Notes

N-Alkylation of Amides. A Novel Procedure

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In view of the known acid-catalyzed reaction of aldehydes[1] and acetals[2] with amides to give methylene diamides it seemed reasonable that the reaction could be adapted to a useful reductive amidation procedure. Thus, when acetamide, acetal, or 2,2-dimethoxypropane, and hydrogen were allowed to react at room temperature in acetic acid solution in the presence of a palladium catalyst and sulfuric acid the corresponding *N*-ethyl- and *N*-isopropylacetamides were produced in about 50% yield. Further investigation will undoubtedly increase the scope and usefulness of this reaction.

Experimental

N-Alkylation of Acetamide.—A mixture of 30 g. (0.51 mole) of acetamide, 62 g. (0.525 mole) of 1,1-diethoxyethane, 2 g. of 10% palladium-on-carbon, and 200 ml. of acetic acid containing 6 g. of concd. sulfuric acid was shaken in an atmosphere of hydrogen (40 p.s.i. initial pressure) for 6 hr., at which time absorption was complete. The catalyst was removed by a filtration and 10 g. of anhydrous sodium acetate added to neutralize the sulfuric acid. After removing the precipitated sulfate, the filtrate was fractionated to yield 20 g. (45%) of pure *N*-ethylacetamide, b.p. 97–98° (8 mm.), $n^{30}D$ 1.4313. The infrared spectrum was identical to that of an authentic sample.

N-Isopropylacetamide was similarly obtained from 2,2-dimethoxypropane in 46% yield, b.p. 87–88° (4.5 mm.), $n^{30}D$ 1.4303, and its identity confirmed by comparison of its infrared spectrum with the spectrum of known material. The use of acetone in place of the ketal or ethanol as a solvent produced none of the desired amide.

(1) For leading references see W. A. Noyes and D. B. Forman, *J. Am. Chem. Soc.*, **55**, 3493 (1933) and W. M. Kraft and R. M. Herbst, *J. Org. Chem.*, **10**, 483 (1945).

(2) C. Bischoff, *Ber.*, **7**, 628 (1874); H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **27**, 2077 (1962).

A New Route to 1-Oxygenated Steroids[1]

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In connection with work currently under way in our laboratory[4] on the relation of mass spectrometric fragmentation patterns and steroid structure, the need arose for a variety of C-1 oxygenated steroids with the 5α-orientation. Oxygenation at C-1 was the last nuclear location for which synthetic procedures were developed in the steroid field and a survey of the literature demonstrates that none of the methods are completely satisfactory.

The starting material for all of the chemical methods is Δ^1-cholesten-3-one (II).[5] Striebel and Tamm,[6] who were the first to develop a feasible route to cholestan-1-one (VIa), converted IIa into the 1α,2α-oxido 3-ketone (IIIa) and reduced it with lithium aluminum hydride. The resulting mixture of glycols (IVa) was partially acetylated at C-3, oxidized at C-1 and the 3-acetoxy group eliminated with alumina to furnish Δ^2-cholesten-1-one (Va), which could be hydrogenated to cholestan-1-one (VI). The Swiss investigators[6] reported an over-all yield of 47% from IIIa to VIa, but Shoppee and collaborators[7] were unable to duplicate the yields in the separation and partial acetylation of the diol mixture (IVa). Their modification involved oxidation of the diols IVa to the 1,3-diketone, preferential mercaptal formation at C-3, followed by desulfurization, the over-all yield of cholestan-1-one (VIa) from the oxido ketone IIa dropping to 14%. Striebell and Tamm[6] also reported that the diol mixture IVa could be completely acetylated and the 1α,3β-diacetoxy component partially saponified at C-3. The free 3β-hydroxy function was removed through the mesylate and iodide to provide cholestan-1α-ol (IXa) in 30% over-all yield.

An alternate scheme was developed by Henbest and Wilson,[8] who reduced Δ^1-cholesten-3-one (IIa) with lithium aluminum hydride, converted the resulting allylic alcohol to the chloride, removed the chlorine atom with lithium aluminum hydride, epoxidized the resulting Δ^1-cholestene and finally opened the oxide ring with lithium aluminum hydride to give cholestan-1α-ol (IXa), the over-all yield from IIa being less than 10%. A second and

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(2) Recipient of a Fulbright Travel Award from the U. S. Educational Commission in the United Kingdom.

(3) Syntex, S. A., Mexico City, Mexico. The present paper represents Part CLXXXXII in the Syntex series on "Steroids."

(4) See H. Budzikiewicz and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1430 (1962), and subsequent papers.

(5) A. Butenandt, L. Mamoli, H. Dannenberg, L. W. Masch, and J. Paland, *Ber.*, **72**, 1617 (1939); C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947).

(6) P. Striebel and C. Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954).

(7) C. W. Shoppee, S. K. Roy, and B. S. Goodrich, *J. Chem. Soc.*, 1583 (1961).

(8) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).

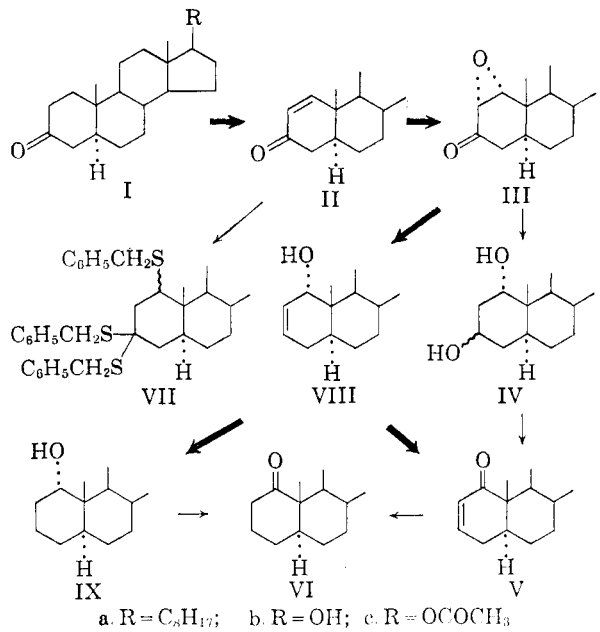
probably inferior approach is due to Plattner,[9a] who prepared a mixture of Δ^1 and Δ^2-cholestenes from IIa *via* the intermediate VIIa, the introduction of the C-1 oxygen function being effected by epoxidation and lithium aluminum hydride reduction. Albrecht and Tamm[9b] simplified this approach by obtaining the mixture of Δ^1- and Δ^2-cholestenes directly through lithium aluminum hydride–aluminum chloride reduction of II. The same authors[9b] also improved the earlier[6] synthesis by developing a seven-step conversion of II into cholestan-1-one (VI) in 30% over-all yield.

In summary, all of the literature procedures suffer either from poor overall yields or a large number of steps, coupled with tedious chromatographic separation of isomers. We should now like to report that application of the recently recorded[10] hydrazine reduction of epoxy ketones to $1\alpha,2\alpha$-oxido-3-keto steroids (III) constitutes the simplest access to a variety of 1-oxygenated steroids.

Cholestan-3-one (Ia) was converted to its 2α-bromo derivative[11] and then dehydrobrominated with calcium carbonate in dimethylacetamide solution.[12] Epoxidation of IIa with alkaline hydrogen peroxide[6] led to $1\alpha,2\alpha$-oxidocholestan-3-one (IIIa),[6] which was reduced in 57% yield with hydrazine hydrate[10] to Δ^2-cholesten-1α-ol (VIIIa). The structure of this allylic alcohol followed from its oxidation[13] with chromium trioxide in acetone solution[14] to the known[6] Δ^2-cholesten-1-one (Va) and from its catalytic hydrogenation in over 90% yield to cholestan-1α-ol (IXa).[6] The over-all yield in the two-step process from the oxido ketone IIIa to cholestan-1α-ol (IXa) is 52%, thus making it by far the most convenient synthetic route to 1-oxygenated 5α-steroids.

The physical constants of our Δ^2-cholestan-1α-ol (VIIIa) proved to be completely different from those recorded by Tamm and Albrecht[15] for the product of the alumina-catalyzed epimerization of 1β-acyloxy-Δ^2-cholestene and to which structure VIIIa had been assigned. Direct comparison with Tamm's specimen[15] showed that the two products were indeed different and that the earlier substance[15] represented a mixture of 3α and 3β-hydroxy-Δ^1-cholestene.[16]

By a similar sequence of reactions, the known[17] Δ^1-androsten-17β-ol-3-one (IIb), was transformed into the oxido ketone IIIb, acetylated at C-17 to give IIIc, and reduced with hydrazine to Δ^2-androstene-$1\alpha,17\beta$-diol 17-acetate (VIIIc). Oxidation with chromium trioxide in pyridine[18] led to Δ^2-androsten-17β-ol-1-one 17-acetate (Vc), an isomer[19] of the male sex hormone testosterone (acetate), which on catalytic hydrogenation provided androstan-17β-ol-1-one 17-acetate(VIc).



Experimental[20]

Δ^2-Cholesten-1α-ol (VIIIa).—$1\alpha,2\alpha$-Oxidocholestan-3-one (IIIa)[6] (2.0 g.) and 12.0 cc. of 100% hydrazine hydrate were heated under reflux for 5 min. while nitrogen was evolved, followed by heating of the two-phase mixture for an additional 15-min. period. Cooling, dilution with water, and extraction with ether provided 1.96 g. of a pale yellow oil, which was passed in benzene solution through a 15-g. column of silica gel (E. Merck AG., Darmstadt, Germany). The benzene-eluted material (1.3 g.) was crystallized from acetone to afford (after drying at 56°/0.1 mm.) 1.1 g. of Δ^2-cholesten-1α-ol (VIIIa) as colorless needles, double m.p. 90–92° and 103–104°, $[\alpha]D$ +124° (*c* 1.4), which possessed no carbonyl absorption in the infrared.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.65; H, 12.11.

Cholestan-1α-ol (IXa).—The above unsaturated alcohol VIIIa (400 mg.) was hydrogenated at room temperature and atmospheric pressure over a period of 4 hr. in 30 cc. of cyclohexane with 100 mg. of 30% palladized charcoal catalyst. Filtration of the catalyst and evaporation to dryness left a crystalline residue, which was recrystallized

(9) (a) P. A. Plattner, A. Fürst, and H. Els, *Helv. Chim. Acta*, **37**, 1399 (1954). (b) R. Albrecht and C. Tamm, *Helv. Chim. Acta*, **40**, 2216 (1957).

(10) P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961); P. S. Wharton, *J. Org. Chem.*, **26**, 4781 (1961).

(11) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935).

(12) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).

(13) Oxidation with dicyanodichlorobenzoquinone [D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Letters*, No. **9**, 14 (1960)] failed, only starting material being recovered.

(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(15) C. Tamm and R. Albrecht, *Helv. Chim. Acta*, **42**, 2177 (1959).

(16) We are indebted to Prof. Tamm (University of Basel) for this information, which will be published elsewhere.

(17) A. Butenandt and H. Dannenberg, *Ber.*, **73**, 206 (1940).

(18) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarrett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(19) W. Schütt and C. Tamm, *Helv. Chim. Acta*, **41**, 1730 (1958), have prepared a similar isomer of progesterone.

(20) All melting points are corrected and were determined in capillaries. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol. The microanalyses are due in part to Mr. E. Meier (Stanford University, Microanalytical Laboratory) and in part to Dr. A. Bernhardt (Mülheim, Germany).

from methanol to furnish 370 mg. of cholestan-1α-ol (IXa) as needles, m.p. 103–105°, $[\alpha]_D$ +33° (*c* 1.2); lit.,[6,8] m.p. 93–95° and 103–105°, $[\alpha]_D$ +35°.

Δ¹-Cholesten-1-one (Va).—A solution of 62.5 mg. of chromium trioxide in 0.09 cc. of 40% sulfuric acid was added dropwise at 22° to a solution of 107 mg. of Δ²-cholesten-1α-ol (VIIIa) in 0.8 cc. of acetone. After shaking for 30 sec., the mixture was diluted with water and ether, the organic phase was separated and washed with water. Evaporation of the dried ether extract and crystallization of the colorless residue (103 mg., $\lambda_{max}^{C_2H_5OH}$ 223 mμ, ε 7100) from methylene chloride–methanol gave 73 mg. of the unsaturated ketone Va as needles or prisms, m.p. 58–60°, $[\alpha]_D$ +128°, $\lambda_{max}^{C_2H_5OH}$ 223 mμ, ε 7700, $\lambda_{max}^{CHCl_3}$ 5.94 μ; lit.,[6] m.p. 58°, $[\alpha]_D$ +124°.

An attempt to oxidize the alcohol VIIIa in benzene solution with dichlorodicyanobenzoquinone[13] (15 hr., 25°) led to recovered starting material (80%), no trace of unsaturated ketone Va being detected by thin-layer chromatography.

Δ²-Androstene-1α,17β-diol 17-Acetate (VIIIc).—A mixture of 15.0 g. of 1α,2α-oxidoandrostan-17β-ol-3-one (IIIb)[21] [m.p. 165–166°, $[\alpha]_D$ +106° (*c* 0.19)], 150 cc. of pyridine, and 70 cc. of acetic anhydride was left at room temperature for 16 hr. and then poured into ice water. Filtration of the precipitate and recrystallization from methylene chloride–heptane afforded 14 g. of the acetate IIIc, m.p. 164–165°, $[\alpha]_D$ +91° (*c* 0.23), λ_{max}^{KBr} 5.78, 5.83, and 8.0 μ; lit.,[21] m.p. 160–161°.

The above 1α,2α-oxidoandrostan-17β-ol-3-one acetate (IIIc) (19 g.) in 400 cc of isopropyl alcohol was mixed with 100 cc. of hydrazine hydrate and 5 cc. of acetic acid, heated on the steam bath for 30 min. (nitrogen evolution), and left at room temperature for 1 hr. Dilution with ice water and isolation with ethyl acetate gave a gummy product, which was chromatographed on 1 kg. of neutral alumina. Elution with benzene-chloroform (1:1) and recrystallization from methylene chloride–heptane provided 7.2 g. of the allylic alcohol VIIIc, m.p. 158–160°, $[\alpha]_D$ +118° (*c* 0.22), λ_{max}^{KBr} 2.95, 5.86, and 8.0 μ.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.74; H, 9.72; O, 14.21.

Δ²-Androsten-17β-ol-1-one 17-Acetate (Vc).—A solution of 1.0 g. of the allylic alcohol VIIIc in 15 cc. of pyridine was added with stirring to a suspension of 1.0 g. of chromium trioxide in 15 cc. of pyridine. After leaving at room temperature overnight, the crystalline product was isolated with ethyl acetate and filtered in benzene solution through 100 g. of neutral alumina. Recrystallization from isopropyl alcohol led to 0.95 g. of 4-Δ²-androsten-17β-ol-1-one 17-acetate (Vc), m.p. 195–196°, $[\alpha]_D$ +116° (*c* 0.32), $\lambda_{max}^{C_2H_5OH}$ 225 mμ, ε 7770, λ_{max}^{KBr} 5.78, 6.01, 6.12, and 8.01 μ.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15; O, 14.53. Found: C, 76.21; H, 8.75; O, 15.03.

Androstan-17β-ol-1-one 17-Acetate (VIc).—A solution of 6.0 g. of the unsaturated ketone Vc in 200 cc. of ethyl acetate was hydrogenated under 30 p.s.i. pressure with 5% palladized charcoal catalyst. After 1 hr., the catalyst was filtered, the solvent evaporated to dryness and the crystalline product (6.0 g., m.p. 140–142°) recrystallized from heptane; m.p. 141–142°, $[\alpha]_D$ +131° (*c* 0.29), λ_{max}^{KBr} 5.77, 5.89, and 8.10 μ. The rotatory dispersion curve closely resembled that[22] of cholestan-1-one (VIa): $[\alpha]_{589}$ +102°, $[\alpha]_{340}$ +313°, $[\alpha]_{317.5}$ +265°, $[\alpha]_{255}$ +1240° (*c* 0.05 in methanol).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.71; H, 9.47.

(21) W. M. Hoehn, *J. Org. Chem.*, **23**, 929 (1958).

(22) C. Djerassi, W. Closson, and A. E. Lippman, *J. Am. Chem. Soc.*, **78**, 3163 (1956).

Reduction of Disulfides with Copper. Preparation of Some Thioethers

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As noted by Adams *et al.*,[1,2] synthetic methods for aryl thioethers lack generality. A necessity for activated reactants and relatively severe experimental conditions are apparent from their summary of known preparative methods. A successful synthesis of both aryl and alkyl aryl thioethers by reaction of various organohalides and certain cuprous mercaptides was described.[1,2] Thus aromatic, heterocyclic, and aliphatic halogens were displaced by cuprous phenyl-, butyl-, ethyl-, and *t*-butylmercaptides and alkylenedimercaptides. While their procedure appeared straightforward, reaction conditions were severe (200–210°) and product isolation was involved. Moreover, isolation of the cuprous mercaptides was a necessary intermediate step. Insolubility of these salts in common organic solvents complicated utility further.

Prior to knowledge of this work a synthesis of thioethers, both aryl and alkyl aryl, which involved direct action of an alkyl or aryl disulfide, an organohalide, and copper powder, was developed in this laboratory. The reactions were conveniently carried out at 160–170° in dimethylacetamide. Most of the reaction intermediates and products were soluble in this medium. Good yields of sulfide were obtained when the solvent was removed by distillation and the residue worked up by appropriate conventional means.

The reaction apparently involves reduction of the disulfide linkage by copper metal forming intermediate cuprous mercaptide which then reacts with halide *via* a typical nucleophilic displacement. As far as can be determined this is the first report of reduction of a disulfide with copper. Disulfides have been reduced by other metals,[3] *e.g.* zinc, sodium, aluminum, and iron, but usually in the presence of acid which generates the corresponding thiols. Arsenic and antimony were used by McLeod[4] and silver by Schönberg *et al.*[5] to cleave certain alkyl and arylacyl disulfides into the corresponding metal mercaptides. None of the latter were employed in further synthesis.

(1) R. Adams, W. Reifschneider, and M. D. Nair, *Croatica Chem. Acta*, **29**, 277 (1957).

(2) R. Adams and A. Ferretti, *J. Am. Chem. Soc.*, **81**, 4927 (1959).

(3) For examples and references see Houben-Weyl, "Methoden der Organischen Chemie," Vol. IX, Georg Thieme Verlag, Stuttgart, pp. 23–25.

(4) G. D. McLeod, U. S. Patent 2,768,192 (1956).

(5) A. Schönberg, E. Rupp, and W. Gumlich, *Chem. Ber.*, **66**, 1932 (1933).

TABLE I

MONOTHIOETHERS

Thioether	Starting Disulfide[a]	B.P. (mm.)	$n^{25}D$	Yield, %	Formula	Sulfur Calcd.	Sulfur Found
n-$C_4H_9SC_6H_5$	$(n$-$C_4H_9S)_2$	123–129 (25)[b]	1.5312	50.8	...	...	...
$C_6H_5SC_6H_5$	$(C_6H_5S)_2$	139–141 (9)	1.631	86.5	...	...	...
m-$BrC_6H_4SC_6H_4CH_3$-p	...[c]	135–145 (0.4)	1.6406	..	$C_{13}H_{11}BrS$	11.48	11.50[d]

[a] Starting halide in every case was bromobenzene. [b] Palladium chloride derivative melts at 107–108°. V. N. Ipatieff, H. Pines, and B. S. Friedman, *J. Am. Chem. Soc.*, **60**, 2731 (1938) report m.p. 106–107° for this derivative, and b.p. 94–97° (4 mm.), $n^{20}D$ 1.5463, for the thioether. [c] By-product from synthesis of m-bis(p-tolylmercapto)benzene (Table II). [d] % Br. Calcd.: 28.62, Found: 28.50.

TABLE II

BISTHIOETHERS

$$RSSR + BrC_6H_4Br \longrightarrow RSC_6H_4SR$$

R	M.P. B.P. (mm.)	Yield, %	Formula	Sulfur Calcd.	Sulfur Found
meta					
C_6H_5	180–185 (0.35)[a]	80.2	$C_{18}H_{14}S_2$	21.78	21.99
p-$CH_3C_6H_4$	240–250 (0.3) 91–92[b]	84.0	$C_{20}H_{18}S_2$	19.87	19.60
o-$NO_2C_6H_4$	151–152[c]	40.0	$C_{18}H_{12}N_2O_4S_2$	16.68	16.70
$C_6H_5CH_2$	180–200 (10) 61–62[d]	46.5	...	...	...
para					
C_6H_5	82–83[e]	32.0[f]	...	...	...

[a] $n^{25}D$ 1.6760. [b] From isopropyl alcohol. [c] From carbon tetrachloride. [d] From ethanol. C. Finzi, *Gazz. chim. ital.*, **44** I, 602 (1914), reports m.p. 60°, prepared in low yield from dithioresorcinol and benzyl bromide. [e] This is the melting point given for this compound in ref. 1. [f] Low yield in this case resulted from utilization of ethylene glycol as solvent.

That reduction of the disulfide bond does occur with subsequent formation of intermediate cuprous mercaptide was proved by conducting one experiment in the absence of any halide. Cuprous phenylmercaptide was isolated in 87.5% yield and proved identical to that prepared by the method of Adams *et al.*[1] It was also shown that the reaction was not one of thermal disulfide cleavage with formation of thiyl radicals. One experiment with phenyl disulfide and dibromobenzene was carried out in the absence of copper powder. No reaction was apparent and no thioether was formed.

While the present synthetic method utilizes disulfides in contrast to the generally more available mercaptans as starting materials, it should be noted that many mercaptans react poorly with cuprous oxide. However, conversion of mercaptans to the corresponding disulfides is almost invariably facile. Moreover some cuprous mercaptides are unstable in the Adam's procedure. For example, Adams and Ferretti[2] found that cuprous benzylmercaptide decomposed into benzyl sulfide and stilbene before it could react with halide present. By our method benzyl disulfide, m-dibromobenzene, and copper gave a 46.5% yield of the expected product, bis(benzylmercapto)-benzene.

An attempt was made to prepare hexaphenylmercaptobenzene from hexachlorobenzene, phenyl disulfide, and copper, but only unidentified black oil was obtained. Evidently, an Ullmann biaryl synthesis occurred between the copper and halide yielding a mixture of products.

In conclusion the thioether synthesis reported here serves as a useful adjunct to that of Adams *et al.* It appears that the only limitation to the present one could be availability of disulfides. At any rate the two related methods provide a general synthesis of aryl and alkyl aryl thioethers.

Experimental[6]

General Procedure for Preparation of Thioethers.—A mixture of 0.1 mole of disulfide, 0.1 mole of dibromide (0.2 mole of monobromide), and 0.2 g.-atom of copper powder in 500–700 ml. of dimethylacetamide was stirred and heated to 135–140° where it was held for 1–2 hr. Reaction started at about 130° and was only mildly exothermic. The copper bronze color gave way to a very light green and cuprous benzenethiolate precipitated.[7] The reaction temperature was then raised to reflux (165–170°). Solids dissolved as the salt reacted and the mixture turned brown. Reflux temperatures were maintained for 10–15 hr. after which dimethylacetamide was distilled. Water and benzene were added to the residue. The insoluble cuprous bromide was collected on a filter and washed with benzene. The latter was combined with the benzene layer, washed with water, and evaporated to a residue, which was purified by distillation or recrystallization. Information regarding the thioethers, their physical properties, analytical data, etc., are presented in Tables I and II.

Little or no yield of thioether was obtained when other solvents–*e.g.*, ethylene glycol and diethylaniline—were tried. Their higher reflux temperatures allowed formation of by-products and they were less effective than dimethylacetamide in dissolving cuprous thiolates.

Refractory impurities were removed from the nitro derivative in Table II by passing a benzene solution through a

(6) All melting and boiling points are uncorrected.

(7) In most cases there was a copious precipitation of solid cuprous thiolate making stirring difficult. Often additional solvent was added to give a stirrable slurry. As reaction progressed, this solid is used up and cuprous halide separates, but it creates no problem.

column of alumina. Some black cupric bromide was formed during the synthesis of the benzyl derivative in Table II indicating that a portion of the dihalide underwent a typical Ullmann biaryl coupling.

Cuprous Benzenethiolate.—Following the same method, but without added halide, a mixture of 15.2 g. (0.07 mole) of phenyl disulfide and 8.9 g. (0.14 g.-atom) of copper powder in 200 ml. of dimethylacetamide was heated to reflux for 3 hr. Water was added to precipitate all the cuprous salt as a light yellow solid, which was collected and washed with ethanol. There was obtained 21 g. (87.5% yield) of dry cuprous benzenethiolate, char point 255°, soluble in pyridine, insoluble in water.

Anal. Calcd. for C_6H_5CuS: S, 18.57. Found: S, 18.4. These results are identical to those produced by the same salt prepared by another method[1] from benzenethiol and cuprous oxide in ethanol.

Acknowledgment.—The author wishes to express his gratitude to Dr. E. E. Campaigne for the basic postulation behind this work. Appreciation is also extended to our Analytical Group who performed all analytical determinations and to Dr. Q. E. Thompson for his helpful suggestions concerning the manuscript.

The Preparation of Cycloheptylamine

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The need in this laboratory for pure cycloheptylamine prompted an investigation of methods of synthesis in which readily available or easily prepared intermediates could be used. Since the Ritter reaction with cycloheptanol gives a mixture of products[1] and chemical reduction of cycloheptanone oxime results in poor yield,[2] they were not considered. A more logical approach appeared to be reductive amination of cycloheptanone (A) or catalytic hydrogenation of its oxime (B). While method A gave a good yield, the resultant product was found to be contaminated with cycloheptanol. High pressure reduction of the oxime in the presence of Raney nickel and ammonia gives a good yield.[3] However, except in small size runs, the exothermicity of the reaction even with a low catalyst ratio made us aware that the reduction could get out of hand. Rhodium-on-alumina on the other hand proved highly satisfactory even with undistilled oxime in low pressure hydrogenations in the absence of ammonia. Under these conditions, uptake of hydrogen was entirely too slow when Raney nickel was used.

(1) R. Jacquier and H. Christol, *Bull. Soc. Chim.*, 560 (1954).

(2) W. Markownikoff, *J. Russ. Phys. Chem. Soc.*, **25**, 365 (1893), and V. Prelog, M. F. El-Neweihy, and O. Häflinger, *Helv. Chim. Acta*, **33**, 365 (1950).

(3) A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Am. Chem. Soc.*, **75**, 3212 (1953).

Experimental

Method A.—A solution of 101.5 g. (0.905 mole) of cycloheptanone,[4] 100 cc. of ethyl alcohol and 100 cc. of liquid ammonia was placed in a 1-l. rocker bomb. Raney nickel (20.0 g.) was added and the mixture hydrogenated at 70° and 100 atm. Uptake of hydrogen was complete in less than 1 hr. The reaction mixture was filtered from the catalyst and the solution and washings concentrated. The residue was treated with 20% hydrochloric acid and the mixture extracted with ether to remove cycloheptanol (about 20 g. of crude alcohol was obtained). The acidic solution was kept at room temperature while adding solid potassium hydroxide until the mixture was strongly basic. The mixture was then extracted thoroughly with ether (some water may be added to dissolve potassium chloride). The extract was dried over potassium hydroxide. The solution was filtered and the ether distilled. The residue on fractionation yielded 61% of cycloheptylamine boiling at 172–175° (750 mm.).[5]

Low pressure reductions with a higher catalyst ratio (30%) required a longer time but gave about the same yield.

Method B. Cycloheptanone Oxime.[6]—A solution of 4000 g. (35.72 moles) of cycloheptanone in 3500 cc. of methyl alcohol was treated with 3000 g. (43.16 moles) of hydroxylamine hydrochloride. It was then stirred for 1 hr. while heating to 80°. While this temperature was maintained, a solution of 1560 g. of sodium hydroxide in 3500 cc. of water was added over a 4-hr. period. The reaction mixture was then refluxed for 1–2 hr. and allowed to cool to room temperature. An oily layer separated, which was removed and dried over anhydrous magnesium sulfate. The oil,[7] after filtration from the drying agent, was dissolved in 9000 cc. of methyl alcohol and placed in a 10-gal. glass-lined reactor, to which 450 g. of 5% rhodium-on-alumina[8] was added. The mixture was hydrogenated under 0.75 to 1.0 atm. The temperature rose gradually to 60° and was maintained there until reduction was complete. The solution was filtered from the catalyst and concentrated. The residue was fractionated. An over-all yield of 80% of cycloheptylamine based on cycloheptanone was obtained.

Hydrogenation of distilled oxime carried out in a Parr shaker under 3 atm. pressure gave about the same over-all yield.

(4) Aldrich Chemical Co., Milwaukee, Wis.

(5) R. Willstatter, *Ann.*, **317**, 204 (1901), reports 169°.

(6) The method is essentially as described for benzophenoneoxime by A. Lachman, *Org. Syntheses*, Coll. Vol. I, 10 (1930).

(7) Cycloheptanoneoxime from a 675-g. run was distilled successfully. An 86% yield of product boiling at 125–130° (22 mm.) was obtained. When distillation of a larger run was attempted, decomposition took place, resulting in the thermometer being blown from the stillhead.

(8) Baker and Co., Division of Engelhard Industries, 113 Astor Street, Newark, N. J.

A Correlation in the Infrared Spectra of Some C-Benzoylated Nitrogen Heterocycles

D. G. FARNUM[1] AND PETER YATES[2]

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In the course of studies related to heterocyclic chemistry[3] we have had occasion to examine the

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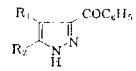
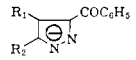
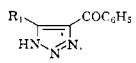
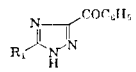
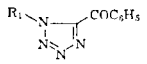
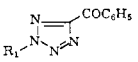
TABLE I

	R_1	R_2	Medium[a]	λ_{max} (μ)[b]	Intensity Ratio (ϵ_r)[c]
	C_6H_5	H	N	6.06 10.88[d]	0.7
	C_6H_5	OH	N	6.13 11.02	0.6
	C_6H_5	C_6H_5	D	6.08 11.05	1.1
	H	C_6H_5	D	6.07 11.20[e]	0.6
	OH	C_6H_5	N	6.16 11.05	0.7
	$OCOCH_3$	C_6H_5	D	6.12 11.00	1.2
	COC_6H_5	COC_6H_5[f]	D	6.02 11.00[d]	0.9
	$N_2^{\oplus}$	C_6H_5	D	6.08 11.15[e]	1.0
	C_6H_5	$N_2^{\oplus}$	D	6.06 11.05[e]	1.6
	$NHCOC_6H_5$	...	N	6.11 10.70	1.1
	COC_6H_5	...	N	6.09 10.81[e]	0.7
	$NHCOC_6H_5$	...	N	6.00 10.82[e]	0.5
	H	...	N	6.03 10.80[e]	0.9
	CH_3[g]	...	D	5.99 10.88	1.1
	$CH_2CO_6H_5$	...	D	5.95 10.82[h]	1.0
	$CH_2COC_6H_5$	...	D	5.97 10.80[h]	0.9

[a] N = Nujol mull; D = dichloromethane solution. [b] Where more than one carbonyl-stretching band occurs, only that assignable to the benzoyl group is given. [c] Ratio of apparent extinction coefficients of the benzoyl band and that in the 10.7–11.2-μ region. [d] Compared with the corresponding 2-pyrazoline. [e] Compared with the compound having the C-benzoyl group replaced by a benzyl group. [f] P. Yates and T. J. Clark, *J. Org. Chem.*, **27**, 286 (1962). [g] This compound is either 1-methyl- or 2-methyl-5-benzoyltetrazole. [h] Compared with the corresponding *N*-phenacyltetrazole.

infrared spectra of sixteen compounds which possess the common feature of a benzoyl group attached to a carbon atom of a heteroaromatic system containing two or more nitrogen atoms. We have observed that the spectra of all of these compounds show a strong band in the region 10.7–11.2 μ whose intensity is of the same order as that of the carbonyl-stretching band due to the benzoyl group. Although we have not established the nature of the vibration which gives rise to this band, we report these data here since the correlation has been found to be useful as a diagnostic aid in structural determinations.[4]

The positions of this band and the carbonyl-stretching band of the benzoyl group in each case are given in Table I together with the ratio (ϵ_r) of the apparent extinction coefficients of the two bands.[7] The latter may be seen to fall in the range 0.5–1.6. In several instances it has been possible to examine the spectra of the corresponding compounds in which the benzoyl group is replaced by a benzyl group; in all of these cases, the spectra show only very weak bands or no bands in the 10.7–11.2-μ region. Further, while the spectra of 3-benzoyl-4-phenylpyrazole and 3,4,5-tribenzoylpyrazole show strong bands in this region, those of the corresponding 2-pyrazolines show only weak absorption, although each possesses a strong band at 11.6 μ. It may also be noted that the spectra of 1- and 2-phenacyltetrazole lack the strong bands at 10.8 μ present in the spectra of their 5-benzoyl derivatives.

We have not examined whether this correlation applies also to C-acyl derivatives of these heterocycles, or is restricted to the benzoyl series. However, recently published spectra[8] of 3-acetylpyrazole and 3-pivaloylpyrazole show bands, in the 10.5–11-μ region, whose intensities appear to be of the same order as those of the corresponding carbonyl-stretching bands.

(3) P. Yates and D. G. Farnum, *Tetrahedron Letters*, No. 17, 22 (1960); D. G. Farnum and P. Yates, *Chem. Ind.* (London), 659 (1960).

(4) It has been suggested[5] that an absorption band at 10.7 μ is characteristic of the pyrazole ring; this view has not been supported by our own studies nor by those of others.[6]

(5) C. S. Rondestvedt and P. K. Chang, *J. Am. Chem. Soc.*, **77**, 6532 (1955).

(6) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **26**, 1716 (1961).

(7) It must be noted that the solvent used for the solution spectra, dichloromethane, is not that of choice since it has a weak absorption band at 11 μ; the values of ϵ_r quoted are thus approximate in nature.

(8) Yu. N. Sheinker, I. Ambrush, and N. K. Kochethov, *Doklady Akad. Nauk S.S.S.R.*, **123**, 709 (1958).

Inductive Constants for the Cyclohexyl and 3-Cyclohexenyl Radicals

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Received February 5, 1962

In connection with another study[2] concerning neighboring double-bond participation in cyclohexenylcarbinyl systems it was desired to have σ^* constants for the cyclohexyl and 3-cyclohexenyl

groups. Although a σ^* value for cyclohexyl has been reported,[3] it is based on a secondary comparison rather than the fundamental definition of σ^* in terms of rates of acidic and basic ester hydrolyses;[4] no σ^* value for the 3-cyclohexenyl group has been reported. This note reports the required acid and base catalyzed rates of hydrolysis of the ethyl esters of cyclohexanecarboxylic acid (I), and 3-cyclohexenecarboxylic acid (II). From these data and the corresponding rates for ethyl acetate are calculated the desired σ^* constants.

I II

Table I summarizes the measured rate data; the footnotes of this table cite relevant literature data for comparison. In making these comparisons, it will be noted that the previous data was for hydrolysis in a slightly more aqueous solvent than that employed here. Consideration of the effect of water on hydrolysis rates in other acetone–water mixtures[6] indicates that the extra water has no significant effect here and that the rates may be compared directly without correction. Although the internal and external agreement in Table I is only fair (± 6–10%) in some cases, it is quite adequate for calculating σ^* constants, since as logarithmic quantities they are insensitive to small changes in rate.

TABLE I

SECOND-ORDER RATE CONSTANTS FOR ACID AND BASE HYDROLYSIS AT 25.0° IN 70% (V./V.) ACETONE–WATER[a]

Compound	Nature of Hydrolysis	k, Mole^{-1} Sec.$^{-1}$
Ethyl acetate[b]	Base	5.4×10^{-2}
Ethyl acetate[c]	Acid	4.6×10^{-5}
Ethyl cyclohexanecarboxylate	Base	$(1.74 \pm 0.03) \times 10^{-3}$
Ethyl cyclohexanecarboxylate[d]	Acid	$(7.2 \pm 0.4) \times 10^{-6}$
Ethyl 3-cyclohexenecarboxylate	Base	$(4.86 \pm 0.00) \times 10^{-3}$
Ethyl 3-cyclohexenecarboxylate	Acid	$(8.8 \pm 0.4) \times 10^{-6}$

[a] This corresponds to *ca.* 65% (w./w.) acetone–water. [b] A rate constant of 4.9×10^{-2} can be estimated from a plot of log k *vs.* $1/T$ for the eight rates measured by Davies and Evans,[5] Nair and Anantakrishnan,[6] and Rylander and Tarbell[7] at eight different temperatures all in *ca.* 62% (w./w.) acetone–water. The slope of this plot yields an E_a of 11.8 kcal. [c] Reported value,[5] 4.6×10^{-5} (extrapolated from 24.8°). [d] Reported value,[8] 7.4×10^{-6}.

Insertion of the data from Table I (using the value of 4.9×10^{-2} for the basic ethyl acetate hydrolysis) into equation (1)[4] yields the σ^* values shown below. The deviations

$$\sigma^* = \frac{1}{2.48}\left[\log(k/k_0)_B - \log(k/k_0)_A\right] \quad (1)$$

$\sigma^* = -0.26 \pm 0.02$

$\sigma^* = -0.12 \pm 0.02$

ascribed to these values are based on the observed deviations in the rate constants of Table I. By way of comparison the average of the probable errors in fit of other σ^* constants is greater than 0.03 unit.[3]

Because of the lack of data for reactions or equilibria of known freedom from steric influences, it is difficult to assess independently the validity of these two σ^* constants. The previously assigned σ^* for cyclohexyl (0.15)[3] was based on the acidity of cyclohexanecarboxylic acid in water at 25°. Unfortunately, as Taft has pointed out,[9] acid equilibria are susceptible to steric influences and both the cyclohexyl and 3-cyclohexenyl groups would be expected to exhibit steric complications. The enhanced acidity of α-ethylbutyric acid (R = diethylcarbinyl) computed from the $\rho^*\sigma^*$ plot corresponds to a σ^* deviation of *ca.* +0.16 unit. If cyclohexyl were assigned the same positive deviation, the corrected σ^* estimated from its pK_a would be −0.31. The less negative observed value of −0.26 is in line with the idea that steric effects are less important with cyclohexyl than with diethylcarbinyl. Moreover, from an inductive point of view, it would be supposed that the cyclohexyl σ^* should be very slightly more negative than that of the diethylcarbinyl group ($\sigma^* = -0.23$) as is observed. Finally, in support for at least the difference between the σ^*'s of cyclohexyl and 3-cyclohexenyl, it should be mentioned that the assigned values correlate well with nine pairs of solvolysis rates.[2]

Experimental

Ethyl 3-Cyclohexene-1-carboxylate (II).—In a steel bomb containing 20 g. (0.2 mole) of ethyl acrylate and 0.5 g. of hydroquinone was condensed 13.5 g. (0.25 mole) of butadiene. The sealed bomb was heated at 160–165° for .5 hr. Distillation of the crude product gave 28.3 g. (93%) of ethyl 3-cyclohexene-1-carboxylate, b.p. 84° (23 mm.), n^{25}D, 1.4540 (lit.,[10] b.p. 194–195°, n^{20}D, 1.4578).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.09; H, 9.15. Found: C, 69.96; H, 9.20.

Ethyl Cyclohexanecarboxylate (I).—A solution of the

(1) Taken from the dissertation submitted by S. S. Chibber to Cornell University for the Ph.D. degree, September, 1961.

(2) C. F. Wilcox, Jr., and S. S. Chibber, manuscript submitted for publication.

(3) R. W. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, Inc., New York, 1956, p. 619.

(4) R. W. Taft, *ibid.*, p. 587.

(5) G. Davies and D. P. Evans, *J. Chem. Soc.*, 339 (1940).

(6) P. M. Nair and S. V. Anantakrishnan, *Proc. Indian Acad. Sci.*, **32A**, 187 (1950).

(7) P. M. Rylander and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 3021 (1950).

(8) H. A. Smith and J. H. Steele, *J. Am. Chem. Soc.*, **63**, 3466 (1941).

(9) R. W. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, Inc., New York, 1956, ref. 5 in Table IX.

(10) N. Chayanov, *Zhur. Obshchei Khim.*, **8**, 460 (1938).

cyclohexenyl ester II in 95% ethanol was reduced over 10% palladium on charcoal in a Parr hydrogenation apparatus. Fractional distillation of the product gave a 62% yield of the saturated ester, b.p. 97° (23 mm.), $n^{25}D$ 1.4387 (lit.,[11] b.p. 195–200, $n^{25}D$ 1.4396).

Alkaline Hydrolyses.—Except in the case of ethyl acetate, approximately 0.1 *M* solutions of the esters were prepared by dissolving the required amount of ester in 70 ml. of anhydrous acetone and diluting with 30 ml. of water. In the case of ethyl acetate an approximately 0.4 *M* aqueous solution was prepared and 30 ml. of this solution diluted with 70 ml. of acetone. The concentration of each ester solution was checked before use by complete hydrolysis with excess base and back titration with acid.

For the alkaline hydrolyzing agent, 30 ml. of *ca.* 0.33 *M* carbonate free sodium hydroxide was diluted with 70 ml. of acetone.[12] The concentration of this solution was determined by titration immediately before use.

After the ester and base solutions had both equilibrated at 25.0°, 50 ml. of each solution was transferred into a 100-ml. volumetric flask which was stoppered, well shaken and quickly returned to the thermostat. The reaction was followed by withdrawing 5-ml. aliquots at suitable time intervals, running them into 10 ml. of 0.05 *N* hydrochloric acid, and finally titrating the excess acid with 0.05 *N* sodium hydroxide solution against phenolphthalein.

The second-order rate constants were computed by the Widequist technique.[13]

Acid Hydrolyses.—The ester and hydrochloric acid solutions were prepared in the same manner as described under the base hydrolyses. Because of the slow rate of reaction and the volatility of the solvent, 5-ml. aliquots were sealed in glass ampoules and these equilibrated at 25.0°. At suitable time intervals the contents of a tube were titrated with sodium hydroxide solution.

The rate constants were calculated in the standard fashion.[5]

(11) S. Ono and T. Yamauchi, *Bull. Chem. Soc. Japan*, **25**, 404 (1952).

(12) In an attempt to prepare 0.2 *N* solutions of sodium hydroxide in 70% acetone–water, a difficulty visible phase separation occurred. The volumes and composition of the two phases appears to be critically dependent on the concentration of base. With the 0.1 *N* base employed here no phase separation was noted.

(13) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, 1953, p. 18.

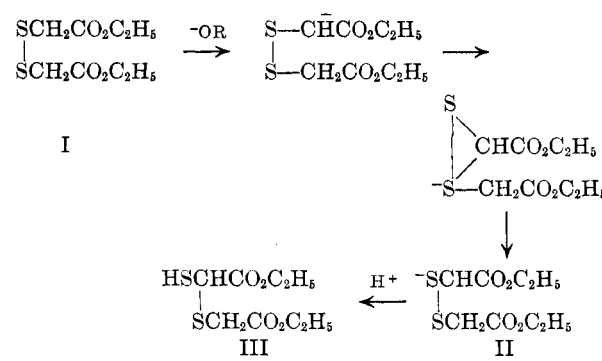
Base-Catalyzed Rearrangement of Diethyl Dithiodiglycolate

E. G. HOWARD

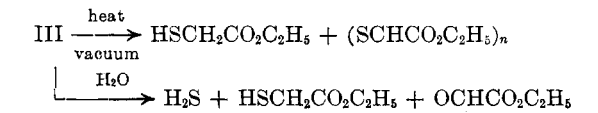
Contribution No. 695 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Del.

Received June 8, 1961

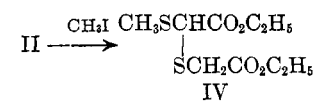
The diethyl ester of dithiodiglycolic acid (I) has been found to undergo a rapid rearrangement, even at −50°, when treated with sodium alkoxide, and the product has proved to be the sodium salt of diethyl 2-mercapto-3-thiaglutarate (II). The ionization of a methylene group is pictured as being the first step in the rearrangement. The carbanion possibly forms a three-membered ring that rearranges to the product II.



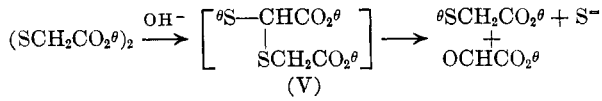
The assignment of structure is based on the following physical and chemical properties of compound III. (1) The infrared absorption spectrum possesses a band at 3.95 μ, which is indicative of the mercaptan group. (2) Slow distillation of III gives ethyl mercaptoacetate and a liquid believed to be a trimer of ethyl thioglyoxylate. (3) Compound III gives a positive sodium nitroprusside test. (4) Titration of III with iodine solution requires more titer when smaller samples or more dilute solutions are used or when the titrations are carried out over an extended period of time. These are conditions which would permit the hydrolysis of an unstable hemimercaptal group to a mercaptan



(5) Methylation of the anion II with methyl iodide gave IV which is stable and easily purified by distillation



It is suggested that compounds of type III are involved in the cleavage of dithiodiglycolic acids by aqueous base where the product is in turn hydrolyzed to salts of hydrogen sulfide, mercaptoacetic acid, and glyoxylic acid.[1] Supporting evidence is found in the fact that I gave the typical yellow color of II even when treated with 30%



aqueous sodium hydroxide at 0°. A yellow color similar to that of II has also been observed in the rearrangement of dithiodiglycolic acid.[2]

(1) A. Schobel, *Ber.*, **70**, 1186 (1937), *et seq.*

(2) N. A. Rosenthal and G. Oster, Organic Section, 126th Meeting of the American Chemical Society, September, 1954, New York, N. Y., report that a chromophore is produced in the reaction. We found the color to be yellow.

Experimental

Rearrangement of Diethyl Dithiodiglycolate (I).—To sodium methoxide prepared by the addition of 2.3 g. (0.1 g.-atom) of sodium to methanol was added 250 ml. of absolute ether. To the stirred mixture was added at −20° a solution of 23.8 g. (0.1 mole) of diethyl dithioglycolate. The mixture immediately turned deep yellow in color and a small amount of solid precipitated. To obtain the free mercaptan, a mixture of ice, 20 ml. of concd. hydrochloric acid, and water was added to the cold reaction mixture. The organic layer was separated and dried over anhydrous magnesium sulfate. Removal of the solvent by vacuum distillation gave a pale yellow oil possessing a mercaptan odor. When the material was distilled rapidly through a short head still, a fraction was obtained, b.p. 103–104° (0.10 mm.), $n^{25}D$ 1.5042, which possessed a penetrating mercaptan odor.

Anal. Calcd. for $C_8H_{14}O_4S_2$: C, 40.31; H, 5.92; S, 26.91; mol. wt., 238. Found: C, 39.68; H, 5.53; S, 29.95; mol. wt., 208.

The infrared absorption spectrum possessed a band at 3.95 μ, which is characteristic of the mercaptan group.

The product (109 g., 92%) from a similar reaction using five times the above quantities was subjected to a slow precision distillation through an 18-in. column. The distillate, b.p. 28–30° (0.4 mm.) (pot temperature, 110°), weighed 42 g. The residue (51 g.) did not distill up to 170° (0.4 mm.) and was a liquid polymer of ethyl thioglyoxylate The distillate was redistilled, b.p. 60–61° (21 mm.), and was ethyl mercaptoacetate.

Anal. Calcd. for $C_4H_8O_2S$: C, 39.98; H, 6.71; S, 26.68. Found: C, 40.08; H, 6.79; S, 26.60.

Addition of diethyl dithiodiglycolate to either 20% aqueous sodium hydroxide at 25° or 30% aqueous sodium hydroxide at 0° gave the characteristic intense yellow color of the anion II.

Methylation of the Sodium Salt of Diethyl 2-Mercapto-3-Thiaglutarate (II).—The rearranged product from 71.5 g. (0.3 mole) of diethyl dithiodiglycolate and 0.33 mole of sodium ethoxide was stirred vigorously at −30°. When 47 g. (0.33 mole) of methyl iodide was added, the temperature rose to −10°. After 1 hr. at 0° and 2 hr. at 30°, the mixture was poured into water. The organic layer was taken up in ether, washed with dilute aqueous sodium hydroxide and water, and dried over anhydrous magnesium sulfate. The fraction (42 g.) boiling between 40 and 150° was rectified by precision distillation through an 8-in. spinning-band column using a reflux ratio of 10:1. The product weighed 21 g. (28%), b.p. 116–118° (0.40 mm.), $n^{25}D$ 1.4990 to 1.5033, proved to be diethyl 2-methylmercapto-3-thiaglutarate (IV). A center cut of this fraction, 4.6 g., b.p. 117–118° (0.40 mm.), $n^{25}D$ 1.4990, was analyzed.

Anal. Calcd. for $C_9H_{16}S_2O_4$: C, 42.84; H, 6.39; mol. wt., 252. Found: C, 42.89; H, 6.45; mol. wt., 250.

Amperometric titration with silver nitrate indicated the presence of less than 0.7% mercaptan group. The infrared absorption spectrum resembled that of compound III except that there was no characteristic band for the mercaptan group. Also the 7.3-μ band for methyl was stronger.

The Synthesis of Tetrahydropalmatrubine[1]

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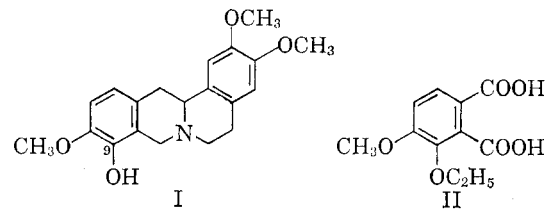
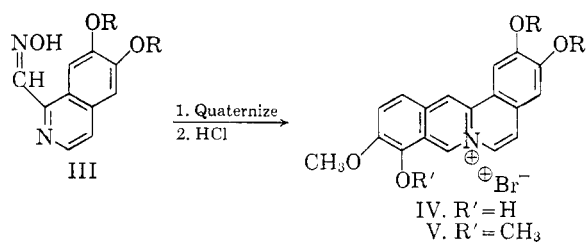
Received August 9, 1961

The chloride salt of the berberine alkaloid palmatine undergoes monodemethylation to yield a red compound, palmatrubine.[2] Späth and Burger[3] reduced palmatrubine to tetrahydropalmatrubine (I), and by ethylation, followed by oxidation to 3-ethoxy-4-methoxybenzene-1,2-dicarboxylic acid (II), established beyond doubt that the free hydroxyl group must have been at position 9.



Since it has been shown that the aromatic cyclodehydration method makes possible the formation of the dehydroberberinium nucleus under very mild conditions,[4–6] it seemed probable that the first unequivocal synthesis of the tetrahydrapalmatrubine nucleus could be effected.

Crude 2-hydroxy-3-methoxybenzyl bromide formed with 6,7-dimethoxyisoquinoline-1-carboxaldoxime[6] (III. R = CH_3), a quaternary salt which cyclized in concentrated hydrochloric acid at 100° in only a few minutes to afford the new dehydropalmatrubinium bromide (IV. R = CH_3). Catalytic reduction of the bromide salt gave tetrahydropalmatrubine[1]:



Dehydroberberubinium bromide (IV. R—R = —CH_2—) and its acetate were prepared also. A comparison of the ultraviolet absorption spectra of the new dehydro systems (IV) with those of the related dehydroberberinium salts (V)[5,6] is shown in Table I.

(1) This research was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health.

(2) K. Feist and G. L. Dschu, *Arch. Pharm.*, **263**, 294 (1925).

(3) E. Späth and G. Burger, *Ber.*, **59**, 1486 (1926).

(4) C. K. Bradsher and J. H. Jones, *J. Org. Chem.*, **23**, 430 (1958).

(5) C. K. Bradsher and N. L. Dutta, *J. Am. Chem. Soc.*, **82**, 1145 (1960).

(6) C. K. Bradsher and N. L. Dutta, *J. Org. Chem.*, **26**, 2231 (1961).

(7) All melting points are uncorrected. The ultraviolet absorption spectra were determined in 95% ethanol using the Warren Spectracord spectrophotometer with 1-cm. silica cells.

(8) N. Mauthner, *J. prakt. Chem.*, **158**, 321 (1941).

TABLE I
COMPARISON OF ULTRAVIOLET ABSORPTION SPECTRA OF DEHYDRORUBINIUM (IV) WITH ANALOGOUS DEHYDROBERBERINIUM SYSTEMS (V)

Dehydro-	max, mμ[a]					min, mμ			
Palmatrubinium	248	281		354	477	263		337	412
Palmatinium	246	285	328	355	464	268	306	344	404
Berberubinium	249	281		352	470	268		334	415
Berberinium[b]	246	278	310	348	460	257	290.5	332	405

[a] Except as noted, bromides were used. [b] As chloride.

Experimental[7]

3-Methoxy-2-hydroxybenzyl alcohol[8] (prepared in 68% yield by sodium borohydride reduction of the aldehyde) was converted to the bromide by treatment with phosphorus tribromide. The crude 3-methoxy-2-hydroxybenzyl bromide was not purified.

Dehydropalmatrubinium (IV. R = CH_3) Bromide.—One gram of 6,7-dimethoxyisoquinoline-1-carboxaldoxime[6] was allowed to react with 1 g. of crude 3-methoxy-2-hydroxybenzyl bromide in 7 ml. of dimethylformamide, at first for a few minutes in the steam bath, and then at room temperature for 24 hr. The yellow crystals of the crude quaternary salt were collected, washed with ether, and then cyclized by heating on the steam bath with 12 ml. of concd. hydrochloric acid. After only 10 min. red crystals started to precipitate. The mixture was cooled and the product collected and recrystallized from methanol–ethyl acetate as red needles, m.p. 218–220° dec. (sealed tube), yield 2 g. (100%).

Anal. Calcd. for $C_{20}H_{18}BrNO_4 \cdot 2H_2O$: C, 53.10; H, 4.86; N, 3.10. Found: C, 53.50; H, 4.69; N, 3.32.

The Perchlorate (IV. R = CH_3) crystallized from dimethyformamide-methanol as red needles, m.p. 313–314° dec. (sealed tube).

Anal. Calcd. for: $C_{20}H_{18}ClNO_8 \cdot 2H_2O$: C, 50.90; H, 4.66; N, 3.00. Found: C, 51.22; H, 4.86; N, 3.16.

Tetrahydropalmatrubine (I).—A suspension containing 200 mg. of dehydropalmatrubinium bromide in 150 ml. of methanol was hydrogenated at atmospheric pressure for 2 days in the presence of 40 mg. of platinum oxide catalyst. The colorless solution was concentrated under reduced pressure and the residue treated with a dilute solution of sodium carbonate and then extracted with ether. The residue obtained by evaporation of the ether was crystallized twice from dilute methanol as colorless prisms, m.p. 148° (lit.,[3] m.p. 148–149°). The base slowly develops color on storage.

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.38; H, 6.74; N, 4.10. Found: C, 70.33; H, 6.93; N, 3.95.

Dehydroberberubinium (IV. R—R= —CH_2—) Bromide.—Quaternization of 1.1 g. of 6,7-methylenedioxyisoquinoline-1-carboxaldoxime[5] with 1.1 g. of crude 3-methoxy-2-hydroxybenzyl bromide was carried out in 9 ml. of dimethylformamide and the product cyclized as in the case of dehydropalmatrubine. Two grams (100%) of red needles were obtained, m.p. 203–205° dec.

Anal. Calcd. for $C_{19}H_{14}BrNO_4$: C, 57.00; H, 3.50; N, 3.50. Found: C, 56.83; H, 3.63; N, 3.35.

The perchlorate (IV. R—R = —CH_2—) crystallized from dimethylformamide–methanol as red needles, m.p. 338° dec.

Anal. Calcd. for $C_{19}H_{14}NClO_8$: C, 54.35; H, 3.33; N, 3.33. Found: C, 54.48; H, 3.46; N, 3.40.

Acetyldehydroberberubinium Bromide.—Dehydroberberubinium bromide was acetylated by refluxing for 3 hr. in acetic anhydride. The product crystallized from methanol as yellow prisms, m.p. 145–146°, and slowly turned to a buff color on keeping.

Anal. Calcd. for $C_{21}H_{16}BrNO_5$: C, 57.01; H, 3.61; N, 3.16. Found: C, 57.32; H, 3.90; N, 3.15.

Diisothiocyanates and Derivatives[1]

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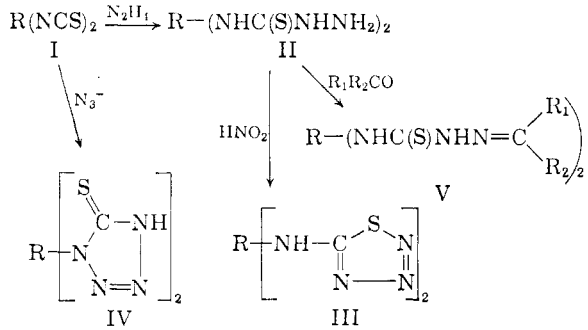
Received August 15, 1961

The present investigation relates to the synthesis of difunctional compounds of the aminothiatriazole and tetrazolinethione series.[4,5] For this purpose, diisothiocyanates (I) were prepared from diamines and their conversion to di-thiosemicarbazides (II), -aminothiotriazoles (III), and -tetrazoline-5-thione (IV) studied. Most of the compounds thus prepared have not been previously reported. Thiosemicarbazones (V) were prepared to characterize II.



The infrared absorption spectra of I, II, III, and IV were determined. All of the diisothiocyanates show a strong or medium band, near 2040 cm.$^{-1}$ or between 2062–2105 cm.$^{-1}$. The 2040-cm.$^{-1}$ band is slightly lower than the characteristic vibrational frequencies for the monofunctional isothiocyanates.[6] It has been suggested that the bands in the 1000–1100-cm.$^{-1}$ region are due to the isothiocyanate stretching vibration.[6] As in the monofunctional compounds[7] the S—H band (2600–

(1) The authors gratefully acknowledge the support of this investigation by the U. S. Army Research Office.

(2) To whom all correspondence should be addressed.

(3) Abstracted from the M.S. Thesis, DePaul University, Chicago, Ill., 1961.

(4) E. Lieber, C. N. Pillai, and R. D. Hites, *Can. J. Chem.*, **35**, 832 (1957).

(5) E. Lieber, C. N. Pillai, J. Ramachandran, and R. D. Hites, *J. Org. Chem.*, **22**, 1750 (1957).

(6) E. Lieber, C. N. R. Rao, and J. Ramachandran, *Spectrochimica Acta*, **13**, 296 (1959).

(7) E. Lieber, C. N. R. Rao, J. Ramachandran, and R. D. Hites, *Can. J. Chem.*, **36**, 801 (1958).

TABLE I
DIISOTHIOCYANATES R(NCS)$_2$

R	Functional Positions, (NCS)$_2$	% Yield[a]	M.P. Found	M.P. Reptd.	Ref.	Cryst. Form	Formula	N Calcd.	N Found	S Calcd.	S Found
C_6H_4	1,4	67	132	130–131	[b]	Pr. ndls.	$C_8H_4N_2S_2$				
2-Cl—C_6H_3[c,d]	1,4	59	58	[e]	[e]	Lt. yel. lftls.	$C_8H_3ClN_2S_2$	12.36	12.56	28.26	27.60
2-CH_3—C_6H_3[c]	1,4	47	75			Lt. yel. ndls.	$C_9H_6N_2S_2$	13.59	13.78	31.07	31.22
C_6H_4[f]	1,3	59	54–55	53, 55	[b]	Wh. ndls.	$C_8H_4N_2S_2$	14.58	14.70	33.33	33.25
4-Cl—C_6H_3[c,g]	1,3	60[h]	33			Wh. lflts.	$C_8H_3ClN_2S_2$	12.36	12.09	28.26	27.45
4-CH_3—C_6H_3	1,3	45	57	56	[b]	Wh. ndls.	$C_9H_6N_2S_2$	13.59	13.81	31.07	30.90
4-CH_3O—C_6H_3[c]	1,3	70	96			Lt. yel. pr.	$C_9H_6N_2OS_2$	12.61	12.42	28.83	28.65
$C_{13}H_{10}$[i,j]	4,4′	69	138–139	143–144 196	[k]	Lt. yel. ndls.	$C_{14}H_{10}N_2S_2$	9.93	10.27	22.70	22.81
$C_{14}H_{12}$[c,l]	4,4′	84	126–127			Lt. yel. ndls.	$C_{16}H_{12}N_2S_2$	9.46	9.55	21.62	21.68
$C_{10}H_6$[c,l,m]	1,5	35	177–178			Wh. ndls.	$C_{12}H_6N_2S_2$	11.57	11.41	26.45	26.59
C_2H_4	1,2	16	B.p. 100/3 mm.	B.p. 141/10 151/15	[n]	Lt. yel. liq.	$C_4H_4N_2S_2$	19.44	19.61	44.44	44.19

[a] Based on pure product. [b] O. Billeter and A. Steiner, *Ber.*, 20, 230 (1887). [c] New compound. [d] Calcd.: Cl, 15.67. Found: Cl, 15.65. [e] Not reported. [f] The monothiourethane was obtained from ethanol–acetone, m.p. 72–73°, calcd. for $C_{10}H_{10}N_2OS$; N, 11.78; S, 26.90. Found: N, 11.90; S, 26.95. [g] Calcd.: Cl, 15.67; Found: Cl, 14.98; the product tend to revert to an oil. [h] Crude. [i] Diphenylmethane, $C_6H_4CH_2C_6H_4$. [j] Calcd.: C, 63.83; H, 3.55. Found: C, 63.98; H, 3.69. [k] Ref. 9 and 11. [l] Bibenzyl group. [m] Naphthalene group. [n] Ref. 10.

2500 cm.$^{-1}$) was not evident. The absence of this band in the spectra of IV supports the structure given. The di(tetrazolinethiones) (IV) showed bands previously observed for this class.[7] Absorption bands near 1500 cm.$^{-1}$ and 1330–1370 cm.$^{-1}$ have been assigned, tentatively, to the N—C=S and C=S structures. Skeletal vibrations of the tetrazole ring are attributed to the bands near 1080 cm.$^{-1}$, 1040 cm.$^{-1}$, and 980 cm.$^{-1}$. The characteristic infrared absorption bands for III were found to be similar to those for the monofunctional derivatives.[7]

Modification of the method[4] for the preparation of substituted-5-aminothiatriazoles by the diazotization of the di(thiosemicarbazides) gave only three derivatives of acceptable analysis (Table V), although many trials were carried out. The direct reaction[4] of hydrazoic acid with the di(isothiocyanates) in a variety of solvents failed to yield any products of acceptable analysis which varied over a wide range and were not consistent. The cause for these failures are not known.

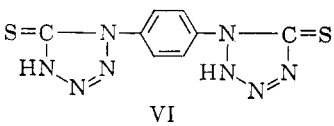
Experimental[8]

Diisothiocyanates.—The aromatic diisothiocyanates were prepared by the method of Dyson.[9,10] In those cases in which the product did not precipitate, it was recovered by neutralization of the acid solution or by extraction with organic solvents. Ethylene diisothiocyanate was prepared by the method of Klöpping.[11] The diisothiocyanates so prepared are listed in Table I. Recrystallization was from acetone or aqueous acetone. **4,4′-Di(isothiocyano)diphenylmethane** has previously been reported to have a melting point of 143–144° [9] and 196°.[12]

Dithiosemicarbazides (II).—The method of Lieber[4] was used. Dimethylformamide was used to effect recrystallization. The crude products are highly insoluble in the usual organic solvents. The crude diisothiosemicarbazide was dissolved in warm dimethylformamide, ethanol was then added to promote crystallization. Benzene or ethanol, instead of ether, can be used as the solvent for reaction. The hydrazine was occasionally added in ethanol rather than in aqueous solution, depending on the solubility requirements. The substances prepared are listed in Table II.

Thiosemicarbazones. (V).—Acetone thiosemicarbazones were prepared by refluxing the components in dimethylformamide on the steam bath for 1 hr. The ketone derivatives were recovered by pouring the clear solution into ice water. The aldehyde derivatives were recovered by diluting the dimethylformamide solution with ethanol. Recrystallizations were effected from ethanol or from dimethylformamide, adding ethanol to the latter if necessary. The compounds so prepared are summarized in Table III. All the substances summarized in this Table are new compounds. In a similar manner, hydrazones were readily prepared from benzaldehyde and other ketones and aldehydes.

Di(1-substituted tetrazoline-5-thiones) (IV).—These are prepared from I by a modification of the method of Lieber.[12] The *p*-phenylene derivative (VI) is described as typical. *p*-Phenylene diisothiocyanate (3.0 g., 0.016 mole) and 3.3 g. (0.05 mole) of sodium azide were used to 100 ml. of water and refluxed for 4 hr., the solution becoming greenish.



VI

(8) Microanalyses by Dr. C. Weiler and Dr. F. B. Strauss, Oxford, England. Melting points were determined in glass capillaries and are uncorrected. Infrared absorptions were recorded on a Perkin-Elmer Model 21 with sodium chloride optics over the range 2–15 μ using an automatic slit drive with a program of 927 and a scanning rate of twenty minutes. Liquids were handled in a demountable cell with a 0.025-mm. silver spacer. Solids were mulled in 2–3 drops of white mineral oil using sufficient sample to provide good absorption intensity. Thiophosgene was supplied by Rapter Laboratories, Chicago, Ill.

(9) G. M. Dyson, *J. Chem. Soc.*, 1702 (1924).

(10) G. M. Dyson and D. W. Browne, *ibid.*, 318 (1934).

(11) H. L. Klöpping and G. J. M. VanderKerk, *Rec. trav. chim.*, **70**, 949 (1951).

(12) F. H. McMillan and J. H. King, *J. Am. Chem. Soc.*, **72**, 4323 (1950).

TABLE II

DI(THIOSEMICARBAZIDES)

R—(NBC(S)NHNH$_2$)$_2$

R	Functional Positions	% Yield[a]	M.P.[b-d]	Formula	N Calcd.	N Found	S Calcd.	S Found
C_6H_4[e]	1,4	93	205–206	$C_8H_{12}N_6S_2$	32.79	33.10	25.10	25.20
2-ClC_6H_3[e,b]	1,4	85	193	$C_8H_{11}ClN_6S_2$	28.92	28.99	22.03	22.34
2-$CH_3C_6H_3$[e]	1,4	95	197–198	$C_9H_{14}N_6S_2$	31.11	31.00	23.70	23.96
C_6H_4[e]	1,3	95	189–190	$C_8H_{12}N_6S_2$	32.79	32.17	25.01	24.72
4-ClC_6H_3[e,g]	1,3	76	201[h]	$C_8H_{11}ClN_6S_2$	28.92	28.61	22.03	21.68
4-$CH_3C_6H_3$	1,3	86	196[i]	$C_9H_{14}N_6S_2$	31.11	30.81	23.70	23.58
4-$CH_3OC_6H_3$[e]	1,3	95	190	$C_9H_{14}N_6OS_2$	29.37	29.29	22.38	22.56
$C_{13}H_{10}$[e,j]	4,4′	94	193–194	$C_{15}H_{18}N_6S_2$	25.00	25.21	19.05	18.81
$C_{14}H_{12}$[e,k]	4,4′	88	209	$C_{16}H_{20}N_6S_2$	23.33	23.60	17.78	17.80
$C_{10}H_6$[e,l]	1,5	95	223	$C_{12}H_{14}N_6S_2$	27.45	27.20	20.92	21.11
C_2H_4[e]	1,2	85	225	$C_4H_{12}N_6S_2$	40.38	40.20	30.76	30.00

[a] Crude. [b] All recrystn. were from dimethylformamide. [c] White amorphous powder except where noted. [d] With decompn. [e] New compound. [f] Calcd.: Cl, 12.22. Found: Cl, 11.92. [g] Calcd.: Cl, 12.22. Found: Cl, 12.10. [h] Tan powder. [i] J. Klarer and R. Behnisch, Ger. Patent **832,891** (1952). [j] Diphenylmethane group. [k] Bibenzyl group. [l] Naphthalene.

TABLE III

ACETONE THIOSEMICARBAZONES

R(NHC(S)NHN=C(CH_3)$_2$)$_2$

R[a]	Functional Positions	% Yield	M.P.	Formula	N Calcd.	N Found	S Calcd.	S Found
C_6H_4	1,4	76	207–208[b,c]	$C_{14}H_{20}N_6S_2$	25.00	24.90	19.05	18.70
2-ClC_6H_3[d]	1,4	78	197–198[e]	$C_{14}H_{19}ClN_6S_2$	22.67	22.67	17.27	17.09
2-$CH_3C_6H_3$	1,4	60	187[e]	$C_{15}H_{22}N_6S_2$	24.00	24.30	18.29	17.96
C_6H_4	1,3	76	198–199[c]	$C_{14}H_{20}N_6S_2$	25.00	24.70	19.05	19.29
4-ClC_6H_3	1,3	67	189[e]	$C_{14}H_{19}ClN_6S_2$	22.76	22.80	17.27	17.10
4-$CH_3C_6H_3$	1,3	69	183–184[c]	$C_{15}H_{22}N_6S_2$	24.00	24.40	18.29	18.26
4-$CH_3OC_6H_3$	1,3	73	192[g]	$C_{15}H_{22}N_6OS_2$	22.95	22.78	17.49	17.61
$C_{13}H_{10}$[h]	4,4′	83	189–190[i]	$C_{21}H_{26}N_6S_2$	19.72	19.56	15.02	14.51
$C_{14}H_{12}$[j]	4,4′	53	208[i]	$C_{22}H_{28}N_6S_2$	19.09	18.78	14.55	14.65
$C_{10}H_6$[k]	1,5	83	210[e]	$C_{18}H_{22}N_6S_2$	21.76	21.58	16.58	16.48
C_2H_4	1,2	56	216[i]	$C_{10}H_{20}N_6S_2$	29.17	28.80	22.22	22.60

[a] New compound. [b] All m.p. all decompn. [c] White amorphous powder. [d] Calcd: Cl, 9.58. Found: Cl, 9.73. [e] Gray powder. [f] Calcd.: Cl, 9.58. Found: Cl, 9.31. [g] White ndls. [h] Diphenylmethane group. [i] Light yellow crystals. [j] Bibenzyl group. [k] Naphthalene.

TABLE IV

DI(TETRAZOLINETHIONES)

R[a]	Functional Positions	% Yield	M.P.	Formula	N Calcd.	N Found	S Calcd.	S Found
C_6H_4	1,4	93	210[b]	$C_8H_6N_8S_2$	40.33	40.50	23.00	22.98
2-ClC_6H_3[c]	1,4	60	173	$C_8H_5ClN_8S_2$	35.84	36.02	20.48	20.40
2-$CH_3C_6H_3$	1,4	81	190	$C_9H_8N_8S_2$	38.36	37.96	21.92	21.73
C_6H_4	1,3	76	179	$C_8H_6N_8S_2$	40.33	41.00	23.00	23.20
4-ClC_6H_3[d]	1,3	61	160	$C_8H_5ClN_8S_2$	35.84	35.35	20.48	19.30
4-$CH_3C_6H_3$	1,3	60	180	$C_9H_8N_8S_2$	38.36	38.20	21.92	21.58
4-$CH_3OC_6H_3$	1,3	67	126	$C_9H_8N_8OS_2$	36.36	36.55	20.78	20.76
$C_{13}H_{10}$[e]	4,4′	82	188	$C_{15}H_{12}N_8S_2$	30.43	30.20	17.39	17.51
$C_{14}H_{12}$[f]	4,4′	53	191	$C_{16}H_{14}N_8S_2$	29.32	29.21	16.76	16.78

[a] New compound. [b] All detonate or decompose violently. [c] Calcd.: Cl, 11.36. Found: Cl, 11.70. [d] Calcd.: Cl, 11.36. Found: Cl, 11.42. [e] Diphenylmethane. [f] Bibenzyl.

The alkaline solution was filtered, extracted twice with ether to remove unchanged isothiocyanate, and acidified with concd. hydrochloric acid (Congo red paper), giving a creamy white solid. The yield was 4.1 g. (93%) melting with detonation at 205°. Recrystallization from ethanol gave white leaflets which detonated at 208°.

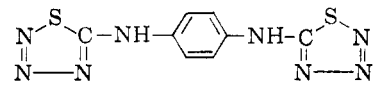
Anal. Calcd. for $C_3H_6N_8S_2$: C, 34.52; H, 2.17; N, 40.27; S, 23.04; neut. equiv., 139. Found: C, 34.50; H, 2.40; N, 40.50; S, 22.98; neut. equiv., 137.

The ultraviolet absorption was taken with a Beckman DU spectrophotometer at a concentration of 11 mg./ml. in 95% ethanol; λ_{max} was 228 mμ; log ϵ_{max} 4.40.

The ditetrazolinethiones derived from diphenylmethane and bibenzyl, because of solubility considerations, were prepared in a benzene–water two-phase system, with recovery of the product from the aqueous alkaline layer.

The di(tetrazolinethiones) are listed in Table IV.

Di(aminothiatriazoles) (III).—These were prepared by a modification of the method of Lieber.[4] The procedure for the



VII

p-phenylene derivative (VII) is typical. The *p*-phenylenedi(thiosemicarbazide), 0.6 g. (0.0023 mole), was dissolved in

TABLE V
DI(AMINOTHIATRIAZOLES)

R[a]	Functional Positions	% Yield	M.P[b]	Formula	N Calcd.	N Found	S Calcd.	S Found
C_6H_4	1,4	80	180	$C_8H_6N_8S_2$	40.33	40.25	23.00	22.90
C_6H_4	1,3	82	162	$C_8H_6N_8S_2$	40.33	40.30	23.00	22.85
$C_{13}H_{10}$[c]	4,4′	86	148	$C_{15}H_{12}N_8S_2$	30.43	30.10	17.39	17.20

[a] New compound. [b] With detonation. [c] Diphenylmethane.

25 ml. of dimethylformamide, cooled to 5°, and agitated by a magnetic stirring bar. There was then added 4 ml. of 4 *N* hydrochloric acid and 0.4 g. (0.006 mole) of sodium nitrite in 5 ml. of water over a 10-min. period. A yellow-green solid precipitated immediately. The reaction was maintained at 5–10° for 20 min. The crude product, 0.51 g. (80%), was recovered as a greenish powder, detonating at 160°. Recrystallization was effected by dissolving in 15 ml. of dimethylformamide, decolorizing with charcoal, filtering, and then diluting with ethanol. A light tan powder, detonating at 180° was obtained. The di(aminothiatriazoles) are listed in Table V.

(13) E. Lieber and J. Ramachandran, *Can. J. Chem.*, **37**, 101 (1959).

Formation of Quinoxalone Dye in the Color Photographic Coupling Reaction

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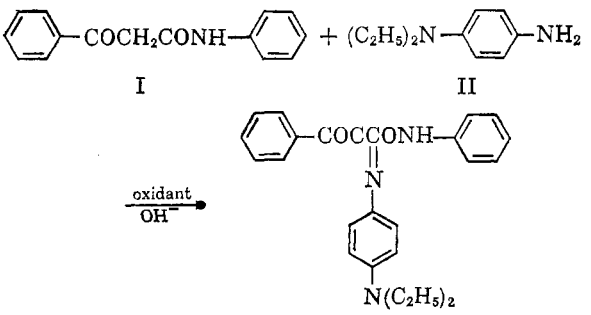
Communication No. 2230 from the Kodak Research Laboratories, Rochester, N. Y.

Received September 25, 1961

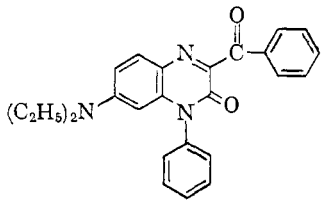
A large class of the compounds ("couplers") giving yellow color photographic image dyes contain the grouping, —$COCH_2CONH$—.[1] Reaction of the oxidized *p*-phenylenediamine derivative developing agent at the activated methylene group of such a coupler gives azomethine dye, as shown.



III

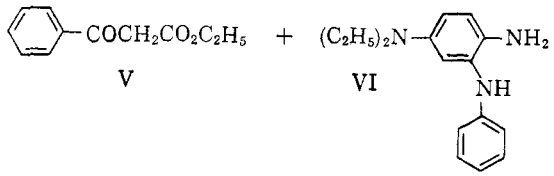
When couplers of this class react with oxidized color developing agents in dilute solution, it is often observed[2] that, in addition to the azomethine dye, a yellow dye of another type is produced. This dye differs from the azomethine dye in its fluorescence, smaller value of λ_{max}, and greater slope of the absorbance *vs.* λ curve on the long wave length side of λ_{max}. The present communication gives a proof of structure or a representative of this type of dye and evidence for a mechanism by which it forms.

On the basis of the fluorescence and absorption spectra, it was suggested[3] several years ago that the fluorescent, yellow dyes formed along with the yellow azomethine dyes are quinoxalones. For example, I and II would give IV. Structure IV

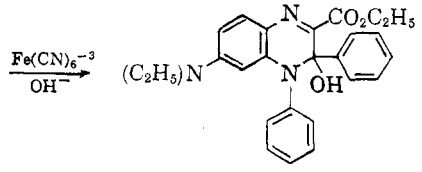


IV

has now been verified by means of the following alternative synthesis:



V VI



VII

Irradiation of the yellow pseudo base, VII, in solution converts it to IV, identical with the fluorescent dye obtained from I and II.

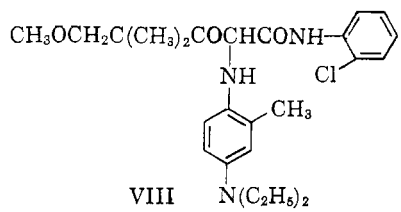
The oxidative condensation of dicarbonylmethylene compounds with *p*-phenylenediamines having a monosubstituted amino group *ortho* to the unsubstituted amino group has been described by Schmidt *et al.*[4] The products are yellow in the presence of alkali and magenta under neutral or weakly acidic conditions. The new dye VII shows this typical behavior. Schmidt *et al.*[4] proposed that in the magenta form the dyes have a quinoxalinium structure, whereas in the yellow form they exist as the corresponding pseudo bases (1,2-

(1) P. W. Vittum and A. Weissberger, *J. Phot. Sci.*, **2**, 81 (1954).
(2) G. H. Brown, private communication.
(3) P. W. Vittum, private communication.
(4) W. A. Schmidt, V. Tulagin, J. A. Sprung, R. C. Gunther, R. F. Coles, and D. E. Sargent, *Ind. Eng. Chem.*, **45**, 1726 (1953).

dihydro-2-quinoxalinols). This structural assignment is supported by the earlier results of Kehrmann and Falke.[5] Their quinoxalinium compounds having substituted amino groups in the 7-position are magenta and give yellow, fluorescent (in solution) pseudo bases.

The conversion of VII to IV takes place when solutions are exposed to radiant energy within the wave-length region, 350–450 mμ. This region corresponds to the long wave length absorption band of VII. Reaction occurs in acetone, acetonitrile, benzene, and cyclohexane. Not all of the VII is converted to IV. Other products are formed, too. The fraction of the photoreacted VII going to IV increases as the intensity of irradiation is decreased. There is little or no reaction in the dark, even in refluxing acetonitrile. The mechanism of the photoreaction is under investigation. It is hoped that the results of this study may be reported at a later date.

Consider now the steps leading to formation of quinoxalone dye in an oxidative condensation reaction such as that of I with II. An intermediate in the formation of azomethine dye by this reaction is the leuco form of the dye. A leuco dye (VIII) of this type has been synthesized. When VIII



VIII

is oxidized with dichloroquinone, both azomethine and quinoxalone dye are formed. The latter dye is recognized by its analysis, characteristic fluorescence, and absorption spectrum, and by the fact that close to the theoretical four equivalents of oxidant are consumed in its formation. It is inferred that, in oxidative condensation reactions such as that of I with II, the leuco dye is a precursor of both the azomethine and quinoxalone dyes. Dichloroquinone does not oxidize the azomethine dye to the quinoxalone dye, showing that the former dye is not an intermediate in the formation of the latter. Therefore, branching in the reaction path must occur either at the leuco-dye stage, or, as seems more likely, at a stage intermediate between the leuco dye and azomethine dye. For example, the leuco dye may undergo a single-electron transfer reaction with the oxidant, giving a dye semiquinone which either undergoes ring closure, leading, on further oxidation, to quinoxalone dye, or is oxidized to azomethine dye.

Experimental

Ethyl 6-Diethylamino-3,4-dihydro-3,4-diphenyl-3-hydroxy-2-quinoxalinecarboxylate (VII).—To 15 ml. of ethyl benzoylacetate (V) (Eastman Grade) and 900 ml. of methanol was added an alkaline slurry of 3-anilino-N^1,N^1-diethyl-*p*-phenylenediamine (VI), prepared by dissolving 15 g. of sodium carbonate monohydrate in a solution of 2.1 g. (0.006 mole) of the sulfuric acid salt of VI[6] in 300 ml. of water. To the stirred mixture was added during 20 min. a solution of 9.0 g. of potassium ferricyanide in 120 ml. of water. Stirring was continued for 5 min. After the mixture was filtered, it was chromatographed on Florisil.[7] The product was very strongly absorbed and had the magenta color of the quinoxalinium ion. The column was washed with 50% aqueous methanol. The product was eluted as the yellow pseudo base first with acetone and finally with a mixture of 90 parts acetone, 10 parts triethylamine, and 4 parts water. The residue from the evaporated eluate was dissolved in benzene, washed with water, and dried over sodium sulfate. This solution was passed through a column of Florisil,[7] which was then washed with acetone. The product was eluted using the 90:10:4 acetone–triethylamine–water mixture. Evaporation of the eluate gave a partly crystalline, dark-colored residue (*ca.* 0.6 g.), which was crystallized three times from cyclohexane. The yellow, nonfluorescent crystals (0.27 g.) give green-fluorescing solutions in organic solvents; m.p. 114–117° dec. This value was determined as follows: The sample on the Fisher-Johns hot stage was heated during 5 min. to within 5° of initial melting. Rate of heating was then 1°/min. until melting started, when the rate was reduced to 0.5°/min. When the crystals are dropped on a preheated stage (Kofler Heizbank, Reichert Co., Austria), the lowest temperature at which rapid melting occurs is *ca.* 130°.

Anal. Calcd. for $C_{27}H_{29}O_3N_3$: C, 73.1; H, 6.6; N, 9.5. Found: C, 73.2; H, 6.3; N, 9.5.

Visible and ultraviolet spectra in acetonitrile (*ca.* 2.5×10^{-5} *M* in potassium hydroxide): 303 mμ (peak, log ε 3.96); 408 mμ (peak, log ε 4.32). Infrared spectrum in Nujol mull: broad hydroxyl band at 3230 cm.$^{-1}$; single carbonyl band at 1700 cm.$^{-1}$ (ester).

3-Benzoyl-7-diethylamino-1-phenyl-2(1)-quinoxalone (IV).—(1). To a stirred solution of 1.6 g. of potassium hydroxide, 0.24 g. of benzoylacetanilide,[8] and 2.8 g. of *N*,*N*-diethyl-*p*-phenylenediamine monohydrochloride (Eastman Grade) in 250 ml. of methanol was added, all at once, a solution of 1.4 g. of potassium ferricyanide in 50 ml. of water. After 4 min., 2 ml. of glacial acetic acid was added. The crude product was precipitated by addition of 1 l. of water, separated by filtration, and washed with water. This procedure was repeated once on the same scale and once on twice this scale. The dried products were combined, dissolved in benzene, and chromatographed on Florisil.[7] Mixtures of benzene and acetone were used as eluting solvent. The azomethine dye, which was readily separated from IV on the column, was discarded. Separation of IV from 4,4′-bis(diethylamino)azobenzene, which is formed as a by-product in the reaction, was not clean. Therefore, the contaminated IV was chromatographed again. The crude IV (0.4 g.) was crystallized from acetone. The residue from the mother liquor was crystallized from ethanol and combined with the crystallized product. This combination was crystallized from acetone. The yellow crystals (0.13 g.) fluoresce green; m.p. 192–193°.

Anal. Calcd. for $C_{25}H_{23}O_2N_3$: C, 75.5; H, 5.8; N, 10.6. Found: C, 75.0; H, 5.9; N, 10.6.

Visible and ultraviolet spectra in acetonitrile: 228 mμ (peak, log ε 4.61); 255 mμ (shoulder, log ε 4.26); 294 mμ (shoulder, log ε 3.79); 427 mμ (peak, log ε 4.43). Infrared spectrum in potassium bromide pressing: two carbonyl bands at 1650 cm.$^{-1}$ and 1675 cm.$^{-1}$.

(2). A solution of 0.050 g. of VII in 500 ml. of benzene in a 15- × 9.5-in. dish was exposed to General Electric Co. Cool

(5) F. Kehrmann and E. Falke, *Helv. Chim. Acta*, **7**, 981 (1924).

(6) Prepared by R. Bent, of these laboratories, using the method of J. C. Arcos and J. A. Miller, *J. Am. Chem. Soc.*, **77**, 3128 (1955).

(7) Floridin Co., Tallahassee, Fla.

(8) C. J. Kibler and A. Weissberger, *Org. Syntheses*, **25**, 7 (1945).

White fluorescent bulbs at a level of *ca.* 20 ft.-candles. After 160 min., all of the VII had disappeared from the solution. Evaporation of the benzene gave 0.045 g. of a brown-yellow, largely crystalline residue, which was crystallized twice from ethanol. The yellow crystals (6.2 mg.) fluoresce green; m.p. 192–193°. The ultraviolet, visible, and infrared spectra are identical with those for the IV prepared by method 1.

The precursors (IX–XIV) of the leuco dye, VIII, were synthesized by Lee J. Fleckenstein of these laboratories.

Methoxypivalic acid (IX) was prepared by a procedure similar to that described for the preparation of methoxyacetic acid;[9] b.p. 105–110° (5.5 mm.); $n^{25}D$ 1.4199. This compound has been prepared previously and characterized analytically at the Tennessee Eastman Co.[10]

Ethyl Methoxypivalate (X).—A mixture of 57.3 g. (0.434 mole) of IX, 70 ml. of absolute ethanol, 170 ml. of benzene, and 1.5 ml. of concd. sulfuric acid was refluxed for 18 hr. in a flask equipped with a short Vigreux column surmounted by a Dean-Stark trap and reflux condenser. The mixture was cooled, washed several times with saturated sodium carbonate solution, dried over potassium carbonate, and distilled to give 55.4 g. (80%) of X; b.p. 161–165°; $n^{25}D$ 1.4060.

Anal. Calcd. for $C_8H_{16}O_3$: C, 60.0; H, 10.0. Found: C, 60.3; H, 9.7.

(Methoxypivalyl)acetonitrile (XI) was prepared from X by the general procedure of Eby and Hauser.[11] From 15.9 g. (0.69 g.-atom) of sodium, 600 ml. of liquid ammonia, 28.3 g. (0.69 mole) of acetonitrile, and 55.2 g. (0.345 mole) of X, there was obtained 42.7 g. (80%) of XI; b.p. 109–112° (1.3 mm.); $n^{25}D$ 1.4400.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.9; H, 8.4; N, 9.0. Found: C, 61.6; H, 8.7; N, 8.9.

Methyl (Methoxypivalyl)acetate (XII).—A solution of 42.6 g. (0.275 mole) of XI in 250 ml. of absolute methanol was cooled in an ice bath and saturated with gaseous hydrogen chloride. After standing 16 hr. at room temperature, the mixture was concentrated to dryness under reduced pressure at room temperature. To the residue was added 200 ml. of benzene, 150 ml. of water, and 3 drops of concd. hydrochloric acid. The mixture was refluxed for 2 hr. and cooled. The phases were separated, and the aqueous phase was extracted twice with benzene. The extracts were added to the original organic phase, washed with saturated salt solution, and dried over sodium sulfate. The solution was concentrated at atmospheric pressure, and the residue was distilled under reduced pressure through a short Vigreux column to yield 29.1 g. (56%) of XII; b.p. 87–94° (1.4 mm.); $n^{25}D$ 1.4398.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.5; H, 8.5. Found: C, 57.7; H, 8.6.

2′-Chloro-2-(methoxypivalyl)acetanilide (XIII).—A mixture of 7.82 g. (0.061 mole) of *o*-chloroaniline, 11.3 g. (0.060 mole) of XII, and 150 ml. of xylene was heated at the boiling point for 3 hr. in a flask equipped with a distillation head. During this time, 75 ml. of distillate was collected. The hot mixture was filtered into 300 ml. of heptane, and the solution was refrigerated. There was obtained 5.5 g. of white crystals; m.p. 51–56°. By concentrating and refrigerating the mother liquors, two additional crops of crystals (6.5 g.) were obtained. The three crops were combined and recrystallized from ether to give 11 g. (65%) of XIII as heavy white prisms; m.p. 50–56°.

Anal. Calcd. for $C_{14}H_{18}O_3NCl$: C, 59.2; H, 6.3; N, 5.0; Cl, 12.5. Found: C, 59.6; H, 6.4; N, 5.3; Cl, 12.9.

2,2′-Dichloro-2-(methoxypivalyl)acetanilide (XIV).—A solution of 10.85 g. (0.0382 mole) of XIII in 100 ml. of chloroform was cooled in an ice bath, and a solution of 5.54 g. (0.041 mole) of sulfuryl chloride in 35 ml. of chloroform was added, with stirring, over a period of 65 min. The mixture was stirred at room temperature for an additional 35 min., then concentrated under reduced pressure at room temperature to a white, crystalline solid. The solid was washed with a little petroleum ether, collected by filtration, dried, and recrystallized from hexane containing a small amount of ethanol to give 10.5 g. (87%) of XIV as large, colorless prisms; m.p. 90–94°.

Anal. Calcd. for $C_{14}H_{17}O_3NCl_2$: C, 52.8; H, 5.3; N, 4.4; Cl, 22.3. Found: C, 52.8; H, 5.2; N, 4.4; Cl, 22.7.

2′-Chloro-2-(4-diethylamino-2-methylanilino)-2-(methoxypivalyl)acetanilide (VIII).—In a closed vessel fitted with inlet and outlet tubes were placed 1.83 g. of XIV and 3.50 g. of N^1,N^1-diethyl-3-methyl-*p*-phenylenediamine monohydrochloride (Kodak Color Developing Agent CD-2). The vessel was swept with nitrogen, and 7 ml. of nitrogen-swept dimethylformamide was introduced, followed 2 min. later by 9.3 ml. of nitrogen-swept 10% methanolic potassium hydroxide solution. Nitrogen was passed through the mixture for 2 min. and then over the mixture while it was held at 32° for 100 min. After adding 125 ml. of nitrogen-swept, 85% aqueous methanol, the solution was cooled in an ice bath and seeded with crystals of VIII from a previous, small-scale experiment. The mixture was stirred with nitrogen for 30 min., and then 15 ml. of nitrogen-swept water was added. After an additional 30 min., the crystals of VIII were filtered off in air and washed with air-saturated 80% methanol, 50% methanol, and with water. The light yellow product was dried over calcium chloride in a nitrogen-filled desiccator; weight, 2.18 g. The product was crystallized three times from methanol, all operations, including drying, being carried out under nitrogen. The very pale yellow crystals (1.1 g.) melt at 84–86°.

Anal. Calcd. for $C_{25}H_{34}O_3N_3Cl$: C, 65.3; H, 7.5; N, 9.1; Cl, 7.7. Found: C, 65.1; H, 7.1; N, 9.3; Cl, 7.6.

Oxidation of Leuco Dye VIII to Azomethine and Quinoxalone Dyes.—The VIII used in this experiment was prepared as described above but was not recrystallized. The VIII (2.36 g.) was dissolved in 150 ml. of warm (*ca.* 40°), nitrogen-swept methanol to which 0.5 ml. of 10% methanolic potassium hydroxide solution had been added. The solution was stirred, and a solution of 2.45 g. of 2,5-dichloro-*p*-benzoquinone (Eastman Grade) in 27 ml. of warm acetone was added all at once. After 5 min., the solution was cooled to 25°, and 300 ml. of water was added. The product was extracted into benzene, and the solution was washed with water. The benzene was allowed to evaporate. The residue was redissolved in a little benzene and chromatographed on Florisil.[7] Mixtures of benzene and acetone were used for elution. The crude azomethine dye, 2′-chloro-2-(4-diethylamino-2-methylphenylimino)-2-(methoxypivalyl)acetanilide, weighed 1.65 g. It was crystallized from methanol, chromatographed on Florisil,[7] and crystallized from methanol; orange crystals, m.p. 113–114°.

Anal. Calcd. for $C_{25}H_{32}O_3N_3Cl$: C, 65.6; H, 7.0; N, 9.2; Cl, 7.7. Found: C, 65.6; H, 7.3; N, 9.5; Cl, 8.0.

Visible spectrum in methanol: 442 mμ (peak, log ε 4.19).

The crude quinoxalone dye, **1-(2-chlorophenyl)-7-diethylamino-3-(methoxypivalyl)-5-methyl-2(1)-quinoxalone,** after one crystallization from 90% aqueous methanol, weighed 0.35 g. It was chromatographed again on Florisil[7] and crystallized from 85% aqueous methanol and from cyclohexane; yellow, green-fluorescing crystals; m.p. 128–129°.

Anal. Calcd. for $C_{25}H_{30}O_3N_3Cl$: C, 65.9; H, 6.6; N, 9.2; Cl, 7.8. Found: C, 65.6; H, 6.8; N, 9.3; Cl, 7.7.

Visible spectrum in methanol: 434 mμ (peak, log ε 4.44)

Equivalents of Oxidant Consumed in the Oxidation of VIII.—The chloro-*p*-benzoquinone used as oxidant in this experiment was prepared by oxidizing chlorohydroquinone (Eastman Organic Chemicals) with potassium dichromate in aqueous sulfuric acid. The crude product was crystallized four times from 50% aqueous ethanol.

(9) T. L. Gresham, J. E. Jansen, F. W. Shaver, J. T. Gregory, and W. L. Beers, *J. Am. Chem. Soc.*, **70**, 1004 (1948).

(10) K. C. Brannock, private communication.

(11) C. J. Eby and C. R. Hauser, *J. Am. Chem. Soc.*, **79**, 723 (1957).

Reactions of the chloroquinone and VIII were carried to completion in a mixture of 12.5 ml. of methanol and 5.0 ml. of water. In each reaction, 4.16×10^{-7} moles of VIII was used. The amounts of the dyes produced were determined spectrophotometrically. Results are shown in Table I.

TABLE I
OXIDATION OF LEUCO DYE VIII BY CHLOROQUINONE

Chloroquinone Used, Moles $\times 10^7$	Azomethine Dye Produced, Moles $\times 10^7$	Quinoxalone Dye Produced, Moles $\times 10^7$	Theoretical Chloroquinone Consumption, Moles $\times 10^7$
6.7	1.15	2.5_5	6.2_5
5.0	0.75	2.0	4.7_5
3.8	0.55	1.5_5	3.6_5
2.2	0.35	0.9	2.1_5

The last column gives the total amount of oxidant needed to produce the azomethine and quinoxalone dyes of the second and third column, on the assumption that 1 mole (two oxidation equivalents) of the oxidant is used for the formation of 1 mole of the azomethine dye and 2 moles (4 oxidation equivalents) for the formation of 1 mole of the quinoxalone dye. The correctness of these assumptions is indicated by the agreement between the figures of columns 1 and 4.

Observations on the Formation of Piperidine Hydrochloride from Chloroform and Piperidine

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The formation of piperidine hydrochloride from the reaction of chloroform and piperidine, with or without a strong base, has been reported by several workers.[2,3] The same product has also been observed in reactions that yield chloroform, when piperidine is present in the reaction mixture, but no effort has been made by previous investigators to establish the source of piperidine hydrochloride.[4,5] Since we are currently investigating similar reactions, we were interested in studying the conditions which lead to the formation of piperidine hydrochloride. Secondary amines have been shown to react with chloroform in the presence of potassium *t*-butoxide to yield amides.[6] Under these conditions, a dichlorocarbene has been shown to be an intermediate.[7]

It is the purpose of this communication to show that chloroform is sufficiently acidic to react with an organic base such as piperidine ($k = 1.2 \times 10^{-3}$)[8] to yield piperidine hydrochloride and *N*-dichloromethylpiperidine, which is instantaneously hydrolyzed to *N*-formylpiperidine. The extent to which this reaction takes place is very small in the absence of a strong base. Equimolecular amounts of piperidine and chloroform yield piperidine hydrochloride and *N*-formylpiperidine to the extent of 1%, after they are allowed to stand together for several days. The presence of *N*-formylpiperidine, as one of the products of the reaction between chloroform and piperidine in the absence of strong bases, has not been previously detected by chemical means since it is not easily identified when formed in minute amounts. We found that *N*-formylpiperidine could be easily detected when no particular attempts were made to keep the reaction mixture anhydrous. However, when precautions were taken to exclude moist air from the reaction mixture, no *N*-formylpiperidine could be detected by gas-liquid chromatography. This observation could be ascribed to the fact that if a dichlorocarbene were an intermediate in this reaction, *N*-dichloromethylpiperidine would be formed and under anhydrous conditions this compound could not be hydrolyzed to *N*-formylpiperidine. On the other hand, the observation could mean that the reaction between chloroform and piperidine proceeds *via* a free radical mechanism, as in the photolysis of diazomethane or ketone, which is believed to yield the methylene diradical.[9] To eliminate the last possibility, similar experiments were carried out, one in the absence of air and light, another in the presence of an inhibitor such as hydroquinone. These conditions did not appear to modify the course of the reaction to any great extent. The addition of hydroquinone to the reaction mixture appears to facilitate the reaction since under these conditions piperidine hydrochloride is obtained in 3% yield. This may be attributed to the increase in the polarity of the medium.

In view of these findings, it is concluded that the reaction between chloroform and piperidine proceeds *via* an ionic mechanism probably similar to that proposed by Saunders and Murray for related reaction.[10]

$$Cl_3CH + \ddot{N}C_5H_{10} \longrightarrow Cl_3C^- + \overset{+}{H_2}\ddot{N}C_5H_{10}$$

$$Cl_3C^- \longrightarrow Cl_2C: + Cl^-$$

$$Cl_2C: + \ddot{N}C_5H_{10} \longrightarrow Cl_2C\overset{-}{\ddot{N}}\overset{+}{C}C_5H_{10}$$

$$\begin{array}{c} H \\ \downarrow \\ O{=}C{-}NC_5H_{10} \xleftarrow{H_2O} Cl_2CNC_5H_{10} \end{array}$$

(1) To whom all inquiries should be addressed.
(2) J. Busz and A. Kekulé, *Ber.*, **20**, 3246 (1887).
(3) F. B. Ahrens, *ibid.*, **27**, 2090 (1894).
(4) Y. Ursy and M. Paty, *Compt. rend.*, **252**, 3812 (1961).
(5) M. M. Joullié, Ph.D. thesis, University of Pennsylvania (1953).
(6) M. Saunders and R. W. Murray, *Tetrahedron*, **6**, 88 (1959).
(7) W. von E. Doering and A. K. Hoffman, *J. Am. Chem. Soc.*, **76**, 6162 (1954).
(8) Y. N. Sheinker and E. M. Peresleni, *Zhur. Fiz. Khim.*, **32**, 2112 (1958).
(9) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, 1959, p. 750.
(10) M. Saunders and R. W. Murray, *Tetrahedron*, **11**, 1 (1960).

These findings appear to be supported by the study of methylene derivative as intermediates in polar reactions, in which it was found that in buffered solutions the hydrolysis of chloroform is independent of pH.[11]

Experimental

Materials.—The chloroform used in this experiment was purified by successive washings with concentrated sulfuric acid and distilled water and then dried over calcium chloride overnight.[12] The drying agent was removed by filtration and the filtrate distilled through a 30-cm. column, 2 mm. in diameter, packed with glass helices, b.p. 61.0–61.5°, n^{25} 1.4457.

Piperidine was purified by allowing it to stand over potassium hydroxide pellets for 1 week. The pellets were removed by filtration and the filtrate distilled through a 30-cm. column, 2 mm. in diameter, packed with glass helices, b.p. 106°, n^{25} 1.4514.

Commercial anhydrous ether was dried more completely by allowing it to stand over calcium hydride for one week.

Reaction of Piperidine and Chloroform.—Chloroform (11.9 g., 0.1 mole) was added to piperidine (8.5 g., 0.1 mole). The reaction was exothermic. Piperidine hydrochloride was isolated by the addition of anhydrous ether to the reaction mixture after 24 hr., yield 1%. Piperidine hydrochloride was identified by its melting point, 244°, and infrared spectrum. The presence of *N*-formylpiperidine was verified by gas-liquid chromatography using a 3-ft. column of 25% carbowax 20-M on chromosorb 30–60 regular mesh packing, or a 6-ft. column of 25% silicone grease on chromosorb 30–60 regular mesh packing on fluoropak, all at 200° and 145 ml. of helium per min. *N*-Formylpiperidine cannot be obtained by distillation when present in small quantities because of its polar nature and its tendency to decompose when distilled under atmospheric pressure. It may be isolated as its mercuric chloride derivative. This derivative is easily prepared by adding small amounts of solutions believed to contain *N*-formylpiperidine to an aqueous solution of mercuric chloride (5 g. of mercuric chloride in 100 ml. of water). A solid forms immediately, m.p. 145°. The identity of this solid was established by comparing its infrared spectrum to that of an authentic sample of the mercuric chloride derivative of *N*-formylpiperidine. A mixture of the two compounds showed no depression in melting point. The authentic sample of the mercury derivative was prepared according to the directions of Farlow and Adkins[13] from *N*-formylpiperidine which had been obtained from the reaction of chloral and piperidine.[14]

Reaction of Piperidine and Chloroform in the Absence of Air and Light.—In a darkroom, nitrogen was bubbled through chloroform (11.9 g., 0.1 mole) and piperidine (8.5 g., 0.1 mole). Chloroform was added to piperidine and the reaction was exothermic. The mixture was allowed to stand in a pressure bottle, under nitrogen, in the darkroom overnight. To a 10-ml. aliquot of this reaction mixture, 200 ml. of *n*-hexane was added, still in the darkroom. A white solid precipitated, m.p. 242°, yield 1%. The infrared spectrum of this compound agreed with an authentic sample of piperidine hydrochloride. The rest of the reaction mixture was analyzed by gas-liquid chromatography using a 3-ft. column containing 25% carbowax 20-M on chromosorb 30–60 regular mesh packing, at 200° and 145 ml. of helium per minute. Three peaks were obtained. They were attributed to chloroform, piperidine, and *N*-dichloromethylpiperidine, respectively. The last peak had a retention time of 0.78 min. under the above conditions. This peak disappeared upon subsequent hydrolysis of the reaction mixture and a new peak corresponding to *N*-formylpiperidine was observed. The presence of *N*-formylpiperidine was verified by addition of an authentic sample of *N*-formylpiperidine in various amounts to the hydrolyzed reaction mixture.

Reaction of Piperidine and Chloroform in the Presence of Hydroquinone.—Chloroform (11.9 g., 0.1 mole) was added to a piperidine solution (8.5 g., 0.1 mole) containing hydroquinone (1.1 g., 0.01 mole). The reaction was exothermic and the solution turned red within 0.5 hr. The reaction mixture was allowed to stand in a pressure bottle overnight, without attempting to exclude light. The solid which formed was removed by filtration. *n*-Hexane (400 ml.) was added to a 10-ml. aliquot of the reaction mixture and the solid which formed was collected by filtration. The solids were combined and washed with chloroform. The chloroform solution was treated with 400 ml. of *n*-hexane. A solid precipitated and was removed by filtration. This solid was recrystallized from absolute ethanol and anhydrous ether, m.p. 242°, yield 3%.

The remaining reaction mixture was analyzed by gas-liquid chromatography using a 3-ft column of 25% carbowax 20-M on chromosorb 30–60 regular mesh, at 200° and 145 ml. of helium per min. Three peaks were observed which were attributed to chloroform, piperidine, and *N*-dichloromethylpiperidine, the last peak having a retention time of 0.78 min. under the above conditions. After subsequent hydrolysis, the peak occurring at 0.78 min. disappeared and the peak corresponding to *N*-formylpiperidine, having a retention time of 7.38 min., was observed. The proof of the presence of *N*-formylpiperidine was carried out in the same manner as described in the previous experiment.

(11) J. Hine and P. B. Langford, *J. Am. Chem. Soc.*, **80**, 6010 (1958).

(12) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, 1957, p. 283.

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(14) F. F. Blicke and C. J. Lu, *ibid.*, **74**, 3933 (1952).

The Synthesis of Certain 7α- and 21-Methylsulfinyl and Methylsulfonyl Steroid Derivatives

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Our interest in the synthesis of steroid hormone analogs and the availability in our laboratory of a number of steroids substituted at C-7[1] or at C-21[2] with a methylthio group prompted us to investigate the preparation of the corresponding sulfoxide and sulfone derivatives. Several attempts to effect the oxidation of 7α-methylthiocortisone acetate with hydrogen peroxide were unsuccessful and crystalline material could not be isolated.[3] However, treatment of this compound with 1.1 molar equivalents of monoperphthalic acid (MPA) smoothly afforded a 65% yield of the desired sulfoxide. The 7α-methylsulfinyl derivatives of testosterone ace-

(1) R. E. Schaub and M. J. Weiss, *J. Org. Chem.*, **26**, 3915 (1961).

(2) R. E. Schaub and M. J. Weiss, *J. Org. Chem.*, **26**, 1223 (1961).

(3) These experiments utilized a modification of the procedure reported by Ralls, Dodson, and Riegel [*J. Am. Chem. Soc.*, **71**, 3320 (1949)] for the oxidation of 3β-ethylthio-5-cholestenone to the corresponding sulfone.

TABLE I

SULFOXIDES

Compound	Yield, %	M.P. (dec.)	$[\alpha]^{\circ}D$	Concn., Solvent	$\lambda_{max}^{CH_3OH}$, mμ	ε	λ_{max}^{KBr}, μ	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
7α-Methylsulfinyltestosterone acetate[a]														
17β-Acetoxy-7α-methylsulfinyl-androstan-3-one	66	205-207	−80.6	1% in $CHCl_3$	...	....	5.78, 5.83, 8.00, 9.60	$C_{22}H_{34}O_4S$	66.96	66.61	8.69	8.93	8.12	8.01
7α-Methylsulfinylcortisone acetate	65	195	+128	0.2% in dioxane	235	13,100	2.94, 5.69, 5.76, 5.83, 5.95, 6.03, 6.14, 8.10, 9.60	$C_{24}H_{32}O_7S$	62.04	61.44	6.95	7.01	6.90	6.83
7α-Methylsulfinylprogesterone	57	179-180	+76.3	0.5% in $CHCl_3$	242	12,200	5.84, 5.97, 6.17, 9.67	$C_{22}H_{32}O_3S \cdot {}^1/_2H_2O$	68.54	68.89	8.63	8.65	8.32	8.02
21-Methylsulfinylprogesterone	67	130-132	+224	0.4% in $CHCl_3$	239	17,500	5.85, 5.96, 6.16, 9.51	$C_{22}H_{32}O_3S$	70.18	69.98	8.57	8.65	8.52	8.66
21-Methylsulfinyl-21-deoxyhydrocortisone	56	164	+204	0.5% in $CHCl_3$	241	16,300	2.89, 5.83, 5.98, 6.14, 9.72	$C_{22}H_{32}O_5S \cdot {}^1/_4H_2O$	63.98	63.81	7.93	8.21	7.76	7.58
21-Methylsulfinyl-21-deoxy-9α-fluorohydrocortisone	53	212	+126	0.4% in dioxane	238	19,600	3.00, 5.85, 5.97, 6.14, 9.60	$C_{22}H_{31}FO_5S$[b]	61.95	62.20	7.33	7.33	7.52	7.56

[a] See Experimental. [b] %F: Calcd. 4.45; found 4.49.

TABLE II

SULFONES

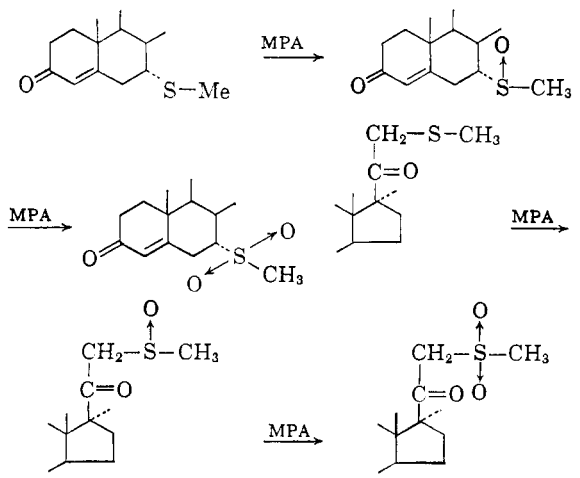
Compound	Yield, %	M.P. (dec.)	$[\alpha]^{\circ}D$	Concn., Solvent	$\lambda_{max}^{CH_3OH}$, mμ	ε	λ_{max}^{KBr}, μ	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
7α-Methylsulfonyltestosterone acetate	65	167-168	+19.7	1.1% in $CHCl_3$	241	15,100	5.77, 6.00, 6.16, 7.33, 8.05, 8.88, 13.00	$C_{22}H_{32}O_5S$	64.68	64.27	7.90	8.25	7.85	8.05
17β-Acetoxy-7α-methylsulfonyl-androstan-3-one	92	265-267	−41.5	0.9% in $CHCl_3$	...	....	5.75, 5.84, 7.73, 8.04, 8.90, 13.04	$C_{22}H_{34}O_5S$	64.35	63.90	8.35	8.58	7.81	7.72
7α-Methylsulfonylcortisone acetate	60	184	+103	0.6% in pyridine	236	18,500	2.86, 5.70, 5.77, 5.86, 5.94, 6.14, 7.68, 7.93, 8.10, 8.87, 13.00	$C_{24}H_{32}O_8S$	59.98	60.31	6.71	6.86	6.67	6.83
21-Methylsulfonylprogesterone	85	197-199	+221	0.9% in $CHCl_3$	242	16,800	5.85, 6.00, 6.15, 7.62, 8.64	$C_{22}H_{32}O_4S$	67.32	67.12	8.22	8.61	8.17	8.61
21-Methylsulfonyl-21-deoxyhydrocortisone	50	196-198	+157	0.9% in CH_3OH	241	15,300	2.81, 5.78, 6.00, 6.15, 7.65, 8.85	$C_{22}H_{32}O_6S$	62.25	62.59	7.60	7.88	7.55	7.85
21-Methylsulfonyl-21-deoxy-9α-fluorohydrocortisone	71	253	+165	0.5% in dioxane	238	19,000	2.84, 2.92, 5.78, 6.01, 6.15, 7.63, 8.78	$C_{22}H_{31}FO_6S$[a]	59.71	59.78	7.06	7.30	7.24	7.33

[a] %F: Calcd. 4.29; found 4.34.

tate and progesterone were then also prepared by this procedure. Such oxidations were equally applicable in the 21-methylthio series, and the 21-methylsulfinyl derivatives of progesterone, 21-deoxyhydrocortisone and 21-deoxy-9α-fluorohydrocortisone were obtained. The various sulfoxide derivatives are listed in Table I.

Subsequent to the preparation of 7α-methylsulfinyltestosterone acetate, Holmlund and coworkers[4] isolated from a microbiological oxidation of 7α-methylthiotestosterone acetate a product which on acetylation appeared to give the sulfur epimer of the synthetic sulfoxide (epimer A), since further oxidation by monoperphthalic acid of both compounds gave 7α-methylsulfonyltestosterone acetate. In view of this observation we reinvestigated the mother liquor from the synthetic preparation, and indeed were able to isolate a second product (epimer B) which proved to be identical with that obtained by microbiological oxidation. However, in general, we can offer no information concerning the *S*-epimeric purity of the other methylsulfinyl derivatives reported in this paper.

Oxidation of the sulfoxides with 1.1 molar equivalents of monoperphthalic acid then gave the corresponding sulfones in good yield. Again, these oxidations proceeded smoothly and the crystalline products were easily isolated from the reaction mixture. Thus the 7α-methylsulfonyl derivatives of testosterone acetate and cortisone acetate, and the 21-methylsulfonyl derivatives of progesterone, 21-deoxyhydrocortisone and 21-deoxy-9α-fluorohydrocortisone were obtained (Table II).



The α-configuration for the parent 7-methylthio derivatives was assigned on the basis of molecular rotation differences.[1] By the same criterion the α-configuration can be assigned to the various 7-methylsulfinyl and 7-methylsulfonyl derivatives of this investigation (see Table III).

(4) C. E. Holmlund, K. J. Sax, B. E. Nielsen, R. E. Hartman, R. H. Evans, Jr., and R. H. Blank, *J. Org. Chem.*, **27**, 1468 (1962).

TABLE III

CHANGES IN MOLAR ROTATION VALUES RESULTING FROM INTRODUCTION OF 7-METHYLSULFINYL AND 7-METHYLSULFONYL GROUPS

Parent Compound	7-Substituent	MD	ΔMD
Testosterone acetate		+307	
	CH_3SO Epimer A	−138	−445
	Epimer B	+ 44	−263
	CH_3SO_2	+ 80	−227
17β-Acetoxyandrostan-3-one		+ 86	
	CH_3SO	−320	−406
	CH_3SO_2	−170	−256
Cortisone acetate		+745	
	CH_3SO	+594	−151
	CH_3SO_2	+495	−250
Progesterone		+603	
	CH_3SO	+287	−316

Finally, it was of some interest to attempt the base-catalyzed epimerization of the 7α-methylsulfonyl derivatives. However, this did not prove possible since the overriding reaction of a 7α-methylsulfonyl-Δ^4-3-ketone with base is apparently an elimination reaction. Thus, even relatively mild base treatment (0.1% methanolic potassium hydroxide at room temperature) of 7α-methylsulfonyltestosterone acetate gave an 89% yield of 6-dehydrotestosterone acetate. In order to circumvent the elimination reaction, 17β-acetoxy-7α-methylsulfonylandrostan-3-one prepared by the above-described procedures from 17β-acetoxy-7α-methylthioandrostan-3-one,[1] was submitted to the epimerization experiments. However, this compound proved resistant to several attempts at base-catalyzed epimerization—the most vigorous of which was treatment for three hours at reflux temperature with 0.1% methanolic potassium hydroxide. In this last experiment the only isolatable product was starting material (after reacetylation) in about 50% yield.

Experimental[5]

General Procedure for the Preparation of Steroidal C-7 and C-21 Methyl Sulfoxides.—The steroidal C-7[1] or C-21[2] methylthio compound was dissolved or suspended in 75 ml. of methylene chloride per 0.01 mole of steroid and 1.1 mole equivalents of ethereal monoperphthalic acid was then added. The reaction mixture, protected from moisture, was allowed to stand at room temperature for 24 hr., during which period phthalic acid separated. The solution showed a negative test with 20% aqueous potassium iodide solution. The phthalic acid was collected by filtration. The filtrate was washed with dilute sodium carbonate solution, water, dried with anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure. The residue was recrystallized from acetone or petroleum ether (b.p. 60–70°)–acetone and collected by filtration. For analysis, the product was recrystallized from acetone or acetone–petroleum ether. The results obtained by this general procedure are shown in Table I.

(5) All melting points were determined in an open capillary tube and are uncorrected. The ultraviolet spectra were obtained on a Cary recording spectrophotometer and the infrared spectra were determined with a Perkin-Elmer spectrophotometer (Model 21). Optical rotations were measured in a 1-dm. semi-micro tube.

7α-Methylsulfinyltestosterone Acetate. Isolation of Two Epimers. Epimer A.—7α-Methylthiotestosterone acetate (1 g.) was treated with monoperphthalic acid by the general procedure for sulfoxide preparations described above. Evaporation of the methylene chloride solvent gave a solid which was dissolved in hot acetone. To the refluxing acetone solution petroleum ether (b.p. 60–70°) was added to the point of crystal formation. The mixture was then chilled and the solid was filtered to give 418 mg. (40%) of product with m.p. 148–150° (gas). (The mother liquor was further investigated; see below.) This product was recrystallized once from methylene chloride–ether and then three times from acetone–petroleum ether (b.p. 60–70°) to a constant m.p. at 142–145°; $[\alpha]^{25}D$ −36.2° (0.6% in chloroform); $\lambda_{max}^{CH_3OH}$ 248 mμ (ε 12,800); λ_{max}^{KBr} 5.75, 6.00, 6.16, 8.0–8.06, 9.55, 9.63 μ, also weak bands at 7.71 and 8.84 μ indicating the presence of some sulfone; $R_f^6 = 0.42$.

Anal. Calcd. for $C_{22}H_{32}O_4S$: C, 67.32; H, 8.22; S, 8.17; O, 16.31. Found: C, 66.85; H, 8.31; S, 7.87; O, 16.64.

Similar material prepared in another experiment with 0.75 molar equivalents of monoperphthalic acid (37% yield) had m.p. 149–151°; $[\alpha]^{25}D$ −6.8° (1.0% in chloroform); $R_f^6 = 0.42$; $\lambda_{max}^{CH_3OH}$ 247 mμ (ε 11,000); infrared spectrum was essentially the same as that above except that the sulfone bands were almost absent. This product was different (mixture melting point and papergram mobility comparisons) from the 7α-methylthiosulfinyltestosterone acetate obtained by Holmlund and co-workers[4] by a microbiological procedure.

Epimer B.—The acetone–petroleum ether mother liquor from the 418-mg. preparation (above) gave, after partial evaporation, a second product (202 mg., 20%) with m.p. 171–173° (gas). Recrystallization from acetone–petroleum ether (b.p. 60–70°) three times to constant melting point gave material with m.p. 175–176° (gas); $[\alpha]^{25}D$ +15.5° (0.6% in chloroform). Further purification of this product was accomplished by partition chromatography on Celite[7] diatomaceous earth using the solvent system cyclohexane–dioxane–water (60:40:8) according to a procedure developed by C. Pidacks and described previously.[8] In the second holdback volume a small amount of 7α-methylsulfonyltestosterone acetate was obtained and in the fourth holdback volume the desired 7α-methylsulfinyltestosterone acetate which was identical by mixed melting point and paper chromatographic comparisons with the microbiological product of Holmlund and co-workers[4] (presumed epimer B) was obtained. This material had the following constants: m.p. 170–171° (gas), $[\alpha]^{25}D$ +11.3° (0.97% in chloroform). $R_f^6 = 0.56$; $\lambda_{max}^{CH_3OH}$ 242 mμ (ε 10,800); λ_{max}^{KBr} 5.75, 5.97, 6.18, 8.05, 9.78 μ (no sulfone bands).

Anal. Calcd. for $C_{22}H_{32}O_4S$: C, 67.32; H, 8.22; S, 8.17. Found: C, 66.97; H, 8.36; S, 8.24.

General Procedure for the Preparation of Steroidal C-7 and C-21 Methyl Sulfones.—The steroidal C-7 or C-21 methyl sulfoxide was dissolved or suspended in 75 ml. of methylene chloride per 0.01 mole of steroid and treated with 1.1 mole equivalents of ethereal monoperphthalic acid according to the procedure described above for the preparation of the steroidal sulfoxides, except that the reaction time was extended to 48 hr. The product obtained was recrystallized from the same solvents described above. The compounds thus prepared by this general procedure are shown in Table II.

Treatment of 17β-Acetoxy-7α-methylsulfonyl-4-androsten-3-one with 0.5% Methanolic Potassium Hydroxide to Give 6-Dehydrotestosterone Acetate.—A suspension of 56 mg. of 17β-acetoxy-7α-methylsulfonyl-4-androsten-3-one in 5 cc. of 0.5% methanolic potassium hydroxide was stirred under nitrogen for 3 min. when solution was completed. After an additional 1 min., the solution was acidified with acetic acid. Dilution with water and filtration afforded 40 mg. (89%) of 6-dehydrotestosterone acetate,[9] m.p. 137–140°. Admixture with an authentic sample did not depress the melting point. The infrared spectra for the two samples were identical.

Acknowledgment.—We wish to thank Mr. L. Brancone and staff for the microanalyses and Mr. W. Fulmor and staff for the spectral and polarimetric determinations.

(6) The solvent system used was benzene, acetic acid, petroleum ether (b.p. 90–100°), water in the volume ratio 13:16:7:4. We thank Dr. Holmlund and his colleagues for these determinations.

(7) Celite is the trademark of Johns Manville Corp. for diatomaceous earth.

(8) W. S. Allen, C. C. Pidacks, R. E. Schaub, and M. J. Weiss, *J. Org. Chem.*, **26**, 5046 (1961).

(9) C. Djerassi, G. Rosencranz, J. Romo, St. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

Formation and Oxidation of 2-(9′-Fluorenyl)-fluorene[1]

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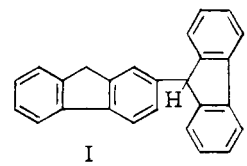
In an earlier paper it was reported that reaction of fluorene and sodium amide yielded two products which were isomers of 9,9′,9′,9″-terfluorene since more than two moles of fluorenone were obtained by oxidation of these products.[2] In the present work, the preparation and oxidation of a related compound, 2-(9′-fluorenyl)fluorene (I) are described. I was isolated as a by-product in the Clemmensen reduction of 9-fluorenol in toluene, was also produced when 9-fluorenol was boiled with fluorene in acetic acid in the presence of sulfuric acid, or was obtained by Friedel-Crafts reaction between fluorene and 9-bromofluorene in carbon disulfide.



I

On oxidation with sodium dichromate in acetic acid, I gave *o*-(fluorenone-2-carbonyl)benzoic acid and 13*H*-indeno[1,2-*b*]anthracene-6,11,13-trione (*lin*-phthaloylfluorenone), but no fluorenone, indicating that two molecules of fluorene were condensed at the 2- and 9- positions, respectively. I gave fluorene by zinc dust distillation, and its ultraviolet absorption spectrum differed from those of dibiphenyleneethane,[3] tribiphenylenepropane,[3] and 2,2′-difluorenyl.[4]

(1) Studies on Fluorene Derivatives XVIII; Part XVII of this series: S. Kajigaeshi, in press.

(2) K. Suzuki, Nippon Kagaku Zasshi, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **70**, 189 (1949).

(3) K. Suzuki, *Technol. Repts. Tohoku Univ.*, **19**, 63 (1955).

(4) M. Barnett, G. Daub, F. Hayes, and D. Ott, *J. Am. Chem. Soc.*, **81**, 4583 (1959).

Barnett's[5] method was employed to synthesize the *lin*-phthaloylfluorenone. *o*-(Fluorenone-2-carbonyl)benzoic acid was formed by oxidation of *o*-(fluorene-2-carbonyl)benzoic acid and was esterified in ethanol.

Experimental[6]

2-(9′-Fluorenyl)fluorene (I).—9-Bromofluorene (2.44 g.) and fluorene (1.66 g.) were dissolved in carbon disulfide (30 ml.). Anhydrous aluminum chloride (1.35 g.) was added in small portions with stirring at the boiling point. The reaction color immediately turned greenish blue and hydrogen chloride gas was evolved. After warming for 0.5 hr. on the water bath, the mixture was cooled and poured into water. The carbon disulfide layer was separated, washed with water, and evaporated to dryness to give colorless needles 1.5 g., m.p. 225–226° (from benzene), soluble in hot benzene, acetic acid, and ethyl acetate, and stable at the melting point. Ultraviolet absorption spectra: $\lambda_{max}^{CHCl_3}$ mμ (log ε); 272.5 (4.52), 296 (4.15), 307 (4.22), 323 (3.27).

Anal. Calcd. for $C_{26}H_{18}$: C, 94.51; H, 5.49; mol. wt., 330. Found: C, 94.15; H, 5.68; mol. wt., 325.

Clemmensen Reduction of 9-Fluorenol.—A mixture of amalgamated zinc (10 g.), water (10 ml.), toluene (40 ml.), concd. hydrochloric acid (35 ml.), and 9-fluorenol (10 g.) was refluxed briskly for 24 hr. Hydrochloric acid was added every 6 hr. After the reaction, fluorene (8 g., m.p. 113–114°) was obtained by steam distillation. A residual product was filtered and recrystallized from ethyl acetate to yield I, 0.8 g., m.p. 224–227°.

Reaction of Fluorene and 9-Fluorenol.—9-Fluorenol (0.8 g.) and fluorene (0.73 g.) in acetic acid (7 ml.) and two drops of concd. sulfuric acid were refluxed for 5 hr. After pouring into cold water, the white amorphous product was filtered off giving 0.8 g. of I, m.p. 224–226° (from benzene).

Oxidation of I.—A solution of I (1.0 g.) in glacial acetic acid (10 ml.) was refluxed with sodium dichromate (3 g.) and concd. sulfuric acid (1 drop) for 3 hr. After cooling and diluting the solution with cold water, the yellow amorphous precipitate was filtered and treated with dilute sodium hydroxide (10%). Acidification of the alkali soluble part gave a precipitate which was recrystallized from acetic acid to yield yellow prisms of *o*-(fluorenone-2-carbonyl)benzoic acid (0.2 g.), m.p. 257–258°, identical with that obtained by oxidation of *o*(fluorene-2-carbonyl)benzoic acid.

Anal. Calcd. for $C_{21}H_{12}O_4$: C, 76.82; H, 3.68. Found: C, 76.67; H, 3.77.

The alkali-insoluble part was recrystallized from acetic acid to afford small orange-red needles, m.p. 367°, 0.5 g., which gave a blue color test with concd. sulfuric acid. This was identical with the *lin*-phthaloylfluorenone which was prepared by Barnett's method.[5]

Anal. Calcd. for $C_{21}H_{10}O_3$: C, 81.28; H, 3.25. Found: C, 81.17; H, 3.47.

Ethyl *o*-(Fluorenone-2-carbonyl)benzoate.—The acid was esterified in the usual manner to give yellow crystals, m.p. 108–110° (from alcohol).

Anal. Calcd. for $C_{23}H_{16}O_4$: C, 77.51, H, 4.53. Found: C, 77.15; H, 4.61.

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(5) E. Barnett, N. Goodway, and J. Waston, *Ber.*, **66**, 1876 (1933); F. Ullmann and I. Dasgupta, *ibid.*, **47**, 566 (1914); G. Goldschmiedt and A. Lipschitz, *ibid.*, **36**, 4034 (1903); A. Dansi and A. Sempronji, *Gazz. chim. ital.*, **63**, 681 (1933); *Chem. Abstr.*, **28**, 1999 (1934).

(6) All melting points are uncorrected.

Fries Rearrangement of 3-Nitrophenyl Butyrate

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Few examples of the Fries isomerization of nitrophenyl esters are reported in the literature.[1–10] The reduced tendency of these esters to undergo Fries rearrangement must be associated with the retarding effect of the nitro substituent in the phenyl ring.[11–16]

The Fries reaction of 3-nitrophenyl acetate,[2,3] propionate,[6] phenylacetate, and benzoate[10] has already been realized. In the present work 3-nitrophenyl butyrate has been subjected to the Fries rearrangement by heating it for 2.5 hr. in the absence of a solvent in the presence of aluminum chloride at 140°. The isomerization yielded 3.5–5% of the so far unknown 4-nitro-2-hydroxybutyrophenone, which was characterized by its phenylhydrazone. The structure of this new ketone was proved by oxidation which gave 4-nitro-2-hydroxybenzoic acid.

Experimental[17]

3-Nitrophenyl butyrate was prepared in 80% yield from sodium 3-nitrophenoxide (obtained from 3-nitrophenol and sodium ethoxide in benzene) and butyryl chloride in benzene. After the removal of the solvent the residual ester[18] was used without further purification, as it decomposed on distilling. The ester (10.5 g., 0.05 mole) was mixed with aluminum chloride (6.55 g., 0.05 mole,) in a flask protected against moisture and heated in an oil bath at 135–140° for 150 minutes. At the beginning of the reaction hydrogen chloride was evolved. The solidified product was dissolved

(1) F. G. Brown, *J. Am. Chem. Soc.*, **68**, 872 (1946).

(2) Á. Gerecs, T. Széll, and M. Windholz, *Acta chim. Acad. Sci., Hung.*, **3**, 459 (1953).

(3) T. Széll, Gy. Sipos, and Gy. Szentgáli, *Magy. Kém. Foly.*, **59**, 148 (1953).

(4) G. C. Amin and A. S. U. Choughulay, *J. Sci. and Industr. Res.* (India), **12 B**, 391 (1953).

(5) Sh. Joshi and H. Singh, *J. Am. Chem. Soc.*, **76**, 4993 (1954).

(6) T. Széll and A. Bajusz, *Acta Phys. et Chem. Szeged*, **2**, 137 (1956).

(7) A. S. U. Choughulay and G. C. Amin, *Sci. and Cult.*, **19**, 614 (1954).

(8) T. Széll, *Ber.*, **91**, 2609 (1958).

(9) T. Széll, Á. Furka, and I. Szilágyi, *J. Sci. and Industr. Res.* (India), **18 B**, 325 (1959).

(10) Á. Furka and T. Széll, *Acta Phys. et Chem. Szeged.*, **6**, 113, 122 (1960); *ibid.*, **7**, 70 (1961).

(11) K. W. Rosenmund and W. Schnurr, *Ann.*, **460**, 56 (1928).

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(13) J. F. Norris and B. M. Sturgis, *J. Am. Chem. Soc.*, **61**, 1413 (1939).

(14) C. R. Hauser and E. H. Man, *J. Org. Chem.*, **17**, 390 (1952).

(15) J. I. Setalvald and N. M. Shah, *J. Indian Chem. Soc.*, **31**, 600 (1954).

(16) T. Széll, Á. Furka, and I. Szilágyi, *J. Sci. and Industr. Res.* (India), **18 B**, 323 (1959).

(17) Melting points are uncorrected.

(18) Ch. Huggins and J. Lapides, *J. Biol. Chem.*, **170**, 467 (1947).

in 20 cc. of ethanol, and poured into a mixture of 10 cc. of concd. hydrochloric acid and 150 cc. of water. The aqueous layer was extracted with four 40- cc. portions of tetrachloromethane and two 15-cc. portions of benzene. The combined extracts were used to dissolve the organic layer. The solution was washed with eight 50-cc. portions of water. It was then dried over sodium sulfate and filtered through cotton. Removal of the solvent gave a brown oily residue. A part of this was dissolved in 70% ethanol, mixed with phenylhydrazine, and boiled for 2–3 min. On allowing to stand it overnight in a refrigerator, red needles melting at 179–180° separated.

Anal. Calcd. for $C_{13}H_{17}O_3N_3$: N, 14.04; mol. wt. 299.3. Found: N, 14.30.

Another part of the residual oil was washed with water again and extracted with petroleum ether. On concentrating the extract yellowish oily crystals separated. They were collected and recrystallized from ethanol to give a solid melting at 63.5–64°.

Anal. Calcd. for $C_{10}H_{11}O_4N$: N, 6.73; mol. wt. 209.2. Found: N, 6.81.

The method of oxidation of 4-nitro-2-hydroxybutyrophenone to 4-nitro-2-hydroxybenzoic acid was the same (potassium permanganate in potassium hydroxide solution) as used for the oxidation of 4-nitro-2-hydroxypropiophenone.[6]

Acknowledgment.—We wish to thank the Hungarian Academy of Sciences for a grant and the Microanalytical Laboratory of the Institute of Organic Chemistry of the University of Szeged (Mrs. K. L. Láng and Mrs. G. B. Bózóki) for the microanalyses.

Mannich Bases Derived from Acetylated Hydantoins

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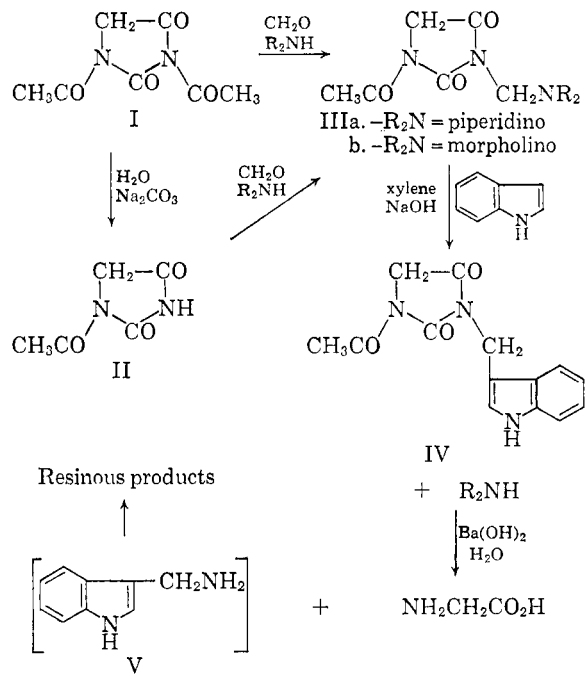
1,3-Diacetylhydantoin (I), prepared by the reaction of hydantoin with acetic anhydride in the presence of fused sodium acetate,[1] has been investigated as a precursor of the tryptophan side chain. Treatment of this compound with aqueous formaldehyde and either piperidine or morpholine was found to yield crystalline Mannich bases in excellent yield. Elemental analysis of these derivatives indicated that one of the acetyl groups had been replaced by an aminomethyl group.

Mannich base formation has also been observed with 1-acetylhydantoin (II), a compound readily prepared by the partial hydrolysis of 1,3-diacetylhydantoin.[1] Treatment of this material with aqueous formaldehyde and either piperidine or morpholine yielded the same Mannich bases obtained with 1,3-diacetylhydantoin.

Reaction of either Mannich base with indole under conditions similar to those described by Butenandt and Hellmann[2] gave a single condensation product in 20–32% yield. The latter compound had an elemental analysis which indicated the dialkylamino group had been replaced by an indolyl group. Upon alkaline hydrolysis[3] the compound yielded glycine along with an insoluble resinous product but no tryptophan.

On the basis of these results the Mannich bases have been identified as 1-acetyl-3-*N*-piperidinomethylhydantoin (IIIa) and 1-acetyl-3-*N*-morpholinomethylhydantoin (IIIb), respectively. The condensation product is indicated as being 1-acetyl-3-(3′-indolylmethyl)hydantoin (IV) since this compound on hydrolysis should be converted into glycine and 3-indolylmethylamine (V). The latter compound, which is relatively unstable, might be expected to form the resin isolated in its place under the conditions used to accomplish the hydrolysis.



The exact course of the reaction forming the Mannich bases from 1,3-diacetylhydantoin has not been determined. A possible intermediate is 1-acetylhydantoin, since this material could be produced by the alkaline conditions employed in the aminomethylation reaction.

Efforts to prepare Mannich bases by the reaction of either piperidine or morpholine and formaldehyde with various other glycine derivatives were unsuccessful. Compounds of the latter type examined include hydantoin, 3-methylhydantoin, aceturic acid, hippuric acid, acetaminoacetonitrile, *N*-phthaliminoacetonitrile, and 2-phenyl-5-oxazolone.

(1) L. Siemonsen, *Ann.*, **333**, 101 (1904).

(2) A. Butenandt and H. Hellmann, *Z. physiol. Chem.*, **284**, 168 (1949).

(3) W. K. Anslow and H. King, *J. Chem. Soc.*, 2463 (1929).

Experimental[4]

1-Acetyl-3-*N*-piperidinomethylhydantoin (IIIa).—1,3-Diacetylhydantoin (5.0 g., 0.027 mole) was dissolved in piperidine (10.0 g., 0.12 mole). To the resulting solution aqueous formaldehyde (5 ml. 36.2% solution equivalent to 1.85 g. or 0.062 mole) was added in one portion. The product precipitated immediately as a white crystalline mass. After cooling to 10–15°, this product was collected by filtration and washed with petroleum ether (four 15-ml. portions). After air drying, the product (6.7 g., 0.026 mole, 98%) melted at 150–152°. A single recrystallization from ethyl acetate raised this melting point to 160–161°.

Anal. Calcd. for $C_{11}H_{17}O_3N_3$: C, 55.25; H, 7.13; N, 17.59. Found: C, 55.48; H, 7.12; N, 17.78.

1-Acetyl-3-*N*-morpholinomethylhydantoin (IIIb).—1,3-Diacetylhydantoin (5.0 g., 0.027 mole) was dissolved in morpholine (10.0 g., 0.12 mole). To this solution aqueous formaldehyde (5 ml. 36.2% solution equivalent to 1.85 g. or 0.062 mole) was added in one portion. The solution which resulted was cooled to 15–20° and stirred to induce crystallization. The product deposited as a mass of white crystals. It was collected by filtration and washed with dry ether (two 5-ml. portions). After air drying it amounted to 6.2 g. (0.025 mole, 91%) and melted at 139–141°. A single recrystallization from ethyl acetate yielded the compound in pure form, m.p. 154–155°.

Anal. Calcd. for $C_{10}H_{15}O_4N_3$: C, 49.87; H, 6.23; N, 17.42. Found: C, 50.17; H, 6.41; N, 17.08.

1-Acetyl-3-(3′-indolylmethyl)hydantoin (IV).—1-Acetyl-3-piperidinomethylhydantoin (7.6 g., 0.030 mole), indole (3.6 g., 0.031 mole), and sodium hydroxide (0.2 g., 0.005 mole) were placed in dry xylene (60 ml.) and heated at 135–145° for 24 hr. under nitrogen. Upon cooling a brown amorphous precipitate deposited and was collected by filtration. After washing with a small amount of petroleum ether, the product was air dried. It weighed 3.6 g. Extraction of this material with ethyl acetate in a Soxhlet apparatus yielded 2.5 g. (0.0097 mole, 32%) of a product which melted at 197–198°.

Anal. Calcd. for $C_{14}H_{13}O_3N_3$: C, 62.00; H, 4.80. Found: C, 61.61; H, 4.96.

The same derivative was obtained in somewhat lower yield by condensing 1-acetyl-3-morpholinomethylhydantoin with indole under the conditions described above.

The hydrolysis of 1-acetyl-3-(3′-indolylmethyl)hydantoin was accomplished by heating the compound with aqueous barium hydroxide. This hydrolysis yielded an appreciable quantity of glycine, identified by paper chromatography, and an insoluble resinous product, which was not characterized. The absence of tryptophan in the hydrolyzate was also established by paper chromatography.

(4) All melting points are uncorrected.

SN2 Reactions of Chloroacetals

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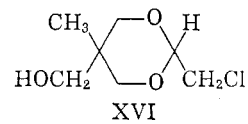
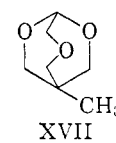
Nucleophilic substitutions of the chlorine atoms of bischloroethylidenepentaerythritol[1] (I) offer promise of producing several interesting difunctional compounds of possible interest in the synthesis of polymers and of fluids of high viscosity and low volatility. Because of the difficulty reported in effecting these reactions with sodium cyanide,[2] a study has been made of the nucleophilic substitution of the following cyclic acetals of chloroacetaldehyde: I; monochloroethylidenepentaerythritol (II); the acetal (III) of chloroacetaldehyde and 2-methyl-2-hydroxymethylpropanediol-1,3; two homologs of the latter (IV and V in Table I); and the chloroacetal of 2,2-dimethylpropanediol-1,3 (VI)[1] (see Table I).

The nucleophilic reagents chosen for study were ammonia and the anions of phenol and cyclohexanol. No difficulty was experienced in effecting S_N2 reactions with these reagents. In the reaction of ammonia with VI, the secondary amine was isolated, probably because the reaction was conducted in a two phase system. The product of the reaction of ammonia with I was a basic material, indicating that the reaction had taken place, but it was an intractable gum from which no pure product could be isolated.

Compounds III, IV, V, and their derivatives, are capable of existing in *cis* and *trans* forms. Distillation of III through a short packed fractionating column failed to effect a separation. If at least a part of III, IV, or V were present as the isomer in which the hydroxymethyl group is *cis* to the chloromethyl group (XVI for III),[3] it should be possible to effect cyclization to a bicyclic triether structure like XVII. However, treatment of III and IV



XVI



XVII

with sodium cyclohexyloxide gave the cyclohexyl ethers, but no product of cyclization. The same results were obtained with II, even though in this case the chloromethyl group would necessarily be *cis* to a hydroxymethyl group. Also, an attempt to cyclize V by refluxing with a solution of sodium hydroxide in diethylene glycol produced no evidence of formation of a cyclic product.

Experimental[4]

Preparation of 2-*n*-Propyl-2-hydroxymethylpropanediol-1,3.[5]—To a stirred mixture of 86.1 g. (1 mole) of *n*-valeralde-

(1) Correct systematic names for compounds I through VI are: I: 3,9-Bischloromethyl-2,4,8,10-tetraoxaspiro[5.5]undecane. II: 2-Chloromethyl-5,5-bishydroxymethyl-1,3-dioxane. III: 2-Chloromethyl-5-ethyl-5-hydroxymethyl-1,3-dioxane. V: 2-Chloromethyl-5-hydroxymethyl-5-propyl-1,3-dioxane. VI: 2-Chloromethyl-5,5-dimethyl-1,3-dioxane.

(2) J. B. Clements and L. M. Rice, *J. Org. Chem.*, **24**, 1958 (1959).

(3) The question whether this ring structure takes the chair, boat, or skew conformation is as yet unresolved.

(4) Microanalyses were performed by Weiler and Strauss Laboratories, Oxford, England; melting points and boiling points were uncorrected.

(5) An adaptation from the preparation of pentaerythritol. H. B. J. Schurink, *Org. Syntheses*, Coll. Vol. I, 425 (1941).

TABLE I
ACETALS OF POLYOLS

	R_1	R_2	R_3	M.P.	B.P.	Mm.	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
IV	$HOCH_2$—	C_2H_5—	Cl	...	106–111	0.2	65	$C_8H_{15}O_3Cl$	49.36	7.76	18.21	49.53	7.92	18.28
V	$HOCH_2$—	*n*-C_3H_7	Cl	...	112–114	0.1	77	$C_9H_{17}O_3Cl$	51.78	8.21	16.99	52.01	8.18	17.10
VII	CH_3—	CH_3—	*O*-Phenyl	50.5–51		...	52	$C_{13}H_{18}O_3$	70.21	8.16		70.15	8.26	
VIII	CH_3—	CH_3—	*O*-Cyclohexyl-	...	78–80	0.05	29	$C_{13}H_{24}O_3$	68.38	10.59		68.84	11.11	
IX	$HOCH_2$—	CH_3—	*O*-Phenyl	98–99	...	...	30	$C_{13}H_{18}O_9$	65.50	7.61		65.56	8.02	
X	$HOCH_2$—	CH_3—	*O*-Cyclohexyl	...	130–132	0.1	25.6	$C_{13}H_{24}O_4$	63.90	9.90		64.65	10.14	
XI	$HOCH_2$—	C_2H_5—	*O*-Cyclohexyl	...	150–160	0.3	55	$C_{14}H_{26}O_4$	65.09	10.15		65.06	9.46	
XII	$HOCH_2$—	$HOCH_2$—	*O*-Phenyl	134–140	...	...	29	$C_{13}H_{18}O_6$	61.38	7.13		61.73	7.15	
XIII	$HOCH_2$	$HOCH_2$—	*O*-Cyclohexyl-	97–98	180–245	0.008	8.1	$C_{13}H_{24}O_5$	59.94	9.28		58.75	9.33	

hyde and 2060 g. of water, was added solid calcium hydroxide and 40% formaldehyde solution in small portions at a rate which kept the temperature of the reaction mixture between 50 and 55°. After 420 ml. of 40% formaldehyde (6 moles) and 44.5 g. (0.6 mole) of calcium hydroxide had been added, the mixture was kept at 50° with an infrared lamp and stirred for 3 hr. The *p*H at this time was 6.8. After filtering the mixture, removing the water by vacuum distillation and the resulting white inorganic precipitate by filtration, the remaining liquid was distilled at 1 mm. When the pot temperature reached 180°, distillation was stopped just as signs of darkening appeared. Attempts to distill beyond this point resulted in decomposition. On cooling, the pot contents (89.5 g.) solidified. On recrystallization from methanol, 43.0 g. (29.1 %) of 2-*n*-propyl-2-hydroxymethylpropanediol-1,3, m.p. 97–100°, was obtained; m.p. of an analytical sample was 100–101°.

Anal. Calcd. for $C_7H_{16}O_3$: C, 56.73; H, 10.88. Found: C, 56.10; H, 10.77.

Preparation of Chloroacetals.—The synthesis of II, III, and VI has been previously reported.[6] The other chloroacetals (I, IV, and V) were made by the same methods. I, which was made in 35% yield by reaction in aqueous solution, was found to have a m.p. 96.0–96.5°. The m.p. previously reported was 91.8°.[7]

Reaction of Chloroacetals with Sodium Phenoxide.—The following may be considered a model for all the reactions of this type which were conducted in this work. A solution of 12 g. (0.3 mole) of sodium hydroxide, 23.1 g. (0.3 mole) of phenol, and 36.82 g. (0.14 mole) of bischloroethylidenepentaerythritol in 200 ml. of ethylene glycol was refluxed for 26 hr. The reaction mixture solidified on cooling and was washed with water, yielding 38.5 g. of water-insoluble solid. On recrystallization from benzene, 20.1 g. (39%) of XIV, m.p. 203–205°, was obtained.

In the reaction of III with sodium phenoxide, the product was soluble in the reaction mixture, so that the solvent was removed by distillation and the sodium chloride was filtered as it precipitated. The product itself (IX) was distilled at 154–160° (0.14 mm.). It then solidified and was recrystallized from methanol and water to a m.p. of 98–99°.

Reactions of Chloroacetals with the Sodium Salt of Cyclohexanol.—The following is a general procedure for the preparation of the cyclohexyl ethers from the chloroacetals. To 250 ml. of cyclohexanol was added 6.9 g. (0.3 g.-atom) of metallic sodium, and the resulting mixture was refluxed until all the sodium dissolved. To this solution was added 58.4 g. (0.3 mole) of III. This mixture was refluxed for 1 hr., and the reaction mixture filtered hot to remove the salt (16.4 g.) formed during reaction. The filtrate was then distilled under reduced pressure.

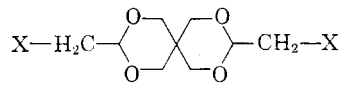
In the reactions of the sodium salt of cyclohexanol with monochloroethylidenepentaerythritol and with bischloroethylidenepentaerythritol, the distillate solidified on cooling. The former was recrystallized to a constant melting point from benzene. The latter could not be recrystallized from any of the common solvents and was sent for analysis without recrystallization. In all of these reactions, no cyclization product was obtained in the boiling point range expected for these compounds.

Reaction of Chloroacetal of 1,1,1-Trimethylolbutane (V) and Sodium Hydroxide.—To a hot solution of 16.3 g. (0.41 mole) of sodium hydroxide in 300 ml. of diethylene glycol (b.p. 244°) was added dropwise 50 g. (0.24 mole) of V. A distillate was collected (7.1 g.) while the sodium hydroxide was being added (b.p. 98–110°). This, as well as another fraction (2.1 g., b.p. 110–135°) was almost entirely water. In the boiling point range expected for the cyclization product (135–210°) nothing was collected. The reaction

(6) W. E. Conrad, B. D. Gesner, L. A. Levasseur, R. F. Murphy, and H. M. Conrad, *J. Org. Chem.* **26**, 3571 (1961).

(7) V. G. Mkhitaryan, *J. Gen. Chem. U.S.S.R.*, **9**, 1923 (1939).

TABLE II
ACETALS OF PENTAERYTHRITOL



	X	M.P.	B.P.	Mm.	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
XIV	*O*-Phenyl	203.5	...	...	39	$C_{21}H_{24}O_6$	67.73	6.45		66.93	6.66	
XV	*O*-Cyclohexyl	40–47	176–200	0.1	50	$C_{21}H_{36}O_6$	65.59	9.43		64.19	9.36	
I	Cl	96–96.5	...	...	35	$C_9H_{14}O_4Cl_2$	42.05	5.49	27.58	42.61	5.17	27.40

mixture was completely soluble in water. No further attempts were made to isolate a reaction product.

Reaction of VI with Ammonia.—A mixture of 82.3 g. (0.5 mole) of the chloroacetal of pentaglycol and 133.2 ml. (2 moles) of concd. ammonium hydroxide in 66.6 ml. of Cellosolve was placed in a sealed iron pipe and heated at 138° for 17 hr. The reaction mixture was then filtered and the filtrate formed two layers. The organic layer was separated and distilled. After a small forerun, a fraction (17.5 g.) was collected at 80–155° (1.3 mm.) which solidified on cooling. On recrystallization from benzene, 15.6 g. (23%) of bis[(5,5-dimethyl-*m*-dioxan-2-yl)methyl]amine, m.p. 60–65°, was obtained. Melting point of an analytical sample was 67–68°.

Anal. Calcd. for $C_{14}H_{27}O_4N$: C, 61.51; H, 9.95; N, 5.12. Found: C, 61.73; H, 10.12; N, 5.11.

Reaction of I with Ammonium Hydroxide.—Reaction of I with ammonia for 8.5 hr. at 140° in a procedure similar to the above, afforded a light-colored gummy material which was soluble in cold dilute hydrochloric acid. The gummy product could not be recrystallized. Attempts to form derivatives by benzoylation and by reaction with picric acid afforded only gummy materials again.

Acknowledgment.—We gratefully acknowledge grants for the support of undergraduate research from the Research Corp., the National Science Foundation, and the Petroleum Research Fund, administered by the American Chemical Society.

Juglone 4-Monooxime, an Isomer of 8-Nitro-1-naphthol

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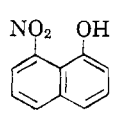
Meldola and Streatfeild[1] were the first to attempt to prepare 8-nitro-1-naphthol (I) by decomposition of the diazonium salt of 8-nitro-1-naphthylamine,



I

but obtained only resinous material. Kozlov and Vorozhtzov[2] repeated this work and obtained a product of m.p. 212° dec., which they considered to be the compound in question. The reaction was later carried out by Luther and Gunzler,[3] and also by Anderson and co-workers[4] and by Bryson,[5] and the product accepted as 8-nitro-1-naphthol.

In the present work, the compound was prepared by the same method for comparison with other products which were suspected of containing this nitronaphthol. From Luther and Gunzler's infrared data, it was seen that the product obtained was identical to theirs. It eventually became apparent, however, that the substance did not have the infrared spectral characteristics nor the chemical properties of a nitronaphthol.

Thus, the spectrum was found to be quite similar to those of a number of naphthaquinone monooximes which had been prepared in this laboratory. Strong nitro bands were missing and three characteristic features of quinone oximes, as indicated by Hadzi,[6] were present: 1. Strong and broad absorption bands centered around 3100 cm.$^{-1}$, with one band appearing at 2830 cm.$^{-1}$. 2. A shoulder at 1655 cm.$^{-1}$, probably due to the C=O stretching mode of the 1,4-monooxime. 3. A strong band at 988 cm.$^{-1}$, ascribed to the N—O bending frequency in quinone oximes. No similar band was found in any of the isomeric nitronaphthols which were examined in this laboratory.

Among various possible structures considered for the compound was that of a 5-hydroxy-1,4-naphthaquinone 4-monooxime (8-hydroxynaphthaquinone 1-oxime) (III), isomeric with 8-nitro-1-naphthol. After further examination, this constitution proved to be compatible with the properties of the substance.

All three of the *ortho* substituted nitronaphthols (1,2- or 2,1- and 3,2-) have melting points below 130° and a peri (1,8-) isomer, with similar possibilities for chelation or H-bonding likewise might be expected to be less polar and therefore lower melting than other nitronaphthols. The m.p. of 212° dec. given by Kozlov and Vorozhtzov[2] is much higher than would be expected and, indeed, later work by Anderson *et al.*[4] and Bryson[5] give a decomp. point of 242° without melting.

(1) R. Meldola and F. W. Streatfeild, *J. Chem. Soc.*, **63**, 1056 (1893).

(2) V. V. Kozlov and N. N. Vorozhtzov, *Ber.*, **69B**, 416 (1936).

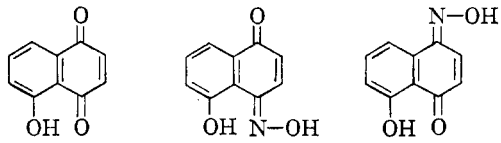
(3) H. Luther and H. Gunzler, *Z. Naturfors.*, **10b**, 445 (1955).

(4) J. R. A. Anderson, A. J. Costoulas, and J. L. Garnett, *Anal. Chim. Acta.*, **20**, 236 (1959).

(5) A. Bryson, *Trans. Faraday Soc.*, in press (from ref. 4).

(6) D. Hadzi, *J. Chem. Soc.*, 2725 (1956).

From the suggested structure of a 5-hydroxy-1,4-naphthaquinone 4-oxime, it is evident that this is a derivative of the long known 5-hydroxy-1,4-naphthaquinone or juglone (II). It might be considered possible, therefore, that the compound would be convertible into, or formed from, juglone.

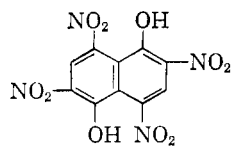


II III IV

In an effort to test this, compound III was steam distilled from dilute sulfuric acid, hoping to hydrolyze the oxime and volatilize any juglone. The latter was isolated from the distillate in greater than 80% yield, and the infrared spectrum matched that of authentic juglone. It is difficult to see how this compound could be derived from a nitronaphthol.

The monooxime III does not seem to be listed in the literature, though the isomeric monooxime (IV) has been claimed to be the product from juglone and hydroxylamine.[7] The orientation IV might have been expected, since the oxime III would be the product of reaction at a more hindered carbonyl, and in addition, this carbonyl would be less reactive because of H-bonding to the peri-hydroxyl group.

The action of nitric acid under mild conditions on some naphthaquinone oximes results in derivatives of 2,4-dinitro-1-naphthol (Martius Yellow), formed by a combined oxidation and nitration.[8] If this reaction succeeded with the quinone oxime III, it might be supposed that the product would be the 2,4,6,8-tetranitro-1,5-dihydroxynaphthalene



V

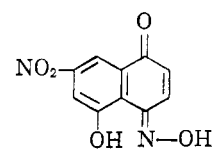
(V) of Thomson, Race, and Rowe.[9] When this was tried with the suspected hydroxyquinone oxime III, it gave a better yield of the tetranitro compound V than was obtained from 1,5-dihydroxynaphthalene by nitration.[9] The infrared spectra of the tetranitro compounds prepared by the two methods were identical. The improved yields with the hydroxyquinone oxime as starting material may be explained by the fact that it is less sensitive to oxidative destruction by nitric acid and also because it is already partly substituted in the desired direction.

8-Nitro-1-naphthol, under the conditions of the nitration, should form 2,4,8 trinitro-1-naphthol. By comparison with authentic material,[8] it was seen that no trace of the infrared peaks of this trinitronaphthol was present in the spectrum of the nitration product of III.

As to the mode of formation of the juglone 4-oxime, it is apparently the result of an internal oxidation-reduction, but a mechanism for its production cannot be discerned at this time.

Further efforts were made to prepare 8-nitro-1-naphthol from the 8-nitro-1-diazonium salts. Attempts to employ the method of Hodgson and Foster[10] involving decomposition of the diazonium zinc chloride complex in acetic anhydride led to intractable tars instead of a nitronaphthyl acetate. No nitronaphthol could be obtained on alkaline hydrolysis of the product. Likewise, the adaptation of Smith and Haller[11] using the diazonium fluoroborate in acetic acid gave a similar result.

In an extension of this work, the diazotization and decomposition of 3,8-dinitro-1-naphthylamine[12] was carried out to determine if 3,8-dinitro-1-naphthol could be formed. However, the properties of the product were best explained by the nitrojuglone oxime formulation, VI. The infrared



VI

spectrum of the material shows two strong absorption bands at 985 cm.$^{-1}$ and 995 cm.$^{-1}$,[6] and a strong band at 1640 cm.$^{-1}$ these wave-numbers probably corresponding to the similar values shown by III. In its property of decomposing at a high temperature with partial fusion, VI also resembles the juglone monooxime. This reaction seems to provide an additional example of the formation of a hydroxyquinone oxime from a nitrodiazonium salt.

It may be noted that another reference exists in the literature describing the synthesis of 8-nitro-1-naphthol, namely that of Bell,[13] who claims its preparation in poor yield by the nitration of the *m*-nitrobenzenesulfonate ester of α-naphthol, followed by hydrolysis. Preliminary attempts to repeat this work have not succeeded.

(7) H. Goldstein and P. Grandjean, *Helv. Chim. Acta.*, **26**, 181 (1943).

(8) C. Graebe and A. Oeser, *Ann.*, **335**, 145 (1904).

(9) R. H. Thomson, E. Race, and F. M. Rowe, *J. Chem. Soc.*, 350 (1947).

(10) H. H. Hodgson and C. K. Foster, *J. Chem. Soc.*, 747 (1942).

(11) L. E. Smith and H. L. Haller, *J. Am. Chem. Soc.*, **61**, 143 (1939).

(12) E. R. Ward, T. M. Coulson, and J. G. Hawkins, *J. Chem. Soc.*, 4541 (1954).

(13) F. Bell, *J. Chem. Soc.*, 286 (1933).

Experimental

Infrared spectra were obtained on a Perkin-Elmer Model 21 Spectrophotometer, using a sodium chloride prism. The samples were examined as potassium bromide discs.

The hydroxyquinone oxime III was prepared as described by Kozlov and Vorozhtzov,[2] any excess of nitrous acid being destroyed by urea before boiling. As to the decomp. point, the higher value favored by Bryson[5] seems to describe better the behavior of the compound on heating. The Russian workers gave adequate analytical values for III and also its lead salt. In the present work, the molecular weight was obtained by the Osmometer method to be sure the substance was not dimeric.

Mol. wt. Calcd. for $C_{10}H_7NO_3$: 189. Found: 190.

Hydrolysis of III.—A mixture of 150 mg. (0.79 mmole) of the juglone 4-oxime and 200 ml. of 2.5 *N* sulfuric acid was steam distilled for 6 hr. The yellow distillate was extracted twice with ether and the extracts dried and evaporated. A residue of 112 mg. of crystalline material was left. Yield: 81.1%. The spectrum of this product was identical to that of authentic juglone. It also formed the characteristic violet solutions in alkalies. Juglone for comparison was obtained by the method of Fieser and Dunn,[14] from 1,5-dihydroxynaphthalene.

Nitration of III.—A suspension of 0.25 g. (1.32 mmoles) of the hydroxy quinone oxime in 15 ml. of acetic acid was heated to boiling and cooled to 40–50°. A good part of the material crystallized at this temperature, and 5 ml. of 70% nitric acid was added slowly with stirring. The temperature was kept below 50°. After 15 min. at 40–50°, the mixture was cooled, diluted with 6 volumes of water, and left 1 hr. The tetranitro compound was filtered, washed with water, and dried. Yield 285 mg. or 63%. This product becomes red with alkali without solution as described by Thomson *et al.*[9] Comparison of infrared spectra with the authentic product showed identity.

To prepare a comparison sample of the tetranitro compound V, Thomson's work was repeated.[9] A poor yield of yellow-orange crystalline powder was produced which decomp. above 250°.

Authentic 2,4,8-trinitro-1-naphthol was prepared by the procedure of Graebe and Oeser.[8]

Preparation of VI.—This was carried out substantially as for III,[2] except that 40% sulfuric acid was used for the diazotization because of the weaker basicity and more sparing solubility of 3,8-dinitro-1-naphthylamine. Urea was added before boiling. The product was obtained as a yellowish crystalline powder in about 37% yield. The mixture of 3,5- and 3,8-dinitro-1-naphthylamines was prepared from 3-nitro-1-naphthylamine as described by Ward and coworkers,[12] and separated as they direct.[15]

The nitroquinone oxime VI was purified by recrystallization from aqueous methanol. On heating, it darkens above 180°, with softening at 225°, and forms a black smear above 250°.

Anal. Calcd. for $C_{10}H_6N_2O_5$: N, 11.966. Found: N, 11.99.

Acknowledgment.—The authors express thanks to Mrs. Dobbie Roisen for infrared spectra, and to W. M. Padgett II and Dr. J. Hyman for suggestions during the work.

(14) L. F. Fieser and J. T. Dunn, *J. Am. Chem. Soc.*, **59**, 1018 (1937).

(15) The diazo decomposition reaction on 3,5-dinitro-1-naphthylamine provides a compound which is probably authentic 3,5-dinitro-1-naphthol.

The Mannich Condensation of 3-Amino-1,2-propanediol with 2,2-Dinitropropanol and the Nitration of the Product

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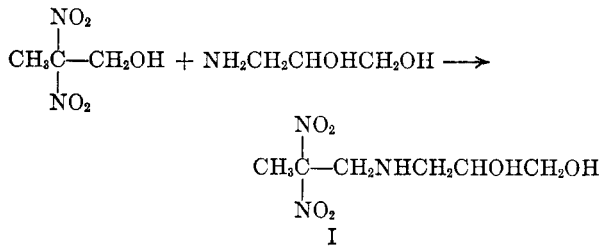
Received November 11, 1961

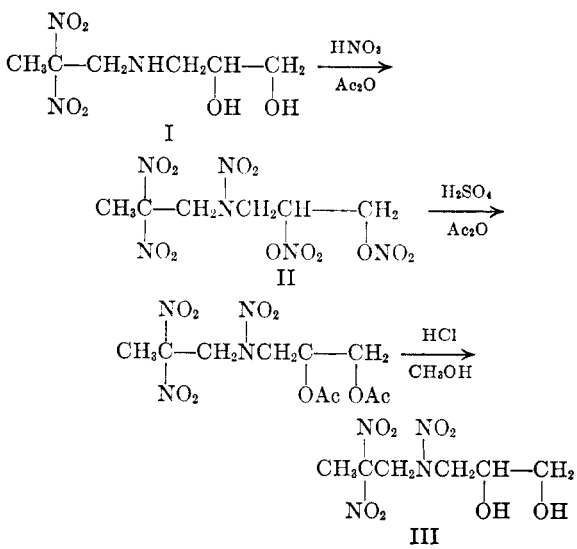
The Mannich condensation of 2,2-dinitro-1-alkanols and some reactions of the products have been reported.[1-4] In the present work, the nitration of the condensate of 3-amino-1,2-propanediol and 2,2-dinitropropanol has yielded a novel product.

Heating an aqueous suspension of 2,2-dinitropropanol with a solution of 3-amino-1,2-propanediol to 50° gave a dark water-insoluble oil, presumably 6,6-dinitro-4-aza-1,2-heptanediol (I). However, since this material could not be purified without decomposition, the crude product was used directly in the subsequent reactions.



I

The nitration of I, which was expected to yield 1,2-dinitroxy-4,6,6-trinitro-4-azaheptane (II), was carried out at 0° in acetic anhydride. An oil was isolated which was sensitive to impact. This oil



III

(1) H. Feuer, G. B. Bachman, and W. May, *J. Am. Chem. Soc.*, **76**, 5124 (1954).

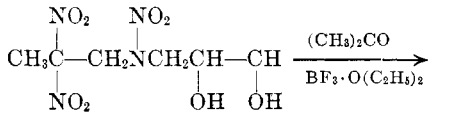
(2) K. Klager, *J. Org. Chem.*, **23**, 1519 (1958).

(3) M. B. Frankel and K. Klager, *J. Am. Chem. Soc.*, **79**, 2953 (1957).

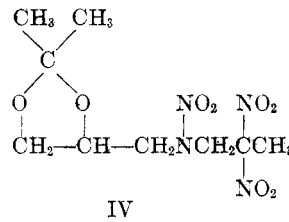
(4) H. Feuer and W. A. Swarts, U. S. 2,981,750 (April 25, 1961).

was acetylated with a 10:1 mixture of acetic anhydride and sulfuric acid in order to prepare 1,2-diacetoxy-4,6,6-trinitro-4-azaheptane, which it was hoped would be a solid derivative. The product, however, was again an oil which could not be crystallized. The acetylated material was then transesterified in refluxing methanolic hydrochloric acid to give 4,6,6-trinitro-4-aza-1,2-heptanediol (III), m.p. 60°.

The reaction of III with acetone in the presence of boron trifluoride etherate gave the cyclic ketal, 2,2 - dimethyl- 4 - (2,4,4 - trinitro - 2 - azapentyl)-dioxalene (IV).

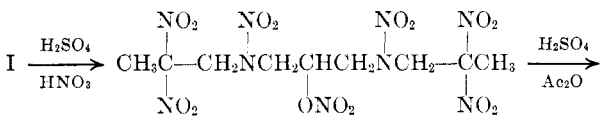


III

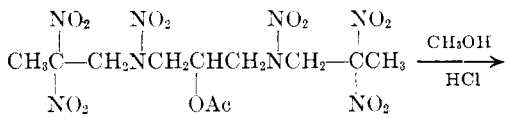


IV

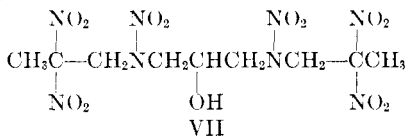
The nitration of I took a different course when a mixture of nitric and sulfuric acids was used as the nitrating agent. This reaction at 50° yielded 6 - nitroxy - 2,2,4,8,10,10 - hexanitro - 4,8 - diaza-undecane (V), m.p. 158–159°. This compound was acetylated at 0° using acetic anhydride and sulfuric acid to prepare 6-acetoxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane (VI), m.p. 145°. The acetate was then transesterified with refluxing methanolic hydrochloric acid to yield 6-hydroxy-2,2,4,8,10,10 - hexanitro - 4,8 - diazaundecane (VII), m.p. 168.5–169°.



V

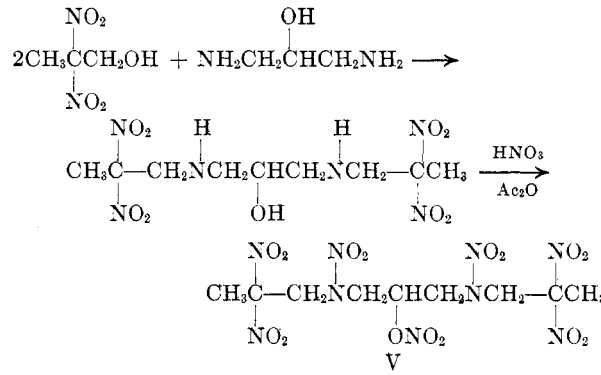


VI



VII

As a final structure proof of V, an independent synthesis was carried out by condensing 1,3-diamino-2-propanol with 2,2-dinitropropanol. The product, an oil, was nitrated under mild conditions, using nitric acid in acetic anhydride at 0 to 5°, to give V. This material was identical to that



V

prepared in the nitration of I with sulfuric acid and nitric acid.

The formation of compound V in the nitration of the condensation product of 3-amino-1,2-propanediol might take place by the alkylation of the amino group of I by a reactive derivative (sulfate or nitrate) of the terminal hydroxyl of a second molecule of I. Nitrolysis of the dihydroxypropyl group of the resulting tertiary amine would lead to compound V.

Experimental[5]

3-Amino-1,2-propanediol.—3-Amino-1,2-propanediol was prepared in 68% yield by the reaction of excess aqueous ammonia with glycidol, as reported by Knorr.[6] Similar yields were obtained by the reaction of ammonia with glycerol α-monochlorohydrin followed by the neutralization of the resulting hydrochloride. This method is preferred because of the commercial availability of the starting material.

Glycerol-α-monochlorohydrin (800 g., 7.23 moles) was added with stirring to 16 l. of 28% ammonia. After 24 hr., the solution was concentrated under vacuum to 5 l., and 478 g. (7.23 moles) of 85% potassium hydroxide pellets in 2 l. of methanol was added. The water and methanol were removed under vacuum, and 2 l. of methanol was added. The potassium chloride precipitate was removed by filtration, and was washed with 1 l. of methanol. The combined filtrate and washings were stripped under aspirator vacuum; the residue was distilled to yield 437 g. (4.80 moles, 66.4% yield) of 3-amino-1,2-propanediol, b.p. 80–106° at 0.1 to 0.15 mm.

Condensation of 3-Amino-1,2-propanediol and 2,2-Dinitropropanol (I).—A solution of 30 g. (0.33 mole) of 3-amino-1,2-propanediol in 30 ml. of water was added slowly to a stirred suspension of 52.4 g. (0.33 mole, 96% assay) of 2,2-dinitropropanol, and this mixture was heated to 50° for 15 min. A dark red oil separated. This oil was then dried under vacuum, and the product (27.05 g., 36.8% yield as 6,6-dinitro-4-aza-1,2-heptanediol) was used in subsequent reactions without further purification.

4,6,6-Trinitro-4-aza-1,2-heptanediol (III).—The crude condensation product of 3-amino-1,2-propanediol and 2,2-dinitropropanol (27.05 g.) was dissolved in 270 ml. of acetic anhydride, and 150 ml. of 100% nitric acid was added dropwise with stirring. The temperature of the solution was maintained at −20 to −25° during the addition, and then at 0° for an additional 3.5 hr. The solution was poured over 2 l. of crushed ice and the ice was allowed to melt. The water was decanted, and the residue was dissolved in 1.5 l. of methylene chloride and dried over sodium

(5) Elemental analysis by Dr. Adalbert Elek, Los Angeles, Calif.
(6) L. Knorr, *Ber.*, **32**, 752 (1899).

sulfate. The solvent was removed leaving 26.4 g. of an oil, impact sensitivity 6 cm. using a 2-kg. weight.[7]

This oil was dissolved in 360 ml. of acetic anhydride and 30 ml. of concd. sulfuric acid was added dropwise with stirring. The temperature was kept at −10 to −20° during the addition, and then at 0° for 2 hr. The reaction mixture was poured into 1.5 l. of ice water, and the gummy residue which separated was filtered off, dissolved in methylene chloride, dried with sodium sulfate, and the solvent was removed.

The residue (10.2 g.) was heated at reflux for 2 hr. in a mixture of 370 ml. of methanol and 17 ml. of concd. hydrochloric acid. The product was stripped under vacuum and recrystallized twice from methylene chloride to yield 3.55 g. of 4,6,6-trinitro-4-aza-1,2-heptanediol (11% over-all yield if it is assumed that the condensation product consisted entirely of 6,6-dinitro-4-aza-1,2-heptanediol), m.p. 60°, with a crystalline phase change at 50°.

Anal. Calcd. for $C_6H_{12}N_4O_8$: C, 26.87; H, 4.48; N, 20.89. Found: C, 26.81; H, 4.79; N, 20.79.

2,2-Dimethyl-4-(2,4,4-trinitro-2-azapentyl)dioxalane (IV).—To a solution of 3.00 g. (0.0112 mole) of 4,6,6-trinitro-4-aza-1,2-heptanediol in 200 ml. of dry acetone was added slowly, with stirring, 1.67 g. (0.0177 mole) of boron trifluoride etherate. The temperature of the solution was kept below 20° by means of an ice bath. After 5 min. the solution was poured into 100 ml. of ice water and a solid crystallized. This solid was filtered, dried, and recrystallized from isopropyl ether to give 2.55 g. (74% yield) of 2,2-dimethyl-4-(2,4,4-trinitro-2-azapentyl)dioxalane, m.p. 84.5–86°.

Anal. Calcd. for $C_9H_{16}N_4O_8$: C, 35.07; H, 520; N, 18.39. Found: C, 34.93; H, 5.00; N, 18.21.

6-Nitroxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane (V) by Nitration of I.—The condensation product of 3-amino-1,2-propanediol and 2,2-dinitropropanol (25 g., 0.11 mole as 6,6-dinitro-4-aza-1,2-pentanediol) was added dropwise to a mixture of 125 ml. of 100% nitric acid and 115 ml. of concd. sulfuric acid at 55°, and the mixture was heated at this temperature for an additional 3 hr. The reaction mixture was then added to 2 l. of ice and water. The product was filtered and slurried with 1.5 l. of boiling ethylene dichloride. A small amount of insoluble residue was filtered from the hot solution, and the filtrate was concentrated and cooled. The product which crystallized was filtered and washed with a small amount of ether to yield 7.6 g. (28% yield assuming this condensation product was pure 6,6-dinitro-4-aza-1,2-heptanediol) of 6-nitroxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane, m.p. 158–159°. An analytical sample was recrystallized from ethylene dichloride.

Anal. Calcd. for $C_9H_{15}N_9O_{15}$: C, 22.08; H, 3.07; N, 25.77. Found: C, 22.42; H, 3.03; N, 25.29.

6-Nitroxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane (V) from 1,3-Diamino-1-propanol.—1,3-Diamino-2-propanol (7 g., 0.0556 mole) was added slowly to a swirled suspension of 17.3 g. (0.112 mole) of 2,2-dinitropropanol (96% assay) in 20 ml. of water. An oil formed, which was separated from the aqueous layer and dried under vacuum. The residue weighed 10.9 g. (55.4% yield). This oil was dissolved in 10 ml. of acetic anhydride and 105 ml. of 100% nitric acid was added dropwise, with stirring, while the temperature was kept at 0–5°. The solution was stirred at 0° for an additional 2 hr. and then was poured over 2 l. of crushed ice. The ice was allowed to melt, and the water was decanted from a gum-like residue. This residue was recrystallized from ethylene chloride, to yield 6.1 g. of V, (40.5% yield assuming the condensation product was pure 6-hydroxy-2,2,10,10-tetranitroundecane), m.p. 158–159°. A mixed melting point with the above product gave no depression.

6-Acetoxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane (VI).—6-Nitroxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane (7.6 g., 0.0155 mole) was dissolved in 80 ml. of acetic anhydride and 8 ml. of concd. sulfuric acid was added dropwise while the temperature of the solution was kept at −10 to −20°. The solution was stored at 0° for 24 hr. and then was poured in to 2l. of ice water. The gum-like precipitate was recrystallized from methylene chloride to yield 6.5 g. (0.0134 mole, 86% yield) of 6-acetoxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane, m.p. 145°.

Anal. Calcd. for $C_{11}H_{18}N_8O_{14}$: C, 27.16; H, 3.71; N, 23.05. Found: C, 26.92; H, 3.31; N, 23.41.

6-Hydroxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane (VII).—6-Acetoxy - 2,2,4,8,10,10 - hexanitro - 4,8 - diazaundecane (6.5 g., 0.0134 mole) was heated under reflux for 4 hr. in a mixture of 390 ml. of methanol and 40 ml. of concd. hydrochloric acid. The volatile materials were removed under vacuum and the residue was recrystallized from methylene chloride to yield 2.7 g. (0.0061 mole, 45.4% conversion, 61% yield) of 6-hydroxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane, m.p. 168.5–169°. Some starting material, 6-acetoxy-2,2,10,10-tetranitro - 4,8 - dinitrazeundecane (1.6 g., 0.0033 mole) was recovered upon concentration of the filtrate.

Anal. Calcd. for $C_9H_{16}N_8O_{13}$: C, 24.32; H, 3.60; N, 25.22. Found: C, 24.51; H, 3.43; N, 25.37.

Acknowledgment.—We are indebted to the Office of Naval Research for the financial support of this work.

(7) Bureau of Mines Bulletin No. 346.

Variations of Alkyl Groups in 4-(4-Dialkylaminostyryl)quinolines[1,2]

CARL TABB BAHNER, LYDIA MOORE RIVES, EMMA BROWN SENTER, WILLIAM LONGMIRE, HAROLD KINDER, DOROTHY BETTIS BALES, FRED HANNAN, BOBBY PETTYJOHN, WILLIAM K. EASLEY, LOVELY FREE, AND HUGH FREE

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Received November 13, 1961

Although slight modifications in the structure of aminostyrylquinolines sometimes destroy their antitumor effects, the replacement of the dimethylamino group in 4-(4-dimethylaminostyryl)quinoline by an $—NH_2$, and $—N(C_2H_5)CH_2C_6H_5$ or an $—N{=}CH—C_6H_4—N(CH_3)_2$, produced compounds with good antitumor activity.[3–6] A series of dialkylaminostyryl compounds, listed in Table I, has been prepared in order to determine the optimum chain length. In the course of these preparations, three monoalkylamino compounds were obtained as by-products and others were then sought.

A number of Schiff bases were prepared by treating 4-(4-aminostyryl)quinoline with a variety

(1) This research was aided by grants from the American Cancer Society and the National Institute of Health.

(2) Presented in part at the Southeastern Region Meeting of the American Chemical Society in Birmingham, Ala., November, 1960.

(3) C. T. Bahner, Lydia Moore Rives, Emma Brown Senter, Dorothy Bettis Bales, Fred Hannan, and Bobby Pettyjohn, *J. Org. Chem.*, **23**, 1060 (1958).

(4) Margaret Reed Lewis, Boland Hughes, Aubrey L. Bates, and Carl Tabb Bahner, *Cancer Res*, **20**, 691 (1960).

(5) A. Haddow, private communication.

(6) K. Sugiura, private communication.

TABLE I
AMINOSTYRYL COMPOUNDS

No.	Alkyl Group on Amino Nitrogen	Formula	M.P.	Reaction Time, Hr.[a]	Yield, %	Calcd. C	Calcd. H	Found C	Found H
	A. 4-(4-Aminostyryl)quinolines								
1	*N,N*-Dipropyl	$C_{23}H_{26}N_2$	76–77	1.5	33	83.61	7.93	83.27	7.80[b]
2	*N,N*-Diallyl	$C_{23}H_{22}N_2$	82.0–83.5	1.5	13	84.64	6.79	84.63	6.65[b]
3	*N,N*-Dibutyl	$C_{25}H_{30}N_2$	81–83	2	23	83.75	8.44	84.16	8.43[c]
4	*N,N*-Diisobutyl	$C_{25}H_{30}N_2$	94.5–95.0	2		83.75	8.44	83.61	8.43[b]
5	*N,N*-Di-*sec*-butyl	$C_{25}H_{30}N_2$	96.0–96.5	3.5					[b,d]
6	*N,N*-Diamyl	$C_{27}H_{34}N_2$	88–89	2	14	83.88	8.86	84.05	8.95[b,e]
7	*N,N*-Dihexyl	$C_{29}H_{38}N_2$	23.0–25.5	2		84.00	9.24	83.79	9.40[b]
8	*N,N*-Diheptyl	$C_{31}H_{42}N_2$	Oil	1	26	84.10	9.56	83.90	9.53[b,f]
9	*N,N*-Dioctyl	$C_{33}H_{46}N_2$	Oil	1.5	31	84.21	9.85	84.51	9.93[b,g]
10	*N,N*-Dinonyl	$C_{35}H_{50}N_2$	Oil	4[h]		84.28	10.10	84.45	10.13[b]
11	*N,N*-Didecyl	$C_{37}H_{54}N_2$	Oil	5[i]	50[j]				
12	*N,N*-Dioctadecyl	$C_{53}H_{86}N_2$	52–53	6[k]	14	84.73	11.54	85.02	11.49[b]
13	*N,N*-Dibenzyl	$C_{29}H_{22}N_2$	99–100	1[l]	8	87.28	6.14	87.18	6.03[b]
14	*N*-Benzyl-*N*-methyl	$C_{24}H_{20}N_2$	118.0–118.5	15.5[m]	8	85.68	6.33	85.49	6.12[b]
15	*N*-Monomethyl	$C_{18}H_{16}N_2$	137–138	1[n]	26	83.04	6.20	82.98	5.99[b]
16	*N*-Monobutyl	$C_{21}H_{22}N_2$	128–130	2		83.40	7.33	83.37	7.27[b]
17	*N*-Monohexyl	$C_{23}H_{26}N_2$	97–98	2	2[o]	83.62	7.93	83.95	7.89[b]
18	*N*-Monoheptyl	$C_{24}H_{28}N_2$	98–99	1	0.4[o]				[b,p]
19	*N*-Monooctyl	$C_{25}H_{30}N_2$	112–113	1.5	2[o]	83.75	8.43	83.88	8.74[b,q]
20	*N*-Methyl-*N*-(2-*N'*,*N'*-diethylaminoethyl)	$C_{24}H_{29}N_3$	54–55	3[r]	12	80.18	8.13	79.91	8.07[b]
21	*N*-Ethyl-*N*-(2-*N'*,*N'*-diethylaminoethyl)	$C_{25}H_{31}N_3$	72–73	7[r]	20	80.38	8.37	80.61	8.39[b]
22	*N*-Ethyl-*N*-(3-*N'*,*N'*-dimethylaminopropyl)	$C_{24}H_{29}N_3$		3[r]	10	80.18	8.13	80.00	8.34[b]
23	*N*-Methyl-*N*-carboxymethyl	$C_{20}H_{18}N_2O_2$	236–237	3[s]	20	75.45	5.70	75.16	6.00[c]
24	*N*-*n*-Butyl-*N*-2-cyanoethyl	$C_{24}H_{25}N_3$	115–116	3	70	81.10	7.09	80.99	7.03[b]
25	*N*-*n*-Butyl-*N*-2-carboxyethyl	$C_{24}H_{26}N_2O_2$	181–182	0.5	52	76.96	7.01	77.26	7.11[c]
	B. 1-(4-Aminostyryl)isoquinolines								
26	None	$C_{17}H_{14}N_2$	196.7–197.7	2	28	82.90	5.72	82.95	5.60[b]
27	*N*-Benzyl-*N*-ethyl	$C_{25}H_{22}N_2$	118.0–119.5	2	8	85.67	6.64	85.70	6.44[c]
	C. Schiff Bases from 4-(4-Aminostyryl)quinoline and:								
28	2-Thiophenaldehyde	$C_{22}H_{16}N_2S$	132	Method A	58	77.61	4.70	77.53	4.79[c]
29	2-Furfuraldehyde	$C_{22}H_{16}N_2O$	125	Method A	8	81.45	4.93	81.71	4.98[c]
30	3,4-Diethoxybenzaldehyde	$C_{28}H_{26}N_2O_2$	147	Method A	73	79.60	6.24	79.59	6.14[c]
31	4-*N,N*-Dimethylamino-3-methylbenzaldehyde	$C_{27}H_{25}N_3$	114	Method A	3	82.85	6.39	83.29	6.10[c]
32	4-*N,N*-Bis-2-chloroethylaminobenzaldehyde	$C_{28}H_{25}N_3Cl_2$	160–161	Method A Method B	41 83	Cl—14.95		Cl—14.68[c]	
	D. Schiff Base from 4-(4-Aminostyryl)pyridine and:								
33	4-*N,N*-Bis-2-chloroethylaminobenzaldehyde	$C_{24}H_{23}N_3Cl_2$	179–180	Method A Method C	47 62	Cl—16.71		Cl—16.82[c]	

[a] At 150–160° unless otherwise indicated. [b] Analyses by Galbraith Microanalytical Laboratories. [c] Analyses by Weiler and Strauss. [d] N: Calcd., 7.82; found, 8.01. [e] N: Calcd., 7.25; found, 7.14. [f] N: Calcd., 6.33; found, 6.55. [g] N: Calcd., 5.95; found, 6.07. [h] At 150–170°. [i] At 160–165°. [j] Isolated and analyzed as maleate salt. See Table II. [k] At 157–176°. [l] At 185–190°. [m] Used lepidine zinc chloride complex instead of hydrochloride and heated at 110°. [n] At 143–158°. [o] By product. [p] N: Calcd., 8.14; found, 8.18. [q] N: Calcd., 7.82; found, 7.83. [r] Dry HCl was passed into the reaction mixture during heating. [s] The required 4-(*N*-methyl-*N*-carboxymethylamino)benzaldehyde was obtained in 33% yield as tan needles, m.p. 223–224°, by heating 0.080 mole 4-*N*-methylaminobenzaldehyde with 0.080 mole bromoacetic acid 2 hr. at 100° and recrystallizing the solid three times from water. *Anal.*: Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74. Found: C, 62.18; H, 5.59. Because of the high melting point of the aldehyde, a small amount of dimethylformamide was used as solvent for the reaction with lepidine hydrochloride. [t] Prepared by refluxing for 6 hr. a mixture containing 10.0 g. of 4-[4-(*N*-*n*-butyl-*N*-2-cyanoethylamino)styryl]quinoline and 25 g. of sodium hydroxide in 150 ml. of methanol and 50 ml. of water, neutralizing with acetic acid, washing the orange crystals with water, and recrystallizing twice from benzene.

of aldehydes, in the hope that one of them might lead to a more favorable distribution of the compound in the animal.

Quinoline derivatives with an *N,N*-dialkylamino-alkylamino group have found favor as antimalarials.[7] Three styrylquinolines containing such groups were prepared. It seemed desirable to examine also compounds with a carboxyl group

(7) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," Interscience Publishers, New York, 1960, p. 228.

TABLE II
SALTS OF 4-(4-AMINOSTYRYL)QUINOLINES

Base No.	M.P.	Formula	Calcd. C	Calcd. H	Calcd. N	Found[a] C	Found[a] H	Found[a] N
			Picrates					
5	231–232	$C_{31}H_{33}N_5O_7$	63.36	5.66		63.10	5.51	
6	186	$C_{33}H_{37}N_5O_7$	64.37	6.06	11.38	64.27	5.96	11.10
7	185–186	$C_{35}H_{41}N_5O_7$	65.30	6.38	10.88	64.97	6.55	10.71
8	181	$C_{37}H_{45}N_5O_7$	66.15	6.75		66.15	6.56	
9	159–160	$C_{39}H_{49}N_5O_7$	66.93	7.06	10.00	66.41	6.91	9.96
20	225–226	$C_{36}H_{35}N_9O_{14}$	52.90	4.31		53.09	4.39	
22	239–240	$C_{36}H_{35}N_9O_{14}$	52.90	4.31		53.05	4.39	
			Malate					
[b]	180	$C_{25}H_{28}N_2O_5$	68.78	6.47		68.27	6.72	
			Maleate					
[b]	183	$C_{25}H_{26}N_2O_4$	71.75	6.26		71.81	6.25	
7	133	$C_{33}H_{42}N_2O_4$	74.68	7.98		74.44	8.01	
8	115	$C_{35}H_{46}N_2O_4$	75.25	8.30		75.19	8.46	
10	103	$C_{39}H_{54}N_2O_4$	76.17	8.85		76.06	8.70	
11	106–107	$C_{41}H_{58}N_2O_4$	76.60	9.09		76.45	9.10	
			Fumarates					
[b]	200	$C_{25}H_{26}N_2O_4$	71.75	6.26		72.05	6.45	
[b]	200	$C_{46}H_{48}N_4O_4$	76.65	6.71		76.76	6.75	
7	112	$C_{62}H_{80}N_4O_4$	78.63	8.51		78.29	8.55	
9	104	$C_{70}H_{96}N_4O_4$	79.50	9.15		79.37	8.91	

[a] Analyses by Weiler & Strauss, Oxford, England. [b] 4-(4-Diethylaminostyryl)quinoline.

on an alkyl radical. 4-[4-(*N*-*n*-Butyl-*N*-2-cyanoethylamino)styryl] quinoline was hydrolyzed to 4-[4-(*N*-*n*-butyl-*N*-2-carboxyethylamino)-styryl] quinoline. 4-[4-(*N*-Methyl-*N*-carboxymethylamino)styryl] quinoline, which may be considered as a substituted glycine, was prepared from the corresponding aldehyde by condensation with lepidine hydrochloride. The presence of the carboxyl group on the side chain increased the solubility in water. 4-[*N*,*N*-Bis(2-chloroethyl)amino]benzaldehyde was used to make a styrylquinoline because the compound so produced would contain two antitumor groupings and might be more effective for that reason. Popp[8] has reported several derivatives prepared from this aldehyde that were active against tumors.

In order to facilitate purification and handling of the basic compounds that were oils at room temperature, several types of salts were prepared (Table II).

Experimental

Dipropylaniline was purchased from Distillation Products Industries, dibutyl-, di-*sec*-butyl-, diamyl-, dinonyl-, didecyl-, and dioctadecylanilines from K & K Laboratories and diallylaniline was purchased from Peninsular Chemresearch, Inc. Dihexyl-, diheptyl-, dioctyl-, and diisopropylaniline were prepared by alkylating aniline with the appropriate halides. The dialkylaminoalkylanilines were prepared by refluxing an amyl alcohol solution of the appropriate dialkylaminoalkyl chloride and the aniline over anhydrous sodium carbonate. (Amyl alcohol gave better yields than ethyl alcohol.) The dialkylanilines were converted to aldehydes by the process of Champaigne and Archer[9] except that the mixture of dimethylformamide, phosphorus oxychloride, and dialkylaniline was heated at 105–110°. The period of heating was doubled for *N*,*N*-dioctadecylaniline. *N*-Benzyl-*N*-methylaminobenzaldehyde and *N*,*N*-dibenzylaminobenzaldehyde were prepared by William K. Easley, L. Free, and Hugh Free at East Tennessee State College. Attempts to prepare monoalkylaminobenzaldehydes from the corresponding anilines by reaction with alloxan and treatment with hot sulfuric acid by the method of Bohringer and Sohn[10] produced little if any of the desired products.

p-*N*-Monomethylaminobenzaldehyde and *p*-*N*-monobutylaminobenzaldehyde were prepared from the corresponding *N*-alkylformanilides by treatment with phosphoryl chloride and phosphorus pentachloride according to the method of Vilsemeier and Haack.[11] The aldehydes were converted into styrylquinolines by heating with lepidine hydrochloride.

The solid styrylquinolines were purified by recrystallization from isohexane or mixed octanes. In addition, chromatography on silica gel or alumina and purification through conversion to the salts were employed. The latter two methods were especially valuable for the products which melted below room temperature.

The dark red salts were prepared by mixing concd. alcoholic solutions of the acid and base, cooling, filtering, and recrystallizing. The bases reacted with picric and maleic acids in a mole to mole ratio, but with fumaric acid some salts contained 2 moles of base per mole of acid, probably because the carboxyl groups are farther apart in the latter acid so that the introduction of the second large molecule of base is less difficult. Tartaric acid tended to give gels instead of satisfactory crystalline salts.

4-{4-[*N*,*N*-Bis(2-chloroethyl)amino]styryl}quinoline.—A mixture of 3.7 g. (0.010 mole) of lepidine picrate with 2.5 g. (0.010 mole) of 4-[*N*,*N*-bis(2-chloroethyl)amino]-benzaldehyde was heated 1.5 hr. in an oil bath at 150–

(8) Frank D. Popp, *J. Org. Chem.*, **26**, 1566 (1961); see also W. C. J. Ross, G. P. Warwick, and J. J. Roberts, *J. Chem. Soc.*, 3110 (1955).

(9) E. Campaigne and W. L. Archer, *Org. Syntheses*, **33**, 27 (1953).

(10) Bohringer and Sohn (DRP 108026).

(11) A. Vilsmeier and A. Haack, *Ber.*, **60B**, 119–122 (1927).

160°. A solution of the red solid in a minimum amount of hot dimethylformamide when cooled in a freezer deposited 2.7 g. of crude product, m.p. 221°. The product after four recrystallizations from dimethylformamide and washing with acetone was obtained as reddish green crystals; yield, 1.3 g.; 21.6%, m.p. 241°.

Anal. Calcd. for $C_{27}H_{23}N_5Cl_2O_7$: C, 54.01; H, 3.86. Found: C, 53.74, 54.03; H, 4.23, 4.39.[12]

The picrate was neutralized with ammonium hydroxide and the precipitate was recrystallized from octane to yield yellow crystals, m.p. 115–116°.

Anal. Calcd. for $C_{21}H_{20}N_2Cl_2$: Cl, 19.10. Found: 19.25, 19.19.[13]

Schiff Bases.—A mole to mole mixture of 4-aminostyryl base and the aldehyde was heated 10–20 min. without solvent (method A), or dissolved in a minimum volume of methanol (method B), or the aldehyde was added slowly with stirring at 110° to a solution of the amine in a minimum amount of dimethylformamide, then heated 15 min. at 120°–130° (method C). The crude product was precipitated by addition of water and was recrystallized from octane or from methanol.

(12) Analyses by Weiler and Strauss, Oxford, England.

(13) Analyses by Galbraith Laboratories, Knoxville, Tenn.

Base-Catalyzed Ring Opening of Diethyl 1,1,2,2-Tetracyanocyclopropane-3,3-dicarboxylate

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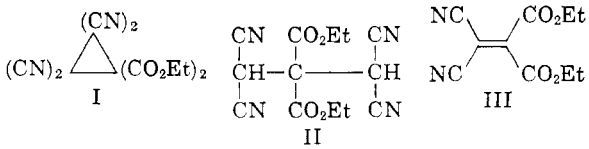
Polycarboxylic esters of cyclopropane are generally stable to bases with respect to ring cleavage.[1] Hydrolysis is often accompanied by decarboxylation but the cyclopropane ring remains intact unless very vigorous reaction conditions are employed. Herewith is reported an example of a cyclopropane ring cleavage under very mild conditions.

Diethyl 1,1,2,2 - tetracyanocyclopropane - 3,3-dicarboxylate (I) was synthesized using the technique of Mariella and Roth.[2] Condensation of malonitrile and diethyl ketomalonate catalyzed by a trace of piperidine yielded diethyl dihydroxymalonate and an intermediate, presumably II. Attempted isolation of this intermediate gave instead a compound assigned the structure diethyl 1,1 - dicyanoethylene - 2,2 - dicarboxylate (III).[3]



I II III

(1) W. E. Truce and L. B. Lindy, *J. Org. Chem.*, **26**, 1464 (1961).

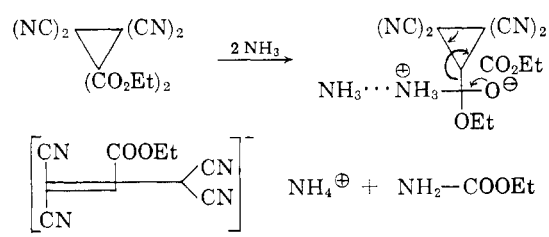
(2) R. P. Mariella and A. J. Roth, *J. Org. Chem.*, **22**, 1130 (1957).

(3) This compound was originally prepared by W. T. Tsatsos of the Central Research Dept., E. I. du Pont de Nemours & Co., *via* the condensation of malonitrile and diethylketomalonate.

Structural assignment was made on the basis of elementary analysis, infrared absorption, and reaction with anthracene to form initially the π-complex and then the Diels-Alder adduct. The reaction with anthracene is analogous to the reactions of tetracyanoethylene with aromatic compounds[4] to give the π-complexes and, where favorable, the Diels-Alder adducts.

Treatment of an ethanol solution of intermediate II with bromine gave the cyclic diester I in 87% yield.[5] When the diester I was added to aqueous or methanolic ammonia, a deep orange solution formed, but no tractable product could be isolated. In anhydrous ether, ammonolysis of the diester gave a nearly quantitative yield of an orange crystalline solid. The orange compound was soluble in water and alcohol and insoluble in nonpolar organic solvents. Its aqueous solutions gave instantaneous colored precipitates on addition of organic bases, *e.g.*, quinoline. The infrared spectrum had a sharp, intense nitrile band at 2190 cm.$^{-1}$ (4.57 μ), no absorption between 1710 and 1650 cm.$^{-1}$, but a strong band at 1510 cm.$^{-1}$ (6.62 μ). Cyclopropane nitriles absorb in the region 2250 cm.$^{-1}$ (4.45μ) and those containing carbethoxy groups characteristically have very weak nitrile bands[6]—*e.g.*, the diester I has only a barely perceptible nitrile band at 2240 cm.$^{-1}$ (4.46 μ). This sharp increase in nitrile band intensity coupled with the shift to lower frequency corresponds to the nitrile absorption of cyanopropenide ions as exhibited by sodium pentacyanopropenide and similar ions[7] which have high intensity absorption in the 2190-cm.$^{-1}$ (4.57μ) region. The polycyanopropanides also exhibit a strong low fequency shift in the C=C-stretching band from the region near 1625 cm.$^{-1}$ (6.1μ) to the region 1550–1400 cm.$^{-1}$ (6.45–7.41 μ)[7]; and in addition they form colored precipitates with organic bases such as quinoline.

These data lead to the structural assignment for the orange compound as ammonium 1,1,3,3-tetracyano-2-carbethoxypropenide. Further buttressing evidence is the fact that the ethereal



(4) T. L. Cairns, R. A. Carboni, D. D. Coffman, V. A. Engelhardt, R. E. Heckert, E. L. Little, E. G. McGeer, B. C. McKusick, W. J. Middleton, R. M. Scribner, C. W. Theobald, and H. E. Winberg, *J. Am. Chem. Soc.*, **80**, 2775 (1958).

(5) This compound was first synthesized in very small yield by Dr. R. M. Scribner of the Central Research Dept., E. I. du Pont de Nemours & Co., using the procedure of L. Ramberg and S. Widequist, *Arkiv. für Kemi*, **12A**, No. 22 (1937); **12B**, No. 37 (1941).

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., Wiley, New York, 1958, p. 266.

(7) C. E. Looney and J. R. Downing, *J. Am. Chem. Soc.*, **80**, 2840 (1958).

supernatant of the ammonolysis mixture gave a 50% yield of ethyl carbamate on work-up. Equation 1 is a rationalization of the reaction sequence.

At first glance the driving force for the reaction would seem to be the release of steric strain to give a resonance-stabilized product. However, construction of molecular models[8] indicates that a planar configuration of the propenide ion is subject to a much larger degree of steric crowding than is the cyclopropane. Even if the carbon-carbon bonds of the propane molecules are allowed to rotate freely, thus destroying allylic resonance, the most favorable conformation is not improved over the cyclopropane with respect to steric crowding. An acceptable rationale for the reaction is not evident.

Experimental

Diethyl 1,1-Dicyanoethylene-2,2-dicarboxylate (III).—Malonitrile (6.6 g., 0.10 mole) was dissolved in diethyl ketomalonate (17.4 g., 0.10 mole, Pierce Chemical Co.) contained a flask protected from moisture and cooled in an ice bath. One drop of base catalyst (2/3 dioxane, 1/3 piperidine) was added. At the end of 3 hr. the contents had become a solid waxy white mass. Filtration under nitrogen gave a white hygroscopic residue and a yellow oily filtrate.

The white solid was shown to be diethyl dihydroxymalonate by comparison (infrared) with an authentic specimen.

The yellow oil was fractionated through a spinning brush column: 1.2 g., b.p. 60–97° (1.5 mm.) and 13.1 g., b.p. 97–99° (1.5 mm.). The 97–99° fraction was redistilled through the spinning brush column: 11.7 g., b.p. 86.0° (1.0 mm.) collected in six fractions, $n^{24}D$ = 1.4620–1.4628. The center fraction, $n^{24}D$ 1.4628, was analyzed.

Anal. Calcd. for $C_{10}H_{10}N_2O_n$: C, 54.0; H, 4.5; N, 12.6; mol. wt., 222. Found: C, 54.23, 54.25; H, 4.56, 4.95; N, 12.80, 12.67; mol. wt., 203, 205.

The NMR spectrum (40 mc./sec.) shows only O—CH_2—CH_3 absorption. The infrared spectrum has a weak nitrile band at 2230 cm.$^{-1}$ (4.48 μ), a strong carbonyl at 1750 cm.$^{-1}$ (5.72 μ), and —C=C— at 1600 cm.$^{-1}$ (6.22 μ). The compound reduces permanganate readily but does not decolorize bromine in carbon tetrachloride, even on boiling. Its solution in benzene is colorless, but addition of anthracene gives a red-brown complex. An equimolar mixture of the compound and anthracene is red-brown, but after heating to 150° and cooling, a white adduct forms. Crystallization from ethanol–water, then from cyclohexane gave white crystals, m.p. 153.6–155.2°.

Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 72.0; H, 5.0; N, 7.0. Found: C, 72.16, 71.84; H, 5.13, 5.19; N, 6.96, 6.94.

The adduct is thermochromic, turning red-brown on melting and white again on resolidifying.

Diethyl 1,1,2,2-Tetracyanocyclopropane-3,3-dicarboxylate (I).—To the product resulting from the reaction of malonitrile (38 g., 0.575 mole) and diethyl ketomalonate (100 g., 0.575 mole) (this time a yellow viscous fluid), ethanol (250 ml., commercial absolute) was added and the mixture stirred to effect solution. While cooling the mixture in an ice bath, bromine (52 g., 0.28 mole) was added dropwise slowly. The resulting dark red-brown solution was poured onto 1 kg. of ice to give a yellow oil, which crystallized on being stirred overnight. The precipitate was washed with water, then dried over phosphorus pentoxide under vacuum to give 71.5 g. (0.25 mole, 87%) of product, m.p. 129.4–130.8°. A sample crystallized from ethanol–water, carbon tetrachloride, and then hexane was sublimed at 1 mm. pressure and 110° to give white crystals, m.p. 129.6–131.2°.

(8) Godfrey Molecular Models, *J. Chem. Ed.*, **36**, 140 (1959).

Anal. Calcd. for $C_{13}H_{10}N_4O_4$: C, 54.5; H, 3.5; N, 19.6; mol. wt., 286. Found: C, 54.80, 54.70; H, 3.81, 3.51; N, 19.44, 19.37; mol. wt., 297, 280.

The NMR spectrum (40 mc./sec.) shows only O—CH_2—CH_3 absorption. The infrared spectrum has only a barely perceptible nitrile band at 2240 cm.$^{-1}$ (4.46 μ), a strong CO at 1765 cm.$^{-1}$ (5.70 μ), and no absorption between 1765 (5.70 μ) and 1500 cm.$^{-1}$ (6.7 μ) (*i.e.*, no —C=C—).

Ammonium 1,1,3,3-Tetracyano-2-carbethoxypropenide (IV).—Diethyl 1,1,2,2-tetracyanocyclopropane-3,3-dicarboxylate (I) (15.0 g., 0.052 mole) was suspended in ether (500 ml., distilled from calcium hydride) in a flask protected from moisture. Dry ammonia (approx. 15 g.) was allowed to distill from a solution of sodium in ammonia and drop from a Dry Ice–acetone cooled condenser into the ethereal suspension of I. The first drops of ammonia gave a yellow oily precipitate which soon solidified to a brown cake. After stirring overnight, the mixture was filtered to give 11.4 g. of brown amorphous solid, m.p. 192–201° dec. The filtrate was evaporated to dryness and the pasty orange residue was stirred with chloroform, leaving a yellow chloroform solution and 0.5 g. of yellow powder, m.p. 203° (decompn.). Mixed m.p. of this latter yellow powder with the first precipitate was 197–204° (decompn.). The chloroform-insoluble material was washed with excess chloroform and dried *in vacuo*.

Anal. Calcd. for $C_{19}H_{13}N_5O_2$: C, 52.1; H, 4.3; N, 30.3. Found: C, 52.34; H, 4.21; N, 30.50.

The chloroform solution was decolorized with charcoal and evaporated to dryness to give white crystals, m.p. 46.6–48.6°, whose infrared spectrum was superimposable on that from an authentic specimen of ethyl carbamate.

The infrared spectrum of the orange solid has a very strong nitrile band at 2190 cm.$^{-1}$ (4.57 μ), a strong CO at 1730 cm.$^{-1}$ (5.78 μ), no absorption between 1730 (5.8 μ) and 16.50 cm.$^{-1}$ (6.5 μ), but a strong band at 1510 cm.$^{-1}$ (6.62 μ) assigned to the —C=C—.

Quinolinium-1,1,3,3-tetracyano-2-carbethoxypropenide.—To an aqueous solution of IV was added a concentrated aqueous solution of quinolinium hydrochloride. An immediate orange precipitate formed, several recrystallizations of which from water gave a product of m.p. 51–52°. Drying in high vacuum over phosphorus pentoxide at 60° gave a product of m.p. 111.5–112.5°.

Anal. Calcd. for $C_{19}H_{13}N_5O_2$: C, 66.5; H, 3.8; N, 20.4. Found: C, 66.79, 66.88; H, 3.77, 4.00; N, 20.03, 20.0.

Recrystallization of the 111.5–112.5° product from water gave a product of m.p. 51–52°, presumably a hydrate.

S-Acylthiosemicarbazones

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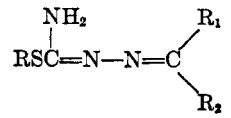
While investigating methods for the preparation of 1-(5-nitro-2-furoyl)thiosemicarbazides,[1] a paper was found wherein the authors[2] treated *p*-nitrobenzoyl chloride and other acid chlorides with thiosemicarbazide in *acetone* to obtain 1-*p*-nitrobenzoyl and other 1-acylthiosemicarbazides. This reaction was verified in our laboratory. However, when 5-nitro-2-furoyl chloride was substituted for the nitrobenzoyl chloride, *S*-(5-nitro-2-furoyl)ace-

(1) W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

(2) M. Ohta and T. Higashijima, *J. Pharm. Soc. Japan.*, **72**, 376 (1952).

TABLE I

S-ACYLTHIOSEMICARBAZONES



R	R_1	R_2	Yield, %	M.P.[a]	Color	Crystallized from
5-Nitro-2-furoyl (I)	CH_3	CH_3	88	204 dec.	Deep red	D.M.F.[c]-H_2O
5-Nitro-2-furoyl (II)	C_2H_5	C_2H_5	36	186–187 dec.	Red	HOAc-H_2O
5-Nitro-2-furoyl (III)	CH_3	C_2H_5	51	190–191 dec.	Red	2-butanone
5-Nitro-2-furoyl (IV)	CH_3	CF_3	18	155–156 dec.	Red	T.H.F.[e]-$(C_2H_5)_2O$
5-Nitro-2-furoyl (V)	CH_3	—CHCH$_2$CH$_2$	60	169–170 dec.	Orange-red	T.H.F.-C_6H_6
5-Nitro-2-furoyl (VI)	CH_3	$—CH_2CH_2COOH$	56	166–167 dec.	Red	T.H.F -$(C_2H_5)_2O$
5-Nitro-2-furoyl (VII)	CH_3	C_6H_5	36	168–169 dec.	Orange-red	D.M.F.-H_2O
5-Nitro-2-furoyl (VIII)	$—CH_2CH_2CH_2CH_2—$		78	192–193 dec.	Red	T.H.F.
5-Nitro-2-furoyl (IX)	H	$—CH=CHC_6H_5$	87	207 dec.	Orange-red	D.M.F.-H_2O
2-Furoyl (X)	CH_3	CH_3	77	145–146	Pale yellow	C_6H_6
p-Nitrobenzoyl (XI)	CH_3	CH_3	55	165 dec.	Yellow	C_2H_5OH
p-Chlorobenzoyl (XII)	CH_3	CH_3	70	169–170 dec.	White	C_2H_5OH

[a] See ref. 6. [b] See ref. 3. [c] Dimethylformamide. [d] Nujol mull. [e] Tetrahydrofuran. [f] 3.5% $CHCl_3$ solution. [g] 1.2% $CHCl_3$ solution.

tone thiosemicarbazone (I) was obtained in 66% yield. This, and other *S*-acylthiosemicarbazones, could also be prepared by treating the appropriate thiosemicarbazone with the required acid chloride (Table I). It is not known why the nitrofuroyl chloride and the nitrobenzoyl chloride follow different courses in the first-described reaction.

The *S*-acyl structure proposed for these substances is supported principally by two facts: the formation of a benzylidene derivative and the infrared spectra[3] of appropriate members of the series.

When I is warmed with benzaldehyde, a compound is formed which has the correct elemental analysis for the benzylidene derivative and which has no major absorption below 3.45 μ (Nujol). Under acid conditions, this readily reverts to I, which has two absorptions in this region (Table I).

The infrared spectra of three *S*-acylacetone thiosemicarbazones which could be determined in solution [2-furoyl (X), *p*-nitrobenzoyl (XI) and *p*-chlorobenzoyl (XII); see Table I] all show two absorptions in the 3-μ region, both of which lie in the proper range[4] for a primary amine. *S*-Benzylacetonethiosemicarbazone[5] shows similar absorption [2.89 (m), 2.98 (m), 7% in chloroform].

Both *S*-(5-nitro-2-furoyl)- and *S*-*p*-nitrobenzoylacetone thiosemicarbazone are insoluble in cold or boiling 25% sodium hydroxide solution, suggesting the absence of —SH, which also supports the *S*-acyl structure.

All of these compounds are highly colored. In particular, the nitrofuryl derivatives are usually a brilliant red. Several of the substances appeared to exist in two different colored modifications. For instance, *S*-*p*-nitrobenzoylacetone thiosemicarbazone can be crystallized from benzene to give orange needles and from ethanol to give a yellow form. Both of these forms have the same melting point and are identical in the infrared, both in Nujol mull and chloroform solution.

The most interesting of this series from a chemotherapeutic standpoint is *S*-(5-nitro-2-furoyl)-acetone thiosemicarbazone (I). This compound was found to protect up to 80% of mice which had been infected with a fatal *Trypanosoma cruzi* parasitemia, when given intraperitoneally, over a fifteen-day period, at a level of 33 mg./kg./day.

Experimental[6]

S-**Acylthiosemicarbazones.**—These compounds, whose properties are described in Table I, were prepared in dry tetrahydrofuran, with the exception of I, X, XI, and XII, where dry acetone was the reaction solvent.

In general, a solution of the appropriate thiosemicarbazone in the proper solvent was stirred at room temperature with 1.4 equivalents of sodium bicarbonate. To this was added a solution, in the same solvent, containing an equimolar quantity of the required acid chloride. After stirring for 2 hr., the reaction mixture was heated under reflux for 30 min., cooled, and filtered. The filter cake was washed with water and the product recrystallized from the proper solvent (Table I).

Occasionally, a quantity of 1-acylthiosemicarbazide could be isolated from these reactions as a minor by-product. Whether this arose by solvolysis of thiosemicarbazone or by thiosemicarbazide present in the starting material is not known, although the latter does not seem likely.

S-(5-Nitro-2-furoyl)acetone Thiosemicarbazone (I).—In

(3) Infrared spectra were determined by W. Washburn of Abbott Laboratories whose aid in the interpretation of these data is acknowledged. Spectra were measured on a Perkin-Elmer Model 21 spectrophotometer.

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., Methuen and Co., Ltd., London, 1959, p. 249.

(5) F. J. Wilson and R. Burns, *J. Chem. Soc.*, **121**, 873 (1922).

(6) All melting points are uncorrected and were determined in capillary tubes. Analyses were carried out at Abbott Laboratories by E. F. Shelberg and his staff.

TABLE I (*Continued*)

Calcd.	Found	Calcd.	Found	Calcd.	Found	Infrared,[b] μ
N, 20.74	N, 20.68	O, 23.69	O, 23.97	S, 11.84	S, 11.91	3.06 (m), 3.18 (m)[d]
C, 44.29	C, 44.47	H, 4.73	H, 4.52	N, 18.78	N, 18.61	...
C, 42.25	C, 42.50	H, 4.26	H, 4.16	N, 19.71	N, 19.91	...
C, 33.34	C, 33.48	H, 2.18	H, 2.33	N, 17.28	N, 17.15	...
C, 44.59	C, 44.77	H, 4.08	H, 3.97	N, 18.91	N, 18.63	...
C, 40.24	C, 40.38	H, 3.68	H, 3.73	N, 17.07	N, 16.82	...
C, 50.59	C, 50.61	H, 3.64	H, 3.89	N, 16.86	N, 16.80	...
C, 44.59	C, 44.85	H, 4.08	H, 4.23	N, 18.91	N, 18.64	...
C, 52.31	C, 52.32	H, 3.51	H, 3.35	N, 16.28	N, 16.32	...
C, 47.98	C, 48.16	H, 4.92	H, 5.19	N, 18.65	N, 18.63	2.86 (m), 2.94 (m)[f]
C, 47.14	C, 47.16	H, 4.32	H, 4.49	N, 19.99	N, 19.80	2.86 (m), 2.94 (m)[f]
C, 48.98	C, 48.73	H, 4.49	H, 4.59	N, 15.58	N, 15.82	2.87 (m), 2.95 (m)[g]

addition to the general procedure described above, this may be prepared in the following way. To a solution of 5.27 g. (0.03 mole) of 5-nitro-2-furoyl chloride in 100 ml. of cold acetone was added, in the following order, 2.73 g. (0.03 mole) of thiosemicarbazide and 7 g. of sodium bicarbonate. After stirring for 3 hr., the suspension was heated under reflux for 1 hr., cooled, and filtered. The filtrate was set aside and the filter cake washed with water to provide 5.41 g. (66%) of I, identical in all ways with material prepared by the general procedure.

Evaporation of the filtrate gave a residue which, after repeated crystallization from ethanol, provided 0.3 g. (4.3 %) of 1-(5-nitro-2-furoyl)thiosemicarbazide, identical with authentic[1] material.

Different Colored Modifications of *S*-(*p*-Nitrobenzoyl)acetone Thiosemicarbazone (XI).—This compound could be obtained in either of two colored modifications. When crystallized from benzene, large orange needles were obtained, which melted at 165° dec., turning yellow at about 140°. This material could not be obtained in an analytically pure state. However, if the orange compound was crystallized from ethanol, small yellow needles were obtained of the same melting point. This product gave the analysis shown in Table I. While the yellow form could be induced to crystallize from benzene, only yellow material could be obtained from ethanol. The infrared spectra of the two different colored forms were identical, both in chloroform solution and in Nujol mull.

***S*-(5-Nitro-2-furoyl)-4-benzylidene-1-isopropylidenethiosemicarbazide.**—One-half gram (0.00185 mole) of *S*-(5-nitro-2-furoyl)acetone thiosemicarbazone (I) was covered with a few milliliters of freshly distilled benzaldehyde and the flask flushed with nitrogen. The benzaldehyde was heated at the boiling point until solution occurred. Cooling and scratching provided material which, after crystallization from ethylene glycol dimethyl ether, weighed 0.33 g. (50%) and melted at 213–214°. Repeated crystallization as before gave yellow platelets, m.p. 217°.

Anal. Calcd. for $C_{16}H_{14}N_4O_4S$: C, 53.63; H, 3.94. Found: C, 53.71; H, 3.92.

Solvolysis of Benzylidene Derivative.—To a suspension of 0.23 g. (0.00064 mole) of pure *S*-(5-nitro-2-furoyl)-4-benzylidene-1-isopropylidenethiosemicarbazide in 10 ml. of ethanol was added 1 small drop of concd. hydrochloric acid. When the suspension was heated to the boiling point, solution occurred. Cooling precipitated 0.16 g. (82%) of *S*-(5-nitro-2-furoyl)acetone thiosemicarbazone (I), identical with authentic I in melting point and infrared spectrum.

Nitric Acid and Perchloric Acid Salts of Aminopyridines[1]

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Very little has been published concerning the preparation and properties of aminopyridine salts with inorganic oxidizer acids. Marckwald[2] reported the preparation of the mononitric acid addition salt of 2-aminopyridine, but no mention was made of reaction conditions or melting point of the product. Monosalts of 2-amino-4-methylpyridine[3] and 2-amino-6-methylpyridine[4] have been prepared by the addition of concentrated nitric acid to an alcoholic solution of the free base. To our knowledge no perchloric acid salts of aminopyridines have been reported.

This paper presents part of a study on amine salts in which the salts of several aminopyridines were prepared through interactions with nitric acid or perchloric acid. The results obtained are shown in Table I. The procedures used were aimed at the isolation, if possible, of the diacid addition compounds, but none were formed. Even electron donating methyl groups in the 6-position or in the 4,6-position did not increase the basicity enough to permit the formation of the diacid salt.

(1) Published with the permission of the Bureau of Naval Weapons, Navy Department. The opinions and conclusions are those of the authors.

(2) W. Marckwald, *Ber.*, **27**, 1321 (1894).

(3) O. A. Seide, *Ber.*, **57**, 791 (1924).

(4) O. A. Seide, *J. Russ. Phys. Chem. Soc.*, **50**, 534 (1920).

TABLE I

Base	Adduct	Calcd., N	Calcd., Anion	Anal., N	Anal., Anion	M.P.[a]
2-Aminopyridine	$C_5H_6N_2 \cdot HNO_3$	26.74	39.46	26.73	39.76	133–139
4-Aminopyridine	$C_5H_6N_2 \cdot HNO_3$	26.74	39.46	26.46	38.82	172–173
3-Aminopyridine	$C_5H_6N_2 \cdot HNO_3$	26.74	39.46	26.83	39.54	128–132
2-Amino-5-methylpyridine	$C_6H_8N_2 \cdot HNO_3$	24.55	36.29	25.25	36.06	139–140
2-Amino-6-methylpyridine	$C_6H_8N_2 \cdot HNO_3$	24.55	36.29	24.11	35.70	168–170[b]
2-Amino-4,6-dimethylpyridine	$C_7H_{10}N_2 \cdot HNO_3$	22.69	33.48	22.45	33.80	177–178
2-Aminopyridine	$C_5H_6N_2 \cdot HClO_4$	14.40		14.02		185–187
4-Aminopyridine	$C_5H_6N_2 \cdot HClO_4$	14.40		13.79		272–274
3-Aminopyridine	$C_5H_6N_2 \cdot HClO_4$	14.40		14.05		190–224
2-Amino-5-methylpyridine	$C_6H_8N_2 \cdot HClO_4$	13.43		13.51		99–103
2-Amino-6-methylpyridine	$C_6H_8N_2 \cdot HClO_4$	13.43		13.57		100–102
2-Amino-4,6-dimethylpyridine	$C_7H_{10}N_2 \cdot HClO_4$	12.58		12.70		186–187

[a] All melting points are uncorrected. [b] A m.p. of 168° was reported by Seide (ref. 4).

Experimental

Perchloric Acid Salts.—The perchloric acid addition salts were made by adding slowly 20 ml. of 70–72% perchloric acid to a solution of 4–5 g. of base in 20 ml. of alcohol. All reagents and the reaction vessel were kept cold in an ice bath. After allowing the mixture to stand in the ice bath for 1 hr., the salts were isolated by filtration and partially dried. They were recrystallized from glacial acetic acid or ethanol.[5]

Nitric Acid Salts.—The nitric acid salts were prepared by slowly adding 25 ml. of ice cold concd. nitric acid to 5 g. of cold anhydrous base. Excess nitric acid was removed by placing the sample in a wide flat dish and passing a gentle current of air over the sample overnight. If the salt were still moist, it was placed in a vacuum desiccator and the latter evacuated with a water pump intermittently. The salt was then recrystallized from commercial anhydrous ethyl alcohol. Occasionally, in order to avoid extensive decomposition, the nitric acid–base mixture was frozen and evaporated down to a thick slurry. An alternative method, especially when the pure monosalts were desired, was to add nitric acid to an ether solution of the free base.

(5) Part of this method was suggested to us in a private communication from T. B. Joyner of the U. S. Naval Ordnance Test Station, China Lake, Calif.

D-Mannoheptulose 1-(N^1-Benzyl-N^1-phenyl)-2-(N^1-phenyl)osazone

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D-Mannoheptulose 1-(N^1-benzyl-N^1-phenyl)-2-(N^1-phenyl)osazone was synthesized in connection with a study on the identification of microgram amounts of D-mannoheptulose.[1] A detailed description of the preparation and structure of this new, characteristic, crystalline osazone is given here because very few hydrazine derivatives of this heptulose are known. The osazone is an acetic acid solvate when synthesized at room temperature, but washing and drying the crude product removes the acetic acid. Recrystallization from glacial acetic acid yields a solvate, but recrystallization from ethyl acetate or absolute ethanol yields the unsolvated osazone.

The osazone was recovered unaltered after attempted formazan formation in alkaline ethanol. The failure to react under these conditions establishes the point of attachment of the primary and secondary hydrazine groups to C-2 and C-1 of the sugar, respectively.[2] The assigned structure is in accord with the conclusions of Henseke and co-workers, who studied some pentose and hexose mixed osazones.[3,4]

Experimental

D-Mannoheptulose 1-(N^1-Benzyl-N^1-phenyl)-2-(N^1-phenyl)osazone (I).—A solution of 210 mg. (1 mmole) of D-mannoheptulose in 0.4 ml. of water was added with stirring to a mixture of 939 mg. (4 mmoles) of recrystallized 1-benzyl-1-phenylhydrazine hydrochloride, 289 mg. (2 mmoles) of ground recrystallized phenylhydrazine hydrochloride, 492 mg. (6 mmoles) of anhydrous sodium acetate, and 5 ml. of glacial acetic acid in a glass-stoppered weighing bottle.[5] After several hours, 2 ml. of glacial acetic acid was added with stirring. The product was removed by filtration after 20 hr.; washed with glacial acetic acid, ether, water, and ether; and air-dried. The yield was 289 mg. (60%). The dried, crude product contained no volatile acid. Recrystallization of 280 mg. of the crude sample from boiling absolute ethanol (7 mg. of sample per ml. of ethanol) gave 242 mg. (87% yield, two crops) of bright yellow, fine needles or filaments. The m.p. was 191–193° dec. (corrected) after two recrystallizations.

Anal. Calcd. for $C_{26}H_{30}N_4O_5$: C, 65.25; H, 6.39; N, 11.71. Found: C, 65.3; H, 6.35; N, 11.8.

D-Mannoheptulose 1-(N^1-Benzyl-N^1-phenyl)-2-(N^1-phenyl)osazone Acetic Acid Solvate.—Recrystallized I was dissolved in hot glacial acetic acid (8 mg. of I per ml. of acid), and the solution was allowed to cool slowly. The fine yellow needles that formed were removed by filtration and washed with cold glacial acetic acid without allowing them to become dry. A thin layer of wet crystals on platinum foil was exposed to air and their weight was recorded at timed intervals. When the weight loss per unit of time decreased

(1) L. M. White and G. E. Secor, *Anal. Chem.*, **33**, 1287 (1961).

(2) L. Mester, *J. Am. Chem. Soc.*, **77**, 4301 (1955).

(3) G. Henseke and H.-J. Binte, *Chimia*, **12**, 103 (1958).

(4) G. Henseke and W. Liebenow, *Ber.*, **87**, 1068 (1954).

(5) The same mixed osazone was obtained when total hydrazine ranged from 3 moles to 9 moles per mole of sugar and with 1 or 2 moles of 1-benzyl-1-phenylhydrazine hydrochloride per mole of phenylhydrazine hydrochloride.

abruptly, samples were taken for the determination of volatile acid.

Anal. Calcd. for $C_{26}H_{30}N_4O_5 \cdot 2^1/_2\ HC_2H_3O_2$: weight loss, 23.88; volatile acid, 23.88. Found: weight loss at 100° (in vacuo), 23.4; volatile acid as acetic, 23.5.

The direction of vibration of the slower component was lengthwise of the crystal in crude I before washing and drying and also in I recrystallized from glacial acetic acid, but the direction of vibration of the slower component was crosswise of the crystal in I recrystallized from ethanol.

Attempted Formazan Formation.—Recrystallized I (from absolute ethanol) was recovered unchanged after attempted formazan formation,[2] as evidenced by comparison of elemental analyses, melting points, and X-ray powder patterns of the original and recovered osazones. Under the same conditions, sugar osazones having a phenylhydrazine group on C-1 underwent a marked color change to produce typical sugar formazans.

Acknowledgment.—We are greatly indebted to Dr. Nelson K. Richtmyer of the National Institutes of Health, Bethesda, Md., for a generous sample of pure D-mannoheptulose; to Dr. Francis T. Jones for microscopical observations; and to Mr. Dale R. Black for X-ray diffraction analyses.

Polyfunctional Aliphatic Compounds. I. The Preparation of 3-Hydroxyglutaronitriles

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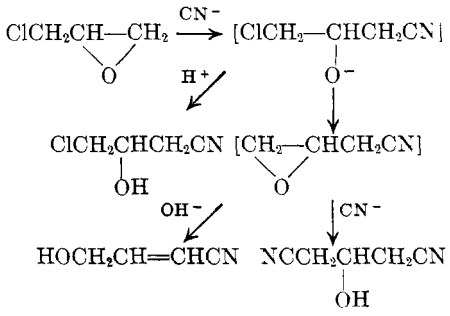
The necessity of obtaining large quantities of the base-sensitive 3-hydroxyglutaronitrile and related three-substituted homologs for cyclization studies has prompted us to re-examine the methods of preparation for these compounds. Previous syntheses of 3-hydroxyglutaronitrile itself have relied on the reaction of aqueous potassium cyanide with 1,3-dichloropropanol-2[1-4] and on the action of a concentrated solution of potassium cyanide on 4-chloro-3-hydroxybutyronitrile.[5,6] Of these only the latter appeared to merit any attention as a preparative method, but even here the reported yields were low (35–40%). This reaction proved to be highly exothermic and required careful control but when the operating temperature was kept around 40°, yields as high as 51.5% were obtained. Nevertheless on a large scale, the difficulties of manipulation and extraction prohibited the use of this method.

We now have found that the required 3-hydroxyglutaronitriles can be prepared by allowing an epichlorohydrin to react with an aqueous solution of potassium cyanide buffered by magnesium sulfate to a pH of approximately 9.5. The best yields were obtained by carrying out these mildly exothermic reactions at 10 to 11° followed by ethyl acetate extraction.

Epichlorohydrin, itself, in this reaction led to 3-hydroxyglutaronitrile in 60% yield accompanied by smaller amounts (18%) of 4-chloro-3-hydroxybutyronitrile and 4-hydroxycrotononitrile. The latter materials, being considerably more volatile, were easily separated by distillation. These two components were the only materials that could be isolated when magnesium sulfate was omitted from the reaction.[7] The various products probably arise according to the scheme shown below.



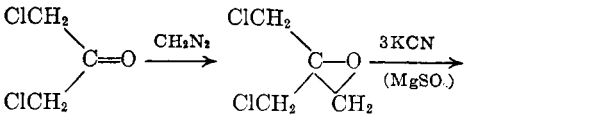
However, on no occasion did we isolate any 3,4-epoxybutyronitriles from our reaction products. Culvenor, Davies, and Haley[7] have commented on the instability to base of epoxy systems of this type, and it appears that they are attacked faster by nucleophiles than the corresponding chloro epoxides.

The use of 1,3-dichloropropanol-2 or 4-chloro-3-hydroxybutyronitrile in the buffered system led to poorer yields of 3-hydroxyglutaronitrile.

The action of the buffered potassium cyanide solution on 2-methyl-, 2-ethyl-, and 2-phenylepichlorohydrin was also examined. The latter two materials were prepared in high yield by the reaction of the appropriate Grignard reagent with 1,3-dichloroacetone at −60°, followed by treatment of the resultant 1,3-dichloroisopropanol with strong base. Under the conditions described above, 2-methyl-, and 2-ethylepichlorohydrin afforded exclusively the corresponding 3-hydroxy-3-alkylglutaronitriles in 71 and 77% yield. However, the reaction with 2-phenylepichlorohydrin did not proceed at any measurable rate. In this case modest yields of the crystalline 3-hydroxy-3-phenylglutaronitrile were realized by employing a mixture of potassium carbonate and bicarbonate (1:1 molar ratio) as the buffering agent.

(1) M. Simpson, *Ann.*, **133**, 74 (1864).
(2) O. Morgenstern and E. Zerner, *Monatsh.*, **31**, 777 (1910).
(3) M. H. Dreifuss and C. K. Ingold, *J. Chem. Soc.*, **123**, 2964 (1923).
(4) G. Braun, *J. Am. Chem. Soc.*, **52**, 3167 (1930).
(5) R. Lespieau, *Bull. soc. chim. France*, [4] **33**, 725 (1923).
(6) R. Legrand, *Bull. soc. chim. Belges*, **53**, 166 (1944) [*Chem. Abstr.*, **40**, 4671 (1946)].
(7) C. C. J. Culvenor, W. Davies, and F. G. Haley, *J. Chem. Soc.*, 3123 (1950).

The ease with which these 3-hydroxyglutaronitriles were produced suggested that the reaction might be capable of extension to more complex system. Accordingly, 2 - chloromethylepichlorohydrin, most easily prepared by reaction of diazomethane on 1,3-dichloroacetone, was treated with three equivalents of potassium cyanide solution buffered by magnesium sulfate. After a mildly exothermic reaction, extraction of the mixture with ethyl acetate afforded a 60% yield of only one product, namely tris(cyanomethyl)carbinol.



$HOC(CH_2CN)_3$

1,4-Dichloro-2,3-epoxybutane was also treated under the same conditions with cyanide ion, but no product could be extracted from the reaction mixture.

All of the 3-hydroxyglutaronitriles prepared by the above methods showed both hydroxyl and nitrile absorptions in the infrared while bands that might be expected for a double bond or a carbonyl group were absent.

The results of cyclization studies on these materials will be presented in subsequent papers.

Experimental

Melting points were determined on a Fisher-Johns melting point block and are not corrected. Infrared spectra were recorded on a Baird spectrophotometer, Model No. 4–55, as films or as Nujol mulls. Epichlorohydrin as supplied by Eastman Kodak was used without further purification.

2-Ethylepichlorohydrin (1,2-Epoxy-2-chloromethylbutane).—1,3-dichloroacetone (84.6 g. 0.66 mole) was dissolved in anhydrous ether (600 ml.) and the solution cooled to −60°. While maintaining this temperature, a solution of ethylmagnesium bromide (0.66 mole) in ether (600 ml.) was added over a period of 2 hr. with vigorous mechanical stirring. Ten minutes after this addition was complete, the reaction mixture, which had remained heterogeneous throughout, was treated with acetic acid (64 g.) in ether (100 ml.) followed by water (50 ml.). With continued stirring the temperature was allowed to rise to 0° and the ether layer separated from the clear biphasic liquid. The aqueous phase was washed once with ether and the organic extract combined, washed with water, and evaporated down to small bulk. The crude 1-chloro-2-hydroxy-2-chloromethylbutane (101.3 g., 97% yield) thus obtained was not purified further but was added below the surface of a slurry of calcium hydroxide (200 g.) and water (500 ml.) during 20 min. During this period the reaction system was maintained at 57° and under a pressure of 160 mm. while the epoxide was distilled as its water azeotrope. The product was isolated *via* ether extraction and fractionally distilled at 40 mm. The fraction (42.4 g.) boiling at 65° was collected and constituted almost pure 1,2-epoxy-2-chloromethylbutane. A sample of this material redistilled at atmospheric pressure for analysis had a boiling point of 137°, $n^{25}D$ 1.4375.

Anal. Calcd. for C_5H_9OCl: C, 49.80; H, 7.52; Cl 29.40. Found: C, 49.6; H, 7.5; Cl, 29.5.

1,3-Dichloro-2-phenylpropanol-2.—To 1,3-dichloroacetone (63.5 g., 0.5 mole) in ether (680 ml.) at −60° there was added phenylmagnesium bromide (0.55 mole) in ether solution (500 ml.) during 1.5 hr. After a further 10 min. glacial acetic acid (53 g.) in ether (80 ml.) was added slowly and the temperature of the reaction mixture allowed to rise to 4°. Water (200 cc.) was run into the flask and the product isolated in the usual way. The viscous oil thus obtained was fractionally distilled and that portion (78.9 g.) boiling at 80–85° (0.1 mm.) collected. This was suitable for further reaction. A sample, distilled at 0.5 mm., had b.p. 102° and $n^{25}D$ 1.4568. The infrared showed a strong band at 2.82 with a shoulder at 2.87 μ.

Anal. Calcd. for $C_9H_{10}Cl_2O$: C, 52.71; H, 4.92; Cl, 34.58. Found: C, 52.6; H, 4.8; Cl, 34.8.

2-Phenylepichlorohydrin.—With rapid stirring *N* sodium hydroxide solution (575 ml.) was added dropwise over a period of 1 hr. to 1,3-dichloro-2-phenylpropanol-2 (102.6 g., 0.5 mole). Stirring was continued for 2.5 hr. and the biphasic liquid extracted with ether (4 × 150 ml.). The product (82.6 g.) isolated in the usual way afforded, after fractional distillation, pure 2-phenylepichlorohydrin (81.3 g.); b.p. 109–109.5° (6 mm.), $n^{25}D$ 1.5461.

Anal. Calcd. for C_9H_9ClO: C, 64.10; H, 5.38; Cl, 21.03. Found: C, 64.4; H, 5.5; Cl, 20.8.

This epoxide has been prepared previously by Adamson and Kenner[8] who recorded b.p. 135–137° (17 mm.).

2-Chloromethylepichlorohydrin.—To a solution of diazomethane prepared from "Diazald" (280 g.), in ether (4 l.) was added a solution of 1,3-dichloroacetone (80 g., 0.63 mole). The mixture was then kept at 5° for 5 days. A small amount of polymethylene was separated by filtration and the solvent then removed by evaporation. The residual light brown oil (97 g.) on fractional distillation afforded a colorless liquid (67.8 g.), b.p. 60–62° (8 mm.), whose infrared spectrum indicated the presence of ketonic material (band at 5.75 μ). To remove this the distilled liquid was dissolved in ether (350 ml.) and the solution stirred vigorously with 1 *M* sodium hydrogen sulfite (165 ml.) for 1.5 hr. After reisolation of the pale yellow product (54 g.) from the ether solution, distillation afforded 2-chloromethylepichlorohydrin (45.4 g., 51% yield); b.p. 78° (23 mm.), $n^{25}D$ 1.4688. [Reported,[9] b.p. 89.5 (31 mm.)].

Anal. Calcd. for $C_4H_6Cl_2O$: C, 34.07; H, 4.29; Cl, 50.29. Found: C, 34.0; H, 4.3; Cl, 50.5.

3-Hydroxyglutaronitrile.—A 12-l. three-necked flask was fitted with a mechanical stirrer, an adapter incorporating a reflux condenser, and a thermometer, and an addition funnel of 500-ml. capacity. The reaction flask was placed in an acetone–Dry Ice cooling bath, and the atmosphere in the flask replaced by pure nitrogen. Magnesium sulfate heptahydrate (4930 g. 20 moles) was dissolved in tap water (7 l.) and the solution filtered into the reaction flask. This liquid was cooled to 10° and potassium cyanide (1430 g., 22 moles) then added with stirring and allowed to dissolve during 45 min. At this point the mixture had an opaque milky white appearance due to the precipitation of a little magnesium hydroxide. With continued stirring and cooling, epichlorohydrin (1018 g., 11 moles) was added over a period of 5.5 hr., the temperature of the reaction mixture being maintained at 10–11° throughout this period. After the addition was complete, stirring was continued for a further 48 hr. at room temperature. The reaction mixture which at this point had a dark red-brown color was extracted continuously with ethyl acetate (5 l.) for a period of 48 hr. The extract was dried over anhydrous magnesium sulfate and the solvent

(8) D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 181 (1939).
(9) G. Hearne and H. W. deJong, *Ind. Eng. Chem.*, **33**, 940 (1941).

removed under vacuum on a steam bath. The residual dark brown oil (950 g.) was then subjected to fractional distillation at reduced pressure. A forerun (207 g.) consisting essentially of 4-chloro-3-hydroxybutyronitrile and 4-hydroxycrotononitrile was collected from 90–115° at 0.4 mm. Pure 3-hydroxyglutaronitrile (723 g.) then distilled at 155–160° at the same pressure (yield 60%). A sample (12 g.) of the dinitrile was purified by fractional distillation through a 6-in. column and the portion boiling at 156° (0.22 mm.) collected (10 g.). $n^{23}D$ 1.4632 (Reported,[5] b.p. 202° (11 mm.) $n^{22}D$ 1.4805). The infrared spectrum of the material showed bands at 2.91 and 4.41 μ.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.3; H, 5.5; N, 25.4.

3-Hydroxy-3-methylglutaronitrile.—Magnesium sulfate heptahydrate (112 g., 0.45 mole) and potassium cyanide (32.5 g., 0.5 mole) were dissolved in water (160 ml.). This solution was cooled to 5° and over a period of 1.25 hr. there was added 1-chloro-2,3-epoxy-2-methylpropane (26.6 g., 0.25 mole) dropwise. After 24 hr., the product was isolated as in the above experiment. The resulting dark brown liquid was distilled at 0.09 mm. and the main fraction (23 g.) consisting of almost pure 3-hydroxy-3-methylglutaronitrile, collected at 128–130°; yield 71%. A sample of this material redistilled for analysis boiled at 131° and 0.07 mm., $n^{25}D$ 1.4596.

Anal. Calcd. for $C_6H_8ON_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.0; H, 6.5; N, 22.3.

The infrared spectrum of the pure material showed bands at 2.91 and 4.41 μ characteristic of hydroxyl and saturated nitrile groups, respectively.

3-Hydroxy-3-ethylglutaronitrile.—This was prepared in exactly the same way as the methyl homolog. From 2-ethylepichlorohydrin (20.1 g., 0.167 mole) and a solution of potassium cyanide (2.17 g., 0.334 mole) and magnesium sulfate heptahydrate (73.8 g., 0.30 mole) there was obtained pure 3-hydroxy-3-ethylglutaronitrile (17.71 g., 77% yield) b.p. 134–137° (0.3 mm.), $n^{25}D$ 1.4658. A sample was redistilled for analysis b.p. 135° (0.35 mm.).

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.3; N, 20.28. Found: C, 60.8; H, 7.4; N, 20.5.

3-Hydroxy-3-phenylglutaronitrile.—A solution of potassium cyanide (19.5 g., 0.3 mole), potassium carbonate (17 g.), and potassium bicarbonate (17 g.) in water (120 ml.) was stirred vigorously with 2-phenylepichlorohydrin (25 g., 0.15 mole) for 1 week at room temperature. The semisolid organic phase was then diluted with a small amount of a 50–50 mixture of ether and petroleum-ether (b.p. 30–60°) and the solid removed by filtration. The filtrate contained mainly unchanged epoxide. Recrystallization of the solid from ethanol gave almost pure 3-hydroxy-3-phenylglutaronitrile (7.8 g.) as feathery white needles, m.p. 117–118°. A sample recrystallized for analysis had m.p. 118–120°.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.9; H, 5.6; N, 15.1.

Tris(cyanomethyl)carbinol.—2-(Chloromethyl)epichlorohydrin (14.1 g., 0.1 mole) was added dropwise over a period of 15 min. to a cooled solution of potassium cyanide (20.4 g., 0.314 mole) and magnesium sulfate heptahydrate (74 g., 0.3 mole) in water (200 ml.). Isolation of the product in the usual way afforded a somewhat oily crystalline solid (10.5 g.). One recrystallization of this material from ethanol afforded tris(cyanomethyl)carbinol (8.0 g., yield 53.5%) m.p. 106–108°, raised to 109° from the same solvent. The infrared spectrum showed hydroxyl absorption at 2.99 μ and a split band at 4.37 and 4.41 μ for nitrile.

Anal. Calcd. for $C_7H_7N_4O$: C, 56.37; H, 4.73; N, 28.18. Found: C, 56.5; H, 4.8; N, 28.0.

Acknowledgment.—We are much indebted to Dr. C. K. Fitz who carried out all microanalyses.

Polycyclic Studies. II. The Ultraviolet Spectra of Some Diels-Alder Adducts[1]

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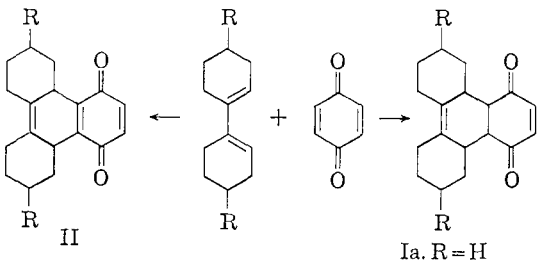
Received November 28, 1961

The bicyclohexenyl-*p*-benzoquinone Diels-Alder adducts I and II have been recently employed[1] as intermediates in the synthesis of triphenylenes.

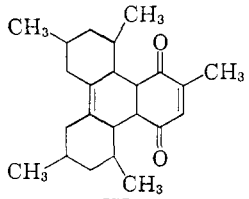


II

Ia. R = H
b. R = CH_3
c. R = OCH_3

Ia. R = H
b. R = CH_3
c. R = OCH_3

The difference in the ultraviolet absorption spectra between adducts I and II is one of the criteria[1] by which these two types of compounds can be distinguished. Whereas the quinones II show the expected maximum at 258–259 mμ (log ϵ 4.1–4.2), the adducts I do not show a definite maximum in the region 220–230 mμ, as would be expected from the data for enediones summarized in Table I. On the other hand, substituted enediones have been shown to exhibit an absorption maximum in the region 235–250 mμ (Table II). Indeed, of the compounds investigated by us, only one, 2,5,7,10,12 pentamethyl-$\Delta^{2,14}$-tetradecahydrotriphenylene-1,4-dione, III, showed such a maximum ($\lambda_{max}^{ethanol}$ 242 mμ, ϵ 11,500).



III

This apparent lack of a maximum has been observed also in other similar unsubstituted Diels-Alder adducts investigated in this laboratory.[3]

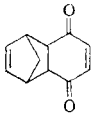
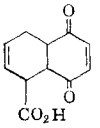
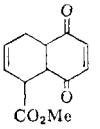
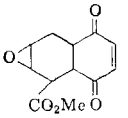
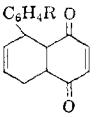
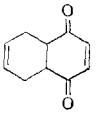
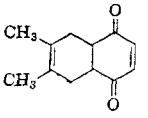
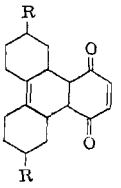
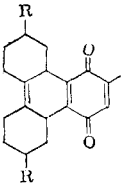
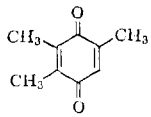
(1) Part I. A. Mandelbaum and Michael Cais, *J. Org. Chem.*, **26**, 2633 (1961).

(2) American Chemical Society–Petroleum Research Fund Fellow, 1959–1961.

(3) Yanina Altman and David Ginsburg, *J. Chem. Soc.*, 1498 (1961).

TABLE I

THE ULTRAVIOLET SPECTRA OF CYCLOHEXENE-1,4-DIONES AND SUBSTITUTED QUINONES

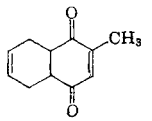
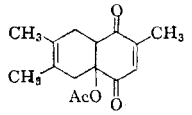
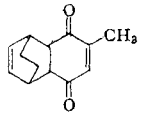
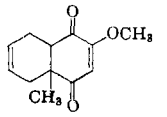
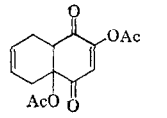
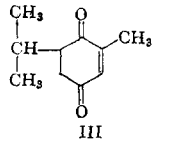
Compound		λ_{max} mμ	ϵ^h
		222[a]	12,800
		224[b]	11,300
		223[b]	10,670
		221[b]	10,380
		218–227[c]	15,000–27,500[i]
		224[d]	12,000
		228	9,800
	Ia	226[e]	11,000
	Ib	226[e]	11,100
	Ic	228[e]	9,450
	R = H	259[f]	16,300
	R = CH_3	258–259[f]	12,700
		253, 260[g]	19,800; 19,400

[a] H. Bastron, R. E. Davis, and L. W. Butz, *J. Org. Chem.*, 8, 515 (1943); [b] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kirstead, *Tetrahedron*, 2, 1 (1958). [c] E. A. Braude, E. R. H. Jones, and E. S. Stern, *J. Chem. Soc.*, 1092 (1947). [d] Prepared according to O. Diels and K. Alder, *Ber.*, 62, 2361 (1929). M.p. 57–58° (lit., 58°) [e] Values obtained by subtraction, see Fig. 1. [f] See ref. 1 for synthesis. [g] E. A. Braude, *J. Chem. Soc.*, 493 (1945). [h] In ethanol solution, except where otherwise indicated. [i] In hexane solution.

A comparison of I with the formulas of the compounds listed in Table I shows that in I the nonconjugated double bond 14:15 is tetrasubstituted and exocyclic to two fused six-membered rings. Such double bonds in the steroid series have been reported[4] to show a rather intense ultraviolet absorption in the region 210–225 mμ. For example $\Delta^{8(14)}$ and $\Delta^{9,10}$ are reported[4] to absorb in the range $\epsilon_{210\ m\mu}$ 6300–10,500 and ϵ_{220} 1900–7000.

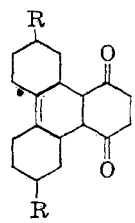
TABLE II

THE ULTRAVIOLÆT SPECTRA OF 2-SUBSTITUTED CYCLOHEX-2-ENE-1,4-DIONES

Compound	λ_{max} mμ	ϵ^f
	237[a]	12,250
	236[a]	20,000
	235[a]	8,200
	269[a]	8,400
	240[b]	8,000
 III	238[c]	15,600[d]
	242[e]	11,500

[a] H. Bastron, R. E. Davis, and L. W. Butz, *J. Org. Chem.*, 8, 515 (1943). [b] J. A. Barltrop and M. L. Burstall, *J. Chem. Soc.*, 2183 (1959). [c] O. Isler, H. Lindlar, M. Montavon, R. Rüegg, G. Saucy, and P. Zeller, *Helv. Chim. Acta*, 39, 2041 (1956). [d] Calculated from reported[c] value $\Sigma^{1\%}_{1\ cm}$ = 942, in petroleum ether solution. [e] See ref. 1 for synthesis. [f] In ethanol solution, except where otherwise indicated.

The nonconjugated 14:15 double bond in the reduced adducts IV, which is similar to the 8:14 and 9:10 double bonds in steroids, shows a similar



IVa. R = H
b. R = CH_3

a. R = H
b. R = CH_3

(4) P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

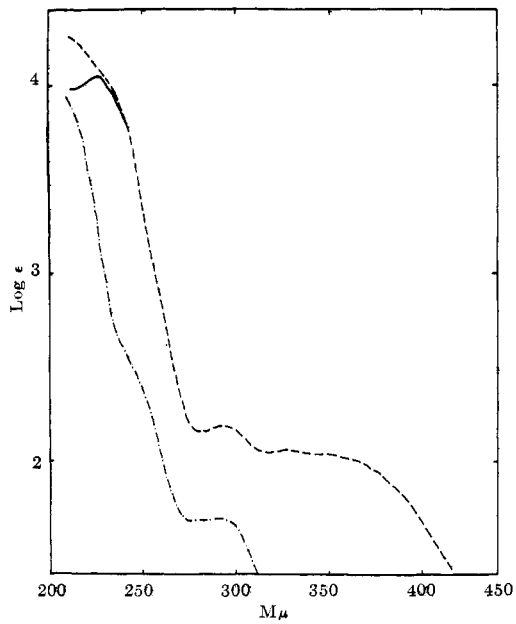


Fig. 1.—Evaluation of enedione chromophore absorption maximum in spectra of bicyclohexenyl-*p*-benzoquinone adducts

(– – – –) Spectrum of $\Delta^{2,14}$ tetradecahydrotriphenylene-1,4-dione (Ia) (in ethanol)

(- · – · –) Spectrum of Δ^{14} hexadecahydrotriphenylene-1,4-dione (IVa) (in ethanol)

(————) Curve obtained by subtracting IVa from Ia

high absorption in the 210–225 mμ region ($\epsilon_{210\ m\mu}$ 8700, $\epsilon_{220\ m\mu}$ 4400).

On the assumption that this high absorption of 14:15 double bond might mask the maximum due to the enedione chromophore, the intensity values of the reduced adducts IV in the 210–240-mμ region were subtracted from those of the adducts I. When the resulting intensity values were plotted against the respective wave lengths (Fig. 1), there was obtained for adducts Ia, Ib, and Ic the expected maximum of the enedione chromophore (Table I).

Experimental

The absorption spectra were measured with a Unicam SP 500 spectrophotometer. Melting points were measured in a capillary and are uncorrected.

6,7-Dimethyl-5,8,9,10-tetrahydronaphthoquinone (Table I).—A mixture of 2,3-dimethylbutadiene (4 g., 0.049 mole) and *p*-benzoquinone (4 g., 0.037 mole) was kept for 1 week at room temperature. Trituration with ethanol (15 ml.) yielded yellow crystals (6.75 g., 96%), m.p. (from ethanol) 115–117° (lit.[5] m.p. 113–115°) $\nu_{C=O}^{CHCl_3}$ 1690 cm.$^{-1}$. λ_{max} 228 mμ, ε 9800.

6,11-Dimethyl-Δ^{14}-hexadecahydrotriphenylene-1,4-dione (IVb).—A solution of 6,11-dimethyl-$\Delta^{2,14}$-tetradecahydrotriphenylene-1,4-dione Ib (4.5 g.) in acetic acid (70 ml.) was shaken with powdered zinc (15 g.) for 15 min. The mixture was then filtered, and the filtrate was poured into cold water (1.5 l.), shaken for 15 min., and kept in the refrigerator overnight. A white precipitate was obtained which upon crystallization from methanol yielded white crystals 3.3 g.), m.p. 107–110°. Recrystallization from methanol gave the analytical sample, m.p. 133.5–135°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 79.95; H, 9.39; O, 10.65. Found: C, 79.69; H, 9.39; O, 10.67.

Acknowledgment.—This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

(5) L. F. Fieser, W. P. Campbell, and E. M. Fry, *J. Am. Chem. Soc.*, **61**, 2217 (1939).

A Method of Tritium Labeling

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Received November 29, 1961

The use of tritium as a tracer in reactions of various organic compounds is of growing interest. Much of the labeling is accomplished by the Wilzbach method which involves the exposure of such compounds to curie quantities of tritium gas for periods of hours or days.[1] In general, the labeling process is accompanied by the appearance of a number of labeled by-products often with specific activities 10–100 times greater than that of the desired material.[2] The presence of these by-products which arise from such processes as polymerization,[3] replacement of substituents,[4] isomerization,[3] and addition of tritium to unsaturated linkages[5] requires careful purification procedures. The times necessary for labeling by the Wilzbach method may be greatly reduced if an electric discharge is employed during the period of gas exposure.[6] Labeling in the presence of uranium hydride containing tritium has also been carried out with certain advantages over the usual procedure.[7]

It is well known that rapid exchange between deuterium gas and the active hydrogen in organic compounds such as acids and alcohols occurs in the presence of certain metal catalysts.[8] The same

(1) K. E. Wilzbach, *J. Am. Chem. Soc.*, **79**, 1013 (1957).

(2) K. E. Wilzbach, "Proceedings of the International Atomic Energy Agency Symposium on the Detection and Use of Tritium in the Physical and Biological Sciences," Vienna, Austria, 1961, paper 83.

(3) P. Riesz and K. E. Wilzbach, *J. Phys. Chem.*, **62**, 6 (1958).

(4) L. Dorfman and K. E. Wilzbach, *ibid.*, **63**, 799 (1959).

(5) H. J. Dutton, E. P. Jones, L. H. Mason, and R. F. Nystrom, *Chem. Ind.* (London), 1176 (1958).

(6) F. L. Jackson, G. W. Kittinger, and F. P. Krause, *Nucleonics*, **18**, 102 (1960).

(7) R. E. Felter and L. A. Currie, "Proceedings of the International Atomic Energy Agency Symposium on the Detection and Use of Tritium in the Physical and Biological Sciences," Vienna, Austria, 1961, paper 121.

(8) L. E. Line, Jr., B. Wyatt, and H. A. Smith, *J. Am. Chem. Soc.*, **74**, 1808 (1952); H. A. Smith and E. L. McDaniel, *ibid.*, **77**, 583 (1955); E. L. McDaniel and H. A. Smith in "Advances in Catalysis and Related Subjects," Vol. IX, Academic Press, Inc., New York, 1957, p. 76; H. A. Smith and B. B. Stewart, *J. Am. Chem. Soc.*, **82**, 3898 (1960).

behavior is expected when tritium gas is employed. The labeling of a compound at the position of an active hydrogen is of little value since the labeled atom is readily lost under mild conditions. However, when the tritium atom can be easily transferred to a position where it is not labile, a satisfactory tagging process results. Furthermore, the position which the tritium atom assumes in the molecule should be reasonably well established by the synthetic route employed. The method has been applied to the synthesis of tritiated acetic acid and tritiated *N*-methylpyrrole.

Experimental

Materials.—Malonic acid was Eastman White Label grade and was used without further purification. *N*-Methylpyrrole-2-carboxylic acid was prepared by metalation of *N*-methylpyrrole with *n*-butyllithium followed by carbonation.[9] C. P. dioxane (Matheson, Coleman, and Bell) was used as solvent. No purification was necessary. The tritium gas of 99+ % purity was obtained from the Oak Ridge National Laboratory. One curie of this isotope (0.45 standard cc.) was added to 4000 standard cc. of hydrogen and the mixture stored in a small metal tank. The isotopic mixture remained in the tank for more than a year before use in the labeling experiments; at this time, gas chromatographic analysis showed that 95% of the tritium was in the form of tritium hydride.[10] The activity was about 0.3 mc. per standard cc.

The catalyst employed in the exchange process was 5% rhodium supported on alumina and was obtained from Baker and Co., Inc., of Newark, N. J.

Exchange Procedure.—All exchange reactions were carried out in heavy-walled 50-ml. Erlenmeyer flasks each fitted with a 6-mm., straight-bore stopcock terminating in a ball and socket joint. The catalyst, substrate, and solvent, in that order, were introduced into the flask through a long-stemmed funnel. The flask was then attached by means of the ball and socket joint to a manifold which contained (1) a source of tritium hydride, (2) a gas sampling chamber of known volume, (3) a mercury manometer, (4) a source of helium, and (5) a 50-ml. Berkowski ionization chamber attached to a Cary Model 31 vibrating reed electrometer equipped for continuous recording. The latter two were used in the analyses of the residual gas after the exchange. The flask was cooled in liquid nitrogen, evacuated, and filled with the hydrogen–tritium hydride mixture to the desired pressure. The exchange vessel was removed from the manifold, warmed to room temperature, and shaken for at least 10 min. The solution was again attached to the manifold, cooled in liquid nitrogen, and the gas sample removed for analysis by gas chromatography.

The flask was taken from the manifold and warmed to room temperature. After removal of the catalyst by filtration through a fritted glass funnel, the solution was concentrated by evaporation of most of the solvent, then transferred to a semimicro distillation apparatus for evaporation of the remaining solvent and decarboxylation.

Decarboxylation Procedure.—The tritiated acids were decomposed by heating followed by product distillation. The distillates were sampled, and the samples diluted with appropriate solvents for counting.

Tritium Analysis of Products.—All tritium activities of labeled compounds were obtained by the liquid scintillation method employing a Baird-Atomic Model 745 system. The scintillation solution contained 4 g./l. of 2,5-diphenyloxazole (PPO) and 50 mg./l. of 2,2′-*p*-phenylenebis(5-phenyloxazole) (POPOP) in toluene.

Elimination of Labile Tritium.—In the preparation involving exchange with malonic acid, the acetic acid produced contained both unlabile tritium (in the methyl group) and labile tritium (in the carboxyl group). The latter type was eliminated by neutralization with sodium hydroxide followed by removal of tritiated water from the salt formed, and acidification to regenerate the organic acid.

Experimental Calculations and Results

As expected, tritium in the presence of rhodium catalyst exchanges rapidly with the hydrogen atom of a carboxyl group. Under the experimental conditions employed, some 60% of the gas phase tritium atoms were exchanged in 10 min. Apparently, equilibrium had been established, since continued shaking for 90 min. gave virtually the same result. The details of three exchange reactions are shown in Table I.

TABLE I

EXCHANGE REACTIONS OF TRITIUM HYDRIDE WITH CARBOXYLIC ACIDS IN THE PRESENCE OF 0.1 G. OF RHODIUM CATALYST AND 25 ML. OF DIOXANE SOLVENT

Acid	Gas Pressure, Cm. Hg at 77°K.	Tritium, Mc.	Acid Concentration, Moles/L.	Exposure Time, Min.	Fraction of tritium Exchanged
Malonic	26	8	0.2	10	0.61
Malonic	43	13	0.2	90	0.63
N-Methylpyrrole-2-carboxylic acid	25	7.5	0.17	90	0.59

The activity of the acetic acid obtained by decomposition of the labeled malonic acid was 36 mc. per mole while that of the *N*-methylpyrrole obtained by decarboxylation of the *N*-methylpyrrole-2-carboxylic acid was 8 mc. per mole. In each case, there appeared to be some loss of tritium activity by exchange of the tritium in the carboxyl group with hydrogen adsorbed on the glass surface of the container. This could undoubtedly be reduced by pretreatment procedures.

Discussion

The success of the method of labeling reported here depends upon the rapid exchange of tritium with carboxyl hydrogen atoms in the presence of a noble metal catalyst such as rhodium. The specific activities of the product obtained are dependent on the fraction of tritium in the hydrogen gas employed in the exchange reaction. With the mole fraction of tritium only around 10^{-4}, the specific activities were about 10% of the 3–90 mc. per gram reported for the Wilzbach gas exposure method[2] when the mole fraction of tritium was essentially

(9) D. A. Shirley, B. H. Gross, and P. A. Roussel, *J. Org. Chem.*, **20**, 225 (1955).

(10) H. A. Smith and E. H. Carter, "Proceedings of the International Atomic Energy Agency Symposium on the Detection and Use of Tritium in the Physical and Biological Sciences," Vienna, Austria, paper 109. in press.

unity. If one expresses the efficiency of tritium labeling in terms of millicuries of incorporated activity per curie-hour of tritium exposure, the efficiency of the exchange-decarboxylation method is some 10^5 times that found when the Wilzbach method is applied to the labeling of toluene.[11]

Because of the low level of tritium activity and short exposure times, the products formed are not contaminated to any appreciable extent by high specific activity materials resulting from side reactions. In addition, the decarboxylation-distillation procedure may be expected to produce some purification. The rhodium catalyst employed in the exchange process is an excellent hydrogenation catalyst, and might be expected to accelerate hydrogenation of unsaturated linkages thus producing saturated by-products. However, the hydrogenation is ordinarily much slower than the desired exchange reaction, so that little contamination results. The tritiated *N*-methylpyrrole prepared by exchange and decarboxylation of *N*-methylpyrrole-2-carboxylic acid was examined for contamination by gas chromatography. This examination revealed the presence of a very small amount (3% or less) of a lower boiling contaminant, probably *N*-methylpyrrolidine. This contaminant can be readily removed by chromatographic processes. Incidentally, the problem of hydrogenation of unsaturated linkages is also present when the Wilzbach method is employed.[5]

While the method of labeling which has been described is not as general as that of Wilzbach, it should be applicable to any compound containing a carboxyl group which can be readily decarboxylated. It has the advantage of employing low activities of tritium and short exposure times and producing products of high purity labeled in specific positions.

A similar method has been used for producing nicotinic acid-2-*t*-through decarboxylation of tritiated quinolinic acid.[12] However, the latter compound was prepared through exchange with tritium oxide rather than the readily available tritium gas.

Acknowledgment.—The authors are indebted to the National Science Foundation for aid through its Research Participation for College Teachers Program and the United States Atomic Energy Commission for support of this work. They are also indebted to Drs. D. A. Shirley and R. G. Thompson for the sample of *N*-methylpyrrole-2-carboxylic acid used in the exchange experiments and to Mr. E. H. Carter, Jr., for the gas chromatographic analyses.

(11) H. J. Ache, W. Herr, and A. Theimann, Proceedings of the Symposium on the Detection and Use of Tritium in the Physical and Biological Sciences, Vienna, Austria, 1961, paper 10, in press.

(12) R. F. Dawson, D. R. Christman, A. D'Adamo, M. L. Solt, and A. P. Wolf, *J. Am. Chem. Soc.*, **82**, 2628 (1960). *Cf.* A. P. Holemann and K. Clusius, *Ber.*, **70**, 819 (1937).

Preparation of *trans*-Stilbene from Benzoin

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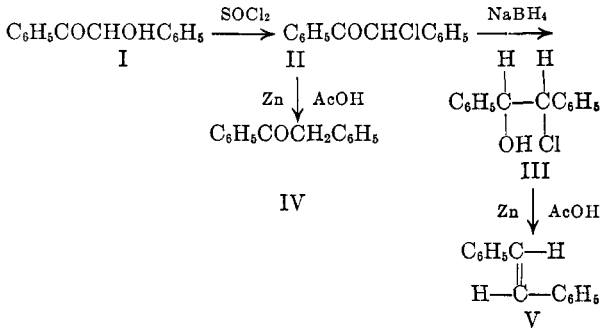
A procedure for the preparation of *trans*-stilbene developed by one of us[1] calls for reaction of benzoin with thionyl chloride to produce desyl chloride (II), reduction with sodium borohydride to give a product rich in the *erythro* chlorohydrin III, and reaction with zinc dust and acetic acid. The two reduction steps are run consecutively in the same ethanol solution. If deteriorated sodium borohydride is used (University of Illinois), the low-melting product is desoxybenzoin (IV). At the

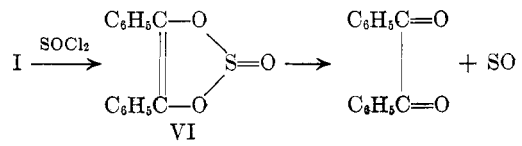


Massachusetts Institute of Technology most members of the class obtained *trans*-stilbene but a few encountered desoxybenzoin. After trying all conceivable variations in the second and third steps to no avail, the author of the manual considered the possibility for variable interpretation of the following direction: "Place four grams of benzoin (crushed to a powder) in a one hundred-milliliter round-bottomed flask, cover it with four milliliters of thionyl chloride, warm gently on the steam bath (hood) . . . ." The comma after "thionyl chloride" represents a pause in operation, as in reading. The pause is ordinarily not more than a second or two, but it could be long, as over the lunch hour or overnight. Trial indeed showed that if the mixture of reagents is let stand at room temperature until reaction is complete and the subsequent steps are then applied, the final product that crystallizes from ethanol is desoxybenzoin. The yield is low; a major product, retained in the mother liquor, is *meso*-hydrobenzoin. For avoidance of trouble at this stage, and to insure removal of all excess thionyl chloride which otherwise affords sulfur in the next step, the present procedure is as follows: "Put four grams of benzoin into a tared one hundred-milliliter flask and mount the

(1) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., revised, D. C. Heath, 1957, pp. 178–180. For an interpretation of the stereochemistry, see L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., 1961, pp. 165–170.

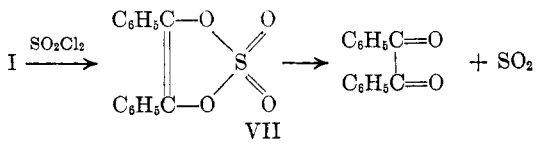
flask on the steam bath under a reflux condenser (hood). Heat the flask containing the benzoin and then pour in four milliliters of thionyl chloride through the condenser. Reflux for five minutes, then remove the condenser and heat for five minutes to drive off gases and thionyl chloride. Then connect the flask with a rubber stopper to the suction pump and heat on the steam bath to constant weight (four grams of benzoin gives four and three tenths grams of desyl chloride)."

A further study of the reaction between benzoin (one mole) and thionyl chloride (three moles) at 20° and at 0° showed that the reaction products are desyl chloride, benzil, and sulfur. We postulate that the initial product is the cyclic endiol sulfite VI, which decomposes to benzil and sulfur



VI

monoxide. This oxide is known to yield sulfur by disproportionation: $2SO \rightleftharpoons SO_2 + {}^1/_2\ S_2$.[2] Borohydride reduction of VI to desoxybenzoin is understandable. Attempts to isolate the intermediate were unsuccessful, as were attempts to isolate the sulfate ester VII from benzoin and sulfuryl chloride.



VII

However, the transient formation of VII is indicated by the observation that when a mixture of benzoin (one mole) and sulfuryl chloride (three moles) was let stand at room temperature, benzil and sulfur dioxide were formed in equivalent amounts and in high yield. That benzil is produced in higher yield in this reaction than in the reaction with thionyl chloride is perhaps due to the greater stability of the gaseous product.

Further evidence in support of the structures postulated including isolation of the crystalline 2,2′-4,4′,6,6′-hexamethyl derivative of VI from reaction of the known endiol[3] with thionyl chloride and pyridine in methylene chloride at −20°, will be presented by the junior author in candidacy for a degree in Japan.

Experimental

Reaction of Benzoin with Thionyl Chloride.—A mixture of 2 g. of benzoin and 2 ml. of thionyl chloride when let stand at 0° for 12 hr. afforded a yellow solution, and evacuation at the water pump afforded a viscous brown oil which solidified on standing. The infrared spectrum showed bands at 1718 cm.$^{-1}$ (desyl chloride) and 1686 cm.$^{-1}$ (benzil). Chromatography on alumina afforded 1.18 g. of desyl chloride, m.p. 68°, 0.71 g. (35%) of benzil, m.p. 96°, and a trace of sulfur.

For quantitative determination of both benzil and the gaseous products, 320.3 mg. of benzoin was placed in a small Claisen flask cooled in an ice bath and supplied with a gas inlet tube. The sidearm was connected through a Dry Ice–acetone trap (to catch thionyl chloride) to two absorption tubes containing 1 *N* sodium hydroxide. The system was flushed with nitrogen and then stopcocks at the ends of the system were closed and 0.45 ml. of thionyl chloride was added to the benzoin. After 12 hr., a slow stream of nitrogen was passed through the system for 3 hr. and then the system was evacuated twice to sweep gas dissolved in the reaction mixture into the absorption tubes. The residual syrup was analyzed spectrophotometrically using the benzil band at 11.52 μ and found to contain 125 mg. (39%) of the diketone. The solution in each absorption tube was neutralized with 1 *N* hydrochloric acid at 0° and titrated iodimetrically. Since the total iodine consumption was 37×10^{-4} equiv., whereas the benzil produced was only 5.9×10^{-4} equiv., considerable thionyl chloride must have been carried over into the absorption tubes. A blank run with benzil in place of benzoin showed this to be the case and afforded 22×10^{-4} equiv. of iodine. The difference, 15×10^{-4} equiv., is in the order of magnitude of the benzil formed.

In a run conducted with benzoin as before but at 20° (12 hr.), the yield of benzil was 29%.

Reaction of Benzoin with Sulfuryl Chloride.—This reaction presents a simpler case than that with thionyl chloride because the sole gaseous product is sulfur dioxide and because reagent swept into the absorption tubes is converted into sodium sulfate. In an experiment conducted like that described above, 226.5 mg. of benzoin treated at 0° with 0.4 ml. of sulfuryl chloride afforded 205 mg. (95%) of benzil, and 1.6×10^{-3} mole (94%) of sulfur dioxide.

(2) H. Zeise, *Z. Physik. Chem.*, **B51**, 120 (1942).

(3) R. C. Fuson, C. H. McKeever, and J. Corse, *J. Am. Chem. Soc.*, **62**, 600 (1940).

DL- and L-Threonine *p*-Toluenesulfonate Benzyl Ester[1]

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For a projected synthesis of the threonine containing chromopeptide actinomycin D, which has carcinostatic activity,[2] we required L- and/or DL-threonine benzyl ester. Since the problem of the synthesis of actinomycins has been solved in principle by the recent total synthesis of actinomycin C_3,[3] which is very closely related to actinomycin D, work on the project has been discontinued. We wish to report here the preparation and properties of DL- and L-threonine *p*-toluenesulfonate benzyl ester since these compounds might be useful for the synthesis of threonine peptides. Although DL-serine benzenesulfonate benzyl ester can be obtained readily as a crystalline solid by the

(1) Supported by a grant (C-2571) from the National Cancer Institute, U. S. Public Health Service.

(2) S. Farber, *Am. J. Path.*, **31**, 582 (1955).

(3) H. Brockmann, *Angew. Chem.*, **72**, 939 (1960).

method of Miller and Waelsch,[4] the literature contains no reference that the procedure also can be applied to the esterification of threonine.[5] The present report indicates that the esterification of threonine with benzyl alcohol by the method of Miller and Waelsch[4] proceeds very slowly and requires a reaction time which is much longer than that necessary for the esterification of other amino acids. If the reaction were carried out for the comparatively short periods of time necessary for the esterification of amino acids, such as glycine, only threonine *p*-toluenesulfonate was isolated. Even with the use of prolonged reaction times crude DL-threonine *p*-toluenesulfonate benzyl ester contained as much as 20% DL-threonine *p*-toluenesulfonate, the estimate being based on the average carbon content of different preparations. The resistance of threonine to yield the benzyl ester may be due to steric factors which are not operative in the case of serine. Molecular models show that the methyl group of threonine crowds the hydroxyl group toward the carbonyl oxygen. Because the formation of L-threonine *p*-toluenesulfonate benzyl ester necessitated heating for a prolonged period, the possibility had to be considered that the compound would racemize. However, conversion of *N*-carbobenzoxy-L-threonine benzyl ester, prepared from L-threonine *p*-toluenesulfonate benzyl ester, to L-threonine of the correct specific rotation proved that racemization did not take place under the experimental conditions. As expected of a primary aliphatic amine,[6] threonine *p*-toluenesulfonate benzyl ester and threonine benzyl ester reacted with ninhydrin. The reaction was very much slower than with threonine *p*-toluenesulfonate or threonine, the compound giving a yellow color at first which changed to the typical purple color within twenty-four hours.

Experimental

DL- and L-Threonine, $[\alpha]^{25}D$ −28.4° (*c* 3, water) were obtained from the Mann Research Laboratories, New York, N. Y. All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Amino nitrogen was determined manometrically.[7] For chromatography, Whatman #1 paper and the solvent system 95% ethanol–benzene–water (4:1:1) were used. Chromatograms were developed routinely by the descending technique. The petroleum ether used had a boiling range of 30–60°.

DL-Threonine *p*-Toluenesulfonate (I).—DL-Threonine, 0.15 g. (1.3 mmoles), and 0.27 g. of *p*-toluenesulfonic acid monohydrate (1.4 mmoles) were dissolved in 10 ml. of benzyl alcohol by warming the mixture on the steam bath to 80°. The solvent was removed slowly by vacuum distillation (80°, 1 mm.). The oily residue was washed three times with 50-ml. portions of dry ether and was then overlaid with dry ether. I, m.p. 143–145°, crystallized on standing at 4° overnight; 0.16 g., 43% yield. On paper chromatograms I migrated as a single component and gave an immediate test with ninhydrin, R_f = 0.45.

Anal. Calcd. for $C_{11}H_{17}O_6NS$: C, 45.3; H, 5.88; NH_2—N, 4.80. Found: C, 45.2; H, 5.83; NH_2—N, 4.94.

Reaction of DL-Threonine with *p*-toluenesulfonic acid in hot ethanol followed by evaporation of the solvent and crystallization of the residual oil from ether gave I in quantitative yield.

DI-Threonine *p*-Toluenesulfonate Benzyl Ester (II).—DL-Threonine, 2.0 g. (1.7 mmoles), and 3.44 g. of *p*-toluenesulfonic acid monohydrate (1.8 mmoles) were dissolved in 28 ml. of benzyl alcohol and 100 ml. of carbon tetrachloride by warming to 80°. The mixture was heated under reflux, the carbon tetrachloride being removed slowly by distillation at atmospheric pressure. After a reaction time of 15 hr. the carbon tetrachloride and approximately one half of the benzyl alcohol were removed by distillation at reduced pressure. II was precipitated as an oil by addition of dry ether. The oil crystallized on triturating the product with dry ether and cooling in an ice bath. The white solid, m.p. 98–101°, was collected, washed with petroleum ether, and dried *in vacuo* over calcium chloride; 5.48 g.; 86% yield. Further analysis of this material by paper chromatography indicated that the product, R_f = 0.86, was contaminated with I, R_f = 0.45. Attempts to separate I from II by chromatography on cellulose columns (Whatman ashless cellulose powder for chromatography) were unsuccessful. The crude material was purified by dissolving 0.38 g. (1 mmole) in 25 ml. of 5% sodium bicarbonate and extracting three times with 40 ml. of benzene. The combined benzene extracts were washed once with 40 ml. of water, and dried over anhydrous sodium sulfate. The solvent was evaporated at reduced pressure yielding the free base as a clear oil which could not be crystallized. The oil was dissolved in 10 ml. of warm ethyl acetate and 0.19 g. of *p*-toluenesulfonic acid monohydrate (1 mmole) in 3 ml. of ethyl acetate was added to this solution. The oil which was obtained on evaporation of the solvent was taken up in a minimum amount of hot benzene and the solution was filtered. Pure II crystallized upon adding dry ether, cooling in ice, and scratching; 0.10 g.; m.p. 115–117°.

Anal. Calcd. for $C_{18}H_{23}O_6NS$: C, 56.6; H, 6.08; N, 3.67. Found: C, 56.6; H, 6.09; N, 3.42.

On paper chromatograms the compound gave a delayed test with ninhydrin, R_f = 0.84. The spot which was initially yellow-brown gave the typical purple ninhydrin color only after 24 hr. Glycine *p*-toluenesulfonate benzyl ester, m.p. 132–133° (reported 132–134°),[8] when chromatographed under the same conditions, likewise gave a delayed reaction, R_f = 0.83. *N*-Carbobenzoxy-DL-threnonine benzyl ester,[9,10] m.p. 62–63°, of the correct elementary composition was prepared by treating II in dilute potassium bicarbonate solution with carbobenzoxy chloride in the usual manner.

L-Threonine *p*-Toluenesulfonate (III).—L-Threonine, 0.30 g. (2.5 mmoles) and 0.48 g. of *p*-toluenesulfonic acid monohydrate (2.5 mmoles) were dissolved in 30 ml. of ethanol with heating on the steam bath. The hot solution was filtered and the solvent removed at reduced pressure. The residual oil crystallized upon adding dry ether and cooling. The hygroscopic solid was collected and recrystallized twice from methanol–ether to yield III, m.p. 138–140°, 0.44 g., 60% yield. For analysis, the compound was recrystallized once more from methanol–ether with no change in melting point and dried *in vacuo* over phosphorus pentoxide at 56°.

(4) H. K. Miller and H. Waelsch, *J. Am. Chem. Soc.*, **74**, 1092 (1952).

(5) N. Izumija and S. Makisumi, *Nippon Kagaku Zasshi*, **78**, 662 (1957); *Chem. Abstr.*, **53**, 5148h (1959), reported that heating of DL-threonine in benzyl alcohol in the presence of one equivalent of *p*-toluenesulfonic acid failed to give a solid product.

(6) F. Feigl, "Spot Tests in Organic Analysis," 5th ed., Elsevier Publishing Co., New York, 1956, p. 283.

(7) D. D. Van Slyke, *J. Biol. Chem.*, **83**, 425 (1929).

(8) L. Zervas, M. Winitz, and J. P. Greenstein, *J. Org. Chem.*, **22**, 1515 (1957).

(9) F. Bergel and R. Wade, *J. Chem. Soc.*, 941 (1959).

(10) D. L. Ross, C. G. Skinner, and W. Shive, *J. Org. Chem.*, **24**, 1440 (1959).

Anal. Calcd. for $C_{11}H_{17}O_6NS$: C, 45.3; H, 5.88; N, 4.80. Found: C, 44.8; H, 6.04; N, 4.34.

On chromatograms III migrated as a single component, R_f = 0.42, and reacted immediately with ninhydrin.

L-Threonine *p*-Toluenesulfonate Benzyl Ester (IV).—L-Threonine, 0.30 g. (2.5 mmoles) and 0.53 g. of *p*-toluenesulfonic acid monohydrate (2.8 mmoles) were dissolved in 5 ml. of benzyl alcohol by heating on the steam bath. Carbon tetrachloride (25 ml.) was added and the mixture heated under reflux for 20 hr., the carbon tetrachloride being distilled from the mixture very slowly. Addition of dry ether precipitated an oil which was partially soluble in ethyl acetate. The material which was insoluble in ethyl acetate was identified as III, m.p. 136–137°. After 5 ml. of fresh benzyl alcohol and 25 ml. of carbon tetrachloride had been added, distillation of the carbon tetrachloride was resumed for an additional 19 hr. Addition of dry ether (100 ml.) precipitated 0.33 g. of a colorless oil after drying *in vacuo* over calcium chloride. Attempts to crystallize the oil from benzene–ether, benzene–petroleum ether, methanol–ether, and/or acetone–ether either at 0° or at −70° were unsuccessful.

Anal. Calcd. for $C_{18}H_{23}O_6NS$: NH_2—N, 3.67. Found: NH_2—N, 3.80.

Chromatography disclosed contamination of IV, R_f = 0.83, with III, R_f = 0.40. The material was dissolved in 40 ml. of benzene and purified by extraction with a dilute solution of sodium bicarbonate as described above for II. Following addition of one equivalent of *p*-toluenesulfonic acid monohydrate and evaporation of the solvent at reduced pressure, chromatographically pure IV, R_f = 0.82, was obtained as an oil, which could not be induced to crystallize. Although pure IV was obtained by this procedure in several runs, attempts to crystallize the resulting oil were unsuccessful.

***N*-Carbobenzoxy-L-threonine Benzyl Ester (V).**—L-Threonine, 0.40 g. (3.4 mmoles), and 0.71 g. of *p*-toluenesulfonic acid monohydrate (3.8 mmoles) were dissolved in 5 ml. of benzyl alcohol and 30 ml. of dry benzene. Esterification was carried out for 25 hr. as described for IV. The remaining benzene was removed by distillation at reduced pressure and IV precipitated by addition of 100 ml. of dry ether. After the ether had been decanted and the oil dried for 12 hr. *in vacuo* over calcium chloride, it was dissolved in 10 ml. of water and cooled in an ice bath. Carbobenzoxy chloride (0.60 ml.) and 1.4 g. of potassium carbonate in 25 ml. of water were added. After a few minutes of shaking, V precipitated from the reaction mixture. Following addition of a few drops of pyridine the reaction mixture was extracted with ethyl acetate. The organic phase was washed with 5% sodium bicarbonate and water in succession and dried over anhydrous sodium sulfate. After the solvent had been evaporated at reduced pressure, the oily residue solidified upon addition of petroleum ether to yield 0.80 g. of crystalline V; m.p. 79–80°, 68% yield. One recrystallization from ethyl acetate–petroleum ether afforded needles, m.p. 79–80°, $[\alpha]^{25}D$ −10.5° (*c* 2.0, 95% ethanol).

Anal. Calcd. for $C_{19}H_{21}O_5N$: C, 66.5; H, 6.17; N, 4.10. Found: C, 66.7; H, 6.23; N, 4.36.

Conversion of V to L-Threonine.—V, 0.71 g. (2.1 mmoles), was dissolved in 25 ml. of methanol. Following addition of three drops of glacial acetic acid, hydrogenolysis was carried out with palladium oxide[11] as catalyst. The product which had precipitated partially during the reaction was brought back into solution by addition of water. After the reaction mixture had been filtered, the solvent was removed at reduced pressure and the residue recrystallized from methanol–ether to yield 0.18 g. of L-threonine, $[\alpha]^{23}D$ −28.2° (*c* 1.5, water); 74% yield.

(11) R. L. Shriner and R. Adams, *J. Am. Chem. Soc.*, **46**, 1683 (1924).

New Synthetic Route to 6-Nitroisatin *via* Nitration of 3-Indolealdehyde

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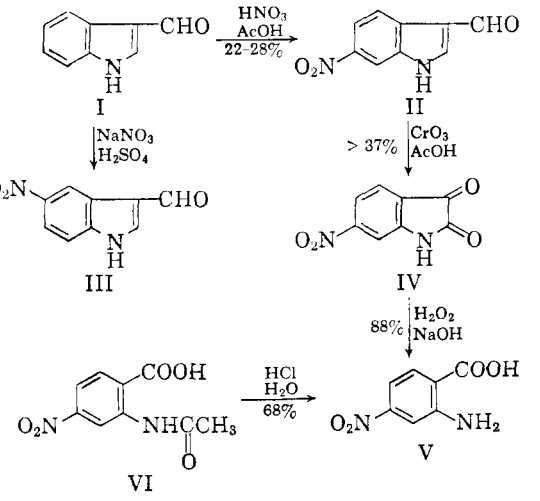
Nitration of 3-indolealdehyde (I) in acetic acid was first reported, by Majima and Kotake,[2] to give in unstated yield a mononitro derivative, having a melting point of 290° with decomposition, in which the position of nitration was not determined. Recently, and subsequent to the completion of our work, Berti and da Settimo[3] have reported that they have repeated the nitration of 3-indolealdehyde in acetic acid, and have obtained in 16% yield a mononitro derivative, having a melting point of 302–304° with decomposition. The mononitro derivative was proved to be 6-nitro-3-indolealdehyde (II), by oxidation to the corresponding acid and decarboxylation to authentic 6-nitroindole.[2] Berti and da Settimo[3] also reported that nitration of 3-indolealdehyde with potassium nitrate in concentrated sulfuric acid gave in 85% yield a mixture of mononitro derivatives, having a melting point of 260–270° with decomposition, shown by ultraviolet analysis to contain 66% 5-nitro-3-indolealdehyde and 34% 6-nitro-3-indolealdehyde. The structure of 5-nitro-3-indolealdehyde (III), isolated in small amount by fractional crystallization, was proved by oxidation to the corresponding acid and decarboxylation to a compound having a



melting point and ultraviolet spectrum in good agreement with those reported for 5-nitroindole.[4]

(1) From the senior thesis research of Reuben D. Rieke, 1960–1961.

(2) R. Majima and M. Kotake, *Ber.*, **63**, 2237 (1930).

(3) G. Berti and A. da Settimo, *Gazz. chim. ital.*, **91**, 728 (1961).

(4) S. M. Parmerter, A. G. Cook, and W. B. Dixon, *J. Am. Chem. Soc.*, **80**, 4621 (1958).

We also repeated the nitration of 3-indolealdehyde in acetic acid, and obtained in 22–28% yield a mononitro derivative, having a melting point of 301.5–302° with decomposition, corresponding to the mononitro derivative previously described.[2,3] We have proved the mononitro derivative to be 6-nitro-3-indolealdehyde (III), but by a different degradative method, and our results confirm the structure proved by Berti and da Settimo.[3] We have also carried out the nitration of 3-indolealdehyde, with sodium nitrate instead of potassium nitrate, in concentrated sulfuric acid, and have obtained in 93% yield a nitration product, from which was isolated the major product, a yellow, crystalline mononitro derivative, having a melting point of 312–314° with decomposition, different from 6-nitro-3-indolealdehyde, and assumed to be 5-nitro-3-indolealdehyde (III). Our crystalline product has a higher melting point than the microcrystalline powder of melting point 301.5–302° with decomposition, described for 5-nitro-3-indolealdehyde,[3] but the infrared and ultraviolet spectra appear to agree with those reported.

Our proof of the structure of 6-nitro-3-indolealdehyde is by chromic acid oxidation in better than 37% yield to 6-nitroisatin (IV), having a melting point in agreement with that reported,[5] followed by alkaline hydrogen peroxide oxidation[6] of the 6-nitroisatin in 88% yield to 4-nitroanthranilic acid[7] (V), identical with a sample prepared by acid hydrolysis of *N*-acetyl-4-nitroanthranilic acid[8] (VI). Our synthesis of 6-nitroisatin by chromic acid oxidation of 6-nitro-3-indolealdehyde appears to be the most convenient method; the previously reported method is by oxidation of 6,6′-dinitroindigo in 26% yield with a mixture of chromic, nitric, and sulfuric acids.[5] Similar chromic acid oxidations of 3-indolecarbonyl derivatives to the corresponding isatins have been described by Majima and Kotake,[2] involving oxidation of 6-bromo- and 5,6-dibromo-3-indolecarboxylic acids to the corresponding 6-bromo- and 5,6-dibromoisatins.

Ethyl 6-nitro-3-indolecarboxylate was prepared in 6% yield, for the purpose of ultraviolet comparison, by nitration of ethyl 3-indolecarboxylate in acetic acid according to the procedure of Majima and Kotake,[2] who did not state the yield. The ultraviolet spectrum was found to be quite similar to that of 6-nitro-3-indolealdehyde and different from that of 5-nitro-3-indolealdehyde (see data in Experimental).

(5) E. Giovannini and P. Portmann, *Hev. Chim. Acta*, **31**, 1375 (1948).

(6) W. C. Sumpter and W. F. Jones, *J. Am. Chem. Soc.*, **65**, 1802 (1943).

(7) (a) A. M. Berkenheim and R. S. Livshits, *J. Gen. Chem. U. S. S. R.*, **6**, 1025 (1936); *Chem. Abstr.*, **31**, 1779 (1937). (b) H. Rupe and L. Kersten, *Helv. Chim. Acta*, **9**, 578 (1926). (c) E. Chapman and H. Stephen, *J. Chem. Soc.*, **127**, 1791 (1925).

(8) Kindly provided by Dr. Lowell R. Smith; prepared by acetylation of Eastman Kodak Co. white label 2-methyl-5-nitroaniline: (a) Lowell R. Smith, Ph.D. thesis, Univ. of Minnesota, May, 1960, pp. 56–57, 70; followed by oxidation. (b) H. L. Wheeler and B. Barnes, *Am. Chem. Soc. J.*, **20**, 217 (1898).

Experimental

Melting points were determined on a calibrated Kofler micro hot stage.

3-Indolealdehyde (I) was prepared through a Vilsmeier reaction from indole and *N*,*N*-dimethylformamide in the presence of phosphorus oxychloride[9]; λ_{max} mμ (log ε) in 95% C_2H_5OH: 242 (4.14), 260 (4.07), 296 (4.12); ν_{NH} 3440 m in $CHCl_3$, 3140 ms in Nujol, $\nu_{C=O}$ 1655 s in $CHCl_3$, 1625 s cm.$^{-1}$ in Nujol.

6-Nitro-3-indolealdehyde (II).—The procedure is essentially that of Majima and Kotake,[2] who did not, however, state the relative quantities of reactants or the yield. Concentrated nitric acid (*d* 1.42, 50 cc.) was added, with rapid stirring, to a solution of 3-indolealdehyde (10.0 g., 0.0692 mole) in acetic acid (100 cc.). The first few cubic centimeters of nitric acid were added dropwise, causing a large amount of the yellow 1:1 addition product[2] of 3-indolealdehyde and nitric acid to precipitate. The remainder of the nitric acid was then added rapidly. The resulting suspension was heated to 65° on a water bath, whereupon a violent reaction took place. The reaction flask was immediately cooled in an ice bath and the solid which precipitated (2.86 g., 0.0150 mole, 22%), m.p. 285–290°, washed with water, dried, and recrystallized three times from acetone–benzene (acetic acid,[2] acetone–ethanol,[3] or ethanol–water may also be used), yielding light yellow needles, m.p. (turns brown at 292°) 301.5–302° dec.; reported: m.p. 290° dec.,[2] 16%, m.p. 302.5–304° dec.;[3] λ_{max} mμ (log ε) in 95% C_2H_5OH: 278 (4.23), 316 infl. (3.72); ν_{NH} 3180 m, $\nu_{C=O}$ 1647 s, ν_{NO_2} 1512 ms, 1340 s cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_9H_6N_2O_3$ (190.15): C, 56.84; H, 3.18; N, 14.73. Found: C, 57.09; H, 3.22; N, 14.67.

In other experiments, under similar conditions, yields of 23–28% were obtained.

5-Nitro-3-indolealdehyde (III).—A solution of sodium nitrate (2.93 g., 0.0345 mole) in concd. sulfuric acid (50 cc.) was added dropwise, with stirring, to a solution of 3-indolealdehyde (5.00 g., 0.0345 mole) in concd. sulfuric acid (60 cc.) cooled to 0° in an ice bath over a period of 1 hr. and 20 min. The solution was then poured onto ice (400 cc.). The cream-colored precipitate (6.1 g., 0.032 mole, 93%) was filtered, washed with water, and dried under vacuum for 2 days. The resulting reddish pink solid was extracted with large amounts of 95% ethanol, leaving a light blue solid residue, m.p. 280–290°. Four or five recrystallizations, once with charcoal, from *N*,*N*-dimethylformamide-water yielded the major product as light yellow needles, m.p. 312–314° dec.; λ_{max} mμ (log ε) in 95% C_2H_5OH: 257 (4.41), 263 infl. (4.40), 312 (3.96); ν_{NH} 3140 m and 3090 m (broad), $\nu_{C=O}$ 1650 s, ν_{NO_2} 1511 m and 1345 s or 1326 ms cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_9H_6N_2O_3$ (190.15): C, 56.84; H, 3.18; N, 14.73. Found: C, 57.22; H, 3.40; N, 14.32, 14.62.

Treatment of the ethanol extracts with charcoal, and subsequent evaporation, left a bright orange-red residue. Two crystallizations from *N*,*N*-dimethylformamide (DMF)–water gave a yellow solid, m.p. 270–280°, which was dissolved in DMF and chromatographed on an alumina column (2.0 × 30 cm.). Elution with 1:1 DMF–benzene removed a light yellow solid. Two crystallizations from DMF–water gave a light yellow solid, m.p. 265–267°, which still did not appear to be a pure compound and was not further characterized.

6-Nitroisatin (IV).—A solution of chromium trioxide (1.93 g., 0.0193 mole) in acetic acid (10 cc.) and water (2 cc.)

(9) P. N. James and H. R. Snyder, *Org. Syntheses*, **39**, 30 (1959).

was added dropwise over a period of 15 min. to a mixture of 6-nitro-3-indolealdehyde (1.00 g., 0.00520 mole) and acetic acid (200 cc.). The light yellow solution turned dark brown and all of the 6-nitro-3-indolealdehyde dissolved. The solution was stirred at room temperature for 30 hr., during which time a bright orange solid precipitated. The solid (0.37 g., 0.00193 mole, 37%), m.p. 287–290°, was filtered, washed with water, dried, and recrystallized three times from 95% ethanol, yielding 6-nitroisatin as a mixture of dark orange needles and light yellow fluffy solid, m.p. 288–290° dec.; reported[5] m.p. 288–290° dec.; λ_{max} mμ (log ϵ) in 95% C_2H_5OH: 239 (4.37), 272 infl. (3.85), 339 infl. (3.20), 395 diffuse infl. (3.06); ν_{NH} 3150 m, $\nu_{C=O}$ 1750 s infl., 1741 s, 1711 ms, 1624 s, ν_{NO_2} 1550 s, and 1360 ms or 1335 s cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_8H_4N_2O_4$ (192.13): C, 50.01; H, 2.10; N, 14.58; C, 50.04; H, 2.29; N, 14.77.

The acetic acid mother liquor was diluted with water (600 cc.) and extracted with ether (6 × 100 cc.). Evaporation of the ether extracts left an orange-brown solid (0.2 g., 0.00104 mole, 20%). One recrystallization from 95% ethanol gave a sample, m.p. 263–273°, shown by its infrared spectrum in Nujol to be 6-nitroisatin contaminated by 6-nitro-3-indolealdehyde starting material.

4-Nitroanthranilic Acid (V). A. By Hydrolysis of *N*-Acetyl-4-nitroanthranilic Acid.—A solution of *N*-acetyl-4-nitroanthranilic acid[8] (1.00 g., 0.00446 mole) and 6 *N* hydrochloric acid (50 cc.) was refluxed for 1.5 hr. The cooled solution was extracted with ether (3 × 125 cc.), and the ether extracts were dried over anhydrous magnesium sulfate and evaporated, leaving a bright orange solid. Recrystallization from 95% ethanol yielded bright orange needles (0.55 g., 0.00302 mole, 68%), m.p. 266–268° dec.; reported: m.p. 263–264°[7a], 264°,[7b] 269°[7c]; ν_{NH} 3460 m, 3360 m, $\nu_{C=O}$ 1683 s, ν_{NO_2} 1528 s, 1362 ms cm.$^{-1}$ in Nujol.

B. By Oxidation of 6-Nitroisatin.—The procedure is essentially that used previously for oxidation of 5-nitroisatin to 5-nitroanthranilic acid.[6] 6-Nitroisatin (0.13 g., 0.00068 mole) was dissolved in aqueous 10% sodium hydroxide solution (5 cc.), 3% hydrogen peroxide solution (4.3 cc.) was added, and the solution was kept at room temperature for 30 min. The solution was filtered through a sintered glass funnel and acidified to *p*H 1 with concd. hydrochloric acid, causing precipitation of a heavy yellow solid (0.11 g., 0.00060 mole, 88%), m.p. 263–266° dec. A mixed melting point with the sample prepared by acid hydrolysis of *N*-acetyl-4-nitroanthranilic acid (see part A, above) was undepressed, and the infrared spectra in Nujol were identical.

Ethyl 3-Indolecarboxylate was prepared by a Grignard coupling reaction from indolemagnesium iodide and ethyl chloroformate.[2,10,11] After elution from alumina with ethyl acetate and three recrystallizations from ethanol–water, our sample had a melting point, 126–127°,[12] higher than the 118–119° reported;[10] λ_{max} mμ (log ϵ) in 95% C_2H_5OH: 213 (4.56), 242 infl. (3.97), 281 (4.06), 286 (4.04); ν_{NH} 3450 m, 3300 m in $CHCl_3$, 3240 ms in Nujol, $\nu_{C=O}$ 1678 s in $CHCl_3$, 1685 m, 1661 s cm.$^{-1}$ in Nujol.[12]

Ethyl 6-nitro-3-indolecarboxylate was prepared in 6% yield by nitration of ethyl 3-indolecarboxylate in acetic acid by the method of Majima and Kotake,[2] who did not state the yield. The product, obtained by elution from alumina and recrystallization from ethanol–water, had a melting point of 200–201°; reported m.p. 198–199°;[2] λ_{max} mμ (log ϵ) in 95% C_2H_5OH: 270 (4.16), 320 (3.72), 329 infl. (3.68); ν_{NH} 3230 m, $\nu_{C=O}$ 1692 s infl., 1679 s, ν_{NO_2} 1521 s, 1349 s cm.$^{-1}$ in Nujol.

(10) R. Majima and M. Kotake, *Ber.*, **55**, 3865 (1922).

(11) We are indebted to Daryl L. Ostercamp for this preparation.

(12) Donald N. Robinson, Ph.D. thesis, Univ. of Minnesota, March, 1959, p. 129.

Sodium Triphenylgermanethiol. Synthesis of Some New Organothiogermanes

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Only a few organogermanium compounds have been synthesized which contain germanium directly linked to sulfur. Of this type the following have been prepared: R_3GeSR,[2a] R_2GeS,[2b] $(RS)_4Ge$,[3a] $(RS)_3GeX$,[3b] $R_3GeSSGeR_3$,[4] $(R_3Ge)_2S$,[4] and $(R_2GeS)_2S$.[5]

Gilman and Lichtenwalter[6] have reported the synthesis of lithium triphenylsilanethiol in tetrahydrofuran solution by treating triphenylsilyllithium with elemental sulfur. Proof of its existence was established by reaction with several RX type compounds. Solutions of triphenylgermyllithium[7] do not react as smoothly with elemental sulphur as the corresponding silyllithium compound.

The sodium salt of triphenylgermanethiol, on the other hand, may be prepared and isolated in good yields after dropwise addition of a benzene solution of triphenylbromogermane to a freshly prepared suspension of sodium sulfide in ethanol:

$$(C_6H_5)_3GeBr + Na_2S \longrightarrow (C_6H_5)_3GeSNa(I) + NaBr$$

The pure salt (I), although hygroscopic, has been stored in a dessicator containing Drierite for over a month without change. It is soluble in benzene, alcohol, and water. An aqueous solution, alkaline to *p*H paper, becomes turbid after several minutes with the liberation of a hydrogen sulfide-like odor. Refluxing in commercial anhydrous alcohol produces bis(triphenylgermanium) sulfide and sodium sulfide. The reaction is reversible since bis(triphenylgermanium) sulphide when refluxed with excess sodium sulfide produces starting material (I):

$$(C_6H_5)_3GeSNa \underset{XS.Na_2S}{\overset{C_2H_5OH}{\rightleftharpoons}} (C_6H_5)_3GeSGe(C_6H_5)_3 + Na_2S$$

The reaction of I with RX type compounds presents a convenient method for the synthesis of sulfur containing organogermanium compounds, Table I:

(1) Research Fellow sponsored by the Germanium Research Committee.

(2) (a) H. H. Anderson, *J. Org. Chem.*, **21**, 869 (1956). (b) *J. Am. Chem. Soc.*, **78**, 1692 (1956).

(3) (a) H. J. Backer and F. Stienstra, *Rec. trav. chim.*, **52**, 1033 (1933), **54**, 607 (1935). (b) **54**, 38 (1935).

(4) R. Burschkies, *Ber.*, **69**, 143 (1936).

(5) H. Bauer and R. Burschkies, *Ber.*, **65**, 956 (1932).

(6) H. Gilman and G. Lichtenwalter, *J. Org. Chem.*, **25**, 1064 (1960).

(7) H. Gilman and C. W. Gerow, *J. Am. Chem. Soc.*, **77**, 4675 (1955).

TABLE I
REACTIONS OF $(C_6H_5)_3GeSNa$

Compound No.	RX	Product	Yield, %	M.P.	Formula	Found C	Found H	Found Ge	Found S	Calcd. C	Calcd. H	Calcd. Ge	Calcd. S
II	CH_3I	(Methylthio)triphenylgermane	62	87–88	$C_{19}H_{18}GeS$	64.88	5.30	20.50	9.24	65.10	5.16	20.70	9.14
III	n-C_4H_9I	(n-Butylthio)triphenylgermane[a]	70	147–150/0.05 mm.	$C_{22}H_{24}GeS$	66.92	6.16	18.62	7.55	67.30	6.16	18.48	8.15
IV	$C_6H_5CH_2Cl$	(Benzylthio)triphenylgermane	59	98.5	$C_{25}H_{22}GeS$	69.92	5.32	17.05	7.55	70.30	5.19	17.00	7.51
V	$C_6H_5C(O)Cl$	(Benzylthio)triphenylgermane	67	145.5	$C_{25}H_{20}GeOS$	67.80	4.69	16.49	7.18	68.10	4.51	16.47	7.26
VI	p-$NO_2C_6H_4C(O)Cl$	(p-Nitrobenzoylthio)triphenylgermane	58	151	$C_{25}H_{19}GeNO_3S$	61.40	4.01	14.80	6.90	61.70	3.95	14.95	6.60
VII	$(C_6H_5)_3GeBr$	Bis(triphenylgermanium) sulfide[b]	67	138.5	$C_{36}H_{30}Ge_2S$								
VIII	CH_3SCH_2Cl	[(Thiomethyl)methylthio]triphenylgermane	65	63.0	$C_{20}H_{16}GeS$	60.35	5.15	18.24	16.30	60.40	5.08	18.28	16.15
IX	CH_3SO_2Cl	Bis(triphenylgermanium) disulfide	50	171–172	$C_{36}H_{30}Ge_2S_2$	63.90	4.55	21.40	9.31	64.20	4.50	21.60	9.55
X	$(C_6H_5)_2GeBr_2$	Diphenyl(bistriphenylgermanethio)germane	52	162	$C_{48}H_{40}Ge_3S_2$	64.19	4.51	24.15	7.11	64.20	4.48	24.25	7.14

[a] Liquid with refractive index = 1.6135. [b] Known compound. Identified by mixed melting point + comparison of infrared spectrum.

$$(C_6H_5)_3GeSNa + RX \longrightarrow (C_6H_5)_3GeSR$$

R = $-CH_3$ (II); $-n$-C_4H_9 (III); $-CH_2C_6H_5$ (IV); $-C(O)C_6H_5$ (V); $-C(O)C_6H_4NO_2$-p (IV); $-Ge(C_6H_5)_3$ (VII); $-CH_2SCH_3$ (VIII)

Carbon disulfide treated with I and methyl iodide did not produce the expected organogermane substituted carbonic acid trithioester. Instead bis(triphenylgermanium) sulfide and disodium trithiocarbonate were formed. It is not clear whether the expected reaction A took place and subsequently, through decomposition, formed bis(triphenylgermanium) sulfide and disodium trithiocarbonate or whether I is unstable in carbon disulfide solution. In the later case, reaction B, the initially formed sodium sulfide could have reacted with carbon disulfide to form the sodium trithiocarbonate.[8] Reaction of I with methanesulfonyl chloride forms the symmetrical disulfide and not the thiosulphonyl compound in a manner similar to that described for the synthesis of organic disulfides[9]:

$$2(C_6H_5)_3GeSNa + CS_2 \xrightarrow{A} [2(C_6H_5)_3GeSC(S)SNa] \longrightarrow [(C_6H_5)_3Ge]_2S + Na_2SC_3$$

$$2(C_6H_5)_3GeSNa + CS_2 \xrightarrow{B} [(C_6H_5)_3Ge]_2S + Na_2S \xrightarrow{CS_2} Na_2SC_3$$

$$2(C_6H_5)_3GeSNa + CH_3SO_2Cl \longrightarrow (C_6H_5)_3GeSSGe(C_6H_5)_3 \text{ (IX)} + NaCl + RSO_2Na$$

When two equivalents of I reacted with one equivalent of diphenyldibromogermane the expected diphenyl(bistriphenylgermanethio)germane (X) was isolated in good yield:

$$2(C_6H_5)_3GeSNa + (C_6H_5)_2GeBr_2 \longrightarrow (C_6H_5)_3GeSGe(C_6H_5)_2SGe(C_6H_5)_3 \text{ (X)}$$

Experimental[10]

Preparation of the Sodium Salt of Triphenylgermanethiol (I).—Excess sodium sulfide pentahydrate, 10 g. (71 mmoles), recrystallized from ethanol, was suspended in 130 ml. of absolute ethanol at room temperature. Triphenylbromogermane, 10 g. (26 mmoles), dissolved in 70 ml. of benzene, was added dropwise over a 10-min. period while stirring. After 15-min. of additional stirring the solution was filtered, the clear solution evaporated to dryness and the resulting white crystalline mass extracted with benzene. Filtration removed the excess sodium sulfide and bromide. The filtrate was evaporated yielding 9 g. of product. This material was dissolved in benzene at approximately 50° and 80 ml. of hexane added. Within minutes white crystals formed which, after filtration, were washed with hexane and vacuum dried

(8) E. Emmett Reid, "Organic Chemistry of Bivalent Sulphur," Vol. I, Chem. Publ. Co., Inc., New York, 1958. p. 31.

(9) D. T. Gibson, C. J. Miller, and S. Smiles, *J. Chem. Soc.*, **127**, 1821 (1925).

(10) Melting points were determined with a Kofler hot stage. Infrared spectra of all organogermanium compounds, in addition to the normal absorptions, contained the characteristic phenyl-germanium absorption at 9.15 μ, J. G. Noltes, M. C. Henry, and M. J. Janssen, *Chem. Ind.* (London), 1959, 298.

to yield 8.2 g. (88%) of the sodium salt of triphenylgermanethiol (I), m.p. 185–195°. The melting point could not be improved by recrystallization.

Anal. Calcd. for $C_{18}H_{15}GeSNa$: Na, 6.45; Found: Na, 6.34.

Typical Reaction Conditions.—A solution of the RX compound (5.8 mmoles) in 10 ml. of benzene was added slowly to a solution of 2.0 g. (5.8 mmoles) of the sodium salt (I) and the mixture stirred for 3 hr. The white precipitate of sodium halide that formed during the reaction was filtered and washed with 2 ml. of benzene. The filtrate was evaporated in vacuum and the crude product recrystallized from hexane.

Reaction of I with Carbon Disulfide.—A 2.0-g. sample (5.8 mmoles) of I was dissolved in 50 ml. of carbon disulfide. The clear solution slowly formed an orange precipitate. After 10 days the mixture was filtered. The yield was 600 mg. The orange-colored compound turned red in moist air, was insoluble in benzene and soluble in water.

Evaporation of the filtrate and recrystallization from hexane yielded 1.3 g. of long, white needles, m.p. 138°, bis(triphenylgermanium) sulfide identified by infrared spectra and mixed melting point using a known sample.

The orange compound (250 mg.) was refluxed with 0.2 ml. of methyl iodide in 30 ml. of benzene for 5 hr. during which time the benzene solution became yellow and a precipitate (400 mg.) of sodium iodide formed. The benzene was evaporated leaving a strong smelling, yellow oil (150 mg.). The mass spectral pattern indicates a molecular weight of 136. This information together with the infrared spectrum tentatively suggests this compound to be dimethyl trithiocarbonate.

Acknowledgment.—The authors are grateful to C. DiPietro of the analytical laboratory of this division for the microanalyses.

The Reaction between 2-Nitro-1-phenylpropene and Cyclohexanone

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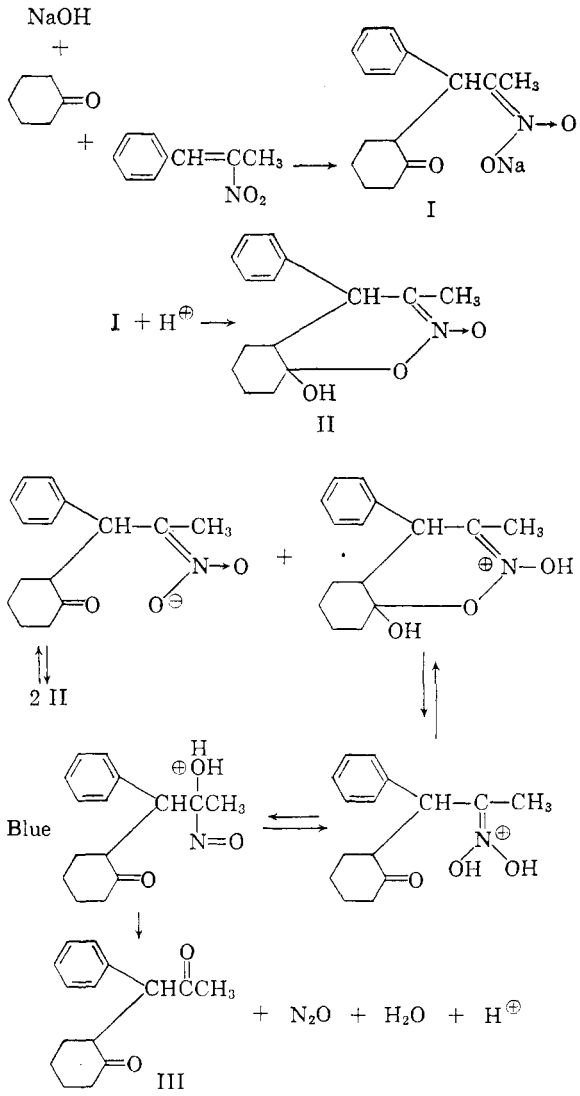
In an attempt to prepare a nitro ketone desired for synthetic work an aqueous solution of one equivalent of sodium hydroxide was added to a solution of one equivalent of 2-nitro-1-phenylpropene in excess cyclohexanone. Upon stirring, a sharp temperature rise occurred and the mixture became one phase. Addition to methanol containing an excess of acetic acid led to a crystalline precipitate which has an analysis corresponding to the expected nitro ketone, but which is now believed to be the cyclic condensation product II.

Compound II melts with decomposition, is only slightly soluble in organic solvents or water, but dissolves readily in aqueous sodium hydroxide. The infrared spectrum is complex, but strong bands are absent from the regions around 1700 cm.$^{-1}$, 1540 cm.$^{-1}$, and 1350 cm.$^{-1}$ where intense bands would be expected from a nitro ketone. Of interest are strong bands at 1615 cm.$^{-1}$ and 3145 cm.$^{-1}$, which we interpret as evidence for a ring C=N,[1] and a hydroxyl group, respectively.

Refluxing II in methanol leads to the development of a blue color, the evolution of nitrous oxide, and finally, to the formation of a crystalline product containing no nitrogen, showing strong carbonyl absorption, and giving the correct analysis for the 1,4-diketone III. Further evidence for the 1,4-diketone structure is the reaction of III with aniline which gives a compound having a nitrogen analysis corresponding to the expected 4,5,6,7-tetrahydroindole.

On dissolving compound II in aqueous sodium hydroxide and adding this solution to a large excess of acetone a crystalline sodium salt forms (as a hexahydrate) which shows strong absorption in the carbonyl region of the infrared spectrum. Reaction of this sodium salt with bromine gives a bromo nitro ketone, while reaction with benzyl chloride gives sodium chloride, a strong odor of



(1) N. E. Boyer, G. M. Czerniak, H. S. Gutowsky, and H. R. Snyder, *J. Am. Chem. Soc.*, **77**, 4238 (1955), found a band for the C=N at 1625–1600 cm.$^{-1}$ in the furoxan ring.

benzaldehyde and what appears to be a cyclic condensation product of the monoxime.[2]

The equations below are suggested as possible routes of the main reactions involved.[3]

This series of reactions might be thought of as an interrupted Nef reaction.

The addition of ketones to 2-nitro-1-phenylpropene appears to be fairly general, since both acetone and diethyl ketone give salts similar to I. Pure compounds corresponding to II have not been isolated from these salts, however.

Experimental[4]

Addition of Cyclohexanone to 2-Nitro-1-phenylpropene.—To 65.2 g. (0.4 mole) of 2-nitro-1-phenylpropene in 160 ml. of cyclohexanone was added a solution of 20 g. (0.5 mole) of sodium hydroxide in 50 ml. of water. The mixture was stirred and cooled for about 30 min. during which time it became one phase and the temperature rose to 60°, and then subsided.

Acidification of Addition Product.—The above reaction mixture was poured slowly with stirring and cooling into 300 ml. of methanol containing 60 ml. of acetic acid. After 30 min. the white, crystalline precipitate (II) was filtered and air-dried. There was 47 g. (45%); m.p. 137–139° dec.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 68.9; H, 7.33; N, 5.36. Found: C, 69.2; H, 7.49; N, 5.22.

Preparation of 1-(2-Oxocyclohexyl)-1-phenyl-2-propanone (III).—A mixture of 100 ml. of methanol and 26 g. (0.1 mole) of compound II was refluxed for 4 hr. A blue color appeared after a few minutes, then this slowly turned to yellow toward the end of the reaction. The solid went into solution gradually, and a gas was evolved. Analysis by a mass spectrometer showed this gas to be pure nitrous oxide. After evaporation of the methanol, addition of 10 ml. of cyclohexane caused crystallization. After filtration and drying there were 16.4 g. (71%), m.p. 79–80° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.2; H, 7.88. Found: C, 78.4; H, 8.02.

Preparation of the Sodium Salt of 1-(2-Oxocyclohexyl)-2-nitro-1-phenylpropene (I).—A solution of 13 g. (0.05 mole) of II in 40 ml. of water plus 2.2 g. (0.055 mole) of sodium hydroxide was filtered into 300 ml. of acetone. A crystalline precipitate formed which weighed 18 g. (92%), m.p. 75–77°. The infrared spectrum of this had a strong band at 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{18}NO_3Na\ 6H_2O$; C, 46.0; H, 7.72; N, 3 58. Found: C, 46.6; H, 7.40; N, 3.52.

Bromination of the Sodium Salt of 1-(2-Oxocyclohexyl)-2-nitro-1-phenylpropene (I).—A solution of 13 g. (0.05 mole) of II in 100 ml. of water plus 2.2 g. (0.055 mole) of sodium hydroxide was added slowly with stirring and cooling to 20–25° to 200 ml. of methanol containing 2.5 ml. (0.05 mole) of bromine. The mixture was left in the refrigerator overnight, filtered to give 14 g. of white crystals. After several recrystallizations from isopropyl alcohol the melting point was 113–115°. This compound showed strong bands at 1710 cm.,$^{-1}$ 1550 cm.,$^{-1}$ and 1330 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{18}BrNO_3$: N, 4.12; Br, 23.5. Found: N, 4.35; Br, 23.8.

Reaction of the Sodium Salt of 1-(2-Oxocyclohexyl)-2-nitro-1-phenylpropene (I) with Benzyl Chloride.—To 8.0 g. (0.02 mole) of the sodium salt of 1-(2-oxocyclohexyl)-2-nitro-1-phenylpropene in 100 ml. of ethanol was added 2.6 g. (0.021 mole) of benzyl chloride. The mixture was heated in a steam bath for 2 hr., then cooled overnight and filtered to give 1 g. of sodium chloride. The filtrate had the odor of benzaldehyde. It was concentrated to 30 ml., 10 ml. of water was added, and the mixture was cooled overnight. This gave 2.5 g. (42%) of a compound which, after two recrystallizations from isopropyl alcohol, melted at 165–166°. The infrared spectrum of this had intense bands in the regions of 3200 cm.$^{-1}$ and 1615 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{20}NO_2$: N, 5.71. Found: N, 5.47.

Preparation of 1,3-Diphenyl-2-methyl-4,5,6,7-tetrahydroindole.—A mixture of 4.0 g. (0.17 mole) of 1-(2-oxocyclohexyl)-1-phenyl-2-propanone (III), 2 g. (0.21 mole) of aniline, 2 drops of hydrochloric acid, and 25 ml. of ethanol was heated on a steam bath for 2 hr., then cooled 2 hr., and filtered to give 4.3 g. (88%) of white crystals. After recrystallization from ethanol the melting point was 77–79°.

Anal. Calcd. for $C_{21}H_{21}N$: N, 4.87. Found: N, 4.97.

Reaction of Acetone with 2-Nitro-1-phenylpropene.—To 100 ml. of acetone with 16.3 g. (0.1 mole) of 2-nitro-1-phenylpropene was added a solution of 4 g. (0.1 mole) of sodium hydroxide in 10 ml. of water. The mixture was stirred for 1.5 hr. during which a crystalline precipitate formed and the temperature rose to 38° and then dropped. Filtration gave a yellow solid which was dissolved in 50 ml. of 50% aqueous methanol. This was filtered into 300 ml. of acetone to give 11 g. (45%) of a white crystalline product, melting point 110–115° dec.

Anal. Calcd. for $C_{12}H_{14}NO_3Na\cdot 3H_2O$: N, 4.71. Found: N, 4.52.

Acidification of this by acetic acid in methanol led to a blue color, but no crystalline product was recovered.

Diethyl ketone gave a similar salt.

(2) See H. B. Hass and M. L. Bender, *J. Am. Chem. Soc.*, **71**, 3482 (1949).

(3) The mechanism of the Nef reaction is discussed by W. E. Noland, *Chem. Rev.*, **55**, 137 (1955).

(4) Melting points are uncorrected. Infrared data were taken with a Perkin-Elmer Model 21 double beam recording spectrophotometer equipped with sodium chloride optics. Potassium bromide disks were used for all determinations. Gas analysis was done with a Model 21-103-C Consolidated Engineering mass spectrometer.

Peptide Synthesis. An Application of the Esterase Activity of Chymotrypsin

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A frequently required step in peptide synthesis is the hydrolysis of an ester function used to block the terminal carboxyl group. The conventional methods for accomplishing this step may cause side reactions.[1] When we hydrolyzed the methyl ester of isoleucine-5 angiotensin octapeptide[2,3] under either acidic or basic conditions, we obtained low yields of the desired peptide. Chymotrypsin[4]

(1) R. Schwyzer, *Chimia*, **12**, 53 (1958); M. Goodman and G. W. Kenner, "Advances in Protein Chemistry," Vol. XII, Academic Press, New York, 1957, p. 474.

(2) Angiotensin is the present name for the substance formerly called angiotonin and hypertensin: E. Braun-Menendez and I. H. Page, *Science*, **127**, 242 (1958).

(3) H. Schwarz, F. M. Bumpus, and I. H. Page, *J. Am. Chem. Soc.*, **79**, 5697 (1957); R. Schwyzer, B. Iselin, H. Kappeler, B. Riniker, W. Rittel, and H. Zuber, *Chimia*, **11**, 335 (1957).

(4) M. Dixon and E. C. Webb, "Enzymes," Academic Press, Inc., New York, 1958, p. 269; and H. Neurath and G. W. Schwert, *Chem. Rev.*, **46**, 69 (1950) review the proteolytic and esterase activities of chymotrypsin.

was found to be an ideal reagent for hydrolysis of this ester without by-product formation.

Isoleucine-5 angiotensin octapeptide[2,3] was synthesized by a sequence requiring, in the final step, hydrolysis of the ester, α-aspartyl-arginyl-valyl-tyrosyl - isoleucyl - histidyl - prolyl - phenylalanine methyl ester. When we hydrolyzed this ester with sodium hydroxide or hydrochloric acid, side reactions took place as shown by paper chromatography and biological assay of the products. We then examined the action of chymotrypsin on this ester. Since the tyrosyl-isoleucine linkage is readily cleaved by chymotrypsin,[5] conditions were required which would allow selective hydrolysis of the ester. It was found that at a chymotrypsin to substrate ratio of 1:1000, both the ester and tyrosyl-isoleucyl bonds were cleaved, while at a ratio of 1:100,000 the ester hydrolyzed at a rate too slow to be practical. But when a ratio of 1:10,000 was used, ester hydrolysis was complete in two hours while no cleavage of a peptide bond or formation of other products was observed. The course of reaction was followed by paper chromatography.

In the course of this work we examined the action of chymotrypsin on four other peptide esters: L-prolyl-L-phenylalanine methyl ester, carbobenzyloxy-L-valyl-L-tyrosine methyl ester, N^{α}-carbobenzyloxy-N^{g}-nitro-L-arginyl-L-valyl-L - tyrosine methyl ester, and carbobenzyloxy methylene L-asparaginyl-L-tyrosine methyl ester. When an aqueous solution of chymotrypsin was added to a solution of L-prolyl-L-phenylalanine methyl ester in methanol, L-prolyl-L-phenylalanine crystallized rapidly in a 90% yield. Carbobenzyloxy-L-valyl-L-tyrosine was obtained in 80% yield from its methyl ester. In this case a solution of the peptide ester in dimethylformamide was added to an aqueous solution of chymotrypsin. Even though the ester had precipitated from the solution, hydrolysis was complete in two hours. Similarly, the tripeptide derivative, N^{α}-carbobenzyloxy-N^{g}-nitro-L-arginyl-L-valyl-L-tyrosine methyl ester was converted to the corresponding acid in 95% yield, and carbobenzyloxy methylene-L-asparaginyl-L-tyrosine methyl ester was hydrolyzed in 80% yield to the corresponding acid. In these cases the blocking groups did not interfere with enzymic hydrolysis and the peptides were obtained rapidly in pure form by procedures readily adapted to large-scale preparations.

These examples point out the preparative practicality of enzymic peptide ester hydrolysis. Depending upon the nature of the C-terminal amino acids, enzymes other than chymotrypsin would be used.

Experimental

Melting points were taken on a Kofler micro hot stage.

Paper chromatograms were done on 32-cm. Whatman No. 1 circles with a 1-cm. center hole.[6]

The compounds were located on the paper by means of ninhydrin (N), diazotized sulfanilic acid (P), or Sakaguchi reagent (S). A compound which has an R_f value of 0.5 in the MPW[7] system and was located with ninhydrin reagent is reported as R_f^{MPW} 0.5 (N).

Hydrolysis of L-Prolyl-L-phenylalanine Methyl Ester.—A solution of 18 mg. of α-chymotrypsin (crystallized, Worthington Biochemical Corp.) in 50 ml. of 0.5 *M* ammonium acetate (*p*H 6.4) was added rapidly to a stirred solution of 1 g. of L-prolyl-L-phenylalanine methyl ester hydrochloride[8] in 5 ml. of methanol.

Crystallization of L-prolyl-L-phenylalanine occurred almost immediately. After the suspension had been stirred at 22° for 15 min., the product was filtered, washed with water and with methanol; 0.9 g. of L-prolyl-L-phenylalanine was obtained. No impurities were detected by radial paper chromatography in two solvent systems: R_f^{BAW} 0.64 (N); R_f^{BAm} 0.26 (N).

A sample crystallized from water and dried at 110° had the following properties: m.p. 234–238°; $[\alpha]^{22}D$ −42° (*c* 2.1, 20% hydrochloric acid).[9]

Hydrolysis of Carbobenzyloxy-L-valyl-L-tyrosine Methyl Ester.—A solution of 0.5 g. of carbobenzyloxy-L-valyl-L-tyrosine methyl ester[10] in 2 ml. of dimethylformamide was added dropwise during a 5-min. period to a stirred solution of 20 mg. of α-chymotrypsin in 22 ml. of 0.5 *M* ammonium acetate to which ammonium hydroxide had been added to adjust the solution to *p*H 8. A precipitate formed immediately. The *p*H of the solution gradually dropped, and after 10 min., the solution was readjusted to *p*H 8 with ammonium hydroxide. After the mixture had been stirred at 22° for 2 hr., a clear solution had formed. The solution was acidified to *p*H 1 with hydrochloric acid, the resulting crystalline precipitate was filtered, washed with water, and dried; 0.4 g. of carbobenzyloxy-L-valyl-L-tyrosine[10] was obtained, R_f^{BAm}[7] 0.69 (P).

A sample was recrystallized from aqueous methanol: m.p. 163–169°; $[\alpha]^{22}D$ +26.5° (*c* 2.1, pyridine).

A similar reaction, but at *p*H 6.4, gave incomplete hydrolysis. A control experiment at *p*H 8 in the absence of enzyme showed no hydrolysis.

Hydrolysis of Carbobenzyloxy Methylene-L-asparaginyl-L-tyrosine Methyl Ester.—A solution of 230 mg. of carbobenzyloxy methylene-L-asparaginyl-L-tyrosine methyl ester[11] in 2 ml. of methanol was added dropwise to a stirred solution of 10 mg. of α-chymotrypsin in 20 ml. of 0.5 *M* ammonium acetate to which ammonium hydroxide had been added to adjust the solution to *p*H 8. The precipitate which formed went rapidly into solution. After the solution had been stirred about 2 hr. at 22°, it was acidified to *p*H 1 with hydrochloric acid. The oily precipitate which formed crystallized slowly on standing overnight to give 177 mg. of carbobenzyloxy methylene-L-asparaginyl-L-tyrosine,[11] m.p. 118–122°, $[\alpha]^{22}D$ −25° (*c* 1.0, pyridine), R_f^{MPW} 0.85 (N).

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(5) A. A. Plentl and I. H. Page, *J. Biol. Chem.*, **163**, 49 (1946) describe cleavage of angiotensin by chymotrypsin.

(6) E. Lederer and M. Lederer, *Chromatography*, 2nd ed., Elsevier Publishing Co., New York, 1957, p. 134.

(7) BAW, butanol–acetic acid–water—4:1:5. The upper phase was used. BAm, butanol–1.5 *N* ammonium hydroxide—1:1. The upper phase was used. MPW, methyl ethyl ketone–pyridine–water—4:1:1.6.

(8) W. Rittel, B. Iselin, H. Kappeler, B. Riniker, and R. Schwyzer, *Helv. Chim. Acta*, **40**, 614 (1957).

(9) E. Fischer and A. Luniak, *Ber.*, **42**, 4752 (1909), report m.p. 252°, $[\alpha]$ −40.9° (*c* 5, 20% hydrochloric acid).

(10) H. Schwarz and F. M. Bumpus, *J. Am. Chem. Soc.*, **81**, 890 (1959).

(11) C. H. Stammer, *J. Org. Chem.*, **26**, 2556 (1961).

Hydrolysis of N^{α}-Carbobenzyloxy-N^{g}-nitro-L-arginyl-L-valyl-L-tyrosine Methyl Ester.—A solution of 500 mg. of N^{α}-carbobenzyloxy-N^{g}-nitro-L-arginyl-L-valyl-L-tyrosine methyl ester[8] in 5 ml. of dimethylformamide was added dropwise to a solution of 50 mg. of α-chymotrypsin in 40 ml. of 0.5 *M* ammonium acetate to which ammonium hydroxide had been added to adjust the solution to *p*H 7.5. The reaction mixture was stirred at 22° for 15 min. during which time a precipitate formed and redissolved. Acidification of the solution to *p*H 2 with hydrochloric acid gave 480 mg. of N^{α}-carbobenzyloxy-N^{g}-nitro-L-arginyl-L-valyl-L-tyrosine,[10] R_f^{BAm} 0.55 (N), $[\alpha]^{22}D$ −13.4° (*c* 0.82, methanol). A sample recrystallized from ethanol melted at 178–182°.

Isoleucine-5 Angiotensin Methyl Ester.—Isoleucine-5 angiotensin has been synthesized[9] by (a) condensation of carbobenzyloxy-β-methyl ester-L-aspartyl-N^{g}-nitro-L-arginine with L-valyl-L-tyrosyl-L-isoleucyl-L-histidyl-L-prolyl-L-phenylalanine methyl ester, (b) alkaline hydrolysis of the condensation product, and (c) removal of the carbobenzyloxy and nitro groups by catalytic hydrogenation. Similarly, we condensed carbonbenzyloxy-β-benzyl ester-L-aspartyl-N^{g}-nitro-L-arginine[12] with the hexapeptide ester using dicyclohexyl-carbodiimide[13] as the condensing agent: hydrogenation of the product over a palladium catalyst yielded a mixture containing isoleucine-5 angiotensin methyl ester. This ester was carried through a 96-plate countercurrent distribution in the system butanol–propanol–acetic acid–water (30:15:5:50) followed by a 196-plate distribution of the peak fractions in butanol–acetic acid–water (4:1:5). The product from the major peak showed only one component, R^{BAW_7} 0.61 (N); $R_f^{MPW_7}$ 0.69 (N); $R_f^{BAm_7}$ 0.40 (N).

Chymotrypsin Hydrolysis of Isoleucine-5 Angiotensin Methyl Ester. Method A. (1–1000).—A 5.3-mg. sample of isoleucine-5 angiotensin methyl ester was added to 0.8 ml. of 0.5 *M* ammonium acetate containing 5.3 γ of chymotrypsin. Samples were examined periodically by radial paper chromatography in MPW; ninhydrin was used to locate the spots. In 2 min. considerable hydrolysis had occurred and chromatography showed that the free octapeptide, $R_f^{MPW_7}$ 0.48 (N,P,S), was being produced. In 40 min., however, cleavage of the peptide chain to give the tetrapeptides α-L-aspartyl-L-arginyl-L-valyl-L-tyrosine, $R_f^{MPW_7}$ 0.39 (N,P,S) and L-isoleucyl-L-histidyl-L-prolyl-L-phenylalanine, $R_f^{MPW_7}$ 0.62 (N, P), had occurred, while an observable amount of octapeptide ester $R_f^{MPW_7}$ 0.69 (N,P,S) remained unhydrolyzed.

Method B. (1–100,000)—A sample was treated as described in A above, except that 0.053 γ of chymotryspin was used. Under these conditions both ester and amide hydrolyses were slow—after 2 hr. only a small amount of ester hydrolysis and no amide hydrolysis was observed.

Method C. (1–10,000).—A 10.2-mg. sample of isoleucine-5 angiotensin methyl ester in 0.8 ml. of 0.05 *M* ammonium acetate was added to 0.28 ml. of water containing 1.0 γ of chymotrypsin. The solution was *p*H 6. In 2 hr. the ester was completely hydrolyzed as indicated by a single spot at R_f^{MPW} 0.48 (N,P,S). No cleavage of the peptide chain was observed. Only after 22 hr. was formation of a small amount of the tetrapeptides, R_f^{MPW} 0.39 (N,P,S) and R_f^{MPW} 0.62 (N,P), detected. The product isolated by lyophilization after 2 hr. of hydrolysis under the above conditions had a high order of biological activity. In normal anesthetized dogs, a dose of 1 γ/kg. produced a 60-mm. mean arterial pressure rise, while the starting octapeptide ester was essentially inactive at dosages up to 100 γ/kg.

The biological assays were carried out by Dr. L. S. Watson in these laboratories.

(12) L. T. Skeggs, Jr., K. E. Lentz, J. R. Kahn, and N. P. Shumway, *J. Exp. Med.*, **108**, 283 (1958).

(13) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

o-Trifluoromethyl- and Some *ortho, meta*-Disubstituted Benzeneboronic Acids and Anhydrides

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In connection with a reaction mechanism study, the organolithium procedure followed by boronation with tri-*n*-butyl borate was satisfactorily employed to prepare a series of known boronic acids and anhydrides[1] and the new ones reported herein.

Except for *o*-trifluoromethylbenzeneboronic acid and its anhydride, these compounds are analogs or isomers of others described in another work,[2] reference to which should be made for general remarks on difficulties of purification and characterization. Unfortunately, no infrared spectral analysis was available to us: we regret the lack of such a facility for improving characterization of our compounds, and because of some discussion[3] on previous observations of one of us.[2]

Dehydration of acids to anhydrides, as it was pointed out,[2,3] in some cases is accomplished simply by moderate heating in anhydrous solvents, but sometimes does require temperatures over 100°.[4] The application of vacuum, even in the presence of dehydrating agents, in our experience was seldom effective.

Another striking example of the influence of substituents on ease of dehydration is offered by the comparison of the two isomeric hydroxybromobenzeneboronic anhydrides reported herein: they both have a bromine atom in the *meta* position with respect to the borono group, but whereas the one brominated *para* to the hydroxyl required a long time of heating above 100° to be obtained from the acid, the other one with bromine *ortho* to hydroxyl is so much more stable that the acid could not even be detected in the product crystallized from water. A hydroxyl *ortho* to the borono group is known to favor stabilization of the anhydride, as compared with the unsubstituted benzeneboronic compound[5]: apparently, the disturbing action of bromine is neutralized when this substituent is *ortho* to the hydroxy group, possibly by hydrogen-bonding.

The only other trifluoromethyl derivative of a boronic acid hitherto reported appears to be the *m*-

(1) L. Santucci, *Boll. Ist. patol. libro*, **20**, 123 (1961).

(2) L. Santucci and H. Gilman, *J. Am. Chem. Soc.*, **80**, 193 (1958).

(3) H. R. Snyder, M. S. Konecky, and W. J. Lennarz, *J. Am. Chem. Soc.*, **80**, 3611 (1958).

(4) See also H. G. Kuivila and A. R. Hendrickson, *J. Am. Chem. Soc.*, **74**, 5068 (1952).

(5) H. Gilman, L. Santucci, D. R. Swayampati, and R. O. Ranck, *J. Am. Chem. Soc.*, **79**, 3077 (1957).

trifluoromethylbenzeneboronic anhydride.[6] The *ortho* isomer we obtained was probably contaminated by the former when crude, according to the literature description[7] of the isolation of carboxylic analogs obtained by metalation and carbonation of the same starting compound, but we made no attempt to isolate it. One noteworthy property of our compound is its remarkable water solubility.

The proof of structure depended on characterization of the corresponding aryllithium compounds, obtained by carbonation of the metalation mixtures.

Experimental

Melting points are uncorrected, and were usually obtained with a bath pre-heated to within 5–15° of the melting temperature, applying heat very slowly: in the case of *o*-trifluoromethylbenzeneboronic acid, however, it was necessary to introduce the capillary tube no more than 1° below melting. All reactions were carried out under a dry, oxygen-free nitrogen atmosphere, and employed ether dried over sodium. The *n*-butyllithium reagent was always prepared according to literature procedures.[8] For the neutralization equivalents, the samples were dissolved in 50% ethanol (except for *o*-trifluoromethylbenzeneboronic acid and anhydride, which could be easily dissolved in water) containing twenty times the sample weight of D-mannitol, and the titration was carried out with standard sodium hydroxide using phenolphthalein to detect the end point.

2-Phenoxy-5-bromobenzeneboronic Acid.—A mixture of 0.026 mole of *n*-butyllithium and 13.0 g. (0.052 mole) of *p*-bromodiphenyl ether in 25 ml. of ether was stirred for 16 hr. at room temperature,[9] and then added very slowly to a stirred solution of 12.0 g. (0.052 mole) of tri-*n*-butyl borate in 15 ml. of ether, previously cooled to −70° by means of a Dry Ice–acetone bath. After 2 hr. at the low temperature, the mixture was allowed to warm to 0° and hydrolyzed with 10% hydrochloric acid. The aqueous layer was separated from the ether and washed four times with fresh ether. The combined ether layers were extracted with 8% sodium hydroxide, but no precipitation occurred upon acidification of the alkaline extracts. The ether solution was then dried and evaporated, thus obtaining 2.5 g. of a residue that was dissolved in water and precipitated by acidification. This yielded 1.03 g. of a boron- and bromine-containing material, which melted at 106–113°, corresponding to a 13% yield based on *n*-butyllithium. Recrystallization from petroleum ether (b.p. 60–80°) gave 0.78 g. of product, m.p. 108–113°. After two additional recrystallizations from 4:1 water–acetone mixture the melting point was 108–110°.

Anal. Calcd. for $C_{12}H_{10}BBrO_3$: C, 49.21; H, 3.44; neut. equiv., 292.83. Found: C, 48.77; H, 3.53; neut. equiv., 296.3.

2-Methoxy-5-bromobenzeneboronic Anhydride.—This anhydride of a previously reported acid[2] was obtained by heating the latter less than 2 hr. at 115–120°, and had a melting point of 176–179°. It should be noted that this compound, presumably owing to volatilization, did not attain constant weight even within 15 hr. of heating, although melting point and neutralization equivalent remained unchanged throughout. Heating at lower temperatures under water vacuum and in the presence of phosphorus pentoxide did not prove to be an equally efficient procedure.

Anal. Calcd. for $C_7H_6BBrO_2$: neut. equiv., 212.87. Found: neut. equiv., 209.4.

2-Hydroxy-5-bromobenzeneboronic Anhydride.—Dehydration of the previously reported acid[2] was accomplished after 34 hr. of heating at 95–110° or 15 hr. at 115–120°: different combinations of lower temperatures, vacuum, and dehydrants were all ineffective. The anhydride melted at 323–325°.

Anal. Calcd. for $C_6H_4BBrO_2$: neut. equiv., 198.86. Found: neut. equiv., 195.0, 200.1.

2-Hydroxy-5-chlorobenzeneboronic Acid.—To a stirred solution of 14.5 g. (0.068 mole) of 2-(*p*-chlorophenoxy)tetrahydropyran[9] in 60 ml. of ether, 0.10 mole of *n*-butyllithium in 70 ml. of ether was added at room temperature over 25 min. The mixture was stirred for another 30 min., then added slowly to a solution of 31.6 g. (0.137 mole) of tri-*n*-butyl borate in 40 ml. of ether while cooling at −70°. After stirring for 3 hr., the reaction mixture was permitted to warm to 0° and hydrolyzed with 10% hydrochloric acid. The ether layer was separated from the aqueous layer, the latter being washed twice with 50-ml. portions of fresh ether which were combined with the main portion, and extracted with 8% sodium hydroxide. Some water had to be added to the alkaline extracts in order to dissolve a solid which had precipitated, then the solution was acidified with 10% hydrochloric acid and the material obtained recrystallized from a 3:1 water–acetone mixture: there was obtained 5.8 g. (63.4%) of a crude material melting over the range 143–180°. Three additional recrystallizations from ethylene chloride gave a final 2.29 g. of white crystals melting at 185–188°. This represents a 36% yield of pure 2-hydroxy-5-chlorobenzeneboronic acid.

Anal. Calcd. for $C_6H_6BClO_3$: neut. equiv., 172.38. Found: neut. equiv., 173.1, 172.6.

2-Hydroxy-5-chlorobenzeneboronic Anhydride.—The anhydride was obtained by heating the acid in an oven at 115–120° to constant weight, which was attained in about 5 hr. The loss in weight corresponded to that expected for the transition of acid to anhydride, and the melting point was raised to 333–337°. No loss in weight was observed after keeping the sample under water vacuum and in the presence of phosphorus pentoxide for periods up to 60 hr. at room temperature.

Anal. Calcd. for $C_6H_4BClO_2$: C, 46.68; H, 2.61; neut. equiv., 154.37. Found: C, 47.91; H, 2.42; neut. equiv., 152.2, 153.6, 153.4.

2-Hydroxy-3-bromobenzeneboronic Anhydride.—A 0.02-mole sample of *n*-butyllithium in 15 ml. of ether were added as fast as possible to a stirred solution of 2.52 g. (0.01 mole) of 2,6-dibromophenol in 40 ml. of ether kept at −18° by means of a salt–ice bath,[9] then the reaction mixture was immediately chilled with a Dry Ice–acetone bath and siphoned over 30 min. into a stirred solution of 6.80 g. (0.03 mole) of tri-*n*-butyl borate in 10 ml. of ether maintained at −70°. After standing overnight at this temperature, the mixture was warmed to 0° and hydrolyzed with 8% hydrochloric acid. The strongly acidic aqueous layer was separated from the ether and washed with fresh ether, which was combined with the main portion. The whole was extracted with 70 ml. of 15% sodium carbonate in nine portions, then the alkaline extract was made strongly acidic with 8% hydrochloric acid and extracted with fresh ether. Upon evaporation of the ether, 0.68 g. (31%) of material melting over the range 150–170° was obtained. This was recrystallized from ethylene chloride, yielding 0.29 g. (9.3%) of crystals melting at 187.5–191°. Another two recrystallizations from the same solvent raised the melting point to 213–214°.

The original ether layer was also extracted with 8% sodium hydroxide, and subsequently evaporated. These two operations yielded an over-all amount of 0.46 g. of oily material, from which no crystalline product could be obtained. In another experiment using the same amounts, the carbonate extract was acidified without extracting with ether, and

(6) K. V. Nahabedian and H. G. Kuivila, *J. Am. Chem. Soc.*, **83**, 2167 (1961).

(7) J. D. Roberts and D. Y. Curtin, *J. Am. Chem. Soc.*, **68**, 1658 (1946).

(8) R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 339 (1951). H. H. Gilman and J. W. Morton, Jr., *Org. Reactions*, **8**, 258 (1954).

(9) L. Santucci, L. Tavoletti, and D. Montalbano, *Ricerca Sci.*, in press.

0.62 g. of precipitate was obtained, with a melting range of 135–180°. One recrystallization from ethylene chloride yielded 9% of product melting at 205–208°.

The product recrystallized three times from ethylene chloride was used as an analytical sample and dried for 1.5 hr. at 108°, which did not affect the weight or the melting point. Neutralization equivalent and elementary contents suggested formulation as an anhydride. An attempt was made to obtain the acid by recrystallization from acetone and water, in the ratio of 1 ml. of acetone and 3.5 ml. of water per 0.1 g. of product, followed by drying at room temperature in the open for 3 hr.: however, although the melting point decreased to 194–195°, the neutralization equivalent remained unchanged.

Anal. Calcd. for $C_6H_4BBrO_2$: C, 36.23; H, 2.03; Br, 40.19; neut. equiv., 198.86. Found: C, 36.02; H, 2.26; Br, 40.34; neut. equiv., 199.0; 195.8, 196.2.

o-Trifluoromethylbenzeneboronic Acid.—To a stirred solution of 23.0 g. (0.10 mole) of tri-*n*-butyl borate in 20 ml. of ether 0.05 mole of *o*-trifluoromethylphenyllithium, prepared by refluxing equimolar amounts of α,α,α-trifluorotoluene and *n*-butyllithium for 6 hr.,[7] was added slowly while cooling at −70°. The mixture was left overnight at this temperature, then hydrolyzed with 30 ml. of 8% hydrochloric acid, and the ether layer extracted with 50 ml. of 15% sodium carbonate and 60 ml. of 8% sodium hydroxide in five portions. Upon acidification to pH 3 and subsequent extraction with ether, the carbonate extracts did not yield any significant amount of product, whereas 4.60 g. (48.5%) of a crystalline material, melting range 50–85°, was obtained from the sodium hydroxide solution. It is worth noting that the etheral extraction of the carefully acidified solution was particularly necessary in this case, since the precipitate was small and appeared to be soluble in excess acid. The crude material was recrystallized from petroleum ether (b.p. 60–80°), to yield 1.80 g. (19%) of crystals melting at 86–94°. Another recrystallization from the same solvent and then from ethylene chloride raised the melting point to 106–107°.

In another experiment, employing the same amounts, the reaction mixture was hydrolyzed with water and the ether layer evaporated to yield 4.54 g. of crude material. Another 0.20 g. was obtained by acidification and ether extraction of the aqueous layer. One recrystallization from petroleum ether yielded a 16% of product melting at 92–98.5°.

Anal. Calcd. for $C_7H_6BF_3O_2$: neut. equiv., 189.95. Found: neut. equiv., 187.2.

o-Trifluoromethylbenzeneboronic Anhydride.—The anhydride was obtained by recrystallizing the acid twice from anhydrous ethylene chloride, and had a melting point of 136.5–141°. Heating at 108° for over 1 hr. failed to attain a constant weight, but the melting point and neutralization equivalent were practically unaffected.

Anal. Calcd. for $C_7H_4BF_3O$: C, 48.89; H, 2.35; F, 33.15; neut. equiv., 171.94. Found: C, 48.95; H, 2.66; F, 32.75; neut. equiv., 172.5.

Grignard Route to 4,4′-Dichlorobenzophenone

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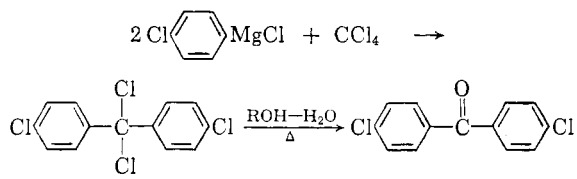
Literature references to the reaction of Grignard reagents with carbon tetrachloride are relatively few. Binaghi[2] isolated triphenylmethyl peroxide, hexaphenylethane, and triphenylcarbinol from the reaction of carbon tetrachloride with phenylmagnesium bromide. Kinney and Spliethoff[3] obtained 1,1,1-trichloropentane from the reaction of butylmagnesium chloride with carbon tetrachloride.

Satisfactory yields of 4,4′-dichlorobenzophenone were obtained in our laboratory by the following sequence of reactions:



The Grignard reagent[4] was added to solutions of carbon tetrachloride in tetrahydrofuran, benzene, pentane–benzene, and toluene over wide temperature ranges without gross differences in yield. Thickening was observed with hydrocarbon solvents. Extensions of the above reaction are under investigation.

Experimental

To a solution of 34 g. (0.222 mole) of carbon tetrachloride in 200 ml. of tetrahydrofuran was added 0.45 mole of *p*-chlorophenylmagnesium chloride[4] over a period of 30 min. with vigorous stirring. The temperature was maintained at 10° utilizing a Dry Ice–acetone bath. The reaction mixture was stirred for 30 min. and then hydrolyzed by the cautious addition of 150 ml. of 10% sulfuric acid at room temperature. The organic phase was separated and the aqueous phase was extracted twice with 100-ml. portions of diethyl ether. Solvents were distilled from the combined organic fractions under reduced pressure leaving a dark brown residue. Hydrolysis of the intermediate 4,4′-dichlorobenzophenone dichloride was effected by adding the residue to 300 ml. of 50% ethanol and refluxing the mixture for 90 min. with stirring. Following cooling to room temperature and decantation of the liquid portion, the tan product was slurried with 100 ml. of petroleum ether. The crude ketone was then filtered and washed with petroleum ether. A crude yield of 23.0g. (41%) melting at ca. 134° was obtained. Recrystallization from absolute ethanol gave white plates melting at 149–150°. Recrystallization from isomeric heptanes did not change the melting point. Admixture with authentic 4,4′-dichlorophenzophenone showed no depression. The 2,4-dinitrophenylhydrazone melted at 237.5–239.5° (lit.,[5] m.p. 238–240°).

(1) Present address: Esso Research & Engineering Co. Research Center, Linden, N. J.

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Synthesis of *N*-(1-Hydroxy-2-fluorenyl-1-C^{14})-acetamide with a High Specific Activity[1]

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Previous work[2-4] has implicated the metabolite *N*-(1-hydroxy-2-fluorenyl)acetamide in a series of reactions resulting in the protein binding of the carcinogen *N*-2-fluorenylacetamide *in vitro*. In connection with further studies concerned with the metabolism and mechanism of action of *N*-2-fluorenylacetamide, carbon-14 ring-labeled *N*-(1-hydroxy-2-fluorenyl)acetamide with a high specific activity was desired.

A chemical synthesis utilizing potassium cyanide-C^{14} for the introduction of carbon-14 into the fluorene nucleus in a route to *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide has been reported by Morgan and Gutmann. The preparation[5] involved treatment of 3-(3-indenyl)propyl bromide with potassium cyanide-C^{14} to give 4-(3-indenyl)butyronitrile-1-C^{14} and cyclization of the nitrile to 1,2,3,4-tetrahydrofluoren-1-one-1-C^{14}. The carbon-14 labeled ketone was dehydrogenated yielding 1-hydroxyfluorene-1-C^{14}, which was converted to *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide in four steps.

In the present paper, a modification of this synthesis, which is more economical than that reported previously, is presented. The major modification is in the use of barium carbonate-C^{14} instead of potassium cyanide-C^{14} for the introduction of the radioactivity. Barium carbonate-C^{14} is available commercially at less than one sixth the cost of potassium cyanide-C^{14} per millicurie of radioactivity.

The Grignard reagent prepared from 3-(3-indenyl)propyl bromide[6] was carbonated with carbon-C^{14} dioxide generated from barium carbonate-C^{14}. Ring closure of the resulting 4-(3-indenyl)butyric-1-C^{14} acid was accomplished with anhydrous hydrogen fluoride yielding 1,2,3,4-tetrahydrofluoren-1-one-1-C^{14}. The radioactive yield from the barium carbonate to the tetrahydrofluorenone was 61% compared to a yield of 42% from the potassium cyanide to the ketone in the previous synthesis.[5] The labeled ketone was converted to *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide in four steps using slight modifications of published methods as indicated below. The over-all radioactive yield from barium carbonate to *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide, having a specific radioactivity of 4.99 millicuries per mmole was 10.6%. Morgan and Gutmann obtained a yield of 5.1%, and the product had a specific radioactivity of 0.66 millicurie per mmole.

Experimental

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Radioactivity measurements were made using a Tri Carb liquid scintillation spectrometer.

4-(3-Indenyl)butyric-1-C^{14} Acid.—3-(3-Indenyl)propylmagnesium bromide was prepared from 0.54 g. (22 mmoles) of magnesium and 4.8 g. (20 mmoles) of freshly redistilled 3-(3-indenyl)propyl bromide[6] (b.p. 130°/0.4 mm., $n^{28}D$, 1.5870) in 30 ml. of anhydrous ether under an atmosphere of dry nitrogen. After stirring and refluxing for 3 hr. the reaction mixture was cooled to room temperature and an aliquot was removed for titration. The mixture contained 0.48 mmole of Grignard reagent per ml. At once, 11.5 ml. of the solution, containing 5.5 mmoles of Grignard reagent, was transferred to a carbonation flask containing 10 ml. of anhydrous benzene in an atmosphere of dry nitrogen. Carbonation was carried out at −5° at a pressure of 0.2 mm. in an apparatus similar to that described by Gutmann *et al.*[7] Carbon-C^{14} dioxide was generated by addition of concd. sulfuric acid to barium carbonate-C^{14} (0.987 g., 5.01 mmoles; 25.4 mc.). After standing at room temperature for several hours, 10 ml. of 10% hydrochloric acid was added to the carbonation reaction mixture with stirring. The ether layer was washed with 5 ml. of water and extracted twice with 2 *N* sodium hydroxide. The sodium hydroxide extracts (25 ml. total) were combined and warmed to remove ether. Activated charcoal was added to the warm solution, which was then filtered through Celite. The filtrate was cooled and acidified with concd. hydrochloric acid. After standing at 4° overnight, the product was collected, washed with water, and dried *in vacuo* over phosphoric anhydride. The yield was 0.922 g. (4.56 mmoles, 91%) of 4-(3-indenyl)-butyric-1-C^{14} acid, m.p. 88–92°. The indenylbutyric acid could be recrystallized from petroleum ether (b.p. 90–100°) but was used without purification for the next reaction step. In some nonradioactive preparations, the melting point of the recrystallized product mixed with authentic 4-(3-indenyl)butyric acid,[6] m.p. 90–92° (reported[6] m.p. 91–93°), was not depressed.

1,2,3,4-Tetrahydrofluoren-1-one-1-C^{14}.—4-(3-Indenyl)-butyric-1-C^{14} acid (0.922 g., 4.56 mmoles) was dissolved in 5–6 ml. of anhydrous hydrogen fluoride, and the solution was allowed to stand overnight at room temperature in a closed 15-ml. polypropylene centrifuge tube. The hydrogen fluoride was evaporated, and the residue was taken up in 25 ml. of ether. The ether solution was washed with 10% sodium carbonate and then with water. Evaporation of the ether under a stream of nitrogen gave 0.560 g. (3.04 mmoles, 67% yield) of 1,2,3,4-tetrahydrofluoren-1-one-1-C^{14}, m.p. 101–105°, after drying *in vacuo* over phosphoric anhydride. Recrystallization of the crude product in some nonradioactive preparations gave pure 1,2,3,4-tetrahydrofluoren-1-one, m.p. 105° (reported[6] m.p. 104–106°) which showed no depression in melting point when mixed with authentic 1,2,3,4-tetrahydrofluoren-1-one.[6] The yield of crude tetrahydrofluorenone was markedly dependent upon the purity of the 4-(3-indenyl)butyric acid used as starting material. In nonradioactive runs using recrystallized indenylbutyric acid, the yield of crude ketone was 90–95%.

(1) This investigation was supported in part by a grant (C5490) from the National Cancer Institute, U. S. Public Health Service.

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1-Hydroxyfluorene-1-C^{14}.—1,2,3,4-Tetrahydrofluoren-1-one-1-C^{14} (0.560 g., 3.04 mmoles) was dehydrogenated according to the method described by Morgan and Gutmann,[5] except dichloromethane instead of ether was used in the extraction of the crude reaction mixture. There was obtained 0.414 g. (2.27 mmoles, 75% yield) of 1-hydroxyfluorene-1-C^{14}.

1-Hydroxy-2-nitrofluorene-1-C^{14}.—1-Hydroxyfluorene-1-C^{14} (0.414 g., 2.27 mmoles) was nitrated by the procedure reported by Weisburger and Weisburger.[8] Chromatography of the crude nitration product on alumina (Merck, acid-washed) gave 0.211 g. (0.93 mmole, 41% yield) of 1-hydroxy-2-nitrofluorene-1-C^{14}.

1-Hydroxy-2-aminofluorene-1-C^{14} Hydrochloride.—1-Hydroxy-2-nitrofluorene-1-C^{14} (0.211 g., 0.93 mmole) was reduced[8] with zinc dust. The hot reaction mixture was filtered through Celite into 1.9 ml. of concd. hydrochloric acid, and the zinc was washed with ethanol. The filtrate and washings were combined and the ethanol was removed under reduced pressure at 40°. The mixture was then cooled in an ice bath, and the product was transferred to a sintered glass funnel with the aid of a small volume of ice-cold concd. hydrochloric acid. After drying *in vacuo* over potassium hydroxide, there was obtained 0.159 g. (0.68 mmole, 73%) of 1-hydroxy-2-aminofluorene-1-C^{14} hydrochloride.

***N*-(1-Hydroxy-2-fluorenyl-1-C^{14})acetamide.**—The hydrochloride of 1-hydroxy-2-aminofluorene-1-C^{14} (0.159 g., 0.68 mmole) was acetylated by the method of Weisburger and Weisburger,[8] yielding 0.160 g. (0.67 mmole, 99%) of crude *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide. Chromatography of the crude product on alumina (Merck, acid-washed) with ethyl acetate as eluent, followed by recrystallization from dilute ethanol, gave 0.126 g. (0.529 mmole, 78% yield) of *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide as white needles, m.p. 211–212° (reported[8] m.p. 208°), after drying *in vacuo* at 78° over phosphoric anhydride. The specific radioactivity of the *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide was 4.99 mc. per mmole.

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Asymmetric Synthesis of (+)-Bicyclo[2.2.2]-octanol-2[1]

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Brown and Zweifel[2] have recently reported that they obtained nearly complete asymmetric stereoselectivity[3] by the addition of diisopinocampheylborane to various olefines. This remarkable achievement prompted us to apply this method to the synthesis of optically active bicyclo[2.2.2]-octanol-2.

We wish to report that the addition of diisopinocampheylborane (from (−)-α-pinene) to bicyclo-[2.2.2]octene-2 produced *S*-(+)-bicyclo [2.2.2]-octanol,[4] m.p. 214–217°, $[\alpha]^{25}D$ +6.9° (*c* 2.37, chloroform).

Based on the known absolute configuration[5] of (−)-α-pinene and by the application of the Prelog-Cram rule[6] one would predict the *R* configuration for the resulting alcohol. This was not found to be the case and is therefore inconsistent with the absolute configurational assignment of *S*-(+)-bicyclo[2.2.2]octanol-2 which has been determined by a different method.[4]

Experimental[7]

***S*-(+)-Bicyclo[2.2.2]octanol-2.**—To a solution of 3.12 g. (0.083 mole) of sodium borohydride in 75 cc. of anhydrous diglyme was added 27.2 g. of α-pinene,[8] $[\alpha]^{25}D$ −47.88. The solution was cooled to 0° and while under an atmosphere of argon 14.2 g. of freshly distilled boron trifluoride-etherate was added at a rate which maintained the temperature between 0–5°. The mixture was stirred for an additional hour at 0–2° and then 10.4 g. (0.1 mole) of bicyclo[2.2.2]-octane-2[9] was added. Stirring was continued for 4 hr. at 0–2° and finally at room temperature for 12 hr.

The reaction mixture was hydrolyzed by the addition of water, 31 cc. of 3 *N* sodium hydroxide and finally, 31 cc. of 30% hydrogen peroxide at a sufficient rate so that the temperature of the solution was kept between 30–35°. The reaction mixture was extracted with pentane, and the extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed and the residue distilled at 85 mm. to yield 3.55 g. of material, b.p. 60–75°. Fractional sublimation of the waxy product gave fractions, the specific rotations of which varied from +6 to +7°. Recrystallization of the sublimed material from pentane yielded 2.61 g. of bicyclo[2.2.2]octanol-2, m.p. 214–217° (s.t.), $[\alpha]^{28}D$ +6.9° (*c* 2.32, chloroform), the infrared spectrum of which was identical with that of an authentic sample. Vapor phase chromatography showed that the sample was not contaminated with isopinocampheol. Recrystallization of the residue from the above distillation yielded an additional 1.04 g. of alcohol, $[\alpha]^{28}D$ +6.3° (*c* 2.15, chloroform) making the total yield of alcohol 30%.

(1) This work was supported by a Research Grant CY-4065, National Institute of Health, Public Health Service.

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Some Free Radical-Catalyzed Additions of Perfluoroalkyl Iodides to Olefins

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The free radical-catalyzed addition of one- and two-carbon perhaloalkyl iodides to simple olefins has been investigated extensively, principally

by Haszeldine.[1] The work presently reported demonstrates that this synthetic method can be extended successfully by use of longer-chain perfluoroalkyl iodides and by functional substitution in the olefin.

Organic peroxides and azobisnitriles are known as highly effective initiators for free radical additions. However, for this investigation ultraviolet irradiation was employed, in order not to introduce minor amounts of side products derived from the initiator; it could be anticipated that the high-boiling desired products might thus be more readily purified. The penalty one pays for this choice is that there is a progressive loss of effective radiation, resulting in incomplete reaction. Reasons for this are that the reaction mixtures tend to darken during the run, and also that the ultraviolet absorption maxima of the products lie only *ca.* 50 Å to shorter wavelengths than that of the starting compound, *n*-perfluoroheptyl iodide. Inasmuch as the relatively low-boiling starting materials were, as expected, readily separable from the desired products, such behavior was here of little concern. For the preparation of the easily distillable adduct of n-C_3F_7I to isobutene, benzoyl peroxide was employed and the reaction proceeded to completion. In a similar addition of dibromodifluoromethane to isobutene an error in the literature was uncovered.

The adducts of perfluoroalkyl iodides to olefins are known to be readily dehydrohalogenated by bases.[2] Some semiquantitative information is given to illustrate the reactivity of the higher molecular weight adducts prepared in this investigation.

Experimental

Materials.—The perfluoro-*n*-heptyl iodide was prepared as has been described.[3] It had $n^{25}D$ 1.3339, not 1.3274 as erroneously given;[3] its ultraviolet absorption spectrum (4.0 mg./ml. isooctane) had λ_{max} 2720 Å, ϵ_{max} 282, and band width at half-height, $W_{1/2}$ 6300 cm.$^{-1}$. Preparation and properties of perfluoro-*n*-propyl iodide have been presented.[4] Octene-1 and octadecene-1 were obtained from the Connecticut Hard Rubber Co., undecylenic acid from the Baker Castor Oil Co., and vinylmethyldiethoxysilane from the Linde Air Products Co. All were vacuum distilled before use, and had $n^{25}D$ 1.4060, 1.4425, 1.4475, and 1.3973, respectively.

1-Perfluoroheptyl-2-iodooctane.—In a stoppered 50-ml. Pyrex test tube equipped with 6-mm. i.d. air condenser was placed n-$C_7F_{15}I$, 20.0 g. (0.04 mole) and octene-1, 4.50 g. (0.04 mole). The reaction mixture was externally irradiated for 15 hr. by an unfiltered "Hanovia" quartz-mercury arc lamp placed at a distance of 6 in. from the test tube. Upon fractional distillation of the mixture the desired adduct, n-$C_7F_{15}CH_2CHIC_6H_{13}$, b.p. 156°/20 mm. $n^{25}D$ 1.3846, was obtained in 87% yield, as calculated on the basis of "conversion," 60% (*i.e.*, $C_7F_{15}I$ not recovered).

Anal. Calcd. for $C_{15}H_{16}F_{15}I$: C, 29.62, F, 46.86; I, 20.87. Found: C, 29.8; F, 46.8; I, 20.8.

Its ultraviolet spectrum in isooctane had λ_{max} 2663 Å, ϵ_{max} 483 and $W_{1/2}$ 5050 cm.$^{-1}$.

1-Perfluoroheptyl-2-iodooctadecane.—Octadecene-1, 0.03 mole, and n-$C_7F_{15}I$, 0.03 mole, were treated as above. The adduct, n-$C_7F_{15}CH_2CHIC_{16}H_{33}$, isolated by vacuum distillation, had b.p. 170–200°/0.01 mm. and $n^{25}D$ 1.4107. The yield was 93%, based on 71% conversion of n-$C_7F_{15}I$.

Anal. Calcd. for $C_{25}H_{36}F_{15}I$: I, 16.96. Found: I, 16.7.

10-Iodo-11-perfluoroheptylhendecanoic Acid.—From undecylenic acid, 0.03 mole, and n-$C_7F_{15}I$, 0.03 mole, the above-described procedure gave n-$C_7F_{15}CH_2CHI(CH_2)_8CO_2H$, b.p. 190–240°/0.01 mm. m.p. 50–51°, (recryst. from cyclo-$C_8F_{16}O$) in a yield of 73% based upon 44% conversion of n-$C_7F_{15}I$.

Anal. Calcd. for $C_{18}H_{20}F_{15}IO_2$: C, 31.78; F, 41.90; I, 18.66. Found: C, 31.8; F, 42.1; I, 18.2.

2,2-Diethoxy-3-iodo-4-perfluoroheptyl-2-silabutane.—Vinylmethyldiethoxysilane, 0.04 mole, and n-$C_7F_{15}I$, 0.04 mole, treated in the above fashion, produced $C_7F_{15}CH_2CHISi(CH_3)(OC_2H_5)_2$, b.p. 150°/20 mm., $n^{25}D$ 1.3795, the yield being 62% based on 37% conversion of n-$C_7F_{15}I$.

Anal. Calcd. for $C_{14}H_{16}F_{15}IO_2Si$: C, 25.66; F, 43.49; I, 19.37. Found: C, 25.5; F, 43.2; I, 19.15.

The ultraviolet spectrum in isooctane had λ_{max} 2685 Å, ϵ_{max} 484, $W_{1/2}$ 5500 cm.$^{-1}$.

1-Perfluoropropyl-2-iodo-2-methylpropane.—Isobutene, 5.7 g. (0.10 mole), n-C_3F_7I, 30.0 g. (0.10 mole), and benzoyl peroxide, 1.0 g., were treated for 6 hr. at 90° in a 43-ml. rocking autoclave. Upon fractional distillation of the product there was obtained n-$C_3F_7CH_2CI(CH_3)_2$, b.p. 63°/40 mm., $n^{25}D$ 1.3963, the yield being 91%, based upon 100% conversion of the perfluoropropyl iodide.

Anal. Calcd. for $C_7H_8F_7I$: C, 23.95; F, 37.60; I, 36.15. Found: C, 24.2; F, 37.9; I, 35.9.

Adduct of CF_2Br_2 to Isobutene.—This compound, $C_5H_8Br_2F_2$, was reported[5] to have $n^{25}D$ 1.4632. When prepared as above, except that ditertiary butyl peroxide was used and the reaction temperature was 140°, the adduct had b.p. 69°/40 mm., in excellent agreement with the literature value,[5] but had $n^{25}D$ 1.4527. Presumably a typographical error was responsible for the discrepancy. Although the cited reference[5] did not mention the formation of telomeric materials, it appears that appreciable 1:2 adduct was formed (about one-fifth as much as the simple adduct); it was not stable under the conditions of handling and eliminated hydrogen bromide. The resulting olefin was principally $BrCF_2CH_2C(CH_3)_2CH{=}C(CH_3)_2$, as indicated by the infrared spectrum. It had b.p. 93°/40 mm. and $n^{25}D$ 1.4414.

Anal. Calcd. for $C_9H_{15}BrF_2$: Br, 33.2. Found: Br, 32.4.

Dehydrohalogenation Studies.—Percentage dehydroiodination of the octene, octadecene, and vinylsilane adducts, measured *via* iodide ion liberated upon 1-hr. reflux in 90% ethanolic potassium bicarbonate (0.01 *M*) were, respectively, 61%, 39%, and 96%. When potassium carbonate was used, values for the latter two adducts were 68% and 99%. Upon treatment for 16 hr. at 25°, the vinylsilane adduct reacted to the extent of 92% with potassium carbonate, but less than 7% with potassium bicarbonate.

Acknowledgment.—I thank B. W. Nippoldt and R. R. Davis of our Analytical Section for, respectively, the elementary analyses and the dehydrohalogenation studies.

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The Structure of Commercial Pyronin B[1]

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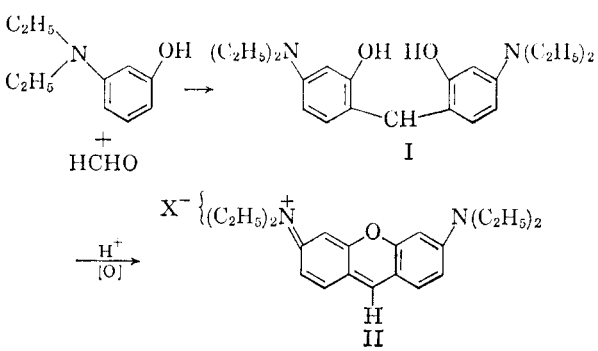
Pyronin B (Color Index 45010),[2] a xanthene dye, has been studied under a variety of circumstances: as a carcinogenic agent,[3a] as a mutagenic agent,[3b] and as a stain for bacteria, molds,[3c] and ribonucleic acids.[3d] Interest in Pyronin B in the cancer chemotherapy program of the National Institutes of Health required a pure sample of the dye as a standard and a crude commercial sample of the dye seemed like a logical source for this although the purification has not been described in the literature. Exploratory experiments indicated that commercial material could not be represented by the simple molecular structure (II) predicted by its synthesis.

Pyronin B is prepared from *meta-N,N*-diethylaminophenol and formaldehyde according to the following scheme.[4a,b]

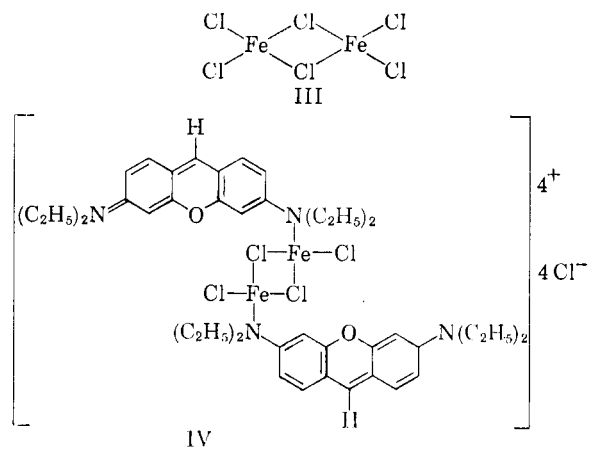


Combustion of a sample of the crude commercial dye gives an ash which is not due to adulteration by inorganic salts as washing with water did not change the ash content; spectrographic analysis indicated the ash was due to iron.

Paper strip electrophoresis in pH 2 buffer exhibits four colored components which migrate to the cathode. Examination of the strips in a recording densitometer showed absorption maxima for two of the spots in the 550-mμ region.

Dialysis against aqueous ethanol (1:1) separates the crude into two components. The nondialyzable material has an ultraviolet absorption maximum at 555 mμ ($E^{1\%}_{1\,cm.}$ 1219), but its solution in aqueous alcohol lacks the characteristic red fluorescence of Pyronin B and it was not examined further. Concentration of the dialysate gave material which had the typical red fluorescense in aqueous alcohol and had an ultraviolet absorption maximum at 542 mμ ($E^{1\%}_{1\,cm.}$ 951). Recrystallization of this latter material from ethyl acetate gives metallic green needles, $\lambda^{50\%\ alc.}_{max}$ 555 mμ, $E^{1\%}_{1\,cm.}$ 2300. The crystalline material on combustion gives an ash of 15.5%, consequently the product cannot be completely represented by structure II.

Biehringer[4] obtained the uncomplexed dye by performing the oxidation (I→II) with chloranil or nitrous acid. When he carried out the oxidation with stannic chloride, a tin complex of the dye was obtained. The iron in our material could originate from an oxidizing agent such as ferric chloride used in the commercial preparation of the dye.



Elemental analysis establishes the emperical formula as $C_{21}H_{27}N_2Cl_4OFe$, and indicates a Pyronin B molecule combined with ferric chloride. Polarography shows a strongly complexed trivalent Fe. Titration with base yields an equivalent weight of 134 (theory for replacement of four chloride ions is 130). Three equivalents of chloride ion are easily replaced by hydroxyl. A fourth equivalent can be replaced only above pH 10 where precipitation of ferric hydroxide indicates a breakup of the complex. That each iron has one chloride ion more strongly bound than the others suggests the bridged structure of Fe_2Cl_6 (III). A nitrogen in the Pyronin B nucleus could replace one of the chlorides around the iron. Since the crystal

(1) This work was done under Contract SA-43-ph-1948 with the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

(2) Color Index, 2nd ed., The American Association of Textile Chemists and Colorists, Lowell Technicological Institute, Lowell, Mass., Vol. 3, p. 3382 (1956).

(3) (a) R. Willheim and A. C. Ivy, *Gastroenterology*, **23**, 1 (1953); (b) B. C. Auerbach, *Am. Nat.*, **89**, 241 (1955); (c) F. Aiquel and F. J. Herrero, *Arch. Farm. y Bioquim. Tucuman*, **4**, 181 (1948); (d) B. Biswas, *Current Sci.*, **22**, 346 (1953), E. Taft, *Expt. Cell Research*, **2**, 312 (1951), L. Abolins, *Expt. Cell Research*, **3**, 1 (1952).

(4) (a) J. Biehringer, *Ber.*, **27**, 3299 (1894); (b) J. Biehringer, *J. Prakt. Chem.*, **54**, 217 (1896).

symmetry established by X-ray analysis requires the molecule to have a center of symmetry, two Pyronin B molecules would have to replace diagonally opposite chlorides in the iron dimer. On the basis of these data we propose the structure IV for Pyronin B. Symmetry and spatial considerations in the unit cell of the crystal eliminate all other chemically logical structures.

From the dialysis experiments, the differential solubility of the two major components of the crude dye in ethyl acetate suggested a simplified extraction procedure for the isolation of pure Pyronin B on a large scale. Extraction of 500 g. of crude dye in a Soxhlet extractor with ethyl acetate gave 120 g. of product which on re-extraction with ethyl acetate gave analytically pure Pyronin B, m.p. 176–178°, $\lambda_{max}^{50\%\ alc.}$ 555 mμ, $E_{1\ cm.}^{1\%}$ 2324. The purity by phase solubility is 99.8 ± 0.2%.

The absorption spectra of the dye was examined in 50% aqueous ethanol in a Beckmann DU spectrophotometer and a Cary recording spectrophotometer. It was found that solutions of the dye of concentrations greater than 10 mg./l. do no obey Beer's law. Principal absorption maximum is at 555 mμ with another at 521 mμ, and multiple absorption from 350 mμ to 210 mμ In addition, a fluorescent emission maximum appears at 580 mμ and an activation maximum at 530 mμ. These latter maxima give rise to erroneous results when measurements are made with the Beckmann DU spectrophotometer.

Experimental

Five hundred grams of commercial Pyronin B[5] was extracted in a Soxhlet extractor with 3-1. portions of ethyl acetate over a period of 14 days. The solvent was changed after the second, fifth, and ninth day. Each extract was worked up separately by concentrating to 500 ml., cooling in ice, filtering the product, washing with ether, and drying. In this way, 120 g. of product was obtained in four crops; 8 g. $\lambda_{max}^{50\%\ C_2H_5OH}$ 555 mμ, $E_{1\ cm.}^{1\%}$ 2185; 34 g. $\lambda_{max}^{50\%\ C_2H_5OH}$ 555 mμ $E_{1\ cm.}^{1\%}$ 2207; 51 g. $\lambda_{max}^{50\%\ C_2H_5OH}$ 555 mμ, $E_{1\ cm.}^{1\%}$ 2383; 27 g., $\lambda_{max}^{50\%\ C_2H_5OH}$ 555 mμ, $E_{1\ cm.}^{1\%}$ 2290.

The combined product was re-extracted with two 3-1. portions of ethyl acetate. The first extraction (7 days) was cooled in ice, filtered, and washed with ether to give 68 g. of metallic green needles, m.p. 176–177°; paper strip electrophoresis[6] (pH 2 buffer, 200 v.)—single spot; phase solubility—slope 1 ± 0.5; $\lambda_{max}^{50\%\ C_2H_5OH}$ 554 mμ, $E_{1\ cm.}^{1\%}$ 2428.

Anal. Calcd. for $C_{42}H_{54}N_4Cl_8O_2Fe_2$ (1,042.28): C, 48.40; H, 5.22; N, 5.38; Cl, 27.22. Found: C, 49.04; H, 5.35; N, 6.66; Cl, 27.33.

The second extraction (14 days) on cooling gave 39 g. of product as green metallic needles, m.p. 176–178°; paper strip electrophoresis (pH 2 buffer, 200 v.)—single spot; phase solubility–slope 0.2 ± 0.2; $\lambda_{max}^{50\%\ C_2H_5OH}$ 555 mμ, $E_{1\ cm.}^{1\%}$ 2324.

Anal. Calcd. for $C_{42}H_{54}N_4Cl_8O_2Fe_2$ (1,042.28): C, 48.40; H, 5.22; N, 5.38; Cl, 27.22; Fe, 10.71. Found: C, 48.60; H, 5.13; N, 5.85; Cl, 27.60; Fe, 10.86.

(5) National Aniline Division of Allied Chemical and Dye Corp. certified dye content 34%.

(6) Spinco Model RB, Durrum type.

Polarographic Analyses.—The half wave potential was determined on a Leeds and Northrup Electrochemograph Type E in 0.2 *M* potassium oxalate containing 0.004% gelatin against a saturated calomel electrode, $E_{1/2}$—0.25 V., i.d.—13.1 μA/mg. of iron added as Pyronin B, a standard Fe(III) solution under the same conditions, gave $E_{1/2}$—0.25V and i.d.—15.1 μA./mg. of iron.

X-Ray Diffraction.—Pyronin B crystallizes as needles, elongated along the *a* axis and developing the {010} and {011} forms. The ends of the needles are normally fractures rather than crystal faces. The crystals are quite opaque, being metallic green by reflected light. Observations on very thin crystals show them to be red by transmitted light.

The unit cell dimensions were determined from rotation and Weissenberg photographs around the *a* and *c* axes. The density was measured by floatation. Monoclinic, a = 9.00, b = 20.84, C = 13.66, B = 108°. Volume of the unit cell = 2562 Å.^{3}. Density calculated = 1.421, measured = 1.398. Systematic absences: *hol* for odd indices of *l*, and *oho* for odd indices, space group $P2_1/c$.

Acknowledgment.—The authors are indebted to Mr. James Wittig for the potentiometric titrations and the solubility analyses; to Mr. R.. N. Boos and his staff for the analytical data.

5-Pyrimidinecarboxylic Acid and Some of Its Derivatives

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The chemical literature seems to be devoid of suitable methods for the preparation of relatively large amounts of simple pyrimidines bearing a carboxy group or its derivative at position 5. In 1904 Gabriel and Colman[1] obtained a small amount of 5-pyrimidinecarboxylic acid during the course of degradative studies on quinazoline. Boarland and McOmie[2] converted this acid to the corresponding amide and methyl ester. Smith and Christensen[3] obtained the compound in 29% yield from the catalytic dehalogenation of 2,4-dichloro-5-pyrimidinecarboxylic acid ethyl ester using a palladium-carbon catalyst in an aqueous sodium hydroxide–ether system.

In our hands the ester was obtained in 60% yield by a modification of the Smith-Christensen procedure and was subsequently hydrolyzed to afford 5-pyrimidinecarboxylic acid. The acid was converted, *via* the acid chloride, to some amides whose counterpart in the pyridine series had been shown to possess biological activities. For example, treatment of a crude, ethereal solution of the acid chloride with diethylamine gave the *N*,*N*-diethylamide, analogous to "Coramine." A similar re-

(1) S. Gabriel and J. Colman, *Ber.*, **37**, 3643 (1904).

(2) M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 1218 (1951).

(3) V. H. Smith and B. E. Christensen, *J. Org. Chem.*, **20**, 829 (1955).

action with *N,N*-diethylethylenediamine gave *N*-(2 - diethylaminoethyl) - 5 - pyrimidinecarboxamide, while the action of ammonia yielded 5-pyrimidinecarboxylic acid amide, resembling niacin.

Success in the dehalogenation of 2,4-dichloro-5-pyrimidinecarboxylic acid ester prompted attempts to extend this reaction to prepare 5-pyrimidinecarbonitrile from the corresponding dihalocyanopyrimidine. However, the hydrogenolysis of this compound, under conditions comparable to the ones employed in the reduction of the carbethoxy analog afforded 5-pyrimidinecarbonitrile in only 9% yield. This same nitrile could also be prepared by the dehydration of the carboxamide by means of phosphorus pentoxide. Furthermore the cyanopyrimidine was found to undergo hydrogen sulfide addition to give 5-pyrimidinethiocarboxamide.

Experimental

5-Pyrimidinecarboxylic Acid, Ethyl Ester.—A mixture of 125 g. (0.568 mole) of 2,4-dichloro-5-pyrimidinecarboxylic acid ester[3] in 1250 ml. of isopropyl alcohol was hydrogenated on a Parr shaker at 15.5 p.s.i. in the presence of 40 g. of calcium oxide and 5 g. of 5% palladium-on-carbon. Only a slight increase in temperature was noted in a run of this size, and the theoretical amount of hydrogen was absorbed after 3 hr. The solids were then filtered off and washed with several portions of fresh isopropyl alcohol. Stripping the filtrate of solvent *in vacuo* left a residue consisting of calcium chloride and product. Ether (500 ml.) was added to this mixture and the inorganic salts were removed by three washings with a minimum of ice-cold water. The organic phase was dried over sodium sulfate, and the solvent was subsequently removed. Very rapid vacuum distillation of the residual oil yielded 54 g. (63%) of crude carbethoxypyrimidine boiling at 80–85°/0.3 mm. which was collected in an ice-cooled receiver. The distillation was terminated when decomposition of the pot residue set in accompanied by the evolution of gases. Refractionation of the crude distillate through a Vigreux column gave 51 g. of pure 5-pyrimidinecarboxylic acid, ethyl ester, b.p. 102.5–103.5°/12 mm. The compound solidified when cooled on ice and melted at 16°. The yield of pure material was 60%.

Anal. Calcd. for $C_7H_8N_2O_2$: N, 18.42. Found: N, 18.15.

5-Pyrimidinecarboxylic Acid.—To 11.5 g. (0.758 mole) of the ester was added 40 ml. (0.080 mole) of 2 *N* sodium hydroxide solution. A mildly exothermic reaction set in, causing the temperature to rise to 50° as the oil went into solution. After a few minutes one equivalent of 1 *N* hydrochloric acid was added, causing immediate precipitation of the acid. The mixture was cooled and filtered to give 8.3 g. (88%) of product, melting at 268–270°. Lit. value: 268–270°.[3]

5-Pyrimidinecarboxylic Acid Chloride.—A mixture of 8.3 g. (0.067 mole) of the acid was refluxed in 50 ml. of reagent grade thionyl chloride until all the material had dissolved. The excess thionyl chloride was removed in vacuum. One equivalent of quinoline was added to the residue which was then distilled to yield 8.1 g. of acid chloride, boiling at 80–85°/3 mm. Atmospheric exposure caused this material to be instantaneously converted to a viscous gum, but it was quite stable if kept in tightly sealed containers. Analytical results were unsatisfactory.

***N*-(2-Diethylaminoethyl) - 5 - pyrimidinecarboxamide.**—A solution of purified 5-pyrimidinecarboxylic acid chloride (8.1 g., 0.056 mole) in 50 ml. reagent grade chloroform was added slowly to an ice-cold solution of 13.2 g. (0.114 mole) of *N,N*-diethylethylenediamine in 30 ml. chloroform. The reaction was allowed to proceed for several days at room temperature, and it was then poured on ice water containing 12 ml. (0.06 mole) of 5 *N* sodium hydroxide solution. The chloroform layer was separated and dried. Stripping of solvent followed by vacuum distillation of the residue yielded 5.5 g. of the amide as a yellow oil boiling at 145–150°/0.160 mm. This corresponds to a 44% yield.

Anal. Calcd. for $C_{11}H_{18}N_4O$: C, 59.43; H, 8.17. Found: C, 59.50; H, 8.51.

***N,N*-Diethyl-5-pyrimidinecarboxamide.**—A crude ethereal solution of 5-pyrimidinecarboxylic acid chloride was prepared by allowing 6.0 g. (0.0485 mole) of the acid to react with 30 ml. of thionyl chloride; the excess thionyl chloride was removed in vacuum and replaced with anhydrous ether.

This solution was added slowly to an ice-cold solution of 24 ml. of diethylamine in 150 ml. dry ether. After allowing the reaction mixture to stand for 1 hr. at room temperature, 3 g. of diethylamine hydrochloride was removed by filtration. The filtrate solvent was subsequently removed and the oily residue was subjected to vacuum distillation to yield 4.5 g. (52% yield) of a pale yellow oil, boiling at 108–113°/0.2 mm.

Anal. Calcd. for $C_9H_{13}N_3O$: N, 23.45. Found: N, 23.50, 23.30.

5-Pyrimidinecarboxamide.—This compound had been previously prepared "in low yield" by the action of aqueous ammonia upon the acid chloride.[2] An improved method is given below.

A crude solution of 5-pyrimidinecarboxylic acid chloride was prepared from 12 g. (0.097 mole) of the acid, as described above. This solution was added dropwise to ether previously saturated with excess gaseous ammonia. The solids, a mixture of product and ammonium chloride, were filtered off after 1 hr. Recrystallization of the solids from 20 ml. of water gave 7.4 g. of the amide. The mother liquor was taken to dryness. The residue was recrystallized from 6 ml. of hot water to give an additional 0.60 g. of product. Both crops melted at 212–213° and the combined yield of 8.0 g. represents 67% of the theoretical amount.

5-Pyrimidinecarbonitrile. A. By the Dehydration of 5-Pyrimidinecarboxamide.—An intimate mixture of 2.5 g. of phosphorus pentoxide and 2.0 g. (0.016 mole) of 5-pyrimidinecarboxamide was placed in a 50-ml. flask equipped with facilities for rapid vacuum distillation. A slight vacuum (50–100 mm.) was applied to the system and the flask was gently heated in a metal bath. At a bath temperature of 250° the product started to distill, boiling at 140°/80 mm., and solidifying in the receiver, which was cooled in an ice bath. The distillate weighed 1.3 g. (77% yield) and melted between 75° and 80°. One recrystallization from alcohol yielded an analytically pure product, m.p. 83.5–84° which weighed 0.80 g. The material crystallized as very long, stout needles.

Anal. Calcd. for $C_5H_3N_3$: C, 57.14; H, 2.87. Found: C, 57.27; H, 3.23.

B. By the Dehalogenation of 2,4-Dichloro-5-pyrimidinecarbonitrile.—A solution of 52.2 g. (0.301 mole) of dihalide (*vide infra*) in 1200 ml. of isopropyl alcohol was shaken under an atmosphere of hydrogen (11 p.s.i.) in the presence of 30 g. of calcium oxide and 3 g. of 5% palladium-on-carbon. The theoretical amount of hydrogen was absorbed after 4 hr. Removal of the solids by filtration, followed by solvent stripping *in vacuo* left a solid residue. This was repeatedly extracted with warm ether as the solids were filtered off. Evaporation of the ether from the filtrate left a residue, but this material failed to yield any 5-pyrimidinecarbonitrile upon distillation. However, when the ether-insoluble material was subjected to exhaustive vacuum sublimation, 2.8 g. (9% yield) of product could be obtained. This material melted at 83–84° and was spectrally identical with 5-pyrimidinecarbonitrile obtained from the dehydration of the amide.

Thio-5-pyrimidinecarboxamide.—A slow stream of hydro-

gen sulfide was passed through a mixture of 0.250 g. (0.0024 mole) of 5-pyrimidinecarbonitrile in 3 ml. of alcohol previously saturated with ammonia. After a short time all the solids went into solution and the product started crystallizing. The hydrogen sulfide addition was continued for another 15 min. Cooling and filtration of the mixture gave 0.230 g. of yellow, well defined crystals melting at 169–170°. An analytical sample prepared from 30 parts of alcohol melted at 170–170.5°.

Anal. Calcd. for $C_5H_5N_3S$: C, 43.15; H, 3.62. Found: C, 43.25; H, 3.68.

2,4-Dichloro-5-pyrimidinecarbonitrile.—A mixture of 123 g. (0.90 mole) of 2,4-dihydroxy-5-pyrimidinecarbonitrile,[4] 290 ml. of diethylaniline, and 720 ml. of phosphoryl chloride was stirred without the application of heat for *ca.* 0.5 hr. After the initial exothermic reaction had subsided, the dark solution was heated under reflux for an additional 1–2 hr. Removal of the excess phosphoryl chloride *in vacuo* and keeping the internal temperature below 65° left a viscous residue. This material was poured on ice and was caused to crystallize by prolonged stirring. The crude product was removed by filtration, and melted between 50° and 58°. Further purification was achieved by dissolving the material in 800 ml. of ether, washing with dilute sodium bicarbonate solution, and drying the ether phase. Subsequent removal of the solvent left a red crystalline mass which was distilled to give 101 g. of a yellow product, b.p. 110–112°/2 mm. solidifying in the receiver. An analytical sample was prepared from isooctane to give lemon-yellow needles, m.p. 62–63°.

Anal. Calcd. for $C_5HCl_2N_3$: N, 24.15. Found: N, 24.19.

Acknowledgment.—Microanalytical determinations were performed by Mr. C. E. Childs and associates. Special thanks are due to Mr. W. M. Pearlman for carrying out the hydrogenations as well as for valuable suggestions in connection therewith.

(4) G. Shaw, *J. Chem. Soc.*, 1827 (1955).

Formation of Copper Phthalocyanine

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It has remained an open question in the formation of copper phthalocyanine from phthalic anhydride and urea whether the α-carbon atoms in the maleic anhydride ring of phthalic anhydride are replaced by the carbon atom in urea, or whether the α-carbon atoms in the maleic anhydride ring in phthalic anhydride remain intact to constitute the eight porphin carbons in the tetraazaporphin ring.

This question relates to the formation of phthalonitrile which has been considered to be a reaction intermediate but the presence of which remains to be detected.[1,2] If the α-carbons supplied by the

TABLE I

Material	Run No. 1			Run No. 2			Run No. 3		
	Weight in G.		Activity counts/ min./mg.	Weight in G.		Activity counts/ min./mg.	Weight in G.		Activity counts/ min./mg.
	Initial	Final		Initial	Final		Initial	Final	
C-14 urea	8.0×10^{-5}	...	...	8.0×10^{-5}	...	...	8.0×10^{-5}	...	...
Urea mix	2.000	...	12 ± 2	2.000	...	12 ± 2	2.000	...	12 ± 2
Phthalic anhydride	1.250	...	0	1.250	...	0	1.250	...	0
Reaction mixture	3.540	...	6.5 ± 1	3.540	...	6.5 ± 1	3.540	...	6.5 ± 1
Reaction crude	...	1.8459	3.2 ± 1	...	1.9090	3.4 ± 1		1.8132	3.2 ± 1
Copper phthalocyanine	...	0.792	0	...	Lost during purification			0.382	0
Drierite	14.9959	15.2425	0	11.7162	11.9406	0	10.9004	11.1839	0
Ascarite in tower	42.4878	43.7240	0.44 ± .05	40.9385	42.0769	0.46 ± .05	42.8473	44.0681	0.41 ± .05
Ascarite in tube	12.4081	12.5040	0	13.6144	13.6912	0	14.1807	14.2718	0
Ammonia in H_2SO_4 tower	0	0.1104	...	0	0.1621	...	0	0.2098	...

phthalic anhydride remain intact, it is postulated no phthalonitrile is formed and the immediate precursors of copper phthalocyanine are either or both monoiminophthalimide or 1-amino-3-imino-isoindolenine.

It is shown, using urea tagged with carbon-14, that under the set of reaction conditions described below, urea does not contribute carbon atoms in the formation of copper phthalocyanine from phthalic anhydride and urea.

Experimental

The reaction was carried out in a 250-ml. flask with nitrogen carrier gas flow through the reactor and downstream gas train at 1–2 ml./sec. The flask was heated in an oil bath held at 200°. The gas train system consisted of an air condenser, to trap sublimed organic by-products, Drierite tube to trap water, Ascarite tower (50:50 mixture of Ascarite and Drierite to prevent clogging of tower from traces of moisture) to trap carbon dioxide, Ascarite tube to test efficiency of Ascarite tower, back-up flask, and concd. sulfuric acid bubbler to collect ammonia gas, followed by exhaustion to atmosphere of the nitrogen purge.

The urea mix for the reaction was prepared as follows: 0.4 mg. of carbon-14 urea (Source: Tracer Laboratories, Inc.; specific activity: 3.69 mc./mM.) and 10 g. of urea were dissolved in 20 ml. of distilled water; the solution was evaporated. The residue was ground in a mortar preparatory to introduction into the crude reaction mix. For each of the three test reactions that were made, 15.93 g. of mix was prepared from which three samples, each weighing 3.54 g., were drawn: 1.25 g. of phthalic anhydride, 2.00 g. of urea mix, 212 mg. of cuprous chloride, 26 mg. of copper, and 52 mg. of molybdic trioxide.[3] The constituents were weighed in a Nettler Balance with stated sensitivity of about ± 0.02 mg. The reaction mixture was ground and blended with mortar and pestle. The reaction mass was heated to temperature 1 hr. and held at 200° for 4 hr. The reaction product in the 250-ml. flask was weighed and purified in sulfuric acid solution. The acid suspension was filtered and the filter cake was washed acid free to Congo Red paper, dried, and weighed to determine the yield. In the second test run there was no filter cake, presumably due to solution or sulfonation of the copper phthalocyanine in sulfuric acid solution. Infrared absorption characteristics of the purified residues of the first and third test runs, made with a Perkin-Elmer Model 21 spectrophotometer, over 2.5 μ to 15.5 μ, gave no evidence of compounds other than copper phthalocyanine. One hundred-milligram samples of reaction mix, crude reaction product, purified reaction product, and contents of Drierite and Ascarite tubes were tested for radioactivity with a Nuclear Corp. Model 2612-P portable radiation survey meter. The only samples that gave radioactive counts were from the reaction mixture, crude reaction product, and Ascarite tower. Copper phthalocyanine gave no count. Drierite and Ascarite tubes gave no count. Although not necessary to the purpose at hand, the amount of ammonia absorbed in the concd. sulfuric acid tower was determined by the formaldehyde method.

Yield data, radioactive counts, and weight of reaction mixture, reaction crude, copper phthalocyanine, Drierite and Ascarite tubes, Ascarite tower, and ammonia are given in Table I.

(1) N. H. Haddock, *J. Soc. Dyers Colourists*, **61**, 68 (1945).
(2) G. Rosch, W. Wolf, and H. Vollman, U. S. Patent 2,739,155 March 20, 1956.
(3) A. Riley, U. S. Patent 2,214,477, September 10, 1940.

Compounds Containing the Trifluoromethyl Group[1]

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Details of the preparation and polymerization of monomers containing the trifluoromethyl group have appeared elsewhere.[3] We would like to report here related work, for the most part concerned with the attempted preparation of compounds bearing a trifluoromethyl group on a tertiary carbon atom. Compounds of this type are not reported in the literature except for the special example of 1,1-bis(trifluoromethyl)cyclobutane. This compound was prepared by Hasek[4] from the reaction of cyclobutane dicarboxylic acid with sulfur tetrafluoride. We were unable to convert α,α-dimethyl substituted carboxylic acids, specifically 2,2-dimethylpent-4-eneoic and 2,2-dimethyl-3-acetoxybutyric acid to the corresponding trifluoromethyl derivatives using sulfur tetrafluoride. Severe reaction conditions caused carbonization and milder conditions gave no reaction. The lack of reactivity in the latter two instances is attributable to steric hindrance of the carboxyl group. The steric requirements are somewhat lessened in the case of cyclobutanedicarboxylic acid because of the presence of fewer interfering hydrogen atoms and the removal of the hydrogen atoms from the site of reaction due to the ring structure.

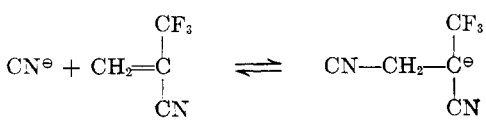
Sulfur tetrafluoride easily converted isobutyric acid to 2-trifluoromethylpropane. This compound was obtained also from hydrogenation of 2-trifluoromethylpropene. The former reaction is preferable for the preparation of large quantities of this material. It was felt that 2-trifluoromethylpropane might be alkylated in a manner similar to that for isobutyronitrile. Alkylation was attempted with phenyllithium and allyl bromide in ether and sodium amide and allyl bromide in ammonia. The reactions were not successful. Ethyl 2-cyano-3-trifluoromethylbutenoate was prepared by condensation of trifluoroacetone with ethyl cyanoacetate in pyridine solvent with piperidine as catalyst. It is interesting to note that the intermediate ethyl 2-cyano-3-hydroxy-3-trifluoromethylbutyrate was not isolated; it dehydrated at room temperature to give the desired product. This can be contrasted to the dehydration of 2-trifluoromethyl-2-propanol which required prolonged heating at

(1) The financial support of the Wright Air Development Division, Dayton, Ohio, is acknowledged (Contract No. AF33(616)-6866).
(2) Present address: Esso Research and Engineering Co., Linden, N. J.
(3) C. G. Overberger and E. B. Davidson, *J. Polymer Sci.* in press.
(4) W. Hasek, W. Smith, and V. Englehardt, *J. Am. Chem. Soc.*, **82**, 543 (1960).

135° over phosphorus pentoxide.[5] Similarly, ethyl 3-hydroxy-3-trifluoromethylbutyrate was prepared by a Reformatsky reaction of trifluoroacetone with zinc and ethyl bromoacetate and did not appreciably dehydrate upon distillation at 176°. Walborsky[6] heated 3-hydroxy-3-trifluoromethylbutyric acid, prepared from the condensation of trifluoroacetone with malonic acid, over phosphorus pentoxide in order to effect dehydration.

The monomer, trifluoromethylacrylonitrile, is known and was prepared according to Buxton.[7] The literature does not reveal much concerning the polymerization of this monomer. Dickey[8] polymerized trifluoromethacrylonitrile with triallyl arsines, stibines, and phosphines at −20° in solvents; di- and trialkylphosphites were reported to polymerize trifluoromethacrylonitrile in bulk at −50°.[9] In the present work, trifluoromethacrylonitrile was polymerized in bulk and solution with a variety of bases to give solid polymers; *e.g.*, bases such as ammonia, *n*-butylamine, and piperidine gave colored polymers from yellow to orange; *n*-butyllithium gave a black polymer; potassium hydroxide gave a white polymer; and sodium cyanide gave a pink polymer. Acetonitrile and pyridine were found to be suitable solvents for homogeneous polymerizations.

Solution polymerizations were characterized by development of a yellow coloration and absorption at 494 mμ. The color appeared instantaneously upon addition of the catalyst and it was felt that the rate of change of absorption at 494 mμ could be used to follow the rate of polymerization. The system, sodium cyanide in dimethylformamide was used for this purpose. It became apparent that the absorption was not related to the rate of propagation when a 1:1 = monomer: catalyst reaction showed the same effect. Evidently the spectrophotomeric method is following the rate of production of the ionic propagating species



Several unsuccessful attempts were made to isolate this species as the sodium salt.

Experimental

Ethyl 3-Hydroxy-3-trifluoromethylbutyrate.—Half of a solution composed of trifluoroacetone 51 g. (0.46 mole), and dry benzene, 250 ml., was added to activated zinc powder, 32 g. (0.5 g.-atom). The materials were heated until reaction commenced, after which the remaining solution was added at a rate such that gentle refluxing was maintained. After an additional 2 hr. of refluxing, the material was poured into a cold solution of sulfuric acid, 49 g. (0.5 mole), in 500 ml. of water. The organic phase was separated and combined with the benzene extracts of the aqueous phase; this solution was water washed until the washes were neutral to litmus. The solution was dried, and after the solvent removed by distillation, ethyl 3-hydroxy-3-trifluoromethylbutyrate was obtained, 50 g. (55% yield), b.p. 176° (atm.), $n^{25}D$ 1.3769, d^{25}_4 1.2207.

Anal. Calcd. for $C_7H_{11}F_3O_2$: C, 42.00; H, 5.59; F, 28.48. Found: C, 41.28; H, 5.69; F, 28.98.

Ethyl 2-Cyano-3-trifluoromethylbutenoate.—Trifluoroacetone, 33 g. (0.28 mole), ethyl cyanoacetate, 33 g. (0.28 mole), piperidine 2 ml., and dry pyridine 150 ml. were mixed and allowed to stand at 0° for 12 hr. After 24 hr. at room temperature the volatile materials were removed under reduced pressure and a solid residue was obtained. The solid was crystallized from 95% ethanol and then from carbon tetrachloride to give ethyl trifluoromethylisopropylidenecyanoacetate, 29 g. (87% yield), m.p. 124–125°.

Anal. Calcd. for $C_8H_8NF_3O_2$: C, 46.38; H, 3.89; N, 6.76; F, 27.52. Found: C, 46.43; H, 4.08; N, 6.54; F, 27.71.

2-Trifluoromethylpropane.—2-Trifluoromethylpropene, prepared according to Henne[5], 25.3 g. (0.23 mole), was condensed into a pressure bottle containing platinum oxide, 0.46 g., and ethanol, 30 ml. The contents were cooled, and the bottle flushed with nitrogen prior to the introduction of hydrogen. After 4 days at room temperature, the hydrogen uptake ceased, the material having absorbed 46% of the theoretical quantity. Low-boiling compounds were removed by flash distillation and passed through bromine which was illuminated with ultraviolet light. 2-Trifluoromethylpropane, 4.4 g. (18% yield), b.p. 11.8–12.7° (atm.) was obtained still contaminated with 2-trifluoromethylpropene as evidenced from the infrared spectrum. An elemental analysis could not be performed on this material because of experimental difficulties. 1,2-Dibromo-2-trifluoromethylpropane, 2 g. (3% yield), b.p. 130° (atm.) was recovered after removal of excess bromine. (b.p. 130–130.8[10]).

A stainless steel bomb was charged with isobutyric acid, 13.2 g. (0.15 mole), and sulfur tetrafluoride, 54 g. (0.50 mole), after which it was heated to 160° for 9 hr. The contents were vented at room temperature through a trap containing 10% sodium hydroxide solution, a trap cooled to 0° and one cooled to −78°. The material in the last trap was distilled to give 2-trifluoromethylpropane, 11 g. (65% yield), b.p. 130° (atm.). This material gave an infrared spectrum identical to that obtained from the catalytic hydrogenation except for the absence of bonds due to unsaturation.

Attempted Preparation of 2-Methyl-2-trifluoromethyl-3-acetoxy-butane and 4-Methyl-4-trifluoromethylpentene-1.—Methyl 2-bromo-isobutyrate was prepared according to Smith and Norton[11] in 65% yield. This was converted to 2,2-dimethyl-3-hydroxybutanoic acid and then to 2,2-dimethyl-3-acetoxybutanoic acid according to Courtot.[12]

4-Methyl-4-cyanopentene-1 was prepared according to Wittig,[13] and was converted to 2,2-dimethylpent-4-eneoic acid according to Brown and van Gulick.[14]

The first of the above compounds reacted by a procedure similar to that described in the preceding section, except that 1,2-dimethoxyethane was used as solvent. The starting material was recovered from this reaction along with a small amount of a yellow crystalline solid which was not identified.

The reaction of 2,2-dimethylpent-4-eneoic acid with sulfur tetrafluoride was characterized by carbonization. The use of diethyl ether or dimethoxyethane as solvent eliminated the

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(6) H. Walborsky, M. Baum, and D. Loncrini, *ibid.*, **77**, 3637 (1955).

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(8) J. Dickey and H. Coover, U. S. Patent 2,652,393, Sept. 15, 1953.

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(10) F. Swarts, *Bull. soc. chim. Belg.*, **36**, 192 (1927).

(11) C. Smith and D. Norton in *Org. Syntheses*, **33**, 29 (1953).

(12) A. Courtot, *Bull. soc. chim.*, [3] **35**, 114 (1906).

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(14) R. Brown and N. van Gulick, *J. Am. Chem. Soc.*, **77**, 1088 (1955).

carbonization; however, the desired product was not obtained.

Polymerization of Trifluoromethacrylonitrile.—Trifluoromethacrylonitrile was prepared from trifluoroacetone according to Buxton.[7] The polymerizations were carried out in a vacuum system. The catalyst, sodium cyanide, was crystallized from water and dried at room temperature at 7×10^{-3} mm. for 1 week. A weighed quantity, 0.018 g. (3.7×10^{-4} mole) was placed in a reaction vessel and degassed for 0.5 hr. at 0.05 mm. Trifluoromethacrylonitrile, 3.47 g. (0.029 mole), was distilled from the reservoir on the vacuum line to a side arm on the reaction flask which, by rotation, could be inverted to discharge its contents into the flask. The monomer was kept frozen in the side arm with liquid nitrogen until needed. Dimethylformamide was refluxed over phosphorus pentoxide and distilled at reduced pressure prior to storage on the vacuum line over methylenebis(*p,p*-diphenyl diisocyanate). Dimethylformamide, 25 ml., was transferred from its reservoir into the reaction flask and the sodium cyanide dissolved to give a clear solution by stirring for 1 hr. at room temperature under an atmosphere of argon. The solution was cooled to −40°; the monomer was thawed and the side arm emptied into the reaction flask causing an immediate production of orange-brown solution. The polymerization was terminated by addition of 3 ml. of a 2% solution of sulfuric acid in dimethylformamide, and the polymer isolated by precipitation into water containing potassium hydroxide. The polymer was obtained as a pink powder. Polymerizations carried out for 30, 9, and 4 min. gave essentially quantitative yields, m.p. 190° dec. Intrinsic viscosities were determined in dimethylformamide and in cyclohexanone. The curves showed an electrolyte effect; $[\eta]$ was of the order 0.1 $\frac{dl}{g}$.

Anal. Calcd. for $(C_4H_2NF_3)_n$: C, 39.68; H, 1.67; N, 11.57; F, 47.08. Found: C, 40.19; H, 2.03; N, 10.75; F, 45.48.

Hydrolysis of an Ester with a Neighboring Carboxyl and a Quaternary Ammonium Group[1]

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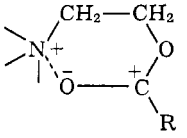
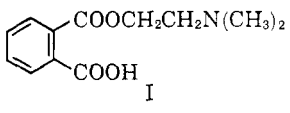
The enhanced reactivity of esters of the choline type[2] has been explained by assuming that the positively charged nitrogen stabilizes a negative charge on the carbonyl oxygen, making the carbonyl carbon more susceptible to attack by a nucleophilic reagent as indicated by:

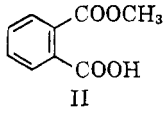


This type of catalysis has been classified by Bender[3] as intramolecular general acid catalysis. The difference in reactivity of esters of cyclohexanol derivatives with a *cis* or a *trans* quaternary nitrogen has been offered as evidence for the above mechanism.[4] By analogy, a neighboring positively charged nitrogen should make the carbonyl carbon more susceptible to neighboring carboxylate attack. It has been shown previously that an ester containing both an ionized and an unionized neighboring carboxyl group is highly reactive, and this effect has been attributed to a stabilization of the transition state by hydrogen bonding between the carbonyl oxygen of the ester and the unionized carboxyl.[5] It was suggested that a similar stabilization might be achieved by ion-pair formation involving the partial negative charge of the carbonyl oxygen and a neighboring cationic group.[5]

To demonstrate this effect, we carried out a study of the *p*H dependence of the rate of hydrolysis of β-*N,N*-dimethylaminoethyl hydrogen phthalate (I). An analogous ester lacking the cationic group, *i.e.*, methyl hydrogen phthalate II has been investigated previously.[6]



I



II

The pseudo-first-order rate constants for the hydrolysis of ester I in various buffers and at different temperatures are given in Table I.

TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE HYDROLYSIS OF β,*N,N*-DIMETHYLAMINO ETHYL HYDROGEN PHTHALATE

*p*H	10^5k Sec.$^{-1}$ (at 75°)	*p*H	10^5k Sec.$^{-1}$	Temp.
1.11	3.3	7.92	41	75.5
2.82	2.8	6.06	3.0	75.5
3.26	2.7	6.06	0.033	34.5
4.92	3.0	6.06	1.13	65.5
6.39	3.8	6.06	6.65	85.4
6.99	8.1			

In Fig. 1 the logarithms of the rate constants obtained at 75.5° are plotted against pH along with a similar plot for the hydrolysis of methyl hydrogen phthalate taken from ref. 6.

An Arrhenius plot of rates obtained at pH 6.06 gave an activation enthalpy of 23.4 kcal./mole as against 33.7 kcal./mole reported for ester II[6].

The results of this study show that the amphoteric ester I is much more reactive than the acid ester II, but that the hydrolysis rate of I unlike that of II, is pH independent in the region of

(1) Financial support of this research by the Office of Naval Research Contract Nonr-839(31) is gratefully acknowledged.

(2) (a) W. Davis and W. C. J. Ross, *J. Chem. Soc.*, 3056 (1950). (b) E. Schätzle, H. Urheim, M. Rottenberg, and Thürkauf, *Experientia*, **17**, 350 (1961).

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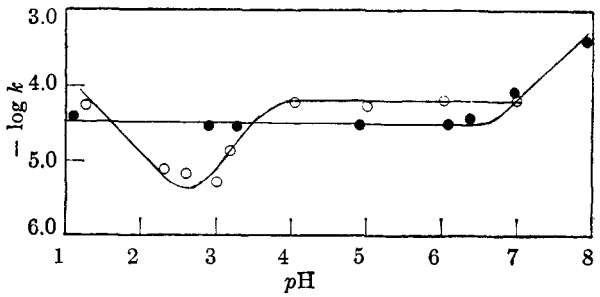

Fig. 1.—The hydrolysis of β-*N*,*N*-dimethylaminoethyl hydrogen phthalate at 75.5°, ●; and of methyl hydrogen phthalate at 109°, ○ (Ref. 6).

carboxyl ionization. It may therefore be concluded that in this *p*H region the bulk of the hydrolysis is due to direct attack of water on the ester group, and that any contribution which intramolecular carboxylate attack may make to the observed hydrolysis rate of I is within the experimental error of the rate constant measurements. If we extrapolate the data from ref. 6 for the fully ionized II at 109° and 84° to a temperature of 75.5°, we find that intramolecular carboxylate attack on the ester group results in a hydrolysis rate constant of 0.079×10^{-5} sec.$^{-1}$. This is less than 3% of the rate constant observed for ester I in the plateau region below *p*H 6.1, so that intramolecular carboxylate attack would not be experimentally detectable in ester I unless it were about four times as efficient as in II. Apparently the cationic group does not produce an effect of this magnitude.

Experimental

β-*N*,*N*-Dimethylaminoethyl Hydrogen Phthalate.—Phthalic anhydride (7.4 g., 0.05 mole) and 17.8 g. (0.2 mole) dimethylaminoethanol were placed in a 250-ml. three-necked round-bottomed flask equipped with a mechanical stirrer. The mixture was stirred at room temperature for 6 hr. The resulting slurry was washed with benzene and recrystallized from ethanol giving small colorless plates, which melt with decomposition 160–170°.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.36; N, 5.90. Found: C, 61.02; H, 6.46; N, 5.81.

Kinetics.—The hydrolysis reactions were carried out in buffer solutions less than 0.02 *M* in ionized acid. The ionic strength was adjusted to 0.1 *M* by addition of sodium chloride and the *p*H was determined with a Cambridge Research Model *p*H meter. The rate of reaction was studied by observing the disappearance of the peak due to the the ester at 280 mμ on a Beckman DU spectrophotometer. In order to follow the rate of reaction in this manner the free phthalic acid had to be ionized, since unionized phthalic acid has approximately the same extinction coefficient as the ester. Therefore, for most runs, 2-ml. aliquots of the reaction solution (containing 24 mg. ester/100 ml.) were transferred into 2 ml. of 0.5 *M* phosphate buffer (*p*H 6.06), and the optical density (D) determined at 25.3°. Plots of $-\ln (D-D_\infty)$ were linear in time in all cases, and were used to calculate the first-order rate constant. The formation of phthalic acid in the reaction was proved by the similarity between the spectrum of the ester after hydrolysis and phthalic acid at the same *p*H.

Quaternary Derivatives of Nitrogen-Mustards[1]

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Phosphorylated *N*-mustards, prepared by Friedman and Seligman[3] as well as Arnold and Burseaux,[4] are examples of cytotoxic substances with a so-called "hidden" or "toxagenic" *N*-mustard group. According to the hypothesis, the *N*-phoshorylation or urethane formation of the bis(β-chloroethyl)-amine eliminates the basic character of the amine, preventing the formation of intermediary ethylenimonium salts, which are considered the true alkylating agent. The compounds are therefore nontoxic, inactive *in vitro*, and activated only *in vivo* by phosphamidases restoring the secondary amine.

We report here the properties of *N*-mustard derivatives, which are capable of quaternerizing prior to the eventual hydrolysis of *N*-acyl groups. Although, they are not "toxagenic" derivatives of originally active *N*-mustards, nevertheless, they contain quaternerized chloroethylamino groups. These differ from ethylenimonium salts in being less strained six-membered rings of novel structure. *N* - Bis(β - chloroethyl)phosphoramidic dichloride[3] (I) was first treated with four moles of 1,1-dimethylhydrazine, affording the *N* - bis(β - chloroethyl)phosphoramidate di(2,2 - dimethylhydrazidate) (II) as an oily base. On standing at room temperature for a few hours, or warming it several minutes on the steam bath, the compound bisquaternerized to the unusual heterocyclic system 2,7 - dimethyl - 9 - phospha - 9 - oxo - 10 - azapyridazo[5,6 - *e*]pyridazine - 2,7 - bischloromethylate (III), a water soluble crystalline substance.

On the other hand, phenyl-*N*-bis(β-chloroethyl)-phosphoramidic chloride[3] (IV), prepared from I was also treated with dimethylhydrazine to the tertiary base (V), which in turn, yielded the quaternary 1 - methyl - 3 - oxo - 3 - phenoxy - 4-(β - chloroethyl) - 3 - phospha - 1,2,4 - triazine - 1-chloromethylate (VI).

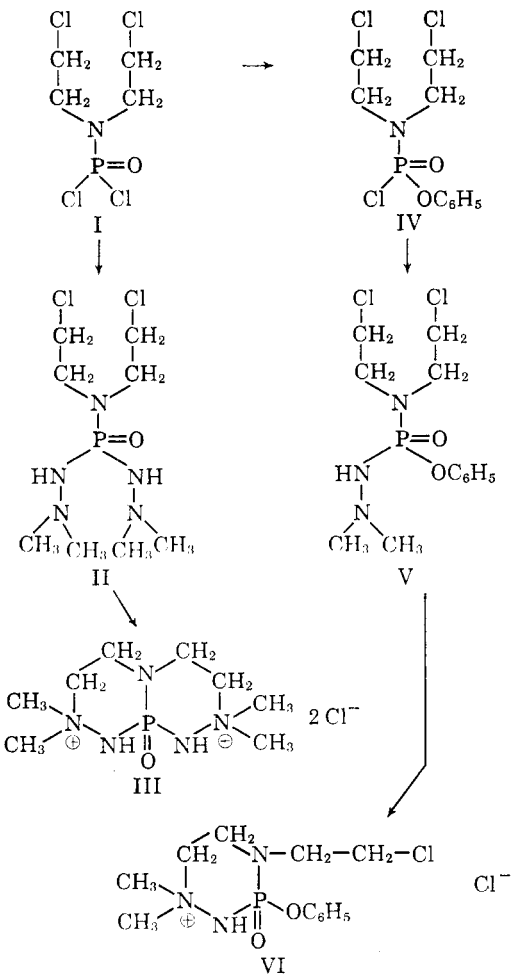
In connection with our investigations about *N*-mustard urethanes,[5] we also prepared the analogous

(1) This investigation was supported by the U. S. Department of Health, Education and Welfare, National Institutes of Health (Grant No. 2260), the National Research Council of Canada (Grant No. MAG40), and by the National Cancer Institute of Canada. We thank the principal investigator of this project, Dr. V. W. Adamkiewicz of the Department of Physiology, University of Montreal, for making this investigation possible, and supplying the toxicity data.

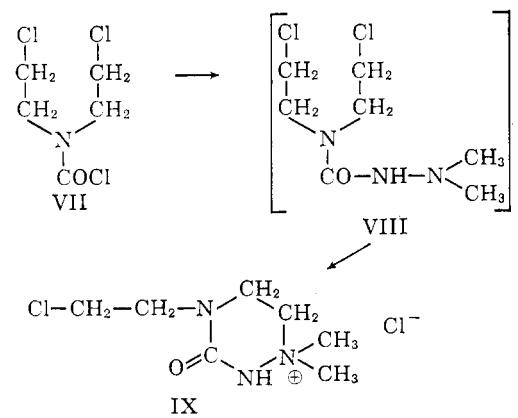
(2) Present address: Department of Chemistry, Loyola College, Montreal 28, Quebec, Canada.

(3) O. M. Friedman and A. M. Seligman, *J. Am. Chem. Soc.*, **76**, 655 (1954).

(4) H. Arnold and F. Burseaux, *Angew. Chemie*, **70**, 539 (1958).



derivative from *N*-chloroformylbis(β-chloroethyl)-amine[6] (VII) with dimethylhydrazine. The reaction in benzene is exothermic, and therefore, besides the dimethylhydrazine hydrochloride, the quaternary salt separates directly. The tertiary urea (VIII) could not be isolated, so the quaternerization was driven to completion by heating, and the 1-methyl-4-(β-chloroethyl)-1,2,4-triazine-3-one-1-chloromethylate (IX) isolated.



The acute toxicity[1] of the two phosphates was surprisingly low. The LD_{50} of III was 1600 mg./kg. (mouse, single intraperitoneal injection), that of VI was 1000 mg./kg. The cancerostatic screening[7] on Sarcoma 180 revealed, however, that both compounds (SK-25,029 and SK-25,030) were completely inactive in doses up to 500 mg./kg. This might be attributed to the assumption, that a six membered quaternary salt is much more stable than an ethylenimonium salt, is therefore incapable of splitting at the C—N bond, and acting as an alkylating agent. The single chloroethyl group in VI can not quaternerize; it is therefore inactive, too.

Experimental[8]

2,7-Dimethyl-9-phospha-9-oxo-10-azapyridazo-[5,6-e]-pyridazine-2,7-chloromethylate (III).—A 1.30-g. sample of *N*-bis(β-chloroethyl)phosphoramidic dichloride[3] and 1.52 ml. of 1,1-dimethylhydrazine were dissolved in 15 ml. of dry benzene. The solution became warm, and dimethylhydrazine hydrochloride started to crystallize. After standing overnight, the salt was filtered off, and the solution evaporated under reduced pressure, affording 1.00 g. (65.4%) of a colorless viscous oil.

Heating this on a steam bath, it solidified immediately to a hard mass. After 30 min., it was triturated with a small amount of boiling ethanol, chilled, filtered, and recrystallized from methanol-ether, yielding 0.47 g. (31.7%) bis-quaternary salt, m.p. 212–215° (dec.)

Anal. Calcd. for $C_8H_{22}Cl_2N_5OP$: C, 31.4; H, 7.2; Cl, 23.2; N, 22.9. Found: C, 31.3; H, 7.4; Cl, 22.9; N, 23.1.

1-Methyl-3-oxo-3-phenoxy-4-(β-chloroethyl)-3-phospha-1,2,4-triazine-1-chloromethylate (VI).—A 15.8-g. sample of phenyl-*N*-bis(β-chloroethyl)phosphoramidic chloride[3] and 8.0 ml. of 1,1-dimethylhydrazine in 100 ml. dry benzene was refluxed for 1 hr., chilled, filtered, and the solution evaporated under reduced pressure. The resulting oil was heated on the steam bath for 30 min., solidifying immediately. This was triturated with acetone, filtered, and recrystallized from ethanol, yielding 6.08 g. (35.8%) of colorless crystals, m.p. 214–215° (dec.).

Anal. Calcd. for $C_{12}H_{20}Cl_2N_3O_2P$: C, 42.4; H, 5.9; Cl, 21.0; N, 12.3. Found: C, 42.5; H, 6.1; Cl, 20.8; N, 12.5.

1-Methyl-4-(β-chloroethyl)-1,2,4-triazine-3-one-1-chloromethylate (IX).—A 2.04-g. sample of chloroformylbis-(β-chloroethyl)amine[6] and 1.6 ml. of 1,1-dimethylhydrazine were dissolved in 10 ml. of dry benzene. The solution became hot. After 1 hr. at room temperature, the benzene was evaporated under reduced pressure from the semisolid reaction mixture, and heated for 20 min. at 95°. It was triturated with cold ethanol, filtered, and recrystallized from a large amount of ethanol, yielding 0.52 g. (22.8%) crystals, m.p. 209–210° (dec.).

Anal. Calcd. for $C_7H_{15}Cl_2N_3O$: C, 36.8; H, 6.6; Cl, 31.3; N, 18.4. Found: C, 36.7; H, 6.7; Cl, 31.4; N, 18.3.

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(7) The cancerostatic screening was performed by the Sloan-Kettering Institute for Cancer Research, Rye, N. Y. We wish to thank Dr. C. C. Stock for making the data available to us.

(8) All melting points are uncorrected. Microanalyses were done by Dr. C. Daessle Microanalytical Laboratory (Montreal), and Dr. G. Papineau-Couture and his staff of Ayerst, McKenna & Harrison Co. Ltd. (Montreal), to whom thanks are due.

D-Ribose Hydrazone

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Received January 8, 1962

For comparison of its properties with those of D-ribosylamine,[2] the title compound was synthesized by condensation of D-ribose with hydrazine. Although innumerable *substituted* hydrazones of sugars (and of reducing, substituted sugars) have been described in the literature, this appears to be the first *unsubstituted* hydrazone of a sugar that has been prepared.

In order to minimize possible formation of 1,2-di-D-ribosylhydrazine or of the azine, the following conditions were used: A ten-fold excess of hydrazine was employed, the reaction solution was quite concentrated, and the condensation was conducted at room temperature.

Experimental

D-Ribose Hydrazone.—Anhydrous hydrazine (16 g.) was weighed into a 50-ml. Erlenmeyer flask and 16 ml. of absolute methanol was added; heat was evolved, and so the solution was cooled in ice–salt. Dry, finely powered D-ribose (7.5 g.) was now added and the flask was quickly stoppered. On swirling, part of the D-ribose dissolved and a new kind of colorless crystals rapidly formed. After the mixture had stood at room temperature for 24 hr., with occasional swirling, all of the crystals had dissolved to a clear, colorless solution. This was transferred to an evaporating dish and evaporated in a vacuum desiccator, over phosphorus pentoxide and soda lime, to a thick, viscous, colorless sirup which was dried at 0.1 mm. (Desiguard). The sirup was redissolved by stirring it with 10 ml. of absolute methanol; addition of 10 ml. of absolute ethanol now gave a white, gummy precipitate. The solution was decanted, and the precipitate was stirred with 20 ml. of absolute methanol, affording a suspension of colorless crystals which was filtered with suction (rubber dam); the crystals were washed with 10 ml. of absolute methanol and dried at 0.1 mm.; wt., 5.4 g.; m.p. 127–129°. The infrared absorption spectrum was recorded; it showed a band at 1613 cm.$^{-1}$, possibly indicative of C=N absorption. (The combined mother liquors were evaporated to dryness and the resulting crystalline mass, on stirring with 10 ml. of absolute methanol, gave a crop (1.9 g.) of less pure crystals, m.p. 115–117°.)

Anal. Calcd. for $C_5H_{12}N_2O_4$: C, 36.58; H, 7.37; N, 17.07. Found: C, 36.63; H, 7.64; N, 16.89.

The compound is practically insoluble in all organic solvents tested, except boiling acetic acid. It is sparingly soluble in water (<1 g. per 100 ml.); the saturated, aqueous solution had $\alpha^{25}D$ −0.13° (l = 2 dm.), and its ultraviolet absorption spectrum was recorded. A band at *ca.* 280 mμ suggested the presence of the open-chain, *aldehydo* form, rather than of a cyclic D-ribosylhydrazine.

(1) Present address: Division of Physical Chemistry, National Bureau of Standards, Washington 25, D. C.

(2) R. S. Tipson, *J. Org. Chem.*, **26**, 2462 (1961).

The Synthesis of *trans*-3-Oxa-4-oxo- and *trans*-4-Oxa-3-oxobicyclo[5.4.0]undecanes

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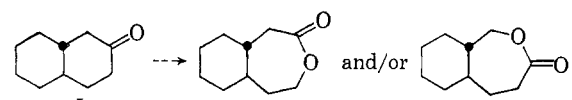
Notable by its absence in the work performed to date on the Baeyer–Villiger reaction[2] is a study of the more subtle differences prevailing in positions other than those alpha to the carbonyl function. In an attempt to study the requirements of the migrating group and yet avoid primary steric effects,[3] we were prompted to consider the Baeyer-Villiger oxidation of *trans*-β-decalone (I). The molecule could further serve as a model for rearrangements in steroids possessing an A/B *trans*-ring fusion.



I II III

Of the various approaches to the problem available to us, we chose first to prepare and characterize authentic samples of the lactones II and III. A knowledge of the physical properties of these substances might subsequently allow a method of composition analysis to be applied directly to the *trans*-β-decalone oxidation mixtures. The purpose of this paper is to report the unequivocal synthesis of *trans*-4-oxa-3-oxobicyclo[5.4.0]undecane (II) and *trans*-3-oxa-4-oxobicyclo[5.4.0]undecane (III).

Reaction of *trans*-β-(2-carboxycyclohexane) propionic acid (IV)[4,5] with diazomethane gave methyl *trans*-β-(2-carbomethoxycyclohexane)propionate (Va) which was selectively saponified with one equivalent of sodium hydroxide in refluxing aqueous methanol to produce *trans*-β-(2-carbomethoxycyclohexane)propionic acid (Vb). Near theoretical quantities of VI were obtained by reduction of Vb with sodium–ethanol–liquid ammonia.[6] Distillation of this hydroxy acid readily furnished *trans*-3-oxa-4-oxobicyclo[5.4.0]undecane (III).

(1) Department of Chemistry, The Upjohn Co., Kalamazoo, Mich.

(2) For a recent review of this reaction see C. H. Hassall, *Org. Reactions*, IX, 73 (1957).

(3) The present status of knowledge on primary steric effects is discussed in R. R. Sauers and J. P. Ahearn, *J. Am. Chem. Soc.*, **83**, 2759 (1961) and references cited therein.

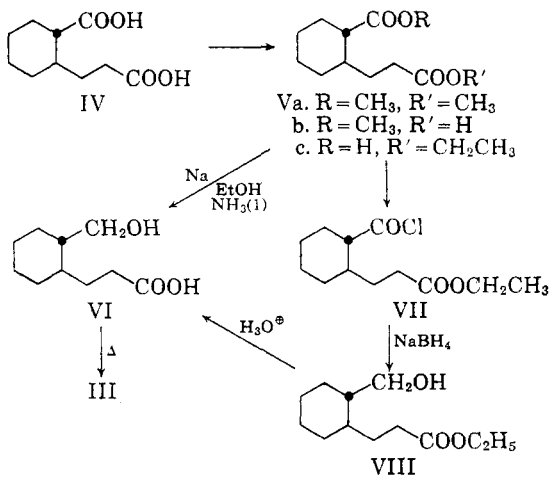
(4) G. A. Page and D. S. Tarbell, *Org. Synthesis*, **34**, 8 (1954).

(5) C. D. Gutsche and H. H. Peter, *J. Am. Chem. Soc.*, **77**, 5971 (1955).

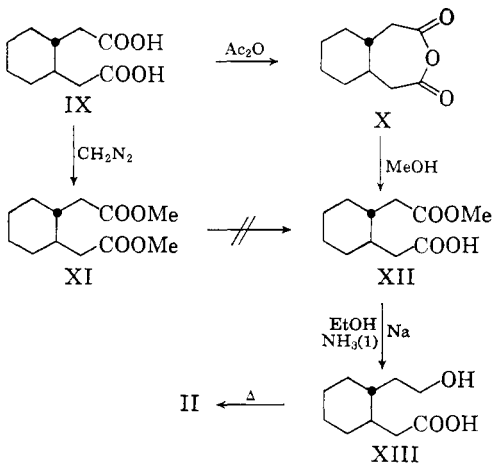
(6) The new selective reduction method described herein is far superior to the Bouveault-Blanc procedure[7,8] presumably because the temperature of the reaction, when performed in this medium, is sufficiently low to allow the reduction to proceed rapidly without the problem of concomitant ester hydrolysis.

(7) P. Chuit and J. Hausser, *Helv. Chim. Acta*, **12**, 463 (1929).

(8) D. C. Sayles and E. F. Degering, *J. Am. Chem. Soc.*, **71**, 3161 (1949).



To establish that no rearrangement had occurred during the sodium–ethanol–liquid ammonia reduction, an alternative approach to the synthesis of III was undertaken. Fisher esterification of IV in ethanol gave the primary monoester Vc which, on treatment with thionyl chloride followed by direct reduction of the acid chloride[9] with sodium borohydride, was transformed to ethyl *trans*-β-(2-hydroxymethylcyclohexane)propionate (VIII).[10] The conversion of VIII to the lactone III was effected by saponification and subsequent distillation of the resulting hydroxy acid.



The synthesis of the lactone II from *trans*-cyclohexane-1,2-diacetic acid (IX)[11] *via* its anhydride (X), acid ester (XII), and hydroxy acid (XIII) was performed in a similar fashion. It is noteworthy that the diester XI could not be selectively hydrolyzed with one equivalent of base to XII, the product being a mixture of diester, acid-ester, and diacid.

Very preliminary attempts to separate artificially compounded mixtures of II and III by vapor phase chromatography have proven disappointing. However, quantitative infrared spectroscopy should be possible as a means of analyzing the composition of β-tetralone oxidation products, because I, II, and III do possess characteristic absorption bands in their respective spectra (*cf.*, Experimental). Because of a change in laboratories[1] no further work on this problem is anticipated.

Experimental[12]

Methyl *trans*-β-(2-Carbomethoxycyclohexane)propionate (Va).—To 20.0 g. (0.10 mole) of *trans*-β-(2-carboxycyclohexane)propionic acid was added an etheral solution of excess diazomethane. The unchanged diazomethane was decomposed with dilute hydrochloric acid solution. The layers were separated and the ethereal layer was washed successively with 5% sodium bicarbonate solution, distilled water, and saturated salt solution. The ether extract was dried, filtered, and concentrated to give a residue which was distilled *in vacuo* to yield 22.7 g. (99.7%) of a colorless liquid, b.p. 105° (0.80 mm.), $n^{25}D$ 1.4555. Redistillation of a small sample gave pure diester, b.p. 98° (0.55 mm.), $n^{25}D$ 1.4558. $\tilde{\nu}_{max}^{CCl_4}$ 1740 cm.$^{-1}$ (s, ester carbonyl).

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.26; H, 8.83.

***trans*-β-(2-Carbomethoxycyclohexane)propionic Acid (Vb).**—In a 100-ml. flask fitted with a condenser was placed 4.56 g. (0.02 mole) of the diester Va, 40 ml. of anhydrous methanol, and 395 ml. of 0.506 *N* sodium hydroxide solution (0.02 mole). The mixture was heated under reflux for 4 hr. The solvent mixture was removed under reduced pressure, water was added, and the solution was extracted with ether. The aqueous layer was acidified with concd. hydrochloric acid and extracted with three 150-ml. portions of ether. The ether extract was dried, filtered, and concentrated to give a residue which was distilled *in vacuo* to yield a colorless liquid, 3.09 g. (72.3%), b.p. 135–138° (0.45 mm.), $n^{25}D$ 1.4690. Redistillation of a small sample gave pure acid ester, b.p. 134° (0.40 mm.), $n^{25}D$ 1.4694. $\tilde{\nu}_{max}^{CCl_4}$ 1700–1740 cm.$^{-1}$ (s, carboxyl and ester carbonyls).

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.50; H, 8.27.

Ethyl *trans*-β-(2-Carboxycyclohexane)propionate (Vc).—In a dry 500-ml. flask was placed 20.0 g. (0.10 mole) of the *trans*-diacid IV, 0.2 g. of *p*-toluenesulfonic acid, 100 ml. of absolute ethanol, and 75 ml. of dry benzene. The solution was refluxed on the steam bath with concurrent slow distillation of the solvent. This process required 17 hr., and the residual solvent was removed under reduced pressure. The remaining material was filtered to remove the *p*-toluenesulfonic acid, which was rinsed with ether. The oil was distilled *in vacuo* to give 19.5 g. (85.5%) of colorless liquid, b.p. 134–138° (0.135 mm.), $n^{25}D$ 1.4636. Redistillation of a small sample gave pure acid ester, b.p. 134° (0.125 mm.), $n^{27}D$ 1.4670. $\tilde{\nu}_{max}^{CCl_4}$ 1710 (s, carboxyl carbonyl) and 1740 cm.$^{-1}$ (s, ester carbonyl).

(9) Although the tautomerism of acid halides of half-esters is observed when the ring is five- and six-membered [*cf.*, B. H. Chase and D. H. Hey, *J. Chem. Soc.*, 554 (1952); J. C. Bardham *ibid.* 2604 (1928); D. L. Turner *et al.*, *J. Am. Chem. Soc.*, **72**, 5654 (1950); S. Stallberger-Stenhagen *ibid.*, **69**, 2568 (1947); J. Cason, *J. Org. Chem.*, **13**, 227 (1948)], this type of isomerization appears unimportant when a seven-membered ring intermediate is required.

(10) Subsequent to the work reported herein, H. C. Brown and W. Korytnyk [*J. Am. Chem. Soc.*, **82**, 3866 (1960)] reported that carboxylic acids are reduced with marked ease by diborane while esters react sluggishly with this reagent. Presumably therefore, the acid ester Vc could also be converted to VIII with diborane. In addition the transformation XII → XIII should also be permissible by this procedure.

(11) R. J. Tudor and A. I. Vogel, *J. Chem. Soc.*, 1250 (1934).

(12) Melting points and boiling points are uncorrected. The infrared spectra were determined with a Baird (Model B) spectrophotometer fitted with a sodium chloride prism. The microanalyses were performed by Dr. S. M. Nagy and his associates. Magnesium sulfate was employed as the drying agent.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.26; H, 8.93.

Ethyl *trans*-β-(2-Hydroxymethylcyclohexane)propionate (VIII).—A mixture of 4.56 g. (0.02 mole) of the acid ester Vc and 4.72 g. (0.04 mole) of redistilled thionyl chloride was refluxed for 2 hr. At the end of this time, the solution was cooled and the thionyl chloride was removed overnight *in vacuo* at room temperature. The resulting crude brown oil was dissolved in 30 ml. of pure, dry dioxane and was added dropwise to a slurry of 1.13 g. of sodium borohydride in 15 ml. of pure, dry dioxane. After refluxing for 2.5 hr., the mixture was cooled in ice and 50 ml. of water was slowly added. The resulting solution was acidified to Congo Red with hydrochloric acid and extracted with three 100-ml. portions of ether. After washing the combined ether layers with water, the organic layer was dried, filtered, and evaporated to yield a residual oil which was distilled *in vacuo* to give 1.80 g. (42.1% over-all) of a colorless oil, b.p. 100–110° (0.7 mm.). Two additional distillations of this material gave pure hydroxy ester, b.p. 86° (0.07 mm.). $\bar{\nu}_{max}^{CCl_4}$ 3525 (m, hydroxyl stretching) and 1740 cm.$^{-1}$ (ester carbonyl).

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.53; H, 10.24.

***trans*-3-Oxa-4-oxobicyclo[5.4.0]undecane (III). A. From VIII.**—A mixture of 0.95 g. (4.44 mmoles) of VIII and 15 ml. of 10% sodium hydroxide solution was refluxed for 4 hr. The reaction mixture was cooled and extracted with ether; the resulting aqueous solution was acidified and re-extracted with ether. The combined ether layers from the latter extraction were washed with water to neutrality, dried, filtered, and evaporated to give an oil which upon distillation *in vacuo* gave 330 mg. (44.3%) of crude lactone as a crystalline distillate. Three recrystallizations of the white solid from benzene–petroleum ether gave pure lactone as white needles, m.p. 77.5–78.0°. $\bar{\nu}_{max}^{CCl_4}$ 1740 cm.$^{-1}$ (lactone carbonyl); analytical bands at 1335, 1125, and 900 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.14; H, 9.58.

B. From Vb.—Into a dry 200-ml. flask was placed 4.28 g. (0.02 mole) of Vb, 10 ml. of absolute ethanol, and 100 ml. of liquid ammonia. To the rapidly stirred solution was added 4.6 g. (0.20 g.-atom) of sodium metal in small portions. Upon completion of the addition, a small amount of absolute ethanol was added to neutralize the remaining sodium. The solution was stirred until most of the ammonia had evaporated, water was added, and the solution was acidified with hydrochloric acid. The acid solution was extracted with ether, and the combined ether layers were washed with water. After the ether extract was dried, filtered, and concentrated, there remained 3.72 g. of a brownish oil which was distilled *in vacuo* to give 2.41 g. (71.7%) of a crystalline distillate, m.p. 65–72°. Recrystallization of this material from benzene–petroleum ether gave white, fluffy needles, m.p. 77–78°. A mixed melting point of this sample with a sample of the material prepared in section A gave no depression.

Dimethyl *trans*-Cyclohexane-1,2-diacetate (XI).—The diacid IX (4.00 g.) was treated with excess etheral diazomethane as described for the preparation of Va. The residual oil was distilled *in vacuo* to yield 4.18 g. (91.8%) of a colorless liquid, b.p. 95° (0.40 mm.), $n^{26}D$ 1.4600. Redistillation of a small sample of this material gave pure diester, b.p. 94° (0.40 mm.), $n^{25}D$ 1.4600.[13]

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.29; H, 8.71.

Methyl Hydrogen *trans*-Cyclohexane-1,2-diacetate (XII). A mixture of 6.0 g. (0.03 mole) of IX, 9.4 ml. (10.2 g., 0.10 mole) of acetic anhydride, and 4 drops of acetyl chloride was heated on the steam bath for 3 hr. At the end of this time, the solution was cooled and 50 ml. of anhydrous methanol was added and the solution heated at reflux for 0.5 hr. After removal of the solvent mixture under reduced pressure, the residue was distilled *in vacuo* to give 4.7 g. (72.8% for the two steps) of colorless liquid, b.p. 135–139° (0.275–0.35 mm.). A small sample was redistilled to give pure acid ester, b.p. 137° (0.14 mm.), $n^{26}D$ 1.4730. $\bar{\nu}_{max}^{CCl_4}$ 1700 (s, carboxyl carbonyl) and 1740 cm.$^{-1}$ (s, ester carbonyl).

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.81; H, 8.44.

***trans*-4-Oxa-3-oxobicyclo[5.4.0]undecane (II). A. By the Sodium in Liquid Ammonia Procedure.**—A 3.50-g. (0.0163 mole) sample of XII was treated with 4.6 g. (0.20 g.-atom) of sodium, 10 ml. of absolute ethanol, and 100 ml. of liquid ammonia as described for the preparation of III. There was obtained 3.04 g. of a brownish oil which was distilled *in vacuo* to give 1.76 g. (64.2%) of colorless oil, b.p 108–113° (0.2 mm.). Redistillation of a small sample gave pure lactone, b.p. 113° (0.2 mm.), m.p. 31–32°, $n^{25}D$ 1.4892 (super-cooled), $\bar{\nu}_{max}^{CCl_4}$ 1740 cm.$^{-1}$ (s, lactone carbonyl); analytical bands at 1430, 1300, 1240, and 1015 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.65.

B. By the Bouveault-Blanc Procedure.—To a solution of 4.0 g. (0.0187 mole) of XII in 250 ml. of refluxing absolute ethanol was slowly added 9.2 g. (0.40 g.-atom) of sodium metal in small portions with rapid stirring. When all the sodium had dissolved, the alcohol was removed under reduced pressure. To the solid residue was added 250 ml. of water. With ice-cooling, the solution was acidified slowly with hydrochloric acid and extracted with three 150-ml. portions of ether. The ether extract was dried, filtered, and evaporated to give 1.5 g. of crude cyclohexane-1,2-diacetic acid, m.p. 158–162°. The remaining aqueous solution was re-extracted with two 150-ml. portions of chloroform. The combined chloroform layers were dried, filtered, and evaporated to give a yellow brown oil. Vacuum distillation of this material gave 0.63 g. (20%) of colorless oil, b.p. 108–110° (0.4 mm.), $n^{26}D$ 1.4850 (super-cooled). A comparison of the infrared spectra of this material with that of the lactone prepared in section A indicated by the virtual superimposability of bands that they were identical in structure.

(13) *After completion of this work, this diester was synthesized via an alternate route by M. E. Ali and L. N. Owen, J. Chem. Soc.,* 2111 (1958); they report for this substance b.p. 115° (0.7 mm.), $n^{19}D$ 1.4625, in excellent agreement with the above work.

Synthesis of Ring C^{14}-Labeled Anthranilic and 3-Hydroxyanthranilic Acid

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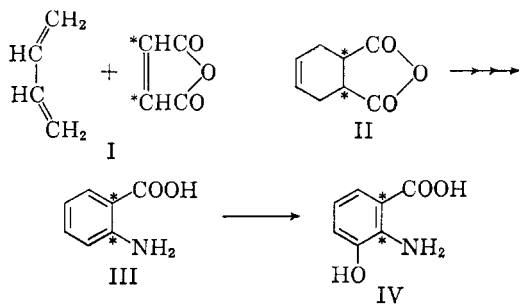
The stimulus for the syntheses reported in this note arose from the desire to study the metabolism of anthranilic and 3-hydroxyanthranilic acid, the latter an important intermediate in tryptophan metabolism and a known precursor of nicotinic acid.[1]

Starting materials used in the preparation of nuclear (1,2)-C^{14}-labeled anthranilic acid (III) were butadiene and maleic anhydride (I, C^{14}-labeled at the ethylenic carbons) which, in benzene underwent Diels-Alder condensation to yield 90% of 1,2,3,6-tetrahydro-*cis*-phthalic anhydride (II).[2]

(1) H. K. Mitchell and J. F. Nyc, *Proc. Soc. Acad. Sc.*, **34**, 1 (1948).

(2) E. F. Jenkins and E. J. Costello. *J. Am. Chem. Soc.*, **68**, 2733 (1946).

Aromatization of II by the method of Newman[3] gave 70–80% yields of 1,2-C^{14}-labeled phthalic anhydride, which on reaction with concentrated ammonium hydroxide yielded 1,2-C^{14}-labeled phthalimide[4] in 95% yield. Reaction of the latter with potassium hypobromite[5] produced 1,2-C^{14}-labeled anthranilic acid (III) in 70–75% yields after a different and simpler isolation procedure than that reported.[5] Finally, persulfate oxidation of III[6] afforded 10–15% yields of the 3-hydroxy derivative (IV) which was separated by ion exchange chromatography and further purified by recrystallization as the hydrochloride. 5-Hydroxyanthranilic acid was a concomitant product of this oxidation reaction.



Experimental

Melting points, taken in a capillary, are corrected.

Ring (1,2)-C^{14}-Labeled Anthranilic Acid (III).—To 1.0 g. of maleic anhydride (cold), 8.4 mg. of maleic anhydride, C^{14}-labeled at the Π-bond carbons (I, 0.5 mc.) and 2 ml. of benzene cooled to 0° was added 2 ml. of butadiene cooled in a Dry Ice–acetone bath. The mixture was stoppered tightly and kept at room temperature for 20 hr., then excess butadiene was expelled on the steam bath. The resultant solution (benzene dilution may be necessary) was filtered and diluted with an equal volume of ligroin (b.p. 30–60°). After cooling to −15°, 1.38 g. (91%) of 1,2-C^{14}-labeled-1,2,3,6-*cis*-tetrahydrophthalic anhydride (II), m.p. 98–100° was obtained.[2]

A refluxing solution of 1.3 g. of II and 2.6 ml. of glacial acetic acid was treated during 30–40 min. (stirring), with 1.1 ml. of bromine in 2.9 ml. of acetic acid. The solution was refluxed for 18 hr., and the solvent was evaporated (bath temperature 60–70°) with a water pump aspirator. The residue was kept (stirring) at 200–210° (oil bath temperature) for 7–9 hr. The dark residue was transferred to a sublimation tube with benzene, the benzene was removed with water pump evacuation, and the residue was dried *in vacuo* over potassium hydroxide to remove hydrogen bromide. Sublimation gave 1.03 g. (79%) of 1,2-C^{14}-labeled phthalic anhydride, m.p. 129–131°.[7] Further purification is usually unnecessary. Benzene–ligroin (b.p. 30–60°) may be used for recrystallization.

To 1.0 g. of the above phthalic anhydride in a small test tube was added carefully 1.0 ml. of 12 *M* ammonium hydroxide and the mixture was dried over a free flame during 5–10 min. The residual melt was heated to 270–280° during 5–10 min. where it was kept for a few more minutes. The material was sublimed at 150°/0.5 mm. to give 0.93 g. (93%) of **1,2-C^{14}-labeled phthalimide,** m.p. 229–232°.[4]

This phthalimide (0.93 g.) was added to an ice-cold solution of 0.34 ml. of bromine in 15.4 ml. of 2 *N* potassium hydroxide. The suspension was stirred to solution (10 min.) while cooling in an ice bath. Then 0.9 g. of potassium hydroxide pellets was added and the mixture again stirred to solution while cooling. The clear solution was stirred at room temperature for 8–10 min. and warmed to 80° during 5 min. Upon cooling in an ice bath and adding 1.8 ml. of acetic acid, crude III separated and was extracted with ether. After removal of the solvent and acetic acid, *in vacuo*, the material was sublimed (105°/0.5 mm.) to give 0.65 g. (77%) of III which melted at 144–146°.[5]

1,2,C^{14}-Labeled 3-Hydroxyanthranilic Acid (IV).[8]—A stirred solution of 0.65 g. of III, 140 ml. of 2 *N* potassium hydroxide and 32 ml. of water was treated during 4 hr. with 2.6 g. of potassium persulfate in 50 ml. of water. Hydrochloric acid (40 ml. of 12 *M*) was added, the dark solution was heated on the steam bath for 30 min., and the solution was evaporated to dryness at the water pump. The residue was extracted with 30 ml. of hot absolute ethanol in five portions. The combined, filtered extracts were evaporated to dryness *in vacuo*, leaving a residue (0.5 g.) which was dissolved in 10 ml. of water and chromatographed on a column (10 × 1 cm.) of Dowex 1-acetate. The column was washed with water, then eluted with a gradient of acetic acid with 50 ml. of water in the mixing bottle into which was added 6 *N* acetic acid; 10-ml. fractions were collected. 5-Hydroxyanthranilic acid (identified by paper chromatography and fluorescence)[9] was recovered from fractions 4 and 5 and 3-hydroxyanthranilic acid (IV)[9] in fractions 8–15. These were pooled and distilled in a flash evaporator. The residue was dissolved in water and the solvent again evaporated to remove acetic acid. Recrystallization from absolute alcohol by addition of a little ether gave 50 mg. of 1,2-C^{14}-labeled-3-hydroxyanthranilic acid (V) hydrochloride, m.p. 226–227° dec., identified by comparison with authentic material, by paper chromatography and by fluorescence.[9] The filtrate was evaporated to dryness. To the residue was added 50 mg. of 3-hydroxyanthranilic acid. Recrystallization gave 60 mg. more material, m.p. 227–228° with sufficient specific activity, for metabolic studies.

(3) M. S. Newman and C. D. McCleary, *J. Am. Chem. Soc.*, **63**, 1542 (1941).

(4) W. A. Noyes and P. K. Porter, *Org. Syntheses*, Coll. Vol. I, 457 (1941).

(5) M. M. S. Hoogewerf and W. A. Van Dorp, *Rec. trav. chim.*, **10**, 5 (1891).

(6) E. Boyland and P. Sims, *J. Chem. Soc.*, 980 (1954).

(7) I. Heilbron, *Dictionary of Organic Compounds*, **4**, 193 (1953).

(8) J. F. Nyc and H. K. Mitchell, *J. Am. Chem. Soc.*, **70**, 1847 (1948).

(9) E. Boyland, P. Sims, and D. C. Williams, *Biochem. J.*, **62**, 546 (1956).

The Steric Course of the Acid-Promoted Addition of Acetic Acid to Norcarane

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Although the unsaturation of cyclopropane and its derivatives has long been known, investigations of the steric course of addition to cyclopropane derivatives appear to be lacking. This report describes preliminary findings of our investigation of the acid-promoted opening of the cyclopropane ring of norcarane and deals primarily with the steric course of the addition reaction.

Norcarane was treated with glacial acetic acid in the presence of *p*-toluenesulfonic acid at 46.5° for eighty-eight hours. An infrared spectrum of the crude product mixture showed the following pertinent bands: carbonyl at 5.76 μ, acetate ester at 8.07 μ and double bond at 6.11 μ. Analysis by gas chromatography showed the product mixture to contain 57% hydrocarbon and 43% acetate. Further analysis by gas chromatography indicated the hydrocarbon fraction was made up of 3- and/or 4-methylcyclohexene (63–66%), 1-methylcyclohexene (26–25%), and cycloheptene (11–8%); no trace of unreacted norcarane could be found.

Saponification of the crude product mixture gave material which proved to be a mixture of cycloalkanols. The infrared spectrum showed the following pertinent bands: hydroxyl at 2.74–2.95 μ, methyl group at 6.90 and 7.30 μ, and bands at 9.37 μ, 9.50 μ, and 9.65 μ. The last three bands are especially characteristic of *trans*-2-methylcyclohexanol and are clearly distinguishable from the bands in the same region which are characteristic of the *cis* isomer.[1] Gas chromatograms of the mixture of cycloalkanols showed the presence of at least five components. Components present in minor amounts were 1) 1-methylcyclohexanol; 2) *cis*-2-methylcyclohexanol, integrated peak area along with 1-methylcyclohexanol—4%; 3) *trans*-3- and/or *trans*-4-methylcyclohexanol—1% and 4) cycloheptanol—15%. The major peak represented 79% of the mixture and was identical in retention time with *trans*-2-, *cis*-3-, or *cis*-4-methylcyclohexanol. Since it was not possible to achieve resolution of these cycloalkanols, the mixture of cycloalkanols was oxidized to a mixture of ketones and these were examined. Chromic acid oxidation of the mixture of cycloalkanols gave material whose infrared spectrum showed an unsymmetrical carbonyl band at 5.85 μ and weak absorption at 2.70–2.95 μ. A gas chromatogram of this material showed the following peaks: 1) 1-methylcyclohexanol—3%; 2) 2-methylcyclohexanone—76%; 3) 3-methylcyclohexanone—5%; 4) 4-methylcyclohexanone—less than 1%; 5) cycloheptanone—15%. The close agreement of the amount of 2-methylcyclohexanone in the mixture of cycloalkanones with the integrated area of the predominant cycloalkanol peak in the mixture of cycloalkanols clearly indicates that this cycloalkanol is largely *trans*-2-methylcyclohexanol.

trans-2-Methylcyclohexanol was also isolated as its 3,5-dinitrobenzoate from the mixture of 3,5-dinitrobenzoates by elution chromatography.

Dependence of the ring opening on the presence of strong acid was demonstrated by the result that only norcarane was recovered from a mixture of glacial acetic acid and norcarane after one week at 46.5°.

Results have been obtained which indicate that formation of *trans*-2-methylcyclohexyl acetate is largely kinetically controlled. A mixture containing 59% *cis*-2-methylcyclohexyl acetate and 41% *trans*-2-methylcyclohexyl acetate was treated with sulfuric acid in glacial acetic acid at 50° for five hundred hours. The product included a hydrocarbon fraction (16%), which consisted largely of 1-methylcyclohexene and 3- and/or 4-methylcyclohexene (less than 1%), and an acetate fraction, 84%, which on saponification afforded a mixture of cycloalkanols made up of 14% 1-methylcyclohexanol, 27% *cis*-2-methylcyclohexanol, and 59% *trans*-2-methylcyclohexanol. These results show that only 46% of the initial *cis*-2-methylcyclohexyl acetate was transformed to other products in five hundred hours. Since the *trans* isomer in the mixture of cycloalkyl acetates from ring opening is present to the extent of 79% after only eighty-eight hours, the *trans* isomer is being formed more rapidly than it could be formed by the isomerization of the less stable *cis*-2-methylcyclohexyl acetate under comparable conditions.

Although addition of acetic acid to 3-methylcyclohexene may account for some of the *trans*-2-methylcyclohexyl acetate, certainly this is not the path by which the preponderant amount of this material is formed. Addition to 3-methylcyclohexene could reasonably be expected to give nearly equal amounts of 2- and 3-methylcyclohexyl acetates, however equal amounts of the two methylcyclohexyl acetates are not afforded in the ring opening reaction.

The nearly exclusive formation of *trans*-2-methylcyclohexyl acetate among the methylcyclohexyl acetates demonstrates that addition of acetic acid to norcarane under the conditions employed proceeds in a stereospecific manner. Final interpretation of all aspects of the ring opening reaction, including olefin formation, ring enlargement, and stereochemistry of addition, awaits the results of experimental work now in progress.

Experimental

Norcarane.—Norcarane was prepared by the method of Simmons and Smith.[2] Purification was effected by double distillation through a Todd column, b.p. 115.8–115.9°. Gas-liquid chromatographic analysis of the purified norcarane showed it contained approximately 2% of an impurity which appeared as a shoulder on the low retention time side of the norcarane peak. Brief treatment of the purified norcarane in ether solution with cold dilute permanganate resulted only in consumption of norcarane with no effect whatsoever on reducing the amount of impurity. Therefore the impurity was considered to be inert material which would not give rise to spurious results in the ring opening reactions of norcarane.

Acid-Promoted Addition of Acetic Acid.—A sealed glass tube containing 1.84 g. of norcarane and 25 ml. of 0.0745 M *p*-toluenesulfonic acid in glacial acetic acid was placed in a constant temperature bath at 46.5°. After 88 hr., the tube was withdrawn, cooled and its contents added to 50 ml. of water and 50 ml. of ether. The aqueous layer was ex-

(1) E. L. Eliel and C. A. Lukach, *J. Am. Chem. Soc.*, **79**, 5986 (1957).

(2) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **81**, 4256 (1959).

tracted three times with 30-ml. portions of ether. The combined ether extracts were washed three times with 30-ml. portions of water, three times with 30-ml. portions of 5% sodium bicarbonate, and finally with saturated salt solution. The ether solution was dried over anhyrous magnesium sulfate. The ether was removed by distillation through a 12-in. Vigreux column. The remaining oil, 2.71 g., was subjected immediately to gas-liquid chromatographic analysis using a 4-ft. diethylene glycol adipate on Celite column at 81°. The column had been calibrated using known amounts of 3-methylcyclohexene and a mixture of *cis*- and *trans*-2-methylcyclohexyl acetates. The chromatogram showed that the product mixture was made up of 27% acetate, 36% hydrocarbon, and 37% residual ether, which amounts to 43% acetate and 57% hydrocarbon excluding residual ether. Gas-liquid chromatographic analysis of the product mixture using an 11-ft. 4% squalane on firebrick column at 80.8°, flow rate 49 ml./min. showed in addition to residual ether, three peaks at 9.8 min. (63%), 12.5 min. (26%), and 14.2 min. (11%); retention times in the order given were identical with retention times of 3-[3] or 4-methylcyclohexene[4] (authentic samples not separable), 1-methylcyclohexene,[4] and cycloheptene.[5] The norcarane peak at 16.8 min. was absent. A chromatogram obtained using a 11.5-ft 15% Silicone 550 on firebrick column at 81.0°, flow rate 54.5 ml./min. showed three peaks at 7.8 min. (66%), 10.0 min. (25%), 11.8 min. (8%); again retention times, in the order given, were identical with 3- or 4-methylcyclohexene (authentic samples not separable), 1-methylcyclohexene and cycloheptene. The norcarane peak at 13.0 min. was lacking.

In the infrared spectrum, the mixture of cycloalkyl acetates and cycloalkenes showed the following bands; 5.76, 6.11, 6.90, 7.30, 8.07, 10.13 (strong), 10.27 μ.

Saponification.—The mixture of cycloalkyl acetates, 2.33 g., and 5 g. of potassium hydroxide in 25 ml. of water were stirred rapidly at about 35° for 6 hr. The aqueous phase was saturated with sodium chloride and 20 ml. of ether was added. The aqueous layer was extracted three times with 15-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Distillation of the ether through a 12-in. Vigreux column and subsequent vacuum distillation of the remaining oil afforded 552 mg. of cycloalkanols, b.p. 72–80° (20 mm.). Pertinent bands in the infrared spectrum were found at 2.74, 2.95, 5.77 (trace), 6.82, 6.83, 7.30, 9.37, 9.50, 9.65, 9.71 (weak), and 10.96 μ (weak). Gas-liquid chromatographic analysis using a 11-ft., 17% glycerol on Celite column at 100°, flow rate 52.6 ml./min., showed five peaks at 7.2 and 8.0 min. (4%), 11.0 min. (79%), 15.5 min. (about 1%), 27 min. (15%); the retention times in the order given were identical with 1-methylcyclohexanol, *cis*-2-methylcyclohexanol,, *trans*-2- or *cis*-3- or *cis*-4-methylcyclohexanol[1] (authentic samples not separable), *trans*-3- or *trans*-4-methylcyclohexanol[1] (authentic samples not separable), and cycloheptanol.[4] No trace of cyclohexylcarbinol[6] at 20.5 min. could be found. Gas-liquid chromatographic analysis using a 13-ft .,5% erythritol on "Celite" column at 86.6°, flow rate 46.8 ml./min. gave four peaks, at 9 min., 11 min., 20 min., and 30 min.; in the order given, these four peaks correspond to the retention times of 1-methylcyclohexanol and *cis*-2-methylcyclohexanol (authentic samples not separable), *trans*-2-methylcyclohexanol, *trans*-3- and *trans*-4- methylcyclohexanol (authentic samples not separable), and cycloheptanol. No trace of cyclohexylcarbinol at 22 min. could be found. A synthetic mixture of 45 mg. of 3-methylcyclohexanol (29% *cis*) and 103 mg. of 2-methylcyclohexanol (88% *trans*) gave only one peak in the immediate region of 11.0–13.0 min. A synthetic mixture containing equal quantities by volume of *cis*-3-methylcyclohexanol and *trans*-2-methylcyclohexanol afforded two peaks at 11.0 and 13.0 min.

Oxidation of Cycloalkanols.—The mixture of cycloalkanols was oxidized by the method of Brown and Garg.[7] To 440 mg. of cycloalkanol (3.85 mmoles) in 7 ml. of ether was added 386 mg. of sodium dichromate dihydrate (1.30 mmoles) in 0.3 ml. of 96% sulfuric acid and 2.0 ml. of water. The chromic acid solution was added slowly over a period of 15 min. with a rapid stirring and in such a manner that the temperature did not exceed 28°. The two phase system was stirred for an additional 2 hr. After work-up by the usual method, the remaining oil was distilled to give 295 mg. of cycloalkanones b.p. 49–55° (10 mm.). Pertinent bands in the infrared were found at 2.75, 2.90, 5.85 (unsymmetrical), 6.90, and 7.30 μ. Gas-liquid chromatographic analysis used an 8′ Carbowax 20M column at 141°; the flow rate was 61.2 ml./min. Peaks were found at 19 min. (1-methylcyclohexanol, 3%), 21 min. (2-methylcyclohexanone,[4] 76%), 23.5 min. (3-methylcyclohexanone[8] 5%), 25 min. (4-methylcyclohexanone,[6] less than 1%), and 35.5 min. (cycloheptanone,[8] 15%). Identification of each peak was made by adding a known amount of authentic sample to a known amount of the mixture of cycloalkanones. In each case addition of authentic sample resulted only in enlarging the peak in question and produced no new peaks.

Preparation and Separation of 3,5-Dinitrobenzoates.—A mixture of cycloalkanols originating from norcarane was produced by the method similar to that described above. Treatment of 446 mg. of cycloalkanols with freshly prepared 3,5-dinitrobenzoyl chloride in anhydrous pyridine gave 821 mg. of the crude 3,5-dinitrobenzoates, m.p. 82–100°. Chromatography of 59.4 mg. of the crude 3,5-dinitrobenzoate mixture on a silicic acid–Celite–rhodamine 6G column,[9] 30 cm. × 12 mm., resulted in incomplete separation of the major component, *trans*-2-methylcyclohexyl 3,5-dinitrobenzoate. The column was eluted with 0.5% ether-*n*-hexane. Results of the chromatography are summarized below. Mixture of fractions 1, 2, or 3 with authentic *trans*-2-methylcyclohexyl 3,5-dinitrobenzoate (m.p. 116.5–117.5°) showed no depression in melting points. Isolation of the next most abundant component, cycloheptyl 3,5-dinitrobenzoate, was not realized. Rechromatography of combined fractions 11–25 effected no separation.

Fractions	Combined Weight in Mg.	M.P. Range of Fractions
1–3	12.8 (22%)	(116.0–117.5)–(113–116°)
4–5	9.0	(107–114)–(103–113°)
6–10	12.4	(99–114)–(66–82°)
11–25	22.2	(57–65)–(56–64)

Acid Treatment of 2-Methylcyclohexyl Acetate.—A mixture of *cis*- (59%) and *trans*-2-methylcyclohexanol (41%, analysis by gas-liquid chromatography) was converted to a mixture of acetates by warming with freshly distilled acetic anhydride. A sealed glass tube containing 3.0 g. of this mixture of acetates and 10 drops of 96% sulfuric acid in 50 ml. of glacial acetic acid remained in a constant temperature bath at 50° for 500 hr. Work-up of the contents of the tube in a manner similar to that employed in the norcarane ring opening furnished 2.23 g. of oil. Gas-liquid chromatographic analysis using a diethylene glycol adipate on Celite column showed the material to consist of 84% acetate and 16% hydrocarbon and in addition some residual ether; gas-liquid chromatographic analysis using a 4% squalene on fire brick column showed that the hydrocarbon content consisted of less than 1% 3- or 4-methylcyclohexene and the remainder 1-methylcyclohexene. Saponification

(3) A. Berlande, *Compt. rend.*, **213**, 437 (1941).

(4) Purchased from the Aldrich Chemical Co. and distilled.

(5) Purchased from the Columbia Organic Chemical Co. and distilled.

(6) Purchased from Eastman Organic Chemicals and distilled.

(7) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

(8) Prepared from cycloheptanol by oxidation according to Brown and Garg.[7]

(9) J. W. White, Jr., and E. C. Dryden, *Anal. Chem.*, **20**, 853 (1945).

of the 2.15 g. of the crude mixture of acetate was accomplished by employing 5 g. of potassium hydroxide in 25 ml. of water. Work-up and distillation yielded 483 mg. b.p. 72–80° (21 mm.). The infrared showed bands at 2.82, 2.95, 6.85, 6.90 in addition to several bands in the 9.0–11.0-μ region. Gas-liquid chromatography on a 5% erythritol on Celite column produced three peaks identical with 1-methylcyclohexanol (14%), *cis*-2-methylcyclohexanol (27%), and *trans*-2-methylcyclohexanol (59%).

Norcarane and Acetic Acid.—A sealed tube containing 1.9 g. of norcarane and 10 ml. of glacial acetic acid remained in a constant temperature bath for 1 week at 46.5°. Work-up in the usual manner furnished an oil which by gas-liquid chromatographic analysis on an 11-ft. 4% squalene on firebrick column showed only the presence of norcarane.

Gas-Liquid Chromatographic Analyses and Infrared Spectra.—A Baird double beam infrared spectrophotometer was employed to determine the infrared spectra. The gas-liquid chromatographic analyses were carried out with an instrument constructed in these laboratories. The instrument contained a Gow-Mac thermal conductivity cell. Helium was employed as the mobile phase.

Acknowledgment.—The work described above was supported by a Frederick Gardner Cottrell Grant-in-Aid. The author wishes to thank Mr. L. S. Forney for the preparation of norcarane.

A Dihydroresorcinol Derivative[1]

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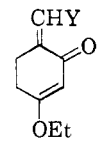
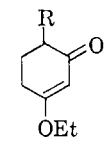
As a result of our need for 6-hydroxymethylene-3-ethoxycyclohex-2-enone (Ia) the formylation of the dihydroresorcinol derivative, 3-ethoxycyclohex-2-enone(IIa), was investigated. Reaction between the latter, ethyl formate, and sodium ethoxide in benzene yielded a single, crystalline $C_9H_{12}O_3$ compound. Its spectral properties, its alcohol solution giving a positive ferric chloride test, and its conversion to a copper chelate revealed the product to be a readily enolizable substance. It could be transformed into an enol acetate with acetic anhydride and pyridine and into an enol ether by base-induced reaction with isopropyl iodide. While *a priori* the formyl group could have entered the dihydroresorcinol nucleus at C-2,-4, or -6, the preliminary evidence favored C-6 as its site of attachment. Nevertheless, a search for more rigorous data was undertaken.

Catalytic hydrogenation of the formylation product yielded a dihydro derivative whose ultraviolet spectrum was identical with that of dihydroresorcinol ethyl ether(IIa). Thus the formyl (or hydroxymethylene) group had been reduced to



Ia. Y = OH
b. Y = O—*i*-Pro
c. Y = OAc
d. Y = H

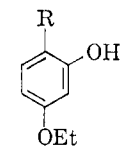


IIa. R = H
b. R = CH_2OH
c. R = CH_2OAc

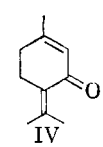
a hydroxymethyl function whose position was limited to C-4 or -6 (IIb), since at C-2 it would have been expected to alter the nuclear chromophore.

Catalytic hydrogenation of the enol acetate of the formylation product yielded a mixture from which a crystalline $C_9H_{12}O_2$ compound was isolated. Its spectral properties showed it to be an aromatic substance. On the assumption of its being 4-ethoxy-2-hydroxytoluene(IIIa) this compound was synthesized. Diazoethane treatment of β-resorcylaldehyde yielded 4-ethoxysalicylaldehyde(IIIb). Reduction of the latter with zinc and acetic acid afforded the cresol IIIa, identical in all respects with the product of hydrogenation of the enol acetate of the formylation product. These results establish firmly the C-6 attachment of the carboxaldehyde (or hydroxymethylene) function in the initial formylation product. They further suggest that the latter's enol ether, enol acetate, and dihydro derivative are represented by Ib, Ic, and IIb, respectively.

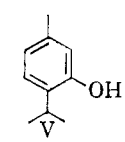
IIIa. R = CH_3
b R = CHO
c. R = CN



The unusual transformation of Ic into IIIa under hydrogenation conditions proceeds most probably *via* Id, produced either by direct hydrogenolysis of Ic or by the latter's hydrogenation to IIc and catalyst-induced β-elimination of acetate to Id.[3] The extraordinary isomerization of an alkylidenecyclohexenone(Id) into a phenol(IIIa) finds precedence in the recent conversion of piperitenone(IV) into thymol(V) under hydrogenation conditions.[4]



IV



V

As an alternate route from the aldehyde IIIb to the cresol IIIa, the Wolff-Kishner reduction of the former's semicarbazone had been examined briefly. This reaction yielded a mixture of prod-

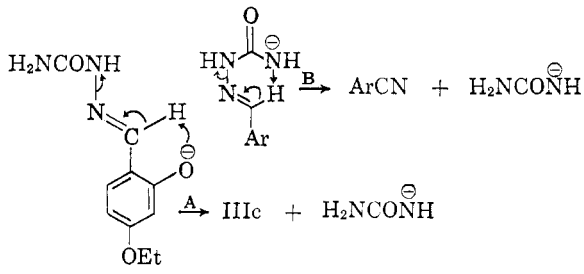
(1) Financial support for this work by Ciba Pharmaceutical Products Inc., Summit, N. J., hereby is gratefully acknowledged.

(2) Present address: Department of Chemistry, Indiana University, Bloomington, Ind.

(3) *Cf.* E. Wenkert, A. K. Bose, and T. L. Reid, *J. Am. Chem. Soc.*, **75**, 5514 (1953).

(4) E. D. Bergmann and P. Bracha, *J. Org. Chem.*, **24**, 994 (1959).

ucts from which the desired phenol and, more interesting, the nitrile IIIc (characterized as its acetate) could be isolated. The latter's identity was established by the synthesis of its acetate through the treatment of the aldoxime (of IIIb) with acetic anhydride. The unusual base-induced nitrile production is rationalized most readily on the basis of mechanisms A or B.[5]



Experimental

6-Hydroxymethylene-3-ethoxycyclohex-2-enone(Ia) and Its Derivatives.—A mixture of dry sodium ethoxide, from 4.6 g. of sodium, 13.4 g. of ethyl formate, and 12.9 g. of 3-ethoxycyclohex-2-enone(IIa) [b.p. 61–64°/0.1 mm.; spectra: ultraviolet (EtOH), λ_{max} 249 mμ (log ε 4.27); infrared ($CHCl_3$), 6.09(s) and 6.24(s)μ][6] in 100 ml. of anhydrous benzene was left standing at room temperature under nitrogen for 22 hr. The reaction mixture then was stirred with cold water and extracted with 5% sodium hydroxide solution. Addition of solid carbon dioxide to the aqueous extract led to a precipitate which was filtered and washed with water. Crystallization of the colorless solid, 8.0 g., m.p. 93°, from aqueous ethanol yielded crystalline Ia, m.p. 93–93.5°; spectra: ultraviolet (EtOH), λ_{max} 256 mμ (log ε 4.05) and 295 mμ (log ε 3.93), λ_{min} 225 mμ (log ε 3.48) and 276 mμ (log ε 3.81); infrared ($CHCl_3$), 3.70(vw), 5.70(w), 6.09(s), and 6.24(s) μ; copper chelate, m.p. 185–187°; semicarbazone, m.p. 203–204°.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.30; H, 7.19. Found: C, 64.28; H, 7.12.

A mixture of 5.0 g. of Ia, 6.4 g. of isopropyl iodide, and 6.2 g. of anhydrous potassium carbonate in 40 ml. of anhydrous acetone was refluxed under nitrogen for 30 hr. After removal of the solvent and addition of cold water the mixture was extracted with ether. The extract was washed with cold 5% sodium hydroxide solution, with water and with saturated brine solution. The ether solution then was dried over anhydrous potassium carbonate and evaporated under vacuum. Crystallization of the solid residue, 4.5 g., m.p. 58–61°, from petroleum ether yielded crystalline 6-isopropoxymethylene-3-ethoxycyclohex-2-enone(Ib), m.p. 62.5–63.5°; ultraviolet spectrum (EtOH), λ_{max} 292 mμ (log ε 4.21), $\lambda_{shoulder}$ 263 mμ (log ε 4.06), λ_{min} 229 mμ (log ε 3.28).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.94; H, 8.73.

A solution of 2.0 g. of Ia and 4 ml. of acetic anhydride in 10 ml. of pyridine was refluxed under nitrogen for 10 min., cooled, and poured onto 40 ml. of ice water. The solid, 1.8 g., was filtered and washed with cold 2% hydrochloric acid solution and with water. Crystallization from aqueous alcohol gave long colorless needles of 6-acetoxymethylene-3-ethoxycyclohex-2-enone(Ic), m.p. 88–89°; spectra: ultraviolet (EtOH), λ_{max} 279 mμ (log ε 4.30), λ_{min} 226 mμ(log ε 2.19); infrared ($CHCl_3$), 5.66(s), 5.98(s) and 6.24(s) μ.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.90; H, 6.72. Found: C, 62.80; H, 6.73.

6-Hydroxymethyl-3-ethoxycyclohex-2-enone (IIb).—A mixture of 500 mg. of Ia and 50 mg. of 5% palladium-charcoal in 20 ml. of ethyl acetate was hydrogenated at atmospheric pressure and room temperature. After hydrogen uptake had ceased, the catalyst was filtered and the solvent removed under vacuum. Chromatography of the residue on a silica column and elution with 4:1 petroleum ether–ether yielded 200 mg. of a solid, m.p. 71–73°. Crystallization of the latter from petroleum ether–ether gave crystalline IIb, m.p. 72.5–73°; spectra: ultraviolet (EtOH), λ_{max} 250 mμ (log ε 4.18); infrared ($CHCl_3$), 2.80(w), 2.88(w), 2.93(w), 6.09(s) and 6.24(s) μ.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.55; H, 8.45.

4-Ethoxy-2-hydroxytoluene (IIIa).—A mixture of 700 mg. of Ic and 100 mg. of 5% palladium-charcoal in 25 ml. of ethyl acetate was hydrogenated at atmospheric pressure and room temperature. After a work-up identical with the above and elution with 19:1 petroleum ether–ether 190 mg. of a solid product was obtained. Crystallization of the latter from benzene yielded colorless needles of IIIa, m.p. 47–48°; infrared spectrum ($CHCl_3$), 2.77(m), 3.00(w), 6.15 (s), and 6.26(s) μ.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.40; H, 8.13.

A 20% excess of ethereal diazoethane solution was added to 3.0 g. of β-resorcyaldehyde in 100 ml. of ether and the mixture was left standing for 1 hr. Upon solvent removal under reduced pressure the residue was chromatographed on silica. The 1:1 petroleum ether–ether eluates were concentrated and the resulting oil exposed to short-path distillation. This led to 2.5 g. of 4-ethoxysalicylaldehyde (IIIb), m.p. 34°; ultraviolet spectrum (EtOH), λ_{max} 230 mμ (log ε 4.17), 278 mμ (log ε 4.31) and 319 mμ (log ε 3.92), λ_{min} 247 mμ (log ε 2.75) and 303 mμ log ε 3.90); oxime, m.p. 87–88°.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.18; H, 6.10.

Zinc dust, 50 g., was added in 10-g. portions at 10-min. intervals to a stirring solution of 700 mg. of 4-ethoxysalicylaldehyde (IIIb) in 50 ml. of glacial acetic acid. After filtration the residue was washed with hot water and ethyl acetate. The combined filtrates were brought to pH 6, the organic phase dried over magnesium sulfate, and its solvent removed under vacuum. Silica chromatography of the residue and elution with 19:1 petroleum ether–ether yielded 105 mg. of starting aldehyde, while elution with a 9:1 solvent mixture afforded 365 mg. of 4-ethoxy-2-hydroxytoluene (IIIa), m.p., m.m.p. 46–47°; spectra identical with those of the above sample.

4-Ethoxysalicylonitrile Acetate.—Crystallization of the semicarbazone of 4-ethoxysalicylaldehyde(IIIb) from ethyl acetate–dimethylformamide produced platelets, m.p. 208–209°; ultraviolet spectrum (EtOH), λ_{max} 232 mμ (log ε 4.14), 288 mμ (log ε 4.25) and 317 mμ (log ε 4.29).

Anal. Calcd. for $C_{10}H_{13}O_3N_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.79; H, 6.11; N, 18.89.

A mixture of 620 mg. of the semicarbazone and 1.5 g. of powdered potassium hydroxide in 10 ml. of ethylene glycol was kept at 180° until the escaping gases no longer turned red litmus blue and then was heated at 210° for 2 hr. Upon cooling 100 mg. of cold water was added and the resulting solution extracted with cold 10% hydrochloric acid solution, with chloroform and with ethyl acetate. After drying of the combined organic solutions over magnesium sulfate, the solvent was removed under vacuum. Silica chromatography of the residue and elution with 4:1 petroleum ether–ether yielded 8 mg. of a solid, m.p. 46–47°, identical in all respects with the phenol IIIa. Elution with ether and ether-methanol gave two unidentified oils, 55 mg. and 38 mg., respectively.

(5) B may be the preferred pathway since aldehyde semicarbazones having no neighboring, potentially reaction-facilitating group have been shown previously to produce nitriles in low yields in attempted Wolff-Kishner reductions (E. Wenkert and J. W. Chamberlin, unpublished results).

(6) E. G. Meek, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 811 (1953).

TABLE I
2-FUROATES OF 4-PHENYLPHENOL AND BROMO-4-PHENYLPHENOLS

Phenol Used[a]	Yield, %	M.P., °C.[b]	Formula	Bromine, % Calcd.	Bromine, % Found
4-Phenyl-	85.1	125–126	$C_{17}H_{12}O_3$	..	..
4-(4-Bromophenyl)-	88.9	153–154	$C_{17}H_{11}O_3Br$	23.3	23.7
2,6-Dibromo-4-phenyl-	85.5	152–153	$C_{17}H_{10}O_3Br_2$	37.9	37.9
2-Bromo-4-(4-bromophenyl)-	93.5	127–128	$C_{17}H_{10}O_3Br_2$	37.9	38.2
2,6-Dibromo-4-(4-bromophenyl)-	87.9	186.5–187.5	$C_{17}H_9O_3Br_3$	47.9	48.2

[a] The bromo-4-phenylphenols were prepared by recorded methods. [b] The esters were purified by crystallization from ethanol.

Further elution with methanol led to 25 mg. of an oil with an intense nitrile infrared absorption peak. It was acetylated by standard means and the product chromatographed on silica. This produced crystalline 4-ethoxysalicylonitrile acetate, m.p. 72.5–73.5°; spectra: ultraviolet (EtOH), λ_{max} 250 mμ (log ε 4.20) and 283 mμ (log ε 3.17), λ_{min} 226 mμ (log ε 3.74) and 280 mμ (log ε 3.09); infrared ($CHCl_3$), 4.48(s), 5.63(s), 6.20(s), and 6.35(m) μ.

Anal. Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.64; H, 5.53; N, 6.67.

A solution of 100 mg. of 4-ethoxysalicylaldoxime and 0.5 ml. of acetic anhydride was refluxed for 2 hr. and then poured onto 5 ml. of ice water. The resulting precipitate was filtered, crystallized from aqueous ethanol, and chromatographed on silica. Elution with 9:1 petroleum ether–ether led to a crystalline solid, m.p., m.m.p. 72–73.5°, identical in all respects with the above sample of 4-ethoxysalicylonitrile acetate.

The Bromination of 4-Phenylphenyl 2-Furoate

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A number of esters of the phenylphenols have been brominated previously, and the results of these studies have been reported.[1] In this investigation, an acyl group of different type than those involved in previous studies has been used, *viz.*, the furoyl group. The results are different. Bromination occurred in the acyl portion of the molecule rather than in the biphenyl group, and 4-phenylphenyl 5-bromo-2-furoate was formed. Such is in agreement with reports by Gilman[2] that the furan ring undergoes substitution reactions more readily than the benzene ring.

Reaction products were identified by mixed melting point procedures.

A number of related esters have been prepared.

(1) S. E. Hazlet and L. C. Hensley, *J. Am. Chem. Soc.*, **69**, 708 (1947) and earlier papers.

(2) See, for example: H. Gilman and E. B. Towne, *Rec. trav. chim.*, **51**, 1054 (1932); H. Gilman and N. O. Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933); and H. Gilman and R. V. Young, *ibid.*, **56**, 464 (1934).

Experimental

2-Furoates of 4-Phenylphenol and Bromo-4-phenylphenols.—4-Phenylphenol (40 g., 0.235 mole) was dissolved in 30 ml. of pyridine and 60 ml. of *p*-dioxane; the solution was cooled to 5°, and 36.8 g. (0.282 mole) of 2-furoyl chloride was added in small portions. The mixture was heated at 70° for 1 hr. and then cooled; 400 ml. of water was added, and the solution was acidified with dilute hydrochloric acid. The crude product was obtained in nearly quantitative yield; purification was effected by crystallizations from ethanol, m.p. 125–126°.

Anal. Calcd. for $C_{17}H_{12}O_3$: C, 77.3; H, 4.55. Found: C, 77.4; H, 4.61.

Several 2-furoic acid esters of bromo-4-phenylphenols were prepared by similar procedures. The results are shown in Table I.

5-Bromo-2-furoic Acid.—Except that only a small excess of bromine was used, this compound was prepared in 64% yield by the method of Whittaker,[3] m.p. 187–187.5°.

5-Bromo-2-furoyl Chloride.—5-Bromo-2-furoic acid (3 g., 0.0157 mole) was treated with thionyl chloride (12 g., 0.101 mole) and a drop of pyridine. The mixture was refluxed on a steam bath for 6 hr., the excess thionyl chloride was removed by distillation, and the acid chloride—the residue—was used without purification.

4-Phenylphenyl 5-Bromo-2-furoate.—To the crude 5-bromo-2-furoyl chloride (*ca.* 0.0157 mole) were added 2 ml. of pyridine, 7 ml.of *p*-dioxane, and 2.67 g. (0.0157 mole) of 4-phenylphenol. The mixture was heated for 1 hr. on a steam bath, cooled, and diluted with 40 ml. of water; the odor of pyridine was discharged by the addition of dilute hydrochloric acid. The solid product was leached with hot water and then with 5% sodium carbonate solution and washed with hot water. Crystallizations from ethanol gave 2.2 g. (0.00641 mole, 40.8% yield) of 4-phenylphenyl 5-bromo-2-furoate, m.p. 152–153°.

Anal. Calcd. for $C_{17}H_{11}O_3Br$: Br, 23.3. Found: Br, 23.9.

Bromination of 4-Phenylphenyl 2-Furoate.—The ester (10 g., 0.0379 mole) was suspended in 30 ml. of glacial acetic acid, which had been heated to 115°. A trace of iron powder was introduced, and 6 g. (0.0375 mole) of bromine dissolved in 10 ml. of glacial acetic acid was added. The temperature of the mixture was maintained at 100° for 50 min.

The mixture was cooled to room temperature, and the precipitated solid (6 g.) was collected by filtration, m.p. 130–139°. Crystallizations from propanol gave 4.8 g. (0.014 mole, 37.3% yield) of 4-phenylphenyl 5-bromo-2-furoate, m.p. 149–150.5°.

The acidic solution was diluted with 250 ml. of water and neutralized with sodium carbonate solution; the precipitated solid (6.1 g.) was collected by filtration, m.p. 107–117°. Several crystallizations from ethanol gave 3.9 g. (0.0148 mole, 39.5% yield) of 4-phenylphenyl 2-furoate, m.p. 123–124°.

Hydrolysis of 4-Phenylphenyl 5-Bromo-2-furoate.—A

(3) R. M. Whittaker, *Rec. trav. chim.*, **52**, 352 (1933).

small sample of 4-phenylphenyl 5-bromo-2-furoate obtained by the bromination of 4-phenylphenyl 2-furoate was refluxed in 20% potassium hydroxide (water–ethanol, 1:1) solution for 20 hr. From the reaction mixture, 4-phenylphenol, m.p. 161–162° (which was converted to the benzoate, m.p. 146–147°[4]), and 5-bromo-2-furoic acid, m.p. 185.5–186.5°, were obtained.

(4) S. E. Hazlet, G. Alliger, and R. Tiede, *J. Am. Chem. Soc.*, **61**, 1447 (1939).

A New Chemical Synthesis of 2-D-Ribofuranosyl-*as*-triazine-3,5(2*H*,4*H*)-dione (6-Azauridine)[1]

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A recent communication[2] describing a synthesis of 6-azauridine prompts us to report a new chemical route to this compound which offers added evidence that attachment of the ribose is at the 2- position of the *as*-triazine ring. An earlier synthesis,[3] resulting from the direct ribosidation of the mercury salt of 6-azauracil led to two isomers, neither of which was obtained crystalline.

This paper describes a method for the chemical synthesis of 6-azauridine based on the findings of E. Cattelain,[4] who demonstrated that alkylation of 6-benzyl-3-(methylthio)-*as*-triazin-5(2*H*)-one[5] occurred at the 2- position of the *as*-triazine ring.

Accordingly, we synthesized the desired intermediate, 3-(methylthio)-*as*-triazin-5 (4*H*)-one (III). Since this work was completed the preparation of III has been reported and assigned the (4*H*) structure, based on a series of pK_a determinations.[6] The same authors report that similar to the experience of Cattelain,[4] methylation of III was found to occur exclusively in the 2- position of the *as*-triazine ring (1-position of the 6-azauracil system).

In this laboratory III was made *via* two routes: first by cyclization of glyoxylic acid, 3-methylisothiosemicarbazone (I), or more conveniently by methylation of glyoxylic acid, 3-thiosemicarbazone (II), with concurrent cyclization.

Condensation of IV (mercuribis salt of III) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride by the method of Fox *et al.*[7] gave, after hydrolytic desulfurization, a product which proved to be 2′,3′,5′ - tri - *O* - benzoyl - 6 - azauridine (V). Debenzoylation in methanolic ammonia led to crystalline 6-azauridine (VI), identical in all respects to material produced by fermentation.

Experimental[8]

3-(Methylthio)*as*-triazin-5(4*H*)-one (III).—A. A solution of 17.2 g. (0.074 mole) of 3-methylisothiosemicarbazide, hydroiodide in 90 ml. of water was added to a solution of 6.8 g. (0.074 mole) of glyoxylic acid, hemihydrate in 75 ml. of *N* sodium hydroxide at room temperature. After a short time, 11.2 g. of glyoxylic acid, 3-methylisothiosemicarbazone (I), m.p. 180–190° dec., separated.

Anal. Calcd. for $C_4H_7N_3O_2S$: C, 29.83; H, 4.38; N, 26.07; S, 19.89. Found: C, 29.60; H, 4.56; N, 25.76; S, 19.56.

After refluxing 11 g. of I in 700 ml. of 95% ethanol for 5 hr. 4.4 g. of unchanged material was filtered off and a total of 2.8 g. (29%) of III was obtained by concentration of the mother liquor.

B. To a solution of 107 g. (1.17 moles) of thiosemicarbazide in 3 l. of 80% ethanol at 70° was added 116.7 g. (1.27 moles) of glyoxylic acid, hemihydrate in 600 ml. of 80% ethanol. After 5 min., a solution of 52 g. (1.3 moles) of sodium hydroxide in 325 ml. of water was added, followed by 189 g. (1.33 moles) of methyliodide. The mixture was refluxed for 2.5 hr. and then concentrated to one third the original volume. After cooling, the crude product was filtered and recrystallized from ethyl acetate to yield 108 g. (64%) of 3-(methylthio)-*as*-triazin-5(4*H*)-one (III); m.p. 222–224°.

Anal. Calcd. for $C_4H_5N_3OS$: C, 33.55; H, 3.52; N, 29.35; S, 22.40. Found: C, 33.54; H, 3.44; N, 29.03; S, 22.56.

The intermediate glyoxylic acid, 3-thiosemicarbazone (II), has been isolated and recrystallized from water; m.p. 165° dec.

Anal. Calcd. for $C_3H_5N_3O_2S$: C, 24.49; H, 3.43; N, 28.56; S, 21.79. Found: C, 24.37; H, 3.41; N, 28.22; S, 21.33.

2,2′-Mercuribis[3-(methylthio)-*as*-triazin-5(2*H*)-one] (IV).—A warm solution of 6.38 g. (0.02 mole) of mercuric acetate in 50 ml. of methanol was added to a warm solution of 5.72 g. (0.04 mole) of III in 120 ml. of methanol. After cooling, the precipitate was filtered and washed successively with water, ethanol, and ether. The product (IV) weighed 8.6 g. (88%) and had a good analysis for a compound containing a ratio of 2 moles of triazine and one mole of mercury.

Anal. Calcd. for $C_8H_8N_6O_2S_2Hg$: N, 17.33; S, 13.22. Found: N, 16.77; S, 13.07.

2′,3′,5′-Tri-*O*-benzoyl-6-azauridine (V).—A suspension of 3.76 g. (0.0078 mole) of IV in 200 ml. of toluene was dried by azeotropic distillation of 100 ml. of the solvent. A dried solution of 15 g. (0.031 mole) of amorphous 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[9,10] in 100 ml. of benzene was added, and the mixture was distilled to remove benzene. The mixture was then refluxed for .75 hr., cooled, and filtered. The filtrate was concentrated to dryness

(1) Since 6-azauridine has become established in the literature as the name for the subject compound, we propose to use the familiar name throughout this paper.

(2) M. Prystaš, J. Gut, and F. Šorm, *Chem. Ind.*, No. **25**, 947 (June 24, 1961).

(3) R. E. Handschumacher, *J. Biol. Chem.*, **235**, 764 (1960).

(4) E. Cattelain, *Bull. Soc. Chim.*, **11**, 249 (1944).

(5) The structure given is the one assigned by E. Cattelain[4] for the product obtained by cyclization of phenylpyruvic acid, 3-methylisothiosemicarbazone.

(6) J. Gut, M. Prystaš, and J. Jonáš, *Collection Czech. Chem. Commun.*, **26**, 986 (1961).

(7) J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956).

(8) Analyses were carried out by the Analytical Division, Squibb Institute for Medical Research: microanalyses by Mr. J. Alicino and his associates; infrared and ultraviolet determinations by Dr. N. Coy and her colleagues. Melting points are uncorrected.

(9) E. F. Recondo and H. Rinderknecht, *Helv. Chim. Acta*, **42**, 1171 (1959).

(10) H. M. Kissman, C. Didaks, and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955).

and the residue extracted into chloroform. The extract was washed with dilute potassium iodide solution, then with water, and, after drying, it was concentrated to a sirupy residue. The residue was dissolved in 200 ml. of 95% ethanol, treated with 20 ml. of concd. hydrochloric acid, and refluxed for 1.5 hr., whereupon methyl mercaptan evolved. After the reflux period, the solution was concentrated slightly, causing precipitation of 2.6 g. (30%) of crude V. A sample for analysis, recrystallized from ethyl acetate, had a m.p. of 191–194°.

Anal. Calcd. for $C_{29}H_{23}N_3O_9$: C, 62.47; H, 4.16; N, 7.55. Found: C, 62.02; H, 4.11; N, 7.53.

6-Azauridine (VI).—A solution of 590 mg. (1.06 mmoles) of V in 200 ml. of methanol, saturated at 5° with ammonia, was held for 3 days at room temperature. After concentration to dryness, the residual sirup was dissolved in water and the solution was washed with ether. The aqueous solution was concentrated to dryness and the residue dissolved in absolute ethanol and reconcentrated. This operation was repeated several times to assure removal of water. Recrystallization of the residue from absolute ethanol afforded 160 mg. (62%) of 6-azauridine (VI); m.p. 157–159°, undepressed by biosynthetic material. The infrared spectrum was identical to that of authentic material as was the ultraviolet spectrum: $\lambda_{max}^{0.2\ N\ NaOH}$ 257 mμ (ε 6988).

Anal. Calcd. for $C_8H_{11}N_3O_6$: C, 39.19; H, 4.52; N, 17.14. Found: C, 39.79; H, 4.56; N, 17.34.

Acknowledgment.—The authors wish to thank Dr. E. T. Stiller and Mr. M. A. Dolliver for their continuing interest in this work. They are also indebted to Dr. J. Bernstein for helpful discussions and consultations.

2,4-Dinitrothiazole. The Boron Trifluoride–Nitrogen Tetroxide Nitration of 2-Nitrothiazole

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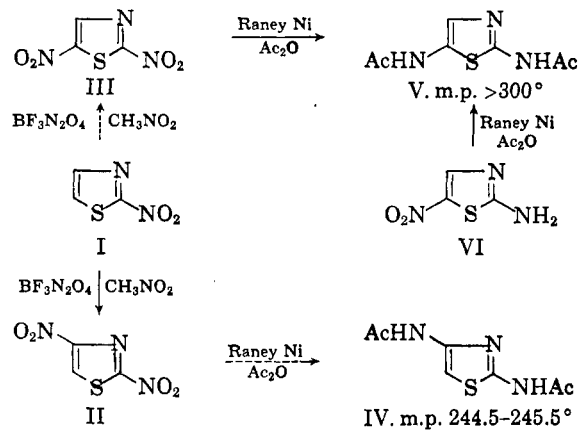
The only C-dinitrothiazoles that have been reported are 2,4-dinitro-5-acetamidothiazole,[1] and 2 - nitramino - 3,4,5 - trinitro - 2 - thiazoline.[2] Ganapathi,[3] however, has presented data that place the structure of the former compound in considerable doubt. In fact, his evidence indicates that this compound is indeed the mononitrothiazole (5-acetamido-4-nitrothiazole). In contrast to the work of Prijs,[4] we have found that 2-nitrothiazole (I) can be nitrated in excellent yield using a complex of boron trifluoride and nitrogen tetroxide.[5] It is curious to note however, that the nitration which is described below, does not proceed satisfactorily unless an excess of boron trifluoride is present in the nitration mixture.[6]

Two isomers are possible from the nitration of 2-nitrothiazole: 2,4-dinitro-(II) and 2,5-dinitrothiazole (III). Since the corresponding acetylated



diamines (IV and V) of the two possible products (II and III) were known,[7–9] the reduction of the dinitro compound seemed the best means of identification. Using 2-amino-5-nitrothiazole (VI) as a model compound, several chemical reductions were attempted in vain. Ultimately, reductive acetylation with Raney nickel catalyst was successful. Contrary to the experience of Ganapathi,[7] this reduction proceeded smoothly yielding the previously described[7] 2,5-diacetamidothiazole (V). When the nitration product (II) was subjected to this same procedure, 2,4-diacetamidothiazole (IV) resulted. This was identified by a mixed melting point determination and comparison of the infrared spectrum with that of an authentic sample prepared according to Davies.[9]

Experimental

2,4-Dinitrothiazole (II).—A stirred solution of 10 ml. of nitrogen dioxide–nitrogen tetroxide (Matheson) in 25 ml. of nitromethane was cooled to 0°, and boron trifluoride gas was bubbled in until dense white fumes were evolved from the condenser. A solution of 2 g. of 2-nitrothiazole[4] (m.p. 74–75°) in 25 ml. of nitromethane was added portionwise with stirring, and the mixture was refluxed for 1 hr. The mixture was then filtered hot, the solids washed with 25 ml. of nitromethane, and the solvent removed by evaporation in a stream of air. The yield was 2.60 g. Crystallization from benzene afforded 2,4-dinitrothiazole (m.p. 145.5–146.5° corr.) in 80% yield.

Anal. Calcd. for $C_3HN_3O_4S$: C, 20.59; H, 0.57; N, 24.00. Found: C, 20.84; H, 0.59; N, 24.25.

Reductive Acetylation of 2-Amino-5-nitrothiazole (VI).—

(1) B. Prijs, W. Menigisen, S. Fallab, and H. Erlenmeyer, *Helv. Chim. Acta*, **35**, 187 (1952).

(2) S. J. Viron and A. Taurins, *Can. J. Chem.*, **31**, 885 (1953).

(3) K. Ganapathi and K. D. Kulkarni, *Proc. Indian Acad. Sci.*, **37A**, 758 (1953).

(4) B. Prijs, J. Ostertag, and H. Erlenmeyer, *Helv. Chim. Acta*, **30**, 1200 (1947).

(5) G. B. Bachman, H. Feuer, B. R. Bluestein, and C. M. Vogt, *J. Am. Chem. Soc.*, **77**, 6188 (1955).

(6) Bachman's nitration procedure involves filtering and pressing the solid complex on a porous plate, thus any excess boron trifluoride dissolved in the solvent is removed.

(7) K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 343 (1945).

(8) K. Ganapathi and A. Venkartaraman, *Proc. Indian Acad. Sci.*, **22A**, 359 (1945).

(9) W. Davies, J. A. Maclaren, and L. R. Wilkinson, *J. Chem. Soc.*, 3491 (1950).

Five grams of 2-amino-5-nitrothiazole (VI) (m.p. 200–201°) was added to sufficient acetic anhydride (about 300 ml.) to effect solution. Approximately 0.5 g. of Raney nickel[10] was added, and the mixture was shaken at 40 p.s.i. of hydrogen for 3 hr. with no observed pressure drop. Additional portions of catalyst were added periodically until the theoretical pressure drop was recorded. (A total of four portions was added over a period of 2 days). The slurry was filtered and the solids were extracted with hot acetic acid. A 65% yield of 2,5-diacetamidothiazole V (4.46 g.) m.p. > 300° (lit., m.p.[7] > 285°) was obtained by evaporation of the acetic acid extracts. This product can be recrystallized from acetic acid–water mixtures.

Anal. Calcd. for $C_7H_9N_3O_2S$: C, 42.20; H, 4.53; N, 21.05. Found: C, 42.47; H, 4.28; N, 21.16.

Reductive Acetylation of 2,4-Dinitrothiazole.—The procedure followed here was that described in the previous example, but the isolation procedure was slightly different because of the solubility of the product in acetic anhydride. After reduction was complete, the catalyst was filtered, the acetic anhydride removed under vacuum, and the residue was recrystallized from hot water. From 5 g. of dinitrothiazole, 4.95 g. (87% yield) of product (m.p. 244.5–245.5° corr.) (lit.,[9] m.p. 240–241°) were obtained.

Anal. Calcd. for $C_7H_9N_3O_2S$: C, 42.20; H, 4.53; N, 21.05. Found: C, 42.42; H, 4.60; N, 20.75.

Acknowledgment.—The author is indebted to J. J. Kobliska and his associates for the microanalyses and to Miss J. L. Gove for the infrared spectra.

(10) Prepared according to L. Covert and H. Adkins, *J. Am. Chem. Soc.*, **54**, 4116 (1932).

A Flavopereirine Synthesis[1]

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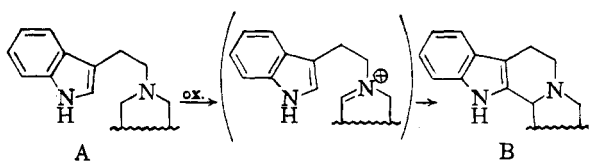
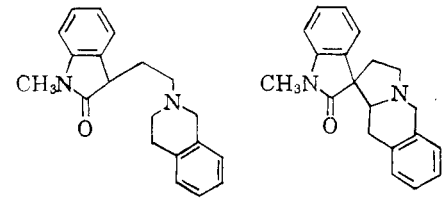
Received January 24, 1962

As part of a general search for new methods of synthesis of indole alkaloids the scheme outlined below (A→B) came under consideration. While two procedures were developed, one using mercuric acetate as the oxidizing agent[1] and the other palladium, the latter is the subject of this communication.



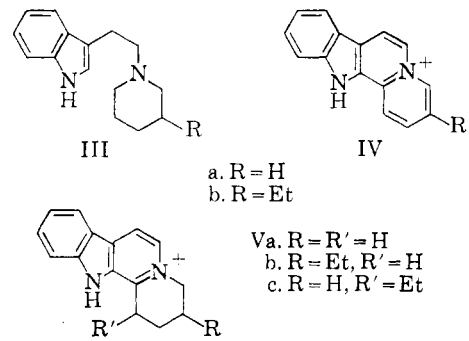
A B

It was decided to model our oxidative cyclization after the strikingly elegant and simple, but unapplied example of a palladium-induced conversion of the oxindole derivative I into II.[3] However, since substances of general type B are known to undergo palladium-catalyzed dehydrogenation,[4] the final products were expected to be anhydronium compounds, tetradehydro and octadehydro derivatives of B.



I II

Exposure of the hydrochloride of *N*-[β-(3-indolyl)ethyl]piperidine (IIIa)[5] to palladium-charcoal at 300° for twenty minutes and conversion of the products to salts led to the anhydronium in compounds IVa and Va. A similar treatment of 1[β-(3-indolyl)-ethyl]-3-ethylpiperidine (IIIb)[6] yielded the salts of flavopereirine (IVb), tetrahydroflavopereirine (Vb), and tetrahydroisoflavopereirine (Vc).



III IV

a. R = H
b. R = Et

Va. R = R′ = H
b. R = Et, R′ = H
c. R = H, R′ = Et

The last reaction constitutes a novel and short synthesis of flavopereirine, one of the alkaloids of the bark of *Geissospermum vellosii* and *laeve*.[7]

Experimental

Dehydrogenations.—A solution of 500 mg. of the piperidinoindole in a minimum amount of methanol was saturated

(1) This work was first presented as one part of a lecture by E. W. at the 17th National Organic Symposium of the American Chemical Society at Bloomington, Ind., June 26–29, 1960. The authors acknowledge gratefully hereby the financial support of the work by a Public Health Service Grant (MY-5815) from the U. S. Department of Health, Education, and Welfare.

(2) Present address: Department of Chemistry, Indiana University, Bloomington, Ind.

(3) P. L. Julian, A. Magnani, J. Pikl, and W. J. Karpel, *J. Am. Chem. Soc.*, **70**, 174 (1948); B. Belleau, *Chem. and Ind.*, 229 (1955); K. T. Potts and R. Robinson, *J. Chem. Soc.*, 2675 (1955).

(4) *Cf.* E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958).

(5) R. C. Elderfield, B. Fischer, and J. M. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957).

(6) Compounds IIIb and Vc were prepared previously by Dr. B. Wickberg[1] in connection with another study.

(7) (a) M.-M. Janot, R. Goutarel, A. LeHir, and L. O. Bejar, *Ann. pharm. France*, **16**, 38 (1958). (b) H. Rapoport, T. P. Onak, N. A. Hughes, and M. G. Reinecke, *J. Am. Chem. Soc.*, **80**, 1601 (1958). (c) N. A. Hughes and H. Rapoport, *ibid.*, **80**, 1604 (1958). (d) A. Bertho, M. Koll, and M. I. Ferosie, *Chem. Ber.*, **91**, 2581 (1958). For previous syntheses see (e) A. LeHir, M.-M. Janot, and D. van Stolk, *Bull. soc. chim. France*, 551 (1958). (f) K. B. Prasad and G. A. Swan, *J. Chem. Soc.*, 2024 (1958). (g) J. Thesing and W. Festag, *Experientia*, **15**, 127 (1959). (h) H. Kaneko, *J. Pharm. Soc. Japan*, **80**, 1374 (1960). (*i*) Y. Ban and M. Seo, *Tetrahedron*, **16**, 5 (1961).

with anhydrous hydrogen chloride gas. Palladium-charcoal, 1 g., was added *cautiously* (to prevent spontaneous ignition!) and the mixture evaporated under vacuum. While maintaining a constant pressure of nitrogen over the mixture of solids, it was heated at 295–305° for 20 min. The cooled mixture was extracted continuously for 18 hr. with anhydrous methanol, to which a few milliliters of glacial acetic acid had been added. The yellow fluorescing solution was evaporated under vacuum and the residue partitioned between 10% sodium hydroxide solution and chloroform. The aqueous solution was extracted repeatedly with chloroform until no more color transferred. The combined chloroform extracts were washed once with water, dried over anhydrous sodium sulfate, and filtered. After addition of enough glacial acetic acid to discharge the bright orange color, the solution was evaporated under vacuum on the steam bath. The residual yellow mixture of gum and crystals was dissolved in a minimum quantity of chloroform and transferred onto a chromatography column whose contents had been prepared from 33 g. of cellulose and 11 ml. of 1% (by volume) of aqueous acetic acid mixed intimately in dry chloroform. Fifty milliliter eluates were collected and treated with a few milliliters of dilute aqueous hydrochloric acid to prevent possible air oxidation of the desired products.

Desethylflavopereirine (IVa) and Its Tetrahydro Product (Va).—Elution of the chromatogram of the reaction mixture from the dehydrogenation of compound IIIa with wet chloroform removed all tars. Elution with 2.5:1 wet chloroform–*n*-butyl alcohol gave solid products. The first three fractions were combined and the solvent evaporated. Dissolution of the residue in a minimum amount of water and addition of a few drops of glacial acetic acid and 10% aqueous sodium perchlorate solution yielded a precipitate. Crystallization of the latter from aqueous ethanol gave 48 mg. of cream-colored crystals of Va perchlorate, m.p. 242–246°, mixed m.p. 241–246°. Its ultraviolet and infrared spectra were identical with those of an authentic sample, m.p. 242–247°, prepared by dissolving crystalline Va hydrobromide, m.p. 278–281° (lit.,[8] m.p. 280° dec.), in 10% sodium hydroxide solution extracting exhaustively with chloroform, adding glacial acetic acid to the organic extract, evaporating the solvent, and converting the residue to a perchlorate in the above manner.

Anal. Calcd. for $C_{15}H_{14}N_2 \cdot HClO_4$: C, 55.82; H, 4.69; N, 8.68. Found: C, 55.74; H, 4.78; N, 8.75.

The last twenty chromatographic fractions from the chloroform–butanol elution were combined, concentrated to a small volume, and divided into two parts. One was treated with a saturated methanol solution of picric acid. Crystallization of the resulting solid from absolute ethanol yielded 21 mg. of crystalline IVa picrate, m.p. and mixed m.p. 250–252° (lit.,[7f] m.p. 252–253°). The other part was concentrated and ether added. This led to 11 mg. of long needles of IVa chloride, m.p. 291–296° dec. (lit.,[7f] m.p. 295° dec.) infrared spectrum identical with that recorded in the literature.[7f]

Flavopereirine (IVb) and the Tetrahydro Products Vb and Vc.—Elution of the chromatogram of the reaction mixture from the dehydrogenation of compound IIIb,[6] m.p. 112–113.5°, with wet chloroform removed all tars, while elution with 5:1 wet chloroform–*n*-butyl alcohol yielded solid products. The first three fractions were combined and evaporated and the residue dissolved in a minimum amount of hot water and a trace of acetic acid. Dropwise addition of 10% sodium perchlorate led to a precipitate which on crystallization from absolute ethanol yielded 31 mg. of tetrahydroflavopereirine (Vb), m.p. and mixed m.p. 219–222°. Its infrared and ultraviolet spectra were identical with those of an authentic sample.[7c,9]

Since the later fractions of the chromatogram yielded a mixture of products, all eluates were combined, the salts reconverted to their organic bases, the latter transformed to acetic acid salts and chromatographed on cellulose as above. Elution with 9:1 wet chloroform–*n*-butyl alcohol yielded at first a solid which on crystallization from isopropyl alcohol-isopropyl ether afforded 9 mg. of Vc perchlorate, m.p. and mixed m.p. 246–252°. Its infrared and ultraviolet spectra were identical with those of an authentic sample.[6] The later chromatographic fractions were combined and concentrated. Crystallization of the precipitate from isopropyl alcohol and from water gave crystals, m.p. 320–325°. Recrystallization of this substance, 3 mg., from water and drying at 80° and 1 mm. pressure for 18 hr., and a similar treatment of an authentic sample[9] of IVb perchlorate yielded crystalline flavopereirine perchlorate, m.p. and mixed m.p. 323–327°. The ultraviolet and infrared spectra of the two specimens were identical.

(8) L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 650 (1952).

(9) The authors are indebted to Professor Henry Rapoport for a gift of a sample of this compound.

Synthesis of Toluene-α-D_3-1-C^{14}; Exchange during an Attempted Catalytic Deuteration

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Toluene-α-D_3-1-C^{14} was needed as a precursor of radioactive *p,p'*-ditrideuteromethylhydrazobenzene. The nondeuterated hydrazotoluene had previously been synthesized from radioactive toluene. In order to comparet he yields of the products from the rearrangement of the two compounds, it was desired to have the compounds with equal specific activity. Accordingly toluene-1-C^{14} was used as the initial precursor of toluene-α-D_3-1-C^{14}.

It was reasoned that the most economical method of synthesis would be to reduce methyl benzoate with deuterium gas in the presence of copper chromite

$$C_6H_5{-}CH_3 \xrightarrow{KMnO_4} C_6H_5CO_2H \xrightarrow{CH_2N_2} C_6H_5CO_2Me \xrightarrow[CuCrO_2]{D_2} C_6H_5CD_3$$

Practice hydrogenations were carried out under different conditions. The experimental data are listed in Table I.

Optimum conditions appeared to involve use of ethanol as a solvent. However, the toluene that was obtained by the reaction of deuterium with radioactive methyl benzoate was shown by infrared analysis to have very little deuterium in the methyl group. Apparently there was a rapid equilibration of the deuterium gas with the hydrogen present in the ethanol, or the ethanol itself was directly responsible for the reduction.

(1) National Institutes of Health Predoctoral Fellow, 1961–1962.

TABLE I

HYDROGENATION OF METHYL BENZOATE IN THE PRESENCE OF COPPER CHROMITE[a]

No.	Solvent	Grams of Methyl Benzoate	Press.[b] of H_2 in P.S.I.	Temp.	Time	Product Composition[c] CH_3OBz	$C_6H_5CH_2OH$	$C_6H_5CH_3$
1	C_2H_5OH, 195 ml. abs.	25	1450–1500	190[d]	15 hr.	100	...	...
2	C_2H_5OH, 195 ml. abs.	25	1500	250–290	12 hr.	67	27	25
3	C_2H_5OH, 200 ml. abs.	25	1500	250–290	67 hr.	...	30	70
4	C_2H_5OH, 200 ml. abs.	25	1450	320–340	64 hr.	...	<2	>98
5	Methylcyclohexane, 200 ml.	27	1450	320–340	63 hr.	100	...	...
6	...	18[e]	1500	320–340	41 hr.	Lg.	...	Sm.
7	...	27	1500	320–340	140 hr.	60–70	...	30–40
8[f]	C_2H_5OH, 250 ml. abs.	25	1650[f]	320–340	73 hr.	...	Trace	>98

[a] Ten grams of catalyst was used in all runs except No. 6. [b] This refers to the initial pressure of the gas before the bomb was heated. The pressure was never allowed to drop below 1100 p.s.i. Considerable amounts of hydrogen dissolved in ethanol, but very little went into methylcyclohexane or methyl benzoate. It is felt that higher pressures of hydrogen would have significantly shortened the reaction time. The practice runs were, however, governed by the size of the bomb and the supply of deuterium gas. [c] All values are approximate and as no other products were detected by vapor phase chromatography, it was assumed that starting material was completely accounted for by the compounds listed here. [d] It is estimated that 5–6 hr. are required for the contents of the bomb to reach the temperature indicated by the thermocouple. [e] Five grams of catalyst was used. [f] Reaction of radioactive methyl benzoate with deuterium. As toluene and ethanol form an azeotrope, the two were separated by addition of an equal volume of water to the solution followed by extraction of the resulting mixture with pentane. The separated pentane solution was then dried with calcium chloride and the toluene was recovered by distillation. The infrared spectrum of the radioactive toluene obtained from the actual deuteration showed only a trace of possible C—D absorption around 2100 cm.$^{-1}$ and the usual C—H absorption of the methyl group in the 2000–3000-cm.$^{-1}$ region.

The following, more standard method of synthesis, was then resorted to:

$$C_6H_5CH_3 \xrightarrow{KMnO_4} C_6H_5CO_2H \xrightarrow{LiAD_4} C_6H_5CD_2OH \xrightarrow{SOCl_2} C_6H_5CD_2Cl \xrightarrow{Mg} C_6H_5CD_3$$

This path proved successful and gave an over-all yield of 63%.

Experimental

Benzoic acid-1-C^{14} was prepared by permanganate oxidation[2] of toluene-1-C^{14}. Yields of 90–98% were obtained. The highest yield was obtained when the reaction mixture was kept just below the reflux temperature.

Methyl benzoate-1-C^{14} was prepared in virtually quantitative yield by the reaction of diazomethane with benzoic acid.

Copper chromite was prepared by the method of Vogel.[3]

Attempted Preparation of Toluene-α-D_3-1-C^{14}.—All hydrogenation were carried out in a 500-cc. bomb. The product compositions were determined by gas chromatography with an Apiezon-J column.

Benzyl Alcohol-α-D_2-1-C^{14}.—A solution of 38 g. (0.316 mole) of benzoic acid-1-C^{14} in several hundred ml. of ether was added with stirring over a period of 1.5 hr. to 20 g. (> 0.45 mole) of $LiAlD_4$ (> 95% purity) in 650–700 ml. of ether. The mixture was stirred for a total of 14 hr. after which time it was worked up by standard techniques. A total of 28.7 g. (83.5% yield) of benzyl alcohol-α-D_2-1-C^{14} was isolated (b.p. 95° at 10 mm).

Benzyl Chloride-α-D_2-1-C^{14}.—To 50 ml. of thionyl chloride (0.69 mole) in 50 ml. of ether was added the 28.7 g. (0.26 mole) of benzyl alcohol in 45 ml. of ether. The resulting solution was stirred at room temperature for 7 hr. and then distilled. The gas that was evolved during distillation probably came from either the formation and resulting decomposition or from the decomposition of the previously formed benzyl chlorosulfite. Thirty grams (91% yield) of benzyl chloride-α-D_2-1-C^{14} was collected at 92–93°, at a pressure of 50 mm.

Toluene-α-D_3-1-C^{14}.—To 5.69 g. (0.234 g.-atom) of magnesium turnings in 80 ml. of anhydrous ether was added gradually over a 20-min. period the 30 g. (0.234 mole) of benzyl chloride. It was necessary to apply gentle heat to initiate the reaction which was then controlled by intermittant cooling with an ice water bath. After all of the benzyl chloride had been added, the reaction mixture refluxed spontaneously for 10–15 min.; heat was then applied for another 25 min. to continue the reflux action. After this time 25 g. of deuterium oxide (1.25 moles) was added over a 30-min. period. The magnesium salts soon coagulated and left a clear ether solution. The mixture was stirred for 100 min. under gentle reflux and was then worked up. A total of 19.6 g. (88% yield) of toluene-α-D_3-1-C^{14}, which contained a trace of ether, was isolated. Analysis by n.m.r. showed 0.15 atom of deuterium in the ring. No hydrogen could be detected in the methyl group by n.m.r., while the infrared spectrum indicated a possible trace. The over-all yield leased on the 30 g. of starting toluene-1-C^{14} was 63%.

(2) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, New York, 1956, p. 250.

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The Reidentification of "Camphene" from the Acid-Catalyzed Isomerization of α-Terpineol as 3-*p*-Menthene

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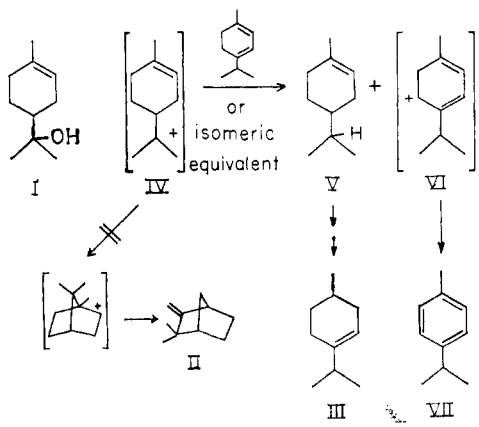
In a recent study of the isomerization of α-terpineol (I) under various acidic conditions it was

reported that about 16% of camphene (II) was formed in a refluxing 4:1 ethanol–sulfuric acid mixture.[1] The identification of this particular fraction as camphene was based on (1) its identical retention time on a rape seed oil gas chromatographic column with authentic camphene, (2) its solidification when seeded with authentic camphene, and (3) the lack of melting point depression of the resulting solid when further camphene was added.

This report was surprising since our own attempts to force bicyclic ring closures of this same and related cyclohexenyl systems under nonequilibrium, kinetically controlled conditions were unsuccessful.[2]

The isomerization of α-terpineol was repeated in the manner described[1] to give a mixture of products whose proportions by gas-liquid chromatographic analysis appeared to be the same as those reported previously. However, when the lower boiling fractions were analyzed on a LAC-446 column, the retention time of the "camphene" peak differed very slightly from that of authentic camphene.[3] Moreover, 1:9 and 9:1 mixtures of this peak with camphene gave distinct shoulders which indicated definitely that the peak could not be camphene and was misidentified. Interestingly, a 1:1 mixture gave a single peak which indicates how similar the retention times of the two materials were to each other. We are unable to explain the seeding results of von Rudolph except to note the tendency of bicyclic molecules to form solid solutions with a large variety of molecules.[4]

The unknown "camphene" peak was isolated by preparative gas-liquid chromatography using a LAC-446 column to give a *liquid* of >95% peak purity. This liquid gave an analysis for a structure close to a $C_{10}H_{18}$ hydrocarbon. Another sample of >97% peak purity obtained with a silicone oil column had infrared and NMR spectra which indicated that it was 3-*p*-menthene (III).[5] Authentic 3-*p*-menthene of greater than 99% peak purity[6] gave infrared and NMR spectra essentially superimposable on that of the unknown.



The formation of 3-*p*-menthene can be readily accommodated into the isomerization scheme[1] of α-terpineol. The initially formed α-terpinyl carbonium ion (IV) could accept a hydride ion from one of the menthadienes to give 1-*p*-menthene (V) which would rapidly isomerize under the acidic conditions to give the more stable[7] 3-*p*-menthene, as observed. The other product of the hydride transfer (VI) is simply a protonated *p*-cymene which would lose its proton to become the observed *p*-cymene (VII).

Experimental

To 80 g. of α-terpineol in 320 ml. of 95% ethanol was added 80 ml. of concd. sulfuric acid. The solution was heated under reflux for 1 hr. and then steam distilled into an ice-cooled flask. The organic portion of the distillate was recovered by extraction and solution in ether. This ethereal solution was washed with bicarbonate solution, then with water, and finally dried over anhydrous magnesium sulfate. The dried solution was distilled through a 2-ft. Podbielniak-type[8] distillation column, and the fractions with b.p. 52–58° (17 mm.) and b.p. 58–60° (17 mm.) were collected. The 3-*p*-menthene, 70% of the first fraction, was isolated by preparative gas chromatography on a 6-ft. × 1/2 in. column packed with 10% LAC-446 (Wilkens Instrument and Research) on Chromosorb W using a flow rate of 600 ml./min. and a column temperature of 81°. Reinjection of the collected sample, $n^{23.5}D$ 1.4519, indicated peak purity >95%.

Anal. Calcd. for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 87.18; H, 12.98.

Commercial camphene was recovered unaltered by this isolation technique.

Another sample of 3-*p*-menthene of >97% peak purity was isolated using a commercial 5-ft. × 1/2-in. column packed with 20% GE-SF-96 silicone oil on acid-washed Chromosorb W (Wilkens Instrument and Research). The infrared spectrum (neat) was identical with the published spectrum[5] and a spectrum obtained with an authentic sample of pure (>99% peak purity) 3-*p*-menthene.[6] The NMR spectrum, determined on a Varian A-60 using a Varian 12-in. magnet, was complex but the three groups of peaks were in the expected ratio of 1:6:9 (with group centers at τ = 4.52, 8.0, and 9.0, respectively). With the exception of two small peaks at τ = 4.34 and 4.42 the spectrum of the isolated sample was identical with that of authentic 3-*p*-menthene.

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Studies on the Chemistry of Aspenwood. IX. *p*-Hydroxybenzoic Acid in Aspen Klason Lignin

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In a previous study on the Klason lignin determination of trembling aspen (*Populus tremuloides*), *p*-hydroxybenzoic acid was found to be a major component of the Klason lignin filtrate.[1] Furthermore, the Klason lignin precipitate resisted alkaline nitrobenzene oxidation and did not yield monomolecular products under these conditions. Other studies in our laboratories[2] indicated that *p*-hydroxybenzoic acid was probably present in aspenwood lignin in a combined form, and therefore an attempt was made to release it by more drastic means than alkaline nitrobenzene oxidation.

Experimental

A number of identical Klason lignin determinations were made on the same extracted wood and in the same manner as reported earlier.[1] The average yield of Klason lignin was 16.8% and the methoxyl value was 20.5%. Five grams of this lignin was added slowly to a fused mixture of 13 g. solid potassium hydroxide and 2 g. of water at 170°. The temperature rose to 190°. After addition was complete, the fused mixture was stirred for five min. between 175 and 190° and allowed to cool. The cooled mixture was dissolved in water, acidified with dilute sulfuric acid, and extracted continuously with ether. The ether extract was dried, and the ether removed to yield 0.21 g. (4.2%) of ether-soluble material. Qualitative paper chromatography in the butanol–2% aqueous ammonia and 10:3:3 butanol–pyridine–water developers[1] indicated *p*-hydroxybenzoic, syringic, and vanillic acids as the chief components of the ether-soluble material and several unidentified phenolic acids as minor components. Quantitative studies by previously described paper chromatographic and spectrophotometric procedures[3] indicated that the ether-soluble material contained 51.0% *p*-hydroxybenzoic acid, 13.1% syringic acid, and 8.7% vanillic acid. Thus, the Klason lignin precipitate of trembling aspenwood comprises over 2% *p*-hydroxybenzoic acid in the combined form.

Results

This finding of the *p*-hydroxybenzoic acid moiety in the Klason lignin precipitate of trembling aspenwood with a methoxyl content of 20.5% indicates that this Klason lignin precipitate must be different from the Klason lignin precipitates of similar methoxyl content from other hardwoods such as birch and maple which do not give *p*-hydroxybenzoic acid under similar alkali fusion conditions. In addition, these data suggest the possibility that hardwood Klason lignin precipitates vary somewhat in composition from species to species.

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