Notes

A department for short papers of immediate interest.

The Trimerization of Hexafluoro-2-butyne

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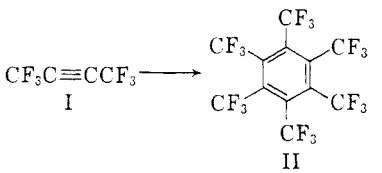
Received October 12, 1959

The trimerization of alkyl and aryl substituted acetylenes to give substituted benzenes is well known,[1] but there appear to be no reports of trimerization of a fluoroalkyl acetylene.[2]

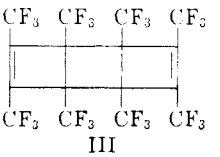
We have found that the novel hexakis(trifluoromethyl)benzene (II) can be obtained in yields of 70 to 75% by heating hexafluoro-2-butyne (I) with trifluoromethyl iodide or iodine at 260° under pressure. Smaller yields have also been obtained by heating the butyne alone at 275°.



I II

Hexakis(trifluoromethyl)benzene (II) is a colorless, crystalline, readily sublimable compound melting at 210–212° (sealed capillary). The fluorine nuclear magnetic resonance spectrum in acetone consists of a single, unsplit resonance line, indicating that the fluorine atoms are all equivalent. The results of cryoscopic molecular weight measurements in benzene were about 4 to 7% higher than the value calculated for the trimer, while the molecular weight determined by the x-ray method was 3% low. However, mass spectrometric analysis showed the parent ion of mass 486 and a series of ions logically derived from it.

The infrared spectrum of the trimer is characterized by many of the bands reported by Brown[3] for a compound, m.p. 208–209°, which was obtained by heating I at 320°, and to which the tetrameric structure III was assigned on the basis of an ebullioscopic molecular weight determination.[4] The

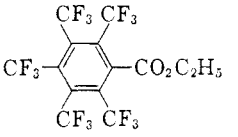


III

ultraviolet spectrum of the trimer is also strikingly similar (λ_{max} 287 mμ, log ε 2.22) to that reported by Ekström[5] for Brown's compound (λ_{max} 287 mμ, log ε 2.24). The similarities in reaction conditions, melting point, and, NMR infrared and ultraviolet spectra lead us to suggest that Brown's compound is actually the trimer (II).

Because of the bulkiness of trifluoromethyl groups, it was not possible to construct a model (Stuart-Briegleb) of the trimer without distorting the benzene ring from its normal planar configuration. It was, in fact, not possible to place more than three trifluoromethyl groups in adjacent positions without ring distortion. The resulting model had the trifluoromethyl groups locked in a highly crowded conformation. The unusual behavior of the trimer toward basic hydrolysis (see below) might be attributed to its highly crowded structure.

The trimer was found to be resistant to hydrolysis by sulfuric acid or by a chlorosulfonic acid–sulfuric acid mixture, in contrast to the ready hydrolysis reported for *m*- and *p*-bis(trifluoromethyl)benzene under these conditions.[6] However, hydrolysis by bases occurs readily; treatment of the trimer with two moles of potassium hydroxide in ethanol led to the formation of ethyl pentakis(trifluoromethyl)-benzoate (IV) in 27% yield.



IV

EXPERIMENTAL

Hexakis(trifluoromethyl)benzene (II). *a. Catalytic.* A mixture of 11.1 g. (0.068 mole) of hexafluoro-2-butyne, 1.8 g. (0.009 mole) of trifluoromethyl iodide, and 0.3 ml. of perfluorodimethylcyclohexane was sealed in a platinum tube under a nitrogen atmosphere, and the tube pressured externally with nitrogen. The tube was heated at 260° under 1000 atm. pressure for 15 hr. The reaction mixture was cooled below 0°, filtered, and the solid residue was air-dried. There was thus obtained 7.89 g. (71.1%) of hexakis(trifluoromethyl)benzene (II), melting at 209–210° (sealed capillary). The melting point was unchanged by recrystallization from acetone, benzene, or methanol.

Anal. Calcd. for $C_{12}F_{18}$: C, 29.65; F, 70.35; mol. wt., 486. Found: C, 29.78; F, 70.45; mol. wt., 505, 522 (cryoscopic in benzene).

Replacement of the trifluoromethyl iodide catalyst with

(1) (a) A. W. Reppe and W. J. Schweckendiek, *Ann.*, **560**, 104 (1948); (b) D. C. McKinley, *Ind. Eng. Chem.*, **44**, 995 (1952)..

(2) Monofluoroacetylene has been reported to trimerize spontaneously; W. J. Middleton and W. H. Sharkey, *J. Am. Chem. Soc.*, **81**, 803 (1959).

(3) H. C. Brown, *J. Org. Chem.*, **22**, 1256 (1957).

(4) Ebullioscopic molecular weight determinations (benzene) on the trimer carried out in our laboratory resulted in very high values (825, 850). This may be due to the volatility of the compound, resulting in the loss of material during the determination.

(5) B. Ekström, *Chem. Ber.*, **92**, 749 (1959).

(6) P. G. Scheurer and G. M. le Fabe, *J. Am. Chem. Soc.*, **72**, 3308 (1950).

iodine (0.1 mole per mole of hexafluoro-2-butyne) gave a 70.5% yield of nearly pure II as a pale yellow solid, m.p. 209–211° (with previous softening).

The infrared spectrum (carbon tetrachloride) has strong absorption at 8.1–8.3, 8.51, and 9.51 μ, with much weaker bands at 7.12, 7.43, 7.61, and 7.73 μ. Additional bands for II at 8.63m, 8.75m, 12.41s, 13.35s and 13.79s μ are detected by use of a potassium bromide wafer. The trimer crystals are monoclinic. X-ray diffraction data were determined from a single crystal grown from acetone. There are four formula weights per unit cell with a space group of $C^5_{2h}P2_1/c$, a_0 = 9.42, b_0 = 16.54, c_0 = 8.98. The β angle is 99.5°. Assuming a molecular weight of 486.24, the x-ray density is 2.33.[7] The density at 25° ("Ultracene") is 2.2603, corresponding to a molecular weight of 470.

The trimer (50% in acetone) has an F^{19} resonance at −945 c.p.s. at 40 mc./sec., relative to trifluoroacetic acid = 0.[8]

b. Thermal. An 80-cc. stainless steel bomb containing 25 g. (0.155 mole) of I was heated for 7 hr. at 275° and 7 hr. at 285°. A pressure drop from 905 p.s.i. at 275° to 390 p.s.i. at 285° occurred during this time. After cooling and venting the bomb, there was obtained 15.1 g. of fluffy solid. Sublimation of 14 g. of this material at 100°, 1 mm. for 2 hr. yielded 5.47 g. of wet crystals. Pentane extraction of this material left 3.53 g. of II, m.p. 210–212° (sealed capillary).

Hydrolysis of II. Approximately one half of 11.0 g. (0.023 mole) of II was dissolved in 1 l. of hot absolute ethanol. Then one third of a solution of 3.4 g. (0.052 mole) of potassium hydroxide in 35 ml. of ethanol and 2 ml. of water was added during 20 min. The rest of the trimer was dissolved in the mixture, and the remainder of the base was added slowly. After standing overnight at room temperature, the volume was reduced to 150 ml., and the hot solution was decanted from precipitated potassium fluoride. Upon cooling the solution in an ice-salt bath, there was obtained 4.22 g. of colorless leaflets, m.p. 72–76°. Recrystallization from pentane gave 3.0 g. (27%) of ethyl pentakis(trifluoromethyl)-benzoate (IV), m.p. 89–90°.

Anal. Calcd. for $C_{14}H_5F_{15}O_2$: C, 34.30; H, 1.03; F, 58.14. Found: C, 34.51; H, 1.40; F, 58.24.

Carbonyl absorption in the infrared was at 5.67 μ (potassium bromide disk) and the proton NMR spectrum indicated the presence of an ethyl group. The fluorine NMR spectrum had complex absorption in the CF_3 region which is consistent with the unsymmetrical, highly crowded structure IV.

Attempts to isolate other hydrolysis products from this reaction were unsuccessful.

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(7) E. A. Braude and F. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press Inc., N. Y., 1955, p. 468.

(8) The convention employed here is that resonances occurring at high field relative to the reference are assigned positive values.

Hexa(trifluoromethyl)benzene[1]

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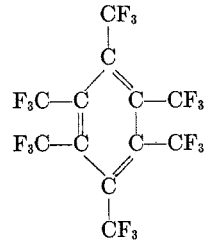
The thermal reaction of perfluorobutyne-2 under autogenous pressure has been reported previously[3] as producing a white, crystalline compound believed to be the polycyclic tetramer. Further examination of this compound by Ekstrom[4] led to the incorrect assignment of the structure as octa(perfluoromethyl)cyclooctatetraene.

A redetermination of the molecular weight of the product, both by ebullioscopic method in benzene and by isothermal distillation in benzene, gave a value of 472, which is reasonably close to the value of 486 expected for the trimer of perfluorobutyne. Further consideration has therefore been given to the structure and additional data obtained which shows conclusively that this compound is actually the previously unreported hexa(trifluoromethyl)benzene (I).



I

The fluorine nuclear magnetic resonance in dilute tetrahydrofuran of two samples of the trimer was determined at 40 megacycles/sec. and about 10,000 gauss and only one, single unsplit peak was found. This peak is found displaced 433 c.p.s. to lower magnetic fields than the fluorine resonance of benzotrifluoride and some 2,320 c.p.s. to higher fields from the fluorine peak of tribromofluoromethane, the latter being used as an internal standard. It was shown conclusively that this one peak contained all the fluorine atoms in the fluorocarbon, as no detectable resonance could be found at ± 5,000 c.p.s. from the observed peak. Furthermore, known solutions of the perfluorobutyne trimer and benzotrifluoride were prepared in which the ratios of the number of fluorine atoms due to the trimer to those due to benzotrifluoride were 0.988 : 1.010. The spectra were run and the integrated areas of the two peaks determined with a planimeter which gave values of 0.99 ± 0.09 and 1.11 ± 0.12 for the ratios. Coupled with the observation that only one peak can be detected, this result shows clearly that the trimer contains only one type of fluorine atom.

The ultraviolet absorption spectrum (max 285 mμ, log ϵ = 2.20) of the perfluorobutyne trimer tends to confirm the presence of an aromatic ring. The ultraviolet extinction coefficient of this com-

(1) This work was supported in part by the Office of Naval Research under Contract N-onr 580(03); NR 356-333 with the University of Florida. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) Present address: U. S. Borax Research Corporation, Anaheim, California.

(3) H. C. Brown, *J. Org. Chem.*, **22**, 1256 (1957).

(4) B. Ekstrom, *Ber.*, **92**, 749 (1959).

pound, when compared with the extinction coefficients for trifluoromethyl benzene and *bis*(trifluoromethyl)benzene, is in the expected range. The ultraviolet curve showed a smoothing out effect with an electron donating solvent such as ether when compared with the spectrum determined in chloroform. The inductive effect of the eighteen fluorine atoms would be expected to make the ring very electron deficient and could account for this phenomenon.

The solubility characteristics of the trimer are appropriate to an electron deficient structure, as it has a low solubility in benzene but is soluble in electron rich solvents. A solubility in tetrahydrofuran greater than that in ethyl ether is consistent with the greater basicity of the former.

The melting point of the perfluorobutyne trimer is in the range expected for hexa (trifluoromethyl)-benzene. A plot of the melting points of the methylbenzenes *vs.* the melting points of the known trifluoromethylbenzenes is linear.

All the evidence shown above is based on the physical properties of the trimer and substantiates the proposed aromatic ring structure. We would like to report, in addition, that unequivocal chemical confirmation of the ring structure was obtained by vapor phase chlorination of the trimer under ultraviolet irradiation to produce chlorotrifluoromethane and hexachlorobenzene.

Preparation of hexa(trifluoromethyl)benzene has been modified to include a relatively cold reservoir in the pyrolysis tube for condensation of the product as formed. Yields of 68% of the resublimed or recrystallized product have been obtained.

Further work on reactions of hexa(trifluoromethyl)benzene promoted by free radical attack and also by the attack of nucleophilic reagents is in progress.

EXPERIMENTAL

Hexa(trifluoromethyl)benzene. Hexafluorobutyne-2 (20 g., 0.123 mol.) was condensed into a previously evacuated heavy wall Pyrex tube 55 cm. × 2.4 cm. designed to project from a vertical tube furnace approximately 6 in. The tube was then sealed and heated at 375° for 60 hr. The autogenous pressure in the 250 ml. tube was calculated to be about 25 atm. As the reaction proceeded, the solid product condensed in the exposed, relatively cool portion of the tube. The tube was cooled, opened, and the condensed solid removed and resublimed. Recrystallization from carbon tetrachloride gave 13.7 g. (68.5%) of pure hexa(trifluoromethyl)benzene, m.p. 209° (sealed tube).

Chlorination of hexa(trifluoromethyl)benzene. Hexa(trifluoromethyl)benzene (4.86 g., 0.01 mol.) was placed in a 500 cc. Vycor flask. Dry chlorine gas, 4.4 g. (0.062 mol.), was condensed into the flask, and the flask was sealed and heated to 260° under ultraviolet radiation supplied by a Hanovia utility lamp for 44 hr. The vessel was cooled and opened into a vacuum system to remove the volatile material which was subsequently bubbled through a 10% solution of sodium hydroxide to remove any unreacted chlorine. The remaining gas was identified by molecular weight determination (Dumas-104) and infrared spectra as chlorotrifluoromethane. The solid product was recrystallized from benzene to give pure hexachlorobenzene, m.p. 229–230°, mixed melting point with authentic samples 229–231°. The infrared spectra of this solid material also corresponded to that of an authentic sample of hexachlorobenzene.

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Quebrachamine. II

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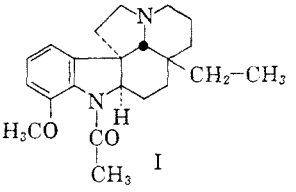
The establishment by x-ray analysis of the structure I for aspidospermine[1–3] makes II an attractive



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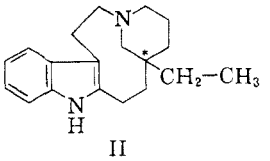


II

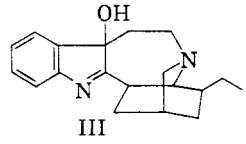
formulation for quebrachamine.[4] This note reports two further experiments designed to clarify the nature of the substituent, H or R, at the α-indole position, and identifies the "*N*(*a*)-acetyldihydroindole base" previously reported,[4] as I.

The positive Ehrlich and Hopkins-Cole reactions of quebrachamine suggested an α-unsubstituted indole ring. Such α-unsubstituted indoles may be characterized or diagnosed by their α,α′-disulfides. Quebrachamine trichloroacetate reacted in benzene with disulfur dichloride to yield a crystalline disulfide, whose ultraviolet absorption peak showed the expected shift to longer wave lengths.[5] Reductive hydrolysis, however, gave back quebrachamine. It must be concluded that quebrachamine disulfide is an abnormal disulfide in which two molecules of quebrachamine are linked together by an S-S bridge attached to an unknown position of the indole part. Tetrahydrocarbazole did not yield a disulfide.

Another reaction characteristic of α-unsubstituted indoles is their oxidation to (di)oxindole derivatives with *N*-bromosuccinimide.[6] Quebrachamine under such conditions gave a tribromo com-

(1) S. C. Nyburg and J. F. D. Mills, *Tetrahedron Letters*, **11**, 1 (1959).
(2) G. F. Smith and J. T. Wrobel, *J. Chem. Soc.*, in press.
(3) H. Conroy, P. R. Brook, and Y. Amiel, *Tetrahedron Letters*, **11**, 4 (1959).
(4) *Cf.* B. Witkop, *J. Am. Chem. Soc.*, **79**, 3193 (1957).
(5) *Cf.* K. Freter, J. Axelrod, and B. Witkop, *J. Am. Chem. Soc.*, **79**, 319 (1957).
(6) A. Patchornik, W. B. Lawson, and B. Witkop, *J. Am. Chem. Soc.*, **80**, 4747 (1958).

pound $C_{19}H_{23}N_2Br_3$, m.p. 290°, whose ultraviolet spectrum (Table I) was similar to that of the hydroxy base $C_{19}H_{26}N_2O$, m.p. 188°. Both these compounds have peaks similar to, but extinctions higher than, the β-hydroxyindolenine III derived from ibogamine (Table I).[7] This type of spectrum, intermediate between indole and indolenine, may



III

point to transannular interaction with N_b. No definite structures are assigned to these products at this time. The failure of *N*-bromosuccinimide to convert quebrachamine to an oxindole derivative is proof for an α-substituted indole nucleus. This is in agreement with the results of recent studies of the nuclear magnetic resonance spectrum of quebrachamine[8] which clearly shows the absence of the peak characteristic of the proton in the α-position of the indole ring.

TABLE I

ULTRAVIOLET SPECTRA IN 95% ETHANOL

Compound	λ_{max}	ε
Hydroxy base $C_{19}H_{26}N_2O$, m.p. 188°, from quebrachamine	295	7,080
	286	7,590
	227	28,200
Tribromo compound $C_{19}H_{23}N_2Br_3$, m.p. 290°, from quebrachamine	293	7,470
	285	7,440
	231	44,000
Hydroxyindolenine III from ibogamine	292	3,020
	281	3,200
	253–254	3,910
	228	13,700
	222	19,800

The same study led to the conclusion that the NMR peaks of possible indolenine tautomers of cycloheptenoindole, cyclooctenoindole and of II, a cyclononenoindole, would be masked by the multiplicity of saturated methylene protons.

The so-called "*N*(*a*)-acetyldihydroindole base," m.p. 213°,[4] and the "isomeric hydroxy base," m.p. 103°,[4] turned out to be aspidospermine and deacetylaspidospermine.[9] Apparently the latter is admixed with samples of "pure" quebrachamine, m.p. 144°, which give a single spot on chromatograms in three different solvent systems. Repeated recrystallization gave a sample, m.p. 145–146°, $[\alpha]_D^{20}$ −116.5°, which with hydrogen peroxide in acetic acid gave solely the hydroxy base, m.p. 188°.

(7) D. F. Dickel, C. L. Holden, R. C. Maxfield, L. E. Paszek, and W. I. Taylor, *J. Org. Chem.*, **80**, 123 (1958).

(8) L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Am. Chem. Soc.*, in press.

(9) We are greatly indebted to Prof. H. Conroy for pointing out first these possibilities.

EXPERIMENTAL[10]

Fractional recrystallization of quebrachamine. A sample of quebrachamine (5 g.) obtained through the courtesy of E. Merck, Darmstadt,[11] was recrystallized twice from methanol and showed then m.p. 143–145°, $[\alpha]_D^{20}$ −117.3° (*c*, 1.0 in 95% C_2H_5). Further recrystallizations from cyclohexane furnished 5 fractions of increasing solubility which had the following melting points: 145–146°; 145–146°; 146–147°; 145–146°; 144–145°. The rotations of the first four fractions were all $[\alpha]_D^{20}$ −116.5 ± 2°. The last fraction and mother liquors had $[\alpha]_D^{20}$ −118.8 ± 2° which slowly increased on standing in solution, since the hydroxy base $C_{19}N_{26}N_2O$, $[\alpha]_D^{20}$ −504°, is formed.

Chromatographic analysis. In three solvent systems (a) 2-butanol–formic acid–water (75:15:10), (b) 99% of a mixture of 2 parts of methanol, 1 part of benzene, 1 part of 1-butanol and 1 part of water, and 1% of a 15% aq. ammonia solution, (c) phenol–formic acid–water (120 g.:1.6 cc.:40 cc.) quebrachamine traveled close to the solvent front (Whatman No. 1 filter paper) showing R_f values >0.9. Deacetylaspidospermine was indistinguishable in these systems. In amyl alcohol–water (90:6) there was a slight separation of quebrachamine (R_f 0.92) and deacetylaspidospermine (0.83) which however was insufficient to detect 10% deacetylaspidospermine in a mixture made up with quebrachamine. The use of filter paper impregnated with borate buffer of *p*H 7.4, 9.3, and 10.4 did not improve the separation.

Electropherograms[12] of mother liquors of quebrachamine in acidic buffer systems showed the presence of small amounts of oxy base $C_{19}H_{26}N_2O$, m.p. 188°, which moved slightly faster than quebrachamine. Deacetylaspidospermine moved (after 50 min.) approximately twice as fast as quebrachamine and was detectable by its coloration on spraying with 1% ethanolic cinnamaldehyde solution and subsequent exposure to hydrogen chloride gas. In mixtures made up of 50% quebrachamine and 50% deacetylaspidospermine separation and detection were still possible, but 10% deacetylaspidospermine admixed to quebrachamine could not be detected in this way.

Identification of "base $C_{21}H_{28}N_2O_2$, m.p. 213°" with aspidospermine. By the action of 6 cc. of acetic acid–30% hydrogen peroxide (1:1) on 0.5 g. of commercial "pure" quebrachamine 40 mg. of the base considered to be an N^a-acetylhydroxy- derivative $C_{21}H_{28}N_2O_2$ of quebrachamine was obtained.[4] The mixed melting point of this base with aspidospermine ($C_{22}H_{30}N_2O_2$) was 213°. The ultraviolet and infrared spectra of the two bases were identical. No aspidospermine was found when the purest sample of quebrachamine obtained by repeated recrystallizations first from methanol and then from cyclohexane was oxidized with peracetic acid. This led only to the formation of the base $C_{19}H_{26}N_2O$, m.p. 188°.

Quebrachamine disulfide. To a cooled solution of 29.2 mg. of quebrachamine in 10 ml. of anhydrous benzene was added 100 mg. of anhydrous trichloroacetic acid and 1 ml. of a solution of 6.8 mg. of disulfur dichloride (S_2Cl_2) in benzene. After 2 hr. the reaction mixture was poured into an excess (*ca.* 100 ml.) of petroleum ether (b.p. 30–40°). The precipitate was removed by centrifugation, washed with ether and petroleum ether, and recrystallized from petroleum ether to colorless crystals (20 mg., 60%), m.p. 166°; R_f 0.25, compared with quebrachamine 0.8 (2,4-lutidine-*t*-amyl alcohol, 1:1, saturated with water). The reactions according to Ehrlich, Hopkins-Cole and with cinnamic aldehyde were

(10) All melting points are corrected. The analyses were performed by the Analytical Services Unit of this laboratory, under the direction of Dr. W. C. Alford.

(11) We are greatly indebted to Dr. Jan Thesing for his assistance and cooperation.

(12) Approximately 50 volts/cm., using the Wieland-Pfleiderer Pherograph [*cf. Angew. Chem.*, **67**, 257 (1955)].

all negative. The Keller reaction, concd. sulfuric acid containing a trace of ferric ion, was positive.

Anal. Calcd. for $C_{33}H_{50}N_4S_2$: C, 72.79; H, 7.99; N, 8.94; S, 10.23. Found: C, 72.50; H, 8.04; N, 9.06; S, 10.33.

Ultraviolet spectrum: λ_{max} (log ϵ) 300 (3.56); 212 (4.30).

Infrared spectrum (potassium bromide): 2.95–2.98 (broad); 3.43; 3.58; 6.05vw; 6.20vw; 6.44s; 6.86vs; 7.25m; 7.39s; 7.52w; 7.86m; 8.10m; 8.28m; 8.39s; 8.56w; 8.74m; 8.86m; 9.08w; 9.37w; 9.74m; 9.88m; 10.0vw; 10.11vw; 10.36m; 10.69w; 11.51m μ.

On reductive hydrolysis of the disulfide (10 mg.) with zinc in acetic acid the ether solution of the crude reaction product showed (in chloroform) a band at 5.81 μ of medium intensity, and 6.20vs, both bands typical of oxindole derivatives. However, on purification of the material *via* the picrate only a small amount of quebrachamine picrate, m.p. 193°, identified by mixed melting point and infrared spectrum, was obtained. The same result was given by the reduction of the disulfide with Raney nickel.

Quebrachamine "tribromide." *N*-Bromosuccinimide (0.222 g.) was added slowly with mechanical stirring to 0.141 g. of quebrachamine in 3 ml. of glacial acetic acid and 2 ml. of water. Stirring was continued for 1 hr. at room temperature and then 4*N* sodium hydroxide was added in the cold until the solution was at *p*H 6. Extraction with dichloromethane and *n*-propyl alcohol yielded a yellow oil which was crystallized from chloroform and benzene to yield 0.08 g. of cotton-like needles, m.p. 287–289°. The analytical sample was prepared by a recrystallization from the same solvents. It displayed m.p. 290°, ultraviolet spectrum λ_{max} 231 (ϵ 44,000), 285 (ϵ 7,440), 293 (ϵ 7,470) and had no carbonyl absorption in the infrared.

Anal. Calcd. for $C_{19}H_{23}N_2Br_3$: C, 43.96; H, 4.47; Br, 46.18. Found: C, 43.99; H, 4.59; Br, 45.99. The formula $C_{19}H_{25}N_2Br_3$ (C, 43.79; H, 4.84; Br, 46.00) is not excluded.

Acknowledgment. We are greatly indebted to Drs. K. Freter and A. A. Patchett for experimental assistance, to Dr. H. Conroy for helpful discussions and to Dr. G. F. Smith for an advance copy of his manuscript prior to publication.

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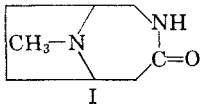
Synthesis of 9-Methyl-3,9-diazabicyclo[4.2.1]-nonane

R. J. MICHAELS AND H. E. ZAUGG

Received September 29, 1959

This note reports the preparation of the title compound, II, by treatment of tropinone with hydrazoic acid to give the bicyclic lactam I which was reduced with lithium aluminum hydride. The overall yield of II was 61%.



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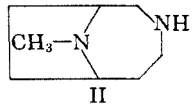

II

This scheme provides access to a bicyclic homopiperazine system of potential value as an intermediate for compounds of pharmacological interest.

EXPERIMENTAL

9-Methyl-3,9-diazabicyclo[4.2.1]nonan-4-one (I). A solution of 11.1 g. (0.08 mole) of tropinone in 100 ml. of chloroform cooled to −5° in an ice-salt bath was treated dropwise with stirring with 25 ml. of concentrated sulfuric acid, keeping the temperature below 15°. After cooling to 5° the stirred reaction mixture was treated with 10.4 g. (0.16 mole) of sodium azide in approximately 0.5–1 g. portions at such a rate that the temperature did not exceed 35°. Addition of the azide required about 2 hr. after which the reaction mixture was stirred at 50° for another 2 hr. It was then poured into a 600 ml. beaker one third filled with ice. Solid potassium carbonate was added portionwise until the mixture was strongly alkaline. This was followed by 50 ml. of a 60% potassium hydroxide solution; the inorganic salts were removed by filtration and washed well with chloroform. The alkaline filtrate was extracted with three portions of chloroform and the combined chloroform washings and extracts were dried over anhydrous sodium sulfate. Filtration of the drying agent followed by removal of the chloroform by distillation gave 11.1 g. (90%) of crude I, m.p. 79–83°. For analysis, a sample was converted to the hydrochloride, m.p. 258–259° dec. (from ethanol).

Anal. Calcd. for $C_8H_{15}ClN_2O$: C, 50.39; H, 7.93; N, 14.69. Found: C, 50.42; H, 7.96; N, 14.59.

9-Methyl-3,9-diazabicyclo[4.2.1]nonane (II). To a solution of 11.0 g. (0.071 mole) of I in 400 ml. of dry ether was added dropwise with stirring under an atmosphere of dry nitrogen, a solution of 6.8 g. (0.18 mole) of lithium aluminum hydride in 200 ml. of dry ether. Addition was complete in 0.5 hr., and the mixture was stirred and refluxed for 46 hr.

Water (25 ml.) was added dropwise to the cooled reaction mixture which was then filtered by suction. The filter cake was washed well with ether and the combined filtrate and washings were dried over anhydrous sodium sulfate. Filtration and removal of the ether by distillation followed by vacuum distillation of the residual oil gave 6.8 g. (68%) of II, b.p. 111–113° (38 mm.), n_D^{24} 1.4992.

Anal. Calcd. for $C_8H_{16}N_2$: C, 68.52; H, 11.50; N, 19.98. Found: C, 68.71; H, 11.91; N, 20.26.

II.Dihydrochloride, m.p. 290–291° dec. (from dry ethanol).

Anal. Calcd. for $C_8H_{18}Cl_2N_2$: C, 45.08; H, 8.51. Found: C, 45.46; H, 8.61.

Acknowledgment. The authors are indebted to Mr. E. F. Shelberg and his associates for the microanalyses.

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Preparation of *m*- and *p*-Diethynylbenzenes

ALLAN S. HAY

Received September 30, 1959

We wished to prepare reasonably large quantities of *m*- and *p*-diethynylbenzenes. Deluchat[1]

(1) R. Deluchat, *Ann. chim.*, 1 [11] 181–255 (1934).

had prepared these compounds by a laborious seven step synthesis starting from the corresponding xylene isomer. This route was obviously not satisfactory for relatively large scale preparation of these materials.

When the commercially available divinylbenzene mixture[2] (40% *m*- and *p*-divinylbenzenes) is brominated in chloroform solution, 1,4-bis(1,2-dibromoethyl)benzene separates on cooling. Recrystallization from chloroform yields the pure material. The bromination residue now contains 1,3-bis-(1,2-dibromoethyl)benzene along with considerable quantities of the dibromodiethylbenzenes from the ethylstyrenes in the starting material. A molecular distillation readily separates the dibromodiethylbenzenes from the tetrabromodiethylbenzene. The latter fraction on crystallization from ethanol yields pure 1,3-bis(1,2-dibromoethyl)benzene. Treatment with four moles of potassium *t*-butoxide in *t*-butanol readily converts the tetrabromodiethylbenzenes to the respective diethynylbenzenes.

EXPERIMENTAL

Bromination of mixed divinylbenzenes. Bromine (1300 g., 8.13 moles) was added over 2 hr. with stirring to a cooled solution of 750 g. mixed divinylbenzene (40% = 2.3 moles *m*- and *p*-divinylbenzene) in 1200 ml. of chloroform. The reaction mixture was then cooled to 5° and a voluminous precipitate settled out which was separated by filtration. Recrystallization from chloroform yielded 264 g. (0.59 mole) of 1,4-bis(1,2-dibromoethyl)benzene, m.p. 155–157° (lit.[1] m.p. 157°). The two filtrates were combined and the chloroform removed on a rotating evaporator at 100° (3 mm.). The residue was then fractionated in a molecular still. Distillation at 50° (40–70 μ) and then at 80° (20–50 μ) separated most of the dibromodiethylbenzenes. The residue which was a viscous sirup was distilled at 150° (12–30 μ). The distillate crystallized when triturated with cold alcohol and after recrystallization from alcohol yielded 420 g. (0.93 mole, combined yield of 66%), 1,3-bis(1,2-dibromoethyl)benzene, m.p. 65–66.5° (lit.[1] m.p. 64°).

p-Diethynylbenzene. To a solution of 18 g. (0.46 mole) of potassium in 1 l. of *t*-butanol at the temperature of reflux was added 50 g. (0.11 mole) of 1,4-bis(1,2-dibromoethyl)-benzene. After 1 hr. the reaction mixture was made up to 4 l. with ice water and the pale yellow solid was removed by filtration. There was isolated 9.8 g. (0.078 mole, 71% yield) of *p*-diethynylbenzene, m.p. 95° (lit.[1] m.p. 95°). Sublimation at 90–100° (2 mm.) gave a colorless solid m.p. 96.5°.

m-Diethynylbenzene was prepared in an identical fashion and in comparable yield from 1,3-bis(1,2-dibromoethyl)-benzene. After flooding with water the product was isolated by ether extraction and distillation to yield *m*-diethynylbenzene, b.p. 78° (14 mm.), n_D^{20} 1.5825 (lit.[1] b.p. 78° (15 mm.) n_D^{18} 1.5841).

Acknowledgment. The distillations were performed by Mr. E. M. Hadsell. It is a pleasure to acknowledge the very capable assistance of Mr. R. J. Flatley.

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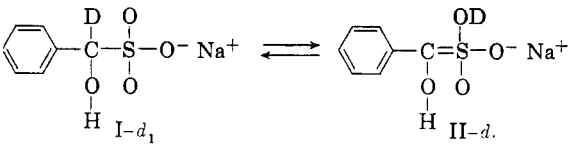
(2) Purchased from Monomer-Polymer Laboratories, 5000 Landgon Street, P.O. Box 9522, Philadelphia 24, Pa.

Absence of Exchange by the "Aldehydic" Hydrogen of Benzaldehyde Sodium Bisulfite

JOHN A. SOUSA AND J. DAVID MARGERUM

Received October 19, 1959

In 1939 Thompson and Cromwell reported that in contrast to the lack of hydrogen-deuterium exchange by aldehydes, benzaldehyde-d_1 sodium bisulfite (I-d_1) exchanged up to 76% with conductivity water in a period of seventeen days.[1] They suggested that this could be evidence for the enolization of the bisulfite complex. Such an enol form (II-d_1) would be of particular interest since it postulates an expanded valence shell of ten electrons for the sulfur atom in the complex.



We desired to prepare some deuterated benzaldehydes by utilizing the reverse of this reported exchange reaction. We first attempted to prepare benzaldehyde-d_1 by placing benzaldehyde sodium bisulfite (I) in excess deuterium oxide for a long period of time, as indicated in experiment 1, Table I. The infrared spectrum of the aldehyde showed that no exchange had occurred.[2] Similar experiments (2, 4, and 5 through 9) were made using different methods of separating the products, and of determining the extent of exchange by infrared analysis. These experiments were conducted under various conditions such as exposure to near ultraviolet light or in the presence of added substances which might somehow have acted as catalysts in the original work. Experiment 3 is essentially a duplication of one experiment of the reported exchange reaction, using benzaldehyde prepared from lithium aluminum deuteride.[2] In every experiment no hydrogen-deuterium exchange was found on the "carbonyl" carbon of I or I-d_1. Thus, there is no evidence for the existence of an enol form, such as II-d_1.

The attempted exchange experiments are summarized in Table I. The infrared spectra of I and I-d_1 are shown in Fig. 1. The deuterated complex is readily distinguished from I by the absence of bands at 1411 and 845 cm.$^{-1}$ and the presence of bands at 1347, 969, 945, and 766 cm.$^{-1}$ [3].

(1) A. F. Thompson, Jr., and N. H. Cromwell, *J. Am. Chem. Soc.*, **61**, 1374 (1939).

(2) K. B. Wiberg, *J. Am. Chem. Soc.*, **76**, 5371 (1954).

(3) Deutero-benzaldehyde is easily distinguished from benzaldehyde by the large shift in the C—H stretching frequency (*cf.* ref. 2), and also shows the absence of bands at approximately 1387, 826, and 714 cm.$^{-1}$ and the presence of bands at approximately 1222, 791, and 733 cm.$^{-1}$.

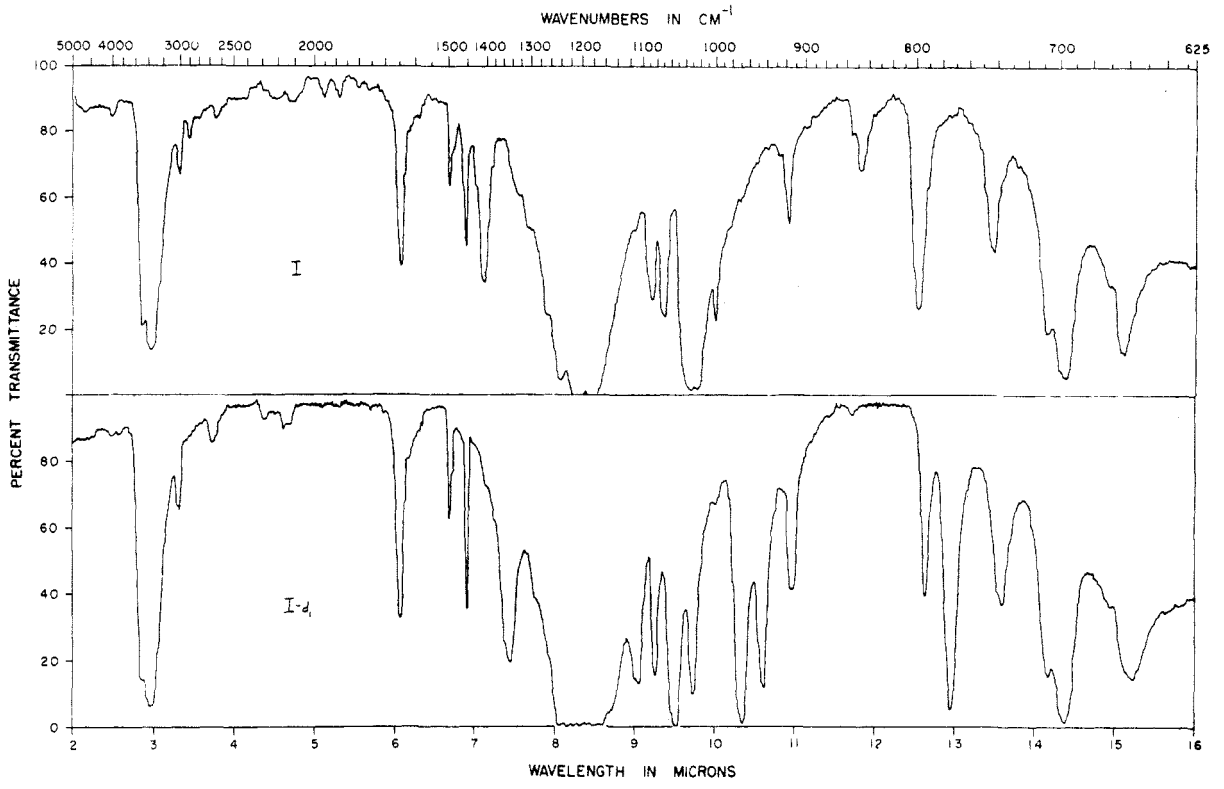


Fig. 1. Infrared spectra of benzaldehyde sodium bisulfite (I) and benzaldehyde-d_1 sodium bisulfite (I-d_1) in potassium bromide disks

TABLE I

ATTEMPTED PROTIUM EXCHANGE IN BENZALDEHYDE SODIUM BISULFITE ADDITION COMPOUND (I)

Expt.	Reactants	Mole Ratio of Reactants	Period, Days	Light	Method of Separation	Products Analyzed
[a]	I-d_1/H_2O	1/11.1	17	—	Vac. distln.	H_2O
1	I/D_2O	1/31.5	28	Dark	Na_2CO_3 rxn.	BzH
2	I/D_2O	1/35	26	Dark	Vac. distln.	BzH
3	I-d_1/H_2O	1/11.7	34	Dark	Vac. distln.	H_2O
					Na_2CO_3 rxn.	BzD
4	I-d_1/H_2O	1/11.1	2	Near UV	Evaporation	I
5	I/D_2O	1/31.5	45	Rm. light	Evaporation	I
6	(Same as 5; 1 drop 6*N* HCl added to 2 ml. of solution)					
7	(Same as 5; 1 drop 6*N* NaOH added to 2 ml. of solution)					
8	(Same as 5; *ca.* 100 mg. 5% Pd-$BaSO_4$ added to 2 ml. of solution)					
9	(Same as 5; *ca.* 50 mg. quinoline-sulfur added to 2 ml. of solution)					

[a] Ref. 1.

The increases in the density of water observed in the work of Thompson and Cromwell[1] could not have been due to an exchange reaction. A possible explanation of their results may be found in our observation that benzaldehyde and sulfur dioxide vapors appear to exist in equilibrium with the benzaldehyde sodium bisulfite complex. In the vacuum distillation of water from a water-complex mixture at room temperature, small but significant amounts of benzaldehyde and sulfur dioxide are carried over into the water, which would increase its density.

EXPERIMENTAL

Benzaldehyde sodium bisulfite (I) was prepared by mixing 40% aqueous sodium bisulfite with a slight excess of freshly distilled benzaldehyde, allowing the complex to separate on standing, filtering it, washing it three times with ether and drying over phosphorus pentoxide at 1 μ for 1.5 hr. Benzaldehyde-d_1 sodium bisulfite (I-d_1) was prepared by Wiberg's method.[2] The 5% palladium-barium sulfate and the quinoline-sulfur were prepared as described in *Organic Reactions*.[4]

Reaction conditions and separation of products. All experiments were carried out in evacuated, out-gassed, sealed-off tubes.[1] These were allowed to stand at room temperature, in the dark or in room light as indicated in Table I, except for experiment 5 in which exposure was made with a water cooled AH-6 mercury arc (glass envelope) for 29 hr. using Corning glass filter No. 5840 followed by 20 hr. without a filter. Separation by vacuum distillation was made at 25° for water and between 60° and 115° for benzaldehyde. In experiments 1 and 3 the complex was treated with an excess

(4) E. Mosettig and R. Mozingo, *Org. Reactions*, **IV**, 386–9 (1948).

of 3% sodium carbonate followed by ether extraction, drying over magnesium sulfate, and distillation of the benzaldehyde at reduced pressure under nitrogen.

Analysis. In all of the experiments infrared absorption spectra were used to analyze for the presence of deuterated and undeuterated products. Most of the spectra were taken with a calcium fluoride prism in a Perkin-Elmer model 112 Spectrometer. The benzaldehyde and benzaldehyde-d_1 were run between sodium chloride plates or in carbon tetrachloride solution; water and deuterium oxide were run in thin calcium fluoride cells[5]; crystals of I and I-d_1 were run using the model 85 microscope attachment to the 112. Spectra of I and I-d_1 (recrystallized from water and dried under vacuum) were also run in potassium bromide disks on a Baird Model A and are shown in Fig. 1.

Instability of the complex under vacuum. At 60° large amounts of benzaldehyde, sulfur dioxide, and water were vacuum distilled from I in a period of several days. These were identified by mass spectral analysis with a Consolidated Electrodynamics model 21-103C mass spectrometer. Similarly, at 25° more than 7% of the benzaldehyde was vacuum distilled from a dry sample of I in 5 days, and was analyzed by its ultraviolet spectrum with a Cary model 11 spectrophotometer. A mixture of 1.86471 g. of I (freshly washed with ether and dried) and 1.48630 g. of water was placed in one arm of a U-tube, which was outgassed and evacuated. The water was vacuum distilled for 2 hr. into the other arm from a maximum temperature of 25°. After dilution to 5.0 ml. the water had a *p*H of 3.1 compared to an initial *p*H of 6.0 and the ultraviolet spectrum (measured in a 0.0107 cm. calcium fluoride cell) showed a total of 0.0016 g. of free benzaldehyde. When diluted again by $^1/_{50}$ (measured in a 1.00 cm. cell) it showed a total of 0.0021 g. of free benzaldehyde. The difference in free aldehyde with concentration can probably be attributed to some benzaldehyde-sulfurous acid complex formation. Thompson and Cromwell, using comparable amounts of water and complex, found that after vacuum distillation the water had increased in total weight between 0.00213 and 0.00756 g. and attributed this to an exchange reaction.

PIONEERING RESEARCH DIVISION
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(5) R. C. Gore, R. B. Barnes, and E. Petersen, *Anal. Chem.*, **21**, 382 (1949).

Unsaturated Four-Membered Ring Compounds. III. The Reactivity of Benzycyclobutene Toward Electrophilic Substitution

FREDERICK R. JENSEN AND GARY MACIEL

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In view of the possible effects of compression of the bond angles in benzene on the rate of substitution, it was of interest to determine the absolute reactivity of benzocyclobutene towards electrophilic substitution. Although the bond angles and interatomic distances have not been determined for benzocyclobutene, it is to be expected that the bond angles to the cycloalkane ring are appreciably smaller than the normal bond angle of 120°.

The electrophilic reaction selected was the aluminum chloride–catalyzed benzoylation reaction using ethylene chloride as solvent. Since substitution of a methyl group in benzene increases the rate of reaction by a factor of 132 (Table I), the benzoylation reaction is very sensitive to substitution effects. Any net effect of the fused ring should give a marked change in the rate of benzoylation. The aromatic compounds selected as standards for reference purposes were *o*-xylene, indane, and tetralin.

For this reaction, individual experiments follow second order kinetics according to expression 1.

$$\text{rate} = k_2(C_6H_5COCl\cdot AlCl_3)(ArH) \qquad (1)$$

However, the value of k_2 depends on the initial concentration of the complex.[1] With benzocyclobutene, the reactions apparently followed second-order kinetics to about 50% reaction and then the rates of reaction fell off rapidly. After ten to fifteen minutes, the reaction mixtures began to darken and turned progressively darker with time. The cause of this behavior was not investigated. The reactions of the other compounds followed second-order kinetics to at least 90% reaction, and the reaction mixtures stayed colorless for at least twenty-four hours.

The results are summarized in Table I.[2] The three compounds with the fused cycloalkane rings react two to three times faster than *o*-xylene. However, benzocyclobutene reacts only slightly faster than indane and tetralin. Since there is no rate acceleration, any decreased stability of benzocyclobutene by the bond compressions must be countered by an equal degree of instability of the transition state.

TABLE I

RATES OF THE ALUMINUM CHLORIDE–CATALYZED BENZOYLATION OF SELECTED BENZENE DERIVATIVES IN ETHYLENE CHLORIDE SOLUTION AT 25°[a]

Aromatic	$k_2 \times 10^3$ (l.m.$^{-1}$ sec.$^{-1}$)	Relative Rate[b]
Benzene	0.00855	1/1700
Toluene	1.13	1/13
o-Xylene	15.1	1
Benzocyclobutene	41[c]	2.8
Indane	28.6	1.9
Tetralin	33.6	2.3

[a] For benzene and toluene, initial concentrations 0.222*M*; for the other compounds, 0.200*M*. [b] The small effect of initial concentration on rate is ignored in calculating the relative rates. [c] Less than 50% reaction. The calculated rate constants for benzocyclobutene decrease sharply after 50% reaction.

There are at least two explanations which could account for the "normal" reactivity of benzocyclo-

(1) F. R. Jensen, *J. Am. Chem. Soc.*, **79**, 1226 (1957).

(2) When no unusual reactivities were observed, the decision was made not to determine the manner in which the benzoyl chloride is consumed. The reported rate constants probably represent the upper limit for aromatic substitution.

butene. One possible explanation is that the bond compressions have no effect on the resonance stabilization of the molecule. The second possibility is that the resonance stabilization of benzocyclobutene is decreased by the bond compressions, but that the stabilization of the transition state by the cycloalkane ring is less for benzocyclobutene than for tetralin and indane.

It is of interest to note that indane and tetralin are both more reactive than *o*-xylene. There is probably very little difference in the steric hindrance to attack in the *ortho-* positions of these molecules. Nor can, the effect be attributed to the substitution of hydrogen by an alkyl group, since ethylbenzene is less reactive than toluene in the benzoylation reaction.[3] The increased reactivity may be due to the presence of more favorable configurations for hyperconjugation[4] with the alkyl groups in the transition states for substitution of indane and tetralin than for *o*-xylene.

EXPERIMENTAL

The benzocyclobutene was prepared by the catalytic hydrogenolysis of 1,2-dibromobenzocyclobutene using the method given by Cava and Napier for the hydrogenolysis of 1,2-diiodobenzocyclobutene.[5] Whereas yields of 20–55% were reported using the diiodo- compound, yields of 80–85% were obtained using the dibromo- compound. The hydrocarbon sample by mass spectral analysis[6] contained 99.6% of material with mass number 104, and the infrared spectrum corresponded to that reported for benzocyclobutene.[4] The benzocyclobutane had b.p. 150.5°/754 mm. (lit.,[4] b.p. 150°/748 mm.). The other hydrocarbons had purities of at least 99.5% as shown by cooling curve determinations. The other reactants and the solvent were purified as described previously.[1] The reactions were followed by determining the rate of disappearance of benzoyl chloride.[3]

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(3) H. C. Brown, B. A. Bolto, and F. R. Jensen, *J. Org. Chem.*, **23**, 414 (1958).

(4) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Am. Chem. Soc.*, **80**, 2326 (1958).

(5) M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **80**, 2255 (1958).

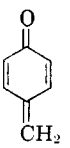
(6) We are indebted to Mr. Seymour Meyerson of the Standard Oil Company (Ind.) for the mass spectra analysis.

Dimer of 10-Methylene-9-phenanthrone

PETE D. GARDNER AND HOSSEIN SARRAFIZADEH R.

Received September 18, 1959

Although several highly substituted homologs of quinone methide (I) are known only one has been reported which contains its double bond terminally II.[1] In an attempt to obtain a compound having the *ortho*-functionality of I for purposes of studying its chemistry, we have directed our efforts toward the synthesis of 10-methylene-9-phenanthrone (III). It might be expected to be stable both by analogy with II and by consideration of the relatively small energy difference between it and the fully aromatic phenanthrene system (10-methyl-9-phenanthrol). Naively, perhaps, one might expect it to have properties similar to those of a hyper-reactive aryl vinyl ketone. Molecular orbital calculations are not helpful in making predictions in cases of this sort because of the oxygen atom; a new parameter is required, the uncertainty in which would permit one to have but little faith in the result. At any rate, one would expect the molecule to have a large delocalization energy and a large free valence value at the terminal carbon atom.[2]



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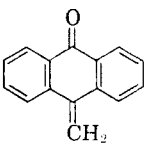

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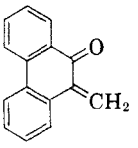
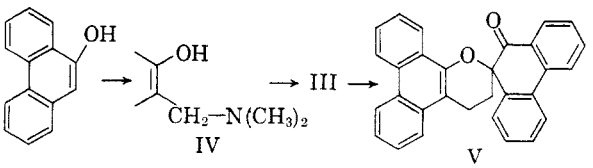


III

The condensation of 9-phenanthrol with formaldehyde and dimethylamine under very mild conditions afforded the expected Mannich base IV which proved to be very unstable. Loss of nitrogen occurred during attempts to purify it and the majority of such experiments gave, directly, a high-melting, nitrogen-free substance V. Treatment of a crude sample of IV with methyl iodide gave the methiodide which was also unstable and afforded, as before, the yellow compound. The reaction of 9-phenanthrol with formaldehyde afforded V directly indicating similar instability of the 10-methylol compound.



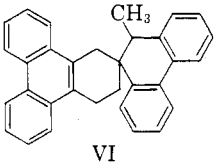
V

The dimeric quinone methide V absorbs at 5.94 μ in the infrared. Its ultraviolet spectrum exhibits high intensity maxima at 250, 275, 295, and 306 mμ with ϵ values ($\times 10^4$) 5.65, 2.74, 1.07, and 0.950, respectively. Low intensity absorption is at 340 and 360 mμ with ϵ ($\times 10^3$) 3.82 and 2.65, respectively. Reduction of V with lithium aluminum hydride afforded the corresponding carbinol. The latter substance absorbs in the infrared at 2.90 μ but the 5.94 band found in the spectrum of V is not present. The ultraviolet spectrum exhibits high intensity absorption at 256, 276, and 297

(1) E. Clar, *Ber.*, **69**, 1686 (1936) and references cited therein.

(2) Compare, for example, with *p*-quinodimethane, predicted by calculations[3] to be nearly as stable as benzene (stable as reflected by delocalization energy) but highly reactive. Experimental evidence bearing only on its reactivity is available.

mμ with ε (× 10^4) 6.35, 3.32, and 1.44 respectively. Low intensity absorption at 343 and 362 mμ has ε 1.92 × 10^3. This spectrum is almost identical with that of the dihydro dimer of 9,10-phenanthraquinodimethane (VI).[4] Extinction coefficients of low intensity absorption make it clear that only one of the phenanthrene nuclei retains the 9,10-double bond. On the basis of these data, and in consistency with characterized quinone methide dimers in other series,[5] the substance is formulated as V.



VI

EXPERIMENTAL[6]

9-Phenanthrol. This substance was prepared by the procedure of Bachman[7] (22–40% yields) and also by application of the method developed by Hawthorne[8] for another phenol (26% yield).

10-Dimethylaminomethyl-9-phenanthrol (IV) *and its methiodide.* A solution of 5.9 g. of 9-phenanthrol in 20 ml. of ethanol was treated with 6.0 ml. of 25% aqueous dimethylamine and 2.3 ml. of 36% aqueous formaldehyde. After standing for 8 hr. at room temperature, the mixture was freed of solvent, without heating, at an aspirator. The solid residue (crude IV) could not be purified without decomposition and so was dissolved in ether and converted to the methiodide using 5.0 g. of methyl iodide. After 12 hr. at room temperature the salt was collected by filtration and washed with ether. The methiodide in this crude state (4.0 g. 35%) melted with decomposition at 225°. Attempts to purify it resulted in the formation of V.

Anal. Calcd. for $C_{18}H_{20}NI$: N, 3.55. Found: N, 3.92.

Dimer of 10-methylene-9-phenanthrone (V). A solution of 7.0 g. of 9-phenanthrol, 3.2 ml. of 38% aqueous formaldehyde and 6.2 ml. of 25% aqueous dimethylamine in 60 ml. of ethanol was heated under reflux for 2 hr. The mixture, containing suspended yellow solid, was filtered and the filtrate was concentrated to a small volume whereupon additional solid crystallized. The combined solids were recrystallized from benzene to give 3.2 g. (43%) of well formed yellow prisms of V, m.p. 251–252°.

Anal. Calcd. for $C_{30}H_{20}O_2$: C, 87.35; H, 4.89. Found: C, 87.13; H, 4.82.

Spectral data are described in the discussion section.

A similar experiment in which the dimethylamine was replaced by a catalytic quantity of pyridine gave the same substance in 40% yield. Reactions conducted in the absence of base of any kind afforded the dimer in 36% yield.

Lithium aluminum hydride reduction of V. One gram of the dimer (V) was heated for 10 hr. under reflux in a suspension of a very large excess of lithium aluminum hydride in 50 ml. of tetrahydrofuran. Excess hydride was destroyed by the cautious addition of water followed by dilute hydrochloric acid. Isolation of the product by ether extraction and the usual processing of the extract afforded 0.90 g. (90%) of the expected carbinol, m.p. 249–250°. This substance appeared as colorless prisms after several recrystallizations from ethyl acetate and had the same melting point. The carbonyl absorption found at 5.94 μ in V was lacking in the spectrum of the carbinol. Hydroxyl absorption appeared at 2.9 μ. The ultraviolet spectrum is described in the discussion.

Anal. Calcd. for $C_{30}H_{22}O_2$: C, 86.93; H, 5.35; mol. wt. 414. Found: C, 86.64; H, 5.15; mol. wt. 480 (cryoscopic in benzil).

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(3) C. A. Coulson, D. P. Craig, A. Maccoll, and A. Pullman, *Discussions Faraday Soc.*, **2**, 46 (1947).

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(5) See for example K. Hultzsch, *J. prakt. Chem.*, **159**, 180 (1941).

(6) Melting points are corrected. Infrared spectra were obtained in potassium bromide wafers. Ultraviolet spectra were of 95% ethanol solutions.

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Condensation of *o*-Benzoylbenzoyl Chloride with Ethyl Malonate

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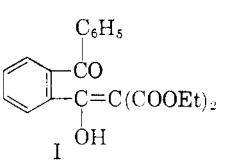
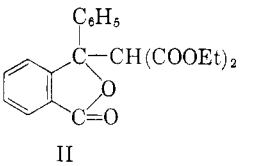
The compound formed by action of *o*-benzoylbenzoyl chloride on ethoxymagnesiomalonic ester, formerly represented as ethyl 3-phenylphthalidylmalonate (II),[1] is actually the enol form of ethyl *o*-benzoylbenzoylmalonate (I).

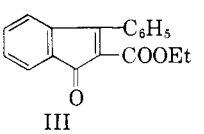


I

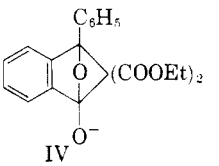


II

Structure I allows simple formulation of the conversion of the substance into ethyl 3-phenylindone-2-carboxylate (III) by aqueous base, whereas with structure II this change requires assumption of a strained intermediate (IV).



III



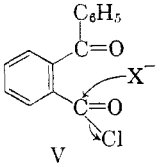
IV

Spectral and chemical properties of the compound are in agreement with I. In chloroform the compound has a sharp absorption band at 3500 $cm.^{-1}$ (enolic OH), a broad band with maxima at 1600, 1650, 1725 and 1770 $cm.^{-1}$ (C=O and C=C—O), and a broad band at 1260–1300 $cm.^{-1}$ (ester). It gives a deep red-brown color with ferric chloride, and it is soluble in cold 1% sodium hydroxide. Acidification of this solution, if it has not been

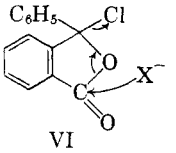
(1) W. L. Yost and A. Burger, *J. Org. Chem.*, **15**, 1113 (1950).

heated or kept too long, precipitates the compound unchanged.

Formation of I has no bearing on the true structure of *o*-benzoylbenzoyl chloride, as illustrated by V and VI.



V



VI

Authentic ethyl 3-phenylphthalidylmalonate (II) can be obtained in good yield from ethyl *o*-benzoylbenzoate and ethyl sodiomalonate in alcohol. The properties of this substance are quite different from those of its isomer. Its infrared spectrum shows absorption at 1720 and 1770 cm.$^{-1}$, corresponding to lactone and ester carbonyl groups. It gives no ferric chloride color and it is insoluble in cold dilute sodium hydroxide. When it is heated with the latter reagent, it dissolves, and acidification then precipitates 3-phenylphthalidyl malonic acid. Heating this acid yields the known[2] 3-phenylphthalidylacetic acid, also obtained directly from the malonic ester by acid hydrolysis.

By analogy with the present results, it is probable that the compound obtained from ethyl benzoylbenzoate and benzyl cyanide is not $C_6H_5COC_6H_4$-$COCHCN$,[3] but rather $HOOCC_6H_4C(C_6H_5)=C(C_6H_5)CN$ or the corresponding lactone. The reported stability to hydrolysis then is easily understandable, and the methylation product is a methyl ester.

EXPERIMENTAL

Ethyl o-benzoylbenzoylmalonate (I). Slight modification of the original preparation[1] enables one to obtain yields of 90–95%. It was not necessary to avoid heating benzoylbenzoyl chloride, and the material was freed of thionyl chloride at 100° under reduced pressure, two portions of dry benzene being added to insure complete volatilization. As I is soluble in and rapidly altered by aqueous sodium carbonate, an excess must be avoided in final washing of the crude product; furthermore, the compound is quite soluble in ether and it is well to use 2:1 ether-ligroin (30–60°) for the first crystallization. The crude product obtained in the present research melted at 80–85°; recrystallization from ethyl acetate–ligroin gave clear prisms, m.p. 86–88° (lit.,[1] 77–79°).

Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.5; H, 5.5. Found[4]: C, 68.4; H, 5.4.

Ethyl 3-phenylphthalidylmalonate (II). A solution of 10 g. of sodium in 100 ml. of absolute alcohol was treated with 70 g. of ethyl malonate and then 100 g. of ethyl benzoylbenzoate. The mixture was boiled for 1.5 hr. and then distilled to a sirup under reduced pressure. Addition of 400 ml. of water gave a cloudy solution from which ether extraction (2 × 100 ml.) removed 9.1 g. of ethyl malonate and 20 g. of ethyl benzoylbenzoate. The product was precipitated by acidification as an oil which soon solidified; recrystallization from alcohol and then from ethyl acetate–ligroin gave 95 g. of colorless needles m.p. 100–102°.

Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.5; H, 5.5. Found: C, 68.5; H, 5.6.

When II was boiled with 10% sodium carbonate for about 5 min., it gave a colorless solution. Acidification gave an oil which solidified when it was dried and rubbed with ether. Crystallization from ethyl acetate–ligroin gave an *acid-ester*, colorless needles, m.p. 97–98° that frothed at about 145°.

Anal. Calcd. for $C_{19}H_{16}O_6$: C, 67.0; H, 4.7. Found: C, 66.7; H, 4.5.

When 1 g. of II was boiled for 1 hr. with 4 ml. of acetic acid and 4 ml. of 48% hydrobromic acid, it gave 3-phenylphthalide-3-acetic acid, needles from toluene, m.p. 177–178° with previous sintering (lit.,[2] m.p. 179–181°); boiling the acid with methanol-sulfuric acid gave *methyl 3-phenylphthalid-3-acetate*, needles from methanol, m.p. 86–87°; b.p. 230–232° at 10 mm.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.3; H, 5.0. Found: C, 72.0; H, 5.0.

When 6.7 g. of II was boiled 15 min. with 4 g. of sodium hydroxide in 25 ml. of water and the resulting solution was then cooled and acidified, there was obtained 5.3 g. crude *3-phenylphthalidylmalonic acid*, a white powder nearly insoluble in hot acetic acid, ethyl acetate, benzene, or chloroform. Acetone dissolved it easily, however, and crystallization from acetone-ligroin gave 4.1 g. of colorless needles, m.p. 160–164° with gas evolution; the melt resolidified and then melted again at 176–178°.

Anal. Calcd. for $C_{17}H_{12}O_6$: C, 65.4; H, 3.9. Found: C, 65.2; H, 3.9.

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(3) W. Wislicenus, H. Eichert, and M. Marquardt, *Ann.*, **436**, 95 (1923).

(4) The author thanks Mrs. O. Hamerston for analytical work.

Condensation Reactions of Phthalaldehydic Acid. I

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On the basis of certain reactions of phthalaldehydic acid several early investigators[1,2] postulated a tautomeric closed-ring form for this compound. This view is substantiated in a recent paper by Wheeler, Young, and Erley,[3] who have examined the infrared absorption of phthalaldehydic acid. These investigators also give data for a considerable number of substituted phthalides prepared by syntheses involving the very reactive 3-position in the 3-hydroxyphthalide form. However, in none of the phthalides which they describe is the carbon atom at the 3-position linked directly to carbon in the substituent.

The solubility and stability of phthalaldehydic

(1) S. Racine, *Ber.*, **19**, 778 (1886).

(2) Bistrzycki and Yessel de Schepper, *Ber.*, **31**, 2790 (1898).

(3) D. D. Wheeler, D. C. Young, and D. S. Erley, *J. Org. Chem.*, **22**, 556 (1957).

acid in concentrated sulfuric acid, and even in mixtures of concentrated sulfuric acid and 20% fuming sulfuric, suggested that condensations might be carried out between phthalaldehydic acid and aromatic hydrocarbons, aryl halides, etc., not unlike the condensation occurring in the production of DDT. A search of the literature revealed that this approach to the synthesis of 3-substituted phthalides from phthalaldehydic acid has been examined only in condensations using certain phenols and phenolic ethers.[2,4,5]

The experiments reported here show that sulfuric acid, which on occasion is bolstered with 20% fuming sulfuric acid, can be employed successfully as the medium for condensing phthalaldehydic acid with a number of aromatic hydrocarbons and aryl halides. Two of the phthalides synthesized and described, namely 3-(2,5-dichlorophenyl)phthalide and 3 - (2,5 - dibromophenyl)phthalide, are apparently unreported in the literature; the others have been prepared by more circuitous methods. Thus the preferred preparation for 3-phenylphthalide, possibly the most important of the phthalides described in this paper, has been the method of Ullman[6,7] which involves the reduction of *o*-benzoylbenzoic acid. 3-Phenylphthalide has also been synthesized by the reaction of phthalaldehydic acid with phenylmagnesium bromide.[8]

The present study is being extended to determine the possibility of similar condensations of phthalaldehydic acid with other aromatics.

EXPERIMENTAL

The phthalaldehydic acid used in these experiments was purified by a single recrystallization from water. This afforded a white crystalline solid, m.p. 99–100°. The fuming sulfuric acid was Merck 20–23%, reagent grade.

3-Phenylphthalide. Five grams (0.033 mole) of phthalaldehydic acid was dissolved in 30 ml. of conc. sulfuric acid, 95–98%. To this solution was added 2.6 g. (0.033 mole) of benzene, and the mixture mechanically stirred at room temperature to disperse the benzene. After about 0.5 hr. the benzene disappeared, giving a homogeneous solution. Stirring was then continued for 0.5 hr.

The reaction mixture, light amber in color, was slowly poured with stirring into about ten times its volume of cold water. The product separated as a thick gum and quickly hardened to a granular solid. After standing until cool the solid was removed, crushed, and thoroughly washed with cold water. The crude product, m.p. 112–114°, weighed 6.9 g. (98%) and was nearly white in color. A single crystallization from ethanol gave 6.0 g. (86%) of white crystals, m.p. 116–117°; lit.,[7] m.p. 115–116°.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79. Found: C, 80.12; H, 4.94.

To verify the product as 3-phenylphthalide 0.5 g. was oxidized with alkaline permanganate solution according to accepted procedure.[9] This gave 0.45 g. of anhydrous *o*-benzoylbenzoic acid, m.p. 127°; lit.,[10] m.p. 127°.

3-Tolylphthalide. Three grams (0.02 mole) of phthalaldehydic acid was dissolved in 30 ml. of 5:1 conc. sulfuric acid–water. To this was added 1.84 g. (0.02 mole) of toluene, and the mixture was mechanically stirred to disperse the insoluble toluene. After approximately 2 hr. the toluene disappeared, giving a clear green solution. This was permitted to stand for 1 hr., then poured into a large volume of cold water. The product separated as a yellow gum, soon hardening to a crumbly solid. When cold the solid was removed, pulverized, and washed with cold water. After air-drying the crude product, ivory in color, weighed 4.5 g. (100%). Crystallization from ethanol yielded 3.8 g. (85%) of a white powdery solid which showed no sharp melting point, but softened at 85° and became a clear liquid at *ca.* 115°. This behavior is not unexpected, as the synthesis permits formation of a mixture of the 3-tolylphthalides, particularly the *o*- and *p*-isomers. Reported melting points[11] for the isomers are as follows: 3-(*p*-tolyl)-phthalide, 130°; *o*-, 111°; *m*-, 86.6°.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.35; H, 5.39. Found: C, 79.86; H, 5.47.

3-(p-Xylyl)-phthalide. Three grams (0.02 mole) of phthalaldehydic acid was dissolved in 20 ml. of 9:1 conc. sulfuric acid-water. To this solution at room temperature was added 2.12 g. (0.02 mole) of *p*-xylene and the mixture was stirred to disperse the insoluble hydrocarbon. After about 30 min. the mixture became orange in color and homogeneous. The reaction product was then isolated in the same manner as described previously for 3-phenylphthalide. After air drying the crude product, ivory in color, weighed 4.5 g. (94%) and melted at 104–111°. Crystallization from ethanol yielded a white powder-like solid, m.p. 111–112°; lit.,[12] m.p. 112°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.84; H, 5.68.

To verify the product as 3-(*p*-xylyl)phthalide 0.5 g. was subjected to alkaline permanganate oxidation.[9] This gave 0.48 g. of 2-(*o*-carboxybenzoyl)terephthalic acid (commonly called benzophenone-2,2′,5′-tricarboxylic acid) m.p. 282° dec. Neut. equiv. Calcd.: 105; found: 108.

3-(Chlorophenyl)phthalide. Five grams (0.033 mole) of phthalaldehydic acid was dissolved in 30 ml. of 2:1 conc. sulfuric acid-20% fuming sulfuric acid. To this was added 3.75 g. (0.033 mole) of chlorobenzene, and the mixture was stirred to disperse the insoluble halide. As a slight temperature rise occurs, the reaction vessel was kept in a water bath at room temperature during the initial stages of the reaction. After some 45 min. the dispersed phase disappeared, leaving a homogeneous solution. The reaction product was then separated and dried as previously described for 3-phenylphthalide. The crude material weighed 8.2 g. (100%) and was nearly white in color. Crystallization from ethanol gave a white, microcrystalline solid. The purified product failed to melt sharply, softening at 85° and becoming completely liquid at 95°. This is to be expected, as the reaction for preparation permits formation of isomeric 3-(chlorophenyl)-phthalides, the *o*- and *p*- in particular. Successive recrystallizations of first crops of crystals from ethanol gave a gradual rise of softening temperature. The melting point of 3-(*p*-chlorophenyl)phthalide reported[13] is 124°. The product melting at 85–95° was used for the analysis.

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(10) W. Hemilian, *Ber.*, **11**, 838 (1878).
(11) Dimeter Ivanov Dalev, *Annuaire univ. Sofia, Fac. phys.-math.*, Livre II, **41**, 37–68 (1944–45); *Chem. Abstr.*, **49**, 4595b (1955).
(12) E. Clar, Fr. John, and B. Howran, *Ber.*, **62**, 940 (1929).
(13) J. O'Brochta and A. Lowy, *J. Am. Chem. Soc.*, **61**, 2765 (1939).

Anal. Calcd. for $C_{14}H_9O_2Cl$: C, 68.72; H, 3.71; Cl, 14.49. Found: C, 68.74; H, 3.90; Cl, 14.67.

3-(Bromophenyl)phthalide. Five grams (0.033 mole) of phthalaldehydic acid was dissolved in 30 ml. of 2:1 conc. sulfuric acid-20% fuming sulfuric acid. To this was added 5.23 g. (0.033 mole) of bromobenzene. Following essentially the same procedure outlined for the preparation of 3-(chlorophenyl)phthalide there was obtained 9.25 g. (96%) of crude product. Crystallization from ethanol yielded a white crystalline solid which did not show a sharp melting point but softened at 92° and finally became completely liquid *ca.* 105°, indicating a mixture of isomers. The reported[14] melting point for 3-(*p*-bromophenyl)phthalide is 139–140°.

Anal. Calcd. for $C_{14}H_9O_2Br$: C, 58.16; H, 3.14; Br, 27.64. Found: C, 58.32; H, 3.07; Br, 27.47.

3-(2,5-Dichlorophenyl)phthalide. Five grams (0.033 mole) of phthalaldehydic acid was dissolved in 36 ml. of 1:1 concentrated sulfuric acid-20% fuming sulfuric acid. To this was added 4.9 g. (0.033 mole) of *p*-dichlorobenzene. In order to keep the insoluble *p*-dichlorobenzene in melted condition the reaction vessel was placed in a water bath maintained at 65–70°. The mixture was mechanically stirred, and after about 2 hr. the dispersed *p*-dichlorobenzene disappeared, yielding a homogeneous reddish-brown solution. The mixture was allowed to stand in the hot water bath for an additional hour, then cooled and poured slowly with stirring into about ten times its volume of cold water. The product separated as a gum which gradually hardened. When cold the solid was removed and the lumps crushed and washed several times with cold water. The crude product, light tan in color, weighed 8.4 g. (90%) and melted at 128–130°. Recrystallization from ethanol, with added Norit, gave colorless needles, m.p. 130–131°.

Anal. Calcd. for $C_{14}H_8O_2Cl_2$: C, 60.24; H, 2.89; Cl, 25.41. Found: C, 59.90; H, 2.80; Cl, 25.54.

3-(2,5-Dibromophenyl)phthalide. Five grams (0.033 mole) phthalaldehydic acid was dissolved in 45 ml. of 2:1 conc. sulfuric acid-20% fuming sulfuric acid. To this solution was added 7.86 g. (0.033 mole) of *p*-dibromobenzene, and the reaction vessel was then placed in an oil-bath at a bath temperature of 90–95° in order to maintain the insoluble *p*-dibromobenzene in a melted state for better dispersion. Following essentially the same procedure used in the preparation of 3-(2,5-dichlorophenyl)phthalide, there was obtained 12.2 g. (99%) of crude product, light ivory in color, m.p. 121–124°. Crystallization from ethanol, with added Norit, afforded colorless crystals, m.p. 124–125°.

Anal. Calcd. for $C_{14}H_8O_2Br_2$: C, 45.69; H, 2.19; Br, 43.43. Found: C, 45.49; H, 2.37; Br, 43.59.

Acknowledgment. The author is indebted to the Dow Chemical Company for supplying the phthalaldehydic acid. Appreciation is expressed to Professor Walter A. Cook who provided some of the microanalytical data.

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Dicyclopropylglycolic Acid

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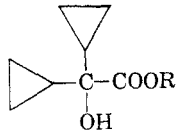
The interesting physiological activity of certain basic esters of benzilic acid is well known.[1] The availability of dicyclopropyl ketone through the convenient procedure of Hart and Curtis[2] has now made possible the preparation of the analog of benzilic acid, dicyclopropylglycolic acid (I).



I. R = H
II. R = CH_3
III. R = $—CH_2CH_2N(C_2H_5)_2 \cdot HCl$

Although Hart and Curtis showed that dicyclopropyl ketone reacts with the usual carbonyl reagents, we have been unable to prepare its cyanohydrin. Nor does it appear to form a chloroform addition product[3] from which the hydroxyacid could be derived. In these respects dicyclopropyl ketone resembles benzophenone.

The desired acid I was finally secured through permanganate oxidation of 1,1-dicyclopropyl-2-propyn-1-ol, derived from dicyclopropyl ketone by addition of sodium acetylide.[4] The yield of the oxidation step was only fair (40–45%).

Direct acid-catalyzed esterification of I could not be accomplished. Use of an ion exchange resin as the acid catalyst was no better. Likewise the action of either methyl iodide or dimethyl sulfate on the sodium salt of I produced no ester. Finally, however, II was obtained in 71% yield using diazomethane. The basic ester III was formed by treating the acid I with diethylaminoethyl chloride in isopropanol according to the method of Horenstein and Pählicke.[5]

EXPERIMENTAL

Dicyclopropylglycolic acid (I). To a stirred suspension of 40.8 g. (0.3 mole) of 1,1-dicyclopropyl-2-propyn-1-ol in 800 ml. of water held at 3–5° by means of an ice bath was added dropwise, over a period of 2.5 hr., a solution of 118.5 g. (0.75 mole) of potassium permanganate in 850 ml. of water. After stirring in the ice bath for another 1.5 hr., a large quantity of a filter aid (filtercel) was added and stirring was continued overnight in a refrigerated room.

The manganese dioxide and filter aid were collected at the filter and washed well with water. The combined filtrate and washings were decolorized with charcoal and extracted with ether from which, after drying and removal of ether by distillation, 6.0 g. (15%) of the acetylenic carbinol was recovered.

The ice-cold alkaline solution was acidified by the dropwise addition of cold concentrated sulfuric acid, and then extracted with five 200-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave

(1) Alfred Burger, *Medicinal Chemistry*, Interscience Publishers, Inc., New York, 1951, Vol. I, p. 423.
(2) H. Hart and O. Curtis, Jr., *J. Am. Chem. Soc.*, **78**, 112 (1956).
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(5) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).

an oily semisolid product (33 g.) which was collected at the vacuum filter. Recrystallization from hexane (Skellysolve B) gave 12.3 g. of first crop, m.p. 83–85° and 6.1 g. of second, m.p. 82–84° (18.4 g. = 46% of theory, based on unrecovered carbinol). Several more recrystallizations for analysis raised the melting point to 84–86°.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75; O, 30.73. Found: C, 61.68; H, 7.97; O, 30.80.

The infrared spectrum was consistent with the assigned structure.

Methyl dicyclopropylglycolate (II). To a solution of 6 g. of diazomethane in 100 ml. of ether was added a solution of 8 g. (0.051 mole) of dicyclopropylglycolic acid (I) in 50 ml. of ether. After standing at room temperature in the dark for 24 hr., the ether was removed by distillation and the residual oil was distilled under reduced pressure. After a forerun, 2.1 g., b.p. 30–124° (60 mm.), the methyl ester II distilled at 124° (60 mm.); yield, 6.2 g. (71%), n_D^{23} 1.4535.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.18; H, 8.51.

The infrared spectrum, including a band at 1.63 μ in the near infrared, characteristic of the cyclopropane ring,[6] was consistent with the assigned structure.

β-Diethylaminoethyl dicyclopropyglycolate hydrochloride (III). A solution of 7.8 g. (0.05 mole) of dicyclopropylglycolic acid (I) and 7.5 g. (0.055 mole) of β-diethylaminoethyl chloride in 60 ml. of isopropanol was refluxed with stirring for 18 hr. On cooling, the product crystallized. It was collected by vacuum filtration and dissolved in 50 ml. of cold water. Addition of excess cold 40% sodium hydroxide solution precipitated an oil (free ester base) which was taken up in ether, washed with water and dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, a slight excess of ethereal hydrogen chloride solution was added and the precipitated hydrochloride was collected. Three recrystallizations from ethanol gave 6.5 g. (45%) of the ester hydrochloride III, m.p. 152–154°.

Anal. Calcd. for $C_{14}H_{26}ClNO_3$: C, 57.62; H, 8.98; N, 4.80; Cl, 12.15. Found: C, 57.77; H, 8.98; N, 4.82; Cl, 12.17.

(6) W. H. Washburn and M. J. Mahoney, *J. Am. Chem. Soc.*, **80**, 504 (1958).

Acknowledgments. The authors are indebted to Mr. E. F. Shelberg and Mr. W. H. Washburn and their associates for the microanalyses and infrared spectra, respectively.

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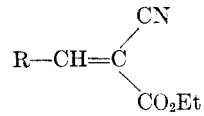
Synthesis of 3-Hydroxypyridines. I. Condensation of Aromatic Aldehydes with Ethyl Cyanoacetate

FRANK D. POPP

Received October 1, 1959

In the course of investigations of methods of syntheses of 3-hydroxypyridines in progress in this laboratory, it was necessary to prepare a series of compounds of type I.



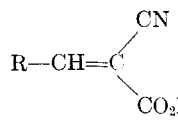
The α,β-unsaturated cyanoesters, I, in which R is an aromatic group, were prepared by condensation of the appropriate aromatic aldehyde with ethyl cyanoacetate by the general Knoevenagel[1] reaction using piperidine as a catalyst.[2] In this

(1) J. Scheiber and F. Meisel, *Ber.*, **48**, 257 (1915).

(2) See for example P. D. Gardner and R. I. Brandon, *J. Org. Chem.*, **22**, 1704 (1957).

TABLE I

CONDENSATION OF ALDEHYDES WITH ETHYL CYANOACETATE



R	Yield, %	M.P.[a]	Calcd. Carbon	Calcd. Hydrogen	Calcd. Nitrogen	Found[b] Carbon	Found[b] Hydrogen	Found[b] Nitrogen
o-ClC_6H_4—	61	54–55[c,d]	61.16	4.28	5.95	61.11	4.03	5.97
3,4-$(C_2H_5O)_2C_6H_3$—	86	126–127[c]	66.42	6.62	4.84	66.40	6.64	4.95
p-$(ClCH_2CH_2)_2NC_6H_4$—	89	174–175[e]	56.31	5.32	8.21	56.38	5.54	7.93
3,4-$(CH_2O_2)C_6H_3$—	77	106–107[c,f]	63.67	4.52	5.71	63.70	4.63	5.47
o-$O_2NC_6H_4$—	68	101–103[c,g]	58.53	4.09	11.38	58.82	4.16	11.60
3-CH_3O-4-HOC_6H_3—	92	108–109[c,h]	63.15	5.30	5.67	63.13	5.39	5.90
p-HOC_6H_4—	58	173–174[c,i]	66.35	5.11	6.45	66.69	5.05	6.23
p-$(CH_3CH_2)_2NC_6H_4$—	81	95–96[c]	70.56	7.40	10.29	70.42	7.49	10.09
o-$O_2NC_6H_4CH{=}CH$—	83	141–142[c]	61.76	4.44	10.29	62.21	4.42	10.42

[a] All melting points are uncorrected. [b] Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Straus, Oxford, Eng. [c] Recrystallized from 95% ethanol. [d] Reported m.p. 53° (from esterification of acid), J. A. McRae and C. Y. Hopkins, *Can. J. Res.*, **7**, 248 (1932). [e] Recrystallized from chloroform. [f] Reported m.p. 104° (from esterification of acid), C. H. Clarke and F. Francis, *Ber.*, **44**, 273 (1911). [g] Reported m.p. 96° (from condensation reaction), F. Reidel, *J. prakt. Chem.*, (2), **54**, 533 (1896). [h] Reported m.p. 111° (from esterification of acid), reference as footnote f. [i] Reported m.p. 162–163° (from condensation reaction), reference as footnote g.

manner, the compounds shown in Table I were prepared.

All of the compounds reported had infrared spectra which exhibited a nitrile band at 2195 ± 10 cm.$^{-1}$ and an ester band at 1700 ± 10 cm.$^{-1}$

EXPERIMENTAL

Reagents. The author thanks Kay-Fries Chemicals, Inc. for a generous gift of ethyl cyanoacetate. The aldehydes used were obtained from commercial sources and used without further purification or were prepared by standard literature methods. Thanks go to the Antara Chemicals Division of General Aniline and Film Corp. for a sample of *p*-diethylaminobenzaldehyde.

Typical condensation. To a mixture of 22.6 g. (0.2 mole) of ethyl cyanoacetate and 0.2 mole of aldehyde in about 60 ml. of dry dioxane at 0° was added dropwise 0.8 ml. of piperidine. After standing overnight at room temperature, crystals had formed (in a few cases cooling was needed to promote crystallization). The solids were filtered, washed, dried, and recrystallized several times from an appropriate solvent.

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Preparation of Various Substituted Pyrimidines[1]

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Received October 29, 1959

During the last decade, numerous pyrimidines and purines have been investigated which might be useful in human cancer chemotherapy, and several have been found to possess tumor-inhibiting properties.[3,4] The pharmacological activity of these compounds has prompted the preparation of various substituted pyrimidines.

The substituted pyrimidines synthesized during the course of this investigation have incorporated the physiologically active ring systems of pyridine and thiophene and were prepared in hopes that some of them would exhibit physiological activity of some type, since they are related to a number of the biological and medicinal agents, such as nucleic acids, several vitamins and enzymes, uric acid, and sulfadiazine.

Pharmacological tests of these substituted pyrimidines are being made.

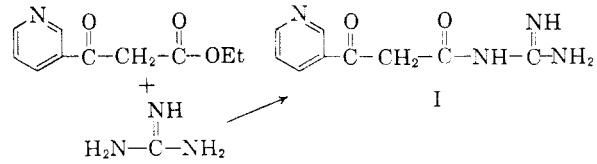
The substituted pyrimidines synthesized are listed in Table I and Table II and were prepared by condensing the appropriate β-diketone or β-keto ester with guanidine carbonate. The general procedure is given in the experimental section.

The 2-amino-4-alkyl-6-(α-thienyl)pyrimidines were prepared by condensing the appropriate acyl-2-thenoylmethane with guanidine carbonate.

The 2-amino-4-alkyl-6-(β-pyridyl)pyrimidines were prepared by the same method, but the appropriate nicotinylacylmethane was employed.

In the case of 2-amino-4-hydroxy-6-(α-thienyl)-pyrimidines, ethyl β-keto-(α-thienyl)propionate was condensed with guanidine carbonate.

In the attempted preparation of 2-amino-4-hydroxy-6-(β-pyridyl)pyrimidine, ethyl nicotinoylacetate was treated with guanidine carbonate, but ring closure did not occur as the intermediate product (I) was obtained instead.



The infrared spectra of these pyrimidines have been recorded and showed prominent peaks near 3200–3100 cm.$^{-1}$ due to CH stretching vibrations. In addition, strong peaks were noted in the region near 1665 cm.$^{-1}$, 1600–1565 cm.$^{-1}$ and 1555–1540 cm.$^{-1}$ which are due to C=C and C=N vibrations, respectively, in this aromatic system. There is some belief that the higher frequency bands are due to NH_2 deformations modes rather than C=C and C=N vibrations themselves.[5] There is also a strong band near 3320 cm.$^{-1}$ and this is assigned to the NH_2 group.

EXPERIMENTAL

Preparation of substituted pyrimidines. The substituted pyrimidines were prepared by heating 3.5 g. of the appropriate β-diketone or β-keto ester with 1.5 g. of guanidine carbonate at 130–140° for 3–4 hr. according to the method of Evans.[6] The molten mass was allowed to cool and then dissolved in hydrochloric acid. The substituted pyrimidine was then precipitated upon the addition of dilute ammonium hydroxide.

The substituted pyrimidine was recrystallized three times from absolute alcohol, and white crystals were obtained. The average yield was 20%.

The respective picrates were prepared by dissolving 0.1 g. of the pyrimidine in 5 ml. of absolute alcohol and adding a saturated solution of picric acid dissolved in absolute alcohol. Upon standing, the picrate settled out and was recrystallized from absolute alcohol.

In the case of the 2-amino-4-hydroxy-6-(α-thienyl)pyrimidine, the acid-base technique was not employed, but the pyrimidine was recrystallized from 80% alcohol.

(1) This work is based on a thesis submitted by James J. Zelko in partial fulfillment for the degree of Master of Science at Loyola University, Chicago, Ill.

(2) Cooperative National Science Foundation Fellow, Summer 1959.

(3) C. Heidelberger, N. C. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven, and J. Scheiner, *Nature*, **179**, 663 (1957).

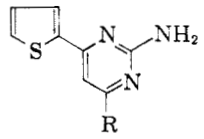
(4) R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Amer. Chem. Soc.*, **79**, 4559 (1957)

(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Second Edition, John Wiley and Sons, (New York, 1956), p. 282.

(6) P. N. Evans, *J. prakt. Chem.* [2] **48**, 513 (1893).

TABLE I

PYRIMIDINES OF TYPE

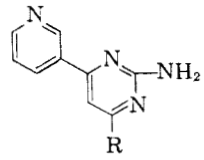


R	Molecular Formula	M.P.	% Nitrogen Calcd.	% Nitrogen Found[a]	Molecular Formula	M.P.[b]	% Nitrogen Calcd.	% Nitrogen Found[a]
—CH_3	$C_9H_9N_3S$	172°	21.97	21.50	$C_{15}H_{12}N_6O_7S$	243–248°	19.93	19.94
—C_2H_5	$C_{10}H_{11}N_3S$	139°	20.47	20.32	$C_{16}H_{14}N_6O_7S$	233–237°	19.34	19.25
—*n*-C_3H_7	$C_{11}H_{13}N_3S$	116°	19.16	19.13	$C_{17}H_{16}N_6O_7S$	213–214°	18.74	18.81
—*i*-C_3H_7	$C_{11}H_{13}N_3S$	115°	19.16	19.03	$C_{17}H_{16}N_6O_7S$	220–222°	18.74	18.65
n-C_4H_9	$C_{12}H_{15}N_3S$	79°	18.01	18.27	$C_{18}H_{18}N_6O_7S$	196–199°	18.17	18.00–
i-C_4H_9	$C_{12}H_{15}N_3S$	110°	18.01	18.17	$C_{18}H_{18}N_6O_7S$	175–176°	18.17	17.92
n-C_5H_{11}	$C_{13}H_{17}N_3S$	82°	16.99	16.88	$C_{19}H_{20}N_6O_7S$	163–164°	17.64	17.60
—OH	$C_8H_7N_3OS$	306° dec.	21.74	21.95	$C_8H_7N_3O_8S$	241–248°	19.90	19.72

[a] Nitrogen analyses by Micro-Tech Laboratories, Skokie, Ill. [b] Melting points of the picrates were taken in a sealed evacuated capillary tube, are uncorrected, and all melt with decomposition.

TABLE II

PYRIMIDINES OF TYPE



R	Molecular Formula	M.P.	% Nitrogen Calcd.	% Nitrogen Found[a]	Molecular Formula	M.P.[b]	% Nitrogen Calcd.	% Nitrogen Found[a]
—CH_3	$C_{10}H_{10}N_4$	205°	30.09	29.83	$C_{16}H_{13}N_7O_7$	245–249°	23.60	23.75
t-Butyl	$C_{13}H_{16}N_4$	138°	24.43	24.43	$C_{19}H_{19}N_7O_7$	210–212°	21.43	21.34
i-Butyl	$C_{13}H_{16}N_4$	149°	24.66	24.66	$C_{19}H_{19}N_7O_7$	206–207°	21.43	21.38
Phenyl	$C_{15}H_{12}N_4$	166°	22.57	22.57	$C_{21}H_{15}N_7O_7$	223–225°	20.53	20.78

[a] Nitrogen analyses by Micro-Tech Laboratories, Skokie, Ill. [b] Melting points of the picrates were taken in a sealed evacuated capillary tube, are uncorrected, and all melt with decomposition.

Preparation of I. A 3.5-g. sample of ethylnicotinoylacetate and 5 g. of guanidine carbonate was heated at 140° for 1 hr. The molten mass was allowed to cool and recrystallized from 80% alcohol, and light colored crystals were obtained melting at 283–288° dec.

Anal. Calcd. for $C_9H_{10}O_2N_4$: N, 27.37. Found: N, 27.17.

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Quaternary Ammonium Salts. IV. Synthesis and Decomposition of *N*-Methyl-*N*,*N*-di-*n*-propylanilinium Salts

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Received August 18, 1959

In continuation of the research done by Fahim and Galaby,[1] Fahim and Fleifel,[2] and Fahim *et al.*,[3] we now have studied the synthesis and decomposition of some *N*-methyl-*N*,*N*-di-*n*-propylanilinium salts. The tertiary bases, used as starting materials in this investigation, were prepared by propylation of the corresponding primary aromatic amines with tri-*n*-propyl phosphate as recommended by Bilman *et al.*[4] for the preparation of dipropylaniline. The dipropylanilines obtained were identified through the picrate. The boiling points and the yields of the tertiary bases are recorded in Table I.

TABLE I
TERTIARY BASES

Primary aromatic amine	Boiling point of the dipropylaniline	Yield, %
p-Anisidine	158–160/15 mm.	70
o-Anisidine	142–145/15 mm.	45
p-Phenetidine	166–168/60 mm.	44
o-Phenetidine	173–175/60 mm.	45
p-Toluidine	165–168/65 mm.	51
m-Toluidine	170–173/60 mm.	51
o-Toluidine	144–146/55 mm.	58

(1) H. A. Fahim and M. Galaby, *J. Chem. Soc.*, 3529 (1950).
(2) H. A. Fahim and A. M. Fleifel, *J. Chem. Soc.*, 2761 (1951).
(3) H. A. Fahim, F. G. Baddar, and M. Galaby, *J. Chem. Soc.*, 317 (1955).
(4) J. H. Bilman, A. Radike, and A. W. Mundy, *J. Am. Chem. Soc.*, **64**, 2977 (1942).

TABLE II

QUATERNARY IODIDES, QUATERNARY PICRATES, PICRATES OF STARTING MATERIALS AND PRODUCTS

Starting Material	Compound	Solvent[c]	M.P.	Yield, %	Formula	Carbon, % Calcd. (Found)	Hydrogen, % Calcd. (Found)	Iodine, % Calcd. (Found)
Ia	*N*-Methyl-*N*,*N*-di-*n*-propyl-*p*-anisidinium iodide	A	142–143	100[a]	$C_{14}H_{24}ONI$			36.39 (36.3)
	N-Methyl-*N*,*N*-di-*n*-propyl-*p*-anisidinium picrate	B	103–104		$C_{20}H_{26}O_8N_4$	53.33 (53.40)	5.77 (5.80)	
	N,*N*-di-*n*-propyl-*p*-anisidine picrate	B	93–94		$C_{19}H_{24}O_8N_4$	52.3 (52.40)	5.50 (5.70)	
	N-Methyl-*N*-propyl-*p*-anisidine picrate	B	102		$C_{17}H_{20}O_8N_4$	50.0 (49.80)	4.90 (4.95)	
Ib	*N*-Methyl-*N*,*N*-di-*n*-propyl-*o*-anisidinium iodide	A	238–239	45	$C_{14}H_{24}ONI$			36.39 (36.9)
	N-Methyl-*N*,*N*-di-*n*-propyl-*o*-anisidinium picrate	B	143–144		$C_{20}H_{26}O_8N_4$	53.33 (53.75)	5.77 (5.90)	
	N,*N*-di-*n*-propyl-*o*-anisidine picrate	B	110		$C_{19}H_{24}O_8N_4$	52.3 (52.14)	5.50 (5.70)	
	N-Methyl-*N*-propyl-*o*-anisidine picrate	B	139–140		$C_{17}H_{20}O_8N_4$	50.0 (49.50)	4.90 (5.0)	
Ic	*N*-Methyl-*N*,*N*-di-*n*-propyl-*p*-phenetidinium iodide	A	241–242	100	$C_{15}H_{26}ONI$			35.59 (36.2)
	N-Methyl-*N*,*N*-di-*n*-propyl-*p*-phenetidinium picrate	B	117		$C_{21}H_{28}O_8N_4$	54.31 (53.90)	6.03 (5.90)	
	N,*N*-di-*n*-propyl-*p*-phenetidine picrate	B	105–106		$C_{20}H_{26}O_8N_4$	53.33 (53.98)	5.77 (6.05)	
	N-Methyl-*N*-propyl-*p*-phenetidine picrate	B	137–138		$C_{18}H_{22}O_8N_4$	51.18 (51.65)	5.21 (5.10)	
Id	*N*-Methyl-*N*,*N*-di-*n*-propyl-*o*-phenetidinium iodide	A	233–234	53	$C_{15}H_{26}ONI$			35.59 (36.2)
	N-Methyl-*N*,*N*-di-*n*-propyl-*o*-phenetidinium picrate	B	139–140		$C_{21}H_{28}O_8N_4$	54.31 (53.80)	6.03 (5.90)	
	N,*N*-di-*n*-propyl-*o*-phenetidine picrate	B	96		$C_{20}H_{26}O_8N_4$	53.33 (53.01)	5.77 (5.79)	
	N-Methyl-*N*-propyl-*o*-phenetidine picrate	B	184–185		$C_{18}H_{22}O_8N_4$	51.18 (51.75)	5.21 (5.30)	
Ie	*N*-Methyl-*N*,*N*-di-*n*-propyl-*p*-toluidinium iodide	A	133–134	80	$C_{14}H_{24}NI$			38.02 (38.76)
	N-Methyl-*N*,*N*-di-*n*-propyl-*p*-toluidinium picrate[b]	B	140–141		$C_{20}H_{26}O_7N_4$	55.27 (55.26)	6.0 (6.09)	
	N,*N*-di-*n*-propyl-*p*-toluidine picrate	B	109		$C_{19}H_{24}O_7N_4$	54.28 (53.97)	5.71 (5.67)	
	N-Methyl-*N*-propyl-*p*-toluidine picrate	B	284–285		$C_{17}H_{20}O_7N_4$	51.0 (50.86)	5.0 (4.85)	
If	*N*-Methyl-*N*,*N*-di-*n*-propyl-*m*-toluidinium iodide	A	148–149	37	$C_{14}H_{24}NI$			38.02 (38.6)
	N,*N*-di-*n*-propyl-*m*-toluidine picrate	B	128–129[d]		$C_{19}H_{24}O_7N_4$	54.28 (54.27)	5.71 (5.74)	
	N-Methyl-*N*-propyl-*m*-toluidine picrate	B	89–90		$C_{17}H_{20}O_7N_4$	51.0 (50.59)	5.0 (5.12)	
Ig	*N*,*N*-di-*n*-propyl-*o*-toluidine picrate	B	140–141		$C_{19}H_{24}O_7N_4$	54.28 (54.29)	5.71 (5.90)	

[a] The yields of *N*-methyl-*N*,*N*-di-*n*-propylanilinium salts were calculated on the basis of the iodide. [b] *N*-Methyl-*N*,*N*-di-*n*-propyl-*m*-toluidinium picrate was obtained as a yellow oil which could not be solidified. [c] A = methanol-ether; B = ethanol. [d] F. J. Wobb, W. S. Cook, H. E. Albert, and G. E. P. Smith, *Ind. Eng. Chem.*, **46**, 1711 (1954) (*Chem. Abstr.*, 14282 (1954)), gave the same m.p. for the picrate, when they prepared the tertiary base (If) by the action of *n*-propyl bromide in aqueous potassium carbonate.

N-Methyl-*N*,*N*-di-*n*-propylanilinium salts of the tertiary bases (Ia–g) were prepared by the action of methyl iodide on the corresponding *N*,*N*-di-*n*-propylanilines.

$$\underset{\text{I}}{ArN(C_3H_7)_2} + CH_3I \longrightarrow \underset{\text{II}}{[ArN(C_3H_7)_2CH_3]^+I^-}$$

Ia.	Ar = *p*-$CH_3OC_6H_4$—	IIa.	Ar = *p*-$CH_3OC_6H_4$—
b.	Ar = *o*-$CH_3OC_6H_4$—	b.	Ar = *o*-$CH_3OC_6H_4$—
c.	Ar = *p*-$C_2H_5OC_6H_4$—	c.	Ar = *p*-$C_2H_5OC_6H_4$—
d.	Ar = *o*-$C_2H_5OC_6H_4$—	d.	Ar = *o*-$C_2H_5OC_6H_4$—
e.	Ar = *p*-$CH_3C_6H_4$—	e.	Ar = *p*-$CH_3C_6H_4$—
f.	Ar = *m*-$CH_3C_6H_4$—	f.	Ar = *m*-$CH_3C_6H_4$—
g.	Ar = *o*-$CH_3C_6H_4$—		

Only in the case of *N*,*N*-di-*n*-propyl-*o*-toluidine, could the formation of the quaternary ammonium salt not be achieved under normal conditions, when the tertiary base was treated with methyl iodide or methyl sulfate, due probably to steric effect.[1,2]

The thermal decomposition of the quaternary ammonium iodides was affected by heating above their melting points. The remaining tertiary bases, left after decomposition, were identified as the corresponding picrates. Mixed melting-point determination of the picrates of the starting materials (Ia–f) and the picrates obtained on thermal decomposition, showed depression in each case. This fact, together with the analytical figures obtained from decomposition picrates, indicated that thermal decomposition led to the formation of the mixed dialkylaniline, i.e., *n*-propyl iodide was always eliminated and *N*-methyl-*N*-propyl aromatic base was left. A similar result has been reported previously.[1–3]

Decomposition of the iodides IIa–f with ethanolic sodium ethoxide followed the same route observed in the thermal decomposition. Mixed melting-point determination of the picrates obtained on thermal decomposition and those from alkaline decomposition showed no depression, indicating that they are identical. The quaternary iodides, the quaternary picrates, the picrates of the starting materials, and the picrates of the products of decomposition are listed in Table II.

EXPERIMENTAL

Preparation of the dipropylanilines (Ia–g). Tri-*n*-propyl phosphate was prepared according to the general procedure described for the synthesis of *n*-alkyl phosphates.[5]

The method used for the preparation of Ia–g was that adopted by Bilman *et al.*[4] The corresponding picrates were prepared by mixing an ethanolic solution of the freshly distilled tertiary base with saturated ethanolic solution of picric acid. The products were filtered and crystallized.

Preparation of the quaternary ammonium iodides. Equimolecular proportions of the tertiary base Ia–g and methyl iodide were mixed in a sealed tube and left for some days at room temperature (20°) (in case of Ia, Ic, and Ie), or heated at 100° for 5–10 hr. (Ib, Id, and If), (40 hr. in case of Ig). The solid products were washed with ether and crystallized.

Preparation of the quaternary ammonium picrates. The quaternary ammonium picrates were obtained when an aqueous solution of the corresponding iodide was added to an excess of a saturated aqueous solution of picric acid. The precipitate was collected, dried, and crystallized.

Decomposition of the quaternary ammonium iodides. (a) *By heat.* The thermal decomposition of the iodides IIa–f was effected by heating 0.5 g. of the pure substance in a Pyrex tube above its melting point until bubbles ceased to evolve. The oily residue was extracted with ether, filtered to remove any undecomposed iodide and the ether removed. A few drops of ethanol were added, followed by a saturated ethanolic solution of picric acid. The picrate was filtered off and crystallized.

(b) *By ethanolic sodium ethoxide.* The decomposition of the iodides IIa–f was carried out by heating (1.5 g.) with ethanolic sodium ethoxide [from metallic sodium (0.3 g.) and absolute ethanol (20 ml.)] for 5 hr. on the steam bath. Sodium iodide, formed as a result of decomposition, was filtered, the ethanol was concentrated and a few ml. of water added. The oil that separated was taken up in ether, dried, and the ether removed. The oily residue was converted into the picrate, which was then filtered and crystallized.

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(5) G. R. Dutton and C. R. Noller, *Org. Synthesis*, **Vol. XVI**, p. 9.

Thiophosgenation of Dimethylammonium Chloride[1]

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Received October 20, 1959

In continuation of studies[3] on the preparation and properties of the thiatriazole ring system a supply of dimethylthiocarbamyl chloride (II) was required. Billiter and Rivier[4,5] report a convenient procedure using dimethylammonium chloride (I) and thiophosgene in the presence of aqueous sodium hydroxide. The thiophosgene (in alcohol-free chloroform) is added to an aqueous solution of I followed by slow addition of sodium hydroxide, the temperature being maintained at 25° by addition of ice. Yields of 65 to 95% of II were reported. Two moles of alkali are used per mole of I and at the end of the reaction the aqueous phase was reported[4] to be alkaline. At this point the chloroform layer changes from red to yellow in color. In our hands the repetition of this procedure failed to confirm any of these observations; only a 7%

(1) The authors gratefully acknowledge the support of these studies by the Air Force Office of Scientific Research.

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(3) E. Lieber, J. Ramachandran, C. N. R. Rao, and C. N. Pillai, *Can. J. Chem.*, **37**, 563 (1959).

(4) O. Billiter and H. Rivier, *Ber.*, **37**, 4319 (1904).

(5) Houben-Weyl, *Methoden der Organischen Chemie*, Georg Thieme Verlog, Stuttgart, Germany, volume IX, page 830 (1955).

yield of II was obtained, the aqueous layer was acidic and the chloroform layer remained red in color. In addition, a nicely crystalline product melting at 104° consistently appeared by fractional recrystallization of the crude II. This was identified as tetramethylthiuram monosulfide (III) and in one experiment (Table I) it became the major product. Tetramethylthiourea was also isolated in this instance. Billiter and Rivier[4] fail to mention the formation of any by-products in their reaction.

TABLE I

THIOPHOSGENATION OF DIMETHYLAMMONIUM CHLORIDE[a]

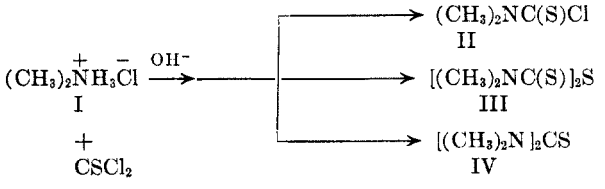
Temp. °	Ratio NaOH/ $Me_2\overset{+}{N}H_3\overset{-}{Cl}$	% Yield of Dimethylthiocarbamyl Chloride
28	1	2
28	2	7
28	2.5	None[b]
20	2.7	25[c]
10	2	15
−5[d]	2	38
−20[e]	2	46–50

[a] In all experiments a one to one molar ratio of thiophosgene to dimethylammonium chloride was maintained. [b] Tetramethylthiuram monosulfide was isolated in 1.6% yield, the major product being an unworkable oil. [c] The major product (47%) was III; 5% of IV was also obtained. [d] The temperature varied from 0° to −5°. [e] The temperature varied from −10° to −20°.

An investigation of this reaction was conducted. The results are summarized in Table I. Increasing the quantity of sodium hydroxide until the aqueous layer became alkaline was without effect, in fact no yield of II was obtained and only 1.6% of III and an intractable oil were the major products. The most important variable was the temperature of the reaction regardless of whether the aqueous phase ended up in an acidic or alkaline condition. The lowest practical temperature with the set of reagents used was found to be −10 to −20° in which case consistent yields of II of 46 to 50% were obtained. At lower temperatures increase in sodium hydroxide reduces the yield of II while favoring the formation of III. This suggests that the formation of III can be accounted for by a nucleophilic displacement of chloride ion by sulfide ion: the sulfide ion arising from the alkaline

$$2\ \mathrm{II} + S^{=} \longrightarrow \mathrm{III} + 2\ Cl^{-}$$

hydrolysis of the thiophosgene.



EXPERIMENTAL[6,7]

Dimethylthiocarbamyl chloride (II). Into a three necked round-bottom flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel and surrounded by acetone-Dry Ice bath was placed 8.3 g. (0.1 mole) of dimethylammonium chloride dissolved in 10 ml. of water. The temperature was adjusted to −10°. Thiophosgene (12 g., 0.1 mole) dissolved in 30 ml. of alcohol-free chloroform was added to the reaction flask with stirring over a period of 30 min. An aqueous solution of sodium hydroxide (100 ml. of a 2*M* solution) was then added over a period of 1 hr., not allowing the temperature to rise above −10°. The mixture was finally stirred for an additional 30 min., the chloroform layer separated and immediately dried over calcium chloride. The chloroform was then removed at reduced pressure at steam bath temperature. The residue (which is semisolid when cooled in an ice bath) was recrystallized from petroleum ether yielding a product melting at 41° in agreement with that reported.[4] The yield varied from about 5 to 5.5 g. (45 to 50% based on I).

Tetramethylthiuram monosulfide (III). This arises (Table I) from the fraction-crystallization of crude II. It was identified by mixture melting point with an authentic specimen of tetramethylthiuram monosulfide prepared according to the procedure of von Braun and Stechele.[8] When using anhydrous ether (as solvent for the thiophosgene) II is recovered as the ether soluble fraction, while recrystallization of the ether-insoluble residue yields III.

Tetramethylthiourea (IV). This was found in several instances as a by-product of the fractional crystallization of II. It was identified by its melting point[9] of 75–76°.

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(6) Melting points are uncorrected.

(7) The thiophosgene was supplied by the Rapter Chemical Company, Chicago, Illinois. Vapor phase chromatography showed this to be 99% plus in thiophosgene content.

(8) J. von Braun and F. Stechele, *Ber.*, **36**, 2274 (1903).

(9) O. Billiter, *Ber.*, **43**, 1856 (1910).

Cyclic Sulfites and the Bissinger Rearrangement

RICHARD G. GILLIS

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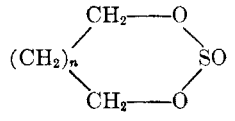
The "Bissinger rearrangement" is a convenient name for the reaction first described by Bissinger, Kung, and Hamilton,[1] in which a dialkyl sulfite gives an alkyl alkanesulfonate on heating with a tertiary base. Dimethyl sulfite gave a 49–56% yield of methyl methanesulfonate after 24 hr. with 1 mol. per cent of tributylamine; the yield decreased with increasing size of alkyl groups. The rearrangement of dimethyl sulfite gave dimethyl ether as by-product, and a mechanism was suggested which accounted for both the rearrangement and the ether formation. We have found triethylamine is also a

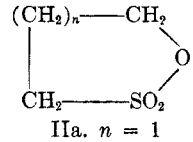
(1) W. E. Bissinger, F. E. Kung, and C. W. Hamilton, *J. Am. Chem. Soc.*, **70**, 3940 (1948).

satisfactory catalyst, but not quinoline or dimethylaniline.

If the Bissinger rearrangement of trimethylene sulfite (Ia) were successful, it would provide a convenient route to



Ia. $n = 1$
Ib. $n = 2$



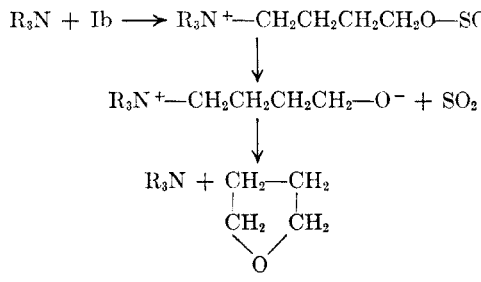
IIa. $n = 1$
IIb. $n = 2$

3-hydroxy-1-propanesulfonic acid sultone (IIa) whose preparation from allyl alcohol has been described.[2] Similarly, a successful rearrangement of tetramethylene sulfite (Ib) would provide a route to 4-hydroxy-1-butanesulfonic acid sultone (IIb) which has been prepared from 4-chlorobutyl acetate.[3]

In an attempt to prepare Ia, Majima and Simanuki[4] obtained mainly trimethylene chloride. Myles and Prichard[5] state that 1,4-butanediol and longer chain glycols give only chain polymers when treated with thionyl chloride and pyridine below 35°. However, successful preparations have been reported by de la Mare and co-workers,[6] and also by Szmant and Emerson.[7] We have prepared both Ia and Ib in reasonable yield from the corresponding glycol and thionyl chloride by the method of Kyrides.[8]

The attempted rearrangement of Ib gave only tetrahydrofuran as an identifiable organic product in 76% yield. It was substantially pure; in one experiment traces of two carbonyl containing impurities were detected by paper chromatography. The attempted rearrangement of Ia gave a mixture of six organic products including acrolein and propionaldehyde, together with water and sulfur dioxide. The same reaction of ethylene sulfite gave seven organic products including acetaldehyde.

The formation of tetrahydrofuran from tetramethylene sulfite is compatible with the mechanism advanced by Bissinger *et al.* for the formation of dimethyl ether as a by-product from dimethyl sulfite. The reaction may be formulated as shown:



The formation of a five-membered ring is favored for steric reasons; trimethylene and ethylene sulfites would lead to four- and three-membered rings, and the decomposition of the zwitterionic intermediate to aldehyde products is understandable.

EXPERIMENTAL[9]

Preparation of cyclic sulfites. Tetramethylene sulfite was prepared from tetramethylene glycol and thionyl chloride by the method of Kyrides[8] in 45% yield. The product had b.p. 119° at 15 mm., n_D^{20} 1.4650; d_4^{20} 1.2537; R_D. Calcd.: 29.90. Found: 30.02 (lit.,[7] n_D^{25} 1.4631).

Trimethylene sulfite was prepared from trimethylene glycol and thionyl chloride by the same method in 42% yield. The product had b.p. 76° at 15 mm., n_D^{20} 1.4567; d_D^{20} 1.3225; R_D. Calcd. 25.25. Found 25.14 (lit., n_D^{25} 1.4509,[6] n_D^{20} 1.4530[7]).

Ethylene sulfite was prepared similarly in 79% yield and had b.p. 70° at 20 mm., n_D^{20} 1.4461 (lit.,[6] n_D^{25} 1.4450).

Analytical methods. Gas chromatography of the products was carried out using a McWilliam-Dewar detector[10] and dioctyl phthalate as stationary phase supported on 30–50 mesh crushed "Insulox"[11]; nitrogen was the carrier gas and the column temperature was 100°. The retention times, q, are given relative to benzene (1.00) under the same conditions.[12] Peak heights relative to the largest peak are shown in parentheses. The organic products were also treated with dinitrophenylhydrazine in methanol, and the mixed dinitrophenylhydrazones were separated by descending paper chromatography in a heptane-methanol system.[13–15] Finally, the products were examined by infrared spectroscopy in a Perkin Elmer Model 12C instrument using sodium chloride optics.

Rearrangement products. The rearrangement was attempted by heating the sulfite (0.2 mol.) with triethylamine (0.01 mol.) at a pot temperature of 180° for 9 hr. The reaction mixture was distilled and the distillate examined. In each case the residue was an intractable tar.

Tetramethylene sulfite gave tetrahydrofuran in 76% yield. The distillate had b.p. 64–70°; n_D^{20} 1.4030 (lit.,[16] b.p. 64–66°; n_D^{20} 1.4070). Gas chromatography showed no trace of contaminants, and the product had retention time identical with an authentic specimen. In one experiment, the paper chromatograph showed very faint traces of two carbonyl components which ran slower than crotonaldehyde; in a second experiment, not even these trace impurities were found. Tetrahydrofuran was characterized as tetramethylene

(2) J. H. Helberger, *Ann.*, **588**, 71 (1954).
(3) W. E. Truce and F. D. Hoerger, *J. Am. Chem. Soc.*, **76**, 5357 (1954).
(4) R. Majima and H. Simanuki, *Proc. Imp. Acad. Japan*, **2**, 544 (1926); *Chem. Abstr.*, **21**, 1796 (1927).
(5) W. J. Myles and J. H. Prichard, U. S. Patent **2,465,915**; *Chem. Abstr.*, **43**, 4835 (1949).
(6) C. A. Bunton, P. B. D. de la Mare, P. M. Greaseley, D. R. Llewellyn, N. H. Pratt, and J. G. Tillett, *J. Chem. Soc.*, 4751 (1958).
(7) H. H. Szmant and W. Emerson, *J. Am. Chem. Soc.*, **78**, 454 (1956).
(8) L. Kyrides, *J. Am. Chem. Soc.*, **66**, 1006 (1944).
(9) Melting points and boiling points are uncorrected.
(10) I. G. Williams and R. A. Dewar, "*Second Symposium on Gas Chromatography*," (ed. D. H. Desty), Butterworths Scientific Publications, London, 1958, p. 174.
(11) "Insulox" is the registered trade name for an insulating firebrick manufactured by Nonporite Pty. Ltd., Hawthorn, Victoria.
(12) R. J. Cvetanovic and K. O. Kutschke, "*Vapor Phase Chromatography*" (ed. D. H. Desty), Butterworths Scientific Publications, London, 1957, p. 87.
(13) F. E. Huelin, *Australian J. Sci. Res.*, **5B**, 328 (1952).
(14) D. F. Meigh, *Nature (London)*, **170**, 579 (1952).
(15) D. A. Forss, E. A. Dunstone, and W. Stark, *Chem. & Ind.*, **42**, 1292 (1954); **45**, 521 (1957).
(16) T. H. Durrans, "*Solvents*," Chapman & Hall Ltd., London, 7th ed., 1957, p. 185.

bis(2-thiopseudourea)dipicrate, prepared from 1,4-diiodobutane made by a modification of the method of Stone and Schechter.[17] To 5 g. of potassium iodide was added 5 ml. of sirupy phosphoric acid (85%) and 1 ml. of rearrangement product. The mixture was refluxed gently for 1.5 hr., then 10 ml. of water was added, and the whole was extracted with 15 ml. of ether. The ether solution was washed with water, sodium thiosulfate solution and again with water; then the ether was removed and replaced by 10 ml. of ethanol. A 1-g. sample of thiourea was added, and after 10 min. refluxing, 0.5 g. of picric acid. The precipitated tetramethylene bis(2-thiopseudourea)dipicrate was filtered, washed with ethanol, and dried, m.p. 240° dec. (lit.[18] 240–242° dec.). A specimen prepared in the same way from authentic tetrahydrofuran also had m.p. 240° dec., and the mixed melting point of the two was the same.

Trimethylene sulfite gave a product which showed five peaks on the gas chromatograph, at q = 0.17 (26), 0.32 (100), 0.42 (48), 0.86 (48), 2.22 (7). The second peak was an unresolved mixture of acrolein (q = 0.29) and propionaldehyde (q = 0.32). In check experiments, these were not resolved on a squalane column at 100° or 64°. Three aldehydes were detected by paper chromatography, acrolein (R_f = 0.21), propionaldehyde (R_f = 0.26) and a third (R_f = 0.35) which is thought to be an aldol condensation product. Infrared spectroscopy of the mixture confirmed the presence of acrolein and propionaldehyde by the C=C and C=O stretching bands in the 6μ region. There were no indications at any time of the presence of acetone.

Ethylene sulfite gave a product which showed seven peaks on the gas chromatograph at q = 0.14 (100), 0.54 (6), 0.60 (6), 0.90 (35), 1.14 (12), 1.64 (94), and 3.18 (6). Two of these were identified as acetaldehyde (q = 0.16) and paraldehyde (q = 0.56). Paper chromatography of the dinitrophenylhydrazone from the product showed only one spot due to acetaldehyde (R_f = 0.12), and the 6μ region of the infrared spectrum confirmed this.

Acknowledgments. The author is indebted to Mr. G. J. Long for experimental assistance and to the Chief Scientist, Australian Defence Scientific Service, Department of Supply, Melbourne, Australia, for permission to publish.

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(17) H. Stone and H. Schechter, *Org. Syntheses*, **30**, 33 (1950).

(18) A. W. Nineham, *J. Chem. Soc.*, 2601 (1953).

Synthesis of Certain Sulfonium Analogs of Meperidine and of the Methadone Class of Analgesics

CORRIS M. HOFMANN AND MARTIN J. WEISS

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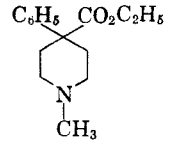
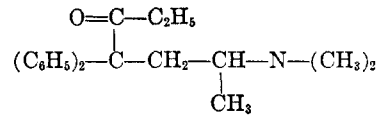
In continuation of our investigations[1] dealing with the preparation of sulfonium analogs of pharmacologically active tertiary and quaternary amines, we wish to report the synthesis of sulfonium analogs of meperidine[3] and also of the methadone class. Both meperidine and methadone are important analgesic agents.



Meperidine



Methadone

The meperidine sulfonium analog VI was prepared from the known 4-cyano-4-phenyltetrahydrothiapyran (III).[7] This nitrile (III) was converted to the 4-carbethoxy intermediate (V) by direct ethanolysis in the presence of sulfuric acid or, more satisfactorily, in two steps by hydrolysis with 70% aqueous sulfuric acid to the corresponding acid[7] (IV) followed by esterification with ethanolic hydrogen chloride. Treatment of V with excess methyl iodide then gave the desired analog (VI); reaction of V with excess ethyl iodide afforded the corresponding ethiodide.

The intermediate nitrile (III) was obtained directly by the sodium amide-catalyzed condensation of phenylacetonitrile (I) with bis(2-chloroethyl) sulfide, a synthesis originally described by Eisleb[7] and which in our hands afforded a 40% yield of III. This nitrile (III) was also prepared from 1,5-dichloro-3-cyano-3-phenylpentane (II)[8] on treatment with sodium sulfide. Although the latter procedure avoids the use of the dangerous mustard gas, the preparation of the 1,5-dichloride (II) requires three steps, and in our experience proceeded in relatively poor over-all yield (11%).[9] It was also possible to prepare the more advanced intermediate, 4-carbethoxy-4-phenyltetrahydrothiapyran (V), by direct condensation of bis(2-chloro-

(1) M. J. Weiss and M. B. O'Donoghue, *J. Am. Chem. Soc.*, **79**, 4771 (1957). This paper contains a review of sulfonium analog work in the pharmaceutical field. The preparation of sulfonium derivatives in the phenazine series has been reported recently.[2]

(2) S. O. Winthrop and M. A. Davis, *J. Am. Chem. Soc.*, **80**, 4331 (1958).

(3) There are two reports in the literature concerning unsuccessful attempts to prepare sulfonium analogs of the 1-methyl-4-acyloxy-4-phenylpiperidine class.[4,5] These piperidines are closely related to meperidine and are active analgesics.[6]

(4) H. M. E. Cardwell, *J. Chem. Soc.*, 1059 (1950).

(5) V. Mychajlyszn and J. O. Jilek, *Chem. Listy*, **50**, 1479 (1956); *Chem. Abstr.*, **51**, 2666 (1957).

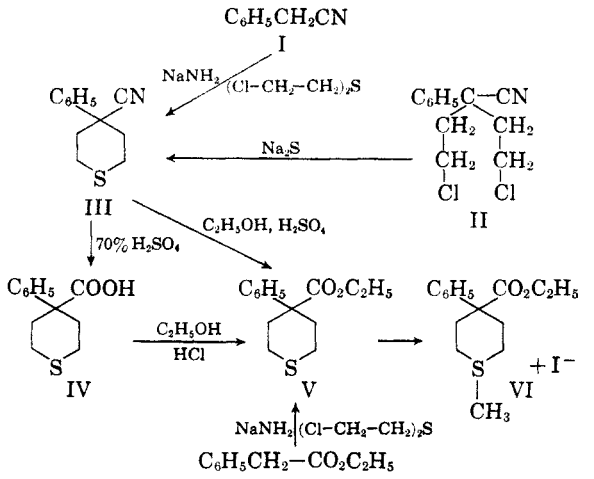
(6) A. Ziering, L. Berger, S. D. Heineman and J. Lee, *J. Org. Chem.*, **12**, 894 (1947).

(7) O. Eisleb, *Ber.*, **74B**, 1433 (1941).

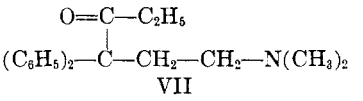
(8) F. Bergel, A. L. Morrison, and H. Rinderknecht, *J. Chem. Soc.*, 265 (1944).

(9) Dichloride II was obtained by condensation (sodium amide) of phenylacetonitrile (I) with 2-vinyloxyethyl chloride, acid hydrolysis of the vinyloxy groups and treatment of the resulting 1,5-diol with thionyl chloride.[8]

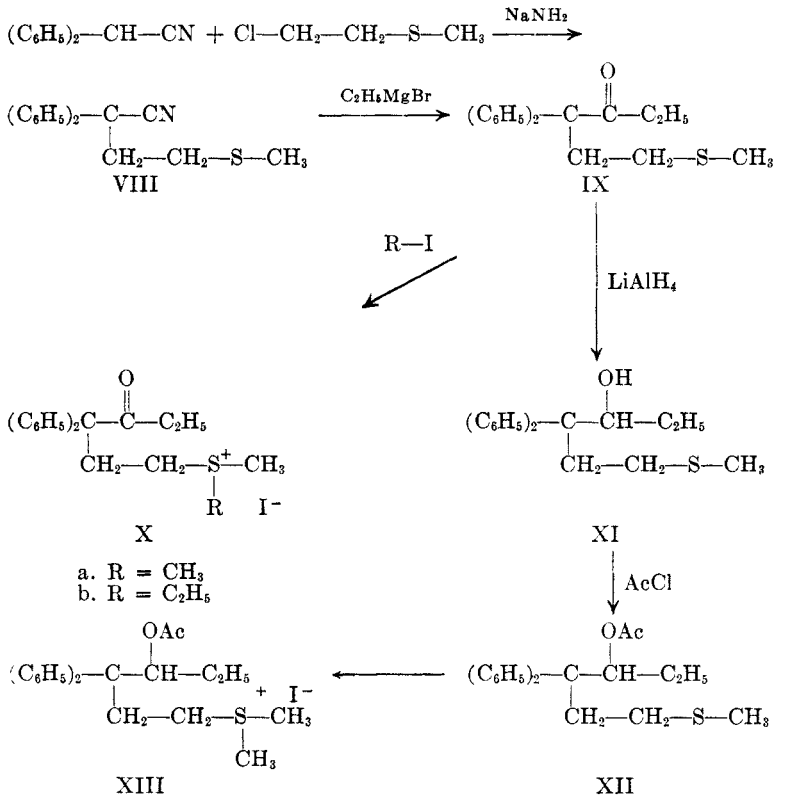
ethyl) sulfide with ethyl phenylacetate in the presence of sodium amide. However, the yield for this reaction was very poor (12% crude).



A sulfonium analog of methadone itself was not prepared because of the potential synthetic difficulties involved in the development of the isopropyl side chain.[10] Instead, analogs of the closely related VII were prepared. This compound has a β-dimethylaminoethyl side-chain instead of the β-dimethylaminoisopropyl side-chain found in methadone, and it is reported to be an effective analgesic agent in experimental animals and man although it is not as active as methadone.[11] Since the completion of our work, the synthesis of one sulfonium analog of VII has been reported.[5] We have also prepared this compound (Xa) although by a somewhat different route, and have in addition prepared several other methadone-type sulfonium analogs.



Condensation of diphenylacetonitrile with (2-chloroethyl)methyl sulfide in the presence of sodium amide afforded the alkylated diphenylacetonitrile-(VIII) in 42% yield. This compound was prepared by the Czechoslovak workers[5] from 3,3-diphenyl-3-cyanopropyl bromide and sodium methyl mercaptide. Conversion of VIII to the dimethyl sulfonium analog (Xa) was carried out in the same manner as reported by these workers;[5] that is, by methyl iodide treatment of the sulfide (IX), prepared by reaction of ethyl magnesium bromide with nitrile (VIII). Reaction of IX with ethyl iodide afforded the ethyl sulfonium analog (Xb).



Although reduction of the carbonyl group in methadone to give methadol generally causes a decrease in analgesic activity, acetylation of meth-

(10) A. Berger, *Medicinal Chemistry*, Interscience Publishers, Inc., New York, N. Y., 1951, p. 182.

(11) C. C. Scott, E. B. Robbins, and K. K. Chen, *Science*, **104**, 587 (1946); E. C. Kleiderer, J. B. Rice, V. Conquest, and J. H. Williams, Report No. 981, Office of the Publication Board, Department of Commerce, Washington, D. C.

adol results in a restoration of this activity.[12] Therefore, it was of interest to prepare a sulfonium analog of the acetyl methadol type structure. Lithium aluminum hydride reduction of ketone IX gave the corresponding carbinol (XI) in 65% yield. Treatment of this carbinol with acetyl chloride produced a 59% yield of the acetate (XII), which on reaction with methyl iodide afforded the desired sulfonium analog (XIII).

None of the sulfonium analogs reported in this paper showed significant analgesic activity.

EXPERIMENTAL[13]

1,5-Dichloro-3-cyano-3-phenylpentane (II). This compound was prepared by the three-step synthesis described by Bergel and coworkers[8] in an over-all yield of 11.4%, m.p. 51–52°.

4-Cyano-4-phenyltetrahydrothiapyran (III). To a solution of 25.3 g. (0.105 mole) of 1,5-dichloro-3-cyano-3-phenylpentane (II) in 125 ml. of ethanol was added a solution of 25.2 g. (0.105 mole) of sodium sulfide nonahydrate in 75 ml. of water. A clear solution did not form. The mixture was refluxed on a steam bath for 27 hr., then cooled and poured into ice water. The milky solution was extracted several times with ether. The combined ether extracts were dried, filtered, and evaporated. The residue consisted of two oily layers. The lower layer was distilled; the main fraction, 7.8 g. (37%), boiled at 137–142° at 1 mm., n_D^{26} 1.5729. Eisleb[7] reports a boiling point of 175° at 6 mm.

4-Carbethoxy-4-phenyltetrahydrothiapyran (V). (A) *By ethanolysis of nitrile* III. A mixture of 20.3 g. (0.1 mole) of 4-cyano-4-phenyltetrahydrothiapyran (III), 30 g. of 98% sulfuric acid, 0.26 g. of water, 46 g. of ethanol, and 5.36 g. of ammonium chloride was heated in a glass-lined autoclave at 160° for 7 hr. The contents of the autoclave were treated with ice water and the mixture was extracted with ether. The ether extracts were dried, filtered, and evaporated to give 5.5 g. (22%) of the ester as an oil.

(B) *By esterification of acid* IV. A mixture of 5.5 g. (0.025 mole) of 4-carboxy-4-phenyltetrahydrothiapyran (IV)[7] and 35 ml. of ethanol, which had been saturated with hydrogen chloride, was placed in a pressure bottle, and warmed on a steam bath for about 14 hr. After cooling, the solvent was removed and the residue was dissolved in ether. The ether solution was washed with a dilute sodium carbonate solution, dried, and evaporated. This gave the ester V as a light brown oil, which was used as such for the preparation of the sulfonium salts VI.

(C) *From ethyl phenylacetate and bis(2-chloroethyl)sulfide.* To a solution of sodium amide,[14] prepared from 16.6 g. (0.72 mole) of sodium and 500 ml. of liquid ammonia, was added 59 g. (0.36 mole) of ethyl phenylacetate in 100 ml. of dry ether. The mixture was stirred and warmed gently to remove the ammonia which was replaced with 300 ml. of ether. A solution of 30 ml. (0.284 mole) of bis(2-chloroethyl)sulfide was then added dropwise during 5 min. The mixture was refluxed on a steam bath for 1 hr., 200 ml. of toluene was added and refluxing was continued for 90 min. (reflux temperature was 95–100°).

After cooling to 10°, water was added cautiously to decompose any unreacted sodium amide, and when the reaction was no longer exothermic, a large amount of ice water was added. The toluene layer was dried over calcium sulfate (Drierite), filtered and distilled. A 10-g. forerun boiling at 82–83° at 1 mm. was followed by the product (8.4 g., 29%) boiling at 160–162° at 1 mm. A small amount of solid which codistilled with the product proved to be phenylacetamide, m.p. 155.5–156.5°, admixture of which with an authentic sample showed no depression in melting point.

4-Carbethoxy-1-methyl-4-phenylhexahydrothiapyrylium iodide (VI). A solution of 4-carbethoxy-4-phenyltetrahydrothiapyran (V), obtained *via* procedure B from 5.5 g. of IV, in 45 ml. of methyl iodide, was allowed to stand at room temperature for 24 hr. The sulfonium salt separated as a crystalline solid (3.5 g., 36%), m.p. 139–140° dec.

In a pilot run, the product was recrystallized from ethanol to give white crystals melting at 135–136° dec.

Anal. Calcd. for $C_{15}H_{21}IO_2S$: C, 45.9; H, 5.40; I, 32.4; S, 8.17. Found: C, 45.9; H, 5.65; I, 32.4; S, 8.00.

4-Carbethoxy-1-ethyl-4-phenylhexahydrothiapyrylium iodide. This compound was prepared in a manner similar to that described above for the methiodide salt except that the ester was dissolved in acetone and then treated with a large excess of ethyl iodide. The ethiodide salt was obtained after drowning the reaction solution in ether. The product melted at 117.5–118°.

Anal. Calcd. for $C_{16}H_{23}IO_2S$: C, 47.3; H, 5.70; I, 31.2; S, 7.89. Found: C, 47.1; H, 5.68; I, 30.5; S, 8.23.

2,2-Diphenyl-4-methylthiobutyronitrile (VIII). A solution of 386.5 g. (2 moles) of diphenylacetonitrile in 1530 ml. of dry benzene was added dropwise with stirring, over a period of 1 hr., to a mixture of 100 g. (2.5 moles) of sodium amide[14] in 1000 ml. of dry benzene. The reaction was not exothermic. The mixture was stirred at 40° for 1 hr., then 221 g. (2 moles) of 2-chloroethyl methyl sulfide[15] was added dropwise at 32–34° during 2.5 hr. The mixture was then stirred at 50–70° for 15 hr. The liquid was decanted from the precipitated solids into a separatory funnel and water was added. The benzene layer was separated and washed three times with small portions of water. The solvent was removed and the residual oil was distilled. After an initial fraction (b.p. 124–170° at 2 mm.) which consisted largely of diphenylacetonitrile (187 g., 49% recovery) and a small intermediate fraction, the product VIII was obtained boiling at 182–185° at 2 mm. (227 g., 42%; n_D^{26} 1.5880).

Anal. Calcd. for $C_{17}H_{17}NS$: C, 76.4; H, 6.41; N, 5.24; S, 12.0. Found: C, 76.3; H, 6.38; N, 5.33; S, 11.2.

Mychajlyszn and Jilek[5] prepared this compound in 71% yield, b.p. 160–165° at 1 mm., by the reaction of sodium methylmercaptide with 2,2-diphenyl-4-bromobutyronitrile.

4,4-Diphenyl-6-methylthiohexanone-3 (IX). Ethyl magnesium bromide was prepared from 36 g. (0.33 mole) of ethyl bromide, 8 g. (0.33 mole) of magnesium and 160 ml. of ether. A solution of 53.5 g. (0.2 mole) of 2,2-diphenyl-4-methylthiobutyronitrile (VIII) in 120 ml. of toluene was added. The solvent was distilled until the internal temperature rose to 102°. The mixture was stirred, warmed at 102–110° for 4.5 hr., and then allowed to stand at room temperature overnight. Ice was cautiously added to decompose the Grignard complex. The reaction was exothermic and the temperature rose to 50–60°. When the heat evolution had subsided, 100 ml. of dilute hydrochloric acid was added and the mixture was warmed on the steam bath for 2 hr. The two layers were separated, and the aqueous layer was extracted three times with small portions of benzene. The benzene extracts were combined with the toluene layer and distilled at reduced pressure. After a small forerun (8.8 g.), the product (IX) boiled at 165–178° at 1 mm., and weighed 39.9 g. (67%), n_D^{30} 1.5823. Mychajlyszn and Jilek[5] report a b.p. of 170–173° at 0.5 mm.

A sample of material boiling at 176–177° at 1 mm., n_D^{29} 1.5828, was analyzed.

Anal. Calcd. for $C_{19}H_{22}OS$: C, 76.5; H, 7.43; S, 10.7. Found: C, 76.5; H, 7.43; S, 10.8.

(12) Ref. 10, p. 184.

(13) Melting points are uncorrected.

(14) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 122 (1954).

(15) *Org. Syntheses*, Coll. Vol. II, p. 136, John Wiley and Sons, New York, N. Y., 1943.

Dimethyl-(3,3-diphenyl-4-oxohexyl)sulfonium iodide (Xa). A solution of 5.8 g. of 4,4-diphenyl-6-methylthiohexanone-3 (IX) in 20 ml. of methyl iodide was allowed to stand for 4 days. The product (Xa) separated as a white crystalline material, which after 2 recrystallizations from 95% ethanol, weighed 5.3 g., m.p. 125.5° (gas evolution). Mychajlyszn and Jilek[5] report a m.p. of 122°.

(3,3-Diphenyl-4-oxohexyl)-ethylmethylsulfonium iodide (Xb). A solution of 25.3 g. (0.085 mole) of 4,4-diphenyl-6-methylthiohexanone-3 (IX) in 75 ml. acetone was treated with 46.8 g. (0.3 mole) of ethyl iodide. The solution was allowed to stand at room temperature for several days. The sulfonium salt separated out during this time as a crystalline solid. The mixture was filtered and the light yellow solid weighed 5.4 g., m.p. 114–115.5°. After recrystallization from 15 ml. of 95% ethanol there was obtained 4.3 g. of a white solid, m.p. 118.5–119°.

Anal. Calcd. for $C_{21}H_{27}IOS$: C, 55.5; H, 5.99; I, 27.9; S, 7.06. Found: C, 55.4; H, 5.61; I, 27.8; S, 7.47.

4,4-Diphenyl-6-methylthiohexanol-3 (XI). A mixture of 4.6 g. (0.12 mole) of lithium aluminum hydride in 200 ml. of ether was refluxed on a steam bath in an atmosphere of nitrogen for 4.5 hr. A solution of 119.3 g. (0.4 mole) of 4,4-diphenyl-6-methylthiohexanone-3 (IX) in 200 ml. of ether then was added dropwise over a period of 40 min. The mixture was refluxed for 2.5 hr. Wet ethyl acetate (40 ml.) was added cautiously to decompose the complex and any unreacted lithium aluminum hydride. After the decomposition was complete, 300 ml. of ice water was added. This gave a milky solution, which separated into 2 layers after standing overnight. The aqueous layer was acidified with dilute sulfuric acid, and then extracted several times with ether. The ether extracts were combined, dried over sodium sulfate, filtered, and evaporated. The residue, a thick viscous oil, was distilled at reduced pressure. The product boiled at 182–184° at 1–2 mm. and weighed 77.4 g. (64.5%). This oil solidified to a white solid, m.p. 66–69°. Recrystallization from a mixture of hexane and petroleum ether gave 75.2 g. of the product XI, m.p. 70–71.5°.

Anal. Calcd. for $C_{19}H_{24}OS$: C, 75.9; H, 8.05; S, 10.7. Found: C, 76.1; H, 8.22; S, 10.6.

4,4-Diphenyl-6-methylthio-3-hexyl acetate (XII). A mixture of 90 g. (0.3 mole) of 4,4-diphenyl-6-methylthiohexanol-3 (XI) in 400 ml. of dry pyridine was stirred and cooled in an ice bath while 27 g. (0.35 mole) of acetyl chloride was added over a period of 30 min. at 10–12°. The ice bath was removed and the temperature raised slowly until a clear solution formed (about 2 hr.). The solution was stirred at room temperature for 3 hr., and then poured onto ice water which had been made slightly acid with dilute hydrochloric acid. The mixture was extracted three times with portions of ether, and the ether extracts were combined, dried, filtered, and evaporated. The residue, a thick viscous amber oil, was distilled at reduced pressure. The product (XII) boiled at 180–188° at 1 mm. and weighed 60.5 g. (59%).

(4-Acetoxy-3,3-diphenylhexyl)-dimethylsulfonium iodide (XIII). This compound was prepared from XII and methyl iodide by the procedure described above for the preparation of Xa. It was obtained in 38% yield after crystallization from 95% ethanol, m.p. 121.5–122.5°.

Anal. Calcd. for $C_{22}H_{29}IO_2S$: C, 54.5; H, 6.03; I, 26.2; S, 6.62. Found: C, 54.2; H, 6.44; I, 26.2; S, 6.21.

Acknowledgment. We wish to thank Mr. O. Sundberg and staff for microanalyses. We are indebted to Dr. A. Osterberg and staff of the Experimental Therapeutics Section of these laboratories for the pharmacological evaluation of these compounds.

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Preparation of 2-Thioöxazolidones from Substituted Dithiocarbamylacetic Acids

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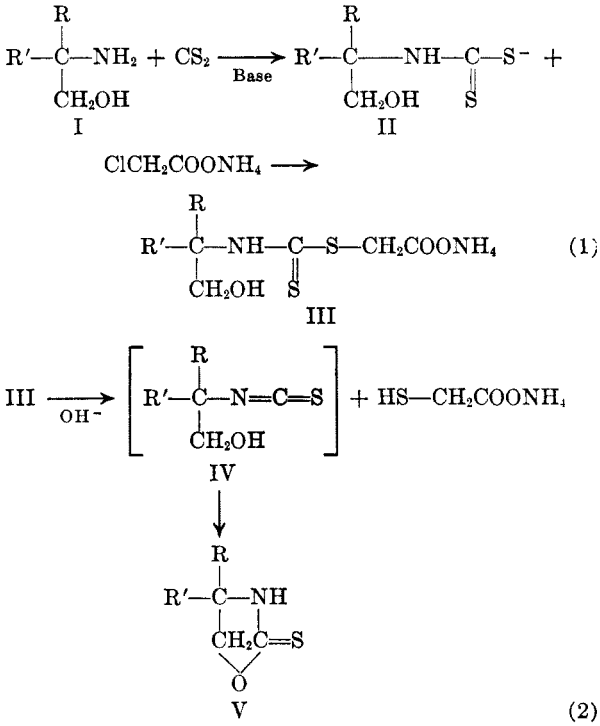
2-Thioöxazolidones[1] substituted in the 4- and 5- positions have been prepared from aminoalcohols by reaction with carbon disulfide and potassium hydroxide[2,3] and by the decomposition of thiuram disulfides derived from 2-aminoalcohols.[3]

We have now found that *N*-substituted dithiocarbamylacetic acid derivatives produced from 2-aminoalcohols, carbon disulfide, and monochloracetic acid (Equation 1) may be decomposed by alkali to form a substituted 2-thioöxazolidone and thioglycolic acid (Equation 2).



The expected product of the scission of the substituted dithiocarbamylacetic acid would be a hydroxyalkyl isothiocyanate (IV), but this apparently cyclizes to the corresponding 2-thioöxazolidone (V).[4]

In the above manner, 2-methyl-2-aminopropanol-1, I R=R′=CH_3, yields 4,4-dimethyl-2-

(1) We have confirmed the work of M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4792 (1950), who has shown by infrared spectra that these materials are thioketones and do not contain SH groups. Therefore, they are more properly termed 2-thioöxazolidones rather than oxazoline-2-thiols.

(2) H. A. Bruson and J. W. Eastes, *J. Am. Chem. Soc.*, **59**, 2011 (1937).

(3) A. A. Rosen, *J. Am. Chem. Soc.*, **74**, 2994 (1952).

(4) B. Holmberg, *J. Prakt. Chem.*, **79**, 263 (1909) observed that dithiocarbamylacetic acid in alkali solution produced thioglycolic acid and thiocyanic acid.

thioöxazolidone whereas the carbon disulfide and alkali process of Bruson[2] produces a mixture of the 2-thioöxazolidone and thiazoline compounds. Similarly 2-aminobutanol-1, (I).R = H, R′ = C_2H_5, produces a thioöxazolidone derivative instead of a substituted thiazoline. The reaction products are thus similar to those obtained by the thiuram procedure.[3]

EXPERIMENTAL[5]

Preparation of substituted 2-thioöxazolidone from 2-amino alcohols. A mixture of 1 mole (89.1 g.) 2-aminobutanol-1, or 2-methyl-2-aminopropanol-1, and 90 g. of ammonium hydroxide was cooled in an ice bath at 10° and 76 g. of carbon disulfide were added over a 15-min. period, and then stirred for 1 hr. or until it became a clear uniform solution. A solution prepared by dissolving 94.5 g. (1 mole) of monochloracetic acid in 70 ml. of water and neutralizing with 70 ml. of ammonium hydroxide solution was added to the above dithiocarbamate solution. This reaction was somewhat exothermic and the temperature rose to 20 to 25°. Stirring was continued for an hour after addition was complete and the mixture was then allowed to stand overnight. The white crystals of the substituted 2-thioöxazolidone which formed, were filtered by suction on a Büchner funnel and washed with a small amount of cold water. The yield was 45 to 55 g. of air dried crystals (35–42% of theory).

4-Ethyl-2-thioöxazolidone, (V), R = H; R′ = C_2H_5. The white crystals prepared above from 2-aminobutanol-1 melted at 72.8 to 73.2° after recrystallization from alcohol (lit.,[3] m.p. 74–75°). These crystals were soluble in alcohol, ethyl acetate, benzene, and acetone.

Anal. Calcd. for C_5H_9NOS: C, 45.77; H, 6.91; N, 10.68; S, 24.44. Found: C, 46.06; H, 6.88; N, 10.35; S, 24.56.

4,4-Dimethyl-2-thioöxazolidone, (V), R = R′ = CH_3. When recrystallized from alcohol, the melting point was 124.6 to 125.8° (lit.,[6] m.p. 123–125°). The compound was soluble in alcohol, benzene, and ethyl acetate.

Anal. Calcd. for C_5H_9NOS: C, 45.77; H, 6.91; N, 10.68; S, 24.44. Found: C, 45.96; H, 6.78; N, 9.90; S, 25.04.

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(5) Microanalysis by the Clark Microanalytical Laboratory, Urbana, Ill.

(6) C. Y. Hopkins, *Can. J. Research*, **B20**, 268 (1942).

Studies on Hydroxybenzotriazoles

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Several compounds containing the grouping >NOH have been reported[2] to be useful as organic precipitating agents. 1-Hydroxy-1,2,3-benzotriazoles also contain a similar grouping. In view of the fact that they can be prepared readily by the action of sodium hydroxide[3,4j] or hydrazine hydrate on *o*-nitrophenylhydrazines[4] or even from *o*-dinitrobenzenes,[4a,j] it was considered worthwhile to synthesize some additional derivatives and study their analytical behavior.

1-Hydroxy-1,2,3-benzotriazoles have been prepared by the action of hydrazine hydrate on *o*-nitrophenylhydrazines and also on *o*-dinitrobenzenes. They are suitable for the estimation of silver ion with which they give a quantitative precipitate.

Details of their analytical behavior shall be published elsewhere.

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(2) (a) F. Ephriam, *Ber.*, **63**, 1928 (1930). (b) G. Denigs, *Bull. soc. pharm. Bordeaux*, **70**, 101 (1932). (c) D. C. Sen, *J. Indian Chem. Soc.*, **15**, 473 (1938). (d) J. F. Flagg and N. H. Furman, *Ind. Eng. Chem., Anal. Ed.*, **12**, 529 (1940). (e) K. J. Keuning and J. V. Dubsky, *Rec. trav. chim.*, **59**, 978 (1940). (f) P. Wenger, R. Duckert, and M. Busset, *Helv. Chim. Acta*, **24**, 889 (1941).

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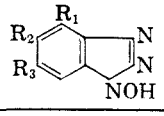
TABLE I

1-HYDROXY-1,2,3-BENZOTRIAZOLES



No.	R_1	R_2	R_3	Formula	Color	M.P.°C	Analysis	
							Calcd.	Found
1	H	Cl	H	$C_6H_4N_3OCl$	Colorless plates	210d[a,b]	Cl: 20.93	20.8
2	H	Br	H	$C_6H_4N_3OBr$	Colorless plates	220d[a]	Br: 37.39	37.2
3	H	I	H	$C_6H_4N_3OI$	Colorless plates	200d[a]	I: 48.66	48.4
4	H	Cl	CH_3	$C_7H_6N_3OCl$	Colorless needles	203d[a]	Cl: 19.34	19.2
5	H	I	CH_3	$C_7H_6N_3OI$	Colorless needles	182[a]	I: 46.18	46.0
6	H	C	Cl	$C_6H_3N_3OCl_2$	Colorless needles	215[a,c]	Cl: 34.81	34.5
7	Br	H	Br	$C_6H_3N_3OBr_2$	Colorless needles	218d[a]	Br: 54.61	54.4

[a] Recrystallized from ethanol. [b] Lit.,[4h] m.p. 204–205°. [c] Lit.,[4g] m.p. 194–196°.

EXPERIMENTAL[5]

5-Bromo-1-hydroxy-1,2,3-benzotriazole. To a solution of 2-nitro-5-bromophenylhydrazine (0.5 g.) in ethanol (20 ml.) was added hydrazine hydrate (2 ml. 50%). It was heated on a water bath for 0.5 hr., concentrated to a small volume, diluted with water and filtered. The filtrate on acidification with dilute hydrochloric acid gave 5-bromo-1-hydroxy-1,2,3-benzotriazole (0.3 g.) as colorless plates from ethanol, m.p. 220° dec. By adopting a similar procedure other hydroxybenzotriazoles were prepared. The data concerning the new compounds are listed in Table I. All of them explode above their melting points.

Acknowledgment The authors wish to express their gratitude to Dr. S. S. Joshi, D.Sc., for his kind interest in this work.

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(5) All melting points are uncorrected.

Identification of Caffeic Acid in Cigarette Smoke

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No previous report has been made of the presence of caffeic acid (3,4-dihydroxycinnamic acid) in cigarette smoke. Several groups of workers[1-3] however, have reported finding free caffeic acid in various cured tobaccos, but Roberts and Wood,[4] using fresh cigar tobacco, and Weaving,[5] using flue-cured tobaccos, could find none in their samples. Dieterman *et al.*[6] have recently pointed out that esculetin (6,7-dihydroxycoumarin) in tobacco may often be confused on paper chromatograms with caffeic acid. In the present study on tobacco in eight brands of cigarettes commonly smoked in the U. S., every sample tested was found to contain free caffeic acid. Also, in every case, the main stream smoke from the cigarette contained free caffeic acid.

In the purification of scopoletin (6-methoxy, 7-hydroxycoumarin) from cigarette smoke and from various tobacco extracts,[7,8] two or more interfering blue fluorescing compounds persisted with the scopoletin through several developments of paper chromatograms. Dieterman *et al.*[6] identified one of these interfering compounds as esculetin. The present identification establishes free caffeic acid as the other blue fluorescing compound.

During paper chromatography in certain acid solvent systems, such as 15% acetic acid–water, caffeic acid appears as two distinct zones. These have been shown to be *cis-* and *trans-* caffeic acid.

EXPERIMENTAL

Caffeic acid from cigarette tobacco. The tobacco obtained from one hundred and twenty cigarettes (three each from forty packs of the same brand) was mixed and ground to a powder. Six 5.5-g. samples of this powder were thoroughly extracted with 85% isopropyl alcohol, as previously described by Yang *et al.*[7] The combined extracts were concentrated under reduced pressure, and the concentrate was then subjected to separation by mass paper chromatography.[7] After the initial chromatography with Whatman 3MM paper, using the solvent system *n*-butyl alcohol–acetic acid–water (6:1:2 v./v.), each zone containing caffeic acid, still mixed with some esculetin and scopoletin, was cut off and then eluted with methanol. The eluates were combined and streaked on S & S No. 589, Red Ribbon, chromatography paper, and developed in the system chloroform–acetic acid–water (2:1:1 v./v., bottom layer). This solvent system proved to be superior to the nitromethane-benzene-water system (2:3:5 v./v., upper layer) used in our previous studies on scopoletin and esculetin. In the chloroform system, the scopoletin (R_f = 0.75) moves in a narrow zone quite removed from those of esculetin (R_f = 0.39) and of caffeic acid (R_f = 0.35). This was also the case with the benzene–propionic acid–water system (2:2:1 v./v., top layer) with R_f values: scopoletin (0.66); caffeic acid (0.32); and esculetin (0.26). The two top zones resulting from paper chromatography with the chloroform system contained primarily caffeic acid and esculetin. They were cut off from each chromatogram together; sewn onto a new sheet of paper; and then developed in ethyl acetate–formic acid–water (10:2:3 v./v.). Each zone containing caffeic acid, with a trace of esculetin still present, was cut off and eluted with the ethyl acetate solvent system. The eluates were combined and again streaked on S & S No. 589 paper and developed in 15% acetic acid–water. Although separation of caffeic acid from esculetin was completed by this chromatography with acetic acid, an isomer of caffeic acid now appeared as a separate, third zone.

The two zones of isomeric caffeic acid were cut from each chromatogram as a unit and sewn onto a new sheet of chromatography paper. Each such sheet was then developed in the ethyl acetate system to obtain one narrow blue zone for identification studies.

Identification of caffeic acid. The combined eluates containing the purified caffeic acid from each single zone obtained in the ethyl acetate system were then co-chromatographed with authentic caffeic acid purchased from California Foundation for Biochemical Research, using the *n*-butyl alcohol–acetic acid–water, chloroform–acetic acid–water, ethyl acetate–formic acid–water, benzene–propionic acid–water, and nitromethane-benzene-water systems already described, and *n*-butyl alcohol–benzene–pyridine–water (5:1:3:3 v./v., upper layer), isopropyl alcohol–pyridine–acetic acid–water (8:8:1:2 v./v.), and 15% acetic

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(7) C. H. Yang, Y. Nakagawa, and S. H. Wender, *J. Org. Chem.*, **23**, 204 (1958).
(8) C. H. Yang, Y. Nakagawa, and S. H. Wender, *Anal. Chem.*, **30**, 2041 (1958).

acid–water. Both the reference and isolated caffeic acid solutions gave the same R_f values in every test. In the 15% acetic acid system, both the reference and unknown caffeic acid samples gave two zones each, with corresponding R_f values.

The isolated and reference caffeic acids behaved similarly towards the chromogenic agents previously reported.[6] In addition, both gave the same color reaction with the Höfner reagent[4] (pink, changing to yellowish-brown) and with 2% alcoholic ferric chloride solution (green changing to gray).

The absorption spectra exhibited by the isolated caffeic acid in ethanol, and in buffer solutions at *p*H 3.5 and 6.8, checked in each case with the corresponding spectrum exhibited by the reference caffeic acid in ethanol and in buffer solutions at *p*H 3.5 and 6.8 in our laboratory and with those reported for these preparations by Sutherland.[9]

Caffeic acid in the mainstream smoke of cigarettes. The smoking of eight brands of cigarettes for caffeic acid analysis was performed by a procedure similar to the one already described for scopoletin in smoke by Yang *et al.*[8] Because caffeic acid, however, was present only in a trace amount in the smoke, samples representing smoke from forty packs of cigarettes were combined and concentrated to obtain sufficient caffeic acid for unambiguous studies by paper chromatography. The separation, purification, and identification of caffeic acid from the cigarette smoke condensates were carried out by mass paper chromatography in the same manner as already described above for determination of caffeic acid in tobacco. Cigarettes analyzed included Camel, Lucky Strike, Philip Morris, Old Gold Straights, Pall Mall, Winston, Viceroy, and Oasis.

Isomerization of caffeic acid. On paper chromatography with 15% acetic acid–water, the reference caffeic acid gave two distinct zones. The farther moving zone (R_f = 0.50) was called "CA-1," and the slower moving zone (R_f = 0.42) was called "CA-2." Each blue fluorescing zone was cut out separately; sewn onto separate new sheets of paper; and again developed in the 15% acetic acid. It was observed that from the slower moving zone (CA-2), the faster moving zone (CA-1) was produced every time that a separated CA-2 zone was rechromatographed in this acid system. If this procedure, involving separation by paper chromatography, cutting, sewing, and rechromatography of the CA-2 was repeated even five or more times, the slower moving zone of caffeic acid, would in every case, continue to change to give both isomers. The fluorescence of this slower moving zone would be weaker on each subsequent chromatogram. The CA-1 zone likewise gave both isomers on rechromatography of the faster moving zones, but produced only a relatively small amount of the CA-2 each time that the CA-1 was developed in the 15% acetic acid–water.

Both CA-1 and CA-2 co-chromatographed with the reference caffeic acid to give only one spot in all the solvent systems mentioned in this paper, except in the 15% acetic acid–water. In this latter system, the major spot from the reference caffeic acid on the first chromatograms was identical with CA-2, and the minor spot was the same as CA-1. Both CA-1 and CA-2 gave the same color reactions when tested with all the chromogenic agents described in this report.

Williams[10] has reported that cinnamic acid derivatives give two spots on paper chromatography with 2% acetic acid–water. He suggested that this was a case of *cis-trans* isomerization on paper. He did not, however, point out which spot corresponded to which isomer. Recently, Butler and Siegelman[11] have reported that the faster moving zone of caffeic acid during paper chromatography with 5% acetic acid–water is *cis*-, and the slower moving zone is *trans*-caffeic acid, on the basis that ultraviolet light converted a part of the slower moving zone into the faster moving one. Our slower moving zone behaved similarly, and based on their conclusions, it would appear that our CA-1 is *cis*- and our CA-2 is *trans*-caffeic acid. For further confirmation of these *cis* and *trans* configuration assignments to CA-1 and CA-2, we undertook ultraviolet and infrared spectral studies as described in following paragraphs.

Ultraviolet absorption spectra of the caffeic acids. Although the isomeric caffeic acids CA-1 and CA-2 could be readily obtained as completely separated zones on paper chromatograms, much difficulty was experienced in getting solutions of either isomer completely free of the other. During the preparation of such solutions by extraction or elution of the individual zones from the paper, and application of heat, isomerization was usually found to occur, and an equilibrium mixture was set up according to the temperature, solvent, etc. used. During such handling, except for the paper chromatography step itself, the CA-1 (*cis*) shifted more readily into the CA-2 (*trans*) than did CA-2 to CA-1. For the ultraviolet spectrophotometry, a solution consisting mainly of isomer CA-1 (but not entirely free of the other isomer) and another preparation consisting mainly of CA-2 were prepared as described in the next paragraph.

Each isomeric zone was cut from the chromatogram separately and eluted with 95% ethanol in an elution chamber. Each eluate was then evaporated to dryness, *in vacuo*, without application of heat. The residue, containing the caffeic acid isomer plus a filter paper impurity, was then dissolved by 1 ml. of hot distilled water, added drop by drop, while the container was kept rotating. A blank solution containing the filter paper impurity, but no caffeic acid, was prepared in exactly the same manner as just described, except that no caffeic acid was present on the sheet of chromatography paper. The aqueous solution of each isomer was then added to cold distilled water in separate cuvettes, drop by drop, with a capillary tube. To the cuvette used as a blank, approximately an equal amount of the blank solution containing the filter paper impurity, but no caffeic acid, was added. The absorption spectra of these CA-1 and CA-2 solutions were then measured with the Beckman spectrophotometer, Model DU. Results are shown in Fig. 1. The CA-1 preparation exhibited its high maximum

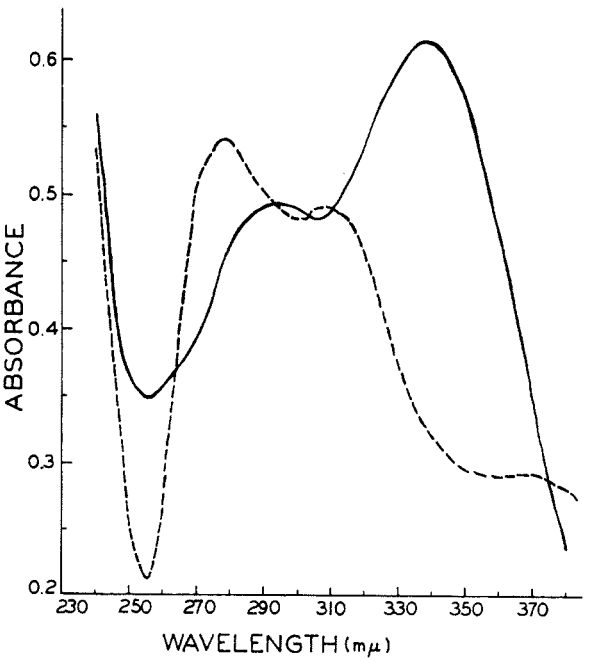

Fig. 1. Absorption spectra of aqueous solutions of caffeic acid prepared from zones CA-1 (- - - -) and CA-2 (———).

(9) G. K. Sutherland, *Arch. Biochem. Biophys.*, **75**, 412 (1958).

(10) A. H. Williams, *Chem. & Ind. (London)*, 120 (1955).

(11) W. L. Butler and H. W. Siegelman, *Nature*, **183**, 1813 (1959).

at 278 mμ, whereas the CA-2 preparation had an even higher maximum at 340 mμ. Mixing of various amounts of CA-1 and CA-2 shifted the 340 mμ maximum of CA-2 to various corresponding lower wave lengths.

To interpret these results, one uses the working rule which states that when the absorption properties of the *cis-trans* isomers of a substance differ, "the more elongated isomer absorbs at somewhat longer wave lengths and more intensely."[12]

Haskins and Gorz[13] recently have found that such absorption data apply in their studies on *cis-* and *trans-o*-cinnamic acid. If this rule should also hold with caffeic acid, CA-1 would then appear to be the *cis* isomer and CA-2 the *trans* isomer of caffeic acid. These assignments of *cis* and *trans* to the caffeic acid isomers check with the designations in above paragraphs.

Infrared absorption spectra of the caffeic acids. To prepare samples of CA-1 and CA-2 for infrared studies, caffeic acid solution was streaked onto S & S No. 589 paper and developed in 15% acetic acid–water. The CA-1 and CA-2 zones were cut out and separately eluted with methyl alcohol. The eluate containing CA-1 was extracted with *n*-hexane, which is supposed to favor solution of the *cis* isomer.[14] The hexane was removed *in vacuo* at room temperature in the dark, and crystals of CA-1 were obtained. The methyl alcohol eluate CA-2 was concentrated *in vacuo* almost to dryness, in the dark at room temperature, and the residue was extracted several times with ethyl ether. Crystals of CA-2 were obtained after evaporation of the ether. Two milligrams of each of the crystalline CA-1 and CA-2 were mixed with 400 mg. of potassium bromide and made into pellets. These were studied with the Perkin-Elmer recording infrared spectrophotometer, Model 21.

At 814 cm.$^{-1}$, the absorption of the compound from CA-2 (*trans*) showed stronger intensity than did the absorption from compound CA-1 (*cis*). Bellamy[15] states that conjugation of the double bond with carbonyl groups has a very marked effect, and that the group —CH=CHCOOR (*cis*) absorbs near 820 cm.$^{-1}$ with sufficient regularity for this to be a useful assignment. He continues by stating that this absorption from the *cis* form is usually much weaker in intensity than that from the *trans* series. Also, at 1640 cm.$^{-1}$, CA-2 showed stronger absorption than did CA-1. Thus, the infrared data confirmed the previous indications that the CA-2 fraction was primarily the *trans* isomer, and the CA-1 fraction was mainly the *cis* isomer of caffeic acid.

Acknowledgment. This work and some previous research on which these findings are based were supported in part by the Tobacco Industry Research Committee, by The National Institute of Health, and by the Atomic Energy Commission. We are grateful to Dr. Alfred Weinheimer, University of Oklahoma, for his many helpful suggestions.

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(12) A. E. Gillam and E. S. Stern, *An Introducton to Electronic Absorption Spectroscopy in Organic Chemistry*, Edward Arnold Publishers Ltd., London, England, 2nd ed., 1957, p. 267.

(13) F. A. Haskins and H. J. Gorz, *Arch. Biochem. Biophys.*, 81, 204 (1959).

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(15) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen & Co. Ltd., London, 1954, p. 48.

Halogenation of Glycoluril and Diureidopentane

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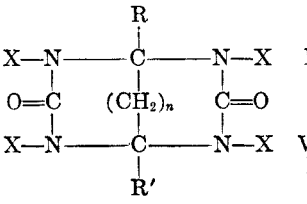
The literature reveals the preparation of 1,3,4,6-tetrachloro-3a,6a-diphenylglycoluril (I),[1,2] 1,3,4,6-tetrachloro-3a,6a-dimethylglycoluril (II),[2,3] and of 1,3,4,6-tetrachloro-3a-methyl-6a-phenylglycoluril (III)[2] but does not disclose 1,3,4,6-tetrachloroglycoluril (IV). This paper deals with the preparation of IV and some related compounds.



	R	R′	X	*n*
I	C_6H_5	C_6H_5	Cl	0
II	CH_3	CH_3	Cl	0
III	CH_3	C_6H_5	Cl	0
IV	H	H	Cl	0
V	H	H	Br	0
VI	H	H	I	0
VII	H	H	H	0
IX	CH_3	CH_3	H	1
X	CH_3	CH_3	Cl	1

We found that chlorination of aqueous suspensions of glycoluril (VII),[4–6] under a variety of conditions, gave IV. Excellent yields were obtained when the chlorination mixture was kept neutral or slightly alkaline (*p*H 7–8) by the addition of various basic materials either as solids or as solutions. Although a wide variety of alkaline materials was successfully used, a 1 to 6*N* sodium hydroxide solution was the most convenient alkali to add.

Bromination of glycoluril to 1,3,4,6-tetrabromoglycoluril (V) required somewhat more alkaline conditions (*p*H 8–11). The use of analogous techniques failed to give tetraiodoglycoluril (VI).

A clear solution resulted on treatment of an aqueous suspension of VII with half the theoretical amount of chlorine required for the preparation of IV. Further chlorination of this solution caused the precipitation of IV. Concentration of the clear solution resulted in the isolation of a dichloroglycoluril (VIII). No attempt was made to separate or characterize the possible isomers.

No material corresponding to a mono- or a trichloroglycoluril was found. Chlorination of VII to a theoretical trichloroglycoluril stage gave a solid which was readily separated into IV and VIII by extraction with water. The water solubility, at

(1) H. Biltz and O. Behrens, *Ber.*, **43**, 1984 (1910).

(2) J. W. Williams, U. S. Patent **2,649,389** (1953).

(3) H. B. Adkins, U. S. Patent **2,654,763** (1953).

(4) H. Biltz, *Ber.*, **40**, 4806 (1907).

(5) R. A. Pingree and M. A. Dahlen, Textile Finishing Treatments, P.B. Report 1576, Appendix III, Hobart Publishing Company, Washington, D. C.

(6) W. Baird, C. B. Brown, and G. R. Perdue, Textile Auxiliary Products of I. G. Farbenindustrie, P.B. Report 32565, Page 12, Hobart Publishing Company, Washington, D. C.

room temperature, of IV was found to be 0.01 g./100 ml. while that of VIII was 0.27 g./100 ml.

This is the first instance that we are aware of in which a dihaloglycoluril has been isolated. Because VII was converted almost entirely into VIII before any significant amount of IV was observed, we are led to believe that other glycolurils could be similarly chlorinated. However, because of different solubility characteristics, the partial chlorination of other glycolurils might not be as easy to follow visually as was our example.

Chlorination of the related diureidopentane (IX), prepared by the method of de Haan,[7] gave tetrachlorodiureidopentane (X) but, because of the great insolubility of the materials involved, the chlorination proceeded with greater difficulty.

The products described are relatively stable. Pure, dry samples of IV and VIII have been kept in stoppered clear-glass vials at room temperature for as long as two years with only a 5–10% loss of available chlorine. However, mixtures with wet, strongly alkaline materials (sodium metasilicate and sodium metasilicate pentahydrate) resulted in rapid decomposition of IV and VIII, which, on occasion, became violent.

EXPERIMENTAL[8]

Glycoluril (VII). A stirred solution of 30% aqueous glyoxal (2250 g., 11.6 mole) and urea (1900 g., 31.7 mole) in 4 l. of water was heated to 85–95° and maintained at this temperature for 20–30 min. while concentrated hydrochloric acid (25–45 ml.) was added as needed to maintain the solution at *p*H 1.5–2.0. Cooling, filtering, and recrystallizing from water with the aid of decolorizing carbon gave 850–900 g. (52–55%) of white crystalline VII, decomposing at 300°.

Tetrachloroglycoluril (IV). A stirred suspension of VII (71 g., 0.5 mole) in 3200 ml. of water was treated with chlorine (150 g., 2.1 mole) at the rate of 20–40 g./hr. while 6*N* sodium hydroxide solution was added at such a rate as to maintain the mixture at *p*H 7–8, as measured with a *p*H meter. The resulting white solid was filtered, washed twice with 1-l. portions of water, and dried to give 136 g. (97%) of IV, decomposing slowly above 280°.

Anal. Calcd. for $C_4H_2Cl_4N_4O_2$: C, 17.2; H, 0.7; Cl, 50.7; N, 20.0. Found: C, 17.5; H, 0.8; Cl, 50.5; N, 20.2. Infrared examination did not show the NH band (3170 cm.$^{-1}$) present in VII.

Dichloroglycoluril (VIII). This was carried out as in the preparation of IV except that 78 g. (1.1 mole) of chlorine was used. The solution was filtered to remove traces of IV and concentrated under vacuum at 50° to a volume of about 200 ml. The resulting solid was filtered, washed with two 100-ml. portions of water, and dried to give 90 g. (85%) of VIII, melting with rapid decomposition at 180°.

Anal. Calcd. for $C_4H_4Cl_2N_4O_2$: C, 22.8; H, 1.9; Cl, 33.6; N, 26.5. Found: C, 22.5; H, 1.6; Cl, 33.0; N, 26.0.

Tetrabromoglycoluril (V). A stirred suspension of VII (7.1 g., 0.05 mole) in 2200 ml. of water was treated with bromine (80.0 g., 0.5 mole) over a 3-hr. period while the mixture was maintained at *p*H 9–10. The resulting solid after filtering, washing with two 500-ml. portions of water, and drying gave 17.2 g. (75%) of V melting at 292–295° with decomposition.

Anal. Calcd. for $C_4H_2Br_4N_4O_2$: C, 9.8; H, 0.4; Br, 69.6. Found: C, 10.5; H, 0.8; Br, 65.5.

Tetrachlorodiureidopentane (X). A stirred suspension of IX (56 g., 0.3 mole) in 3 l. of water was treated with chlorine (110 g., 1.55 mole) over a 4-hr. period while the mixture was maintained at *p*H 5–8. The white solid was filtered, washed with several portions of water and dried to give 87 g. (90%) of X melting at 210° with decomposition.

Anal. Calcd. for $C_7H_8Cl_4N_4O_2$: Cl, 44. Found: Cl, 41.5.

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(7) T. de Haan, *Rec. trav. chim.*, **27**, 162 (1908).

(8) All melting points are uncorrected. Elemental and infrared analysis by the Diamond Alkali Company Research Analytical Laboratory.

C-73: A Metabolic Product of *Streptomyces albulus*

KOPPAKA V. RAO

Received August 11, 1959

C-73 is a crystalline compound which accompanies cycloheximide and E-73 in the broths of *Streptomyces albulus*. The three compounds have identical carbon skeletons. C-73 has an aromatic ring in place of the cyclohexanone ring which is common to cycloheximide and E-73. The structure of C-73 is shown (I.)

The isolation of the five fractions designated as A-73 (fungicidin), B-73, C-73, D-73 (cycloheximide), and E-73 from the culture filtrates of *Streptomyces albulus* has been described earlier.[1] Among these, E-73 showed pronounced antitumor activity in experimental animals and its structure has been elucidated.[2] The present paper deals with the chemical nature of C-73.

C-73 (I) is a pale yellow crystalline solid sparingly soluble in common organic solvents. Elementary analysis corresponds to the empirical formula $C_{15}H_{17}O_4N$. Its occurrence with cycloheximide in the culture broths and the close similarity between their empirical formulae $C_{15}H_{17}O_4N$ and $C_{15}H_{23}O_4N$ suggested a possible structural relationship between the two.

The ultraviolet spectrum of C-73 has maxima at 262 and 345 mμ (ϵ = 10,870 and 4,550 respectively). The infrared spectrum shows bands at 5.80, 5.90, 6.10, and 6.26 μ among others. The substance shows bright yellow fluorescence under ultraviolet light. It gives a dark green color with alcoholic ferric chloride, indicating the presence of a phenolic group. C-73 is soluble in aqueous alkali to give bright yellow solutions.

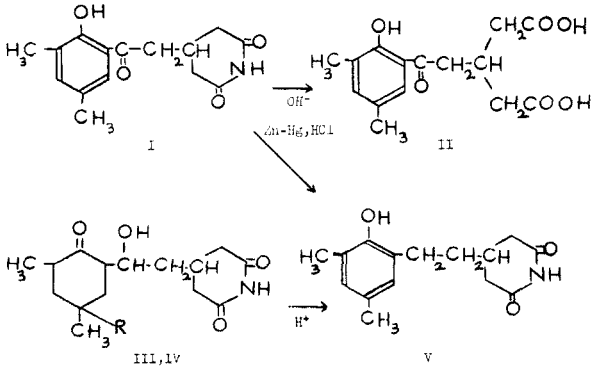
(1) K. V. Rao and W. P. Cullen, *J. Am. Chem. Soc.*, in press.

(2) K. V. Rao, *J. Am. Chem. Soc.*, in press.

Acetylation of C-73 yields a colorless mono acetate, $C_{17}H_{19}O_5N$. C-73 forms an orange red 2,4-dinitrophenylhydrazone as evidence for the presence of the carbonyl group. The color reaction with ferric chloride, the ultraviolet spectrum and the diminished hydroxyl band in the infrared spectrum suggest that the carbonyl group is *ortho* to the phenolic hydroxyl. Boiling C-73 with aqueous alkali produces one molar equivalent of ammonia and an acidic compound (II). This acid, which is dibasic (N = 147) has the molecular formula $C_{15}H_{18}O_6$. It has ultraviolet absorption maxima at 262 and 345 mμ (ϵ = 11,000 and 4600 respectively, similar to the original compound). It also retains the fluorescence and the ferric chloride reaction typical of C-73.

Methylation of C-73 yields a colorless methylation product $C_{17}H_{21}O_4N$ which contains one methoxyl and one methylimide group.

The properties described thus far indicate the presence of a phenolic group, a keto group and an imide group in C-73. It may be recalled that both cycloheximide (III) and E-73 (IV) contain an imide group. As C-73 differs from cycloheximide only by the lack of six hydrogen atoms, the possibility appeared that the former is an aromatized analogue of cycloheximide. Among the alternatives considered, structure I appeared most probable. During the course of the work on the structure of E-73, some of the phenolic transformation products of the latter became available and it appeared that C-73 could be related to one of them. Accordingly C-73 was reduced by the Clemmensen procedure whereby a colorless crystalline product (V) was obtained. This was shown to be identical in all respects to desacetyl dehydro E-73 described earlier.[2] The formation of this common intermediate is considered as a proof for structure I for C-73. The reactions are described in Fig. 1. Unlike cycloheximide or E-73, C-73 has little or no antitumor activity in experimental animals.



III. R = H
IV. R = O Ac

Fig. 1. Comparaison of C-73 with cycloheximide and E-73

EXPERIMENTAL

C-73 was purified by crystallization from a mixture of methanol and chloroform. The product separated out as pale yellow needles, m.p. 198–199°.

Anal. Calcd. for $C_{15}H_{17}O_4N$: C, 65.44; H, 6.22, N, 5.09. Found: C, 65.57; H, 6.33; N, 5.10.

For acetylation, C-73 (0.2 g.) was left at room temperature with acetic anhydride (2 ml.) and pyridine (0.5 ml.) for 24 hr. The reagents were removed by a current of air and the residue crystallized from a mixture of methylene chloride and ether. The acetyl derivative separated as colorless needles, m.p. 149–150°.

Anal. Calcd. for $C_{17}H_{19}O_5N$: C, 64.34; H, 6.04; N, 4.41. Found: C, 63.34; H, 6.52; N, 4.42.

The 2,4-dinitrophenylhydrazone of C-73 was prepared by the action of 2,4-dinitrophenylhydrazine in 2*N* methanolic hydrochloric acid. The derivative separated as orange red rectangular plates which did not melt below 280°.

Anal. Calcd. for $C_{21}H_{21}O_7N_5$: C, 55.38; H, 4.65; N, 15.38. Found: C, 55.84; H, 4.84; N, 15.00.

Alkaline hydrolysis of C-73. A solution of C-73 (0.5 g.) in aqueous sodium hydroxide (25 ml.) was refluxed for 2 hr. A current of nitrogen was passed through the solution during the hydrolysis and the exit gases trapped in 1*N* hydrochloric acid. The distillate was concentrated to dryness and the residue crystallized from methanol-acetone.

Anal. Calcd. for NH_4Cl: N, 26.17; Cl, 66.28. Found: N, 26.85; Cl, 66.10.

The alkaline hydrolysis mixture was acidified and the precipitated solid crystallized from aqueous methanol. The product separated as long, colorless needles, m.p. 126–127°.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.23; H, 6.16. Found: C, 61.16; H, 6.20.

Methylation of C-73. A mixture of C-73 (0.5 g.), acetone (50 ml.), dimethyl sulfate (2 ml.), and anhydrous potassium carbonate (8 g.) was refluxed for 12 hr., the solvent was distilled, the residue treated with water and the mixture extracted twice with methylene chloride. Concentration of the solvent extract gave a colorless crystalline solid which was recrystallized from a mixture of ether-isopropyl ether. The methyl ether separated as colorless rectangular prisms, m.p. 100–101°.

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.32; H, 6.97; N, 4.61; OMe,[1] 10.21; NMe,[1] 9.56. Found: C, 67.46; H, 7.10; N, 4.77; OMe, 10.48; NMe, 8.0.

Reduction of C-73. Zinc amalgam was prepared from zinc dust (5 g.) and a 0.5% solution of mercuric chloride. The supernatant liquid was decanted and a solution of C-73 (0.3 g.) in a mixture of ethanol (20 ml.) and 6*N* hydrochloric acid (20 ml.) was added and the whole refluxed for 4 hr. After 2 hr., an additional quantity (5 ml.) of the acid was added. At the end of the reaction, the mixture was filtered, the residue washed with ethanol, and the filtrate concentrated to remove the ethanol. Extraction of the aqueous concentrate with ether followed by evaporation of the extract gave a colorless crystalline solid. When recrystallized from aqueous methanol, V separated as colorless glistening rectangular plates, m.p. 147–148°. A mixed melting point with desacetyl dehydro E-73[2] (V) (obtained by heating E-73 (IV) with 6*N* hydrochloric acid) was undepressed. The ultraviolet spectra (λ_{max} at 280 mμ, ϵ = 2000) and the infrared spectra were identical.

Anal. Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.43; H, 7.52; N, 5.67.

Acknowledgment. The author is grateful to Dr. R. L. Wagner for analyses.

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Ethanolysis of 2-Substituted-4-arylidene-5-oxazolones. Effect of Trifluoromethyl Substitution on the Arylidene Ring

ROBERT FILLER AND HERMAN NOVAR

Received September 17, 1959

The ultraviolet absorption spectra of azlactones are usually measured in 95% ethanol, chloroform, ether, or acetic acid as solvents. A hypsochromic shift of the principal maximum of unsaturated azlactones has been observed[1] when dilute ethanolic solutions were allowed to stand at room temperature for several days. This shift is due to the noncatalyzed solvolysis of the oxazolone to form the open chain ester and this change offers a convenient means for following the course of the reaction spectrophotometrically.

Thus, 2-phenyl-4-benzylidene-5-oxazolone (Ia), λ_{max}^{EtOH} 360 mμ[2] was gradually converted into ethyl α-benzamidocinnamate (IIa), λ_{max}^{EtOH} 282 mμ. After three to four days, about 50% conversion had occurred and the reaction was complete within twenty-one days.[1] We have confirmed these results and have further observed that 2-methyl-4-benzylidene-5-oxazolone (Ib), λ_{max} 328 mμ, was much more readily solvolyzed to IIb, λ_{max} 281 mμ, with conversion almost complete after twenty-eight hours. This increased rate of alcoholysis of 2-methyl analogs has been observed previously with another oxazolone[1] and is consistent with the facile hydrolysis of Ib with boiling water-acetone to give the α-acetamido acid.[3] Ia is stable under the latter conditions.

In the course of our studies on trifluoromethyl-substituted aromatic amino acids, we have prepared and similarly examined several analogs of Ia and Ib (see Table I), possessing trifluoromethyl groups in the *ortho* and *meta* positions of the arylidene ring. The preparation of these compounds will be discussed in a forthcoming paper.[4]

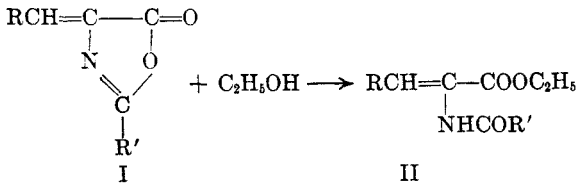
Ic (λ_{max} 359 mμ) was largely converted to the open-chain, α,β-unsaturated ester after twenty-four hours and had reacted completely within seventy-two hours, while the *meta* trifluoromethyl compound, Id (λ_{max} 358 mμ), and the 2-methyl counterparts, Ie (λ_{max} 324 mμ) and If (λ_{max} 322 mμ), showed no evidence of unchanged oxazolone after twenty four hours.

These results reflect the enhancement of solvolysis due to the electronic influence of the trifluoromethyl group in labilizing the oxazolone ring. The site of attack is the lactone carbonyl moiety and it is difficult, as the results are not quantitative, to evaluate, particularly in the case of the *o*-trifluoromethyl compound, the relative importance of the *inductive* and *field* effects in the total electrical effect. Such an evaluation has been made by Roberts[5] for *o*-substituted phenylpropiolic acids and esters.

It is also of interest to note that the spectra of the 2-phenyl-4-trifluoromethylbenzylidene-5-oxazolones (Ic and Id) did not reveal any sign of *trans*-acylation during their preparation by the Erlenmeyer-Plöchl reaction, in contrast to the observations of Bennett and Niemann in the preparation of the 4-(*p*-fluorobenzylidene) analog.[6]

Concentrations of solutions were about 5 μg oxazolone/cc. Measurements were made with a Beckman DK-2 spectrophotometer.

TABLE I



I II

Compound	Substituents R	R'
a	C_6H_5	C_6H_5
b	C_6H_5	CH_3
c	*o*-$C_6H_4CF_3$	C_6H_5
d	*m*-$C_6H_4CF_3$	C_6H_5
e	*o*-$C_6H_4CF_3$	CH_3
f	*m*-$C_6H_4CF_3$	CH_3

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(1) E. L. Bennett and E. Hoerger, *J. Am. Chem. Soc.*, **74**, 5975 (1952).

(2) D. A. Bassi, V. Deulofeu, and F. A. F. Ortega, *J. Am. Chem. Soc.*, **75**, 171 (1953).

(3) *Org. Syntheses*, **Coll. Vol. II**, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 1.

(4) R. Filler and H. Novar, in press.

(5) J. D. Roberts and R. A. Carboni, *J. Am. Chem. Soc.*, **77**, 5554 (1955).

(6) E. L. Bennett and C. Niemann, *J. Am. Chem. Soc.*, **72**, 1803 (1950).

The Synthesis of a Novel Ester of Phosphorus and of Arsenic

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Received September 28, 1959

Stetter and Steinacker[2] report the synthesis of 1-phospha-2,8,9-trioxa-adamantane (II) and the corresponding 1-oxide and 1-sulfide. Using a modification of their synthetic method, we have pre-

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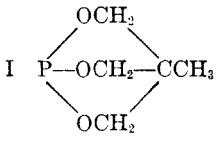
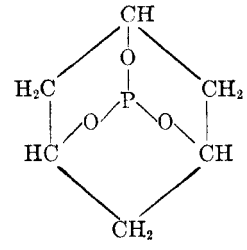
(2) H. Stetter and K. Steinacker, *Ber.*, **85**, 451 (1952).

pared the heretofore unknown 1-methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane (I) in which the phosphorus-oxygen bond angles are even more restricted and the organic group less bulky.



I



II

Compounds I and II function as excellent donors. This is the consequence of the minimal steric hindrance, increased availability of the phosphorus lone-pair electrons, and the high symmetry of the ligands. By contrast, the trialkoxyphosphorus compounds of comparable molecular weight are relatively poor donors.[3] It has been found[4] that I and II form stable complexes with various metal ions and addition compounds with Group III Lewis acids. The arsenic analogues of I and II are also presently being investigated in this respect.

Despite the opportunity for polymer formation in the preparation, it is possible to obtain I in 40% yield. The preparation is effected by allowing phosphorus trichloride to react with 2-hydroxymethyl-2-methyl-1,3-propanediol at high dilution in tetrahydrofuran in the presence of a base (pyridine). Because of its volatility, I is separated from the reaction products by sublimation *in vacuo*. Contrary to expectation, I is very stable to air oxidation over a period of months, although it is quite hygroscopic. On the other hand, II is quite unstable in air.[2]

The slightly soluble 1-methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane - 4 - sulfide is obtained in nearly quantitative yield when sulfur is allowed to react with I at 140° in a sealed tube. The solid product remains after any unreacted starting materials have been extracted with carbon disulfide.

The previously unknown -4-arsa- analogue of I is obtained in 38% yield by using arsenic trichloride instead of phosphorus trichloride in the preparation of the bicyclic arsenic compound. The volatile product is separated from the polymeric reaction mixture by sublimation *in vacuo*. The colorless crystalline sublimate is quite unstable to moisture and hydrolyzes readily.

Attempts to synthesize the 4-oxide and the 4-sulfide of the -4-arsa- compound have thus far been unsuccessful.

The infrared spectra of these compounds are commensurate with the assigned structures. The P=O stretching frequency appears as a strong band at 1325 cm^{-1}. It is interesting to note that this frequency lies somewhat above the range generally assigned to this band.[5] The P=S stretching frequency occurs as a band of medium intensity at 800 $cm.^{-1}$ which lies within the range generally assigned to such compounds.[6]

(3) A. Arbuzov and V. Zoroastrova, *Doklady Akad. Nauk S.S.S.R.*, **84**, 503 (1952).

(4) To be published elsewhere.

EXPERIMENTAL[7,8]

1-Methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane. Tetrahydrofuran was distilled after refluxing over lithium aluminum hydride for 3 hr.; the portion boiling from 65–66° was taken. Pyridine was distilled after refluxing over barium oxide for 3 days; the portion boiling at 115° was taken. Two solutions were prepared: (1) a solution of 8.8 ml. (0.1 mole) freshly distilled phosphorus trichloride diluted to 75 ml. with tetrahydrofuran and (2) a solution of 12 g. (0.1 mole) 2-hydroxymethyl-2-methyl-1,3-propanediol in 24.2 ml. (0.3 mole) pyridine. The latter solution was also diluted to 75 ml. with tetrahydrofuran. These two solutions were simultaneously added dropwise over a period of 45 min. to 100 ml. of vigorously stirred tetrahydrofuran under dry nitrogen. The white reaction mixture was then stirred for 30 min., after which the pyridinium hydrochloride was allowed to settle. The clear supernatant liquid was filtered and the residue washed with two 30-ml. portions of tetrahydrofuran. Tetrahydrofuran was then distilled from the solution *in vacuo* until the residue became a white syrupy mass. The product was sublimed at 1 mm. pressure and room temperature on to a water-cooled finger until sublimation ceased. The temperature was then gradually raised by means of an oil bath to 80° and held constant within 2° of this temperature until no more product sublimed. To effect purification, the crude product was sublimed three times at 50° and 1 mm. pressure, yield, 5.9 g. (40%), m.p. of the colorless prismatic crystals 97–98°.

Instead of further sublimation, the product may be recrystallized from hot *n*-heptane.

Anal. Calcd.: C, 40.60; H, 6.08. Found: C, 40.55; H, 6.07. Mol. wt. Calcd.: 148. Found: 157.

1-Methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane-4-oxide. To a solution of 1.48 g. (0.01 mole) 1-methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane in 5 ml. absolute ethanol was added dropwise 1.13 ml. (0.01 mole) of 100 volume hydrogen peroxide. The crystals formed on cooling the solution were filtered, washed with 4 ml. cold absolute ethanol, dried, and sublimed three times at 155° and 1 mm. pressure, yield, 1.5 g. (92%), m.p. of the colorless acicular crystals 249–250°.

Anal. Calcd.: C, 36.60; H, 5.48. Found: C, 36.90; H, 5.48.

Mol. wt. Calcd.: 164. Found: 171.

The residue may also be recrystallized from absolute ethanol instead of subliming to effect purification.

1-Methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane-4-sulfide. A glass tube containing a mixture of 1.48 g. (0.01 mole) of I and 0.32 g. (0.01 mole) sulfur was evacuated, sealed, and heated to 140° in an oil bath for 5 min. After the vigorous reaction subsided, the tube was allowed to cool and the contents ground to a fine powder. The yellow powder was allowed to stand under 30 ml. of carbon disulfide for 24 hr. in order to dissolve any unchanged starting materials. The

(5) L. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, Ed. 2, 1958, p. 312.

(6) L. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, Ed. 2, 1958, p. 321.

(7) Melting points are uncorrected.

(8) Molecular weights were obtained by cryoscopic determination in nitrobenzene.

white powder was further extracted with three 20-ml. portions of carbon disulfide, dried and sublimed three times at 140° and 1 mm. pressure, yield, 1.6 g. (89%), m.p. of the colorless acicular crystals 224–225°.

Anal. Calcd.: C, 33.40; H, 5.00. Found: C, 33.56; H, 5.18.

Mol. wt. Calcd.: 180. Found: 174.

1-Methyl-4-arsa-3,5,8-trioxabicyclo[2.2.2]octane. The preparation of this compound involved arsenic trichloride and was analogous to that of the -4-phospha- compound. The first sublimation of the crude syrup, however, was carried out at room temperature. The solid sublimate, contaminated with a small amount of oily material, was dissolved in ether, in which the oily substance was insoluble. The ether solution was decanted and evaporated to dryness. The residual white solid was sublimed three times at room temperature and 1 mm. pressure, yield, 38%, m.p. of the colorless prismatic crystals 41–42°.

Anal. Calcd.: C, 31.25; H, 4.68. Found: C, 31.15; H, 4.68.

Mol. wt. Calcd.: 192. Found: 185.

Infrared Spectra. Spectra were taken in chloroform and carbon disulfide solutions as well as in nujol mulls on a Perkin-Elmer Model 21 Spectrophotometer.

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Phosphonic Acid and Esters. II. Formation of Telomers in Olefin/Phosphorous Acid Reactions

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In Part I it was shown that alkylphosphonic acids (I) could be formed by the addition of phosphorous acid to olefins in the presence of peroxides or ultraviolet irradiation (steps 1–2).[1] The low

$$RCH{=}CH_2 + \underset{II}{\cdot P(O)(OH)_2} \longrightarrow \underset{III}{RCHCH_2P(O)(OH)_2} \quad (1)$$

$$III + HP(O)(OH)_2 \longrightarrow \underset{I}{RCH_2CH_2P(O)(OH)_2} + II \quad (2)$$

yields of products obtained were attributed to the occurrence of polymerization, inhibition by allylic abstraction and telomerization (steps 3–4). Specific evidence for the occurrence of telomerization was provided by the isolation of a telomeric 2:1 adduct,

$$III + RCH{=}CH_2 \longrightarrow \underset{IV}{RCHCH_2CHRCH_2P(O)(OH)_2} \quad (3)$$

$$IV + HP(O)(OH)_2 \longrightarrow \underset{V}{RCH_2CH_2CHRCH_2P(O)(OH)_2} + II \quad (4)$$

2-hexyldecylphosphonic acid (VI; V, R = *n*-hexyl), as well as the primary reaction product (*n*-octylphosphonic acid) from the reaction of 1-octene and phosphorous acid. Similar telomers have been shown to arise in the peroxide initiated addition of dialkyl phosphonates to olefins.[2] In order to determine the extent of telomer formation, the previous investigation[1] has now been extended to a study of the reactions of 1-hexene, 1-decene, and cyclohexene.

1-Hexene was treated with phosphorous acid in the presence of dibenzoyl peroxide at reflux temperature; fractionation of the products led to the isolation of *n*-hexylphosphonic acid (23%) and the 2:1 adduct, 2-butyloctylphosphonic acid (VII; V, R = *n*-butyl). Reaction with 1-decene gave *n*-decylphosphonic acid (18%) and 2-octyldodecylphosphonic acid (VIII: V, R = *n*-octyl). A reinvestigation of the cyclohexene/phosphorous acid reaction led to the isolation of 2-cyclohexylcyclohexylphosphonic acid (IX) and the primary reaction product, cyclohexylphosphonic acid. Thus, telomerization appears to be generally characteristic of the olefin/phosphorous acid reactions and additional evidence for the low transfer constant of phosphorous acid is provided.

The structures proposed for the telomeric acids (V) are those which would arise from telomerization of conventional (head to tail) orientation, i.e., attack of the radical (III) at the terminal olefinic carbon.[3] The identity of the acids (V) was confirmed by comparison with samples prepared by an independent route: peroxide initiated addition of diethyl phosphonate to the appropriate olefin and acidic hydrolysis of the resulting diethyl alkylphosphonate. The requisite olefins, including

$$RCH_2CH_2CR{=}CH_2 + HP(O)(OC_2H_5)_2 \longrightarrow V$$

the previously unreported 2-hexyl-1-decene, were conveniently prepared from the corresponding ketones by means of the Wittig reaction. In each case the acid prepared independently was identical with the 2:1 adduct isolated from the olefin/phosphorous acid reactions.

The independent route employed above is, however, capable of yielding two produts: V by attack of the phosphonate radical at the terminal olefinic carbon and the isomeric 2-methyl alkylphosphonic acid $RCH_2CH_2CR(CH_3)P(O)(OH)_2$ by attack at carbon two. On the basis of the known chemistry and orientation of this and similar free radical addition reactions, terminal attack is most probable.[2,4,5] A conclusive demonstration was

(1) C. E. Griffin and H. J. Wells, *J. Org. Chem.*, **24**, 2049 (1959).

(2) A. R. Stiles, W. E. Vaughan, and F. F. Rust, *J. Am. Chem. Soc.*, **80**, 714 (1958).

(3) Alternatively, the attack of III at carbon two of the olefin would yield a primary radical (less stable than the secondary radical IV) and, ultimately, the isomeric acid $RCH(CH_3)CHRCH_2P(O)(OH)_2$.

(4) P. C. Crofts, *Quarterly Revs.*, **12**, 363 (1958).

(5) C. Walling, *Free Radicals in Solution*, John Wiley and Sons, Inc., New York, 1957, pp. 239–89.

provided by the synthesis of VII by an unequivocal route: Arbuzov reaction between 1-bromo-2-butyloctane and triethyl phosphite followed by hydrolysis. A sample of the acid prepared in this manner was identical with VII prepared by the addition of diethyl phosphonate to 2-butyl-1-octene. By analogy structure V is proposed for the acids VI, VIII, and IX.

EXPERIMENTAL

The olefin/phosphorous acid reactions were conducted according to the method previously reported[1]; a 1:1 molar ratio of olefin to phosphorous acid was employed. The 1:1 adducts were isolated by direct crystallization, while the 2:1 adducts were most conveniently isolated by anion exchange chromatography of reaction residues. Reactants and products are listed.

1-Hexene: n-hexylphosphonic acid (23%), m.p. 105–106° (from ligroin) (reported[6] m.p. 104.5–106°); *2-butyloctylphosphonic acid* (VII) (8%), m.p. 99–100° (from 50% ethanol).

1-Decene: n-decylphosphonic acid (18%), m.p. 101.5–103° (from ligroin) (reported[6] m.p. 102–102.5°); *2-octyldodecylphosphonic acid* (VIII) (6%), m.p. 94–95° (from H_2O).

Cyclohexene: cyclohexylphosphonic acid (20%)[1]; *2-cyclohexylcyclohexylphosphonic acid* (IX) (9%), m.p. 98–99.5° (from 50% ethanol).

1-Octene experiments are reported in Part I.

2-Alkyl-1-alkenes were prepared from the appropriate ketones[7] and triphenylphosphine methylene by the modification of a method described in the literature.[8] Products were isolated directly by distillation after removal of triphenylphosphine oxide by filtration.

2-Butyl-1-octene (from undecanone-5)[9] b.p. 83–84°/12 mm. (reported[9] b.p. 88–89°/14 mm.).

2-Octyl-1-dodecene (from nonadecanone-9)[7] b.p. 184–186°/10 mm. (reported[10] b.p. 193–195°/12 mm.).

2-Hexyl-1-decene (from pentadecanone-7)[11] b.p. 165–166°/9 mm.

Anal. Calcd. for $C_{16}H_{32}$: C, 85.63; H, 14.37; mol. wt., 224.4. Found: C, 85.60; H, 14.49; mol. wt. (Rast), 225.9.

1-Cyclohexylcyclohexene was prepared according to the method of Truffault.[12]

Alkylphosphonic acids were prepared from the corresponding olefins and diethyl phosphonate (1:4 molar ratio) in the presence of di-*t*-butyl peroxide according to established procedure.[2] Upon completion of reaction, unchanged diethyl phosphonate was removed by distillation under reduced pressure; the residue was hydrolyzed with concd. hydrochloric acid. Filtration and recrystallization gave the phosphonic acid.

2-Hexyldecylphosphonic acid (VI) m.p. 100.5–101.5° (from ligroin) (reported[1] m.p. 100.5–101.5°).

Anal. Calcd. for $C_{16}H_{35}O_3P$: C, 62.71; H, 11.51; neut. equiv., 153.2. Found: C, 62.84; H, 11.38; neut. equiv., 153.6.

2-Butyloctylphosphonic acid (VII) m.p. 99–100° (from 50% ethanol).

Anal. Calcd. for $C_{12}H_{27}O_3P$: C, 57.57; H, 10.87; neut. equiv., 125.2. Found: C, 57.59; H, 11.01; neut. equiv., 125.9.

2-Octyldodecylphosphonic acid (VIII) m.p. 94–95° (from H_2O).

Anal. Calcd. for $C_{20}H_{43}O_3P$: C, 66.26; H, 11.96; neut. equiv., 181.3. Found: C, 66.30; H, 11.76; neut. equiv., 182.9.

2-Cyclohexylcyclohexylphosphonic acid (IX) m.p. 98–99.5° (from 50% ethanol).

Anal. Calcd. for $C_{12}H_{23}O_3P$: C, 58.50; H, 9.41; neut. equiv., 123.1. Found: C, 58.61; H, 9.43; neut. equiv., 124.2.

In each case the alkylphosphonic acid prepared in this manner was identical with the 2:1 adduct isolated from the olefin/phosphorous acid reactions. Mixture melting points and infrared spectra were employed as criteria of identity.

2-Butyloctylphosphonic acid (VII) was prepared independently by a conventional Arbuzov reaction. 1-Bromo-2-butyloctane was prepared by the action of phosphorus tribromide on the corresponding alcohol in pyridine; after removal of solvent under reduced pressure, the reaction mixture was filtered and dissolved in ether. The ethereal extract was washed with water, dilute hydrochloric acid, and dilute ammonium hydroxide and dried over anhydrous sodium sulfate; removal of ether under reduced pressure gave the crude alkyl bromide. A mixture of the alkyl bromide and a three fold excess of triethyl phosphite was heated at 150° for 30 hr. The reaction mixture was treated as above to isolate the acid. A sample of acid from this preparation was identical with the product of the 2-butyl-1-octene/diethyl phosphonate reaction.

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(6) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **67**, 1180 (1945).

(7) Prepared according to the method of F. L. Breusch and F. Baykut, *Chem. Ber.*, **86**, 684 (1953).

(8) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **79**, 5029 (1957).

(9) J. v. Braun and H. Kroper, *Ber.*, **62B**, 2880 (1929).

(10) J. v. Braun and G. Manz, *Ber.*, **67B**, 1696 (1934).

(11) M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1949).

(12) R. Truffault, *Bull. soc. chim. France*, (5), **3**, 442 (1936).

Potential Anticancer Agents.[1] XXX. Analogs of *N,N',P*-Triphenylphosphonothioic Diamide

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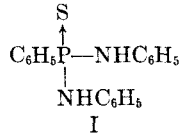
One of the compounds found in the mass screening program of the Cancer Chemotherapy National Service Center to have slight antitumor activity is *N,N',P*-triphenylphosphonothioic diamide (I). This compound showed borderline activity against adenocarcinoma 755. The synthesis of a number of



I

analogs of I for test evaluation was undertaken in this laboratory. The compounds were selected to give the widest possible diversity of structural types (Table I). These compounds were made by interaction of the appropriate phosphorus chloride and amine by one of several methods described in the Experimental.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper in this series, *cf.* E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, in press.

TABLE I

No.	R	R′	R″	M.P., °C.	Procedure	Yield,[b] %	Analysis					
							Carbon, %		Hydrogen, %		Nitrogen, %	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
II	C_6H_5—	*p*-ClC_6H_4NH—[f]	*p*-ClC_6H_4NH—	181–182	A	62[c]	55.0	54.7	3.85	4.30	7.13	7.33
III	C_6H_5—	*o*-ClC_6H_4NH—[f]	*o*-ClC_6H_4NH—	113–114	B[g]	52[c]	55.0	54.8	3.85	4.00	7.13	7.15
IV	C_6H_5—	3,4-$Cl_2C_6H_3NH$—	3,4-$Cl_2C_6H_3NH$—	145	B[g]	47[c]	46.8	46.4	2.83	3.03	6.06	6.08
V	C_6H_5—	3,4-$(CH_3)_2C_6H_3NH$—	3,4-$(CH_3)_2C_6H_3NH$—	132–133	A	70[c]	69.2	69.4	6.62	6.66	7.37	7.22
VI	C_6H_5—	*p*-$CH_3OC_6H_4NH$—	*p*-$CH_3OC_6H_4NH$—	112–114	A	32[c]	62.5	62.6	5.51	5.66	7.29	7.34
VII	C_6H_5—	*p*-$O_2NC_6H_4NH$—	*p*-$O_2NC_6H_4NH$—	198–200	C[h]	30[e]	52.2	52.3	3.65	3.98	13.5	13.3
VIII	C_6H_5—	*p*-$(C_2H_5O_2C)C_6H_4NH$—	*p*-$(C_2H_5O_2C)C_6H_4NH$—	Amorph.	B[g]	87	61.5	61.8	5.38	5.64	5.98	6.11
IX	C_6H_5—	—NH_2	—NH_2	38–40	D	50[c]	41.8	42.2	5.27	5.40	16.3	16.3
X	C_6H_5—	C_2H_5NH—	C_2H_5NH—	80–81[i]	A	79[c]	52.6	52.7	7.50	7.40	12.3	12.2
XI	C_6H_5—			111–112	A	62[c]	53.8	53.9	6.78	6.92	8.97	8.90
XII	C_6H_5—	C_6H_5O—	C_6H_5NH—	93–96[j]	E	53[c]	66.4	66.6	4.96	5.12	4.31	4.67
XIII	C_6H_5NH—	C_6H_5NH—	C_6H_5NH—	150–151	A	43[d]	63.7	64.0	5.35	5.44	12.7	12.7
XIV	C_6H_5O—	C_6H_5NH—	C_6H_5NH—	122–123	E	74[c]	63.5	63.3	5.04	5.15	8.23	8.42
XV	$C_6H_5PO(NHC_6H_5)_2$			207–210[k]	A	61[c]						

[a] All the compounds contained the proper infrared bands for the type of phenyl substituent as well as P—N bands at 11.0–13.3 μ. Compounds with a P → S bond showed a band at 13.5–14.5 μ. [b] Yields are after at least one recrystallization. [c] Recrystallized from absolute ethanol. [d] Recrystallized from 95% ethanol. [e] Recrystallized from aqueous acetone. [f] The *m*-chloro analog failed to crystallize and the crude product could not be obtained in an analytically pure condition. [g] Procedure A failed to give a crystallizable product or gave a much lower yield. [h] Procedures A and B failed to give any appreciable reaction. [i] Reported[4] m.p. 85.7–86°. [j] Reported[5] m.p. 103°. [k] Reported[6] m.p. 211°.

Although compound I showed activity against adenocarcinoma 755 when tested in these laboratories, none of the analogs showed any appreciable activity against this tumor, sarcoma 180, or leukemia L-1210.[2]

EXPERIMENTAL[3]

Procedure A. To a solution of 1.12 g. (9.2 mmoles) of 3,4-xylidene in 20 ml. of anhydrous ether was added 0.50 g. (2.4 mmoles) of phenylphosphonothioic dichloride dropwise with stirring. The reaction mixture was allowed to stand overnight at room temperature protected from moisture, then the precipitated 3,4-xylidine hydrochloride was removed by filtration. Evaporation of the filtrate to dryness *in vacuo* gave a solid, which was recrystallized from absolute ethanol to give 0.70 g. (77%) of white crystals of V, m.p. 128–130°. Further recrystallizations raised the melting point to 132–133°. The analytical data are recorded in Table I.

Procedure B. A flask containing a mixture of 26.4 g. (0.207 mole) of *o*-chloroaniline and 10.0 g. (0.048 mole) of phenylphosphonothioic dichloride was placed in an oil bath at room temperature and the temperature raised to 165° over 15–20 min., then held at that temperature for 1 hr. The mixture was cooled, then dissolved in 150 ml. of chloroform. Treatment of the chloroform solution with 100 ml. of 1*N* hydrochloric acid caused the precipitation of *o*-chloroaniline hydrochloride. After the removal of the hydrochloride by filtration, the layers were separated and the chloroform layer was washed with two 60-ml. portions of 2*M* aqueous ammonia and 100 ml. of water. The chloroform layer was dried over magnesium sulfate, then concentrated to dryness *in vacuo* to yield 14.8 g. of a white solid. Recrystallization from absolute ethanol gave 9.6 g. (52%) of III as white crystals, m.p. 112–114°. An analytical sample was prepared from a similar run and recrystallized to constant melting point, 113–114°. The analytical data are recorded in Table I.

Procedure C. To a mixture of 12.98 g. (0.094 mole) of *p*-nitroaniline and 7.44 g. (0.094 mole) of pyridine in 400 ml. of dry benzene was added 10.0 g. (0.047 mole) of phenylphosphonothioic dichloride dropwise with stirring over a period of about 10 min. After the addition was complete, the reaction was heated at reflux for 7 hr., then cooled and concentrated to dryness *in vacuo*. The residue was dissolved in 200 ml. of ethyl acetate and washed with two 100-ml. portions of 1*N* hydrochloric acid, 150 ml. of 2*M* aqueous ammonia, and finally with two 100-ml. portions of water. The ethyl acetate solution was dried over magnesium sulfate, then evaporated to dryness *in vacuo*. The solid residue was dissolved in 200 ml. of acetone, then water (approximately 50 ml.) was added until the solution became slightly turbid. The solution was cooled to 0° overnight, then filtered to yield 5.95 g. (30%) of pale yellow crystals of VII, m.p. 196–200°. An analytical sample was prepared from a similar run and recrystallized to constant melting point, 198–200°. The analytical data are recorded in Table I.

Procedure D. To 40 ml. of concentrated ammonium hydroxide was added 2.0 g. (9.5 mmoles) of phenylphosphonothioic dichloride dropwise with stirring. An oily layer separated which slowly crystallized on standing. The reaction was heated on a steam bath for 0.5 hr., then concentrated to dryness *in vacuo* and the residue was taken up in 20 ml. of water. The aqueous layer was extracted with two 10-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate, then evaporated to dryness *in vacuo* to yield 0.91 g. (57%) of an oil. Crystallization from absolute ethanol gave 0.80 g. (50%) of IX as white crystals, m.p. 30–35°. Recrystallization from absolute ethanol raised the melting point to 38–40°. The analytical data are recorded in Table I.

Procedure E. A solution of 7.3 g. (0.078 mole) of phenol and 6.2 g. (0.078 mole) of pyridine in 20 ml. of anhydrous ether was added dropwise with stirring to a solution of 13.2 g. (0.078 mole) of thiophosphoryl chloride in 20 ml. of anhydrous ether over a period of about 10 min. The reaction mixture was heated at reflux for 1 hr., then cooled to 0° and the precipitated pyridine hydrochloride was removed by filtration. The filtrate was concentrated to dryness *in vacuo* to yield 15.6 g. (88%) of crude *o*-phenylphosphorothioic dichloride as an oil.

To a cold (5–10°) solution of 15.6 g. of this dichloride in 10 ml. of dry benzene was added 28.1 g. (0.30 mole) of aniline in 30 ml. of benzene dropwise with stirring. The reaction mixture was stirred for 2 hr. in an ice bath, then filtered to remove aniline hydrochloride. The filtrate was concentrated to dryness *in vacuo* to yield a solid, which was recrystallized from absolute ethanol to give 17.4 g. (74%) of XIV as white crystals, m.p. 118–120°. An analytical sample was prepared from a similar run and recrystallized to constant melting point, 122–123°. The analytical data are recorded in Table I.

Acknowledgment. The authors are indebted to Dr. Peter Lim for interpretation of the infrared spectra.

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(2) These tests were performed at Stanford Research Institute by Dr. Joseph Greenberg and staff under a contract with the Cancer Chemotherapy National Service Center.

(3) Melting points were taken on a Fisher-Johns block and are uncorrected.

(4) E. J. Kohn, U. E. Hanninen, and R. B. Fox, Naval Research Laboratory *Rept.* **C-3180,** 1947.

(5) M. F. Hersman and L. F. Audrieth, *J. Org. Chem.*, **23,** 1889 (1958).

(6) A. Michaelis, *Ann.*, **293,** 215 (1896).

Selective Oxidation of Alkyl Groups

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Previous workers[2] have shown that the oxidation of *p*-dialkylbenzenes with nitric acid will yield alkylbenzoic acids, but no generalization has been expressed concerning the relative ease of oxidation of the alkyl groups. Cullis[3] reported the relative rates of oxidation of some monoalkylbenzenes by permanganate. However, other than with *t*-butyl groups, the literature reveals that permanganate oxidizes dialkylbenzenes to benzene dicarboxylic acids. It would be useful sometimes in organic synthesis to be able to oxidize selectively only one alkyl group of dialkylbenzenes. For this reason,

(1) Taken from the M.S. Thesis of Andrew I. Wims, Howard University, 1959. Present position: Teaching Assistant, Pennsylvania State University.

(2) *Cf.* W. F. Tuley and C. S. Marvel, *Org. Syntheses*, **Coll. Vol. III.** Wiley and Sons, N. Y., 1955, p. 822; G. F. Hennion, A. J. Driesch, and P. L. Dee, *J. Org. Chem.*, **12,** 1102 (1952).

(3) C. F. Cullis and J. W. Ladbury, *J. Chem. Soc.*, 555 4186 (1955).

and to seek some principle for predicting the relative ease of oxidizing alkyl groups, a study was made of the selective oxidation of dialkylbenzenes with nitric acid. The identity and purity of the products were verified by mixed melting points and infrared spectra.

EXPERIMENTAL

Preparation of compounds. Those dialkylbenzenes not readily available commercially were prepared by the Wurtz-Fittig reaction.[4] Of the required substituted benzoic acids, only *p*-ethylbenzoic acid had to be synthesized, which was prepared by carbonating *p*-ethylphenylmagnesium bromide.[5]

The melting or boiling points of the compounds used in this study are listed in Table I. All liquids were distilled at reduced pressures and a constant boiling fraction taken. The boiling point of a small sample was then determined at atmospheric pressure. All solids were recrystallized from ethanol to constant melting points.

Oxidations with nitric acid. A typical oxidation with nitric acid can be described for *p*-cymene. A mixture of 15 g. of *p*-cymene, 70 ml. of water, and 20 ml. of concentrated nitric acid was placed in a flask. The mixture was allowed to reflux gently for 8 hr. After cooling, the solid was collected and dissolved in 60 ml. of 1*N* sodium hydroxide. The alkaline solution was distilled over zinc dust until the distillate ran clear, in order to reduce any nitrated products. The solution was then acidified with dilute hydrochloric acid. The precipitate was recrystallized from ethanol to a constant melting point of 180°. The literature value for *p*-toluic acid is 181°. A mixed melting point with an authentic sample of *p*-toluic acid was 180–180.5°. Its infrared spectrum in spectro grade dimethylformamide had the characteristic band of *p*-toluic acid at 13.14 μ, while the characteristic band of cumic acid at 12.88 μ was absent.

Other dialkylbenzenes were oxidized similarly. Little attention was given to per cent yields, although the yields were sufficiently large to make the reactions suitable for a preparation. In all cases, only one of the two potential acids was recovered, and it was identified by mixed melting point with an authentic sample and infrared spectra.

Permanganate oxidations. A few attempts were made to use potassium permanganate for oxidizing one alkyl group of a given dialkylbenzene, but except when a *t*-butyl group was one of the alkyl groups, only the respective dicarboxylic acid was obtained. For example, *p*-*t*-butyltoluene yielded *p*-*t*-butylbenzoic acid, whereas *p*-cymene gave terephthalic acid. Experiments were made using a 10:1 molar ratio of hydrocarbon to permanganate at temperatures of 60–70°.

Infrared spectra. Spectra of the substituted benzoic acids were measured in spectro grade *N*,*N*-dimethylformamide in a Perkin Elmer spectrophotometer 12C using a rock salt optical system. Characteristic bands for the acids were found as follows: *p*-Toluic acid 13.14 μ; *p*-ethylbenzoic acid 13.04 μ; *p*-cumic acid 12.88 μ; *p*-*t*-butylbenzoic acid 12.80 μ.

DISCUSSION

Nitric acid oxidation of *p*-methyl-, *p*-ethyl, and *p*-isopropyl-*t*-butylbenzenes always gave *p*-*t*-butylbenzoic acid as the only isolated product. This inertness of the *t*-butyl group to oxidation has been observed previously. For example, Ligge[6] attempted to oxidize *p*-di-*t*-butylbenzene with chromic oxide, aqueous potassium permanganate, and several concentrations of nitric acid. Only 50% nitric acid at 180° brought about a significant oxidation of the *p*-di-*t*-butylbenzene.

Initial experiments on the oxidation of diethylbenzenes with 15% nitric acid gave the following results:

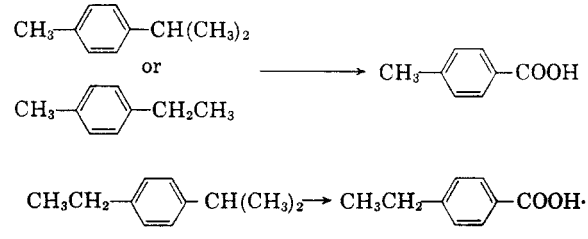

TABLE I

PHYSICAL PROPERTIES OF COMPOUNDS USED IN THIS STUDY

Compound	Observed	Literature
	B.P.	
p-Ethylcumene	194–194.5	194[a]
p-*t*-Butylethylbenzene	206–206.5	205.4[b]
p-*t*-Butylcumene	222–222.5	220[c]
p-*n*-Propylethylbenzene	204	202–206[d]
p-Isobutylethylbenzene	211	210[e]
p-Ethyltoluene[f]	162.5	161–162[g]
p-Cymene[h]	176	177[i]
p-*t*-Butyltoluene[h]	191.5	192–193[j]
p-Bromoethylbenzene[f]	187–188	188–189[k]
Isopropyl bromide[h]	60	59.4[l]
t-Butylbromide[h]	74	73.3[m]
p-Bromocumene[f]	218	216[n]
n-Propylbromide[h]	70	71[l]
Isobutyl bromide[h]	92	91[p]
o-Ethyltoluene[f]	164–165	164.8–165[q]
	M.P.	
p-Toluic acid[h]	180.5	181[r]
Cumic acid[h]	118–119	117–118[s]
p-*t*-Butylbenzoic acid[h]	165.5	164[j]
p-Ethylbenzoic acid	111–112	110–111[t]
o-Toluic acid[h]	104–105	102–103[u]
	n_D	
p-Methylbenzyl methyl ether	1.4991	1.4990[v]

[a] D. Todd, *J. Am. Chem. Soc.*, **71**, 1356 (1949). [b] G. F. Hennion, A. J. Driesch, and P. L. Dee, *J. Org. Chem.*, **12**, 1102 (1952). [c] V. N. Ipatev, N. A. Orlov, and A. D. Petrov, *Chem. Zentr.*, I, 2081 (1930). [d] Ng. Ph. Bun-Hou, Ng. Hoan, and Ng. D. Xuong, *Rec. trav. chim.*, **71**, 285 (1952). [e] O. Wallach, *Ann.*, **414**, 210 (1917). [f] Purchased from Aldrich Chemical Co. [g] F. Richter and W. Wolff, *Ber.*, **63**, 1723 (1930). [h] Purchased from Eastman Kodak Co. [i] K. T. Serijan, H. F. Hipsher, and L. C. Gibbons, *J. Am. Chem. Soc.*, **71**, 873 (1949). [j] P. S. Varma, *J. Indian Chem. Soc.*, **14**, 157 (1937). [k] E. L. Skaw and R. MacCullogh, *J. Am. Chem. Soc.*, **57**, 2439 (1935). [l] R. S. Schwartz, B. Post, and I. Fankuchen, *J. Am. Chem. Soc.*, **73**, 4490 (1951). [m] J. W. Copenhauer, M. F. Roy, and C. F. Marvel, *J. Am. Chem. Soc.*, **57**, 1311 (1935). [n] A. L. Soloman and H. C. Thomas, *J. Am. Chem. Soc.*, **72**, 2028 (1950). [p] K. Auwers, *Ann.*, **419**, 109 (1919). [q] O. Herb, *Ann.*, **258**, 10 (1890). [r] L. Bert, *Bull. soc. chim.*, **37**, 1400 (1925). [s] Org. Synthesis, **Coll. Vol. III**, 822 (1955). [t] M. J. Schlatter and R. D. Clark, *J. Am. Chem. Soc.*, **75**, 361 (1953). [u] R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, p. 250 (1957). [v] C. D. Gutsche and H. E. Johnson, *J. Am. Chem. Soc.*, **77**, 109 (1955).

(4) *Cf.* E. Wertheim, *A Laboratory Guide for Organic Chemistry*, 3rd ed., McGraw-Hill, N. Y., 1948, p. 128.

(5) *Cf.* H. Gilman, N. B. St. John, and F. Schulze, *Org. Syntheses*, **Coll. Vol. II**, Wiley and Sons, N. Y., 1943, p. 425.

(6) D. I. Ligge, *J. Am. Chem. Soc.*, 69, 2088 (1947).

It can be seen that, exclusive of the *t*-butyl groups, the preferential oxidation of these respective alkyl groups decreases in the order, isopropyl, ethyl, methyl. This is the order of increasing electronegativity of the groups and also of the increasing number of *alpha* hydrogens. Hence, to explore further the selectivity shown, groups were chosen which have the same number of *alpha* hydrogens but a third group of varying electronegativity. For example, *p*-isobutylethylbenzene, has a methyl group and an isopropyl group, attached to the *alpha* carbons. In this case, oxidation produced *p*-ethylbenzoic acid. Thus, it appears that the relative ease of oxidation of the alkyl groups, provided there is at least one α-hydrogen atom, is determined by the relative electronegativity of the alkyl groups attached to the *alpha* carbon atoms. To test this idea, *p*-*n*-propylethylbenzene, was oxidized. *p*-Ethylbenzoic acid was obtained, again supporting the idea expressed above. In all cases, mixed melting points and infrared spectra of the oxidation products showed no sign of other *p*-alkylbenzoic acids being present.

The nitric acid oxidations in this study can be summarized as follows:

$$p\text{-}CH_3C_6H_4CH_2CH_3 \longrightarrow p\text{-}CH_3C_6H_4COOH$$

$$p\text{-}CH_3C_6H_4CH(CH_3)_2 \nearrow$$

$$o\text{-}CH_3C_6H_4CH_2CH_3 \longrightarrow o\text{-}CH_3C_6H_4COOH$$

$$p\text{-}R_1\text{—}C_6H_4\text{—}R_2 \longrightarrow p\text{-}R_1\text{—}C_6H_4COOH$$

R_1 = ethyl; R_2 = *n*-propyl, isopropyl, and isobutyl

R_1 = *t*-butyl; R_2 = methyl, ethyl, isopropyl

This generalization about the relative ease of oxidation of carbon-attached side chains only applies to hydrocarbon groups. Once a carbon-oxygen, carbon-nitrogen, or carbon halogen bond is formed, the carbon is easily oxidized. For example, the CH_2OH, CH=O, and CH_2Cl groups are probably much more easily oxidized than alkyl groups in spite of the fact that there are highly electronegative atoms attached to the α-carbon. To test this idea, *p*-methylbenzyl methyl ether was prepared and oxidized with 15% nitric acid. As expected, the product was *p*-toluic acid.

In summary, it can be generalized that 15% nitric acid will oxidize dialkylbenzenes to alkylbenzoic acids, and with groups containing at least one α-hydrogen atom, the relative ease of oxidation increases with decreasing electronegativity of the groups attached to the α-carbon.

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Oxidation of a Secondary Alkyl Tosylate by Dimethyl Sulfoxide

MANUEL M. BAIZER

Received October 29, 1959

In the course of a study of the thermal decomposition of tosylates of secondary alcohols as a route to olefins, we had occasion in one instance to examine the modification reported by Nace.[1] In his procedure dimethyl sulfoxide is used as a medium and sodium hydrogen carbonate is optionally used to protect the olefin formed from the action of the liberated sulfonic acid.

When the tosylate (I) of 1,3-diphenoxy-2-propanol (II) was heated with dimethyl sulfoxide and sodium bicarbonate for six hours at a maximum temperature of 103°, the only product recovered was unchanged starting material. When the reaction temperature was allowed to rise to 150°, 10% of the input of I was recovered as its saponification product II; the remainder was converted to a yellow oil which, after distillation followed by crystallization of the distillate, was found to be 1,3-diphenoxy-2-propanone (III). III showed carbonyl absorption in the infrared; its melting point and that of its 2,4-dinitrophenylhydrazone agreed with the values reported in the literature.[2]

While the oxidation by dimethyl sulfoxide of phenacyl[3] and benzyl halides[4] and of tosylates of benzyl alcohols[5] to aldehydes has been reported,[6] the oxidation of a secondary alkyl tosylate to the corresponding ketone seems not to have been noted before.

Attempts to oxidize II directly by dimethyl sulfoxide were unsuccessful.

EXPERIMENTAL[7]

Dimethyl sulfoxide was obtained from the Stepan Chemical Co. and used without purification.

1,3-Diphenoxy-2-propyl p-toluenesulfonate (I) was prepared from the alcohol and *p*-toluenesulfonyl chloride in pyridine according to the usual procedure. The crude yield was 95%, m.p. 117–119°. After recrystallization from 2-propanol the product melted at 121°.

Anal. Calcd. for $C_{22}H_{22}O_5S$: C, 66.32; H, 5.57. Found: C, 66.08; H, 6.08.

(1) H. R. Nace, *Chemistry & Industry (London)*, 1629 (1958).

(2) J. Munch-Petersen, *Acta Chem. Scand.*, **5**, 519 (1951).

(3) N. Kornblum, *et al.*, *J. Am. Chem. Soc.*, **79**, 6562 (1957).

(4) H. R. Nace, U. S. Patent **2,888,488**, May 26, 1959.

(5) N. Kornblum, *et al.*, *J. Am. Chem. Soc.*, **81**, 4113 (1959).

(6) I. M. Hunsberger and J. M. Tien, *Chemistry & Industry (London)*, 88 (1959) also report the oxidation of ethyl bromoacetate to ethyl glyoxylate and propose a mechanism for the reaction.

(7) Melting points were taken on a Fisher-Johns block and are uncorrected.

Attempted preparation of 1,3-diphenoxy-2-propene. A suspension of 19.9 g. (0.05 mole) I and 4.2 g. (0.05 mole) sodium bicarbonate in 75 ml. dimethyl sulfoxide was stirred vigorously and warmed slowly, so that it reached 90° in 63 min. and 100° in 140 min. Carbon dioxide evolution was fairly brisk beginning at the former temperature. After 4 hr. at 100° the reaction mixture was poured onto ice. The gummy solid was broken up, washed thoroughly with water and dried *in vacuo*, wt. 17.3 g. Recrystallization from 2-propanol yielded unchanged I, melting point and mixture m.p. 121–122°.

Oxidation of I *by dimethyl sulfoxide.* The reaction mixture was prepared as in the experiment above and heated more strongly so that it remained in the range 138–150° for 2 hr. It was then poured onto ice. The precipitated tar was dissolved in benzene and the solution washed several times with water, dried over sodium sulfate and filtered. Evaporation of the benzene at room temperature left 11.6 g. of a brown semisolid residue. Trituration with 2-propanol at room temperature followed by filtration removed 1.2 g. of solid which, after purification, was found to be identical with II. After removal of the propanol from the filtrate, the residual liquid was distilled, b.p. 158–163°/0.30–0.36 mm. Trituration of the distillate with Skellysolve F induced crystallization. The solid after two recrystallizations from 50% 2-propanol melted at 57° (reported[2] 59–60°). The infrared spectrum showed strong absorption at 5.90 μ.

The *2,4-dinitrophenylhydrazone* after recrystallization from ethanol containing a little ethyl acetate melted at 128° (reported[2] 125–126°).

Anal. Calcd. for $C_{21}H_{17}N_4O_6$: N, 13.30. Found: N, 13.96.

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Crystalline Racemic Bornyl Acetate

WILLIAM J. CONSIDINE

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Although optically pure bornyl acetate has long been known to be a low melting solid with a tendency to supercool, nothing is known about the melting behavior of mixtures of the two optical antipodes. A search of the literature uncovered only a statement by Haller[1] that racemic bornyl acetate did not crystallize, even at −17°. Having samples of pure *d*-bornyl acetate and *l*-bornyl acetate available, the melting point behavior of mixtures of the two was investigated.

When a mixture of equal parts of the dextro and laevo isomers was stored in a freezing chest for a week, crystallization occurred to give a solid mass which had a melting point of 7.0°. With this assurance, a series of mixtures was prepared and the melting points taken: % levo isomer (m.p.); 100%, m.p. 27°; 75%, 18.5°; 62.5%, m.p. 12°; 50%, m.p. 7°; 37.5%, m.p. 12°; 25%, m.p. 17.5°, 0% (i.e. 100% dextro isomer), m.p. 26.5°.

A plot of these melting point data gives a symmetrical fusion curve with a single eutectic point demonstrating[2] the formation of a simple conglomerate or racemic mixture. This behavior is to be contrasted with the much more common occurrence of a racemic compound, or, rarely, a solid solution.

EXPERIMENTAL[3]

The *d*-bornyl acetate, [α] + 41.2°, used in this study had a melting point of 26.5° (lit.[1] [α] + 44.38°; m.p. 24°). The *l*-bornyl acetate, [α] − 42.0°, had a melting point of 27.0° (lit.[1] [α] − 44.45°; m.p. 24°). Each sample, and mixture, was originally crystallized by storage in a freezing chest (−10°) for periods up to one week. Thereafter recourse was had to seeding when necessary.

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(1) M. A. Haller, *Comp. rend.*, **109**, 29 (1889).

(2) A. Findlay (ed. Campbell and Smith), *The Phase Rule and Its Applications*, 9th Ed., Dover, New York, 1951, p. 190.

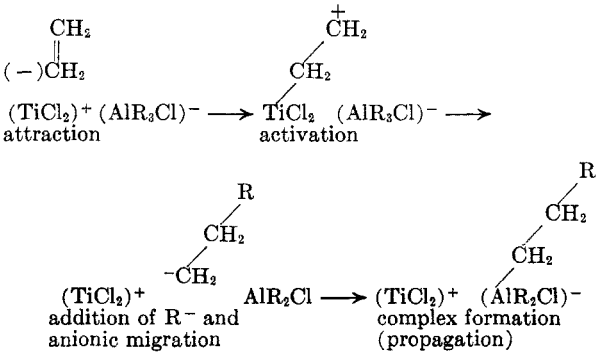
(3) All melting points are uncorrected and rotations (D line) are determined on the supercooled liquid at ambient temperatures. The temperature at which the last crystal disappeared was recorded as the melting point.

Interpretation of Some Reactions on Complex Ionic Bonds[1a]

HEINZ UELZMANN

Received July 16, 1959

The mechanism of olefin polymerization with Ziegler catalysts has been considered to occur on complex ions, such as $(TiCl_2)^+(AlR_3Cl)^-$ from $TiCl_3/AlR_3$, with the direct participation of the cation metal and anion metal.[1b] The initiating step of the polymerization is the activation of the monomer on a cation of a transition element. The second step is the migration of the activated monomer to the anion metal (aluminum for instance, or titanium) which occurs at the moment when the propagation starter (R^-, H^-) neutralizes the cationic transition state of the monomer. The migration can be compared with the addition of a metal alkyl to a Lewis type metal alkyl with the formation of more stable complex ions. The polymerization mechanism of ethylene on $(TiCl_2)^+(AlR_3Cl)^-$ complex is formulated below.



The addition of the propagation starter and the migration of the monomer are concerted reactions.

The principal reasons why this mechanism proceeds are the following:

1. Special activity of transition metal cations for the activation of the monomer (low temperature initiation) can be based on the fact that inner orbitals (3*d*) participate in resonance stabilization of the electrons accepted from the monomer.

2. Migration of the monomer from titanium to aluminum is explained by the formation of a more stable aluminum carbon bond.

3. The addition of the carbanion chain end of the polymer to the cationically activated monomer (propagation) occurs continuously because it is still activated (excited) from the previous migration.

4. Very high molecular weight polymers are obtained because the growing chain end is resonance-stabilized in the complex anion, thus diminishing termination reactions.

The cation can be blocked by electron donors (ethers, amines, etc.) which form more stable coordination complexes with the cation than the monomer does.

The formation of a four valent titanium cation can be expected when titanium tetrachloride and aluminum triisobutyl are allowed to react at −78°. The ionic structure below has been proposed for the red, soluble complex formed under these conditions.[1b,2]

$$TiCl_4 + AlR_3 \xrightarrow[-78°]{} (TiCl_3)^+(AlR_3Cl)^-$$

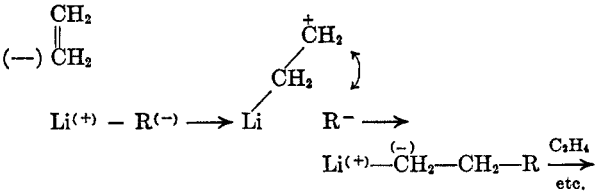
R = isobutyl

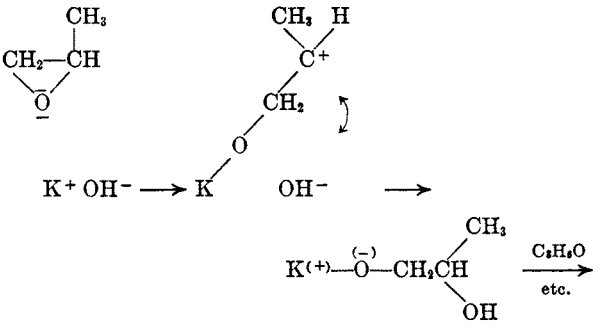
This complex decomposes above −30° yielding $TiCl_3R$ and AlR_2Cl which can form another complex. The driving force for the decomposition in this direction is the formation of a more stable aluminum-chlorine bond.[2]

The ionic nature of the complex solution at −78° has been proven by A. Malatesta[3] in conductivity measurements.

Polymerization on simple and complex ionic bonds. The catalytic site in ionic polymerizations can be a simple or a complex ionic bond.

When a simple ionic bond is involved the polymerization takes place on one metal atom only. Catalysts with simple ionic bonds are, for instance, $Li^{(+)}—R^{(-)}$ or $R_2Al^{(+)}—R^{(-)}$ for ethylene polymerization or K^+OH^-, $Zn(C_2H_5)_2/H_2O$,[4] and strontium carbonate[5] for epoxides





No migration of the monomer, therefore, is likely to occur in a simple ionic mechanism and it can be expected that both activation and propagation proceed on the same metal-oxygen bond (K—O, Zn—O, Sr—O, etc.).

The active site can also be a complex ionic bond which can be represented by a complex acid, such as $H^+(AlBr_4)^-$ for α-olefins (cationic propagation), $H^+(FeCl_2OR)^-$, $H^+(BF_4)^-$ for cyclic ethers, or a complex salt, such as a Ziegler catalyst from $TiCl_3/AlR_3$ for olefins or Price's catalyst $ZnCl_2/Al(OR)_3$ for epoxides.[6] The increase in reactivity by complex formation is generally known[7] and is due to a strong ionic or polarized complex bond on which monomers or other reactive molecules are activated according to their polarization.

In olefin polymerization reactions complex ionic bonds generally offer better control of propagation than simple ionic bonds. The growing chain is more effectively resonance-stabilized as a member of a complex ion than as a simple ion. Therefore, complex catalysts allow the chain to grow longer yield-

(1a) This treatise is based on a paper presented at the Symposium on Stereoregulated Polymerizations at the Polytechnic Institute of Brooklyn, Brooklyn, N. Y., Nov. 22, 1958.

(1b) H. Uelzmann, *J. Polymer Sci.* **32**, 457 (1958).

(2) H. Uelzmann, *J. Polymer Sci.* **37**, 561 (1959). The heat of formation for the aluminum-chlorine bond (based on aluminum chloride) is 55.6 kcal., and for the titanium chlorine bond 44.8 kcal. (based on titanium tetrachloride). However, the heat of formation of titanium-chlorine in titanium trichloride is 55 kcal. and in titanium dichloride 57 kcal. which is close to the aluminum-chlorine value. Weak addition complexes can be expected to be formed, and an equilibrium according to

$$TiCl_2 + AlR_3 \rightleftarrows (TiCl)^+(AlR_3Cl)^-$$

$$TiCl_3 + AlR_3 \rightleftarrows (TiCl_2)^+(AlR_3Cl)^-$$

$$RTiCl_3 + AlR_2Cl \rightleftarrows (RTiCl_2)^+(AlR_2Cl_2)^-$$

$$RTiCl_2 + AlR_2Cl \rightleftarrows (RTiCl)^+(AlR_2Cl_2)^-$$

is possible. The nature of the R group, its stability, polarity, and steric factor is not accounted for in these formulations and will influence the complex formations.

(3) A. Malatesta, paper presented at the Ninth Canadian Polymer Forum, Oct. 26–28, 1959, Toronto, Ontario, Canada.

(4) Junji Furukawa *et al.*, *J. Polymer Sci.*, **36**, 541 (1959).

(5) F. N. Hill, F. E. Bailey, Jr., and J. T. Fitzpatrick, *Ind. Eng. Chem.*, **50**, 5 (1958). Belgian Patent No. 557,766.

(6) C. C. Price and Maseh Osgan, *J. Polymer Sci.*, **34**, 153 (1959). Belgian Patent No. 566,583.

(7) G. Wittig, *Angew. Chem.*, **70**, 65 (1958).

ing high degrees of polymerization. This is particularly true in anionic propagations where the cation or the anion portion of the catalytic bond can be efficiently complexed and where termination reactions by hydride ion abstraction require higher activation energies. In cationic propagations low temperatures are usually required for the formation of long chains in order to avoid proton eliminations or hydride shifts.

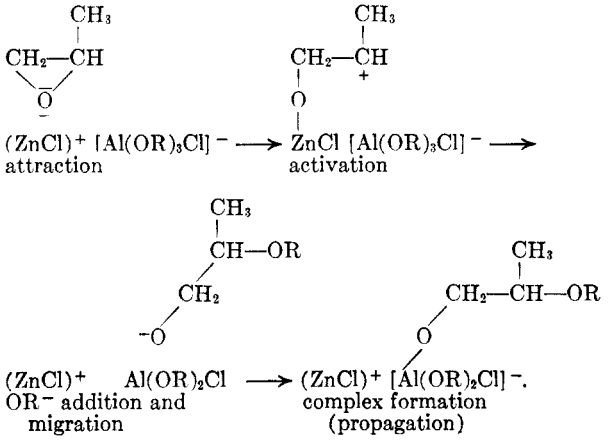
K. Ziegler and co-workers[8] obtained only low molecular weight polyethylenes with aluminum alkyls, but polymers of high molecular weight resulted when these metal alkyls were complexed with compounds of transition elements.

A similarity in structure can be expected between Ziegler catalysts, such as $TiCl_3/AlR_3$, and Price's catalyst $ZnCl_2/Al(OR)_3$. In both cases an electron donor reacts with a Lewis acid to form complex ions with two metal atoms:

$$\underset{\text{donor}}{TiCl_3} + \underset{\text{acceptor}}{AlR_3} \longrightarrow (TiCl_2)^+ (AlR_3Cl)^-$$

$$\underset{\text{donor}}{ZnCl_2} + \underset{\text{acceptor}}{Al(OR)_3} \longrightarrow (ZnCl)^+ (Al(OR)_3Cl)^-$$

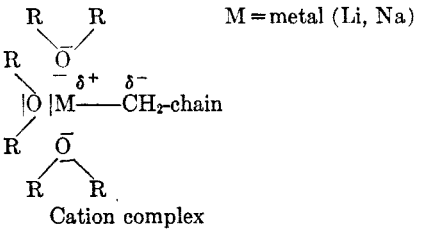
Therefore, it is likely that propylene oxide polymerizes similarly to ethylene when Price's catalyst is used:



The migration of the monomer is comparable to the addition of an alcoholate anion to a Lewis type alcoholate. Other epoxides would polymerize similarly.

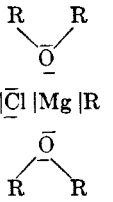
The ionic bond on which the polymerization proceeds offers two possibilities for complexing: the cationic or the anionic part. The mechanism of polymerization and consequently the properties of the resulting polymers can be strongly influenced by either kind of complexing.

Cation complexes. Electron donors, such as ethers or tertiary amines, will react with the cation to form association complexes. The complexing could go so far that the cation completes its outer electron shell to form an octet:



Cation complex

Similar complexes are generally known to be formed by the interaction of Grignard compounds and ethers:



Cation complexes are also formed from lithium or sodium cations and ethers [Szwarc catalysts,[9] Dainton catalysts], or alcoholate and chlorine anions [Alfin catalysts[10]]. The differences in the polymerization of butadiene (or styrene) in the presence or absence of these cation complexes (ether solvents) are generally known. Propagation on an ether-complexed or salt-complexed sodium cation gives usually high molecular weight polymers and promotes stereo-preserving polymerizations [formation of *trans*-1,4-polybutadiene from *trans* conformational monomeric butadiene[1b]]. However, when the energy level of the complexed cation is lower than the energy level required for the activation of the monomer no polymerization will occur. This is possibly the reason why conjugated dienes or styrene but not ethylene or α-olefins can be polymerized with Szwarc-type or Alfin-type catalysts. Since less energy is required for the activation of a conjugated system the complexed cations can activate dienes but not mono-olefins. The same seems to be true for lithium alkyls which normally polymerize ethylene to a certain degree. In the presence of ethers no polymerization of ethylene is observed.

Anion complexes. If the propagation starter (R^-, H^-, OR^-, OH^-) is a member of a Lewis acid it can become a member of a complex anion by adding a negative ion.

$$TiCl_3 + AlR_3 \longrightarrow (TiCl_2)^+ (AlR_3Cl)^- \text{ (olefins)}$$

$$TiCl_3 + TiCl_3R \longrightarrow (TiCl_2)^+ (TiCl_4R)^- \text{ (olefins)}$$

$$ZnCl_2 + Al(OR)_3 \longrightarrow (ZnCl)^+ (Al(OR)_3Cl)^- \text{ (epoxides)}$$

$$R\text{—}OH + FeCl_3 \longrightarrow H^+ (FeCl_3OR)^- \text{ (epoxides)}$$

The activation would be cationic, followed by a migration and anionic propagation of the monomer.

Prerequisites for this type of anionic propagation are:

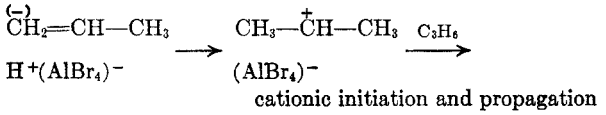
(8) K. Ziegler *et al.*, *Angew. Chem.*, **68**, 721 (1956).

(9) M. Szwarc *et al.*, *J. Am. Chem. Soc.*, **78**, 2656 (1956).

(10) A. A. Morton, *Ind. Eng. Chem.* **42**, 1488 (1950).

1. The cation must always be reformed for the activation of new monomers.
2. The complex anion must contain a propagation starter which neutralizes the cationically activated monomer.
3. The bond of the polymer chain to the metal of the complex anion must be more stable than the bond to the activating cation to assure migration and propagation.

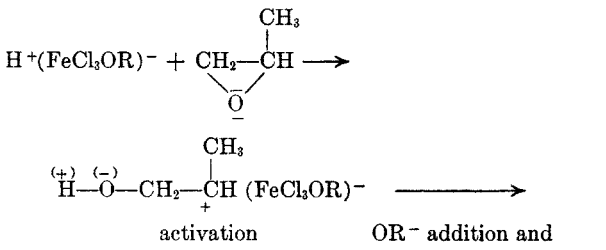
If the afore mentioned prerequisites are not fulfilled the following course of reactions for α-olefins could be concluded. The cation can not be reformed when a complex acid such as $H^+(AlBr_4)^-$ is used because of the elimination of the proton with the formation of a stable methyl group and a rather homopolar bond.

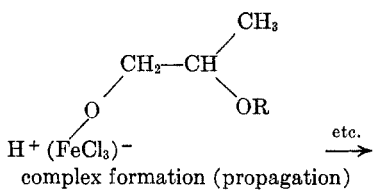


cationic initiation and propagation

The carbonium ion formed allows cationic propagation only. If activated on a metal cation the bond of propylene to the cation is still ionic and allows migration, propagation, and reformation of the metal cation.

Contrary to olefins the anionic polymerization of epoxides by complex acids seems to be possible. The activating proton of the complex acid is not destroyed after the initiation of the monomer because of the formation of an ionizable hydroxyl group.





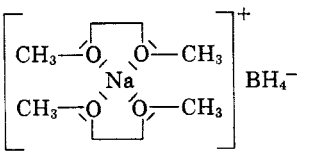
complex formation (propagation)

A cationic propagation would occur if the negative complex ion does not contain a propagation starter which would neutralize the cationically activated monomer. Such a complex acid could be $H^+BF_4^-$. On the other hand $H^+(BF_3OR)^-$ or $H^+(BF_3OH)^-$ could propagate anionically.

Cationic mechanisms with $H^+BF_4^-$ as a catalyst for the polymerization of cyclic ethers are generally known.

Reductions with complex metal hydrides. It can be deduced from the mechanisms discussed in the foregoing section that a similar migration of ionized groups or molecules from one metal to another is much more common in organic chemistry than hitherto expected.

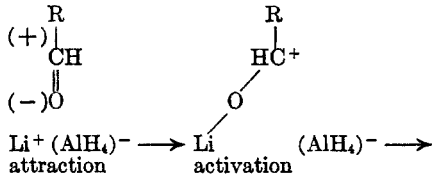
In reduction mechanisms of organic compounds with complex hydrides (lithium aluminum hydride, sodium aluminum hydride, sodium borohydrides, etc.) a direct participation of both the cation metal and anion metal would explain why there can be differences in reactivities when the cation metals are changed. H. C. Brown and co-workers[11] found that lithium borohydride reduces ester groups but sodium borohydride does not. Since different cations also differ in energy levels or steric factors their participation in the reduction mechanism as the initiating or activating site (attracting negatively polarized atoms, such as oxygen, nitrogen) explains their deviating behavior and selectivity in the above-mentioned complex ions. A reaction mechanism which proceeds solely on the complex anion allows no interpretation of this phenomenon. As already discussed the energy level of the cation can be modified additionally by the formation of coordination complexes with solvents which act as electron donors (ethers, amines). H. C. Brown *et al.*[11] have found that sodium borohydride in ethyleneglycol dimethylether reduces aldehydes but not ketones. It can be assumed that the sodium cation forms a coordination complex (octet formation) with the ether:

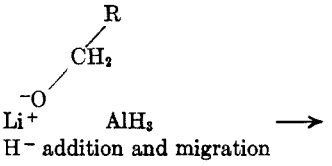


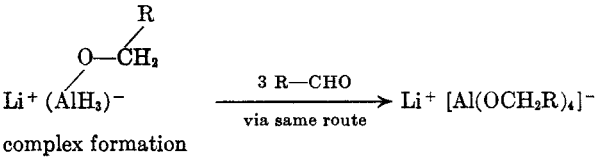
The activity of the sodium cation is decreased to such an extent that it can still activate aldehydes but not ketones. The latter apparently require higher activation energies than aldehydes and are more sterically hindered. The complete mechanism of the reduction of an aldehyde by lithium aluminum hydride is explained by the sequence of reactions shown below.

The negatively polarized oxygen atom, as the most exposed reactive atom of the aldehyde, is attracted and activated by the cation with the formation of a lithium-oxygen bond and a carbonium ion (cationic transition state). A hydride ion adds to the carbonium ion and the resulting alcoholate ion migrates and adds to the aluminum. The driving force is the reformation of stable complex ions. Here the migration compares with a simple addition of lithium alcoholate to AlH_3:

(11) H. C. Brown, Lecture series "Frontiers in Chemistry," April 24, 1959, Western Reserve University, Cleveland, Ohio.







It can be expected that many other reactions of complex ionic bonds follow a similar mechanism, particularly in those cases where exposed reactive atoms are negatively polarized and, therefore, are subject to a cationic activation.

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