Notes

Reactions of Enamines. IX. Benzoylation of 1-Ethyl-2-methylene-1,2-dihydroquinoline[1]

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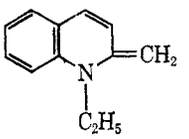
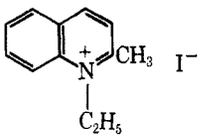
The methylene base I[2,3] obtained by treatment of quinaldine ethiodide (II) with strong aqueous sodium hydroxide has been shown to undergo many reactions characteristic of an enamine.[3,4] Our attention was

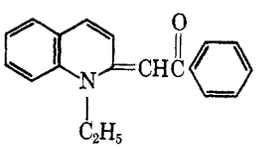


I

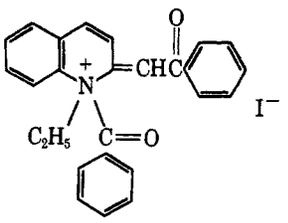


II

drawn to a report[5] that benzoylation of II under Schotten–Baumann conditions[6] gave a salt isolated as the iodide with elemental analyses corresponding most closely to $C_{26}H_{22}INO_2$. On the basis of the empirical formula and its easy hydrolysis to III, the compound was assigned structure IV.



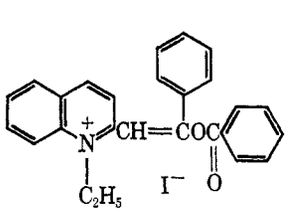
III



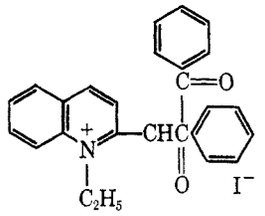
IV

It seemed to us in view of the well-known acylation reactions of enamines[7,8] and enamino ketones[8,9] that structure IV was probably not correct. Presumably the reaction proceeded by benzoylation of the enamine I to the enamino ketone III and by further benzoylation of III to give the isolated compound. Structures V and VI which correspond to O- and C-benzoylation of III are in better accord with the known behavior of enamino ketones.

On repeating the previous work a compound having the reported properties was isolated and elemental analysis confirmed the empirical formula $C_{26}H_{22}INO_2$. The compound showed infrared absorption at 5.72 μ consistent with the carbonyl absorption of an enol ester. An enol ester structure is also in accord with the previously noted facile acid hydrolysis. The compound may, therefore, be assigned structure V. Structure VI or its enol may be excluded as they would be expected to exhibit infrared carbonyl absorption above 6 μ and to resist acid hydrolysis.



V



VI

The intermediacy of III in the formation of V from II was established by benzoylation of III by 1 mole of benzoyl chloride to give a hygroscopic salt which was converted to V by treatment with sodium iodide. This product was identical with the benzoylation product of II under Schotten–Baumann conditions. Thus it appears that II is indeed converted to the enamino ketone III which then undergoes further benzoylation.[10]

Experimental Section[11]

Reaction of Quinaldine Ethiodide with Benzoyl Chloride and Base.—Quinaldine ethiodide (10.0 g, 0.0335 mole) in water (50 ml) was treated successively with 200 ml of 4% sodium hydroxide solution and 9.4 g (0.067 mole) of benzoyl chloride keeping the temperature below 20° by external cooling. The reaction mixture was stirred vigorously for 2 hr and allowed to stand overnight. The tarry solid which had separated was allowed to settle and the aqueous layer was removed by decantation. The solid was taken up in 30 ml of glacial acetic acid and a solution of 10 g of sodium iodide in 20 ml of water was added. Addition of water induced a yellow-green solid to crystallize which was removed by filtration and washed with ethanol to give 5 g of V: mp 195–197° dec. Recrystallization from ethanol gave analytically pure V as gold-yellow plates: mp 200–202° dec; λ_{max}^{EtOH} 361 mμ (ϵ 26,500), 245 mμ (ϵ 39,000) (sh) at 298 mμ (ϵ 9000). The nmr spectrum in trifluoracetic acid showed absorption at τ 8.08 (3 H, triplet), τ 4.70 (2 H, quadruplet), and between τ 2.65 and 1.00 (17 H, complex series of multiplets). The compound showed carbonyl absorption at 5.72 μ in the infrared.

Anal. Calcd for $C_{26}H_{22}INO_2$: C, 61.55; H, 4.37; I, 25.01; N, 2.76. Found: C, 61.37; H, 4.36; I, 25.12; N, 2.80.

Vongerichten and Rotta[5] reported mp 197° but no satisfactory analysis.

Acid Hydrolysis of V.—Compound V (2.5 g, 0.005 mole) was heated under reflux with 125 ml of concentrated hydrochloric acid for 1 hr. The reaction mixture was extracted with three 50-ml portions of ether giving 600 mg (98%) of benzoic acid, mp and mmp 122°. The aqueous layer was made alkaline with ammonia. The precipitated yellow solid was isolated by filtration and crystallized from ethanol to give 800 mg of III as yellow plates: mp 137–139° (lit.[5] mp 139°). The nmr spectrum in deuteriochloroform showed absorption at τ 8.57 (3 H, triplet), τ

(1) Part XIII: G. H. Alt and A. J. Speziale, *J. Org. Chem.*, in press.
(2) E. Vongerichten and C. Höfchen, *Ber.*, **41**, 3054 (1908).
(3) F. M. Hamer, R. J. Rathbone, and B. S. Winton, *J. Chem. Soc.*, 954 (1947).
(4) M. Coenen, *Angew. Chem.*, **61**, 11 (1949).
(5) E. Vongerichten and W. Rotta, *Ber.*, **44**, 1419 (1911).
(6) C. Schotten and E. Baumann, *ibid.*, **19**, 3218 (1886).
(7) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
(8) S. Hünig, E. Benzing, and E. Lücke, *Ber.*, **90**, 2833 (1957).
(9) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **29**, 798 (1964).
(10) The only other reported case of O-acylation of an enamino ketone is that of Hünig, *et al.*, ref 8.
(11) Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were taken on Perkin-Elmer Infracord Model 137 in chloroform solution. Ultraviolet spectra were taken with a Beckman DK2A spectrophotometer in ethanol solution. Nmr spectra were taken with a Varian A-60 instrument in the solvent stated using tetramethylsilane as internal standard.

5.86 (2 H, quadruplet), τ 4.05 (1 H, singlet), and between τ 2.95 and 1.95 (11 H, complex series of multiplets). The compound showed carbonyl absorption at 6.15 μ in the infrared.

Benzoylation of III.—The enamino ketone III (1.4 g, 0.005 mole) in chloroform (10 ml) was treated with benzoyl chloride (0.8 g, 0.0057 mole) at reflux temperature for 30 min. Evaporation of the chloroform gave a hygroscopic, tarry residue which was taken up in a minimum amount of glacial acetic acid and treated with a concentrated solution of sodium iodide. On standing, 1.2 g (48%) of V, mp 197–199° dec, crystallized. The melting point was not depressed on admixture with authentic material above.

Acknowledgment.—Thanks are due to Dr. A. J. Speziale for many helpful and stimulating discussions.

Intramolecular Cyclization of N-Formyl-1-carboxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

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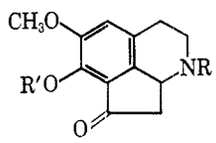
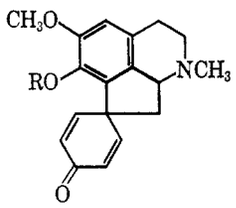
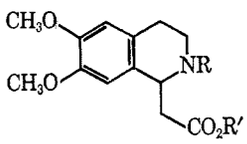
The announcement[2] of the total synthesis of the spirodienone alkaloid pronuciferin, utilizing an intermediate of type I (R = R′ = CH_3), prompts this report of an independent effort to prepare derivatives of the tricyclic ketone I.



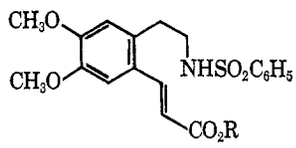
Ia, R = CHO; R′ = CH_3
b, R = CHO; R′ = H



pronuciferin, R = CH_3
glaziovine, R = H



IIa, R = H; R′ = C_2H_5
b, R = $SO_2C_6H_5$; R′ = H
c, R = $SO_2C_6H_5$; R′ = C_2H_5
d, R = CHO; R′ = C_2H_5
e, R = CHO; R′ = H



IIIa, R = C_2H_5
b, R = H

Initial attempts to cyclize 1-carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIa) with concentrated sulfuric acid or polyphosphoric acid gave only amphoteric water-soluble products. Cyclization of the benzenesulfonamide IIc with sulfuric acid was attempted, but the only products isolated were the cinnamic acid derivatives IIIa and b, resulting from β elimination. Assignment of structure to IIIa and b was based on elemental analyses, the presence of extended ultraviolet absorption relative to IIa and b, infrared bands corresponding to N–H and conjugated carbonyl stretching vibrations, and the presence of olefinic proton absorption in the nmr spectra. Intramolecular acylation of the acid chloride of IIb, using aluminum chloride or stannic chloride, was also unsuccessful.

However, cyclization could be effected by using the N-formyl derivatives IId or e. Treatment of either IId or e with polyphosphoric acid at 90–100° produced the ketone Ia. Longer reaction times and higher temperatures brought about selective ether cleavage to the monophenol Ib. The lack of sharp O–H absorption in the infrared spectrum of Ib is a familiar property of *o*-hydroxy aryl ketones, and there is ample precedent for selective cleavage of a methoxyl group adjacent to a carbonyl.[3] Methylation of Ib with diazomethane gave Ia.

Further transformations toward the proaporphine skeleton were discontinued because of the close similarity of this approach to the published synthesis. Compounds Ia and b appear well suited for elaboration, using Bernauer's method, to a variety of N- and O-substituted relatives of pronuciferin, or other alkaloids of this series, particularly glaziovine.[4]

Experimental Section

1-Carboxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Benzenesulfonamide (IIb).—1-Carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIa)[5] (3.00 g) was dissolved in a 10% solution of potassium hydroxide in 25 ml of 2:1 dioxane–water; the solution was refluxed for 3 hr. Excess benzenesulfonyl chloride was added to the cooled solution and the mixture was shaken for several minutes. The mixture was acidified with 1:1 hydrochloric acid and kept for 3 days at room temperature. The colorless sulfonamide was collected; it weighed 1.30 g (26.6%), mp 168–172°. Three recrystallizations from benzene gave the pure sulfonamide, mp 171–172°, λ_{max} 285 mμ.

Anal. Calcd for $C_{19}H_{21}NO_6S$: C, 58.29; H, 5.41; N, 3.58; S, 8.20. Found: C, 58.55; H, 5.49; N, 3.45; S, 7.95.

1-Carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Benzenesulfonamide (IIc).—To 3.00 g of IIa in 8 ml of pyridine was added 2.5 g of benzenesulfonyl chloride. The solution was kept at room temperature for 15 min, cooled, poured into water, and extracted with ether (3 × 25 ml). The combined extracts were washed with 5% hydrochloric acid. Addition of ice-cold brine caused immediate precipitation of the colorless sulfonamide (3.46 g), mp 70–75°. Recrystallization from absolute ethanol gave pure material, mp 90.5–91.5°, ν 1710 cm.$^{-1}$

Anal. Calcd for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.00; N, 2.99; S, 7.66. Found: C, 59.89; H, 6.03; N, 3.19; S, 7.80.

Benzenesulfonamide of Ethyl 3,4-Dimethoxy-6-(β-aminoethyl)-cinnamate (IIIa).—Benzenesulfonamide IIc was prepared as before, and the crude product (3.53 g) was added directly to 20 ml of concentrated sulfuric acid. After 10 min at room temperature the mixture was cautiously poured into 200 ml of water, depositing a white oil. The mixture was made basic with 20% sodium hydroxide and extracted with ether (3 × 100 ml). The extracts were dried over sodium sulfate and concentrated *in vacuo*, leaving a colorless oil. Trituration with absolute ethanol gave the crystalline ester IIIa (0.34 g, 7.5%), mp 147–151°. Three recrystallizations from ethanol gave the pure ester: mp 152.5–153°; λ_{max} 297, 232 mμ; ν 1690, 3230 cm^{-1}.

Anal. Calcd for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.00; N, 2.99; S, 7.66. Found: C, 60.17; H, 6.12; N, 3.20; S, 7.79.

Benzenesulfonamide of 3,4-Dimethoxy-6-(β-aminoethyl)cinnamic Acid (IIIb).—The alkaline layer remaining in the above preparation was acidified with concentrated hydrochloric acid to give an oily, white solid. Trituration with absolute ethanol gave 1.80 g (43%), mp 199–203°. Recrystallization from absolute

(1) Public Health Service Predoctoral Fellow, 1963–1965.
(2) K. Bernauer, *Experientia*, **20**, 380 (1964).
(3) (a) G. C. Morrison and J. Shavel, Jr., *J. Org. Chem.*, **29**, 2486 (1964); (b) S. Karady, *ibid.*, **27**, 3720 (1962); (c) R. H. F. Manske and H. L. Holmes, *J. Am. Chem. Soc.*, **67**, 97 (1945); (d) A. Brossi, F. Schenker, and W. Leimgruber, *Helv. Chim. Acta*, **47**, 2089 (1964).
(4) B. Gilbert, M. Gilbert, M. M. DeOliverira, O. Ribeiro, E. Wenkert, B. Wickberg, U. Hollstein, and H. Rapoport, *J. Am. Chem. Soc.*, **86**, 694 (1964).
(5) We are indebted to Dr. A. Brossi of Hoffmann-La Roche, Inc., Nutley, N. J., for a generous sample of this compound.

ethanol gave the analytical sample: mp 203.5–205°; λ_{max} 295, 328 mμ; ν 1695, 3230 cm^{-1}.

Anal. Calcd for $C_{19}H_{21}NO_6S$: C, 58.29; H, 5.41; N, 3.58; S, 8.20. Found: C, 58.36; H, 5.51; N, 3.43; S, 8.42.

N-Formyl-1-carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IId).—Compound IIa (27.93 g) was mixed with 350 ml of ethyl formate and heated under reflux for 1 hr. Removal of the solvent under reduced pressure left the N-formyl derivative as a yellow oil which readily crystallized. Trituration with ether gave a pale yellow solid (28.03 g, 91%), mp 104–107°. The colorless analytical sample, obtained by recrystallization from ether, had mp 107.5–108°; λ_{max} 285 mμ; ν 1725, 1655 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.55; H, 6.97; N, 4.53.

N-Formyl-1-carboxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIe).—To a solution of IId (10 g) in 75 ml of 50% aqueous ethanol was added 7.5 g of potassium hydroxide, and the solution was refluxed for 30 min. The solution was cooled, diluted with 200 ml of water, and washed with chloroform, then acidified with 30% sulfuric acid, and saturated with sodium chloride. Extraction with chloroform (3 × 50 ml) and concentration of the extracts gave a viscous oil which slowly solidified (5.3 g, 58%). Three recrystallizations from absolute ethanol gave a pure sample of IIe: mp 153–155° with gas evolution; λ_{max} 285 mμ; ν 1740, 1625 cm^{-1}.

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.11; H, 6.18; N, 5.00.

1-Formyl-1,2,3,7,8,8a-hexahydro-5,6-dimethoxy-7-oxocyclopent[*ij*]isoquinoline (Ia). A.—A mixture of IId (5.00 g) in 50 g of polyphosphoric acid was stirred and heated at 100–110° for 80 min. The red-brown solution was cooled, decomposed with ice, and extracted with chloroform (4 × 50 ml). The extracts were dried over sodium sulfate, filtered through charcoal, and concentrated at reduced pressure. The residue was dissolved in 50 ml of benzene and stirred for 10 min with 3 g of alumina, then filtered, and concentrated. The residue was recrystallized from benzene–heptane to afford 0.20 g (4.7%) of a pale yellow solid, mp 138–144°, whose infrared spectrum was identical with that of the ketone prepared in part B.

B.—A solution of 100 mg of Ib in 20 ml of a 1:1 mixture of benzene and tetrahydrofuran was warmed while an ethereal solution of diazomethane was added over 15 min. Most of the solid material dissolved during the addition. The solvents were evaporated in a stream of nitrogen, and the light brown residue was recrystallized from benzene–heptane. The pale yellow plates of Ia (0.05 g), mp 145–146°, were recrystallized twice more to give the analytical sample: mp 146–147°; ν 1705, 1655 cm^{-1}; λ_{max} 236, 263, 346 mμ.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.44; H, 5.93; N, 5.15.

1-Formyl-1,2,3,7,8,8a-hexahydro-5-methoxy-6-hydroxy-7-oxocyclopent[*ij*]isoquinoline (Ib).—A mixture of 1.00 g of IId and 10 g of polyphosphoric acid was heated at 140–150° for 30 min. The red-brown solution was poured over ice and extracted with chloroform. The orange extracts were dried over sodium sulfate, filtered through charcoal, and concentrated, yielding an oil which readily crystallized. The solid was washed with a few milliliters of benzene, leaving 170 mg (21%) of light brown ketone. Recrystallization from benzene–heptane gave the analytical sample: mp 203–205° dec; λ_{max} 265, 344 mμ; ν 1722, 1651 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.08; H, 5.43; N, 5.50.

Heating the acid IIc in polyphosphoric acid at 90–100° for 16 hr and working up as described gave a 2% yield of Ib.

On the Decomposition of Hindered Quinone Methides

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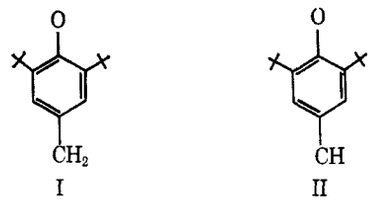
The esr spectrum of a 3,5-di-*t*-butyl-*p*-quinone methide has previously been interpreted by Coppinger, *et al.*,[1,2] to consist of equal parts of two free-radical species One is a triplet of triplets with approximate splitting constants of 9 and 2 gauss. These are said to represent the partial structures I and II. Our interest

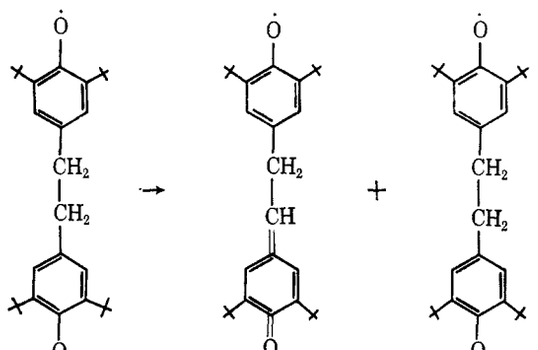


I II

in the reaction mechanisms of polymerization inhibitors[3–6] and the revival[7] of an earlier proposal[8] that the 2,6-di-*t*-butyl-4-methyl phenoxyl radical rearranged to form the 3,5-di-*t*-butyl-4-hydroxybenzyl radical has prompted a repetition of the above experiment.

The esr spectra obtained from varied concentrations of quinone methide indicate that the interpretation leading to radical II was an error which was probably due to low signal/noise ratio.

For the 0.25 *M* solution of 3,5-di-*t*-butyl-*p*-quinone methide, Figure 1 shows only a triplet of triplets with splitting constants of 7.67 and 1.67 gauss. From the experimental splittings in several phenoxy radicals,[9] it is reasonable to assign this spectrum, "A," to structure I in agreement with Coppinger. However, it is interesting that partial structure I can include such forms as the ones that are shown below (III–V).



III IV V

These should give nearly identical spectra since the π systems in the biradical III may be treated as separate entities.[9] Of course, esr cannot differentiate between any of these, but the presence of III is strongly inferred from a series of experiments by Neureiter.[10] Hydrogen abstraction from IV and/or III by V and/or III could lead to the final products, VI, 3,3′,5,5′-tetra-*t*-butylstilbene-4,4′-quinone, and VII, 1,2-bis(3,5-di-*t*-butyl-4-hydroxyphenyl)ethane. This step is suggested from experiments by Brodskii, *et al.*,[7] who found that

(1) G. M. Coppinger, *J. Am. Chem. Soc.*, **86**, 4385 (1964).
(2) R. H. Bauer and G. M. Coppinger, *Tetrahedron*, **19**, 1201 (1963).
(3) R. H. Hoskins and B. R. Loy, *J. Chem. Phys.*, **28**, 2461 (1955).
(4) R. H. Hoskins, *ibid.*, **25**, 788 (1956).
(5) R. H. Hoskins, *ibid.*, **23**, 1975 (1955).
(6) R. H. Hoskins and B. R. Loy, unpublished Dow Chemical report, PRL No. 54126-3.
(7) A. I. Brodskii, V. D. Pokhodenko, and L. N. Ganyuk, *Roczniki Chemii*, **38**, 105 (1964).
(8) C. D. Cook, N. G. Nash, and H. R. Flanagan, *J. Am. Chem. Soc.*, **77**, 1783 (1955).
(9) See, for example, "Free Radicals," D. J. E. Ingram, Ed., Academic Press Inc., New York, N. Y., 1958, p 230.
(10) N. P. Neureiter, *J. Org. Chem.*, **28**, 3486 (1963).

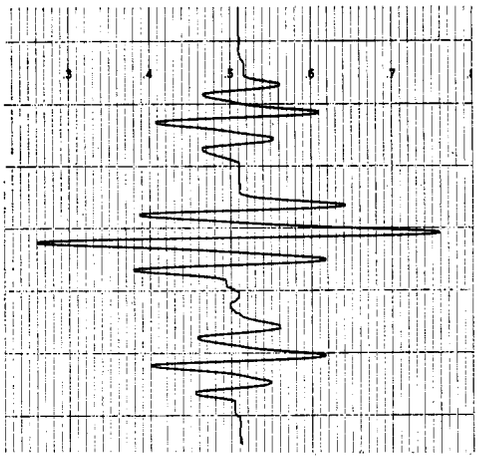


Figure 1.—Solution (0.25 M) of 3,5-di-t-butyl-p-quinone methide in carbon disulfide containing 3×10^{-5} M radicals represented by structure I. Splitting constants are 1.67 and 7.67 gauss.

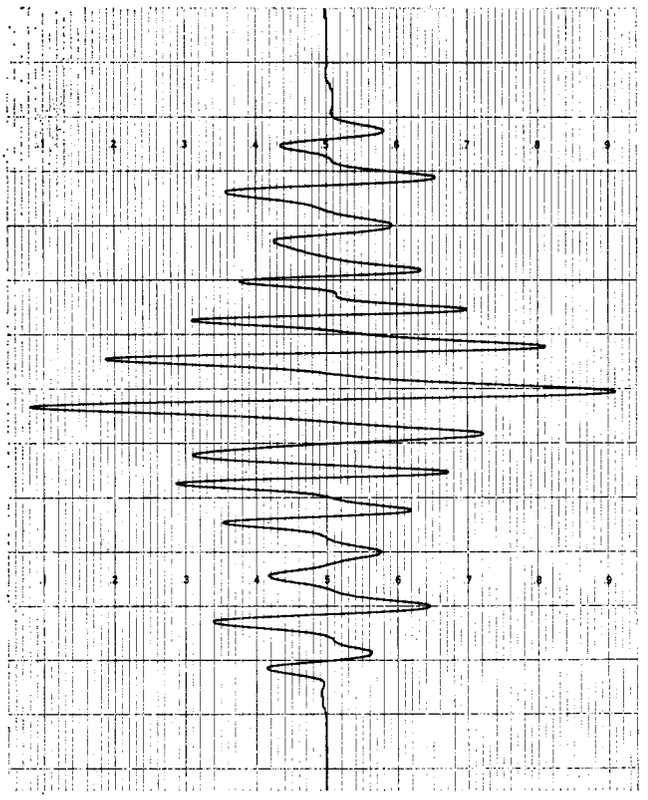
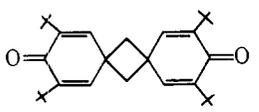


Figure 2.—Solution (0.10 M) of 3,5-di-t-butyl-p-quinone methide in carbon disulfide. Approximately 10^{-5} M in free radicals. Contains I plus galvinoxyl radical.

the phenolic-OD group in the parent 2,6-di-t-butyl-4-methyl phenol was replaced by OH in the oxidation product VII.

The experiments of Chandross and Kreilick[11] indicate that III would probably be in equilibrium with the internally dimerized structure that is shown below.



From a 0.1 M solution of the quinone methide, the spectrum shown in Figure 2 was found. This spectrum

(11) E. A. Chandross and R. Kreilick, *J. Am. Chem. Soc.*, **85**, 2530 (1963).

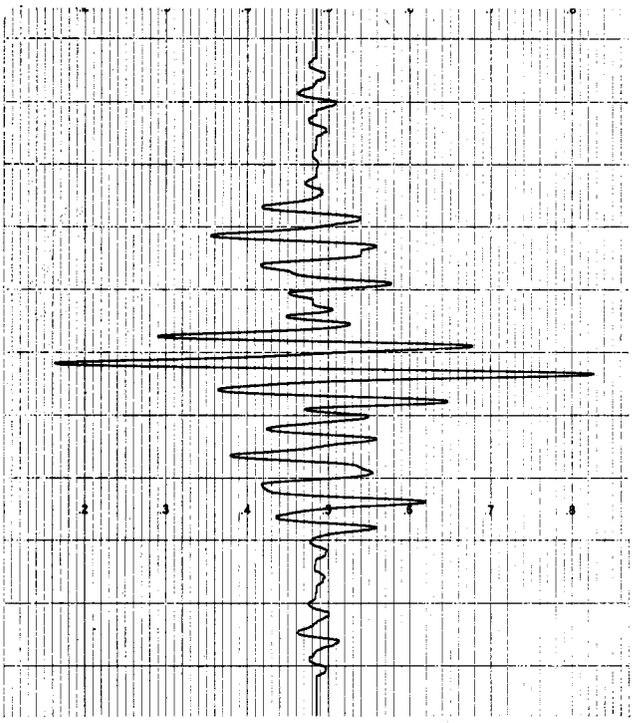


Figure 3.—All of the free radicals normally encountered in the (HgO in CS_2) oxidation of the parent phenol are present in this 0.05 M CS_2 solution of the quinone methide.

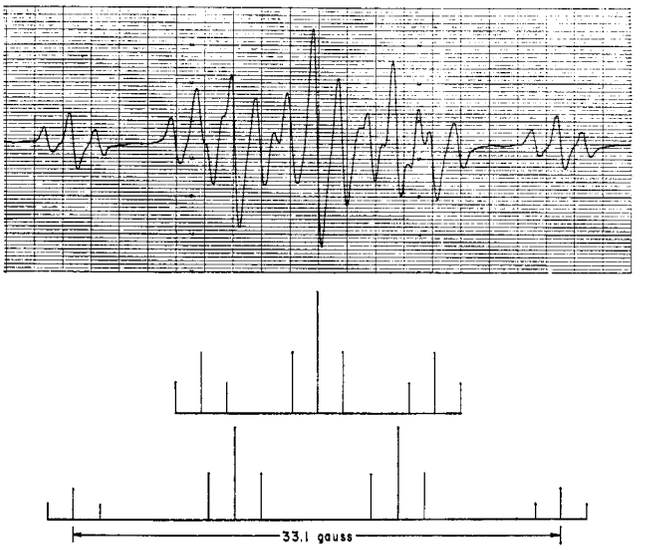


Figure 4.—Esr of reaction mixture during the (HgO–CS_2) oxidation of 2,6-di-t-butyl-4-methyl phenol shows primarily the 2,6-di-t-butyl-4-methyl phenoxyl radical and the radical in Figure 1.

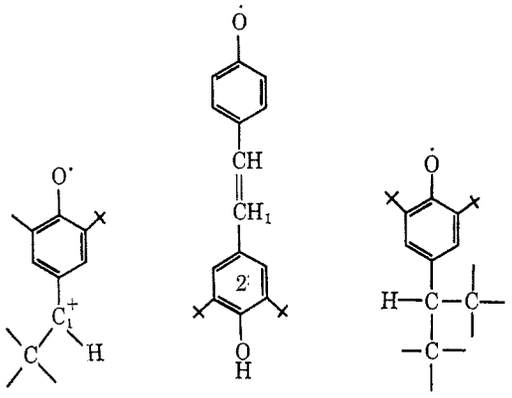
was also simulated by a computer program for summing gaussian lines which plotted the spectrum "A" plus another spectrum called "B," which is a pair of quintets with relative intensities of 1:4:6:4:1, splitting constants of 5.66 and 1.34 gauss and a line width of 0.4 gauss. The relative concentration of A/B is 1.7/1. "B" has been previously identified by Becconsall, *et al.*, to be the galvinoxyl radical,[12] which is relatively stable in this reaction media and may be ignored as an active intermediate.

Figure 3 shows the esr spectrum of a 0.05 M solution of the quinone methide. One recognizes that the pair

(12) J. K. Becconsall, S. Clough, and G. Scott, *Trans. Faraday Soc.*, **56**, 461 (1960).

of triplets, located at the extrema of the spectrum and which are 33.6 gauss apart, belong to the 2,6-di-*t*-butyl-4-methyl phenoxyl radical.[12] This is a quartet of triplets with splittings of 11.2 and 1.67 gauss and a line width of 0.53 gauss and is referred to as spectrum "C." Thus, Figure 3 is comparable to a computer simulated spectrum with relative concentrations A/B/C of 3.5/1.1/1. Figure 3 leaves no doubt that the phenoxyl radical is present even though its presence is difficult to explain except perhaps by the principle of microscopic reversibility. If one examines the spectrum shown in ref 1 it is apparent that, because of the poor signal–noise ratio, the "pair" of triplets was probably the two center triplets belonging to the phenoxyl radical.

Therefore, it is unlikely that II is a radical intermediate in the decomposition of the quinone methide. Further difficulties arise when one inquires about the nature of II. Possibly more complete structures include VIII–X.



VIII IX X

If VIII, then C_1 is sp^3 and only ring hydrogens will contribute to hyperfine splitting (hfs).[12,13] If IX, then H_1 and ring (2) hydrogens will contribute to hfs. X would produce the "observed" hfs but such a structure is unlikely.

In summary, one concludes that spectrum A is always noted in the decomposition of the quinone methide. B and C are present occasionally but these are identified as radicals which are not likely to be primary participants. A may be identified as the partial structure I[1] which in turn may represent the three structures III, IV and IV. Esr cannot distinguish between these but in view of known reactions,[7,10] it is likely that all three are present.

Perhaps, it is worthwhile to report that spectrum A has also been recorded during the oxidation of the parent phenol. Figure 4 was recorded after 131 min of reaction with mercuric oxide in carbon disulfide solution. The components are unambiguously interpreted to be equal parts of A and C.

Experimental Section

Preparation of 2,6-Di-*t*-butyl-4-bromomethylphenol (XI).—2,6-Di-*t*-butyl-4-methyl-4-bromo-2,5-cyclohexadienone, prepared after Coppinger and Campbell,[14] was heated in an evacuated, sealed Pyrex tube for 10 min at 100°. The nmr spectrum of the product dissolved in carbon disulfide showed the OH and CH_2Br peaks at τ 4.89 and 5.64 and indicated complete conversion to the benzyl bromide.

4-Methylene-2,6-(Di-*t*-butylcyclohexa-2,5-dienone (Quinone Methide).—After Filar and Winstein,[15] equivalent amounts of XI and triethylamine in carbon disulfide were mixed in the absence of air and filtered into a Varian sample tube. The nmr sample tube was welded to one end of a medium porosity Pyrex filter tube and a 4-mm glass tube fitted with a syringe cap was welded to the other end. The benzyl bromide solution was added through the syringe cap and frozen with liquid nitrogen. The triethylamine solution was similarly added. The argon atmosphere, which was previously added, was evacuated with a vacuum pump and the 4-mm glass tube was flame sealed. The contents were allowed to melt, shaken for 1 min at approximately −10°, and filtered by cooling the nmr tube in a Dry Ice bath. Finally the contents were frozen in liquid nitrogen while the nmr tube was flame sealed. The nmr spectrum was similar to that reported in ref 10 and indicated quantitative conversion to the quinone methide. In the case of the more concentrated solution (0.25 *M*), the radical (Figure 1) appeared to be in a steady-state concentration for about 3 hr and finally tailed off to a negligible concentration after 4 hr.

Oxidation of 2,6-Di-*t*-butyl-4-methylphenol (XII).—The mixture (0.0060 g of XII, 0.0250 g of mercuric oxide, and 0.18 ml of carbon disulfide) was sealed in a 4-mm Pyrex tube and examined in the esr spectrometer at 102° over a period of 24 hr. A similar mixture was prepared for nmr mesurements using the filtreing device described above. After 24 hr at 100° the hot mixture was filtered into the nmr tube. There was no precipitate formed after cooling to room temperature. The nmr spectrum of the filtrate showed the filtrate to be two parts VI and one part VII.

Instrumental.—The nmr[16] and esr[17] have been previously described.

Acknowledgments.—The author wishes to thank Dr. E. B. Baker for the use of the nmr spectrometer as well as Professor Earl Huyser and Dr. Corwin Bredeweg for helpful discussions. He also wishes to thank the reviewer for calling the work of Chandross and Kreilick[11] to his attention.

(13) E. J. Burrell, Jr., *J. Am. Chem. Soc.*, **83**, 574 (1961).
(14) G. M. Coppinger and T. D. Campbell, *ibid.*, **75**, 734 (1953).
(15) L. J. Filar and S. Winstein, *Tetrahedron Letters*, **No. 25**, 9 (1960).
(16) E. B. Baker and L. W. Burd, *Rev. Sci. Instr.*, **28**, 313 (1957).
(17) B. R. Loy and C. R. Noddings, *J. Catalysis*, **3**, 1 (1964), and references cited therein.

A New Preparation of 4-(*p*-Tolyl)-1,2-dithiole-3-arylimines

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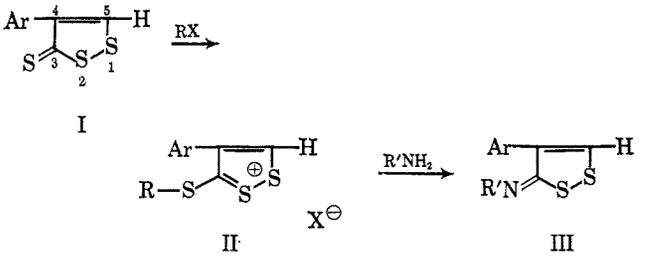
Trithionium salts (II), formed by the reaction of alkyl halides with 1,2-dithiole-3-thiones (I), react with amines to yield the 3-imines (III) and a mercaptan.[2a]



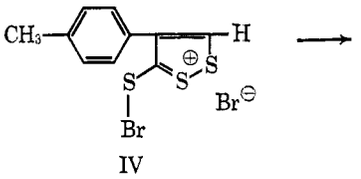
I II III

(1) Arapahoe Chemicals Inc., Boulder, Colo.
(2) (a) A. Luttringhaus and U. Schmidt, *Chem.-Ztg.*, **77**, 135 (1953); see *Chem. Abstr.*, **47**, 4836a (1953); (b) W. R. Diveley, K. Brack, and A. D. Lohr, *J. Agr. Food Chem.*, **12**, 251 (1964).

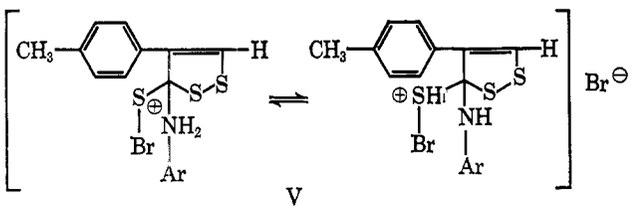
On the other hand, the 4-(*p*-tolyl)-1,2-dithiole-3-thione hydrobromide gave only trithione upon addition of aniline, and the trithione reacted very slowly with aniline in refluxing benzene solution. Direct refluxing with aniline opened the dithiole ring to provide materials that absorb in the 3.0-μ region.

The types of halogenated derivatives formed from trithiones depend on the solvent and the halogen. Chlorination in refluxing chloroform gives a 3,3,5-trichlorodithiole,[2b] whereas in acetic acid the 3,3-dichlorodithiole and a monochloro intermediate are formed.[3] Bromine and iodine trithione adducts have also been reported.[4]

In the work reported here, the room-temperature addition of 1 mole of bromine in carbon tetrachloride or benzene solution to 4-(*p*-tolyl)-1,2-dithiole-3-thione quantitatively precipitated a tan, high-melting solid. The solid did not absorb in the 8.9-μ region, evidence for reaction at the thiocarbonyl group. Isolation of trithione by aqueous acetic acid hydrolysis of the solid showed that the thione sulfur atom remained attached during the bromination. Reaction of the solid with primary aryl amines gave the 3-imines. Assuming that the solid is the bromotrithionium bromide IV, V was formed by addition of the amine. Loss of hydrogen bromide and sulfur yielded the imine hydrobromide. Aliphatic amines produced intractable tars.



IV



V

Experimental Section

Nuclear magnetic resonance spectra were measured at 52 Mc with a Varian Associates DP-60 spectrophotometer, with tetramethylsilane as internal standard.

4-(*p*-Tolyl)-1,2-dithiole-3-anil.—A solution of 2.24 g (0.010 mole) of 4-(*p*-tolyl)-1,2-dithiole-3-thione in 75 ml of carbon tetrachloride was treated with 1.70 g (0.0106 mole) of bromine dissolved in 25 ml of carbon tetrachloride. The tan solid that formed was collected, washed with carbon tetrachloride and pentane, and mixed with 10 ml of aniline; then ether was added. The ether-insoluble salt was collected and hydrolyzed with water, and the product was dissolved in benzene. The ether filtrate was diluted with pentane, and the small amount of solid that formed was collected and added to the benzene solution. The benzene was decolorized with Norit and concentrated. The addition of pentane produced 2.33 g (82%) of 4-(*p*-tolyl)-1,2-dithiole-3-anil: mp 139–141°, yellow-orange crystals; nmr ($CDCl_3$), 8.18 (singlet, 1 proton), 7.39 (complex 9 aromatic protons), and 2.34 ppm (singlet, 3 methyl protons); nmr for 4-(*p*-tolyl)-1,2-dithiole-3-thione (CCl_4), 8.26 (singlet, 1 proton), 7.28 (*para*-substituted aromatic, 4 protons), and 2.41 ppm (singlet, 3 methyl protons).

Anal. Calcd for $C_{16}H_{13}NS_2$: C, 67.80; H, 4.62; N, 4.94; S, 22.6. Found: C, 67.61; H, 4.57; N, 48.3; S, 22.9.

(3) R. S. Spindt, D. R. Stevens, and W. E. Baldwin, *J. Am. Chem. Soc.*, **73**, 3693 (1951).

(4) A. S. Broun, M. D. Voronkov, and K. P. Katkova, *J. Gen. Chem. USSR*, **20**, 765 (1950).

4-(*p*-Tolyl)-1,2-dithiole-3-benzylimine.—The trithione dibromide was prepared by addition of 4.89 g (0.0305 mole) of bromine in 30 ml of benzene to 6.72 g (0.030 mole) of the trithione in 120 ml of benzene. The crude dibromide was washed with benzene and treated with 11 ml of benzylamine. After the exothermic reaction had subsided, ether was added and the insoluble salt was collected and thoroughly washed with ether. The salt was hydrolyzed with water and the imine was dissolved in benzene and crystallized from benzene–hexane to yield 4.65 g (52%) of 4-(*p*-tolyl)-1,2-dithiole-3-benzylimine: mp 111–113°; nmr ($CDCl_3$), 7.91 (singlet, 1 proton), 7.31 (complex, 9 aromatic protons), 4.87 (singlet, 2 methylene protons), and 2.31 ppm (singlet, 3 methyl protons).

Anal. Calcd for $C_{17}H_{15}NS_2$: C, 68.64; H, 5.08; N, 4.71; S, 21.6. Found: C, 68.67; H, 5.44; N, 4.60; S, 21.8.

4-(*p*-Tolyl)-1,2-dithiole-3-(*p*-carboxyphenyl)imine.—The dibromide prepared from 8.96 g (0.040 mole) of trithione was treated with 16.5 g of *p*-aminobenzoic acid dissolved in 200 ml of methanol. The mixture was stirred for 15 min and the solid that formed was collected and washed with methyl ethyl ketone, benzene, and hexane. The crude imine was dissolved in 250 ml of pyridine, decolorized with Norit, and crystallized by the addition of 650 ml of ether. The yield of 4-(*p*-tolyl)-1,2-dithiole-3-(*p*-carboxyphenyl)imine was 9.85 g (75%): mp 252–258° dec; λ_{max}^{mull} 6.00 and 6.25 μ.

Anal. Calcd for $C_{17}H_{13}NO_2S_2$: C, 62.35; H, 4.01; N, 4.28; S, 19.6. Found: C, 62.40; H, 3.92; N, 4.30; S, 19.5.

4-Mercapto-5-(*p*-tolyl)-2H-thiapyrans

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Received November 23, 1965

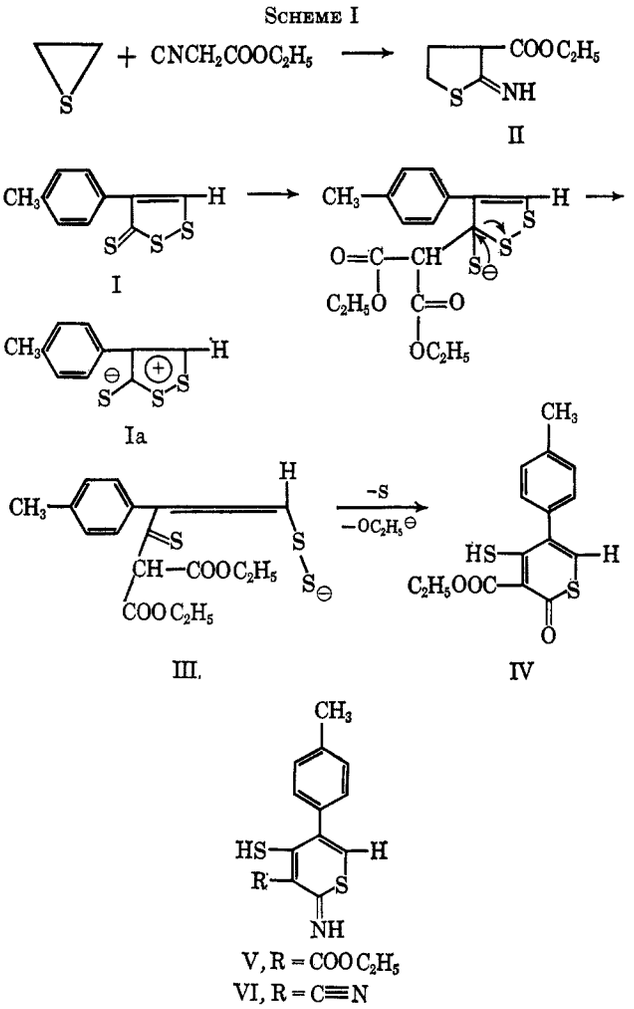
4-Aryl-1,2-dithiole-3-thiones,[2a] readily available from the reaction of sulfur with the appropriate cumene or α-methylstyrene, are a source of a large number of new sulfur chemicals. 4-(*p*-Tolyl)-1,2-dithiole-3-thione (I) reacted with several active methylene compounds to provide high yields of orange or red compounds containing two sulfur atoms. Condensations were carried out at room temperature using sodium ethoxide in benzene–ethanol solution. Other condensing agents were also used. *E.g.*, malonic ester condensed in a dimethoxyethane–benzene solvent pair with sodium amide as the condensing agent. Ethyl cyanoacetate and the trithione condensed very rapidly in benzene solution when piperidine was added. Acetoacetic ester or ethyl benzoylacetate did not react but malononitrile condensed very readily. In these condensations both the methylene and ester or cyano groups are involved and sulfur is lost.

The addition of ethyl cyanoacetate to ethylene sulfide,[2b] gives an imino tetrahydrothiafuran existing as a mixture of tautomers. In a similar manner the addition of malonate ion to the trithione I caused cleavage of the dithioester to yield the intermediate III. Successive loss of sulfur, ring closure, and loss of ethoxide gave the 3-carbethoxy-4-mercapto-5-(*p*-tolyl)-2H-thiapyran-2-one (IV) in 86% yield. The 2-imino-2H-thiapyrans V and VI were obtained in 86 and 77% yield, respectively. (See Scheme I.)

(1) Arapahoe Chemicals Inc., Boulder, Colo.

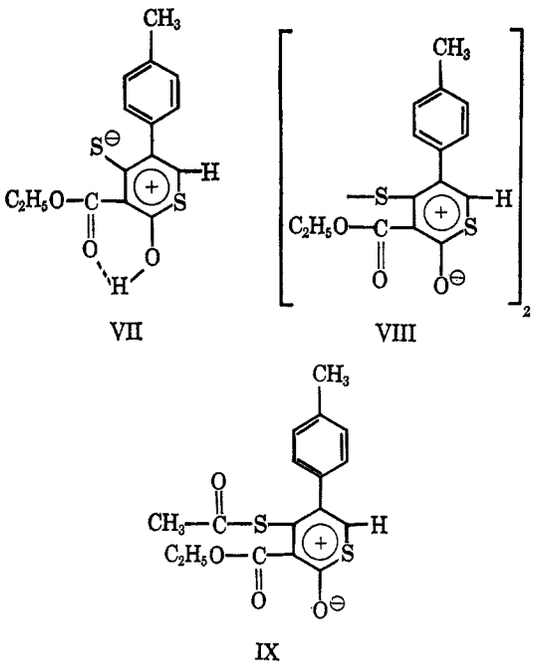
(2) (a) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co., Inc., New York, N. Y., 1960, pp 43–58; (b) H. R. Snyder and Wyvona Alexander, *J. Am. Chem. Soc.*, **70**, 217 (1948).

SCHEME I



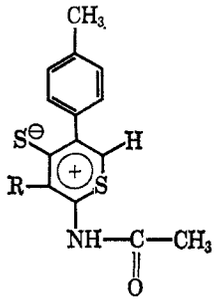
The thiapyran-2-one IV is acidic and formed stable salts that yield the original thiapyran upon acidification. The favored tautomer of IV is the hydrogen-bonded enol where a polarized structure VII, similar to Ia, accounts for the observed spectral properties. The solid is a vivid red, and the thiocarbonyl absorption is strong in the 8.9-μ region, while the carbonyl region exhibits only a single, somewhat polar carbonyl band at 5.98 μ. The aromatic character of the hydrogen atom at the 6 position was confirmed by the nuclear magnetic resonance band at 7.6 ppm. The acidic hydrogen can be removed by oxidation with either hydrogen peroxide or iodine to yield the yellow disulfide VIII. This material could not be readily purified but gave the expected doublet carbonyl absorption at 5.75 and 6.05 μ.

Acetylation of IV by acetyl chloride in pyridine yielded the thioacetate IX, a light yellow compound which hydrolyzes with cold alcohol and pyridine. The triplet carbonyl absorptions occur at 5.75, 5.85, and 6.02 μ and there is no absorption in the 8.9-μ region. The 3-μ region of the infrared spectra of V and VI, measured using Fluorolube mulling agent, exhibited a single band for the former, and the latter gave a well-defined doublet. The amino hydrogens of VI provide a single nuclear magnetic resonance signal and exchange with deuterium oxide. Study of VI in solution was hindered by low solubilities. It is possible that the second amino absorption is obscured by carbon–hydrogen absorptions. In this case, both V and VI



would probably be best described by structures similar to VII.

The acetates, prepared with acetyl chloride in pyridine, are deep red and absorb strongly in the 8.9-μ region, indicating reaction at the nitrogen atom. The ester amide X does not absorb in the 3.0-μ region while XI exhibits a moderately strong singlet. The acetate XI is an imide analog and the remaining hydrogen atom is acidic. Aqueous ammonium hydroxide gives a salt that returns the imide upon acidification. The acetate X is not soluble in ammonium hydroxide.



X, R = $COOC_2H_5$
XI, R = C≡N

Experimental Section

Infrared spectra were measured with a Perkin-Elmer Model 21 spectrophotometer with sodium chloride optics. Ultraviolet spectra were determined with a Cary Model 11-MS recording spectrophotometer. Nuclear magnetic resonance measurements were carried out with the Varian Associates DP 60 spectrophotometer, with tetramethylsilane as internal standard.

3-Carbethoxy-4-mercapto-5-(*p*-tolyl)-2H-thiapyran-2-one (IV).—A solution of 6.10 g (0.265 mole) of sodium dissolved in 200 ml of absolute ethanol was treated with 43.5 g (0.27 mole) of diethyl malonate. After standing for 15 min the mixture was added to 35.8 g (0.16 mole) of 4-(*p*-tolyl)-1,2-dithiole-3-thione (I) dissolved in 200 ml of benzene. The reaction was allowed to stand at room temperature for 1 hr and the solid that formed upon addition to ice water was collected and washed with benzene and ether. The resulting yellow salt was decomposed with aqueous hydrochloric acid and the product was dissolved in benzene. Crystallization from benzene–hexane provided 42.0 g (86%) of 3-carbethoxy-4-mercapto-5-(*p*-tolyl)-2H-thiapyran-2-one (IV): mp 121–124°, as red needles; infrared (mull), 5.98 (C=O) and 8.86 μ (C=S); nmr (carbon tetrachloride) (parts per million from

TMS), 10 (broad OH), 7.60 (CH=), 7.16 (C_6H_4), 4.39 (CH_2 quadruplet), 2.38 (CH_3), 1.41 (CH_3 triplet); $\lambda_{max}^{CH_3OH}$ 270, 313, and 455 mμ (log ε 3.72, 3.60, and 3.99).

Anal. Calcd for $C_{15}H_{14}O_3S_2$: C, 58.81; H, 4.61; S, 20.9. Found: C, 58.15; H, 4.65; S, 20.8.

Treatment of IV with acetyl chloride and pyridine yielded an acetate that crystallized as yellow needles from benzene–hexane: mp 96–97.5°; infrared (mull), 5.75, 5.85, and 6.02 μ (C=O); nmr (carbon tetrachloride) (parts per million from TMS), 7.93 (CH=), 7.06 (C_6H_4), 4.20 (CH_2 quadruplet), 2.35 (CH_3C=O), 2.25 (CH_3), 1.35 (CH_3 triplet). The acetate was unstable in methanol solution when exposed to ultraviolet radiation, and rapidly hydrolyzed to IV in the presence of alcohol and pyridine.

Anal. Calcd for $C_{17}H_{16}O_4S_2$: C, 58.60; H, 4.63; S, 18.4. Found: C, 58.22; H, 4.70; S, 18.2.

2-Imino-3-carbethoxy-4-mercapto-5-(*p*-tolyl)-2H-thiapyran (V).—Ethyl cyanoacetate, 1.80 g (0.015 mole), was added to a solution of 0.015 mole of sodium ethoxide in 10 ml of ethanol and the resulting mixture was treated with 1.70 g (0.0076 mole) of 4-(*p*-tolyl)-1,2-dithiole-3-thione dissolved in 15 ml of benzene. Reaction was immediate and the orange-yellow solid that formed was collected and washed with water, benzene, and ether. The yield of crude 2-imino-3-carbethoxy-4-mercapto-5-(*p*-tolyl)-2H-thiapyran, mp 240–245° dec, was 2.0 g (86%). A purified sample, mp 246–248° dec, was obtained by crystallization from methyl ethyl ketone: infrared (mull), 3.02 (NH), 5.91 (C=O), and 8.90 μ (C=S); $\lambda_{max}^{CH_3OH}$ 334 and 390 mμ (log ε 3.95 and 3.34).

Anal. Calcd for $C_{16}H_{15}NO_2S_2$: C, 58.99; H, 4.95; N, 4.59; S, 21.0. Found: C, 59.59; H, 4.91; N, 4.29; S, 21.5.

The acetate, prepared with acetyl chloride in pyridine solution, was isolated as dark red crystals from ethyl acetate: mp 193–196°; infrared (mull), 5.85 (C=O), 6.00 (C=O), and 8.88 μ (C=S).

Anal. Calcd for $C_{17}H_{17}NO_3S_2$: N, 4.03. Found: N, 3.98.

2-Imino-3-cyano-4-mercapto-5-(*p*-tolyl)-2H-thiapyran (VI).—A solution of 24.6 g (0.110 mole) of 4-(*p*-tolyl)-1,2-dithiole-3-thione and 9.1 g (0.14 mole) of malononitrile in 330 ml of benzene was added to 8.9 g (0.165 mole) of sodium methoxide in 500 ml of methanol. After standing for 1 hr the reaction mixture was added to an excess of dilute hydrochloric acid and the red solid was collected and washed with water and benzene. The yield of crude product, mp 245–250° dec, was quantitative. Samples of VI were purified in 77% yield, by crystallization from acetone–benzene, without any change in the melting point: infrared (fluorolube), 3.06 and 3.23 μ (NH_2); (mull), 4.50 (C≡N), 6.03 (C=N), and 8.92 (C=S); nmr (deuterated DMSO) (ppm from TMS), 9.09 (NH_2), 7.34 (CH=), 6.85 (C_6H_4), 2.30 (CH_3) (all singlets); $\lambda_{max}^{CH_3OH}$ 248, 331, and 472 mμ (log ε 4.08, 4.36, and 4.30).

Anal. Calcd for $C_{13}H_{10}N_2S_2$: C, 60.43; H, 3.90; N, 10.85; S, 24.8. Found: C, 60.55; H, 3.90; N, 10.73; S, 24.9.

With ammonium hydroxide the thiapyran gives a yellow solution from which the starting material can be recovered upon acidification. The amino hydrogens, observed *via* nmr spectroscopy, readily exchange with deuterium oxide in deuterated dimethyl sulfoxide. Acetylation with acetyl chloride–pyridine gives a purple-red monoamide that was crystallized from acetone–benzene: mp 245–248°; infrared (mull), 3.08 (NH), 4.50 (C≡N), 5.82 (C=O), and 8.95 μ (C=S). The amide is soluble in aqueous ammonium hydroxide giving an orange-red solution. Acidification with hydrochloric acid precipitates the amide.

Anal. Calcd for $C_{15}H_{12}N_2OS_2$: C, 59.98; H, 4.03; N, 9.33; S, 21.4. Found: C, 60.47; H, 4.35; N, 9.33; S, 21.6.

A Rational Synthesis of 4-Hydroxy-2,5-dimethyl-3(2H)-furanone, a Flavor Component of Pineapple

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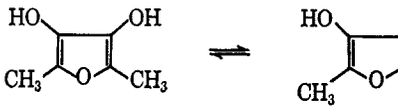
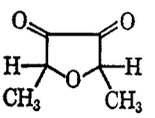
The title compound (I), recently isolated from pineapple flavor concentrate by Rodin, *et al.*,[1] was identified on the basis of its spectral characteristics. It was known also from the work of Hodge, *et al.*, to be produced by a complex reaction between piperidine acetate and the deoxy sugar, rhamnose.[2,3] The product of this reaction was identified on the basis of its spectral properties and on a degradative sequence.[3,4] This Note presents a rational synthesis of furanone I, which confirms the previous structural assignments.

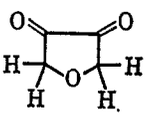
4-Hydroxy-2,5-dimethyl-3(2H)-furanone may be considered as one of three possible tautomers (I, Ia, and Ib). Dienolic tautomer Ia is formally a furan, and a synthetic approach utilizing intermediates containing this relatively stable heteroaromatic ring could be



Ia I



Ib



II

expected to avoid some of the well-documented instability problems associated with the monoenolic final product.[1,5,6] Almost all α- or β-hydroxyfurans tend to assume the carbonyl tautomeric form[7]; thus, the lower homolog of I, tetrahydrofuran-3,4-dione (II), is reported to exist solely in the diketo form.[8] In the special case where carbalkoxy groups are present in the 2 and 5 positions, however, 3,4-dihydroxyfurans exist as such, and several examples of this class of compound are known.[9] The behavior of these hydroxyl groups parallels that of phenols and they may be alkylated or acylated in the normal manner.[9]

In the present work, dimethyl 3,4-dihydroxyfuran-2,5-dicarboxylate (III), prepared by base-catalyzed condensation of dimethyl oxalate and dimethyl diglycolate,[10] was readily converted to dibenzyl derivative IV by treatment with excess benzyl chloride in the presence of base. Reduction of IV with lithium aluminum hydride gave a viscous diol (V), which was transformed directly to dibenzoate ester VI with benzoyl chloride and pyridine (see Scheme I). Catalytic hydrogenolysis of a tetrahydrofuran solution of the dibenzoate,

(1) J. O. Rodin, C. M. Himel, R. M. Silverstein, R. W. Leeper, and W. A. Gortner, *J. Food Sci.*, **30**, 280 (1965).

(2) J. E. Hodge, B. E. Fisher, and E. C. Nelson, *Proc. Am. Soc. Brewing Chemists*, **84** (1963).

(3) J. E. Hodge and B. E. Fisher, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, p 3D.

(4) B. E. Fisher and J. E. Hodge, Abstracts, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1965, p 4D.

(5) J. E. Hodge, personal communication.

(6) B. Willhalm, M. Stoll, and A. F. Thomas, *Chem. Ind.* (London), **38**, 1629 1965.

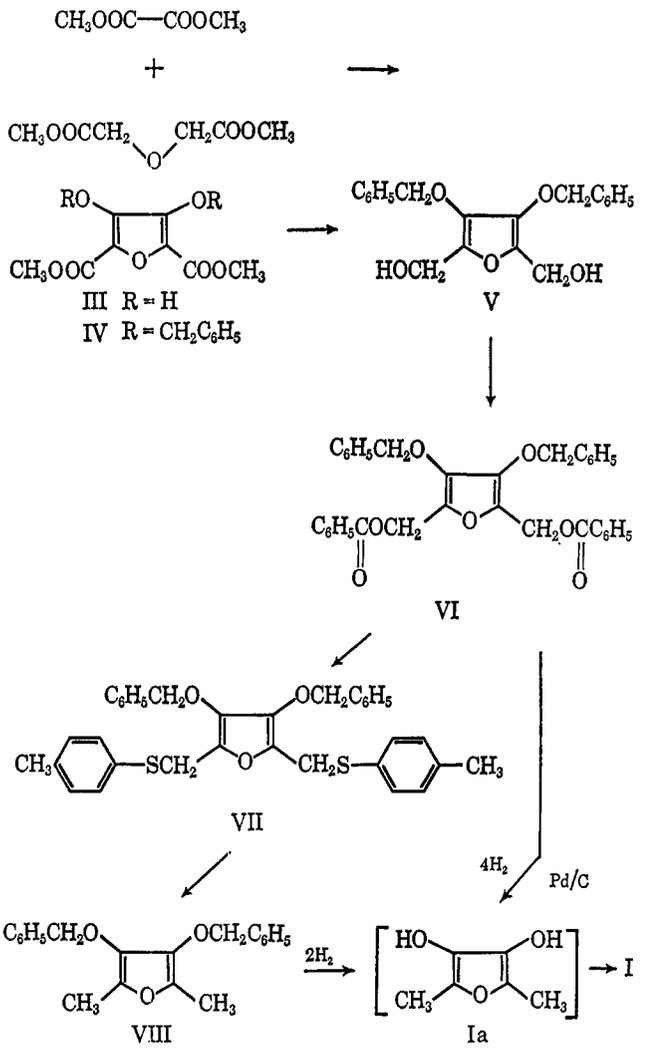
(7) R. Rosenkranz, K. Allner, R. Good, W. V. Philipsborn, and C. Eugster, *Helv. Chim. Acta*, **46**, 1259 (1963), and references therein.

(8) E. C. Kendall and Z. G. Hajos, *J. Am. Chem. Soc.*, **82**, 3219 (1960).

(9) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, pp 180–183.

(10) O. Hinsberg, *Chem. Ber.*, **45**, 2413 (1912).

SCHEME I



in the presence of palladium on charcoal and anhydrous potassium carbonate, resulted in rapid uptake of 4 moles of hydrogen to give the desired furanone I. The use of potassium carbonate in the reaction gave improved yields due to removal, as the potassium salt, of the benzoic acid formed during the hydrogenolysis. Isolation of I from the reaction mixture by conventional means proved to be quite difficult. Although gas phase chromatography indicated that good yields (*ca.* 70%) were obtained in the reaction, much of the product was lost during the work-up. The best method for obtaining pure samples was gas phase chromatography. Samples thus prepared gave excellent analyses and had nmr, mass, and infrared spectra in agreement with those obtained by the previous workers.[1,5] The ultraviolet spectrum of the synthetic product [λ_{max}^{MeOH} 291 mμ, (ϵ_{max} 8700)] differed slightly from the spectrum obtained by Rodin, *et al.*[1] [λ_{max}^{MeOH} 289 mμ, (ϵ_{max} 6700)], but their sample had had the opportunity to partially decompose. Hodge[5] reported $\lambda_{max}^{H_2O}$ 286 mμ, (ϵ_{max} 9100) for his compound, which is in substantial agreement with the synthetic product reported here [$\lambda_{max}^{H_2O}$ 289.5 mμ (ϵ 9500)].

A fully satisfactory melting point was not obtained, and the best samples melted at 75–78°. These samples were obtained when the collection tube on the gas chromatograph was seeded with previously crystallized product, thus causing the effluent to crystallize directly from the gas stream. Without seeding, a liquid was obtained that crystallized on scratching and, subsequently, melted at 50–70°. Correct combustion analyses were obtained on samples collected under both conditions, however. Hodge[3,5] reported a melting point of 82–84° for freshly crystallized (ether) or sublimed samples. Crystalline samples, as reported previously,[1,5,6] changed to viscous liquids of altered odor within 1 or 2 days if stored at room temperature in the presence of air. Storage under nitrogen at subzero temperatures improved stability markedly, and samples have been stored in such a manner for several months with only slight decomposition. Larger samples prepared by Hodge's method[2] were appreciably easier to handle and, as a preparative method, his procedure is clearly the one of choice.

A variation on the above synthetic scheme also led to furanone I. Dibenzoate VI, when treated with the sodium salt of *p*-toluenethiol, underwent displacement of the benzoate groups to give bissulfide VII. Careful treatment of this thio compound with Raney nickel resulted in desulfurization to 3,4-dibenzyloxy-2,5-dimethylfuran (VIII). This compound absorbed 2 moles of hydrogen to yield I. It was necessary to add the Raney nickel in small portions while following the progress of the desulfurization by thin layer chromatography. Excess nickel caused debenzylation as indicated by the characteristic odor of I. No furanone could be isolated from such over-treated reaction mixtures, however.

An attempt to reduce diol V directly to I with hydrogen and palladium on charcoal resulted in rapid uptake of only 2 moles of hydrogen and slow uptake of the remaining two. Although the aroma of the product was obvious, gas phase chromatography showed only traces to be present.

Experimental Section[11]

Dimethyl Diglycolate.—A solution of 203.4 g (1.52 moles) of diglycolic acid in 760 ml of methanol, 354 g (3.4 moles) of acetone dimethyl acetal, and 15 ml of concentrated sulfuric acid was held for 2 hr at room temperature. Most of the solvent was removed *in vacuo* and the residue was taken up in *ca.* 2 l. of water. Threefold extraction of the aqueous solution with ether, followed by drying of the combined extracts with sodium sulfate and removal of solvent *in vacuo*, left a crystalline residue of 126.2 g. Distillation *in vacuo* (10 mm) gave 119.3 g (48.5%) of product boiling at 116–119°, which crystallized in the receiver. Material prepared in a similar manner showed a single peak on gas phase chromatography (0.25 in. × 5.5 ft column, 15% DC 550 on Chromosorb W, 171°, 70 cc of He/min, retention time 4.0 min); a sample collected by this method melted at 37.5–39°, lit.[12] mp 36°, bp 130° (12 mm).

Dimethyl 3,4-Dihydroxyfuran-2,5-dicarboxylate (III).—A stirred solution of 27.6 g (0.17 mole) of dimethyl diglycolate and 20.4 g (0.17 mole) of dimethyl oxalate in dimethylformamide (400 ml) was treated in portions with 8.6 g (0.36 mole) of sodium hydride. After addition of methanol (0.5 ml), the mixture was warmed to *ca.* 50° when a mild exothermic reaction began, accompanied by hydrogen evolution. The temperature was held

(11) Melting points were taken in capillary tubes on a Mel-Temp apparatus and are corrected. Nmr spectra were obtained on either Varian HR-60, A-60, or HA-100 instruments and were taken in carbon tetrachloride solution with tetramethylsilane as the internal reference. Infrared spectra were taken on a Perkin-Elmer Model 137 Infracord. Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 recording spectrophotometer. The mass spectrum was provided by a CEC 21-103C instrument.

(12) R. Anschutz and S. Jaeger, *Chem. Ber.*, **55**, 676 (1922).

at 50–55° by occasional cooling with an ice bath. When the temperature had dropped spontaneously to 40°, the thickened mixture was poured into water (1500 ml) containing 60 ml of 3*N* HCl. Thorough chilling in an ice bath caused precipitation of 15.3 g (41.5%) of tan crystals melting at 216–220° after oven drying at 120°, lit.[10] mp 220°.

On one occasion out of three, the spontaneous reaction failed to occur, and the mixture required heating at 85–95° for 1.5 hr to conclude the slow hydrogen evolution. The same work-up gave a 34% yield in this instance.

Dimethyl 3,4-Dibenzyloxyfuran-2,5-dicarboxylate (IV).—A stirred solution of 21.6 g (0.10 mole) of dimethyl 3,4-dihydroxyfuran-2,5-dicarboxylate and 50 ml (0.44 mole) of benzyl chloride in dimethylformamide (175 ml) was treated slowly and in small portions with 52% sodium hydride in oil (9.8 g, 0.21 mole). The mixture was heated at 100° for 1 hr, poured into water (*ca.* 1.5 l.), and the partially crystalline precipitate was removed by extraction with ether. The ether solution was dried over Na_2SO_4, the ether was removed by boiling, and the residue was treated with 30–60° petroleum ether (*ca.* 100 ml). Swirling the mixture caused crystallization and, after cooling, the product was filtered off and washed with petroleum ether. Recrystallization from methanol gave 31.2 g (79%) melting at 95–97°. This product was analyzed after drying *in vacuo*.

Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.83; H, 5.12.

3,4-Dibenzyloxy-2,5-dihydroxymethylfuran (V).—A solution of dimethyl 3,4-dibenzyloxyfuran-2,5-dicarboxylate (14.0 g, 0.035 mole) in anhydrous ether (500 ml) was added dropwise over 0.5 hr to a stirred mixture of 5.0 g (0.13 mole) of lithium aluminum hydride in anhydrous ether (150 ml). Stirring was continued for an additional 0.5 hr. Water (*ca.* 15–20 ml) was then added carefully dropwise until the gray color of the inorganic salts had changed to white. The mixture was gravity-filtered and the precipitate was washed several times with ether. The solvent was removed from the combined filtrate and washings *in vacuo* to leave 9.7 g of viscous, pale-yellow, crude diol. Thin layer chromatography (silica gel, ether) showed a major component at R_f 0.3 (presumably the diol) and two very minor impurities with R_f 0.05 and 0.15. The infrared spectrum of this material showed a strong, broad hydroxyl band at 3.0 μ. This unstable product was immediately converted to the dibenzoate without further purification.

2,5-Dibenzoyloxymethyl-3,4-dibenzyloxyfuran (VI).—Crude 3,4-dibenzyloxy-2,5-dihydroxymethylfuran (9.7 g, 0.0285 mole) in 25 ml of dry pyridine was treated in small portions with 10 ml (12 g, 0.085 mole) of benzoyl chloride with swirling and intermittent cooling. After 1 hr at room temperature, the mixture was poured into dilute aqueous sodium bicarbonate (*ca.* 250 ml, excess). The oily precipitate crystallized almost immediately and was filtered off. Recrystallization of the wet product from methanol gave 9.3 g (48%, based on dimethyl 3,4-dibenzyloxyfuran-2,5-dicarboxylate) of product, mp 82–83.5°. Infrared spectrum: λ (Nujol mull) 5.79 (C=O), 6.23 (C=C), 7.68, 7.95, 9.15, 9,36, 9.75, 13.5, 14.2, and 14.4 μ. Nmr spectrum: τ 4.97 (singlet, 8 protons, α to phenyl and furyl rings), 2.04 (ill-defined doublet, 4 protons α to aromatic carbonyls), 2.5–2.9 (multiplet, 16 protons, aromatic).

Anal. Calcd for $C_{34}H_{28}O_7$: C, 74.44; H, 5.14. Found: C, 74.18; H, 5.17.

4-Hydroxy-2,5-dimethyl-3(2H)-furanone (I).[13]—A stirred solution of 1.10 g (2.0 mmoles) of 3,4-dibenzyloxy-2,5-dibenzoyloxymethylfuran in tetrahydrofuran (33 ml) was hydrogenated at atmospheric pressure and room temperature in the presence of 10% palladium on charcoal (160 mg) and powdered anhydrous potassium carbonate (0.63 g, 4.6 mmoles). During 2 hr, 175 ml of hydrogen (91% of theoretical) was taken up and absorption then ceased. Vapor phase chromatography (3/8 in. × 6 ft column, Chromosorb W, 50/60 mesh, 143°, 150 cc of He/min) of an aliquot of the reaction mixture indicated a yield of 73% by comparison with a standard solution prepared from rhamnose-derived furanone.[2] Retention times for the hydrogenolysis product and the reference compound were 10.5 and 10.4 min, respectively. The catalyst and inorganic salts were removed by centrifugation and the supernatant was reduced to a volume of *ca.* 2 ml, without heating, by a stream of nitrogen. Vapor phase chromatography was used to isolate samples from this concentrate for the various analytical procedures. Fresh individual samples were collected immediately before use in uncooled glass tubes seeded with traces of crystalline product. A 220-μl. aliquot of the concentrate gave 17 mg of crystalline product melting at 75–78°. Without seeding, a liquid product was obtained. The infrared spectrum was taken on such a sample in order to compare it with the liquid film spectrum of Rodin, *et al.*[1] Infrared spectrum: λ (liquid film) 3.1 (OH, broad), 5.90 (C=O), 6.16, 7.66, 8.33, 9.97, 10.71, and 13.15 μ. Nmr spectrum: τ 2.76 (1 proton, broad singlet), 5.67 (1 proton, quartet, J = 7 cps), 7.81 (3 protons, singlet), 8.60 (3 protons, doublet, J = 7 cps). Ultraviolet spectrum: λ_{max}^{MeOH} 291 mμ (ϵ_{max} 8700); $\lambda_{max}^{H_2O}$ 289.5 mμ (ϵ_{max} 9500). The mass spectrum gave a molecular ion of m/e 128 and fragment peaks in agreement with those previously obtained.[1] A small, long-range coupling effect (0.75 cps) was noted in the nmr spectrum between the C-2 proton and the C-5 methyl protons.

Anal. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.25; H, 6.40.

3,4-Dibenzyloxy-2,5-di(*p*-tolylthiomethyl)furan (VII).—A solution of sodium *p*-toluenethiolate was prepared by adding 54 mg of 52% sodium hydride in oil (1.2 mmoles) to 135 mg (1.1 mmoles) of *p*-toluenethiol in dimethylformamide (2 ml). To this solution was added 3,4-dibenzyloxy-2,5-dibenzoyloxymethylfuran (266 mg, 0.49 mmole) and the mixture was heated *ca.* 5 min on the steam bath. The gelled reaction mixture was diluted with 8 ml of water and the oily precipitate was isolated by ether extraction. The 248-mg residue, obtained after drying the ether extracts over Na_2SO_4 and removal of the solvent *in vacuo*, was chromatographed over Merck basic alumina (8.7 g). Petroleum ether (lys 30–60°) and 10% ether in petroleum eluted a total of 8 mg of low-polarity impurities. Elution with 25–50% ether gave 165 mg (61%) of colorless, oily product, which displayed only a single spot on thin layer chromatography (alumina, 5% ether in petroleum ether, R_f 0.7). This material gave a very clean nmr spectrum: τ 2.6–3.1 (18 aromatic protons, multiplet), 5.36 (4 protons, singlet, benzyloxy methylenes), 6.25 (4 protons, singlet, furyl methylenes), 7.72 (6 protons, singlet, aromatic methyls).

Anal. Calcd for $C_{34}H_{32}O_3S_2$: C, 73.88; H, 5.84. Found: C, 73.77; H, 5.95.

3,4-Dibenzyloxy-2,5-dimethylfuran (VIII).—A stirred solution of 2.0 g (3.7 mmoles) of 3,4-dibenzyloxy-2,5-di(*p*-tolylthiomethyl)-furan in 60 ml of 1:1 absolute alcohol–benzene was treated at room temperature with small portions of Raney nickel. After each portion was added (the desulfurization was very rapid), the progress of the reaction was monitored by thin layer chromatography (alumina, 5% ether in 30–60° petroleum ether). The R_f values of the bissulfide and the product were 0.7 and 0.85, respectively. During the reaction, a third spot (R_f 0.78), presumed to be the monodesulfurized intermediate, was also present in low concentration. When essentially all of the starting material was gone, the catalyst was removed by filtration and the solution was evaporated to an oily residue (1.0 g). Chromatography over Merck basic alumina (20 g) using 30–60° petroleum ether intially, then 30% ether in petroleum ether to elute the product, gave a colorless oil (487 mg), which was estimated to be >99% pure by thin layer chromatography. A trace of starting bissulfide could be detected, however. Nmr spectrum: τ 2.67 (10 aromatic protons, singlet), 5.08 (4 benzyloxy protons, singlet), 8.06 (6 methyl protons, singlet).

Before this product could be catalytically hydrogenated, it was necessary to treat it with a small amount of Raney nickel to remove the sulfur-containing residual starting material. Apparently this impurity was enough to poison the catalyst and no hydrogen uptake occured.

Catalytic hydrogenolysis of 3,4-Dibenzyloxy-2,5-dimethylfuran (VIII).—A solution of 96 mg (0.31 mmole) of 3,4-dibenzyloxy-2,5-dimethylfuran in tetrahydrofuran (5 ml) was hydrogenated at atmospheric pressure and room temperature in the presence of 31 mg of 10% palladium on charcoal. Hydrogen uptake slowed markedly but did not stop after 2 moles had been absorbed. The reaction was stopped after 16.4 ml (theoretical 15.4 ml) had been taken up, and, after removal of the catalyst by centrifugation, the mixture was concentrated under a nitrogen stream to 2.3 ml. Vapor phase chromatography of an aliquot (previous conditions) indicated a yield of 57%. A sample isolated by vapor phase chromatography had an infrared spectrum identical with that of 4-hydroxy-2,5-dimethyl-3(2H)-furanone obtained previously.

(13) NOTE ADDED IN PROOF.—The title compound was recently isolated from the hydrogenolysis products of acetylformoin: A. Hofman and C. Eugster, *Helv. Chim. Acta*, **49**, 53 (1966).

Acknowledgment.—The nuclear magnetic resonance spectra were performed by Mr. W. R. Anderson, Jr. The mass spectrum was obtained by Mr. F. M. Church. Microanalyses were carried out by the Stanford Research Institute analytical department.

Stereochemistry of the Palladium-Catalyzed Hydrogenation of 3-Oxo-4-ene Steroids[1]

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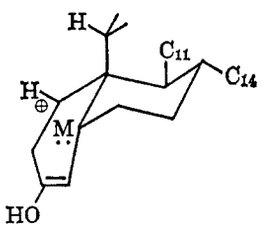
Recently, the effect of solvents on the stereochemistry of the catalytic hydrogenation of α,β-unsaturated ketones has been reported with two series of ketones.[3,4] Augustine has shown that under acidic conditions $\Delta^{1,9}$-2-octalone and 2-benzoyl-1,2,3,4,8,8a-hexahydro-6-isoquinolone give the corresponding saturated *cis* ketones predominantly in the hydrogenation with a 10% palladium–charcoal as a catalyst.[3] On the other hand, McQuillin, Ord, and Simpson have reported that the use of less polar solvents or the presence of acid causes the decrease of the formation of 5β ketones, the ring A/B-*cis* isomers, in the hydrogenation of cholest-4-en-3-one and testosterone with a palladium–charcoal catalyst.[4] Thus, the effect of acid on the stereochemistry of the hydrogenation led to completely different results with the two series of ketones. Apparently the main difference in these studies seems to come from the fact that the former deals with the ketones having no angular methyl group, while the latter with those having such a group at C-10 position. In order to obtain more comparable data and to clarify the cause of this difference in results, three steroid ketones with and without the C-19 angular methyl group, cholest-4-en-3-one (I), testosterone (II), and 19-nortestosterone (III), have been hydrogenated using prereduced palladium oxide and palladium hydroxide as catalysts. Unsupported catalysts were used in this study, because supported catalysts seemed to be more difficult to be prepared in a state free from alkaline or acidic substances. The acetates of II and III have also been subjected to hydrogenation in order to know the effect of the 17-hydroxyl group on the stereochemistry of the hydrogenation.

Table I summarizes the ratio of saturated 5β to 5α ketone formed in the hydrogenation of I, II, III, and the acetates of II and III with palladium black catalysts at 25° and atmospheric pressure of hydrogen. The hydrogenation in ethanol was complicated by an unexpected reaction: the resulting saturated ketones are easily liable to further reduction to give the corresponding ethoxy compounds along with slight amounts of saturated alcohols.[5] This reaction is strongly depressed with addition of alkali or hydrochloric acid. Because of an extensive occurrence of this reaction, the results obtained in ethanol will not be reliable ones, although the hydrogenations were carried out under the conditions to minimize the formation of the ethoxy compounds by using a smaller ratio of catalyst to substrate and a shorter reaction time. Palladium hydroxide was used preferentially in the hydrogenations in neutral alcoholic solutions, because palladium oxide of the Adams type probably contains a small amount of alkaline substances,[6] which may affect the formation of 5β ketone to increase.[4,7]



M = Catalyst metal

Figure 1.

TABLE I

RATIO OF 5β TO 5α KETONE FORMED IN THE HYDROGENATION OF 3-OXO-4-ENE STEROIDS WITH PALLADIUM CATALYSTS

	Compd				
Solvent	I	II	III	Acetate of II	Acetate of III
EtOH + 20% NaOH, 0.1 ml	11.5	6.3[a]	2.09	...	...
t-BuOH	1.35[a]	...	...	...	...
i-PrOH	1.38[a]	0.74[a]	1.68[a]	0.80[a]	1.10[a]
EtOH	1.34[a]	0.52[a]	1.25[a]	1.43[a]	2.04[a]
EtOH + 3 *N* HCl, 0.1 ml	1.44	0.46	1.18	1.95[a]	3.93[a]
AcOH	2.85	0.52	2.02	1.48[a]	4.44[a]
CF_3COOH	3.12	...	...	...	...
AcOH + 3 *N* HCl, 0.1 ml	4.56	0.95	3.17	2.70[a]	12.1[a]

[a] Palladium hydroxide was used as the catalyst. In other cases palladium oxide catalyst was used.

From the results of Table I it is obvious that the formation of 5β-ketone increases under acidic conditions irrespective to the ketones investigated. These results are in line with those reported by Augustine,[3] but not with those reported by McQuillin and his coworkers that the presence of acid decreased the yield of 5β-ketone in the hydrogenation of I and II.[4] For the predominant formation of *cis* ketones in acidic medium, Augustine[3] has proposed a mechanism which involves a 1,4 addition of hydrogen *via* the protonated ketone as an intermediate. When his explanation is applied to the steroid ketones having the C-19 methyl

(1) Presented in part at the 18th Annual Meeting of the Chemical Society of Japan in Osaka, Japan, April 1965.

(2) (a) Department of Industrial Chemistry, Tokyo University of Agriculture and Technology, Koganei, Tokyo, Japan; (b) Chemical Laboratory, Ochanomizu University, Bunkyo-ku, Tokyo, Japan.

(3) R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958); R. L. Augustine and A. D. Broom, *ibid.*, **25**, 802 (1960); R. L. Augustine, *ibid.*, **28**, 152 (1963).

(4) F. J. McQuillin, W. O. Ord, and P. L. Simpson, *J. Chem. Soc.*, 5996 (1963).

(5) A direct formation of the ethoxy compounds from the starting unsaturated ketones may also be possible, since such compounds were found in the products at the intermediate stages of the hydrogenation. Details of this reaction will be published elsewhere.

(6) The palladium hydroxide used in this study probably contains a smaller amount of alkali than the palladium oxide of Adams type, since the resulting catalyst catalyzes the formation of ethoxy compounds from ketones in ethanol more efficiently than the catalyst from the oxide, the reaction being depressed by the presence of alkali. *Cf.* C. W. Keenan, B. W. Giesemann, and H. A. Smith, *J. Am. Chem. Soc.*, **76**, 229 (1954).

(7) A. L. Wilds, J. A. Johnson, Jr., and R. E. Sutton, *ibid.*, **72**, 5524 (1950).

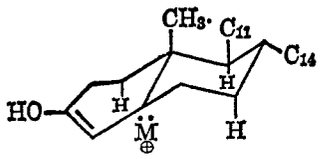


Figure 2.

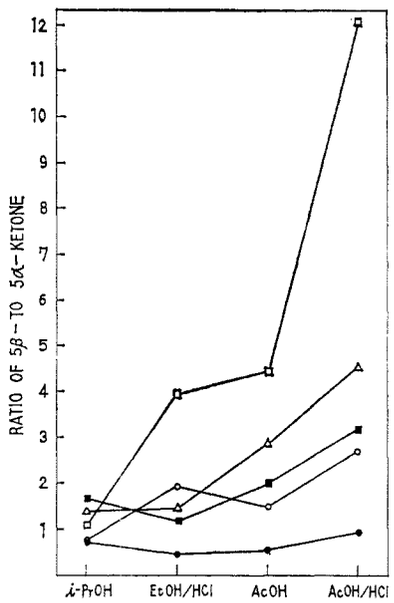


Figure 3.—Effect of acidic solvents on the $5\beta/5\alpha$ ratio of ketones formed in hydrogenation of 3-oxo-4-ene steroids with palladium catalyst: △, cholest-en-3-one; ●, testerone; ○, testerone acetate; ■, 19-nortesterone; □, 19-nortesterone acetate.

group, there exist two 1,3 interactions between two hydrogen atoms, one axial and one methyl hydrogen, and the catalyst surface at the position of the methyl group giving the greatest interaction in the intermediate leading to the 5β isomer as shown in Figure 1. On the other hand, there are three such interactions in the structure leading to the 5α isomer (Figure 2). Thus, the formation of 5β ketone will be more favored sterically even in the ketones having the angular methyl group.[8] The hydrogenation in the absence of alkali or acid will proceed with a less stereospecificity because the species hydrogenated may be a less polarized ketone in which the $5\beta/5\alpha$ ratio of the product will be controlled by an interaction of the π electrons of the unsaturated ketone and the catalyst surface. The fact that I gives much greater yields of 5β ketone than II and even than III in acidic media suggests that the 17-hydroxyl group may have some effect to decrease the formation of 5β ketone probably in combination with acids. This may be presumed further by the finding that in acidic media the acetates of II and III give much greater yields of 5β ketone than II and III, respectively (see Figure 3).

Experimental Section

Materials.—The substances hydrogenated are all known compounds of the following melting points:[9] cholest-4-en-3-one, 80.0–80.5° (lit.[10] 82°); testosterone, 155–156° (lit.[10] 155°); testosterone acetate, 140–140.5° (lit.[11] 140–141°); 19-nortestosterone, 124–125° (lit.[10] 124°); 19-nortestosterone acetate, 62–67° (lit.[12] 91–93°). Purity of these compounds was further ascertained by gas–liquid partition chromatography.

Catalysts.—Palladium oxide was prepared by the method of Shriner and Adams.[13] Palladium hydroxide was prepared by adding a slight excess of lithium hydroxide solution to a hot aqueous solution of palladium chloride, the precipitate being washed with hot distilled water thoroughly until the filtrate became neutral to thymol blue.

Hydrogenation.—The substrate (30–100 mg) dissolved in 10–15 ml of a solvent was shaken in a glass bottle with 10–30 mg of prereduced palladium oxide or palladium hydroxide at 25° and atmospheric pressure of hydrogen until hydrogen uptake ceased. In the hydrogenation using ethanol as the solvent, the absorption of hydrogen did not cease with the uptake of 1 mole, and so when 1 mole of hydrogen was absorbed, the reaction was stopped to examine the products at that stage.

Analysis of Products.—The products were analyzed by means of gas–liquid partition chromatography using a column of 1% SE-52 silicone on Chromosorb W (30–60 mesh). The following conditions were used for the analyses: for the products from cholestenone, column length 1.5 m, column temperature 238°; for the products from testosterone, 19-nortestosterone and its acetate, column length 2.25 m, column temperature 218°; for the products from testosterone acetate, column length 2.25 m, column temperature 228°. Small amounts of hydrogenolyzed products (1–5%) were formed in all the hydrogenations, but the products contained saturated alcohols in only slight amounts. This, if necessary, was confirmed by the analysis of the products treated with acetic anhydride and pyridine, since the retention times of the saturated 5α alcohols obtained from I and II were nearly the same with those of the corresponding saturated 5β ketones.

Acknowledgment.—The authors are grateful to Teikoku Hormone Manufacturing Company, Ltd., for providing testosterone, 19-nortestosterone, and some of their derivatives.

(8) The same conclusion may also be deduced in hydrogenation of 4,5-unsaturated steroids in neutral media [H. I. Hadler, *Experientia*, **11**, 175 (1955)]. However, it may be suggested that the steric control will be more pronounced in the formation of the intermediates as shown in Figures 1 and 2, since the adsorption between a carbonium ion and the catalyst surface is involved.

(9) All melting points were measured on a hot-stage apparatus and were not corrected.

(10) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959.

(11) L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 1275 (1935).

(12) J. A. Hartman, *J. Am. Chem. Soc.*, **77**, 5151 (1955). The acetate was prepared from the 19-nortestosterone of mp 124–125°. Although the melting point of the resulting acetate was considerably lower than that reported in the literature, it was confirmed by gas chromatography that the acetate contained only a trace of impurities.

(13) R. L. Shriner and R. Adams, *ibid.*, **46**, 1683 (1924).

Steroids. CCXCV. A Novel Ring A Aromatization Reaction[1]

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The aromatization of ring A in steroids containing a CH_3 group at C-10 has been mainly accomplished starting either from $\Delta^{1,4}$-3 ketones[2] or more recently through microbiological transformation of 19-oxygenated steroids.[3] The reactions involved in these trans-

(1) Steroids. CCXCIV: C. Beard, I. Harrison, L. Kivkham, and J. Fried, *J. Am. Chem. Soc.*, in press.

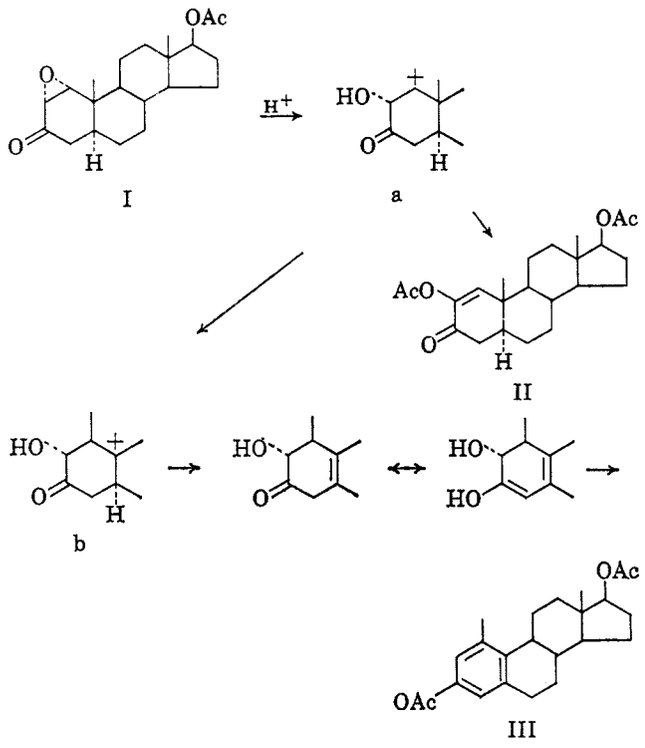
(2) L. F. Fieser and M. Fieser, "Steroids," Rheinhold Publishing Corp., New York, N. Y., 1959, p 479.

(3) R. M. Dodson and R. D. Muir, *J. Am. Chem. Soc.*, **83**, 4627, 4631 (1961). C. J. Sih, S. S. Lee, Y. Y. Tsong, K. C. Wang, and F. N. Chang, *ibid.*, **87**, 2765 (1965), and earlier papers.

formations have been thoroughly studied and rationalized. We wish to report the aromatization of ring A achieved by the action of acid on 1α,2α-epoxy-3-keto steroid.

When we subjected 17β-acetoxy-1α,2α-epoxy-5α-androstan-3-one (I,[4] Scheme I) to rearrangement

SCHEME I



with *p*-toluenesulfonic acid in acetic anhydride, the expected 2,17β-diacetoxy-5α-androst-1-en-3-one (II) could be isolated from the reaction mixture by chromatographic separation. Surprisingly, II was accompanied by another substance which was identified as the diacetate of 1-methylestradiol (III) by its physical characteristics and mixture melting point comparison with an authentic sample.[5] The compound III was obtained in a higher yield than II and consequently should be considered as the main reaction product.

The formation of these two widely different compounds can be explained by the following mechanism. Acid-catalyzed opening of the epoxy ring at C-1 generates the intermediate carbonium ion a which passes over to II by proton loss from C-2 and acetylation. Alternatively, migration of the C-19 angular methyl group in the ion a to C-1 leads to the carbonium ion b which then undergoes aromatization by enolization and proton loss at C-5 followed by elimination of the C-2 oxygen function as water or acetic acid. The formation of 1-methylestradiol diacetate (III) is reminiscent of the acid-catalyzed rearrangement of 3α-acetoxy-16α,17α-epoxy-pregn-5-en-20-one to 3α,16α-diacetoxy-17β-methyl-17α-pregna-5,13-dien-20-one.[6] In the latter case, however, Wagner–Meerwein rearrangement is initiated by cleavage of the epoxide ring at C-17.

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

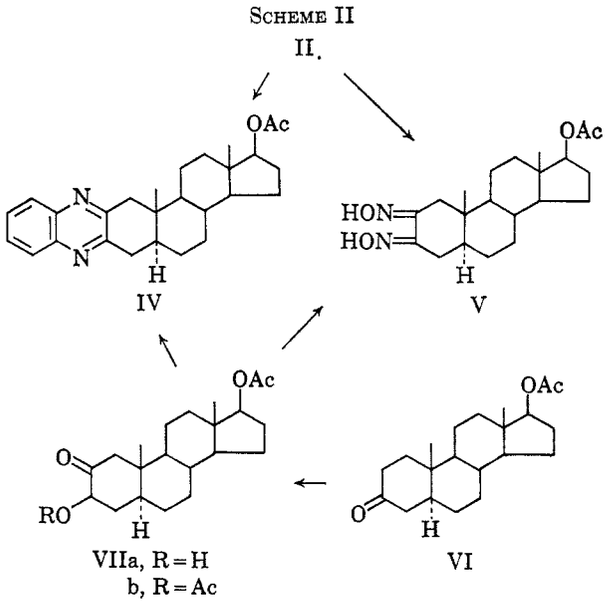
(5) C. Djerassi, J. Romo, J. Pataki, and S. Kaufmann, *J. Am. Chem. Soc.*, **72**, 4540 (1950).

(6) K. Heusler and A. Wettstein, *Ber.*, **87**, 1301 (1954).

The structure of compound II was established by its ultraviolet spectrum [λ_{max} 237 mμ (log ε 4.00)][7] and by the formation of the crystalline quinoxaline and dioxime derivatives IV and V.

For comparison purposes we have prepared the free diosphenol (VIIa) *via* selenium dioxide oxidation of 17β-acetoxy-5α-androstan-3-one (VI) in accordance with a method originally described by Stiller and Rosenheim.[8] VIIa forms the same quinoxaline derivative (IV, Scheme II) and dioxime (V) as those prepared from II. Mild acetylation of VIIa with acetic anhydride in pyridine leads to the isomeric diacetate 3,17β-diacetoxy-5α-androst-3-en-2-one (VIIb) which is not identical with II as expected.

SCHEME II



Experimental Section[9]

2,17β-Diacetoxy-5α-androst-1-en-3-one (II) and 1-Methylestradiol Diacetate (III).—A solution of 5.0 g of 17β-acetoxy-1α,2α-epoxy-5α-androstan-3-one (I) in 50 ml of acetic anhydride was treated with 5.0 g of *p*-toluenesulfonic acid and the mixture was heated for 2 hr on the steam bath. After cooling, the reaction mixture was poured into water and extracted with ether. The organic layer was washed with water and a solution of sodium bicarbonate until neutral. The solvent was evaporated to dryness and the oily residue was crystallized by addition of methanol. The crude crystalline product (1.5 g) was separated into two fractions by chromatography on 50 g of silica gel.

Elution with benzene containing 2% ether yielded 1-methylestradiol diacetate (III, 0.7 g), which recrystallized from methanol as plates: mp 177–78°, $[\alpha]_D$ +108.2°, λ_{max} 269 mμ (log ε 2.529) [lit.[5] mp 178–180°, $[\alpha]_D$ +111°, λ_{max} 268 mμ (log ε 2.53)] identical by mixture melting point and infrared comparison with an authentic sample.[5] Continued elution with the same solvent mixture afforded compound II (0.4 g). Several recrystallizations from methanol yielded a pure specimen as prisms: mp 189–190°; $[\alpha]_D$ +40.5°; λ_{max} 237 mμ (log ε 4.00); ν_{max} 2900, 1770, 1730, 1640, 1375, 1250, and 1095 cm^{-1}.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.04; H, 8.29.

Preparation of the Quinoxaline Derivative IV.—A solution of 2 g of II in 50 ml of alcohol was treated with 2 g of *o*-phenylenedi-

(7) L. F. Fieser and M. Fieser, ref. 2, p 304.

(8) E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938).

(9) Melting points were recorded in a Thomas–Hoover melting point apparatus and are corrected. Except where stated otherwise rotations and infrared spectra were determined in chloroform, and ultraviolet spectra in ethanol solution. Microanalysis were performed by Midwest Micro Laboratories, Indianapolis, Ind., or by A. Bernhardt, Mühlehim (Ruhr), West Germany.

amine and a solution of 1 g of potassium bicarbonate in 5 ml of water. The mixture was heated under reflux for 2 hr. On cooling, IV crystallized from the reaction mixture in slightly yellow plates (1.8 g). Recrystallization from methylene chloride–methanol yielded a pure sample: mp 242–244°; $[\alpha]_D$ +68.3°; λ_{max} 239, 263, and 321 mμ (log ε 4.503, 3.339, and 4.074).

Anal. Calcd for $C_{27}H_{34}N_2O_2$: C, 77.55; H, 8.11; N, 6.69. Found: C, 77.53; H, 8.32; N, 6.52.

Preparation of the Dioxime Derivative V.—A solution of 1 g of II in 50 ml of methanol was treated with a solution of 2 g of hydroxylamine acetate in 10 ml of methanol. After a few minutes of heating on the steam bath the dioxime V precipitated in fine needles, mp 272.5–275° dec, $[\alpha]_D$ +57.4 (pyridine).

Anal. Calcd for $C_{21}H_{32}N_2O_4$: C, 67.00; H, 8.58; N, 7.43. Found: C, 67.54; H, 8.35; N, 8.01.

3,17β-Diacetoxy-5α-androst-3-en-2-one (VIIb).—To a solution of 15 g of 17β-acetoxy-5α-androstan-3-one in 300 ml of alcohol there was added 120 g of selenium dioxide dissolved in 70 ml of water and 300 ml of alcohol. The mixture was heated under reflux for 15 min and then cooled. The precipitated selenium was removed by filtration and the filtrate was diluted with 1 l. of ether. The organic layer was washed first with 1 l. of a concentrated salt solution and then with 500 ml of a concentrated solution of sodium bicarbonate. The potassium salt of the diosphenol (VIIa) precipitated at the interface by shaking the etheral layer with 300 ml of 20% aqueous potassium hydroxide.

The resinous, dark precipitate was separated from the liquid layers and washed thoroughly with ether. The free diosphenol was liberated from its potassium salt by treatment with dilute hydrochloric acid followed by extraction with ether. The organic layer was washed with water, dried, and decolorized with activated charcoal. Upon concentration of the ether solution the diosphenol was crystallized in small, yellow plates. Recrystallization from ether yielded 3.5 g of pure VIIa: mp 151.5–153°, $[\alpha]_D$ +80.5°, λ_{max} 272 mμ (log ε 3.753).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.81; H, 8.73. Found: C, 72.99; H, 8.58.

Treatment of the diosphenol VIIa with *o*-phenylenediamine and hydroxylamine acetate afforded the quinoxaline (mp 242–244°) and dioxime (mp 272.5–275°), respectively, which were identical in all respects with the corresponding derivatives obtained from II.

The enol acetate VIIb was prepared from the diosphenol by dissolving the latter in acetic anhydride and pyridine at room temperature. After standing for 24 hr the reaction mixture was worked up in the usual way. Crystallization from methanal yielded well-formed prisms: mp 184–184.5°; $[\alpha]_D$ +82.4°; λ_{max} 240 mμ (log ε 3.898); ν_{max} 2900, 1770, 1730, 1640, 1375, 1250, 1155, 1135, and 1065 cm^{-1}.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.78; H, 8.22.

The Synthesis of Nitrogen-Containing Steroids. I. Diels–Alder Adducts of Steroids and 4-Phenyl-1,2,4-triazoline-3,5-dione[1]

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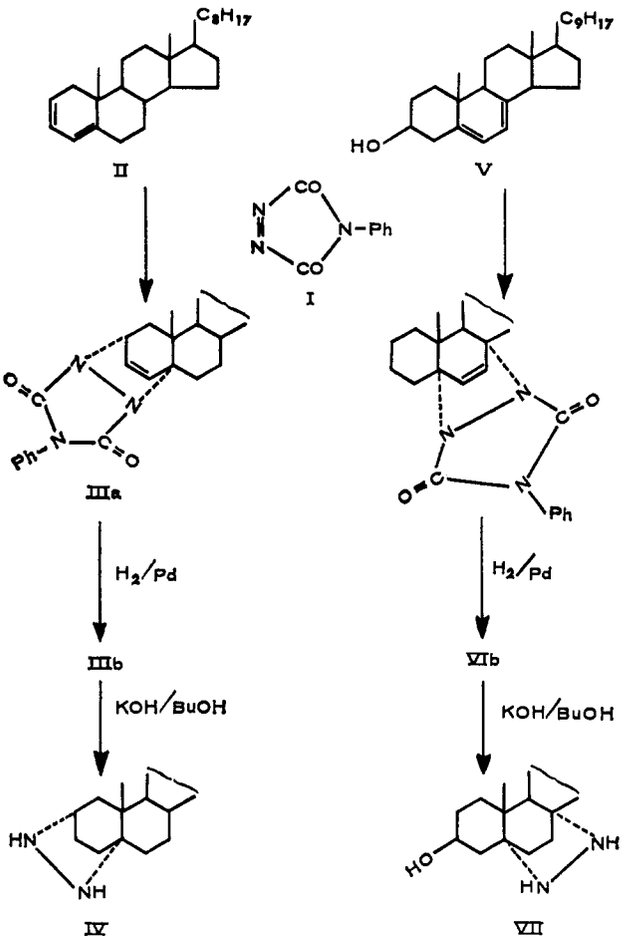
As part of a general program for the investigation of nitrogen-containing steroids, we have investigated the incorporation of azo and hydrazo bridges into rings A and B of $\Delta^{2,4}$-cholestadiene (II) and ergosterol (V). respectively, by the use of the dienophilic reagent 4-phenyl-1,2,4-triazoline-3,5-dione (I) (see Scheme I), Despite reports that the Diels–Alder reaction between

SCHEME I



ergosterol and maleic anhydride is slow[2] and that hydrogen abstraction–addition constitutes an undesirable side reaction in the ergosterol–ethyl diazocarboxylate reaction,[3] it was hoped that I would behave normally on the basis of its reactivity in various systems[4] including steroids.[5]

I reacted instantly with $\Delta^{2,4}$-cholestadiene in acetone–benzene solution at 0° as shown by disappearance of the red color of I. The adduct IIIa was isolated and characterized as such by several lines of evidence: the diene ultraviolet absorption pattern of II (λ_{max} 275 and 267 mμ) had disappeared; in the infrared spectrum, a carbonyl doublet at 1705 and 1760 cm^{-1} typical of adducts of I[4,5] had appeared; the pmr spectrum showed peaks at δ 6.25 and 6.34 (doublet integrating for two protons, J = 4 cps) assigned to ring A vinyl protons and a singlet at δ 7.4 assigned to N-phenyl; and finally, absence of NH peaks in the infrared spectrum and elemental analysis lend strong support to structure IIIa.

The adduct IIIa was hydrogenated at 3-atm pressure (5% Pd–C) to give the dihydro adduct IIIb which was isolated and characterized by analysis, absence of peaks for vinyl protons at δ 6.25 and 6.34 in the pmr spectrum, and the presence of the N-phenyl peak at δ 7.4. Hy-

(1) This work was supported by Grant GM 11603 from the National Institutes of Health, U. S. Public Health Service.

(2) H. H. Inhoffen, *Ann.*, **508**, 81 (1934).

(3) A. Van Der Gen, J. Lakeman, M. A. M. P. Gras, and H. O. Huisman, *Tetrahedron*, **20**, 2521 (1964).

(4) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Letters*, 615 (1962).

(5) A. J. Solo, H. Sachdev, and S. S. H. Gilani, *J. Org. Chem.*, **30**, 769 (1965).

drolysis of IIIb with 2 *N* potassium hydroxide in butan-1-ol (43 hr) gave the hydrazine IV in good yield as evidenced by absence of carbonyl peaks and appearance of NH peaks in the infrared spectrum, absence of N-phenyl peaks at δ 7.4 in the pmr spectrum, satisfactory elemental analysis, and the trapping of the aniline formed in the hydrolysis as diphenylurea.

I also reacted instantly with ergosterol (V) in acetone–benzene solution at 0° as shown by disappearance of the color of I. The adduct VIa was characterized by the disappearance of the ring-diene absorption pattern for ergosterol at λ_{max} 282 mμ, appearance of a carbonyl doublet at 1675 and 1735 cm^{-1}, and the pmr spectrum which showed peaks at δ 7.4 (N-phenyl), 5.2 and 5.26 (multiplet, integrating for the two vinyl protons at C-22 that were in the same position in ergosterol), and 6.24 and 6.33 (two vinyl protons at C-6 and C-7, J = 4 cps). No hydrogen abstraction–addition product[3] could be isolated.

The adduct VIa was hydrogenated to the tetrahydro adduct VIb, whose pmr spectrum failed to reveal vinylic protons. Hydrolysis of VIb to the hydrazine VII required more drastic conditions compared to IIIb, namely, 120-hr reflux in 3 *N* potassium hydroxide in butan-1-ol. VII was characterized by absence of the N-phenyl peak in the pmr spectrum, by the absence of a carbonyl doublet and the presence of NH peaks in the infrared spectrum, and by elemental analysis.

It has been established that adduct formation in rings A and B of $\Delta^{2,4}$-cholestadiene and ergosterol takes place from the less hindered α side[6] and we therefore assume that the stereochemistry of IIIa and VIa is as depicted.

Experimental Section[7]

$\Delta^{2,4}$-Cholestadiene (II).—The procedure of Stavely and Bergmann[8] was employed with some modification. A cholesterol–alumina (Fischer chromatographic grade) mixture (3:2) was heated for 2.5 hr at 225° (0.4 mm). The yellow mixture was cooled and extracted with methylene chloride, and the extracts were chromatographed (Woelm neutral alumina) using benzene as the eluent to give II in 64% yield: mp and mmp 60–62°.

Adduct IIIa of II with 4-Phenyl-1,2,4-triazoline-3,5-dione (I).—To a solution of II (0.368 g) in dry acetone (25 ml) and a little benzene (to homogeneity) was added dropwise at 0° a freshly prepared[3] solution of I in dry acetone until the reaction mixture remained pale pink. The reaction mixture was chromatographed (Woelm neutral alumina) using benzene and ethyl acetate (95:5) as eluent and recrystallized from ethanol to give IIIa (0.47 g, 90%): mp 200–204°; ν^{Nujol} 1705, 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{35}H_{49}N_3O_2$: C, 77.30; H, 9.08; N, 7.7. Found: C, 77.3; H, 9.3; N, 7.4.

Catalytic Reduction of Adduct IIIa.—IIIa (0.9 g) in ethanol (100 ml) was hydrogenated for 19 hr at 45 psi with 5% Pd–C (300 mg). The solution was evaporated *in vacuo* and the solid material was chromatographed (Woelm neutral alumina) using benzene and ethyl acetate (95:5) as eluent and crystallized from ethanol to give IIIb in near quantitative yield: mp 208–209°; ν^{Nujol} 1705, 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{35}H_{51}N_3O_2$: C, 77.00; H, 9.42; N, 7.7. Found: C, 77.26; H, 9.42; N, 7.4.

Alkaline Hydrolysis of Reduced Adduct IIIb.—IIIb (1.08 g) and potassium hydroxide–butan-1-ol (40 ml, 2 *N*) were refluxed in a nitrogen atmosphere for 43 hr. The solution was evaporated *in vacuo* and the solid material was extracted into methylene chloride, chromatographed (Woelm neutral alumina) using benzene and ethyl acetate (80:20) as eluent, and crystallized from ethanol–ether to give IV (0.439 g, 60%): mp 115–118°, ν^{Nujol} 3400 cm^{-1} (NH) (br).

Anal. Calcd for $C_{27}H_{48}N_2$: C, 80.91; H, 12.08; N, 6.99. Found: C, 80.97; H, 11.90; N, 6.93.

Adduct VIa of V and 4-Phenyl-1,2,4-triazoline-3,5-dione (I).—This was prepared in a similar manner to adduct IIIa from 0.8 g of ergosterol in acetone–benzene. The reaction mixture was evaporated under reduced pressure and crystallized three times from aqueous acetone to give VIa (0.93 g, 85%): mp 190–191.5°; ν^{Nujol} 1675, 1735 (C=O), 3450 cm^{-1} (OH).

Anal. Calcd for $C_{36}H_{49}N_3O_3$: C, 75.63; H, 8.64; N, 7.35. Found: C, 75.47; H, 8.77; N, 7.54.

Catalytic Reduction of Adduct VIa.—VIa (0.57 g) in ethanol (40 ml) was hydrogenated for 16 hr at 50 psi with 5% Pd-C (300 mg). The solution was evaporated under reduced pressure, chromatographed (Woelm neutral alumina) using benzene and ethyl acetate (95:5) as eluent, and crystallized from ethanol to give VIb (0.49 g, 86%): mp 178–182°; ν^{Nujol} 1675, 1740 (C=O), 3435 cm^{-1} (OH).

Anal. Calcd for $C_{36}H_{53}N_3O_3$: C, 75.1; H, 9.2; N, 7.3. Found: C, 74.89; H, 9.02; N, 6.8.

Alkaline Hyrolysis of Reduced Adduct VIb.—VIb (1.7 g) and potassium hydroxide–butan-1-ol (100 ml, 3 *N*) were refluxed in a nitrogen atmosphere for 120 hr and extracted as for adduct IIIb to give VII (0.3 g, 25%): mp 189–192°, ν^{Nujol} 3410 cm^{-1} (NH) (br).

Anal. Calcd for $C_{28}H_{50}N_2O$; C, 78.1; H, 11.6; N, 6.5. Found: C, 77.92; H, 11.66; N, 6.4.

Acknowledgment.—We thank Mr. S. C. Dubickas for his competent assistance.

(6) R. Antonucci and K. J. Sax, *J. Org. Chem.*, **16**, 1356 (1951); K. Tsuda and S. Nozoe, *Chem. Pharm. Bull.* (Tokyo), **8**, 1128 (1960).

(7) Melting points were recorded on a Thomas–Kofler hot stage and are corrected. Infrared and ultraviolet spectra were recorded on Perkin-Elmer spectrophotometers, Models 237 and 202, respectively. Pmr spectra were recorded on a Varian A-60 spectrophotometer and are reported as δ values in deuteriochloroform with tetramethylsilane as internal standard. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn.

(8) H. E. Stavely and W. Bergmann, *J. Org. Chem.*, **1**, 575 (1936).

The Preparation of Triazines Related to 6-Cyano-2,2′-bipyridine[1]

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Received February 8, 1966

For the preparation of 6-cyano-2,2′-bipyridine,6-chloro- or -bromobipyridine was needed. The chloro compound was prepared by converting 2,2′-bipyridine methiodide by an alkaline oxidation with potassium ferricyanide to the hitherto unreported 1-methyl-2,2′-bipyridin-6-one and treating the latter with phosphoryl chloride and phosphorus pentachloride. However, since the halogen in this compound was too unreactive to yield the cyanobipyridine, 6-bromo-2,2′-bipyridine was prepared from the bipyridinone using phosphoryl bromide, phosphorus tribromide, and bromine. This compound had previously been prepared by direct vapor phase bromination of 2,2′-bipyridine.[2] The bromobipyridine was then converted smoothly to 6-cyano-2,2′-bipyridine by cuprous cyanide in pyridine. The melting point observed for the cyanobipyridine was considerably lower than that previously reported.[2]

Starting from 6-cyano-2,2′-bipyridine and using reactions previously described[3,4] for cyanopyridine

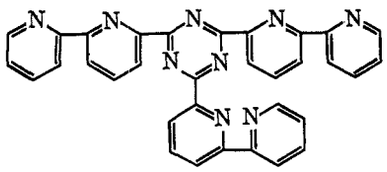
(1) This work was supported by a grant (G-9645) from the National Science Foundation.

(2) F. H. Burstall, *J. Chem. Soc.*, 1662 (1938).

(3) F. H. Case and E. Koft, *J. Am. Chem. Soc.*, **81**, 905 (1959).

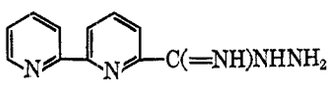
(4) F. H. Case, *J. Org. Chem.*, **30**, 931 (1965).

derivatives there were synthesized 2,4-diamino-6-(2,2′,6-bipyridyl)-1,3,5-triazine (by the action of dicyanodiamide), 2-amino-4,6-bis(2,2′,6-bipyridyl)-1,3,5-triazine (from guanidine), and 2,4,6-tris(2,2′-6-bipyridyl)-1,3,5-triazine (I) (by the action of sodium hydride). The hydrazidine (II) was prepared by the



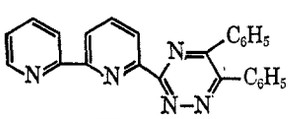
I

action of hydrazine and from it 3-(2,2′,6-bipyridyl)-

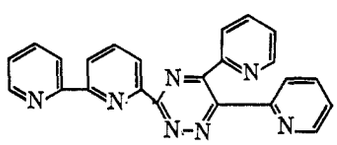


II

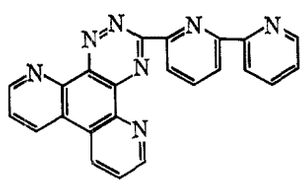
5,6-diphenyl-*as*-triazine (III) (by the action of benzil), 3-(2,2′,6-bipyridyl)-5,6-bis(2-pyridyl)-*as*-triazine (IV) (on treatment with pyridil), and 3-(2,2′,6-bipyridyl)-*as*-triazino[5,6-*f*][4,7]phenanthroline (V) (on treatment with 4,7-phenanthroline-5,6-dione). The triazines de-



III



IV



V

scribed in this paper, all of which contain the ferroin group (=N—C(=)—C(=)—N=), will be tested for metal-chelating ability.

Experimental Section

1-Methyl-2,2′-bipyridin-6-on.—To a stirred saturated solution of potassium ferricyanide maintained at 25° there was added in alternate portions 50 g of 2,2′-bipyridine methiodide[5] and sufficient concentrated sodium hydroxide solution to maintain a constant alkalinity. The reaction was completed by stirring for 0.5 hr at this temperature. Repeated extraction of the aqueous solution with chloroform, removal of solvent, and vacuum distillation yielded 17 g (54.3%) of product, bp 205–210° (8 mm). A sample of the solidified compound, crystallized from benzene–petroleum ether (bp 60–70°), melted at 74–75°.

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.97; H, 5.38. Found: C, 71.28; H, 5.53.

6-Chloro-2,2′-bipyridine.—A mixture of 16 g of 1-methyl-2,2′-bipyridin-6-one, 16 g of phosphorus pentachloride, and 90 g of phosphoryl chloride was heated at reflux for 3 hr. After removal of excess phosphoryl chloride using an aspirator at 100°, the contents of the flask were poured on ice and neutralized with ammonium hydroxide. The precipitate was removed by filtration, dried, and crystallized from petroleum ether (bp 60–70°). The yield of pure product, melting at 61–62°, was 13 g (79.3%).

Anal. Calcd for $C_{10}H_7N_2Cl$: C, 62.98; H, 4.12. Found: C, 62.68; H, 3.91.

6-Bromo-2,2′-bipyridine.—To 3.4 ml of ice-cold phosphorus tribromide was added 2.3 ml of bromine, followed by 50 g of phosphoryl bromide and 7.5 g of 1-methyl-2,2′-bipyridin-6-one. The mixture was heated at 120–130° for 2.5 hr, then poured onto ice and made alkaline with ammonium hydroxide. The dried precipitate, after crystallization from petroleum ether (bp 60–70°), melted at 70–71° (lit.[3] 74°). The yield was 4.5 g (47.4%).

Anal. Calcd for $C_{10}H_7N_2Br$: C, 51.06; H, 3.00. Found: C, 51.15; H, 3.12.

6-Cyano-2,2′-bipyridine.—A mixture of 9 g of 6-bromo-2,2′-bipyridine, 3.9 g of cuprous cyanide, and 15 ml of pyridine was heated at 140–150° for 3 hr. The contents of the flask were then poured into an excess of a concentrated solution of potassium cyanide and allowed to stand overnight. The resulting precipitate was filtered, dried, and extracted with benzene. The residue from the removal of benzene on crystallization from methanol yielded 4.5 g (65.2%) of pure product, mp 130–131° (lit.[2] 151°).

Anal. Calcd for $C_{11}H_7N_3$: C, 72.89; H, 3.90. Found: C, 72.76; H, 4.04.

2,4,6-Tris(2,2′,6-bipyridyl)-1,3,5-triazine.—6-Cyano-2,2′-bipyridine (1.5 g) and sodium hydride (0.15 g) were heated at 130–140° in a test tube in absence of air for 9 hr. After cooling 5 ml of ethanol was added, and the solution was evaporated and treated with water. The precipitate, after extraction with ethanol to remove soluble material, was crystallized from dimethylformamide. The yield of pure product melting at 312–313° was 0.4 g (26.7%).

Anal. Calcd for $C_{33}H_{21}N_9$: C, 72.89; H, 3.90. Found: C, 72.97; H, 4.29.

2,4-Diamino-6-(2,2′,6-bipyridyl)-1,3,5-triazine.—A mixture of 0.75 g of dicyanodiamide, 1.3 g of 6-cyano-2,2′-bipyridine, 0.1 g of potassium hydroxide, and 5 ml of Methyl Cellosolve was heated at 130–140° for 3 hr, and then poured into water. The resulting precipitate, on crystallization from aqueous dimethylformamide, yielded 1.6 g (72.7%) of pure dihydrate, melting at 284–285°.

Anal. Calcd for $C_{13}H_{11}N_7 \cdot 2H_2O$: C, 51.79: H, 5.01. Found: C, 51.38; H, 5.21.

Drying at 120° for 24 hr yielded the anhydrous material.

Anal. Calcd for $C_{13}H_{11}N_7$: C, 59.07; H, 4.11. Found: C, 58.85; H, 4.18.

2-Amino-4,6-bis(2,2′,6-bipyridyl)-1,3,5-triazine.—To a cooled solution of 0.55 g of guanidine hydrochloride in 20 ml of absolute ethanol was added 0.15 g of sodium. After complete solution of the sodium, 1.8 g of 6-cyano-2,2′-bipyridine was added and the mixture was refluxed for 20 hr. The solution was then poured into water, and the precipitate was removed by filtration and dried. Crystallization from dimethylformamide yielded 0.8 g (20%) of pure product melting at 318–319°.

Anal. Calcd for $C_{23}H_{16}N_8$: C, 68.28; H, 3.99. Found: C, 68.05; H, 4.12.

Hydrazidine of 6-Cyano-2,2′-bipyridine.—A mixture of 1.6 g of 6-cyanobipyridine, 5 ml of ethanol, and 5 ml of 95% hydrazine was stirred at room temperature for 2.5 hr. The contents of the flask were then poured into water, and the resulting precipitate was removed by filtration and dried. Crystallization from benzene yielded 1.1 g (57.9%) of product melting at 155–156°.

Anal. Calcd for $C_{11}H_{11}N_5$: C, 61.97; H, 5.21. Found: C, 62.25; H, 5.46.

3-(2,2′,6-Bipyridyl)-5,6-diphenyl-*as*-triazine.—A mixture of 1 g of the hydrazidine of 6-cyano-2,2′-bipyridine and 1 g of benzil in 25 ml of ethanol was refluxed for 2 hr. It was then poured into water, and the precipitate was removed by filtration and dried. Crystallization from ethanol yielded 1.6 g (88.9%) of triazine melting at 184–185°.

Anal. Calcd for $C_{25}H_{17}N_5$: C, 77.48; H, 4.43. Found: C, 77.48; H, 4.66.

3-(2,2′,6-Bipyridyl)-5,6-bis(2-pyridyl)-*as*-triazine.—A solution of 1 g of the hydrazidine of 6-cyano-2,2′-bipyridine and 1.3 g of pyridil in 20 ml of ethanol was allowed to stand overnight. The resulting precipitate was removed by filtration, dried, and crystallized from methanol. The yield of triazine was 1.2 g (66.7%) melting at 164–165°.

Anal. Calcd for $C_{23}H_{15}N_7$: C, 70.92; H, 3.88. Found: C, 71.07; H, 4.08.

(5) F. H. Westheimer and O. T. Benfey, *J. Am. Chem. Soc.*, **78**, 5309 (1956).

3-(2,2′,6-Bipyridyl)-*as*-triazino[5,6-f][4,7]-phenanthroline.—A mixture of 1 g of 6-cyano-2,2′-bipyridine hydrazidine, 1 g of 4,7-phenanthroline-5,6-dione, and 30 ml of ethanol was refluxed 3 hr. The contents of the flask were then poured into water, and the precipitate was removed by filtration, dried, and crystallized from dimethyl sulfoxide, yielding 1.2 g of product melting at 369–370° (57.1%). An analytical sample, melting at 372°, was prepared by crystallization from dimethylformamide.

Anal. Calcd for $C_{23}H_{13}N_7$: C, 71.28; H, 3.88. Found: C, 71.66; H, 3.69.

The Structure of α-Nitro Ketones

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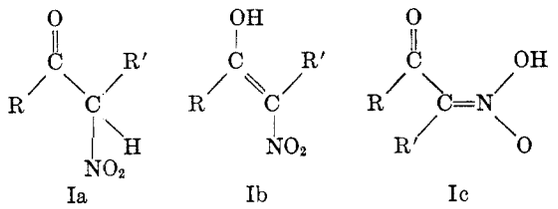
Received January 17, 1966

Based on work done in 1914[1] it has been thought that α-nitro ketones could best be represented by three tautomeric structures, Ia, b, and c.[2] This early work done by bromine titration indicated that α-nitroacetophenone existed in solution as a mixture of material of ketonic and enolic structures. The compound was found to be most enolic in toluene (10.3%) and least so in aqueous methanol (2.7%).



Ia Ib Ic

R = alkyl or aryl; R′ = alkyl or H

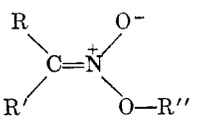
Using spectral techniques Campbell and Pitzer[3] have shown that 2-nitro-1-indanone is isolable as a pure nitro enol. These authors found that the pure enol partially isomerized on standing to a mixture of nitro ketone and nitro enol. Schaub, *et al.*,[4] have determined that 2α-nitro-17β-hydroxy-17α-methyl-5α-androstan-3-one and 2α-nitro-17β-hydroxy-5α-androstan-3-one are mixtures of material of nitro ketone and nitro enol structure. In addition, these workers showed that due to steric interactions the corresponding 4-nitro-3-keto and 16-nitro-17-keto steroids were not enolic. We would like to present data which demonstrates that in general acyclic α-nitro ketones exist in neutral media in the nitro ketone form Ia and that α-nitrocyclohexanone, representative of the cyclic compounds, which was isolatable in the nitro ketone form, isomerizes under mild conditions to a mixture of tautomers.

The proton magnetic resonance (pmr) spectra[5] of 1-nitro-2-pentanone, 2-nitro-3-pentanone, and 3-methyl-3-nitrobutanone in carbon tetrachloride of α-nitroacetophenone and α-nitrocyclohexanone[6] in deuteriochloroform and of α-nitroacetophenone in benzene show only the presence of material of nitro ketone structure. The neat pmr spectra of 1-nitro-2-pentanone, 2-nitro-3-pentanone, and α-nitropropiophenone also give no indication of the presence of enol or *aci*-nitro species in the system. In Table I is given the pmr data on the several α-nitro ketones.

The infrared spectra of the α-nitro ketones also indicated that only material of nitro ketone structure was present. The spectra were run neat and in carbon tetrachloride solution. In neither case was any absorption due to enolic OH observed, no absorption being found below 3.2 μ. The principal absorptions of the compounds occurred at 5.76 μ (ε ~300) and 6.41 μ (ε ~800). These bands are assignable to the carbonyl stretching and the asymmetric nitro stretching vibrations of the molecules. The locations and intensities of these bands were unaltered in going from primary to secondary to tertiary α-nitro ketones.

Isomerization of α-nitrocyclohexanone was carried out either by heating [vacuum distillation at ~100° (0.1 mm)] or by passing the compound through a silica gel column. The other nitro ketones were stable to both the distillation and chromatography conditions. In addition, treatment of the acyclic nitro ketones with excess aqueous sodium hydroxide or excess triethylamine in carbon tetrachloride did not cause isomerization. The compounds were recovered unchanged.

In agreement with other workers[3,4] the infrared spectrum of the cyclic enol showed strong absorption at 6.14 μ and weak absorption at 6.55 μ. Though the 6.14-μ band has been assigned[3,4] to olefin absorption it is equally consistent with C=N absorption. Kornblum[7] has found that nitronic esters II absorb in the region 6.05–6.2 μ and therefore no definite conclusion as to enol structure of the α-nitro ketones can be drawn. The pmr spectrum of the tautomeric mixture shows sharp absorption at τ −3.93. This has been assigned[4] to the OH proton of the nitro enol but is equally consistent with the *aci*-nitro ketone structure; *via* pmr the mixture was determined to be 30.6% enol.



II

R, R′ = H, alkyl or aryl; R″ = alkyl

The isomerization of the cyclic α-nitro ketone to an enolic structure is best interpreted in terms of the instability of the cyclic α-nitro ketone rather than to the stability of the enol. Stuart–Briegleb models indicate that there is severe crowding of the nitro and carbonyl groups in the boat and both chain conformers of the molecule; enolization alleviates this. Enolization also decreases the unfavorable electrostatic interactions between the two polar functionalities.

That the acyclic α-nitro ketones do not substantially exist in a stable enolic form is interpretable in terms of the known weak hydrogen bonding ability of aliphatic nitro compounds. It has been shown *via* infrared and ultraviolet spectra that aliphatic nitro groups form

(1) K. H. Meyer and P. Wertheimer, *Ber.*, **47**, 2374 (1914).

(2) G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p 633.

(3) R. D. Campbell and C. L. Pitzer, *J. Org. Chem.*, **24**, 1531 (1959).

(4) R. E. Schaub, W. Fulmor, and M. J. Weiss, *Tetrahedron*, **20**, 373 (1964).

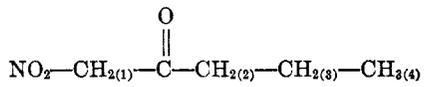
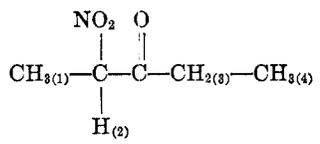
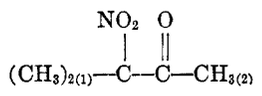
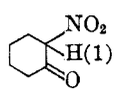
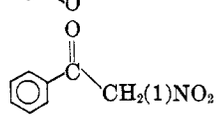
(5) It is estimated that an enol concentration of >1% would have been observable in both the pmr and infrared spectra. We have determined by neat pmr spectra that ethyl acetoacetate contains 7.5% enol. This is in excellent agreement with Burdett and Rogers [J. L. Burdett and M. T. Rogers, *J. Am. Chem. Soc.*, **86**, 2105 (1964)] who determined the compound to be 8% enolic.

(6) The pure nitro ketone isomer.

(7) N. Kornblum and R. A. Brown, *J. Am. Chem. Soc.*, **86**, 2681 (1964).

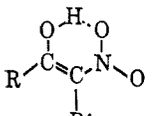
TABLE I

THE PROTON MAGNETIC RESONANCE SPECTRA OF α-NITRO KETONES

Compound	Solvent	τ[a]	Relative areas
	CCl_4	(1) 4.72, (2) 7.49 (3) 8.35, (4) 9.06	...
	Neat	...	(1) 2.00, (2) 1.96 (3) 2.16, (4) 2.88
	CCl_4	(1) 8.32, (2) 4.73 (3) 7.40, (4) 8.89	...
	Neat	...	(1) 2.93, (2) 1.01 (3) 2.00, (4) 3.05
	CCl_4	(1) 8.31, (2) 7.83	(1) 5.95, (2) 3.06
	$DCCl_3$[b]	(1) 4.66 (multiplet) (ring protons) multiplet main peaks at 7.42 and 7.97	(1) 0.95 (ring protons) 8.05
	$DCCl_3$[b]	(1) 4.08 (ring protons) multiplet main peaks at 2.18 and 2.37	(1) 2.05 (ring protons) 4.94

[a] All the signals had multiplicities and coupling constants consistent with the structural assignments. [b] The compound was insoluble in carbon tetrachloride.

weak hydrogen bonds[8] to proton donors. Schleyer[9] has suggested, to account for this weak hydrogen-bonding ability, that the nitro group is an electron-demanding rather than an electron-rich function. In light of this it is reasonable to expect that a hydrogen-bonded nitro enol (III) would not be stable relative to material of *trans* nitro ketone[10] structure and that this structure would not significantly contribute to the ground state of the molecule.



III, R = alkyl or aryl
R′ = alkyl or H

Experimental Section

The alkyl α-nitro ketones were prepared by the method of Hurd and Nilson[11] and were purified by column chromatography on silica gel using 1:1 (v/v) methylene chloride–isohexane as eluent; see Table II for physical data. α-Nitrocyclohexanone,[6] mp 37.5–38.5° (lit.[12] mp 37°), was synthesized by chromic acid oxidation[11] of 2-nitrocyclohexanol prepared by the method of Levy and Scarfe.[13] It was purified by recrystallization from ether–pentane at −70°. Partial isomerization was effected by vacuum distillation[14] or column chromatography through silica gel using methylene chloride–isohexane as eluent. No attempt was made to determine the thermodynamic equilibrium composition.

TABLE II

Compound	Bp or mp, °C	Found, %[a] C	H	N
1-Nitro-2-pentanone	31–31.5	45.72	6.85	10.47
2-Nitro-3-pentanone	88 (10.5 mm) lit.[11] 82–85 (8 mm)[b]	45.91	6.94	10.49
3-Methyl-3-nitrobutanone	29.5–30	45.90	7.02	10.61

[a] Calcd for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.68. [b] 2,4-DNPH mp 102–103° (lit.[11] mp 105–106°).

Anal. Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.29; N, 9.79. Found: C, 50.18; H, 6.40; N, 9.83.

The aromatic α-nitro ketones, α-nitroacetophenone and α-nitropropiophenone, were prepared from benzoyl cyanide by the method of Bachman and Hokama[15]: α-nitroacetophenone, mp 106–106.5° (lit.[16] mp 105–106°); α-nitropropiophenone, bp 124° (2 mm) (lit.[15] bp 124° (2 mm)).

The pmr spectra were run on a Varian Associates Model V-4311 spectrometer operated at 60 Mcps. The τ values were determined using tetramethylsilane (τ 10) as internal standard. No determinations of peak locations were made in the neat spectra. The infrared spectra both neat and in solution were run on a Beckman IR 4 equipped with sodium chloride optics.[17] Molar extinction coefficients were determined in carbon tetrachloride solution.

(8) M. Kuhn, W. Luttke, and R. Mecke, *Z. Anal. Chem.*, **57**, 680 (1963); T. Urbanski, *Bull. Acad. Polon. Sci., Class III*, **1**, 239 (1953); **4**, 87, 381 (1956); Z. Eckstein, T. Urbanski, and W. Sobotka, *ibid.*, **5**, 679 (1957); T. Urbanski, *Tetrahedron*, **6**, 1 (1959); T. Urbanski and D. Ciercierska, *Roczniki Chem.*, **29**, 11 (1955); T. Urbanski, *ibid.*, **31**, 37 (1957); W. F. Baitinger, P. von R. Schleyer, T. S. S. R. Murty, and L. Robinson, *Tetrahedron*, **20**, 1635 (1964); H. E. Ungnade, E. M. Roberts, and L. W. Kissinger, *J. Phys. Chem.*, **68**, 3225 (1964).

(9) W. F. Baitinger, P. von R. Schleyer, T. S. S. R. Murty, and L. Robinson, *Tetrahedron*, **20**, 1635 (1964).

(10) In the acyclic compound a *trans* juxtaposition of the carbonyl and nitro groups eliminates both the unfavorable steric and electronic interactions.

(11) C. D. Hurd and M. E. Nilson, *J. Org. Chem.*, **20**, 927 (1955).

(12) H. Wieland, P. Garbsch, and J. J. Chavan, *Ann.*, **461**, 295 (1928).

(13) N. Levy and C. W. Scarfe, *J. Chem. Soc.*, 1093 (1946).

(14) "Kugelrohr" distillation at ~100° (0.1 mm).

(15) A. B. Bachman and T. Hokama, *J. Am. Chem. Soc.*, **81**, 4882 (1959).

(16) A. J. Jakubowitsch, *J. Prakt. Chem.*, **142**, 37 (1935).

(17) The authors are indebted to Mr. E. Poti and Mr. G. Taylor, Jr., respectively, for their assistance in the determination of the infrared and pmr spectra.

Acid-Catalyzed Rearrangement of Certain 2-Amino-1-tetralones[1]

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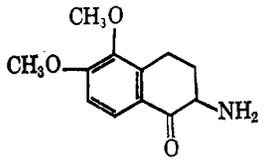
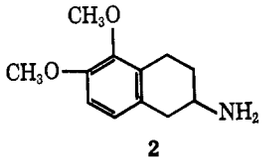
Received February 1, 1966

As a part of a continuing study of emetic agents related to apomorphine, it was desired to convert 2-amino-3,4-dihydro-5,6-dimethoxy-1(2H)-naphthalenone (**1**) to 2-amino-1,2,3,4-tetrahydro-5,6-dimethoxynaphthalene (**2**). When the hydrochloride of **1** was



1



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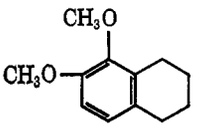

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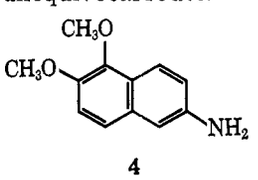
subjected to conditions of the Clemmensen reduction, a complex mixture of substances resulted, from which two products were isolated in low yields: 1,2,3,4-tetrahydro-5,6-dimethoxynaphthalene (**3**) and a second compound which contained nitrogen and whose infrared spectrum indicated the presence of a primary amine and the absence of carbonyl. A nuclear magnetic resonance spectrum of this product precluded the possibility that it was **2**. Elemental analytical data were consistent with the suggested structure of a dimethoxynaphthylamine system, $C_{12}H_{13}NO_2$. It was apparent, however, that the compound was not 2-amino-5,6-dimethoxynaphthalene (**4**), since its physical and spectral properties did not agree with those which had been found for **4** which had been prepared by an unequivocal route.[3]



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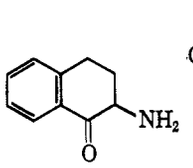

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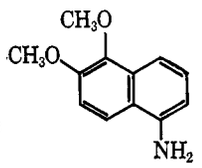

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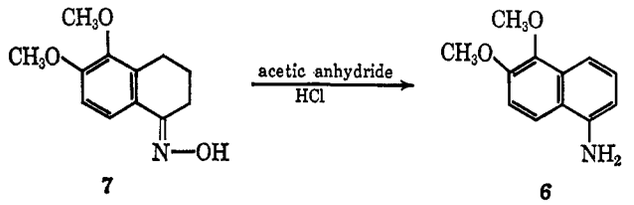
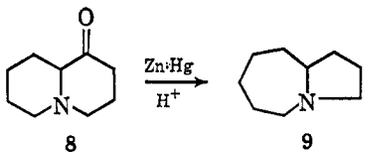
A simpler system, 2-amino-3,4-dihydro-1(2H)-naphthalenone (**5**), when subjected to Clemmensen conditions identical with those employed for **1**, gave rise to low yields of 1,2,3,4-tetrahydronaphthalene and 1-naphthylamine. This result strongly suggested that the amine isolated from Clemmensen treatment of **1** was 5,6-dimethoxy-1-naphthylamine (**6**). That this was indeed the case was confirmed by synthesis of



7 **6**

6 by a Semmler–Wolff reaction on **7**. An infrared spectrum of the Semmler–Wolff product was superimposable upon a similar spectrum of the amino product of the Clemmensen reduction of **1**.

Compound **5** was refluxed in ethanol containing hydrochloric acid; the resulting reaction mixture afforded 1-naphthylamine, but no identifiable tetralone derivative could be isolated. In the Clemmensen reduction of 2-amino-1-tetralones, two reaction paths are involved: reduction of the carbonyl function with accompanying loss of the amino group; and a sequence in which the amino function migrates from the 2 position to the 1 position with concomitant aromatization of the ring. No studies have been conducted to elucidate the mechanism(s) of these transformations. Rearrangement of α-amino ketones under conditions of the Clemmensen reaction has been extensively studied by Clemo and co-workers[4] and by Leonard and co-workers;[5] however, these investigations have been limited to ketones having tertiary amino groups α to the carbonyl, as typified by the conversion of **8** to **9**. No compounds bearing *primary* amino groups α to the ketonic function were reported. Although



8 **9**

this rearrangement of the nitrogen to the carbon bearing the carbonyl group is similar to that observed in the present study, subsequent aromatization or introduction of other unsaturation was not observed. Vorozhtsov and Koptiug[6] and Bhatt[7] have found that oximes of 1-tetralone derivatives undergo the Semmler–Wolff aromatization under acidic conditions, to give aromatic systems having an amino group on the carbon which originally bore the ketonic group.

It would appear that the amino group migration–aromatization reported herein represents a novel rearrangement without precedent in the literature.

Experimental Section[8]

Attempted Clemmensen Reduction of 2-Amino-3,4-dihydro-5,6-dimethoxy-1(2H)-naphthalenone Hydrochloride (1).—Amal-

(1) This investigation was supported in part by a grant (NB-04349), National Institute of Neurological Diseases and Blindness and in part by National Institutes of Health Predoctoral Fellowship GM-19445 (W. K. S.). Abstracted in part from a portion of a thesis submitted by W. K. S. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Iowa, 1966.

(2) To whom all correspondence should be addressed.

(3) W. K. Sprenger and J. G. Cannon, unpublished data.

(4) G. R. Clemo, R. Raper, and H. J. Vipond, *J. Chem. Soc.*, 2095 (1949), and preceeding papers in the series.

(5) (a) N. J. Leonard and W. C. Wildman, *J. Am. Chem. Soc.*, **71**, 3089 (1949); (b) N. J. Leonard, J. W. Curry, and J. J. Sagura, *ibid.*, **75**, 6249 (1953), and preceeding papers in the series.

(6) N. N. Vorozhtsov and V. A. Koptiug, *J. Gen. Chem. USSR*, **28**, 1697 (1958).

(7) M. V. Bhatt, *Experientia*, **13**, 70 (1957).

(8) All boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas–Hoover Uni-Melt apparatus, and are corrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Nuclear magnetic resonance spectra were recorded with a Varian A-60 spectrometer at 60 Mc relative to an internal standard of tetramethylsilane. Infrared spectra were obtained with a Beckman IR 5A spectrophotometer. Vapor phase chromatographic analyses were performed on a F and M Model 500 programmed gas chromatograph apparatus using a silicone gum rubber column and a flame ionization detector.

gamated zinc[9] (15.0 g), 3.0 g (0.012 mole) of 1,[3] 50 ml of ethanol, and 25 ml of concentrated HCl were refluxed for 6 hr, an additional 20 ml of concentrated HCl being added after 3 hr. The reaction mixture was decanted from the remaining zinc amalgam, diluted with 100 ml of water, made strongly alkaline with 20% NaOH, and extracted with four 100-ml portions of ether. The combined ether extracts were washed once with water, dried ($MgSO_4$), filtered, and concentrated to give a dark red liquid (1.5 g) which was dissolved in benzene and was chromatographed on neutral alumina (Merck No. 71707) wet with benzene. The column was eluted with benzene, benzene–ether, and ether–methanol. The eluate fractions yielded 0.28 g of a colorless liquid, 1,2,3,4-tetrahydro-5,6-dimethoxynaphthalene, the infrared spectrum of which was identical with that of an authentic sample; 0.26 g of a yellow liquid, 5,6-dimethoxy-1-naphthylamine **6**, which crystallized on standing; and 0.5 g of a highly impure dark oil which showed bands in the N—H stretching region of its infrared spectrum. Recrystallization of **6** from ethanol gave small, colorless prisms, mp 97.5–98°. An infrared spectrum of **6** ($CHCl_3$) showed a doublet at 2.90 and 2.97 μ (NH_2 stretching) and a strong band at 6.20 μ (NH_2 deformation). A nmr spectrum of **6** ($CDCl_3$) showed a pair of singlets at δ 3.90 and 3.95, superimposed upon a broad band between δ 3.7 and 4.3 (eight protons), and a series of broad, overlapping signals between δ 6.4 and 7.8 (five protons).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.10; H, 6.49; N, 7.11.

A hydrochloride salt of **6** was prepared in ether and was recrystallized from ethanol, mp 254–255° dec.

Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; Cl, 14.79; N, 5.84. Found: C, 60.40; H, 5.95; Cl, 15.31; N, 5.93.

1,2,3,4-Tetrahydro-5,6-dimethoxynaphthalene (3).—This compound was obtained by a modification of the method employed by Stork[10] to prepare 1,2,3,4-tetrahydro-6-methoxynaphthalene. A mixture of 117.4 g (0.625 mole) of 1,2-dimethoxynaphthalene,[11] 2 ml of glacial acetic acid, and 20 ml of Raney nickel catalyst W-2[12] in 400 ml of anhydrous ethanol was hydrogenated in a Parr shaker apparatus at a maximum pressure of 45 psig. Approximately 4 days was required for completion of the hydrogenation. The product was isolated by filtration from the catalyst, concentration of the filtrate under reduced pressure, and distillation, to give 115.5 g (96%) of a colorless liquid, bp 81–83° (0.45 mm), $n^{25}D$ 1.5379, d^{20} 1.060. Schroeter and co-workers[13] reported synthesis of this compound by another route, bp 137–138° (12 mm). Vapor phase chromatographic analysis indicated 96% of the product to be a single component. A nmr spectrum (CCl_4) showed a multiplet centered at δ 1.70 (four protons), a multiplet centered at δ 2.65 (four protons), a pair of singlets at δ 3.70 and 3.73 (six protons), and a series of bands between δ 6.5 and 7.2 (two protons).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 75.20; H, 8.29.

Attempted Clemmensen Reduction of 2-Amino-3,4-dihydro-1(2H)-naphthalenone Hydrochloride (5).—Amalgamated zinc (50 g), 10.0 g (0.051 mole) of 5,[14] 150 ml of ethanol, and 50 ml of concentrated HCl were refluxed 6 hr, an additional 25 ml of concentrated HCl being added after 3 hr. The reaction mixture was decanted from the remaining amalgam, diluted with 250 ml of water, made strongly alkaline with 20% NaOH, and extracted with four 250-ml portions of ether. The combined ether extracts were washed once with water, then were dried ($MgSO_4$). Filtration and concentration of the filtrate under reduced pressure gave 5.1 g of a dark red liquid which was dissolved in benzene and chromatographed as previously described for the Clemmensen reaction mixture of **1**. The eluate fractions yielded 1.7 g (25%) of 1,2,3,4-tetrahydronaphthalene and 1.5 g (21%) of 1-naphthylamine (identified by comparing their infrared spectra with those of authentic samples) and 0.9 g of a highly impure, dark green liquid, which showed weak bands in the N—H stretching region of its infrared spectrum. The alkaline aqueous solution from which 1,2,3,4-tetrahydronaphthalene and 1-naphthylamine had been extracted was made strongly acidic with concentrated HCl, but extraction of this solution with ether failed to provide any identifiable product.

Rearrangement of 2-Amino-3,4-dihydro-1(2H)-naphthalenone Hydrochloride (5) in Ethanol–Hydrochloric Acid.—A solution of 2.0 g (0.01 mole) of **5** in 100 ml of ethanol and 20 ml of concentrated HCl was refluxed for 6 hr. The reaction mixture was cooled, then was made strongly alkaline with 20% NaOH, and was extracted with three 100-ml portions of ether. The combined ether extracts were swirled with $MgSO_4$ for 10 min, then were filtered and concentrated under reduced pressure to give 0.95 g of a yellow-brown liquid which was dissolved in benzene and immediately chromatographed as previously described. The eluate fractions yielded 0.17 g (12%) of 1-naphthylamine (the infrared spectrum of which was superimposable upon that of an authentic sample), and a variety of unidentifiable substances, all of which showed similar infrared spectra: multiple absorption bands in the 2.7–3.1-μ region (N—H and/or O—H stretching) and a broad band in the 5.8–6.2-μ region (C=N and/or C=O stretching).

5,6-Dimethoxy-1-naphthylamine (6).—A modification of the method of Bauer and Hewitson[15] was employed. 3,4-Dihydro-5,6-dimethoxy-1(2H)-naphthaleneone oxime (**7**,[3] 5.0 g, 0.023 mole) was heated in a mixture of 2.5 ml of acetic anhydride and 20 ml of glacial acetic acid for 10 min at 110°, then anhydrous HCl was passed through the solution for 30 min, while maintaining the temperature at 100°. The reaction mixture was cooled overnight in a refrigerator and the gray crystals which separated were collected on a filter. These were washed twice with 10-ml portions of anhydrous ethanol and were air dried to yield 0.6 g (13%) of 5,6-dimethoxy-1-naphthylamine hydrochloride, mp 253–255° dec. An infrared spectrum (Nujol) was superimposable upon a similar spectrum of the hydrochloride salt of the product of the attempted Clemmensen reduction of **1**. The hydrochloride salt obtained above was warmed gently in 5% Na_2SO_3, and the resulting solution was extracted with chloroform, dried ($MgSO_4$), and filtered. The solvent was removed from the filtrate under reduced pressure and the residue was recrystallized repeatedly from ethanol (charcoal), to afford white crystals of 5,6-dimethoxy-1-naphthylamine (**6**), mp 97–98°. An infrared spectrum ($CHCl_3$) of this product was superimposable upon a similar spectrum of the free base form of the amino product isolated from the attempted Clemmensen reduction of **1**.

Acknowledgment.—We acknowledge with thanks the helpful discussions with Professor Ludwig Bauer, University of Illinois, regarding the Semmler–Wolff reaction.

(9) Prepared by shaking 15 g of clean mossy zinc with a solution of 1.5 g of mercuric chloride in 15 ml of water and 15 ml of 5% HCl, followed by thorough washing with water.

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The Conformational Inversion of D-Mannopyranosides Caused by Certain Aglycons

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D-Mannopyranose is found in nature as a constituent of certain polysaccharides, of nucleotides, and of certain glycoproteins. The elucidation of the conformation of D-mannopyranose moiety in these molecules will be very important in studying their structures, biosyntheses, and biological functions. Both α- and β-D-mannopyranoses are believed to have C1 conforma-

TABLE I

CHEMICAL SHIFTS OF METHINE AND METHYLENE PROTONS (δ)

		Chemical shifts[a] (integral of protons)											
		H-1		H-2		H-3		H-4		H-5			
Compd	Solvent	a	e	a	e	a	e	a	e	a	e	Ha-6	Hb-6
I	$CDCl_3$[b]	6.50 d		5.95 q		5.09 q		5.52 t		←4.14–4.86c (3 H)→			
II	D_2O	6.32 d		←3.66–4.70c (6 H)→									
IV	$CDCl_3$		4.60 d	5.51 q	←4.93–5.39c (2 H)→					3.75[c]	←4.20–4.38c (2 H)→		
VI	$CDCl_3$		5.66 d	←5.17–5.59c (3 H)→						←3.63–4.50c (3 H)→			
VIII[d]	$CDCl_3$	5.91 d		5.50 q	5.70 q		5.33[c]			3.82[c]		4.32 q	4.16 q
IX[d]	$CDCl_3$		6.32 d	5.43 q	5.70 q		5.33 t			4.15[c]		4.30 q	4.18 q
X	$CDCl_3$	6.66 d		←5.87–6.32c (3 H)→						←4.32–4.91c (3 H)→			
XI	$CDCl_3$		5.47 d	←4.54–4.97c (4 H), 3.68–4.22c (2 H)→									
XII	$CDCl_3$	6.20 d		←5.10–5.87c (3 H)→						←3.90–4.32c (3 H)→			

[a] For compounds I and II, the position numbers 1, 2, 3, 4, 5, and 6 should be taken to mean 1′, 2′, 3′, 4′, 5′, and 6′, respectively; d, doublet; t, triplet; q, quarter; c, complex, overlapping, or incompletely resolved multiplet; a, axial; e, equatorial. [b] There was no significant change of the proton signals as measured in pentadeuteriopyridine and in various mixtures of deuteriochloroform and benzene. [c] A multiplet center. [d] Reported by Horton and Turner.[4e]

TABLE II

FIRST-ORDER COUPLING CONSTANTS OF METHINE PROTONS[a]

	Coupling constants (cps)[b]			
Compd	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
I	8.7	3.3	3.7	3.7
II	6.5	c	c	c
IV	1.0	2.5	c	c
VI	1.3	c	c	c
VIII[c]	1.1	3.0	9.5	9.0
IX[c]	1.6	3.0	10.0	9.4
X	1.5	c	c	c
XI	1.5	c	c	c
XII	7.5	c	c	c

[a] Measured in the solvents described in Table I. [b] For compounds I and II, the position numbers 1, 2, 3, and 4 should be taken to mean 1′, 2′, 3′, and 4′, respectively; c, the coupling constants could not be determined because of complex, overlapping, or incompletely resolved multiplets. [c] Reported by Horton and Turner.[4e]

tion as predicted on the basis of optical rotatory data[1,2] and the Reeves' conformational instability factors.[3] The conformation has also been confirmed with the derivatives by the nmr spectral analysis,[4] but Lemieux and Morgan[5] have recently reported 1C conformation for *N*-(3′,4′,6′-tri-*O*-acetyl-2′-deoxy-2′-iodo-α-D-mannopyranosyl)pyridinium perchlorate.

In the course of the synthesis of 1,2-*cis* glycosides,[6] we observed by nmr and infrared spectral analyses a conformational inversion of D-mannopyranosides from C1 to 1C by modifying the aglycons. The present paper describes the evidences for the conformational inversion. The derivatives of D-mannopyranose examined are as follows: 7-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosyl)theophylline (I), 7-α-D-mannopyranosyltheophylline (II), 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-mannopyranose (III), methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (IV), methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside (V), *p*-nitrophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (VI), *p*-tolyl 2,3,4,6-tetra-*O*-acetyl-D-mannopyranosylamine (VII), 1,2,3,4,6-penta-*O*-acetyl-β-D-mannopyranose (VIII), 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (IX), and 1,2,3,4,6-penta-*O*-benzoyl-β-D-mannopyranose (X). In addition to these compounds, 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (XI) and 7-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-theophylline (XII) were examined.

Spin–Spin Coupling Constants of Methine and Methylene Protons.—The signals of the ring hydrogens in the nmr spectra were assigned in the usual manner. The chemical shifts of methine and methylene protons are given in Table I, and the first-order coupling constants are given in Table II. As shown in Figure 1, the H-1′ signal in I appears at δ 6.50 as doublet of $J_{1',2'} = 8.7$ cps, which indicates[7–9] the diaxial orientation of H-1′ and H-2′ with a projected angle of *ca.* 180° between the C-1′ and C-2′ carbon–hydrogen bonds. The H-2′ signal appears at δ 5.95 as quartet through coupling with H-1′ and with H-3′. The small value (3.3 cps) of the $J_{2',3'}$ indicates the axial–equatorial orientation of H-2′ and H-3′. The H-3′ signal in I is observed at δ 5.09 as quartet with $J_{3',4'} = 3.7$ cps, which indicates a projected angle of *ca.* 60° between the C-3′ and C-4′ carbon–hydrogen bonds. The H-4′ signal in I is observed at δ 5.52 as triplet with a small spacing of 3.7 cps between the lines, due to equal coupling with the equatorial protons at C-3′ and at C-5′. Owing to the equatorial orientation of the hydrogen at C-2′ in the C1 conformation of D-mannopyranose, the value of $J_{1',2'}$ should be small, without the distinction of α- and β-D configurations. Therefore, the large values of $J_{1',2'}$ in I and II exclude the possibilities of α- and β-D-mannopyranosides in C1 conformation and of the β-D anomer in 1C conformation, and are in good agreement with α-D anomer in 1C conformation. The α-D configuration is also confirmed with the ORD curve of II. The small values of $J_{2',3'}$, $J_{3',4'}$, and $J_{4',5'}$ in I fully support the 1C conformation. On the other hand, the small values of $J_{1,2}$ and $J_{2,3}$, and the large values of $J_{3,4}$ and $J_{4,5}$ in other com-

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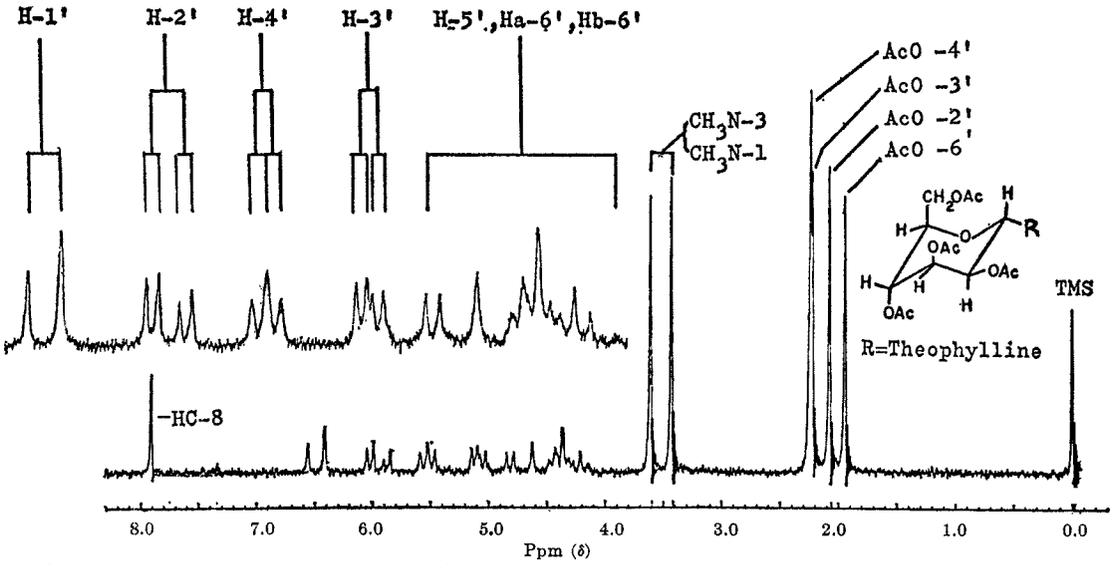

Figure 1.—The nmr spectrum of 7-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosyl)theophylline (I) recorded at 60 Mc in $CDCl_3$.

pounds examined are in good agreement with the theoretical values of the C1 conformation.

Chemical Shifts of Acetate-Methyl Signals.—Equatorial acetate-methyl signals (δ 2.11–2.02) in pyranose ring had been confirmed to shift to smaller δ values than those of axial ones (δ 2.19–2.15),[5,8–14] and acetate-methyl signals on axial and equatorial orientations above the plane of D-hexopyranose ring had been confirmed to shift to relatively a little smaller δ values than those on their orientations below the plane of pyranose ring.[10,13] This tentative rule was applied to the assignment of acetate-methyl signals of the acetylated derivatives to be examined. As shown in Table III, two acetate-methyl signals of axial orientation and one signal of equatorial one appear in I: the two axial signals were assigned to the acetate-methyl signals at C-3′ and C-4′ and one equatorial signal to that at C-2′. The acetate-methyl signals in other compounds examined are in good agreement with those of C1 conformation having one axial orientation at C-2 and two equatorial ones at C-3 and C-4. Therefore, these acetate-methyl signals in I fall within the range expected as 1C conformation.[5,8–14]

C–H Deformation Vibration at the Anomeric Carbon in the Infrared Spectra.—It had been found by the infrared spectral analysis to be able to distinguish the orientation of anomeric hydrogens due to the axial and equatorial C–H deformation vibrations at the anomeric carbon and equatorial C–H deformation vibrations other than the anomeric one.[15–17] The analytical results are shown in Table IV. Compounds I and II show absorption bands in the range from 890 to 895 cm^{-1}, indicating the axial orientation of C–H at the anomeric carbon. On the other hand, IV, X, and XI show absorption bands in the range from 840 to 860 cm^{-1}, indicating the equatorial orien-

TABLE III

CHEMICAL SHIFTS OF ACETATE-METHYL PROTONS[a]

	Chemical shifts (δ)[b]							Presumed conformation
	AcO-2		AcO-3		AcO-4			
Compd	a	e	a	e	a	e	AcO-6	
I		2.06	2.14		2.16		1.93	1C
III[c]		2.06	2.14		2.16			1C
IV	2.20			2.70		2.01	2.00	C1
V[d]	2.15			2.10		2.04	1.99	C1
VI	2.23			2.08		2.07	2.03	C1
VII	2.23			2.02		2.02	2.00	C1
XI	2.13		2.11		2.15			1C
XII		2.06		2.02		2.06	1.90	C1

[a] Measured in $CDCl_3$. The assignments of the acetate-methyl resonances are carried out only on the basis of the empirical rule as described in the text. Recently, D. Horton has shown that the acetate-methyl resonance in the highest field to the C_6 substituents may be erroneous (150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965) but the exact assignment is not definitely settled. [b] For the compound I, the position numbers 2, 3, 4, and 6 should be taken to mean 2′, 3′, 4′, and 6′, respectively; a, axial; e, equatorial. [c] Reported by Hall and Hough.[10] [d] Reported by Sowden, Bowers, Hough, and Shute.[13]

TABLE IV

ABSORPTION BANDS IN THE INFRARED SPECTRA OWING TO THE C–H DEFORMATION VIBRATION AT ANOMERIC CARBON (cm^{-1})[a]

	Deformation vibration		
	Anomeric C–H		
Compd	Axial[b]	Equatorial[c]	Other equatorial C–H
I	895 (m)	...	870 (w)
II	890 (m)	...	880 (w)
IV	...	860 (m)	875 (w)
X	...	840 (w)	883 (w)
XI	...	840 (w)	880 (m)

[a] m, moderate absorption; w, weak absorption. [b] Reported value: 891 ± 7.[15,16] [c] Reported value: 844 ± 8.[15,16] [d] Reported value: 880 ± 8.[15,16] Recently the C–H deformation vibration at C-1 has been amended. A vibration of the whole grouping at the aromeric carbon atom has been found to be responsible for each of these bands, but the exact nature of the vibration is still not definitely settled.[17]

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tation of C–H at the anomeric carbon. These data also support the 1C conformation for I and for II.

All of these data described above fully support the 1C conformation for I and for II, and are inconsistent with any other conformational assignments.

As an essential factor for the conformational inversion, Lemieux and Morgan[5] suggested that a quaternized nitrogen on axial orientation at the anomeric carbon might be necessary for the inversion arising from the electrostatic interaction between the C-1 to N and C-5 to O bonds. From our observation, it is clear that methyl, *p*-nitrophenyl, and bromine molecules as aglycon on axial orientation at the anomeric carbon of D-mannopyranose have no effect on the conformational inversion, and that theophylline molecule as aglycon, on the other hand, has effect on the inversion. In due consideration of these data and of the existing states of pyranoses in natural products, it seems that there might be a relationship between the configurations and molecular weights of substituents on axial orientation and the conformational inversion. But this problem will have to be studied further, in viewpoint of the mechanism and biological meanings.

Experimental Section

All nmr spectra were recorded at 60 Mc with a Varian A-60 spectrometer at its normal operating temperature, and chemical shifts in the nmr spectra were expressed on δ scale in parts per million downfield displacement from tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard. All infrared spectra were measured with a Shimadzu AR-6 spectrophotometer (sodium chloride optics). All compounds were examined in Nujol as phase. An ORD curve was measured with an optical rotatory dispersion recorder (Model ORD/UV-5, Japan Spectroscopic Co., Ltd.). Paper chromatographic examination was carried out on Toyo Roshi No. 51 filter paper by the descending technique, using 1-butanol–water (86:14, v/v) as developing solvent. All melting points are uncorrected.

7-(2′,3′,4′,6′-Tetra-*O*-acetyl-α-D-mannopyranosyl)theophylline (I).[18]—Syrupy 1,2,3,4,6-penta-*O*-acetyl-D-mannopyranose (3.9 g) was treated with theophylline (1.8 g) in an oil bath at 150–160° in the presence of about 0.1 g of freshly fused zinc chloride according to the procedure previously reported.[19,20] The reaction product was dissolved in a small volume of boiling methanol. Unreacted theophylline, which was immediately precipitated, was removed by filtration. The filtrate was allowed to stand in a refrigerator to produce a crystalline product. The product was recrystallized from ethanol: yield 2.1 g (41%); mp 136°; $[\alpha]^{22}D$ +39° (*c* 1.0, $CHCl_3$); R_f 0.77; ν_{max}^{Nujol} 1760 (OAc), 1705 (C=O), and 1550 (C=N) cm^{-1}.

Anal. Calcd for $C_{21}H_{26}N_4O_{11}$: C, 49.41; H, 5.13; N, 11.00. Found: C, 49.16; H, 5.26; N, 11.18.

7-α-D-Mannopyranosyltheophylline (II).—Deacetylation of I was carried out in methanol saturated with ammonia, according to the usual procedure. The reaction product was recrystallized from water: mp 199–200°; $[\alpha]^{22}D$ +86° (*c* 1.0, H_2O); R_f 0.21–0.22; ν_{max}^{Nujol} 3300 (OH), 1700 (C=O), and 1545 (C=N) cm^{-1}; $\lambda_{max}^{H_2O}$ 275 mμ (ϵ_{max} 7.6 × 10^3); ORD (*c* 1.0, H_2O), 17°, $[\phi]_{700}$ +219°, $[\phi]_{600}$ −301°, $[\phi]_{500}$ +356°, $[\phi]_{400}$ +793°, $[\phi]_{350}$ +1230°, and $[\phi]_{300}$ +2330°.

Anal. Calcd for $C_{13}H_{18}N_4O_7$: C, 45.61; H, 5.30; N, 16.37. Found: C, 45.73; H, 5.43; N, 16.17.

The other compounds examined were prepared according to each of the authorized methods: methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside (V),[21] mp 161°, $[\alpha]^{22}D$ −46° (*c* 1.0, $CHCl_3$); *p*-nitrophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (VI),[22] mp 156–157°, $[\alpha]^{22}D$ +103° (*c* 1.5, $CHCl_3$); *p*-tolyl-2,3,4,6-tetra-*O*-acetyl-D-mannopyranosylamine (VII),[23] mp 127–128°; 1,2,3,4,6-penta-*O*-benzoyl-β-D-mannopyranose (X),[24] mp 147–148°; and 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (XI),[25] mp 111°, $[\alpha]^{22}D$ −55° (*c* 2.0, $CHCl_3$). The nmr spectral data of III,[10] of IV,[13] of VIII,[4a] and of IX[4a] are obtained from the reported ones, respectively.

Acknowledgment.—The authors are greatly indebted to Dr. T. Shingu, Department of Pharmacology, Kyoto University, for the measurement of the nmr spectra.

(18) The α configuration was assigned from the data of the nmr spectra of I and II and of the ORD curve of II.
(19) K. Onodera and H. Fukumi, *Agr. Biol. Chem.*, **27**, 526, 864 (1963).
(20) K. Onodera, S. Hirano, and H. Fukumi, *ibid.*, **28**, 173 (1964).
(21) D. F. Mowery, Jr., *Methods Carbohydrate Chem.*, **II**, 328 (1963).
(22) O. Westphal and H. Feier, *Chem. Ber.*, **89**, 582 (1965).
(23) G. P. Ellis and J. Honeyman, *J. Chem. Soc.*, 1490 (1952).
(24) E. Fischer and R. Oetker, *Ber.*, **46**, 4029 (1913).
(25) G. H. Coleman, *Methods Carbohydrate Chem.*, **II**, 397 (1963).

Tagatosazine. A Condensation Product Prepared from 2-Amino-2-deoxy-D-galactose

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Fructosazine,[1] 2,5-bis(D-*arabino*-tetrahydroxybutyl)-pyrazine, is a condensation product of 2 moles of 2-amino-2-deoxy-D-glucose (D-glucosamine), and has been previously prepared from 2-amino-2-deoxy-D-glucose in aqueous solution[2] and in methanol solution.[3] It is also prepared from 2-amino-2-deoxy-D-mannose and an evidence is offered that 2-amino-2-deoxy-D-glucose is epimerized to 2-amino-2-deoxy-D-mannose under the alkaline conditions besides the condensation to the fructosazine.[4]

It is expected that 2-amino-2-deoxy-D-galactose would similarly produce the corresponding pyrazine derivative, 2,5-bis(D-*lyxo*-tetrahydroxybutyl)pyrazine, designated as tagatosazine. This compound has been obtained actually by heating 2-amino-2-deoxy-D-galactose in methanolic alkaline solution. The product has the similar composition as fructosazine but the melting point, 198° dec, and rotatory power, $[\alpha]^{20}D$ −14.5° (*c* 1.0, water), are different from the corresponding physical constants, mp 237° and $[\alpha]^{20}D$ −84.1°, of fructosazine. The infrared spectra of both pyrazine derivatives differ from each other.

Tagatosazine and fructosazine gave the identical oxidative cleavage product, pyrazine-2,5-dicarboxylic acid, which was characterized by converting into the methyl ester. By acetylation with acetic anhydride and pyridine, tagatosazine was converted to the octaacetate, mp 143°, $[\alpha]^{11}D$ −3.6° (*c* 1.0, chloroform). These constants differ from those of fructosazine octaacetate, mp 174°, $[\alpha]^{11}D$ −7.2° (*c* 1.0, chloroform). The infrared spectra of both octaacetates do not overlap each other.

The nmr spectrum[5] of tagatosazine octaacetate is given in Figure 1. The C-3 proton of the pyrazine system (C-1 hydrogen of the 2-amino-2-deoxy-D-

(1) K. Stolte, *Beitr. Chem. Physiol. Pathol.*, **11**, 19 (1908).
(2) M. I. Taha, *J. Chem. Soc.*, 2468 (1961).
(3) C. A. Lobry de Bruyn, *Rec. Trav. Chim.*, **18**, 77 (1899).
(4) S. Fujii, R. Kikuchi, and H. Kushida, *J. Org. Chem.*, in press.
(5) Nmr spectrum was measured with Varian A-60 60-Mcps nmr spectrometer. Tetramethylsilane (τ 10.00) was used as the internal reference standard.

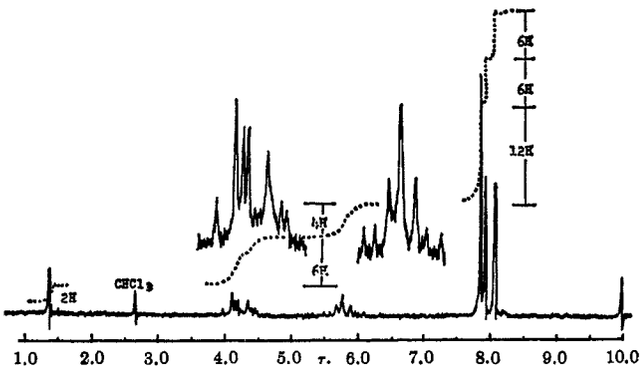
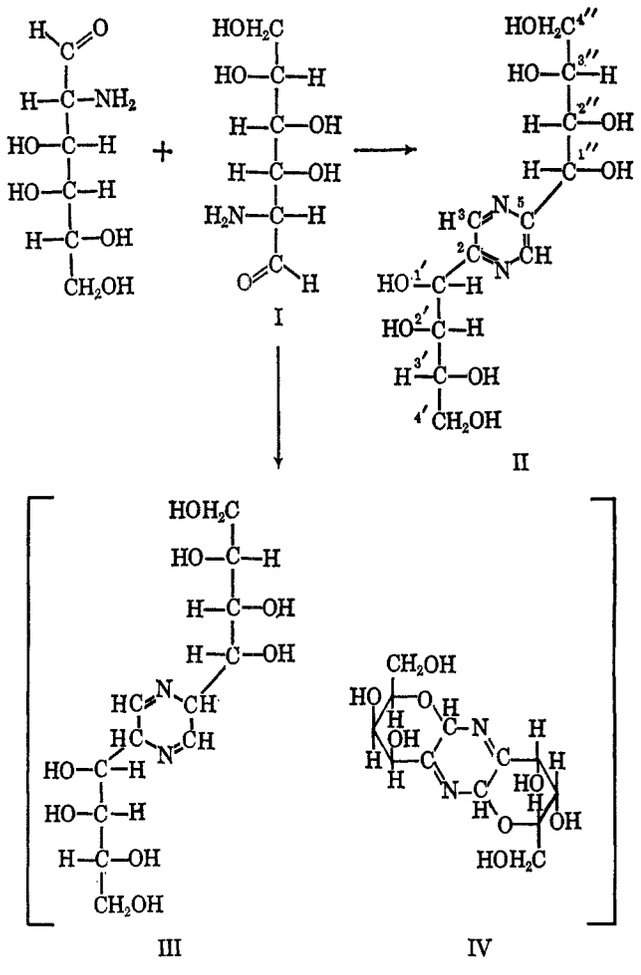


Figure 1.—Nmr spectrum of 2,5-(D-*lyxo*-tetraacetoxybutyl)-pyrazine.

SCHEME I



galactose) appears as a low field singlet, τ 1.04, as in the case of fructosazine. This fact supports the structure II, for in the structure III the proton at C-3 would appear as a doublet through coupling with the proton at C-2. The integral value of protons appears between τ 4.0 and 6.0, corresponding to six methine protons at C-1′, C-2′, C-3′, C-1″, C-2″, C-3″, and four methylene protons at C-4′, C-4″, and between τ 7.8 and 8.2, corresponding to 24 protons of eight acetyl groups. These data exclude the possibility of structure III and IV. (See Scheme I.)

Experimental Section[6]

Tagatosazine.—Thirty grams of 2-amino-2-deoxy-D-galactose hydrochloride was suspended in 150 ml of hot methanol containing 3.6 g of sodium, and after shaking, sodium chloride deposited was filtered off. The filtrate was warmed to 60–65° in water bath under reflux and oxygen was bubbled into the solution for 6 hr. After allowing to stand overnight, this reaction mixture was dissolved in 500 ml of water and passed through an Amberlite infrared-120 (H^+) column (3 × 70 cm). The eluate together with washings was neutralized with Dowex 1 × 8 (HCO^-), 200–400 mesh, and the resin was removed by filtration. After treatment with charcoal, the solution was concentrated *in vacuo* to a syrup. This syrup was dissolved in small amount of methanol, and ethanol was added to this solution to turbidity. Then crystals were deposited; the yield was 2.2 g (9.6%). Recrystallization from water and ethanol furnished pure crystals, mp 198° dec, $[\alpha]^{20}D$ −14.5° (*c* 1.0, water), $\lambda_{max}^{H_2O}$ 274 mμ.

Anal. Calcd for $C_{12}H_{20}N_2O_8$: C, 45.00; H, 6.29; N, 8.75. Found: C, 44.92; H, 6.55; N, 8.68.

2,5-Bis(D-*lyxo*-tetraacetoxybutyl)pyrazine.—This compound was prepared according to the method reported by Taha,[2] for fructosazine octaacetate, by acetylation of tagatosazine (220 mg) with acetic anhydride and pyridine. Recrystallization from acetone and petroleum ether afforded pure crystals, in the yield of 270 mg (61%): mp 143°; $[\alpha]^{11}D$ −3.6° (*c* 1.0, chloroform); ν_{max}^{Nujol} 1740 (C=O), 1230, 1060, and 870 cm^{-1}. For nmr spectrum, see Figure 1.

Anal. Calcd for $C_{28}H_{36}N_2O_{16}$: C, 51.22; N, 5.53; N, 4.27. Found: C, 51.18; H, 5.53; N, 4.25.

2,5-Dimethoxycarbonylpyrazine (Pyrazine-2,5-dicarboxylic Acid Dimethyl Ester) from Tagatosazine.—Tagatosazine (500 mg) was treated with potassium permanganate according to the method of Mager and Berends,[7] and 70 mg of pyrazine-2,5-dicarboxylic acid thus gained was converted to 2.5-dimethoxycarbonylpyrazine by boiling in methanolic hydrogen chloride. Recrystallization from methanol gave 58 mg of pure product: mp 168°; the over-all yield, 19.4%; ν_{max}^{Nujol} 1720 (C=O), 1286, 1153, 1030 (C—O—C), 968, 830 (C=CH), and 763 cm^{-1}.

Anal. Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.03; H, 4.19; N, 13.98.

No depression in the melting point was observed when this material was mixed with a sample of the authentic one from fructosazine, and they showed the identical infrared spectrum.

(6) All melting points are uncorrected.

(7) H. I. X. Mager and W. Berends, *Rec. Trav. Chim.*, **77**, 827 (1958).

An Unusual Wittig Reaction with Benzil

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The reaction of benzil with triphenylphosphine-phenylmethylene, according to Parrick,[1] leads to unilateral condensation, giving *cis*- and *trans*-1,2,3-triphenyl-1-propen-3-one. In a study of synthetic routes to pseudo-aromatic, polycyclic ring systems, we have investigated the reactions of the bisphosphorane (III), derived from 1,8-bis(bromomethyl)-naphthalene (I) *via* (II) (Chart I). Since the only reaction of III which had been reported so far, was its oxidative transformation to acenaphthylene,[2] condensations with benzaldehyde and 2-naphthaldehyde were studied. 1,8-Distyrylnaphthalene (IV, Ar = C_6H_5) and 1,8-di-[β-(2-naphthyl)vinyl]naphthalene (IV, Ar = 2-$C_{10}H_7$) were obtained.[3] In the reaction with benzil, however, a yellow-greenish hydrocarbon $C_{38}H_{22}$ (mp

(1) J. Parrick, *Can. J. Chem.*, **42**, 190 (1964).

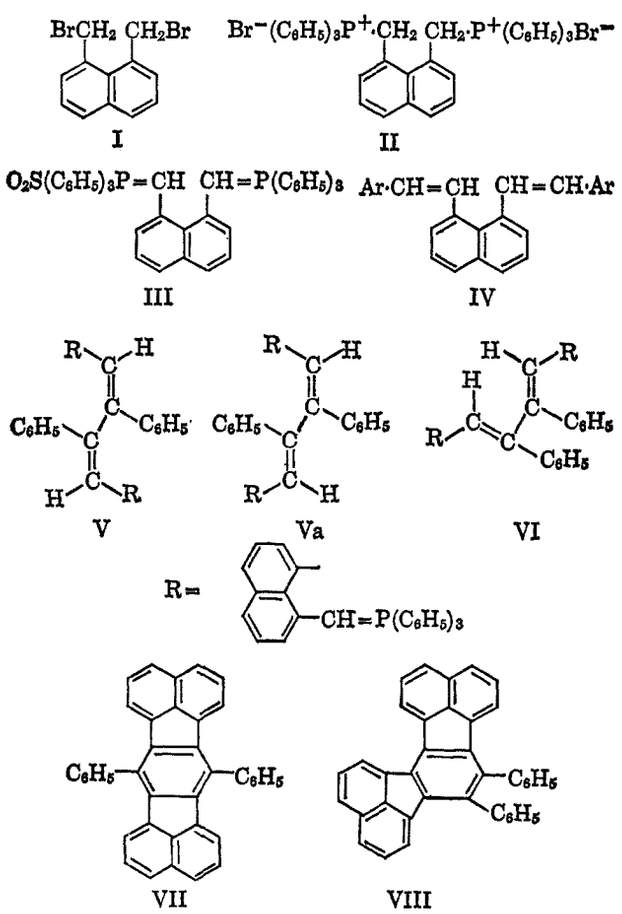
(2) H. J. Bestmann, H. Haeberlein, and O. Kratzer, *Angew. Chem. Intern. Ed. Engl.*, **3**, 226 (1964); J. Bestmann, *ibid.*, **4**, 830 (1965).

(3) The configuration of the compounds, IV, has not been elucidated; the infrared spectrum indicates that at least one of the double bonds (and probably both) has the *trans* configuration, which would have been expected under the experimental conditions used.

TABLE I
ULTRAVIOLET SPECTRA

Compd	Solvent	λ, mμ (log ε)							
Acenaphtho[1,2-*k*]fluoranthene	C_6H_6	417 (4.24)	394 (4.10)			325 (4.72)			
Acenaphtho[1,2-*j*]fluoranthene	C_6H_6		400 (3.92)	354 (4.74)	337 (4.56)		282 (4.14)		
	EtOH			352 (4.74)	336 (4.60)		281 (4.15)	270 (4.18)	242 (4.68)
Our hydrocarbon	C_6H_6		400 (3.93)	358 (4.57)	337 (4.50)		280 (4.29)		
	$CHCl_3$		400 (3.94)	357 (4.58)	339 (4.45)			275 (4.32)	
	CH_3CN			353 (4.65)	335 (4.62)		282 (4.33)	273 (4.33)	240 (4.78)	225 (4.95)
4,5-Di(*p*-chlorophenyl)acenaphtho-[1,2-*j*]fluoranthene	Dioxane		400 (4.01)	355 (4.74)	337 (4.61)	325 (4.23)	282 (4.42)	273 (4.43)	244 (4.84)	224 (5.06)

CHART I



290°) was formed, obviously by reaction of 1 mole of benzil with 2 moles of III and spontaneous dehydrogenation or hydrogen transfer of the product, involving the elimination of four hydrogen atoms. Three intermediary diene compounds can formally be expected from this stoichiometry, *viz.* the *trans–trans* (V), the *cis–trans* (Va), and the *cis–cis* (VI) configurations. V and Va would cyclize to 7,14-diphenylacenaphtho[1,2-*k*]fluoranthene (VII) and VI to 4,5-diphenylacenaphtho[1,2-*j*]fluoranthene (VIII). The decision between these two formulas can be based on the fact that the spectra of the two nonphenylated parent substances of VII and VIII are known[4]; they are characteristically different from each other, and it is justified to assume that the phenyl groups, being in highly hindered positions, will not substantially alter these spectra. Table I shows that formula VIII is preferable. Table I also contains the spectrum of the analogous product prepared from 4,4′-dichlorobenzil and III.

In fact, compounds VII and VIII have been described before[5,6] as having mp >400 and 290–291°, respectively. The latter product is identical with our hydrocarbon (mixture melting point and superimposable ultraviolet and infrared spectra).

(4) See E. Clar, "Polycyclic Hydrocarbons," Vol. 2, Academic Press Inc., New York, N. Y., 1964, pp 357–360.

Experimental Section[7]

(1,8-Naphthylenedimethylene)bis[triphenylphosphonium Bromide] (II).—A solution of 26.2 g of triphenylphosphine in 150 ml of dry xylene was added to a solution of 15.7 g of 1,8-bis(bromomethyl)naphthalene (I)[8] in 50 ml of the same solvent and the mixture refluxed in an inert atmosphere for 1 hr. After cooling, the colorless precipitate was filtered, washed with xylene and petroleum ether and, for the analysis, recrystallized from nitromethane: yield, 37.7 g (90%), mp >300°.

Anal. Calcd for $C_{48}H_{40}Br_2P_2$: C, 68.7; H, 4.8; Br, 19.1; P, 7.4. Found: C, 68.7; H, 4.9; Br, 19.4; P, 6.4.

1,8-Distyrylnaphthalene (IV, Ar = C_6H_5).—In an inert atmosphere, 60 ml of 0.2 *M* lithium ethoxide solution was added slowly to a suspension of 4.2 g of II in a solution of 1.6 g of benzaldehyde in 60 ml of ethanol. The vivid color of the phosphoran disappeared towards the end of the reaction, and upon standing the product crystallized from the solution. After recrystallization from cyclohexane, clusters of colorless needles, mp 148°, were formed which exhibited a strong violet fluorescence in benzene solution: $\lambda_{max}^{dioxane}$ 250 (4.72), 342 mμ (4.34); ν_{max}^{KBr} 960 cm^{-1} (*trans*-C=C).

Anal. Calcd for $C_{26}H_{20}$: C, 93.9; H, 6.1. Found: C, 93.7; H, 6.2.

1,8-Di[β-(2-naphthyl)vinyl]naphthalene (IV, Ar = 2-$C_{10}H_7$).—In the same manner, the reaction of 4.2 g of the bisphosphonium bromide and 1.6 g of 2-naphthaldehyde in 50 ml of ethanol with 60 ml of 0.2 *M* lithium ethoxide solution gave an 80% yield of IV (Ar = 2-$C_{10}H_7$), from benzene yellowish needles of mp 214°: $\lambda_{max}^{dioxane}$ 252 (4.94), 280 (4.40, sh), 300 (4.30, sh), 350 mμ (4.46); ν_{max}^{KBr} 962 cm^{-1} (*trans*-C=C); fluorescence spectrum, 440 mμ (in dioxane).

Anal. Calcd for $C_{34}H_{24}$: C, 94.4; H, 5.6. Found: C, 94.2; H, 5.4.

4,5-Diphenylacenaphtho[1,2-*j*]fluoranthene (VIII).—In the manner described above, 4.2 g of benzil in 200 ml of ethanol was condensed with 16.8 g of II by addition of 200 ml of 0.2 *M* lith-

(5) W. Dilthey, S. Henkels, and A. Schaefer, *Ber.*, **71**, 974 (1938).
(6) D. B. Clapp, *J. Am. Chem. Soc.*, **61**, 2733 (1939).
(7) All melting points are uncorrected.
(8) E. D. Bergmann and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **75**, 2760 (1953).

ium ethoxide solution during 10 min. The solution turned first orange, then dark red, and upon standing for 48 hr, deposited the orange-yellow crystals of VIII. Recrystallization from butanol gave needles of the same color and mp 272°; the compound sublimed at 230–240° (0.2 mm). Even so, the product was not completely pure, and only chromatography of the benzene solution on alumina gave the pure product in yellow-greenish needles of mp 290° (lit.[6] mp 290–291°); it sublimed at 230–240° (0.2 mm) [(lit.[6] 255–260° (3 mm)]; yield, 0.6 g (12%); fluorescence, 485 mμ (in chloroform).

Anal. Calcd for $C_{38}H_{22}$: C, 95.4; H, 4.6. Found: C, 95.5; H, 4.7.

From the mother liquor, no other defined products could be isolated apart from triphenylphosphine oxide which was identified by melting point and mixture melting point. For comparison, the hydrocarbon VIII was synthesized according to Clapp.[6] Chromatography of the benzene solution on neutral alumina and recrystallization from a benzene–methanol mixture gave yellow-greenish needles of mp 290°. The mixture melting point with VIII showed no depression, and the ultraviolet and infrared spectra (in chloroform and potassium bromide, respectively) were identical.

4,5-Di(*p*-chlorophenyl)acenaphtho[1,2-*j*]fluoranthene.—In a similar reaction, using 5.6 g of 4,4′-dichlorobenzil and completed by refluxing the mixture for 5 hr, yellow needles were obtained by recrystallization from benzene (0.4 g, 7%): mp >305°; fluorescence, 480 mμ (in dioxane).

Anal. Calcd for $C_{38}H_{20}Cl_2$: C, 83.4; H, 3.7; Cl, 13.0. Found: C, 83.4; H, 3.5; Cl, 13.0.

Metallocene Polymers. XIV. Metal–Ring Bond Cleavage by Water-Promoted Zinc Chloride[1]

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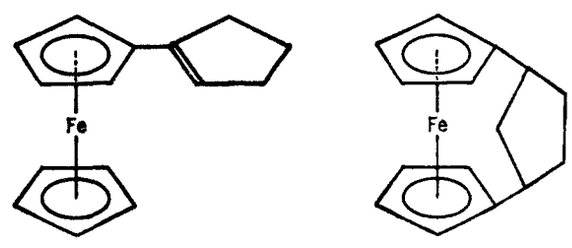
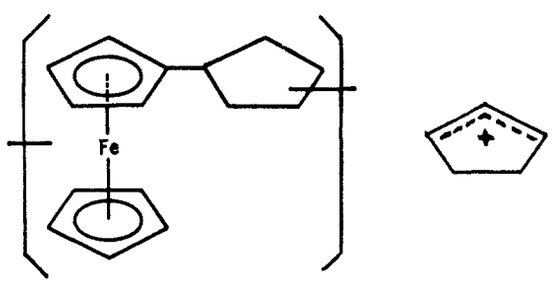
The deleterious effects of strong Lewis acids on the ferrocene system in various solvent media, resulting in cleavage of the metal–ring bond, have been amply documented in the literature. Thus, hydrogen fluoride was reported to cleave ferrocene[2] to give, *via* intermediary cyclopentadiene, cyclopent-1-enylferrocene (I)[3] and a compound independently prepared from ferrocene and aluminum chloride in benzene solution and identified as the heterobridged 1,1′-(1,3-cyclopentylene)-ferrocene[3b] (II). Additional cleavage reactions were described,[3b,c,4,5] some of them giving rise to oligomeric and polymeric cleavage products believed to be composed of such recurring units as exemplified by III. All of these reported reactions proceeded in solution. To this date, however, no mentioning has been made in the literature of analogous cleavage reactions in the melt phase. Such information would be useful in connection with reactions in which molten ferrocene is exposed to the attack of Lewis acids, *e.g.*, in the melt-phase polycondensations of ferrocene with aldehydes.[6] In these Lewis acid catalyzed polycondensation reactions, which for some time have been a major area of interest in this laboratory, the experimental conditions of temperature and heating time occasionally were severe enough to render cleavage of the metallocene system a definite possibility. Such cleavage, with subsequent further involvement of the intermediary cyclopentadiene or its protonated species, the cyclopentenyl cation IV, could conceivably affect the course



I II



III IV

of polycondensation by causing side-chain and cross-link formation or, under less drastic conditions, merely the incorporation of cyclopentenyl and cyclopentylene groups into the products. Analytical evidence for the presence of cyclopentylene moieties in some of the polymers was indeed obtained in this earlier work.[6d]

We have, therefore, undertaken to study the effect of the same catalyst system used in these ferrocene–aldehyde polycondensations, *viz.* water-promoted[7] zinc chloride, on ferrocene in the molten state and in the absence of any additional reactants. When fused for 0.5–2.0 hr at 180° with zinc chloride and water in molar ratios comparable with those generally employed in the ferrocene–aldehyde condensations (*e.g.*, ferrocene–$ZnCl_2$–H_2O, 1.0:0.3:0.1), ferrocene was indeed found to undergo cleavage as expected. Work-up by selective extraction, chromatography, and reprecipitation furnished, aside from 70–90% unreacted ferrocene, the cyclopentylene derivatives II, V, and VI in 1–3% combined yield. The heterobridged II was identified by direct comparison with an authentic product.[8]

(1) Parts I–XIII of this series appeared under the general title: "Ferrocene-containing Polymers." (Part XIII: E. W. Neuse, and K. Koda, *J. Polymer Sci.*, in press.)

(2) V. Weinmayr, *J. Am. Chem. Soc.*, **77**, 3009 (1955).

(3) Structure independently ascertained by (a) K. L. Rinehart, Jr., *et al.*, *ibid.*, **82**, 4111 (1960); (b) S. G. Cottis and H. Rosenberg, *Chem. Ind.* (London), 860 (1963); (c) A. N. Nesmeyanov, N. S. Kochetkova, P. V. Petrovsky, and E. I. Fedin, *Dokl. Akad. Nauk SSSR*, **152**, 875 (1963).

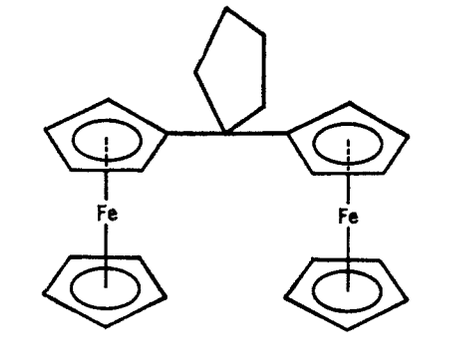
(4) (a) A. N. Nesmeyanov and N. S. Kochetkova, *ibid.*, **126**, 307 (1959); (b) A. N. Nesmeyanov, N. S. Kochetkova, and R. B. Materikova, *ibid.*, **136**, 1096 (1960); (c) S. J. Goldberg, *J. Am. Chem. Soc.*, **84**, 3022 (1962); (d) S. G. Cottis and H. Rosenberg, *J. Polymer Sci.*, **B2**, 295 (1964).

(5) A. N. Nesmeyanov, N. S. Kochetkova, and R. B. Materikova, *Dokl. Akad. Nauk SSSR*, **147**, 113 (1962).

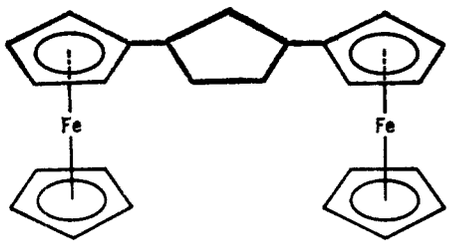
(6) (a) E. W. Neuse and D. S. Trifan, Abstracts, 148th National Meeting of the American Chemical Society, Sept 1964, p 5S; (b) E. W. Neuse, *Nature*, **204**, 179 (1964); (c) E. W. Neuse, K. Koda, and E. Carter, *Makromol. Chem.*, **84**, 213 (1965); (d) E. W. Neuse and E. Quo, *Bull. Chem. Soc. Japan*, in press.

(7) Water formed according to the equation (R = alkyl, aryl, etc.; see ref 6b): $(n + 1)\ C_{10}H_{10}Fe + n\text{RCHO} \rightarrow \text{H}{+}C_{10}H_8Fe\text{–CH(R)}{+}_n C_{10}H_9Fe + nH_2O$.

(8) The CH out-of-plane deformation region in the infrared spectrum of II was characterized by two distinctly separated band groups, a triplet centered near 11.6 μ and a singlet at 12.50 μ, replacing the broad absorption usually exhibited by ferrocene derivatives at 12.2–12.3 μ. We have observed a similar pattern in this region with a large number of heterobridged ferrocene compounds.



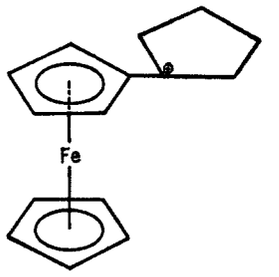
V



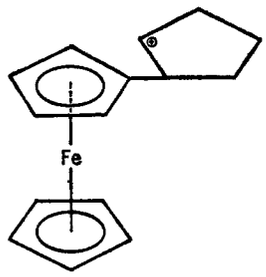
VI

The assignment of V (1,1-diferrocenylcyclopentane) was based on elemental analyses, molecular weight determinations, and spectroscopic evidence. The infrared spectrum (KBr pellet) was closely related to that of ferrocenylcyclopentane,[2] showing moderately strong aliphatic CH stretching absorption at 3.39 and 3.48 μ, the corresponding bending absorption near 6.9 μ, and the well-known bands typical of homoannularly substituted ferrocene. The nmr spectrum (at 60 Mc/sec in $CDCl_3$), while lacking methinyl proton absorption, gave ferrocene (τ 5.85–6.12) and complex alicyclic methylene (τ 7.6–8.3) signals in the approximate 18:8 area ratio. VI was found by elemental composition, molecular weight, and infrared spectrum to be isomeric with V. Independent synthesis by hydrogenation of 1,4-diferrocenylcyclopenta-1,3-diene[9] identified the product as a 1,3-diferrocenylcyclopentane. The fact that only a single saturated product could be isolated in this hydrogenation suggests the *cis* configuration for VI because of greater probability of formation under these conditions, taking both 1,2 and 1,4 addition into account. The position of the methinyl proton nmr signal (two protons) at τ 6.9–7.4, practically coinciding with that of ferrocenylcyclopentane, also supports the *cis* structure,[10] as does the broad, complex methylene resonance (six protons) in the τ region 7.7–8.5, lacking the superimposing triplet signal expected in the *trans* case for the equivalent C-2 methylene protons coupling with the two likewise equivalent methinyl protons. For an unambiguous steric assignment, however, a direct comparison of the nmr spectra of both 1,3 isomers would be required. It is unfortunate that the second 1,3 species, undoubtedly present (along with 1,2 isomers) in one of the several multicomponent, chromatographic fractions left unidentified, could not be isolated in this work.

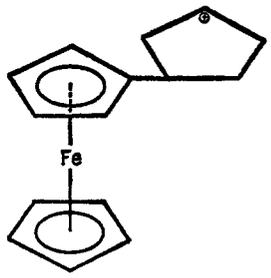
In addition to the mono- and dinuclear ferrocenylcyclopentanes described in the foregoing, polymers were separated in 5–15% yield, which had number-average molecular weights, M_n, of 2000–2500 and roughly corresponded in elemental composition to the unit III much as did the polymers formed in $AlCl_3$-catalyzed solution reactions.[3c,4d] These polymers probably arose from Friedel–Crafts type polyalkylation of intermediary cyclopentenylferrocenes *via* the same equilibrating cations VII believed to be the precursors of II and the



VIIa

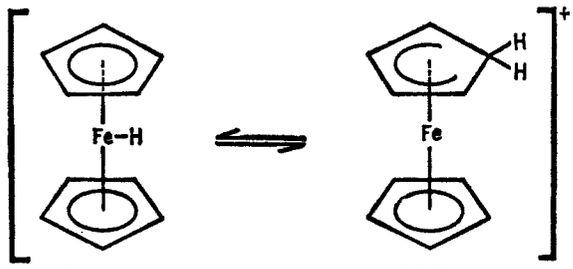


VIIb



VIIc

various diferrocenylcyclopentanes. (In other experiments, an increase above unity of the cyclopentyl–ferrocenyl ratio was observed, indicating additional immediate attack of cyclopentenyl cations IV on ferrocene groups of the original recurring units III.) The



VIIIa VIIIb

relatively high yields in which, despite the low instantaneous concentrations of their precursor cations VII, these polymers were obtained in successful competition with the rapid first-order reactions of these cations by cyclialkylation (to give II) or attack on ferrocene (to give diferrocenylcyclopentanes) are not surprising in view of the enhanced nucleophilicity expected for cyclopentyl substituted, as compared to unsubstituted, ferrocenyl rings. Oligomers with M_n in the 700–1000 range and compositions similar to those of the polymers were also separated (by column chromatography) in these experiments. The methylene–methinyl proton area ratio, on the average in the vicinity of 4, suggests *ca.* 20% of the units in these oligomers to possess the *gem*-diferrocenyl substituent disposition. Since only hexane-soluble material was originally placed on the column used for the separation (whereas the oligomers isolated showed very limited solubility in hexane), one may

(9) E. W. Neuse and R. K. Crossland, paper in preparation.

(10) In the *trans* compound, an upfield displacement would be expected for this signal as a consequence of the ever so limited residence time of each methinyl proton in the positive shielding cone of the corresponding *cis*-ferrocenyl substituent. *Cf.* in this connection D. Y. Curtin, H. Gruen, and B. A. Shoulders, *Chem. Ind.* (London), 1205 (1958).

conclude that these oligomers were generated on the alumina in the column from cyclopentenylferrocenes unstable under these conditions. Failure to isolate I or any of its isomers, which were doubtlessly formed as cleavage products, is consistent with this inference.

It is of interest to note that, while the cleavage reactions discussed above proceeded readily in the presence of the zinc chloride–water system, no such reactions were observed with zinc chloride under anhydrous conditions. This suggests initiation by a protonation step, possibly one involving Fe–H bond formation, with subsequent cleavage *via* the protonated species VIIIa[11] and the tautomeric σ-complex VIIIb leading to the cyclopentenyl cation IV. The latter will immediately attack surrounding ferrocene to give cyclopentenylferrocenes[3b] or their respective cations VII, with further reaction then occurring as proposed.

The demonstrated ease with which the ferrocene system is cleaved by the zinc chloride–water catalyst[12] confirms the earlier suggestion that the presence of cyclopentylene groups should quite generally be expected in ferrocene polymers prepared under comparable experimental conditions. To what extent this competing side reaction will become significant is, then, merely a question of relative reactivities.

Experimental Section

The experiment described below, while not necessarily representing optimal cleavage conditions, may exemplify the general procedure.

The mixture of ferrocene (0.3 mole), zinc chloride (fused, anhydrous, 0.1 mole), and water (0.03 mole), contained in a round-bottom flask, was quickly heated to 180°, and the resulting melt was stirred for 1 hr at this temperature under N_2. The reaction product was washed with water, dried, and extracted with hexane. Extraction of the hexane-insoluble residue with benzene, followed by precipitation with isopropanol from the concentrated extract, gave a tan polymer in 5.9% yield (up to 15% under more rigorous conditions), which was soluble in dioxane, benzene, and chlorohydrocarbons: melting range, 125–135°; M_n, 2030 (determined by vapor pressure osmometry in benzene).

Anal. Calcd for $(C_{15}H_{16}Fe)_n$ (III): C, 71.45; H, 6.40; Fe, 22.15. Found: C, 71.88; H, 6.61; Fe, 21.30.

The hexane extract from the foregoing operations was chromatographed on Alcoa Grade F-20 activated alumina, using hexane as eluent. The first, fast-moving zone eluted gave ferrocene (87.6% recovery). The second band furnished 0.9% yield of crude II, which, after vacuum sublimation, had mp 139° (undepressed by admixture of authentic sample,[2,3b] identical X-ray diffractograms). The third band was rechromatographed on alumina slightly deactivated by a 4-hr exposure to air of 50% relative humidity. In addition to small amounts of unidentified orange oils and a few milligrams of two compounds melting at 74–76° (25.19% Fe, infrared spectrum indicates isomer of V, VI) and 167° (trinuclear; mol wt, 620), the two diferrocenylcyclopentanes V (mp 168–169°) and VI (mp 104–105°, both compounds recrystallized from ethanol) were eluted successively in yields of 0.4 and 0.2%, respectively.

Anal. Calcd for $C_{25}H_{26}Fe_2$ (V and VI: mol wt, 438): C, 68.53; H, 5.98; Fe, 25.49. Found for V: C, 68.54; H, 6.01; Fe, 25.55; mol wt, 445. Found for VI: C, 68.43; H, 5.99; Fe, 25.27; mol wt, 450.

The fourth, multilayer band was extracted with ether–benzene. Reprecipitation of the resinous evaporation residue from dioxane by aqueous isopropyl alcohol (1:1) provided yellow, powdery oligomer (3.9%) which dissolved readily in benzene, dioxane, and halohydrocarbons, but only with difficulty in hexane: melting range, 95–105°; M_n, 790.

Anal. Calcd for $(C_{15}H_{16}Fe)_n$ (III): C, 71.45; H, 6.40; Fe, 22.15. Found: C, 71.01; H, 6.71; Fe, 22.50.

Acknowledgment.—The authors are grateful to Mr. G. P. Kazokas and his staff for obtaining the infrared spectra and molecular weights. Dr. V. Weinmayr, E. I. du Pont de Nemours and Company, kindly provided a sample of ferrocenylcyclopentane for spectroscopic comparison.

(11) M. Rosenblum and J. O. Santer, *J. Am. Chem. Soc.*, **81**, 5517 (1959). One is tempted to propose similar intermediary involvement of protonated species analogous to VIII in the facile aluminum chloride catalyzed ring exchange recently observed with ferrocene compounds [A. N. Nesmeyanov, N. A. Volkenau, and I. N. Bolesova, *Tetrahedron Letters*, **No. 25**, 1725 (1963); *Dokl. Akad. Nauk SSSR*, **149**, 615 (1963); D. E. Bublitz, *Can. J. Chem.*, **42**, 2381 (1964)]. Probably related herewith are the displacement reactions discussed by I. G. Morrison and P. L. Pauson [*Proc. Chem. Soc.*, 177 (1962)], in which the intermediacy of cations of the type VIIIa was postulated by the authors. It would not appear unreasonable to assume that in the last-named reactions, metal–ring bond cleavage, rather than simple substituent displacement, occurred much as in Nesmeyanov's and Bublitz's work, this cleavage being followed by π-cyclopentadienyl ring exchange.

(12) It should be of interest to study analogous reactions involving the more powerfully protonating ZnCl–HCl system, for which enhanced cleavage of the iron-ring bond and, hence, increased abundance of cyclopentylene groups in the products, can be predicted.

Metal–Olefin Complexes. A Convenient Synthesis of *syn*-7-Norbornenol[1a]

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Central Basic Research Laboratory, Esso Research and Engineering Company, Linden, New Jersey

Received November 18, 1965

The preparation of vinyl esters, most notably vinyl acetate, by the reaction of the palladium chloride–ethylene π complex has been reported[2] (eq 1). Re-

$$CH_2{=}CH_2 + NaOOCCH_3 \xrightarrow[PdCl_2]{} CH_2{=}CHOOCCH_3 + Pd + NaCl + HCl \quad (1)$$

cent experiments in these laboratories[3] have revealed that the reaction of palladium chloride complexes of olefins higher than ethylene are sensitive to both olefin structure and reaction medium. The influence of these factors is reflected in some instances by the formation of mixtures of isomeric unsaturated acetates[4] (eq 2)

$$RCH_2CH{=}CH_2 \xrightarrow[NaOOCCH_3]{C_5H_{12},\ PdCl_2} RCH_2CH{=}CHOOCCH_3 + RCH{=}CHCH_2OOCCH_3 \quad (2)$$

and in others by the formation of saturated bifunctional compounds such as di- and haloacetates (eq 3). Subjecting norbornene to the general reaction illustrated by eq 3 leads to the formation of *exo*-2-chloro-*syn*-7-acetoxynorbornane (I), a convenient precursor

(1) (a) Presented in part at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966; (b) Enjay Chemical Laboratories, Linden, N. J.

(2) (a) I. I. Moiseev, M. N. Vargaftik, and Y. K. Sirkin, *Dokl. Akad. Nauk SSSR*, **133**, 377 (1960); (b) E. W. Stern and M. L. Spector, *Proc. Chem. Soc.*, 370 (1961).

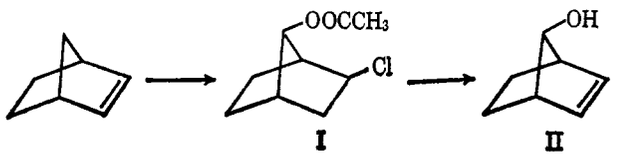
(3) W. C. Baird, Jr., unpublished results. A manuscript entitled, "Metal–Olefin Complexes. The Synthesis of Acetate Esters," is in preparation.

(4) The formation of isomeric acetates had also been previously noted. See ref 2b.

$$RCH{=}CH_2 + NaOOCCH_3 \xrightarrow[X^-]{CH_3COOH} RCHCH_2X + Pd + NaCl + HCl \quad (3)$$

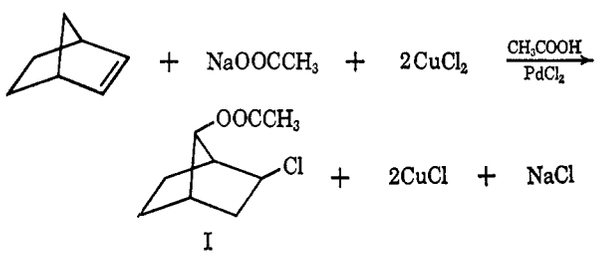
(PdCl$_2$ coordinated to the alkene; OOCCH$_3$ on the adjacent carbon; X = Cl, OOCCH$_3$)

for *syn*-7-norbornenol (II). This two-step synthesis of the *syn*-alcohol offers a convenient and improved route to this difficultly accessible compound.[5]



I II

The chloroacetate (I) is prepared in 50–84% yields by heating norbornene with sodium acetate and cupric chloride in glacial acetic acid containing a catalytic quantity of palladium chloride. The utilization of a large excess of cupric chloride as an oxidation–reduction reagent for the palladium catalyst provides a convenient source of chloride ion, and the reaction stoichiometry is illustrated by eq 4. The high concentration of chloride



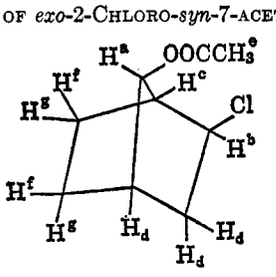
I

ion relative to that of acetate ion accounts for the detection of only 5–10% of diacetate in the reaction product.

The proof of structure of *exo*-2-chloro-*syn*-7-acetoxynorbornane resides in its nmr spectrum (Table I) and in its chemical behavior.

TABLE I

NMR SPECTRUM OF *exo*-2-CHLORO-*syn*-7-ACETOXYNORBORNANE



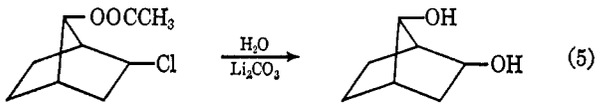
Hydrogen assignment	Cps (δ, ppm)	Area, % Calcd	Area, % Found	Ratio	S_H,[a] (cps)
a	278 (4.63)	7.7	7.1	1	3
b	240 (4.00)	7.7	7.5	1	13
c	153 (2.55)	7.7	7.6	1	7
d	133 (2.21)	23.0	22.8	3	..
e	119 (1.98)	23.0	24.8	3	..
f	96 (1.60), 72 (1.20)	30.8	30.3	4	..

[a] S_H = sum total of coupling constants. See ref 7.

(5) S. Winstein and E. T. Stafford, *J. Am. Chem. Soc.*, **79**, 505 (1957).

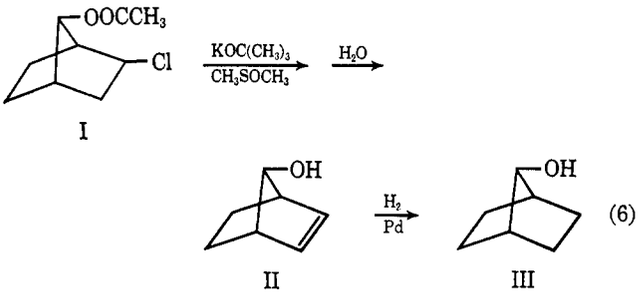
The skeletal positions and stereochemistry of the CHCl and CHOOCCH$_3$ protons were established by the similar nature of their chemical shifts and coupling constants compared to those of *exo*-2-acetoxy-*syn*-7-chloro-5-norbornene;[6] the isomeric 2,3-chloroacetate can be excluded on the same basis.[6] The chlorine atom has been assigned an *exo* configuration since the sum total of the coupling constants of the CHCl proton, S_b[7] = 13 cps, approximates the total coupling constants observed for similar *endo* protons (S = ~11–14 cps).[6–8] If the chlorine atom were to occupy an *endo* position (*exo* proton), then the value of S_b should lie in the range ~14–20 cps.[7,8] Furthermore, the CHCl proton in I does not appear as a doublet of triplets as has been reported for other *endo*-2-substituted norbornyl derivatives,[8] but rather as a broadened triplet.[9]

Hydrolysis of I with aqueous lithium carbonate[10] produced *exo,syn*-2,7-dihydroxynorbornane (eq 5), a result totally consistent with the structure of I and one



that has been previously observed for other *exo,syn*-disubstituted norbornanes.[10,11]

Treatment of I with potassium *t*-butoxide in dimethyl sulfoxide gave *syn*-7-norbornenol (II) in 70% yield (eq 6). The structure of II was established by



II III

its nmr spectrum,[7a] and by comparison of its tosylate and that of its reduction product, 7-hydroxynorbornane (III), with those of authentic samples. No carbonyl-containing compound was detected in the isolated *syn*-alcohol (II), a result which demonstrates chemically the nonexistence of 2,3 substitution since norcamphor would be the anticipated product arising from such a structure.[12]

(6) R. S. Neale and E. B. Whipple, *ibid.*, **86**, 3130 (1964).

(7) Similar treatments of complex spectra have been reported by (a) E. I. Snyder and B. Franzus, *ibid.*, **86**, 1166 (1964); (b) P. M. Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965).

(8) (a) P. Laszlo and P. V. R. Schleyer, *J. Am. Chem. Soc.*, **86**, 1171 (1964); (b) J. C. Davis, Jr., and T. V. van Auken, *ibid.*, **87**, 3900 (1965); (c) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

(9) Treatment of proton H_b as the X portion of an ABX pattern leads to a value of 11 cps for (J_{AX} + J_{BX}). Since the total coupling constant, S_b, is 13 cps, the difference (2 cps) is too small to be attributed to an *exo* H_b coupled with bridgehead proton H_c (J = 2.9–4.3 cps[7b]). A long-range coupling between *endo*-2H–*anti*-7H, J = 2.8 cps, in norbornanes has been observed.[7b] It is suggested that the additional coupling found for H_b in I arises from this source. Thus, the nmr evidence supporting *endo* H_b (*exo* chlorine) appears sound.

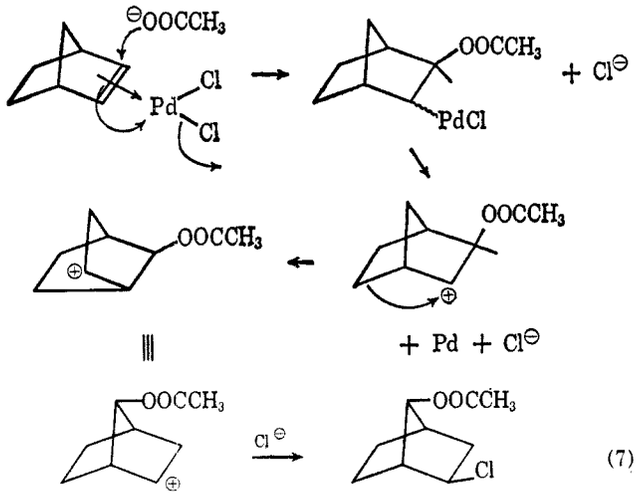
(10) H. M. Walborsky and D. F. Loncrini, *J. Org. Chem.*, **22**, 1117 (1957).

(11) J. D. Roberts, F. O. Johnson, and R. A. Carboni, *J. Am. Chem. Soc.*, **76**, 5692 (1954).

(12) The cleavage of nonenolizable ketones by potassium *t*-butoxide in dimethyl sulfoxide to carboxylic acids has been observed by P. G. Gassman and F. V. Zalar, *Tetrahedron Letters*, **No. 40**, 3031 (1964). A control experiment with norcamphor has shown this ketone to experience only self-condensation under our reaction conditions. The presence of the condensation product was not noted in the *syn*-alcohol reaction mixture.

The preparation of *exo*-2-chloro-*syn*-7-acetoxynorbornane by the reaction of the palladium chloride–norbornene π complex may be of significance regarding the mechanism of the reactions of such complexes, a topic of some controversy. Previous interpretations of the chemistry of palladium chloride complexes have invoked both noncarbonium[13-15] and carbonium ion[16] mechanisms based on deuterium labeling and kinetic studies. Noncarbonium ion mechanisms are considered to involve hydride shifts occurring as the metal–olefin π complex experiences nucleophilic attack.[13,15] Other interpretations favor concurrent nucleophilic attack and rearrangement of the π complex to a σ complex as the rate-determining step. The reaction is subsequently completed by the σ complex undergoing a hydride shift, or by ionization of the σ complex to form a carbonium ion as the reactive intermediate.[16]

The reaction of the palladium chloride–norbornene complex described above provides good evidence in support of the carbonium ion mechanism, for it is difficult to rationalize the formation of *exo*-2-chloro-*syn*-7-acetoxynorbornane on any basis other than rearrangement of a norbornyl cation. The reaction path, as illustrated by eq 7, involves nucleophilic attack by acetate ion on the π complex to generate a β-acetoxyalkyl palladium chloride (σ complex) which subse-



(7)

quently experiences heterolytic cleavage to produce the acetoxynorbornylcarbonium ion.[17] Rearrangement and combination with chloride ion (or acetate ion) leads to the observed product. Reaction paths invoking hydride shift mechanisms[13-15] would yield in this case 2-acetoxy-2-norbornene or 1-acetoxy-2-chloronorbornane (bridgehead acetate), neither of which were detected in this reaction.

Experimental Section

Infrared spectra were recorded using a Beckman IR-5 spectrophotometer. Vapor phase chromatographic analysis was carried out on a Perkin–Elmer Model 154-D fractometer; preparative gas chromatography was performed using a Wilkens Aerograph Autoprep Model A-700. Nmr spectra were determined with a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard. All melting points with the exception of those taken in sealed capillaries are corrected; boiling points are not corrected.

***exo*-2-Chloro-*syn*-7-acetoxynorbornane (I).**—To 200 ml of glacial acetic acid were added 20.0 g (0.21 mole) of norbornene, 16.0 g (0.20 mole) of anhydrous sodium acetate, 50.0 g (0.37 mole) of anhydrous cupric chloride, and 1.0 g (0.056 mole) of anhydrous palladium chloride. The reagents were heated and stirred at 80° for 72 hr. The cooled reaction mixture was filtered, and the filter cake was washed twice with 50–100-ml portions of glacial acetic acid. The filtrate and the washings were combined and added to 1500 ml of water; the product was extracted five times with 100-ml portions of pentane. The combined pentane extracts were washed twice with 25 ml of 10% sodium carbonate solution and twice with 25 ml of water. The pentane solution was dried over magnesium sulfate, and the solvent was removed on a rotary evaporator to give 32.5 g of crude product. Vacuum distillation yielded 29.3 g (84%) of *exo*-2-chloro-*syn*-7-acetoxynorbornane: bp 63–65° (0.1 mm); $n^{20}D$ 1.4833; purity by vpc, 95% (2 m × 0.25 in. diethyleneglycol succinate column, 170°, 30 psig of helium); retention time from air, 10.0 min.

Anal. Calcd for $C_9H_{13}ClO_2$: C, 57.30; H, 6.94; Cl, 18.80. Found: C, 57.81; H, 7.02; Cl, 18.6.

Decreasing the reaction period to 16–24 hr gave product yields of 50–65%; the product purity in these cases was 85–92%.

Hydrolysis of *exo*-2-Chloro-*syn*-7-acetoxynorbornane.[10]—To a solution of 2.5 g (0.037 mole) of lithium carbonate in 50 ml of water was added 2 g (0.011 mole) of 2-chloro-7-acetoxynorbornane. The reaction was refluxed for 36 hr. The reaction mixture was filtered, and the filtrate was extracted continuously with ether for 24 hr. The ether was removed by distillation to yield 1.5 g of crude *exo,syn*-2,7-dihydroxynorbornane. After sublimation at 120° (1.0 mm) the diol melted at 175–176° (lit.[10] 181°). The bisphenylurethane recrystallized from benzene had mp 222–223° (lit.[10] 221°).

***syn*-7-Norbornenol (II).**—To a solution of 10 g (0.053 mole) of *exo*-2-chloro-*syn*-7-acetoxynorbornane in 25 ml of dimethyl sulfoxide was added all at one time a solution of 14 g (0.12 mole) of potassium *t*-butoxide in 75 ml of dimethyl sulfoxide. The reaction was stirred at room temperature overnight (22 hr). To the reaction mixture was added 100 ml of water, and the mixture was steam distilled until 300–500 ml of distillate had been collected. The distillate was extracted five times with 100-ml portions of ether. The combined ether extracts were washed twice with 50 ml of water and once with 50 ml of saturated sodium chloride solution. The ether solution was dried over magnesium sulfate, and the solvent was removed on a rotary evaporator to give 4.1 g (70%) of crude *syn*-7-norbornenol, which crystallized upon standing at room temperature. The alcohol was 83% pure by vpc analysis (2 m × 0.25 in. ethylene glycol succinate column, 125°, 60 ml/min), retention time from air, 6.4 min. The impurities were *t*-butyl alcohol (8.3%), an unknown alcohol[18] (4%), and an unknown hydrocarbon[19] (4.7%). No carbonyl-containing compounds could be detected by infrared analysis. Sublimation [75° (150–200 mm)] increased the purity of the alcohol to 88%. Preparative vpc[20] provided *syn*-alcohol of purity >98%, mp (sealed capillary) 88.5–89.5°. The nmr spectrum was identical with that previously reported.[9]

Anal. Calcd for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 75.64; H, 9.17.

The tosylate of the *syn*-7-norbornenol was prepared and recrystallized from pentane, mp 67.5–68.5° (lit.[5] 67–68°). A sample of *syn*-alcohol was hydrogenated in ethanol over 10% palladium on carbon; the product was identical with an authentic sample of 7-hydroxynorbornane[21] (infrared, vpc, melting point). The tosylate of the reduced alcohol recrystallized from pentane

(13) J. Smidt, *Chem. Ind. (London)*, 54 (1962).
(14) P. M. Henry, *J. Am. Chem. Soc.*, **86**, 3246 (1964).
(15) E. W. Stern, *Proc. Chem. Soc.*, 111 (1963).
(16) I. I. Moiseev and M. N. Vargaftik, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 759 (1965); *Chem. Abstr.*, **63**, 2862 (1965).
(17) The reaction path is similar to that encountered in the oxythallation of norbornene: K. C. Pande and S. Winstein, *Tetrahedron Letters*, **No. 46**, 3393 (1964).
(18) The alcohol was not the corresponding *anti* isomer as evidenced by vpc.
(19) Comparative vpc studies suggested that this material may be cycloheptadiene or cycloheptatriene.
(20) Preparative vpc conditions: 12 ft × ⅜ in. 30% FFAP column (Wilkens Instrument, Walnut Creek, Calif.); column temperature, 125°; injector temperature, 160°; detector temperature, 180°; flow rate, 100 ml/min.
(21) Kindly provided by Dr. B. Franzus of these laboratories.

had mp 52–53° (lit.,[22] 54–55°); a mixture melting point with the tosylate of authentic 7-hydroxynorbornane was 52–53°.

Reaction of Norcamphor with Potassium *t*-Butoxide and Dimethyl Sulfoxide.—To a solution of 1.6 g (0.014 mole) of potassium *t*-butoxide in 15 ml of dimethyl sulfoxide was added 1.28 g (0.012 mole) of norcamphor. The reaction was stirred under nitrogen at room temperature for 18 hr. The reaction mixture was neutralized with concentrated hydrochloric acid and extracted three times with 20-ml portions of ether. The ethereal solution was washed twice with 10 ml of 10% sodium bicarbonate solution from which 0.052 g of oil (3.4% yield) was isolated by neutralization with 6 *N* hydrochloric acid followed by ether extraction. Infrared analysis indicated the material to be a mixture of ketones and carboxylic acid. From the original ether extract 0.92 g (74.5% yield) of neutral material was isolated; infrared analysis indicated a mixture of norcamphor and its self-condensation product.

Acknowledgment.—The author gratefully acknowledges useful discussions with Professors H. C. Brown and S. J. Cristol and Dr. Boris Franzus regarding this work.

(22) S. Winstein and M. Shatavsky, *J. Am. Chem. Soc.*, **78**, 592 (1956).

Thermal Isomerization of Bicyclo[3.2.0]hept-6-en-2-ols[1]

ROBERT L. CARGILL AND DAVID M. POND

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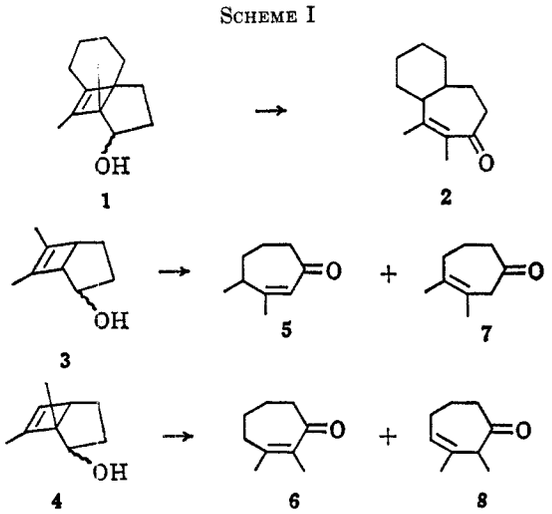
Received March 2, 1966

We have previously reported that pyrolysis of alcohol **1** (Scheme I) provides, along with dehydration products, the α,β-unsaturated ketone **2**.[2] We have also investigated the pyrolysis of alcohols **3** and **4**, obtained by reduction of the corresponding ketones,[3] and we now report our findings.

SCHEME I



Pyrolysis of alcohol **3** at 405° gave a mixture of which ketones **5** and **7** (ratio 3:7) amounted to 38%. Each ketone was isolated by gas chromatography and identified by analysis of the infrared, ultraviolet, nmr, and mass spectra[4] (see Experimental Section for pertinent spectral data). In a similar manner, pyrolysis of **4** gave a mixture containing ketones **6** and **8** (ratio 4:1) as 38% of the pyrolysate. The ratios of ketones **5** and **7**, and **6** and **8**, in the respective pyrolysates are the same as these ratios at thermodynamic equilibrium (25°) in accord with the suggested mode of formation of these ketones.[2] As in the case of **2** the isomer having a tetrasubstituted double bond is the more stable regardless of the α,β or β,γ nature of the double bond.[5]

The ultraviolet spectra of ketones **7**, λ_{max} 295 mμ (ϵ 450), and **8**, λ_{max} 290 mμ (ϵ 236), when compared with those of cycloheptanone, λ_{max} 274 mμ (ϵ 20), and 3-cycloheptenone, λ_{max} 284 (ϵ 80),[6] show marked shifts to longer wavelength and increased extinction. These data indicate efficient overlap of double bond and carbonyl in the excited state which is possible only in the chair conformation.[5,7]

Experimental Section[8]

1,7-Dimethylbicyclo[3.2.0]hept-6-en-2-ol (4).—A solution of 540 mg (3.97 mmoles) of 1,7-dimethylbicyclo[3.2.0]hept-6-en-2-one[3] in 5 ml of anhydrous ether was mixed with a suspension of lithium aluminum hydride. After the reaction was complete the excess reagent was destroyed by addition of water. The ether layer was separated and dried ($MgSO_4$), and the product was obtained by short-path distillation: 470 mg, 86.5%, bath temperature 100° (6 mm), mp 36–37°. Gas chromatography (DEGS, 10 ft, 170°) indicated the presence of a single compound.[2]

Anal. Calcd for $C_9H_{14}O$ (138.11): C, 78.21; H, 10.21. Found: C, 78.11; H, 10.27.

The nmr spectrum of **4** has absorptions at τ 4.43 (1 H, vinyl, coupling with vinyl methyl unresolved), 6.43 (1 H, triplet, $J_{ax} + J_{bx}$ = 8 cps, carbinol), 7.58 (1 H, br, bridgehead), 8.33 (3 H, triplet, vinyl methyl coupled to vinyl H and bridgehead H with equal J = 1.7 cps), and 8.79 (3 H, singlet, bridgehead methyl).

6,7-Dimethylbicyclo[3.2.0]hept-6-en-2-ol (3).—Reduction of 6,7-dimethylbicyclo[3.2.0]hept-6-en-2-one[3] in the above manner gave **3**, bp 110–115° (22 mm) (bath temperature), in 79.5% yield. The clear oil appeared to be a single isomer by glpc.

Anal. Calcd for $C_9H_{14}O$ (138.11): C, 78.21; H, 10.21. Found: C, 78.57; H, 10.33.

The nmr spectrum of **3** has τ 6.15 (1 H, multiplet, carbinol), 7.26 (2 H, br, bridgeheads), 8.35 and 8.47 (broadened singlets over broad multiplet, vinyl methyls).

Pyrolysis of Alcohols 3 and 4.—In general, sealed, evacuated (0.75 mm) Pyrex tubes with an average volume of 1.5 ml containing 30–40 mg of sample were heated in an electric furnace maintained at 405 ± 5°.

Pyrolysis of 3 for 23 min gave a mixture containing at least 13 compounds. Ketones **5** and **7** (ratio 3:7, respectively) amounted to 38% of the volatile pyrolyzate (from glpc areas, uncorrected). Collection gave 55 mg of **7** and 81 mg of **5** from the contents of 35 tubes.

(1) We thank the donors of the Petroleum Research Fund administered by the American Chemical Society for support of this research.

(2) R. L. Cargill, M. E. Beckham, A. E. Siebert, and J. Dorn, *J. Org. Chem.*, **30**, 3647 (1965).

(3) P. E. Eaton, *Tetrahedron Letters*, 3695 (1964); R. Criegee and H. Furrer, *Ber.*, **97**, 2949 (1964).

(4) We thank Professor A. L. Burlingame for mass spectra of ketones **5**, **6**, **7**, and **8**, all of which appeared to be consistent with the assigned structures and Professor G. Büchi who also provided a mass spectrum of **6**.

(5) I. Maclean and R. P. A. Sneeden, *Tetrahedron*, **21**, 31 (1965).

(6) A. C. Cope, S. Moon, and C. H. Park, *J. Am. Chem. Soc.*, **84**, 4843 (1962).

(7) For chemical evidence of this interaction in β,γ-unsaturated ketones, see R. L. Cargill, J. R. Damewood, and M. M. Cooper, *ibid.*, **88**, 1330 (1966), and references cited there.

(8) Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken on a Perkin-Elmer Model 337 grating spectrophotometer in carbon tetrachloride solution. Ultraviolet spectra in 95% ethanol were recorded on a Perkin-Elmer Model 202 spectrophotometer. The nmr spectra were recorded on a Varian A-60 nmr spectrometer[9] in carbon tetrachloride using tetramethylsilane and chloroform as internal standards. Gas–liquid partition chromatographic analyses and separations were performed with an Aerograph, Model A-90-P-3, gas chromatograph. Melting points and boiling points are uncorrected.

(9) We thank the National Science Foundation for funds toward the purchase of the nmr spectrometer.

3,4-Dimethyl-2-cycloheptenone (5), $C_9H_{14}O$, had mol wt 138; λ_{max} 238 mμ (ϵ 11,300); ν_{max} 1660 and 1650 cm^{-1}; and τ 4.28 (1 H, vinyl, coupling with vinyl methyl unresolved), 7.5 (3 H, br, allylic and methylene adjacent to carbonyl), 8.09 (3 H, doublet, J = 1.5 cps, vinyl methyl coupled with vinyl), 8.15 (4 H, multiplet, methylene), and 8.82 (3 H, doublet, J = 6.8 cps, *sec*-methyl).

3,4-Dimethyl-3-cycloheptenone (7), $C_9H_{14}O$, had mol wt 138; λ_{max} 295 mμ (ϵ 450); ν_{max} 1705 and 1661 cm^{-1}; and τ 6.98 (2 H, singlet, methylenes at C_2), 7.6 (4 H, multiplet, methylenes at C_5 and C_7), and 8.00 (2 H, multiplet, C_6), 8.20 (6 H, singlet, vinyl methyls).

Pyrolysis of 4 for 18 min gave a mixture of 13 compounds. Ketones **6** and **8** (ratio 4:1, respectively) amounted to 38% of the volatile pyrolysate. Collection gave 75 mg of **6** and 24 mg of **8** from the contents of 29 tubes.

2,3-Dimethyl-2-cycloheptenone (6), $C_9H_{14}O$, had mol wt 138; λ_{max} 248 mμ (ϵ 8700); ν_{max} 1665 and 1630 cm^{-1}; and τ 7.60 (4 H, multiplet, methylenes at C_4 and C_7), 8.16 (3 H, singlet, α-vinyl methyl), and 8.28 (3 H, broad singlet, β-vinyl methyl). Methylenes at C_5 and C_6 are obscured by methyl signal at 8.28. Ketone **6** formed a red dinitrophenylhydrazone, mp 146–147°. Attempts to form crystalline derivatives of the other cycloheptenones failed.

2,3-Dimethyl-3-cycloheptenone (8), $C_9H_{14}O$, had mol wt 138; λ_{max} 290 mμ (ϵ 236); ν_{max} 1710 and 1680 cm^{-1}; and τ 4.41 (multiplet, vinyl), 8.23 (singlet, vinyl methyl), and 8.82 (doublet, J = 7.0 cps, *sec*-methyl at C_2). The remainder of the spectrum was too ill defined to be of diagnostic value.

Isomerization of Ketones 5 and 7.—To a solution of 26.1 mg of **7** in 25 ml of ethanol was added 150 mg of solid sodium hydroxide and the ultraviolet spectrum was measured peridically over a period of several weeks. The extinction coefficient at 238 mμ increased from an initial value of 3040 to 6050. In like manner the extinction coefficient at 238 mμ of a solution of 3.4 mg of **5** in 25 ml of ethanol fell from 11,300 to 5300. The equilibrium concentration of **5** is, therefore, 28 ± 4%.

Isomerization of ketone 6 was carried out as above. The equilibrium extinction coefficient at 248 mμ was 7250, indicating 80% **6** at equilibrium (ketone **8** had ϵ_{248} 1700).

The Synthesis of 2-Phenyl-1,3-di(4-pyridyl)-2-propanol

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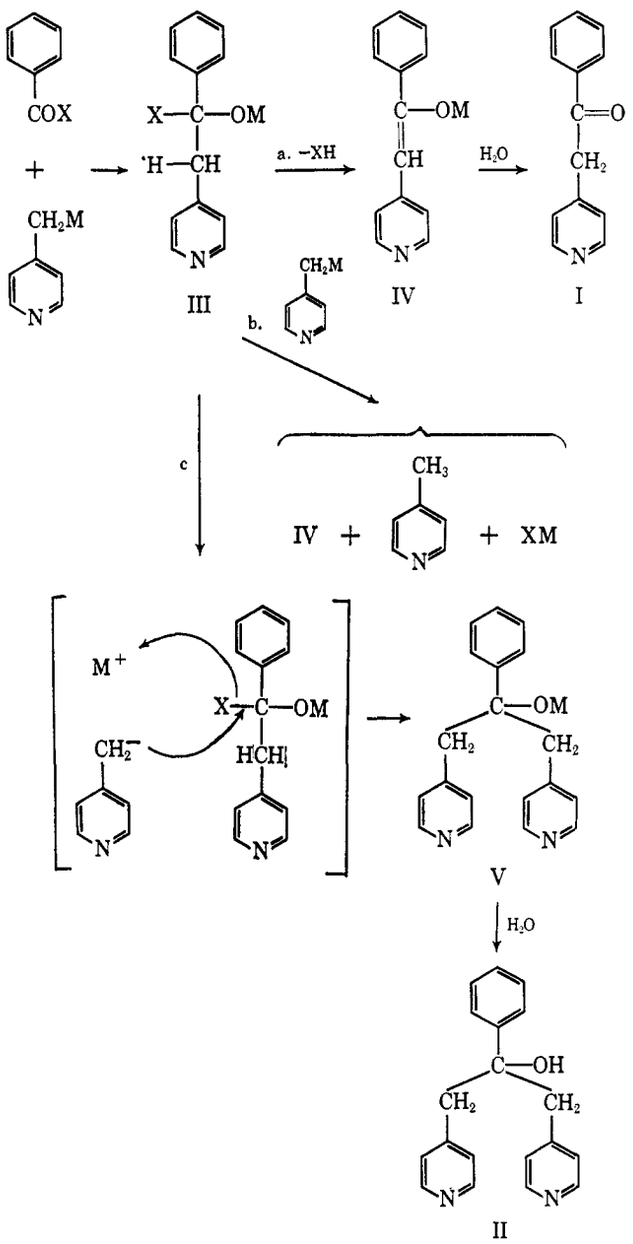
In connection with other work[1] large quantities of 4-(phenacyl)pyridine (I) were required. Using a variation of the method of Raynolds and Levine[1,2] we prepared compound I in several large batches, and isolated in some of these reactions small amounts (<2%) of the less soluble 2-phenyl-1,3-di(4-pyridyl)-2-propanol (II).

Since it had been reported that tertiary carbinols of this type were not formed under these conditions and could not be prepared from phenacylpyridines,[2] we studied this reaction and found that these substituted propanols can in fact be readily prepared by the reaction of picolyllithium with esters or acid chlorides. However, when we reexamined the reaction of picolylsodium and picolyllithium with phenacylpyridine under a wide variety of conditions (varying time, temperature, and solvents), we isolated only unchanged starting materials and therefore concur with Raynold's and Levine's,[2] explanation that picolylsodium (or picolyllithium) adds to phenacylpyridine by a process of anion formation to give the sodium (or lithium) enolate of I.[3]

It is apparent therefore, that in this instance, formation of the tertiary carbinol II cannot proceed *via* the ketone I. The yields of I and II, respectively, in such a reaction must depend on the relative ease with which an intermediate (III) can either be attacked further by picolyllithium to give the salt of II, or can undergo elimination to form the stable enolate IV.



By varying both M and X, we have shown that the formation of the carbinol from such an intermediate is strongly influenced by the metal in the order Mg < Na < Li. We have also shown that the over-all yield

(1) R. I. Fryer, R. A. Schmidt, and L. H. Sternbach, *J. Pharm. Sci.*, **53**, 264 (1964).

(2) S. Raynolds, and R. Levine, *J. Am. Chem. Soc.*, **82**, 472 (1960).

(3) The yield of tertiary carbinol formed by the reaction of a ketone with a Grignard reagent has been reported to be substantially increased when carried out in the presence of an excess of metal halide: C. G. Swain and H. B. Boyles, *ibid.*, **73**, 870 (1951). We have also attempted to form compound II from I by the addition of a large excess of lithium chloride to the reaction mixture but were unable to detect any trace of the carbinol on work-up.

TABLE I

COMPARATIVE YIELDS OF 4-PHENACYLPYRIDINE (I) AND 2-PHENYL-1,3-DI(4-PYRIDYL)-2-PROPANOL (II)

	Yield of products, %									
	X = OCH_3		X = OC_2H_5		X = $OCH_2C_6H_5$		X = OC_6H_5		X = Cl[a]	
M	I	II	I	II	I	II	I	II	I	II
MgBr	24	1.4	NI[b]	1.2	NI	5	19.5	2.0	...	...
Na[c]	...	...	56 ± 11	11 ± 1	77 ± 4	11 ± 3	62 ± 2	15 ± 1	NI	8.3 ± 1
Li[c]	55 ± 6	37 ± 6	56 ± 2	41 ± 2	55 ± 3	35 ± 4	42 ± 5	48 ± 2	48 ± 4	48 ± 5

[a] For the synthesis of II from esters there was no temperature dependence, while for the acid chloride the reaction was best carried out at −20°. [b] NI = not isolated. [c] Per cent yields are reported as averages of results from several experiments carried out under identical conditions.

of II obtained in these reactions was relatively independent of X (Table I). All of these reactions were carried out in the normal manner used for the preparation of carbinols; *i.e.*, the acid chloride or the ester was added to an excess of picolyllithium.

In order to obtain some insight into the mechanism of attack of the second molecule of picolyllithium on the intermediate, two comparative experiments were carried out. Two solutions of benzoyl chloride were first treated with an equimolar amount of picolyllithium. In one experiment the intermediate thus formed was treated immediately with 1 additional mole of picolyllithium. In the other experiment the intermediate was stirred for 5 hr at −20° in an atmosphere of dry nitrogen before the second mole of picolyllithium was added. Comparison of the yields of compounds I and II obtained in each case (58:40% and 84:12%, respectively) suggests that the intermediate formed (III) is probably unstable and can undergo intramolecular elimination to the enolate IV as shown by path a.

Intermolecular attack of III by additional picolyllithium (in an acid–base type of reaction) could again lead to IV as illustrated by path b. An indication that the major reaction can proceed by this second route was demonstrated in Raynold's and Levine's work,[2] where a low yield of I was obtained when the molar ratio of reactants was 1:1,[4] whereas an extremely high yield of I was isolated when the molar ratio of reactants was 2:1. In our own work, where picolyllithium and benzoyl chloride were used, it would appear that I is formed by the intramolecular route since optimal yields of I were obtained when an equimolar ratio of reactants was employed. Furthermore, an excess of picolyllithium had an adverse effect on the yield of I while the yield of II was increased. For the preparation of II a molar ratio of 5:2 was optimal.

Thus for an optimal yield of I in the case where conditions are unfavorable for the synthesis of II (path b), a 2:1 molar ratio of reactants would be required. For an optimal yield of I under conditions favorable for the synthesis of II (path c) a 1:1 molar ratio would be required (making path a the operative mechanism). We have in fact prepared I under conditions favorable for the synthesis of II using an equimolar ratio, and obtained a 54% yield of I and an 11% yield of II.[5] These yields are comparable to those obtained where we allowed the intermediate to stand for 5 hr.

It is reasonable to assume from the above discussion, that the course of the reaction by either path b or c would depend on the relative electrophilic character of the two carbon atoms involved. Only the OM and X groups are variable and both would be expected to have an effect on the carbon atom to which they are attached. This was verified by the sequence for OM, which we found for path b to be Na > Li and for path c to be Li > Na.

We were unable to detect any substantial increase in the carbonium ion character of the carbon atom attached to the phenyl ring by making R a better leaving group. We observed differences in the yields of products only for X = OC_6H_5 and X = Cl where M = Li (Table I). Thus it would appear qualitatively, that for increasing the carbonium ion character of the adjacent carbon atom $OCH_3 \simeq OCH_2C_6H_5 < OC_6H_5 \simeq Cl$.

Experimental Section

This section describes the synthesis of 2-phenyl-1,3-di(4-pyridyl)-2-propanol II from benzoyl chloride and 4-picolyllithium.[6] This reaction gave optimal yields of the carbinol. The only difference in reaction conditions when esters were employed was the addition of the ester to the picolyllithium at room temperature. Melting points were determined microscopically on a hot stage and were corrected.

2-Phenyl-1,3-di(4-pyridyl)-2-propanol (II).—A commercial (Foote Mineral Co.) ether–benzene solution of phenyllithium (0.25 mole, total volume 135 ml) was added over 1 hr to a stirred solution of 4-picoline (23.4 g, 0.25 mole) in tetrahydrofuran[7] (100 ml) in an atmosphere of dry nitrogen. The reaction mixture changed from blood red to dark brown during the addition. There was no appreciable heat of reaction (the temperature was kept at approximately 30°). When the addition of phenyllithium had been completed, the solution of picolyllithium was stirred for 15 min longer, and then cooled to −20° in a Dry Ice–acetone bath. A mixture of benzoyl chloride (14.1 g, 0.1 mole) and tetrahydrofuran[6] (50 ml) was added over 50 min, while the temperature was kept at −20 ± 1°. The pale green reaction mixture was stirred at −20° for 1 hr and at room temperature for 1 hr and then 15 ml of water was added dropwise. Ice (50 g) was added followed by 100 ml of ether with vigorous stirring. The mixture was next transferred to a large separatory funnel and acidified with 3 *N* hydrochloric acid (200 ml). The acid layer was separated and the organic phase was extracted with 3 *N* hydrochloric acid (three 50-ml portions). The combined acid extracts were washed with ether (three 100-ml portions). Ice (200 g) was added to the acid solution which was then made basic with ammonium hydroxide while the temperature was kept about 10°. The two products (I and II) precipitated as solids which were filtered and washed with water (three 75-ml portions). The precipitate was partitioned between methylene chloride (60 ml) and water (80 ml) and the mixture was shaken thoroughly to remove inorganic salts and the methylene chloride soluble 4-(phenacyl)pyridine I. The insoluble residue (II) was removed by filtration, washed with water (two 300-ml portions), methylene chloride (two 25-ml portions), and ether (30 ml), and was dried in a vacuum oven at 50° for

(4) The ratios throughout are given for picolylmetal–acid derivatives, respectively.

(5) Also isolated from this reaction was 16% of the known enolate ester of IV, α-4-pyridylmethylenebenzyl alcohol benzoate: W. von E. Doering and W. E. McEwen, *J. Am. Chem. Soc.*, **73**, 2104 (1951).

(6) During the course of this investigation a number of analogous di(4-pyridyl)-2-propanols were prepared. Physical data for these compounds are given by B. Brust, R. I. Fryer, and L. H. Sternbach, in Belgium Patent 645,241 (Sept 16, 1964); *Chem. Abstr.*, **63**, 13223e (1965).

(7) Purified by filtration through grade I neutral alumina.

15 hr to give 16.5 g of product, mp 92–99°[8] (resolidifies and remelts at 166–168°). Recrystallization from an acetone–water mixture gave 15.5 g (53.4%) of the pure carbinol II, as white prisms, mp 167.5–169°.

Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: 78.90; H, 6.04; N, 9.59.

The methylene chloride solution obtained from the separation of the mixture of products was washed with water, dried, and evaporated. Recrystallization of the residue from a mixture of dichloromethane and hexane gave 8.6 g (43.7%) of pure 4-(phenacyl)pyridine (I) as white prisms, mp 113–115°.[2]

Acknowledgment.—We are indebted to Dr. A. Steyermark and his staff for the microanalyses and to Mr. S. Traiman for the determination of infrared spectra.

(8) The compound is polymorphic and melting points of 117–118° and 126–127° have also been observed. Recrystallization from acetone however raises the melting point to 167.5–169°.

1,3-Dipolar Cycloaddition of Carbon Disulfide to a Nitrile Oxide[1]

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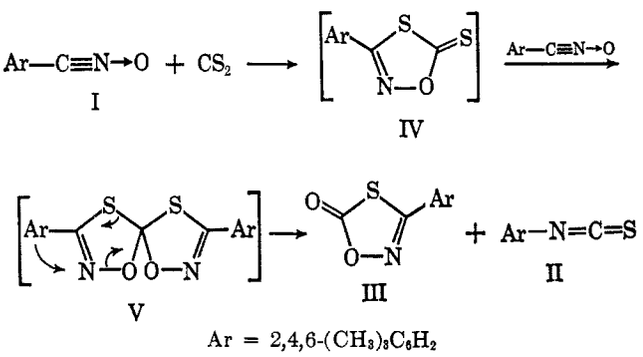
Reports on the reactions of nitrile oxides with thiocarbonyl functions[2] have not heretofore included carbon disulfide. We have found that 2,4,6-trimethylbenzonitrile oxide[3] (I) reacts with carbon disulfide at 80–90° to form mesityl isothiocyanate (II) and 3-mesityl-1,4,2-oxathiazoline-5-one (III). The latter compound is analogous to the 5,5-disubstituted (alkyl, alkoxyl, or alkylthio) 1,4,2-oxathiazolines which have been obtained using other thiocarbonyl compounds.[2] See Scheme I.

SCHEME I



These products could arise by prior formation of the thione (IV) by a conventional 1,3-dipolar cycloaddition, followed by rapid reaction of the thione with a second mole of nitrile oxide to give the spiro intermediate (V),[4] and thermal decomposition of V to form the observed products. A "thionecarbonate" such as IV would be expected[2] to react with a nitrile oxide under much milder conditions than were required to cause reaction of I with carbon disulfide. The isothiocyanate is a well-known compound and has been observed[2,5] as a product in reactions of nitrile oxides with various sulfur compounds. The oxathiazoline-5-one has infrared absorption at 1796 cm^{-1}, which is characteristic of a "carbonate" carbonyl group in a five-membered ring,[6] and shows no absorption above 3100 cm^{-1}. This compound decomposes above 150° with evolution of an odorless gas and forms mesityl isothiocyanate.

An attempt to obtain the same heterocycle using carbon oxysulfide in toluene under the same reaction conditions returned only the starting mesitonitrile oxide. Anthracene-9-nitrile oxide[3] under the same reaction conditions with carbon disulfide gave only the isothiocyanate.

Production of mesityl isothiocyanate from the nitrile oxide and thiocyanate ion as recently reported[5] has been verified. Use of buffered solutions at pH 5–7 in our case gave the same result.

Compounds I and III will be screened for radioprotective activity, since they possess reactive functions that should readily combine with cellular thiols.

Experimental Section

Melting points were determined in capillaries on a Mel-Temp aluminum block. Infrared spectra were obtained from a Perkin-Elmer Infracord 137B with sodium chloride optics. Evaporations were carried out with a rotary evaporator and water aspirator. Analyses were done by Carol K. Fitz, Needham Heights, Mass.

Reaction of 2,4,6-Trimethylbenzonitrile Oxide with Carbon Disulfide.—A 250-ml conical flask was charged with 8.05 g of 2,4,6-trimethylbenzonitrile oxide[3] (0.05 mole) and 100 ml of dry carbon disulfide,[7] capped with aluminum foil and sealed in a 1000-ml Parr bomb. The bomb was placed in a water bath preheated to 80°, maintained at 80–90° for 22 hr, then cooled to room temperature before opening. The light yellow solution was freed of carbon disulfide on a water bath, and the clear oil remaining was taken up in 50 ml of hexane and cooled overnight at −15° to complete crystallization. The large, white prisms were recrystallized from 50 ml of hexane to give **3-mesityl-1,4,2-oxathiazoline-5-one (III)**: 1.71 g (31%); mp 72–73.5°; ν_{min}^{Nujol} 1796, 1741, 1052, 900, 857, and 725 cm^{-1}. Five recrystallizations from hexane gave the analytical sample: mp 75–76°; dec pt 150°.

Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.8; H, 5.0; N, 6.3. Found: C, 60.0; H, 5.2; N, 6.3.

Heating a sample in a 200° oil bath for a few seconds produced **mesityl isothiocyanate**: mp 59–61° (lit. 63°,[8] 61–62°[5]).

The hexane liquors were combined and concentrated to about 20 ml, cooled, and seeded. This yielded 0.40 g of **mesityl isothiocyanate**, mp 57–59°; a second crop of less pure material comprised 4.78 g. The crude material (6 g) was recrystallized twice from hexane and once from methanol giving 1.75 g of large, white spars, mp 60–62°.

Anal. Calcd for $C_{10}H_{11}NS$: C, 67.8; H, 6.2; N, 7.9. Found: C, 67.3; H, 6.2; N, 8.1.

Reaction of Anthracene-9-nitrile Oxide with Carbon Disulfide.—The above reaction conditions were applied to 1.1 g of anthracene-9-nitrile oxide.[3] There was obtained 1.3 g of yellow solid, mp 125–136°, $\nu_{min}^{CHCl_3}$ 2090 cm^{-1}, characteristic of isothiocyanates, and a sodium fusion test for sulfur was strongly

(1) Part of a project supported by grant RH 00297 from the Division of Radiological Health, Bureau of State Services, U. S. Public Health Service, Bethesda, Md.

(2) R. Huisgen, W. Mack, and E. Anneser, *Angew. Chem.*, **73**, 656 (1961).

(3) C. Grundmann and J. M. Dean, *J. Org. Chem.*, **30**, 2809 (1965).

(4) A stable spiro adduct has been obtained from the reaction of a nitrilimine with carbon disulfide: R. Huisgen, R. Grashey, M. Seidel, H. Knupfer, and R. Schmidt, *Ann.*, **668**, 169 (1962).

(5) C. Grundmann and H.-D. Frommeld, *J. Org. Chem.*, **31**, 157 (1966).

(6) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, Inc., New York, N. Y., 1964, p 255.

(7) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, pp 282–283.

(8) G. M. Dyson and R. F. Hunter, *J. Soc. Chem. Ind.*, **45**, 81T (1926).

positive. Recrystallization did not sharpen the melting point of this product which was concluded to be **anthracene 9-isothiocyanate.**

Anal. Calcd for $C_{15}H_9NS$: C, 76.7; H, 3.8; N, 5.96. Found: C, 76.0; H, 4.1; N, 5.95.

Asymmetric Induction in a 1,4-Cycloaddition Reaction. Influence of Variation of Configuration of the Asymmetric Center

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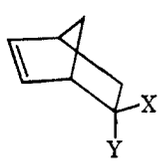
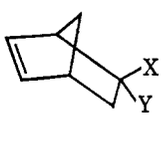
Partial asymmetric syntheses have been achieved in 1,4-cycloaddition reactions.[1-3] With the application of Lewis acid catalysis to promote reaction rate acceleration came the discovery of greatly enhanced asymmetric synthesis. Walborsky, Barash, and Davis presented an effective rationale for the steric course of a particular cycloaddition reaction and examined solvent, temperature, and catalyst effects.[2]

We wish to report our investigation of a system well suited for the study of the effect of variation of substituents about the influencing asymmetric center. This system consists of the reaction between 1,3-cyclopentadiene and acrylic acid esters. The four possible products are represented by I and II. In



Ia, X = H; Y = COOR
b, X = COOR; Y = H



IIa, X = H; Y = COOR
b, X = COOR; Y = H

particular the reaction of esters derived from (*R*)-(−)-menthol, (*S*)-(+)-2-octanol, and (*S*)-(+)-2-butanol were studied. Both catalytic and noncatalytic additions were run. Anhydrous stannic chloride was employed as the Lewis acid catalyst because homogeneous reaction solutions were obtained. The ester adducts were reduced with lithium aluminum hydride to the corresponding alcohols and their rotations were measured. The absolute rotations and configurations of the alcohols derived from the reduction of esters I and II have been assigned.[4] The alcohol obtained from Ia has the *S* configuration and in 95% alcohol the absolute $[\alpha]D$ −76.6°. Our results are summarized in Table I.

Reactions with stannic chloride catalysis were run at 4–8° because at much lower temperatures the catalytic effect on enhancement of optical purity appears to diminish. Walborsky[2] obtained a 75% optical yield for the reaction of 1,3-butadiene with (−)-dimenthyl fumarate using $SnCl_4$ catalysis in toluene at 25°, but at −70° the catalyst was ineffective.

TABLE I

REACTION OF CYCLOPENTADIENE WITH CH_2=CHCOOR

R	Solvent	Yield,[a] %	*endo*[a] %	*endo*[a] $[\alpha]^{25}D$, deg	Optical yield, %
(*R*)-(−)-Menthyl	0.6 *M* in toluene[b] and 1 equiv of $SnCl_4$	76	89	+31.4	41
(*S*)-(+)-2-Octyl		78	92	−11.1	15
(*S*)-(+)-2-Butyl		77	94	−18.4	24
(*R*)-(−)-Menthyl	Neat[c]	77	69	+6.1	8[d]
(*S*)-(+)-2-Octyl	Neat	77	71	−2.3	3
(*S*)-(+)-2-Butyl	Neat	70	74	−4.2	5

[a] Determined by glpc. [b] Temperature maintained at 4–8° for 0.5 hr. [c] Temperature maintained at 24–26° for 6 hr. [d] Agrees with ref 3.

It is noted that for a given acrylate there is a large difference in the amount of *endo* isomer formed in the catalytic and noncatalytic reactions. This gives further support to the contention[2] that the bulky Lewis acid catalyst participates in close coordination with the carboxyl group during cyclization as its steric requirement would result in a higher *endo* yield.[5a] Sauer and Kredel[5b] have reported similar results in a study of solvent and catalyst effects on the *endo–exo* product ratio of the (*R*)-(−)-menthyl acrylate reaction.

It is also seen that the (*R*)-acrylate gives an adduct with excess *R* configuration, and (*S*)-acrylates give adducts of excess *S* configuration. If one attempts to predict the configuration of the adducts from a consideration of diene steric approach control exerted by a dienophile of Cram–Prelog design, it is found that the (*R*)-acrylate should yield an excess of *S* isomer and the (*S*)-acrylate an excess of *R*. Walborsky[2] postulates that the (*R*)-(−)-methyl group exerts a steric control force in a manner deviating from that predicted because of the steric influence of substituents on the menthyl moiety which are not directly attached to the asymmetric carbon. The (*R*)-(−)-menthyl group, he argues, behaves as if the groups about the asymmetric carbon were of *S* configuration. Our data for the (*R*)-acrylate reactions are thus seen to agree with similar results obtained by Walborsky.[2] It is not feasible from the available evidence to rationalize the unexpected observations of the (*S*)-acrylates.

Experimental Section

Materials.—*l*-Menthol, *d*-2-octanol, and acrylyl chloride were purchased from Aldrich Chemical Co. Rotations of the alcohols conformed with literature values.[6] Optically pure *d*-2-butanol was prepared by brucine resolution of the acid phthalate.[7] Cyclopentadiene was freshly distilled before each use. Anhydrous stannic chloride employed was Baker Analyzed reagent. Boiling points are uncorrected.

Preparation of the Optically Active Acrylates.—To an ice-cooled solution of 19.0 g (0.21 mole) of acrylyl chloride and 21.3 g (0.21 mole) of triethylamine in 100 ml of anhydrous ether was added dropwise with stirring to a solution of 0.20 mole of alcohol in 100 ml of anhydrous ether. Triethylammonium hydrochloride precipitated. The addition was controlled to maintain mild reflux and then heated at reflux for an additional 0.5 hr. The ether solution was filtered from the hydrochloride precipitate and washed with 10% aqueous sodium bicarbonate. The ether layer was dried over anhydrous sodium sulfate and the ether was

(1) A. Korolev and V. Mur, *Dokl. Akad. Nauk SSSR*, **59**, 251 (1949).
(2) H. M. Walborsky, L. Barash, and T. C. Davis, *Tetrahedron*, **19**, 2333 (1963).
(3) J. Sauer and J. Kredel, *Angew. Chem. Intern. Ed. Engl.*, **4**, 989 (1965).
(4) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *J. Am. Chem. Soc.*, **83**, 3989 (1961).
(5) (a) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961); (b) J. Sauer and K. Kredel, *Tetrahedron Letters*, **7**, 731 (1966).
(6) "Handbook of Chemistry and Physics," 45th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1964.
(7) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

then removed. The acrylates were then distilled under vacuum, 0.3% hydroquinone was added, and the product was stored in a freezer until used. The following acrylates were prepared: (*R*)-(−)-menthyl acrylate, 85% yield, bp 102–104° (11 mm), $[\alpha]^{23}D$ −77.0° (*c* 8.4, dioxane), lit.[8] bp 78–80° (5 mm), $[\alpha]^{28}D$ −80.2° (*c* 10, dioxane); (*S*)-(+)-2-octyl acrylate, 78% yield, bp 73–75° (5 mm), $[\alpha]^{25}D$ +10.4° (*c* 3.3, dioxane), lit.[9] bp 79° (5.4 mm) for racemic ester; (*S*)-(+)-2-butyl acrylate, 73% yield, bp 54–56° (45 mm), $[\alpha]^{25}D$ +23.5° (*c* 2.0, dioxane), lit.[9] bp 60° for racemic ester (50 mm). All rotations were taken with a Gaertner polarimeter.

Reaction between Cyclopentadiene and Optically Active Acrylates.—To 0.05 mole of acrylate was added with stirring 0.06 mole of freshly distilled 1,3-cyclopentadiene. The reaction flask was immersed in a large water bath maintained at room temperature and allowed to sit for 6 hr. Yields were determined by diluting the reaction solution to a known volume with chloroform and comparing peak areas of gas chromatograms with that of a standard solution. The standard solutions were prepared by dilution of adducts previously isolated by fractional vacuum distillation. Boiling points of the ester adducts (*endo* and *exo* isomers inseparable without spinning column or preparative gc) are 1-menthyl, 134° (0.5 mm); 2-octyl, 112–114° (0.5 mm); 2-butyl, 72° (0.5 mm). Glpc measurements were made on a Perkin-Elmer Model 810 gas chromatograph equipped with hydrogen flame detector. Separation of *endo–exo* isomers was possible using a 6 ft × 1/8 in. column of 10% silicone DC-710 on 80–100 mesh Chromosorb W at temperatures of 200, 190, and 150°, respectively.

Lewis Acid Catalyzed Reaction between Cyclopentadiene and Optically Active Acrylates.—To a stirred solution of 0.06 mole of stannic chloride in 20 ml of dry toluene cooled to 3° was added dropwise a solution of 0.06 mole of acrylate in 30 ml of dry toluene. The temperature never rose above 8°. A change in color from clear to light yellow was noted. Then 0.10 mole of freshly distilled 1,3-cyclopentadiene in 40 ml of anhydrous toluene was added dropwise over 15 min so that the temperature never rose above 8°. The solution changed in color from yellow to red as the addition proceeded. The solution was allowed to react while stirred at 4° for 0.5 hr before 50 ml of dilute hydrochloric acid was added to hydrolyze the complex. The toluene layer was separated, washed with water, dried over sodium sulfate, and subjected to glpc analysis. The toluene was then distilled and the resulting solution was treated with lithium aluminum hydride without further isolation.

Reduction of Cyclopentadiene–Acrylate Adducts.—The products of the catalytic and noncatalytic reactions were taken up in 100 ml of anhydrous ether and added dropwise to a rapidly stirred solution of 2.5 g of lithium aluminum hydride (large excess) and stirred for 10 hr. The excess hydride was decomposed, the ether layer was separated and dried over sodium sulfate, and the ether was distilled. The resulting solution of isomeric bicyclo[2.2.1]-hept-2-enecarbinols was separated by preparative gas chromatography using an Aerograph Autoprep A-700 with a 3/8 in. × 10 ft 30% Carbowax 20M on 60–80 mesh Chromosorb W column maintained at 185°, He flow of 180 cc/min. The *endo* isomer was preferentially heart-cut for maximum purity and rotation measured in 95% ethanol. The *endo* isomer was characterized by its retention time being identical with the product obtained by reduction of the adduct of cyclopentadiene and acrylic acid (74% *endo*).[10]

(8) C. S. Marvel and Robert L. Frank, *J. Am. Chem. Soc.*, **64**, 1675 (1942).

(9) C. E. Rehberg, W. A. Faucette, and C. H. Fisher, *ibid.*, **66**, 1723 (1944).

(10) C. D. Ver Nooy and C. S. Rondestvedt, Jr., *ibid.*, **77**, 3583 (1955).

1(7)-Terpinen-4-ol

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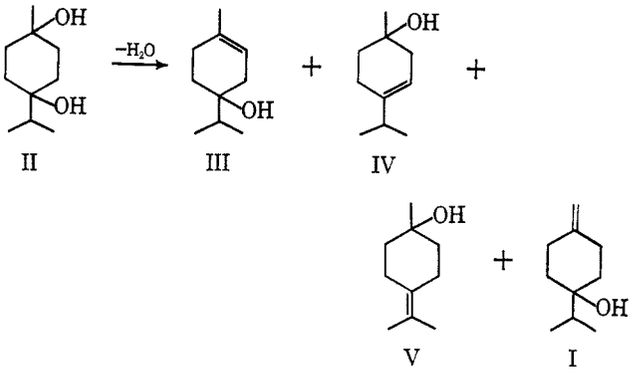
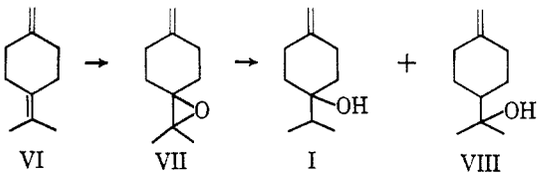
1(7)-Terpinen-4-ol (I) was previously unknown, but has been predicted to occur upon partial dehydration of terpinene terpin (II).[1] 1-Terpinen-4-ol (III), 3-terpinen-1-ol (IV), and 4(8)-terpinen-1-ol (γ-terpineol) (V) have been well documented.[1]



We were able to isolate the 1(7)-terpinen-4-ol from the dehydration products of terpinene terpin (approximately 0.3%) in an impure form and have also prepared it synthetically. We have also observed a peak in a capillary gas chromatogram of commercial terpineol that corresponds in elution time to 1(7)-terpinen-4-ol.

The attempted syntheses of 1(7)-terpinen-4-ol by conventional methods were unsuccessful owing to migration of the exocyclic double bond into the more stable internal position. The 1(7)-terpinen-4-ol was obtained from 1(7),4(8)-*p*-menthadiene VI[2] by conversion to the corresponding epoxide (VIII) which was reduced with lithium aluminum hydride to a mixture of 1(7)-terpinen-4-ol (I) and δ-terpinenol (VIII).[3] The exocyclic double bond was not epoxidized.



Proof of Structure.—The infrared spectrum (Figure 1) clearly shows the presence of the exocyclic double bond at 11.3 and 6.05 μ. The splitting pattern at 7.25 confirms the presence of a *gem*-dimethyl group.

The nmr spectrum (Figure 2) is self-explanatory.

Approximately 100 mg. of 1(7)-terpinen-4-ol was hydrogenated at atmospheric pressure using a 10% palladium-on-charcoal catalyst. A rearrangement to 1-terpinen-4-ol was observed prior to hydrogen uptake (indicating the facile isomerization of the exocyclic double bond to the internal position). Subsequently the *cis*- and *trans*-dihydroterpinenols were obtained. These were separated by gas chromatography and characterized by infrared analysis.

The mass spectrum of the 1(7)-terpinen-4-ol (I) indicated a molecular weight of 154 ($C_{10}H_{18}O$).

(1) J. L. Simonson and L. M. Owen, "The Terpenes," Vol. I, Cambridge University Press, London, 1947, p 274.

(2) B. M. Mitzner, E. T. Theimer, and S. Lemberg, *Can. J. Chem.*, **41**, 2097 (1963).

(3) B. M. Mitzner and S. Lemberg, *J. Org. Chem.*, **31**, 2022 (1966).

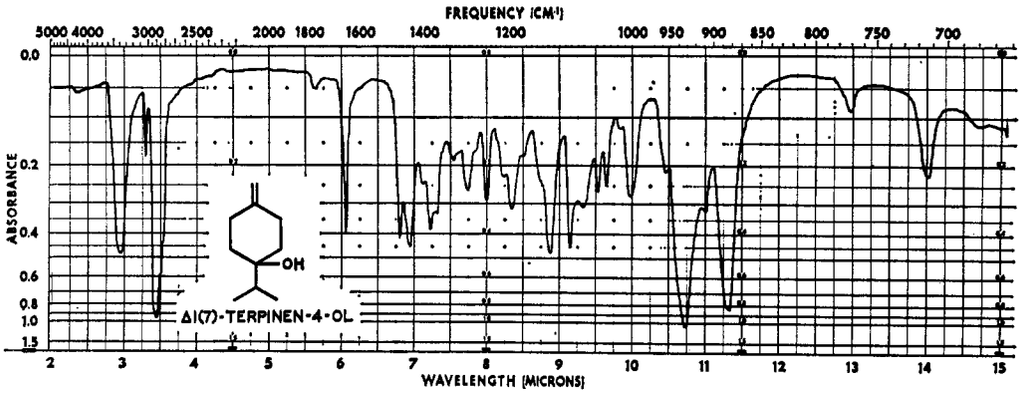


Figure 1.

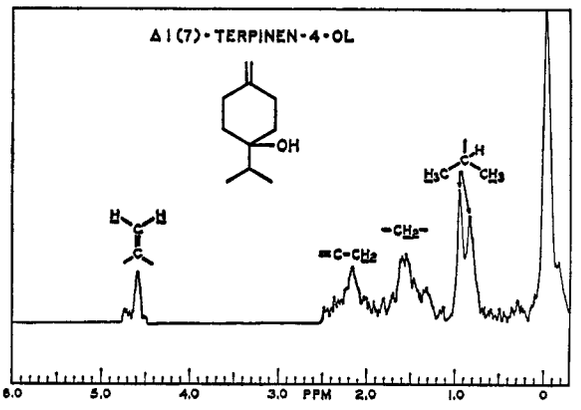


Figure 2.

Experimental Section

Approximately 7 g of 1(7),4(8)-*p*-methadiene was prepared as previously described.[2] This was placed into a 250-ml reaction flask equipped with a stirrer, thermometer, reflux condenser, dropping funnel, and Dry Ice bath. Anhydrous sodium acetate (8.2 g) and 40 ml of methylene chloride were added. The mixture was cooled to 0° and 10 g of 40% peracetic acid was added at 0–5° over a period of 2 hr. Stirring was continued at 0–5° for 3 hr. Water (30 ml) was added to the reaction mixture, and stirring was continued for 1 hr. The organic layer was washed with sodium bicarbonate and salt solutions and dried; the solvent was evaporated. The resulting 8 g of oil was then added (over a period of 1.25 hr) to 38 g of lithium aluminum hydride in 38 g of tetrahydrofuran in a 250-ml reaction flask, equipped with a stirrer, thermometer, reflux condenser, nitrogen purge, dropping funnel, and heating mantle.

The reaction mixture was then heated at reflux for 3 hr and cooled to 0–5°, and 20 ml of H_2O was added over a 1-hr period.

The product, isolated by extraction and solvent recovery, was passed through a preparative gas chromatograph which consisted of a 10 ft × 3/8 in. o.d. column containing 20% Carbowax 20M on silane-treated Celite at 150° with a helium flow rate of 250 cc/min. Successive 100-mg injections were made until 400 mg of 1(7)-terpinen-4-ol was obtained. Approximately 100 mg of δ terpinenol was also obtained which elutes after the 1(7)-terpinen-4-ol.

The product was then passed through a preparative gas chromatograph which consisted of a 10 ft × 0.25 in. o.d. column containing 20% Se-30 on 60–80 mesh silane-treated Chromosorb W, at 125° with a helium flow rate of 100 cc/min. Repeated 10-μl injections were employed and 200 mg of very pure product was thus obtained.

Acknowledgment.—The authors wish to express their gratitude to Mr. M. Jacobs for his nmr analysis.

The Shielding Effect of the Nitro Group

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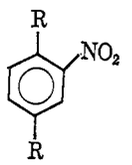
In recent years, the long-range shielding effect of the nitro group has been observed in *t*-butylnitrocyclohexanes,[1] nitrotestosterones,[2] nitrocholestenes,[3] nitroporphyrins,[4] nitronaphthalenes,[5] and nitromethylbenzenes.[6] We have examined the nmr spectra of the 2-nitro derivatives of *p*-xylene (**2**) and of the *p*-diethyl- (**3**), *p*-diisopropyl- (**4**), and *p*-di-*t*-butylbenzenes (**5**).



1, R = H
2, R = CH_3
3, R = CH_2CH_3
4, R = $CH(CH_3)_2$
5, R = $C(CH_3)_3$

In Table I there is presented the difference in chemical shift (downfield) (determined in two inert solvents) of the *ortho* proton in the nitro compound relative to the corresponding proton in the parent hydrocarbon. Also presented is the degree of twist φ of the nitro group from coplanarity with the aromatic ring as calculated by Wepster[7] from ultraviolet data. The corresponding shift difference of the *meta* and *para* protons is also tabulated. The observed signals in the nitro compounds are broad singlets (two unre-

(1) A. Huitric and W. F. Trager, *J. Org. Chem.*, **27**, 1926 (1962).
(2) K. Tori and K. Kuriyama, *Tetrahedron Letters*, 3939 (1964).
(3) J. McKenna, J. M. McKenna, and P. B. Smith, *Tetrahedron*, **21**, 2983 (1965).
(4) R. Bonnett and G. F. Stephenson, *J. Org. Chem.*, **30**, 2791 (1965).
(5) P. R. Wells, *Australian J. Chem.*, **17**, 967 (1964).
(6) I. Yamaguchi, *Mol. Phys.*, **6**, 105 (1963).
(7) B. M. Wepster, "Progress in Stereochemistry," W. Klyne and P. B. D. de la Mare, Ed., Academic Press, Inc., New York, N. Y., 1958, p 110. The angles are calculated from the equation $\epsilon/\epsilon_0 = \cos^2 \varphi$. ϵ is the extinction of the substituted nitro compound and ϵ_0 is the value for nitrobenzene.

TABLE I

SHIFT DIFFERENCES OF RING PROTONS

Compd	Δppm, CCl_4	*ortho*, cyclohexane	φ, deg, isooctane	Δppm, CCl_4	*meta, para*,[a] cyclohexane
1[b]	...	0.95	0	...	0.21 *meta*, 0.33 *para*
2	0.75	0.72	34	0.25	0.18
3	0.63	0.63	40	0.23	0.18
4	0.42	0.45	47	0.30	0.27
5	−0.02	0.00	65	0.18	0.13

[a] Except for **1**, the *meta* and *para* shifts were not resolved and are recorded as one peak. [b] Data of H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 721 (1961).

solved regions which should be the AB and X portions of an ABX spectrum).

In Table II there is recorded the difference in chemical shifts of the *o*- and *m*-benzylic protons relative to the corresponding protons in the parent hydrocarbons. The values were determined in CCl_4 because the cyclohexane resonance interfered with the determination in that solvent.

TABLE II

SHIFT DIFFERENCES OF BENZYLIC PROTONS

Compd	Δppm, *o*-benzylic	Δppm, *m*-benzylic
2	0.25	0.13
3	0.30	0.13
4	0.55	0.12

The data in Table I concerning the *ortho* proton shifts can be evaluated if two reasonable assumptions are made. First, since the *meta,para* resonance is relatively constant through the series, these protons serve as internal standards that demonstrate that change of ring anisotropy, ring electron density, dipole moment, etc., does not make the major contribution to change in *ortho* shift as a function of nitro twist. Second, we assume that in nitrobenzene, a large part of the deshielding of the *ortho* proton, in the light of previous work, can be attributed to anisotropic deshielding. Then, the decrease in deshielding in nitroxylene, as the nitro group is twisted 34° out of the plane, can be explained by suggesting that the *ortho* proton is no longer in the center of the deshielding region. The increasing deviation of the nitro group from coplanarity with the ring in the ethyl and isopropyl cases further removes the *ortho* proton from the region of maximum deshielding and the chemical shift difference decreases in a consistent manner. Finally, in the *t*-butyl case, the nitro group has twisted far enough so that its *shielding* region now affects the *ortho* proton, the signal of which is at higher field than the *meta* and *para* proton signal. The interesting datum in Table II is the seemingly disproportionate deshielding of the *o*-benzylic proton in the isopropyl system. The shift is explained by postulating the existence of a preferred (and model-justified) rotamer of the isopropyl group that keeps the methyl groups away from the nitro group. The benzylic hydrogen is then in the plane of the benzene ring and always subject to the large anisotropic deshielding arising out of the ring current. In the parent compound, the proton is in a freely rotating system and is not maximally deshielded. The experiment testing this hypothesis, that is, obtaining spectra at 70 and 150°, showed no significant shift of the *o*-benzylic proton signal (relative to the other signals). Therefore, the barrier to free rotation of the isopropyl group is very high.

The entire chemical shift of the *ortho* proton in the nitroaromatics relative to the hydrocarbons is not only due to anisotropic effects. Our data has been subjected to some calculations. Attempts were made to separate out the nonanisotropic contributions based on the correlation of inductive and resonance parameters with chemical shift[8] and on an electric field hypothesis.[9] The derived numbers were used to evaluate magnetic susceptibilities.[10] However, these calculations are of dubious merit because the separation of effects at *ortho* positions is speculative, and the theory for the evaluation of magnetic susceptibilities is not valid at small distances.

Experimental Section

The *p*-xylene, 2-nitro-1,4-dimethylbenzene (**2**), and *p*-diisopropylbenzene were commercial samples used without further purification. A sample of *p*-diethylbenzene, bp 184°, was prepared by Wolff–Kishner reduction[11] of the semicarbazone of *p*-ethylacetophenone, mp 188–191° (lit. 191°).[12] Nitration of the hydrocarbon according to a published procedure afforded 2-nitro 1,4-diethylbenzene (**3**), bp 100–103° (1 mm) [lit. 137–140° (12 mm)].[13] A small sample obtained by subsequent chromatography on silica (Davison) was used for nmr analysis. Fractional distillation of the nitration product of *p*-diisopropylbenzene did not yield pure 2-nitro-1,4-diisopropylbenzene (**4**) as had been reported.[14] A fraction, bp 152–158° (25 mm), was chromatographed on silica (Davison) and yielded a homogeneous product. The *p*-di-*t*-butylbenzene, mp 77° (lit. 77–79°),[15] and its nitro derivative (**5**), mp 89–90° (lit. 75–78°),[15] were prepared according to published procedures. The nitro derivative formed solid solutions with the hydrocarbon and the high-melting product was obtained by chromatography on silica.

The nmr spectra were determined with a Varian A-60 instrument using 10% (by weight) solutions in CCl_4 and 7% solutions in cyclohexane. Tetramethylsilane was the internal reference in the first solvent and the solvent absorption itself was used in

TABLE III

SHIFTS OF HYDROCARBONS

Compd	Ring, CCl_4	Ring, Cyclohexane	Benzylic CCl_4	Other CCl_4
Xylene	416	330	135	
Diethylbenzene	419	333	154[a]	72[b]
Diisopropylbenzene	422	335	169[c]	74[d]
Di-*t*-butylbenzene	433	347		76

[a] Quartet, J = 7 cps. [b] Triplet, J = 7 cps. [c] Heptet, J = 7 cps. [d] Doublet, J = 7 cps.

TABLE IV

SHIFTS OF NITRO COMPOUNDS

Compd	Ring *ortho*, CCl_4	Ring *ortho*, Cyclohexane	Ring *meta, para*, CCl_4	Ring *meta, para*, Cyclohexane	Benzylic CCl_4, *ortho*	Benzylic CCl_4, *meta*	Other CCl_4
2	461	373	431	341	150	143	
3	457	371	433	344	172[a]	162[a]	76[b]
4	447	362	440	351	202[c]	176[c]	77[d]
5	432	347	444	355			77, 82

[a] Overlapping quartets. [b] Distorted triplet. [c] Overlapping heptets. [d] Distorted doublet.

(8) (a) R. W. Taft, *et al.*, *J. Am. Chem. Soc.*, **85**, 709, 3146 (1963); (b) J. J. Martin and B. P. Dailey, *J. Chem. Phys.*, **39**, 1722 (1963).
(9) A. D. Buckingham, *Can. J. Chem.*, **38**, 300 (1960).
(10) (a) P. T. Narasimhan and M. T. Rogers, *J. Phys. Chem.*, **63**, 1388 (1959); (b) H. N. McConnell, *J. Chem. Phys.*, **27**, 226 (1957).
(11) D. Todd, *Org. Reactions*, **4**, 379 (1948).
(12) G. Baddeley, *J. Chem. Soc.*, 232 (1944).
(13) W. J. Gaudion, W. H. Hook, and S. G. P. Plant, *ibid.*, 1631 (1947).
(14) A. Newton, *J. Am. Chem. Soc.*, **65**, 2434 (1943).
(15) P. D. Bartlett, M. Roha, and R. M. Stiles, *ibid.*, **76**, 2349 (1954).

the second case. The raw nmr data is assembled in two tables. Table III records proton signals for the hydrocarbons in cycles per second relative to the internal reference. Table IV records the signals for the nitro derivatives.

Acknowledgment.—We wish to thank the National Science Foundation (GP 5160) for support and Messrs. R. DeMartino, A. Durante, E. Gibbons, and E. Reilly for technical assistance.

Chlorosulfonation of Triphenyl Phosphate, Diphenyl Methylphosphonate, and Triphenylphosphine Oxide

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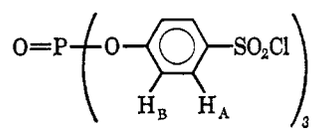
Reports of substitution reactions on aryl groups either attached directly to phosphorus or through carbon as in tertiary phosphine oxides are quite meager. The majority of such reactions have been confined to nitration of the aryl substituent.[1] Stachlewska–Wroblowa and Okon[2] have, in addition to nitration, investigated the sulfonation and chlorosulfonation of triphenylphosphine oxide and its derivatives. The chlorosulfonation of 4-methoxyphenylphosphonic acid to yield 3-chlorosulfonyl-4-methoxyphenylphosphonic acid was also reported in a patent.[3]

Of particular interest to us was the chlorosulfonation of triphenylphosphine oxide and the possible extension of the chlorosulfonation reaction to neutral pentavalent phosphorus esters containing at least one aryl group. The subject of electrophilic substitution reactions involving such phosphorus esters has received even less attention than that afforded tertiary phosphine oxides. In both cases substitution on the pendant aryl group is most often effected prior to formation of the phosphorus ester or phosphine oxide. This is usually desirable especially in the case of the somewhat labile phosphorus esters. In view of this lability, the stability of aryloxy phosphorus bonds, particularly toward chlorosulfonic acid and the attending conditions, was somewhat questionable.

Subsequently, it was found that triphenyl phosphate can be chlorosulfonated readily with apparently little deleterious effect on the aryloxy phosphorus bond. Addition of the phosphate to excess chlorosulfonic acid at room temperature caused a readily controlled exotherm, and hydrogen chloride was evolved. Moderate heating of the reaction mixture, until hydrogen chloride evolution subsided, followed by conventional work-up, yielded chlorosulfonated triphenyl phosphate. The reaction product was identified by elemental analysis, molecular weight determination, and infrared and pmr spectra as tris(*p*-chlorosulfonylphenyl) phosphate (**1**). The reaction conditions were not optimized. However, variation of the molar ratio of reactants, while maintaining reaction time and temperature constant, indicated that a 30:1 mole ratio of chlorosulfonic acid to phosphate reacted at 50° for 6 hr afforded high yields (>80%) of crude **1**. The reaction was repeated several times using these conditions with comparable results. When chlorosulfonic acid and triphenyl phosphate were allowed to react at molar ratios of 24:1, 18:1, and 12:1, the yields of crude chlorosulfonated phosphate (**1**) were 77, 73, and 54%, respectively. Reported[4] methods for reducing the amount of excess chlorosulfonic acid, such as the utilization of sodium chloride, alone or in combination with inert organic solvents (*e.g.*, carbon tetrachloride), were not investigated.

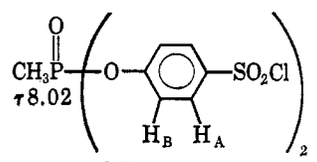
The chlorosulfonation of diphenyl methylphosphonate was also found to proceed readily, utilizing reaction conditions that produced high yields of chlorosulfonated triphenyl phosphate (**1**) and a mole ratio of chlorosulfonic acid to phosphonate of 20:1. The reaction product identified as bis(*p*-chlorosulfonylphenyl) methylphosphonate (**2**) by elemental analysis, molecular weight determination, and infrared and pmr spectra was obtained in better than 79% crude yield.

That chlorosulfonation of triphenyl phosphate and diphenyl methylphosphonate occurs predominately at the *para* position was demonstrated by the infrared and pmr spectra of the reaction products. *para* substitution of both the chlorosulfonated phosphate (**1**) and phosphonate (**2**) was manifested by characteristic infrared absorption in the regions 6.3–7.2 μ and 11.5–12.5 μ. The pmr spectrum of **1** in $CDCl_3$ (TMS as internal reference) exhibited the characteristic AB quartet of a *para*-substituted benzene (τ_A 1.82, τ_B 2.42 ppm; J_{AB} = 8.7 cps). The chlorosulfonated



τ_B 2.42 τ_A 1.82

1



τ_B 2.51 τ_A 1.90

2

phosphonate (**2**) in $CDCl_3$ showed the expected methyl doublet (τ = 8.02 ppm,[2] J_{PH} = *ca.* 18 cps) for P–CH_3 and the characteristic AB pattern of a *para*-substituted benzene (τ_A = 1.90, τ_B = 2.51 ppm; J_{AB} = 8.7 cps). In both **1** and **2**, a long-range coupling of phosphorus to H_B ($^4J_{PH}$ = 1.0 cps) was observed and provided further support for the assigned structures. Similar four-bond couplings have been observed in a number of other organophosphorus compounds.[5] In neither case was there any evidence for the presence of other isomers in amounts greater than *ca.* 5%. In the case of the

(1) K. D. Berlin and G. B. Butler, *Chem. Rev.*, **60**, 243 (1960).

(2) (a) A. Stachlewska-Wroblowa and K. Okon, *Biul. Wojskowej Akad. Tech.*, **10**, No. 4, 3 (1961); *Chem. Abstr.*, **56**, 14322*d* (1962); (b) A. Stachlewska-Wroblowa and K. Okon, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, **9**, 281 (1961).

(3) E. M. Hardy, U. S. Patent 3,017,321 (1962).

(4) E. E. Gilbert, "Sulfonation and Related Reactions," Interscience Publishers, Inc., New York, N. Y., 1965, p 84.

(5) (a) M. Gordon, Ph.D. Thesis, University of Pittsburgh, 1965; (b) C. E. Griffin, R. B. Davison, and M. Gordon, *Tetrahedron*, **22**, 561 (1966).

chlorosulfonated phosphate **1** the crude reaction product, melting over a rather broad range (115–119°) after one recrystallization, gave a pmr spectrum comparable to that of analytically pure material.

In addition to the spectral evidence for *para* substitution, basic hydrolysis of the chlorosulfonated phosphate (**1**) gave 1-phenol-4-sulfonic acid in 48% yield. The sulfonic acid was identified as its S-benzylthiuronium salt by melting point and mixture melting point with an authentic sample.

In the case of tris(*p*-chlorosulfonylphenyl) phosphate (**1**), an alternate synthesis was briefly considered, involving reaction of phosphorus pentachloride or phosphorus oxychloride with 1-phenol-4-sulfonic acid. This route was abandoned in view of the reported[6] initial formation of *p*-chlorosulfonylphenyl phosphorodichloridate and desulfonation under more forceful conditions.

The chlorosulfonation of triphenylphosphine oxide was investigated in order to confirm earlier reports.[2] Repetition of the reported procedure gave negligible amounts of the desired chlorosulfonated triphenylphosphine oxide. Use of longer reaction times and a larger excess of chlorosulfonic acid than reported[2] resulted in improved yields (Table I) of the chlorosulfonated triphenylphosphine oxide.

TABLE I

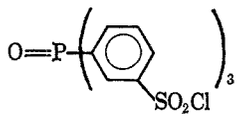
EFFECT OF REACTION TIME AND MOLE RATIO OF REACTANTS ON THE YIELD OF CHLOROSULFONATED TRIPHENYLPHOSPHINE OXIDE (**3**)[a]

Run no.	$ClSO_3H$:Ph_3PO mole ratio	Reaction time, hr	Yield of **3**, %[c]
Lit.[2]	12:1	3	30
1[b]	12:1	3	...
2	25:1	3.5	24 (13)
3	25:1	20	78 (58)

[a] Reaction temperature 130°. [b] Repeat of reported procedure.[2] [c] Yield of purified reaction product (**3**) in parenthesis.

Identification of the reaction product as tris(*m*-chlorosulfonylphenyl)phosphine oxide (**3**) was made by elemental analysis and infrared and pmr spectra.

The pmr spectrum of **3** in DMSO-d_6 gave a pattern in the aromatic region that is characteristic of *meta* substitution; the multiplet structure was quite similar to that observed in tetramethyl *m*-phenylenediphosphonate and dimethyl *m*-carboxyphenylphosphonate. The chemical shifts and coupling constants for the individual aromatic protons could not be determined by inspection due to the complexity of the spectrum. It was estimated that less than 10% of other isomers was present.



3

In none of the chlorosulfonation reactions investigated were reaction products isolated bearing more than a single sulfonyl chloride group per phenyl ring of the organophosphorus moiety. In addition, the results indicated that the phenyl esters of phosphoric and phosphonic acids undergo a more facile chlorosulfonation than do tertiary phosphine oxides bearing at least one phenyl group attached directly to phosphorus. Since the phosphoryl group of the phosphine oxide is electron withdrawing and, therefore, deactivating to electrophilic substitution, more forceful chlorosulfonating conditions are required than for either the phosphate or phosphonate.

(6) C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, p 459.

Experimental Section[7]

Starting Materials.—Triphenyl phosphate practical grade (Eastman Organic Chemicals) was recrystallized from 95% ethyl alcohol (168 g/100 ml of solvent). Material melting at 48–50° (lit.[8] mp 50°) was used in our work. Diphenyl methylphosphonate, bp 137–139° (0.05 mm), $n^{20}D$ 1.5533 [lit.[9] bp 151° (0.8 mm)], was prepared in 54% yield according to the procedure of Morgan and Herr.[9] Triphenylphosphine oxide, mp 155.5–157° (lit.[10] mp 156–157°), was obtained in 83% yield by allowing the corresponding phosphine (Metal and Thermit Co.) to react with hydrogen peroxide. Chlorosulfonic acid, practical grade, (Eastman Organic Chemicals), was distilled; the fraction, bp 149–156° (752.8 mm), was retained.

Chlorosulfonation of Triphenyl Phosphate.—Triphenyl phosphate (195.8 g, 0.6 mole) was added in 20 min under a positive nitrogen pressure to stirred, chlorosulfonic acid (2093 g, 18 moles) maintained at 22–24° by means of a cold-water bath. The phosphate dissolved immediately and hydrogen chloride was evolved. Upon completing the addition, the clear, pale yellow reaction mixture was heated to 50 ± 1° and maintained at these temperatures for 6 hr. The cooled, clear, pale amber reaction mixture when carefully added dropwise to a suitable quantity of crushed ice caused a white solid to precipitate. The white precipitate was filtered and pressed dry; the slightly yellow clear acidic aqueous filtrate was discarded. Chloroform (2900 ml) was added to the filter cake causing most of the solid to dissolve. Chloroform insolubles, a small quantity of gelatinous semisolid and an equally small aqueous phase, were extracted with portions of fresh solvent. The combined chloroform extracts were washed consecutively with two 50-ml portions of aqueous 10% sodium bicarbonate and three 100-ml portions of aqueous saturated sodium chloride, and dried over anhydrous magnesium sulfate.

Concentration of the dried chloroform layer to *ca.* 500 ml gave a white, solid slurry that upon dilution with 500 ml of hexane and cooling gave a white solid. The filtered and dried crude tris(*p*-chlorosulfonylphenyl) phosphate (**1**), 304.4 g, 82%,) softened at 103° and melted at 110–118°. Recrystallization of the crude reaction product **1** from 3000 ml of a 3:1 (v/v) carbon tetrachloride–benzene solution gave 265.3 g of a white solid, mp 115–119°.

An analytical sample (mp 119–121°) was prepared by repeated recrystallization from a benzene–hexane mixture. The recrystallized product **1** was very soluble in acetonitrile, dioxane, methyl ethyl ketone, methylene chloride, and diglyme. Infrared absorption (KBr) occurred at 6.32 (s), 6.74 (s), 7.1 (m), 7.26 (s), 7.61 (s), 7.73 (m), 8.0 (m), 8.32 (s), 8.45 (s), 8.60 (s), 9.25 (m), 10.16 (s), 10.42 (s), 10.67 (m), and 11.85 (s) μ. *Anal.* Calcd for $C_{18}H_{12}Cl_3O_{10}PS_3$ (**1**): C, 34.77; H, 1.95; Cl, 17.11; P, 4.98; S, 15.47; mol wt, 621.83. Found: C, 34.96; H, 1.96; Cl, 17.19; P, 4.99; S, 15.70: mol wt, 593.3 (determined in THF by vapor phase osmometry).

Hydrolysis of Tris(*p*-chlorosulfonylphenyl) Phosphate (1).—A stirred mixture of alcoholic potassium hydroxide (25.8 g, 0.46 mole of base in 400 ml of 95% ethyl alcohol) and 18.6 g (0.03 mole) of **1** was refluxed for 15 hr in a stainless steel reactor. Neutralization of the cooled hydrolysate with concentrated hydrochloric acid (14 ml) precipitated a cream-colored solid. The filtered precipitate washed consecutively with alcohol and ether left 34.03 g (after drying) of an insoluble solid.

(7) Melting and boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville 21, Tenn. Infrared absorption spectra were obtained with a Perkin-Elmer Infracord Model 137B spectrophotometer. Pmr spectra were determined with a Varian Associates A-60 spectrometer.

(8) S. Sugden, J. Reed, and H. Wilkins, *J. Chem. Soc.*, **127**, 1525 (1925).

(9) P. Morgan and B. Herr, *J. Am. Chem. Soc.*, **74**, 4526 (1952).

(10) R. J. Kennedy and A. M. Stock, *J. Org. Chem.*, **25**, 1901 (1960).

S-Benzylthiuronium chloride (5.06 g, 0.02 mole) was allowed to react with a portion (3.92 g) of the insoluble solid dissolved in water to precipitate a solid (4.61 g). After one recrystallization from hot water, the crude product (1.1 g) was identified as the S-benzylthiuronium salt of 1-phenol-4-sulfonic acid by melting point and mixture melting point with the authentic salt (lit.[11] mp 168.7°).

Chlorosulfonation of Diphenyl Methylphosphonate.—The procedure described for the chlorosulfonation of triphenyl phosphate was repeated using 63.3 g (0.26 mole) of diphenyl methylphosphonate and 602 g (5.16 moles) of chlorosulfonic acid. Addition of the reaction mixture to ice, extraction with chloroform, and concentration of the combined, washed, and dried chloroform extracts followed by dilution of the concentrate (250 ml) with pentane precipitated an oil. The solvent layer was decanted and the oil on trituration with fresh ice-cold pentane solidified. The filtered, washed, and dried white solid (78.3 g) melted at 81–86°. A second crop of product (13.6 g), melting at 85–87.5°, was obtained upon dilution of the chloroform–pentane filtrate with the nonsolvent pentane. The combined fractions (91.9 g) of crude bis(*p*-chlorosulfonylphenyl) methylphosphonate (**2**) melted at 83–86°.

Two recrystallizations of the crude reaction product **2** from a 50:50 benzene–ligroine mixture raised the melting point to 84.5–87°. Infrared absorptions (KBr) appeared at 3.23 (w), 6.33 (s), 6.76 (s), 7.07 (m), 7.28 (s), 7.55 (m), 7.73 (m), 7.85 (m), 8.04 (s), 8.26 (s), 8.45 (s), 8.59 (s), 9.24 (w), 10.50 (m), 10.81 (s), 11.81 (m), 11.96 (m), and 13.45 (s) μ. *Anal.* Calcd for $C_{13}H_{11}Cl_2O_7PS_2$ (**2**): C, 35.07; H, 2.49; Cl, 15.92; P, 6.95; S, 14.40; mol wt, 445.24. Found: C, 35.08; H, 2.60; Cl, 15.82; P, 7.02; S, 14.45; mol wt, 457.0 (determined cryoscopically in benzene).

Chlorosulfonation of Triphenylphosphine Oxide.—Excess chlorosulfonic acid (289 g, 2.48 moles) was added dropwise to triphenylphosphine oxide (27.8 g, 0.1 mole) with stirring and cooling. Upon completing the addition, the reaction mixture was heated to 130°. The reaction temperature was maintained for *ca.* 20 hr. The cooled reaction mixture was added dropwise to crushed ice and a solid precipitated. The filtered solid was washed consecutively with water, ethyl alcohol, and ether. After drying *in vacuo* at 45°, the crude reaction product (44.6 g) was recrystallized from a chloroform–hexane mixture to give 33 g (57.5%) of tris(*m*-chlorosulfonylphenyl)phosphine oxide (**3**), mp 217–221° (lit.[2] mp 210–212°). Repeated recrystallization from chloroform–hexane raised the melting point to 220–225°. The product **3** showed infrared absorption (KBr) at 3.2 (w), 6.3 (w), 6.4 (w), 6.83 (w), 7.09 (s), 7.24 (s), 7.65 (w), 7.86 (w), 8.37 (s), 8.47 (s), 8.82 (s), 9.24 (m), 10.08 (w), 12.31 (s), 12.44 (s), and 14.66 (s) μ. *Anal.* Calcd for $C_{18}H_{12}Cl_3O_7PS_3$ (**3**): C, 37.67; H, 2.11; Cl, 18.54; P, 5.40; S, 16.76. Found: C, 37.20; H, 2.40; Cl, 18.34; P, 5.22; S, 16.41.

Acknowledgment.—The author wishes to thank Mr. W. E. Byrne for the pmr spectra and their interpretation and Messrs. W. Whitmore and D. Hershey for carrying out some of the experiments.

(11) N. Cheronis and J. Entrikin, "Semi-micro Qualitative Organic Analysis," Interscience Publishers, Inc., New York, N. Y., 1958, p 697.

Chloromethylphosphine[1]

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It has recently been suggested that α-fluoroalkylphosphines undergo reactions with nucleophiles by an elimination–addition reaction sequence.[2,3] To test the generality of this reaction pattern for compounds containing the grouping CX–PH (X = halogen) the previously unknown chloromethylphosphine has been prepared and its reactions with some nucleophiles have been examined.

The preparation of primary phosphines by the thermal decomposition of phosphinic acids has found its widest application in the aromatic series. The yields of primary aliphatic phosphines from the corresponding phosphinic acids are generally low.[4] The production of primary phosphines can be represented by the following disproportionation. The other product is an alkylphosphonic acid.

$$3RPO_2H_2 \xrightarrow{\Delta} RPH_2 + 2RP(O)(OH)_2$$

Chloromethylphosphinic acid, synthesized from chloromethylphosphonic dichloride by the method of Uhing, Rattenbury, and Toy[5] decomposed violently, *even explosively*, when heated *in vacuo*. However, if the reaction was carried out by allowing the acid to drop slowly into an evacuated flask heated to 150–160°, a steady evolution of a mixture of hydrogen chloride and chloromethylphosphine was obtained. The chloromethylphosphine was separated from hydrogen chloride by washing with water. The yield of chloromethylphosphine was somewhat variable and, at best, was only about 35%.

The gas-phase infrared spectrum of chloromethylphosphine (see the Experimental Section) contained bands attributable to CH, PH, and CCl stretching modes. The proton magnetic resonance spectrum of neat chloromethylphosphine consisted of a complex multiplet attributed to the $ClCH_2$ group (δ_{ClCH_2} = 3.78 ppm (downfield from internal $(CH_3)_4Si$)), and two widely separated multiplets attributed to the PH_2 group (δ_{PH} = 3.40 ppm and J_{HP} = 206 cps). The area ratios agreed with this interpretation. The four protons of chloromethylphosphine probably constitute an A_2B_2 system which is further complicated by coupling of all four protons to phosphorus. A full analysis of this spectrum is in progress.

The reaction between chloromethylphosphine and aqueous sodium hydroxide solution gave hydrogen as the only volatile product. The other reaction product was methylphosphinic acid $CH_3P(O)(H)(OH)$. The identity of this product was suggested by its proton magnetic resonance spectrum, which consisted of four equal peaks attributed to CH_3P (J_{HCP} = 15.3 cps; J_{HCPH} = 2.0 cps) and two widely spaced quartets attributed to PH (J_{PH} = 530 cps). Fiat, *et al.*,[6] reported the following values for aqueous solutions of methylphosphinic acid: CH_3P (J_{HCP} = 15.7 cps; J_{HCPH} = 2.15 cps) and PH (J_{PH} = 561 cps). Oxidation of the phosphinic acid gave methylphosphonic acids, $CH_3P(O)(OH)_2$; the proton magnetic resonance spectrum of the aqueous solution of this compound was identical with that of a sample prepared by the alkaline hydrolysis of chloromethyl phosphinic acid.[5]

(1) This investigation was supported by Public Health Service Research Grant CA 07182 from the National Cancer Institute.

(2) G. M. Burch, H. Goldwhite, and R. N. Haszeldine, *J. Chem. Soc.*, 572 (1964).

(3) H. Goldwhite, R. N. Haszeldine, and D. G. Rowsell, *ibid.*, 6875 (1965).

(4) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p 12.

(5) E. Uhing, K. Rattenbury, and A. D. F. Toy, *J. Am. Chem. Soc.*, **83**, 2299 (1961).

(6) D. Fiat, M. Halmann, L. Kuzel, and J. Reuben, *J. Chem. Soc.*, 3837 (1962).

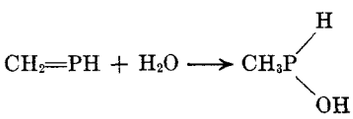
An elimination–addition mechanism has been suggested in order to account for the reactions of primary and secondary polyfluoroalkylphosphines with nucleophilic reagents.[2,3] A similar type of mechanism is one possibility for the alkaline hydrolysis of chloromethylphosphine. The first step could be the removal of a proton attached to phosphorus. Loss of chloride

$$CH_2ClPH_2 + \bar{O}H \longrightarrow CH_2Cl\bar{P}H + H_2O$$

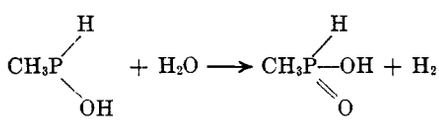
ion could then give a phosphaalkene intermediate.

$$CH_2Cl\bar{P}H \longrightarrow CH_2{=}PH + Cl^-$$

Addition of water across the phosphorus–carbon double bond would give an unstable acid. The production of

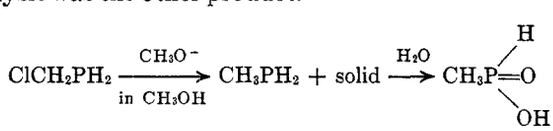


hydrogen and methylphosphinic acid can be represented by the following equation. A number of phosphorus



acids containing P–H bonds are known to react with aqueous sodium hydroxide solution to produce hydrogen,[7] but the mechanisms involved have not been investigated in detail.

The reaction between chloromethylphosphine and sodium methoxide in methanol solution gave methylphosphine accounting for approximately 40% of the phosphorus. The other reaction product was an apparently polymeric involatile material which could not be dissolved without decomposition; hydrolysis of this material gave only methylphosphinic acid. Methylphosphine (31%) was again obtained as the only volatile product when chloromethylphosphine was treated with trimethylamine; an involatile polymeric material which also gave only methylphosphinic acid on hydrolysis was the other product.



It is difficult to suggest adequate mechanisms for these reactions, especially since the nature of the involatile solid precluded establishment of its structure. However, it is significant that in both reactions the eventual fate of the $ClCH_2P$ group was conversion into a CH_3P group, and some type of elimination–addition process would certainly account for this.

Experimental Section

Materials.—Chloromethylphosphonic acid was prepared from chloromethylphosphonic dichloride by the published procedure.[5]

Spectra.—The proton magnetic resonance spectra were determined on a Varian A-60 spectrometer at ambient probe temperature.

The infrared spectrum of chloromethylphosphine in the gas phase was determined on a Beckman IR-12 spectrometer; the following bands (frequencies given in cm^{-1}; sh = shoulder) were observed and tentatively assigned as follows: 2960, 2955, 2950 (CH str); 2328, 2314, 2300, 2290, 2283 (PH str); 1420, 1411, 1405 (CH def); 1232, 1216, 1208, (sh), 1202 (sh); 1090, 1079, 1075 (sh); 943, 940, 935; 883, 878, 872, 854, 847, 843, 839; 764, 760, 750 (CCl str); 630 (sh), 611, 596 (sh).

Molecular weights were determined by measurement of gas densities.

Preparation of Chloromethylphosphine.—A 250-ml, three-necked flask was connected to a conventional vacuum system and evacuated. The flask was heated to 150–160° and chloromethylphosphinic acid (20.0 g, 175 mmoles) was slowly added *via* a dropping funnel. When the acid came in contact with the heated flask a smooth evolution of gas occurred. The volatile products passed into the vacuum system and were condensed in a trap cooled to −196°. When the addition of acid was complete, the contents of the −196° trap were subjected to vacuum fractionation. Hydrogen chloride (1.90 g, 52 mmoles) condensed at −196° and chloromethylphosphine, containing some hydrogen chloride, condensed at −80°. The −80° fraction was condensed into a 50-ml bulb containing water (10 ml). The bulb was allowed to attain room temperature and was shaken. The water-insoluble volatile fraction was taken into the vacuum system, fractionated, dried by condensing onto phosphoric oxide, and finally refractionated to give chloromethylphosphine (1.50 g, 18.2 mmoles, 31%) condensing at −65°, bp (isoteniscope) 68°. *Anal.* Calcd for CH_2ClPH_2: Cl, 43.0; mol wt, 82.5. Found: Cl, 43.7; mol wt, 83.0.

Reaction between Chloromethylphosphine and Aqueous Sodium Hydroxide Solution.—Chloromethylphosphine (0.17 g, 2.0 mmoles) was condensed into a 100-ml bulb containing sodium hydroxide (1.0 g, 25 mmoles) in water (10 ml). The mixture was allowed to attain room temperature. The evolution of noncondensable gas was complete in approximately 30 min. The gas was removed using a Sprengel pump and was identified by combustion over copper oxide as hydrogen (1.4 mmoles). The ^1H nmr spectrum of the aqueous residue showed only four peaks of equal height centered at δ_{CH_3P} = 1.37 ppm, with J_{HCP} = 15.3 cps, and J_{HCPH} = 2.0 cps, and two quartets centered at δ_{PH} = 7.40 ppm, with J_{PH} = 530 cps and J_{HCPH} = 2.0 cps. This solution was refluxed with an excess of hydrogen peroxide for 2 hr. The ^1H nmr of the reaction mixture then consisted solely of a doublet at δ = 1.20 ppm with J_{HP} = 17.0 cps.

A solution of sodium methylphosphonate was prepared by the reaction between chloromethylphosphinic acid and aqueous sodium hydroxide solution.[5] The ^1H nmr of the solution was identical with that of the product obtained above, showing that the oxidation product was methylphosphonic acid (lit.[5] J_{HCP} = 17.3 cps for methylphosphonic acid).

Reaction between Chloromethylphosphine and Sodium Methoxide.—Chloromethylphosphine (0.50 g, 6.0 mmoles) was condensed into a 50-ml bulb containing a solution of sodium methoxide (0.72 g, 13.3 mmoles) in methanol (10 ml). The bulb was kept at −80° for 15 min during which time a white precipitate was slowly produced. The mixture was kept at room temperature for 1 hr. The volatile products were taken into the vacuum system and fractionated. The −80° fraction was identified by infrared spectroscopy as methanol. The −196° fraction was shown by infrared and nmr spectroscopy to be methylphosphine (0.11 g, 2.3 mmoles). *Anal.* Calcd for CH_3PH_2: mol wt, 48.0. Found: mol wt, 49.0. The solid residue in the reaction vessel was dissolved in water (5 ml). The nmr spectrum of the solution confirmed the presence of methylphosphinic acid; no other species containing phosphorus bound to an organic group was detected. It is estimated that this method would have detected such compounds if they were present in an amount not less than 10% of the methylphosphinic acid present.

Reaction between Chloromethylphosphine and Trimethylamine.—Chloromethylphosphine (0.53 g, 6.4 mmoles) and trimethylamine (0.81 g, 13.8 mmoles) were condensed into a glass reaction tube (50-ml capacity). The tube was allowed to attain room temperature. After 1 hr the volatile products were taken into the vacuum system and fractionated. The volatile fraction condensed at −196° and was shown by nuclear magnetic resonance spectroscopy to be a mixture of trimethylamine (0.53 g, 8.9 mmoles) and methylphosphine (0.10 g, 2.0 mmoles). The solid residue was dissolved in water; nmr spectroscopy of the solution indicated that methylphosphinic acid was the sole species containing an organic group bound to phosphorus present.

(7) J. VanWazer, "Phosphorus and Its Compounds," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1958, p 363.

Acknowledgment.—We thank Victor Division of the Stauffer Chemical Company for generous gifts of chloromethylphosphonic dichloride.

Reactions of Triphenylsilyl Azide with Tetraphenyldiphosphine and Diphenylphosphine

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Triphenylsilyl azide reacts readily with triphenylphosphine to give the phosphinimine.[2,3] With chlorophosphines exchange of the azido and chloro groups occurs concurrently with nitrogen evolution resulting in the formation of phosphonitriles and quantitative recovery of the alkyl- or arylsilyl moiety in the form of the chloride.[4] The reaction of phosphine with phenyl azide investigated by Staudinger and Hauser[5] is the only case in which the behavior of a P–H bond during the interaction with an azide could be studied. Although the authors seem to have failed in the isolation of a pure material, they point out that the initial reaction product is probably susceptible to rearrangement.

$$C_6H_5N_3 + PH_3 \longrightarrow \{C_6H_5N{=}PH_3\} + N_2 \longrightarrow C_6H_5NH{-}PH_2$$

No results have as yet been published on the reactivity of azides toward diphosphines, which are known to be prone to rearrangements originating in the breaking of the phosphorus–phosphorus bond.[6]

The present work was thus undertaken to investigate the behavior of the two different types of phosphines toward triphenylsilyl azide.

Tetraphenyldiphosphine was prepared following the procedure of Kuchen and Buchwald;[7] however, the product exhibited a somewhat different infrared spectrum from that reported by the above-mentioned authors. Of special significance is the weakness of the absorption in our spectrum at 1180 cm^{-1}, where a strong band was observed by Kuchen and Buchwald. We attribute the absorption at 1180 cm^{-1} to the presence of the oxide.[8,9] Since other analytical data given by these authors show their material to be pure, we believe that oxidation evidenced in their infrared spectrum occurred during either sample preparation or the actual recording of the spectrum.

Interaction of tetraphenyldiphosphine with triphenylsilyl azide afforded the desired doubly oxidized product I. No other material was isolated from the reaction mixture.

$$(C_6H_5)_3SiN{=}P(C_6H_5)_2P(C_6H_5)_2{=}NSi(C_6H_5)_3$$
I

The reaction of diphenylphosphine with triphenylsilyl azide did not proceed very readily. From the equimolar reaction mixture two products were isolated with Si:P ratios of 1:1 and 2:1. The reaction sequence can be best explained by the equation depicted below, wherein the monoadduct II reacts with an additional mole of silyl azide to give compound III, which now

$$(C_6H_5)_2PH + (C_6H_5)_3SiN_3 \longrightarrow (C_6H_5)_3SiNHP(C_6H_5)_2 \xrightarrow{(C_6H_5)_3SiN_3} (C_6H_5)_3SiNHP(C_6H_5)_2{=}NSi(C_6H_5)_3$$
II III

contains the phosphorus in a pentavalent state. The second step appears to proceed more readily than the first step, since even though equimolar quantities of triphenylsilyl azide and diphenylphosphine were employed a 45% yield of the disubstituted material was isolated together with unreacted diphenylphosphine. If the reaction is conducted using an excess of triphenylsilyl azide only the diadduct is obtained. The proposed structures of compounds II and III are based on their infrared and P^{31} nmr spectra. The presence in compound II of a weak but sharp absorption at 3315 cm^{-1} in conjunction with a strong absorption at 905 cm^{-1} [10,11] points to the presence of the P–NH moiety. This is further supported by the absence of characteristic P–H absorption at 2440–2350 cm^{-1} and the lack of splitting in P^{31} nmr, which would be expected from a P–H group. The formation of $(C_6H_5)_3SiNHP(C_6H_5)_2{=}NSi(C_6H_5)_3$ is an additional proof of the proposed structure for compound II, since in $(C_6H_5)_3SiN{=}P(H)(C_6H_5)_2$ the phosphorus is already in a pentavalent state. The postulated structure of the diadduct III is again in agreement with its infrared and P^{31} nmr spectra (sharp band at 3315 cm^{-1}, strong absorption at 935 cm^{-1}, no absorption at 2440–2350 cm^{-1}, and lack of splitting in the nmr).

Reactions of other types of azido compounds with diphenylphosphine and other secondary phosphines are currently being investigated in order to elucidate the mechanism which leads to the formation of $(C_6H_5)_3SiNHP(C_6H_5)_2$ (II). This reaction is probably an exchange process with a peculiar mechanism due to the electronegativities involved, or a complex oxidation–reduction reaction involving more diphenylphosphine than stoichiometrically required.

Experimental Section

The reactions were conducted either in a vacuum system or in a nitrogen atmosphere with rigid exclusion of moisture and oxygen. All chemicals were purified by applicable methods. Triphenylsilyl azide, mp 84.5–85.5°, was prepared in 83% yield following the procedure of Wiberg, *et al.*;[3] diphenylphosphine, bp 163–163.5° (14.8 mm), was obtained by the method of Kuchen and Buchwald[7] in 51% yield. Melting points were determined in sealed capillaries and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer double-beam (Model 21) infrared

(1) MHD Research, Inc., Newport Beach, Calif. 92663.

(2) R. West and J. S. Thayer, *J. Am. Chem. Soc.*, **84**, 1763 (1962).

(3) N. Wiberg, F. Raschig, and R. Sustmann, *Angew. Chem. Intern. Ed. Engl.*, **1**, 551 (1962).

(4) R. H. Kratzer and K. L. Paciorek, *Inorg. Chem.*, **4**, 1767 (1965).

(5) H. Staudinger and E. Hauser, *Helv. Chim. Acta*, **4**, 861 (1921).

(6) R. S. Hayter and L. F. Williams, *Inorg. Chem.*, **3**, 717 (1964), and references cited therein.

(7) W. Kuchen and H. Buchwald, *Chem. Ber.*, **91**, 2871 (1958).

(8) The infrared spectrum of $(C_6H_5)_2P(O)P(O)(C_6H_5)_2$, given by Kuchen and Buchwald,[7] exhibits a very strong band at 1180 cm^{-1}.

(9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1956, p 312, reports absorption in the vicinity of 1200 cm^{-1} for phosphine oxides.

(10) $(C_6H_5)_2P(O)NH_2$ exhibits a strong absorption at 910 cm^{-1}: K. L. Paciorek and R. H. Kratzer, unreported results.

(11) E. Steger, *Chem. Ber.*, **94**, 266 (1961).

spectrophotometer. The elemental analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Preparation of Tetraphenyldiphosphine.—Following the procedure of Kuchen and Buchwald[7] a 70% yield of tetraphenyldiphosphine was obtained, mp 126–127°. The infrared spectrum (Nujol oil mull, 1430–670-cm^{-1} region) exhibited the following bands: 1430 m, 1380 m, 1325 w, 1300 w, 1183 vw, 1088 vw, 1065 m, 1020 m, 997 m, 919 w, 905 w, 744 m, 734 s, and 692 s cm^{-1}.

Anal. Calcd for $C_{24}H_{20}P_2$: C, 77.83; H, 5.44; P, 16.73; mol wt, 370.37. Found: C, 77.59; H, 5.60; P, 16.89; mol wt, 355 (cryoscopic in benzene).

Preparation of $(C_6H_5)_3SiN{=}P(C_6H_5)_2P(C_6H_5)_2{=}NSi(C_6H_5)_3$.—In a capsule was sealed *in vacuo* triphenylsilyl azide (6.02 g, 20 mmoles), benzene (50 ml), and tetraphenyldiphosphine (3.70 g, 10 mmoles). The mixture was heated at 80–115° (gradually raising the temperature) over the period of 14 days. On opening to a vacuum system only 17.13% of nitrogen was collected. Subsequently, benzene was removed *in vacuo* at room temperature, and the residue was heated at 140° for 3 days (until no additional increase in pressure was observed). Total amount of nitrogen collected was 18.57 mmoles (93% yield). The product was crystallized from benzene–heptane mixture followed by boiling with acetonitrile. This material was then dried overnight at 70° *in vacuo*, mp 236–238°. The infrared spectrum (Nujol mull, 1430–670-cm^{-1} region) exhibited the following bands: 1430 w, 1370 m, 1300 m, 1250 w, 1100 m, 740 w, 722 m, and 700 s cm^{-1}.

Anal. Calcd for $C_{60}H_{50}P_2Si_2N_2$: C, 78.56; H, 5.50; P, 6.76; Si, 6.13; N, 3.06; mol wt, 916.61. Found: C, 78.70; H, 5.59; P, 6.96; Si, 6.41; N, 3.18; mol wt, 847 (in chloroform, using a Mechrolab osmometer).

Treatment of $(C_6H_5)_2PH$ with $(C_6H_5)_3SiN_3$. A. Using Equimolar Quantities.—In a nitrogen atmosphere $(C_6H_5)_3SiN_3$ (9.04 g, 0.03 mole) in ether (90 ml) was treated with $(C_6H_5)_2PH$ (5.5 g, 0.03 mole) in ether (10 ml); the solution was then refluxed overnight. Subsequently, the ether was removed *in vacuo* and the residue was heated to 100° for 10 days. On cooling a solid mass was obtained. This material failed to show in its spectrum any absorption in the vicinity of 2130 cm^{-1}, indicating an absence of azido moieties. Repeated crystallization from heptane gave 4.67 g (45% yield, based on triphenylsilyl azide employed) of $(C_6H_5)_3SiNHP(C_6H_5)_2{=}NSi(C_6H_5)_3$: mp 161–162°; P^{31} nmr, a single peak at −43 ppm (in benzene solution, referenced to 85% H_3PO_4). The infrared spectrum (Nujol oil) exhibited the following bands: 3315 w (N–H), 2900 s, 2858 w (Nujol), 1587 w (C=C), 1460 s (Nujol), 1430 s (PC_6H_5), 1375 s (Nujol), 1290 s, 1250 s, 1180 m, 1155 w, 1105 s, 1025 m, 997 m, 935 s (PNH), 791 m, 744 s, 735 s, and 694 s cm^{-1}.

Anal. Calcd for $C_{48}H_{41}PSi_2N_2$: C, 78.65; H, 5.64; P, 4.23; Si, 7.41; N, 3.55; mol wt, 733.03. Found: C, 78.26; H, 5.72; P, 4.25; Si, 7.41; N, 3.55; mol wt, 670 (in benzene, using a Mechrolab osmometer).

The compound $(C_6H_5)_3SiNHP(C_6H_5)_2{=}NSi(C_6H_5)_3$ was heated in air above its melting point; no change resulted.

The mother liquors, from the recrystallization of $(C_6H_5)_3SiNHP(C_6H_5)_2{=}NSi(C_6H_5)_3$, were freed from solvent on the vacuum line. Unreacted $(C_6H_5)_2PH$ was removed *in vacuo* at *ca.* 95°; subsequent sublimation at 135° afforded $(C_6H_5)_3SiNHP(C_6H_5)_2$ (2.14 g, 19% yield). This sublimate was recrystallized from heptane: mp 148–149°; P^{31} nmr, a single peak at −26.6 ppm (in benzene solution, referenced to 85% H_3PO_4). The infrared spectrum (Nujol oil mull) exhibited the following bands: 3320 w (N–H), 2900 s, 2855 s (Nujol), 1460 s (Nujol), 1430 (PC_6H_5), 1380 m (Nujol), 1307 w, 1220 m, 1212 m, 1190 w, 1117 s, 1030 w, 1000 w, 905 s (P–NH), 741 s (shoulder), 733 s, and 698 s cm^{-1}.

Anal. Calcd for $C_{30}H_{26}PSiN$: C, 78.40; H, 5.70; P, 6.74; Si, 6.11; N, 3.05; mol wt, 459.61. Found: C, 78.62; H, 5.83; P, 6.63; Si, 5.75; N, 2.92; mol wt, 455 (in benzene, using a Mechrolab osmometer).

B. Excess $(C_6H_5)_3SiN_3$.—In a sealed, evacuated ampoule $(C_6H_5)_2PH$ (582.0 mg, 3.126 mmoles) was heated with $(C_6H_5)_3SiN_3$ (2.541 g, 8.430 mmoles) at 110–115° for 90 hr. On opening to the vacuum system, nitrogen (6.349 mmoles) was obtained, thus N_2:$(C_6H_5)_2PH$ = 2.03:1, showing that only the diadduct $(C_6H_5)_3SiNHP(C_6H_5)_2{=}NSi(C_6H_5)_3$ was formed. The reaction mixture on washing with ether, followed by crystallization of the ether-insoluble material from heptane, afforded 1.62 g (71% of the diadduct, mp 161–162°). Additional quantities of the product remained in ether and heptane mother liquors admixed with the excess of $(C_6H_5)_3SiN_3$.

Acknowledgments.—This investigation was partially supported by the Bureau of Naval Weapons, Department of the Navy, through Foundational Research Program. We are indebted to Dr. Kurt Moedritzer of Monsanto Chemical Company for the determination and interpretation of the P^{31} nmr spectra.

The Synthesis of 19-Oxygenated Cardenolides. I. A Convenient Preparation of 19-Hydroxydesoxycorticosterone

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In the recently described total synthesis of periplogenin[1] we took advantage, as an alternative and practical shortcut, of the microbiological hydroxylation in 14α of desoxycorticosterone as a means of introducing the 14,15 double bond and subsequently, by a sequence of steps well known in the steroid literature,[2] the 14β-hydroxyl group characteristic of this class of cardioactive substances.

It seemed attractive therefore to prepare by an efficient method 19-hydroxydesoxycorticosterone as a substrate for 14α-hydroxylation. By applying essentially the already disclosed synthetic sequence used for periplogenin,[1] 19-hydroxy-DOC could be considered a starting material for the synthesis of strophanthidol and related 19-oxygenated cardenolides.

It is of interest that 19-hydroxy-DOC was first obtained by degradation of strophanthidin itself.[12]

The commercially available 21-hydroxypregnenolone diacetate I was converted to the chlorohydrin II in 70% yield by allowing it to react with freshly prepared and chlorine-free hypochlorite solution in acetone. The 6,19-oxide III was obtained in 70% yield from chlorohydrin II by the iodine–lead tetraacetate reaction[13] and saponified to the diol IV with $KHCO_3$ in aqueous methanol in about 90% yield.

(1) R. Deghenghi, A. Philipp, and R. Gaudry, *Tetrahedron Letters*, 2045 (1963).

(2) A recent statement[3] claiming priority over a number of steps well documented in the previous literature (*e.g.*, for the addition of HOBr to a 14,15 double bond followed by Raney nickel debromination, *cf.* Ringold, *et al.*;[4] followed by β-epoxide formation, *cf.* Meister,[5] Bloom, *et al.*,[6] and Reichstein;[7] *cf.* also Meyer[8] and Bernstein;[9] for the hydride reduction of a 14,15β epoxide without epimerization of the 17β chain, *cf.* Meyer[10] and ref 5; also Kondo[11] and references cited therein), deserves little comment.

(3) C. R. Engel and G. Bach, *Steroids*, **3**, 593 (1964).

(4) H. J. Ringold, F. Sondheimer, and G. Rosenkrantz, U. S. Patent 2,889,346 (June 2, 1959; priority Dec 23, 1953).

(5) P. D. Meister, U. S. Patent 2,930,791 (March 29, 1960; applied June 7, 1955).

(6) B. M. Bloom, E. J. Angello, and G. D. Laubach, *Experientia*, **12**, 27 (1956).

(7) A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **45**, 943 (1962).

(8) P. Hofer, H. Linde, and K. Meyer, *ibid.*, **45**, 1041 (1962).

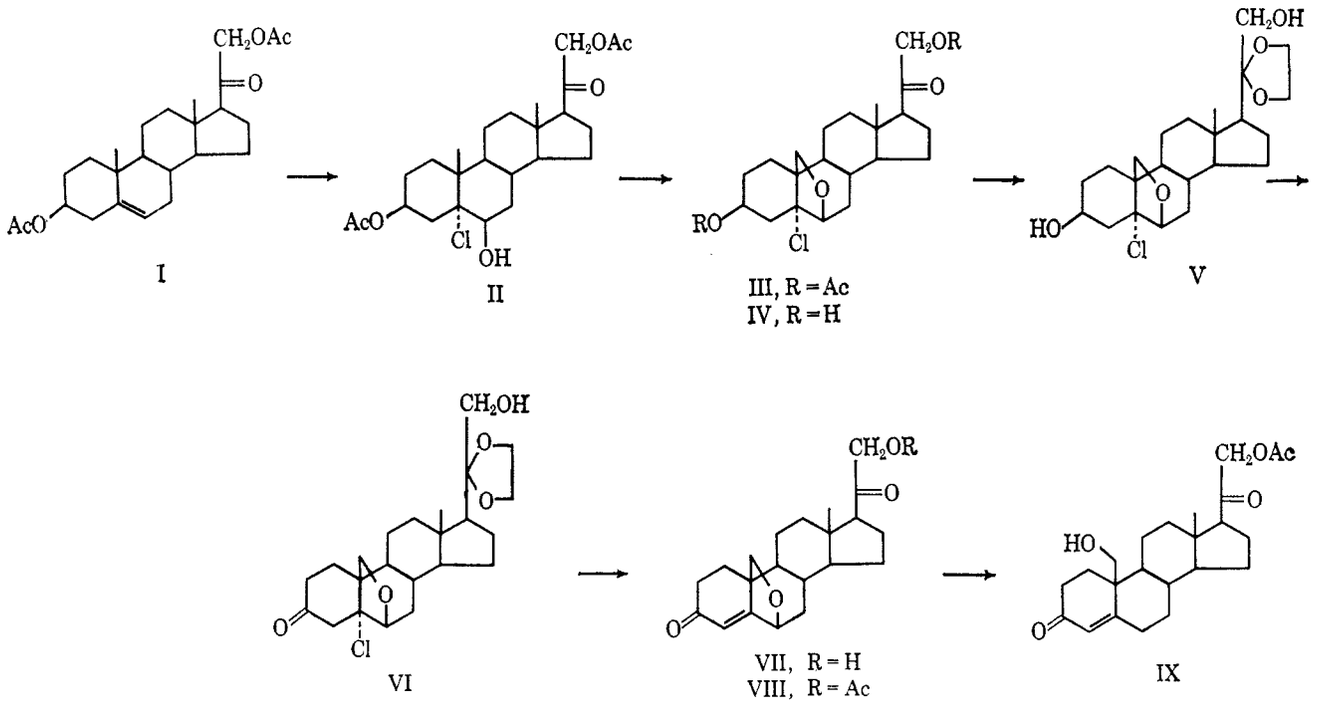
(9) M. Heller, F. J. McEvoy, and S. Bernstein, *Steroids*, **3**, 193 (1964).

(10) H. Linde and K. Meyer, *Helv. Chim. Acta*, **42**, 807 (1959).

(11) H. Kondo, U. S. Patent 3,134,772 (May 26, 1964; priority May 1, 1961).

(12) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **19**, 1758 (1954).

(13) J. Kalvoda, K. Heusler, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 1017 (1963).



The procedure of selective oxidation of secondary *vs.* primary alcohol as described by Bernstein[14] was followed by preparing the 20-ketal V in about 70% yield from IV, and treating it with chromic anhydride in pyridine thus securing the 3-keto compound VI in about 50% yield. This route proved superior to the more obvious protection of the primary alcohol by a variety of selective esterifications. Acid treatment of crude VI provided in 80% yield 6,19-oxido-DOC (VII), characterized as the acetate VIII.

Reductive opening of the oxide bridge with zinc and acetic acid[13] gave 19-hydroxy-DOCA[12] (IX) in good yield.[15]

The microbiological hydroxylation of this compound and its application to the synthesis of 19-oxygenated cardenolides will be reported at a later date.

Experimental Section

5α-Chloro-3β,6β,21-trihydroxypregnan-20-one 3,21-Diacetate (II).—A solution of 160 g of sodium bicarbonate in 1.5 l. of water was saturated at 0° with a stream of chlorine for 15 min. Excess chlorine was removed by bubbling through the solution a stream of air and by repeated chloroform extraction until the organic and aqueous layers were colorless. This solution was found to contain 16.4 g of NaClO/l. by thiosulfate titration of an aliquot.[16]

To a solution of 21-hydroxypregnenolone diacetate (I, 110 g) in 3 l. of acetone was added 1320 ml of the hypochlorite solution (10% excess), and the mixture was stirred at room temperature for 30 min. Addition of a few milliliters of aqueous potassium iodide solution gave a weakly positive active chlorine reaction (iodine color), decolorized by addition of some thiosulfate solution. The bulk of the acetone was evaporated *in vacuo* at moderate temperature and the residue was extracted with ether and washed with thiosulfate and bicarbonate solution and water. Evaporation of the solvent afforded 70.0 g of crystalline II, mp 190–191.5°. Concentration of the mother liquor gave additional quantities of the chlorohydrin. A sample was recrystallized from acetone–hexane for analysis, mp 193–194°, $[\alpha]^{23}D$ +36.0° ($CHCl_3$). *Anal.* Calcd for $C_{25}H_{37}ClO_6$: C, 64.02; H, 7.95; Cl, 7.56. Found: C, 63.95; H, 8.03; Cl, 7.62.

5α-Chloro-3β,21-dihydroxy-6β,19-oxidopregnan-20-one 3,21-Diacetate (III).—Lead tetraacetate, 44 g, and 5.0 g of calcium carbonate were suspended in 1.8 l. of cyclohexane and refluxed for 30 min. A quantity of the chlorohydrin II, 10.0 g, and 13.0 g of iodine were subsequently added. The stirred mixture was refluxed and illuminated with photoflood lamp (750 w) for 2 hr. The cooled mixture was filtered through Celite and the filtrate was washed twice with thiosulfate solution and water. Evaporation of the dried solvent gave 11.8 g of a foamy residue which crystallized from acetone–ether–hexane to give 5.6 g of needles, mp 145–147°. The analytical sample melted at 146–147°, $[\alpha]^{23}D$ +73.5° ($CHCl_3$). *Anal.* Calcd for $C_{25}H_{35}ClO_6$: C, 64.30; H, 7.55; Cl, 7.59. Found: C, 64.42; H, 7.77; Cl, 7.66.

5α-Chloro-3β,21-dihydroxy-6β,19-oxidopregnan-20-one (IV).—The diacetate III, 1.0 g, was dissolved in 30 ml of methanol and refluxed in the presence of 470 mg of potassium bicarbonate in 10 ml of water for 1 hr. The solvent was removed *in vacuo* and the residue was extracted with ether. Evaporation of the solvent furnished 836 mg of a residue which crystallized from acetone–ether–hexane.

The analyzed sample had mp 166–168°, $[\alpha]^{23}D$ +57.8° ($CHCl_3$). *Anal.* Calcd for $C_{21}H_{31}ClO_4$: C, 65.87; H, 8.16; Cl, 9.26. Found: C, 66.07; H, 8.06; Cl, 9.21.

5α-Chloro-20-ethylenedioxy-6β,19-oxidopregnane-3β,21-diol (V).—The diol IV, 0.5 g, was dissolved in 25 ml of benzene and stirred and refluxed in presence of 25 ml of ethylene glycol and 75 mg of *p*-toluenesulfonic acid for 3.5 hr with a water separator. The cooled mixture was extracted with methylene dichloride, and the extract was washed with sodium bicarbonate and water. Evaporation of the solvent gave 0.526 g of a crystalline residue. One recrystallization from methylene dichloride–ether–hexane gave 0.374 g of needles, mp 225–227°.

The analyzed sample melted at 223.5–225°, $[\alpha]^{23}D$ +15.1° (dioxane). *Anal.* Calcd for $C_{23}H_{35}ClO_5$: C, 64.70; H, 8.26; Cl, 8.30. Found: C, 64.68; H, 8.20; Cl, 8.70.

21-Acetoxy-6β,19-oxido-4-pregnene-3,20-dione (VIII).—The diol V, 4.6 g, dissolved in 50 ml of pyridine was added to a slurry of 6.3 g of chromic oxide in 70 ml of pyridine and stirred at room temperature for 16 hr. The mixture was poured into water and extracted to give 2.2 g of amorphous residue, representing crude VI. This product was dissolved in 40 ml of acetone and treated at room temperature for 2 hr in the presence of concentrated sulfuric acid (6 drops). Extraction with methylene dichloride, washing with sodium bicarbonate solution and water, and evaporation of the dried solvent gave 1.830 g of crude

(14) S. Bernstein and R. Lenhard, *J. Am. Chem. Soc.*, **77**, 2331 (1955).

(15) 19-Hydroxylation of DOC by adrenal perfusion [*cf.* R. Neher and A. Wettstein, *Helv. Chim. Acta*, **39**, 2062 (1956)] and by fermentation in low yield [*cf.* M. Nishikawa and H. Hagiwara, *Chem. Pharm. Bull.* (Tokyo), **6**, 226 (1958)] has been described.

(16) Successive runs have shown that a reproducible hypochlorite content is difficult to obtain. This experiment describes the best yield in pure chlorohydrin.

VII, which was acetylated with acetic anhydride, 2.5 ml in 20 ml of pyridine, at room temperature for 16 hr. Usual work-up afforded 1.73 g of crystalline VIII (from acetone–hexane), mp 189–193°. The analyzed sample melted at 193–196°, $[\alpha]^{23}D$ +4.3° ($CHCl_3$). *Anal.* Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.48; H, 8.07.

19,21-Dihydroxy-4-pregnen-3,20-dione 21-Acetate (IX).—The oxide VIII, 0.675 g in 20 ml of acetic acid, was treated with 16.9 g of zinc powder prewashed with diluted acetic acid, with stirring on a steam bath for 10 min. The metal was filtered and washed with acetic acid; the filtrate taken to dryness *in vacuo* and the residue was dissolved in methylene dichloride and washed to neutrality with sodium bicarbonate and water. Evaporation of the solvent gave 0.578 g of amorphous IX, which crystallized from acetone: mp 196–198°, $[\alpha]^{23}D$ +176.5° ($CHCl_3$); lit.[12] mp 197–199°, $[\alpha]^{24}D$ +178°.

19,21-Dihydroxy-4-pregnene-3,20-dione (19-Hydroxydeoxycorticosterone).—Alkaline hydrolysis of the monoacetate IX according to the procedure described by Barber and Ehrenstein[12] gave the title compound: mp 160–162° (from acetone–ether), $[\alpha]^{23}D$ +179° ($CHCl_3$); lit.[12] mp 163–165°, $[\alpha]^{25}D$ +180°.

Acknowledgments.—The technical cooperation of Messrs. Heinz Haenni and Werner Wirz is gratefully acknowledged.

Carboxamidation of β-Dicarbonyl Compounds

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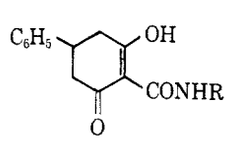
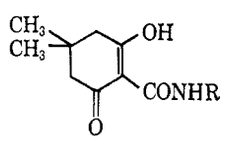
At the beginning of our work on the total synthesis of tetracycline antibiotics we were faced with the problem of constructing a 2-carboxamido 1,3-diketone moiety.[1] Although in the meantime the general synthetic approach has been changed[2] this Note describes some model experiments carried out previously in connection with this problem.

It has been known for a long time that organic isocyanates react with β-dicarbonyl compounds in the presence of catalytic amounts of base to yield N-substituted 2-carboxamido-1,3-dicarbonyl compounds. For instance, the reaction between 5-phenylcyclohexane-1,3-dione and phenyl isocyanate gave I.[3] Under the same conditions dimedon gave II.[3] Furthermore, dimedon reacts with acetyl isocyanate or carbomethoxy isocyanate to yield III and IV, respectively, which can be hydrolyzed with ammonia to V.[4,5]



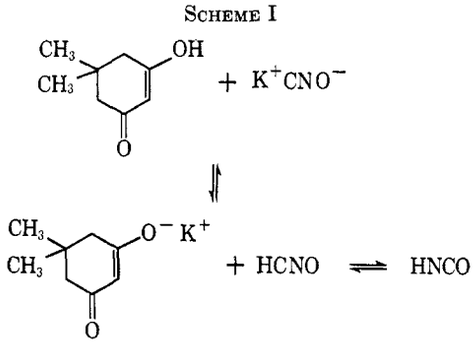
I, R = C_6H_5
VII, R = H



II, R = C_6H_5
III, R = $COCH_3$
IV, R = CO_2CH_3
V, R = H

At the outset of our work we tried to treat isocyanic acid with dimedon to form V. If dimedon was treated with isocyanic acid in chloroform–ether, a very slow reaction to V took place with most of the isocyanic acid polymerizing to cyamelide. However, if triethylamine was added to a chloroform–ether solution of dimedon and isocyanic acid, a faster reaction to V was observed. The fact that the polymerization of isocyanic acid is a main side reaction during these processes led to an attempt to find a system in which only a relatively low concentration of isocyanic acid would be available at a given time which might react in the wanted direction in preference to polymerization. Expecting that a solution of potassium cyanate and dimedon in water might establish the equilibrium outlined in Scheme I and that during and after establishment of this equilibrium V might be formed, dimedon and potassium cyanate were allowed to react in a mixture of dimethylformamide and water.[1b] The best

SCHEME I



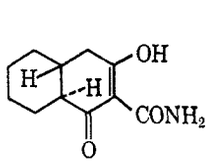
results were obtained by dropping a water solution of potassium cyanate into a solution of dimedon in dimethylformamide. This way a 51% yield of V was obtained. If a greater amount of potassium cyanate was used or the reaction time was prolonged, the yields were lower. This may be due to the fact that potassium carbonate is formed by heating potassium cyanate in water and that potassium carbonate might degrade V. A control experiment showed that V is degraded by potassium carbonate in water.

In order to extent the potassium cyanate reaction to other systems, *trans*-decalin-1,3-dione[6] and 5-phenylcyclohexane-1,3-dione were used. In both cases the expected reaction took place and compounds VI and VII, respectively, were isolated. Furthermore, compound VIII, prepared during attempts to synthesize tetracycline antibiotics,[7] reacted with potassium cyanate to give IX.

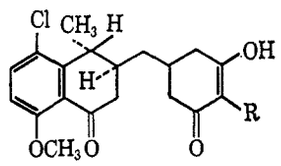
In all the cases mentioned so far, carboxamidation also occurred with lead cyanate in acetonitrile, but no markedly better results were obtained.

The reaction products V–VII and IX could be isolated directly or *via* their crystalline, water-insoluble copper chelates. Compounds V–VII show, even in dilute solution, no infrared absorption maxima of carbonyl groups <6.2 μ and are therefore completely enolized and chelated. The same is true for IX,

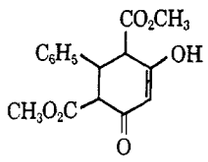
(1) (a) For a general discussion of this problem, see H. Muxfeldt, *Angew. Chem.*, **74**, 443 (1962); *Angew. Chem. Intern. Ed. Engl.*, **1**, 372 (1962).
(2) H. Muxfeldt and W. Rogalski, *J. Am. Chem. Soc.*, **87**, 933 (1965).
(3) W. Dieckmann, J. Hoppe, and R. Stein, *Ber.*, **37**, 4627 (1904).
(4) M. M. Shemyakin, J. A. Arbuzow, M. N. Kolosov, G. A. Shatenshteyn, W. W. Onopienko, and J. V. Konnova, *Zh. Obshch. Khim.*, **30**, 542 (1960).
(5) Compound V was also prepared by fusing a mixture of dimedone and urea: H. C. Scarborough and W. A. Gould, *J. Org. Chem.*, **26**, 3720 (1961).
(6) C.-K. Chuang and H.-L. Tien, *Ber.*, **69**, 25 (1936).
(7) H. Muxfeldt and W. Rogalski, *ibid.*, **95**, 2581 (1962).



VI



VIII, R = H
IX, R = $CONH_2$



X

except that IX has an additional absorption band at 5.96 μ from its tetralone carbonyl.

β-Dicarbonyl compounds of different types, such as compound X,[8] methyl benzoyl acetate, or methyl acetyl acetate did not react in the described manner.

Experimental Section

Carboxamidodimedon (V). A. From Dimedon and Isocyanic Acid in the Presence of Triethylamine.—To a solution of 2 g of dimedon and 2 ml of triethylamine in 200 ml of chloroform, 100 ml of an ether solution of isocyanic acid (prepared by thermal decomposition of 5 g of anhydrous cyanuric acid) was added. The mixture was stirred at room temperature for 10 days.[9] After filtration (cyamelide) the filtrate was acidified with dilute hydrochloric acid and washed with water. The organic phase was dried with sodium sulphate and evaporated. The remaining yellow, crystalline residue was recrystallized from ether–petroleum ether (bp 60–80°). A total of 758 mg (33%) of V was obtained: mp 148–149°; $\lambda_{max}^{0.01\ N\ MeOH-HCl}$ 258 mμ (ϵ 17,700); $\lambda_{max}^{0.01\ N\ MeOH-NaOH}$ 267–270 mμ (ϵ 18,600); $\lambda_{max}^{CHCl_3}$ 2.9, 3.1, 3.4, 6.2 μ.

Anal. Calcd for $C_{19}H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.95; H, 7.16; N, 7.62.

B. From Potassium Cyanate and Dimedon.—A solution of 50 g of potassium cyanate in 150 ml of water was added dropwise during a period of 30 min with stirring to a solution of 50 g of dimedon in 500 ml of dimethylformamide at 100°. The mixture was heated for another 30 min at 100° and was then acidified with dilute hydrochloric acid and diluted with 300 ml of water. The mixture was cooled in an ice bath for 2 hr and the crystalline V was filtered off, washed with water, and dried in a desiccator. The dry V was recrystallized once from ether–petroleum ether. A total of 33.4 g (51%) of V was obtained, mp 148–149°.

C. From Dimedon and Lead Cyanate.—A suspension of 300 mg of dimedon and 900 mg of lead cyanate in 40 ml of acetonitrile was heated to reflux for 3 days. The mixture was diluted with 40 ml of water, acidified with dilute hydrochloric acid, and immediately filtered. The filtrate was further diluted with 100 ml of water and extracted three times with chloroform. The combined extracts were dried over sodium sulphate and evaporated to dryness. The crystalline residue was dissolved in methanol and an excess of a solution of copper acetate in water was added. The crystalline copper chelate of V was filtered off, washed with water–methanol (1:1), and then suspended in water. The suspension was acidified with dilute hydrochloric acid and extracted with chloroform. After drying the extracts and evaporating the solvent there remained 242 mg (63%) of crude V: mp 146–147°; after recrystallization from ether–petroleum ether, mp 148–149°.

D. From Dimedon and Silver Cyanate.—If 300 mg of dimedon was treated with 1 g of silver cyanate as described under C, 240 mg (63%) of V was obtained.

Carboxamidation of 5-Phenylcyclohexane-1,3-dione with Potassium Cyanate.—Within a period of 30 min a solution of 2.5 g of potassium cyanate in 40 ml of water was added with stirring to a solution of 4 g of 5-phenylcyclohexane-1,3-dione in 40 ml of dimethylformamide at 100°. The mixture was kept at this temperature for another 90 min and worked up as described above. The crude material was crystallized from chloroform and ether. A total of 1.4 g (35%) of VII was obtained: mp 162–164°; $\lambda_{max}^{0.01\ N\ MeOH-HCl}$ 257–258 mμ (ϵ 17,900); $\lambda_{max}^{0.01\ N\ MeOH-NaOH}$ 268–269 mμ (ϵ 19,000); $\lambda_{max}^{CHCl_3}$ 2.9, 3.1, 3.4, 6.2 μ.

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67. Found: C, 67.41; H, 5.70.

Carboxamidation of *trans*-Decalin-1,3-dione with Potassium Cyanate.—A solution of 5 g of *trans*-decalin-1,3-dione in 50 ml of dimethylformamide was treated with a solution of 3.75 g of potassium cyanate in 50 ml of water as described above. The crude reaction product was recrystallized from ether. A total of 2.32 g (37%) of VI was obtained: mp 114–116°; $\lambda_{max}^{0.01\ N\ MeOH-HCl}$ 259 mμ (ϵ 16,700); $\lambda_{max}^{0.01\ N\ MeOH-NaOH}$ 267–269 mμ (ϵ 18,700); $\lambda_{max}^{CHCl_3}$ 2.9, 3.1, 3.45, 6.2–6.4 μ.

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.26; N, 6.54. Found. C, 63.27; H, 7.25; N, 6.91.

Carboxamidation of VIII with Potassium Cyanate.—A solution of 250 mg of potassium cyanate in 2.5 ml of water was added with stirring during a period of 25 min to a solution of 720 mg of VIII in 3.5 ml of dimethylformamide at 100°. The mixture was kept at this temperature for another 3 hr, diluted with water, acidified with dilute hydrochloric acid, and extracted with chloroform. The combined extracts were washed with water and evaporated after drying over sodium sulphate. The crude amorphous residue (680 mg) was then dissolved in benzene–ether (1:1) and shaken with 10 ml of a 10% solution of copper acetate in water for 20 min. The crystalline copper chelate of IX was filtered off and suspended in 20 ml of a 1:1 mixture of methanol–2 *N* hydrochloric acid and extracted with chloroform. The combined chloroform extracts were dried over sodium sulphate and evaporated and the residue was crystallized from acetone and ether. A total of 280 mg (35%) of IX was obtained: mp 209–214° dec; $\lambda_{max}^{0.01\ N\ MeOH-HCl}$ 328 mμ (ϵ 4400), 258 (ϵ 23,200), 226 (ϵ 27,000); $\lambda_{max}^{0.01\ N\ MeOH-NaOH}$ 328 mμ (ϵ 4400), 262 (ϵ 22,600), 227 (ϵ 25,400); $\lambda_{max}^{CHCl_3}$ 2.85, 3.05, 3.30, 3.40, 5.96, 6.33 μ.

Anal. Calcd for $C_{20}H_{22}ClNO_5$: C, 61.30; H, 5.66; Cl, 9.05; N, 3.57. Found: C, 61.41; H, 5.80; Cl, 9.15; N, 3.62.

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(8) H. Muxfeldt, G. Grethe, K. Uhlig, and H. Zeugner, *Ber.*, **96**, 2943 (1963).

(9) During preliminary experiments the reaction was run as described above and samples were taken at different times. It was found that after 10 days no increase of the yield of V could be detected.