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Preparation of Nitriles from Halides and Sodium Cyanide. An Advantageous Nucleophilic Displacement in Dimethyl Sulfoxide[1a]

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Reaction of primary and secondary chlorides with sodium cyanide in dimethyl sulfoxide occurs rapidly and efficiently to result in an improved general method for preparing nitriles. Advantages are also realized in conversion of primary and secondary bromides to their corresponding nitriles. Use of dimethyl sulfoxide allows preparative displacement of halides of the neophyl and neopentyl types by cyanide ion without rearrangement. Typical procedures which illustrate the various experimental methods are described.

Sodium or potassium cyanide reacts slowly (twenty-four to ninety-six hours) with primary chlorides in aqueous ethanol to give the corresponding nitriles in good yields, accompanied by alcohols, ethers, and olefins.[2] The procedure is unsatisfactory for low boiling nitriles[3] because of the difficulty of isolating the products from the solvent. The method has been improved by use of higher boiling solvents such as ethylene glycol,[3] methyl Cellosolve,[4a,b] tetrahydrofurfuryl alcohol,[4a] and dimethylformamide;[4b] however, the reaction is still slow because of the insolubility of the inorganic cyanides and offers disadvantages for the usual laboratory synthesis. Secondary chlorides give nitriles in only 30% yield in aqueous ethanol;[5] substitution also occurs slowly and in poor yield in methyl Cellosolve and dimethylformamide.[4b,6] Primary bromides are converted efficiently to nitriles in aqueous ethanol[7a] or ethylene glycol (better).[3,7b] Secondary bromides, however, in aqueous ethanol[8a] or ethylene glycol[3] give nitriles in unsatisfactory (27–39%) yields, and separation of the product from accompanying alcohols and ethers is difficult.[8b]

It is now reported that typical primary chloroalkanes (Table I) react rapidly and exothermically[9] with sodium cyanide in partial solution in dimethyl sulfoxide to give the corresponding nitriles in excellent yields. The nitriles are conveniently isolated from the reaction mixture by dilution with water followed by suitable extraction. At the preferred reaction temperatures of 120–140° the conversion of primary chlorides to nitriles may usually be completed in one half to two hours. The reaction is applicable to the slow conversion of 1-chloro-2-methyl-2-phenylpropane(neophyl chloride)[10] to 3-methyl-3-

(1) (a) Abstracted in part from the Ph.D. Dissertation of L. Friedman, The Ohio State University, 1959. (b) Present address: Department of Chemistry, New York University, University Heights, N. Y. (c) To whom inquiries should be made.

(2) (a) H. B. Hass and J. R. Marshall, *Ind. Eng. Chem.*, **23**, 352 (1931); (b) H. E. Fierz-David and W. Kuster, *Helv. Chim. Acta*, **22**, 82 (1939); (c) H. Suida and F. Drahowzal, *Chem. Ber.*, **75**, 991 (1942); (d) K. Ahmad and F. M. Strong, *J. Am. Chem. Soc.*, **70**, 1699 (1948); (e) K. Ahmad, F. M. Bumpus, and F. M. Strong, *J. Am. Chem. Soc.*, **70**, 3393 (1948).

(3) R. N. Lewis and P. V. Susi, *J. Am. Chem. Soc.*, **74**, 840 (1952).

(4) (a) A. O. Rogers, U. S. Patent **2,415,261**, Feb. 4, 1947; (b) H. B. Copelin, U. S. Patent **2,715,137**, Aug. 9, 1955.

(5) Ref. 2a; no experimental details were given.

(6) 2-Chlorobutane does not react with sodium cyanide in ethylene glycol.[3]

(7) (a) C. S. Marvel and E. M. McColm, *Org. Syntheses*, **5**, 103 (1925); (b) F. B. LaForge, N. Breen, and W. A. Gersdoff, *J. Am. Chem. Soc.*, **70**, 3709 (1948).

(8) (a) M. T. Rogers and J. D. Roberts, *J. Am. Chem. Soc.*, **68**, 843 (1946); (b) T. Moritsugu, M.S. Thesis, The Ohio State University, 1951.

(9) Cooling is sometimes required to keep the reaction under control.

(10) Halides of the neopentyl type are reported to be unreactive to cyanide ion; A. Franke, *Monatsh. Chem.*, **34**, 1893 (1913); F. C. Whitmore and G. H. Fleming, *J. Am. Chem. Soc.*, **55**, 4161 (1933).

phenylbutyronitrile (69% conversion, 29% yield). The secondary chloro compounds, 2-chlorobutane and chlorocyclopentane (Table I), react relatively slowly (*ca.* three hours) to give the corresponding nitriles in moderate yields (65–70%). As a general method for preparing nitriles from primary or secondary chlorides, the reaction in dimethyl sulfoxide is much superior to that in the previous solvents.

t-Butyl chloride and cyclohexyl chloride in dimethyl sulfoxide react either in the presence or absence of sodium cyanide to give olefins, malodorous decomposition products, and tars.[11] Benzyl chloride gave the corresponding nitrile (Table I) in excellent yield. Better yields of benzyl cyanide were obtained at lower temperatures because reaction between the halide and the solvent was minimized.[12] *p*-Nitrobenzyl chloride reacted with sodium cyanide in dimethyl sulfoxide to give 4,4′-dinitrostilbene.[13]

The reaction of sodium cyanide and alkyl halides was extended to representative bromides.[14] 1-Bromobutane reacts rapidly at 60–90[c] with sodium cyanide to give valeronitrile in excellent yield (Table I). The reaction is exothermic and, if the temperature is too high (>90°), the yield is lowered because of reaction of the halide with the solvent.[15,16] 2-Bromobutane reacts to give 2-methylbutyronitrile in 41% yield. The reaction mixtures are dark brown and noxious; the relatively poor yield and the complex products probably result from competing reactions with dimethyl sulfoxide. The yield with the secondary bromide is slightly superior, however, to those reported when ethanol and ethylene glycol are used as solvents, and there are experimental advantages in terms of reaction rate and isolation of products.

TABLE I

REACTION OF ALKYL AND CYCLOALKYL HALIDES WITH SODIUM OR POTASSIUM CYANIDE IN DIMETHYL SULFOXIDE

Halide	Cyanide[a]	Reaction Temp., °	Reaction Time, hr.[b]	Yield of Nitrile, %
1-Chlorobutane[c]	NaCN	140	0.25	93
1-Chlorobutane[c]	KCN	120–140	10	69
1-Chloro-2-methylpropane	NaCN	140[d]	0.5	88[e]
1-Chloro-3-methylbutane	NaCN	100–140	2	85[f]
1-Chloro-2-methyl-2-phenylpropane[c]	NaCN	120	24	26
Benzyl chloride	NaCN	35–40[g]	2.5	92[h]
p-Nitrobenzyl chloride	NaCN	35–40	1	0[i]
2-Chlorobutane	NaCN	120–145	3	64[j]
2-Chlorobutane	KCN	120–138[k]	24	42
Chlorocyclopentane[c]	NaCN	125–130	3	70
Chlorocyclohexane[l]	NaCN	130–80	4	0[l]
2-Chloro-2-methylpropane	NaCN	130–105	4	0[m]
1-Bromobutane[n]	NaCN	60–90[n]	0.6	92[o]
1-Bromo-2-methylpropane[c]	NaCN	70	2	62
2-Bromobutane	NaCN	70	6	41[p]

[a] The ratio of halide (moles), cyanide (moles), and DMSO (ml.) usually used was 1:1.1:250. [b] The reaction time listed is the sum of that for addition of the halide and subsequent reaction at the given temperature. [c] See Experimental. [d] The halide was added in 10 min. to the initial mixture at 80°. The reaction is mildly exothermic and was completed by heating to 140° until refluxing ceased. [e] B.p. 128°, n_D^{20} 1.3926; see ref. 23. [f] B.p. 151–155°, n_D^{20} 1.4047–1.4051; lit. b.p. 150–155°, H. Rupe and K. Glenz, *Helv. Chim. Acta*, **5**, 939 (1922). [g] The reaction mixture was cooled externally. [h] B.p. 90.5–91° (5 mm.), n_D^{20} 1.5237-1.5238; lit. b.p. 115–120° (10 mm.), n_D^{20} 1.5242; J. W. Bruhl, *Z. physik Chem.*, **16**, 218 (1895). [i] 4,4′-Dinitrostilbene is formed in 78% crude yield, m.p. 286–288°; lit. 288°; P. Ruggli and F. Lang, *Helv. Chim. Acta*, **21**, 42 (1938); R. Walden and A. Kernbaum, *Chem. Ber.*, **23**, 1959 (1890). [j] B.p. 123.5–124° (742 mm.), n_D^{20} 1.3898–1.3900; lit. b.p. 125°; M. Hanriot and L. Bouveault, *Bull. soc. chim. France*, (3) **1**, 172 (1889). [k] The halide was added dropwise in 6 hr. to the mixture at 120–125°; the mixture was then heated for 18 hr. until it reached 138°. [l] The reaction mixture became dark and gave cyclohexene, gases, and a black intractable product. [m] Upon initiating reaction at 130°, gases (2-methylpropene, hydrogen cyanide, and formaldehyde) were evolved, the temperature dropped to 105°, and black resinous materials were formed. The desired product was not obtained at lower reaction temperatures. [n] The bromide was added in 30 min. to the cyanide mixture at 60° while effecting cooling of the reaction; the mixture was then heated for 15 min. at 90°. [o] B.p. 138–139° (742 mm.), n_D^{20} 1.3970; see Ref. 19. [p] Upon addition of the 2-bromobutane, the temperature was maintained at 55–60° by intermittent cooling. In subsequent reaction gases were evolved and the mixture became progressively darker and malodorous.

(11) (a) These results are consistent with current substitution theory, the results in related systems, and the effects of ionizing solvents on such halides. (b) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 319, 426. (c) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951). (d) S. Smith and J. Takahashi, unpublished work as quoted in ref. 12b.

(12) Reactions of halides with dimethyl sulfoxide have been investigated by (a) R. Kuhn and H. Trischmann, *Ann.*, **611**, 117 (1958); (b) S. G. Smith and S. Winstein, *Tetrahedron*, **3**, 317 (1958) and (c) N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Am. Chem. Soc.*, **81**, 4113 (1959) and related previous paper.

(13) This reaction also occurs with cyanide ion in ethanol. Its mechanism has been discussed by C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956) and G. Hahn, *Chem. Ber.*, **62**, 2485 (1929).

(14) Reaction of 1-bromobenzocyclobutene with sodium cyanide in dimethyl sulfoxide to give 1-cyanobenzocyclobutene has been reported by our colleagues, M. P. Cava, R. L. Little, and D. R. Napier, *J. Am. Chem. Soc.*, **80**, 2260 (1958). Their use of dimethyl sulfoxide was based on suggestions and experimental details of prior observations by the present authors (Nov. 26–Dec. 21, 1955) on the advantageous use of the solvent in effecting conversions of chlorides and bromides to nitriles. The absence of any reference resulted from the fact that knowledge of the unpublished method was so common in this laboratory that it had assumed routine use. NOTE ADDED IN PROOF: R. A. Smiley and C. Arnold, *J. Org. Chem.*, **25**, 257 (1960) have also described the advantageous use of dimethyl sulfoxide in preparing nitriles from alkyl chlorides.

(15) In the absence of sodium cyanide, extensive reaction of the bromide occurs with the solvent; see ref. 12.

The reaction of alkyl chlorides and bromides with potassium cyanide in partial solution in dimethyl sulfoxide is of significance with respect to preparative purposes in that displacement occurs much more slowly when compared with sodium cyanide.[17] The reason for this difference was not investigated. The synthesis of nitriles from halides and cyanides was also attempted in dimethylformamide, sulfolane, and dimethyl sulfolane. Because the yields are lower and longer reaction times are required, these solvents are not as advantageous as dimethyl sulfoxide.

EXPERIMENTAL[18]

Reaction of 1-chlorobutane and sodium or potassium cyanide. Valeronitrile. (Sodium Cyanide). 1-Chlorobutane (93 g., 1 mole) was added in 10–15 min. to a rapidly stirred partially-soluble mixture of sodium cyanide (53 g., 1.08 moles, Reagent) in dimethyl sulfoxide (250 ml., technical; Stepan Chemical Company) at 80°. The temperature of the mixture rose rapidly and was kept at 140 ± 5° by cooling with water when necessary. During the reaction the mixture became more fluid, and the insoluble salts more crystalline. After the 1-chlorobutane had been added, the temperature dropped rapidly, and the reaction was apparently complete. The brown reaction mixture was cooled, diluted with water to a volume of *ca.* 1000 ml., and extracted with ether (3 × 150 ml.). The pale yellow ether extracts were washed with 6*N* hydrochloric acid (to hydrolyze the small amount of noxious isocyanide) and water, and dried over calcium chloride. After removal of ether, the residue was rectified over phosphorus pentoxide to give forerun (6.0 ml.), b.p. 110–138° (747 mm.), and valeronitrile (77 g., 0.93 mole, 93%), b.p. 138–139° (747 mm.), n_D^{20} 1.3970–1.3972; lit., b.p. 140.75°,[19a] n_D^{15} 1.3990.[19b]

In a similar manner, 1-chlorobutane (465 g., 5 moles), sodium cyanide (95% purity, 265 g., 5.5 moles) and dimethyl sulfoxide (475 ml.) gave valeronitrile (388 g., 4.7 moles), b.p. 138–139°, in 94% yield. In large runs the relative volume of dimethyl sulfoxide was thus lowered.

(16) T. Dougherty, Ph.D. Thesis, The Ohio State University, 1959 has found that 1,3-dibromo-2,2-dimethylpropane (neopentyl dibromide) reacts with equivalent amounts of sodium cyanide in dimethyl sulfoxide in 66 hr. at 90–95° to give 4-bromo-3,3-dimethylbutanenitrile (23% conversion) and 2,2-dimethyl-1,3-propanedinitrile (26–30% conversion). The initial dibromide recovered ranged from 35–50%. The details of this experiment will be published elsewhere.

(17) (a) In using potassium cyanide with chlorides, the temperature of the mixture had to be maintained above 120° in order to effect reaction. Low boiling halides thus had to be added dropwise to a heated mixture of potassium cyanide in dimethyl sulfoxide at a rate such that the temperature is not significantly lowered. (b) Sodium and potassium cyanides are appreciably soluble in warm DMSO; the actual solubilities at various temperatures were not determined.

(18) The preparative examples described are representative of the various experimental procedures summarized in Table I.

(19) (a) G. Lievens, *Bull. soc. chem. Belges*, **33**, 126 (1924); (b) S. Sugden, *J. Chem. Soc.*, **125**, 1186 (1924).

(Potassium cyanide). 1-Chlorobutane (93 g., 1.0 mole) was added *dropwise* in 2 hr. to a stirred suspension of potassium cyanide (70 g., 1.06 moles) in dimethyl sulfoxide (250 ml.) maintained at 120–125°. The mixture was then heated until the pot temperature rose to 140° (8 hr.) and refluxing ceased. The dark-brown evil-smelling mixture was diluted with water and worked up as described in the preceding experiments to give a small forerun (4.0 g., b.p. 110–138°) and valeronitrile (57.5 g., 0.69 mole, 69%), b.p. 138–139° (747 mm.).

Reaction of 1-chloro-2-methyl-2-phenylpropane and sodium cyanide. 3-Methyl-3-phenylbutyronitrile. A stirred mixture of 1-chloro-2-methyl-2-phenylpropane (neophyl chloride, 84.39 g., 0.5 mole, b.p. 110–112° (12 mm.), n_D^{25} 1.5216), sodium cyanide (40.0 g., 0.82 mole) and dimethyl sulfoxide (250 ml.) was heated at 120° for 24 hr. The resulting dark-brown mixture was cooled, diluted with water and worked up for product. Rectification gave 1-chloro-2-methyl-2-phenylpropane (28.0 g., 0.163 mole, 32.6%; b.p. 115–135° (18 mm.), n_D^{25} 1.5216–1.5220) and *3-methyl-3-phenylbutyronitrile* (14.1 g., 0.089 mole, 26% yield, 69% conversion of neophyl chloride), b.p. 135–137° (18 mm.), n_D^{25} 1.5130–1.5132. The physical constants of an analytical sample are b.p. 136° (18 mm.), n_D^{25} 1.5130.

Anal. Calcd. for $C_{11}H_{13}N$: N, 8.80. Found: N, 8.83.

The structure of the 3-methyl-3-phenylbutyronitrile was confirmed by its conversion (99%) to 3-methyl-3-phenylbutyric acid, m.p. 54–56°, by saponification in refluxing aqueous ethylene glycol (12 hr.) and subsequent acidification; m.p. 58–59° (from carbon tetrachloride-hexane); lit.,[20] m.p., 58–59.5°. The mixed melting point with an authentic sample was undepressed.

Reaction of chlorocyclopentane and sodium cyanide. Cyclopentanecarbonitrile. Chlorocyclopentane (210 g., 2.0 moles) was added in 20 min. to a stirred mixture of sodium cyanide (110 g., 2.25 moles) in dimethyl sulfoxide (530 ml.) at 115°. The reaction was mildly exothermic. The mixture was heated at 125–130° for 3 hr. and low boiling material began to reflux. A portion was collected and identified as cyclopentene, b.p. 44–46°, n_D^{20} 1.4208; lit.,[21] b.p. 44.24°, n_D^{20} 1.4224. The dark-brown reaction mixture was cooled and worked up for product. Rectification gave cyclopentanecarbonitrile (133 g., 1.4 moles, 70%), b.p. 74–74.5° (28 mm.), n_D^{20} 1.4429; lit.[8a] b.p. 74.5–75° (30 mm.), n_D^{25} 1.4404.

Reaction of 1-bromo-2-methylpropane and sodium cyanide. 3-Methylbutyronitrile. 1-Bromo-2-methylpropane (137 g., 1 mole) was added in 20 min. to a warm (60°) stirred mixture of sodium cyanide (55 g., 1.12 moles) in dimethyl sulfoxide (400 ml.); the temperature was maintained between 55 and 60° by intermittent cooling. Sodium bromide began to gel near the end of the addition. The mixture was then maintained at 70° for 2 hr. to allow completion of the reaction. During this period gases were evolved and the mixture became progressively darker and malodorous. Isolation of the product in the usual manner gave 3-methylbutyronitrile (51 g., 0.615 mole, 62%), b.p. 128° (743 mm.), n_D^{20} 1.3927; lit.,[22] b.p. 128–129°.

When the reaction was effected at 90–100°, more 1-bromo-2-methylpropane reacted with dimethyl sulfoxide, and the yield of nitrile dropped to 48%.

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(20) F. C. Whitmore, C. A. Weissgerber, and A. C. Shabica, Jr., *J. Am. Chem. Soc.*, **65**, 1471 (1943).

(21) *Selected Values of Properties of Hydrocarbons*, API Research Project 44, 1958, Table 58a.

(22) H. Rupe and E. Hodel, *Helv. Chim. Acta*, **7**, 1023 (1924).

[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Free Radical Rearrangements in the Decarbonylation of Aldehydes[1]

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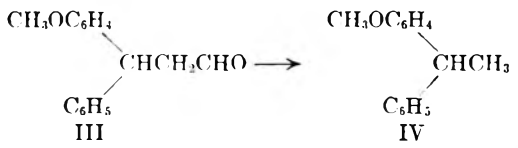
The reaction of β-deutero-β-(*p*-anisyl)-β-phenylpropionaldehyde with di-*t*-butyl peroxide has been found to give decarbonylation without rearrangement of the deuterium atom. A reinvestigation of the decarbonylation of β,β,β-triphenylpropionaldehyde has shown that in addition to the 1,1,2-triphenylethane previously reported there are present lesser amounts of triphenylethylene and 3,3-diphenyl-1-indanone. Decarbonylation of β-(*p*-nitrophenyl)-β,β-diphenylpropionaldehyde proceeded to only a small extent and led to the rearranged olefin, 2-(*p*-nitrophenyl)-1,1-diphenylethylene, as the only product which could be characterized.

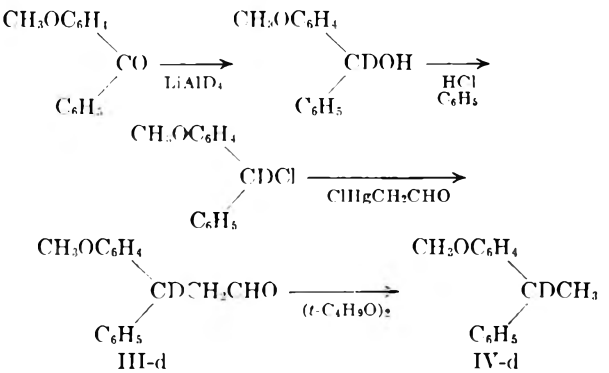
In a previous investigation[3] β,β,β-triphenylpropionaldehyde (I) was found to undergo decarbonylation on treatment with di-*t*-butyl peroxide to yield 1,1,2-triphenylethane (II) with migration of a phenyl group as the only reaction path detected. On the other hand, β-(*p*-anisyl)-β-phenylpropionaldehyde yielded only the unrearranged hydrocarbon, 1-(*p*-anisyl)-1-phenylethane. The present study was initiated to clarify several features of these two reactions.

$$\underset{\text{I}}{(C_6H_5)_3CCH_2CHO} \longrightarrow \underset{\text{II}}{(C_6H_5)_2CHCH_2C_6H_5}$$



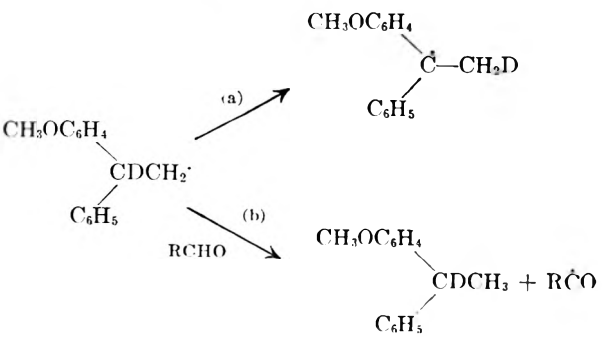
III IV

In view of the observed rearrangement of the triphenylaldehyde I it seemed quite possible that the aldehyde III was also undergoing rearrangement but with the migration of a hydrogen atom. The structure of the product does not distinguish between this possibility and a reaction without rearrangement. The aldehyde III-d was therefore synthesized with a deuterium atom on the β-carbon atom by the same general route employed previously[3] for the undeuterated compound. The steps in the synthesis are shown below. Treatment of the deuterated aldehyde III-d with 10 mole % of di-*t*-butyl peroxide at 140° resulted in the evolution of 40% of the theoretical amount of carbon monoxide. The infrared spectrum of the product mixture indicated that unchanged aldehyde was present to the extent of 50–55% and 46% of it was actually recovered. The only other component found was the hydrocarbon 1-deutero-1-(*p*-anisyl)-1-phenylethane (IV-d), formed without rearrangement of either a phenyl ring or a deuterium atom.



III-d IV-d

The position of the deuterium atom was established with the aid of infrared and nuclear magnetic resonance absorption spectroscopy.[4] It is estimated that within the limits of the method employed not more than 5% of the aldehyde molecules being decarbonylated could have undergone rearrangement of a deuterium atom. However, the extent of rearrangement is probably determined by the relative rates of the two processes shown. It will be seen that path (b) leading to nonrearrangement but not (a) leading to rearrangement should depend



on the aldehyde concentration. Such dependence has been demonstrated experimentally in the decarbonylation leading to the neophyl radical by Seubold.[5] The failure of deuterium to undergo migration is here demonstrated for a medium con-

(1) Taken from the Ph.D. thesis of James C. Kauer, University of Illinois, 1955.

(2) We are indebted to the Rohm and Haas Co. for a Fellowship held by J. C. K. in 1953–54 and to the E. I. du Pont de Nemours & Co., Inc., for a Grant-in-Aid which supported a part of this work.

(3) D. Y. Curtin and M. J. Hurwitz, *J. Am. Chem. Soc.*, **74**, 5381 (1952).

(4) We are indebted to Dr. H. S. Gutowsky and Dr. Jerry Heeschen for the NMR spectra and for assistance with their interpretation. See H. S. Gutowsky, "Physical Methods of Chemical Analysis" Edited by W. G. Berl, Academic Press, Inc., New York, N. Y., 1956, pp. 362, 363.

(5) F. H. Seubold, Jr., *J. Am. Chem. Soc.*, **75**, 2532 (1953).

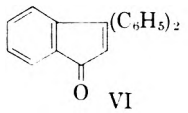
sisting of undiluted aldehyde, conditions less favorable to rearrangement than others which are attainable.[5] A second point to be considered is that path (a) but not (b) might be expected to be subject to a primary isotope effect.[6] It follows that hydrogen migration in the undeuterated radical obtained from the aldehyde (III) might be appreciably more important than deuterium migration in the corresponding deuterated radical. It is clear, however, that even with these complications hydrogen migration is not the dominant reaction of the intermediate radical from the aldehyde (III). An investigation of the behavior of the 2-phenylethyl-1-C^{14} radical has been reported by Slaugh[7] who found that in *o*-dichlorobenzene there was as much as 5% of phenyl migration but that there was no significant amount of hydrogen migration.

The reinvestigation of the decarbonylation of β,β,β-triphenylpropionaldehyde (I) previously reported[3] to give only 1,1,2-triphenylethane (II) was prompted by the failure to observe products of a termination step even though 10 mole % of di-*t*-butyl peroxide was employed as initiator. A second point was that the reaction went to only about 25% completion in contrast to the 90% of decarbonylation of β-phenylisobutyraldehyde observed by Winstein and Seubold[8] under otherwise comparable conditions. When the aldehyde (I) was treated with 20 mole % of di-*t*-butyl peroxide in a bath at 140° under reflux for twenty-eight hours, 32% of the theoretical amount of carbon monoxide was liberated, and in addition to 40% of recovered aldehyde there was obtained in agreement with the previous work[3] 20% of the rearranged triphenylethane (II). There were also formed 4% of triphenylethylene (V) and 3% of a ring-closed product, 3,3-diphenyl-1-indanone (VI). The indanone (VI) was identical with that prepared from triphenylpropionic acid and sulfuric acid by Moureu, Dufraisse, and Dean.[9] The infrared spectrum (in carbon tetrachloride) of triphenylethylene (V) is nearly superimposable on that of the triphenylethane (II), but the unsaturated hydrocarbon (V) could be readily determined quantitatively by the ultraviolet absorption at 298 mμ. The presence of weak absorption in the C-methyl deformation region suggested that as much as 10% of the hydrocarbon fraction might be the unrearranged hydrocarbon, 1,1,1-triphenylethane, but no more definite evidence for its presence was obtained.

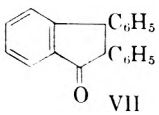
The formation of the indanone (VI) is of interest since it apparently came from a radical version of the Friedel-Crafts acylation. Another example has been reported by Denny and Klemchuk.[10] Other

$$\text{I} \xrightarrow[(t\text{-}C_4H_9O)_2]{} \text{II} + (C_6H_5)_2C{=}CHC_6H_5 +$$

V



VI



VII

related radical cyclizations have been described.[11] With the hope that the temperature dependence of the rates of cyclization and decarbonylation might be such that cyclization should be favored at lower temperatures, the aldehyde (I) was treated with dibenzoyl peroxide at 80°. Under conditions in which 35% of aldehyde failed to react about 13% decarbonylation and less than 9% indanone formation were observed.

It seemed possible that accumulation of acetone and *t*-butyl alcohol from the decomposition of di-*t*-butyl peroxide might be responsible for the decrease in rate after 25% reaction.[12] For this reason the decarbonylation of the aldehyde (I) was carried out as before except that a steam-jacketed condenser was used to permit the removal of low-boiling products as they were formed. A run carried out with 15 mole % of di-*t*-butyl peroxide for twenty-three hours gave 72% recovery of the aldehyde (I) together with 20 mole % of carbon monoxide. There were obtained 7 mole % of the triphenylethane (II), 3 mole % of triphenylethylene (V), and 3 mole % of the indanone (VI). Finally a reaction was carried out with a full mole of di-*t*-butyl peroxide per mole of aldehyde over a five-day period with a steam-jacketed condenser. No aldehyde was recovered. Only 50 mole % of carbon monoxide was obtained, together with 29 mole % of the triphenylethane (I), 12 mole % of triphenylethylene (V), and 25 mole % of the indanone (VI). In addition, there was a small amount of a substance believed to be 2,3-diphenyl-2-indene-1-one (VII) which was not obtained in pure form but which had infrared and ultraviolet spectra very similar to the spectra of an authentic sample of this substance. It seems likely that the indenone (VII) came from a radical rearrangement of the indanone (VI). The indanone (VI) had previously been reported[13] to undergo a thermal rearrangement to VII. Furthermore, the rearrangement of 3,3,5,6-tetraphenylindanone to 2,3,5,6-tetraphenylindene-1-one on heating with sulfur had been observed.[14]

(6) K. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

(7) L. H. Slaugh, *J. Am. Chem. Soc.*, **81**, 2262 (1959).

(8) S. Winstein and F. H. Seubold, Jr., *J. Am. Chem. Soc.*, **69**, 2916 (1947).

(9) C. Moureu, C. Dufraisse, and P. M. Dean, *Bull. soc. chim. France*, **43**, 1367 (1928).

(10) D. B. Denny and P. P. Klemchuk, *J. Am. Chem. Soc.*, **80**, 3289 (1958).

(11) S. Winstein, R. Heck, S. Lapporte, and R. Baird, *Experientia*, **12**, 141 (1956); D. F. DeTar and C. Weis, *J. Am. Chem. Soc.*, **78**, 4297, 4302 (1956); J. W. Wilt and D. D. Oathoudt, *J. Org. Chem.*, **21**, 1550 (1956); *J. Org. Chem.*, **23**, 218 (1958).

(12) We are indebted to Professor W. H. Urry for this suggestion.

(13) C. Moureu, C. Dufraisse, and F. Baylocq, *Bull. soc. chim., France*, **43**, 1371 (1928).

(14) C. F. H. Allen and J. A. Van Allen, *J. Org. Chem.*, **20**, 315 (1955).

To determine whether one of the products had a marked inhibiting effect on the reaction, di-*t*-butyl peroxide was decomposed with the aldehyde (I) in mixtures containing the triphenylethane (II), the diphenylindanone (VI), and triphenylethylene (V). None of these substances showed any large effect on the rate of carbon monoxide evolution.

With the objective of obtaining information about the migration ratio of the *p*-nitrophenyl group in a radical carbon-carbon rearrangement it was desired to prepare and submit to the rearrangement conditions β-(*p*-nitrophenyl)-β,β-diphenylpropionaldehyde (VIII). The synthesis of this compound had been previously attempted unsuccessfully by Bartlett and Cotman.[15] It was prepared by the reaction of *p*-nitrotriphenylmethyl bromide with chloromercuriacetaldehyde in benzene with stannic chloride as a catalyst, a modification[3] of a reaction employed by Nesmeyanov, Lutsenko, and Tumanova.[16] The structure of the aldehyde (VIII) was confirmed by the infrared spectrum which showed absorption at 700 cm.$^{-1}$ (monosubstituted phenyl), 850 cm.$^{-1}$ (*p*-disubstituted phenyl), 1355 and 1530 cm.$^{-1}$ (nitro), and 1720 and 2730 cm.$^{-1}$ (aldehyde). When the aldehyde (VIII) was heated at 140° with 19 mole % of di-*t*-butyl peroxide only about 10% of the theo-

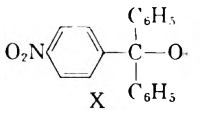
$$(NO_2C_6H_4)(C_6H_5)_2CBr + ClHgCH_2CHO \xrightarrow[SnCl_4]{} (NO_2C_6H_4)(C_6H_5)_2CCH_2CHO$$

VIII

$$VIII \xrightarrow[(t\text{-}C_4H_9O)_2]{} (C_6H_5)_2C{=}CHC_6H_4NO_2$$

IX

retical amount of carbon monoxide had been evolved although the infrared spectrum of the total product suggested that about 50% of the aldehyde (VIII) had been destroyed. Chromatography gave a nitrohydrocarbon fraction, 65% of which crystallized and was characterized as 2-(*p*-nitrophenyl)-1,1-diphenylethylene (IX) (3.3% over-all yield). There was also present an unidentified nitrohydrocarbon (17% of the chromatographic fraction) and a nonnitro-containing liquid ketone. If it is assumed that all of the *p*-nitrotriphenylethyl radicals formed in the decarbonylation ultimately ended in the nitrohydrocarbon fraction (a rather uncertain assumption) then, making a statistical correction for the two phenyl groups, the *p*-nitrophenyl/phenyl migration ratio is at least as great as 8. The happy agreement of this number with the factor of 8 found by Bartlett and Cotman[15] in the rearrangement of the radical X and with the partial rate factor of 6.6 for attack in the *p*-position of nitrobenzene by a phenyl radical[17] can only be regarded as coincidental.[18]



X

EXPERIMENTAL[19]

α-Deutero-p-methoxybenzhydrol. *p*-Methoxybenzophenone[22] (40 g., 0.20 mole) was reduced in 200 ml. of dry diethyl ether with 5.0 g. of lithium aluminum deuteride (93% D) and 2.0 g. of lithium aluminum deuteride (98% D), a total of 0.16 mole, in 300 ml. of dry ether. After 8 days water was added followed by 5% aqueous sulfuric acid. The ether layer was separated, dried, and the ether was distilled. Crystallization of the resulting oil from 1500 ml. of hexane gave 36 g. (82%) of the deuterobenzhydrol, m.p. 66.5–67.5°. Evaporation of the filtrate to a volume of 150 ml. gave 2.5 g. (6%) of additional benzhydrol, m.p. 65.5–66.5°.

Anal. Calcd. for $C_{14}H_{13}DO_2$: D, 7.1 atom %. Found: D, 8.5.

(The presence of residual O-deuterated material from incomplete exchange with water during the workup in a two-phase system probably accounts for the high deuterium analysis. The excess deuterium is then lost in the next step.)

α-Deutero-p-methoxybenzhydryl chloride. The benzhydrol (39 g., 0.19 mole) in 50 ml. of benzene was treated with dry

(15) P. D. Bartlett and J. D. Cotman, Jr., *J. Am. Chem. Soc.*, **72**, 3095 (1950).

(16) A. N. Nesmeyanov, I. F. Lutsenko, and Z. M. Tumanova, *Izvest. Akad. Nauk S.S.S.R. Otdel Khim. Nauk*, 601 (1949). [*Chem. Abstr.*, **44**, 7225c (1950)].

(17) Chang Shih, D. H. Hey, and G. H. Williams, *J. Chem. Soc.*, 4403 (1958). A summary of partial rate factors in the phenylation of monosubstituted benzenes is given by C. S. Rondestvedt, Jr., and H. S. Blanchard, *J. Org. Chem.* **21**, 229 (1956).

(18) For other studies of migration ratios in carbon-to-oxygen rearrangements see M. S. Kharasch, A. C. Poshkus, A. Fono, and W. Nudenberg, *J. Org. Chem.*, **16**, 1458 (1951); W. H. Urry, *Abstracts of the 12th National Organic Chemistry Symposium*, Denver, Colo., 1951. Bartlett and Cotman (Ref. 15) have a particularly rewarding discussion of migration ratios.

(19) All melting points are corrected. Microanalyses were carried out by Mr. Josef Nemeth, Mrs. Katherine Pih, Mrs. Esther Fett, and Mrs. Lucy Chang. Deuterium analyses were performed by the falling-drop method and are reported as absolute atom per cent deuterium $= \frac{D}{D + H} \times 100\%$ where D and H refer to the numbers of deuterium and hydrogen atoms, respectively, in the molecule.[20] Unless otherwise specified the infrared spectra were obtained with 10% solutions in carbon tetrachloride in 0.1-mm. matched cells in a Perkin-Elmer Model 21 Double Beam Spectrophotometer by Miss Helen Miklas, Mrs. Beverly Thomas, Mr. James J. Brader, and Mrs. Louise Griffing. The ultraviolet spectra were obtained in 95% ethanol in 1-cm. cells with a Cary Double Beam Spectrophotometer by Miss Geraldine Meerman. The NMR spectra were obtained on a high resolution spectrophotometer[21] at an adjustable field strength of 4170 gauss with a maximum resolution of about one milligauss by Dr. Jerry Heeschen. Many traces were observed and visually averaged in drawing the conclusions described herein.

Most of the spectra are included in the thesis of JCK[1] which is available on microfilm as Univ. Microfilms Publ. No. 13, 505 [*Chem. Abstr.*, **50**, 2419*b* (1956)] Univ. Microfilms, Ann Arbor, Mich.

(20) A. S. Keston, D. Rittenberg, and R. Schoenheimer, *J. Biol. Chem.* **122**, 227 (1937).

(21) H. S. Gutowsky, L. H. Meyer, and R. E. McClure, *Rev. Sci. Instr.*, **24**, 644 (1953).

(22) P. P. Peterson, *Am. Chem. J.*, **46**, 335 (1911).

hydrogen chloride for 1 hr. Solvent was distilled, and the resulting oil was crystallized from benzene to yield 30 g. (65%) of the deuterobenzhydryl chloride, m.p. 64–64.5°. The absence of absorption at 1218 cm.$^{-1}$ in the infrared, characteristic of the undeuterated benzhydryl chloride indicated that the product was at least 90% deuterated.

Anal. Calcd. for $C_{14}H_{12}DClO$: D, 7.7. Found, D, 7.1.

β-Deutero-β-(p-anisyl)-β-phenylpropionaldehyde (III-d), b.p. 154–155.5° at 0.28 mm., n_D^{20} 1.5808, m.p. 17–19°, was prepared in 75% yield by the method previously reported[3] for the undeuterated compound. The aldehyde was stored under nitrogen since it undergoes air oxidation.

Anal. Calcd. for $C_{16}H_{15}DO_2$: D, 6.3. Found: D, 6.5.

p-Nitrotriphenylmethane. This modification of the procedure of Baeyer and Löhr[23] led to a product which was easier to purify. A solution of 102 g. of *p*-nitrobenzaldehyde in 1500 ml. of dry benzene was stirred for 6 days with 170 g. of phosphorus pentoxide and was then heated to reflux for 1 hr. The solution was cooled, and the benzene layer was decanted and washed thoroughly with 10% sodium carbonate, 5% sodium bisulfite, and water. Solvent was distilled, and the residue was crystallized from 500 ml. of ethanol to yield 75 g. m.p. 90–92°. Treatment of the brown phosphoric acid residue with water and benzene followed by the above treatment of the benzene layer yielded an additional 37 g., m.p. 89.5–91.5°. Recrystallization of both crops from 1 l. of hexane yielded 97.2 g. (50%) of *p*-nitrotriphenylmethane, m.p. 92–93° (lit., m.p. 93°).

β-(p-Nitrophenyl)-β,β-diphenylpropionaldehyde (VIII). A suspension of 65 g. (0.23 mole) of chloromercuriacetaldehyde[15] in dry benzene was added to a solution of 85 g. (0.23 mole) of *p*-nitrotriphenylmethyl bromide[24] in 400 ml. of dry benzene and 90 ml. of hexane cooled with an ice bath. The reaction mixture was protected from moisture with a calcium chloride tube and purged with nitrogen. Anhydrous stannic chloride (60 g., 0.23 mole) was added dropwise, and the mixture was stirred at 0° for 30 hr. and then at 25° for 10 hr. It was then stirred with water and with 10% sodium carbonate solution, and after filtration the benzene layer was washed with 5% sulfuric acid, water, 10% sodium carbonate and water. Solvent was distilled to a volume of 130 ml., and the brown solution was chromatographed on a column of Merck alumina which had been activated at 300° for 1 hr. at 25 mm. pressure. Elution with benzene-hexane (1:1) yielded a 300-ml. forerun followed by a 200-ml. fraction from which solvent was removed by distillation. The resulting solid was washed with 10 ml. of cold carbon tetrachloride and recrystallized from 25 ml. of carbon tetrachloride to yield 13 g. of aldehyde (VIII), m.p. 119–121°. Further elution yielded an additional 5.5 g. The crystalline products were dissolved in 100 ml. of hot ethyl acetate, and 100 ml. of hexane was added. The white crystalline aldehyde (m.p. 122.5–124°) weighed 14 g. (18%).

Anal. Calcd. for $C_{21}H_{17}NO_3$: C, 76.1; H, 5.2; N, 4.2. Found: C, 75.9; H, 5.0; N, 4.1.

β-(p-Nitrophenyl)-β,β-diphenylpropionaldehyde 2,4-dinitrophenylhydrazone,[25] bright yellow crystals, melted at 227–228°.

Anal. Calcd. for $C_{27}H_{21}N_5O_6$: N, 13.7. Found: N, 13.4.

Decarbonylation of the β-deutero aldehyde (III-d). In a flask maintained at 140° ± 1°, the aldehyde III-d (7.0 g., 0.029 mole) was allowed to react with 0.60 g. (0.0041 mole) of freshly distilled di-*t*-butyl peroxide for 11.8 hr. during which time 280 ml. (0.0109 mole, 38%) of gas was liberated.[26] The infrared spectrum of the product indicated by the absorption at 1730 and 2725 cm.$^{-1}$ that 50–55% of unchanged aldehyde III-d was present. Distillation through a 30-cm. spiral wire column[27] gave 1.8 g. of colorless liquid, b.p. 115–122° at 0.55 mm., m.p. −1.5–(+)2° whose infrared spectrum indicated that it contained 2.5% of starting aldehyde but was otherwise identical with that of 1-deutero-1-*p*-anisyl-1-phenylethane (IV-d), prepared as described below. Comparison (using an expanded scale) of the C-D stretching absorption of a solution 510 mg./ml. in carbon tetrachloride at 2119 cm.$^{-1}$ (characteristic of the tertiary C-D of IV-d) and at 2178 cm.$^{-1}$ (where the primary C-D of β-deuteroethylbenzene described below absorbed) confirms the presence only of tertiary C-D. The NMR spectrum[4] showed no splitting of the methyl absorption to be expected if there were coupling with a proton on an adjacent carbon atom. This splitting is prominent in the undeuterated hydrocarbon (IV). Allowing for the small amount of aldehyde (III-d) there was 29% of the deuteroethane (IV-d).

Anal. Calcd. for $C_{15}H_{15}DO$: D, 6.3. Found: D, 6.3.

Recovered aldehyde (III-d) obtained by continuing the distillation above amounted to 2.6 g., b.p. 145–152° at 0.55 mm. and an estimated 0.55 g. in the residue or a total of 46% of the starting material.

1-Deutero-1-(p-anisyl)-1-phenylethane (IV-d). The procedure used was an adaptation of that used by Gomberg and Cone[28] for 1,1,1-triphenylethane. α-Deutero-*p*-methoxybenzhydryl chloride (4.4 g., 0.019 mole) in 150 ml. of dry ether was added dropwise over a period of 1.5 hr. with stirring to a solution of methylmagnesium iodide prepared from 25 g. (0.18 mole) of methyl iodide and 4.3 g. (0.18 mole) of magnesium in 150 ml. of ether. After 0.5 hr. at 0° under a nitrogen atmosphere the solution was allowed to warm to 25° and then heated under reflux for 10 min. Addition of 5% aqueous hydrochloric acid, separation of the ether layer and distillation through a 30-cm. spiral wire column[27] gave 0.8 g. (20%) of IV-d, b.p. 102–103° at 0.3 mm., m.p. 5–6°.

Anal. Calcd. for $C_{15}H_{15}DO$: D, 6.3. Found: D, 6.3.

β-Deuteroethylbenzene was prepared by an adaptation of the method of Turkevich, McKenzie, Friedman, and Spurr[29] for α-deuterotoluene. In an atmosphere of dry nitrogen 20 g. (0.15 mole) of freshly distilled β-phenylethyl chloride in 150 ml. of dry ether was added to 3.6 g. (0.15 mole) of magnesium in 50 ml. of dry ether. After no further reaction was apparent the mixture was refluxed for 2 hr. and then cooled in a Dry Ice-acetone bath and 8 g. of 99.8% deuterium oxide was added dropwise. After 3 hr. 150 ml. of 5% aqueous hydrochloric acid was added, and the ether layer was separated and washed with sodium bicarbonate solution and water. After drying over sodium sulfate and removal of the solvent the residue was distilled through a 30-cm. spiral wire column.[27] The β-deuteroethylbenzene, b.p. 135–136.5°, $n_D^{20.3}$ 1.4950 amounted to 7.7 g. (52%).

Anal. Calcd. for C_8H_9D: D, 10.0. Found: D, 9.7.

Decarbonylation of β,β,β-triphenylpropionaldehyde. (a) *Under partial reflux with excess peroxide.* In a flask maintained at 140 ± 1° and equipped with a steam-jacketed condenser followed by a Dry Ice trap and finally an inverted graduated cylinder arranged to collect noncondensable gases was placed 53 g. (0.18 mole) of the aldehyde I, and 28 g. (0.19 mole) of freshly distilled di-*t*-butyl peroxide was added in small portions over a period of 5 days. The gas liberated amounted to 3.0 l. (0.12 mole). The distillate (25 g.) in the Dry Ice trap was fractionated through a 30-cm. spiral wire column[27] and found to consist of acetone (1.4 g., 0.025 mole, b.p. 49.5–50.5°), *t*-butyl alcohol (22 g., 0.30 mole, b.p. 76–76.5°) and di-*t*-butyl peroxide (1.07 g., 0.007 mole, b.p. 100–106°, n_D^{20} 1.3882). The acetone was further

(23) A. Baeyer and R. Löhr, *Ber.*, **23**, 1621 (1890).

(24) V. A. Izmail'skiĭ and D. K. Surkov, *J. Gen. Chem.* (U.S.S.R.) **13**, 848 (1943). [*C.A.* **39**, 1407 (1945)].

(25) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, 3rd ed., John Wiley and Sons, Inc., New York, 1948, p. 171.

(26) Throughout this work the gas was collected over water, and the volume was corrected for the vapor pressure of water.

(27) C. W. Gould, Jr., G. Holzman, and C. Niemann, *Anal. Chem.* **20**, 361 (1948).

(28) M. Gomberg and L. H. Cone, *Ber.*, **39**, 2963 (1906).

(29) J. Turkevich, H. A. McKenzie, L. Friedman, and R. Spurr, *J. Am. Chem. Soc.*, **71**, 4045 (1949).

identified by its infrared spectrum and by the 2,4-dinitrophenylhydrazone, m.p. 124–125°. The *t*-butyl alcohol formed a phenylurethan, m.p. 133–134°. The noncondensable gas was not analyzed but was assumed to consist of methane and carbon monoxide,[30] the amount of methane being estimated from the amount of acetone to amount to 0.025 mole, thus leaving 0.092 mole (50%) as the amount of carbon monoxide. In other experiments the gas was analyzed by an Orsat volumetric gas apparatus and found to consist of carbon monoxide with traces of oxygen, carbon dioxide, and small amounts of an inflammable gas, presumably methane.

Chromatography of the thick orange oily product (a 2.2-g. aliquot) on a 300 × 17 mm. column of Harshaw Al-0109P activated alumina gave on elution with hexane a hydrocarbon fraction of 0.65 g. Further elution with 20% ether in hexane gave 0.11 g. of red oil with a strong infrared absorption maximum at 1715 cm.$^{-1}$ and an ultraviolet maximum at 258 mμ. Both the infrared and ultraviolet spectra were very similar to the spectra of the diphenylindenone (VII) but on rechromatography the compound still failed to crystallize. Finally 0.64 g. of oil was obtained which when triturated with hexane deposited crystals of the indanone (VI). The indanone was isolated in small amount as crystals, melting point and mixed melting point with an authentic sample, 130.5–131°, and the infrared spectrum was identical with that of the authentic sample. It was estimated from the intensity of the characteristic infrared absorptions of the indanone (VI) at 1240 and 1290 cm.$^{-1}$ in the crude reaction mixture that about 20% of the indanone (VI) was present. From the absence of absorption at 2740 cm.$^{-1}$ it was concluded that less than 5% of aldehyde remained.

Distillation of a 16.8-g. aliquot of the product through a 30-cm. spiral wire column[27] gave 6.3 g. of yellow liquid, b.p. 133–137° at 0.2 mm. which was purified by chromatography on Merck alumina (elution with 2500 ml. of hexane) to give with 98% recovery a clear colorless liquid whose infrared spectrum was almost identical with the rearranged triphenylethane (II). However, the ultraviolet absorption at 296 mμ indicated that it consisted to the extent of 29% of triphenylethylene. The infrared showed that no significant amount (less than 0.5%) of carbonyl-containing compounds could be present. A small absorption at 1380 cm.$^{-1}$ indicated that 1,1,1-triphenylethane might be present but not to an extent of more than 10%. The infrared spectrum of a mixture of 62% of the rearranged triphenylethane (II), 10% of 1,1,1-triphenylethane and 28% triphenylethylene (V) was nearly identical with the spectrum of the mixture except that the product had somewhat more intense absorption at 2980 cm.$^{-1}$ than did the known mixture. Continuation of the distillation gave, after an intermediate fraction of 0.16 g. (b.p. 140–168° at 0.25 mm.), 4.9 g. of viscous orange oil, b.p. 168° at 0.25 mm. which solidified on standing. Its absorption at 1240, 1290, and 1720 cm.$^{-1}$ showed that it consisted to the extent of about 80% of the indanone (VI). The nonvolatile residue was a brown, glassy solid amounting to 4.6 g. and estimated from its infrared spectrum to contain less than 3% of the aldehyde (I) and about 8% of the indanone (VI). The reaction mixture was thus concluded to contain about 0.022 mole (12%) of triphenylethylene, 0.047 mole (25%) of the indanone VI and 0.053 mole (29%) of triphenylethanes chiefly II with not more than 4% of the 1,1,1-isomer.

(b) *Under partial reflux with a catalytic amount of peroxide.* The reaction of 15 g. (0.052 mole) of aldehyde I with 1.2 g. (0.0079 mole) of di-*t*-butyl peroxide added at once was carried out as above for 23 hr. after which gas evolution had ceased. There were obtained 274 ml. (0.011 mole) of carbon monoxide (21%) and 15.4 g. of a liquid product mixture which was found by the method outlined above to contain 11 g. (72%) of starting material (I), 0.0036 mole (6.9%) of saturated triphenylethanes [chiefly the rearrangement product (II)], 0.0017 mole (3.2%) of triphenylethylene, and 0.0018 mole (3.4% of the indanone (VI).

(c) *Under total reflux.* A reaction of 10.0 g. (0.035 mole) of aldehyde I with 0.98 g. (0.0067 mole) of di-*t*-butyl peroxide was carried out for 28 hr. when 290 ml. (0.11 mole) of gas had been liberated (corresponding to 32% decarbonylation if the gas were entirely carbon monoxide). The products estimated as before were 0.0068 g. (20%) of triphenylethane (I) (and any 1,1,1-triphenylethane, if formed), 0.0015 mole (4.3%) of triphenylethylene, and 0.0011 mole (3.2%) of the indanone (VI). The aldehyde (I) was recovered to the extent of 40%, and 0.06 g. of a compound with infrared absorption at 1677 cm.$^{-1}$ was obtained. A reaction was carried out as above with the exception that 0.0116 mole of the triphenylethane (II) was added initially. After 24 hr. 370 ml. (0.14 mole) of gas had been evolved corresponding to 39% decarbonylation. A similar experiment with 3.1 g. (0.011 mole) of the indanone (VI) gave 260 ml. (27% of the theoretical amount of carbon monoxide) after 6.3 hr. and 420 ml. (44%) after 21 hr. With the addition of 3.0 g. (0.012 mole) of triphenylethylene there was 125 ml. of gas (13%) after 4.75 hr. and 317 ml. (33%) after 23 hr. The addition of 1.6 g. (0.022 mole) of *t*-butyl alcohol retarded the reaction (by lowering the temperature) as shown by the fact that after 6 hr. only 90 ml. of gas had been evolved (10%) and 84% of the aldehyde (I) could be recovered.

3,3-Diphenyl-1-indanone (VI), prepared by the method of Moureu, Dufraisse, and Dean,[9] melted at 130–131°. The infrared spectrum[19] showed strong absorption at 1725 cm.$^{-1}$ and the ultraviolet spectrum[19] showed λ_{max} 297 ϵ 2230.

2,3-Diphenylindenone (VII), prepared by the method of Moureu, Dufraisse, and Baylocq,[13] melted at 151.5–152°, with infrared absorption[19] at 1712 cm.$^{-1}$ and a maximum in the ultraviolet at 258 mμ, ϵ 35,000.

Decarbonylation of β-(p-nitrophenyl)-β,β-diphenylpropionaldehyde (VIII). The reaction of 13.1 g. (0.040 mole) of the aldehyde (VIII) was carried out with 1.1 g. (0.0075 mole) of di-*t*-butyl peroxide at 140° for 22.5 hr. as described for the reactions under total reflux discussed above. A total of 112 ml. of gas was evolved corresponding to 11% decarbonylation. The residue of 13.5 g. had absorption at 2730 cm.$^{-1}$ the intensity of which, measured in a 20% carbon tetrachloride solution, indicated that 50% of the starting aldehyde (VIII) was unchanged. Chromatography of 11.8 g. of the product on a 350 × 43 mm. column of alumina activated for 1 hr. at 300° and 25 mm. with 5 l. of 1:1 hexane-benzene gave separation into a yellow band (100 mm. long) followed by two brown bands (each about 50 mm.). These were separated and the yellow band rechromatographed by elution with 1:1:1 hexane-benzene-ether. After elution with 1 l. of the solvent and evaporation of the solvent there was obtained 0.22 g. of 1,1-diphenyl-2-(*p*-nitrophenyl)ethylene (IX), m.p. 153.5–155°. Further elution with 1 l. of the same solvent gave 0.24 g. of yellow oil containing crystals, and further elution with 2.5 l. more of the same solvent gave 0.13 g. of yellow oil. Recrystallization of the solid from the second fraction from 2 ml. of carbon tetrachloride and 5 ml. of petroleum ether gave 0.02 g. of the nitroolefin (IX), m.p. 153–154°. Rechromatography of the combined noncrystalline portions of the eluate gave 0.11 g. more of the nitroolefin (IX) and 0.19 g. of orange oil. Thus, from an 11.8 g. aliquot a total of 0.35 g. (0.0012 mole, 3.3%) of the rearranged nitroolefin (IX) and 0.19 g. of unidentified orange oil were obtained. Further recrystallization of IX from hexane showed m.p. 156–156.5° (reported[31] for brown form, m.p. 148°, for yellow form, m.p. 158–160°). The nitroolefin (IX) was characterized by bromination in 60% yield to 1-bromo-2,2-diphenyl-1-(*p*-nitrophenyl)ethylene, m.p. 181–182° (reported,[31] m.p. 178°) when recrystallized from ethyl acetate-hexane. Oxidation of 100 mg. of IX in 7 ml.

(30) See C. Walling, *Free Radicals in Solution*, John Wiley and Sons, New York, 1957, p. 470f.

(31) F. Bergmann, E. Dimant, and H. Japhe, *J. Am. Chem. Soc.*, **70**, 1618 (1948).

of acetone with 130 mg. of potassium permanganate in 1 ml. of water and 7 ml. of acetone gave on treatment with 2,4-dinitrophenylhydrazine after 18 hr. at 25°, 48 mg. (40%) of benzophenone 2,4-dinitrophenylhydrazone, m.p. 242–243° and undepressed when admixed with an authentic sample, and 20 mg. (36%) of *p*-nitrobenzoic acid, m.p. 240–241° (reported,[32] m.p. 241°).

(32) Ref. 24, p. 225.

The 0.19 g. of orange oil remaining after separation of IX was distilled in a microdistillation apparatus to give 0.10 g. of colorless oil, b.p. 140° at 5 mm. and 0.09 g. of brown residue. The colorless oil had strong infrared absorption at 1682 cm.$^{-1}$ and ultraviolet absorption at 253 mμ. The brown residue had strong peaks at 1350 and 1530 cm.$^{-1}$ (nitro group) and 850 cm.$^{-1}$ (*p*-disubstituted benzene derivative).

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Free Radical Rearrangements. Di(3,3,3-triphenylpropionyl)diimide, Methylazo-2,2,2-triphenylethane, and 2,2,2,-Triphenylethylhydrazine as Radical Sources[1]

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In a search for other methods of preparing the 2,2,2-triphenylethyl radical the thermal decomposition of di(3,3,3-triphenylpropionyl)diimide (I), and methylazo-2,2,2-triphenylethane (II) and the air oxidation of 2,2,2-triphenylethylhydrazine (III) were investigated. Decomposition of I at temperatures between 110 and 180° in the melt or in nonpolar solvents gives 1,1,1,6,6,6-hexaphenyl-3,4-hexandione (IV) in yields of 25–45%. In addition at 160–180° there are formed 1,1,2-triphenylethane and triphenylethylene in nearly equal amounts (11 and 14%, respectively). The thermal decomposition of II leads to triphenylmethane (23% yield), presumably formed by a free radical cleavage reaction, and benzophenone (6–10%) as the only products thus far identified. Air oxidation of III in boiling benzene gives benzophenone in an amount which accounts for some 30% of the triphenylmethyl groups initially present. Attempts to prepare the diketone IV by the more conventional acyloin condensation have led to another cleavage (presumably free radical) resulting in triphenylmethane in 42% yield. Infrared spectra of the diacyldiimide I, diacetyldiimide, and dibenzoyldiimide show their carbonyl stretching absorptions at 1780, 1770, and 1730 cm.$^{-1}$, respectively.

Although a number of studies of carbon-to-carbon free radical rearrangements of the neophyl radical,[3] the 2,2,2-triphenylethyl radical,[4] and other similar radicals[5] have been reported, none of these has been ideally suited to a detailed study of such rearrangements. The present work was undertaken with the hope that a survey of other methods of producing the 2,2,2-triphenylethyl radical might provide a system more amenable to such a study. To this end the syntheses and thermal decomposition of di(3,3,3-triphenylpropionyl)diimide (I) and methylazo-2,2,2-triphenylethane (II) and also the preparation and air oxidation of 2,2,2-triphenylethylhydrazine (III) were investigated.

$$(C_6H_5)_3CCH_2CON{=}NCOCH_2C(C_6H_5)_3$$
I

$$(C_6H_5)_3CCH_2N{=}NCH_3 \qquad (C_6H_5)_3CCH_2NHNH_2$$
II III

$$(C_6H_5)_3CCH_2\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}CH_2C(C_6H_5)_3$$
IV

The thermal decomposition of diacyl- and diaroyldiimides had been investigated previously without very promising results. Thus Stollé[6] reported that dibenzoyldiimide when heated gave benzil in small but unspecified amounts and a more recent and careful study by Leffler and Bond[7] has demonstrated that in benzene solution the major products were 2,5-diphenyl-1,3,4-oxadiazole, biphenyl, dibenzoylhydrazine and a large amount of a mixture of what was presumably di- and tribenzoylhydrazines. In other solvents small amounts of benzil could be obtained. Inhoffen, Pommer, and Bohlmann[8] have investigated the possible

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(2) Standard Oil Company of California Fellow, 1957–58.

(3) (a) W. H. Urry and M. S. Kharasch, *J. Am. Chem. Soc.*, **66**, 1438 (1944); (b) S. Winstein and F. H. Seubold, *J. Am. Chem. Soc.*, **69**, 2916 (1947); (c) F. H. Seubold, *J. Am. Chem. Soc.*, **75**, 2532 (1952); (d) W. H. Urry, 12th National Organic Symposium, ACS, Abstracts, p. 30.

(4) (a) D. Y. Curtin and M. J. Hurwitz, *J. Am. Chem. Soc.*, **74**, 5381 (1952); (b) D. Y. Curtin and J. C. Kauer, *J. Org. Chem.*, **25**, 880 (1960); H. Meislich and J. Costanza, Abstracts of the 132nd Meeting, ACS, New York, N. Y., 1957, p. 9P.

(5) (a) W. H. Urry and N. Nicolaides, *J. Am. Chem. Soc.*, **74**, 5163 (1952); (b) S. Winstein, R. Heck, S. Lapporte, and R. Baird, *Experientia*, **12**, 138 (1954); (c) J. Weinstock and S. N. Lewis, *J. Am. Chem. Soc.*, **79**, 6243 (1957); (d) W. D. Smith and J. D. Anderson, *J. Am. Chem. Soc.*, **82**, 656 (1960); (e) L. H. Slaugh and J. H. Raley, *J. Am. Chem. Soc.*, **82**, 1259 (1960).

(6) R. Stollé, *Ber.*, **45**, 273 (1912).

(7) J. E. Leffler and W. B. Bond, *J. Am. Chem. Soc.*, **78**, 335 (1956).

(8) H. H. Inhoffen, H. Pommer, and F. Bohlmann, *Ber.*, **81**, 507 (1948).

synthetic utility of the conversion of diacyldiimides to diketones. They were able to convert, *N,N'*-dipropionyl- and *N,N'*-dibutyrylhydrazine by way of the diimide, which was not isolated, to diacetyl, dipropionyl, and dibutyroyl (isolated as the bis-phenylhydrazone or bis-*p*-nitrophenylhydrazone) in over-all yields of 0.5 to 1.4%. Cramer[9] has shown that such decompositions lead to radicals which catalyze polymerization.

In spite of these discouraging reports it seemed worth-while to examine the decomposition of the diacyldiimide (I), particularly in dilute solution and at elevated temperatures. The diimide I was prepared by oxidation with iodine of the mercury salt of the corresponding hydrazine, a method previously employed[6] for the preparation of other diacyldiimides. The structure of I was confirmed by its infrared, visible, and NMR spectra as described in the Experimental section and by its ready reduction to the diacylhydrazine from which it had been obtained. It is of interest that the carbonyl stretching frequency in the infrared was 1780 cm.$^{-1}$ Since, apparently, there have been no previous reports of the spectra of compounds with the —CON=NCO— functional group, the spectra of diacetyl- and dibenzoyldiimide were also obtained. These showed strong absorption attributed to the carbonyl group at 1770 and 1730 cm.,$^{-1}$ respectively, in reasonable agreement with the value obtained with I. The diimide I was found to melt with gas evolution which was noticeable even when the sample was heated at 160°. When the solid was heated to 175° for one hour, 70% of the theoretical amount of nitrogen was evolved and treatment of the residue with boiling acetone gave a 45% yield of 1,1,1,6,6,6-hexaphenyl-3,4-hexanedione (IV). No other product could be identified and no hydrocarbon portion was obtained on chromatography. The structure of IV was established by its cleavage to 3,3,3-triphenylpropionic acid with alkaline hydrogen peroxide and by the following spectral evidence. There was strong carbonyl absorption at 1723 cm.$^{-1}$ (chloroform solution). Biacetyl has absorption at 1718 cm.$^{-1}$ in carbon tetrachloride solution.[10] The absorption maximum of a chloroform solution at 440 mμ (ϵ 29) is in fair agreement with λ_{max} 420 mμ (ϵ 10) reported for biacetyl in ethanol.[11] The NMR spectrum of a 20% solution in deuterochloroform showed a singlet at −238 p.p. 10^8 (rel. to water) due to the aromatic protons and another singlet at +88 p.p. 10^8 due to the methylene group.

With the objective of producing 3,3,3-triphenylpropionyl radicals under circumstances which would favor to the maximum extent their decarbonylation rather than their recombination to diketone, the diimide I dissolved in a small volume of chloroform was added very slowly to decalin at 180°. The concentration of diimide was estimated to have been very much less than 0.01*M* and perhaps as low as $10^{-5}M$, throughout the reaction. Again the diketone was formed in 43% yield but there were also significant amounts of hydrocarbons. These, when separated by chromatography and examined with the aid of ultraviolet and NMR spectroscopy were estimated to account for 11% of the initial triphenylethyl groups as 1,1,2-triphenylethane and 14% as triphenylethylene. No hydrocarbon products formed with an unrearranged carbon skeleton could be detected. There was also 4% of di(3,3,3-triphenylpropionyl)-hydrazine formed by reduction of the diimide I. A reaction carried out similarly except that the solvent temperature was 160° gave similar amounts of the two hydrocarbons and di(3,3,3)triphenylpropionyl)hydrazine, but only 31% of the diketone IV. Another experiment at 137° in xylene gave 29% of diketone IV and lesser amounts of rearranged hydrocarbons. At 111° 25% of diketone IV was formed but no hydrocarbon was isolated. The failure of the 3,3,3-triphenylpropionyl radicals to undergo decarbonylation under conditions more vigorous than are required for similar acyl radicals[9,12a] might be attributed to the rapid primary combination of the two acyl radicals produced together, behavior reminiscent of azobisisobutyronitrile decomposition.[12a,13] The activation energy for the decomposition of acetyl radical to methyl radical and carbon monoxide has been estimated to be about 17 kcal.[14] The failure of the relative amount of diketone produced to vary greatly over the temperature range investigated suggests that the diketone is being produced by a process which has an energy of activation not too different from that of decarbonylation. One possibility is the isomerization of the azo compound to the *cis* isomer followed by a simultaneous loss of nitrogen and formation of a carbon-carbon bond by a molecular mechanism similar to that previously proposed by Hammond, Sen, and Boozer[13] as a possibility for part of the azobisisobutyronitrile decomposition. The decomposition of the diimide I requires further study, however, before conclusions about the mechanism may be drawn with any assurance.

It appears that the utility of the thermal decomposition of diacyldiimides for the synthesis of 1,2-diketone is greater for more complex structures than would be anticipated from the earlier studies of structurally simple examples. In particular the tendency of the acyl radical first formed to attack

(9) R. Cramer, *J. Am. Chem. Soc.*, **79**, 6215 (1957).

(10) R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Am. Chem. Soc.*, **71**, 1068 (1949).

(11) R. T. Holman, W. D. Lundberg, and G. O. Burr, *J. Am. Chem. Soc.*, **67**, 1669 (1945).

(12) See C. Walling, *Free Radicals in Solution*, John Wiley & Sons, N. Y., 1957, (a) pp. 278 ff., (b) pp. 76 ff., (c) p. 584 ff.

(13) G. S. Hammond, J. N. Sen, and C. E. Boozer, *J. Am. Chem. Soc.*, **77**, 3244 (1955).

(14) See T. L. Cottrell, *The Strengths of Chemical Bonds*, Butterworths Publications, Ltd., London, 1954, p. 204.

the starting diimide to give oxadiazole and triacylhydrazine which seems to be responsible to a considerable extent for the low yields of diketone, at least in the case of the diaroyldiimides,[7] appears to be greatly reduced in the decomposition of I. It should be noted in this connection that moderately good yields (40–55%) of diketone were obtained by Horner and Naumann[15] by the irradiation of the *p,p'*- or *o,o'*-dichlorodibenzoyldiimide but no diketone was obtained with dibenzoyldiimide or with its methyl and methoxyl substituted derivatives. The synthesis of the diketone IV by the thermal decomposition of I is of particular interest since the more conventional synthesis by the acyloin condensation fails in this case as will be discussed later in this paper.

The second compound to be studied (II) was synthesized by the following route from triphenylacetaldehyde. The structure was confirmed by the

$$(C_6H_5)_3CCH{=}O \xrightarrow[CH_3NHNH_2]{} (C_6H_5)_3CCH{=}NNHCH_3 \xrightarrow[CH_3COOH]{H_2/Pt} [(C_6H_5)_3CCH_2NHNHCH_3 \xrightarrow[NaHCO_3]{H_2O_2} \text{II}$$

infrared, ultraviolet, and NMR spectra described in the Experimental section. When the decomposition was carried out at 206° without a solvent the only identifiable products were triphenylmethane and benzophenone accounting for 23% and 6–10%, respectively, of the starting triphenylmethyl groups. It seems likely that the origin of the triphenylmethane is due to cleavage of the type shown.

$$(C_6H_5)_3CCH_2N{=}NCH_3 \longrightarrow (C_6H_5)_3C\cdot + \left[\cdot CH_2{-}N{=}NCH_3 \leftrightarrow CH_2{=}N{-}NCH_3\right]$$

A radical chain version is also possible.

$$(C_6H_5)_3CCH_2N{=}NCH_3 + R\cdot \longrightarrow (C_6H_5)_3C\cdot + CH_2{=}NH{=}CH_2 + HR$$

The formation of isopropylbenzene in the decomposition of 2-azobis-3-methyl-3-phenylbutane reported by Overberger and Gainer[16] is suggestive of a similar cleavage in that case.

The previously reported observation[17] that 9-hydrazino-9,10-ethano-9,10-dihydroanthracene was oxidized by stirring in tetrahydrofuran solution for several days at room temperature to the corresponding hydrocarbon, 9,10-ethano-9,10-dihydroanthracene, in 60% yield suggested that the mild oxidation of the hydrazine III might be a further method of preparing the 2,2,2-triphenylethyl radical. Attempts to prepare the triphenylethylhydrazine III by reduction of triphenylacetaldehyde hydrazone failed because of the strong tendency of the hydrazone to be converted to triphenylacetaldehyde azine. However, the acetylhydrazone of triphenylacetaldehyde was readily reduced and hydrolyzed to the hydrazine III isolated as the hydrochloride. When the free hydrazine was liberated in benzene solution and air bubbled through the refluxing solution for eight hours the major product found was benzophenone, isolated as the 2,4-dinitrophenylhydrazone and estimated by the use of ultraviolet and infrared examination of the crude product to account for 30% of the triphenylmethyl groups initially present. Small amounts of hydrocarbons also obtained were not identified. It seems likely that the benzophenone was formed from the rearranged radical, $(C_6H_5)_2CCH_2C_6H_5$, but a great deal more information about the mechanism of these reactions is desirable before any conclusions can be drawn as to the nature of the oxidation and possible radical rearrangement.

An attempt to prepare the hexaphenylhexandione IV during the course of the work just described led to an interesting example of a possible complication in the acyloin condensation. When ethyl 3,3,3-triphenylpropionate was treated with sodium in boiling xylene the only identifiable product was triphenylmethane in 42% yield. It is suggested that the ketyl supposed to be the first intermediate in the normal acyloin condensation[9c] lost triphenylmethyl radical (the reversal of the well known addition of a free radical to an olefin) to leave as the other product the sodium derivative of ethyl acetate. The reaction is thus apparently

$$(C_6H_5)_3CCH_2C(O^-)OC_2H_5\ Na^+ \longrightarrow (C_6H_5)_3C\cdot + CH_2{=}C(O^-Na^+)OC_2H_5$$

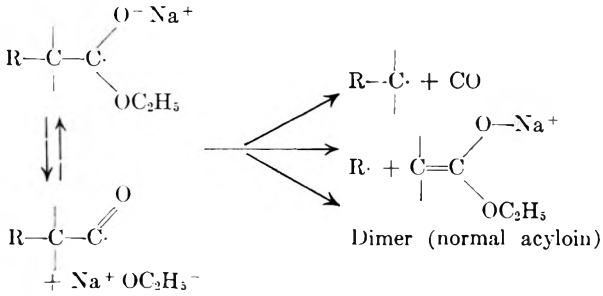
similar to the cleavage of the azo compound II. The generalization can then be noted that there are two alternative reaction paths for the ketyl intermediate formed under the conditions of the acyloin reaction. The first, loss of carbon monoxide,[18] can be expected when the resulting radical is relatively stable and the second, cleavage with rupture of the α,β carbon-carbon bond, the choice being determined to a large extent by the relative stabilities of the radicals to be formed by these processes.

(15) L. Horner and W. Naumann, *Ann.*, **587**, 93 (1954).

(16) C. G. Overberger and H. Gainer, *J. Am. Chem. Soc.*, **80**, 4561 (1958).

(17) M. Wilhelm and D. Y. Curtin, *Helv. Chim. Acta*, **40**, 134 (1957).

(18) E. Van Heyningen, *J. Am. Chem. Soc.*, **74**, 4861 (1952); *J. Am. Chem. Soc.*, **77**, 4016 (1955).



The detailed ordering of the necessary steps and, in particular, the point at which the ethoxide ion is lost cannot be specified with certainty for any of these three reactions.

EXPERIMENTAL[19,20]

N,N'-Di(3,3,3-triphenylpropionyl)hydrazine. To a rapidly stirred mixture of hydrazine hydrate (3.25 g., 0.0650 mole) and 50 ml. of pyridine was added a solution of 3,3,3-triphenylpropionyl chloride[21,22] (40.2 g., 0.125 mole, m.p. 129–131°) in 200 ml. of pyridine. After 1 hr. of heating on a steam bath the pyridine was distilled under reduced pressure and the resulting brown solid was triturated with ether, 5% hydrochloric acid, and 1% sodium hydroxide solution. The tan solid remaining (37.5 g.) was recrystallized by heating under reflux with 500 ml. of glacial acetic acid (in which it dissolves only slowly) to give 22 g. (59%) of *N,N'*-di(3,3,3-triphenylpropionyl)hydrazine, m.p. 276–277°. The infrared spectrum (Nujol mull) showed N—H absorption at 3200 cm.$^{-1}$ and strong carbonyl absorption at 1620 cm.$^{-1}$

Anal. Calcd. for $C_{42}H_{36}N_2O_2$: C, 84.0; H, 6.0; N, 4.7. Found: C, 84.0; H, 6.3; N, 4.6.

Mercury N,N'-di(3,3,3-triphenylpripionyl)hydrazine. A solution of *N,N'*-di(3,3,3-triphenylpropionyl)hydrazine (21.9 g., 0.0365 mole) in 500 ml. of dioxane and yellow mercuric oxide (8.01 g., 0.0370 mole) was stirred for 12 hr. on the steam bath. The fine, white precipitate which resulted was filtered, washed with ether, and dried. The yield of product, m.p. 229–232°, was 25.7 g. (89%). An infrared spectrum (Nujol mull) showed no absorption in the 3200 cm.$^{-1}$-region. There was strong absorption at 1500 cm.,$^{-1}$ (shoulder at 1515 cm.$^{-1}$).

Anal. Calcd. for $C_{42}H_{34}HgN_2O_2$: C, 63.1; H, 4.3; N, 3.5. Found: C, 62.8; H, 4.4; N, 3.5.

Di(3,3,3-triphenylpropionyl)diimide (I). A suspension of mercury *N,N'*-di(3,3,3-triphenylpropionyl)hydrazine (5.00 g., 0.00625 mole) in 100 ml. of reagent ether was stirred for 12 hr. at 25° with iodine (1.59 g., 0.0125 mole). The resulting suspension of pale yellow solid was decanted from the denser mercuric iodide and collected by filtration. About 300 ml. of acetone was required to dissolve the diimide, leaving a small amount of unchanged starting material behind. On cooling the red-orange acetone solution in Dry Ice, 2.04–2.91 g. (54–78% yield) of tiny, pale yellow prisms, m.p. 169–170° with decomposition and gas evolution, was obtained. The infrared spectrum of a 10% solution in chloroform showed strong absorption at 1780 cm.$^{-1}$ The visible spectrum of a chloroform solution showed a broad maximum at 474 mμ (ε 56). The NMR spectrum (20% solution in deuterochloroform) showed a sharp singlet at −243 (phenyl absorption) and a singlet at +85 (methylene group) p.p. 10^{8}.[20]

Anal. Calcd. for $C_{42}H_{34}N_2O_2$: C, 84.3; H, 5.7; N, 4.7. Found: C, 84.4; H, 5.9; N, 4.6.

The diimide I (195 mg., 0.326 mole) in 20 ml. of benzene containing 9.7 mg. of platinum oxide was hydrogenated at 25° and 1 atm. to give 138 mg. (70% yield) of *N,N'*-di-(3,3,3-triphenylpropionyl)hydrazine; the infrared spectrum was identical with that of an authentic sample.

Dibenzoyldiimide, m.p. 118.5–120° (lit.[23] m.p. 119.5–121.5°), was prepared in 40% yield by bubbling chlorine through an alkaline solution of *N,N'*-dibenzoylhydrazine. The infrared spectrum of a 5% solution in chloroform showed strong absorption at 1730 cm.$^{-1}$ The visible spectrum in chloroform showed a broad maximum at 463 mμ, ε 48.

Diacetyldiimide,[8] prepared for infrared spectral examination, was not isolated, but a carbon tetrachloride solution of the crude diimide showed intense infrared absorption at 1765 cm.$^{-1}$

Thermal decomposition of solid di(3,3,3-triphenylpropionyl)-diimide. 1,1,1,6,6,6-Hexaphenyl-3,4-hexandione (IV). Di-(3,3,3-triphenylpropionyl)diimide (2.32 g., 0.00388 mole) was placed in a 50-ml. flask equipped with a gas-collection buret and the air in the flask was replaced by nitrogen. The flask was heated to 175° for 1 hr. Rapid evolution of gas began at about 160° and little evolution was observed thereafter. Assuming that the gas was exclusively nitrogen 68% of the theoretical amount was evolved. The crude product was dissolved in 30 ml. of boiling reagent acetone and the solution was filtered while hot. On standing 0.97 g. (45% yield) of the hexandione IV, m.p. 217–219°, crystallized. Recrystallization gave bright yellow prisms, m.p. 218–220°.

The infrared spectrum of a 10% chloroform solution showed carbonyl absorption at 1723 cm.$^{-1}$ The NMR spectrum (20% solution in deuterochloroform) showed singlets at −238 and +88 p.p. 10^{8}.[20] The visible spectrum of a chloroform solution showed a broad absorption maximum at 440 mμ, ε 29.

Anal. Calcd. for $C_{42}H_{34}O_2$: C, 88.4; H, 6.0. Found: C, 88.0; H, 6.1.

Chromatography of the remainder of the reaction mixture after removal of IV failed to give any hydrocarbon fraction or any other identifiable products.

Oxidation of IV with alkaline hydrogen peroxide. The procedure was similar to that of Geissman and Koelsch.[24] To a solution of diketone IV (102 mg., 0.179 mole) in 10 ml. of acetone were added 0.20 ml. of 30% hydrogen peroxide and 1 ml. of 20% sodium hydroxide. After the addition of 30 ml. of water and distillation of the acetone the solution was filtered to remove unchanged starting material. Acidification of the filtrate gave 57 mg. (53% yield) of 3,3,3-triphenylpropionic acid which after one recrystallization from

(19) All melting points are corrected. Microanalyses were performed by Mr. J. Nemeth, Mrs. H. Stingl, Miss C. Higham, Mrs. F. Ju, and Miss J. Liu. Infrared spectra were measured in part by Mr. J. Brader, Mr. P. McMahon, Miss M. DeMott, and Miss C. Luebke, with a Perkin-Elmer Model 21 spectrophotometer using 0.1 mm. cells. Ultraviolet spectra were measured with a Cary Model 14M spectrophotometer by Mr. M. Chao and Mr. J. Chiu. The NMR spectra were measured by Mr. B. Shoulders with a Varian Associates V-4300-C high resolution spectrophotometer equipped with a VK-3606 flux stabilizer and operated at 40 Mc. Audiofrequency side bands generated with a Hewlett-Packard 200-CD oscillator together with an external methylene chloride standard were used to determine positions of absorption maxima. Most of the pertinent spectra will be available in the Ph.D. thesis of T.C.M.[1]

(20) All NMR spectra are reported in parts per 10^{8} relative to water.

(21) Triphenylpropionic acid, best prepared (in 80% yield) from malonic acid (20% excess) and triphenylcarbinol [C. Moureu, C. Dufraisse, and P. M. Dean, *Bull. soc. chim. France,* **43**, 1367 (1928)], was converted to the acid chloride with thionyl chloride.[22]

(22) L. Hellerman, *J. Am. Chem. Soc.*, **49**, 1735 (1927).

(23) L. Horner and W. Naumann, *Ann.*, **587**, 81 (1954).

(24) T. A. Geissman and C. F. Koelsch, *J. Org. Chem.*, **3**, 489 (1938).

TABLE I

THERMAL DECOMPOSITION OF DI(3,3,3-TRIPHENYLPROPIONYL)DIIMIDE (I)

Temp., °	Time, hr.	Max. Initial concn., mole/l.	Percent Yields of Products Based on Diimide[a]				
			Di(3,3,3)triphenylpropionyl)hydrazine	1,1,1,6,6,6-Hexaphenyl-3,4-hexandione (IV)	1,1,2-Triphenylethane	Triphenylethylene	Total
175[b]	1	<1.7	None	45	None	None	45
111[c]	7	0.019	2	25	None	None	27
137[d]	3	0.015	None	29	<17[f]	8	37–54
160[e]	2	<0.01	6	31	10	13	60
180[e]	1.3	<0.01	4	43	11	14	72

[a] For 1,1,2-triphenylethane and triphenylethylene, % yield = (100)(moles of hydrocarbon) ÷ (2)(moles of diimide). [b] No solvent. [c] Solvent toluene. [d] Solvent xylene. [e] Solvent decalin. [f] The NMR spectrum of this fraction showed contamination by unidentified hydrocarbon impurities.

methanol melted at 178–180° and showed no melting point depression when mixed with an authentic sample.

Decomposition of di(3,3,3-triphenylpropionyl)diimide in solution. (a) *Decalin at 160°.* The solvent, cis-decalin (Eastman Kodak practical grade) was purified by washing with concd. sulfuric acid, then with 5% sodium bicarbonate solution, and finally with distilled water, drying over calcium chloride, and distilling under reduced pressure. A solution of diimide I (0.93 g., 0.0016 mole) in 20 ml. of reagent chloroform was added over a period of 2 hr. to 30 ml. of initially refluxing decalin at such a rate that the temperature of the solution did not drop below 160°. The chloroform was flashed into a Dry Ice trap. A dense black precipitate of palladium was observed as the nitrogen used to sweep the reaction mixture was passed through a dilute aqueous solution of palladous chloride, indicating the presence of carbon monoxide.[25] When the yellow decalin solution was cooled, a voluminous white precipitate was observed. Suction filtration afforded 0.06 g. (6%) of the *N,N'*-di(3,3,3)triphenylpropionyl)hydrazine, which was recrystallized from acetic acid, m.p. 270–273°. Its infrared spectrum was identical with that of authentic material. Most of the decalin was then removed by distillation under reduced pressure. The residue was taken up in boiling acetone, from which the hexandione IV (0.23 g., 31%, m.p. 218–220°) crystallized on cooling. The acetone was removed on the steam bath, finally under reduced pressure, and the residue was chromatographed on ethyl acetate–washed alumina, previously activated 24 hr. at 130°. The first fraction (eluent, hexane) was decalin. An infrared spectrum indicated the absence of phenyl group bands at 1600 cm.$^{-1}$, 1500 cm.$^{-1}$, and 700 cm.$^{-1}$ An ultraviolet spectrum indicated the absence of triphenylethylene. The second fraction (0.19 g.; eluent, hexane) contained 0.11 g. (13% yield based on diimide) of triphenylethylene, as determined by examination of the absorption intensity at 298 mμ (ϵ of the pure compound taken as 19,500)[4b] in the ultraviolet spectrum in ethanol. The NMR spectrum of a 20% solution in carbon tetrachloride showed absorption at −238, −215 and −205 p.p. 10^8 characteristic of triphenylethylene and also at −228, +63 (triplet) and +155 (doublet) due to 1,1,2-triphenylethane. The crude hydrocarbon fraction was submitted for carbon and hydrogen microanalyses after removal of low-boiling solvents by heating 1.5 hr. at 78° at 1 mm.

Anal. Calcd. for a mixture of 63.8% $C_{20}H_{16}$ and 36.2% $C_{20}H_{18}$: C, 93.5; H, 6.6. Found: C, 93.0; H, 6.6.

(b) *Decalin at 180°.* The decomposition of diimide I was repeated as above except that with stronger heating the temperature of the solution was maintained at 180–185° while the diimide (1.491 g., 0.00249 mole) in 25 ml. of reagent chloroform was added to 30 ml. of decalin. Isolation of the products as described above gave 0.055 g. (4% yield) of *N,N'*-di(3,3,3-triphenylpropionyl)hydrazine, 0.603 g. (43% yield) of dione IV, m.p. 214–219°, and 0.333 g. of a hydrocarbon mixture containing 55% of triphenylethylene (14% yield) and 45% 1,1,2-triphenylethane (11% yield) as estimated from the ultraviolet and NMR spectra.

(c) *Decompositions in toluene and xylene* were carried out similarly. The results of these decompositions together with those described in detail above are presented in Table I.

Triphenylethylene, kindly supplied by Mr. J. A. Kampmeier, melted at 68–70° after recrystallization from ethanol (lit.,[26] m.p. 67–68°). The ultraviolet maximum in carbon tetrachloride was at 298 mμ, ϵ 19,500. The NMR spectrum (20% in carbon tetrachloride) showed aromatic resonance at −243 and −220. A maximum at −208 is believed to be due to the olefinic hydrogen atom.

1,1,1-Triphenylethane, prepared from methylmagnesium iodide and triphenylmethyl chloride,[27] melted at 94.5–95.5° (lit.[28] m.p. 94–95°). The infrared spectrum (10% in carbon tetrachloride) showed a sharp moderately intense C-methyl absorption at 1378 cm.$^{-1}$, a region which was completely clear in both the spectra of 1,1,2-triphenylethane and triphenylethylene. The NMR spectrum (20% in carbon tetrachloride) showed sharp singlets at −225 and +263 p.p. 10^8 due to the phenyl and methyl group protons, respectively.[20]

1,1,2-Triphenylethane, kindly supplied by Mr. H. Gruen, melted at 54.5–55°, after recrystallization from 95% ethanol (lit.,[29] m.p. 54°). The NMR spectrum (20% solution in carbon tetrachloride) showed aromatic proton absorption at −233 and −220. The CH group gave rise to a triplet at +63 and the CH_2 to a doublet at +155. (J was 8 c.p.s.).

Triphenylacetaldehyde. Triphenylacetaldehyde was prepared by the acid-catalyzed dehydration of triphenylethylene glycol.[30] Triphenylethylene glycol,[31] m.p. 166–167°, (128 g., 0.441 mole) was heated with stirring at reflux 24 hr. with 2.6 l. of 20% sulfuric acid. The resulting lumps of white crystals were filtered, crushed, washed with water, and dried to give 117 g. (97% yield). Comparison of the infrared absorption of the crude product with pure benzhydryl phenyl ketone and pure triphenylacetaldehyde at 1720 cm.$^{-1}$ (aldehyde carbonyl group) and 1685 cm.$^{-1}$ (ketone carbonyl group) indicated that the mixture consisted of 60 per cent of ketone and 40 per cent of aldehyde. In another preparation, using similar amounts of starting materials and a creased flask for more efficient stirring, and allowing refluxing to continue for 8 hr. instead of 24 hr., a dehydration product

(25) V. J. Altieri, *Gas Analysis and Testing of Gaseous Materials,* American Gas Association, Inc., New York, 1945, p. 257.

(26) J. van de Kamp and M. Sletzinger, *J. Am. Chem. Soc.,* **63** 1880 (1941).

(27) M. Gomberg and L. H. Cone, *Ber.,* **39,** 2963 (1906).

(28) E. Spath, *Monatsch,* **34,** 2013 (1913).

(29) A. Klages and B. Heilmann, *Ber.,* **37,** 1455 (1904).

(30) (a) C. J. Collins, *J. Am. Chem. Soc.,* **77,** 5517 (1955). (b) S. Danilov, *J. Russ. Phys. Chem. Soc.,* **49,** 282 (1917).

(31) S. F. Acree, *Ber.,* **37,** 2762 (1905).

whose infrared spectrum indicated the presence of 55% of ketone and 40% of aldehyde was obtained.

Benzhydryl phenyl ketone crystallized much more rapidly from 95% ethanol than did triphenylacetaldehyde. Advantage was taken of this phenomenon in separating the two compounds. Thus, pure triphenylacetaldehyde (white prisms, 32.9 g., 27.4% yield based on triphenylethylene glycol) was obtained; m.p. 105–105.5°; reported[30b] m.p. 105°.

Triphenylacetaldehyde methylhydrazone. A solution of methylhydrazine sulfate (Eastman Kodak White Label, m.p. 141.5–142.5°, 5.300 g., 0.0368 mole) in 10 ml. of distilled water was neutralized with 3.895 g. (0.0368 mole) of reagent sodium carbonate. Absolute ethanol (10 ml.) was added and the supernatant liquid was filtered into a solution of 5.00 g. (0.0184 mole) of triphenylacetaldehyde in 50 ml. of absolute ethanol. The resulting solution was heated 12 hr. on the steam bath. The white, crystalline product which precipitated on cooling was filtered and recrystallized from 95% ethanol; 4.62 g., 84% yield, m.p. 108–133°. Apparently decomposition occurred during melting.

Anal. Calcd. for $C_{21}H_{20}N_2$: C, 84.0; H, 6.7; N, 9.3. Found: C, 83.9; H, 6.9; N, 9.5. C, 83.7; H, 7.0; N, 9.1.

Methylazo-2,2,2-triphenylethane. A solution of triphenylacetaldehyde methylhydrazone (4.62 g., 0.0154 mole) in 50 ml. of glacial acetic acid containing 50 mg. of platinum oxide (estimated uptake of hydrogen, 24 ml., 27°/703 mm.) was shaken for 3.5 hr. with hydrogen supplied to the reaction flask from a water-filled buret equipped with a leveling bulb. The total uptake of hydrogen was 414 ml. (27°/703 mm.; 95%, corrected for temperature, atmospheric pressure, vapor pressure of water and acetic acid, and catalyst uptake). The catalyst was filtered and the solvent was distilled on the steam bath under reduced pressure, leaving a pale yellow oil containing some solid. The hydrazine was not isolated but was oxidized as follows by a modification of the procedure employed by Overberger and Gainer[16] for the preparation of 2,2′-azobis-2-methyl-2-phenylbutane. A solution of the pale yellow oil from the hydrogenation in 50 ml. of reagent ether was stirred for 4.5 hr. with a solution of 10 ml. of 30% hydrogen peroxide (*ca.* 0.1 mole) and 6 g. of sodium bicarbonate in 50 ml. of distilled water. The ether layer was washed with distilled water and dried over sodium sulfate. The ether was removed carefully on the steam bath, then overnight in vacuum at room temperature, leaving 4.41 g. of a viscous pale yellow oil, much of which crystallized on standing for 72 hr. Pure product, m.p. 70–72°, was obtained by recrystallization from methanol. The recrystallization was greatly hampered by the separation of the product as an oil. Therefore, the yield of pure product was low (1.62 g., 36% yield based on triphenylacetaldehyde methylhydrazone). The infrared spectrum measured in carbon tetrachloride showed no absorption maximum above 3100 cm.$^{-1}$ The NMR spectrum of a 20% solution in carbon tetrachloride showed three sharp singlets at −233 (aromatic), 0 (methylene group), and +130 (methyl group).[20]

Anal. Calcd. for $C_{21}H_{20}N_2$: C, 84.0; H, 6.7; N, 9.3. Found: C, 84.0; H, 6.6; N, 9.4.

Thermal decomposition of methylazo-2,2,2-triphenylethane (II). The azo compound II (202 mg., 0.672 mmole) was placed in a tube which was evacuated to 0.1 mm. and filled with nitrogen several times and then heated for 12 hr. at 205 ± 5° in refluxing tetralin vapor. Effluent gases were collected over silicone oil. The theoretical amount of nitrogen is 16.5 ml. but only 4 ml. of gas was evolved. The crude product was dissolved in chloroform to effect its transfer and the chloroform was then removed under reduced pressure to give 171 mg. of dark brown oil with an amine-like odor. Chromatography on ethyl acetate–washed alumina with pentane gave 38 mg. (23% yield) of triphenylmethane, m.p. 89–92°, as shown by comparison of its infrared and NMR spectra with those of an authentic sample and by the fact that a mixed melting point showed no depression. Further elution with pentane-ether (9/1) gave 66 mg. of yellow oil of which the infrared spectrum showed all the bands present in the spectrum of benzophenone. Using the bands at 1320 cm.$^{-1}$ and 1310 cm.$^{-1}$ it was estimated that the fraction contained 11–18% benzophenone (6–10% of the initial triphenylmethyl groups). Further elution with increasing amounts of ether and finally with methanol gave 69 mg. of additional red and brown oils which could not be identified.

Triphenylacetaldehyde acetylhydrazone. To a solution of triphenylacetaldehyde hydrazone[32] (112 mg., 0.390 mmole, m.p. 138–140°) in 2 ml. of reagent pyridine was added *ca.* 0.2 ml. of reagent acetyl chloride. Excess distilled water was added and the resulting white solid was filtered and washed with distilled water. Two recrystallizations from 95% ethanol gave 57 mg. (45% yield) of white platelets, m.p. 238.5–239°.

Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.5; H, 6.1; N, 8.5. Found: C, 80.1; H, 6.2; N, 8.3.

The compound could also be prepared from triphenylacetaldehyde (5.00 g., 0.0184 mole) and acetylhydrazide (1.63 g., 0.0220 mole) which were heated overnight at reflux in 75 ml. of 95% ethanol, during which time white crystals separated from the hot solution. The mixture was chilled and filtered and the product was washed with generous quantities of 95% ethanol. The yield of product, m.p. 237–239°, after drying was 5.50 g., 91.2% yield. Admixture with the product prepared from triphenylacetaldehyde hydrazone and acetyl chloride gave no depression of the melting point. The infrared spectra of the two products were identical.

N-(2,2,2-Triphenylethyl)-N′-acetylhydrazine. A solution of triphenylacetaldehyde acetylhydrazone (3.572 g., 0.01087 mole) in 150 ml. of glacial acetic acid containing 201 mg. of platinum oxide (estimated uptake of hydrogen, 99 ml., 24°/697 mm.) was shaken for 6.3 hr. with hydrogen at 1 atm. The total uptake of hydrogen was 395 ml. (24°/697 mm.; 102%, corrected for temperature, atmospheric pressure, vapor pressure of water and acetic acid, and catalyst uptake). The catalyst was filtered and the solvent was distilled under reduced pressure, leaving a white solid, which on drying weighed 3.513 g. (97.8% yield) and whose infrared spectrum was identical with that of the product recrystallized once from 95% ethanol. Repeated recrystallizations caused air oxidation with formation of triphenylacetaldehyde acetylhydrazone, the appearance of whose strong infrared bands at 1385 cm.$^{-1}$ and 1330 cm.$^{-1}$ was noted. The melting point was dramatically dependent on the rate of heating. When heated at 1–2°/min. at 140–150°, the product began to melt at 151°, while when heated rapidly the melting point was around 170°.

Anal. Calcd. for $C_{22}H_{22}N_2O$: C, 80.0; H, 6.7; N, 8.5. Found: C, 80.3; H, 6.9; N, 8.4.

2,2,2-Triphenylethylhydrazine hydrochloride. A solution of *N*-(2,2,2-triphenylethyl)-*N′*-acetylhydrazine (508 mg., 1.54 mmoles) in 18 ml. of 95% ethanol and 2 ml. of concd. hydrochloric acid was heated for 12 hr. under reflux. The solvents were distilled at reduced pressure, leaving a white solid which was washed exhaustively with ether and dried (78°/1 mm.) over potassium hydroxide; 463 mg. (92.7% yield), m.p. 197–199° dec. The hydrochloride could be sublimed slowly under high vacuum (150°/0.2 mm.), but sublimation did not raise the melting point.

Anal. Calcd. for $C_{20}H_{21}ClN_2$: C, 73.9; H, 6.5; N, 8.6. Found: C, 73.5; H, 6.4; N, 8.4.

Attempted isolation of 2,2,2-triphenylethylhydrazine. 2,2,2-Triphenylethylhydrazine hydrochloride (198 mg., 0.610 mmole) was shaken in a 50-ml. of reagent ether. During this step, no matter how finely ground beforehand, some of the hydrochloride formed lumps which were neutralized slowly. Thus, the next step was carried out before the neutralization was complete. The ether layer was washed with distilled water until the washings were neutral (three or four times), dried over sodium sulfate, and filtered. The solvent

(32) L. Hellerman and R. L. Garner, *J. Am. Chem. Soc.*, **57**, 139 (1935).

was removed in a stream of nitrogen, leaving fine, white needles, which were dried overnight under high vacuum at room temperature; 111 mg. (76.1% yield), m.p. 86–88° with decomposition and gas evolution. An accurate elemental analysis could not be made because the compound lost weight on the analytical balance. Thus, the decomposition in air is very rapid, with apparent loss of nitrogen. On standing in air the white crystals reverted to a pale yellow gum with entrained gas bubbles. An infrared spectrum run after 2 days' standing exhibited bands characteristic of the infrared spectrum of benzophenone. A calculation using the carbonyl group stretching frequency at 1655 cm.$^{-1}$ indicated the presence of 4.5–7.5% benzophenone.

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83.3; H, 7.0; N, 9.7. Found: C, 79.6; H, 6.5; N, 4.7.

Air oxidation of 2,2,2-triphenylethylhydrazine. A solution of 2,2,2-triphenylethylhydrazine in 30 ml. of reagent benzene prepared by the neutralization of 2,2,2-triphenylethylhydrazine hydrochloride (535 mg., 1.62 mmoles) was heated for 10 hr. under reflux. The benzene was distilled at reduced pressure, leaving 320 mg. of a light yellow oil, whose infrared spectrum, when compared with that of benzophenone, revealed the presence of 12% (13% yield calculated for the stoichiometry in which 1 mole of benzophenone is formed from 1 mole of hydrazine and based on 2,2,2-triphenylethylhydrazine hydrochloride) of benzophenone. Chromatography of 285 mg. of the yellow-orange oil on 15 g. of ethyl acetate–washed alumina, activated overnight at 130°, gave 64 mg. of a hydrocarbon fraction shown by examination of the ultraviolet spectrum to contain no more than 9% (1% yield) of triphenylethylene. Absence of absorption in the infrared at 1380 cm.$^{-1}$ indicated that no significant amounts of 1,1,1-triphenylethane were present. The NMR spectrum gave no evidence of the presence of 1,1,2-triphenylethylene nor dibenzyl, although a maximum at +90 p.p. 10[8] indicated the possible presence of diphenylmethane. The second fraction obtained by elution with 600 ml. of benzene amounted to 145 mg. and the ultraviolet spectrum showed absorption at 252 mμ indicating that it consisted to the extent of about 33% of benzophenone. No other products were isolated. From another run carried out in a similar fashion, except that air was bubbled through the solution, benzophenone, estimated from the infrared to have been formed in about 20% yield, was isolated as the 2,4-dinitrophenylhydrazone, m.p. 236–238°, and a mixed melting point with an authentic sample, m.p. 240–241°, showed no depression.

Reaction of ethyl 3,3,3-triphenylpropionate and sodium in xylene. The procedure was similar to that used in the preparation of lauroin.[33] A solution of ethyl 3,3,3-triphenylpropionate[34] (5.00 g., 0.0151 mole, m.p. 79–80.5°) in 30 ml. of reagent xylene was added dropwise to a rapidly stirred suspension of 0.7 g. (0.03 g. atom) of freshly-cut sodium in 100 ml. of reagent xylene heated in an oil bath held at 119°. The addition required 5 min. and heating was continued for 30 min., while the reaction flask was constantly swept with nitrogen. The reaction mixture was then cooled to room temperature and 10 ml. of reagent methanol was added to decompose the excess sodium. The xylene solution was extracted with 5% hydrochloric acid and water. The xylene was distilled on the steam bath under reduced pressure, leaving 4.07 g. of a viscous light brown residue. The crude product was chromatographed on 200 g. of untreated alumina. Triphenylmethane (1.50 g., 42% yield, m.p. 89–93°) was eluted with 4:1 hexanebenzene. Several recrystallizations from absolute ethanol gave pure triphenylmethane; m.p. 93–93.5°, reported, m.p. 92.5–93°. An infrared spectrum was identical with a spectrum of authentic triphenylmethane. The NMR spectrum (50% solution in carbon tetrachloride) showed a singlet at −55 p.p. 10[8]. The subsequent fractions of the chromatography were not examined.

Anal. Calcd. for $C_{19}H_{16}$: C, 93.4; H, 6.6. Found: C, 93.4; H, 6.9.

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(33) S. M. McElvain, *Org. Reactions*, IV, 256 (1948).

(34) A. T. Blomquist, R. W. Holley, and O. J. Sweeting, *J. Am. Chem. Soc.*, **69**, 2356 (1957).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF LOYOLA UNIVERSITY OF CHICAGO]

Ring Size Effects in the Neophyl Rearrangement[1,2]

JAMES W. WILT AND BROTHER HERBERT PHILIP, F.S.C.[3]

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1-Phenylcyclopentylacetaldehyde (I) and 1-phenylcyclohexylacetaldehyde (II) have been prepared and characterized. The rearrangement percentages upon di-*t*-butyl peroxide-induced decarbonylation in the liquid phase under various conditions have been determined (Table V). The results indicate that the 1,2-phenyl shift is markedly more facile in II than in I. Arguments are presented that this ring size effect results from differences in steric interference with the formation of the requisite transition states and from differences in the hydrogen donor abilities of the aldehydes. The reactions follow the course of other neophyl-type rearrangements and do not appear to involve bridged radicals as intermediates.

The production of a radical site on the cyclohexane ring is generally rather difficult and, in some of the comparisons known, less ready than on the cyclopentane ring, a situation common also to carbonium ion and carbanion formation[4] on these rings. Cyclopentene, for instance, is three to seven times more reactive than cyclohexene toward addition of trichloromethyl radicals in the photochemical addition of bromotrichloromethane[5] while cyclopentaneazobisnitrile undergoes thermal decomposition at 80° about 11.5 times as fast as does the cyclohexane analog.[6] Commonly these ring size effects have been ascribed to conforma-

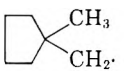
(1) Abstracted from the thesis of Brother Herbert Philip (Hogan), F.S.C., presented to the faculty of the Graduate School of Loyola University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1959.

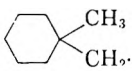
(2) A preliminary report of this work appeared in *J. Org. Chem.*, **24**, 441 (1959).

(3) An Arthur Schmidt Pre-doctoral Fellow, 1957–58.

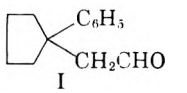
(4) For a survey of much work in these areas, see E. L. Eliel in *Steric Effects in Organic Chemistry*, edited by M. S. Newman, John Wiley and Sons, New York, N.Y., 1956, pp. 121 ff.

tional strain differences between these rings.[4,7] Some recent studies give apparently opposite conclusions, however. Cyclohexane adds to formaldehyde in greater yield than does cyclopentane in a radical process with di-*t*-butyl peroxide[8] and the peroxide of cyclohexanecarboxylic acid decomposes nearly twice as fast as the cyclopentane analog in carbon tetrachloride.[9] There does not, however, appear to be any data on the ease of radical production on cycloalkyl rings by rearrangement. Two earlier studies are inconclusive in this regard. In the first,[10] the decarbonylation of cyclohexanecarboxaldehyde and cyclopentylacetaldehyde led to no observed rearrangement (cyclohexyl $\rightleftharpoons$ cyclopentylcarbinyl) in either case, only the parent skeletal hydrocarbons being obtained. In the second,[11] neither of the radicals shown (likewise produced by decarbonylation of the alde-

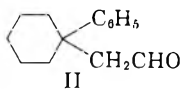




hydes) underwent rearrangement.[12] Thus far, only aryl (and not alkyl) rearrangement has been reported in the radical-chain decarbonylation reaction.[13] For this reason, it was felt that the decarbonylation reaction involving aryl migration *from* a cycloalkyl ring would be a suitable system in which to study various cycloalkyl radicals and the differences among them arising from ring size and conformation. Such rearrangements (1,2-phenyl shifts) in decarbonylations are well known and the reaction has been of interest to several workers in the field since its discovery.[14] While both steric and electronic factors seem operative in this rearrangement, the evidence favors the former as the more important.[15] Thus, an investigation of the neophyl rearrangement in substances containing incorporated cycloalkyl rings would help also to delineate the steric requirements of this process in addition to providing information on cyclic radicals as mentioned above. This report concerns the synthesis of the cyclopentyl and cyclohexyl model compounds (I and II following) and their behavior upon decarbonylation. Work



I



II

is in progress on analogous compounds in other ring sizes.

RESULTS

The aldehydes I and II proved elusive in synthesis. Many routes were attempted and at length most rejected, although a new aldehyde synthesis was developed in the course of this research.[16] Because the skeletal systems desired are quite

(5) For a table of olefin reactivities toward trichloromethyl radicals, see C. Walling, *Free Radicals in Solution*, John Wiley and Sons, New York, N.Y., 1957, p. 254. This increased rate, however, reflects wholly or in part the ground state energy difference between the two cyclic olefins. From heat of hydrogenation data [G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith, and W. E. Vaughan, *J. Am. Chem. Soc.*, **58**, 146 (1936) and M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky, and W. E. Vaughan, *J. Am. Chem. Soc.*, **59**, 831 (1937).] It has been shown that cyclopentene is less stable than cyclohexene by 1.7 kcal./mole. These addition processes, then, do not bear significantly on the relative stabilities of the intervening substituted cyclopentyl and cyclohexyl radicals themselves.

(6) C. G. Overberger, H. Biletch, A. B. Finestone, J. Liker, and J. Herbert, *J. Am. Chem. Soc.*, **75**, 2078 (1953).

(7) Such conformational strain differences are predicated on the unreal planar cyclopentane ring. What puckering exists in this ring has been disregarded as unimportant to the comparisons made. That the nature and degree of the nonplanarity in the cyclopentane ring is of importance to its chemistry is indicated by F. V. Brutcher, Jr., T. Roberts, S. J. Barr, and N. Pearson, *J. Am. Chem. Soc.*, **81**, 4915 (1959).

(8) G. Fuller and F. Rust, *J. Am. Chem. Soc.*, **80**, 6149 (1958). This report was preliminary and made no comparisons, but the reaction would seem to depend on the relative ease of hydrogen abstraction from the cycloalkanes by the *t*-butoxy radical.

(9) H. Hart and D. Wyman, *J. Am. Chem. Soc.*, **81**, 4891 (1959). This result is of special interest in view of the results with the azonitriles,[6] although the rate-determining steps may differ in each case.

(10) F. H. Seubold, Jr., *J. Am. Chem. Soc.*, **76**, 3732 (1954).

(11) M. A. Muhs, dissertation (University of Washington, 1954) quoted by H. Breederveld and E. C. Kooyman, *Rec. trav. chim.*, **76**, 305 (1957).

(12) Interestingly, rearrangement was observed when these radicals were produced in the Kolbe electrolysis reaction. For a discussion of this point see the journal reference in footnote 11.

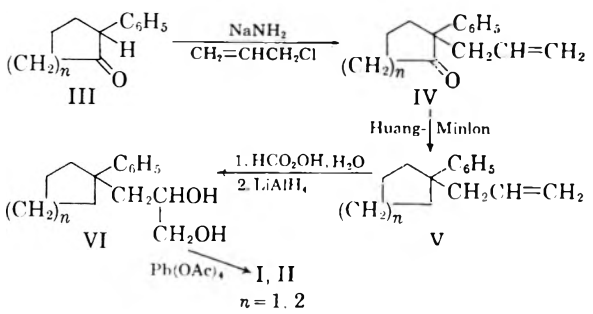
(13) With certain cyclic structures alkyl double bond participation may occur, however. Thus, while cyclohexene-4-carboxaldehyde decarbonylated to cyclohexene exclusively, norbornene-5-carboxaldehyde yielded both norbornene and nortricyclene (J. W. Wilt, A. Wysocki, and A. Levin, unpublished work).

(14) The rearrangement of a radical in solution was first demonstrated by W. H. Urry and M. S. Kharasch, *J. Am. Chem. Soc.*, **66**, 1438 (1944) with the β-phenylisobutyl radical in a cobaltous chloride-Grignard reaction. This β-phenylisobutyl moiety was termed neophyl, apparently first by F. C. Whitmore, C. A. Weisgerber, and A. C. Shabica, Jr., *J. Am. Chem. Soc.*, **65**, 1469 (1943) and gave rise to the term neophyl rearrangement for the reaction observed. This rearrangement during the decarbonylation of aldehydes was first recorded by S. Winstein and F. H. Seubold, Jr., *J. Am. Chem. Soc.*, **69**, 2916 (1947) and has been studied in related series by W. H. Urry and N. Nicolaides, *J. Am. Chem. Soc.*, **74**, 5163 (1952); D. Y. Curtin and M. J. Hurwitz, *J. Am. Chem. Soc.*, **74**, 5381 (1952); and F. H. Seubold, Jr., *J. Am. Chem. Soc.*, **75**, 2532 (1953).

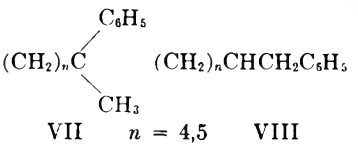
(15) See E. S. Gould, *Mechanism and Structure in Organic Chemistry*, Henry Holt and Co., New York, N. Y., 1959, pp., 755 ff. Although steric compression in the radical and an overall transition to an electronically preferred radical assist rearrangement markedly, neither is necessary for rearrangement since L. H. Slaugh, *J. Am. Chem. Soc.*, **81**, 2262 (1959) has found that the 2-phenylethyl-1-C^{14} radical rearranges to the 2-phenylethyl-2-C^{14} radical to the extent of 2–5% in the decarbonylation reaction.

(16) J. W. Wilt and Bro. H. Philip, F.S.C., *J. Org. Chem.*, **24**, 616 (1959).

prone to ionic rearrangements of the Wagner-Meerwein type,[17] synthetic procedures were designed so that reactions which placed charge on the carbinyl carbon (α to the cycloalkyl ring) were avoided. The route used, actually a modified Hershberg[18] synthesis, is shown in the following diagram.



The appropriate 2-phenylcycloalkanone (III-5, III-6[19]) was alkylated in the α-position[20] using allyl chloride with sodium amide as the condensing agent. The yields and properties of the ketones (IV) so produced, together with their 2,4-dinitrophenylhydrazone derivatives, are given in Table I. The basic medium of this step introduced the possibility of an allylic shift in the position of the double bond in IV. No absorption at 7.3 μ (C—CH_3) was noted in these products, however, and the rearrangement was therefore considered absent. The Huang-Minlon[21] reduction of the ketones proceeded acceptably to the hydrocarbons (V), whose properties are given in Table II. Here, interestingly, some allylic shift was detected in the infrared spectra of the hydrocarbons at 7.3 μ. Presumably, lengthy contact with hot alkali under these conditions isomerized the material in part. While the degree of rearrangement was seemingly slight as evidenced by the shallow C—methyl absorption, this point was not checked and the products were used as obtained. The hydroxylation of the allylic double bond to give the diols (VI) was achieved quite satisfactorily with performic acid, using with slight modification the literature procedures.[22] It was found that basic workup of the glycol formates led to discoloration and generally unsatisfactory material. On the other hand, acidic conditions were considered unsafe, as pinacol rearrangements were likely. The diols were therefore obtained by reductive hydrolysis of the intermediate formates with lithium aluminum hydride.[23] The properties of the diols are given in Table III. The last step, the oxidative cleavage of the diols to the required aldehydes (I and II), involved reaction with lead tetraacetate in benzene.[24] The cleavages were satisfactory, although the conditions for the cleavage of VI-6 were not considered optimum and the yield of II could probably be increased. Periodic acid cleavage led to iodinated intractable substances and was not investigated further. The properties of the aldehydes and their derivatives are listed in Table IV. While the absence of rearrangement in this route rests ultimately upon the found identity of the hydrocarbon mixtures of VII and VIII (from the decarbonylation of I and II) with authentic mix-



tures (see Experimental), two additional facts substantiate this belief. The autoxidation of II led in excellent yield to 1-phenylcyclohexylacetic acid identical in melting point with that reported[25] for this substance prepared in another way. The 2,4-dinitrophenylhydrazone of II from this route was identical with a sample obtained earlier in this study by a published route.[16] The autoxidation of I, however, led in quantitative yield to an acid having the correct analysis for 1-phenylcyclopentylacetic acid but melting at 88–89°. The literature value[26] is 120°. We believe the earlier compound is an isomer, obtained by a rearrangement in the Friedel-Crafts-type reaction used in its production,[27] and that our sample is correctly this acid.

(17) For the parent neophyl system, see S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Am. Chem. Soc.*, **74**, 1113 (1952). Unpublished work by one of us (J.W.W.) in the cyclic analogs indicates comparable rearrangement reactivity in these compounds also.

(18) E. B. Hershberg, *Helv. Chim. Acta*, **17**, 351 (1934).

(19) The numeral refers to the type of compound, the number to the cyclopentyl (5) or cyclohexyl (6) example.

(20) The position of alkylation here is in accord with several literature studies: a similar alkylation by V. Boekelheide and W. M. Schilling, *J. Am. Chem. Soc.*, **72**, 712 (1950); the increased acidity of hydrogen *alpha* to both an aromatic ring and the carbonyl group, A. C. Cope, H. L. Holmes, and H. O. House, *Organic Reactions*, IX, 109 (1957); and the Haller rule that alkylations generally occur at the carbon already more alkylated, A. Haller and E. Benoist, *Ann. Chim.* (Paris), **17**, 25 (1922).

(21) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(22) J. D. Roberts and C. W. Sauer, *J. Am. Chem. Soc.*, **71**, 3927 (1949) and W. R. Newhall, *J. Org. Chem.*, **23**, 1274 (1958).

(23) This rapid and effective method of hydrolysis of ester functions has found much use in the steroid field (see *e.g.*, H. Hirschmann and M. A. Daus, *J. Org. Chem.*, **24**, 1114 (1959)) and is to be recommended generally.

(24) R. J. Speer and H. R. Mahler, *J. Am. Chem. Soc.*, **71**, 1133 (1949).

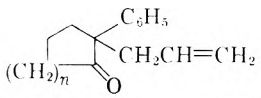
(25) G. F. Woods, E. B. Carton, H. F. Lederle, L. H. Schwartzmann, and G. F. Woods. *J. Am. Chem. Soc.*, **74**, 5126 (1952).

(26) M. A. Saboor, *J. Chem. Soc.*, 922 (1945).

(27) In the earlier study[26] (1-carbomethoxycyclopentyl)-acetyl chloride was treated with benzene in the presence of aluminum chloride. An ester, purportedly methyl 1-phenylcyclopentylacetate, was obtained and saponified to the acid melting at 120°. In view of the rearrangements obtained by Woods[25] and others [see C. D. Nenitzescu and J. Gavat, *Ber.*, **70**, 1883 (1937) for example] in attempts to synthesize 1-phenylcyclohexyl acetic acid by Friedel-Crafts methods, we feel Saboor's reaction led to isomerization at some point.

TABLE I

2-PHENYL-2-ALLYLCYCLOALKANONES (IV)

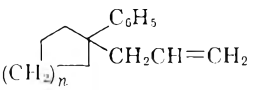


					Analyses			
					Calculated		Found	
n	B.p./mm.	n_D^t	d_4^{20}	Yield, %	C	H	C	H
1[a]	116°/1.0	1.5390[23]	1.046	79	83.96	8.05	83.91	7.98
2[b]	101°/0.5	1.5365[23]	1.040	85	84.07	8.46	83.93	8.50

[a] 2,4-Dinitrophenylhydrazone, m.p. 134.5–135°. *Anal.* Calcd. for $C_{20}H_{20}N_4O_4$: N, 14.73. Found: N, 14.75. [b] 2,4-Dinitrophenylhydrazone, m.p. 141–141.5°. *Anal.* Calcd. for $C_{21}H_{22}N_4O_4$: N, 14.21. Found: N, 14.22.

TABLE II

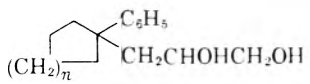
1-PHENYL-1-ALLYLCYCLOALKANES (V)



					Analyses			
					Calculated		Found	
n	B.p./mm.	n_D^t	d_4^{20}	Yield, %	C	H	C	H
1	98°/2.9	1.5340[26]	0.958	63	90.26	9.74	90.49	9.57
2	90°/0.8	1.5315[23]	0.964	70	89.94	10.06	90.05	10.10

TABLE III

1-PHENYL-1-(β,γ-DIHYDROXYPROPYL)CYCLOALKANES (VI)

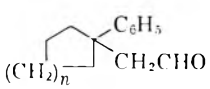


					Analyses			
					Calculated		Found	
n	B.p./mm.	n_D^t	d_4^{20}	Yield, %	C	H	C	H
1[a]	162°/1.2	1.5482[23]	[b]	75	76.32	9.15	76.44	9.05
2[c]	165°/0.4	1.5457[24]	[b]	90	76.88	9.46	76.63	9.66

[a] Mono-*p*-nitrobenzenesulfonate, m.p. 72–73°. *Anal.* Calcd. for $C_{20}H_{23}NO_6S$: C, 59.24; H, 5.72. Found: C, 58.81; H, 5.40. [b] Too viscous to measure in a densitometer. [c] No crystalline derivative was obtained.

TABLE IV

1-PHENYLCYCLOALKYLACETALDEHYDES (I,II)



					Analyses			
					Calculated		Found	
n	B.p./mm	n_D^t	d_4^{20}	Yield, %	C	H	C	H
1[a,b]	106°/1.0	1.5352[22]	1.065	60	82.93	8.57	82.69	8.37
2[c,d]	112°/0.5	1.5395[22]	1.080	32	83.14	8.95	82.95	9.09

[a] 2,4-Dinitrophenylhydrazone, m.p. 132–133°. *Anal.* Calcd. for $C_{19}H_{20}N_4O_4$: N, 15.21. Found: N, 15.25. [b] Oxidizes in air to the acid (100%), m.p. 88–89°. *Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.26; H, 7.69. [c] 2,4-Dinitrophenylhydrazone, m.p. 163–164°. *Anal.* Calcd. for $C_{20}H_{22}N_4O_4$: N, 14.65. Found: N, 14.53. [d] Oxidizes in air to the acid (85%), m.p. 85–86°. *Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.36; H, 8.31.

TABLE V

DECARBONYLATION OF ALDEHYDES

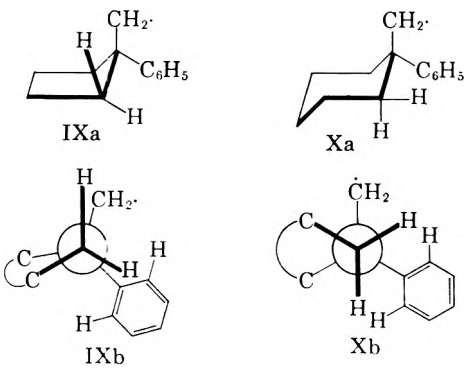
Acetaldehyde	Expt.	Temp. (Bath)	Time (Hr.)	% CO	Hydrocarbons (% VII, VIII)	Rearrangement[a] (% VIII in VII, VIII)
1-Phenylcyclopentyl (I)	I-1	140°	4	87	74	63[b]
	I-2	190°	2	91	70	71[b]
	I-3[c]	132°	20	77	58	92[b]
	I-4[d]	160°	22	64	64	<3[b]
1-Phenylcyclohexyl (II)	II-1	140°	9	48	47	89
	II-2	190°	8	43	41	91
	II-3[c]	132°	20	43	42	94
	II-4[d]	160°	23	22	21	50

[a] Maximum error for I, 2.5%; for II, 1%. See Experimental. [b] With β-phenylisovaleraldehyde, 57% at 130°, 150°; 63% at 170°; ~80% when 1M in chlorobenzene (see F. H. Seubold, Jr. footnote 14); and ". . . rearrangement decreases as benzyl mercaptan is added" (see S. Lapporte, Lit.[38]). [c] Aldehyde 1M in chlorobenzene. [d] Benzyl mercaptan (20 mole-%) added initially.

The decarbonylations of I and II were initiated with di-*t*-butyl peroxide and carried out in the usual fashion.[14,28] The results of these reactions are given in Table V where literature data on the rearrangement of β-phenylisovaleraldehyde to mixtures of *iso*- and *t*-butylbenzene has also been included for comparison purposes.

Discussion. The results in Table V indicate several things, each of which will be discussed in turn: (1) the size of the ring in the decarbonylated radicals does affect rearrangement percentages, the radical $(CH_2)_5C(C_6H_5)CH_2\cdot$ (Xa following) rearranging more than the radical $(CH_2)_4C(C_6H_5)$-$CH_2\cdot$ (IXa following); (2) the rearrangement of IXa shows the greater temperature dependence; and (3) bridged radicals are not significantly involved in either case.

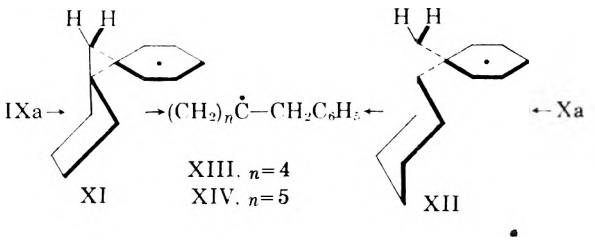
Ring size effect. I approximates somewhat β-phenylisovaleraldehyde in the amount of rearrangement observed, while II has significantly more rearrangement. *If* steric compression at the quaternary carbon center in the generated radical (*i.e.*, IXa or Xa) were the predominant factor in determining rearrangement, then the results obtained here and elsewhere would indicate the following order of increasing β-compression: neophyl< IXa<Xa<β,β,β-triphenylethyl.[29] A study of molecular models substantiates this order, though the models of the cycloalkyl radicals do not appear different in this regard to the degree indicated by their different rearrangement percentages. While increased β-compression undoubtedly raises the potential energy of a radical compared with some standard (in this case the neophyl radical), in certain structures the free energy barrier to rearrangement may also be raised and the net effect is no increase in rearrangement. When the greater strain is not counterbalanced by a raised barrier, rearrangement increases. IXa and Xa below illustrate these points. The cyclopentane ring, while nonplanar and somewhat flexible, still maximizes adjacent bond oppositions compared with the strainless cyclohexane ring. In Newman[30] projection such maximized and minimized bond opposition states may be represented by the following structures (IXb and Xb). The chair form of the cyclohexane ring has been used for Xa–Xb and the phenyl group has been placed in the more likely equatorial position because of its size. These representations show, as do the actual models (Fisher Taylor-Hirschfelder scale models), that rotation of the aromatic ring about its C-1 bond is severely restricted in IXa because of the interference between the *ortho* ring hydrogens and the adjacent cyclopentane ring hydrogen (as is seen in IXb). Such rotation is relatively free in Xa, however, and is in fact comparable to that in the neophyl radical itself. Since migration of the phenyl group to the carbinyl carbon atom will be easiest when the overlap of the orbitals involved is maximized, the lowest-lying transition states for the rearrangement may be shown by XI and XII for the 5- and 6-case, respectively. These states require that the plane of the migrating phenyl group lie perpendicular to the axis of the exocyclic bond of the cycloalkane. As rotation of the phenyl group about its C-1 bond to achieve such geometry is restricted in IXa, while much less so in Xa, the rate of conversion of Xa to



(28) These reactions undoubtedly follow the path given by earlier workers and discussed in Walling (ref. 5), pp. 278–280.

(29) D. Y. Curtin and M. J. Hurwitz, ref. 14, found 100% rearrangement of this radical in decarbonylation.

(30) M. S. Newman, *J. Chem. Ed.*, **32** 344 (1955).



XIV should be (and is) faster than that of IXa to XIII.[31] The similarity of IXa to the neophyl radical, moreover, becomes fortuitous. While the conversion IXa → XIII probably has the higher activation enthalpy, the entropy change would seem less unfavorable because IXa is more strained than the neophyl radical. The apparent net effect is to equate the systems in rearrangement.

The rearrangements above are in competition with processes involving abstraction of hydrogen by the radicals from the solvent, leading to unrearranged hydrocarbons. If this abstraction is easier in one of the systems than the other, the amount of rearrangement will accordingly decrease. Three observations indicate that such indeed is the case: (a) the rates of decarbonylation; (b) the rates of autoxidation; and (c) the presence of acetone from the initiator. At 140° I (pure liquid) decarbonylated nearly four times faster than II (pure liquid) (see Table V). Decarbonylation under these conditions is a free-radical chain process[28] and its rate is determined largely by the rates of primary initiation and chain transfer. Initiation was more effective with I since only ~3 mole per cent di-*t*-butyl peroxide sufficed for 90% of the carbon monoxide evolved, while II required seven-fold more peroxide for less decarbonylation (see Experimental). Therefore initiation and transfer steps are presumably faster with I and imply that the aldehydic hydrogen is more readily homolyzed in I than II. The same conclusion is reached when the rates of autoxidation (a reaction also involving hydrogen abstraction from the aldehyde[32]) are compared. I was oxidized quantitatively in air in twelve hours, while II was oxidized in 85% yield in air in seven days. In a similar way, the formation of acetone is informative here. The amount of acetone resulting from di-*t*-butyl peroxide-initiated processes is determined by the cleavage of *t*-butoxy radicals in competition with hydrogen-atom transfer with the solvent as shown.[33] The more acetone found, the more difficult the hydrogen abstraction must be. No acetone was found in the reactions with I, while 37–41% yields of acetone (based on initial di-*t*-butyl peroxide) were found with II.[34] The longer chain length apparent with I was no doubt due to the *primary* nature of the chain carrier IXa, while with II the chain would be propagated most frequently by the *tertiary* radical XIV, as rearrangement was so extensive here. This argument is irrelevant, however, to the autoxidation rate and the acetone amounts produced and does not exclude the postulated greater hydrogen-donor ability of I.[35]

$$(CH_3)_3C{-}O\cdot \longrightarrow (CH_3)_2CO + CH_3\cdot$$
$$\xrightarrow{\text{solvent}} (CH_3)_3COH + (\text{solvent})\cdot$$

Temperature dependence. With a 50° increase in temperature, the rearrangement of II rose 2%, while that of I rose more than 12%, a six-fold greater response (all values relative to the 140° experiments, see Table V). The greater temperature dependence of rearrangement in I is in accord with the postulated greater $\Delta H^{\pm}$ here.[31] Calculations[36] show that the difference in activation enthalpies for rearrangement and abstraction processes with IXa (*i.e.*, $\Delta(\Delta H^{\pm}) = \Delta H^{\pm}_{\text{rearrangement}} - \Delta H^{\pm}_{\text{abstraction}}$ is ~1 kcal. mole^{-1} greater than the analogous difference with Xa.

Absence of bridged radicals. The neophyl rearrangement is not synchronous with decarbonylation as the amount of rearranged product is inversely related to the initial aldehyde concentration.[37] Active chain transfer agents (*e.g.*, mercaptans) also affect this rearrangement, allowing hydrogen abstraction by the unrearranged radical faster than does the aldehyde itself and consequently decreasing the extent of rearrangement.[38] The decarbonylations of I and II were investigated

(31) The work reported here does not allow a quantitative determination of entropic and enthalpic factors in these rates. An inspection of the above representations of the radicals involved (or their actual models), however, indicates that the transformation Xa → XIV would probably have a larger $-\Delta S^{\pm}$ than IXa → XIII, as both XI and XII are comparably constrained at the reaction zone, while Xa has a higher entropy (because staggered) than IXa (eclipsed). The *rate* for Xa → XIV is greater than IXa → XIII and therefore the former process would have the smaller $\Delta H^{\pm}$ for rearrangement at a given temperature.

(32) Ref. 5, p. 401.

(33) G. A. Russell, *J. Org. Chem.*, **24**, 300 (1959).

(34) Because equal mole per cents of initiator were ultimately present in each system, the acetone in the decarbonylation of II did not arise from thermal decomposition of excess initiator. In fact, the di-*t*-butyl peroxide was "in excess" with I more than II because initiation was so much more efficient in the former (see text).

(35) The lower hydrogen-donor ability of II is most probably steric in origin, although the exact nature of the effect is obscure. Speculatively, the axial position of the —CH_2CHO in II might render aldehydic hydrogen abstraction by bulky radicals (such as XIV) more difficult.

(36) See the doctoral thesis of Bro. H. Philip, F.S.C. (Loyola University), 1959, p. 61–62.

(37) F. H. Seubold, Jr., ref. 14. Other instances of rearrangement involving neophyl-like substances have also indicated that rearrangement is not concerted with radical generation, but rather is a step-wise process involving discrete unrearranged and rearranged radicals. See J. Weinstock and S. N. Lewis, *J. Am. Chem. Soc.*, **79**, 6243 (1957) and C. G. Overberger and H. Gainer, *J. Am. Chem. Soc.*, **80**, 4561 (1958).

(38) S. Lapporte, unpublished work mentioned by S. Winstein, R. Heck, S. Lapporte, and R. Baird, *Experientia*, **12**, 138 (1956); L. H. Slaugh, ref. 15.

in this regard also. Both concentration changes and added mercaptan did affect the extent of rearrangement noticeably (see Table V). A decrease in the initial concentration of I and II from the pure liquids (5.8 and 5.4*M*, respectively) to 1*M* solutions in chlorobenzene increased the rearrangement in each case to nearly the same value. These rearrangement percentages may be the limiting values in chlorobenzene, as this solvent does undergo radical attack itself[39] and could allow a path (although a more difficult one) for abstraction of hydrogen by the unrearranged radicals leading to unrearranged product. The addition of benzyl mercaptan lowered the percentage of rearrangement in both cases, although significantly less in II. The amount of mercaptan added (20 mole per cent) was much greater than that employed in earlier studies,[40] where concentrations of 3 mole per cent effected striking *catalysis* of decarbonylation. The reaction of the acyl radicals with excess mercaptan to regenerate the parent aldehyde would perhaps account for the *slower* rate and decreased percentage of carbon monoxide evolution observed under our conditions. Presumably the high concentration of thiol radicals that resulted in our cases also led to increased disulfide (dimer product), as reflected in the heavier pot residues in these runs (see Experimental). The merit of the excess mercaptan is seen, nonetheless, in the convincing demonstration that these rearrangements can be controlled dramatically in this manner. The virtual disappearance of rearrangement in I contrasts with the equalization of rearrangement and nonrearrangement with II. As hydrogen abstraction from I itself competed favorably in rate with the rearrangement of IXa, it is not surprising that abstraction from the much more active donor material, benzyl mercaptan, effectively swamped out the rearrangement process in this instance. With Xa, however, rearrangement was faster than the abstraction of hydrogen from II and, apparently even in the presence of mercaptan, proceeded at an equal rate with abstraction, illustrating the ease of skeletal rearrangement here. The effects of concentration changes and added mercaptan are thus those noted by others[37,38] for the neophyl rearrangement itself. Hence, in the present processes also the rearrangements proceed through the primary radicals (IXa and Xa), discretely produced and rearranging with a certain rate to the tertiary radicals (XIII and XIV). Bridged radicals, such as XI and XII, are not involved as reaction intermediates but probably as activated complexes in the transitions of the primary radicals during rearrangement.

Investigations are under way in other rearrangement reactions involving 1,2-phenyl shifts to see if the ring size effect 6>5 is operative to the same extent found in these decarbonylations.

(39) A. L. Beckwith and W. A. Waters, *J. Chem. Soc.*, 1665 (1957).

(40) K. E. Barrett and W. A. Waters, *Discussions Faraday Soc.*, **14**, 221, 255 (1953).

EXPERIMENTAL

All melting and boiling points are uncorrected. The combustion analyses were performed by the Galbraith Laboratories, Knoxville, Tennessee. Infrared spectra were determined on a Perkin-Elmer Model 21 Spectrophotometer with sodium chloride optics and were taken on the pure liquids unless otherwise stated. Vapor phase chromatographic work was done on a Perkin-Elmer Model 154 Fractometer using a silicone oil column. Because the synthetic steps followed were usually identical in both ring series, general descriptions of the procedures are given below. Several preparations of all the substances described were carried out, but the departures from the given procedure were slight.

2-Phenylcycloalkanones (III). 2-Phenylcyclopentanone was obtained by the method of Mousseron[41] and by that of Arnold.[42] The former method was found preferable, both in yield (70%) and in quality of product (colorless solid, m.p. 37–38°, semicarbazone m.p. 213–214° dec., lit.,[42] m.p. 37°, semicarbazone m.p. 213° dec.). 2-Phenylcyclohexanone was also obtained in two ways: the phenyl Grignard method of Newman[43] and the oxidation method of Price.[44] Neither route was very successful in our hands, although the latter was preferred because commercially available starting material could be used (Matheson, mixed *cis-trans* 2-phenylcyclohexanol). The ketone was obtained therefrom in a 70% yield, with 30% conversion, as a colorless solid (m.p. 64–65°, 2,4-dinitrophenylhydrazone, m.p. 137–138°, lit.,[44] m.p. 63°, 2,4-dinitrophenylhydrazone m.p.[43], 139°).

2-Phenyl-2-allylcycloalkanones (IV). The appropriate 2-phenylcycloalkanone (1 mole) in dry ether-benzene solution (1:1 by volume, 200 ml.) was added dropwise to a stirred, refluxing suspension of sodium amide (Farchan, 42.9 g., 1.1 moles) in more dry ether-benzene solution (200 ml.). Reflux was continued for 8 hr. To the cooled solution, allyl chloride (freshly distilled, 84 g., 89 ml., 1.1 moles) dissolved in further dry ether-benzene solvent (100 ml.) was added dropwise and with stirring. After 10 hr. of further reflux, water was added cautiously to the cooled mixture. The organic phase was separated, washed with water, and dried over sodium sulfate. The solvents were removed by distillation and the product ketones obtained by vacuum distillation of the residual oil. The physical constants, yield data, analyses, and derivatives of these substances are given in Table I. The infrared spectra of the products were consistent with their proposed structures, having carbonyl (5.75–5.85 μ) and unconjugated carbon-carbon unsaturation (6.09 μ) absorption. C-methyl absorption at 7.3 μ was absent, indicating no allyl to propenyl isomerization during this reaction.

1-Phenyl-1-allylcycloalkanes (V). The appropriate 2-phenyl-2-allylcycloalkanone (0.068 mole), diethylene glycol (90 ml.), hydrazine hydrate (85%, 33.5 ml.) and potassium hydroxide (12.9 g., 0.23 mole) dissolved in water (12 ml.) were refluxed together for three hours. Water was then removed by use of a Dean-Stark separator until the pot temperature reached 200°, whereupon reflux was continued for 6 hr. longer. The reaction mixture was cooled, poured into cold water (700 ml.), and extracted with ether. The extracts were washed with water and dried over sodium

(41) M. Mousseron, R. Jacquier, and H. Christol, *Compt rend.*, **236**, 927 (1953).

(42) R. T. Arnold, J. S. Buckley, and E. M. Dodson, *J. Am. Chem. Soc.*, **72**, 3154 (1950).

(43) M. S. Newman and M. D. Farbman, *J. Am. Chem. Soc.*, **69**, 1550 (1944).

(44) C. C. Price and J. V. Karabinos, *J. Am. Chem. Soc.*, **62**, 1160 (1940).

sulfate. Removal of the ether by distillation left the hydrocarbons as residual oil which was then fractionated. The physical properties of these substances are given in Table II. Their infrared spectra showed absorption at 6.09 μ (C=C) and a slight peak at 7.3 μ (C—CH_3). No trace of carbonyl absorption was present. The C—CH_3 absorption indicated allyl to propenyl isomerization had occurred under these reaction conditions. The weak intensity of the peak, however, indicated this isomerization was minor.

1-Phenyl-1-(β,γ-dihydroxypropyl)cycloalkanes (VI). Into the stirred 1-phenyl-1-allylcycloalkane (0.75 mole) in formic acid (88%, 100 ml.), a solution of hydrogen peroxide (Becco Chemical Division, Food Machinery and Chemical Corporation, 30%, 130 ml.) was added at a rate such that the temperature remained below 35°.[45] After the addition, the material was held at 35° for 1 hr. and then stirred for an additional 12 hr. Excess formic acid was removed by vacuum distillation and the residual oil held at 40° and 1 mm. pressure for 2 hr. more. The crude product (0.65 mole, calculated as diformate ester) was then taken up in dry ether (100 ml.) and added dropwise to a cold, stirred suspension of lithium aluminum hydride (0.64 mole) in dry ether (300 ml.). After the addition, the material was stirred for 2 hr. and then cautiously hydrolyzed with ice-cold hydrochloric acid (5%, 250 ml.). The organic layer was separated, washed with aqueous sodium bicarbonate (10%, 25 ml.), then water, and finally dried over sodium sulfate. The ether solvent was stripped off and the glycols then obtained as viscous oils by vacuum distillation. All attempts to crystallize these substances failed. The properties of the diols are given in Table II. A solid derivative, apparently the mono-*p*-nitrobenzenesulfonate, was obtained from VI-5. No solid derivatives were obtained from VI-6. Their infrared spectra showed broad absorption at 2.9–3.0 μ (O—H). No absorption remained at 6.09 μ (C=C), indicating the absence of the olefinic starting material.

1-Phenylcycloalkylacetaldehydes (I, II). Into a stirred solution of the appropriate 1-phenyl-1-(β, γ-dihydroxypropyl)-cycloalkane (0.51 mole) in benzene (300 ml.) was added a slurry of lead tetraacetate (Arapahoe, 226 g., 0.51 mole) in additional benzene (300 ml.). The reaction mixture was then stirred for 12 hr. and hydrolyzed with excess water. The organic phase was separated, washed with water, aqueous sodium bicarbonate (5%), again with water, and finally dried over sodium sulfate. The benzene was removed by distillation and the residual aldehydes were obtained by fractionation of the residues. The properties of these compounds are given in Table IV. Their infrared spectra showed absorption at 5.75–5.85 μ (C=O) and 3.65 μ (aldehyde C—H). The aromatic C—H rocking absorption (out-of-plane deformation) was found at 13.1 μ, in accord with a phenyl attached to a tertiary carbon (*i.e.*, a quaternary site). This correlation is developed further below.

Autoxidation of the aldehydes. The aldehydes were allowed to stand undisturbed in air (I, 12 hours; II, 7 days). The solid which formed was taken up in aqueous sodium hydroxide (10%). This solution was extracted with ether and the separated aqueous phase was then heated to remove the last traces of the ether. Acidification with dilute (10%) hydrochloric acid precipitated the corresponding acids in a crystalline state. Recrystallization was effected from ethanol. The yields of these products are included in Table IV.

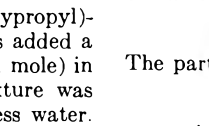
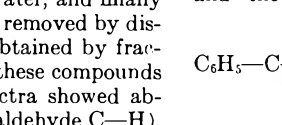
Preparation of the reference hydrocarbons. 1-Phenyl-1-methylcyclopentane (VII-5). The method of Sidorova and Dudnikova[46] was used to obtain this hydrocarbon (40%, b.p. 97° at 11.2 mm., n_D^{20} 1.5190, d_4^{20} 0.942; MR_D calcd. 51.9, found 51.6; lit.,[46] b.p. 110–112° at 25 mm., n_4^{20} 1.5193, d_4^{20} 0.9396). The aromatic C—H rocking absorption in the infrared spectrum was observed at 13.1 μ.

1-Phenyl-1-methylcyclohexane (VII-6). This substance was prepared by the method of Linsk[47] as a colorless oil (38%, b.p. 88° at 2 mm., n_D^{25} 1.525, d_4^{20} 0.946); MR_D calcd. 56.4, found 56.4; lit.,[47] b.p. 103° at 9.5 mm., n_D^{20} 1.5278. In the infrared spectrum the aromatic C—H rocking absorption was again found at 13.1 μ.

Benzylcyclopentane (VIII-5). This hydrocarbon was obtained by the Huang-Minlon reduction of phenyl cyclopentyl ketone.[48] To phenyl cyclopentyl ketone (8.7 g., 50 mmoles) in hydrazine hydrate (85%, 10 ml.) there was added a solution of potassium hydroxide (10 g., 180 mmoles) in diethylene glycol (70 ml.) and water (10 ml.). This mixture was refluxed for 1 hr. and the water was then removed with a Dean-Stark separator. Reflux was continued for 3 hr. at 190° (pot temperature), whereupon the material was cooled and poured into cold water (200 ml.). The water solution was treated with ether and the ether extracts were separated, washed, and dried. After removal of the ether, the hydrocarbon was distilled as a colorless oil (4 g., 50%, b.p. 80° at 3 mm., n_D^{20} 1.5180, d_4^{20} 0.930; MR_D calcd. 51.9, found 51.7; lit.,[49] b.p. 234–236° at 750 mm., n_D^{21} 1.5170, d_4^{21} 0.9283). The infrared spectrum of this hydrocarbon showed the aromatic C—H rocking absorption at 13.5 μ.

Benzylcyclohexane (VIII-6). The material used was obtained from K and K Laboratories, Long Island, N. Y. A wash with concd. sulfuric acid did not alter the infrared spectrum of this sample and the hydrocarbon was therefore used as received. The aromatic C—H rocking absorption was again noticed at 13.5 μ.

Determination of hydrocarbon structure by the 13.1 μ and 13.5 μ absorption. A correlation was observed in this work between the structure of a hydrocarbon and the position of its aromatic C—H out-of-plane deformation (rocking) absorption. Such correlations are not new, but this one was of value in the analytical process employed in this study.

The partial structure  always gave rise to the aromatic C—H rocking absorption at 13.1 μ, *e.g.*, I, II, and the pairs IV, V, and VI. The partial structure  however exhibited this absorption at 13.5 μ, *e.g.* VIII-5 and -6. While these absorption positions may not be unique to the partial structures shown, nonetheless the position of this absorption allowed a simple and ready distinction between unrearranged and rearranged hydrocarbons obtained in this study. A plot of the log transmission at 13.1 μ against the mole per cent of the 1-phenyl-1-methylcycloalkane (VII-5, -6) in mixtures with the appropriate benzylcycloalkane (VIII-5 or -6) gave a linear relationship over the concentrations of interest with a maximum deviation of 2.5% for the cyclopentyl compounds and 2.0% for the cyclohexyl compounds. The average deviation was 1.6% for the former and 1.3% for the latter.

Determination of hydrocarbon structure by the 7.3 μ absorption. Because the rearrangement of I gave appreciable unrearranged product (VII-5), an analytical method based on C—CH_3 absorption was devised. A plot of the log transmission at 7.3 μ (C—CH_3 absorption) against the mole

(45) On one occasion this temperature was apparently not adequately controlled and a violent (although not explosive) reaction ensued.

(46) N. G. Didorova and E. A. Dudnikova, *Zhur. Obshchei. Khim.*, **23**, 1399 (1953). *Cf. Chem. Abstr.*, **47**, 12268c (1953).

(47) J. Linsk, *J. Am. Chem. Soc.*, **72**, 4256 (1950).

(48) This ketone was kindly supplied by Dr. R. P. Mariella of this department and was a sample prepared as in R. P. Mariella and R. Raube, *J. Am. Chem. Soc.*, **74**, 521 (1952).

(49) Y. I. Denisenko, *J. Gen. Chem.* (*U.S.S.R.*), **9**, 1068 (1939). *Cf. Chem. Abstr*, **33**, 8578[2] (1939).

per cent of VII-5 in mixtures with VIII-5 was linear over the concentrations of interest with a maximum deviation of 1.0% and an average deviation of 0.7%. This served as a supplementary check on the analysis based on absorption at 13.1 μ. As II gave primarily rearranged product (little C—CH_3), this additional check was not used in the cyclohexane series.

Decarbonylation of the aldehydes (I and II). A solution of di-*t*-butyl peroxide (0.47 g., 0.6 ml., 3 mmoles, n_D^{20} 1.3890) in the appropriate aldehyde (I or II, 30 mmoles) was heated in a Wood's metal bath held at some constant temperature (see Table V for the specific temperatures used). Portions of more peroxide (to a limit of 9 mmoles) were added periodically, although such additions were not needed for I because of its rapid rate of decarbonylation. The gas liberated in the reaction was passed through a cold trap (−80°) and collected over water. Analysis of the gas for carbon monoxide was performed in a Fisher-Orsat apparatus using cuprous chloride absorbent. When no further gas was evolved, distillation was commenced under reduced pressure, all volatile materials being collected in the cold trap. The distillation was continued until the head temperature decreased, a temperature which in all cases was at least 20° below the boiling point of the parent aldehyde. The purification of the distillate from nonhydrocarbon contaminants was attempted by column chromatography, Girard-T separations, steam distillation, and permanganate oxidations. None of these methods were satisfactory. The distillate was, however, effectively and simply purified by the following technique: distillate (1 g.) was taken up in petroleum ether (10 ml.) and extracted twice with concd. sulfuric acid (10 ml.). The organic phase was separated and washed with sodium bicarbonate solution (10%), then with water, and dried over sodium sulfate. The solvent was removed at room temperature under reduced pressure and the residual oil held at 1 mm. for 5 min. This procedure was shown in control experiments not to affect the hydrocarbons VII and VIII in that the infrared spectra of the hydrocarbons and their mixtures were not altered. The purified hydrocarbons were then analyzed by use of infrared by comparison with the calibration curves obtained using authentic samples (see above). In one instance (an early experiment with II), vapor phase chromatography was employed in the analysis. The silicone oil column failed to resolve the hydrocarbon mixture at the temperature used (225°) although the curve obtained matched that of a synthetic mixture of VII-6 and VIII-6 made up in the proportions indicated by infrared analysis.

The acetone produced in each reaction was determined by the weight of its 2,4-dinitrophenylhydrazone derivatives obtained from the cold trap material: for experiment I-1 (0%), I-2 (0%); II-1 (37%), II-2 (41%), II-3 (37%), all based on the final amount of initiator used. No determinations were made in the other experiments.

The dilution experiments (I-3 and II-3) were performed as above except that the aldehyde (30 mmoles) was dissolved in distilled chlorobenzene (30 ml.). The experiments with mercaptan present (I-4 and II-4) were also performed as above, except that benzyl mercaptan (Eastman, 1.24 g., 10 mmoles) was added initially. The pot residues from all of these reactions were dark viscous materials ranging from 19–25% of the initial aldehyde weight in the case of I to 29–46% in the case of II. These figures do not include the experiments I-4 and II-4 where much of the residue was sulfur-containing material derived from the added mercaptan. The residues contained some unchanged aldehyde in every case as evidenced by the isolation of the correct 2,4-dinitrophenylhydrazone. Other than this, no further work was done on these residues.[50]

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(50) The possibility exists that dimeric hydrocarbons are present in these residues and that the relative rearrangement data might be thereby affected. Such dimer production has been reported by Curtin,[4] although such is normally not the course of the decarbonylation process because the concentration of radicals is kept low by the small amount of initiator present and by control of its rate of homolysis through the use of moderate temperatures for the decarbonylations. The intractable nature of these residues precluded effective work-up, but no crystalline or otherwise easily isolable substances appeared present.

[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY, THE UNIVERSITY OF CHICAGO]

Reactions of *t*-Butyl Peresters. II. The Reactions of Peresters with Compounds Containing Activated Hydrogens[1]

GEORGE SOSNOVSKY AND N. C. YANG

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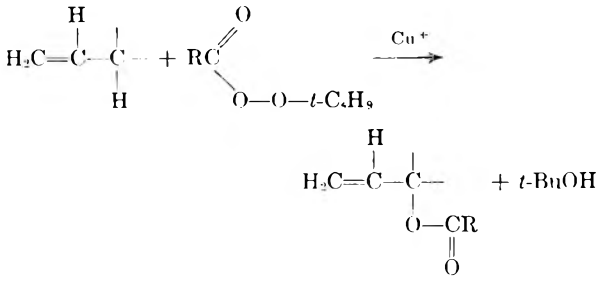
The reactions of *t*-butyl peresters with esters, ethers, aldehydes, ketones, tetralin, benzyl alcohol, dimethylaniline, and thiophenol were investigated. Cuprous bromide exerts a marked influence on both the nature and the rate in most of these reactions, and some of these reactions may be applied advantageously for preparative purposes.

In a previous communication, the reactions of *t*-butyl peresters with olefins in the presence of transition metal salts were described.[2] These reactions may be formulated as the displacement of an allylic hydrogen atom by an acyloxy group. Contrary to the results obtained by conventional free radical reactions, reactions with terminal olefins yielded only one type of allylic esters with terminal unsaturation. In the present investigation, the reactions of *t*-butyl peresters have been extended to substrates containing activated hydrogen atoms other than olefins. The compounds employed are esters, ethers, aldehydes, ketones, tetralin, benzyl alcohol, dimethylaniline, and thiophenol. Cuprous bromide was found to exert a

(1) This investigation was supported by a grant from the Office of Naval Research, Contract No. N6ori-02040. It was presented in part at the 134th Meeting of the American Chemical Society in Chicago, Illinois, September, 1958.

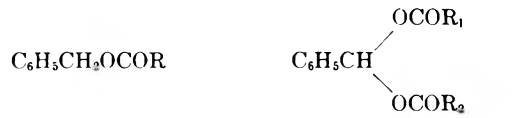
(2) M. S. Kharasch and G. Sosnovsky, *J. Am. Chem. Soc.*, 80, 756 (1958); M. S. Kharasch, G. Sosnovsky, and N. C. Yang, *J. Am. Chem. Soc.*, 81, 5819 (1959).



marked influence on both the nature and the rate in most of these reactions,[3] and some of these reactions may be used for preparative purposes

(a) *Reactions with ethers and esters.* Benzoyl peroxide[4] and *t*-butyl perbenzoate[5] decompose following first order kinetics in aromatic solvents. When the decompositions were carried out in aliphatic solvents, such as ethers and esters, the rate processes became more complex. The radicals derived from the solvents interacted with peroxides causing induced decomposition of the peroxy compounds, and the products of such interactions, acylals, had been isolated in few instances.[6] We found that the reaction of *t*-butyl peresters with ethers and esters bearing activated hydrogen atoms adjacent to the oxygen function may be advantageously used as a new method for the preparation of certain acylals.

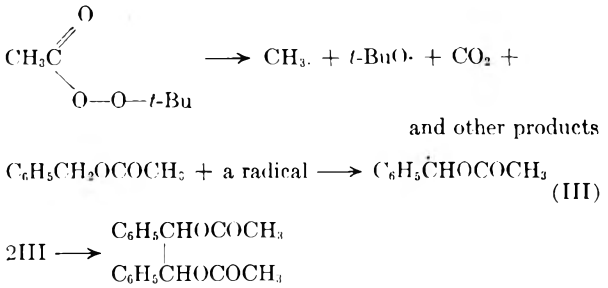
Benzyl acetate (Ia) reacts with *t*-butyl perbenzoate in the presence of cuprous bromide to give benzylidene acetate benzoate (IIa). The same product (IIa) is obtained from the reaction of benzyl benzoate (Ib) with *t*-butyl peracetate, and benzylidene diacetate (IIb) can be prepared from benzyl acetate and *t*-butyl peracetate. In the absence of a copper catalyst, the decomposition of *t*-butyl peracetate in benzyl acetate proceeds at a



Ia. R = CH_3
Ib. R = C_6H_5

IIa. $R_1 = CH_3$, $R_2 = C_6H_5$
IIb. $R_1 = R_2$, $R_2 = CH_3$

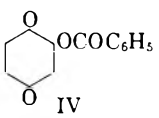
much slower rate and a typical free radical type of reaction takes place.[7] The principal product from the reaction is a 1,2-dihydrobenzoin ester besides much carbon dioxide. The glycol ester is presumably formed by the dimerization of the intermediate benzyl radical (III).



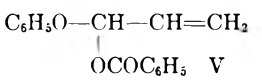
and other products

(III)

1,4-Dioxane reacts sluggishly with benzoyl peroxide after a prolonged heating of twenty one days at 40° to give a poor yield of dioxanyl benzoate (IV).[6] The reaction of dioxane with *t*-butyl perbenzoate remains incomplete after 72 hours of reflux, and only traces of IV are formed. These reactions may be accelerated, however, by the addition of cuprous bromide. The reaction of *t*-butyl perbenzoate and dioxane in the presence of cuprous bromide proceeds smoothly, and the product, IV, crystallized after one simple distillation. Under similar conditions, phenyl allyl ether gives 3-benzoyloxy-3-phenoxy-1-propene (V).

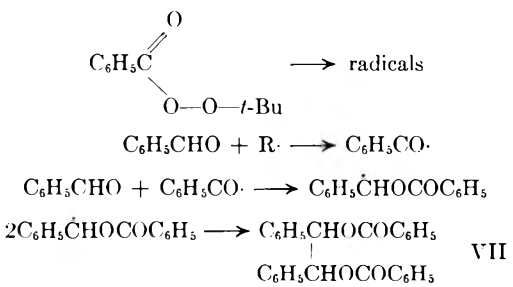


IV



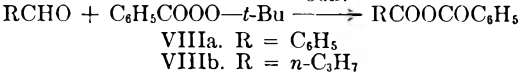
V

(b) *Reactions with aldehydes and ketones.* The decomposition of *t*-butyl perbenzoate in benzaldehyde corresponds closely to the decomposition of other peroxy compounds in the same solvent,[7] and dihydrobenzoin dibenzoate (VII) was found as the major product. Presumably VII is formed by the following reaction path.



VII

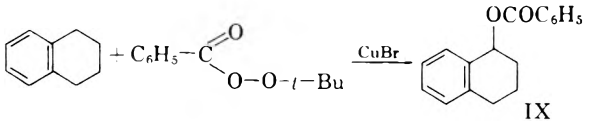
In the presence of cuprous bromide, benzaldehyde reacts smoothly with *t*-butyl perbenzoate to give benzoic anhydride (VIIIa), and butyraldehyde reacts with the same perbenzoate to give a mixture of anhydrides derived possibly from the disproportionation of the intermediate mixed anhydride (VIIIb). Under similar conditions, cyclohexanone and 2-methylcyclohexanone give good yields of benzoic acid and a small amount of high boiling material while the major portions of these ketones are recovered unchanged.



VIIIa. R = C_6H_5
VIIIb. R = n-C_3H_7

(3) M. S. Kharasch and A. Fono, *J. Org. Chem.*, **24**, 606 (1959).
(4) K. Nozaki and P. D. Bartlett, *J. Am. Chem. Soc.*, **68**, 1686 (1946).
(5) A. T. Blomquist, A. F. Ferris and I. A. Berstein, *J. Am. Chem. Soc.*, **73**, 3408, 3421, 5546 (1951).
(6) W. E. Cass, *J. Am. Chem. Soc.*, **69**, 500 (1947).
(7) F. F. Rust, F. H. Seubold, and W. E. Vaughan, *J. Am. Chem. Soc.*, **70**, 3258 (1948).

(c) *Reaction with tetralin.* *t*-Butyl perbenzoate reacts with tetralin in the presence of cuprous bromide to give 1-benzoyloxytetrahydronaphthalene (IX).

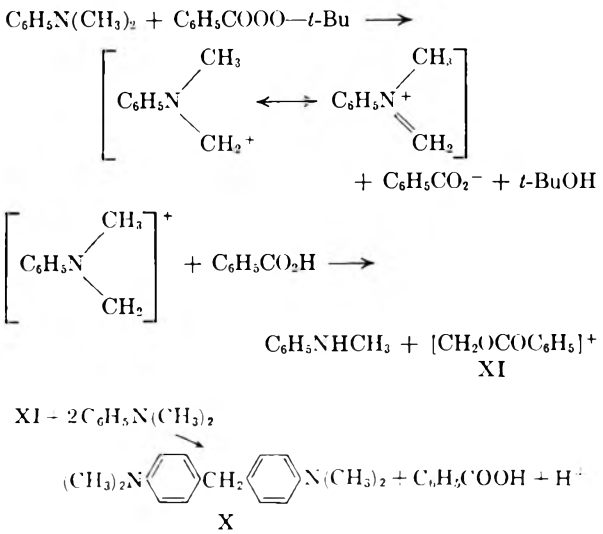


IX

(d) *Reaction with dimethylaniline.* It has been demonstrated thus far that transition metal salts play a significant role in the reactions of peresters. However, these metal catalysts exert no effect on the reaction of *t*-butyl perbenzoate with dimethylaniline, benzyl alcohol, or thiophenol.

A moderate yield of bis(*p*-dimethylaminophenyl)-methane (X) can be easily isolated by distillation from the reaction of *t*-butyl perbenzoate, and dimethylaniline as well as monomethylaniline is also detected in the reaction mixture. Horner and Betzel[8] obtained the same product (X) from the reaction of benzoyl peroxide and dimethylaniline. Their yield was lower (12%) and the method of isolation cumbersome.

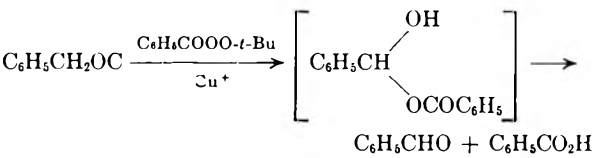
The formation of X from the reaction of benzoyl peroxide and dimethylaniline has been reviewed by Walling.[9] A similar mechanism may apply in the reaction of *t*-butyl perbenzoate with dimethylaniline, such that a one carbon fragment in the oxidation stage of formaldehyde is an intermediate with monomethylaniline as the by-product. This intermediate (XI) reacts with dimethylaniline to form X.



XI

(e) *Reaction with thiophenol.* There was no effect of copper salt on the oxidation of thiophenol to diphenyl disulfide by *t*-butyl perbenzoate. Diphenyl disulfide is formed by the dimerization of phenylmercapto radicals which are generated from the oxidation of thiophenol by a radical or cupric ion.

(f) *Reaction with benzyl alcohol.* *t*-Butyl perbenzoate reacts with benzyl alcohol to form benzaldehyde. A hemiacylal (XII) may be formulate as an intermediate which decomposes to give benzaldehyde and benzoic acid.



EXPERIMENTAL[10]

t-Butyl perbenzoate and *t*-butyl peracetate, purchased from Wallace Tiernan, Inc., were used without further purification. When freshly distilled peresters were used in these reactions, indistinguishable results were obtained.[2] The progress of the reactions was followed by periodic infrared analyses, and all experiments were conducted under an atmosphere of nitrogen.

General procedure for the reactions of peresters in the presence of cuprous bromide. *t*-Butyl perester (0.15–0.3 mole) was added over a period of 1 hr. to a stirring mixture of the substrate (0.27–0.5 mole) and cuprous bromide (0.1 g., 0.35 mmole) maintained at 105–110°. Heating was continued for 0.5 hr. after the perester band had disappeared from the infrared spectrum of the reaction mixture. The time required was approximately 3 hr. for *t*-butyl perbenzoate reactions and 17 hr. for *t*-butyl peracetate reactions. There was little or no gaseous evolution during these reactions. The cooled mixture was washed with 2*N* sodium carbonate followed by water. Benzoic acid might be recovered from the carbonate extract by neutralization. The products were isolated by distillation. The reactions were carried out in an excess of substrates which were partly recovered during the distillations. The results are tabulated in Table I and the listed yields were based on the amounts of peresters used.

Reaction of t-butyl peracetate and benzyl acetate. When benzyl acetate (0.5 mole) was treated with *t*-butyl peracetate (0.2 mole) in the absence of cuprous bromide according to the general procedure described previously, a different result was obtained. After 24 hr. of heating, the reaction mixture still contained 38% of unchanged perester. A large volume of gas was collected during the reaction. Following the usual work up, there were obtained unchanged benzyl acetate (0.34 mole), 13 g. of a high boiling residue, and 6 g. of dihydrobenzoin diacetate (IIb), b.p. 140–142° (0.2 mm.), m.p. 133° (from acetone) which was identical in all respects with an authentic sample.

Reaction of t-butyl perbenzoate and benzaldehyde. *t*-Butyl perbenzoate (0.2 mole) was added over a period of 1 hr. to benzaldehyde (0.5 mole) maintained at 115°. The reaction mixture was heated for 6 hr. During this period there was a continuous evolution of carbon dioxide (2 *l.*, 58%). The mixture was then diluted with benzene and the benzene solution from which benzoic acid (14 g., 58%) was recovered. During washing, a white solid separated between the aqueous and the organic layers. The solid (3 g.) was collected by filtration and washed well with hot acetone, m.p. 242–244°. It was identified as *meso*-dihydrobenzoic dibenzoate by comparison with an authentic sample.[7]

Reaction of t-butyl perbenzoate and dioxane. A mixture of

(8) L. Horner and C. Betzel, *Ann.*, **579**, 175 (1953).

(9) C. Walling, *Free Radicals in Solution*, John Wiley and Sons, New York, 1957, p. 590.

(10) Melting and boiling points are uncorrected. The molecular weights were determined cryoscopically in benzene.

TABLE I

Substrate (mole)	Perester (mole)	Benzoic Acid (%)	Yield Residue (g.)	Structure	Product, g.	%	B.P.	Mm.	n_D^{20}	M.P., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Mol. Wt. Calcd.	Mol. Wt. Found
Benzyl acetate (0.5)	Perbenzoate (0.2)	25		IIa	18.7	35	135–138	0.2		70–71	$C_{16}H_{14}O_4$	71.10	71.12	5.22	5.14	270	268
Benzyl benzoate (0.5)	Peracetate (0.3)		20	IIa	15.0	18											
Benzyl acetate (0.5)	Peracetate (0.3)		8.5	IIb	24.5	40	133–135	10		43.5–44.0	$C_{11}H_{12}O_4$	63.45	63.75	5.81	5.87	208	211
Phenyl allyl ether (0.27)	Perbenzoate (0.15)	8.5	8.5	V	19.0	50	110–112	0.15	1.5662		$C_{16}H_{14}O_3$	75.57	75.37	5.55	5.73	254	244
Benzaldehyde (0.5)	Perbenzoate (0.2)	17		Benzoic anhydride	32.0	70	140–142	0.2								226	228
Tetralin (0.4)	Perbenzoate (0.2)	86		IX	7.4	15	130–135	0.05	1.5780		$C_{17}H_{12}O_2$	80.92	80.92	6.39	6.71	252	248

t-butyl perbenzoate (0.2 mole), dioxane (0.5 mole), and cuprous bromide (0.1 g.) was allowed to react in the usual manner. The cooled reaction mixture was diluted with ether (100 ml.) and extracted with carbonate to remove benzoic acid (2.5 g., 10%). The ethereal solution was washed with water, dried over sodium sulfate, and concentrated on a steam bath. The remaining oil was distilled under reduced pressure. There were obtained 6 g. of a gummy residue and 23 g. (56%) of the product (IV), b.p. 105–107° (0.1 mm.), which crystallized upon standing, m.p. 54° (methanol) (lit.[6] b.p. 108–110° at 0.3 mm.).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; mol. wt., 208. Found: C, 63.29; H, 6.07; mol. wt., 211.

When the reaction was carried out in the absence of cuprous bromide, a different reaction was observed. The reaction mixture contained 3.5% of the unchanged perester after 72 hr. of reflux. Following the usual work up there were obtained 600 ml. of carbon dioxide, traces of IV, and 18 g. of an oily alkali soluble material consisting mainly of benzoic acid.

Reaction of benzoyl peroxide and dioxane in the presence of cuprous bromide. A mixture of dioxane (0.6 mole), benzoyl peroxide (0.1 mole), and cuprous bromide (0.1 g., 0.35 mmole) was stirred at 55–60° for 13 hr. The temperature was raised slowly until the mixture began to boil. After 4 hr. of reflux, the reaction mixture was worked up as described in the preceding experiment. There were obtained 13 g. (55%) of benzoic acid, 800 ml. of carbon dioxide, 4 g. of a gummy residue, and 7 g. (34%) of IV.

Reaction of t-butyl perbenzoate and n-butyraldehyde in the presence of cuprous bromide. *t*-Butyl perbenzoate (0.2 mole) was added to a refluxing mixture of butyraldehyde (0.6 mole) and cuprous bromide (0.1 g., 0.35 mmole) over a period of 45 min. After 2 hr. of reflux, the mixture was worked up by the usual procedure. There were obtained benzoic acid (5 g., 20.5%), butyric anhydride (4 g., b.p. 75–78° at 10 mm. and n_D^{20} 1.4150), benzoic anhydride (9 g., b.p. 125–128° at 0.1 mm. and n_D^{20} 1.5778), and an intermediate fraction (11 g.) which was shown to be a mixture of anhydrides by infrared spectral analysis.

bis(p-Dimethylaminophenyl)methane (X). Over a period of 2 hr., *t*-butyl perbenzoate (0.2 mole) was added to dimethylaniline (0.6 mole) maintained at 105–115°. After the reaction mixture had been heated for 2 additional hr., *t*-butyl alcohol, 9.5 g., b.p. 81°, n_D^{20} 1.3870, was removed by distillation. The remaining liquid was washed with a solution of 2*N* sodium carbonate to remove benzoic acid (23 g., 96%) followed by water, dried over sodium sulfate, and distilled at reduced pressure. There was obtained 29 g. of an oil consisting of mono- and dimethylaniline, b.p. 75° (10 mm.). An aliquot of this mixture (2.14 g.) was acetylated with acetic anhydride at room temperature, and 0.6 g. of *N*-methylacetanilide was obtained, m.p. 99° alone or admixed with an authentic sample. Further distillation of the reaction mixture gave, beside 10 g. of a high boiling residue, 16.5 g. (32%) of X, b.p. 155–157° (0.1 mm.) which solidified on standing, m.p. 89° (from petroleum ether). The compound is identical in all respects with an authentic sample.[8]

When the reaction was carried out in the presence of cuprous bromide, the same result was obtained.

Reaction of t-butyl perbenzoate and thiophenol. To thiophenol (0.5 mole) maintained at 105–115°, *t*-butyl perbenzoate (0.2 mole) was added over a period of 1 hr. After the mixture had been heated for another 2 hr., *t*-butyl alcohol (11 ml.) was removed by distillation. The residual mixture was then diluted with ether and extracted with a 2*N* solution of sodium carbonate to remove benzoic acid (22 g., 92%). The organic phase was concentrated under reduced pressure and the remaining solid was recrystallized from acetone. There were obtained 40 g. (90%) of diphenyl disulfide, m.p. 58.5–59.0°.

When the reaction was carried out in the presence of cuprous bromide, the same result was obtained.

Reaction of t-butyl perbenzoate and benzyl alcohol. When a mixture of *t*-butyl perbenzoate (0.2 mole) and benzyl alcohol (0.5 mole) was treated in the usual manner, there were obtained benzoic acid (24 g., 99%), benzaldehyde (7 g., identified through its 2,4-dinitrophenylhydrazone, m.p. 237°), recovered benzyl alcohol (15 g.), and a higher boiling fraction (13 g., b.p. 50–90° at 0.2 mm.) which was not further investigated. When this reaction was carried out in the presence of cuprous bromide, a similar result was obtained.

Acknowledgment. This work is a continuation of the reactions of *t*-butyl peresters initiated by the late Professor M. S. Kharasch to whom this work is dedicated. The authors are indebted to Mr. William Saschek for the microanalyses and to Mr. Ihor Masnyk for the molecular weight determination.

CHICAGO 37, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

γ-Radiation-Induced Addition of Aldehydes to Esters of Maleic, Fumaric, and Acetylenedicarboxylic Acids

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The γ-radiation (Co-60) initiated addition of aldehydes to maleates and fumarates gives acylsuccinates identical with those obtained with peroxide initiation. The reaction has been extended for the first time to additions with isobutyraldehyde and to the addition of aldehydes to acetylenedicarboxylates. Both radical and radiation initiation give products having a 2 3-diacyl structure from the acetylenedicarboxylates.

The radical initiated addition of aldehydes to maleates and fumarates has been described[1,2] using benzoyl peroxide and ultraviolet light as initiators. The only similar peroxide-initiated addition to an acetylenic bond that has been reported[3] is that with propionaldehyde and acetylene. We have studied these reactions using γ-rays from cobalt-60 as the initiator and wish to record the results of these studies at this time.

The γ-radiation induced addition of aldehydes to diethyl maleate takes place readily with butyraldehyde, isobutyraldehyde, and benzaldehyde. Yields from 14% (G = 9) for benzaldehyde, 27% (G = 35) for isobutyraldehyde, and 84% (G = 70) for butyraldehyde were observed at total dose levels of 17.4–27.6 megarep. The product from butyraldehyde, diethyl 2-butyrylsuccinate, was identical with that obtained by the peroxide initiated reaction.[1] On saponification it gave γ-oxoheptanoic acid, m.p. 50°.[4] Dimethyl fumarate gives the same product from butyraldehyde but in lower yield 36% (G = 23). The isobutyraldehyde product, diethyl 2-isobutyrylsuccinate, has not been described previously. It was obtained in liquid and solid (m.p. 134–136°) forms thought to be tautomeric.

The addition of aldehydes to acetylenedicarboxylic acids has not been described previously. It has been observed that butyraldehyde, isobutyraldehyde, and acetaldehyde add to dimethyl or diethyl acetylenedicarboxylate in yields varying from 9–31% with G values of 11–54 at total dose levels of 10.4–18.8 megarep. The product from acetaldehyde, diethyl 2,3-diacetylsuccinate, m.p. 90°, has been shown to have the 2,3-diacetyl structure by comparison with an authentic sample of this material, m.p. 89°, prepared by coupling ethyl acetoacetate.[5] The infrared spectra of the two samples are superimposable and identical in all respects. Identical products have also been obtained using peroxide initiation.

It is believed that these data indicate that the γ-radiation initiated addition of aldehydes to acetylenedicarboxylic ester proceeds *via* a free-radical mechanism. The first acyl radical to add

$$RCHO \longrightarrow RCO\cdot + H\cdot$$

$$RCO\cdot + R'O_2CC{\equiv}CCO_2R' \longrightarrow R'O_2C{-}\underset{\displaystyle COR}{\underset{|}{C}}{=}\dot{C}{-}CO_2R'$$

$$R'O_2C{-}\underset{\displaystyle COR}{\underset{|}{C}}{=}\dot{C}CO_2R' + RCHO \longrightarrow R'O_2C{-}\underset{\displaystyle COR}{\underset{|}{C}}{=}CHCO_2R' + RCO\cdot$$

$$R'O_2CC{=}CHCO_2R' + RCO\cdot \longrightarrow R'O_2C{-}\dot{C}{-}\underset{\displaystyle COR}{\underset{|}{C}}HCO_2R'$$

$$R'O_2C{-}\dot{C}{-}\underset{\displaystyle COR}{\underset{|}{C}}HCO_2R' + RCHO \longrightarrow RCO\cdot + R'O_2C{-}\underset{\displaystyle COR}{\underset{|}{C}}H{-}\underset{\displaystyle COR}{\underset{|}{C}}H{-}CO_2R'$$

(1) T. M. Patrick, *J. Org. Chem.* **17**, 1009 (1952).
(2) T. M. Patrick, *J. Org. Chem.* **17**, 1269 (1952).
(3) H. H. Schlubach, V. Franzen, and E. Dahl, *Ann.* **587**, 124 (1954).
(4) A. Franke and A. Kroupa, *Monatsh.* **69**, 167 (1936).
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gives an acyl maleate (or fumarate) as an intermediate which reacts with a second acyl radical to give the 2,3-diacyl structure. An ionic mechanism would presumably have resulted in the addition at the second stage to give a 2,2-diacyl structure.

EXPERIMENTAL[6]

Commercial samples of the aldehydes and esters were fractionated through 17-cm. columns packed with helices under partial take-off and dried before use. The dimethyl acetylenedicarboxylate was prepared from the commercial monopotassium salt of the acid with sulfuric acid as catalyst; b.p. 120°/20 mm., n_D^{24} 1.4432. The diethyl ester was prepared similarly; b.p. 123°/23 mm., $n_D^{24.5}$ 1.4405.

The radiations were made in vacuum dried 2.5 × 10 cm. glass tubes with 8 mm. inlet tubes. The reactants were placed in the tubes, frozen, evacuated, thawed, refrozen, and re-evacuated six to eight times to degas completely. The tubes were sealed under vacuum and irradiated at 22° in a standard source[7] at dose rates of 400,000–450,000 rep per hr. The source positions were calibrated with ferric-ferrous dosimetry and the G value calculated with the usual conversion constants.[8]

The infrared spectra were determined using a Baird double beam recording spectrometer with approximately 5% solutions in the stated solvents.

Diethyl 2-butyrylsuccinate. Butyraldehyde (20.2 g., 0.28 mole) and diethyl maleate (12.4 g., 0.072 mole) were degassed and irradiated for a total dose of 27.6 megarep. Fractionation gave 14.6 g. (84%; G = 70) of the product, b.p. 121°/1–2 mm., n_D^{25} 1.4344 leaving a residue (telomer) of 1.95 g. The product prepared as previously described[1] with peroxide initiation boiled at 125°/2 mm., n_D^{25} 1.4340. Infrared absorption characteristics of the two products were identical with a strong maximum in chloroform at 1720 cm.$^{-1}$ (keto carbonyl) and a shoulder at 1740 cm.$^{-1}$ (ester carbonyl). Saponification of the radiation product gave γ-oxoheptanoic acid, m.p. 50°; reported[4] m.p. 49.8°. Using diethyl fumarate in place of the maleate 5.4 g. (36%, G = 23) of the same product, b.p. 126°/2 mm., n_D^{25} 1.4345, and 8 g. of residue (telomer) were obtained. The molecular weight of the residue was 576 and its saponification equivalent 98.7 indicating a composition of three fumarate units to one aldehyde unit.

Diethyl 2-isobutyrylsuccinate. Isobutyraldehyde (15.4 g., 0.21 mole) and diethyl maleate (9.3 g., 0.054 mole) were degassed and irradiated for a total dose of 17.4 megarep. Fractionation gave 3.5 g. (27%, G = 35) of the product, b.p. 99°/2 mm.

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.16; H, 8.26.

Infrared absorption maxima in carbon tetrachloride are at 1721 cm.$^{-1}$ (keto carbonyl) and 1739 cm.$^{-1}$ (ester carbonyl).

Diethyl 2-benzoylsuccinate. Benzaldehyde (20.5 g., 0.193 mole) and diethyl maleate (7.2 g., 0.042 mole) were degassed and irradiated for a total dose of 25.9 megarep. Fractionation gave 1.66 g. (14%, G = 9) of the product, b.p. 159°/1 mm.; n_D^{27} 1.5012; reported[1] b.p. 158°/0.8 mm.; n_D^{25} 1.5028. Infrared absorption maxima in chloroform occur at 1686 cm.$^{-1}$ (keto carbonyl) and at 1730 cm.$^{-1}$ (ester carbonyl).

Dimethyl 2,3-dibutyrylsuccinate. Butyraldehyde (19 g.; 0.264 mole) and dimethyl acetylenedicarboxylate (9.35 g., 0.06 mole) were degassed and irradiated for a total dose of 10.4 megarep. Fractionation gave 4.3 g. (23%, G = 54) of product, b.p. 170–175°/2 mm. which solidified on standing. The oil gave a positive ferric chloride test; the crystals did not. Recrystallization from methanol-water gave crystals, m.p. 112.5°.

Anal. Calcd. for $C_{14}H_{22}O_6$: C, 58.72; H, 7.75. Found: C, 58.91; H, 7.71.

In other runs the solid separated from the crude reaction mixture. Yields of only 8% were obtained with equimolar ratios of reactants.

Dimethyl 2,3-dibutyrylsuccinate, m.p. 111°, was obtained in 22% yield by refluxing (87–94°) butyraldehyde with dimethyl acetylenedicarboxylate and benzoyl peroxide. The two products gave identical infrared spectra (keto and ester carbonyl absorption in carbon tetrachloride, at 1718 cm.$^{-1}$ and 1747 cm.$^{-1}$ (respectively) and showed no depression in melting point on admixture.

Dimethyl 2,3-diacetylsuccinate. Acetaldehyde (13.4 g., 0.304 mole) and dimethyl acetylenedicarboxylate (10.2 g., 0.072 mole) were degassed and irradiated for a total dose of 18.8 megarep. The residue left on evaporation of the excess acetaldehyde deposited a white solid which was collected and found to be identical with a fraction obtained from the oil, b.p. 120–135°/1 mm., which also solidified, m.p. 148°, from methanol-water. The total yield was 5.1 g. (31%, G = 54).

Anal. Calcd. for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.00; H, 6.15.

Diethyl 2,3-diacetylsuccinate. Replacing the dimethyl with the diethyl ester in the preceding experiment gave 4.4 g. (26%, G = 46) of crude product. Recrystallization from ligroin and from 50% acetic acid gave the pure product, m.p. 90°.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.8; H, 7.03. Found: C, 55.87; H, 7.09.

Diethyl 2,3-diacetylsuccinate, m.p. 89°, was also prepared as previously described[5] from ethyl acetoacetate, sodium, and iodine. The infrared spectra, in carbon tetrachloride, of the two samples were superimposable with carbonyl absorption at 1724 cm.$^{-1}$ (keto carbonyl) and 1747 cm.$^{-1}$ (ester carbonyl) and the melting points showed no depression on admixture.

Diethyl 2,3-diisobutyrylsuccinate. Isobutyraldehyde (16.2 g., 0.225 mole) and diethyl acetylenedicarboxylate (8.6 g., 0.051 mole) were degassed and irradiated for a total dose of 17.4 megarep. Fractionation gave a crude product, b.p. 127–134°/2 mm. which was refractionated to give 1.4 g. (9%, G = 11), b.p. 112°/1 mm.

Anal. Calcd. for $C_{16}H_{26}O_6$: C, 61.13; H, 8.33. Found: C, 61.27; H, 8.08.

A solid, m.p. 134–136°, separated from the refractionated material. The solid gave a positive ferric chloride test, whereas the liquid gave only a faint test, and is presumed to be a tautomeric form of the product. Infrared absorption maxima in carbon tetrachloride occur at 1712 cm.$^{-1}$ (keto carbonyl) and 1739 cm.$^{-1}$ (ester carbonyl).

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LOUISVILLE 8, KY.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE VIRGINIA POLYTECHNIC INSTITUTE]

Synthesis and Reactions of Some 9-Trichloromethyl-9,10-dihydroanthracenes[1,2]

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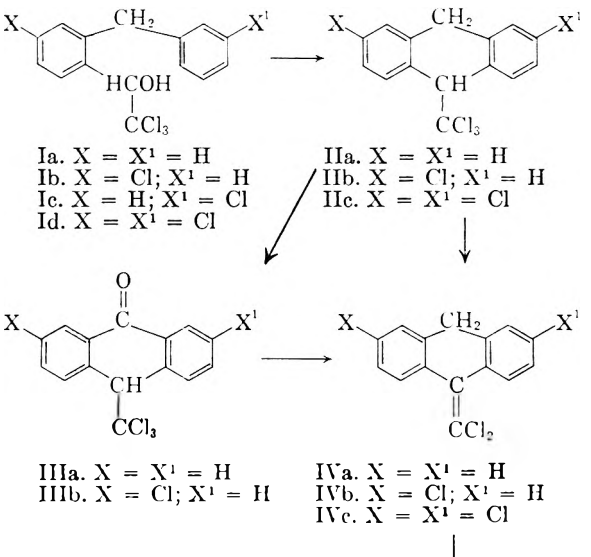
A series of new 9-trichloromethyl-9,10-dihydroanthracenes, which can be considered as analogues of the DDT-type molecule, have been prepared and several of their reactions studied. From the toxicity data against German cockroaches it would appear that these compounds have little if any insecticidal activity.

In connection with our preparation of compounds which are structurally and chemically analogous to the DDT-type molecule,[3,4] we have prepared a new series of 9-trichloromethyl-9,10-dihydroanthracenes (IIa–IIc). Essentially, the structural difference between DDT and the compounds under investigation is that of a methylene bridge linked across the positions of DDT *ortho* to the trichloromethyl moiety.

Although much work has been done in an attempt to relate structure to activity in the case of DDT,[5] it is still not possible to present a completely satisfactory theory of general applicability. Hass *et al.*[6,7] concluded that ascribing the quasi-independent toxic and lipoid-solubilizing properties to parts of the DDT molecule, as was done by many authors, is untenable and that the whole molecule must be considered *per se*. We thought compounds of the type II would be especially interesting to study in view of the suggestion of Riemschneider and Otto[8] and the important characteristics for the toxicity of compounds related to DDT are: molecular weight between 270 and 450; melting point below 180°; good lipoid solubility; and the type, number, and position of auxocontact substituents in the contactophore rings. Compounds of the type II meet all these requirements for high insecticidal activity.

Cyclization of Ia–Id[3] was effected essentially by the method of Ray *et al.*[9] The carbinol was heated with phosphoric anhydride, *in vacuo*, followed by distillation of the product from the reaction mixture. It was interesting to find that the cyclization could not be accomplished with sulfuric acid,[10,11] alumina,[12] or polyphosphoric acid.[13] The highest yield of IIa *via* phosphoric anhydride was obtained by carrying out the reaction in the dry state (61%); with xylene (45%); with toluene (7%). Thus all following cyclizations were carried out in the dry state. As was anticipated, cyclization of Ib under these conditions gave a comparable yield (54%) of IIb.



Ia. X = X¹ = H
Ib. X = Cl; X¹ = H
Ic. X = H; X¹ = Cl
Id. X = X¹ = Cl

IIa. X = X¹ = H
IIb. X = Cl; X¹ = H
IIc. X = X¹ = Cl

IIIa. X = X¹ = H
IIIb. X = Cl; X¹ = H

IVa. X = X¹ = H
IVb. X = Cl; X¹ = H
IVc. X = X¹ = Cl

Va. X = X¹ = H
Vb. X = Cl; X¹ = H
Vc. X = X¹ = Cl

On examination of the structure of Ic cyclization could be seen to afford two products, the desired

(1) Presented before the Division of Organic Chemistry at the 136th Meeting of the American Chemical Society, Atlantic City, New Jersey, September, 1959.

(2) This paper has been abstracted from the Doctorate thesis of P. E. Newallis presented to the Virginia Polytechnic Institute in 1957.

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product IIb and one corresponding to cyclization into the position *ortho* to the chlorine substituent. Only the desired product, IIb, was obtained, *albeit* in low yields (26%). As expected, this cyclization into a ring containing a chlorine atom results in a marked decrease in yield.

Similarly, cyclization of Id could be expected to result in the formation of two products. Apparently this was the case, as a yield of 27% of a mixture was realized. The desired compound, IIc, was obtained after the mixture was chromatographed on alumina and recrystallized numerous times from ethanol. As the known anthraquinone Vc was obtained as the oxidation produce of IIc, the positions of the chlorine atoms were established.

Attempted oxidation of IIa with either selenium dioxide or alkaline potassium permanganate yielded starting material along with a trace of the quinone Va. Heating IIa with a potassium dichromate–acetic acid mixture under reflux conditions gave 28% of anthrone IIIa. Employing a chromic anhydride–acetic acid mixture resulted in an increase in the yield of anthrone IIIa to 60%. Compound IIb was oxidized in the same manner to IIIb in 71% yield. Apparently, the trichloromethyl group exerts a stabilizing effect which makes the adjacent carbon atom resistant to oxidation.[14]

Dehydrochlorination of IIa with alcoholic potassium hydroxide under reflux conditions gave only a yellow gum. A good yield (89%) of IVa could be realized however, by heating a pyridine solution of IIa under reflux for twenty-four hours. Compound IVb was obtained in 75% yield in like manner. Compound IVc, which contains the dichloromethylene group, was not isolated but was subjected to oxidation. Our only interest in compounds IVa–IVc was that they provided a good means of preparing the anthraquinones which were needed for proof of structure.

The oxidation of compounds IVa–IVc with a chromic anhydride–acetic acid mixture proceeded smoothly and in fair yields, Va (42%), Vb (54%), and Vc (53%).

Entomological testing[15] of the new DDT analogs was undertaken by Dr. James M. Grayson and his staff at the Virginia Polytechnic Institute Entomology Department using standard methods of assay. From the toxicity data against German cockroaches it would appear that the new compounds have little if any insecticidal activity.

This work corroborates the view of many workers in this field that the correlation of chemical structure with insecticidal activity is a complex problem. It also indicates that hypotheses assigning specific properties to portions of the molecule are of doubtful value and that the entire molecule must be considered as a unit. Of the compounds prepared and tested, 2,7-dichloro-9-trichloromethyl-9,10-dihydroanthracene (IIc) has the strongest structural semblance of the DDT molecule. It also fulfills most of the requirements proposed for insecticidal activity by various authors, yet this compound is inactive.

Although any conclusion regarding the inactivity of IIc drawn at this time would necessarily be speculative, we feel that the ease of dehydrochlorination exhibited by IIc may be pertinent and that a detoxification mechanism *via* premature dehydrochlorination is a plausible explanation for the failure of IIc to show insecticidal activity.

EXPERIMENTAL[16,17]

9-Trichloromethyl-9,10-dihydroanthracene (IIa). A mixture of 4.35 g. (0.014 mole) of the alcohol Ia[3] and 4.35 g. (0.032 mole) of phosphoric anhydride was heated *in vacuo* (5 mm.) in a metal bath kept at 130–140° for 1 hr. The temperature of the bath was then gradually raised so that a yellow oil distilled. This oil crystallized on standing for a few minutes and was recrystallized from ethanol (Norit) yielding white needles, m.p. 122–123°; yield 2.48 g. (60%). The compound displayed a weak green fluorescence in ethanol and was only slightly soluble in concd. sulfuric acid.

Anal. Calcd. for $C_{15}H_{11}Cl_3$: C, 60.53; H, 3.73. Found: C, 60.35; H, 3.86.

2-Chloro-10-trichloromethyl-9,10-dihydroanthracene (IIb). A. *Via* Ib. This compound (IIb) was prepared using substantially the procedure given above for IIa with Ib being used in place of Ia. The product (54%) melted at 107.5–108.5°.

Anal. Calcd. for $C_{15}H_{10}Cl_4$: C, 54.25; H, 3.04. Found: C, 54.47; H, 3.06.

B. *Via* Ic. Repeating the above experiment using Ic as the starting material instead of Ib gave the same product (IIb) (26%), m.p. 107.5–108.5°. A melting point determination of a mixture of this product with that obtained from Ib showed no depression.

2,7-Dichloro-10-trichloromethyl-9,10-dihydroanthracene (IIc). This compound was prepared using substantially the procedure given above for IIa. This gave a mixture (27%) which was chromatographed in the usual way on alumina using petroleum ether (b.p. 30–60°) as the eluent. This gave a solid, m.p. 142–146°, which after fifteen recrystallizations from ethanol gave long, fine white needles, m.p. 152–153°.

Anal. Calcd. for $C_{15}H_9Cl_5$: C, 49.15; H, 2.48. Found: C, 49.17; H, 2.58.

9-Keto-10-trichloromethyl-9,10-dihydroanthracene (IIIa). A mixture of 1.0 g. (0.003 mole) of IIa, 3.5 g. (0.035 mole) of chromic anhydride,[18] and 35 ml. of glacial acetic acid was heated under reflux for 6 hr. This was poured into an ice

(14) The DDT molecule was also found to be resistant to oxidation when a chromic anhydride–acetic acid mixture was employed under reflux conditions. However, oxidation to the corresponding benzophenone was effected *via* the ethylenic derivative under comparable conditions. O. Grummitt, A. Buck, and A. Jenkins, *J. Am. Chem. Soc.*, **67**, 155 (1945).

(15) Dr. James M. Grayson of the Entomology Department at the Virginia Polytechnic Institute was responsible for conducting the assays. We are grateful to him for this work.

(16) All melting points were taken on a Fisher-Johns melting point block and are uncorrected.

(17) All analyses were carries out by the Micro-Tech Laboratories, Skokie, Illinois.

(18) In another experiment, the ratio of chromic anhydride to the dihydro compound was 5 to 1. A small amount of anthraquinone was isolated in addition to the main product.

water mixture and the greenish solid was filtered. The solid was washed with water and recrystallized from ethanol (Norit). Colorless rods, m.p. 172–174°, were obtained; 0.54 g. Concentration of the mother liquor gave an additional 0.09 g. A total of 0.63 g. (60%) was obtained.

An analytical sample was obtained by repeated recrystallization from ethanol; m.p. 177–178°.

Anal. Calcd. for $C_{15}H_9Cl_3O$: C, 57.82; H, 2.91. Found: C, 57.87; H, 3.34.

2-Chloro-9-keto-10-trichloromethyl-9,10-dihydroanthracene (IIIb). This compound was prepared using substantially the procedure given above for IIIa. The product, IIIb, (71%) melted at 144–145° (from ethanol).

Anal. Calcd. for $C_{15}H_8Cl_4O$: C, 52.06; H, 2.33. Found: C, 51.83; H, 2.21.

Preparation of 9-dichloromethylene-9,10-dihydroanthracene (IVa) *and oxidation to* Va. A mixture of 0.4 g. of the dihydro compound IIa and 20 ml. of anhydrous pyridine was protected from moisture and heated under reflux for 24 hr. The mixture was poured into an ice water mixture. The white precipitate was filtered and recrystallized from ethanol to give 0.18 g. of white needles, m.p. 84–86°. Concentration of the mother liquor gave an additional 0.13 g. for a total yield of 0.31 g. (89%).

A mixture of 0.12 g. of the above olefin, 0.6 g. of chromic anhydride, and 10 ml. of glacial acetic acid was heated under reflux for 4 hr. Worked up in the usual way this mixture gave 42% of the known anthraquinone Va; m.p. 282–284°.

2-Chloro-10-dichloromethylene-9,10-dihydroanthracene (IVb). This compound was prepared using substantially the procedure given above for IVa. The dihydro compound IIb on dehydrohalogenation with pyridine gave IVb (75%); m.p. 131–132°.

Anal. Calcd. for $C_{15}H_9Cl_3$: C, 60.94; H, 3.07. Found: C, 60.74; H, 3.12.

Oxidation of 2-chloro-10-dichloromethylene-9,10-dihydroanthracene (IVb). This oxidation was effected using chromic anhydride in substantially the way IVa was oxidized. The yield of the known 2-chloroanthraquinone (Vb), m.p. 212–213° was 54%.

Dehydrohalogenation of 2,7-dichloro-10-trichloromethyl-9,10-dihydroanthracene (IIc) *and subsequent oxidation to* Vc. The dihydrocompound IIc was dehydrohalogenated with pyridine as was IVa above. The tan solid was then oxidized with chromic anhydride in 53% yield to the known 2,7-dichloroanthraquinone, m.p. 231–232°.

BLACKSBURG, VA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY]

Addition of Halogens and Halogen Compounds to Allylic Chlorides. IV. Effect of Reactivity upon the Orientation of Electrophilic Olefinic Addition

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The orientation of electrophilic olefinic addition is governed by the various electronic effects (such as electromeric, hyperconjugative, and inductive) which are in turn influenced both by the presence of substituents in the olefinic compound and by the nature of the electrophilic reagent. Three generalizations summarize the experimentally observed behavior with a series of allylic chlorides and related compounds: (1) When both the reagent and the olefinic compound are of low reactivity, the orientation is controlled by electromeric or hyperconjugative electron displacements. If this type of displacement cannot be induced, the orientation is controlled by the inductive effect. (2) When either the reagent or the olefinic compound is of high reactivity, the orientation is controlled chiefly by the inductive effect, although hyperconjugative effects may also be involved. (3) When both the reagent and the olefinic compound are of high reactivity, the normal orientation is controlled by the inductive effect, plus a certain amount of random orientation. Increasing the number of chlorine atoms in the allylic position does not appear to reduce the electron density of the double bond sufficiently to alter the nature of the attack by electrophilic reagents.

The literature of organic chemistry provides an abundance of information on the orientation and mechanism of additions of halogen and halogen compounds to unsaturated compounds containing various kinds and numbers of substituents. Some apparent contradictions and inconsistencies in the results reported prompted the present investigation of the addition of halogens and halogen compounds to a selected series of allylic chlorides and related compounds. Part I of this series of papers[2] was concerned with the addition of hydrogen chloride and hydrogen iodide, Part II dealt with the additions of hypochlorous acid, and Part III involved a study of the relative rates of halogen addition. The object of this concluding paper of the series is to review the experimental results and point out the relationships and possible theoretical interpretations of the data. A comparison of olefinic addition and certain aspects of aromatic substitution will be made as an aid to the interpretation of the observed behavior.

DISCUSSION

Effect of allylic halogen. The principal products obtained by the addition of hydrogen chloride, hydrogen iodide, and hypochlorous acid to a series of allylic chlorides and related compounds are summarized in Table I. The addition of hydrogen chloride and hydrogen iodide to propene is according to Markownikoff's rule. Similar orientation of the additions of hydrogen chloride and hydrogen iodide is observed in the case of allyl chloride in

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(2) Part I, *J. Org. Chem.*, **23**, 1876 (1958); Part II, *J. Org. Chem.*, **24**, 1271 (1959); Part III, *J. Org. Chem.*, **25**, 428 (1960).

TABLE I

ADDITION PRODUCTS OF ALLYLIC CHLORIDES AND RELATED COMPOUNDS

Reagents	HCl	HI	HOCl (Cl^+)	
			Primary Chloride	Secondary Chloride
Propene	$CH_3—CH(Cl)—CH_3$	$CH_3—CH(I)—CH_3$	$ClCH_2—CH(OH)—CH_3$ 90%	$CH_3(OH)—CH(Cl)—CH_3$ 10%
Allyl chloride	$CH_3—CH(Cl)—CH_2Cl$	$CH_3—CH(I)—CH_2Cl$	$ClCH_2—CH(OH)—CH_2Cl$ 30%	$CH_2(OH)—CH(Cl)—CH_2Cl$ 70%
3,3-Dichloropropene	$ClCH_2=CH—CH_2Cl$[a]	$CH_3—CH(I)—CHCl_2$	$ClCH_2—CH(OH)—CHCl_2$ 2%	$CH_2(OH)—CH(Cl)—CHCl_2$ 98%
3,3,3-Trichloropropene	$Cl_2C=CH—CH_2Cl$[a]	$ICH_2—CH_2—CCl_3$	...	$CH_2(OH)—CH(Cl)—CCl_3$ 100%
1,3-Dichlorochloropropene	...	$I(Cl)CH—CH_2—CH_2Cl$	$Cl_2CH—CH(OH)CH_2Cl$	...
1,1,3-Trichloropropene	...	$I(Cl_2)C—CH_2—CH_2Cl$	$Cl_3C—CH(OH)CH_2Cl$	...

[a] Isomerized product.

spite of the electron-attracting effect of the *alpha* chlorine atom which might be expected to polarize the double bond in the opposite direction. This has been explained[3] on the basis that the hyperconjugative effect associated with the *alpha* hydrogen atoms is the controlling factor, and makes electrons available at the demand of the electrophilic reagent.

Under the experimental conditions employed, hydrogen chloride added only with difficulty to 3,3-dichloropropene, and no addition product was obtained with 3,3,3-trichloropropene. This inactivity may be attributed in part to the deactivating effect of the additional allylic halogen. The inertness of this compound to electrophilic addition has been confirmed by others.[4] The products isolated in each case were isomers of the starting material resulting from an allylic rearrangement:

$$CH_2=CH—CHCl_2 \rightleftharpoons [CH_2=\overset{\frown}{CH}—CHCl]^+ Cl^- \rightleftharpoons ClCH_2—CH=CHCl$$

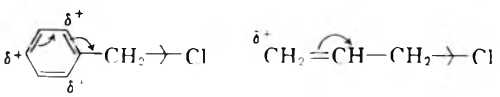
This isomerization (which may result from a nucleophilic attack by chloride ion) provides an additional explanation for the decreased reactivity toward addition of electrophilic reagents since a strongly deactivating vinyl halide is formed.

Allylic isomerization also was observed in the presence of hydrogen iodide, but by using a large excess of hydrogen iodide, addition to the allylic chlorides was effected in each case. However, the excess hydrogen iodide tended to reduce a portion of the product to the corresponding chloroalkane. The addition products of hydrogen iodide to propene, allyl chloride, and 3,3-dichloropropene are all secondary iodides and again illustrate the controlling influence of the hyperconjugative effect. With 3,3,3-trichloropropene, a primary iodide was obtained as a result of the strong inductive electron-attracting effect of the $—CX_3$ group in the absence of *alpha* hydrogen. This finding is in accord with Henne and Kay's[5] observation on the addition of hydrogen chloride to 3,3,3-trifluoropropene.

The results obtained with hypochlorous acid as shown in Table I are quite different from those obtained with hydrogen chloride and hydrogen iodide. With propene, allyl chloride and 3,3-dichloropropene, two products were obtained by attack of the positive halogen of hypochlorous acid on both primary and secondary carbon atoms. The relative amount of primary alcohol formed (as a result of initial attack of positive halogen on the secondary carbon) increases in a regular manner with the number of allylic chlorines present in the starting material. This increasing trend is analogous to the increase in the amount of *meta* substitution observed in aromatic substitution with the corresponding benzylic chlorides in the series from toluene to benzotrichloride.

The orientations in electrophilic aromatic substitution and in electrophilic addition to allylic halides (as well as to other olefinic compounds) are thus governed by the same electronic effects. The inductive effects and hyperconjugation appear to be the controlling factors. In propene and toluene the two effects supplement each other, but in the benzylic and allylic compounds the direction of the two effects are opposite (+T and −I):

Inductive effect (−I)

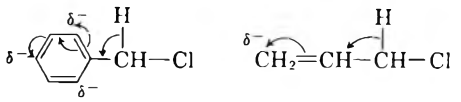


(3) E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., New York, 1954. (a) p. 76; (b) p. 364.

(4) A. N. Nesmeyanov, R. Kh. Friedlina, L. I. Zakharkin, V. N. Kost, R. G. Petrova, A. B. Belyavsky, and A. B. Terentiev in *Vistas in Free-Radical Chemistry* by W. A. Waters, Pergamon, New York, 1959, pp. 235–41.

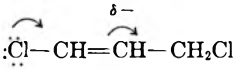
(5) A. L. Henne and S. Kay, *J. Am. Chem. Soc.*, 63, 2558 (1941).

Hyperconjugative effect (+T)

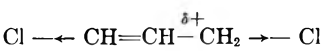


With an increase in the number of electron-attracting substituents on the *alpha* carbon atom, the inductive effect increases, while the opportunity for hyperconjugation decreases with the diminishing number of *alpha* hydrogens. This change is reflected in the increasing amount of *meta* substitution in benzylic halides and in the increasing amount of primary alcohol in the addition products of hypochlorous acid with allylic halides. In 3,3,3-trichloropropene (and benzotrichloride) only the −I effect remains. This is confirmed by similar results reported for the addition of hypobromous acid to this compound.[4]

Effect of vinylic halogen. The effect of vinylic halogen in combination with allylic halogen upon the orientation and rate of addition was also investigated. The retarding effect upon rate is discussed in Part III,[2] and the effect upon orientation is included in Table I. With hydrogen iodide addition, the entering halide went to the carbon atom to which the vinyl halogen was attached in each case, as is usually observed. Thus, while hyperconjugation appeared to control the addition of hydrogen iodide to allyl chloride, in the case of 1,3-dichloropropene and 1,1,3-trichloropropene, the electromeric effect associated with the vinyl halogen (and induced by the electrophilic reagent at the moment of attack) appeared to be the predominant effect.



The addition of hypochlorous acid to these same two compounds containing vinyl halogen along with allylic halogen was more difficult and gave opposite results in that attack by the electrophilic reagent was on the carbon atom bearing the vinyl halogen. This result can be explained on the basis of the combined inductive effects of both the vinylic and allylic halogen which lower the electron density around the central carbon and thus serve to direct the electrophilic attack to the other end of the double bond. The strong inductive



effect of the vinylic halogen has been shown in Part III[2] and by others[6a] to be 1000 times more effective than allylic halogen in deactivating the double bond. The fact that a change in the nature of the reagent can change the relative importance of the electronic effects which govern the mode of addition to a given olefin requires further explanation.

Effect of nature and reactivity of reagent. A comparison of the results in Table I with hydrogen iodide and hypochlorous acid shows other instances in which a change in the nature of the reagent changes the point of electrophilic attack. For example with hypochlorous acid two products were obtained with propene, allyl chloride, and 3,3-dichloropropene where hydrogen iodide gave predominantly single products. With both allyl chloride and 3,3-dichloropropene hydrogen iodide gave evidence of initial electrophilic attack on the primary carbon while hypochlorous acid attacked predominantly on the secondary carbon. De la Mare and Pritchard[7] demonstrated that a small portion of the chlorohydrin with the primary alcohol group formed by addition of hypochlorous acid to allyl chloride comes from exchange of the substituent and entering groups, and suggested that the rest of the product could be explained by a migration of the entering group from the point of initial attack to the neighboring carbon. An alternative explanation is available in terms of the effect of the nature and reactivity of the reagent upon the relative contribution of the various electronic effects involved.

Brown and his co-workers[8,9] have found that the nature and reactivity of the reagent is an important factor in determining the isomer distribution in electrophilic aromatic substitution. In a similar way, a highly reactive reagent like the Cl^+ ion from hypochlorous acid might be expected to show less selectivity in electrophilic addition to reactive olefinic compounds, such as propene, due to an increased random attack to form both possible isomers. This is in accord with the results in Table I for hypochlorous acid addition as compared with the addition of the less reactive halide molecules.

Higher reactivity may also reduce the necessity of a stage of rigorous polarization of the π-electrons of the double bond prior to reaction. This would explain why the mode of addition of hypochlorous acid to allylic chlorides appears to be mainly controlled by the permanent inductive effect rather than by conjugative effects induced at the time of reaction.

Electrophilic mechanism. The interpretation of the experimental results obtained in this series of studies is based on the assumption that the attack is electrophilic in each case. As the number of allylic halogens is increased, the electron density of the double bond is reduced so that the possibility

(6) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953. (a) p. 667; (b) p. 666; (c) p. 650, Hughes and Peeling, unpublished work. (d) p. 258, Cohn, Hughes, and Jones, unpublished work.

(7) P. B. D. De la Mare and J. G. Pritchard, *J. Chem. Soc.*, 3910, 3990 (1954).

(8) H. C. Brown and K. L. Nelson, *J. Am. Chem. Soc.*, **75**, 6292 (1953).

(9) H. C. Brown and C. W. McGary, Jr., *J. Am. Chem. Soc.*, **77**, 2300, 2306, 2310 (1955).

of a change in the nature of the reaction from electrophilic to nucleophilic attack by the reagent must be considered. Two evidences suggest that the nature of the attack remained unchanged. First, the addition of bromine[10] to the di- and trichloropropenes was found to be slower than that of chlorine (Part III).[2] Second, no evidence of addition of nucleophilic reagents, such as sodium bisulfite and ammonia to 3,3-dichloropropene and 3,3,3-trichloropropene was found in this study.

Some instances of nucleophilic attack on allylic halides have been reported. For example, 3,3,3-trifluoropropene does react with ethanol in a base-catalyzed reaction to give some addition by nucleophilic attack[11] along with solvolysis of allylic fluoride. Similarly, 3,3,3-trichloropropene is subject to nucleophilic attack in basic media[12] to give isomerized substitution products by an S_N2' mechanism. In the present study, some 3,3-dichloro-2-propen-1-ol was obtained by an analogous substitution in the attempted reaction with aqueous sodium bisulfite.

Substitution also occurred in the attempted reaction of the di- and trichloropropenes with anhydrous ammonia. However, the failure to observe nucleophilic addition reactions with 3,3,3-trichloropropene is convincing evidence that, with the reagents and conditions used in this study, the addition products obtained resulted from electrophilic attack in each case.

Combined effect of reactivities of both reactants. Kinetic studies[6b] show that the order of reactivity for halogen addition is: $X^+ > X\text{-}Y > X_2 > HX$. When reagents of different reactivities are combined with olefins of different reactivities, three situations are encountered as demonstrated in part III of this series:

1. When both the reagent and the olefin are relatively unreactive, as in the case of hydrogen halides with the di- and trichloropropenes (both vinyl and allylic types), an electromeric or hyperconjugative electron displacement must be induced in order to polarize the π-electrons of the double bond and produce reaction. Thus, these dynamic effects control the orientation of addition except for the case of 3,3,3-trichloroprene where no electromeric shift or hydrogen-hyperconjugation is possible, and consequently, the inductive effect controls the mode of addition.

2. When either the reagent or the olefin is of high reactivity, as in the case of hypochlorous acid with the di- and trichloropropenes, or hydrogen halides with propene, the permanent polarization of the molecule due to the inductive effect is sufficient to permit reaction and to determine the orientation of addition. Hyperconjugation may also be involved to some extent but it is apparently not a controlling factor for such a combination of reactivities. This is in accord with the results reported[6c] for the combination of hydrogen iodide with reactive olefins, and for the mononitration of alkylbenzenes.[6d]

3. When both the reagent and the olefinic compound are of high reactivity, as in the case of hypochlorous acid and propene, the reaction is very rapid and the permanent polarization of the molecule due to the inductive effect is sufficient to give reaction and to determine the predominant orientation of the addition. The greater rate of reaction results in lower selectivity as reflected in the increased random attack to give both possible isomers.

Thus, the orientation of electrophilic addition is governed by combinations of the various electronic effects possible. The relative contribution of the individual effects is dependent upon the nature and reactivity of both the olefinic compound and the electrophilic reagent.

EXPERIMENTAL

A. *Additions to allylic chlorides and related compounds.* The methods of preparation of the chloropropenes used for this study are described in Part I of this series of papers.[2] The procedures and the experimental results discussed in this paper are presented in Parts I–III.

B. *Attempted reactions with nucleophilic reagents.* 1. *Sodium bisulfite and 3,3,3-trichloropropene.* 3,3,3-Trichloropropene (3 g., 0.021 mole) containing hydroquinone (0.006 g.) was refluxed with 10 ml. of a saturated (30%) solution of sodium bisulfite (0.028 mole) for 20 hr. (Hydroquinone was used to inhibit free-radical addition.) After the reaction was completed, the organic layer was separated and washed with water and dried over sodium sulfate. The aqueous portion was evaporated to dryness and extracted with ethyl alcohol. The extract was treated with barium chloride. The organic portion was found to be 3,3-dichloro-2-propen-1-ol, a hydrolyzed product of 1,1,3-trichloropropene. No addition product was found in the aqueous portion.

2. *Anhydrous ammonia with di- and trichloropropene.* Anhydrous ammonia (4 ml., 0.19 mole) was condensed into two Carius tubes. Tube 1 contained 3,3-dichloropropene (3 g., 0.029 mole); tube 2 contained 3,3,3-trichloropropene (5 g., 0.034 mole). Both tubes were sealed and left standing at room temperature for 114 hr. At the end of the reaction, crystalline ammonium chloride was found in both tubes. The contents were washed with water and dried over anhydrous sodium sulfate. In both tubes, only the substituted chlorides were found, and no addition products were detected.

Acknowledgment. This study was made possible by a fellowship grant for fundamental research on organic halogen chemistry established by the Lubrizol Corporation.

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(11) A. L. Henne, M. A. Smook, and R. L. Pelley, *J. Am. Chem. Soc.*, **72**, 4756 (1950).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF IOWA STATE UNIVERSITY]

The Steric Course of Hydration of 1,2-Dimethylcyclohexene

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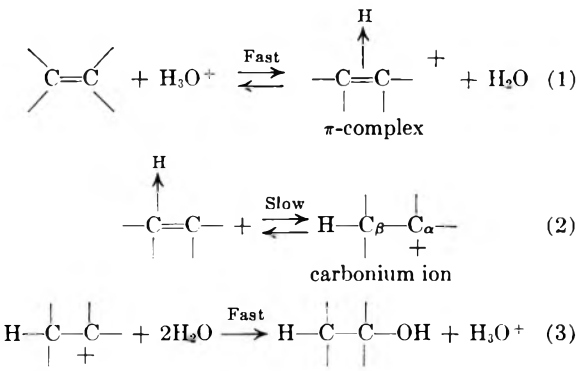
Hydration of 1,2-dimethylcyclohexene in aqueous nitric acid gives nearly equal amounts of *cis*- and *trans*-1,2-dimethylcyclohexanol. The result is consistent with any mechanism in which the product-determining step involves hydration of a carbonium ion.

Much information, both kinetic[3-12] and isotopic,[13] has been presented on the mechanism of the acid-catalyzed hydration of olefins to tertiary alcohols. On the basis of this evidence, Taft[8] proposed a mechanism for the hydration which involved both a π-complex and a classical carbonium ion, as shown in equations 1-3. Step 1, the protonation of the double bond to form the π-complex, and step 3, the conversion of the carbonium ion to to the alcohol, are considered to be relatively rapid; while step 2, the interconversion of the π-complex and the classical carbonium ion, is regarded as rate-determining.



(1)

(2)

(3)

Further refinements by Taft have described the π-complex as nearly olefinic, with a trigonal, coplanar structure and the proton embedded in the electron cloud,[14] *i.e.*, a nonequivalent proton.[13] This is distinguished from both the bridged-hydrogen species[15] and the transition state of Equation 2, which resemble the π-complex in geometry but have more of the electronic character of carbonium ions.[16] Kinetic evidence indicates, but does not compel, the conclusion that the rate-determining step does not involve a proton transfer[13] and that no water is tightly bound to the system in the transition state.[10,11]

Such a mechanism would not be expected to be highly stereospecific if a planar carbonium ion is formed in reaction 2. Even if the lifetime of the cation were short in comparison with rotation about the C_α—C_β bond, the direction of approach of the water molecule should be determined largely by steric interactions with the substituents attached to C_β. Any steric preference introduced by such an effect would probably result in preferential *cis* addition.

Recently, work with several strong acids has shown a *trans* stereospecificity to the addition reaction. Thus, Hammond and Nevitt[17] have observed a clean, stereospecifically *trans* addition of hydrogen bromide to 1,2-dimethylcyclohexene; Hammond and Collins[18] have observed a similar *trans* stereospecificity with hydrogen chloride and 1,2-dimethylcyclopentene; Winstein and Holness[19] have observed a stereospecific attack of formic acid on 4-*t*-butylcyclohexene, and Schleyer[20] has observed a stereospecific proton addition in the reaction of 1-methylnorbornene with formic acid and with ethanolic hydrochloric acid. In each case, the stereospecificity observed was explained by direct attack of the anion on the π-complex or, at least, a sufficiently concerted opening of the complex, coupled with attack of the anion, to yield stereochemically pure product.

The current work on the hydration of 1,2-

(1) Department of Chemistry, University of Wisconsin.

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(14) L. G. Cannell and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **78**, 5812 (1956).

(15) M. J. S. Dewar, *J. Chem. Soc.*, 406 (1946).

(16) P. Riesz, R. W. Taft, Jr., and R. H. Boyd, *J. Am. Chem. Soc.*, **79**, 3724 (1957).

(17) G. S. Hammond and T. D. Nevitt, *J. Am. Chem. Soc.*, **76**, 4121 (1954).

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(20) P. von R. Schleyer, *J. Am. Chem. Soc.*, in press.

TABLE I

PRODUCT COMPOSITION IN HYDRATION OF 1,2-DIMETHYLCYCLOHEXENE

Run No.	Concn. Nitric Acid	Time, Days	Temp.	Alcohol		Recovered Alkene,[a] %	
				trans	*cis*	1,2-	2,3-
1	0.1*M*	1	50	52	48		
2	0.1*M*	7	50	64	36		
3	0.1*M*	30	50	58	42	89	11
4	0.1*M*	5	50	55	45		
5	1.0*M*	5	28	55	45	93	7

[a] Original mixture contained 85% 1,2-dimethylcyclohexene and 15% 2,3-dimethylcyclohexene.

dimethylcyclohexene was undertaken to resolve the question of the stereochemistry.

RESULTS AND DISCUSSION

Table I lists the relative amounts of the *cis*- and *trans*-1,2-dimethylcyclohexanols formed in the hydration experiments. Although the total conversion to alcohols was small (less than 10% of the total sample analyzed), with virtually all of the rest of the material being unchanged olefin, the percentages observed for the *cis*- and *trans*-alcohols indicate nearly equal amounts of each isomer in both 0.1*M* and 1.0*M* nitric acid solutions. The composition of the remaining olefin is also noted. Thus, it is seen that the olefin composition changes little from its original value (85% 1,2-dimethylcyclohexene) in the more dilute acid, while some isomerization is detectable in the more concentrated acid solution. The actual equilibrium mixture contains even greater amounts of the symmetrical alkene.

To determine if equilibration of the *cis*- and *trans*-1,2-dimethylcyclohexanols were causing the near equivalence of the isomeric composition in the hydration experiments, several different alcohol mixtures were subjected to similar treatment. Results are given in Table II and indicate that, within experimental error, no (dilute) acid-catalyzed isomerization was taking place.

TABLE II

EQUILIBRATION STUDIES WITH 1,2-DIMETHYLCYCLOHEXANOLS IN 0.1*M* NITRIC ACID

Run No.	% Composition: Starting Material		% Composition: Recovered Material		Time, Days
	trans	*cis*	*trans*	*cis*	
1	100	0	100	0	1
2	100	0	100	0	1
3	43	57	48	52	1
4	43	57	42	58	1
5	27	73	23	77	3
6	27	73	26	74	1

As the nearly equivalent amounts of *cis*- and *trans*-1,2-dimethylcyclohexanol found in the hydration of 1,2-dimethylcyclohexane are not the result of an isomerization of a stereospecifically formed alcohol but rather are the actual results of the hydration itself, the results are in agreement with any mechanism, including that of Taft,[8] in which the product determining step involves hydration of an open carbonium ion.[21]

As the stereochemical course of hydration is different from that observed in addition of certain acids in organic solvents, there must be some mechanistic differences. However, the variations suggested are both small and of a character which might be anticipated. Both types of reaction can be reasonably formulated as involving complexes between an alkene and a proton (or molecular acid). If it is granted that such complexes maintain their integrity and react directly with a nucleophile in organic solvents, one could hardly devise conditions more favorable for allowing the complexes to isomerize to a carbonium ion than those obtaining in the hydration studies. The reaction is carried on in a medium (water) of high dielectric constant with a good capacity for specific solvation of cations, and the nucleophile (water) ultimately involved in the reaction is less reactive than those involved in most of the stereo-specific reactions.

The fact that two electrophilic addition reactions, hydrogen bromide adition and hydration, with a single substrate, 1,2-dimethylcyclohexene, give different stereochemical results indicates that predictions of the stereochemistry of such reactions will probably be unsafe unless they are based upon very close analogies. Similar pessimism is probably also warranted concerning other problems, such as prediction of the likelihood of molecular rearrangements in the course of addition reactions.

EXPERIMENTAL

Materials. cis- and trans-1,2-Dimethylcyclohexanol were prepared by the method of Nevitt and Hammond.[22] Physical constants were: *cis*-alcohol, b.p. 78.9–79.6° at 25 mm.

(21) A referee has suggested that, if the rate of hydration of 2,3-dimethylcyclohexene is much faster than that of the 1,2-isomer, most of the alcohols could come from that compound and mixtures could be produced by concerted, *trans*-addition. We agree, but feel that this is unlikely in view of the usual reactivity relationships among variously substituted alkenes.

(22) T. D. Nevitt and G. S. Hammond, *J. Am. Chem. Soc.*, 76, 4124 (1954).

(lit.,[22] b.p. 95.7 at 53 mm.) and *trans*-alcohol, b.p. 72.4–72.9° at 25 mm. (lit.,[22] b.p. 86.8° at 52 mm.).

1,2-Dimethylcyclohexene was prepared by dehydration of the mixed alcohols by heating the mixture with iodine. The distilled olefin, b.p. 136.0–136.1° at 735 mm. (lit.,[17] b.p. 135.4–135.9°) was shown to contain 85% 1,2-dimethylcyclohexene and 15% 2,3-dimethylcyclohexene by gas chromatographic analysis on a 6-foot column using Apiezon L grease as the liquid phase. The olefin peaks were distinct and well separated. Calculation was by triangulation,[23] and the results are reproducible to ±2%. The infrared spectrum of this sample was identical with that obtained by the previous workers.[17]

Procedure. For the hydration experiments, 15 ml. of aqueous nitric acid (1.0 or 0.1*M*) was placed in a small flask and 1 g. of 1,2-dimethylcyclohexene added. The flask was fitted with a condenser and magnetic stirring bar and placed in a constant temperature bath (28° or 50°) where the solution was stirred for periods varying from 1 to 30 days. At the end of these intervals, the sample was extracted with pentane. The pentane solution was washed with water and sodium bicarbonate solution and dried briefly over anhydrous calcium sulfate. The pentane was then removed by distillation, and the products were analyzed by gas chromatography at 150° on a 6-foot column with Apiezon L grease as the liquid phase. The *cis*- and *trans*-alcohol peaks showed some overlapping but calculation (by triangulation)[22] of the amounts present was possible. However, because of this overlapping, the results are probably accurate only to ±3–4%.

For the equilibration experiments, 1 g. of an alcohol mixture of known composition was placed in 15 ml. of 0.1*M* nitric acid solution. Further treatment was identical with that of the hydration experiments.

(23) A. I. M. Keulemans, *Gas Chromatography*, Reinhold Publishing Corp., New York, N. Y. (1957), p. 32.

Acknowledgment. We gratefully acknowledge support of this reasearch by the United States Army Office of Basic Ordinance Research. We are also indebted to Dr. Paul Schleyer for prepublication material and to Professor Robert Taft for many enlightening discussions of this subject.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MONTANA STATE UNIVERSITY]

Addition of Nucleophilic Reagents to *o*- and *p*-Cyanostyrene

JOHN M. STEWART, IRWIN KLUNDT, AND KENNETH PEACOCK

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A new improved synthesis of *o*-cyanostyrene was developed. Reactions of a variety of amines and thiols with both *o*- and *p*-cyanostyrene were carried out and the yields were compared to those of similar reactions previously performed with α-cyanostyrene[3] and 2,4-pentadienenitrile.[2] Results indicate a considerable diminishing of the electron-withdrawing effect of the cyano group when passed through the benzene ring conjugation.

o-Cyanostyrene and *p*-cyanostyrene may be considered to be vinylogs of acrylonitrile. Vinylogs are related compounds of the type formula $A(CH{=}CH)_nB$, in which the groups A and B are linked through one or more conjugated vinylene groups. An empirical rule developed by Angeli[1] has been useful in correlating the relations observed in reactions of certain vinylogs. It states that substituent groups situated *ortho* or *para* to each other on a benzene nucleus behave qualitatively as though they were joined directly. Accordingly, it would be predicted that *o*-cyanostyrene might correspond closely to the open chain vinylog, 2, 4-pentadienenitrile ($CH_2{=}CH{-}CH{=}CH{-}CN$), of acrylonitrile—one conjugated vinylene group being part of the benzene ring.

Compounds which contain an alkene linkage directly connected to a highly electron-withdrawing group, or conjugated with it through other vinylene linkages, react by addition across the alkene linkage with nucleophilic reagents which contain labile hydrogen atoms—for example, with primary and secondary amines, thiols, and phenols. Thus, reactions of this type have been carried out with 2,4-pentadienenitrile[2] and atroponitrile[3] (α-cyanostyrene), and the results have been compared with the familiar cyanoethylation reactions of acrylonitrile. It was of interest, therefore, to study the addition of nucleophilic reagents to *o*-cyanostyrene and *p*-cyanostyrene and to determine whether the electron-withdrawing effect of the cyano group upon the alkene linkage is diminished when passed through the benzene ring conjugation.

o-Cyanostyrene has been prepared by Marvel and Hein[4] by the decarboxylation of *o*-cyanocinnamic acid following a sequence of reactions starting with *o*-tolunitrile. The compound has also been reported as prepared in a British patent to the Wingfoot Corporation[5] by direct chlorination of *o*-ethylbenzonitrile, followed by pyrolysis of the chloroethyl derivative to give *o*-cyanostyrene. It was impossible to duplicate the latter procedure in this investigation. The over-all yield in method

(1) A. Angeli, *Atti. accad. Linei* [v] 32i, 443 (1923), *Chem. Abstr.*, **18**, 1118 (1924); R. C. Fuson, *Chem. Revs.* **16**, 1 (1933).

(2) J. M. Stewart, *J. Am. Chem. Soc.* **76**, 3228 (1954).

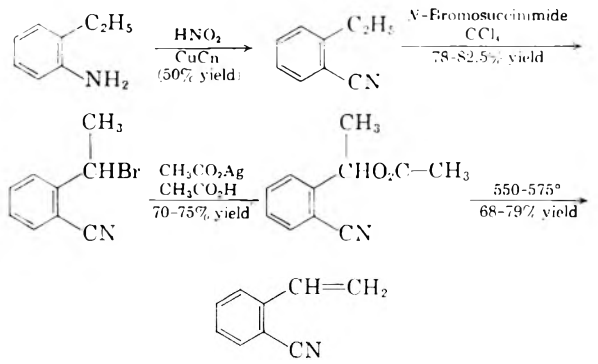
(3) J. M. Stewart and C. H. Chang, *J. Org. Chem.* **21**, 635 (1956).

(4) C. S. Marvel and D. W. Hein, *J. Am. Chem. Soc.* **70**, 1895 (1948).

(5) Wingfoot Corporation, Brit. Pat. **571**, 829 *Chem. Abstr.* **41**, 3322 (1947).

by Marvel and Hein was extremely low (5%). Therefore, the first step in this investigation was the development of a better synthesis of *o*-cyanostyrene.

Numerous routes to a new synthesis of *o*-cyanostyrene were investigated before a satisfactory method was developed. The method finally used involved the following sequence of reactions:



This route gave an overall yield of 18.5–24.4% of *o*-cyanostyrene, which represents a substantial improvement over the method of Marvel and Hein.[4] In the final pyrolysis step an inhibitor was necessary to prevent polymerization of the styrene as it formed. Hydroquinone proved to be a poor inhibitor, *N*-phenyl 2-naphthyl amine was only fair, and picric acid appeared to prevent polymerization almost completely.

By use of several modifications in the method of Marvel and Hein, the principal one being the preparation of *o*-cyanobenzaldehyde by alcoholic silver nitrate hydrolysis of *o*-cyanobenzal bromide, the over-all yield by this route was raised to 12–16%.

Several other methods which were tried but which proved unsatisfactory were: (1) pyrolysis of *o*-(α-bromoethyl)benzonitrile; (2) dehydrohalogenation of *o*-(α-bromoethyl)benzonitrile, or the chlorination product of *o*-ethylbenzonitrile, with quinoline, pyridine, or sodium amide; (3) pyrolysis of the trimethyl quaternary ammonium hydroxide prepared from *o*-(α-bromoethyl)benzonitrile; (4) selective reaction of methyl magnesium iodide with the aldehyde group in *o*-cyanobenzaldehyde to be followed by dehydration of the carbinol; (5) the sequence,

phthalyl chloride $\xrightarrow[H_2O]{NH_3}$ *o*-cyanobenzoic acid $\xrightarrow[0°]{PCl_5}$ *o*-cyanobenzoyl chloride $\xrightarrow{(CH_3)_2Cd}$ *o*-cyanoacetophenone $\longrightarrow$ *o*-cyanophenylmethylcarbinol $\longrightarrow$ *o*-cyanostyrene.

The last method (5) failed to give good results in the preparation of *o*-cyanoacetophenone from the acid chloride.

The *o*-cyanostyrene produced by new methods as well as that produced by the method of Marvel and Hein in this work had the same boiling point as that reported by those investigators but a widely different refractive index, n_D^{20} 1.5650, as compared to their value of n_D^{20} 1.5756. It reacted with bromine to give the same dibromo derivative. It appears that in the work of the previous investigators two small samples of *o*-cyanostyrene were prepared and that the one actually analyzed had a value of n_D^{20} 1.5705 and not n_D^{20} 1.5756 as reported. (Private communication from Prof. C. S. Marvel.)

p-Cyanostyrene was made by the method of Overberger and Allen[6] by pyrolysis of *p*-cyanophenyl methyl carbinol acetate following the sequence of reactions:

bromobenzene $\longrightarrow$ *p*-bromoacetophenone $\longrightarrow$ *p*-cyanoacetophenone $\longrightarrow$ *p*-cyanophenylmethylcarbinol $\longrightarrow$ *p*-cyanophenylmethylcarbinol acetate.

The over-all five-step yield was 26.4%.

A number of secondary amines, primary amines, and thiols were tried as nucleophilic addition reactants with *o*-cyanostyrene. A 40% water solution of Triton B was first used as catalyst since it had proved extremely successful in similar addition reactions of arylonitrile, 2,4-pentadienenitrile and atroponitrile (α-cyanostyrene). In the amine reactions, high yields were obtained only with dimethylamine (75%). Fair yields were obtained with piperidine (23%) and low yields with ethylamine, *n*-butylamine, and morpholine (8–14%). Others which apparently failed to react included diethylamine, di-*n*-butylamine, benzylamine, cyclohexylamine, and 40% aqueous methylamine. Use of other basic catalysts, including sodium methoxide, sodium, and anhydrous tetramethylguanidine did not give improved yields. Use of anhydrous cupric acetate as catalyst resulted in little, if any, addition reaction.

In the addition reactions of thiols with *o*-cyanostyrene, using 40% Triton B as catalyst, the more reactive thiols added quite readily—thiophenol, β-mercaptoethanol, and thioglycolic acid giving fair yields (30–60%) of addition products and butanethiol-1 giving a low yield (9%).

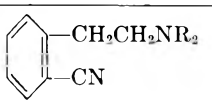
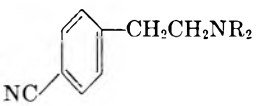
p-Cyanostyrene gave very similar results in its addition reactions with amines and thiols. As seen in Tables I and II, yields were significantly different only in the case of the *n*-butanethiol reaction, and the same amines again failed to give any addition product under the conditions used.

Upon comparison of these addition reactions of amines and thiols to *o*-cyanostyrene and to *p*-cyanostyrene with addition of the same reagents to α-cyanostyrene[3] or 2,4-pentadienenitrile,[2] it appears that the electron-withdrawing effect of the cyano group upon the alkene group is considerably diminished when passed through the benzene ring conjugation. Except in the case of dimethylamine, yields from the same amines were much smaller or

(6) C. G. Overberger and R. E. Allen, *J. Am. Chem. Soc.* 68, 722 (1946).

TABLE I

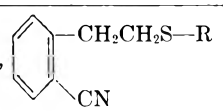
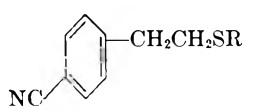
ADDITION PRODUCTS OF AMINES AND *o*- OR *p*-CYANOSTYRENE

Amine	Adduct Yield, %	Adduct B.P.°	Adduct n_D^{20}	Hydrochloride Prepared Direct from Crude Adduct Yield, %	M.P.°	Chlorine Analysis, % Calcd.	Chlorine Analysis, % Found
A. With *o*-Cyanostyrene (*N*-substituted-β-(*o*-cyanophenethyl)amines, 							
Dimethyl	75	98–101(2)	1.5266	46	153–155	16.83	16.66
Piperidine	23	130(2)	1.5425	34	209–212	14.14	14.19
Morpholine	14[a]			3	237–240	13.98	14.23
Ethyl	8.5[a]			6	174–176	16.83	16.71
n-Butyl	10–11[a]			8	188–190	14.78	14.55
Diethyl, Dibutyl, Methyl (40% soln.), *tert*-Butyl, Cyclohexyl, Benzyl	0			0			
B. With *p*-Cyanostyrene (*N*-substituted-β-(*p*-cyanophenethyl)amines, 							
Dimethyl	90	118–121(3)	1.5274		176–178	16.83	16.50
Piperidine	60[b]	168–169(1)	1.5413	21	199–201	14.14	14.03
n-Butyl	15[a]			11	211–212	14.85	15.12
Ethyl	22[a]			14	212–214	16.83	17.05
Diethyl, Di-*n*-butyl and Benzyl	0			0			

[a] This is yield of undistilled product which was then converted directly to the hydrochloride. [b] This run was heated at 70–75° for 24 hr., and let stand a further 48 hr.

TABLE II

ADDITION PRODUCTS OF THIOLS AND *o*- OR *p*-CYANOSTYRENE

Thiol	B.P.°	Refractive Index	Yield, %	Analysis, % Calcd.	Analysis, % Found
A. With *o*-Cyanostyrene [Alkyl (or Aryl)-β-(*o*-cyanophenethyl) sulfides], 					
n-Butyl	151–153(2)	n_D^{20} 1.5450	9	C, 71.18; H, 7.81	C, 71.97; H, 7.50
Thiophenol	165–170(2)	n_D^{31} 1.6072	30.4	S, 13.40	S, 13.18
β-Mercaptoethanol	185–190(2)	n_D^{20} 1.5756	52.4	*Anal.* of 3,5-dinitrobenzoate derivative (m.p. 86.5–88)	
				C, 53.85; H, 3.76	C, 53.90; H, 3.75
Benzyl			0		
B. With *p*-Cyanostyrene [Alkyl (or Aryl)-β-(*p*-cyanophenethyl) sulfides], 					
n-Butyl	165–168(2)	n_D^{20} 1.5497	54.8	C, 71.18; H, 7.81	C, 71.01; H, 7.71
Thiophenol			27.7[a]	*Anal.* of sulfone (m.p. 137–140°)	
				C, 66.40; H, 4.83	C, 66.68; H, 4.81
Thioglycolic acid			91 (crude)	*Anal.* of benzylisothiouronium salt (m.p. 165–166°)	
				C, 58.89; H, 5.46	C, 58.35; H, 4.78

[a] Crude yield. Decomposed on attempted distillation.

no reaction at all took place. Some amines which gave 30–50% yields of addition products with α-cyanostyrene or 2,4-pentadienenitrile failed to react under comparable conditions or even more drastic conditions with both *o*-cyanostyrene and *p*-cyanostyrene.

EXPERIMENTAL[7]

o-Ethylbenzonitrile. A Sandmeyer reaction was used, following the general procedure of H. T. Clarke and R. R. Reed.[8] *o*-Ethylaniline (Eastman) was converted to *o*-ethylbenzonitrile in a yield of 50%, b.p. 91–93°/12 mm.; n_D^{24} 1.5218; lit.,[9] b.p. 103°/19 mm.; n_D^{20} 1.5232.

o-(α-Bromoethyl)benzonitrile. In a 1-l. flask fitted with a reflux condenser (protected by a calcium chloride drying tube) was placed 60 g. (0.46 mole) of *o*-ethylbenzonitrile, 82 g. (0.46 mole) of *N*-bromosuccinimide, 5.5 g. (5 mole % based on *N*-bromosuccinimide) of benzoyl peroxide, and 350 ml. of carbon tetrachloride. The reaction was illuminated with a 235 watt sun lamp and heated under reflux for 2.5 hr., cooled, and filtered to remove the succinimide. The solvent was then removed under reduced pressure and the residual material was fractionally distilled to yield 79.4 g. (82.5%) of a pale yellow liquid, b.p. 99° (2–3 mm.), n_D^{20} 1.5759.

Anal. Calcd. for C_9H_8BrN: Br, 38.04. Found: Br, 38.04.

o-Cyano-α-phenethyl acetate. In a 1-l. flask fitted with a reflux condenser (protected with a calcium chloride drying tube), stirrer, and dropping funnel was placed 83 g. (0.50 mole) of silver acetate and 400 ml. of glacial acetic acid. To this was added dropwise over 2 hr. 79 g. (0.38 mole) of *o*-(α-bromoethyl)benzonitrile. The addition was carried out with the acetic acid just starting to reflux and with rapid stirring. After the addition was complete, the reaction mixture was stirred for an additional 9 hr., cooled, and the silver bromide filtered off. The solution was then diluted with 4 l. of water and extracted with ether six times. The ether was stripped and the crude product was distilled at reduced pressure to yield 53 g. (75%) of colorless liquid, b.p. 95–97° (0.5 mm.), n_D^{20} 1.5120.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.84; H, 5.82; N, 7.43. Found: C, 68.94; H, 5.88; N, 8.15.

o-Cyanostyrene. A Vicor pyrolysis tube filled with pieces of Vicor tubing was heated to a temperature of 550–575° in a vertical electrical heater and 26 g. (0.14 mole) of *o*-cyano-α-phenethyl acetate containing a small amount of picric acid was dropped through it over a period of 35 min. The receiver contained some picric acid and was cooled in an ice bath. Distillation of the pyrolysis mixture in an Argon atmosphere gave 14.28 g. (78%) of a colorless liquid, b.p. 70–72° (3 mm.), n_D^{20} 1.5650; lit.,[4] b.p. 53°/0.15 mm.; n_D^{20} 1.5756. (see Discussion).

o-(α,β-Dibromoethyl)benzonitrile. A sample of *o*-cyanostyrene was dissolved in glacial acetic acid and an excess of bromine was added. The reaction mixture was allowed to stand for 15 min., diluted with water, cooled, and extracted with ether. The ether was dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure and the crude material was recrystallized from an ethanol-water mixture to yield a white solid, m.p. 85–86°; lit.,[4] m.p. 86–86.5°.

Anal. Calcd. for $C_9H_7Br_2N$: Br, 55.30. Found: Br, 55.09.

o-Cyanobenzal bromide. The procedure of Fuson[10] was followed. From 117 g. (1 mole) of *o*-tolunitrile there was obtained 265 g. of crude black crystalline product which was used without purification.

o-Cyanobenzaldehyde. The procedure of Blicke and Patelski[11] for hydrolysis of *o*-cyanobenzal bromide was used with some modifications. A solution of 340 g. (2 moles) of silver nitrate in 2200 ml. of 95% ethanol was added fairly rapidly with stirring to a solution of 263 g. crude *o*-cyanobenzal bromide in 1500 ml. of ethanol maintained at about 60°. After the addition was completed, stirring was continued at 60° for 1 hr. A solution of sodium chloride was then added to remove excess silver nitrate, and the mixture was filtered. The silver halide residue was washed several times with ether and the washings were added to the filtrate. The filtrate was then added to an equal volume of concd. sodium chloride solution, and the mixture was extracted four times with ether. The ether solution was dried over anhydrous magnesium sulfate and the ether was removed under partial vacuum, leaving 110 g. of crude solid product. A sample recrystallized from cyclohexane melted at 104–106°, lit.,[11] m.p. 107–108°.

o-Cyanocinnamic acid. The method used by Rapoport[12] for preparation of *p*-cyanocinnamic acid was followed. Yields of crude product ranged from 60 to 70%. Recrystallization from 95% ethanol gave crystals, m.p. 255–257°; lit.,[4] m.p. 253–254°.

o-Cyanostyrene (by decarboxylation of o-cyanocinnamic acid). The general procedure of Walling and Wolfstirn[13] was modified considerably.

A mixture of 120 ml. freshly distilled quinoline, 3 g. of copper powder (freshly prepared by hydrogen reduction of cupric oxide), and 0.5 g. of cuprous cyanide was heated to about 200° in a 500-ml. 3-necked round-bottomed flask, fitted with thermometer, mechanical stirrer and a short take-off head. A 10-g. portion of *o*-cyanocinnamic acid was added, stirring was begun, and the temperature was raised until distillation occurred. The distillation temperature rose slowly from 220° to 228° (680 mm.) at which time the reaction temperature was lowered to 200° and a second 10-g. portion of *o*-cyanocinnamic acid was added. This process was repeated a third time and finally all the liquid present was allowed to distill. The distillate was added to excess 3*N* hydrochloric acid, and the mixture was extracted three times with ether. The combined ether extracts were washed with 3*N*, hydrochloric acid, 3*N* sodium hydroxide, and saturated sodium chloride solution and dried over calcium chloride. Distillation gave yields varying from 35–45% of *o*-cyanostyrene, b.p. 68–71° (3 mm.); n_D^{20} 1.5648, lit.,[4] b.p. 53°/0.15 mm.; n_D^{20} 1.5756. (See discussion and other method of preparation of *o*-cyanostyrene.)

Reactions of o- and p-cyanostyrene with primary and secondary amines. The cyanostyrene (0.02 mole) was mixed with 0.04 mole of the amine and 3 drops of 40% Triton B solution in a pressure bottle. The bottle was sealed and heated at 60–70° for 24 hr. The mixture was taken up in ether and washed four times with water to remove unchanged amine. The ether solution was then extracted with 3*N* hydrochloric acid and the combined acid extracts were extracted once with ether. The acid solution was made basic with 3*N* sodium hydroxide and the crude product was extracted with ether. The ether solution was dried over anhydrous magnesium sulfate. In most cases the products could not be distilled without some decomposition and were isolated as the hydrochloride salts by bubbling dry hydrogen chloride through the ether solutions.

The hydrochloride salts of the addition products were analyzed for chloride by the Volhard method.

(7) Carbon, hydrogen, nitrogen, and bromine analyses were done by Geller Microanalytical Laboratories, Bardonia, N. Y. Chlorine analyses were done by the authors.

(8) H. T. Clarke and R. R. Read, *Org. Syn.*, Coll. Vol. I, p. 514 (1932).

(9) H. R. Snyder and G. I. Poos, *J. Am. Chem. Soc.* 71, 1057 (1949).

(10) R. C. Fuson, *J. Am. Chem. Soc.*, 48, 1093 (1926).

(11) F. F. Blicke and R. A. Patelski, *J. Am. Chem. Soc.*, 58, 559 (1936).

(12) H. Rapoport, *J. Am. Chem. Soc.*, 75, 1125 (1953).

(13) C. Walling and K. B. Wolfstirn, *J. Am. Chem. Soc.*, 69, 852 (1947).

Reactions of o- and p-cyanostyrene with thiols. These reactions were carried out as with the amines. Except in the case of the addition product of thioglycolic acid, ether solutions of the product mixtures were washed first with 5% sodium hydroxide to remove unchanged thiol, dried over calcium chloride and either distilled directly to give the addition product or stripped of ether and converted to a derivative for analysis. The ether solution of the thioglycolic acid adduct was washed repeatedly with water to remove unchanged thioglycolic acid. The crude product was then isolated by extraction from the ether by 10% sodium hydroxide solution, followed by reacidification, ether extraction, drying, and stripping of the ether. A part of this crude product was converted to a benzylisothiouronium salt derivative (see Table II).

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MISSOULA, MONT.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF STANFORD UNIVERSITY AND WAYNE STATE UNIVERSITY]

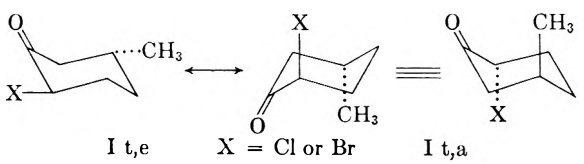
Optical Rotatory Dispersion Studies. XXXIII.[1] α-Haloketones (Part 6).[2] *trans*-2-Bromo-5-*t*-butylcyclohexanone[3]

CARL DJERASSI, E. J. WARAWA, ROBERT E. WOLFF,[4] AND E. J. EISENBRAUN

Received November 30, 1959

Resolution of *cis*-3-*t*-butylcyclohexanol was accomplished through the brucine salt of its acid phthalate, while *trans*-3-*t*-butylcyclohexanol (prepared by catalytic hydrogenation of *m*-*t*-butylphenol) was resolved *via* its 3β-acetoxy-Δ⁵-etienate. Oxidation of either resolved alcohol provided optically active 3-*t*-butylcyclohexanone, which was transformed into *trans*-2-bromo-5-*t*-butylcyclohexanone. Rotatory dispersion and ultraviolet and infrared measurements in different solvents indicated the complete absence of conformational mobility (due to the anchoring effect of the equatorial *t*-butyl group) in this system, in marked contrast to the behavior observed (ref. 5) with *trans*-2-halo-5-methylcyclohexanones.

In an earlier investigation,[5] we have demonstrated by the remarkable changes in the rotatory dispersion Cotton effect curves in solvents of different polarity that there exists a mobile equilibrium in the *trans*-2-halo-5-methylcyclohexanone system (I) between the two chair forms I, t,e and I t,a.[6] This was confirmed by dipole moment, infrared and ultraviolet measurements,[7] and quantitative calculations (in the case of I. X=Br) of the conformer composition (I, t,e *vs.* I t,a) in different solvents.



I t,e X = Cl or Br I t,a

A second, independent verification of these conclusions would involve the synthesis of a relative of *trans*-2-bromo-5-methylcyclohexanone (I, X=Br), where conformational mobility is inhibited on steric grounds, and to subject such a substance to the same physical measurements. In spite of recent comments,[8] the most straightforward approach appeared to be to replace the methyl group in I by a *t*-butyl function. Winstein and Holness[9] pointed out that such a bulky substituent would invariably anchor the cyclohexane ring in that conformation in which the *t*-butyl group occupies the equatorial orientation.[10]

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(1) Paper XXXII, C. Djerassi, *Rec. Chem. Progress*, **20**, 101 (1959).

(2) Part 5, C. Djerassi, N. Finch, and R. Mauli, *J. Am. Chem. Soc.*, **81**, 4997 (1959).

(3) Grateful acknowledgment is made to the National Cancer Institute of the National Institutes of Health for financial support (grant No. CY-2919 at Wayne State University and grant No. CY-4818 at Stanford University). The major portion of the experimental work was carried out in the Department of Chemistry of Wayne State University.

(4) Present address: Institut de Biologie Physicochimique, Paris V.

(5) C. Djerassi and L. E. Geller, *Tetrahedron*, **3**, 319 (1958); C. Djerassi, L. E. Geller, and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 1 (1960).

(6) As proposed to us by Dr. W. Klyne, we are employing two suffixes, the first denoting the relationship between the halogen atom and the alkyl group (c = *cis*, t = *trans*) and the second the orientation of the halogen atom (e = equatorial, a = axial).

(7) N. L. Allinger, J. Allinger, L. E. Geller, and C. Djerassi, *J. Org. Chem.*, **25**, 6 (1960).

(8) W. Hückel and M. Hanack, *Ann.*, **616**, 18 (1958).

(9) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

(10) For other examples where a *t*-butyl group was employed to fix the conformation of a cyclohexane ring see: H. L. Goering, R. L. Reeves, and H. H. Espy, *J. Am. Chem. Soc.*, **78**, 4926 (1956); E. L. Eliel and C. A. Lukach, *J. Am. Chem. Soc.*, **79**, 5986 (1957); R. A. Pickering and C. C. Price, *J. Am. Chem. Soc.*, **80**, 4931 (1958); N. L. Allinger and J. Allinger, *J. Am. Chem. Soc.*, **80**, 5476 (1958).

Because optical rotatory dispersion measurements played an important role in our arguments,[5,7] the hitherto undescribed optically active 3-*t*-butylcyclohexanone was required. Furthermore, in view of the complexity of the monobromination of 3-methylcyclohexanone,[5] it was necessary to demonstrate—and this could be done with the racemic ketone—that bromination of 3-*t*-butylcyclohexanone does, in fact, yield some of the required *trans*-2-bromo-5-*t*-butylcyclohexanone. The present report deals with the experimental answers to these problems.

Initially, we prepared 3-*t*-butylcyclohexanone (IV)[11] by the 1,4-addition of *t*-butyl magnesium chloride to Δ^2-cyclohexenone. In agreement with Winstein and Holness,[9] our yields (20–30%) were far below those (*ca.* 70%) reported in the original literature,[12] and an alternate procedure is described in the sequel. Attempts to resolve the ketone IV by means of D-tartramidic acid hydrazide[13] failed, as the amorphous tartramazone could not be purified successfully. Consequently the ketone was reduced with lithium aluminum hydride to *cis*-3-*t*-butylcyclohexanol (V), whose acid phthalate has already been described.[9] Resolution through the brucine salt and regeneration of the alcohol yielded the pure (+)-antipode V and this was oxidized to (+)-3-*t*-butylcyclohexanone (IV).

In view of the poor overall yield to the resolved ketone IV, the following alternate procedure was selected. Catalytic hydrogenation of *m*-*t*-butylphenol (II)[14] with a rhodium catalyst proceeded in excellent yield to furnish the known[6] *trans*-3-*t*-butylcyclohexanol (III), which upon oxidation led to 3-*t*-butylcyclohexanone (IV), thus representing by far the best method for the synthesis of the racemic ketone. The formation of the *trans* alcohol (III) implies that the hydrogenation of the phenol (II) proceeded either stepwise with possible detachment from the catalyst surface and readsorption at an intermediate stage on the opposite side of the molecule or through the intermediacy of the ketone IV.

In contrast to the behavior of *cis*-3-*t*-butylcyclohexanol (V), we were unable to effect resolution of the *trans* isomer III through alkaloid salts of its acid phthalate. Recourse was therefore taken of the long neglected employment of steroid acids for the resolution of alcohols, and 3β-acetoxy-Δ^5-etienic acid was selected because of its recent successful use[15] for a similar purpose. Fractional crystallization provided the pure levorotatory *trans*-3-*t*-butylcyclohexyl 3β-acetoxy-Δ^5-etienate (VI), which was cleaved by means of lithium aluminum hydride into an easily separable mixture of 17β-hydroxymethyl-Δ^5-androsten-3β-ol (VII) and (+)-*trans*-3-*t*-butylcyclohexanol (III). Oxidation of the latter gave the same dextrorotatory antipode of 3-*t*-butylcyclohexanone (IV) as had been obtained earlier from (+)-*cis*-3-*t*-butylcyclohexanol (V).

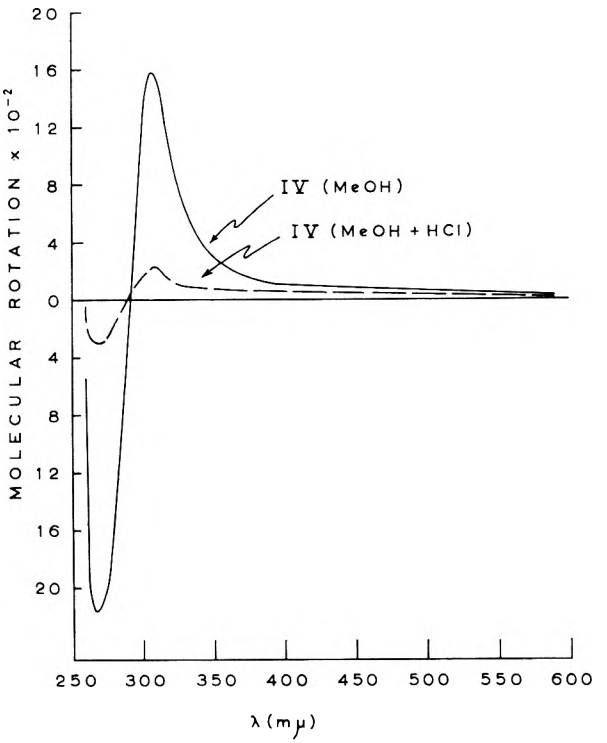


Fig. 1. Optical rotatory dispersion curve of (+)-3-*t*-butylcyclohexanone (IV) in methanol solution before and after the addition of one drop of concd. hydrochloric acid

The rotatory dispersion curve in methanol solution of (+)-3-*t*-butylcyclohexanone (IV) is reproduced in Fig. 1 and except for a somewhat increased amplitude[16,17] is identical with that of (+)-3-methylcyclohexanone measured[18] under similar conditions. It follows,[1,19] therefore, that the absolute configurations of (+)-3-*t*-butylcyclohexanone

(11) For all structural formulas, we are employing absolute configurational representations (steroid notation: solid line implying bond above the plane of the paper and dotted line referring to bond below that plane) corresponding to the resolved antipode employed in our work.

(12) F. C. Whitmore and G. W. Pedlow, *J. Am. Chem. Soc.*, **63**, 758 (1941).

(13) F. Nerdel and E. Henkel, *Ber.*, **85**, 1138 (1952); P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal, O. Weaver, U. C. Quarck, R. R. Chauvette, and R. Monahan, *J. Am. Chem. Soc.*, **79**, 6062 (1957).

(14) Generously donated by Dow Chemical Company, Pittsburgh, California, and by Stepan Chemical Company, Chicago, Illinois.

(15) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(16) For nomenclature and recording of experimental data see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, **55** (1957) and Chapter 2 in ref. 19.

(17) The increased molecular amplitude can be ascribed to the more powerful dextrorotatory contribution of the *t*-butyl group as compared with the methyl group. These quantitative differences in the rotatory contribution of substituents of various size and polarity will be covered in a future paper.

(18) C. Djerassi and G. W. Krakower, *J. Am. Chem. Soc.*, **81**, 237 (1959).

(19) C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw Hill Book Co., New York, 1960. See especially chapter 10.

(IV) and (+)-3-methylcyclohexanone must be identical and, as this problem has already been solved for the latter ketone by classical means,[20] the stereoformulas III, IV, and V are correct in terms of absolute configuration.[11]

By employing the recently reported[1,19,21] rotatory dispersion technique for the determination of methyl ketal formation—measurement of the diminution of the Cotton effect amplitude upon addition of hydrochloric acid—the results shown in Fig. 1 were obtained. These show the formation of 85% of methyl ketal as compared with 93%[21] for (+)-3-methylcyclohexanone. This difference is probably just barely within experimental accuracy of the method and indicates that if the 3-*t*-butyl group has an effect upon the reactivity of the keto function—as has been suggested recently[10]—it is rather small.

With the resolution problem solved, it was necessary to turn to the preparation of the required bromo derivative. Most of the studies were conducted with the racemic 3-*t*-butylcyclohexanone (IV), as the optically active material was required only for the rotatory dispersion measurements (*vide infra*). Just as in the earlier recorded[5] bromination of (+)-3-methylcyclohexanone, a mixture was produced from which one pure, crystalline monobromo derivative (VIII) could be separated in poor yield. The *location* of the bromine atom was established by the course of the dehydrobromination with 2,4-dinitrophenylhydrazine[22] which led smoothly to a 2,4-dinitrophenylhydrazone of 3-*t*-butylcyclohexenone. Its ultraviolet absorption spectrum ($\lambda_{max}^{CHCl_3}$ 383 mμ) was most compatible[23] with the Δ^2-5-*t*-butylcyclohexenone formulation (IX) and complete confirmation came from a repetition of this dehydrobromination with the optically active bromo ketone VIII. The resulting 2,4-dinitrophenylhydrazone (IX) was optically active, which would not have been the case if the alternate 2-bromo-3-*t*-butylcyclohexanone formulation had obtained.

The *orientation* of the bromine atom in VIII was established as equatorial by ultraviolet and infrared spectral measurements (see Tables I and II) in a wide variety of solvents of different polarity. The ultraviolet spectral shift in going from 3-*t*-butylcyclohexanone (IV) to its monobromo derivative (VIII) ranged from 1–4 mμ (Table 1), which is consistent[24] only with an equatorial bromo substituent. Similarly, the infrared shift towards lower wave length of 0.05–0.07 μ in six different solvents (Table II) in going from the ketone IV to VIII again requires[25] an equatorial orientation for the halogen atom.

TABLE I

POSITIONS OF ULTRAVIOLET ABSORPTION CARBONYL MAXIMA

Solvent	3-*t*-Butylcyclohexanone (IV) λ_{max} (mμ)	log ε	*trans*-2-Bromo-5-*t*-butylcyclohexanone (VIII) λ_{max} (mμ)	log ε
Isoöctane	287	1.25	286	1.39
Carbon tetrachloride	290	1.28	290	1.42
Dioxane	285	1.30	281	1.40
Methanol	279	1.21	281	1.41

TABLE II

POSITIONS OF INFRARED ABSORPTION CARBONYL MAXIMA

Solvent	3-*t*-Butylcyclohexanone (IV) λ_{max} (μ)	*trans*-2-Bromo-5-*t*-butylcyclohexanone (VIII) λ_{max} (μ)
Isoöctane	5.80	5.75
Carbon tetrachloride	5.81	5.75
Dioxane	5.82	5.75
Chloroform	5.82	5.77
Methanol	5.82	5.77
Dimethyl sulfoxide	5.84	5.77

The optical rotatory dispersion results of (+)-*trans*-2-bromo-5-*t*-butylcyclohexanone (VIII) are collected in Fig. 2. In the 3-methylcyclohexanone series[5] a strongly negative Cotton effect is observed in a nonpolar medium (e.g. octane) because of the axial conformer I t,a, while a large shift towards positive rotation is encountered in a polar solvent (methanol) because of an increased proportion of the conformer I t,e, with an equatorial halogen atom. As shown in Fig. 2, (+)-*trans*-2-bromo-5-*t*-butylcyclohexanone (VIII) exhibits in both methanol and isoöctane solution a positive Cotton effect, which according to the axial haloketone rule (or its extension, the octant rule)[1,19] is only consistent with the conformation VIII.[26] Even more important is the observation that within the limit of experimental error, the molecular amplitudes of the Cotton effect curves of VIII in two solvents of widely differing polarity (methanol *vs.* isoöctane) are identical. These results do not only

(20) For pertinent references see E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955).

(21) C. Djerassi, L. A. Mitscher, and B. J. Mitscher, *J. Am. Chem. Soc.*, **81**, 947 (1959).

(22) V. R. Mattox and E. C. Kendall, *J. Am. Chem. Soc.*, **70**, 882 (1948); C. Djerassi, *J. Am. Chem. Soc.*, **71**, 1003 (1949).

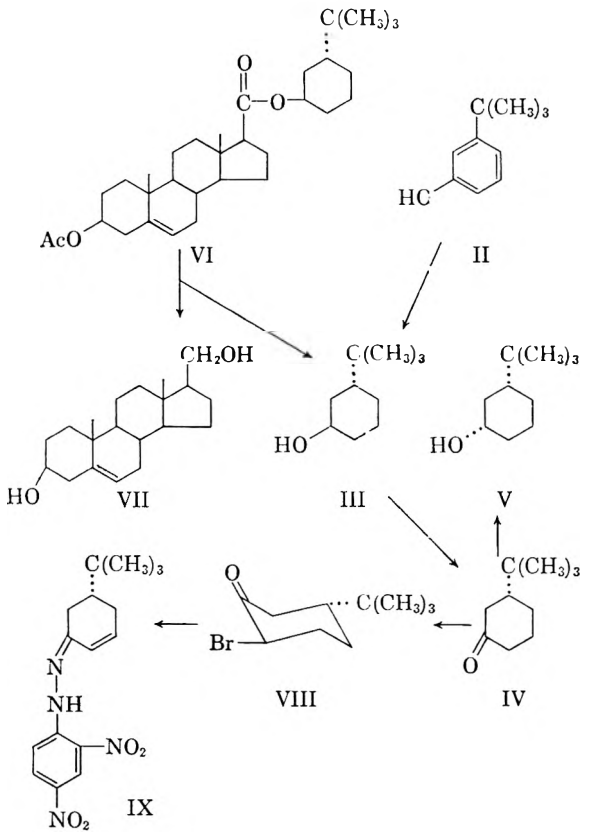
(23) See C. Djerassi and E. Ryan, *J. Am. Chem. Soc.*, **71**, 1000 (1949).

(24) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(25) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952); E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301, 3297 (1953).

(26) There is practically no wave length shift (in any given solvent) in the position of the rotatory dispersion extrema in going from the ketone IV to its bromo derivative (VIII), which again represents an important criterion (see Chapter 9 in ref. 19) of an equatorially oriented halogen atom.

confirm fully our earlier conclusions[5,7] about conformational mobility in the 2-bromo-5-methylcyclohexanone series (I t,e ⟷ I t,a), but they also demonstrate the complete absence of such mobility in the *t*-butyl analog. Fig. 2 represents a clear-cut graphic illustration of the validity of using[9] a bulky *t*-butyl substituent as an effective anchoring device to achieve a frozen conformation.



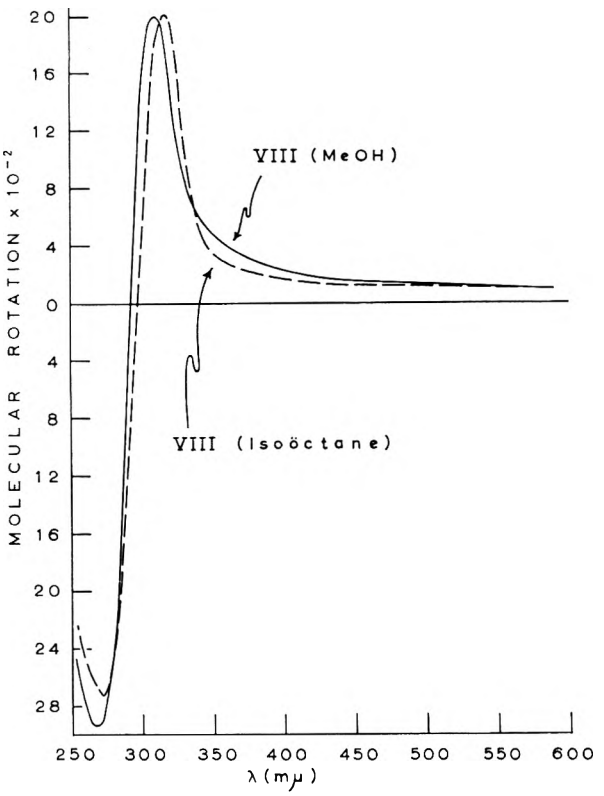


Fig. 2. Optical rotatory dispersion curve of (+)-*trans*-2-bromo-5-*t*-butylcyclohexanone (VIII) in methanol and in isoöctane solution

EXPERIMENTAL[27]

Resolution of cis-3-t-butylcyclohexanol (V). Reduction[9] of 21.5 g. of 3-*t*-butylcyclohexanone (IV) with lithium aluminum hydride provided 20 g. of the crude alcohol which was converted directly into its acid phthalate. Two recrystallizations from 66% aqueous methanol led to 24 g. of *cis*-3-*t*-butylcyclohexyl acid phthalate, m.p. 134–136° (lit.,[9] m.p. 136–136.8°).

A mixture of 15.0 g. of the above acid phthalate and 19.7 g. of brucine was dissolved in 30 cc. of acetone and heated for 40 min. at 40°. After cooling, scratching, and standing overnight in the refrigerator the precipitated brucine salt was collected and recrystallized by triangular fractional crystallization using benzene as the solvent. The separation was followed by the melting point of the brucine salt (purest specimen, m.p. 117–120°) and by the rotation (maximum $[\alpha]_D$ +14°) of the derived acid phthalate obtained upon acid treatment of the salt. In this manner, 6.4 g. of pure brucine salt was secured and this was dissolved in methanol and treated with 10 cc. of 2*N* hydrochloric acid. After heating for 5 min., water was added, the mixture was left overnight in the refrigerator, and the crystals were filtered and washed well with water, the absence of brucine being demonstrated by a negative nitric acid-acetic acid color reaction. The constants (m.p. 104.5–107°, $[\alpha]_D^{30}$ +14°, c = 1.7 in chloroform) of dried solid (86% yield based on brucine salt) were not altered upon recrystallization from aqueous methanol and the infrared spectrum in chloroform solution was identical with that of the racemic acid phthalate.

A 1.78-g. sample of the resolved acid phthalate was steam distilled in the presence of 50 cc. of 50% potassium hydroxide solution, water being added continuously to maintain a constant volume. Ether extraction of the distillate and distillation at 25 mm. and a bath temperature of 130–150° afforded 0.87 g. of (+)-*cis*-3-*t*-butylcyclohexanol (V) $[\alpha]_D^{30}$ +7.9° (c = 3.1 in chloroform), which crystallized in the ice box but melted at room temperature; the infrared spectrum in chloroform solution was identical with that of the racemic material.[9]

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.38; H, 12.49.

trans-3-t-Butylcyclohexanol (III). Hydrogen uptake ceased after 14 hr. when a solution of 10.68 g. of *m*-*t*-butylphenol (II)[14] in 75 cc. of methanol was shaken at 14° and atmospheric pressure in the presence of hydrogen with 1.78 g. of a 10% rhodium sesquioxide on carbon catalyst.[28] After filtration of the catalyst, the solvent was removed by distillation through a Vigreux column and the residue was taken up in ether and washed well with 10% sodium hydroxide solution and then with water. The dried ether solution was evaporated to dryness and the residue (9.40 g.) crystallized completely upon cooling in Dry Ice; m.p. 56–59° (with sublimation at 53°). Vapor phase chromatography at 150° on a silicone grease-firebrick support showed the material to be homogeneous and it was used directly for the oxidation and

(27) Melting points were determined on the Kofler block. The infrared (Beckman spectrophotometer model IR 4) and ultraviolet (Perkin Elmer spectrophotometer model 4000A) spectral determinations were performed by Miss B. Bach.

(28) We are indebted to Mr. William Pearlman of Parke, Davis and Co., Detroit, for a gift of this catalyst.

resolution experiments described below. Sublimation of a 100 mg. sample at 0.1 mm. yielded 82 mg. of colorless solid with m.p. 59–60°; its infrared spectrum in chloroform solution was identical with that of the unsublimed specimen. A small amount of the alcohol was converted to the acid phthalate and recrystallized from acetic acid–hexane (1:5), whereupon it exhibited m.p. 152–153°, undepressed upon admixture with an authentic specimen (lit.,[9] m.p. 154.5–155.5°) of *trans*-3-*t*-butylcyclohexyl acid phthalate which was kindly supplied by Prof. S. Winstein.[9]

Resolution of trans-3-t-butylcyclohexanol (III). Addition of 200 g. of thionyl chloride to 25 g. of 3β-acetoxy-Δ⁵-etienic acid[29] resulted in complete solution. After 6 hr. at room temperature the excess thionyl chloride was removed *in vacuo* and the acid chloride, dissolved in 210 cc. of pyridine, was added to 11.8 g. of *trans*-3-*t*-butylcyclohexanol (III) in 25 cc. of pyridine. The mixture was stirred for 18 hr. and was then poured into a solution of 265 cc. of concd. hydrochloric acid in 1.4 l. of water. The precipitated solid was filtered (yield of air dried material, 32.7 g.) and freed from adhering alcohol by steam distillation. The residual, crude (28.2 g.) *trans*-3-*t*-butylcyclohexyl 3β-acetoxy-Δ⁵-etienate (VI) was extracted with benzene, leaving *ca.* 5 g. of unchanged acid as a residue. The benzene solution was chromatographed on Merck acid-washed alumina and eluted with benzene-ether mixtures, ether, and finally ether containing some methanol. A total of 18 g. of colorless, solid material was obtained, the various fractions ranging in m.p. from 60–140° to 127–141°. Each fraction was purified separately by repeated recrystallization from acetone, leading eventually to a total of 2.30 g. of the pure diasteroisomer VI, m.p. 157–158.5°, $[\alpha]_D^{24}$ −30.4° (c = 0.093 in chloroform), $\lambda_{max}^{CHCl_3}$ 5.80 and 7.90 μ.

Anal. Calcd. for $C_{32}H_{50}O_4$: C, 77.06; H, 10.11; O, 12.83. Found: C, 76.65; H, 9.89; O, 13.52.

The above ester VI (0.44 g.) in ether solution was heated under reflux for 2 hr. with an excess of lithium aluminum hydride. After processing in the usual manner, the reduction product was leached with pentane which left undissolved 0.24 g. of the steroid diol VII. Removal of the pentane by careful distillation and sublimation of the residue (0.16 g.) at 50°/0.1 mm. furnished 0.1 g. of (+)-*trans*-3-*t*-butylcyclohexanol (III), m.p. 61.5–63°, $[\alpha]_D^{28}$ +19.8° (c = 0.85 in chloroform).

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90; O, 10.24. Found: C, 76.70; H, 12.97; O, 10.03.

3-t-Butylcyclohexanone (IV). To an ice cold solution of 240 mg. of *trans*-3-*t*-butylcyclohexanol (III) in 25 cc. of pure acetone was added dropwise, with stirring, a standard chromium trioxide–sulfuric acid solution,[30] small quantities of anhydrous magnesium sulfate being added during the titration. Upon formation of a permanent orange coloration, the solution was stirred for an additional 30 min., excess acid was neutralized with sodium bicarbonate, and the solution was filtered and then dried with magnesium sulfate. The acetone was distilled off carefully, the last traces being removed by codistillation with hexane until the distillate failed to respond to Brady's solution. Distillation of the residue gave 208 mg. of 3-*t*-butylcyclohexanone, b.p. 75–80°/3.5–3.7 mm. The substance was homogeneous by vapor phase chromatography and the relevant ultraviolet and infrared spectral properties are listed in Table I and II.

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol, m.p. 161–162.5°, $\lambda_{max}^{CHCl_3}$ 366 mμ, log ε 4.40.

Anal. Calcd. for $C_{16}H_{22}N_4O_4$: C, 57.48; H, 6.63; N, 16.76. Found: C, 56.98; H, 6.52; N, 16.25.

(29) Grateful acknowledgment is made to Dr. H. L. Herzog and Dr. A. L. Nussbaum of Schering Corporation, Bloomfield, N. J., for a supply of this acid.

(30) See K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

Similar oxidation of 442 mg. of the (+)-antipode of III (or V) yielded 427 mg. of (+)-3-*t*-butylcyclohexanone, $[\alpha]_D^{24.5}$ +25° (c = 0.489 in chloroform); its infrared spectrum (chloroform solution) was identical with that of the racemic ketone. Rotatory dispersion (see Fig. 1) in methanol (c, 0.115): $[\alpha]_{700}$ +6.9°, $[\alpha]_{589}$ +24°, $[\alpha]_{305}$ +1010°, $[\alpha]_{267.5}$ −1400°, $[\alpha]_{255}$ −337°; after addition of one drop of concd. hydrochloride acid: $[\alpha]_{589}$ +10°, $[\alpha]_{315}$ +116°, $[\alpha]_{272.5}$ −210°, $[\alpha]_{260}$ −29°. Rotatory dispersion in isooctane (c, 0.130): $[\alpha]_{700}$ +30°, $[\alpha]_{589}$ +16°, $[\alpha]_{320}$ +902°, $[\alpha]_{315}$ +726°, $[\alpha]_{310}$ +768°, $[\alpha]_{275}$ −1010°, $[\alpha]_{252.5}$ −740°.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.33; H, 11.60.

The semicarbazone of the (+)-ketone IV exhibited m.p. 179–182°, $[\alpha]_D$ +4° (chloroform).

Anal. Calcd. for $C_{11}H_{21}ON_3$: C, 62.52; H, 10.02. Found: C, 62.93; H, 10.41.

trans-2-Bromo-5-t-butylcyclohexanone (VIII). To a cold (10°) solution of 1.015 g. of 3-*t*-butylcyclohexanone (IV) in 7 cc. of anhydrous ether containing 3 drops of 10% hydrogen bromide–acetic acid solution was added dropwise with stirring 1.058 g. of bromine dissolved in 0.26 cc. of glacial acetic acid. The rate of addition was adjusted to the rate of decolorization and the entire reaction was complete in 5 min., whereupon the colorless solution was poured into saturated salt solution and the bromoketone extracted with ether. After thorough washing and drying, the ether was removed at room temperature by bubbling nitrogen gas through the solution under a slight vacuum. The liquid, lachrymatory residue (1.43 g.) was treated with 1 cc. of dry pentane and cooled in a Dry Ice–acetone bath, crystallization being promoted by scratching. The resulting crystals were filtered rapidly after about 5–10 min. and this process was repeated 10 times until no more crystals formed. The total solid material (140 mg.) melted at 54–57° with prior sublimation at 48°. When sublimed at 70°/0.1 mm., 70 mg. of colorless crystals, m.p. 71.5–72.5°, were obtained and these were unchanged upon repeated sublimation. This material was used for the spectral studies (Tables I and II) as well as for the dehydrobromination described below.

Anal. Calcd. for $C_{10}H_{17}BrO$: C, 51.48; H, 7.35; O, 6.86; Br, 34.30. Found: C, 51.21; H, 7.32; O, 6.98; Br, 34.22.

When the bromination was repeated with 310 mg. of (+)-3-*t*-butylcyclohexanone, there was isolated 48 mg. of solid bromoketone with m.p. 64–68°. Sublimation at 70°/0.1 mm. afforded 25 mg. of the pure bromoketone VIII, m.p. 82–83°, whose infrared spectrum in chloroform solution was identical with that of the racemic bromoketone. Rotatory dispersion (Fig. 2) in methanol (c, 0.099): $[\alpha]_{700}$ +8°, $[\alpha]_{589}$ +42°, $[\alpha]_{310}$ +856°, $[\alpha]_{265}$ −1265°, $[\alpha]_{250}$ −1055°. Rotatory dispersion in isooctane (c, 0.0975): $[\alpha]_{700}$ +29°, $[\alpha]_{589}$ +45°, $[\alpha]_{317.5}$ +862°, $[\alpha]_{272.5}$ −1168°, $[\alpha]_{255}$ −964°.

Δ²-5-t-Butylcyclohexenone 2,4-dinitrophenylhydrazone (IX). To a solution of 22 mg. of *trans*-2-bromo-5-*t*-butylcyclohexanone (VIII) in 5 cc. of glacial acetic acid[22] was added 20 mg. of 2,4-dinitrophenylhydrazine; the mixture was warmed for 15 min. in a current of nitrogen and then poured into water. The product was extracted with benzene, dried, and passed through a column of Fischer activated alumina to yield 30 mg. of bright red dinitrophenylhydrazone. Two recrystallizations from ethanol gave the analytical specimen of IX, m.p. 155.5–156.5°, $\lambda_{max}^{CHCl_3}$ 383 mμ, log ε 4.35.

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.76; H, 6.07; N, 16.20.

Repetition of this reaction with 10 mg. of (+)-*trans*-2-bromo-5-*t*-butylcyclohexanone (VIII) furnished the optically active form of the 2,4-dinitrophenylhydrazone IX, m.p. 150.5–151°, $[\alpha]_D^{25}$ −111° (c = 0.235 in chloroform), $\lambda_{max}^{CHCl_3}$ 382 mμ, log ε 4.34.

STANFORD, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Relative Stabilities of *cis* and *trans* Isomers. VIII.[1a] Optical Rotatory Dispersion Studies. XXXIV.[1b] Kinetic and Equilibrium Measurements on Some Steroidal Hydrindanones

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Utilizing optical rotation measurements in the ultraviolet region as a tool, the kinetics for the equilibration of a number of *cis*- and *trans*-hydrindanones in steroidal systems have been measured. The reactions are first order in ketone and first order in base. The equilibrium constants were also found. Approximate methods for predicting energy differences in hydrindane and hydrindanone systems are proposed and compared with experiment, and the agreement between theory and experiment is satisfactory.

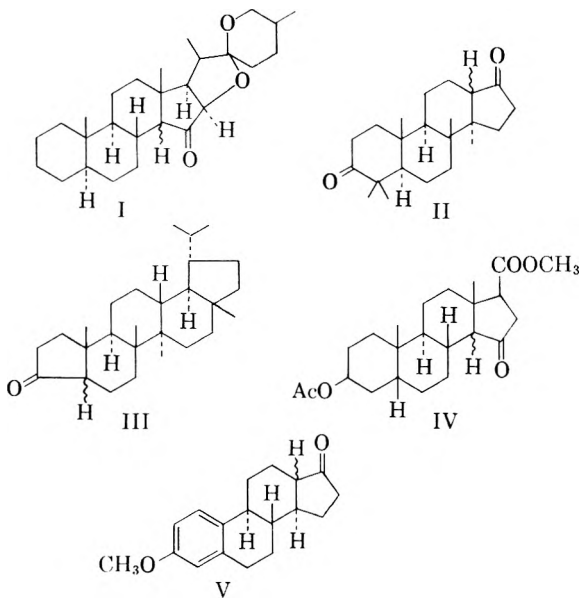
INTRODUCTION

The relative stabilities of *cis* and *trans* hydrindanone systems when these are fused into more complicated structures have been studied by a number of workers.[3] For the most part the available data were obtained by product isolation, and are qualitative at best.

The present work is concerned with quantitative studies on the relative stabilities of a number of fused hydrindanone systems. Compounds I–V were selected for study and these comprise a fair cross section of known hydrindanone systems.

The ketones were obtained from various sources cited in the experimental section. Compound I was obtained by catalytic hydrogenation of the previously described[3d] Δ^2-5α,25α-spirosten-15β-ol followed by oxidation of the saturated alcohol.

The *cis* isomer of compound V is unexceptional, but the *trans* isomer requires comment. The latter was obtained[4] by retroaldolization of 18-hydroxyestrone. Although no stereochemistry was previously assigned to this compound at C-13, the rotatory dispersion curve (Fig. 3) is nearly identical with that of *trans* II and shows clearly that the compound has the 13β configuration (C/D *trans*). The equilibrium mixture of V contains essentially equal amounts of *cis* and *trans* isomers, but the material isolated here was a single compound and not the equilibrium mixture. It was obtained pure in a yield of only 15%, and was the only product isolated. This then is a case where the less stable product alone has been isolated under equilibration conditions, presumably because of some physical factor such as ease of crystallization.



The rotatory dispersion curves were first determined from both isomers in methanol solution except in the case of II, which was available in insufficient quantity. The curves for the *cis*- and *trans*-isomers of I and II have been reported[5] while those of III–V are reproduced in Figs. 1–3. From these curves the wave lengths were chosen which appeared to be best suited for analysis of mixtures of each pair.

It was desirable to use a wave length at which the difference between the rotations of the isomers was large, but other factors had to be considered

(1) (a) Paper VII, N. L. Allinger, and J. L. Coke, *J. Am. Chem. Soc.*, in press. (b) Paper XXXIII, C. Djerassi, E. J. Warawa, R. E. Wolff, and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 917 (1960).

(2) Present address: Department of Chemistry, Stanford University, Stanford, California.

(3) (a) G. Quinkert, *Exper.*, **13**, 381 (1957). (b) N. L. Allinger, *J. Org. Chem.*, **21**, 915 (1956). (c) W. G. Dauben and G. J. Fonken, *J. Am. Chem. Soc.*, **78**, 4736 (1956). (d) C. Djerassi, T. T. Grossnickle, and L. B. High, *J. Am. Chem. Soc.*, **78**, 3166 (1956). (e) A. S. Dreiding, *Chem. and Ind.*, 992 (1954). (f) D. H. R. Barton and G. F. Laws, *J. Chem. Soc.*, **52**, (1954). (g) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4386 (1949). (h) W. E. Bachmann and A. S. Dreiding, *J. Am. Chem. Soc.*, **72**, 1323 (1950). (i) R. P. Linstead, *Ann. Rep. Chem. Soc.* (London), 305 (1935). (j) A. Windaus, *Ann.*, **447**, 233 (1926).

(4) K. H. Loke, G. F. Marrian, W. S. Johnson, W. L. Meyer, and D. D. Cameron, *Biochem. et Biophys. Acta*, **28**, 214 (1958).

(5) C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw Hill, Inc., New York, New York, 1960, p. 59.

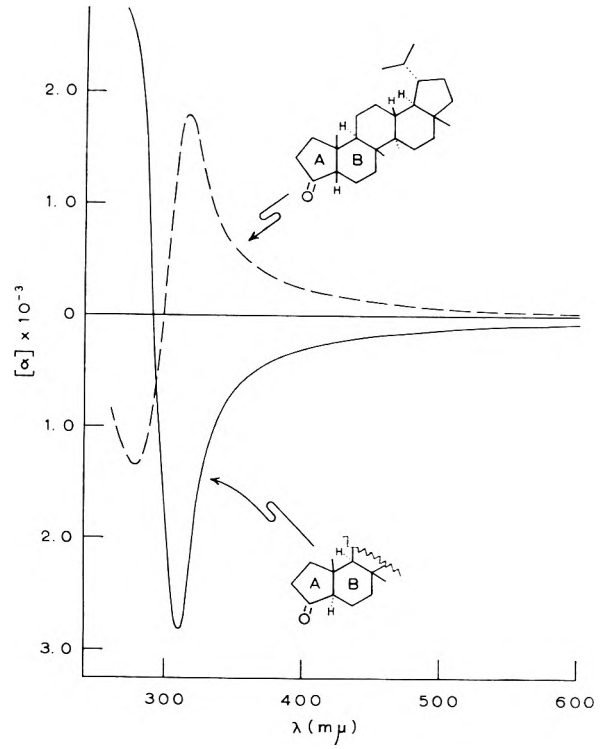


Fig. 1. Rotatory dispersion curves of A/B *cis* and *trans* III in methanol

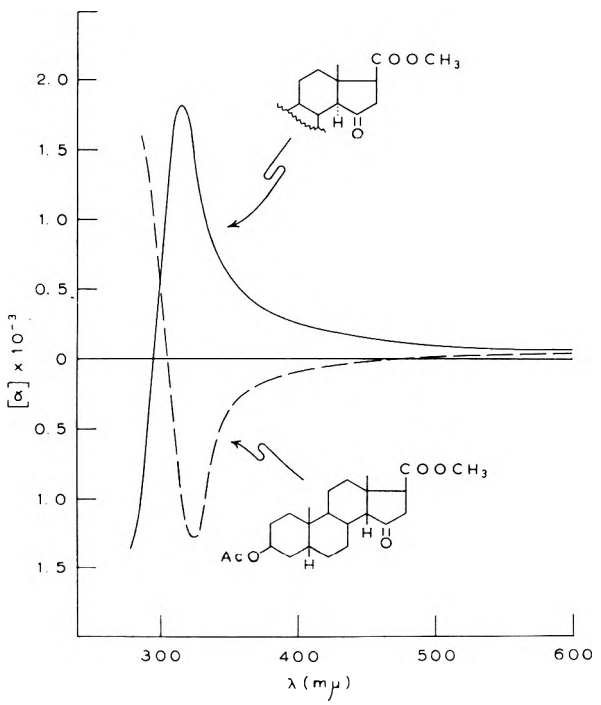


Fig. 2. Rotatory dispersion curves of C/D *cis* and *trans* IV in methanol

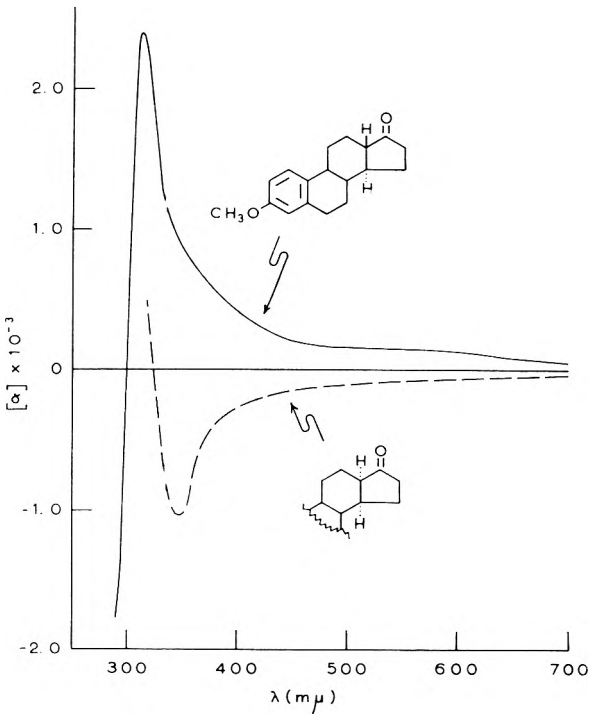


Fig. 3. Rotatory dispersion curves of C/D *cis* and *trans* V in methanol

also. It was not desirable to choose a wave length where either of the curves had a very steep slope as this would make the rotation difference very sensitive to errors in wave length setting, thereby increasing the error when different runs were compared. Also, the stability of the light source was better at wave lengths above 320mμ. By measuring the optical rotation of both pure epimers and the equilibrium mixture of the two at the wave length judged most suitable, the position of equilibrium was determined.

Optical rotation measurements in the ultraviolet region also appeared to be ideally suited for kinetic as well as equilibrium measurements.[5,6] Polarimetric rate constants obtained at the sodium D line have often been reported in the literature. As for most compounds the rotation in the ultraviolet is much larger than that at the D line, there are in general certain advantages in making the measurements at shorter wave length. In the present cases many of the compounds studied were available to the extent of only a few milligrams, and studies at the D line would have been impossible. Because of the enormous difference between the specific rotations for the isomers of a given hydrindanone at the proper wave length (on the order of 3000° near 315mμ), it was possible to carry out a kinetic run with approximately 1 mg. of compound. As the epimerization in base is a very fast reaction (observed second order rate constants are around 10^{+2} moles^{-1} l. sec.$^{-1}$), it was necessary to keep the concentrations rather low. Ordinarily the amount of hydroxide ion in the polarimeter tube was 10^{-5} to 10^{-6} moles. Special precautions therefore had to be taken to keep carbon dioxide out of the system efficiently. The rate and equilibrium constants ob-

(6) C. Djerassi, *Rec. Chem. Progress*, **20**, 101 (1959).

TABLE I[a]

EQUILIBRIUM AND RATE DATA FOR EPIMERIZATION REACTIONS

Compound	Equilib., % *cis*[b]	Rate Constants in Methanol (l., moles^{-1} sec.$^{-1}$) at t°K.		*Trans* ⇄ *Cis*				Rate Constants in Methanol (l., moles^{-1} sec.$^{-1}$) at t°K.		*Cis* ⇄ *Trans*			
		293°	303°	$\Delta F_{293}^{\ddagger}$	$\Delta F_{303}^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	293°	303°	$\Delta F_{293}^{\ddagger}$	$\Delta F_{303}^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
I	>98	85.4	164.3	14.57	14.68	11.0	−12	—	—	—	—	—	—
II	61.4[c]	61.2	123.9	14.76	14.85	12.1	−9	(38.5)[d]	77.8[e]	15.03	15.13	12.1	−10
III	>99	457.2	939.9	13.59	13.63	12.3	−4	—	—	—	—	—	—
IV[f]	87	—	66.1	—	15.23	—	—	—	9.9[f]	—	16.37	—	—
V	55[g]	—	1160[f]	—	13.48[g]	—	—	—	930	—	13.62	—	—

[a] The values for $\Delta F^{\ddagger}$ and $\Delta H^{\ddagger}$ are in kcal./mole while those for $\Delta S^{\ddagger}$ are in cal./mole degree. Average probable errors in various quantities: $\Delta F^{\ddagger}$, 0.03 kcal./mole; $\Delta H^{\ddagger}$, 1 kcal./mole; $\Delta S^{\ddagger}$, 3 e.u.; ($T_{303} - T_{293}$), 0.1°. [b] The equilibrium constants were all measured at 303°K., and are assumed to be essentially independent of temperature over the range used. [c] The equilibrium composition of this compound has been found to be 58% *cis* in acetic acid-hydrochloric acid (private communication from Dr. G. Ourisson of the University of Strasbourgh). [d] This is a calculated value obtained from the data at 303° and the data for the *trans* isomer. [e] This is a calculated value obtained from the experimental equilibrium constant and the experimental rate of the *trans* isomer. An experimental value for the rate was found from the very small amount of *cis* compound available, and was 73 ± 10 The calculated value is believed to be more accurate. [f] This is a calculated value obtained from the data for the other isomer. [g] The *trans* isomer was available in such small amounts that the rotatory dispersion curve had to be determined at very low concentration. The accuracy of the curve is therefore probably less than usual, and the equilibrium constant and dependent quantities such as $\Delta F^{\ddagger}$ of expimerization of the *trans* (which was calculated from the data on the *cis*) may also be somewhat inaccurate.

tained are for the most part considered reliable to about ±2%. As the rates were measured at two temperatures in a few cases, the thermodynamic quantities for the epimerization could be found.

RESULTS

The equilibrium data, together with the rate constants for the epimerization reaction and the derivable thermodynamic quantities, are summarized in Table I.

For all of the hydrindanones studied in the present work, the equilibrium mixture contained predominantly the *cis* isomer, varying in amount from 55 to 99%. In the former case (V) the *cis* is more stable than the *trans* by only 0.1 kcal./mole, while in the latter (III), this difference is no less than 2.7 kcal./mole. This variation is far larger than has previously been generally recognized and is not accounted for by any of the previous theoretical discussions on the subject. One group of hydrindanones (cholestan-15-ones) is known in which the *trans* isomer appears to be the more stable.[3f,7]

The reactions were clearly second order under the conditions used, first order in ketone and first order in hydroxide ion. The rate constants were obtained from the data utilizing the standard methods for reversible or irreversible reactions as appropriate,[8] and the thermodynamic constants were found in the usual way.[9]

DISCUSSION

A priori it would seem that the epimerization reaction in basic solution must formally follow one (or both) of the following kinetic schemes[10,11]:

Mechanism A

$$(+)\text{R—H} + \text{B}^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (+)\text{R}^- + \text{H—B}$$

$$(+)\text{R}^- \xrightarrow{k_2} (\pm)\,\text{R}^-$$

$$(\pm)\text{R}^- + \text{H—B} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} (\pm)\,\text{R—H} + \text{B}^-$$

Mechanism B

$$(+)\,\text{R—H} + \text{B}^- \xrightarrow{k_1} (\pm)\text{R}^- + \text{H—B}$$

$$(\pm)\,\text{R}^- + \text{HB} \rightleftharpoons (\pm)\,\text{R—H} + \text{B}^-$$

In mechanism A the optically active carbanion exists as a discrete intermediate, and its epimerization is rate determining (k_2). In mechanism B the carbanion is epimerized as fast as it is formed. These appear to be the only reasonable alternatives consistent with the observed kinetics.

Earlier studies by Hsü, Wilson, and Ingold have shown that, at least in the particular case they studied, the rate of racemization of a ketone (optically active at the α-carbon) was the same as the rate at which the ketone took up deuterium from a deuteroxylated solvent, which would not be consistent with mechanism A.[10] Cases are known

(7) The *cis* isomers are unknown.

(8) A. A. Frost and R. G. Pearson, *Kinetics and Mechanism*, John Wiley and Sons, New York, N. Y., 1953, p. 172.

(9) Ref. 8, p. 95.

(10) S. K. Hsü, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.*, 78 (1938).

(11) S. K. Hsü and C. L. Wilson, *J. Chem. Soc.*, 623 (1936).

in which reactions appear to proceed via a benzyl carbanion intermediate, and yet are stereospecific.[12]

One interpretation of these facts is that the carbanion is planar when adjacent to a carbonyl function, but pyramidal if adjacent to a group which can offer no better resonance stabilization than can a phenyl substituent. The isoelectronic situation of a nitrogen atom in place of the carbanion is informative, and appears to be quite analogous. Thus, an amide has a planar nitrogen atom[13] while aniline does not.[14]

The observed rate constants vary over a total factor of about 120, but $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ do not vary by significantly more than experimental error. The number of cases studied was too small to yield a discernible correlation between rate and structure.

The relative stabilities of *cis* and *trans* junctures in substituted hydrindanone systems present an apparently anomalous situation which had led to a considerable amount of speculation.[3] As little quantitative data have been available previously, the exact status of the problem has been unclear. One of the aims of the present work is to develop and apply to the available data a simple approximate theoretical treatment of the stabilities of these systems.

Conformational analysis has been applied extensively and with considerable success to six-membered rings,[15] but applications to rings of other sizes have been meager.[16,17] Studies carried out with the cyclopentane ring,[17] with which the present work is in part concerned, have served mainly to show how difficult the problem really is. Consequently, the approach used in this work has been what might be called a perturbation method. Instead of trying to deduce properties of the five-membered ring from basic principles, work is begun by comparing the parent decalin and hydrindane systems, for which data are available, and considering that the properties of the hydrindane are those of the decalin plus the perturbation. The perturbation is taken to be constant from one system to another and is then evaluated empirically. The properties of any substituted hydrindane can then be evaluated if the properties of the corresponding decalin are known (or can be predicted) by adding in the perturbation. Obviously such a simplified treatment is to be regarded as a first approximation, and whether it yields results of sufficient accuracy to be useful can only be judged empirically.

The available data for the decalins[18] show that for the reaction *cis*⇌*trans*, the thermodynamic quantities are $\Delta H^{586} = -2.72$ kcal./mole and $\Delta S^{586} = -0.55$ e.u.

The entropy effect appears small enough that in general when considering decalin systems it may be neglected[18] and ΔH can be equated with ΔF. This approximation is made for decalin systems throughout the remainder of this paper.

The thermodynamic quantities for the isomerization *cis*⇌*trans*-hydrindane are[19]: $\Delta H^{522} = -1070$ kcal./mole, $\Delta S^{522} = -2.3$ e.u. The entropy difference between the isomeric hydrindanes is therefore not negligible, and it should be taken into account. The value −440 kcal./mole at 273°K. is consequently used for ΔF. Part of the entropy effect may be a result of the symmetry of *trans*-hydrindane, but in the absence of more definite data a good approximation is to take $\Delta F = -0.4$ kcal./mole for isomerization of a *cis*- to a *trans*-juncture in a hydrindane in the vicinity of room temperature. If the corresponding value for the decalin juncture is taken as −2.7 kcal./mole, then the difference between these values (2.3 kcal.) can be regarded as a perturbation constant which includes entropy, and which can be used for free energy calculations in hydrindane systems.

Turning now to the structures I–V, it is possible to calculate by standard methods what the enthalpy of the epimerization of the ring juncture adjacent to the ketone would be if the ring were six-membered, using the energy 0.9 kcal. per *gauche* interaction. Adding the perturbation constant, the value for the actual system is obtained. The 2-alkyl and 3-alkyl ketone effects must be taken into account.[3a,20,21] In the cyclopentanone ring, the carbonyl angle is considerably compressed from the preferred value of 120°, even if the ring is planar. The planar form of cyclopentanone has the carbonyl oxygen placed favorably in a staggered position between the adjacent hydrogens, and it seems likely that the cyclopentanone ring will be

(12) D. J. Cram, J. Allinger, and A. Langemann, *Chem. and Ind.*, 919 (1955).

(13) For a summary of available data, see W. J. Orville-Thomas, *Chem. Rev.*, 57, 1179 (1957).

(14) C. A. Coulson, *Valence*, Oxford University Press, London, 1952, p. 244.

(15) For recent reviews see (a) W. G. Dauben and K. S. Pitzer in M. S. Newman's *Steric Effects in Organic Chemistry*, John Wiley and Sons, New York, N. Y., 1956, p. 1 (b) D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, 10, 44 (1956).

(16) (a) N. L. Allinger, *J. Am. Chem. Soc.*, 81, 5727 (1959); N. L. Allinger and S. Greenberg, *J. Am. Chem. Soc.*, 81, 5733 (1959); N. L. Allinger and J. Allinger, *J. Am. Chem. Soc.*, 81, 5736 (1959); (b) N. L. Allinger and J. Allinger, *J. Org. Chem.*, 25, 262 (1960).

(17) (a) K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.*, 81, 3213 (1959). (b) F. V. Brutcher, Jr., T. Roberts, S. J. Barr, and N. Pearson, *J. Am. Chem. Soc.*, 81, 4915 (1959). (c) C. G. LeFevre and R. J. W. LeFevre, *J. Chem. Soc.*, 3549 (1956).

(18) (a) K. S. Pitzer and T. Miyazawa, *J. Am. Chem. Soc.*, 80, 60 (1958). (b) J. P. McCullough, H. L. Finke, J. F. Messerly, S. S. Todd, T. C. Kincheloe, and G. Waddington, *J. Phys. Chem.*, 61, 1105 (1957). (c) N. L. Allinger and J. Coke, *J. Am. Chem. Soc.*, 81, 4080 (1959).

(19) N. L. Allinger and J. L. Coke, *J. Am. Chem. Soc.*, in press.

(20) W. Klyne, *Experientia*, 12, 119 (1956).

(21) P. A. Robins and J. Walker, *J. Chem. Soc.*, 1789 (1955), *Chem. and Ind.*, 772 (1955).

TABLE II

$-\Delta F$ Kcal./mole for *trans* ⟶ *cis* FOR VARIOUS HYDRINDANONE SYSTEMS

Compound	II		III		IV		V	
	cis	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
gauche	3	0	5	4	5	4	3	0
2-Alkyl ketone	1	1	1	1	1	1	1	1
3-Alkyl ketone	1	1	1	1	1	1	1	0
$-\Delta F$ (calcd.)	−0.4		1.4		1.4		0.0	
$-\Delta F$ (found)	0.4		2.7		1.0		0.1	

more nearly planar than the corresponding cyclopentane, and furthermore such puckering as does occur is expected to be brought about by having one (or both) of the β carbons move out of the plane.[17b] Thus, the 2-alkyl ketone effect will probably be less important here than in cyclohexanone systems. Similarly, a 3-alkyl ketone effect is of reduced importance in the five-membered ring. As numerical data are not yet available, the value 0.4 kcal./mole (approximately half that assigned in the cyclohexanone system) has been tentatively and somewhat arbitrarily assigned to each of these effects.

Effect of substituents. The above considerations apply as a first approximation to simple hydrindanones. Compound I, with the D/E *cis* fusion, is at present too complicated a system in which to predict relative stabilities. For the remaining systems (II–V), such predictions can be made as outlined, and the required data are summarized in Table II. In the *cis* isomer of IV there is a *gauche* interaction involving the B and D rings (between carbons 7 and 15) which is also present in the *trans* isomer, and in each compound there are various numbers of *gauche* interactions between the two rings of the hydrindanone systems, as listed in Table II. 2-Alkylketone interactions increase and 3-alkylketone interactions decrease the energy of the system.[20] Summarizing these energies and adding the perturbation constant gave the calculated values of $-\Delta F$, and these are compared with the experimental values in Table II.

For compound II the prediction is straight forward and in fair agreement with experiment. In compound III the *cis* isomer is predicted to predominate over the *trans* by about 10/1, and experimentally it predominates by 100/1. The abnormally large amount of *cis* isomer may be due to the 1,3-diaxial interaction between the methyl groups at carbon atoms 8 and 10. This interaction is known to distort the system considerably.[22] For structures IV and V, the agreement between prediction and experiment is good. The outstanding anomalies reported in the literature for hydrindanones are the 15-keto stanols.[3f] With these substances a *cis* C/D ring juncture forces the 18-methyl group to be very nearly eclipsed by the side chain. The *trans* compound in which ring D is less planar has this strain relieved to some extent, and it is probably the side chain which is displacing the equilibrium in this case. The carbomethoxy group in IV is flat and can apparently twist out of the way of the methyl substituent with the result that the carbomethoxy group is effectively too small to exert an energetically important eclipsing effect.

The simple perturbation method outlined in this paper offers a means of attempting to correlate the observed stabilities of the hydrindanone systems in so far as data are available. Some rather severe approximations were made in developing and applying the theory, and it is intended only as a starting point for the quantitative understanding of these systems. This treatment is only moderately consistent with the limited available data, and it may be too crude to be generally useful.

EXPERIMENTAL

Ketones. The *cis* and *trans* isomers of I were synthesized in the present work, while compounds II,[23] IV,[24] and V[4,25] have been reported in the literature, and were donated by the respective authors. The two isomers of III were furnished by Dr. T. G. Halsall of Oxford University.

5α,25a-Spirostan-15β-ol (I). Digitonin was converted to Δ^2-5α,25a-spirosten-15β-ol as described.[3d] The latter compound, 11.8 g., was reduced in 600 ml. of ethyl acetate using 1.0 g. of platinum oxide. The reaction was complete after 15 min. The solution was filtered and the solvent was evaporated. The residue, 11.4 g., m.p. 180–185°, was used directly in the next step. For analysis a sample was crystallized from acetone, m.p. 184–186°.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.40; H, 10.65.

5α,25a-Spirostan-15-one. One and one-half grams of the alcohol (I) was dissolved in 300 ml. of acetone (purified by treatment with potassium permanganate) and oxidized at 19–21° by adding 1.6 ml. of 8*N* chromic acid reagent[26] dropwise during 45 min. The solution was allowed to stand for 3 hr., and then was poured into water. The precipitate was collected and taken up in chloroform. The chloroform layer was washed and dried, and the solvent was evaporated with the concurrent addition of methanol. The product crystallized, wt. 1.30 g., m.p. 183–191° (block) or 189–196° (capillary). It was found that the compound partially isomerized

(22) Private Communication from Dr. G. Ourisson.

(23) J. Biellmann, P. Crabbé, and G. Ourisson, *Tetrahedron*, **3**, 303 (1958).

(24) A. Lardon, H. P. Sigg, and T. Reichstein, *Helv.*, **42**, 1457 (1959).

(25) W. F. Johns, *J. Am. Chem. Soc.*, **80**, 6456 (1958).

(26) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 461 (1953).

at its melting point (by infrared spectra). The observed melting points of different samples were somewhat variable.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.46; H, 9.88.

22a,25a,14β-Spirostan-15-one. Epimerization of the 14α compound was carried out by dissolving 150 mg. in 10 ml. of methanol containing 127 mg. of potassium hydroxide, and refluxing the resulting solution for 15 min. The solution was diluted with water and extracted with chloroform. The chloroform extracts were washed to neutrality, dried, and the solvent was evaporated. The product, wt. 142 mg., m.p. 166–168°, was recrystallized from methanol, m.p. 166–169°.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.02; H, 10.32.

General polarimetric procedure. A zirconium lamp was used for all of the 20° runs, and also for I at 30°. A xenon lamp was used at 30° for the other compounds. The wave length chosen for each compound was as follows: I, 345 mμ; II, 314 mμ; III, 314 mμ, IV, 327 mμ, and V, 330 mμ.

The polarimeter tube used was center filling, equipped with quartz windows and a water jacket. It had a length of 1 decimeter and a volume of slightly less than 1 ml. Water from a thermostated bath was circulated through the polarimeter jacket, and the temperature was measured as the water left the jacket. The polarimeter tube was first prepared by allowing it to stand for 4 hr. containing a solution of potassium hydroxide in methanol at the same concentration that was to be used in the kinetic run. The tube was then rinsed thoroughly with methanol, dried, and filled with nitrogen. A weighed sample of the ketone (about 5 mg.) was dissolved in 10 ml. of spectroscopic grade methanol at the desired temperature, and 1.00 ml. of standard potassium hydroxide (0.01 or 0.02*N* in methanol) at the desired temperature was added and the mixture was shaken. A 1-ml. aliquot was then transferred to the thermostated polarimeter tube and the rest of the solution was placed in a thermostated bath at the same temperature. Zero time was taken from when 0.5 ml. of the standard base had been added (about 10 seconds) to the solution of the compound. The first polarimetric reading was taken at about $t = 4$ min. Air was kept away from the solutions at all times by filling the pipettes, polarimeter tube, etc., with nitrogen, and storing and transferring the solutions under nitrogen. In all runs the polarimeter tube was emptied after about one-half life, and another aliquot of the solution in which the reaction had been proceeding in the thermostat was put in the tube, and the reaction was followed as before. If a plot of rotation *vs.* time for both samples could be fit by a single line, it was clear that no contamination of the reaction solution had occurred after the solution was prepared. This check was most important, as in the preliminary work the solution transfers were made in air in the ordinary way and the rate was inevitably much slower in the transferred solution. Any runs showing such contamination were discarded.

TABLE III

EPIMERIZATION OF COMPOUND I; A TYPICAL RATE RUN

t = 30.05° I = 0.001337 *M*, Time (Min.)	OH^- = 0.000822 M Solvent Methanol ("Spectra grade") α obs.°	t = 30.05° I = 0.001337 *M*, Time (Min.)	OH^- = 0.000822 M Solvent Methanol ("Spectra grade") α obs.°
0	—	121.8	0.116
4.5	0.353	129.5	0.102
9.3	0.345	145.0	0.072
11.8	0.336	160.0[a]	0.047
16.3	0.330	167.5	0.036
20.0	0.311	171.0	0.023
27.0	0.304	174.5	0.018
33.8	0.295	188.5	−0.009
40.0	0.288	191.3	−0.009
62.5	0.231	209.3	−0.036
72.0	0.205	220.2	−0.055
77.0	0.205	223.0	−0.057
95.5	0.167	00.0	−0.658
107.5	0.136		

[a] After this reading the polarimeter tube was emptied and refilled with another aliquot of reaction solution which had been kept in the thermostat. The points obtained after this time were not used to calculate the rate constant, but only to demonstrate qualitatively the absence of gross contamination of the original aliquot in transfer.

The results of a typical rate run are given in Table III.

The change in rotation in each case followed pseudo first order kinetics. The order of the reaction with respect to base was found by using different base concentrations in a few cases. It was concluded that, as expected, the reactions were second order overall, first order in ketone and first order in base.

The second order rate constants for the reversible reactions

$$A \underset{k'}{\overset{k}{\rightleftharpoons}} B$$

were found using equations (1), (2), and (3), where t is elapsed time, α is the observed rotation at time t, α_0 and α_∞ are the values of rotation at $t = 0$ and $t = \infty$ respectively. For the irreversible reactions the expression simplifies to (4).

$$k + k' = \frac{\ln(\alpha - \alpha_\infty) - \ln(\alpha_0 - \alpha_\infty)}{(t)\,(OH^-)} \quad (1)$$

$$k + k' = k_0 \quad (2)$$

$$k = k_0 \frac{(B)}{(A + B)} \quad (3)$$

$$k = \frac{\ln(\alpha_0 - \alpha_\infty) - \ln(\alpha - \alpha_\infty)}{(t)\,(OH^-)} \quad (4)$$

In cases where the rates were determined at two temperatures the thermodynamic quantities were found from equation (5)–(7).

$$\Delta F_1{\ddagger} = -RT_1 \ln K_1{\ddagger} \text{ where } K_1{\ddagger} = \frac{hk_1}{kT_1} \quad (5)$$

$$\Delta S{\ddagger} = R(T_2 \ln K_2{\ddagger} - T_1 \ln K_1{\ddagger})/(T_2 - T_1) \quad (6)$$

$$\Delta H{\ddagger} = \frac{RT_1T_2 \ln (K_2{\ddagger}/K_1{\ddagger})}{T_2 - T_1} \quad (7)$$

Where k is Boltzmann's constant, k_1 is the rate constant at a temperature T_1, and the other symbols have the usual meanings.

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DETROIT 2, MICH.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Acid-Base Effects in the Ring-Chain Tautomerism of α-[(β-Hydroxyethyl)-amino]desoxybenzoins[1]

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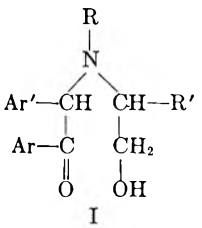
In three α-(hydroxyethyl) secondary amino ketones it has been shown by ultraviolet absorption studies that the ring chain equilibria in $5 \times 10^{-5}M$ 95%-ethanol solution are shifted by acid consistently in the direction of the cyclic hemiketal forms, and it has been shown by infrared absorptivities that in the solid state the hydrochlorides of these three compounds are entirely cyclic. The promotion of cyclization by protonation is explained in terms of the steric effect of the second hydrogen and the positive charge on the nitrogen.

Acidities of the hemiketal hydroxyls of the cyclic compounds in 95% ethanol were demonstrated by conductimetric titrations which gave relative pK'_a values of 9.5–10.4 for this group.

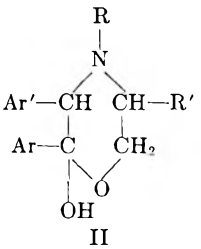
Sodium isopropoxide reduced six cyclic hydroxyethylamino ketones which had resisted reduction by aluminum isopropoxide.

Previous studies on the effect of structure on ring-chain tautomerism in the α-[(β-hydroxyethyl)-amino]desoxybenzoins (I–II)[3] have demonstrated that in certain arrangements a mobile equilibrium exists which depends upon and is affected by sterically active substituents (R and R′) and by *para* substituents in the aroyl group (Ar).[4] This investigation was undertaken to determine acid and base effects on the equilibrium position.



I

(chain form)



II

(ring form)

	R	R′	Ar[a]	Ar′[a]
a.	H	C_2H_5	C_6H_5	C_6H_5
b.	H	C_2H_5	ClC_6H_4	ClC_6H_4
c.	H	C_2H_5	$CH_3OC_6H_4$	$CH_3OC_6H_4$
d.	C_2H_5	H	C_6H_5	C_6H_5
e.	C_2H_5	H	$CH_3OC_6H_4$	C_6H_5
f.	H	H	C_6H_5	C_6H_5
g.	$CH_2C_6H_5$	H	C_6H_5	C_6H_5
h.	C_2H_5	H	C_6H_5	H
i.	C_2H_5	H	ClC_6H_4	ClC_6H_4
j.	H	$CH_2C_6H_5$	C_6H_5	C_6H_5

[a] Indicated substituents are *para*.

α-[2-(1-Hydroxybutyl)amino]desoxybenzoin (Ia–IIa) was chosen for study because the ring-chain equilibrium of its hydrochloride in $5 \times 10^{-5}M$ 95% ethanol solution where extensive hydrolysis or alcoholysis must occur has been shown by the significant aroyl-type ultraviolet absorptivity of ϵ 3980 at 246 mμ to be evenly balanced.[5] A $5 \times 10^{-5}M$ solution of the base Ia–IIa (which has not been isolated in crystalline form), prepared by adding the calculated amount of standardized sodium hydroxide to a 95% ethanol solution of the hydrochloride and adjusting the volume, showed an aroyl-type absorptivity of ϵ 6920 at 248 mμ which corresponds to an equilibrium ratio of approximately 40:60 of ring *vs.* chain tautomer, a significantly higher ratio of chain tautomer than is present in a solution of the pure hydrochloride under these conditions. Neutralization of the base with exactly one equivalent of alcoholic hydrogen chloride restored the characteristic absorptivity of the solution of the hydrochloride and showed the change to be reversible. Acidification of the initial solution of the hydrochloride by adding one equivalent quantity of alcoholic hydrogen chloride lowered ϵ to 1940 at 249 mμ, a result which indicated a marked shift in the equilibrium position in the opposite direction to a point of predominance of the cyclic form. In these experiments there were no significant changes either in the shape of the curve or in the wave length of the absorption maximum which would indicate involvement in solution of any molecular species other than I and II and their hydrochlorides.

The generality of the effect of acid on the equilibrium position was tested by a similar study of solutions of the hydrochlorides of the di-*p*-chloro

(1) This work was initiated under a research grant from the Eli Lilly Co.

(2) Holder of E. I. du Pont de Nemours Company Postgraduate Fellowship 1954–55. Present location: Department of Chemistry, University of Pittsburgh.

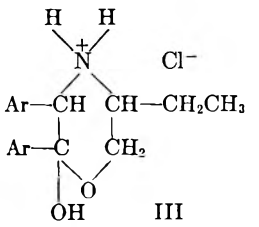
(3) (a) R. E. Lutz, J. A. Freek, and R. S. Murphy, *J. Am. Chem. Soc.*, **70**, 2015 (1948); (b) R. E. Lutz and R. S. Murphy, *J. Am. Chem. Soc.*, **71**, 996 (1949); (c) R. E. Lutz and R. H. Jordan, *J. Am. Chem. Soc.*, **71**, 478 (1949); (d) W. L. Truett, Dissertation, University of Virginia (1950); (e) C. D. Lunsford, R. E. Lutz, and E. E. Bowden, *J. Org. Chem.*, **20**, 1513 (1955); (f) R. E. Lutz and J. W. Baker, *J. Org. Chem.*, **21**, 49 (1956).

(4) C. E. Griffin and R. E. Lutz, *J. Org. Chem.*, **21**, 1131 (1956).

(5) The method of determination of equilibrium mixture composition from the absorption spectral curves has been described previously.[4] The calculation is a rough approximation and is based on the assumption that the aroyl group molar ultraviolet absorptivity of both the ring and the chain tautomers approximate those of reference compounds existing exclusively in ring or chain forms.

and di-*p*-methoxy analogs, Ib and Ic. In the case of the di-*p*-chloro compound where the activating effect of the *p*-chlorine of the aroyl group causes predominance of the cyclic form in $5 \times 10^{-5}M$ solution, acidification shifted the equilibrium position still further in that direction as shown by the depression of ϵ at 261 mμ from 1700 to 1580. In the case of the di-*p*-methoxy compound which is largely acyclic due to the deactivating influence of the *p*-methoxyl on the carbonyl group activity, the effect of one equivalent of excess acid was sufficient to counteract almost completely the marked electronic effect and to shift the equilibrium dramatically toward the cyclic form, as shown by the depression of ϵ at 285 mμ from 17,300 to 1900.

Since excess acid would suppress hydrolysis of the hydrochlorides to bases, maintaining a relatively high degree of protonation of the nitrogen, it seemed probable that the hydrochlorides in the solid state would be completely in the cyclic form, III, because in the crystal lattice the proton would be held at the nitrogen. The absence of benzoyl type bands in the 6 μ region of the infrared absorption spectra[6] of the three crystalline hydrochlorides of Ia, Ib, and Ic, in potassium chloride pellets, proves this to be so. Incidentally, only the di-*p*-chloro compound (IIIb) showed the characteristically strong and sharp bands in the 2.85 μ region which is normal for a free or single-bridge bonded hydroxyl group. In the cases of the other two (IIIa and IIIc) the hydroxyl bands were drastically shifted bathochromically to 3.12 and 3.16 μ respectively, and they were relatively broad and suggestive of polymeric association.



III

a. Ar = C_6H_5
b. Ar = $ClC_6H_4(p)$
c. Ar = $CH_3OC_6H_4(p)$

From the above studies it is clear that the ring-chain equilibrium positions in solutions of the base Ia–IIa and others of this type are shifted in very significant degree in the direction of the cyclic forms by protonation and development of a positive charge on the nitrogen atom. However, similar protonation of the parent hydroxyethyl-secondary-amino ketone If which is without a substituent on the hydroxyethyl chain, although presumably (also) inducing increased activity of the carbonyl group of the acyclic form, does not overcome the factors favoring that form. The effect of protonation therefore appears to be important only when the molecule is so substituted as already to be predisposed or able to cyclize and where a moderately balanced ring-chain equilibrium exists in solutions of the base. The phenomenon may be explained in part in terms of the appreciable added steric restrictions of freedoms of motion in the molecules by the second *N*-hydrogen which completes the tetrahedral onium-ion structure, an effect which would presumably be relatively more important in the chain than in the cyclic tautomer; and it may be explained in part in terms of the inductive effect of the positive charge on nitrogen which should increase the activity at the carbonyl carbon more effectively than it would diminish the donor activity of the alcoholic oxygen. There is an analogy to the significant electronic effect of *para* substitution in the aroyl group which likewise becomes evident and significant *only* when the ring-chain equilibrium is a moderately balanced one.[4,7] The steric effect of the onium-*N*-hydrogen, if it is important, would be analogous to the dramatic steric effect of substitution of an *N*-alkyl group for *N*-hydrogen by which cyclization is promoted in the predominantly acyclic hydroxyethyl secondary amino ketones such as If.

Attempts to study spectrophotometrically the effect of excess of strong base, sodium hydroxide, on compounds of the type I–II at 5×10^{-5} *M* dilution in 95% ethanol, have not been explored fully because of the sensitivity of alkaline solutions of these compounds. It may reasonably be postulated that the cyclic or hemiketal forms of the bases would have appreciable though weak acidity like that of fructose,[10,11] whereas the acyclic forms like ordinary alcohols would not be acidic in this sense. Concomitantly it may be postulated that the alkoxide ions of the acyclic forms would cyclize to hemiketal anions if maintained in sufficient concentration and if favorable steric elements existed, as in Ia–IIa.

To demonstrate experimentally the expected hemiketal acidities of the predominantly cyclic compounds of type II, acid-base titrations were made[12,13] of a number of examples of ethanolamino ketones representing different ring-chain equilibrium positions (I–II, a–d) and also of the compound If which is important for reference because

(6) The infrared determinations were made by Dr. Bernard J. Haske.

(7) It should be pointed out that complete separation of electronic and steric factors cannot be made because one necessarily affects the other. Furthermore there may be a difference in effectiveness of intramolecular hydrogen bondings in the two forms and in the cation *vs.* the bases, where nitrogen may donate to the hydroxylic hydrogen and the oxygen may donate to an *N*-hydrogen.[8,9]

(8) E. D. Bergmann, E. Gil-Av, and S. Pinchas, *J. Am. Chem. Soc.*, **75**, 68 (1953).

(9) A. Gero, *J. Org. Chem.*, **16**, 1222 (1951).

(10) T. Madsen, *Zeit. Phys. Chem.*, **36**, 290 (1901).

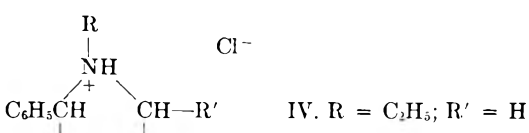
(11) H. Lunden, *Zeit. Phys. Chem.*, **54**, 532 (1906).

(12) Potentiometric titration of the compound was attempted initially but it was found that at the neutralization point of the hemiketal hydroxyl the *p*H of the solution was too high to be measured accurately because of the sensitivity of the glass electrode in strongly alkaline solutions.

(13) The procedure used was that of E. B. Leffler, H. M. Spencer, and A. Burger, *J. Am. Chem. Soc.*, **73**, 2611 (1951).

the evidence indicates that it is entirely acyclic and does not exist in the cyclic form under any of the conditions involved here. It is necessary to use non-aqueous media for titrations because of the water insolubility of the organic bases involved. The most satisfactory solvent was 95% ethanol, and the courses of titrations were followed conductimetrically. The acidities thus measured are not true pK_a values, and therefore are only qualitatively comparable with the true pK_a 12.1 of fructose determined in water;[10,11] but they may be expressed as relative pK_a' values which are significant in the comparison limited to the series I–II.

Under such conductimetric titrations the hydrochlorides of the three compounds IIa, IIb, and IId which had absorption characteristics indicating considerable or high degrees of cyclization, were shown each to possess two acidic groups by their relative pK_a' values in the two ranges, 6.2–6.7 for the amine-onium ion group, and 9.5–10.4 for the hemiketal hydroxyl group of the cyclic forms. Benzyl alcohol itself showed no detectable acidity under these conditions, and the aminodialcohol hydrochlorides IV and V each showed only one inflection point and that for the more strongly acidic amine-onium group, and no inflection in the weakly acid range. Two α-ethanolaminodesoxybenzoin hydrochlorides, Ic–IIc, and the α-(β-hydroxyethylamino) compound If, which had previously been shown to exist, the former predominantly and the latter exclusively in the acyclic form I, showed only one relatively strongly acidic group of the amine-onium type and showed no weakly acidic hemiketal group of sufficient acid strength or availability to detect by titration. Thus these studies demonstrate that the hemiketals of type II have definite though weak acidities which are of a distinctly higher order than those of compounds carrying ordinary benzyl alcohol groups such as are present in the more stable acyclic or chain types (I) and in the carbonyl-reduced types IV and V; and that acidity with ready anion formation is a property peculiar to the cyclic tautomer of the ring-chain tautomeric pair I–II and may be some measure of occurrence and/or stability of the cyclic form.



IV. R = C_2H_5; R′ = H

V. R = H; R′ = C_2H_5

Sodium isopropoxide reductions. Incidental to the study of the effect of base on the ring-chain equilibria in α-[(β-hydroxyethyl)amino]desoxybenzoins, six ethanolamino desoxybenzoins and acetophenones (Ib, d, g, h, i, j) which had been shown to exist chiefly in the cyclic forms II and to be resistant to reduction by aluminum isopropoxide,[3,4] were successfully reduced by means of sodium isopropoxide[14] to dialcohols corresponding to IV–V. Although these results might be accounted for in terms of the greater reducing power or speed of action of sodium isopropoxide as compared with aluminum isopropoxide,[14] it would be of importance in any attempt at explanation to know the effect of aluminum isopropoxide as a Lewis acid and of sodium isopropoxide as a strong base on the ring-chain equilibrium position[cf. 15] and on cyclic (hemiketal) anion formation, and to know to what extent if any the more powerful reagent sodium isopropoxide may directly reduce the cyclic form or its anion.

EXPERIMENTAL

The preparations of the compounds employed in these studies have been previously described.[3,4]

The *ultraviolet absorptivities* were determined using a Beckmann Model DU quartz spectrophotometer. For the spectra of compounds in the presence of acid or base, solutions were prepared by dissolving weighed amounts in 95% ethanol, adding the calculated amount of standardized acid or base from a micro buret, and making up the volume by addition of more ethanol.

Infrared absorption spectra of the hydrochlorides of the three compounds IIa, IIb, and IIc in potassium chloride pellets were determined using a Perkin-Elmer Model 21 spectrophotometer.[6]

Conductimetric titrations at 23.5° were followed by means of an Industrial Instruments Conductivity Bridge Model RC 16 using unplatinized electrodes and a frequency of 1000 cycles per second. The samples were weighed directly on an analytical balance, dissolved in 95% ethanol and titrated with 0.0213*N* sodium hydroxide in 95% ethanol. Equivalence points were obtained from a plot of corrected conductance *vs.* equivalents of base added. Apparent *dissociation constants* of the conjugate acids of the amines were determined[13] by measuring the apparent *p*H of a solution at 23.5° containing equivalent concentrations of amine and salt. Solutions were prepared by the addition of an amount of 95% ethanolic sodium hydroxide calculated for half neutralization, to a solution of known amount of the salt in 95% ethanol. For the determination of the second acidic group, a total of 1.5 equivalents of base was added. Solutions were made up to a constant volume of 200 ml. by the addition of 95% ethanol. Concentrations of salt and free base at the half neutralization point were in the range 5–10 × $10^{-4}M$. The *p*H values were determined by means of a Leeds and Northrup *p*H Meter employing calomel and glass electrodes.

Relative pK_a' values for the amine-onium ion group thus determined at 23.5° were: Ia,[4] 6.63; Ib,[4] 6.30; Ic,[4] 6.72; Id,[3a] 6.22; If,[3a] 6.22; and for 2,3-diphenylmorpholine hydrochloride,[3f] 6.18. Corresponding relative pK_a' values for the more weakly acidic hemiketal hydroxyls were: Ia, 9.50; Ib, 10.00; Ic, none; Id, 10.23; If, none; the others of the above series showed no second inflection for a weakly acidic group.

Sodium isopropoxide reductions. A mixture of 0.1 mole of freshly prepared sodium isopropoxide, 0.03 mole of the amino ketone and 100 ml. of dry toluene, was refluxed for 10 hr. in an atmosphere of nitrogen, allowed to cool to room temperature, hydrolyzed with ice-cold 5% hydrochloric acid, neutralized with 10% aqueous sodium carbonate, and extracted with ether. The ethereal extracts were washed with

(14) R. B. Woodward, N. L. Wendler, and F. J. Brutschy, *J. Am. Chem. Soc.*, **67**, 1425 (1945).

(15) R. H. Jordan, Dissertation, University of Virginia (1948).

water, dried over sodium sulfate, decanted, and acidified with ethereal hydrogen chloride. The solid products were recrystallized until constant melting points were obtained and they were identified by mixture melting points with authentic samples of the hydrochlorides of the known di-alcohols.

The following amino ketones were successfully reduced, and the yields of identified products (corresponding to IV–V) were: α-[*N*-ethyl-*N*-(β-hydroxyethyl)amino]desoxybenzoin[3a] (IId) (51%); α-[*N*-benzyl-*N*-(β-hydroxyethyl)amino]-desoxybenzoin[3d] (IIg) (43%); α-[*N*-ethyl-*N*-(β-hydroxy-ethyl)amino]acetophenone[3c] (IIh), product isolated as the picrate (61%); α-[*N*-ethyl-*N*-(β-hydroxyethyl)amino]-*p,p'*-dichlorodesoxybenzoin[3b] (IIi) (58%); α-[*N*-(1-hydroxy-2-butyl)amino]-*p,p'*-dichlorodesoxybenzoin[4] (IIb) (64%); α-[*N*-2(3-phenyl-1-hydroxypropyl)amino]desoxybenzoin[4] (IIj) (49%); the recrystallization solvents and physical characteristics of the dialcohols prepared, are those given in the references.

Acknowledgment. We wish to thank Dr. Thomas I. Crowell for helpful discussions and criticism during the course of this investigation and Dr. C-K. Dien for checking some of the experiments.

CHARLOTTESVILLE, VA.

[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH LABORATORY, THE DOW CHEMICAL COMPANY]

Adducts of *tert*-Alcohols Containing an Ethynyl Group with Dihydropyran. Potentially Useful Intermediates

DALE N. ROBERTSON

Received December 22, 1959

Acetylenic alcohols of the type RR'C(OH)C≡CH have been found to add smoothly and in high yield to dihydropyran to form tetrahydropyranyl compounds of the general structure RR'C(C≡CH)O—(C_5H_9O). The tetrahydropyranyl grouping is stable to alkali but easily removed by aqueous acid or exchangeable with lower alcohols by acid catalysis. Organometallic intermediates are easily formed by reaction at the acetylenic hydrogen and compounds such as the γ-hydroxy-α,β-acetylenic acids, esters, and ketones thus are readily available.

Woods and Kramer[1] introduced dihydropyran for the protection of hydroxyl groups. Alcohols and phenols were added to dihydropyran by acid catalysis and the resulting adducts were found to be stable to alkali.

Later (1948), Parham and Anderson[2] extended this work to include adducts of other monohydric phenols and some dihydric phenols. The adducts were found to be stable to lithium alkyls. For example, the *p*-bromophenol–dihydropyran adduct was treated with butyllithium and carbonated. Removal of the tetrahydropyranyl group was then accomplished with aqueous acid.

In 1950, Henbest, Jones, and Walls[3] prepared an adduct with propargyl alcohol and in 1953, Jones and Mann[4] used the same adduct in the preparation of 4,4-diethoxy-2-butyn-1-ol.

On hydrolysis, the tetrahydropyranyl group is converted to γ-hydroxyvaleraldehyde.[2] Alcoholysis gives 2-alkoxytetrahydropyrans.[1] Both are easily separated from the desired products.

A British patent (698,736) claims the addition of primary and secondary alcohols to selected dihydropyrans but gives no examples with secondary alcohols.

Crombie and Jocklin[5] have reported the addition of a secondary alcohol to dihydropyran.

In each of the above cases, either concentrated hydrochloric acid or phosphorus oxychloride was employed as catalyst and the products worked up with ether. We have extended this work to include a number of tertiary ethynyl alcohols of the general formula RR'C(OH)C≡CH, where R is alkyl or phenyl and R' is methyl and where R and R' make up a cycloalkyl ring. Although tertiary alcohols are known to present steric problems in some reactions, we have found that each of the alcohols employed here gave pure products in good yield (see Table I).

In order to avoid volatile catalysts and to simplify work-up of the reaction mixture, *p*-toluenesulfonic acid was used as catalyst. Anhydrous potassium carbonate was added to the cooled reaction mixture to neutralize the acid and the product could then be distilled after a simple filtration.

If ether or other solvents are used in the work-up it should be noted that a basic or neutral drying agent *must* be employed. *Magnesium sulfate* is sufficiently *acid* to reverse the addition in only a few hours.

The tetrahydropyranyl compound thus formed provides protection for the hydroxyl group and, even where the hydroxyl group may not need protection, provides a degree of solubility which can be useful. For example, in the carbonation

(1) G. F. Woods and D. N. Kramer, *J. Am. Chem. Soc.* **69**, 2246 (1947).

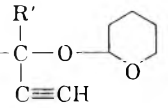
(2) W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.* **70**, 4187 (1948).

(3) H. B. Henbest, E. R. H. Jones, and I. M. S. Walls, *J. Chem. Soc.*, 3646 (1950).

(4) R. G. Jones and M. J. Mann, *J. Am. Chem. Soc.* **75**, 4048 (1953).

(5) L. Crombie and A. G. Jocklin, *Chem. & Ind. (London)*, **1954**, 1197.

TABLE I

TETRAHYDROPYRANS:[a] 

R	R′	B.P.°	Press., mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	CH_3	64.5–65.5	8	$C_{10}H_{16}O_2$	71.39	71.16	9.59	9.45
CH_3CH_2	CH_3	62.5–64.5	3.3	$C_{11}H_{18}O_2$	72.49	72.62	9.95	9.67
$(CH_3)_2CHCH_2$	CH_3	47–50	0.6–0.2	$C_{12}H_{22}O_2$	74.24	73.94	10.55	10.24
$CH_3(CH_2)_5$	CH_3	76–77	0.12	$C_{15}H_{26}O_2$	75.58	75.08	10.99	10.45
	CH_3	99–100.5	0.02	$C_{15}H_{18}O_2$	78.22	78.37	7.88	7.85
R,R′= 		101.5–102.5	3.6–3.7	$C_{13}H_{20}O_2$	74.96	74.67	9.68	9.52

[a] Yields ranged from 60.4 to 84.4%.

of the Grignard derivative of the ethynyl alcohols, the magnesium derivatives of the free alcohols are so insoluble, even in tetrahydropyran, as to present contact problems and thus inordinate reaction times. The dihydropyran adducts, however, are quite soluble, even at −70°.

EXPERIMENTAL

General procedure. The appropriate alcohol (1 mole) and dihydropyran (1.2–2 moles) are mixed in a round-bottomed flask fitted with a thermometer or thermocouple well and a reflux condenser with drying tube. A few crystals of *p*-toluenesulfonic acid are added and dissolved by swirling. With the lower molecular weight alcohols, the exothermic addition begins almost at once and the reaction is usually complete within 0.5–1 hr. With higher molecular weight alcohols, the mixture may be heated on the steam bath for 0.5–1 hr. to ensure complete addition.

A gram or two of anhydrous potassium carbonate is added to the cooled mixture and stirred well for 0.5 hr. or allowed to stand overnight. A magnetic stirrer is most convenient for stirring. The salts are removed by filtration, excess dihydropyran recovered by distillation at atmospheric pressure and the product by distillation at reduced pressure (Table I).

The products are colorless, slightly to very viscous and indefinitely stable in the absence of acid.

It should be mentioned that, in a test tube experiment, evidence was obtained that even *tert*-butyl alcohol adds readily to dihydropyran, though no attempt was made to isolate the product.

Since an equimolar mixture of the two reactants would contain the same carbon and hydrogen values as the products, the infrared spectrum of each product was obtained. The spectra were consistent with their formulation as adducts; no hydroxy groups were detected and the acetylenic linkage and its reactive hydrogen were undisturbed.

MIDLAND, MICH.

[CONTRIBUTION FROM THE INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

Synthesis of 3-Methyl-5,6,7,8-tetrahydro-1-naphthol

DILIP K. DATTA AND P. BAGCHI

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Cyclization of the dienic acid obtained by dehydration followed by hydrolysis of ethyl γ-(Δ′-cyclohexenyl)-β-methyl-β-hydroxybutyrate with phosphorus pentoxide leads to the formation of 3-methyl-5,6,7,8-tetrahydro-1-naphthol whose structure was proved by dehydrogenation to 3-methyl-1-naphthol and also by an unambiguous synthesis.

A case of cyclization reaction involving an oxocarbonium ion belonging to an unsaturated side chain forming the part of a ring system and an ethylenic double bond was first studied by Bagchi, Bergmann, and Banerjee[1] in connection with the synthesis of 9-hydroxy-*sym*-octahydrophenanthrene. This observation has now been extended to the study of a case involving the cyclization of an ethylenic double bond present in a six-membered ring and a carboxyl group in a linear unsaturated side chain resulting in the formation of 3-methyl-5,6,7,8-tetrahydro-1-naphthol.[2]

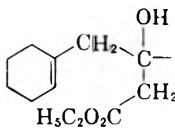
As a suitable system, the dienic acid (III, R = H) obtained by the dehydration and hydrolysis of ethyl γ-(Δ′-cyclohexenyl)-β-methyl-β-hydroxybutyrate (I) was prepared for this work. Cyclohexenyl acetone required as the starting material was prepared according to the method of

(1) P. Bagchi, F. Bergmann, and D. K. Banerjee, *J. Am. Chem. Soc.*, **71**, 989 (1949).

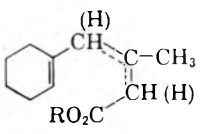
(2) D. K. Datta and P. Bagchi, *Sci. and Culture (Calcutta)*, **17**, 525 (1952).

Jupp, Kon, and Lockton[3] with modifications. The ketone showed the following ultraviolet absorption characteristics: λ max 235–245 mμ (log ε 2.8), indicating the presence of cyclohexylidene acetone to the extent of about 6.%. Our product is, therefore, essentially cyclohexenyl acetone. The ketone underwent a smooth reaction with ethyl bromoacetate in the presence of zinc in benzene solution to give ethyl γ-(Δ′-cyclohexenyl-β-methyl-β-hydroxybutyrate) (I) in 53% yield. This on dehydration with phosphorus pentoxide furnished a dienic ester (II, R = C_2H_5; yield 87%), which in turn on hydrolysis with ethanolic alkali gave the dienic acid (III, R = H) as a thick liquid which failed to crystallize. It may be noticed that the second double bond in II and III might assume a position of conjugation with respect to either the double bond of the cyclohexene ring or the carbethoxyl or carboxyl. The actual product might also represent a mixture of the bond and/or geometric isomers. Because of these reasons and our inability to obtain the acid III in a crystalline form we have not assigned the position of the second double bond with certainty in our products.

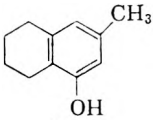
The dienic acid on heating with phosphorus pentoxide in benzene solution underwent cyclization to yield after treatment with ethanolic potassium hydroxide, acidification and washing with bicarbonate and distillation, a solid which on crystallization melted at 98.5° and had as analysis corresponding to methyltetrahydronaphthol. That the above compound possesses structure IV was proved by dehydrogenation over palladium-charcoal at 250° when 3-methyl-1-naphthol(V), melting point 91–92° was obtained.[4] The structures of IV and V were also confirmed by independent unambiguous syntheses described below:



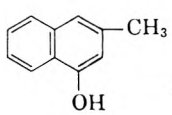
I



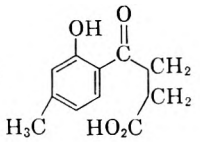
II. R = C_2H_5
III. R = H



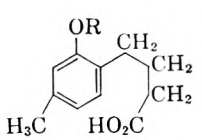
IV



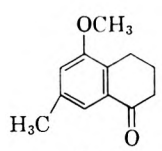
V



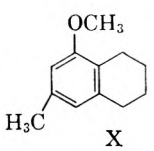
VI



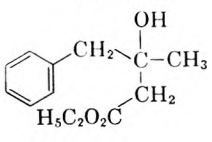
VII. R = H
VIII. R = CH_3



IX

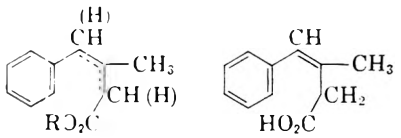


X



XI

(3) L. G. Jupp, G. A. R. Kon, and E. H. Lockton, *J. Chem. Soc.*, 1638 (1928).



XII. R = C_2H_5
XIII. R = H

XIV

Synthesis of 3 - methyl - 5,6,7,8 - tetrahydro - 1-naphthol.[5] For the preparation of a suitable starting material for the synthesis, the condensation between *m*-cresol and succinic anhydride was investigated; this led to the isolation of β-(2-hydroxy-4-methylbenzoyl)propionic acid (VI), m.p. 154°. The proof of the structure of the condensation product will be published in a subsequent communication. The keto acid (VI) was then reduced by Clemmensen's method using benzene as the immiscible solvent to yield γ-(2-hydroxy-4-methylphenyl)butyric acid (VII, R=H) almost quantitatively. Attempts to cyclize this acid directly with sulfuric acid under various experimental conditions failed, presumably due to sulfonation of the benzene nucleus. The acid was, therefore, methylated with dimethyl sulfate and alkali to γ-(2-methoxy-4-methylphenyl)butyric acid (VIII, R = CH_3) in an almost quantitative yield. Methylation of this acid was smooth, unlike the methylation of the keto acid (VI). The difficulty of methylation of VI no doubt arises from the existence of an internal hydrogen bond between the hydrogen of the phenolic hydroxyl and the oxygen of the carbonyl. The acid (VIII, R = CH_3) was cyclized with phosphorus oxychloride in tetrachloroethane to 1-methoxy-3-methyl-5-keto-5,6,7,8-tetrahydronaphthalene (IX, yield 64%). Reduction of IX according to the Hueng-Minlon method gave 3-methyl-5,6,7,8-tetrahydro-1-naphthol methyl ether (X, yield 60%) with only slight demethylation. The latter on demethylation with hydrobromic acid–acetic acid furnished 3-methyl-5,6,7,8-tetrahydro-1 naphthol, m.p. 98° (yield 80%) identical in every respect with the cyclized product IV.

Subsequent to our preliminary publication[5] of the above results, preparations of the compounds VII, VIII, and IX have been described by Cooke and Dowd[6] and Davies and Roberts[7] using almost identical procedures.

Synthesis of 3-methyl-1-naphthol. This compound has been prepared by various workers[4] by more or less roundabout methods. Our method[8] for the synthesis of this compound consists of four steps

(4) M. Tishler, L. F. Fieser, and N. L. Wendler, *J. Am. Chem. Soc.*, **62**, 2866 (1940); J. Cason, *J. Am. Chem. Soc.*, **63**, 828 (1941).

(5) D. K. Datta and P. Bagchi, *Sci. and Culture (Calcutta)*, **18**, 95 (1952).

(6) R. G. Cooke and H. Dowd, *Australian J. Chem.*, **6**, 53 (1953).

(7) J. E. Davies and J. C. Roberts, *J. Chem. Soc.*, 2173 (1956).

(8) D. K. Datta and P. Bagchi, *Sci. and Culture (Calcutta)*, **18**, 243 (1952).

only which are easily carried out. Benzyl methyl ketone prepared according to the method of Julian and Oliver[9] was condensed with ethyl bromoacetate under Reformatsky conditions to give ethyl γ-phenyl-β-methyl-β-hydroxybutyrate (XI, yield 97%). Dehydration of this compound with phosphorus oxychloride in pyridine yielded an unsaturated ester (XII, R= C_2H_5; yield almost quantitative), which furnished on hydrolysis with ethanolic alkali an acid (XIII, R = H; yield 77%) which partially crystallized. The crystalline acid, m.p. 113°, showed the following ultraviolet absorption characteristics: $\lambda_{max.}$ 249 mμ (log ε 4.1), proving it to be an open-chain styrene derivative,[10] and hence to possess the structure XIV. The absorption properties of the gummy portion indicate the presence of both bond isomers in it, since a considerable amount of absorption is observed between 220 and 250 mμ. When the mixture of acids (XIII, R = H) was cyclized with phosphorus oxychloride in tetrachloroethane, 3-methyl-1-naphthol, m.p. 92°, was obtained in 28% yield. This product did not show any melting point depression on admixture with the product V described above.

EXPERIMENTAL

All melting and boiling points are uncorrected.

Cyclohexenyl acetone. To a cooled solution of sodium (23 g., 1 atom) in dry ethanol (300 ml.), a cold mixture of cyclohexanone (98 g., 1 mole) and ethyl acetoacetate (130 g., 1 mole) was added with shaking. After keeping overnight, the solution was refluxed for 24 hr. Water (300 ml.) was added and the resulting mixture was refluxed again for 3 hr. The reaction mixture was then acidified with cold hydrochloric acid and worked up as usual, and the resulting oil was finally distilled. The fraction boiling at 60–110°/15 mm. was collected. The product (66 g.) was carefully fractionated and collected at 58–65°/3 mm.; yield 46 g. *Semicarbazone,* m.p. 144–145° (lit.,[3] m.p. 145°). Under atmospheric pressure, the ketone could be distilled at 195–205° without much decomposition; λ_{max}^{alc} 235–245 mμ (log ε 2.8).

Ethyl γ-(Δ¹-cyclohexenyl)-β-methyl-β-hydroxybutyrate (I). A mixture of cyclohexenylacetone (27.6 g., 0.2 mole), ethyl bromoacetate (50 g., 0.3 mole), and activated zinc wool (26 g., 0.4 atom) in dry benzene (160 ml.) was heated on a water bath, when a vigorous reaction set in. After the initial vigor had subsided, the reaction mixture was refluxed for 2 hr. The greenish-yellow liquid was decanted from the unchanged zinc, acidified strongly with cold hydrochloric acid and shaken vigorously. The benzene solution was then separated and washed consecutively with water, dilute ammonia, and water. The solvent was removed, and the residue distilled to yield 24 g. (53%) of I, b.p. 139–142°/3 mm., n_D^{32} 1.4846.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 69.0; H, 9.7. Found: C, 69.3; H, 9.6.

Dehydration to the dienic ester (II, R = C_2H_5). To a boiling solution of the hydroxy ester (I, 18 g., 0.08 mole) in dry benzene (125 ml.), phosphorus pentoxide (17 g., 0.12 mole) was added in three portions during 1 hr. Thereafter, the mixture was refluxed for 2.5 hr. The benzene layer was decanted and the dark-brown residue was extracted three times with boiling benzene. The pentoxide was then decomposed carefully with cold water and extracted with benzene. The combined benzene layer was washed with water and fractionated to yield 14.5 g. (87%) of the dienic ester, b.p. 125–132°/3 mm.; n_D^{32} 1.4903.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 75.0; H, 9.6. Found: C, 74.8; H, 9.5.

Hydrolysis to the dienic acid (III. R = H). The dienic ester (II, 10.4 g., 0.05 mole) was added to a solution of potassium hydroxide (5.6 g., 0.1 mole) in methanol (60 ml.) and the resulting solution was refluxed for 4 hr. and then evaporated on the water bath. The dark viscous residue was dissolved in water from which any unsaponified matter was extracted with ether. On acidification of the alkaline solution with cold hydrochloric acid, a dark brown oil separated which was extracted with benzene. After washing the benzene solution with water, the solvent was evaporated *in vacuo*, and the dienic acid (*ca.* 8 g.) was obtained as a thick liquid which failed to crystallize.

3-Methyl-5,6,7,8-tetrahydro-1-naphthol (IV). To a boiling solution of the dienic acid (III, 8 g., 0.045 mole) in dry benzene (120 ml.), phosphorus pentoxide (12.7 g., 0.09 mole) was added in three small portions during 1.5 hr. After refluxing for 2.5 hr., the reaction mixture was worked up as usual. The benzene solution was then evaporated and the residue was refluxed with a solution of potassium hydroxide (5 g.) in methanol (45 ml.) for 1 hr. The residue obtained on evaporating the solution was dissolved in water and acidified with dilute hydrochloric acid at 0°, when an oil separated which was extracted with ether. The ethereal layer was washed successively with water, 5% sodium bicarbonate solution and water and dried over anhydrous sodium sulfate. Distillation gave 1.4 g. of a light-yellow thick liquid, b.p. 127–132°/2 mm., which solidified on cooling. After removing the oily material on a porous tile, the solid melted at 97–98°. The solid was crystallized from petroleum ether (40–60°) to yield colorless long needles of the tetrahydronaphthol, m.p. 98.5°; the melting point was not raised on further crystallization.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.4; H, 8.6. Found: C, 81.2; H, 8.5.

The naphthol produced a deep violet coloration with a drop of ferric chloride in ethanolic solution.

3-Methyl-1-naphthol (V). The mixture of tetrahydronaphthol (IV, 0.5 g.) and palladium-charcoal (0.3 g., 30%) was taken in a small dehydrogenation apparatus, and heated on a metal bath initially kept at a temperature of 220°, and finally at 300°. Carbon dioxide gas was swept through the system and the evolved hydrogen was collected and measured by the displacement of a 40% solution of potassium hydroxide. After heating for 4 hr., the calculated volume of hydrogen was liberated. The residue was extracted with chloroform. The solvent was removed and the residue was evaporatively distilled at 160–165° (bath temperature)/40 mm. The solid distillate was crystallized from petroleum-ether (40–60°) to yield the naphthol as pale-yellow flakes, m.p. 91–92° [lit.,[4] m.p. 91–92°].

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.5; H, 7.5. Found: C, 82.4; H, 7.3.

γ-(2-Hydroxy-4-methylphenyl)butyric acid (VII, R = H). To amalgamated zinc (from granulated zinc, 21.4 g., mercuric chloride, 2.14 g., water, 36 ml. and concd. hydrochloric acid, 1 ml.) was added successively water (14 ml.), concd. hydrochloric acid (31 ml.), benzene (36 ml.), and β-(2-hydroxy-4-methylbenzoyl)propionic acid (10.4 g., 0.05 mole). The mixture was gently refluxed over a free flame for 30 hr., adding concd. hydrochloric acid (12-ml. portions) every 6 hr. After decanting the liquid, the benzene layer was separated and the aqueous portion extracted with ether. From the combined organic extract, the solvent was removed and the residue was triturated with a few drops of glacial acetic acid to yield VII as a white powder, weighing 9.6 g. (99%), m.p. 77°. Two crystallizations from benzene–petroleum ether gave white flakes, m.p. 80.5°.

(9) P. L. Julian and J. J. Oliver, *Org. Syn.*, Coll. Vol. II, p. 391.

(10) M. A. Ramart-Lucas and P. Amagat, *Bull. Soc. Chim.*, [4] 51, 119 (1932).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.2. Found: C, 68.1; H, 7.1.

γ-(2-Methoxy-4-methylphenyl)butyric acid (VIII, R = CH_3). The hydroxy acid (VII, 8 g., 0.04 mole) was methylated with dimethyl sulfate (15 g., 0.12 mole) in a 10% solution of sodium hydroxide (10 g., 0.24 mole) in the usual manner. After extracting the alkaline solution with ether, it was acidified with cold hydrochloric acid and the precipitate was filtered. The solid weighed 8.3 g. (almost quantitative). The methoxy acid crystallized from light petroleum ether (40–60°) as white flakes, m.p. 53°; the melting point was not raised on further recrystallization.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.6. Found: C, 68.9; H, 7.3.

1-Methoxy-3-methyl-5-keto-5,6,7,8-tetrahydronaphthalene (IX). To a solution of the methoxy acid (VIII, 6 g.) in dry tetrachloroethane (120 ml.) was added phosphorus oxychloride (3 ml.) dropwise with shaking and the mixture was boiled for 2.5 hr. Water was added and the tetrachloroethane was distilled in steam. The semisolid residue was dissolved in ether, the ethereal layer was washed successively with water, 5% sodium carbonate solution and water, and dried over sodium sulfate. Distillation gave 3.5 g. (64%) of a pale-yellow liquid, b.p. 132–136°/2 mm., $n_D^{32.5}$ 1.5596.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.8; H, 7.3. Found: C, 75.9; H, 7.5.

The *2,4-dinitrophenylhydrazone* crystallized from glacial acetic acid as bright-red needles, m.p. 229–230°, unchanged on further crystallization.

Anal. Calcd. for $C_{18}H_{18}N_5O_4$: N, 15.1. Found: N, 15.1.

1-Methoxy-3-methyl-5,6,7,8-tetrahydronaphthalene (X). A solution of the tetralone (IX, 3.6 g.) in diethylene glycol (10 ml.) was reduced according to the Huang-Minlon method[11] using potassium hydroxide (3.8 g., diethylene glycol (20 ml.), and 50% solution of hydrazine hydrate (5.6 ml.). After distilling the reaction mixture in steam, the distillate was extracted with ether, the ethereal layer was dried over anhydrous sodium sulfate, and the solvent was removed. The residue was distilled to yield 2.1 g. (60%) of a colorless mobile oil, b.p. 106–108°/3 mm., $n_D^{32.5}$ 1.5388.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.8; H, 9.1. Found: C, 82.2; H, 9.1.

3-Methyl-5,6,7,8-tetrahydro-1-naphthol (IV). A solution of the methyl ether (X, 1.6 g.) in glacial acetic acid (30 ml.) and 48% hydrobromic acid (12 ml.) was refluxed on an oil bath kept at 130° for 6 hr. The cooled solution was then poured into ice water and the pink solid was filtered. The naphthol weighed 1.2 g. (80%), m.p. 94°. The melting point rose to 98° after crystallization from petroleum ether (40–60°) and remained undepressed on admixture with the sample obtained previously through cyclization.

Ethyl γ-pheryl-β-methyl-β-hydroxybutyrate (XI). The Reformatsky reaction was carried out as before using benzyl methyl ketone (20 g., 0.15 mole), ethyl bromoacetate (31.4 g., 0.188 mole), activated zinc wool (19.5 g., 0.3 atom), and dry benzene (180 ml.). Distillation gave 32 g. (97%) of a colorless oil, b.p. 140–146°/3 mm., n_D^{22} 1.4994.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.2; H, 8.1. Found: C, 70.2; H, 8.2.

Dehydration to the unsaturated ester (XII, R = C_2H_5). To a solution of the β-hydroxy ester (XI, 8 g., 0.036 mole) in dry pyridine (18 ml.) cooled in ice, was added phosphorus oxychloride (2.8 g., 0.018 mole) dropwise with shaking. After allowing to stand overnight the mixture was warmed on the steam bath for 1 hr. and acidified with cold dilute hydrochloric acid. The organic matter was extracted with ether, the ethereal layer was separated, washed with a solution of sodium bicarbonate and water, and dried over sodium sulfate. On distillation, 7.5 g. (99%) of XII, b.p. 124–126°/1.5 mm. was obtained as a colorless oil, $n_D^{27.5}$ 1.5090.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.4; H, 7.8. Found: C, 76.6; H, 7.7.

Saponification to the unsaturated acids (XIII, R = H, and XIV). To a solution of potassium hydroxide (4.2 g., 0.074 mole) in ethanol (50 ml.), the unsaturated ester (XII 7.5 g., 0.037 mole) was added, and the resulting solution was refluxed for 5 hr., and then worked up as usual. Distillation gave 5 g. (77%) of the acidic material, b.p. 156–162°/3 mm. The distillate solidified to a white mass admixed with an oily material. A portion of the solid was dissolved in petroleum ether (40–60°) from which crystals were deposited, m.p. 110°. Recrystallization from the same solvent yielded the acid (XIV) as white flakes, m.p. 113°; λ_{max}^{alc} 249 mμ (log ε 4.1).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.8. Found: C, 74.8; H, 6.6.

3-Methyl-1-naphthol (V). Phosphorus oxychloride (2 ml.) was added to a solution of the acid (XIII, 4 g.) in dry tetrachloroethane (80 ml.) and the solution was refluxed for 2.5 hr., and then distilled in steam. The residue was dissolved in ether, the ethereal layer washed with water, and evaporated. The residue was hydrolyzed with a solution of potassium hydroxide (3 g.) in ethanol (40 ml.) and worked up as usual. On distillation, the product (1 g.), b.p. 140–144°/3 mm., solidified to a yellow mass, m.p. 89–90°. Crystallization from petroleum ether (60–80°) raised the melting point to 92°, which was not depressed on admixture with the sample obtained previously.

(11) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

JADAVPUR, CALCUTTA 32, INDIA

[CONTRIBUTION FROM THE CHEMICAL THERAPEUTICS RESEARCH LABORATORY, MILES LABORATORIES, INC.]

Spiro[cyclohexane-1,9′-fluoren]-4-one and Some 4-Amino Derivatives

DALE A. STAUFFER AND OTIS E. FANCHER

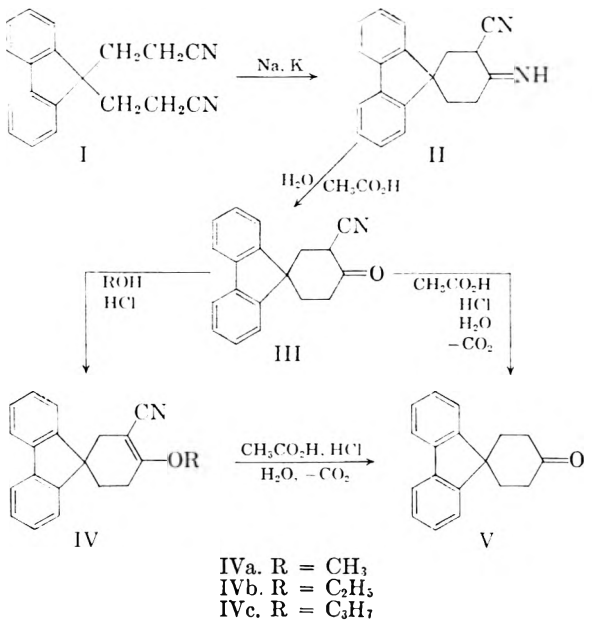
Received December 10, 1959

Spiro[cyclohexane-1,9′-fluoren]-4-one has been synthesized by two methods and a number of 4-amino derivatives have been prepared for pharmacological examination. The compounds showed no outstanding activity.

Spiro[cyclohexane-1,9′-fluoren]-4-one (V) was obtained by two different series of reactions, one starting with 9,9-fluorenedipropionitrile (I).[1] This was cyclized in the presence of metallic sodium and a small quantity of potassium metal to give 4-iminospiro[cyclohexane-1,9′-fluorene]-3-carbonitrile in good yield. The imino compound (II) was hydrolyzed readily to the cyanoketone (III) which, on refluxing with a mixture of acetic and hydrochloric acids, was hydrolyzed with the sub-

(1) H. A. Bruson, *J. Am. Chem. Soc.*, **64**, 2457 (1942).

sequent loss of carbon dioxide to V in rather poor yield.



IVa. R = CH_3
IVb. R = C_2H_5
IVc. R = C_3H_7

The conversion of III to V through the imido ester was attempted but III was too insoluble to allow the desired intermediate to form at the usual temperatures. When anhydrous hydrogen chloride was passed into a hot solution of III in methanol an excellent yield of the enol ether (IVa) was deposited as hard crystals. The structure of IVa was confirmed by the infrared spectrum of the compound. A band at 4.47 μ was attributed to the nitrile group; a peak at 6.09 μ corresponds to the conjugated double bond; and strong absorbance at 7.95 μ was associated with the ether grouping.

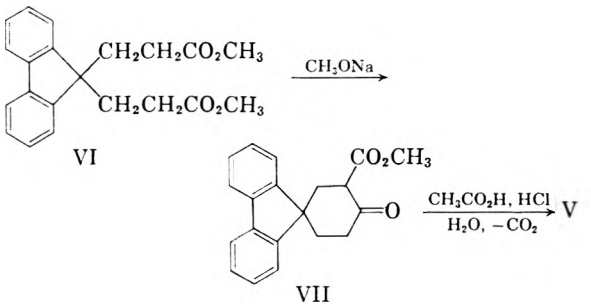
Furthermore the spectrum obtained from NMR studies is consistent with structure IVa. A sharp peak at 3.13 p.p.m. below tetramethylsilane (the reference) was assigned to the hydrogens of the enol ether on the basis of its sharpness, intensity, chemical shift, and relative area.

When ethanol and propanol were used in place of methanol the corresponding ethoxy (IVb) and propoxy (IVc) compounds were obtained.

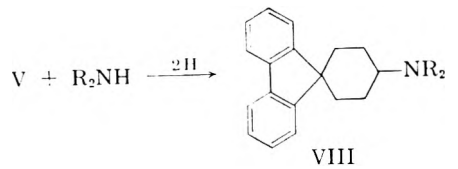
IVa was hydrolyzed to V by prolonged refluxing with a mixture of acetic and hydrochloric acids. The ketone was best isolated as the thiosemicarbazone from which it was readily regenerated.

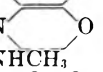
The second synthesis of V started with methyl 9,9-fluorenedipropionate (VI)[2] from which the keto ester (VII) was obtained in good yield by means of the Dieckmann reaction using sodium methoxide in toluene. Hydrolysis and decarboxylation of the keto ester (VII) by refluxing with a mixture of acetic and hydrochloric acids yielded the desired ketone (V).

(2) H. A. Bruson, U. S. Patent 2,339,373 (Jan. 18, 1944) [*Chem. Abstr.*, **38**, 3665 (1944)].



A number of 4-amino derivatives of V were prepared by means of the Leuckart reaction (A) or by catalytic reductive alkylation (B) of the appropriate amine.



VIIIa. $-NR_2 = -NH_2$
VIIIb. $-NR_2 = -N(CH_3)_2$
VIIIc. $-NR_2 = -N$ 
VIIId. $-NR_2 = -N$ 
VIIIe. $-NR_2 = -NHCH_3$
VIIIf. $-NR_2 = -NHCH_2CH_2OH$
VIIIg. $-NR_2 = -NHCH_2CH_2Cl$

The *N*-(2-chloroethyl) compound (VIIIg) was obtained by treating the hydroxy derivative (VIIIf) with thionyl chloride. In addition the dimethylamino compound (VIIIb) was quaternized with methyl chloride.

The amine derivatives were quite toxic and exhibited weak analgetic, antihistaminic and hypotensive properties.

EXPERIMENTAL

4-Iminospiro[cyclohexane-1,9'-fluorene]-3-carbonitrile (II). A finely divided suspension of sodium (12.7 g., 0.55 g.-atom) and potassium (1.3 g.) was stirred at 80° and a solution of 9,9-fluorenedipropionitrile (I) (150 g., 0.55 mole) in 300 ml. of dry toluene was added in one portion. After keeping the mixture at 80–85° for 4 hr., 150 ml. of 95% ethanol was added to destroy the unchanged metals. Then the cold mixture was treated with 700 ml. of water. The crude product (120 g., 80%) melted at 261–264°. After two recrystallizations from isopentyl alcohol the fine colorless needles melted at 264–265°.

Anal. Calcd. for $C_{19}H_{16}N_2$: N, 10.29. Found: N, 10.31.

3-Cyanospiro[cyclohexane-1,9'-fluoren]-4-one (III). A hot solution of II (83.3 g.) in 500 ml. of acetic acid and 25 ml. of water was poured onto 1 kg. of cracked ice. The solid material was collected, slurried with 500 ml. of hot water, and washed thoroughly with additional water. The product amounted to 80 g. (96%) and melted at 184–186°.

Anal. Calcd. for $C_{19}H_{15}NO$: N, 5.13. Found: N, 5.06.

Preparation of the enol ethers (IV). *4-Methoxyspiro[3-cyclohexene-1,9'-fluorene]-3-carbonitrile* (IVa). Anhydrous hydrogen chloride was passed into a solution of III (50 g.) in 500 ml. of hot methanol for 1.5 hr. while the temperature of the mixture was kept near the boiling point. Crystals began to separate after 30 min. The mixture was cooled and the product was collected and washed with methanol. The

crude enol ether (52 g., 99%) melted at 224–226°. The product melted at 226–227° after recrystallization from acetic acid.

Anal. Calcd. for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.87. Found: C, 83.39; H, 5.86; N, 4.87.

4-Ethoxyspiro[3-cyclohexene-1,9'-fluorene]-3-carbonitrile (IVb). This compound was prepared from 5.0 g. of III and 50 ml. of absolute ethanol. The product separated on cooling and was recrystallized from absolute ethanol. The colorless crystals (1.5 g., 27%) melted at 130–131°.

Anal. Calcd. for $C_{21}H_{19}NO$: N, 4.65. Found: N, 4.59.

4-Propoxyspiro[3-cyclohexene-1,9'-fluorene]-3-carbonitrile (IVc). This compound was prepared in a similar way from 5.0 g. of III and 25 ml. of propanol. The crystals separated slowly from the mixture on standing at room temperature for 2 days. The product amounted to 3.2 g. (56%) and melted at 122–123°.

Anal. Calcd. for $C_{22}H_{21}NO$: N, 4.44. Found: N, 4.39.

Methyl 4-oxospiro[cyclohexane-1,9'-fluorene]-3-carboxylate (VII). A mixture of methyl 9,9-fluorenedipropionate (253.5 g., 0.75 mole), sodium methoxide (81.0 g., 1.5 moles) and 800 ml. of dry toluene was stirred under a nitrogen atmosphere and heated in an oil bath at 105–110°. After about 1.5 hr. the mixture suddenly solidified almost completely. The mixture was cooled and 150 ml. of acetic acid was added. Then a mixture of 50 ml. of hydrochloric acid and 500 ml. of water was added and the stirring was continued until all of the solid material had dissolved. The toluene layer was washed free of acidic materials with 10% sodium bicarbonate and dried over calcium chloride. The solid residue which remained when the solvent was removed was recrystallized from a mixture of acetone and methanol. The keto ester was obtained as colorless crystals (205 g., 90%) which melted at 122–123°.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.35; H, 6.19.

Spiro[cyclohexane-1,9'-fluoren]-4-one (V). (A) *Hydrolysis of* VII. The keto ester (10.0 g.) was refluxed for 6 hr. with a mixture of 50 ml. of acetic acid and 25 ml. of hydrochloric acid. The supernatant liquid was decanted from the hot mixture onto 200 g. of cracked ice. The sirupy residue was extracted with another 10 ml. of hot acetic acid which was also decanted into the cold mixture. The crude material was recrystallized from ethanol to give 6.7 g. (83%) of the almost colorless ketone (V) which melted at 198–202°. After two recrystallizations from 2-propanol the product melted at 209–210°.

Anal. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 86.63; H, 6.52.

(B) *Hydrolysis of* III. The cyano ketone (3.0 g.) was heated under reflux for 5 hr. with a mixture of 30 ml. of acetic acid and 15 ml. of hydrochloric acid, and the hot solution was poured onto 100 g. of cracked ice. The crude product was washed with water, dried, and slurried with 15 ml. of a hot 10% sodium carbonate solution. After recrystallization from ethanol the colorless crystals of V (0.6 g., 22%) melted at 200–205°.

(C) *Hydrolysis of* IVa. The enol ether (IVa) (50 g.) was heated under reflux for 48 hr. with 500 ml. of acetic acid and 200 ml. of hydrochloric acid. Most of the acetic acid was removed by distillation and the residue was mixed with 1 kg. of ice and water. The crude ketone (44.3 g., m.p. 185–195°) was dissolved in hot ethanol and a hot solution of thiosemicarbazide (16.3 g.) in 400 ml. of ethanol was added. The mixture was kept near the boiling point for 30 min. and then cooled. The thiosemicarbazone (29.5 g.) melted at 216–217°.

Anal. Calcd. for $C_{19}H_{19}N_3S$: S, 9.98. Found: S, 9.94. The thiosemicarbazone was stirred under reflux for 18 hr. with 150 ml. of concd. hydrochloric acid. Then the mixture was cooled and diluted with 500 ml. of water. The ketone (V) was obtained as faintly yellow crystals (22.5 g., 53% based on the enol ether) which melted at 195–200°.

Samples of the crude ketone (V) obtained by methods B and C melted at 209–210° after repeated recrystallizations from 2-propanol. No depression in the melting point was observed where the materials thus purified were mixed with a sample of V prepared by method A.

(A) *Preparation of amines* (VIII) *by the Leuckart reaction. Spiro[cyclohexane-1,9'-fluoren]-4-amine hydrochloride*(VIIIa). A mixture of the ketone (V) (10.0 g., 0.044 mole), formamide (9.9 g., 0.22 mole), formic acid (20.2 g., 0.44 mole), and diethylene glycol (10 ml.) was heated in an oil bath, so that water and formic acid were slowly removed by distillation through a short Vigreux column. The bath temperature was raised gradually to 185° and that temperature was maintained for 4.5 hr. The mixture was cooled and diluted with 100 g. of ice and water. The solid material was collected and heated under reflux for 2 hr. with 100 ml. of ethanol and 50 ml. of hydrochloric acid. The mixture was cooled and the solid material was removed by filtration. Most of the ethanol was distilled and the residue was extracted with two 200-ml. portions of boiling water. The insoluble tarry material was discarded and the combined extracts were cooled. The hydrochloride was collected, dried and recrystallized from a mixture of methanol and 2-propanol. The colorless crystals (7.5 g., 65%) melted at 326–327°.

Anal. Calcd. for $C_{18}H_{20}ClN$: Cl, 12.41. Found: Cl, 12.27.

N,N-Dimethylspiro[cyclohexane-1,9'-fluoren]-4-amine hydrochloride (VIIIb). This compound was prepared in a similar manner starting with the ketone (V) (37.2 g., 0.15 mole), dimethylformamide (46.8 g., 0.75 mole), and formic acid (69.0 g., 1.5 moles). The mixture was heated at 180° for 1 hr., 190° for 1 hr., 200° for 1 hr., and finally at 210° for 2 hr. The clear solution was allowed to cool and then was heated to reflux with 600 ml. of water and 100 ml. of hydrochloric acid. The hot mixture was clarified by filtration and the hydrochloride separated from the filtrate on cooling. The crude product was recrystallized twice from a mixture of methanol and 2-propanol. The colorless crystals thus obtained (32.0 g., 68%) melted at 295–296°.

Anal. Calcd. for $C_{20}H_{24}ClN$: Cl, 11.30. Found: Cl, 11.29.

4-(1-Piperidyl)spiro[cyclohexane-1,9'-fluorene] hydrochloride (VIIIc). The ketone (V) (6.2 g., 0.025 mole), formopiperidide (15.0 g., 0.125 mole), and formic acid were heated at 200° (bath temperature) for 1 hr. Then the mixture was heated under reflux at a bath temperature of 250° for 5 hr. The clear yellow solution was cooled and heated to boiling with 100 ml. of water and 10 ml. of hydrochloric acid. The salt was not appreciably soluble in the hot mixture. After cooling, the crude product was collected, dried, and recrystallized from a mixture of methanol and 2-propanol. The colorless crystals (6.7 g., 76%) melted at about 345°.

Anal. Calcd. for $C_{23}H_{25}ClN$: Cl, 10.02. Found: Cl, 9.98.

4-(4-Morpholinyl)spiro[cyclohexane-1,9'-fluorene] hydrochloride (VIIId). This compound was prepared in the same way as the piperidine analog starting with the ketone (V) (9.92 g., 0.04 mole), morpholine (17.4 g., 0.2 mole), and formic acid (18.4 g., 0.4 mole). The hydrochloride was obtained as colorless crystals from aqueous methanol. The product (11.5 g., 90%) melted at about 340°.

Anal. Calcd. for $C_{22}H_{26}ClNO$: Cl, 9.96. Found: Cl, 9.97.

(B) *Preparation of amines* (VIII) *by catalytic reductive alkylation. N-Methylspiro[cyclohexane-1,9'-fluoren]-4-amine hydrochloride* (VIIIe). Gaseous methylamine was passed into a hot mixture of the ketone (V) (7.44 g., 0.03 mole) and 50 ml. of 2-propanol until 1.0 g. (0.032 mole) of the amine had been absorbed. The clear yellow solution was added to a suspension of reduced platinum catalyst (from 0.2 g. of the oxide) in 50 ml. of 2-propanol and another 50 ml. of 2-propanol was added. The mixture was reduced under 3 atmospheres. The theoretical quantity of hydrogen was taken up in 3 hr. The catalyst and solvent were removed, and the oily free base was dissolved in a hot mixture of 100 ml. of water and 15 ml. of hydrochloric acid. The crude salt which separated on cooling was collected and recrystallized once from aqueous methanol and three times from a mixture

of methanol and 2-propanol. The colorless crystals (2.5 g., 28%) melted at 287–288°.

Anal. Calcd. for $C_{19}H_{22}ClN$: Cl, 11.83. Found: Cl, 11.65.

N-(2-Hydroxyethyl)spiro[cyclohexane-1,9'-fluoren]-4-amine hydrochloride (VIIIf). This compound was prepared by a procedure similar to that described for the methylamino analog from the ketone (V) (9.92 g., 0.04 mole) and ethanolamine (2.14 g., 0.035 mole). The colorless hydrochloride, recrystallized from a mixture of methanol and 2-propanol, amounted to 9.2 g., (80%) and melted at 290–291°.

Anal. Calcd. for $C_{20}H_{24}ClNO$: Cl, 10.75. Found: Cl, 10.89.

N-(2-Chloroethyl)spiro[cyclohexane-1,9'-fluoren]-4-amine hydrochloride (VIIIg). Compound VIIIf (8.0 g.) was mixed with 20 ml. of thionyl chloride. After the initial reaction was over the mixture was heated under gentle reflux for 3 hr. The excess thionyl chloride was evaporated under reduced pressure and the residue was diluted with 100 ml. of dry ether. The crude salt was collected and recrystallized from aqueous methanol as colorless crystals (4.3 g., 51%) which melted at about 355°.

Anal. Calcd. for $C_{20}H_{23}Cl_2N$: Cl, 20.36. Found: Cl, 20.24.

N,N,N-Trimethylspiro[cyclohexane-1,9'-fluoren]-4-ammonium chloride. Compound VIIIb (11.5 g.) and 10% sodium hydroxide solution (100 ml.) were mixed and warmed. The mixture was cooled and the oily amine was extracted with ether. The extract was dried over calcium chloride and the solvent was evaporated. The solid base which remained as a residue (6.0 g.) was sealed in a glass tube with 20 ml. of methyl chloride. The amine dissolved and the quaternary ammonium salt soon began to separate. After standing overnight the almost solid mixture was crystallized from a mixture of methanol and 2-propanol. The colorless crystals (3.2 g., 27%) melted at about 290° with decomposition.

Anal. Calcd. for $C_{21}H_{26}ClN$: Cl, 10.81. Found: Cl, 10.85.

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ELKHART, IND.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

2-Substituted 1,3-Indandiones

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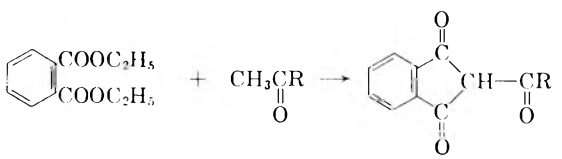
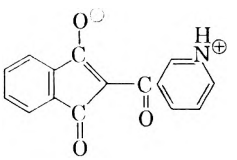
Various 2-aryl- and 2-acyl-1,3-indandiones were prepared. 3-(α-Hydroxy-2,3-dimethoxybenzyl)phthalide (IV) was established as a probable intermediate in the synthesis of 2-(2,3-dimethoxyphenyl)-1,3-indandione (V) from phthalide and 2,3-dimethoxybenzaldehyde. 1,3-Dioxo-2-indancarboxamide (IX) was sought because of its structural relationship with the tetracycline antibiotics. It was accessible from the corresponding nitrile but not from the ethyl ester. Fusion of the sodium enolate of this ester with ammonium acetate gave ethyl 1-imino-3-oxo-2-indancarboxylate (VIII).

In a search for improved blood anticoagulants in the 1,3-indandione series[2–7] we have prepared a number of new 2-substituted-1,3-indandiones. The 2-acyl derivatives listed in Table I were prepared by the sodium methoxide–catalyzed condensation of diethyl phthalate with the appropriate methyl ketone (Method A).[8,9]



4-Chloroacetophenone and 4-ethylacetophenone reacted satisfactorily in refluxing benzene or toluene, but with methyl 4-chloro-1-naphthyl ketone and 4-hydroxyacetophenone it was necessary to use an excess of diethyl phthalate as the solvent. Methyl 3-pyridyl ketone was unusually reactive; the very high melting point and low solubility of the product suggest that it exists as a zwitterion such as:



It is amphoteric. As an acid it is readily soluble in dilute alkali but as a base it is so feeble that it is precipitated from aqueous solution when diluted to an acid strength less than 3*N*.

The 2-aryl-1,3-indandiones of Table I were prepared by the alkoxide-catalyzed condensation of phthalide with aromatic aldehydes (Method B).[10,11] Even though the yields were low this approach was found to be both versatile and convenient.

(1) Present address: Process Development Department, American Cyanamid Co., Bound Brook, N. J.

(2) W. H. Seegers, *Pharmacol. Revs.*, **3**, 278 (1951).

(3) J. T. Correll, L. L. Coleman, S. Long, and R. F. Willy, *Proc. Soc. Exptl. Biol. Med.*, **80**, 139 (1952).

(4) K. C. Murdock, *J. Org. Chem.*, **24**, 845 (1959).

(5) S. R. Heisy, J. P. Saunders, and K. C. Olson, *J. Agr. Food Chem.*, **4**, 144 (1956).

(6) W. Cavallini, E. Milla, E. Grumelli, and F. Ravenna, *Il Farmaco (Pavia), Ed. sci.*, **10**, 710 (1955); *Chem. Abstr.*, **50**, 10707 (1956).

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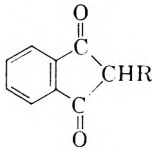
(8) E. Schwerin, *Ber.*, **27**, 104 (1894).

(9) L. B. Kilgore, J. H. Ford, and W. C. Wolfe, *Ind. Eng. Chem.*, **34**, 494 (1942).

(10) W. Dieckmann, *Ber.*, **47**, 1439 (1914).

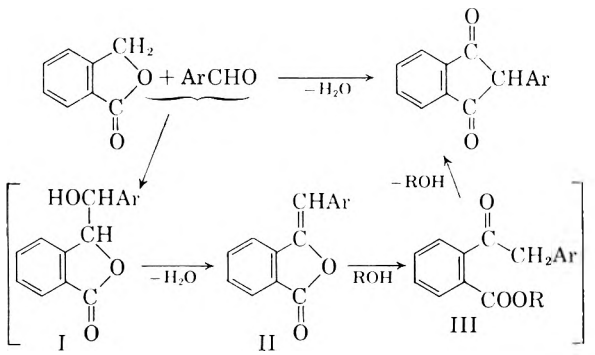
(11) C. F. Koelsch, *J. Am. Chem. Soc.*, **58**, 1331 (1936).

TABLE I

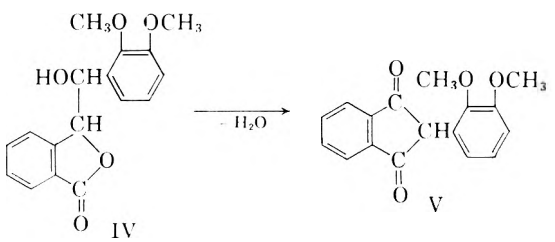
2-SUBSTITUTED-1,3-INDANDIONES 

R	Method	Reaction Temp., °C	Yield, %	M.P., °[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
2-Acyl-1,3-indandiones										
4-Chlorobenzoyl[b]	A	Reflux	5[c]	184	66.5	66.0	3.43	3.34	12.1	12.1
4-Chloro-1-naphthoyl	A	100–120	8[d]	200–201	71.8	71.8	3.31	3.33	10.6	10.8
4-Ethylbenzoyl	A	Reflux	9[e]	87	77.7	77.9	5.07	5.26		
4-Hydroxybenzoyl	A	100–110	60[d]	279	72.2	72.4	3.79	3.76		
Nicotinoyl	A	30–40	7[f,g]	306–308	71.8	72.0	3.63	3.70		
2-Aryl-1,3-indandiones										
2-Chlorophenyl	B	Reflux	31[h]	185	70.2	70.2	3.53	3.53	13.8	13.6
2,6-Dichlorophenyl	B	Reflux	25[h]	158	61.9	61.8	2.77	2.74	24.4	24.2
2,3-Dimethoxyphenyl	B	65	27[h]	148–149	72.3	72.1	5.00	4.93		
4-Hydroxy-3-methoxyphenyl	B	Reflux	17[d]	225–231	71.6	71.9	4.51	4.45		
4-Hydroxyphenyl	B	62	11[d]	178–179[i]	75.7	75.5	4.23	4.42		
2-Methoxyphenyl	B	55	24[d]	172[j]	76.2	76.3	4.80	4.67		
3,4-Methylenedioxyphenyl	B	Reflux	29[h]	160	72.2	72.1	3.79	3.49		

[a] All melting points are corrected. [b] Hemihydrate. [c] Product recrystallized from 80% 2-ethoxyethanol. [d] Recrystallized from 2-ethoxyethanol. [e] Recrystallized from 80% ethanol. [f] The molar ratio of diethyl phthalate, sodium methoxide, and methyl 3-pyridyl ketone was 2:4:1. An exothermic reaction began spontaneously. After 2.3 hr. water was added and extraneous material was removed by extraction with chloroform. The product was precipitated by acidification, washed with acetone, and recrystallized from dimethylformamide. In another run at 100° the yield was 1.5%. [g] Calcd. % N, 5.58. Found, 5.60. [h] Recrystallized from absolute ethanol. [i] Lit. m.p. 174–176° (ref. 6) for material prepared by a different route. [j] Resolidified, then remelted at 175–177°.



Of the indicated intermediates in this condensation the literature provides support for both II and III. Both benzalphthalide[12–15] and methyl 2-phenylacetylbenzoate,[15] prepared by other methods, rearrange in the presence of alkoxides to form 2-phenyl-1,3-indandione. Moreover, both compounds rearrange at the same rate.[15] Dieckmann attempted to isolate benzalphthalide after allowing benzaldehyde and phthalide to react in the presence of milder bases such as amines or potassium carbonate, but was not successful.[10] We have now isolated the probable aldol-type precursor, I, of a substituted benzalphthalide. In the reaction of phthalide with ethanolic solutions of sodium methoxide and 2,3-dimethoxybenzaldehyde the mixture was not refluxed but was held at 65° to see if lower reaction temperatures might give improved yields. In addition to 27% of the expected 2-(2,3-dimethoxyphenyl)1,3-indandione (V) there was also obtained 13% of 3-(α-hydroxy-2,3-dimethoxybenzyl)phthalide (IV). The presence



of hydroxyl and γ-lactone functions was supported by infrared absorption maxima at 2.86 and 5.70 μ.[16] Sodium ethoxide in refluxing ethanol converted the hydroxylactone (IV) to V in 19% yield.

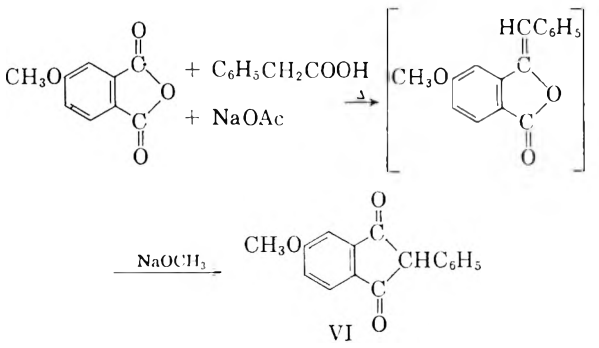
A molecule of water is necessarily generated in the synthesis of V from either the hydroxylactone, IV, or from 2,3-dimethoxybenzaldehyde. It is probable that the low yields obtained in such reactions are due to the saponification of intermediate lactones caused by water produced in the reaction. This view is supported by Nathanson's observa-

(12) F. Nathanson, *Ber.*, 26, 2576 (1893).
(13) A. Eibner, *Ber.*, 39, 2203 (1906).
(14) R. Weiss, *Org. Syntheses*, **Coll. Vol. II**, 61 (1943).
(15) S. Escola, T. Lahikainen, and A. Korhanen, *Suomen Kemistilehti*, 20B, 21 (1947); *Chem. Abstr.*, 41, 7213 (1947).

(16) The infrared spectrum was determined in chloroform solution by Mrs. Cecilia Jorgensen.

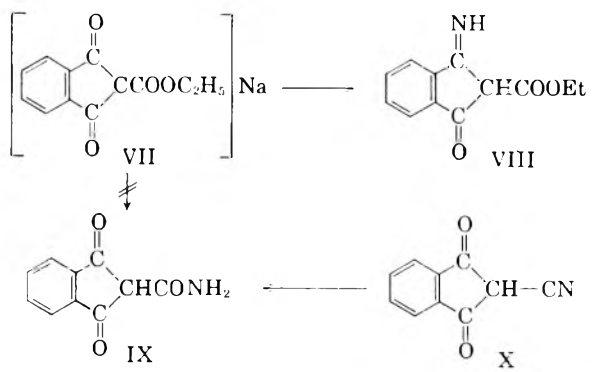
tion that benzalphthalide in absolute ethanol could be rearranged almost quantitatively to 2-phenyl-1,3-indandione, but in 96% ethanol the yield was only one fourth as great.[12]

5 - Methoxy - 2 - phenyl - 1,3 - indandione (VI) was prepared as follows:



This method[6,12,14] was not successful with phthalic anhydrides substituted in the 4-position with hydroxyl-, benzoyl- or sulfonic acid groups.

A consideration of the 1,3-dioxo-2-carboxamide grouping in the tetracycline antibiotics suggested that 1,3-dioxo-2-indancarboxamide (IX) might show antibacterial activity. An attempt to prepare this amide by treating the sodium salt of ethyl 1,3-dioxo-2-indancarboxylate[17] (VII) with concentrated ammonia in an autoclave at 100° was unsuccessful. When VII was fused with ammonium acetate the product obtained was not an amide,



but an imino ester, VIII.[18] In another approach diethyl phthalate and acetonitrile were condensed to give 1,3-dioxo-2-indancarbonitrile (X),[19] an enolic acid with a pK_a of 2.9. The nitrile (X) was readily hydrolyzed to the desired amide (IX) by dissolving it in concentrated sulfuric acid and pouring this solution into cold water. This amide was active *in vitro* against a variety of gram-positive and gram-negative bacteria, but only at relatively high concentrations (*ca.* 1 mg./ml.).[20]

The anticoagulant activities of the compounds listed in Table I will be reported separately.[21]

EXPERIMENTAL

Method A. 2-(4-Hydroxybenzoyl)-1,3-indandione. A well stirred suspension of 48.6 g. (0.9 mole) of sodium methoxide in 300 ml. (1.52 moles) of diethyl phthalate was heated to about 70° during the cautious addition of a solution of 40.8 g. (0.3 mole) of *p*-hydroxyacetophenone in 100 ml. of diethyl phthalate. After stirring at 100–110° for 7 hr. the mixture became too thick to stir. This temperature was maintained for another 6 hr., the mixture was allowed to cool, and 300 ml. of water and 100 ml. of benzene were added. The mixture was warmed until the solids had dissolved, the organic (upper) layer was extracted with 100 ml. of water and the resulting organic (lower) layer was discarded. The combined aqueous solutions were washed with 50 ml. of benzene, diluted with 400 ml. of 95% ethanol, heated to boiling, acidified with 80 ml. of concd. hydrochloric acid, and chilled to 10°. The solid product was washed with ethanol, with water, and then with more ethanol; 48.1 g. (60%), m.p. 279° dec., unchanged after recrystallization from 2-ethoxyethanol.

Method B. 2-(2,3-Dimethoxyphenyl)-1,3-indandione (IV). Hot solutions of 83.1 g. (0.5 mole) of 2,3-dimethoxybenzaldehyde in 50 ml. of absolute ethanol and 67.1 g. (0.5 mole) of phthalide in 50 ml. of absolute ethanol were combined, cooled to 20°, and maintained at this temperature during the gradual addition of a solution of 27.0 g. (0.5 mole) of sodium methoxide in 100 ml. of absolute ethanol. The reaction mixture was loosely stoppered and kept for 50 hr. in an oven maintained at about 65°. The resulting thick red slurry was diluted with 150 ml. of ethanol, heated to boiling, then acidified by the gradual addition with stirring of a slight excess (51 ml.) of concd. hydrochloric acid. The mixture was chilled to 5°, the solid collected, washed with ethanol and then with water. Two recrystallizations from ethanol gave 38.5 g. (27%) of elongated prisms, m.p. 148–149°.

Analogous reactions run at the reflux temperature (Table I) were stopped after 1–3 hr. The higher yields were obtained with the shorter reaction times.

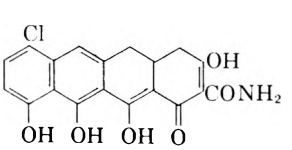
3-(α-Hydroxy-2,3-dimethoxybenzyl)phthalide (IV). The acidic, alcoholic filtrate from the above reaction mixture was allowed to stand for 2 weeks in an unstoppered, wide-mouthed flask. It had then deposited 19.6 g. (13%) of large, tan prisms. Two recrystallizations from ethanol, using decolorizing charcoal, gave 14.1 g. of prisms, m.p. 141°.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 68.0; H, 5.38; mol. wt., 300.3. Found: C, 67.6, 67.7; H, 4.91, 4.99; mol. wt., 321.

A solution of 0.051 g. (0.0022 mole) of sodium in 3.5 ml. of absolute ethanol was combined with 0.601 g. (0.002 mole) of the above hydroxyphthalide (IV) and heated under reflux for 20 min. The resulting thick orange slurry was cooled, agitated during the dropwise addition of 1.9 ml. of concd. hydrochloric acid, then evaporated to dryness. Extraction with 4 ml. of chloroform, evaporation of the extract, and crystallization of the residual sirup from 2 ml. of ethanol gave 0.105 g. (19%) of rods, m.p.

(17) W. Wislicenus, *Ber.*, 20, 593 (1887).

(18) In later work in these laboratories directed toward the total synthesis of tetracycline antibiotics, the product isolated from a similar fusion of a keto ester with ammonium formate was not an imine, but was the desired keto amide,



[J. H. Boothe, A. S. Kende, T. L. Fields, and R. G. Wilkinson, *J. Am. Chem. Soc.*, 81, 1006 (1959)].

(19) This compound was first prepared in another investigation by Dr. R. S. Long.

(20) Antibacterial testing was done by Mr. A. C. Dornbush and his co-workers in the Microbiology Department of these laboratories.

(21) V. Downing *et al.*, to be published.

147–148°. Admixture with 2-(2,3-dimethoxyphenyl)-1,3-indandione (V) did not depress the melting point.

5-Methoxy-2-phenyl-1,3-indandione (VI). A mixture of 13.9 g. (0.078 mole) of 4-methoxyphthalic anhydride, 11.8 g. (0.087 mole) of phenylacetic acid, and 0.5 g. of freshly fused sodium acetate was stirred at 230–245° for 2 hr.; about 1 ml. of a distillate was collected. The partially cooled mixture was diluted with 100 ml. of absolute ethanol, the temperature was adjusted to about 60° and a solution of 4.9 g. (0.091 mole) of sodium methoxide in 50 ml. of hot absolute ethanol was slowly added. After heating the mixture at 70–80° for 5 min. there were added 70 ml. of water and (slowly) 50 ml. of 2*N* hydrochloric acid. The mixture was allowed to stand at 5°, the solid was collected by filtration and washed with water until free of halides; 14.9 g. (76%), m.p. 183–185°. Recrystallization from ethanol gave 12.7 g., m.p. 187°.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.2; H, 4.80. Found: C, 76.1; H, 4.98.

Ethyl 1-imino-3-oxo-2-indancarboxylate (VIII). To a beaker containing 231.2 g. (3.0 moles) of partially molten ammonium acetate at 100° there was added with stirring 72.1 g. (0.3 mole) of the powdered sodium salt of crude ethyl 1,3-dioxo-2-indancarboxylate (VII).[17] After continuous manual stirring at 110–115° for 40 min. the original yellow dough was all liquefied. Mechanical stirring at 110–115° was continued for 1.4 hr. The hot melt was poured with swirling into 450 ml. of hot water. The dark solid which separated on cooling was collected by filtration and the filtrate extracted twice with chloroform. Solids had separated overnight from both the aqueous solution and the chloroform extracts. These solids and the earlier, dark solid were recrystallized repeatedly from dimethylformamide (2.5 ml./g.) or 2-ethoxyethanol (15 ml./g.), combining fractions as purity warranted. Two insoluble, orange by-products were also encountered; one was almost infusible, the other melted at 239–240° dec. The product amounted to 7.2 g. (13%) of yellow-orange crystals, m.p. 242–244° dec.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.4; H, 5.10; N, 6.45; O, 22.1. Found: C, 65.8, 66.0; H, 4.41, 4.70; N, 6.47; O, 21.9.

1,3-Dioxo-2-indancarbonitrile (X).[19] A mixture of 216 g. (4.0 moles) of sodium methoxide, 205 g. (5.0 moles) of acetonitrile, and 444 g. (2.0 moles) of diethyl phthalate was stirred under reflux for 6 hr. (After 2 hr. the mixture had become so thick that it was diluted with another 200 ml. of acetonitrile.) The mixture was cooled and 400 ml. of ether was added. The solid was collected by filtration, washed with ether, dried, dissolved in 3.6 l. of water, acidified with 250 ml. of concd. hydrochloric acid, and allowed to stand at 5° for several hours. The product was collected and washed with water; 232 g. (68%), bright yellow, m.p. 194–195° dec. Recrystallization from tetrahydrofuran-benzene, using decolorizing charcoal, raised the m.p. to 202–204° dec. An analytical sample was obtained by sublimation at 0.2 mm. and *ca.* 180°; m.p. 205–206° dec.

Anal. Calcd. for $C_{10}H_5O_2N \cdot {}^1/_2H_2O$: C, 66.66; H, 3.36; N, 7.78; moisture, 5.00%; neut. equiv., 180. Found: C, 66.71; H, 3.52; N, 8.13; moisture (Karl Fischer), 4.24%; neut. equiv., 190; pK_a 2.9. The infrared absorption spectrum[22] showed an intense peak at 4.51 μ, confirming the presence of the nitrile function.

1,3-Dioxo-2-indancarboxamide (IX). Eight ml. of concd. sulfuric acid was kept cold while 2.0 g. of unpurified 1,3-dioxo-2-indancarbonitrile was dissolved therein. The deep orange solution was allowed to stand overnight, then poured into 200 ml. of cold water. The resulting solid was collected, washed with water and ethanol, and recrystallized from dimethylformamide-water to give 0.9 g. of yellow-orange needles; these sintered from 160 to 220°. After extraction with 200 ml. of boiling benzene the extract was allowed to stand at 5°. It deposited 0.2 g. of an orange powder which sintered from 180 to 220°.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.5; H, 3.73; N, 7.41. Found: C, 63.9; H, 4.00; N, 7.42.

The infrared spectrum[22] showed no absorption in the nitrile range (4–5 μ); absorption maxima at 2.90, 2.98, and 6.05 μ were compatible with the presence of a primary amide grouping.

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PEARL RIVER, N. Y.

(22) Solids were pressed with potassium bromide for infrared spectral determinations.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE FRANCIS DELAFIELD HOSPITAL]

Synthesis of Some Substituted Benzimidazoles, Benzotriazoles, and Quinoxalines

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The synthesis of 3,4-diamino-5-nitrotoluene and 2,3-diamino-5-nitrobenzoic acid is described. These new *o*-diamines, and also 5-chloro-3-nitro-*o*-phenylenediamine, have been subjected to ring closure with appropriate reagents to prepare the derived benzimidazoles, benzotriazoles, and quinoxalines. The derivatives have been used to continue an investigation on the inhibition of developing embryos of the frog, *Rana pipiens*, by such heterocyclic compounds.

The inhibition of the development of *Rana pipiens* by substituted benzimidazoles, benzotriazoles, and quinoxalines has been actively investigated in our laboratories for some time. The work so far completed[1] seemed to indicate that each of the three types of heterocyclic compounds elicits a different morphological response and that the introduction of a nitro group into the parent ring system increases the activity. This effect of the nitro group is diminished by the simultaneous presence of an alkoxy group. Woolley,[2] summarizing his experience with structural analogs as inhibitors of naturally occurring vitamins, suggested that replacing a methyl or carboxyl group by a chlorine atom might result in a more active compound. It seemed of interest, therefore, to prepare derivatives of benzimidazole, benzotriazole, and quinoxaline in which the nitro group was retained but in which the alkoxy group was replaced respectively by methyl, carboxyl, and chlorine. The synthesis of the desired substances required the preparation of two new substituted *o*-phenylenediamine intermediates: 3,4-diamino-5-nitrotoluene and 2,3-diamino-5-nitrobenzoic acid.

Reduction of 4-amino-3,5-dinitrotoluene[3] with alcoholic ammonium sulfide gave a 70% yield of 3,4-diamino-5-nitrotoluene. The *o*-diamine was treated with formic acid, nitrous acid, glyoxal, diacetyl, and benzil to produce respectively, 6-methyl-4-nitrobenzimidazole, 6-methyl-4-nitrobenzotriazole, 7-methyl-5-nitroquinoxaline, 5-nitro-2,3,7-trimethylquinoxaline, and 2,3-diphenyl-7-methyl-5-nitroquinoxaline. No attempt was made to isolate an acetyl derivative of the base but, when the *o*-diamine was dissolved by warming in acetic anhydride, the solution cautiously diluted with cold 3*N* hydrochloric acid, and then refluxed for one-half hour, a good yield of 2,6-dimethyl-4-nitrobenzimidazole was obtained.

2,3-Diamino-5-nitrobenzoic acid was formed in 78% yield when 2-amino-3,5-dinitrobenzoic acid[4] was warmed with aqueous ammonium sulfide and the resulting solution filtered and acidified with the acetic acid. The desired 6-nitrobenzimidazole-4-carboxylic acid, 2-methyl-6-nitrobenzimidazole-4-carboxylic acid, 6-nitrobenzotriazole-4-carboxylic acid, and 2,3-dimethyl- (and 2,3 diphenyl)-7-nitroquinoxaline-5-carboxylic acids were obtained on ring closure of the *o*-diamine with appropriate reagents as indicated in the case of 3,4-diamino-5-nitrotoluene. Attempts to prepare 7-nitroquinoxaline-5-carboxylic acid by treating the *o*-diamine with glyoxal in alcohol or glyoxal bisulfite in water resulted only in resin formation.

The chloronitro substituted benzimidazoles, benzotriazole, and quinoxalines were obtained from 5-chloro-3-nitro-*o*-phenylenediamine in a similar fashion. 6-Chloro-4-nitrobenzimidazole has previously been described by Hoover and Day.[5]

The carboxylic compounds have been found to be completely inactive against developing *Rana pipiens* embryos. The methyl-nitro derivatives of each heterocyclic type appear to be about as active as the alkoxynitro substituted compounds and the chloronitro derivatives are more active than the compounds in which only a nitro group is present. The details of the biological work will be reported elsewhere.

EXPERIMENTAL[6]

The analytical results on the compounds prepared are listed in Table I.

3,4-Diamino-5-nitrotoluene (I). To 200 ml. of freshly prepared 6% ammonium sulfide, there was added 200 ml. of ethanol and 6 g. (0.03 mole) of 4-amino-3,5-dinitrotoluene. The mixture was refluxed for 30 min., diluted with 200 ml. of water, and kept at 5° for several hours. The precipitate was collected, washed with water, and extracted with 400 ml. of hot 0.5*N* hydrochloric acid. When the cooled acid extract was neutralized with concd. (28%) aqueous ammonia, there separated 3.5 g. (70%) of 3,4-diamino-5-nitrotoluene. The diamine crystallized from 25% ethanol as long, red needles, m.p. 152–154°.

6-Methyl-4-nitrobenzimidazole (II). A mixture of 500 mg. (3 mmoles) of I and 1.5 ml. of 98% formic acid in 25 ml. of

(1) K. Liecke, M. Engelman, and S. Graff, *J. Embryol. Exp. Morph.*, **5**, 368 (1957).

(2) D. W. Woolley, the Harvey Lectures, 1945–46, p. 212.

(3) C. L. Jackson and M. H. Ittner, *Am. Chem. J.*, **19**, 6 (1897).

(4) P. Cohn, *Monatshefte fuer Chemie*, **22**, 387 (1901).

(5) J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc.*, **77**, 4324 (1955).

(6) Melting points are uncorrected.

TABLE I

ANALYTICAL DATA OF COMPOUNDS SYNTHESIZED

Compd. No.	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Chlorine, %	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
I	$C_7H_9O_2N_3$	50.30	50.16	5.39	5.37	25.15	25.38		
II	$C_8H_7O_2N_3$	54.24	54.25	3.96	4.27	23.73	23.96		
III	$C_9H_9O_2N_3$	56.54	56.48	4.71	4.66	21.99	22.17		
IV	$C_7H_6O_2N_4$	47.19	47.30	3.37	3.58	31.46	31.64		
V	$C_9H_7O_2N_3$	57.14	57.34	3.70	3.86	22.22	22.51		
VI	$C_{11}H_{11}O_2N_3$	60.83	61.13	5.07	5.16	19.35	19.42		
VII	$C_{21}H_{15}O_2N_3$	73.90	73.61	4.40	4.42	12.32	12.28		
VIII	$C_7H_7O_4N_3$	42.64	42.92	3.55	3.73	21.32	21.22		
IX	$C_8H_5O_4N_3$	46.38	46.25	2.42	2.51	20.29	20.28		
X	$C_9H_7O_4N_3$	48.87	49.12	3.17	3.26	19.00	18.73		
XI	$C_7H_4O_4N_4$	40.38	40.24	1.92	2.24	26.92	26.75		
XII	$C_{11}H_9O_4N_3$	53.44	53.54	3.64	3.94	17.00	16.93		
XIII	$C_{21}H_{13}O_4N_3$	67.92	68.14	3.50	3.81	11.22	11.27		
XIV	$C_8H_3O_2N_4Cl$					28.21	27.89	17.88	17.80
XV	$C_8H_6O_2N_3Cl$					19.86	20.10	16.78	16.72
XVI	$C_8H_4O_2N_3Cl$					20.05	19.90	16.95	16.89
XVII	$C_{10}H_8O_2N_3Cl$					17.68	17.81	14.95	14.86
XVIII	$C_{20}H_{12}O_2N_3Cl$					11.62	11.35	9.81	9.81

3*N* hydrochloric acid was refluxed for 1 hr. The resulting yellow solution was diluted with 75 ml. of hot water, clarified with Darco, and neutralized with 28% ammonium hydroxide solution. After cooling, the yellow precipitate was collected, washed with water, and dried in air. The yield was 465 mg. (87.6%). The 6-methyl-4-nitrobenzimidazole was recrystallized from ethanol, yellow needles, m.p. 288–290°.

2,6-Dimethyl-4-nitrobenzimidazole (III). Three millimoles (501 mg.) of I was dissolved in 4.5 ml. of acetic anhydride by warming on the steam bath. To the cooled solution, there was slowly added 15 ml. of 3*N* hydrochloric acid. The mixture was refluxed for 30 min., diluted with 30 ml. of hot water, boiled briefly with Darco, and filtered. The filtrate was neutralized with strong ammonium hydroxide solution and cooled. There was precipitated 541 mg. (94%) of 2,6-dimethyl-4-nitrobenzimidazole. The compound crystallized from 25% ethanol as a felted mass of tiny, colorless needles, m.p. 238–240°.

6-Methyl-4-nitrobenzotriazole (IV). A suspension of 501 mg. (3 mmoles) of I in 25 ml. of 3*N* hydrochloric acid was stirred at room temperature and treated during the course of 10 min. with a solution of 282 mg. (4 mmoles) of sodium nitrite in 5 ml. of water. Stirring was continued for 1 hr. The 6-methyl-4-nitrobenzotriazole was collected, washed with water and recrystallized from ethanol (Nuchar), m.p. 277–278°. The yield was 405 mg. (75.8%).

7-Methyl-5-nitroquinoxaline (V). A mixture of 835 mg. (5 mmoles) of I and 2.0 g. (7.5 mmoles) of glyoxal bisulfite in 100 ml. of hot water was stirred and heated on the steam-bath for 2 hr. The hot, red solution was filtered by gravity to remove a red resin and the cooled filtrate was made basic by the addition of 10% sodium hydroxide solution. After being kept at 5° for several hours, the tan precipitate was collected, washed with water, and dried *in vacuo* at room temperature. The yield was 648 mg. (69.3%). The 7-methyl-5-nitroquinoxaline was recrystallized from 25 ml. of 50% ethanol (Nuchar), m.p. 134–135°.

2,3,7-Trimethyl-5-nitroquinoxaline (VI). A mixture of 501 mg. (3 mmoles) of I and 363 mg. (4.2 mmoles) of diacetyl in 25 ml. of ethanol was refluxed for 1 hr. The resulting solution was clarified with Nuchar and cooled. The 2,3,7-trimethyl-5-nitroquinoxaline separated as short, almost colorless needles, m.p. 150–151°. The yield was 514 mg. (79%).

2,3-Diphenyl-7-methyl-5-nitroquinoxaline (VII). A mixture of 501 mg. (3 mmoles) of I and 700 mg. (3.3 mmoles) of benzil in 25 ml. of glacial acetic acid was heated on the steam bath for 30 min. To the resulting solution hot water was added to incipient turbidity. The mixture was boiled briefly with Darco and filtered. On cooling the filtrate, there separated 937 mg. (91.6%) of 2,3-diphenyl-7-methyl-5-nitroquinoxaline. It crystallized from ethanol as short needles, m.p. 172–173°.

2,3-Diamino-5-nitrobenzoic acid (VIII). To 150 ml. of freshly prepared 6% ammonium sulfide, there was added 9.1 g. (0.04 mole) of 2-amino-3,5-dinitrobenzoic acid.[4] The mixture was heated with stirring on the steam bath for 1 hr. and then boiled to remove the bulk of the ammonia with hot water being added occasionally to keep the original volume. The hot solution was filtered to remove sulfer. After cooling to 5°, the filtrate was acidified with acetic acid. The precipitate of 2,3-diamino-5-nitrobenzoic acid was filtered off, washed with water, and recrystallized from 75% ethanol. The compound, which separates as dark, red needles, decomposes above 245°. The yield was 6.8 g. (78%).

6-Nitrobenzimidazole-4-carboxylic acid (IX). A mixture of 985 mg. (5 mmoles) of VIII and 1.02 g. (15 mmoles) of sodium formate in 15 ml. of 3*N* hydrochloric acid was refluxed for 1 hr., treated with Darco, and filtered. From the filtrate on cooling, there separated 874 mg. (85.3%) of rhombic, orange crystals of 6-nitrobenzimidazole-4-carboxylic acid. The compound decomposes above 300°. An analytical sample was recrystallized from ethanol.

2-Methyl-6-nitrobenzimidazole-4-carboxylic acid (X). Two millimoles (394 mg.) of VIII was dissolved by warming in 4.5 ml. of acetic anhydride. To the cooled solution, there was cautiously added 15 ml. of 3*N* hydrochloric acid. The mixture was refluxed for 30 min. and clarified with Darco. The filtrate was concentrated to dryness *in vacuo* at 50° and the residue dissolved in 20 ml. of 0.5*N* sodium hydroxide. When the alkaline solution was acidified with acetic acid, there was obtained 272 mg. (61.5%) of 2-methyl-6-nitrobenzimidazole-4-carboxylic acid. The compound dissolved in hot ethanol (60 ml.) and separated on cooling as a colorless powder which does not melt below 300°.

6-Nitrobenzotriazole-4-carboxylic acid (XI). This compound was prepared by the procedure described for IV. From 333 mg. (1.7 mmoles) of VIII, there was isolated 313 mg. (88.4%) of 6-nitro-benzotriazole-4-carboxylic acid. The compound was dissolved in 75 ml. of hot 25% ethanol, treated with Nuchar, and the solution filtered. From the filtrate on cooling, it separated as a colorless powder which decomposes at about 300°.

2,3-Dimethyl-7-nitroquinoxaline-5-carboxylic acid (XII). The procedure employed for VI was followed. From 394 mg. (2 mmoles) of VIII and 288 mg. (3.3 mmoles) of diacetyl in 75 ml. of ethanol, the yield of 2,3-dimethyl-7-nitroquinoxa-

line-5-carboxylic acid was 352 mg. (71.3%); fine, grayish needles, m.p. 222–224° dec.

2,3-Diphenyl-7-nitroquinoxaline-5-carboxylic acid XIII. Two millimoles (394 mg.) of VIII treated with an equivalent quantity of benzil in 25 ml. of glacial acetic acid as described for VII, yielded 526 mg. (70.8%) of 2,3-diphenyl-7-nitroquinoxaline-5-carboxylic acid in the form of yellow plates, m.p. 235–236°. A sample for analysis was recrystallized from methanol.

6-Chloro-4-nitrobenzotriazole XIV. A solution of 940 mg. (5 mmoles) of 5-chloro-3-nitro-*o*-phenylenediamine in 100 ml. of hot 1*N* sulfuric acid was treated with Darco and filtered. The sulfate of the base which separated on cooling the filtrate was kept in suspension by vigorous stirring while a solution of 450 mg. of sodium nitrite in 5 ml. of water was added over a period of 10 min. Stirring was continued for 1 hr. The 6-chloro-4-nitrobenzotriazole was collected, washed with water, and recrystallized from 50% ethanol (75 ml.), m.p. 238–239°. The yield was 619 mg. (62.3%).

6-Chloro-2-methyl-4-nitrobenzimidazole XV. Three millimoles (563 mg.) of 5-chloro-3-nitro-*o*-phenylenediamine, treated with acetic anhydride and then hydrochloric acid as described for III, yielded 548 mg. (86.3%) of 6-chloro-2-methyl-4-nitrobenzimidazole; it was recrystallized from benzene, m.p. 229–230°.

7-Chloro-5-nitroquinoxaline (XVI). To a solution of 940 mg. (5 mmoles) of 5-chloro-3-nitro-*o*-phenylenediamine in 50 ml. of hot ethanol, there was added 1.5 ml. of a 30% aqueous solution of glyoxal. The solution was refluxed for 1 hr., treated with Nuchar, and filtered. On cooling the filtrate, the 7-chloro-5-nitroquinoxaline crystallized as long, yellow needles, m.p. 174–175°. The yield was 690 mg. (65.8%).

7-Chloro-2,3-dimethyl-5-nitroquinoxaline (XVII). Five millimoles (940 mg.) of 5-chloro-3-nitro-*o*-phenylenediamine in 75 ml. of 50% ethanol treated with 605 mg. (7 mmoles) of diacetyl as outlined for VI gave 815 mg. (68%) of 7-chloro-2,3-dimethyl-5-nitroquinoxaline; pale, yellow needles, m.p. 140–141°.

7-Chloro-2,3-diphenyl-5-nitroquinoxaline (XVIII). When a mixture of 563 mg. (3 mmoles) of 5-chloro-3-nitro-*o*-phenylenediamine and 700 mg. (3.3 mmoles) of benzil in 25 ml. of glacial acetic acid was processed as described for VII, a yield of 882 mg. (81.4%) of 7-chloro-2,3-diphenyl-5-nitroquinoxaline was obtained. The compound was recrystallized from ethanol: short, yellow needles, m.p. 184–185°.

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE AND FRENCH LABORATORIES]

Synthesis of Phenothiazines. IV.[1-3] 10-Aminoalkyl Derivatives of 2-Substituted Phenothiazines and 2-Azaphenothiazines

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The present paper describes various 10-aminoalkyl derivatives of the following phenothiazines: 2-hydroxyphenothiazine, 2-methylthiophenothiazine, 2-methylsulfonylphenothiazine, 2-trifluoromethylsulfonylphenothiazine, 2-trifluoromethylthiophenothiazine, 2-azaphenothiazine, and 8-chloro-2-azaphenothiazine.

Paper II[2] of this series describes the preparation of 2-azaphenothiazine and 8-chloro-2-azaphenothiazine. Paper III describes the preparation of 2-hydroxyphenothiazine, 2-benzoyloxyphenothiazine, 2-methylthiophenothiazine, 2- and 4-trifluoromethylthiophenothiazine, 2-methylsulfonylphenothiazine, and 2-trifluoromethylsulfonylphenothiazine. In Tables I and II of the present paper are reported the preparation and physical properties of eighteen different 10-aminoalkyl derivatives of the substituted phenothiazine intermediates described in papers II and III. Biological data concerning these compounds will be published elsewhere.

EXPERIMENTAL[4]

The alkylations were carried out in the usual manner[1] with the following exceptions. The direct alkylation of 2-hydroxyphenothiazine was not attempted. Instead 2-benzoyloxyphenothiazine was alkylated using sodamide in xylene and the ester group was removed by basic hydrolysis during the workup. The alkylation of 2-trifluoromethylsulfonylphenothiazine with 3-(4-methylpiperazinyl)propyl chloride required 48 hr. instead of the usual 2 to 10 hr. The preparation of the β-acetoxyethyl compounds was accomplished as shown.

Preparation of 4-[3-(2-azaphenothiazin-10-yl)propyl]-1-piperazineethanol, acetate dimaleate. (Compound 17). A mixture of 15 g. of 2-azaphenothiazine,[2] 6.8 g. of sodamide, and 500 ml. of dry toluene was refluxed and stirred under a nitrogen atmosphere for 45 min. To the mixture was added a slurry of 21 g. of 3-chloro-1-(1-formyl-4-piperazinyl)propane hydrochloride and 300 ml. of dry toluene which had been previously azeotroped together for 1 hr. The mixture was cooled and 150 ml. of water was added. The toluene layer was extracted with dilute hydrochloric acid. The acid extracts were made alkaline and extracted with benzene. The benzene was evaporated to give 21 g. of an oil. The oil was dissolved in a solution of 250 ml. of ethanol, 60 ml. of water, and 7 ml. of 40% sodium hydroxide solution. The mixture

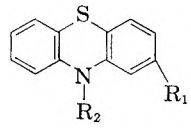
(1) Paper I. P. N. Craig *et al.*, *J. Org. Chem.* **22**, 709 (1957).

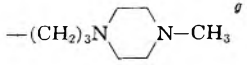
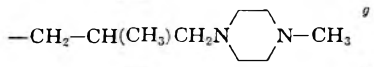
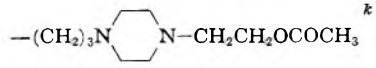
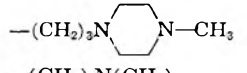
(2) Paper II. A. J. Saggiomo *et al.*, *J. Org. Chem.* **23**, 1906 (1958).

(3) Paper III. E. A. Nodiff *et al.*, *J. Org. Chem.*, **25**, 60 (1960).

(4) All melting points are uncorrected.

TABLE I



Compound Number	R_1	R_2	M.P. and B.P.	Yield, %	Molecular Formula	Analyses					
						Calcd.			Found		
						C	H	N	C	H	N
1	$-SCH_3$	$-(CH_2)_3N(CH_3)_2$[g]	220–223°/0.7 mm.[c] 149–150°[b] (lit. 160°)[g]	88%	$C_{18}H_{23}ClN_2S_2$[b]	58.91	6.32	—	58.77	6.52	—
2	$-SCH_3$	$-CH_2-CH(CH_3)CH_2N(CH_3)_2$[g]	218–221°/0.1 mm.[c] 173–174°[b]	93%	$C_{19}H_{25}ClN_2S_2$[b]	59.89	6.61	—	59.91	6.81	—
3	$-SCH_3$	 [g]	239–242°/0.1 mm.[c] 224–225°[f] (lit. 220°)[g]	92%	$C_{21}H_{29}Cl_2N_3S_2$	55.01	6.38	—	55.29	6.20	—
4	$-SCH_3$	 [g]	200–220°/0.03 mm.[c] 174–175°[e] (lit. 199°)[g]	44%	$C_{30}H_{37}N_3O_8S_2$[e]	57.03	5.90	6.65	56.83	5.78	6.70
5	$-SCH_3$	 [k]	165–166°[e] (Lit. 173–175°)[g]	33%	$C_{32}H_{39}N_3O_{10}S_2$[e]	55.72	5.70	—	56.01	5.98	—
6	$-SO_2CH_3$	$-(CH_2)_3-N(CH_3)_2$[h]	115–116°[a] 112–115°[b] (lit. 158–168°)[h]	62%	$C_{18}H_{22}N_2O_2S_2$[a]	59.64	6.12	—	59.73	6.33	—
7	$-SO_2CH_3$	$-CH_2CH(CH_3)CH_2N(CH_3)_2$[h]	234–235°[b] (lit. 229–230°)[h] 255–260°/0.2 mm.[a]	60%	$C_{19}H_{25}ClN_2O_2S_2$[b]	55.25	6.10	—	55.50	6.12	—
8	$-SCF_3$	$-(CH_2)_3N(CH_3)_2$	153–157°/0.1 mm.[c]	64%	$C_{18}H_{19}N_2F_3S_2$[a]	56.23	4.98	7.29	56.37	5.23	7.52
9	$-SCF_3$	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	153–157°/0.1 mm.[c] 158.5–159.5°[d]	54%	$C_{19}H_{21}F_3N_2S_2$[a] $C_{23}H_{24}F_3N_5O_7S_2$[d]	57.26 47.84	5.31 3.85	7.03 11.16	57.55 47.88	5.57 4.16	7.24 11.48
10	$-SCF_3$		220–223°/0.3 mm.[c] 182–183°[e]	63%	$C_{29}H_{32}F_3N_3O_8S_2$[e]	51.85	4.80	—	52.05	4.95	—
11	$-SO_2CF_3$	$-(CH_2)_3N(CH_3)_2$	235–240°/0.4 mm.[c] 174–175°[b]	15%	$C_{18}H_{20}ClF_3N_2O_2S_2$[b]	47.73	4.45	—	47.93	4.68	—
12	$-SO_2CF_3$	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	182–184°/0.2 mm.[a] 203–204°[d]	19%	$C_{19}H_{21}F_3N_2O_2S_2$[a] $C_{28}H_{24}F_3N_5O_9S_2$[d]	53.01 45.52	4.92 3.67	6.51 10.62	53.06 45.84	5.12 3.76	6.71 10.06
13	$-SO_2CF_3$		249.5° dec.[f] (not distilled)	16%	$C_{21}H_{26}F_3Cl_2N_3O_2S_2$[f]	46.32	4.81	7.72	46.17	5.37	7.72
14	$-OH$	$-(CH_2)_3N(CH_3)_2$	220–225°/0.05 mm.[c] 90–91°[c] 132–133°[e]	49%	$C_{21}H_{24}N_2O_5S$[j]	60.56	5.81	—	60.56	5.94	—

See Table II for footnotes.

TABLE II

DERIVATIVES OF 2-AZAPHENOTHIAZINE

Compound Number	X	R	M.P. or B.P.	Yield, %	Molecular Formula	Analyses					
						Calcd.			Found		
						C	H	N	C	H	N
15	H	$-(CH_2)_2N(CH_3)_2$[f]	165–170°/0.007 mm.[c] 240.5–244.5° dec.[f]	63%	$C_{16}H_{21}Cl_2N_3S$[f]	53.63	5.91	—	53.43	5.80	—
16	H	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	190–195°/0.6 mm.[e] 234–235°[f]	82%	$C_{17}H_{23}Cl_2N_3S$[f]	54.68	6.21	—	54.48	6.51	—
17	H	$-(CH_2)_3N$(piperazinyl)$NCH_2CH_2OCOCH_3$	147 148°[dec.]	9%	$C_{30}H_{36}N_4O_{10}S \cdot H_2O$[e]	54.37	5.78	—	54.40	5.78	—
18	Cl	$-(CH_2)_3N(CH_3)_2$[i]	215–220°/1 mm.[c] 249–250°[f]	66%	$C_{16}H_{20}Cl_2N_2S$[f]	48.92	5.13	—	48.81	5.36	—

[a] Free base. [b] Hydrochloride. [c] B.p., sausage flask distillation. [d] Picrate. [e] Dimaleate. [f] Dihydrochloride. [g] British Patent 802,725, October 8, 1958. [h] R. M. Jacob and G. L. Regnier, U. S. Patent 2,889,322, June 2, 1959. [i] P. J. C. Buisson, Canadian Patent 569,806, January 27, 1959. [j] Maleate. [k] J-P. Bourquin, *et al.*, *Helv. Chim. Acta*, **41**, 1072 (1958).

was refluxed for 2 hr. to remove the formyl protecting group. The solvents were removed under vacuum and the residual oil dissolved in benzene. The benzene solution was extracted with dilute hydrochloric acid. The acid extracts were made alkaline with 10% sodium hydroxide solution and extracted with benzene. The benzene was evaporated and the residual oil distilled at 240–270° (70–90 μ). The yield of distilled 10-[3-(1-piperazinyl)propyl]-2-azaphenothiazine was 11 g. (45%). The distilled material was dissolved in 250 ml. of methanol and refluxed for 90 min. with 1.8 g. of ethylene oxide. The solvent was evaporated under vacuum and the residue dissolved in 250 ml. of benzene. The solution was azeotroped for 1 hr., cooled, filtered, and treated with 6.5 g. of acetyl chloride followed by a reflux period of 1 hr. The solvents were evaporated under vacuum and the residual gum treated with 10% sodium hydroxide solution and benzene. The benzene was evaporated and the resulting oil dissolved in ethyl acetate. The solution was added to sufficient maleic acid, dissolved in ethyl acetate, to form a dimaleate salt. The salt was removed by filtration and recrystallized from ethanol; m.p. 147–148° dec. The overall yield of analytically pure salt based on 2-azaphenothiazine was 4.3 g. (9%).

Anal. Calcd. for $C_{30}H_{36}N_4O_{10}S \cdot H_2O$: C, 54.37; H, 5.78. Found: C, 54.44, 54.35; H, 5.70, 5.85.

Preparation of 3-chloro-1-(1-formyl-4-piperazinyl)propane. 1-Piperazinepropanol (57.6 g.) was refluxed for 1 hr. with 48.0 g. of methyl formate. After removal of excess methyl formate on the steam bath, the residue was quickly fractionated through a small Vigreux column to give 65.3 g. (95%) of an oil; b.p. 174.5–177°/1.1 mm; $n_D^{24°} = 1.5072$. Prolongation of the distillation time was accompanied by formation of gases, with a lower yield of the formamide. A solution of 42.8 g. of this oil in 300 cc. of chloroform was treated with excess gaseous hydrogen chloride to form a slurry. While

stirring the slurry, 19 g. of thionyl chloride was added and the mixture was refluxed for 0.5 hr. A further addition of 3 g. of thionyl chloride was added and refluxing was continued for 2.5 hr. Complete removal of volatile solvents *in vacuo* at room temperature left the hygroscopic crystalline hydrochloride which could be used without further purification. Recrystallization of this salt separated about 5% impurities.

Conversion of this hydrochloride to the free base, 1-formyl-4-(3-chloropropyl)piperazine, was accomplished with potassium hydroxide. Benzene extracts were distilled; approximately 60% yields were obtained of a pale yellow oil; b.p. 144.5–148.5°/0.4 mm; $n_D^{25°}$ = 1.5053, which was not further characterized.

Acknowledgment. The authors wish to express their appreciation to Dr. James W. Wilson for his help, and to Messrs. E. A. Nodiff and A. J. Saggiomo, Research Institute of Temple University, and Dr. H. Reiff, Smith, Kline and French Laboratories, for the preparation of chemical intermediates. Analyses were obtained by the Analytical and Physical Chemistry Section of Smith, Kline and French Laboratories.

PHILADELPHIA 1, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, AIN SHAMS UNIVERSITY]

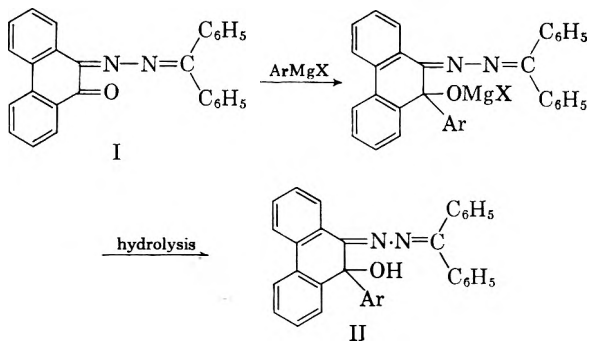
Studies of Quinoid Structures. V. Action of Grignard Reagents on Phenanthrenequinone Benzophenone Azine

WILLIAM IBRAHIM AWAD AND (MRS.) AIDA MOUSTAFA KAMEL

Received September 28, 1959

Arylmagnesium halides add preferentially to the carbonyl group of phenanthrenequinone benzophenone azine (I). When excess Grignard reagent is used, cleavage-condensation reaction takes place with the formation of 9,10-diarylphenanthrene.

In continuation of the previous study[1,2,3,4] of the action of Grignard reagents on derivatives of *ortho*-quinoid structures, the authors have now investigated the action of Grignard reagents on phenanthrenequinone benzophenone azine (I). In molecular proportion or slight excess, Grignard reagents add preferentially to the carbonyl group as it has been previously stated[1,2,3,4] (*cf.* Scheme A).



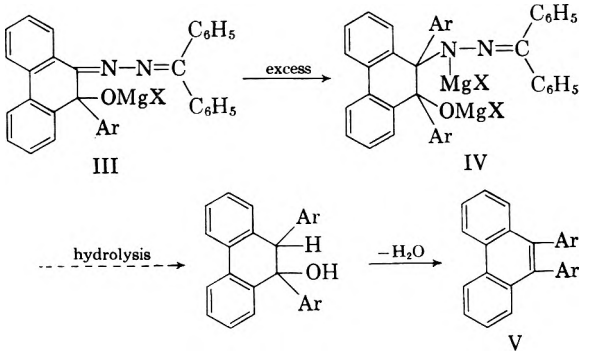
IIa. Ar = C_6H_5, IIb. Ar = $C_{10}H_7$-(α)

Scheme A

The constitution of II is based on 1) the preferential addition to the carbonyl group,[1,2,3,4,5,6a] 2) the carbonyl stretching frequency[6b] (at 1661 cm.$^{-1}$),[7] which is present in the infrared spectrum of the azine, is absent from the spectra of IIa and IIb, 3) an —OH stretching frequency at 3508 cm.$^{-1}$ appeared which was not present in the infrared spectrum of the starting material, and 4) elemental analysis.

However, excess of phenyl or anisylmagnesium bromide gave, in good yield, as a final product 9,10-diphenyl or 9,10-dianisylphenanthrene respectively as proved by 1) mixture melting point with an authentic sample of 9,10-diphenylphenanthrene,[8] and 2) elemental analysis.

It is to be noticed that the cleavage-condensation reaction takes place when acetone anil or acetophenone anil is treated with some Grignard reagents.[9] A possible series of steps for the reaction is:



Va. Ar = C_6H_5, Vb. Ar = C_6H_4—OCH_3(p)

Scheme B

(1) W. I. Awad and A. R. A. Raouf, *J. Org. Chem.*, **22**, 881 (1957).

(2) W. I. Awad and A. R. A. Raouf, *J. Org. Chem.*, **23**, 282 (1958).

(3) W. I. Awad, A. R. A. Raouf, and A. M. Kamel, *J. Org. Chem.*, **24**, 1777 (1959).

(4) W. I. Awad, A. K. Fateen, and M. A. Zayed, *J. Org. Chem.*, in press.

(5) O. Diels and F. ter Meer, *Ber.*, **42**, 1940 (1909).

(6) (a) O. Diels and J. M. Johlin, *Ber.*, **44**, 403 (1911). (b) The infrared measurements were carried out on Perkin-Elmer infracord, model 137 in nujol mulls.

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Metheun, London, 1957, p. 114.

(8) A. Werner and A. Grob., *Ber.*, **37**, 2887 (1904).

V might have been formed during the hydrolysis of IV or by loss of water after hydrolysis. As a fact the final product is the hydrocarbon V.

IIa on treatment with phenylmagnesium bromide yields Va in poor yield. This indicates that the halomagnesium complex of II may be the intermediate product in the formation of V.

During the preparation of phenanthrenequinone benzophenone azine[10a] (red), a yellow, highly crystalline product is formed if excess benzophenone hydrazone is used. We believe that it may be phenanthrenequinone diazine. This compound gave concordant nitrogen analysis for such a formula, but its carbon content showed less carbon than the theoretical value. The constitution of this product is under investigation.

EXPERIMENTAL[10b]

Action of phenylmagnesium bromide on phenanthrenequinone benzophenone azine. A solution of phenanthrenequinone benzophenone azine (3.8 g.) in dry benzene (100 ml.) was added to an ethereal solution of phenylmagnesium bromide (from 1.6 g. bromobenzene, 0.23 g. magnesium) and the reaction mixture was heated under reflux for 2 hr. and left overnight. The reaction mixture was hydrolyzed with a saturated solution of ammonium chloride and the ether-benzene layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated. The product was precipitated by addition of methyl alcohol and was recrystallized from benzene-methyl alcohol to give 2.5 g. of IIa as yellow crystals, m.p. 178–180°.

Anal. Calcd. for $C_{33}H_{24}ON_2$: C, 85.32; H, 5.21; N, 6.03. Found: C, 84.80; H, 5.38; N, 5.91.

The product gave a brownish-yellow color with concd. sulfuric acid.

Action of naphthylmagnesium bromide on phenanthrenequinone benzophenone azine. A solution of phenanthrenequinone benzophenone azine (3.8 g.) in dry benzene (100 ml.) was added to an ethereal solution of naphthylmagnesium bromide (from 2.1 g. α-bromonaphthalene and 0.23 g. magnesium) and the reaction mixture was heated under reflux for 2 hr. and left overnight. The reaction mixture was worked up as before. The product was recrystallized from benzene-methyl alcohol mixture to give 2.9 g. of IIb as yellow crystals, m.p. 208–210°.

Anal. Calcd. for $C_{37}H_{26}ON_2$: C, 86.38; H, 5.05; N, 5.44. Found: C, 86.74; H, 5.25; N, 5.13.

The product gave a brownish coloration with concd. sulfuric acid.

Action of excess phenylmagnesium bromide on phenanthrenequinone benzophenone azine. A solution of phenanthrenequinone benzophenone azine (1 g.) in dry benzene (25 ml.) was added to an ethereal solution of phenylmagnesium bromide (from 6.3 g. bromobenzene and 0.9 g. magnesium) and the reaction was completed as before. The product was precipitated on addition of methyl alcohol and recrystallized from benzene-methyl alcohol mixture to give 0.8 g. of Va as colorless needles, m.p. 231–233°.

Anal. Calcd. for $C_{26}H_{18}$: C, 94.51; H, 5.49. Found: C, 93.67; H, 5.36.

It gave no depression on admixture with an authentic specimen of 9,10-diphenylphenanthrene.

Action of excess anisylmagnesium bromide on phenanthrenequinone benzophenone azine. A solution of phenanthrenequinone benzophenone azine (1 g.) in dry benzene (25 ml.) was added to an ethereal solution of anisylmagnesium bromide (from 9.3 g. *p*-bromoanisole and 0.9 g. magnesium) and the reaction was completed as before. The product was precipitated by the addition of methyl alcohol and recrystallized from benzene-methyl alcohol mixture to give 0.85 g. of Vb as colorless needles, m.p. 250–251°.

Anal. Calcd. for $C_{28}H_{22}O_2$: C, 86.12; H, 5.68. Found: C, 85.81; H, 5.64.

Action of phenylmagnesium bromide on IIa. A solution of IIa (1.1 g.) in dry benzene (25 ml.) was added to an ethereal solution of phenylmagnesium bromide (from 1.5 g. bromobenzene and 0.5 g. magnesium) and the reaction was completed as before. On addition of methyl alcohol, two products were precipitated. On extraction with cold benzene and concentration of the benzene solution, a colorless product was obtained. Recrystallization from benzene-methyl alcohol mixture gave colorless needles in poor yield. It proved to be 9,10-diphenylphenanthrene Va by melting point and mixture melting point. The product which was insoluble in cold benzene was recrystallized from hot benzene-methyl alcohol mixture and proved to be the starting material.

Action of excess benzophenone hydrazone on phenanthrenequinone. Phenanthrenequinone (2 g.) and benzophenone hydrazone (5 g.) in dry benzene (50 ml.) were heated under reflux on the water bath for 20 min. The solution acquired a reddish coloration. On addition of methyl alcohol a yellow product was obtained (2 g.). Recrystallization from benzene-methyl alcohol mixture gave a product with yellow crystals, m.p. 160–162°.

Anal. Calcd. for $C_{40}H_{28}N_4$: N, 9.92. Found: N, 9.77.

The product gave a yellowish-brown coloration with concd. sulfuric acid.

ABBASSIA, CAIRO, EGYPT, U.A.R.

(9) M. S. Kharasch and Otto Reimuth, *Grignard Reactions of Nonmetallic Substances.* New York, Prentice-Hall, Inc., 1954, p. 1209.

(10) (a) O. Gerhardt, *Monatsh. Chem.*, **42**, 63 (1921); *Chem. Abstr.*, **15**, 3834 (1921). (b) Melting points are not corrected. Microanalyses were carried out by Alfred Bernhardt, in the Max-Planck Institut, Mülheim (Ruhr), Germany.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

Photochemical Reactions in Sunlight. Experiments with 2-*N*-Phenyl-α,β-naphtho-1,2,3-triazolequinone and Monoxime Derivative in Sunlight and in Dark

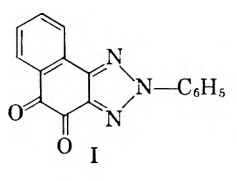
AHMED MUSTAFA, ABDEL KADER MANSOUR, AND HUSSEIN ABDEL AZIM ZAHER

Received December 1, 1959

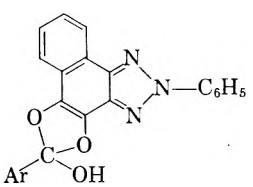
The photochemical addition of aldehydes to heterocyclic nitrogen *o*-quinones, such as 2-*N*-phenyl-α,β-naphtho-1,2,3-triazolequinone (I), has now been investigated and the photoproducts (IIa–b) are obtained. The oxazole (Va) has been obtained either by heating the photoproduct of the reaction of 2-*N*-phenyl-α,β-naphtho-1,2,3-triazolequinone monoxime (IV) and *p*-methoxybenzaldehyde and/or by allowing IV to react with the aldehyde in the dark in the presence of piperidene. The photochemical addition of I to olefins, e.g., stilbene and benzalphthalide, has been investigated and the photoproducts VI and VII are obtained respectively.

In continuation of our previous work, the action of aromatic aldehydes on heterocyclic nitrogen *o*-quinones has been extended.[1–3]

We now have allowed the orange 2-*N*-phenyl-α,β-naphtho-1,2,3-triazolequinone (I) to react with aromatic aldehydes, namely, *p*-methoxybenzaldehyde and 3,4-diethoxybenzaldehyde, in the absence of oxygen and have found that addition takes place in molecular proportions. The colorless photoproducts (IIa–b) are obtained in good yield in most cases and separate during exposure. It is believed that these photoproducts have constitutions such as II or the corresponding open form.

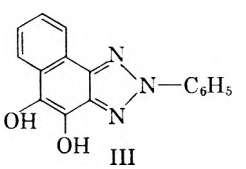


I



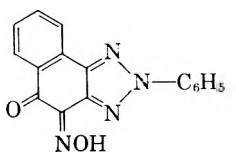
IIa, Ar = *p*-$CH_3OC_6H_4$
b, Ar = 3,4-diethoxyphenyl

Compound IIa is colorless, insoluble in cold aqueous sodium hydroxide solution, and gives no color with ferric chloride. It yields *p*-methoxybenzoic acid and I on heating with concentrated hydrochloric acid in acetic acid. The formation of I may be attributed to the ready oxidation of the intermediate hydroquinone (III) by atmospheric oxygen.[4]

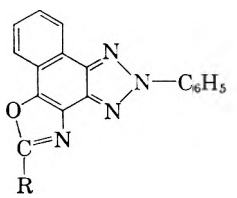


III

2-N-Phenyl-α,β-naphtho-1,2,3-triazolequinone monoxime and aromatic aldehydes. While the mechanism of the action of aromatic aldehydes on *o*-quinone monoximes is not known, the over-all results may be summarized: The oxime (IV or isomer) and *p*-methoxybenzaldehyde do not react in benzene in the dark at room temperature; in sunlight, however, a product was obtained which on heating yielded the corresponding oxazole (Va or isomer).[3,5]



IV (or isomer)



V (or isomer)
Va, R = *p*-$CH_3OC_6H_4$
b, R = 3,4-diethoxyphenyl

We have also investigated the action of aromatic aldehydes, *e.g.*, *p*-methoxybenzaldehyde and 3,4-diethoxybenzaldehyde, on IV and have found that the corresponding oxazoles (Va–b) are formed when the reactants are heated without a solvent in the presence of piperidine.

2-N-Phenyl-α,β-naphtho-1,2,3-triazolequinone and ethylenes. In an extension of our previous work on the action of ethylenes on *o*-quinones in sunlight,[3,6,7]

(1) A. Mustafa, A. H. Harhash, A. K. Mansour, and S. M. Omran, *J. Am. Chem. Soc.*, **78**, 4306 (1956).

(2) A. Schönberg, A. Mustafa, and S. M. Zayed, *J. Am. Chem. Soc.*, **75**, 4302 (1953).

(3) A. Mustafa, A. K. Mansour, and A. F. Shalaby, *J. Am. Chem. Soc.*, **81**, 3409 (1959).

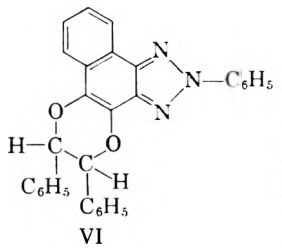
(4) G. Charrier and A. Manfredi, *Gazz. chim. ital.*, **56**, 196–207 (1926); *Chem. Abstr.*, **20**, 2859 (1926).

(5) This reaction is similar to the formation of 2-phenylphenanthroxazole by the action of heat on the product obtained by exposing a mixture of phenanthraquinone monoxime and benzaldehyde to sunlight; *cf.* A. Schönberg *et al.*, *J. Chem. Soc.*, 374 (1950).

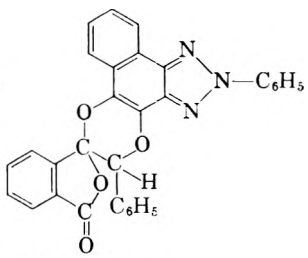
(6) A. Schönberg, A. Mustafa, and co-workers, *J. Chem. Soc.*, 387 (1944); 551 (1945), 2126 (1948); *Chem. Revs.*, **40**, 190 (1948); A. Mustafa and A. M. Islam, *J. Chem. Soc.*, S81 (1949); A. Mustafa, *J. Chem. Soc.*, S83 (1949); 1034 (1951).

(7) For the mechanism of such photo-additions (*cf.* G. O. Schenk, *Naturwissenschaften*, **40**, 229 (1953); G. O. Schenk and G. A. Schmidt Thomee, *Ann.*, **584**, 199 (1953), and A. Schönberg *et al.*, *J. Am. Chem. Soc.*, **77**, 3850 (1955); *cf.* also *Preparative Organische Photochemie*, A. Schönberg, Springer-Verlad, Berlin, Göttingen, Heil Heidelberg, 1958, p. 93.

we now have studied the action of stilbene and/or benzalphthalide on I and have found that, whereas no reaction takes place in the dark, in sunlight colorless products VI and VII or isomer are formed. Compound VI regenerated the starting materials on heating.



VI



VII (or isomer)

EXPERIMENTAL

Preparation of 2-N-phenyl-α,β-naphtho-1,2,3-triazolequinone (I). The quinone was prepared according to the procedure described by Charrier and Manfredi,[4] in 35% yield, m.p. 207–209°.

Photochemical reactions with 2-N-phenyl-α,β-naphtho-1,2,3-triazolequinone in sunlight.[7a] *General remarks.* The photochemical reactions were carried out as described in the previous publications.[3]

Photochemical reaction of 2-N-phenyl-α,β-naphtho-1,2,3-triazolequinone with p-methoxybenzaldehyde. A mixture of the quinone (0.8 g.) and *p*-methoxybenzaldehyde (0.7 g.) in benzene (35 ml.) was exposed to sunlight for 7 days (December). The photoproduct (IIa) separated during irradiation as almost colorless crystals. Recrystallization from xylene gave colorless crystals, m.p. 227–228°. Yield ca., 76%.

Anal. Calcd. for $C_{24}H_{17}N_3O_4$: C, 70.07; H, 4.13; N, 10.12. Found: C, 69.79; H, 4.13; N, 10.07.

IIa is insoluble in aqueous sodium hydroxide solution and gives no color with ferric chloride.

Photochemical reaction of I *and 3,4-diethoxybenzaldehyde.* A mixture of the quinone I (0.7 g.) and 3,4-diethoxybenzaldehyde (0.9 g.) in benzene (40 ml.) was exposed to sunlight for 10 days (December). The photoproduct (IIb), separated during irradiation as almost colorless crystals. It was filtered and recrystallized from xylene as colorless crystals, m.p. 230°. Yield ca. 80%.

Anal. Calcd. for $C_{27}H_{23}N_3O_6$: C, 69.08; H, 4.90; N, 8.95. Found: C, 69.22; H, 4.76; N, 8.52.

IIb is insoluble in aqueous sodium hydroxide solution; it gives a yellow color with concd. sulfuric acid and develops no color with ferric chloride.

Action of hydrochloric acid on IIa. To a solution of 0.5 g. of IIa in 30 ml. of glacial acetic acid, was added 3 ml. of concd. hydrochloric acid. The reaction mixture was refluxed for 5 hr., cooled and poured into water. It was then neutralized with sodium bicarbonate solution and allowed to stand overnight. The orange residue formed was collected and crystallized from acetic acid. It was identified as the quinone (I) (m.p. and mixed m.p.). Acidification of the alkaline filtrate yielded *p*-methoxybenzoic acid (m.p. and mixed m.p.).

Photochemical reaction of I *with stilbene.* A mixture of the quinone (0.9 g.) and stilbene (0.8 g.) in benzene (35 ml.) was exposed to sunlight for 7 days (December). The photoproduct (VI) separated as almost colorless crystals during exposure to sunlight. It was collected and recrystallized from benzene as almost colorless crystals, m.p. 253–254°. Yield ca., 82%.

Anal. Calcd. for $C_{30}H_{21}N_3O_2$: C, 79.12; H, 4.39; N, 9.23. Found: C, 79.31; H, 4.46; N, 9.05.

VI is insoluble in aqueous sodium hydroxide solution and gives no color with ferric chloride.

Thermal decomposition of VI. VI (0.2 g.) was heated at 265–270° (bath temperature) for 1 hr. under reduced pressure. The colorless sublimate on the upper part of the containing vessel was collected and proved to be stilbene (m.p. and mixed m.p.). The reddish sublimate on the lower part of the vessel was collected and proved to be the quinone (m.p. and mixed m.p.).

Photoreaction of the quinone I *with benzalphthalide.* The quinone (0.7 g.) and benzalphthalide (1.0 g.) in benzene (45 ml.) was irradiated for 7 days (March). The photoproduct VII separated during irradiation as colorless crystals. It was recrystallized from chlorobenzene, m.p. 333°. Yield, ca., 78%.

Anal. Calcd. for $C_{31}H_{19}N_3O_4$: N, 8.45. Found: N, 8.28.

VII is insoluble in aqueous sodium hydroxide solution and develops no color with ferric chloride.

Photoreaction of 2-N-phenyl-α,β-naphtho-1,2,3-triazolquinone monoxime (IV) *and p-methoxybenzaldehyde.* A mixture of the oxime (IV) (0.8 g.) and *p*-methoxybenzaldehyde (0.9 g.) in benzene (80 ml.) was exposed to sunlight for 28 days (March). A colorless photoproduct separated during irradiation. It was recrystallized from xylene as almost colorless crystals, m.p. 250–251°. Yield ca., 48%.

Anal. Calcd. for $C_{24}H_{18}N_4O_4$: N, 13.14. Found: N, 12.70.

The product is insoluble in cold aqueous sodium hydroxide solution; it gives a yellow color with concd. sulfuric acid and develops no color with ferric chloride.

This photoproduct was heated at 255° (bath temperature) under reduced pressure (oil-pump) for 0.5 hr. The containing vessel was then cooled and the substance obtained after heating was identified as Va.

Action of p-methoxybenzaldehyde on the monoxime IV *in the dark.* A mixture of the monoxime (IV) (0.3 g.), anisaldehyde (0.4 g.) and a few drops of piperidene was heated at 160–170° (bath temperature) for 2 hr. The reaction mixture was then cooled, rubbed with benzene, filtered on the pump, and washed with cold benzene. The product was recrystallized from xylene as colorless crystals, m.p. 275°. Yield, ca., 71%.

Anal. Calcd. for $C_{24}H_{16}N_4O_2$: C, 73.46; H, 4.08; N, 14.28. Found: C, 73.68; H, 4.00; N, 14.41.

Va is insoluble in aqueous sodium hydroxide solution; it gives a yellow color with concd. sulfuric acid and developed no color with ferric chloride.

Action of 3,4-diethoxybenzaldehyde on the monoxime in the dark. A mixture of the monoxime (0.5 g.), 3,4-diethoxybenzaldehyde (0.6 g.), and 2 drops of piperidene was heated at 165–170° (bath temperature) for 2 hr. It was then cooled and the dark residue obtained washed with cold ethanol. Recrystallization from acetic acid gave almost colorless crystals m.p. 219°. Yield, ca., 41%.

Anal. Calcd. for $C_{27}H_{22}N_4O_3$: N, 12.44. Found: N, 12.03.

Vb is insoluble in aqueous sodium hydroxide solution and develops no color with ferric chloride.

GIZA, EGYPT, U.A.R.

(7a) The photoreactions were carried out in Schlenk tubes of pyrex glass [W. Schlenk and A. Thal, *Ber.*, **46**, 2840 (1913)]. The benzene used for the photochemical experiments was thiophen-free and dried over metallic sodium. Parallel experiments were carried out in the dark under the same experimental conditions and proved to be negative.

[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF FLORIDA]

A New Compound for Cancer Research. Synthesis of 2-Fluoro-5-acetylaminofluorene[1]

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Received December 3, 1959

To investigate its carcinogenicity, 2-fluoro-5-acetylaminofluorene was synthesized from diphenic acid. In the process the following new compounds were prepared: methyl 2-nitrofluorene-5-carboxylate, methyl 2-aminofluorene-5-carboxylate, methyl 2-fluorofluorene-5-carboxylate, 2-fluorofluorene-5-carbohydrazide, 2-fluorofluorene-5-urethan, and 2-fluorofluorene-5-phthalimide.

Experimental evidence has revealed that not only the nature of the group or groups present but also their position has a considerable influence on the carcinogenicity of a compound. For example: 2-Acetylaminofluorene is a known carcinogen of fairly high potency causing a wide variety of tumors[2] while 4-acetylaminofluorene has little activity.[3] It was further shown that introduction of fluorine in the 7-position of 2-acetylaminofluorene increased its potency.[4] It is thus of interest, to determine whether the introduction of fluorine in a similar position in 4-acetylaminofluorene would similarly increase its potency.

The synthesis of the compound 2-fluoro-5-acetylaminofluorene was carried out by the following series of reactions: diphenic acid → fluorenone-4-carboxylic acid → fluorene-4-carboxylic acid → 2-nitrofluorene-5-carboxylic acid → methyl 2-nitrofluorene-5-carboxylate → methyl 2-aminofluorene-5-carboxylate → methyl 2-fluoroborodiazoniumfluorene-5-carboxylate → methyl 2-fluorofluorene-5-carboxylate → 2-fluorofluorene-5-carbohydrazide → 2-fluorofluorene-5-urethan → 2-fluorofluorene-5-phthalimide → 2-fluoro-5-aminofluorene → 2-fluoro-5-acetylaminofluorene.

Preparation of methyl 2-nitrofluorene-5-carboxylate was necessary because attempts to convert 2-aminofluorene-5-carboxylic acid directly to 2-fluoroborodiazoniumfluorene-5-carboxylic acid and subsequently to 2-fluorofluorene-5-carboxylic acid failed because of production of a large amount of tar in the pyrolysis of the diazoniumfluoroborate. Hence, the carboxyl group had to be protected. This increased the yield, although isolation of pure methyl 2-fluorofluorene-5-carboxylate still proved to be a problem which was solved by column chromatography. Next, difficulty was encountered in the acid hydrolysis of 2-fluorofluorene-5-urethan to 2-fluoro-5-aminofluorene. Conversion of the hydrazide to the isocyanate, then to the acetylated amine by refluxing with acetic anhydride[5] gave only a 20% overall yield. Hence, the modified procedure of first converting 2-fluorofluorene-5-urethan to 2-fluorofluorene-5-phthalimide was employed.

The biological activity of 2-fluoro-5-acetylaminofluorene will be reported elsewhere.

EXPERIMENTAL

Methyl 2-nitrofluorene-5-carboxylate. To 150 ml. of thionyl chloride was added in small portions 20 g. (0.078 mole) of 2-nitrofluorene-5-carboxylic acid,[6] with occasional shaking. The mixture was refluxed for 1 hr. The thionyl chloride was distilled off, then three portions of 75 ml. each of hexane were added to the flask successively and distilled again under reduced pressure to dryness. The cooled residue of acid chloride was treated with 300 ml. of dry methanol and refluxed for 17 hr. Filtration of the mixture on cooling gave a pale yellow compound, m.p. 186–187°, yield 20 g. (95%). After recrystallization from benzene brightly shining crystals, m.p. 188–189° were obtained.

Anal. Calcd. for $C_{15}H_{11}O_4N$: C, 66.91; H, 4.08; N, 5.20. Found: C, 67.26; H, 3.52; N, 5.18.

Methyl 2-aminofluorene-5-carboxylate.[7] Thirty grams (0.11 mole) of dry powdered methyl 2-nitrofluorene-5-carboxylate was made into a thin paste with 1 l. of 78% alcohol. A solution of 10 g. of calcium chloride in 15 ml. of water together with a mixture of 300 g. of zinc dust and 10 g. of Norit was added to it; the whole was thoroughly shaken and vigorously refluxed for 4 hr. At the end of the period a solution of 1 ml. of 85% hydrazine hydrate in 2 ml. of water was added; the sludge of zinc dust and charcoal was filtered from the boiling solution and extracted with 50 ml. portions of boiling 78% alcohol. The combined filtrates were then poured into 2 l. of water, whereupon a white flocculent precipitate was obtained, which was filtered and dried. Yield: 24 g. (90%), m.p. 140–141°.

A small amount of this amine was acetylated by refluxing it with acetic anhydride in ether solution. Crystallization from benzene gave white shiny plates m.p. 186°.

Anal. Calcd. for $C_{17}H_{15}O_3N$: C, 72.59; H, 5.33; N, 4.98. Found: C, 72.45; H, 5.41; N, 5.27.

Methyl 2-fluoroborodiazoniumfluorene-5-carboxylate.[8] To 240

(1) This investigation was supported by research grant C-1066 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

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(5) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **18**, 864 (1953).

(6) Prepared from diphenic acid by the procedure of E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **20**, 1396 (1955).

(7) W. E. Kuhn, *Org. Syntheses*, **Coll. Vol. II**, 47 (1943).

(8) Procedure described by E. D. Bergmann, S. Berkovic, and R. Ikan, *J. Am. Chem. Soc.*, **78**, 6037 (1956).

ml. of 48% fluoroboric acid, cooled in an ice-salt bath, were added simultaneously a solution of 8 g. of sodium nitrite in a minimum quantity of water and a thick paste of 24 g. (0.1 mole) of methyl 2-aminofluorene-5-carboxylate in water in small portions, so that the mixture always contained an excess of nitrite. During the whole operation, the mixture was stirred efficiently and kept at −6°. The diazonium salt which precipitated as an emerald green mass was filtered, washed with some fluoroboric acid and then with ether, and dried; yield 36.1 g., m.p. 111–114° dec.

Methyl 2-fluorofluorene-5-carboxylate. The diazoniumfluoroborate was decomposed at 140° (bath temp.) and the product taken up with acetone. The acetone was removed by distillation; the residue was mixed with 30 g. of sodium bicarbonate and then extracted with heptane in a Soxhlet extractor. The extract was passed through a 40 × 2½ cm. column of magnesium trisilicate.[9] The filtrate on evaporation gave crude methyl 2-fluorofluorene-5-carboxylate, m.p. 118–122°, yield 9 g. (37%, calculated on amine). A sample recrystallized several times from methanol melted at 119–120°.

Anal. Calcd. for $C_{15}H_{11}O_2F$: C, 74.38; H, 4.54; F, 7.85. Found: C, 74.25; H, 4.47; F, 8.10.

2-Fluorofluorene-5-carboxylic acid was prepared by hydrolysis of the ester with sodium hydroxide and was purified by sublimation *in vacuo*, m.p. 185–186°.

Anal. Calcd. for $C_{14}H_9O_2F$: C, 73.68; H, 3.94; F, 8.33. Found: C, 73.69; H, 3.84; F, 8.48.

2-Fluorofluorene-5-carboxamide was prepared from the acid chloride and ammonia. It was recrystallized from ethanol and formed shining needles, m.p. 215°.

Anal. Calcd. for $C_{14}H_{10}ONF$: C, 74.00; H, 4.40; N, 6.16; F, 8.37. Found: C, 73.86; H, 4.28; N, 6.11; F, 8.63.

2-Fluorofluorene-5-carbohydrazide.[10] A mixture of 10 g. (0.04 mole) of methyl 2-fluorofluorene-5-carboxylate, 10 ml. of *n*-butanol, and 19.2 ml. of 85% hydrazine hydrate was refluxed for 6 hr. under anhydrous conditions. Within 15 min. a solid appeared and increased with time. On cooling, the mixture solidified *en masse*. It was then transferred to a Büchner funnel, all the liquid was pressed out under suction, and the residue was washed with water, ether and dried; yield 8.5 g. (85%), m.p. 200–201°. Recrystallization from ethanol gave a pure white substance, m.p. 201°.

Anal. Calcd. for $C_{14}H_{11}N_2FO$: C, 69.42; H, 4.54; N, 11.57; F, 7.85. Found: C, 69.90; H, 4.82; N, 11.68; F, 7.83.

2-Fluorofluorene-5-carbonazide. The hydrazide (0.1 g.) in 10 ml. of 6*N* hydrochloric acid was treated with an aqueous solution of sodium nitrite (0.1 g.) with stirring at 0–5°. The pale yellow precipitate which formed was filtered and air-dried. It decomposed at 87°.

2-Fluorofluorene-5-urethan. A suspension of 7.3 g. (0.03 mole) of 2-fluorofluorene-5-carbohydrazide in 200 ml. of 6*N* hydrochloric acid was placed in an ice-salt bath and 400 ml. of ether was added followed by 4 g. of sodium nitrite in 15 ml. of water at a moderate rate, while being stirred rapidly. The temperature was kept between 0–5°. After 0.5 hr. the ether layer was separated and the aqueous layer extracted with 50-ml. portions of fresh ether. The combined etherea] extract was washed with water, then with 5% solution of sodium bicarbonate, then again with water, and finally dried over calcium chloride. The dry ether solution was decanted into a flask containing 250 ml. of absolute ethanol and the ether distilled until the residual volume was about 250 ml. The full heat of the steam bath was then applied and the mixture was refluxed for 1 hr. to complete the decomposition of the azide. Evaporation of ethanol under reduced pressure left 6.9 g. of urethan (yield 84.4%), m.p. 123–125°. On recrystallization from a mixture of ethanol and water the pure urethan, m.p. 132°, was obtained.

Anal. Calcd. for $C_{16}H_{14}NO_2F$: C, 70.84; H, 5.16; N, 5.16; F, 7.01. Found: C, 70.56; H, 4.97; N, 5.17; F, 7.58.

2-Fluorofluorene-5-phthalimide.[11] A mixture of 5 g. (0.018 mole) of 2-fluorofluorene-5-urethan and 10 g. of pure phthalic anhydride (freshly prepared)[12] was heated in an oil bath at 230° until the evolution of gases ceased (~45 min.). The reaction mixture was cooled to 100°, treated with small volume of alcohol and then neutralized with excess aqueous sodium bicarbonate (5%). The yellow precipitate of phthalimide thus obtained was filtered, thoroughly washed with water and dried; yield 6.3 g., m.p. 245–250°. Recrystallization from alcohol gave bright yellow crystals, m.p. 253–254°, yield 4.5 g. (75%).

Anal. Calcd. for $C_{21}H_{12}O_2NF$: C, 76.59; H, 3.64; N, 4.25; F, 5.77. Found: C, 76.53; H, 3.71; N, 4.29; F, 5.69.

2-Fluoro-5-aminofluorene hydrochloride. An alcoholic suspension of 4.5 g. (0.013 mole) of 2-fluorofluorene-5-phthalimide was warmed with 1.5 ml. (0.027 mole) of hydrazine hydrate (85%). The substance slowly dissolved and after some time a white gelatinous precipitate was thrown down. The mixture was warmed with excess of hydrochloric acid with occasional shaking and filtered. The residue was boiled with water and filtered again. The filtrate on cooling gave a thick pinkish-white fluffy precipitate of amine hydrochloride; yield 2.6 g. (80.7%) which sublimed at 250–255°.

2-Fluoro-5-acetylaminofluorene. An aqueous suspension of 2.3 g. (0.0097 mole) of 2-fluoro-5-aminofluorene hydrochloride was stirred with excess aqueous ammonium hydroxide (15%) and then allowed to stand for 15 min. The mixture was extracted with ether, using several small portions. The combined ethereal extract was dried over solid caustic soda and its volume was reduced to about 50 ml.

The solution of amine thus obtained was acetylated by refluxing it with 5.75 ml. of acetic anhydride for 1 hr. The thick white precipitate of the 2-fluoro-5-acetylaminofluorene was filtered, washed with water, and dried, yield 1.9 g. (81%), m.p. 205–207°. Repeated crystallization from ethanol gave pure creamy white needles, m.p. 207–208°.

Anal. Calcd. for $C_{15}H_{12}ONF$: C, 74.68; H, 4.97; N, 5.80; F, 7.88. Found: C, 74.63; H, 4.82; N, 5.79; F, 7.67.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XXXIII. Analogs of Chlorambucil. III. Monofunctional Alkylating Agents Derived from 3-(*p*-Acetylphenyl)propionic Acid

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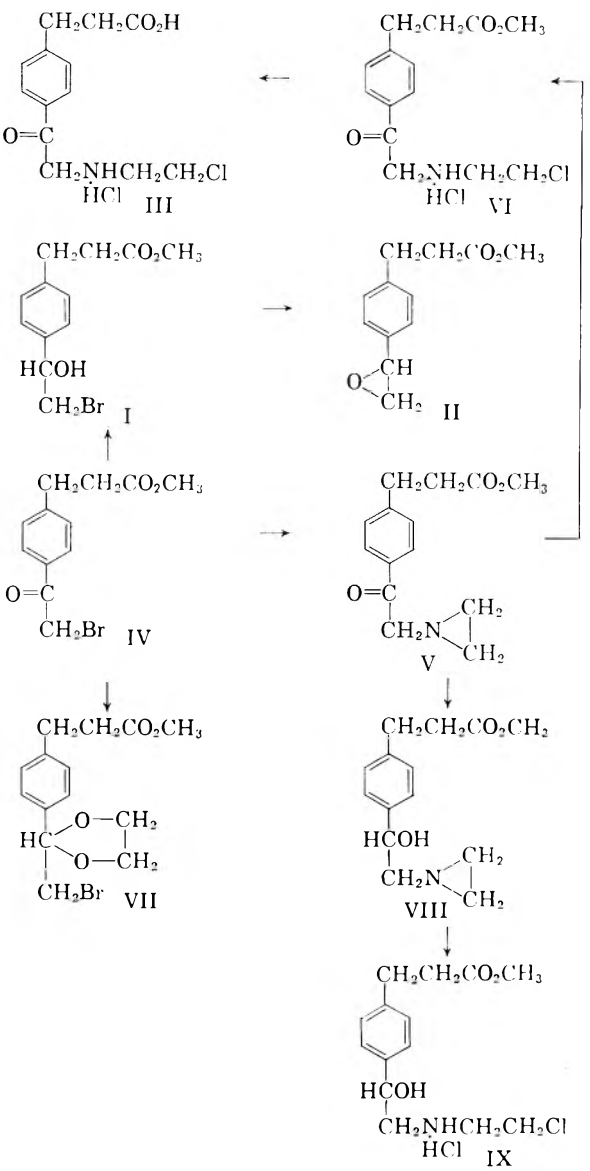
The following monofunctional alkylating agents were synthesized from 3-(*p*-acetylphenyl)propionic acid: 3-{*p*-[*N*-(2-chloroethyl)glycyl]phenyl}propionic acid hydrochloride (III), methyl 3-{*p*-[2-(1-aziridinyl)-1-hydroxyethyl]phenyl}propionate (VIII), and methyl 3-{*p*-[2-(2-chloroethylamino)-1-hydroxyethyl]phenyl}propionate hydrochloride (IX). These compounds can be considered as analogs of chlorambucil, 4-{*p*-[bis(2-chloroethyl)amino]phenyl}butyric acid, and in addition, compound VIII can be considered as an analog of tetramin, α-vinyl-1-aziridinethanol.

In 1953, Everett, Roberts and Ross,[2] reported that a series of *p*-[bis(2-chloroethyl)amino]phenylcarboxylic acids inhibited the growth of the transplanted Walker rat Sarcoma 256, the most active compound being the 4-butyric acid derivative (chlorambucil). The synthesis of derivatives of chlorambucil and norchlorambucil (substituted 3-phenylpropionic acids) has been undertake in these Laboratories.[3a]

Whereas most active anticancer agents of the alkylating type contain bis-alkylating groups, a few anticancer agents can be considered as monofunctional alkylating agents, namely, azaserine[4] (*o*-diazoacetyl-L-serine), DON[5] (6-diazo-5-oxo-L-norleucine), and tetramin[6] (α-vinyl-1-aziridineethanol). With the proper carrier group (metabolite), monofunctional alkylating agents could function as irreversible enzyme inhibitors.[3b] This paper reports the preparation of three monofunctional alkylating agents synthesized from 3-(*p*-acetylphenyl)propionic acid,[3a] namely, 3-[*p*-[*N*-(2-chloroethyl)glycyl]phenyl]propionic acid hydrochloride (III), methyl 3-{*p*-[2-(1-aziridinyl)-1-hydroxyethyl]phenyl}propionate (VIII), and methyl 3-{*p*-[2-(2-chloroethylamino)-1-hydroxyethyl]phenyl}propionate hydrochloride (IX).

The reaction between methyl 3-(*p*-bromoacetylphenyl)propionate (IV)[3a] and ethylenimine was carried out in benzene at 0–5° using triethylamine



(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center of the National Cancer Institute, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper of this series, *cf.* W. A. Skinner, H. F. Gram, and B. R. Baker, *J. Org. Chem.*, **25**, 000 (1960).

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as an acid acceptor. This reaction yielded methyl 3-{*p*-[(1-aziridinyl)acetyl]phenyl}propionate (V) as a semisolid which proved to be too unstable to purify for analysis. However, when V was treated with anhydrous hydrogen chloride in absolute ethanol and chilled in ice, methyl 3-{*p*-[*N*-(2-chloroethyl)glycyl]phenyl}propionate hydrochloride (VI) separated in 52% yield as a crystalline solid, which melted at 180–189° dec. after recrystallization from absolute ethanol.

Hydrolysis of the ester group of VI was accomplished by treatment with hot concentrated hydrochloric acid for two hours. Upon chilling of the acid solution, 3-{*p*-[*N*-(2-chloroethyl)glycyl]phenyl}propionic acid hydrochloride (III) separated in 89% yield as a white solid, m.p. 195–208° dec.

Earlier attempts in these laboratories to treat ethylenimine with methyl 3-(*p*-bromoacetylphenyl)-propionate (IV) in ethanol, using potassium carbonate as the acid acceptor, failed to give the desired product (V) in sufficient yields. That polymeric products were produced even at 0–5°, was shown by treatment of the crude ethylenimino compound with anhydrous hydrogen chloride gas in chloroform, as the resultant product did not move when chromatographed on paper using solvent system A or B.[7]

Tetramin (α-vinyl-1-aziridinethanol) is an anticancer agent active in various experimental systems, whereas the related α-ethyl-1-aziridinethanol is inactive.[6] As methyl 3-(*p*-bromoacetylphenyl)-propionate (IV) was available, it seemed desirable to convert it to VIII, which can be considered an analog of tetramin in which the double bond has been replaced by an aromatic ring. This tetramin analog (VIII) would also be considered an analog of chlorambucil containing a monofunctional alkylating group.

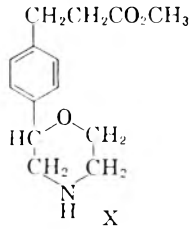
The reduction of methyl 3-(*p*-bromoacetylphenyl)propionate (IV) to methyl 3-[*p*-(2-bromo-1-hydroxyethyl)phenyl]propionate (I) was accomplished in 66% yield by heating with sodium borohydride in aqueous methanol for one hour. The product was a yellow oil that showed OH (2.85μ), C—OH (9.70 μ), C=O ester (5.78 μ), and the absence of C=O ketone (5.90μ) in the infrared spectrum. Without further purification, this oil was treated at 0° in ether with powdered potassium hydroxide to yield quantitatively a yellow sirup which showed the presence of epoxy bands at 7.59 and 11.38μ and no hydroxyl bands in the infrared absorption spectrum. Vacuum distillation of this sirup furnished methyl 3-[*p*-(epoxyethyl)-phenyl]propionate (II) in 58% yield, as a colorless sirup which crystallized upon standing.

Earlier attempts in these laboratories to dehydrobrominate I with ethanolic potassium hydroxide yielded mainly the corresponding glycol or hydroxyether rather than the desired epoxide.

The reaction between methyl 3-[*p*-(epoxyethyl)-phenyl]propionate (II) and ethylenimene failed to yield the desired tetramin analog (VIII). Starting material (II) was recovered when the epoxide and ethylenimine were refluxed in ether for eighteen hours or when a benzene solution of II and ethylenimine was refluxed for eighteen hours. The epoxide (II) did, however, react with anhydrous hydrogen chloride in ethanol to give a compound that showed OH (2.95μ) and C—OH (9.60-μ) in the infrared absorption spectrum and that gave a positive alcohol silver nitrate test for halogen.

Attempts to prepare VIII by a direct reaction between ethylenimine and methyl 3-[*p*-(2-bromo-1-hydroxyethyl)phenyl]propionate (I) by refluxing in benzene in the presence of triethylamine as an acid acceptor failed, starting material and ethylenimine polymer being the only isolable compounds. Without the activation by the keto group, as in the conversion of IV to V, the bromine does not apparently react with the highly heat sensitive ethylenimine.

A successful synthesis of VIII was accomplished by the selective reduction of methyl 3-{*p*-[(1-aziridinyl)acetylphenyl}propionate (V) with sodium borohydride in aqueous methanol. Methyl 3-{*p*-[2-(1-aziridinyl)-1-hydroxyethyl]phenyl}propionate (VIII) was obtained as an analytically pure solid, m.p. 109–112°, in 40% yield by this method. As the OH band in VIII at 2.9μ in the infrared absorption spectrum was very weak, it was necessary to prove that the compound obtained by the sodium borohydride reduction still contained the ethylenimino and hydroxy groupings rather than being the isomeric morpholine derivative (X). Treatment of VIII with hydrogen chloride in benzene successfully opened the ethylenimine ring to form the chloroethylamino derivative (IX) in 85% yield, m.p. 139–140°. The ring of the isomeric morpholine derivative (X) could not be expected to open to IX under the conditions used.



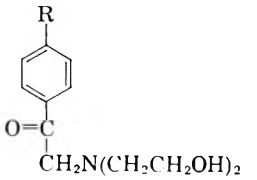
X

The successful reduction of V with sodium borohydride to VIII in which the keto group was selectively reduced without destroying the ethyl-

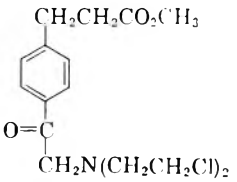
(7) Paper chromatograms were run by the descending technique on Whatman No. 1 paper with the spots being detected by their ultraviolet absorption. In this series, once the ketone has been reduced, the compounds no longer absorb strongly enough in the ultraviolet to be detected on paper chromatograms. The solvent systems used were: Solvent A, *n*-butanol saturated with water, or solvent B, *n*-butanol-acetic acid-water (5:2:3).

enimino group introduces a new route to tetramin analogs via bromoketones rather than from epoxides. This route should prove useful when the epoxides either are too unreactive towards ethylenimine or polymerize too easily.

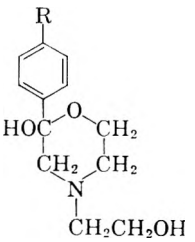
Attempts were made to convert methyl 3-(*p*-bromoacetylphenyl)propionate (IV) to the bis-mustard, methyl 3-{*p*-[*N*,*N*-bis(2-chloroethyl)glycyl]phenyl}propionate (XII) via treatment of IV with diethanolamine followed by chlorination.



XI. R = $CH_2CH_2CO_2CH_3$
XIV. R = H



XII



XIII. R = $CH_2CH_2CO_2CH_3$
XV. R = H

Diethanolamine reacted completely with IV at 90° in one hour, but instead of producing methyl 3-{*p*-[*N*,*N*-bis(2-hydroxyethyl)glycyl]phenyl}propionate (XI), the hemiketal (XIII) was apparently formed. The infrared absorption spectrum of the oily product showed the presence of hydroxyl bands (3.42, 9.50 μ) and an ester band (5.77 μ) but no band for ketone carbonyl (5.90 μ). No ultraviolet-absorbing material could be detected by paper chromatography of this product in solvent system A or B.[7]

Brighton and Reid[8] reported that the reaction of diethanolamine with 2-chloroacetophenone yielded 2-[bis(2-hydroxyethyl)amino]acetophenone (XIV), m.p. 44°. Only analytical data were presented as proof of the structure. This reaction was repeated in this laboratory and the product, m.p. 70–80°, showed no carbonyl absorption near 5.90μ but hydroxyl bands at 3.00 and 9.50μ in the infrared absorption spectrum. This spectrum indicates that the reaction yielded the isomeric hemiketal (XV). Mikhailov and Makarova[9] reported a melting point of 77–78° for this compound and assigned it structure XV. They also converted XV to the ethyl and methyl ketals.

Attempts to effect reaction between diethanolamine and the ethylene ketal VII failed because of the unreactivity of the bromine in that molecule. No reaction with the amine other than amide formation occurred, even when the ketal was heated at 100° for five hours with diethanolamine. The addition of potassium iodide did not increase the reactivity of the compound sufficiently for reaction to occur.

(8) K. W. Brighton and E. Reid, *J. Am. Chem. Soc.*, 65, 479 (1943).

(9) B. M. Mikhailov and A. N. Makarova, *J. Gen. Chem. (USSR)*, 28, 149 (1958).

EXPERIMENTAL

Methyl 3-{p-[N-(2-chloroethyl)glycyl]phenyl}propionate hydrochloride (VI). To a solution of 7.13 g. (0.025 mole) of methyl 3-(*p*-bromoacetylphenyl)propionate[3a] in 50 ml. of benzene containing 2.55 g. (0.025 mole) of triethylamine held at 0–5° was added with stirring 2.15 g. (0.055 mole) of ethylenimine. Stirring was continued for 2 hr. and the precipitated triethylamine hydrobromide was removed by filtration. Upon concentration of the filtrate *in vacuo* at room temperature, 6.35 g. of a dark yellow sirup (V) was obtained. This sirup was taken up in benzene and chilled in ice and anhydrous hydrogen chloride gas was bubbled into the solution, causing it to darken. Ether was added to turbidity and the brown solid that separated after chilling was collected on a filter and recrystallized from absolute ethanol to yield 3.25 g. (52%) of white platelets, m.p. 174–188° dec. An analytical sample was obtained by two more recrystallizations from absolute ethanol, m.p. 180–189° dec.; $\lambda_{max(\mu)}^{Nujol}$ 3.65, 3.75 (NH, NH_2^+), 5.72 (ester C=O), 5.90 (ketone C=O), 3.58 (ester C—O—C), 12.00 (*p*-disubstituted phenyl), 13.85 (C—Cl).

Anal. Calcd. for $C_{14}H_{18}ClNO_3 \cdot HCl$: C, 52.5; H, 5.98; Cl, 22.1. Found: C, 52.2; H, 6.27; Cl, 22.2.

3-{p-[N-(2-chloroethyl)glycyl]phenyl}propionic acid hydrochloride (III). A solution of 0.60 g. (2.4 mmoles) of methyl 3-{*p*-[*N*-(2-chloroethyl)glycyl]phenyl}propionate hydrochloride (VI) in 6 ml. of concd. hydrochloric acid was refluxed for 2 hr. and then chilled. The precipitate that formed was collected on a filter and washed with ether; yield, 0.50 g. (89%), m.p. 195–208° dec. A portion, recrystallized twice from 95% ethanol, melted at 198–208° dec.; $\lambda_{max(\mu)}^{Nujol}$ 5.81 (acid C=O), 5.91 (ketone C=O), 6.49 (NH_2^+), 11.67, 12.00 (*p*-disubstituted phenyl), 13.40, 13.70 (C—Cl).

Anal. Calcd. for $C_{13}H_{16}ClNO_3 \cdot HCl$: C, 51.0; H, 5.55; Cl, 23.2; N, 4.57. Found: C, 51.0; H, 5.71; Cl, 22.9; N, 4.52.

Methyl 3-[p-(epoxyethyl)phenyl]propionate (II). To a solution of 2.20 g. (8 mmoles) of methyl 3-(*p*-bromoacetylphenyl)propionate (IV)[3a] in 20 ml. of methanol was added dropwise over a period of about 10 min. 1.2 ml. (5 mmoles) of 15% aqueous sodium borohydride. The solution was refluxed for 1 hr. and then poured into 20 ml. of water. The oil that separated was collected by two extractions with ether. Dried with anhydrous magnesium sulfate, the combined ether extracts were evaporated *in vacuo* to a yellow sirup (I); yield 1.45 g. (66%); $\lambda_{max(\mu)}^{film}$ 2.85 (OH), 5.78, 8.35 (ester), 9.70 (COH), 11.90 (*p*-disubstituted phenyl), and no ketone absorption near 5.90. Because of its weak ultraviolet absorption, it could not be detected on paper chromatograms.

A solution of 3.6 g. (12.5 mmoles) of crude I in 5 ml. of ether was stirred for 1 hr. with 1 g. (16 mmoles) of freshly powdered (under nitrogen) potassium hydroxide. The filtered solution was evaporated to dryness *in vacuo*. The residual oil (2.6 g.) was distilled to give 1.58 g. (58%) of product, b.p. 94–108° (1 mm.), that crystallized on standing and was of sufficient purity for further transformations. Recrystallization from methanol-water gave white crystals, m.p. 33–34°; $\lambda_{max(\mu)}^{film}$ 5.72 (ester C=O), 7.59, 11.38 (epoxy), 8.31, 8.53 (ester C—O—C), and no OH absorption near 2.90.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.9; H, 6.84. Found: C, 70.0; H, 7.03.

Methyl 3-{p-[2-(1-aziridinyl)-1-hydroxyethyl]phenyl}propionate (VIII). To a solution of 1.0 g. (4 mmoles) of V, pre-

pared as reported in the preparation of VI, in 10 ml. of methanol was added in small portions 0.15 g. (3.8 mmoles) of sodium borohydride. When effervescence had ceased, the solution was allowed to stand at room temperature for 2 hr. and then concentrated *in vacuo* to a light brown solid. The material was dissolved in benzene and petroleum ether (b.p. 30–60°) added until a dark brown oil formed. The colorless solution was decanted from the oil and more petroleum ether added until it became turbid. Upon being chilled, the mixture deposited a sandy precipitate that was collected on a filter and washed with petroleum ether; yield 0.40 g. (40%), m.p. 108.5–110.5°. This solid, after two recrystallizations from benzene-petroleum ether, melted at 109–112°; $\lambda_{max(\mu)}^{KBr}$ 3.20 (OH), 5.72 (ester C=O), 8.52, 9.98 (ester C—O—C), 11.92 (*p*-disubstituted phenyl), and no ketone C=O near 5.90.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.4; H, 7.68; N, 5.62. Found: C, 67.3; H, 7.66; N, 5.69.

Methyl 3-{p-[2-(2-chloroethylamino)-1-hydroxyethyl]-phenyl}propionate hydrochloride (IX). Anhydrous hydrogen chloride gas was passed through a solution of 1.0 g. (4 mmoles) of methyl 3-[*p*-(2-aziridinyl-1-hydroxyethyl)-phenyl]propionate (VIII) in 5 ml. of benzene. A brown gum separated upon adding ether to turbidity and chilling. The solution was decanted from the gum and more ether added. After trituration with ether several times and placing in a refrigerator for 1 hr., the gum solidified, yield 1.1 g. (85%) m.p. 133–140°. Recrystallization from 7 ml. of absolute ethanol by adding ether until turbid and chilling yielded 1.0 g., m.p. 139–140°. An analytical sample, m.p. 140–141°, was prepared by a further recrystallization; $\lambda_{max(\mu)}^{KBr}$ 3.00 (OH), 3.60, 4.00 (NH_2^+), 8.61 (ester C—O—C), 9.59 (C—OH), 12.04 (*p*-disubstituted phenyl).

Anal. Calcd. for $C_{14}H_{20}ClNO_3 \cdot HCl$: C, 52.2; H, 6.52; Cl, 22.0; N, 4.35. Found: C, 52.3; H, 6.52; Cl, 21.8; N, 4.53.

Attempts to acid-hydrolyze IX to the corresponding acid were unpromising.

Acknowledgments. The authors wish to thank Dr. Peter Lim for interpretation of the infrared absorption spectra and his staff for the paper chromatography and spectrophotometry. The authors are also indebted to Mr. O. P. Crews, Jr., and his staff staff for large-scale preparation of certain intermediates.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

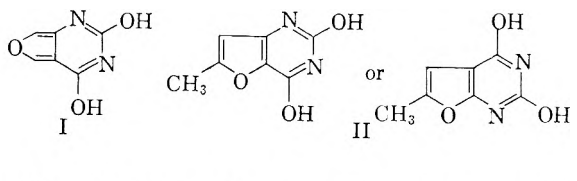
Reaction of Some Heterocyclic *vic*-Dicarboxamides with Alkaline Hypobromite

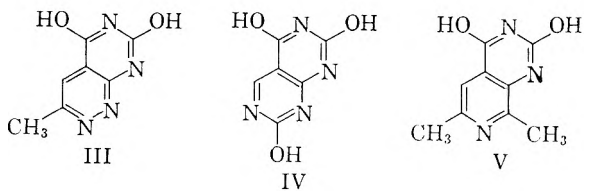
REUBEN G. JONES

Received January 5, 1960

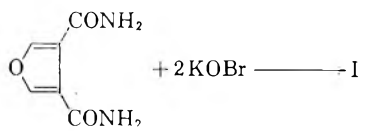
The reaction of alkaline hypobromite with some heterocyclic 1,2-dicarboxamides has led to the preparation of several bicyclic compounds containing the pyrimidine ring fused to furan, pyridazine, and pyrimidine.

This paper concerns the preparation of the new bicyclic pyrimidine derivatives I to V.[1] These were made and tested as possible chemotherapeutic agents against viruses and cancer because of their structural resemblance to certain of the biologically important purines and pteridines.





The compounds were obtained from appropriate 1,2-dicarboxamides by reaction with alkaline hypobromite under the conditions described by Baxter and Spring.[1] This Hofmann reaction on 1,2-dicarboxamides appears to be a rather general method for the synthesis of the 2,4-dihydroxypyrimidine ring system.[1]



The yields of compounds III, IV, and V were quite satisfactory (70 to 80%), but the yield of compound II was only 20 to 25% and the yield of I was 5 to 8%. One experiment was carried out in which 3,4-thiophenedicarboxamide was allowed to react with hypobromite. A crude product was obtained, but it could not be purified.

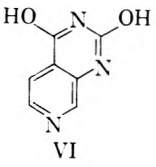
From each of the reactions leading to II, III, IV, and V, two isomeric products would appear to be possible. In each case, however, only one compound was isolated. The assignment of structure V is based on analogy with compound VI, which is the exclusive product from the reaction of 3,4-pyridinedicarboxamide with hypobromite.[2] The isomeric 2,3-pyridinedicarboxamide reacts with hypobromite to give exclusively compound VII.[3] By analogy with this latter reaction structures III and

(1) R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 229 (1945). This reference gives the earlier literature on these reactions.

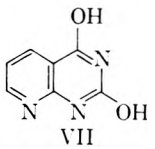
(2) S. Gabrial and J. Cohnan, *Ber.*, **35**, 2831 (1902).

(3) A. C. McLean and F. S. Spring, *J. Chem. Soc.*, 2582 (1949).

IV have been assigned, but it is to be emphasized that these structure assignments are only tentative. In the case of compound II both possible structures are shown.



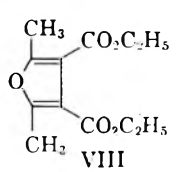
VI



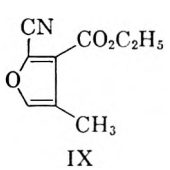
VII

Compounds I and IV retained water of crystallization. From I the water was removed readily by heating at 150°, but from IV the water was only partially removed by heating at 200° for three hours.

Preparation of the starting dicarboxamides deserves some comment. 3,4-Furandicarboxamide, 5-methyl-2,3-furandicarboxamide, 3,4-thiophenedicarboxamide, 2,6-dimethyl-3,4-pyridinedicarboxamide, and 6-methyl-3,4-pyridazinedicarboxamide were all obtained in excellent yields (80 to 98%) by simply allowing the corresponding diethyl esters to stand at room temperature in methanol saturated with ammonia. 2-Hydroxy-4,5-pyrimidinedicarboxamide was prepared with concentrated aqueous ammonia. It would appear to be unnecessary to prepare 3,4-furandicarboxamide by going through the acid chloride as recommended by Stork.[4] Earlier workers have experienced great difficulty in trying to prepare amides by reaction of ammonia with diethyl 2,5-dimethyl-3,4-furandicarboxylate[5,6] (VIII) and ethyl 2-cyano-4-methyl-3-furancarboxylate[5] (IX), and Bilton and Linstead[5] have stated: "the resistance to amide formation appears to be a general property of furan esters. . . ." More likely the resistance to amide formation in these cases is due to steric hinderance. The very appreciable steric effects of the methyl groups on the reactions of VIII and the related monomethyl compound with hydrazine have been noted previously.[7] The present preparation of 2,6-dimethyl-3,4-pyridinedicarboxamide in 80% yield by reaction of the diethyl ester in methanolic ammonia at room temperature contrasts sharply with the 54% yield obtained by Mumm and Hüneke[8] by heating the ester in ethanolic ammonia for eight hours at 150°.

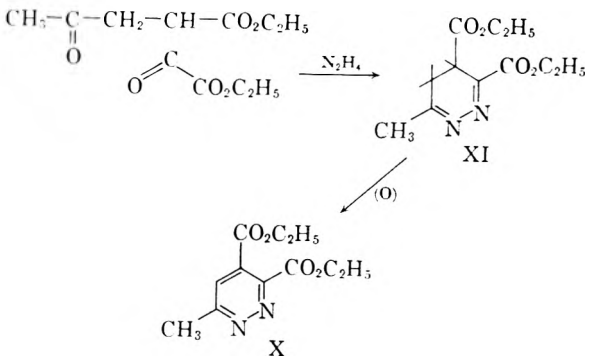


VIII



IX

Diethyl 6-methyl-3,4-pyridazinedicarboxylate (X), from which was prepared III *via* the diamide, is a new compound. It was obtained by the accompanying reactions starting from ethyl 2-ethoxalyl-4-ketovalerate.[9] Compound XI was obtained in good yield, but its oxidation to X by either the permanganate[10] or nitrous acid[11] method was only moderately satisfactory.



XI

X

EXPERIMENTAL

Diethyl 6-methyl-4,5-dihydro-3,4-pyridazinedicarboxylate. A solution of 24.5 g. (0.10 mole) of ethyl 2-ethoxalyl-4-ketovalerate[9] in 500 ml. of 95% ethanol was cooled in an ice bath and to it was added, with rapid stirring, a solution of 5.0 g. (0.10 mole) of hydrazine hydrate in 50 ml. of ethanol. After addition was complete, the solution was allowed to stand at room temperature for about 1 hr. and then was evaporated under reduced pressure to a volume of about 50 ml. The solution was diluted with 300 ml. of water and extracted with three 100-ml. portions of ether. After the ether extract had been dried with magnesium sulfate, it was evaporated, finally under reduced pressure, leaving an oil that crystallized after standing. The product was washed with petroleum ether (b.p. 60–68°) and air dried to yield 20 g. (84%) of soft white crystals. A sample recrystallized from petroleum ether melted at 86–87°.

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.22; H, 6.73; N, 11.54.

Diethyl 6-methyl-3,4-pyridazinedicarboxylate. To a solution of 345 g. (1.40 moles) of distilled ethyl 2-ethoxalyl-4-ketovalerate[9] in 3 l. of alcohol was added, with stirring and cooling during 1.5 hr., a solution of 70 g. (1.40 moles) of hydrazine hydrate in 1 l. of alcohol. The resulting solution was allowed to stand overnight and was then evaporated under reduced pressure to a sirup. This was warmed on the steam bath under reduced pressure for 0.5 hr. to remove all the alcohol. After cooling, the crude diethyl 6-methyl-4,5-dihydro-3,4-pyridazinedicarboxylate partially crystallized.

The crude product (315 g.) was dissolved in 2.75 l. of acetone and the solution was rapidly stirred while a hot solution of 65 g. of potassium permanganate in 900 ml. of water was added during 1 hr. The mixture was cooled and kept saturated with carbon dioxide by continuous addition of small pieces of solid carbon dioxide.

The resulting mixture was filtered on a large suction funnel and the manganese dioxide cake was washed by suspension in 1 l. of acetone. The total filtrate was evaporated under reduced pressure on the steam bath to remove acetone. The residue was extracted with ether and the ether solution was dried and evaporated. The product was distilled under reduced pressure to yield 35 g. of forerun, b.p. 112–115° (0.6

(4) G. Stork, *J. Am. Chem. Soc.*, **67**, 884 (1945).
(5) J. A. Bilton and R. P. Linstead, *J. Chem. Soc.*, 922 (1937).
(6) R. Seka, *Ber.*, **57**, 1864 (1924).
(7) R. G. Jones, *J. Am. Chem. Soc.*, **78**, 159 (1956).
(8) O. Mumm and H. Hüneke, *Ber.*, **50**, 1568 (1917).
(9) R. G. Jones, *J. Am. Chem. Soc.*, **77**, 4069 (1955).
(10) C. Paal and J. Ubber, *Ber.*, **36**, 497 (1903).
(11) C. Paal and C. Koch, *Ber.*, **36**, 2538 (1903).

mm.) which was shown to be diethyl 5-methyl-2,3-furandicarboxylate, and 128 g. of diethyl 6-methyl-3,4-pyridazinedicarboxylate. This was recrystallized by dissolving it in 100 ml. of ether, diluting with 200 ml. of petroleum ether (b.p. 60–68°), and keeping it in the refrigerator overnight. The yield was 114 g. (37%). A sample for analysis was recrystallized again from petroleum ether (b.p. 60–68°), long white needles, m.p. 53–53.5°.

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92. Found: C, 55.27; H, 5.77.

6-Methyl-3,4-pyridazinedicarboxylic acid. The diethyl ester, 12 g. (0.5 mole), was hydrolyzed by warming with a solution of 5 g. of sodium hydroxide in 50 ml. of water. The resulting solution was acidified with 12 ml. of 12*N* hydrochloric acid and cooled in the refrigerator to yield 8.75 g. (95%) of the acid. It was recrystallized from water, m.p. 235–237° dec.

Anal. Calcd. for $C_7H_6N_2O_4$: N, 15.38. Found: N, 15.55.

6-Methyl-3,4-pyridazinedicarboxamide. To 400 ml. of methanol saturated with ammonia was added 47.6 g. (0.2 mole) of diethyl 6-methyl-3,4-pyridazinedicarboxylate. The flask was tightly stoppered and allowed to stand at room temperature for 3 days. The crystalline precipitate of diamide was collected and air dried, yield 35 g. (97%). A sample was recrystallized from aqueous alcohol, m.p. 245–246°.

Anal. Calcd. for $C_7H_8N_4O_2$: N, 31.10. Found: N, 31.10.

2,6-Dimethyl-3,4-pyridinedicarboxamide.[8] A solution of 70 g. of diethyl 2,6-dimethyl-3,4-pyridinedicarboxylate[8] in 500 ml. of methanol saturated with ammonia was allowed to stand in a stoppered flask for 3 days. The mixture was evaporated under reduced pressure and the white crystalline residue of diamide was washed with ether, yield 42 g. (81%), m.p. 213–214° (lit.,[8] m.p. 220°).

2-Hydroxy-4,5-pyrimidinedicarboxamide. To 300 ml. of concd. aqueous ammonia was added 48 g. (0.20 mole) of diethyl 2-hydroxy-4,5-pyrimidinedicarboxylate.[12] The resulting solution was allowed to stand in a stoppered flask for 2 days during which time a mass of large crystals separated. The mixture was chilled and the crystalline product was collected. It was the ammonium salt of 2-hydroxy-4,5-pyrimidinedicarboxamide, yield 32 g. (80%). A sample was recrystallized from dilute ammonium hydroxide solution; it did not melt but decomposed above 300°.

Anal. Calcd. for $C_6H_9N_5O_3$: N, 35.17. Found: N, 34.53.

The ammonium salt, 30 g., was ground to a fine powder and suspended in 100 ml. of 20% acetic acid. The suspension was heated on the steam bath for 2 hr., cooled, and the 2-hydroxy-4,5-pyrimidinedicarboxamide collected, yield 24.3 g. (89%). A sample was recrystallized from water in which it was somewhat soluble. It had no sharp melting point but decomposed above 300°.

Anal. Calcd. for $C_6H_6N_4O_3$: N, 30.76. Found: N, 30.64.

2-Methyl-4,5-furandicarboxamide. A solution of 45.2 g. (0.20 mole) of diethyl 2-methyl-4,5-furandicarboxylate[9] in 150 ml. of methanol, to which had been added 40 g. of ammonia, was kept in a stoppered flask for 3 days. The mass of white crystalline precipitate was collected by filtration and air dried, yield 30 g. (89%). A sample was recrystallized from aqueous ethanol, m.p. 257–258°.

Anal. Calcd. for $C_7H_8N_2O_3$: N, 16.68. Found: N, 16.79.

3,4-Furandicarboxamide.[4] A solution of 63.6 g. (0.30 mole) of diethyl 3,4-furandicarboxylate[13] in 500 ml. of methanol saturated with ammonia was allowed to stand at room temperature in a stoppered flask for 4 days. A mass of white crystalline precipitate had separated. To the mixture was added another 50 ml. of liquid ammonia and it was allowed to stand an additional 4 days. The finely divided white precipitate was collected and air dried, yield 45 g. (97%). A sample for analysis was recrystallized three times from water in which it was very sparingly soluble.

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.92; N, 18.18. Found: C, 47.24; H, 3.92; N, 18.04.

3,4-Thiophenedicarboxamide. A solution of 20 g. (0.10 mole) of dimethyl 3,4-thiophenedicarboxylate[13] in 250 ml. of methanol saturated with ammonia was allowed to stand in a stoppered flask for 5 days. The methanol was evaporated under reduced pressure and the residual crystalline diamide was washed with ether, yield 16.7 g. (98%). A sample was recrystallized from water, m.p. 237–239°.

Anal. Calcd. for $C_6H_6N_2O_2S$: N, 16.46. Found: N, 16.46, 16.50.

4,6-Dihydroxy-2-oxa-5,7-diazaindene. A hypobromite solution was made by dissolving 61.6 g. (1.1 moles) of potassium hydroxide in 160 ml. of water, adding 400 g. of crushed ice, and then stirring in 32 g. (0.20 mole) of bromine. To the resulting pale yellow solution was added all at once 15.4 g. (0.10 mole) of 3,4-furandicarboxamide. With stirring almost all the solid went into solution. The mixture was kept in the refrigerator overnight but did not appear to undergo any change. It was allowed to stand at room temperature for 2 days during which time some white crystalline solid separated. The mixture was heated on the steam bath for 1 hr. and acidified with 70 ml. of acetic acid. After 5 days at room temperature a little tan crystalline solid had separated. This was collected, dissolved in 50 ml. of hot, dilute ammonium hydroxide solution, and reprecipitated with acetic acid as a white crystalline solid, yield 1.4 g. (8.2%). In another experiment the yield was 4.7%. It did not melt below 300°.

Anal. (dried 2 hr. at 125°). Calcd. for $C_6H_4N_2O_3 \cdot H_2O$: C, 42.45; H, 3.53; N, 16.50. Found: C, 42.68; H, 3.67; N, 16.64, 16.70. (Dried 3 hr. at 150°). Calcd. for $C_6H_4N_2O_3$: N, 18.42. Found: N, 18.37.

4,6-Dihydroxy-2-methyl-1-oxa-5,7-diazaindene or 5,7-dihydroxy-2-methyl-1-oxa-4,6-diazaindene. Finely powdered 2-methyl-4,5-furandicarboxamide was allowed to react with potassium hypobromite as described above for the preparation of 4,6-dihydroxy-2-oxa-5,7-diazaindene. The crude product was purified by dissolving it in dilute ammonium hydroxide solution and precipitating with acetic acid. The yields in two experiments were 25% and 20%. A sample for analysis was recrystallized from water.

Anal. (dried 2 hr. at 100°). Calcd. for $C_7H_6N_2O_3$: C, 50.60; H, 3.64; N, 16.86. Found: C, 50.47; H, 3.89; N, 16.66.

1,3-Dihydroxy-5,7-dimethyl-2,4,6-triazanaphthalene. 2,6-Dimethyl-3,4-pyridinedicarboxamide was allowed to react with hypobromite as described above for the preparation of 4,6-dihydroxy-2-oxa-5,7-diazaindene. After standing overnight in the refrigerator, the mixture containing a large quantity of white precipitate was heated on the steam bath for 1 hr. The solid dissolved. The solution was acidified with acetic acid, and the resulting white crystalline precipitate was collected and air dried, yield 75%. An analytical sample was recrystallized from glacial acetic acid, m.p. 355–357°.

Anal. (dried 1 hr. at 100°). Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.73; N, 21.98. Found: C, 56.59; H, 5.05; N, 22.02.

1,3-Dihydroxy-7-methyl-2,4,5,6-tetrazanaphthalene. 3-Methyl-5,6-pyridazinedicarboxamide (0.1 mole) was added all at once to a hypobromite solution prepared as described under 4,6-dihydroxy-2-oxa-5,7-diazaindene. The solid quickly dissolved. After standing in the refrigerator overnight, the solution was heated on the steam bath for 1 hr. and then acidified with acetic acid. A crystalline precipitate separated slowly. The mixture was kept in the refrigerator overnight; then the product was collected and air dried, yield 79%. In another experiment the reaction mixture was neither cooled nor heated prior to acidification, but was allowed to stand at room temperature for 12 hr. The yield of 1,3-dihydroxy-7-methyl-2,4,5,6-tetrazanaphthalene was only 22%. An analytical sample was recrystallized from water.

Anal. (dried 2 hr. at 100°). Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.40; N, 31.45. Found: C, 46.89; H, 3.15; N, 31.64.

(12) R. G. Jones and C. W. Whitehead, *J. Org. Chem.*, **20**, 1342 (1955).

(13) E. C. Kornfeld and R. G. Jones, *J. Org. Chem.*, **19**, 1671 (1954).

1,3,6-Trihydroxy-2,4,5,7-tetrazanaphthalene. 2-Hydroxy-4,5-dicarbamylpyrimidine was allowed to react with hypobromite as described above for the preparation of 1,3-dihydroxy-7-methyl-2,4,5,6-tetrazanaphthalene. The product was obtained, in 74% yield, as a finely divided, light brown crystalline solid, insoluble in boiling water but readily soluble in dilute base. A sample for analysis was taken up in hot dilute ammonium hydroxide and reprecipitated with acetic acid. This was repeated three times. It remained unmelted up to 360°.

Anal. (dried 2 hr. at 100°). Calcd. for $C_6H_4N_4O_3 \cdot H_2O$: C, 36.35; H, 3.04; N, 28.30. Found: C, 36.02; H, 3.20; N, 28.28. (Dried 3 hours at 200°). Calcd. for $C_6H_4N_4O_3$: N, 31.11. Found: N, 29.35.

Acknowledgment. The author is grateful to W. L. Brown, G. Maciak, H. L. Hunter, and R. Hughes for the microanalyses.

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[CONTRIBUTION FROM THE DIVISION OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF WISCONSIN]

Esters of Benzilic Acids and Congeners Having Potential Psychotomimetic Activity

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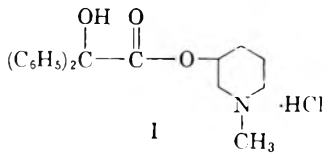
A series of heterocyclic alcoholic esters of benzilic acids and related compounds has been prepared as a part of a study of the structure-activity relationship of certain compounds having hallucinogenic activity.

In 1955, Biel and his co-workers[1] reported the synthesis of a series of disubstituted glycolic acid esters of *N*-alkyl-3-piperidols. Several of these had marked anticholinergic activity; *N*-methyl-3-piperidyl benzilate hydrochloride (I) had 60% of the spasmolytic activity of atropine against actylcholine-induced spasms in the guinea pig ileum.



I

In 1958, Abood, Ostfeld, and Biel[2] reported that compound I produced bizarre psychic effects in a test population of normal human volunteers. The compound is an extremely potent auditory and visual hallucinogen when given in small oral doses. A number of subjects exhibited paranoid and megalomanic delusions; the affective states were reported to range from a feeling of unpleasantness to one of extreme terror. Abood, Ostfeld, and Biel[3] found that the psychotomimetic activity of I was abolished or greatly diminished if the nitrogen-methyl were replaced by ethyl or hydrogen, if the nitrogen were quaternized, or if the hydroxyl group of benzilic acid portion were replaced by hydrogen. The replacement of one of the benzene rings by a cyclohexane or a cyclopentane moiety increased the hallucinogenic activity. These workers made no study of the effects of substitution on the phenyl rings on the potency of the molecule, nor did they report the effects of modifying the hydroxyl group of the benzilic acid portion, other than its replacement by hydrogen.

A number of derivatives and congeners of structure *I* have been prepared in this laboratory, for a further study of structure-activity relationship in this new class of psychotomimetic agents. Attention in the work reported herein has centered chiefly on modifying the acid portion of *I* rather than the amino alcohol portion. A series of esters of disubstituted glycolic acid derivatives has been prepared, and in addition a biologically isosteric α,α-diphenyl propionic acid ester has been prepared. One ester of 2-(1-methyl-4-piperazino) ethanol is listed; with this single exception, the alcoholic portion of the esters if *N*-methyl-3-piperidol.[4] Pharmacological findings will be reported in some detail elsewhere. None of the heterocyclic esters listed has been reported previously in the literature; however, Buehler and his coworkers[5] have reported the preparation of *N*-ethyl-3-piperidyl esters of 2,2′-dimethylbenzilic, 3,3′-dimethylbenzilic, and 4,4′-diphenylbenzilic acids as potential anticholinergic agents.

3,4,3′,4′-Tetramethoxybenzilic acid has apparently never been obtained in an analytically pure state, because of its tendency to undergo decarboxylation during attempted purification. It was possible to convert the crude acid to its methyl ester with diazomethane, and this methyl ester was purified so as to yield a correct analysis.

The general method for preparation of the substituted benzilic esters 1–9 (Table II) was as fol-

(1) J. H. Biel, E. P. Sprengeler, H. A. Leiser, J. Horner, A. Drukker, and H. Friedman, *J. Am. Chem. Soc.*, **77**, 2250 (1955).

(2) L. G. Abood, A. M. Ostfeld, and J. H. Biel, *Proc. Soc. Exptl. Biol. Med.*, **97**, 483 (1958).

(3) L. G. Abood, A. M. Ostfeld, and J. H. Biel, *Arch. Int. Pharmacodynam.*, **120**, 186 (1959).

(4) Generously supplied by Dr. John H. Biel, Lakeside Laboratories, Milwaukee.

(5) C. A. Buehler, H. A. Smith, D. M. Glenn, and K. V. Nayak, *J. Org. Chem.*, **23**, 1432 (1958).

TABLE I

METHYL ESTERS OF BENZILIC ACIDS

$(RC_6H_4)_2C(OH)COOCH_3$

No.	R′	B.P. or M.P.[a]	n_D^t	Formula	Analysis, % Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
1	2,2′-Dichloro	65–67[b]	—	$C_{15}H_{12}O_3Cl_2$	57.8	3.86	22.9	58.1	3.96	23.2
2	3,3′-Dichloro	172–180 (0.5 mm.)	1.5854 (23°)	$C_{15}H_{12}O_3Cl_2$	57.8	3.86	22.9	57.9	4.08	22.6
3	2,2′-Dimethyl	83–85[c]	—	$C_{17}H_{18}O_3$	75.6	6.68		75.8	6.82	
4	3,3′-Dimethyl	63–65[d]	—	$C_{17}H_{18}O_3$	75.6	6.68		75.1	6.54	
5	3,4,3′,4′-Tetramethoxy	132–133[e]	—	$C_{19}H_{22}O_7$	63.0	6.08		63.3	6.13	
6	3,4,3′,4′-Bis-methylenedioxy	130–131[c]	—	$C_{17}H_{14}O_7$	62.0	4.26		62.5	4.36	

[a] All melting points uncorrected. [b] From aqueous methanol. [c] From Skelly-C. [d] From Skelly-B. [e] From Skelly-C-benzene.

lows: treatment of the appropriately substituted benzyldehyde with potassium cyanide; oxidation of the resulting crude benzoin; and rearrangement of the benzil thus formed to the benzilic acid. All of the amino alcohol esters (1–14) were obtained by transesterification of the corresponding methyl ester. Those methyl esters which are new compounds are listed in Table I. When hydrohalide salts of an amino ester proved to be hygroscopic, the bifumarate salt was prepared for pharmacological evaluation.

EXPERIMENTAL

Benzoin condensations. One mole of freshly distilled aromatic aldehyde was dissolved in 150 ml. of 95% ethanol in a round bottom flask, and a solution of 15 g. of potassium cyanide in 120 ml. of water was added. The mixture was refluxed 1 hr., then an additional 15 g. of solid potassium cyanide was added and refluxing was continued for 1.5 hr. The mixture was permitted to cool and was diluted with water to a total volume of 1 l. After standing 15–20 min., the upper aqueous layer was decanted and discarded and the lower heavy, oily layer was washed twice with water. This crude benzoin was oxidized to the benzil without further purification.

Benzils. Method A. The crude benzoin was refluxed with an excess of Fehling's solution for 15 hr. The resulting mixture of cuprous oxide and benzil was collected on a suction filter, washed with copious amounts of water, and air dried. This material was transferred to the extraction thimble of a Soxhlet apparatus and was extracted to exhaustion with acetone. In most instances, the benzil precipitated from the acetone solution on cooling; if not, the solvent was removed by distillation. The crude benzils were recrystallized from ethanol, ethanol-chloroform, or ethanol-benzene.

Method B. The crude benzoin derived from 1 mole of aromatic aldehyde was placed in a 1-l. Erlenmeyer flask and to it was added cautiously in 50 ml. portions a total of 350 ml. of concd. nitric acid. After all of the nitric acid had been added, the mixture was heated on a steam bath until no more brown fumes were evolved. The solid crude benzil was collected on a suction filter, washed with copious amounts of water, dried, and recrystallized as in Method A.

Benzilic acids. A modification of the method of Ford-Moore[6] was found to be of general utility. An 8.5-g. sample of potassium hydroxide was dissolved with heating in 65 ml. of 1-butanol, and the boiling solution was added to 0.05 mole of the purified benzil contained in a 200-ml. round bottom flask fitted with a condenser. The resulting mixture was refluxed vigorously for 10 min., then it was cooled to room temperature. The potassium salt of the benzilic acid precipitated from solution, and it was collected on a suction filter and washed with two portions of cold 1-butanol, then with several portions of dry ether. The crude potassium benzilate was dissolved in 200–300 ml. of water; the solution was filtered, and was extracted three times with ether. Air was bubbled through the aqueous solution for some minutes to remove the dissolved ether; an excess of concd. hydrochloric acid was then added to precipitate the benzilic acid. The acids often separated as gums, but on standing for some time, they crystallized. The crude acid was collected on a suction filter, dried, and was converted to its methyl ester without purification.

9-Hydroxyfluorene-9-carboxylic acid (Esters 10 and 11). This compound was prepared from phenanthrenequinone in 34% yield by the method of Staudinger.[7]

α,α-Diphenyl propionic acid (Ester 12). This compound was prepared by the method of Wegmann and Dahn[8] in 42% yield.

Diphenyl methoxyacetic acid (Ester 13). This acid was prepared in the form of its methyl ester. Diphenyl bromoacetyl bromide was prepared according to the method of Klingler[9] and the crude product was recrystallized several times from Skelly A. A 46.5-g. sample (0.13 mole) of the purified product was placed in a 1-l. round bottom flask equipped with a condenser and a calcium chloride tube. Anhydrous methanol (600 ml.) was added, and the mixture was refluxed 5 hr. The solvent was removed under reduced pressure on a steam bath and the residue of amber-colored oil was distilled, b.p. 124–127 (0.3 mm.).[10] The yield was 17.5 g. (40%) of a water-white, viscous liquid.

O-Acetyl N-methyl-3-piperidyl benzilate (Ester 14). A 2.5-g. sample (0.0069 mole) of *N*-methyl-3-piperidyl benzilate hydrochloride[1] was refluxed 1 hr. with 10 ml. of freshly distilled acetic anhydride, and the reaction mixture was permitted to stand overnight. The resulting clear liquid was poured into 100 ml. of distilled water to destroy the excess acetic anhydride. Ice was added, and an excess of concd. ammonia water was then added to precipitate the acetylated crude product as a white, flocculent solid. The mixture was extracted twice with ether, and the ethereal solutions were combined and dried with anhydrous magnesium sulfate. The bifumarate salt of the ester was prepared from this solution.

2-(1-Methyl-4-piperazino)ethanol (Ester 11). This amino alcohol was prepared by an unpublished method devised

(6) A. H. Ford-Moore, *J. Chem. Soc.*, 1947, 952.

(7) H. Staudinger, *Ber.*, 39, 3062 (1906).

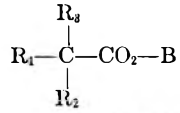
(8) J. Wegmann and H. Dahn, *Helv. Chim. Acta*, 29, 425 (1946).

(9) H. Klingler and G. Nickell, *Ann.*, 390, 365 (1912).

(10) H. Klingler, *Ann.*, 390, 371 (1912) b.p. 191–192 (19 mm.).

TABLE II

Salts of Benzilic Esters and Congeners



No.	R_1	R_2	R_3	B	Method of Prepn. of Benzil	Salt Prepd.	M.P.[b]	Yield,[h] %	Formula	Analysis	Calcd.	Found
1	2-ClC_6H_4	2-ClC_6H_4	OH	*N*-Methyl-3-piperidyl	B	HCl	237–238 dec.[c]	21	$C_{20}H_{22}O_3NCl_3$	N	3.25	3.14
										Cl	24.4	23.7
2	3-ClC_6H_4	3-ClC_6H_4	OH	*N*-Methyl-3-piperidyl	B	HCl	181–182[c]	30	$C_{20}H_{22}O_3NCl_3$	N	3.25	3.0
										Cl	24.4	24.0
3	2-$CH_3C_6H_4$	2-$CH_3C_6H_4$	OH	*N*-Methyl-3-piperidyl	A	Bifumarate	180–183[c]	32	$C_{26}H_{31}O_7N$	C	66.8	67.0
										H	6.68	6.98
										N	2.99	2.71
4	3-$CH_3C_6H_4$	3-$CH_3C_6H_4$	OH	*N*-Methyl-3-piperidyl	A	HCl	193–194[d]	73.5	$C_{22}H_{28}O_3NCl$	N	3.60	3.75
										Cl	9.10	8.94
5	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	OH	*N*-Methyl-3-piperidyl	A	HCl	211–214 dec.[c]	33	$C_{22}H_{28}O_3NCl$	N	3.60	3.75
										Cl	9.10	9.51
6	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	OH	*N*-Methyl-3-piperidyl	A	Bifumarate	188–190[c]	10	$C_{26}H_{31}O_9N$	C	62.3	62.5
										H	6.19	6.43
										N	2.79	3.10
7	3,4-$(CH_3O)_2C_6H_3$	3,4-$(CH_3O)_2C_6H_3$	OH	*N*-Methyl-3-piperidyl	A	Bifumarate	191–193[d]	16.1	$C_{28}H_{35}O_{11}N$	C	61.7	61.6
										H	6.48	6.57
										N	2.56	2.86
8	3,4-$(OCH_2O)_2$-C_6H_3	3,4-$(OCH_2O)_2C_6H_3$	OH	*N*-Methyl-3-piperidyl	A	HCl	236–238 dec.[e]	40	$C_{22}H_{24}O_7NCl$	N	3.13	3.11
										Cl	7.88	7.55
9	4-$C_6H_5C_6H_4$	4-$C_6H_5C_6H_4$	OH	*N*-Methyl-3-piperidyl	A	HCl	221–223 dec.[f,a]	25	$C_{32}H_{32}O_3NCl$	N	2.73	3.02
										Cl	6.90	7.30
10	see footnote[a]			*N*-Methyl 3-piperidyl	—	HCl	255–256 dec.[c]	26.7	$C_{20}H_{24}O_3NCl$	N	3.89	3.78
										Cl	9.89	9.51
11	see footnote[a]			2-(1-Methyl-4-piperazino) ethyl	—	2HCl	221–224 dec.[c]	42.4	$C_{21}H_{26}O_3N_2Cl_2$	N	6.58	6.27
										Cl	16.69	16.30
12	C_6H_5	C_6H_5	CH_3	*N*-Methyl-3-piperidyl	—	Bifumarate	156–158[g]	13.6	$C_{25}H_{29}O_6N$	C	68.7	69.1
										H	6.4	6.8
										N	3.2	3.3
13	C_6H_5	C_6H_5	CH_3O	*N*-Methyl-3-piperidyl	—	HCl	109–111[d]	22	$C_{21}H_{26}O_3NCl$	N	3.72	3.55
										Cl	9.45	9.12
14	C_6H_5	C_6H_5	Acetyl	*N*-Methyl-3-piperidyl	—	Bifumarate	205–207[f]	45	$C_{26}H_{29}O_5N$	C	64.7	64.5
										H	6.0	6.35
										N	2.9	3.36

[a] The acid portion is 9-hydroxyfluorene-9-carboxylic acid. [b] All melting points uncorrected. [c] From absolute ethanol-ether. [d] From 1-butanol-ether. [e] From aqueous ethanol. [f] From 1-butanol. [g] From 1-butanol-Skelly C. [h] Yield of salt based on the amount of methyl ester taken for transesterification.

by Leiser and Biel.[11] To 100.2 g. (1.0 mole) of *N*-methyl piperazine dissolved in 1 l. of anhydrous methanol was added dropwise and with stirring a solution of 44 g. (1.0 mole) of ethylene oxide in 100 ml. of dry toluene. The mixture was stirred for an additional 3 hr. and was permitted to stand overnight. The solvents were removed by distillation, and the residue was fractionated, the liquid boiling at 90–92 (3.0 mm.) being collected. The yield was 91 g. (63%).

Methyl esters. All of the methyl esters except methyl α,α-diphenylmethoxyacetate were prepared by treating an ethereal solution or suspension of the acid with an eightfold excess of an ethereal solution of diazomethane. After effervescence had ceased, the ether and excess diazomethane were removed on a steam bath, and the crude methyl ester was purified by recrystallization or distillation to give an almost quantitative yield. See Table I.

Transesterifications. The methyl ester of the carboxylic acid (0.02 mole) was placed together with an equimolecular portion of the amino alcohol in a 1-l. three necked flask seated in a mantle, and equipped with a Hershberg stirrer and a Dean-Stark moisture determination apparatus topped with a condenser and a calcium chloride tube. Dry *n*-heptane (600 ml.) and 100 mg. of solid sodium methoxide were added to the flask, and the contents were heated and stirred. After an hour's refluxing, an additional 100 mg. of sodium methoxide was added. From time to time, the contents of the Dean-Stark apparatus were drained and discarded, and fresh portions of *n*-heptane were added to the flask so as to maintain the original volume. After 8 hr. refluxing, an additional 50 mg. portion of sodium methoxide was added. Refluxing was continued for a total of 15 hr.; the reaction mixture was then cooled and transferred to a separatory funnel. The organic mixture was extracted repeatedly with water until the washings were approximately *p*H 7. The solvent was removed from the organic solution under reduced pressure from a steam bath; the residue of crude heterocyclic ester was dissolved in ether and this solution was dried over anhydrous magnesium sulfate and filtered. The salt of the ester was prepared from this solution.

Hydrochlorides of the heterocyclic esters. A saturated solution of anhydrous hydrogen chloride in anhydrous ether was added to the dried ethereal solution of the crude amino ester until no more precipitation occurred. The crude hydrochloride was collected on a suction filter, washed with anhydrous ether, and recrystallized.

Bifumarates of the heterocyclic esters. An excess of recrystallized, dried fumaric acid was stirred with 1.5 l. of anhydrous ether for 1 hr., so as to prepare a saturated solution. This solution was filtered through a gravity filter directly into a 3-l. Erlenmeyer flask containing 0.01–0.05 mole of crude amino ester dissolved in 500 ml. of dried ether. The resulting clear solution was placed in a refrigerator for several days, during which time the bifumarate salt slowly crystallized from solution. It was collected on a suction filter and recrystallized.

Acknowledgment. This investigation was supported in part by a grant from Lakeside Laboratories, Milwaukee, Wisconsin, and in part by a grant from the Institute of Mental Health, National Institutes of Health.

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(11) H. A. Leiser and J. H. Biel, Lakeside Laboratories, Milwaukee. Personal communication. J. Cymerman-Craig R. J. Harrisson, M. E. Tate, R. H. Thorp, and R. Ladd [*Australian J. Chem.*, 9, 89 (1956)] prepared this compound from 1-(2-hydroxyethyl)piperazine by a Leuckart Reaction. b.p. 88° (3 mm.).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTH TEXAS STATE COLLEGE]

Amebicides. I. Some 1-(1,4-Dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)-pyridinium Betaines

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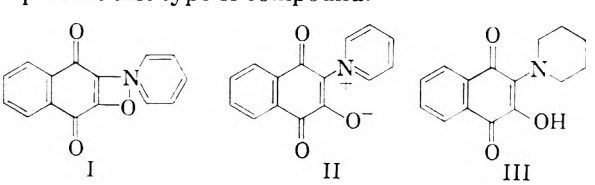
The reaction of 2,3-dichloro-1,4-naphthoquinone with pyridine has been extended to various 2-, 3-, and 4-substituted pyridines and corresponding 1-(1,4-dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)-substituted pyridinium betaines were obtained when acetic acid was used as the solvent for the reaction. The reduction of some of these betaines to 2-hydroxy-3-piperidino-1,4-naphthoquinones is described. The amebicidal activities of these compounds are summarized.

A study and use of the reaction between 2,3-dichloro-1,4-naphthoquinone and pyridine as reported by Ullman and Ettisch,[3] was undertaken in order to obtain a number of pyridinium compounds of a heretofor unstudied group for evaluation as antitubercular and amebicidal agents.[4] Ullmann and Ettisch reported the isolation of 3-hydroxy-1,4-naphthoquinone-2-pyridinium anhydride (I) from the reaction of pyridine and 2,3-dichloro-1,4-naphthoquinone in refluxing alcohol. We prefer to use structure II, 1-(1,4-dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)pyridinium betaine, to represent this type of compound.



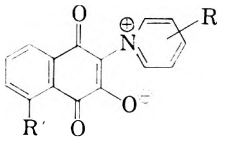
I II III

When we attempted to extend the reaction by the use of 4-(1-octyl)pyridine, a dark red oil was obtained, which was converted with much difficulty to a reddish-purple solid. However, when the initial reaction between 4-(1-octyl)pyridine and 2,3-dichloro-1,4-naphthoquinone was performed in

(1) Research Fellows of Research Corporation, 1950–52.
(2) Research Fellows of Parke, Davis & Co., 1950–53.
(3) F. Ullmann and M. Ettisch, *Ber.*, **54B**, 259 (1921).
(4) Price Truitt, Burl Bryant, William E. Goode, and B. Arnwine, *J. Am. Chem. Soc.*, **74**, 2179 (1952).

TABLE I

1-(1,4-DIHYDRO-1,4-DIOXO-3-HYDROXY-2-NAPHTHYL)PYRIDINIUM BETAINES



	R′	R	M.P.°	Yield, %	Formula	Analysis, % Nitrogen Calcd.	Found
1	H	H	302–303	80	$C_{15}H_9O_3N$	5.58	5.64
2	H	2-Methyl	160–161	33	$C_{16}H_{11}O_3N$	5.29	5.40
3	H	3-Methyl	263–265	65	$C_{16}H_{11}O_3N$	5.29	5.37
4	H	4-Methyl	319 dec.	80	$C_{16}H_{11}O_3N$	5.29	5.42
5	H	4-(1-Pentyl)	239–241	70	$C_{20}H_{19}O_3N$	4.36	4.41
6	H	4-(1-Hexyl)	229–230	80	$C_{21}H_{21}O_3N$	4.18	4.20
7	H	4-(1-Octyl)	230–231	70	$C_{23}H_{25}O_3N$	3.86	3.91
8	H	4-(1-Nonyl)	208–210	75	$C_{24}H_{27}O_3N$	3.74	3.80
9	H	4-(1-Tridecyl)	155–157	65	$C_{28}H_{35}O_3N$	3.24	3.20
10	H	2,4-Dimethyl	161–163	40	$C_{17}H_{13}O_3N$	5.00	5.11
11	H	2,6-Dimethyl	172–173	30	$C_{17}H_{13}O_3N$	5.00	4.92
12	H	2-(1-Pentyl)	171–172	55	$C_{20}H_{19}O_3N$	4.36	4.45
13	H	2-(1-Hexyl)	184–185	60	$C_{21}H_{21}O_3N$	4.18	3.89
14	H	4-(Cyclohexylmethyl)	201–207	85	$C_{22}H_{21}O_3N$	4.03	3.56
15	H	4-(3-Cyclohexylpropyl)	218–219	65	$C_{24}H_{25}O_3N$	3.74	3.69
16	H	4-(1-Cyclohexylbutyl)	215–220	65	$C_{25}H_{27}O_3N$	3.59	3.66
17	H	4-(1-Cyclohexylpentyl)	178–183	78	$C_{26}H_{29}O_3N$	3.47	3.64
18	H	4-(3-Methylcyclohexylmethyl)	169–172	63	$C_{24}H_{25}O_3N$	3.88	3.97
19	H	4-(4-Ethylcyclohexylmethyl)	193–195	61	$C_{24}H_{25}O_3N$	3.74	3.87
20	H	4-(4-Methylcyclohexylmethyl)	199–200	60	$C_{23}H_{23}O_3N$	3.88	3.95
21	H	4-(2-Methylcyclohexylmethyl)	184–187	55	$C_{23}H_{23}O_3N$	3.88	3.91
22	H	4-(3,4-Dimethylcyclohexylmethyl)	167 dec.	35	$C_{24}H_{25}O_3N$	3.74	3.93
23	H	4-(3,5-Dimethylcyclohexylmethyl)	152–153	45	$C_{24}H_{25}O_3N$	3.74	3.86
24	H	4-(2-Phentylethyl)	277–278	90	$C_{23}H_{17}O_3N$	3.94	3.92
25	H	4-(3-Phenylpropyl)	175–179	80	$C_{24}H_{19}O_3N$	3.80	3.94
26	H	4-(4-Phenylbutyl)	224–227	85	$C_{25}H_{21}O_3N$	3.62	3.74
27	H	4-(2-Chlorophenylethyl)	213–214	75	$C_{23}H_{16}O_3N$	3.60	3.69
28	H	4-Carbomethoxy	310–313	49	$C_{17}H_{11}O_5N$	4.53	4.46
29	H	3-Carboxamide	>340	48	$C_{16}H_{10}O_4N_2$	9.52	9.43
30	H	4-Carboxy	>340	73	$C_{16}H_9O_5N$	4.73	4.69
31	H	3-Carboxy	>340	55	$C_{16}H_9O_5N$	4.73	5.02
32	H	4-Acetylamino	>356	65	$C_{17}H_{12}O_4N_2$	9.10	8.94
33	H	4-*N*-Phenylcarbamyl	>340	93	$C_{22}H_{14}O_2N_2$	7.56	7.41
34	H	4-*N*-(4-Methylphenyl)-carbamyl	>340	42	$C_{23}H_{16}O_4N_2$	7.23	7.22
35	H	4-*N*-(2,5-Dichlorophenyl)-carbamyl	121–125	32	$C_{22}H_{12}O_4N_2Cl_2$	6.38	6.34
36	H	3-*N*-(2,5-Dichlorophenyl)-carbamyl	138–139	79	$C_{22}H_{12}O_4N_2Cl_2$	6.38	6.29
37	NO_2	H	280 dec.	65	$C_{15}H_8O_5N_2$	9.44	9.31
38	NO_2	4-Methyl	320 dec.	60	$C_{16}H_{10}O_5N_2$	9.02	8.82
39	NO_2	4-(1-Pentyl)	220–224	62	$C_{20}H_{18}O_5N_2$	7.67	7.78
40	NO_2	4-(1-Hexyl)	192–194	73	$C_{21}H_{20}O_5N_2$	7.36	7.70
41	NO_2	4-(1-Octyl)	179–182	60	$C_{23}H_{24}O_5N_2$	6.86	6.78
42	NO_2	4-(1-Nonyl)	173–176	60	$C_{24}H_{26}O_5N_2$	6.63	6.55
43	NO_2	4-Cyclohexylmethyl	227–230	70	$C_{22}H_{20}O_5N_2$	7.14	6.95
44	NO_2	4-(4-Ethylcyclohexylmethyl)	180–183	35	$C_{24}H_{24}O_5N_2$	6.66	6.60
45	NO_2	4-Ethyl-3-methyl	295–297	35	$C_{18}H_{14}O_5N_2$	8.28	8.05

acetic acid solution, a good yield of orange product (II) was obtained. Although acetic acid mixed with other solvents could be used in the reaction, acetic acid (1–2% water) was superior to the various other mixtures.

The betaine structure II is evidenced by its high

melting point and considerable water solubility. However, the melting point is lowered when an alkyl radical is attached to the pyridinium ring and the water solubility also decreases. On the other hand, when a carboxyl group is on the pyridinium ring, the melting point is higher. This is probably due to the fact that the betaine formation involved the carboxylate ion.

The colored compounds of structure II are insoluble in sodium hydroxide but dissolve in concentrated hydrochloric acid to give faintly yellow solutions; the original compound is regenerated by dilution with water. A white compound can be precipitated from the concentrated acid solution, and it is extremely hygroscopic and contains ionic halogen in excess of one ion per molecule. Water converts this material to the original orange compound.

When a 2-alkylpyridine was used in the reaction a dark gummy mass was obtained, and only when the reaction mass was heated for several hours was it possible to secure a deep red, crystalline product. 3- or 4-Alkylpyridines gave bright yellow to orange colored compounds. The 2-alkylpyridinium compounds were less soluble in concentrated hydrochloric acid than were the 3- and 4-alkylpyridinium products. 2-Chloropyridine did not react even after prolonged heating with 2,3-dichloro-1,4-naphthoquinone. 2,3-Dichloro-5-nitro-1,4-naphthoquinone[5] reacted very readily with pyridine and substituted pyridines although the yields of betaines (II) were generally lower than when 2,3-dichloro-1,4-naphthoquinone was used.

The catalytic reduction of 1-(1,4-dihydro-1,4-dioxo - 3 - hydroxy - 2 - naphthyl)pyridinium betaine has been studied. This compound readily absorbs four moles of hydrogen in the presence of platinum catalyst which indicates the reduction of the quinone to hydroquinone and the pyridinium ring to the piperidine ring. The ease of this reduction is further indication of the pyridinium structure (II) since it is well known that pyridinium compounds are readily reduced to piperidine compounds under these conditions.[6] However, the orange quinone (III), and not the colorless hydroquinone, was isolated from the reduction since the hydroquinone was readily oxidized by air during the filtration process.

The 1-(1,4-dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)pyridinium inner salts described in the present communication were tested by Dr. Paul E. Thompson and co-workers[7] at Parke, Davis and Company against *Endamoeba histolytica in vitro*[8] and when indicated against experimentally induced *E. histolytica* infections in rats.[9] Although details of these test results will be reported elsewhere, it is of interest to note that while the parent 1-(1,-4-dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)pyridinium inner salt was essentially devoid of antiamebic activity, related compounds with alkyl groups containing from six to twelve carbon atoms *para* to the pyridine nitrogen (compounds 6, 7, 15, 18, 20, and 23) were amebicidal *in vitro* at concentrations of 2 to 37 μg./ml., and all of them were active against intestinal amebiasis in rats.

EXPERIMENTAL

1-(1,4-Dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)-4-(1-octyl)-pyridinium betaine (II). Twenty grams of 4-(1-octyl)pyridine in 20 ml. of acetic acid was added rapidly to a solution of 23 g. of 2,3-dichloro-1,4-naphthoquinone in 250 ml. of acetic acid at 100°. The temperature of the solution was maintained at 100–110° for 1 hr. The mixture was cooled and diluted with 250 ml. of ice water. The crystals were removed and recrystallized from acetic acid–water solution, then from dimethyl formamide. The yield was 70%, m.p. 230–231° (corrected).

Other compounds of this type were prepared in the essentially same manner except that with the 2-alkylpyridines the reaction time was extended to 5 or 6 hr. The data are summarized in Table I.

The pyridines used in the work were obtained from Reilly Tar and Chemical Corporation and were distilled or recrystallized before use.

2-Hydroxy-3-piperidine-1,4-naphthoquinone. A suspension of 10 g. of 1-(1,4-dihydro-3-hydroxy-1,4-dioxo-2-naphthyl)-pyridinium betaine and 0.2 g. of platinium oxide in 100 ml. of ethanol was reduced by shaking at room temperature with hydrogen at the pressure of 45 p.s.i. Four moles of hydrogen were absorbed in about 15 min. The solution was colorless but turned red when exposed to air. The solution was evaporated and cooled and 4.7 g. (50%) of orange crystals, which melted at 192–193°, was obtained. This compound formed a red-purple solution with dilute sodium hydroxide and was insoluble in dilute hydrochloric acid.

Anal. Calcd. for $C_5H_{15}NO_3$: C, 70.02; H, 5.87; N, 5.44. Found: C, 69.88; H, 5.92; N, 5.51.

2-Hydroxy-3-(4-n-octylpiperidino)-1,4-naphthoquinone. This compound was prepared by the previous precedure in 60% yield. The orange crystals melted at 152–153°.

Anal. Calcd. for $C_{22}H_{31}NO_3$: C, 74.79; H, 8.41; N, 3.74. Found: C, 74.71; H, 8.63; N, 3.75.

2-Hydroxy-3-(4-n-hexylpiperidino)-1,4-naphthoquinone. A 60% yield of orange crystals of this compound, m.p. 155–157°, were obtained in a like manner.

Anal. Calcd. for $C_{21}H_{26}NO_3$: N, 4.12. Found: N, 4.15.

DENTON, TEX.

(5) O. Y. Imray, British Pat. No. 288,927, April 19, 1928.

(6) F. Krohnke (with S. Fosold), *Ber.*, 67, 656 (1934).

(7) The authors are indebted to Dr. Paul E. Thompson, Miss Anita Bayles, and Mr. D. A. McCarthy for the antiamelic testing.

(8) For a description of test methods, see P. E. Thompson, J. W. Reinertson, D. A. McCarthy, A. Bayles, and A. R. Cook, *Antibiotics and Chemotherapy*, 5, 433 (1955).

(9) For a description of test methods, see P. E. Thompson, M. C. Dunn, A. Bayles, and J. W. Reinertson, *Am. J. Trop. Med.*, 30, 203 (1950).

[CONTRIBUTION FROM THE MERCK SHARP AND DOHME RESEARCH LABORATORIES, DIVISION OF MERCK AND CO., INC.]

Diuretics: Aminobenzenedisulfonamides

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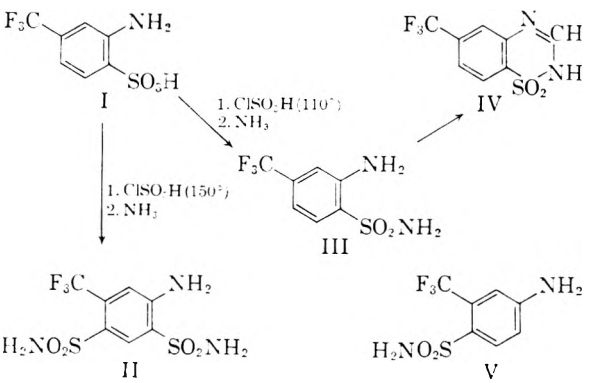
Chlorosulfonation of a number of substituted aniline derivatives followed by reaction of the resulting disulfonyl chlorides with ammonia or amines gave a series of aniline-2,4-disulfonamides possessing diuretic activity.

The diuretic activity of representative benzenedisulfonamides has been reported previously.[1,2,3] Compounds of greatest interest lie in the *meta* series, derivatives of benzene-1,3-disulfonamide. The activity is markedly influenced by further substitution in the benzene ring; halogen, amino, and acylamino groups were found to be particularly desirable. The preparation and some of the structure-activity relations of a series of aminobenzenedisulfonamides are now reported.

Anilinedisulfonyl chlorides were prepared by the reaction of *ortho*, *meta*, or *para*-substituted anilines with excess chlorosulfonic acid. Generally, the addition of sodium chloride was used to insure maximum dichlorosulfonation.[1,4] However, the use of a large excess of chlorosulfonic acid alone may suffice in certain instances.[5] A further modification[6] which permitted chlorosulfonation in the liquid phase was employed also and involved addition of thionyl chloride in place of sodium chloride. Acetanilides rather than the anilines offered no advantage as, under these conditions, the acetyl group was cleaved during the reaction. The disulfonamides were obtained by treatment of the crude disulfonyl chlorides with ammonia or appropriate amines. Compounds prepared in this manner are recorded in Table I and further examples are described in the Experimental.

Among the aniline derivatives that were chlorosulfonated only *m*-trifluoromethylaniline required special attention. The desired 5-trifluoromethylaniline-2,4-disulfonyl chloride was obtained by stepwise introduction of the two sulfonyl chloride groups. Chlorosulfonation of *m*-trifluoromethylaniline with one mole of chlorosulfonic acid in *sym*-tetrachloroethane at 125° according to the procedure of Kracker and Herrlein[7] gave a monosulfonic acid. This acid by further treatment with chlorosulfonic acid at 150° was converted to disulfonyl chloride which with ammonia gave the desired disulfonamide[8] (II) (Compound 16, Table I).



The intermediate monosulfonic acid was assigned the *para* structure, 2-trifluoromethyl-4-aminobenzenesulfonic acid, by Kracker and Herrlein. However, the monoacid obtained by us was shown to have the *ortho* structure (I) as follows. The monoacid was converted to the amide (III) by treatment with chlorosulfonic acid at 110° followed by the action of aqueous ammonia on the resulting sulfonyl chloride. This amide (III) melted at 144–146°. Caldwell and Sayi[9] prepared 2-trifluoromethyl-4-aminobenzenesulfonamide (V) by a different route and reported it to melt at 196–197°. Furthermore, our amide upon treatment with formic acid was readily converted to 6-trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide (IV), which could only occur with the *ortho* amide (III).

The monochlorosulfonation of aniline and acetanilide is known to occur readily under mild conditions to yield the *para* sulfonyl chloride. However, the conditions necessary for introduction of a second sulfonyl group led only to the 2,4,6-trisulfonyl chloride, which upon conversion to the trisulfonamide afforded a compound devoid of diuretic activity. Halogen-substituted anilines proved to be especially valuable; they yielded biologically active disulfonamides and provided a

(1) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.* **79**, 2028 (1957).

(2) F. C. Novello and J. M. Sprague, 132nd Meeting of the American Chemical Society, New York, N. Y., September 8–13, 1957; abstracts, p. 32–0.

(3) J. M. Sprague, *Ann. N. Y. Acad. Sci.* **71**, 328 (1958).

(4) O. Lustig and E. Katscher, *Monatsh.*, **48**, 87 (1927).

(5) W. Logemann, P. Giraldi, and S. Galimberti, *Ann.* **623**, 157 (1959).

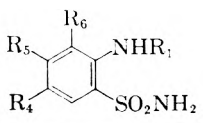
(6) We are indebted to Drs. E. F. Schoenewaldt, A. E. Erickson, and J. M. Chemerda for this modification.

(7) H. Kracker and F. Herrlein, U. S. Patent No. 2119882.

(8) After completion of this work, C. T. Holdrege, R. B. Babel, and L. C. Cheney, *J. Am. Chem. Soc.* **81**, 4807 (1959), described a preparation of 2,4-disulfamyl-5-trifluoromethylaniline by a different procedure.

(9) W. T. Caldwell and A. N. Sayi, *J. Am. Chem. Soc.* **73**, 5125 (1951).

TABLE I

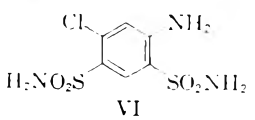


No.[a,b]	R_1	R_6	R_5	R_4	M.P.°	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	Cl	SO_2NH_2	251–252	$C_6H_8ClN_3O_4S_2$	25.22	25.48	2.82	2.81	14.71	14.68
2	H	Cl	H	SO_2NH_2	242–244	$C_6H_8ClN_3O_4S_2$	25.22	25.52	2.82	2.75	14.71	14.59
3	H	H	Br	SO_2NH_2	265–267	$C_6H_8BrN_3O_4S_2$	21.82	22.04	2.44	2.72	12.73	12.72
4	H	H	F	SO_2NH_2	227.5–228.5	$C_6H_8FN_3O_4S_2$	26.76	27.15	2.99	2.98	15.62	15.57
5	H	H	CH_3	SO_2NH_2	246–247	$C_7H_{11}N_3O_4S_2$	31.69	31.68	4.18	3.97	15.84	15.84
6	H	H	OCH_3	SO_2NH_2	252–253	$C_7H_{11}N_3O_5S_2$	29.89	30.12	3.94	4.09	14.94	14.93
7	H	H	NO_2	SO_2NH_2	260–262	$C_6H_8N_4O_6S_2$	24.32	24.53	2.72	2.71	18.91	19.11
8	CH_3	H	Cl	SO_2NH_2	248–249	$C_7H_{10}ClN_3O_4S_2$	28.05	28.09	3.36	3.35	14.02	14.00
9	H	SO_2NH_2	H	Br	252	$C_6H_8BrN_3O_4S_2$	21.83	22.28	2.44	2.81	12.73	12.64
10	H	H	SO_2NH_2	Cl	289–290	$C_6H_8ClN_3O_4S_2$	25.22	25.51	2.82	2.88	14.71	14.58
11	H	H	Cl	Cl	175–178	$C_6H_6Cl_2N_2O_2S$	29.89	29.99	2.51	2.56	11.62	11.50
12	H	H	CH_3	Cl	202–203	$C_7H_9ClN_2O_2S$	38.10	38.20	4.11	4.14	12.70	12.76
13	H	H	Cl	CH_3	191–193	$C_7H_9ClN_2O_2S$	38.10	38.32	4.11	4.13	12.70	12.70
14	H	Cl	Cl	SO_2NH_2	289	$C_6H_7Cl_2N_3O_4S_2$	22.51	22.65	2.20	2.34	3.12	3.16
15	H	I	Cl	SO_2NH_2	308–309[c]	$C_6H_7ClIN_3O_4S_2$	17.51	17.96	1.71	1.83	10.21	10.10
16	H	H	CF_3	SO_2NH_2	241–242	$C_7H_8F_3N_3O_4S_2$	26.33	26.30	2.53	2.77	13.16	13.14
17[d]	H	H	Cl	H	138.5–140.5	$C_6H_7ClN_2O_2S$	34.87	35.22	3.41	3.56	13.56	13.53
18	H	H	SO_2NH_2	H	216–217	$C_6H_9N_3O_4S_2$	28.68	29.14	3.61	3.66	16.72	16.72
19	H	SO_2NH_2	H	H	206–207	$C_6H_9N_3O_4S_2$	28.68	29.03	3.61	3.64	16.72	16.62

[a] Aqueous ethanol was employed for recrystallization. [b] Compounds 9–13 were prepared according to the general sulfonation method described in the Experimental from the following intermediates: (9) *p*-bromoaniline; (10) 5-amino-2-chlorobenzenesulfonic acid (Eastman Kodak Co.); (11) 3,4-dichloroaniline; (12) 2-amino-5-chloro-4-methylbenzenesulfonic acid (Eastman Kodak Co.); (13) 2-amino-4-chloro-5-methylbenzenesulfonic acid (Eastman Kodak Co.). [c] Corrected melting point. [d] Prepared by reduction of 5-chloro-2-sulfamylnitrobenzene according to procedure described in the Experimental for the preparation of 3-chloro-4-methylmercaptoaniline.

convenient route to other anilinedisulfonamides. Both *o*- and *m*-chloroaniline readily yielded the corresponding disulfonamides, 6-chloro-2,4-disulfamylaniline and 5-chloro-2,4-disulfamylaniline. Thus, the chlorine atom in *o*- and *m*-chloroaniline effectively blocks introduction of the third sulfonyl group. In addition, halodisulfamylanilines provided a convenient route to the isomeric disulfamylanilines which are not readily accessible by other synthetic routes. Catalytic dechlorination of both 5-chloro- and 6-chloro-2,4-disulfamylaniline using palladium-charcoal catalyst gave 2,4-disulfamylaniline. 4-Bromo-2,6-disulfamylaniline, prepared from *p*-bromoaniline, upon catalytic debromination yielded 2,6-disulfamylaniline. 2,5-Disulfamylaniline was obtained similarly from the 4-chloro derivative.

The haloaniline-2,4-disulfonamides exhibited superior activity within the series and 5-chloro-2,4-disulfamylaniline (VI) was studied more extensively. Acylation with one equivalent of an

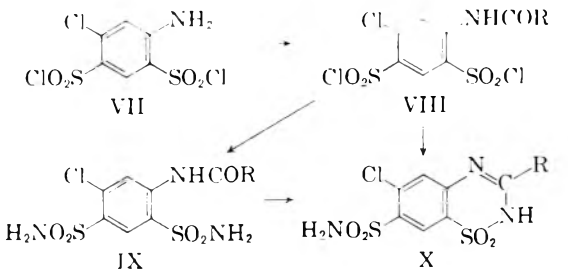


VI

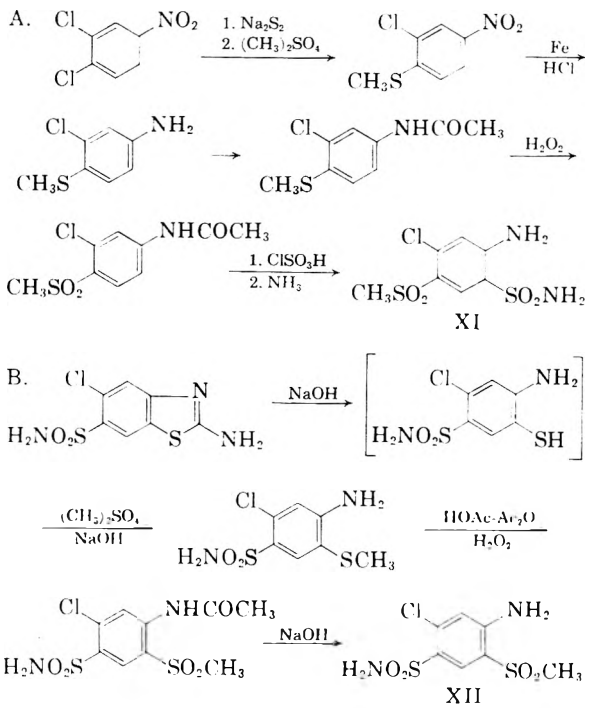
acyl chloride yielded monoacyl derivatives having the amino group acylated. In this manner a series of 5-chloro-2,4-disulfamyl-*N*-acylanilines was prepared from acetyl, chloroacetyl, butyryl, palmitoyl, benzoyl, and *o*- and *p*-chlorobenzoyl chlorides. An excess of the acylating agent resulted in acylation of both sulfamyl groups as well as the amino group to give the triacyl derivative 5-chloro-2,4-di(acylsulfamyl)-*N*-acylaniline. Acylation of the amino group was substantiated by means of a negative color test for diazotizable amine[10] and ultraviolet spectroscopy.

Acylation of the aniline-2,4-disulfonyl chloride (VII) to the *N*-acylaniline-2,4-disulfonyl chloride (VIII) followed by reaction of the acylated sulfonyl chlorides with ammonia or amines offered an attractive alternate route to the disulfamyl-*N*-acylanilines (IX). In this manner, the possibility of acylation of the sulfamyl groups would be avoided. However, treatment of the acylated disulfonyl chloride with ammonia (or secondary amines) invariably resulted in a mixture of the expected sulfamyl compound (IX) together with a benzothiadiazine-1,1-dioxide (X) resulting from cyclodehydration between the acylamino group and the adjacent sulfamyl group.[1]

(10) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, 128, 537 (1939).



Because of the high order of diuretic activity of 5-chloro-2,4-disulfamylaniline (VI), it was of interest to determine the effect of replacing the sulfamyl groups in turn by a methylsulfonyl group. The two isomeric methylsulfonyl analogs XI and XII were prepared as indicated in the following series of reactions.



Biologic evaluation of these compounds was determined in dogs following intravenous or oral administration by measuring sodium, chloride, and potassium excretion and urine volume.[11]

The disulfamylanilines are generally more active than monosulfamyl derivatives previously investigated. This is particularly true of compounds where the sulfamyl groups are *meta* to each other and one sulfamyl group is *ortho* to the amino group. Detailed study of 2,4-disulfamylanilines showed that additional substitution into the benzene nucleus enhances activity. Substitution into the 5-position *ortho* to the second sulfamyl group has the most favorable effect. 5-Chloro-, 5-bromo-, 5-trifluoromethyl-, and 5-nitro-2,4-disulfamylaniline are highly active by both intravenous and oral routes, whereas the 5-fluoro, 5-amino, 5-methyl, and 5-methoxy analogs are somewhat less effective.

Derivatives of 5-chloro-2,4-disulfamylaniline,[12] a representative of the highly active group, were studied further. An additional halogen in the 6-position does not improve activity. Alkylation of the aniline amino group by a methyl or an allyl group gave compounds that are active when administered intravenously, but are less active when given orally. Acylation of this amino group gave compounds of varying activity, depending upon the nature of the acyl group. Aromatic acyl derivatives are less active than the best aliphatic members. In the aliphatic acyl series, activity reaches a maximum with the butyryl and hexanoyl members. Any of a variety of substitutions into one or both sulfamyl groups generally reduces activity.[13] Complete acylation, to give 2,4-di(acylsulfamyl)-*N*-acylanilines, lowers the activity. Replacement of either sulfamyl group by a methylsulfonyl group results in structures of little activity.

EXPERIMENTAL[14,15]

The following procedure illustrates the general method for preparation of aniline-2,4-disulfonamides listed in Table I and not described elsewhere in the Experimental. The yield is typical.

5-Chloro-2,4-disulfamylaniline (No. 1, Table I) *m*-Chloroaniline (64 g., 0.5 mole) was added dropwise with stirring to 670 g. (6.0 moles) of chlorosulfonic acid in a 3-l. round bottomed 3-necked flask cooled in an ice bath. Sodium chloride (350 g., 6 moles) was added portionwise over a period of 1–2 hr. and the mixture then heated gradually in an oil bath to 150°. After 3 hr. at 150–160° the flask was cooled thoroughly in an ice bath and the contents treated with 1 l. of cold water. The product was extracted with ether and dried over sodium sulfate. After removal of ether on the steam bath, the residual 5-chloroaniline-2,4-disulfonyl chloride, which may be crystallized from benzene-hexane, m.p. 139–142°, was added to 150 ml. of cold concd. ammonium hydroxide and heated on the steam bath for 1 hr. The mixture was cooled and the product recrystallized from aqueous ethanol; yield, 44 g. (30%) of colorless needles, $\lambda_{max}^{C_2H_5OH}$ 223.5–224.5, 265–266, and 312–314 mμ, ε 41,776, 18,633, and 3874 respectively.

Acetylation of 5-chloro-2,4-disulfamylaniline by acetic anhydride and concd. sulfuric acid (trace) gave *5-chloro-2,4-di(acetylsulfamyl)acetanilide;* colorless needles from alcohol, m.p. 222–224°.

Anal. Calcd. for $C_{12}H_{14}ClN_3O_7S_2$: C, 34.99; H, 3.43; N, 10.20. Found: C, 34.91; H, 3.77; N, 10.10.

5-Chloro-2,4-disulfamyl-N-methylaniline (No. 8, Table I). *m*-Chloro-*N*-methylaniline (26.7 g., 0.15 mole) was added to 110 ml. of chlorosulfonic acid, cooled in an ice bath over 15 min., and then heated at 125–130° for 3 hr. The mixture was

(11) We are indebted to Drs. John E. Baer and Karl H. Beyer and their associates for the biological data that are summarized here.

(12) Alf Lund and Karen Størling, *Acta Pharm. Tox.* 15, 300 (1959) have recently reported this compound to be highly active in animals and man.

(13) W. Logemann, P. N. Geraldi, and M. A. Parenti, *Nature* 182, 1510 (1958) and ref. 5 report 5-chloro-2,4-di(methylsulfamyl)aniline to be an effective diuretic in rats.

(14) Melting points are uncorrected. Data shown in Table I are not reproduced in the Experimental.

(15) We are indebted to Mr. K. B. Streeter and his associates for analytical and spectral data.

cooled and 44 ml. of thionyl chloride[6] was added. After heating an additional hour on the steam bath, the mixture was cooled and poured onto ice. The solid was collected, washed with water, added to 100 ml. of concd. ammonium hydroxide, and heated on the steam bath for 1 hr. Recrystallization of the product from aqueous ethanol gave colorless needles; yield, 16.5 g. (37%).

2,4-Disulfamyl-5-fluoroaniline (No. 4, Table I) was prepared from *m*-fluoroaniline according to the procedure described for 5-chloro-2,4-disulfamyl-*N*-methylaniline; yield, 39% of colorless needles from aqueous alcohol.

5-Chloro-2,4-di(methylsulfamyl)aniline. 5-Chloroaniline-2,4-disulfonyl chloride (6.5 g., 0.02 mole) was added to 50 ml. of 40% aqueous methylamine and heated on the steam bath for 1–2 hr. The mixture was cooled and the product collected and recrystallized from alcohol; yield, 6.0 g. (96%) of colorless needles, m.p. 175.5–178°.

Anal. Calcd. for $C_8H_{12}ClN_3O_4S_2$: C, 30.62; H, 3.86; N, 13.39. Found: C, 30.85; H, 3.81; N, 13.34.

5-Chloro-2,4-bis(dimethylsulfamyl)aniline was prepared in a similar manner with dimethylamine (25%) in place of methylamine; yield, 54% of colorless needles from ethanol-water, m.p. 181–182°, $\lambda_{max}^{C_2H_5OH}$ 227.5, 271.5, and 314–317 mμ, ε 29,363, 19,177, and 4205 respectively.

Anal. Calcd. for $C_{10}H_{16}ClN_3O_4S_2$: C, 35.14; H, 4.61; N, 12.29. Found: C, 35.21; H, 4.89; N, 12.26.

Acetylation of 5-chloro-2,4-bis(dimethylsulfamyl)aniline by acetic anhydride and concd. sulfuric acid (trace) gave *5-chloro-2,4-bis(dimethylsulfamyl)-N-acetylaniline;* colorless needles from alcohol-water, m.p. 193–195°, $\lambda_{max}^{C_2H_5OH}$ 231–234 and 267–270 mμ, ε 26,601 and 17,098 respectively.

Anal. Calcd. for $C_{12}H_{18}ClN_3O_5S_2$: C, 37.54; H, 4.73; N, 10.95. Found: C, 37.86; H, 4.76; N, 10.90.

5-Chloro-2,4-di(pentamethylenesulfamyl)aniline. A solution of 9.7 g. (0.03 mole) of 5-chloroaniline-2,4-disulfonyl chloride in 200 ml. of benzene was added over 10 min. to 50 ml. (0.05 mole) of piperidine and heated on the steam bath for 3 hr. The solution was cooled, washed with water, dilute hydrochloric acid, water, and dried over sodium sulfate. Solvent was removed *in vacuo*. Recrystallization of the residue from ethanol gave colorless needles, m.p. 162–164°.

Anal. Calcd. for $C_{16}H_{24}ClN_3O_4S_2$: C, 45.75; H, 5.76; N, 10.00. Found: C, 46.04; H, 5.67; N, 10.00.

2-Amino-4-trifluoromethylbenzenesulfonic acid. A solution of 12.0 g. (0.10 mole) of chlorosulfonic acid in 50 ml. of *sym*-tetrachloroethane was added dropwise with stirring over 15 min. to a solution of 16.1 g. (0.10 mole) of *m*-trifluoromethylaniline in 200 ml. of *sym*-tetrachloroethane cooled in an ice bath. After heating in an oil bath at 125° for 3 hr., the mixture was cooled and the product collected and purified by reprecipitation from sodium carbonate solution; yield, 18 g. (75%) pale yellow powder, m.p. 330° dec. A sample recrystallized from water was obtained as colorless needles, m.p. 333–334° dec.

Anal. Calcd. for $C_7H_6F_3NO_3S$: N, 5.81; S, 13.29. Found: N, 5.79; S, 13.38.

*2-Sulfamyl-5-trifluoromethylaniline. 2-Amino-4-trifluoromethylbenzenesulfonic acid (24.1 g., 0.1 mole) was added portionwise with stirring to 75 ml. of chlorosulfonic acid at 0° and then the mixture was heated in an oil bath at 110–115° for 3 hr. The mixture was cooled and thionyl chloride (30 ml.) was added. After heating on the steam bath for 30 min., the solution was poured onto ice and the aqueous layer decanted. The residual solid was heated on the steam bath with 500 ml. of concd. ammonium hydroxide for 1 hr., cooled and the product (12.5 g.) collected and digested with hot toluene (500 ml.) to separate toluene insoluble 2,4-disulfamyl-5-trifluoromethylaniline (3.0 g.). Concentration of the toluene extract to 250 ml. gave 8.0 g. of 2-sulfamyl-5-trifluoromethylaniline, m.p. 144–146°.

Anal. Calcd. for $C_7H_7F_3N_2O_2S$: C, 35.00; H, 2.94; N, 11.66. Found: C, 35.30. H, 3.16; N, 11.75.

A solution of 2-sulfamyl-5-trifluoromethylaniline (4.0 g.) in 98–100% formic acid (100 ml.) was heated under reflux for 2 hr. The mixture was cooled and the product recrystallized from ethanol water. *6-Trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide* was obtained as colorless needles in 96% yield; m.p. 262–264°.

Anal. Calcd. for $C_6H_5F_3N_2O_2S$: C, 38.40; H, 2.01; N, 11.20. Found: C, 39.05; H, 2.04; N, 11.15.

2,4-Disulfamyl-5-trifluoromethylaniline (No. 16, Table I). 2-Amino-4-trifluoromethylbenzenesulfonic acid (32 g., 0.132 mole) was added portionwise with stirring to chlorosulfonic acid (100 ml.), cooled in an ice bath, over a 5–10 min. period. The solution was heated in an oil bath at 150° for 3 hr., and then cooled to room temperature. Thionyl chloride (40 ml.) was added and the mixture heated on the steam bath for 1 hr., cooled, and poured onto ice. The solid was collected and heated on the steam bath with 500 ml. of concd. ammonium hydroxide for 2 hr. The mixture was cooled and the product was collected, washed with water, and dried. To remove a trace amount of 2-sulfamyl-5-trifluoromethylaniline, the crude product was digested with 500 ml. of hot benzene, filtered, and the benzene-insoluble residue recrystallized from aqueous alcohol to give 2,4-disulfamyl-5-trifluoromethylaniline as colorless needles; yield, 15.3 g. (36%).

Dehalogenations. Catalytic dehalogenation of the halodisulfamylanilines was accomplished in 78–94% yield according to the following procedure for *2,4-disulfamylaniline.* A solution of 5.7 g. (0.02 mole) of 5-chloro-2,4-disulfamylaniline in a mixture of 100 ml. of water and 35 ml. of 5% sodium hydroxide was hydrogenated (25 min.) in the presence of 2 g. of 5% palladium-charcoal catalyst. After removal of catalyst, the solution was neutralized with concd. hydrochloric acid to give 3.9 g. of colorless needles, m.p. 230–231.5°, rep.[16] m.p. 235°.

Catalytic dehalogenation of 6-chloro-2,4-disulfamylanilline in similar manner gave the same product.

Acetylation of 2,4-disulfamylaniline by acetic anhydride and sulfuric acid (trace) gave 2,4-di(acetylsulfamyl)acetanilide, m.p. 234–235°.

Anal. Calcd. for $C_{12}H_{15}N_3O_7S_2$: C, 38.19; H, 4.01; N, 11.13. Found: C, 38.20; H, 4.17; N, 10.62.

5-Chloro-2,4-disulfamyl-N-acylanilines. A solution of 5.7 g. (0.02 mole) of 5-chloro-2,4-disulfamylaniline in 75 ml. of dioxane and 2.34 g. (0.022 mole) of butyryl chloride was heated under reflux for 20 hr. and concentrated to dryness *in vacuo*. Recrystallization of the residue from alcohol-water gave 5.2 g. (73%) of *5-chloro-2,4-disulfamyl-N-butyrylaniline,* colorless needles, m.p. 236–237°, $\lambda_{max}^{C_2H_5OH}$ 227–228.5 and 261–265 mμ, ε 38,249 and 19,843 respectively.

Anal. Calcd. for $C_{10}H_{14}ClN_3O_5S_2$: C, 33.75; H, 3.97; N, 11.81. Found: C, 33.80; H, 4.02; N, 11.81.

By this procedure the reaction with the appropriate acyl chlorides gave the following acyl derivatives.

5-Chloro-2,4-disulfamyl-N-acetylaniline, 80% yield, m.p. 240–242°, $\lambda_{max}^{C_2H_5OH}$ 226–228 and 261–263 mμ, ε 37,017 and 18,389 respectively.

Anal. Calcd. for $C_8H_{10}ClN_3O_5S_2$: C, 29.31; H, 3.08; N, 12.82. Found: C, 29.72; H, 3.21; N, 12.80.

5-Chloro-2,4-disulfamyl-N-chloroacetylaniline, 84% yield m.p. 243–244°, $\lambda_{max}^{C_2H_5OH}$ 227–228 and 260–263 mμ, ε 25,752 and 13,447 respectively.

Anal. Calcd. for $C_8H_9Cl_2N_3O_5S_2$: C, 26.53; H, 2.50; N, 11.60. Found: C, 26.84; H, 2.56; N, 11.62.

5-Chloro-2,4-disulfamyl-N-palmitoylaniline, 95% yield, m.p. 213°.

Anal. Calcd. for $C_{22}H_{38}ClN_3O_5S_2$: C, 50.41; H, 7.31; N, 8.02. Found: C, 50.67; H, 7.18; N, 7.99.

5-Chloro-2,4-disulfamyl-N-p-chlorobenzoylaniline, 76% yield, m.p. 269–270° dec.

Anal. Calcd. for $C_{13}H_{11}Cl_2N_3O_5S_2$: C, 36.80; H, 2.61; N, 9.90. Found: C, 36.94; H, 2.46; N, 9.90.

5-Chloro-2,4-disulfamyl-N-o-chlorobenzoylaniline, 85% yield, m.p. 272–273° dec.

(16) P. Fischer, *Ber.* 24, 3785 (1891).

Anal. Calcd. for $C_{13}H_{11}Cl_2N_3O_5S_2$: C, 36.80; H, 2.61; N, 9.90. Found: C, 36.92; H, 2.79; N, 9.94.

When excess butyryl chloride (10 ml.) was employed *5-chloro-2,4-di(butyrylsulfamyl)-N-butyrylaniline* was obtained in 63% yield, m.p. 182.5°.

Anal. Calcd. for $C_{18}H_{26}ClN_3O_7S_2$: C, 43.59; H, 5.28; N, 8.47. Found: C, 43.56; H, 5.38; N, 8.44.

5-Chloro-2,4-disulfamyl-N-benzoylaniline was obtained by the above procedure or as follows: a solution of 5.7 g. (0.02 mole) of 5-chloro-2,4-disulfamylaniline in 75 ml. of dioxane and an excess of benzoyl chloride was heated under reflux for 8 hr. Crystals began to separate within 2 hr. The mixture was cooled and the product (7.0 g., m.p. 266–267° dec.) collected and recrystallized from dimethylformamide-water; yield, 5.4 g. (69%), m.p. 275–276° dec.

Anal. Calcd. for $C_{13}H_{12}ClN_3O_5S_2$: C, 40.05; H, 3.10; N, 10.78. Found: C, 40.49; H, 3.06; N, 10.79.

5-Chloro-N-acylaniline-2,4-disulfonyl chlorides. A solution of 5 g. of 5-chloroaniline-2,4-disulfonyl chloride in 10–15 ml. of the acid anhydrides with and without benzene (10 ml.) was allowed to stand at room temperature for 1–2 hr. Brief warming of the mixture may be employed. The product separated from the reaction mixture and was recrystallized from hexane or a benzene-hexane mixture.

5-Chloro-N-acetylaniline-2,4-disulfonyl chloride, 78% yield, m.p. 137–139°.

Anal. Calcd. for $C_8H_6Cl_3NO_5S_2$: C, 26.21; H, 1.65; N, 3.82. Found: C, 26.39; H, 1.77; N, 3.79.

5-Chloro-N-butyrylaniline-2,4-disulfonyl chloride, 69% yield, m.p. 121–122°.

Anal. Calcd. for $C_{10}H_{10}Cl_3NO_5S_2$: C, 30.43; H, 2.55; N, 3.55. Found: C, 30.72; H, 2.51; N, 3.55.

5-Chloro-N-caproylaniline-2,4-disulfonyl chloride, 69% yield, m.p. 91–93°.

Anal. Calcd. for $C_{12}H_{14}Cl_3NO_5S_2$: C, 34.09; H, 3.34; N, 3.31. Found: C, 34.58; H, 3.56; N, 3.40.

3-Chloro-4-methylmercaptonitrobenzene.[17] A solution of sodium disulfide, prepared from 175 g. (0.72 mole) of sodium sulfide nonahydrate and 23.4 g. (0.73 g. atom) of sulfur dissolved in 1.3 l. of hot ethanol, was added with stirring over 20 min. to a boiling solution of 192 g. (1 mole) of 3,4-dichloronitrobenzene in 250 ml. of ethanol. A solution of 40 g. (1 mole) of sodium hydroxide in 900 ml. of 95% ethanol was then added over 10 min. and heating was continued for another 5 min. The mixture was cooled in an ice bath and diluted with 1.5 l. of ice water and 200 ml. of 20% aqueous sodium hydroxide. Dimethyl sulfate (126 g., 1 mole) was added over 15 min. and the mixture was stirred at room temperature for 45 min. The solid was collected, washed with water, and recrystallized from alcohol; yield, 150 g. (74%) of yellow needles, m.p. 85–91°; analytical sample, m.p. 92–94°.

Anal. Calcd. for $C_7H_6ClNO_2S$: C, 41.28; H, 2.97; N, 6.88. Found: C, 41.47; H, 3.17; N, 6.85.

3-Chloro-4-methylmercaptoaniline. Iron powder (56.4 g.) and concd. hydrochloric acid (236 ml.) were added in six portions over 4 hr. to a suspension of 48.8 g. (0.24 mole) of 3-chloro-4-methylmercaptonitrobenzene and 8 g. of cupric chloride in 190 ml. of water and 100 ml. of methanol, maintained at 70°. The mixture was heated at 80–85° for 1.5 hr. and transferred to a flask suitable for steam distillation. Sodium hydroxide (140 g.) was added and steam distillation carried out for 10 hr. The distillate was extracted with ether and afforded colorless needles from ether-petroleum ether; yield, 31.6 g. (73%), m.p. 73–75°.

Anal. Calcd. for C_7H_8ClNS: C, 48.41; H, 4.64; N, 8.07. Found: C, 48.65; H, 4.74; N, 8.07.

3-Chloro-4-methylmercaptoacetanilide was prepared in quantitative yield from 3-chloro-4-methylmercaptoaniline (45 g.) and acetic anhydride (150 ml.) at room temperature; colorless needles from alcohol-water, m.p. 130–132°.

Anal. Calcd. for $C_9H_{10}ClNOS$: C, 50.11; H, 4.67; N, 6.49. Found: C, 50.32; H, 4.85; N, 6.50.

3-Chloro-4-methylsulfonylacetanilide. To a suspension of 43 g. (0.2 mole) of 3-chloro-4-methylmercaptoacetanilide in 200 ml. of glacial acetic acid–acetic anhydride mixture (1:1), cooled in an ice bath, 55 g. (0.44 mole) of 30% hydrogen peroxide was added with stirring over 20 min. After 24 hr. at room temperature, excess hydrogen peroxide was destroyed by addition of manganese dioxide. The solution was filtered, concentrated to dryness *in vacuo*, and the residue recrystallized from benzene-alcohol; yield, 42 g. (85%) of colorless needles, m.p. 127–130°.

Anal. Calcd. for $C_9H_{10}ClNO_3S$: C, 43.64; H, 4.07; N, 5.66. Found: C, 43.73; H, 3.93; N, 5.62.

5-Chloro-4-methylsulfonyl-2-sulfamylaniline was prepared in 30% yield from 3-chloro-4-methylsulfonylacetanilide by the general chlorosulfonation procedure described for the preparation of 5-chloro-2,4-disulfamylaniline; colorless needles from alcohol-water, m.p. 242–244°.

Anal. Calcd. for $C_7H_9ClN_2O_4S_2$: C, 29.53; H, 3.19; N, 9.84. Found: C, 29.54; H, 3.49; N, 9.79.

2-Amino-5-chloro-6-sulfamylbenzothiazole. A solution of 24 g. (0.15 mole) of bromine in 50 ml. of acetic acid was added slowly to a stirred solution of 31 g. (0.15 mole) of 2-chlorosulfanilamide and 58.2 g. (0.6 mole) of potassium thiocyanate in a liter of 90% acetic acid maintained at 0–5°. The solution was allowed to warm to room temperature slowly and stand overnight. The yellow suspension then was heated under reflux for 2 hr. and concentrated under reduced pressure. The residue upon recrystallization from dilute alcohol yielded 20.8 g. of product, m.p. 285–287°.

Anal. Calcd. for $C_7H_6ClN_3O_2S_2$: C, 31.88; H, 2.29; N, 15.93. Found: C, 32.11; H, 2.40; N, 15.84.

5-Chloro-2-methylmercapto-4-sulfamylaniline. A solution of 7.9 g. (0.03 mole) of 2-amino-5-chloro-6-sulfamylbenzothiazole and 16.8 g. (0.3 mole) of potassium hydroxide in 35 ml. of water was heated under reflux for 6 hr. The solution was cooled and acidified. The product was collected on the filter (7.3 g., m.p. 218–223°) and methylated without further purification, as recrystallization from 90% alcohol or dimethylformamide-water always gave the *disulfide,* m.p. 298–300°.

Anal. Calcd. for $C_{12}H_{12}Cl_2N_4O_4S_4$: C, 30.31; H, 2.55; N, 11.79. Found: C, 30.77; H, 2.55; N, 11.76.

Dimethylsulfate (3.8 g., 0.03 mole) was added in three portions to a stirred solution of the crude 5-chloro-2-mercapto-4-sulfamylaniline (7.2 g., 0.03 mole) in 80 ml. of 5% sodium hydroxide maintained at 5–10°. After 1 hr., the solution was acidified and the product recrystallized from alcohol; yield, 3.2 g., m.p. 160–162°.

Anal. Calcd. for $C_7H_9ClN_2O_2S_2$: C, 33.26; H, 3.59; N, 11.09. Found: C, 33.39; H, 3.46; N, 11.06.

5-Chloro-2-methylsulfonyl-4-sulfamylaniline. One gram (0.9 ml., 0.03 mole) of 30% hydrogen peroxide was added slowly to a suspension of 5-chloro-2-methylmercapto-4-sulfamylaniline (3.0 g., 0.0125 mole) in a mixture of 30 ml. of acetic acid and 25 ml. of acetic anhydride maintained at 0–5°. The solution was allowed to stand at room temperature overnight. Solvent was removed on the steam bath *in vacuo* and the residue poured into water. The product was recrystallized from alcohol-water to give 1.1 g. of *5-chloro-2-methylsulfonyl-4-sulfamylacetanilide,* m.p. 283–285°.

Anal. Calcd. for $C_9H_{11}ClN_2O_5S_2$: C, 33.08; H, 3.39; N, 8.57. Found: C, 33.11; H, 3.38; N, 8.59.

A solution of 2 g. (0.006 mole) of the above acetanilide in 20 ml. of 5% sodium hydroxide was heated on the steam bath for 2 hr. and acidified; yield, 1.4 g., m.p. 229–231°. Recrystallization from water did not change the melting point.

Anal. Calcd. for $C_7H_9ClN_2O_4S_2$: C, 29.52; H, 3.19; N, 9.84. Found: C, 29.69; H, 3.39; N, 9.87.

5,6-Dichloro-2,4-disulfamylaniline (No. 14, Table I). A solution of 25.7 g. (0.09 mole) of 5-chloro-2,4-disulfamylaniline in a mixture of 100 ml. of water, 200 ml. of glacial acetic acid, and 150 ml. of concd. hydrochloric acid was

(17) Based on the procedure for *p*-nitrothiophenol. C. C. Price and G. W. Stacy, *J. Am. Chem. Soc.*, 68, 498 (1946).

treated with 9 ml. of 30% hydrogen peroxide at 75–80° and allowed to cool to room temperature (2 hr.). The mixture was cooled and the crystalline precipitate collected, washed with water, and recrystallized from alcohol-water: yield, 12 g. (42%) of colorless needles.

5-Chloro-2,4-disulfamyl-6-iodoaniline[18] (No. 15, Table I). A solution of iodine monochloride (21.1 g., 0.13 mole) in coned. hydrochloric acid (50 ml.) was added dropwise over 30 min. to a solution of 5-chloro-2,4-disulfamylaniline (25.3 g., 0.089 mole) in coned. hydrochloric acid (350 ml.) maintained at 98°. After stirring at 98° for 24 hr., the mixture was cooled to 5° and the product collected on a sintered glass funnel, washed with water, and dried; yield, 27 g. (82%), m.p. 308–309° dec. (corr.). An analytical sample prepared by recrystallization from ethanol-water showed no change in melting point.

(18) We are indebted to Dr. E. J. Cragoe for this preparation.

WEST POINT, PA.

[CONTRIBUTION FROM THE MERCK SHARP AND DOHME RESEARCH LABORATORIES DIVISION OF MERCK AND COMPANY, INC.]

Diuretics: 1,2,4-Benzothiadiazine-1,1-dioxides

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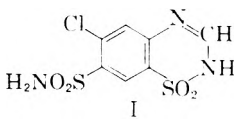
Ring closure of aniline-2,4-disulfonamides with acylating agents, aldehydes, or urea to give sulfamylbenzothiadiazine-1,1-dioxide derivatives is described. Sulfamylbenzothiadiazine-1,1-dioxides promote excretion of sodium chloride in animals and man and constitute a novel class of orally effective diuretic agents. Several aspects of the chemistry of this class of compounds are reported in detail.

6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide[1] (I) is an orally effective diuretic and is

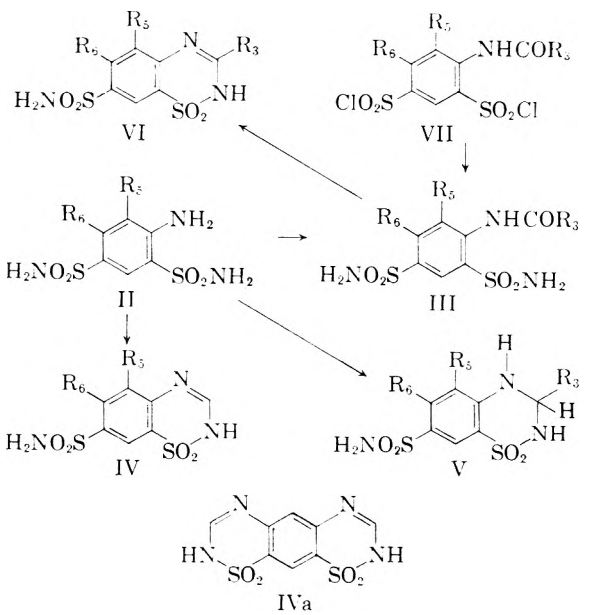


I

being employed currently in therapy for conditions associated with fluid and electrolyte retention such as congestive heart failure and hypertension. Preliminary communications have reported some of the chemistry and biological properties of this compound and some closely related derivatives.[2,3,4] The present paper reports on these more fully and describes the extension of this series of compounds.

1,2,4-Benzothiadiazine-1,1-dioxides as a class have been known since 1902[5–9] and a number of derivatives have been prepared from the appropriately substituted orthanilamide by the general procedures involving ring closure of the orthanilamide by reaction with acylating agents, aldehydes or urea. However, no compound of this class has been reported where a sulfamyl group is present. The only biologic property previously noted for any 1,2,4-benzothiadiazine-1,1-dioxide is the sweet taste of 3-oxodihydro-1,2,4-benzothiadiazine-1,1-dioxide.[6,7,9]

In our studies, compounds of greatest interest have the general structures IV, V and VI where a sulfamyl group occupies the 7 position. Benzothiadiazine-1,1-dioxides of types IV and VI and related isomers having the sulfamyl group in the 5 or 6 position as well as representative reference compounds lacking a sulfamyl group are recorded in Table I.



(1) The generic name of chlorothiazide has been given to this compound and Diuril is the trademark of Merck and Co., Inc., for chlorothiazide.

(2) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, **79**, 2028 (1957).

(3) F. C. Novello and J. M. Sprague, 132nd Meeting of the American Chemical Society, New York, N. Y., September 8–13, 1957; abstracts, pp. 32-40.

(4) J. M. Sprague, *Ann. N. Y. Acad. Sci.* **71**, 328 (1958).

(5) Ekbom, *Bih. Svensk Vetenskakad Handl.*, **27**, (II), 3 (1902).

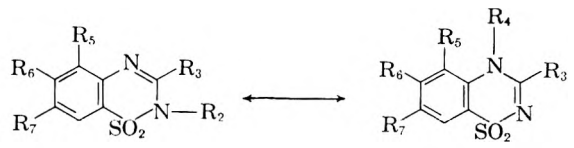
(6) E. Schrader, *J. prakt. Chem.* (2) **95**, 392 (1917).

(7) D. V. Parke and R. T. Williams, *J. Chem. Soc.*, 1760 (1950).

(8) J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, **16**, 815 (1951).

(9) L. Raffa, *Farmaco (Pavia), Ed. sci.*, **9**, 661 (1954); E. Grana and L. Lilla, *Ed. Sci.*, **12**, 65 (1957).

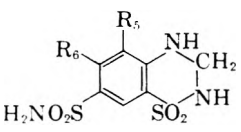
TABLE I.



No.	R_2	R_3	R_4	R_5	R_6	R_7	Recrystn. Solvent[a]	M.P.°	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	—	H	H	SO_2NH_2	A	319–320	$C_7H_7N_3O_4S_2$	32.18	32.19	2.70	2.94	16.08	15.91
2	H	H	—	H	F	SO_2NH_2	A	304–305	$C_7H_6FN_3O_4S_2$	30.10	30.14	2.17	2.50	15.05	14.88
3	H	H	—	H	Cl	SO_2NH_2	A	342.5–343	$C_7H_6ClN_3O_4S_2$	28.48	28.65	2.05	2.23	14.21	14.11
4	H	H	—	H	Br	SO_2NH_2	B	347–349	$C_7H_6BrN_3O_4S_2$	24.71	24.91	1.78	1.93	12.35	12.24
5	H	H	—	H	CF_3	SO_2NH_2	C	294–295	$C_8H_6F_3N_3O_4S_2$	29.18	28.95	1.84	2.24	12.76	12.80
6	H	H	—	H	CH_3	SO_2NH_2	D	344–345	$C_8H_9N_3O_4S_2$	34.90	35.05	3.30	3.32	15.26	15.17
7	H	H	—	H	OCH_3	SO_2NH_2	A	305–307	$C_8H_9N_3O_5S_2$	32.98	33.22	3.11	3.03	14.43	14.42
8	H	H	—	H	NO_2	SO_2NH_2	A	338–339	$C_7H_6N_4O_6S_2$	27.45	27.73	1.98	2.28	18.30	18.17
9[b]	H	H	—	H	NH_2	SO_2NH_2	A	323–324	$C_7H_8N_4O_4S_2$	30.43	30.62	2.92	3.16	20.28	20.16
10	CH_3	H	—	H	Cl	SO_2NH_2	E	217–220	$C_8H_8ClN_3O_4S_2$	31.02	30.98	2.60	2.74	13.57	13.41
11	H	CH_3	—	H	Cl	SO_2NH_2	F	332	$C_8H_8ClN_3O_4S_2$	31.02	31.27	2.60	2.53	13.57	13.50
12	H	n-C_3H_7	—	H	Cl	SO_2NH_2	A	305–307	$C_{10}H_{12}ClN_3O_4S_2$	35.55	35.89	3.58	3.56	12.44	12.43
13	H	n-C_5H_{11}	—	H	Cl	SO_2NH_2	A	269–270	$C_{12}H_{16}ClN_3O_4S_2$	39.39	39.21	4.41	4.70	11.30	11.33
14	H	$ClCH_2$	—	H	Cl	SO_2NH_2	A	323–326	$C_8H_7Cl_2N_3O_4S_2$	27.91	28.45	2.05	2.28	12.21	12.23
15	H	C_6H_5	—	H	Cl	SO_2NH_2	B	>350	$C_{13}H_{10}ClN_3O_4S_2$	41.99	42.64	2.71	2.93	11.30	11.36
16	H	o-ClC_6H_4	—	H	Cl	SO_2NH_2	A	>330	$C_{13}H_9Cl_2N_3O_4S_2$	38.43	38.62	2.23	2.39	10.34	10.33
17	H	p-ClC_6H_4	—	H	Cl	SO_2NH_2	A	>350	$C_{13}H_9Cl_2N_3O_4S_2$	38.43	38.76	2.23	2.36	10.34	10.35
18	—	H	CH_3	H	Cl	SO_2NH_2	G	325–326	$C_8H_8ClN_3O_4S_2$	31.02	31.24	2.60	2.72	13.57	13.49
19	—	H	Allyl	H	Cl	SO_2NH_2	A	257.5–258.5	$C_{10}H_{10}ClN_3O_4S_2$	35.77	35.79	3.00	3.08	12.51	12.48
20	—	CH_3	CH_3	H	H	SO_2NH_2	H	258–260	$C_9H_{11}N_3O_4S_2$	37.36	37.43	3.83	3.86	14.52	14.50
21	H	H	—	Cl	H	SO_2NH_2	A	276.5–277.5	$C_7H_6ClN_3O_4S_2$	28.43	28.64	2.05	2.25	14.21	14.11
22	H	H	—	Cl	Cl	SO_2NH_2	A	355–356	$C_7H_5Cl_2N_3O_4S_2$	25.46	25.88	1.53	1.61	12.72	12.74
23[c]	H	H	—	I	Cl	SO_2NH_2	B	376–377[d]	$C_7H_5ClIN_3O_4S_2$	19.94	20.40	1.20	1.24	9.97	9.85
24	CH_3	H	—	H	Cl	SO_2NHCH_3	F	219–221	$C_9H_{10}ClN_3O_4S_2$	33.38	33.69	3.11	3.25	12.98	13.01
25	p-ClC_6H_4	H	—	H	Cl	$SO_2NHC_6H_4Cl$-p	I	247–249	$C_{19}H_{13}Cl_2N_3O_4S_2$	44.15	44.17	2.34	2.55	8.13	8.11
26	H	H	—	H	Cl	$SO_2N(CH_3)_2$	A	265–267	$C_9H_{10}ClN_3O_4S_2$	33.39	33.09	3.11	3.15	12.98	12.85
27	H	H	—	SO_2NH_2	H	H	J	249–250	$C_7H_7N_3O_4S_2$	32.18	32.48	2.70	2.79	16.08	15.96
28	H	H	—	SO_2NH_2	H	Br	K	291–292	$C_7H_6BrN_3O_4S_2$	24.71	24.58	1.78	1.92	12.35	12.35
29	H	H	—	SO_2NH_2	H	SO_2NH_2	A	316–318	$C_7H_8N_4O_6S_3$	24.70	24.89	2.37	2.58	16.46	16.43
30	H	H	—	H	SO_2NH_2	H	A	309–312	$C_7H_7N_3O_4S_2$	32.18	32.44	2.70	2.75	16.08	16.08
31	H	H	—	H	SO_2NH_2	Cl	L	327–330	$C_7H_6ClN_3O_4S_2$	28.43	28.90	2.05	2.09	14.21	14.15
32	H	H	—	H	Cl	H	M	253–254	$C_7H_5ClN_2O_2S$	38.80	38.89	2.33	2.40	12.93	12.90
33	H	H	—	H	Cl	Cl	L	293–294	$C_7H_4Cl_2N_2O_2S$	33.48	33.73	1.61	1.53	11.16	11.15
34	H	H	—	H	Cl	CH_3	A	287–288	$C_8H_7ClN_2O_2S$	41.65	41.94	3.06	3.18	12.15	12.14
35	H	H	—	H	CH_3	Cl	I	260–261	$C_8H_7ClN_2O_2S$	41.65	41.80	3.06	3.17	12.15	12.07
36	H	H	—	H	Cl	CH_2SO_2	A	329–331	$C_8H_7ClN_2O_4S_2$	32.60	32.62	2.39	2.61	9.51	9.46
37[e]	CH_3	H	—	H	H	H	F	95–97	$C_6H_8N_2O_2S$	48.97	49.05	4.11	4.05	14.28	14.15

[a] A = alcohol-water, B = dimethylformamide-water, C = alcohol-hexane, D = acetic acid-water, E = dimethylformamide-ether, F = alcohol, G = acetone-alcohol, H = dimethylformamide-alcohol, I = acetonitrile, J = acetone-benzene, K = acetone, L = acetone-petroleum ether, M = butanone. [b] Prepared by hydrogenation of No. 8 in ethanol in presence of platinum oxide catalyst in 73% yield. [c] We are indebted to Dr. E. J. Cragoe for preparation of this compound. [d] Corrected melting point. [e] 2-Methylsulfamylaniline was prepared in 80% yield by hydrogenation of 2-methylsulfamylnitrobenzene in ethanol in presence of platinum oxide catalyst; m.p. 56–56.5°. *Anal.* Calcd. for $C_7H_{10}N_2O_2S$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.29; H, 5.42; N, 15.00.

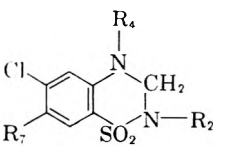
TABLE II



No.[a]	R_5	R_6	M.P.°	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1[b]	H	H	216–217	$C_7H_9N_3O_4S_2$	31.93	31.90	3.45	3.35	15.96	15.80
2	H	Cl	262–263	$C_7H_8ClN_3O_4S_2$	28.24	28.55	2.71	2.78	14.11	13.93
3	H	Br	287–288	$C_7H_8BrN_3O_4S_2$	24.56	24.86	2.36	2.50	12.27	12.27
4	H	CF_3	263–264	$C_8H_8F_3N_3O_4S_2$	29.00	29.22	2.43	2.67	12.68	12.52
5	H	CH_3	253–254	$C_8H_{11}N_3O_4S_2$	34.65	35.07	4.00	4.11	15.15	15.13
6	H	NO_2	263.5–264.5	$C_7H_8N_4O_6S_2$	27.27	27.61	2.62	2.96	18.17	17.80
7	Cl	Cl	288–289	$C_7H_7Cl_2N_3O_4S_2$	25.31	25.63	2.12	2.31	12.65	12.62

[a] Alcohol-water employed for recrystallization. [b] Prepared also by catalytic dehalogenation of No. 2, Table II, in dilute sodium hydroxide solution in presence of palladium-charcoal catalyst; 90% yield.

TABLE III



No.	R_2	R_4	R_7	M.P.°	Recrystn. Solvents[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	H	164–166	A	$C_7H_7ClN_2O_2S$	38.45	38.76	3.23	3.29	12.81	12.78
2	H	CH_3	SO_2NH_2	249–250	B	$C_8H_{10}ClN_3O_4S_2$	30.82	31.21	3.23	3.35	13.48	13.45
3	CH_3	H	SO_2NH_2	239–241	B	$C_8H_{10}ClN_3O_4S_2$	30.82	31.06	3.23	3.42	13.48	13.39
4	CH_3	H	SO_2NHCH_3	195–197	C	$C_9H_{12}ClN_3O_4S_2$	33.18	33.28	3.71	3.77	12.90	12.75
5	H	H	$SO_2N(CH_3)_2$	202–204	B	$C_9H_{12}ClN_3O_4S_2$	33.18	33.38	3.71	3.84	12.90	12.85
6	H	H	CH_3SO_2	248–249	B	$C_8H_9ClN_2O_4S_2$	32.38	32.63	3.06	3.10	9.44	9.41

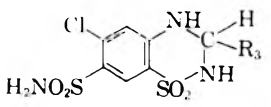
[a] A = toluene, B = alcohol-water, C = alcohol.

The preparation of sulfamylbenzothiadiazine-1,1-dioxides (VI) was generally accomplished by cyclization of 2,4-disulfamyl-*N*-acylanilines (III) in presence of base. Ammonium hydroxide was employed in most instances. For some ring closures, potassium fluoride in dimethylformamide proved more satisfactory. As either liquid ammonia or ammonium hydroxide were convenient for ring closure, the cyclized products (VI) were prepared directly from the *N*-acylaniline-2,4-disulfonyl chlorides (VII) in these media, thus accomplishing the formation of the disulfonamide (III) and the ring closure in one step. The required intermediates II, III and VII have been described.[10]

When formic acid was employed as the acylating agent in reactions with II, the formyl derivative III (R_3=H) was not obtained but only the corresponding cyclic product IV (VI. R_3=H) resulted. Any formyl derivative (III. R_3=H) apparently has only transitory existence. Ring closure of 5-amino-2,4-disulfamylaniline (II. R_6=NH_2, R_5=H) gave the tricyclic compound (IVa), benzo[1,2-e, 5,4-e']bis[1,2,4-thiadiazine-1,1-dioxide], which has a melting point above 500°. With compounds in which the sulfamyl group *ortho* to the amino group held a substituent (*e.g.*, methyl), formic acid proved less satisfactory for ring closure and in these instances (*e.g.*, 2-methylsulfamylaniline, 5-chloro-2-methylsulfamyl-4-sulfamylaniline, and 5-chloro-2,4-di(methylsulfamyl)-aniline) ethyl orthoformate was the reagent of choice.[8] This reagent also effected a smooth and rapid ring closure when the *ortho* sulfamyl group was unsubstituted. However, with reactants having a second unsubstituted sulfamyl group not amenable to cyclization, a further reaction occurred. Under conditions affecting ring formation, ethyl orthoformate reacted also with the unsubstituted sulfamyl group to yield ethoxymethylene derivatives of the type VIII. Where the cyclization reaction was rapid, the formation of appreciable amounts of VIII could be avoided by short reaction times; prolonged reaction led to VIII, exclusively. The same type of compounds (VIII) resulted from treatment of the sulfamylbenzothiadiazines I, IV, and VI with ethyl orthoformate. Similar reaction occurred between V and ethyl orthoformate. Mild alkaline hydrolysis removed the ethoxymethylene group to yield the desired products. Upon treatment with ammonia, VIII gave the formamidine IX.

(10) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.* 25, 965 (1960).

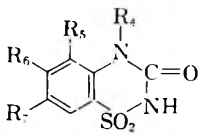
TABLE IV



No.	R_3	M.P.°	Recrystn. Solvent[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	CH_3	252–253	A	$C_8H_{10}ClN_3O_4S_2$	30.82	30.94	3.23	3.23	13.48	13.33
2	C_2H_5	265	A	$C_9H_{12}ClN_3O_4S_2$	33.17	33.40	3.71	3.79	12.90	12.75
3	Cl_3C	287	B	$C_8H_7Cl_4N_3O_4S_2$	23.15	23.56	1.70	1.93	10.12	10.13
4	$HOCH_2$	225–226	C	$C_8H_{10}ClN_3O_5S_2$	29.31	29.59	3.08	3.25	12.82	12.72
5		233–235	C	$C_9H_{10}ClN_3O_5S_2$	31.81	32.03	2.97	3.24	12.37	12.18
6	$(CH_2)_6$[b]	259–260	D	$C_{12}H_{16}ClN_3O_4S_2$	39.39	39.70	4.41	4.60	11.49	11.35
7	$C_6H_5CH_2$	260–262	A	$C_{14}H_{14}ClN_3O_4S_2$	43.35	43.43	3.64	3.96	10.83	10.70
8	p-ClC_6H_4	250–251	A	$C_{13}H_{11}Cl_2N_3O_4S_2$	38.24	38.48	2.72	2.95	10.29	10.26
9	p-$NO_2C_6H_4$	268–269	E	$C_{13}H_{11}ClN_4O_6S_2$	37.28	37.47	2.65	3.14	13.38	13.18
10	2-Pyridyl	260	F	$C_{12}H_{11}ClN_4O_4S_2$	38.45	38.87	2.95	3.05	14.95	14.91
11	5-Nitro-2-furyl	239–240	E	$C_{11}H_9ClN_4O_7S_2$	32.32	32.89	2.22	2.38	13.70	13.01

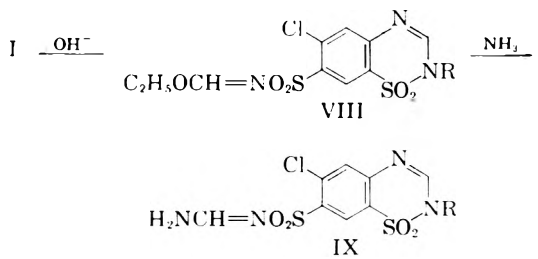
[a] A = acetic acid-water, B = ethylene glycol monomethyl ether-water, C = acetone-water, D = dimethylformamide-water, E = acetone-ether, F = acetonitrile. [b] R_3 and H replaced by this group.

TABLE V



No.[a]	R_4	R_5	R_6	R_7	M.P.°	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	Cl	SO_2NH_2	313	$C_7H_6ClN_3O_5S_2$	26.97	27.29	1.94	2.10	13.48	13.44
2	H	Cl	H	SO_2NH_2	314–315	$C_7H_6ClN_3O_5S_2$	26.97	27.09	1.94	2.20	13.48	13.48
3	H	H	SO_2NH_2	Cl	323–324	$C_7H_6ClN_3O_5S_2$	26.97	27.23	1.94	2.06	13.48	13.47
4	H	H	Br	SO_2NH_2	323–324	$C_7H_6BrN_3O_5S_2$	23.60	23.76	1.70	1.97	11.80	11.83
5	H	H	CH_3	SO_2NH_2	307–308	$C_8H_9N_3O_5S_2$	32.98	32.98	3.11	3.29	14.42	14.37
6	H	H	CH_3O	SO_2NH_2	291–293	$C_8H_9N_3O_6S_2$	31.27	31.32	2.95	3.10	13.67	13.66
7	H	H	NO_2	SO_2NH_2	>350	$C_7H_6N_4O_7S_2$	26.08	26.47	1.88	2.14	17.38	17.99
8	CH_3	H	Cl	SO_2NH_2	315	$C_8H_8ClN_3O_5S_2$	29.49	29.58	2.48	2.59	12.90	12.87

[a] Alcohol-water employed for recrystallization.



VIII

IX

Preparation of dihydrobenzothiadiazine-1,1-dioxides (V) was accomplished by ring closure of representative 2,4-disulfamylanilines with appropriate aldehydes in the presence of catalytic amounts of acid or base. In Tables II and III are listed compounds prepared by ring closure of various 2,4-disulfamylanilines with formaldehyde. From this series a second clinically useful diuretic agent has resulted—6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide,[11–13] the dihydro derivative of I (V. R_6=Cl, R_3=R_5=H). Derivatives of V (R_6=Cl, R_5=H) prepared by ring closure of 5-chloro-2,4-disulfamylaniline with various aldehydes are listed in Table IV. Chloral underwent reaction with 5-chloro-2,4-disulfamylaniline in either of two ways. In the absence of acid or base and in dimethylformamide solution, the product was 6-chloro-7-sulfamyl-3-trichloromethyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (V. R_3=CCl_3, R_6=Cl, R_5=H), the expected product from such an aldehyde. However, under the general procedure employing a basic catalyst, chloral behaved as a formylating agent and the product was 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-di-

(11) This compound has been given the generic name of hydrochlorothiazide; HydroDIURIL is the trademark of Merck and Co., Inc. for hydrochlorothiazide.

(12) Preparation of this compound has been reported by G. de Stevens, L. H. Werner, A. Halamandaris, and S. Ricca, Jr., *Experientia* **14**, 463 (1958).

(13) Preparation of 6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide has been reported by C. T. Holdrege, R. B. Babel, and L. C. Cheney, *J. Am. Chem. Soc.*, **81**, 4807 (1959).

TABLE VI

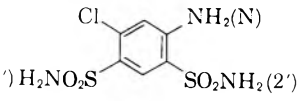
ULTRAVIOLET ABSORPTION SPECTRA OF 1,2,4-BENZOTHIADIAZINE-1,1-DIOXIDES[a]

	R_2	R_3	R_4	R_6	R_7	Solvent[b]	λ_{max}, mμ	$\epsilon \times 10^{-3}$	λ_{max}, mμ	$\epsilon \times 10^{-3}$	λ_{max}[f], mμ	$\epsilon \times 10^{-3}$
1	H	H	—	H	H	A[c]			267–269	8.12		
						B			277	9.47	298–300	4.45
2	H	H	—	Cl	H	A	221–222	30.5	266–269	7.37		
3	H	H	—	H	SO_2NH_2	A			277 278	11.6		
4[e]	H	H	—	Cl	SO_2NH_2	A	226	30.0	280	11.1		
						B	224–226	22.8	291–293	13.1		
5	H	CH_3	—	Cl	SO_2NH_2	A	225–226	30.8	275–277	11.8		
							228.5–229	30.3				
						B	224–227	23.1	289–292	11.7		
6	H	H	—	F_3C	SO_2NH_2	A			278–279	11.0		
			4-Substituted Series									
7	—	CH_3	CH_3	H	H	A			266–268	8.37		
8	—	CH_3	CH_3	H	SO_2NH_2	A			277.5	12.6		
9[g]	—	H	CH_3	Cl	SO_2NH_2	A	228–229	27.9	284	11.3		
10	—	H	allyl	Cl	SO_2NH_2	A	228.5	28.0	283–285	11.2		
						B[d]	229	35.8	269.5	17.7	319–322	4.77
			2-Substituted Series									
11	CH_3	H	—	H	H	A			262–264	7.94	296–298.5	5.35
12	CH_3	H	—	Cl	SO_2NH_2	A	228–230	26.4	283–286	10.3	302–305	8.83
						C	228–229	24.5	282–286	9.81	305–307	8.88
13	CH_3	H	—	Cl	SO_2NH_2	A	227–228	26.1	288–289	10.6	308–310	9.52
			3,4-Dihydro Series (cf. V)									
14	H	H	H	Cl	SO_2NH_2	A	226	36.7	269–271	19.8	315–318	3.10
15	CH_3	H	H	Cl	SO_2NH_2	A	225	36.5	267–269	19.5	312–316	3.14
16	H	H	CH_3	Cl	SO_2NH_2	A	228	34.5	276	21.9	322–325	3.72
17	H	$HOCH_2$	H	Cl	SO_2NH_2	A	226	39.7	268–270	20.8	310–315	3.13
18	H	$C_6H_5CH_2$	H	Cl	SO_2NH_2	A	226.5	42.4	270–271	23.5	314–316	3.05
19	H	p-$NO_2C_6H_4$	H	Cl	SO_2NH_2	A	225	39.7	271	35.1	307–313[j]	3.83
20	H	Cl_3C	H	Cl	SO_2NH_2	A	225	43.0	264–266	19.3	302–308	2.75
21	H	=O	H	Cl	SO_2NH_2	A	223–224	48.4	259–260	16.1		
22	6-Chloro-3,3-pentamethylene-7-sulfamyl					A	226–227.5	33.8	272–273.5	21.8	315–321	2.73

[a] Determined with Cary Recording Spectrophotometer, Model 11. [b] A = ethanol, B = 0.1N aqueous sodium hydroxide, C = acetonitrile. [c] D. V. Parke and R. T. Williams, ref. 7 found λ_{max} 207, 269 mμ, $\epsilon \times 10^{-3}$ 13.4, 7.6 respectively. [d] Gives ring-opened compound, see Table VII. [e] The spectra in ethanol of the derivatives bearing an acetyl, butyryl, or ethoxymethylene group on the 7-sulfamyl were identical with the unsubstituted compound recorded here. [f] The spectra of compounds 2–10 inclusive in ethanol showed pronounced shoulders in the region 290–310 mμ. [g] Prepared either by methylation of chlorothiazide (I) or by the ring closure synthesis starting with m-chloro-N-methylaniline. [j] Shoulder.

TABLE VII

ULTRAVIOLET ABSORPTION SPECTRA OF 5-CHLORO-2,4-DISULFAMYLANILINE AND RELATED COMPOUNDS

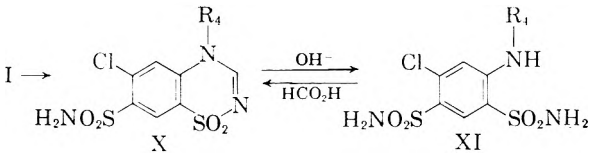


		Solvent[a]	λmax, mμ	ε × 10⁻³	λmax, mμ	ε × 10⁻³	λmax, mμ	ε × 10⁻³
1	5-Chloro-2,4-disulfamylaniline	A	223–224	41.8	265–266	18.6	312–314	3.87
		B	222–223	32.2	262	14.8	305–309	3.11
2	*N*-Methyl[b]	A	225–227	38.2	269–271	20.3	317–322	4.49
3	*N*-Acetyl	A	226–228	37.0	261–263	18.4		
4	*N*-Butyryl[c]	A	227–228	38.3	261–265	19.8		
5	*N*-Acetyl-2′,4′-tetramethyl	A	231–234	26.6	267–270	17.1		
6	2′-Methyl	A	224–225	38.6	264–265	18.2	309–312	3.85
7	2′,4′-Tetramethyl	A	227.5	29.4	271.5	19.2	316–319	4.20
8	2′,4′-Bis(pentamethylene)	A	228	28.0	272	19.0	317–320	4.29
9	*N*-Allyl-2′-formyl	A	229	36.9	269–270	17.6	321–327	4.49
		B[d]	229	35.8	269.5	17.7	319–322	4.77
10	*N*-Formyl-2′,4′-dimethyl	A	230.5	33.1	266–268	18.4		
11	*N*-Methyl-2′-acetyl-5-deschloro	A	215–217	24.2	267–269	19.5	323–328	4.47
12	2-(*N*-Methyl-*N*-formylsulfamyl)aniline	A			246–247	12.3	284.5–286.5	3.33

[a] A = ethanol, B = 0.1*N* aqueous sodium hydroxide. [b] The *N*-allyl analog gave identical values. [c] The chloroacetyl analog had the same spectra as the acetyl and butyryl derivatives. [d] 4-Allyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 0.1*N* sodium hydroxide.

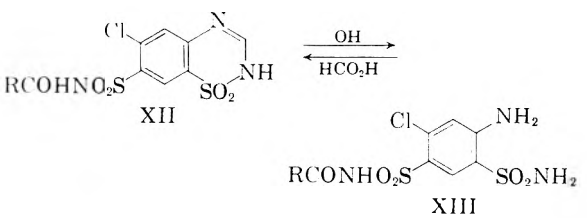
oxide (I). This property of chloral has been employed for preparation of *N*-formylamines.[14] Further ramifications in the dihydrobenzothiadiazine-1,1-dioxide series included preparation of 3-oxodihydro-1,2,4-benzothiadiazine-1,1-dioxides (Table V) by fusion of the disulfamylanilines with urea.

Using 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (I, chlorothiazide) and certain of its derivatives as illustrative examples of the series, several aspects of the chemistry of this type of structure were investigated.



Alkylation of I with methyl sulfate or with allyl bromide in aqueous or alcoholic alkali yielded the 4-methyl and 4-allyl derivatives (X) respectively. The position of the entering group was established by hydrolysis of X (R_4=CH_3) to XI (R_4=CH_3) and by ring closure of XI (R_4=CH_3) prepared from *N*-methyl-*m*-chloroaniline. The ultraviolet spectra of these substances and of pertinent reference compounds (Tables VI and VII) also support the 4 position of the alkyl group in X.

Acylation with either acetic or butyric anhydride in pyridine at room temperature yielded the 7-acylsulfamyl derivative XII (R=CH_3, C_3H_7) which exhibits two acid dissociations, pK'_a 3.7 and pK'_a 7.2, consistent with this structure. Con-



trolled alkaline hydrolysis of XII (R=CH_3) gave XIII which upon treatment with formic acid was recyclized to XII.

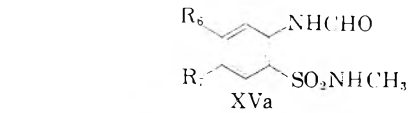
The benzothiadiazine-1,1-dioxides (IV, VI) are readily cleaved by hot aqueous alkali to yield as final products the disulfamylaniline II. This reaction, which has been established chemically and spectrophotometrically, is the basis of an analytical method[15] for the determination of I in biological specimens through the quantitative diazo color reaction of 5-chloro-2,4-disulfamylaniline (II) (R_6=Cl, R_5=H). In 1.0*N* sodium hydroxide ring opening was complete in thirty minutes at steam-bath temperature but required 26–48 hours at room temperature. In 0.1*N* sodium hydroxide with heating the reaction was complete in three hours but at room temperature it was not complete in 168 hours. In acid media the heterocyclic ring proved more stable; I in hydrochloric acid-acetic acid at the boiling point for one hour was recovered essentially unchanged.

The presence of an alkyl substituent on either nitrogen atom in positions 2 or 4 greatly increased lability of the heterocyclic ring to hydrolytic cleavage. The 2-methyl derivatives (XIV) underwent ring fission upon recrystallization from hot

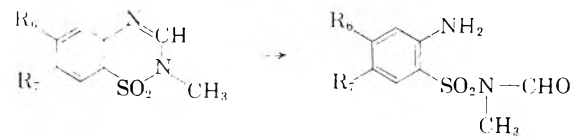
(14) F. F. Blicke and C. J. Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).

(15) J. E. Baer, L. Leidy, A. V. Brooks, and K. H. Beyer, *J. Pharmacol. Exp. Therap.*, **125**, 295 (1959).

aqueous ethanol. Two structures, XV and XVa, are possible for these products. Comparative ultraviolet spectral data (Table VII) indicate that the product (Table VII, No. 12) isolated from XIVa has structure XV, whereas the product (Table VII, No. 10) from XIVb is probably XVa as its spectrum resembles that of the 2,4-disulfamyl-*N*-acylanilines. The 4-substituted derivatives, X, underwent analogous cleavage. Mild treatment of the allyl compound (X. R_4=allyl) with aqueous alkali yielded XVI. The formation of XVI rather than XVIa is supported as follows. The ultraviolet absorption spectra (Table VII) of XVI differ from those of the disulfamyl-*N*-acylanilines (Table VII) by the presence of a distinct band of low intensity in the 300–325 mμ region. XVI (R_4=allyl) titrates as a dibasic acid, pK'_a 2.9, 10.1, consistent with the presence of the strongly acidic —SO_2NHCHO group. Acid titration of an alkaline solution of both the 4-methyl and 4-allyl compounds (X. R_4=CH_3 and allyl) reveals two acidic dissociations for each compound, pK'_a 2.8, 10.0 and 3.0, 10.2 respectively, consistent with ring opening to give XVI.

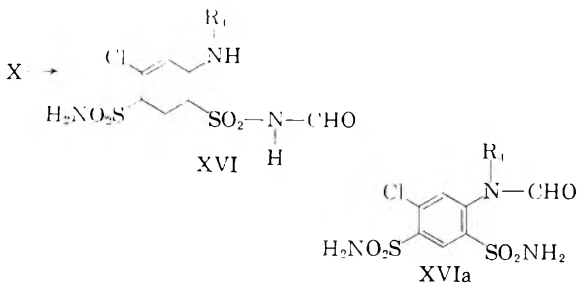


XVa



XIV a. R_6=R_7=H
XIV b. R_6=Cl, R_7=SO_2NHCH_3

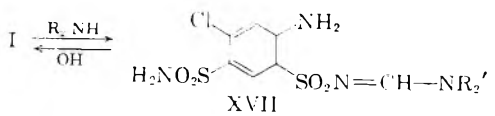
XV



XVI

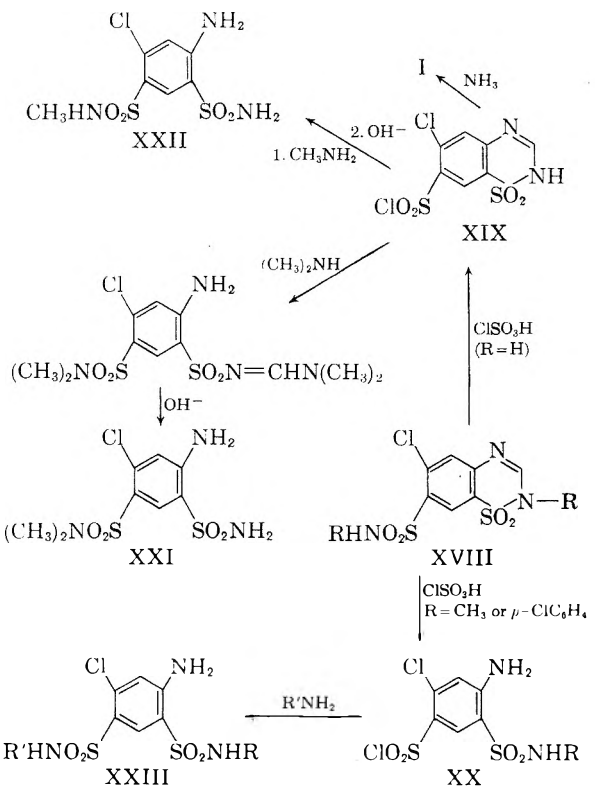
XVIa

On reaction with anhydrous dimethylamine or piperidine, I underwent ring opening to give the substituted formamidine derivative, XVII (R'$_2$N=$(CH_3)_2N$ or $C_5H_{10}N$). Primary amines gave only mixtures of products that were not further characterized and no ring opening occurred with anhydrous liquid ammonia. The products, XVII, are stable to boiling water but reform the benzothiadiazine with loss of the secondary amine upon mild treatment with aqueous alkali.



XVII

The well-known conversion of a sulfamyl group to the sulfonyl chloride by the action of chlorosulfonic acid has proved useful in the benzothiadiazine-1,1-dioxide series. In this manner, the 7-sulfamyl group was converted to the sulfonyl chloride without attack upon the sulfamyl group that is a part of the thiadiazine ring. However, the nature of the final sulfonyl chloride that was obtained after treatment of the chlorosulfonic acid reaction mixture with ice and water varied with the substituent on the nitrogen in the 2 position. When this position was unsubstituted (XVIII. R=H), the heterocyclic ring remained intact and the sulfonyl chloride, XIX, was obtained (96%). As pointed out previously, a substituent in the 2 position labilizes the ring toward hydrolytic cleavage. Where R = CH_3 or *p*-ClC_6H_4, the product of the chlorosulfonic acid reaction was the corresponding 2-substituted-sulfamyl-5-chloroaniline-4-sulfonyl chloride XX (60%) resulting from such ring opening. The sulfonyl chlorides, XIX and XX, reacted with ammonia or various amines, as expected from the properties discussed above, and provided satisfactory routes to several derivatives of 2,4-disulfamylaniline (XXI, XXII, XXIII) variously substituted in the sulfamyl groups as shown in the following series of reactions. Acylation and cyclization of these compounds led to further examples of the benzothiadiazine-1,1-dioxide series.



XXII

XIX

XXI

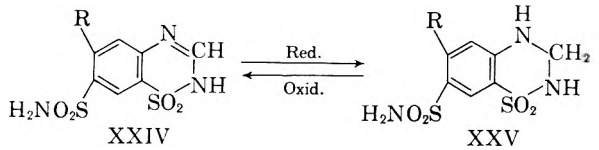
XVIII

XXIII

XX

The interconversion of benzothiadiazine-1,1-dioxides and dihydrobenzothiadiazine-1,1-dioxides was accomplished with representatives of each series. Catalytic hydrogenation of XXIV (R=Cl)

using ruthenium on charcoal catalyst gave the dihydro compound XXV (R=Cl) in 83% yield. Sodium borohydride reduction of XXIV (R=Cl) to XXV (R=Cl) has been reported.[12] Conversely, permanganate oxidation of XXV (R=Cl, CH_3) yielded the corresponding dehydrogenated compound XXIV (R=Cl, CH_3) in good yield.



XXIV XXV

The structure of the thiadiazine ring of 1,2,4-benzothiadiazine-1,1-dioxides has not been studied in detail or extensively. It is undoubtedly a tautomeric system (A⇌B). The double bond may occupy either the 2,3 or the 3,4 positions and the anion would be expected to be a resonance hybrid. A comparison (Table VI) of the ultraviolet spectra of the parent compound, 1,2,4-benzothiadiazine-1,1-dioxide and several of its derivatives, including I and related compounds having the nitrogen atoms in positions 2 and 4 unsubstituted, with the spectra of derivatives where the double bond is fixed in the 2,3 or 3,4 locations by appropriate substitution at positions 2 or 4 permits some tentative conclusions. These comparative data indicate that in ethanol solutions the benzothiadiazine-1,1-dioxides (A⇌B) that are unsubstituted on either nitrogen exist predominantly in the form B with the double bond at the 2,3 position. In aqueous alkali, however, there is a shift toward the spectra of form A in ethanol where the double bond is at the 3,4 position.

A B

In ethanol solution, the spectra of compounds having the unsubstituted nitrogen bear a close resemblance to the spectra of those compounds which have the double bond fixed in the 2,3 position. They show absorption maxima of similar intensity in the region 265–280 mμ. The presence of chlorine (but not of trifluoromethyl) in the benzenoid ring at position 6 produces a strong band at 220–230 mμ. Most of the compounds have a detectable shoulder at 290–310 mμ. In aqueous sodium hydroxide solution, the spectra of the 2 and 4 unsubstituted compounds show a shift of the 265–280 mμ band to higher wave lengths by 8–17 mμ; the 220–230 mμ band, if present, is unaffected and the shoulder at 290–310 mμ becomes more pronounced. In the 2-methyl derivatives which have the double bond fixed at the 3,4-position, a distinct band now appears at 295–310 mμ where only a shoulder exists in the other compounds.

The spectra of the dihydro derivatives (V) have three distinct maxima of decreasing intensity at 224–226 mμ, 264–273 mμ and 302–325 mμ (Table VI) comparable to the spectra of the aniline-2,4-disulfonamides (Table VII). The 3-*p*-nitrophenyl and 3-oxo derivatives present exceptions. In the spectra of the *p*-nitrophenyl compound (Table VI, No. 19), the maximum at 307–313 mμ appears only as a shoulder. The spectra of the 3-oxo derivatives, *e.g.*, 6-chloro-7-sulfamyl-3-oxo-dihydrobenzothiadiazine-1,1-dioxide (Table VI, No. 21), resemble closely the disulfamyl-*N*-acylanilines (Table VII). For spectral comparison, two anils of 2,4-bis(dimethylsulfamyl)-5-chloroaniline were prepared from *p*-nitrobenzaldehyde and phenylacetaldehyde. These compounds cannot undergo cyclization to the dihydrobenzothiadiazine system and exhibit spectra markedly different from the analogous cyclic structures (Table VI), thus lending further support to the heterocyclic structure for V.

A tabular summary of the comparative activity of many of these compounds on electrolyte excretion in the dog following oral and intravenous administration has been presented previously.[4,16] A sulfamyl group is essential for any degree of activity; benzothiadiazine-1,1-dioxides without this group are inactive. High activity is obtained when this group is in the 7 position—that is, when it is in the *meta* relation to the sulfamyl that is part of the thiadiazine ring. For maximum activity an augmenting group must also be present in the benzene ring. This is most striking when such a group is in the 6 position adjacent to the sulfamyl group. Chlorine, bromine, trifluoromethyl, and nitro groups in this position yield highly active compounds. Methyl, fluorine, methoxy, and amino are less effective as augmenting substituents. Conversion of chlorothiazide (I) to the dihydro derivative (V. R_6=Cl, R_3=R_5=H) results in a ten-fold increase in potency. Oxygen at the 3-position depresses activity. In both the dihydro and 3-oxodihydro series the influence of substituents parallels that observed in the benzothiadiazine-1,1-dioxides.

Compounds with an alkyl group in the 3 position retain a high order of activity but the 3-phenyl derivatives are less effective. Substitution on either nitrogen atom in positions 2 and 4 gives compounds with lower activities. The order of activity of compounds substituted (alkyl or acyl) on the 7-sulfamyl group is consistent with the assumption that the substituent is removed metabolically. That metabolic removal of such groups from substituted sulfonamides can occur has been clearly demonstrated in the acetazolamide series.[17] Replacement of the

(16) We are indebted to Drs. John E. Baer and Karl H. Beyer and their associates for the biological data that are summarized here.

(17) T. H. Maren, *J. Pharmacol. Exp. Therap.*, 117, 385 (1956).

7-sulfamyl group by a methylsulfonyl group produces little change in many of the chemical and physical properties and some of the biological properties of the original sulfonamide. However, the methylsulfonyl analogs are exceedingly weak carbonic anhydrase inhibitors and do not promote electrolyte excretion in the dog.

EXPERIMENTAL[18,19]

The following procedure is illustrative of the formic acid ring closure of aniline-2,4-disulfonamides to benzothiadiazine-1,1-dioxides listed in Table I and not described elsewhere in the Experimental. The yield is typical.

6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 3, Table I). A solution of 5-chloro-2,4-disulfamylaniline (5.7 g., 0.02 mole) in 75 ml. of 98–100% formic acid was heated under reflux for 24 hr. After cooling, water (100 ml.) was added and the product collected, washed with water, and recrystallized. Colorless needles were obtained in 90% yield.

Benzo[1,2-e,5,4-e']bis[1,2,4-thiadiazine-1,1-dioxide]. A solution of 5-amino-2,4-disulfamylaniline (1.3 g., 0.005 mole) in 98–100% formic acid (20 ml.) was heated under reflux for 2.5 hr. and cooled. Recrystallization of the precipitate, 1.14 g. (82%), from dimethylformamide-water afforded pale yellow needles, m.p. >500°.

Anal. Calcd. for $C_8H_6N_4O_4S_2$: C, 33.56; H, 2.11; N, 19.57. Found: C, 34.03; H, 2.37; N, 19.55.

2-Methyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 37, Table I). Following the procedure of Freeman and Wagner,[8] a mixture of 2 g. of 2-methylsulfamylaniline and 5 ml. of ethyl orthoformate was heated in an open flask at 125–135° for 30 min., concentrated to dryness *in vacuo* and the residue recrystallized from ethanol; yield, 1.6 g. (76%) of colorless needles.

Recrystallization of *2-methyl-1,2,4-benzothiadiazine-1,1-dioxide* from hot (50%) aqueous ethanol gave *2-(N-formyl-N-methylsulfamyl)aniline;* colorless needles, m.p. 116–118°.

Anal. Calcd. for $C_8H_{10}N_2O_3S$: C, 44.86; H, 4.71; N, 13.08. Found: C, 45.04; H, 4.57; N, 13.14.

Ring closure of 5-chloro-2,4-dimethylsulfamylaniline was carried out in like manner to give *6-chloro-2-methyl-7-methylsulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* (No. 24, Table I). When this compound was recrystallized from hot aqueous ethanol, 5-chloro-2,4-di(methylsulfamyl)-*N*-formylaniline was obtained; colorless plates, m.p. 192–195°.

Anal. Calcd. for $C_9H_{12}ClN_3O_5S_2$: C, 31.63; H, 3.54; N, 12.29. Found: C, 31.99; H, 3.68; N, 12.29.

6-Chloro-7-ethoxymethylenesulfamyl-1,2,4-benzothiadiazine-1,1-dioxide. A suspension of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (15 g., 0.05 mole) in 100 ml. of ethyl orthoformate was heated under reflux with stirring for 24 hr. Upon cooling to room temperature, the product was collected and washed with alcohol; yield, 15.4 g. (87%), m.p. 207–210° with softening at 195°. A sample recrystallized from acetonitrile-ether melted at 195–196° with resolidification and remelting at 210–211°.

Anal. Calcd. for $C_{10}H_{10}ClN_3O_5S_2$: C, 34.14; H, 2.87; N, 11.94; OC_2H_5, 12.81. Found: C, 34.35; H, 2.95; N, 11.96; OC_2H_5, 12.70.

6-Chloro-7-ethoxymethylenesulfamyl-2-methyl-1,2,4-benzothiadiazine-1,1-dioxide was prepared according to the above procedure from 6-chloro-2-methyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide and ethyl orthoformate, m.p. 155–157°.

Anal. Calcd. for $C_{11}H_{12}ClN_3O_5S_2$: C, 36.11; H, 3.31; N, 11.49; OC_2H_5, 12.32. Found: C, 35.48; H, 3.68; N, 11.35; OC_2H_5, 12.94.

6-Chloro-7-ethoxymethylenesulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide was prepared in like manner from 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide and ethyl orthoformate, m.p. 222–230° eff.

Anal. Calcd. for $C_{10}H_{12}ClN_3O_5S_2$: C, 34.94; H, 3.42; N, 11.88. Found: C, 34.67; H, 3.60; N, 11.82.

7-Aminomethylenesulfamyl-6-chloro-1,2,4-benzothiadiazine-1,1-dioxide. Ammonia was passed into a suspension of 6-chloro-7-ethoxymethylenesulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (6.5 g., 0.0185 mole) in 50 ml. of anhydrous alcohol for 30 min. Complete solution occurred within a few minutes with subsequent separation of product; yield, 3.6 g. (60%), m.p. 308–310°. Recrystallization from alcohol raised the melting point to 309–311°.

Anal. Calcd. for $C_8H_7ClN_4O_4S_2$: C, 29.77; H, 2.19; N, 17.36. Found: C, 29.89; H, 2.52; N, 17.04.

7-Aminomethylenesulfamyl-6-chloro-2-methyl-1,2,4-benzothiadiazine-1,1-dioxide was prepared from 6-chloro-7-ethoxymethylenesulfamyl-2-methyl-1,2,4-benzothiadiazine-1,1-dioxide according to the above procedure, m.p. 233–234°.

6-Chloro-3-methyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 11, Table I). 5-Chloroacetanilide-2,4-disulfonyl chloride (4.4 g.) was added portionwise to 50 ml. of 10% alcoholic ammonia. After the initial reaction had subsided, the solution was evaporated to dryness on the steam bath and the residue recrystallized from aqueous ethanol.

In like manner, using concd. ammonium hydroxide in place of alcoholic ammonia, *6-chloro-3-n-propyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* (No. 12, Table I) and *3-n-amyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* (No. 13, Table I) were prepared from the corresponding *N*-acylanilinedisulfonyl chlorides.

3-Chloromethyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 14, Table I). A solution of 5-chloro-2,4-disulfamyl-*N*-(chloroacetyl)aniline (7.2 g.) in dimethylformamide (30 ml.) was heated on the steam bath with stirring with 2.3 g. of anhydrous potassium fluoride for 1.5 hr., cooled, and diluted with water; yield, 5.5 g. (80%).

6-Chloro-3-phenyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 15, Table I). *Method A.* 5-Chloroaniline-2,4-disulfonyl chloride (8.4 g.) was dissolved in 13 ml. of benzoyl chloride by warming briefly on the steam bath and allowed to stand at room temperature overnight. 5-Chloro-*N*-benzoylaniline-2,4-disulfonyl chloride (10.9 g.) was collected, washed with benzene, added to 50 ml. of concd. ammonium hydroxide, and heated on the steam bath for 2 hr. Recrystallization of the precipitate from dimethylformamide-water gave 2.7 g. of 6-chloro-3-phenyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide as colorless needles.

Acidification of the ammoniacal filtrate and recrystallization of the precipitate from aqueous ethanol gave 5-chloro-2,4-disulfamyl-*N*-benzoylaniline.[10]

Method B. A solution of 1 g. of 5-chloro-2,4-disulfamyl-*N*-benzoylaniline[10] in 25 ml. of concd. ammonium hydroxide was allowed to stand at room temperature for 48 hr. and concentrated to dryness *in vacuo*. The residue was washed with water and afforded 84% yield of product identical with that prepared by Method A.

In like manner, ring closure of 5-chloro-2,4-disulfamyl-*N*-*p*-chlorobenzoylaniline gave *3-(p-chlorophenyl)-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* (No. 17, Table I) in 85% yield.

3-(o-Chlorophenyl)-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 16, Table I) was prepared in 56% yield from 5-chloro-2,4-disulfamyl-*N*-*o*-chlorobenzoylaniline according to the procedure described for compound No. 14.

General procedure for 3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxides (Tables II and III). *Method A. Base catalyzed ring closure.* A solution of 0.02 mole of the orthanilamide compound and 0.025 mole of 37% formaldehyde in 50 ml. of 90% ethanol-water containing 300 mg. of sodium hy-

(18) Melting points are uncorrected. Data shown in the tables are not reproduced in the Experimental.

(19) We are indebted to Mr. K. B. Streeter and Mr. Y. C. Lee and their associates for analytical and spectral data and pK'_a determinations.

droxide was heated on the steam bath for 2 hr. and acidified. This mixture was cooled and the product collected, washed with water, dried, and recrystallized; yield, 80%.

Method B. Acid catalyzed ring closure. A suspension of 0.02 mole of the orthanilamide compound and 0.04 mole of paraformaldehyde in 60 ml. of ethanol and 60 ml. of 6.0*N* hydrochloric acid was heated on the steam bath. Complete solution occurred with subsequent separation of product. Reaction was complete in 1 hr.; average yield, 85–90%.

Compounds listed in Table IV were prepared by ring closure of 5-chloro-2,4-disulfamylaniline with the appropriate aldehyde. Acid cyclization was employed for compounds No. 1, 2, 9 and base cyclization for the remainder.

6-Chloro-7-sulfamyl-3-trichloromethyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (No. 3, Table IV). A solution of 11.4 g. (0.04 mole) of 5-chloro-2,4-disulfamylaniline in 20 ml. of dimethylformamide and 17.6 g. (0.12 mole) of chloral was heated on the steam bath for 24 hr. Water (100 ml.) was added and the semisolid reprecipitated from dilute ammonium hydroxide; yield, 14.5 g. (87.5%) of colorless needles, m.p. 278–279°.

When this reaction was carried out in 60 ml. of dimethylformamide in the presence of 4.6 g. (0.08 mole) of anhydrous potassium fluoride for 3 hr. on the steam bath, *6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* was obtained in 76% yield; m.p. 330°, mixed melting point with chlorothiazide was not depressed, $\lambda_{max}^{C_2H_5OH}$ 225 and 279–280 mμ, ε 29,592 and 11,465.

6-Chloro-7-sulfamyl-3,3-pentamethylene-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (No. 6, Table IV). A solution of 5.7 g. (0.02 mole) of 5-chloro-2,4-disulfamylaniline and 5.9 g. (0.06 mole) of cyclohexanone in 30 ml. of dimethylformamide was heated with stirring with 2.3 g. (0.04 mole) of anhydrous potassium fluoride on the steam bath for 2 hr. and diluted with 100 ml. of water; yield, 4.7 g. (57%), m.p. 259–261°.

6-Chloro-3-oxo-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (No. 1, Table V). The following procedure is illustrative of the method[7] employed for preparation of compounds in Table V. Compounds were recrystallized from aqueous ethanol and obtained in yields of 35–73%.

An intimate mixture of 5-chloro-2,4-disulfamylaniline (8.4 g., 0.03 mole) and urea (3.5 g., 0.06 mole) was heated in an oil bath at 200° for 45–60 min. The mixture liquified with evolution of ammonia and solidified after 30 min. The solid was cooled, dissolved in water, filtered, and acidified. Recrystallization from aqueous alcohol afforded colorless plates.

6-Chloro-4-methyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 18, Table I). *Method A. Methylation of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide.* A filtered solution of 5.9 g. (0.02 mole) of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 25 ml. of water containing 0.88 g. (0.022 mole) of sodium hydroxide was shaken with 3.0 g. (0.024 mole) of methyl sulfate in a stoppered flask at room temperature for 10 min. The precipitate was collected, washed with water, alcohol, and dried; yield, 2.8 g. (45%), m.p. 308°. Admixture of analytical specimen (m.p. 325–326°) and product obtained by Method B showed no depression in melting point.

A sample when heated on the steam bath with 10% sodium hydroxide for 2.5 hr. gave 5-chloro-2,4-disulfamyl-*N*-methylaniline[10]; no depression in mixed melting point.

Method B. A solution of 5-chloro-2,4-disulfamyl-*N*-methylaniline (5 g.) in 98–100% formic acid (70 ml.) was heated under reflux for 24 hr. and cooled to room temperature; yield, 4.7 g. (90.5%), m.p. 325–327°.

4-Allyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 19, Table I). 6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (32.2 g., 0.11 mole) was added portionwise with stirring to a cold solution of 2.5 g. (0.11 mole) of sodium dissolved in 200 ml. of ethanol. Allyl bromide (16.3 g., 0.135 mole) was added and the solution heated on the steam bath for 24 hr. with the intermittent addition of 4.0 g. of allyl bromide after 6 hr. of heating. The mixture was cooled, filtered, and the precipitate washed with water, alcohol, and dried; yield, 27.2 g., m.p. 244–246°, cloudy melt. Repeated extraction of this material with acetone (1 l. total) at room temperature afforded 11.9 g. of starting material (insoluble fraction) and 12.5 g. of 4-allyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (soluble fraction), m.p. 243–245°. Final purification was accomplished by recrystallization from aqueous ethanol.

A sample (1.0 g.) of 4-allyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 20 ml. of 10% aqueous sodium hydroxide was heated on the steam bath for 2 hr., cooled, and acidified. Recrystallization of the precipitate from water gave *5-chloro-2,4-disulfamyl-N-allylaniline*; yield, 0.5 g. of colorless needles, m.p. 181–183°; negative test[20] for diazotizable amine.

Anal. Calcd. for $C_9H_{12}ClN_3O_4S_2$: C, 33.18; H, 3.71; N, 12.90. Found: C, 32.92; H, 3.71; N, 12.90.

5-Chloro-2-formylsulfamyl-4-sulfamyl-N-allylaniline. A solution of 1.0 g. of 4-allyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 70 ml. of water and 9 ml. of 1.0*N* sodium hydroxide was allowed to stand at room temperature for 30 min., cooled in an ice bath, and acidified with dilute hydrochloric acid. The precipitate was collected, washed with water, and dried in a vacuum desiccator over sulfuric acid. Recrystallization from chloroform-acetone yielded 0.4 g. of colorless needles, m.p. 142.5–143.5°, with effervescence; readily soluble in bicarbonate solution.

Anal. Calcd. for $C_{10}H_{12}ClN_3O_5S_2$: C, 33.94; H, 3.42; N, 11.88. Found: C, 33.72; H, 3.52; N, 11.40.

Recrystallization of a sample from water yielded a bicarbonate insoluble product which gave no depression in melting point upon admixture with *5-chloro-2,4-disulfamyl-N-allylaniline.*

3,4-Dimethyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (No. 20, Table I). A solution of 3,4-dimethyl-1,2,4-benzothiadiazine-1,1-dioxide[5] (11.4 g., 0.054 mole) in 35 ml. of chlorosulfonic acid was heated in an oil bath at 150–160° for 2.5 hr., cooled, and poured onto ice. The precipitate was collected and added to 50 ml. of concd. ammonium hydroxide. After brief standing (30–60 min.), the product was collected and recrystallized from dimethylformamide-water.

Reprecipitation of a sample from dilute sodium hydroxide gave 2-acetylsulfamyl-4-sulfamyl-*N*-methylaniline, colorless needles from acetone-petroleum ether, m.p. 208–210°.

Anal. Calcd. for $C_9H_{13}N_3O_5S_2$: C, 35.17; H, 4.26; N, 13.67. Found: C, 35.27; H, 4.27; N, 13.68.

7-Acetylsulfamyl-6-chloro-1,2,4-benzothiadiazine-1,1-dioxide. Acetic anhydride (25 ml.) was added to a suspension of 8.9 g. (0.03 mole) of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 75 ml. of pyridine at room temperature. Complete solution occurred within 20 min. and was followed by gradual separation of colorless needles. After standing at room temperature overnight, the product was collected, washed with alcohol, and dried; yield, 7.7 g., m.p. 314°. Recrystallization from either acetone-alcohol or alcohol-water gave colorless needles, soluble in bicarbonate solution; melting point, dependent on rate of heating, 299° (rapid heating), 289° (slow heating); pK'_a 3.7, 7.2.[21]

Anal. Calcd. for $C_9H_8ClN_3O_5S_2$: C, 32.00; H, 2.39; N, 12.44. Found: C, 32.20; H, 2.56; N, 12.36.

A solution of 7-acetylsulfamyl-6-chloro-1,2,4-benzothiadiazine-1,1-dioxide (2 g.) in 10 ml. of 10% aqueous sodium hydroxide when heated on the steam bath for 15 min., cooled, and acidified gave *4-acetylsulfamyl-5-chloro-2-sulfamylaniline;* colorless plates from acetone-alcohol, m.p. 221°; positive test for diazotizable amine.

Anal. Calcd. for $C_8H_{10}ClN_3O_5S_2$: C, 29.31; H, 3.08; N, 12.82. Found: C, 29.54; H, 3.20; N, 12.73.

(20) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537 (1939).

(21) pK'_a values were determined according to the method described by T. V. Parke and W. W. Davis, *Anal. Chem.* **26**, 642 (1954).

Cyclization of 4-acetylsulfamyl-5-chloro-2-sulfamylaniline with formic acid in the usual manner gave 7-acetylsulfamyl-6-chloro-1,2,4-benzothiadiazine-1,1-dioxide; no depression in mixed melting point.

7-Butyrylsulfamyl-6-chloro-1,2,4-benzothiadiazine-1,1-dioxide. Butyric anhydride (25 ml.) was added to a suspension of 8.9 g. (0.03 mole) of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 75 ml. of pyridine at room temperature. Complete solution occurred in 4 hr. After standing at room temperature overnight, the solution was poured into 200 ml. of ice water and acidified with concd. hydrochloric acid. The solid was collected, washed with water, and recrystallized from alcohol-water; yield, 8.1 g. (74%), colorless needles, soluble in bicarbonate solution, m.p. 286°.

Anal. Calcd. for $C_{11}H_{12}ClN_3O_5S_2$: C, 36.11; H, 3.31; N, 11.49. Found: C, 36.31; H, 3.38; N, 11.47.

5-Chloro-2-dimethylaminomethylenesulfamyl-4-sulfamylaniline. 6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (10 g., 0.034 mole) was added to 50 ml. of anhydrous dimethylamine and allowed to stand at room temperature until all the amine had evaporated (2 hr.). The residue was dissolved in 50 ml. of 50% aqueous ethanol and then acidified with dilute hydrochloric acid. Recrystallization of the precipitate from ethanol-water (9:1) gave 5.8 g. (50%) of product, m.p. 208–210°.

Anal. Calcd. for $C_9H_{13}ClN_4O_4S_2$: C, 31.71; H, 3.84; N, 16.44. Found: C, 32.10; H, 3.86; N, 16.35.

5-Chloro-2-piperidinomethylenesulfamyl-4-sulfamylaniline. A mixture of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (10 g., 0.034 mole) and piperidine (13.6 g., 0.16 mole) was heated on the steam bath for 1 hr., diluted with water, and acidified with dilute hydrochloric acid. The resinous product was dissolved in dilute sodium hydroxide and the solution washed with ether and then acidified. The initial precipitate (4.3 g.) was starting material. Upon prolonged standing, the filtrate yielded 3.8 g. (30%) of product, m.p. 208–210°, which was purified by recrystallization from aqueous alcohol, m.p. 210–212°.

Anal. Calcd. for $C_{12}H_{17}ClN_4O_4S_2$: C, 37.84; H, 4.50; N, 14.71. Found: C, 37.96; H, 4.58; N, 14.69.

6-Chloro-1,2,4-benzothiadiazine-1,1-dioxide-7-sulfonyl chloride. 6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (29.6 g., 0.1 mole) was added in portions to chlorosulfonic acid (150 ml.) and heated on the steam bath for 2 hr. Upon cooling to room temperature, the reaction mixture was poured onto crushed ice. The precipitate was collected on the filter, washed by suspension in 2 l. of ice water, filtered, and air-dried; yield, 30.3 g. (96%), m.p. 250–253°. A sample (10 g.) purified by reprecipitation from acetone (200 ml.) with hexane melted at 259–261°.

Anal. Calcd. for $C_7H_4Cl_2N_2O_4S_2$: C, 26.67; H, 1.28; N, 8.89. Found: C, 26.98; H, 1.43; N, 8.83.

5-Chloro-2-methylsulfamylaniline-4-sulfonyl chloride. 6-Chloro-2-methyl-7-methylsulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (68.3 g., 0.21 mole) was added in portions to 200 ml. of chlorosulfonic acid and heated on the steam bath for 5 hr. Upon cooling, the solution was poured onto crushed ice and the precipitate collected on the filter, washed with water, and dried. Recrystallization from acetone-benzene gave 60 g. (90%) of product, m.p. 150°, with effervescence. Repeated recrystallization from acetone-benzene raised the m.p. to 158°, with effervescence.

Anal. Calcd. for $C_7H_8Cl_2N_2O_4S_2$: C, 26.34; H, 2.53; N, 8.78. Found: C, 26.99; H, 2.64; N, 8.72.

5-Chloro-2-methylsulfamyl-4-sulfamylaniline. 5-Chloro-2-methylsulfamylaniline-4-sulfonyl chloride (43.2 g., 0.135 mole) was added portionwise to 250 ml. of concd. ammonium hydroxide and heated on the steam bath for 1 hr. Upon concentration *in vacuo*, the product was collected and recrystallized from water; yield, 17.9 g. (45%). The compound was obtained in two crystalline modifications; m.p.'s 168–170° and 188–190°. A mixture of both melted at 188–190°.

Anal. Calcd. for $C_7H_{10}ClN_3O_4S_2$: C, 28.05; H, 3.36; N, 14.02. Found: C, 28.19; H, 3.41; N, 13.95.

5-Chloro-4-methylsulfamyl-2-sulfamylaniline. 6-Chloro-1,2,4-benzothiadiazine-1,1-dioxide-7-sulfonyl chloride (10 g., 0.031 mole) was added to 30 ml. of anhydrous methylamine and allowed to stand at room temperature until excess methylamine had evaporated. The residue was dissolved in 200 ml. of 5% sodium hydroxide, heated on the steam bath for 2 hr. and acidified. Recrystallization of the precipitate from water gave 6.4 g. of product, m.p. 181–183°.

Anal. Calcd. for $C_7H_{10}ClN_3O_4S_2$: C, 28.05; H, 3.36; N, 14.02. Found: C, 28.22; H, 3.54; N, 14.05.

5-Chloro-2-dimethylaminomethylenesulfamyl-4-dimethylsulfamylaniline. 6-Chloro-1,2,4-benzothiadiazine-1,1-dioxide-7-sulfonyl chloride (30 g., 0.095 mole) was added to 150 ml. of anhydrous dimethylamine and allowed to stand at room temperature until excess amine had evaporated. Recrystallization of the residue from alcohol yielded 22.8 g. (64%) of product, m.p. 195–197°.

Anal. Calcd. for $C_{11}H_{17}ClN_4O_4S_2$: C, 35.81; H, 4.65; N, 15.19. Found: C, 35.81; H, 4.72; N, 15.10.

5-Chloro-4-dimethylsulfamyl-2-sulfamylaniline. A suspension of 5-chloro-2-dimethylaminomethylenesulfamyl-4-dimethylsulfamylaniline (6.7 g., 0.018 mole) in 20 ml. of 10% sodium hydroxide was heated on the steam bath for 1 hr., cooled, and acidified with dilute hydrochloric acid. Recrystallization of the precipitate from aqueous alcohol gave 4.0 g. (71%) of product, m.p. 158–160°.

Anal. Calcd. for $C_8H_{12}ClN_3O_4S_2$: C, 30.62; H, 3.86; N, 13.39. Found: C, 30.75; H, 3.93; N, 13.41.

Catalytic hydrogenation[22] *of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* (3.0 g.) was performed in methanol (100 ml.) in the presence of 5% ruthenium on charcoal catalyst (1.0 g.) at room temperature and at an initial hydrogen pressure of 39 lb./sq. in. Upon completion of reduction (10 hr.), the mixture was heated to boiling, filtered, and concentrated. An 83% yield of product was obtained which showed no depression in melting point upon admixture with a sample of 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide prepared from 5-chloro-2,4-disulfamylaniline and formaldehyde.

Oxidation of 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide to 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide. Potassium permanganate (3.75 g.) was added portionwise, with stirring, over 10 min. to a solution of 8.9 g. (0.03 mole) of 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide in 150 ml. of water and 10 ml. of 20% sodium hydroxide. The solution was stirred at room temperature for 15 min. and warmed on the steam bath for 5 min. Excess permanganate was destroyed by addition of 2–3 ml. of ethanol. Upon filtration, acidification of the filtrate afforded 7.4 g. (84%) of product, m.p. 337°; mixed melting point with 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine was not depressed.

In like manner oxidation of *6-methyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide* gave *6-methyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide* in comparable yield, m.p. 345°; no depression in mixed melting point with material prepared by formic acid ring closure of 5-methyl-2,4-disulfamylaniline.

5-Chloro-2,4-bis(dimethylsulfamyl)-N-(2-phenylethylidene)-aniline. A mixture of 3.4 g. (0.01 mole) of 5-chloro-2,4-bis-(dimethylsulfamyl)aniline and 10 g. (0.04 mole) of 50% phenylacetaldehyde in alcohol was heated at 150° for 30 min. in an open flask. Complete solution occurred as alcohol distilled from the reaction mixture. Upon cooling, the residue was triturated with acetonitrile and the solid collected on the filter; yield, 2.4 g. (55%), m.p. 193–196°. Recrystallization from acetonitrile raised the melting point to 203–205°, $\lambda_{max}^{C_2H_5OH}$ 226–228 and 337–340 mμ, ε 27,351 and 36,106.

(22) We are indebted to Dr. W. H. Jones for this experiment.

Anal. Calcd. for $C_{18}H_{22}ClN_3O_4S_2$: C, 48.69; H, 5.00; N, 9.46. Found: C, 48.95; H, 4.98; N, 9.70.

5-Chloro-2,4-bis(dimethylsulfamyl)-N-(p-nitrobenzylidene)-aniline. A mixture of 3.4 g. of 5-chloro-2,4-bis(dimethylsulfamyl)aniline, 3.0 g. of *p*-nitrobenzaldehyde, and 60 ml. of toluene was heated under reflux with a water separator for 20 hr. Upon cooling, the crystalline solid was collected, triturated with 200 ml. of boiling alcohol, and recrystallized from acetonitrile; yield, 3.6 g. (76%), m.p. 221–223°, $\lambda_{max}^{C_2H_5OH}$ 276–281 mμ, ε 25,270.

Anal. Calcd. for $C_{17}H_{19}ClN_4O_6S_2$: C, 42.99; H, 4.03; N, 11.80. Found: C, 43.03; H, 4.26; N, 11.72.

WEST POINT, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ANDHRA UNIVERSITY]

New Alkaloids from *Tiliacora racemosa* (Colebr.). III.[1,2a] Constitution[2b] of Tiliacorine and Tiliarine

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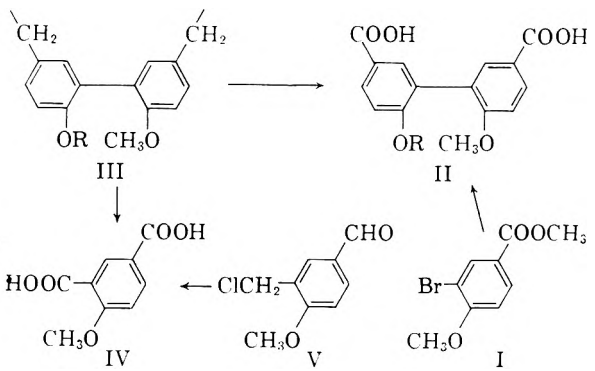
Permanganate oxidation of *O*-methyltiliacorine and *O,N*-dimethyltiliarine gives rise to 2,2′-dimethoxydiphenyl-5,5′-dicarboxylic acid. Tiliacorine and tiliarine yield, on the other hand, 4-methoxyisophthalic acid and no diphenyldicarboxylic acid. It is, therefore, felt that the free hydroxyl is present in the 2-position of the diphenyl system. This was confirmed by the oxidation of *O*-ethyl ethers of the two alkaloids, which yielded 2′-ethoxy-2-methoxy-diphenyl-5,5′-dicarboxylic acid. On this basis, a structure is suggested for tiliacorine which is derived from two coclaurine units and contains a dibenzo-*p*-dioxin system as in menisarine but with a 2′-hydroxy-2-methoxydiphenyl system in place of 2-methoxydiphenyl oxide group. Tiliacorine and tiliarine are thus the only two bisbenzyl isoquinoline alkaloids isolated from nature with 11,11′-diphenyl link.

In parts I[1] and II[2] of this series, tiliacorine and tiliarine were assigned the molecular formulas $C_{32}H_{23}O_3(OH)(2\text{-}OCH_3)(2\text{-}NCH_3)$ and $C_{32}H_{23}O_3(OH)(2\text{-}OCH_3)(1\text{-}NCH_3, 1\text{-}NH)$ respectively. The hydroxyl is phenolic in character, and may be in a sterically hindered position as it resisted methylation with diazomethane. Both alkaloids exhibit a prominent blue color with sulfur-nitric acid reagent[3] indicating a dibenzo-*p*-dioxin system in the molecule. Furthermore, a study of their ultraviolet absorption spectra[2] suggested a close resemblance with trilobine or menisarine.

Confirmation of the above formulas was sought by a study of the permanganate oxidation of these two alkaloids and their *O*-methyl derivatives. *O*-Methyltiliacorine and *O,N*-dimethyltiliarine furnished the same carboxylic acid (m.p. 338–340°; dimethyl ester 171–173°) during oxidation with 2% permanganate at laboratory temperature. Analysis indicated a dicarboxylic acid with two methoxyls in it and it was identified as 2,2′-dimethoxydiphenyl-5,5′-dicarboxylic acid (II. R = CH_3) by direct comparison with a synthetic sample obtained by Ullmann's reaction with methyl-3-bromo-4-methoxybenzoate[4] (I).



The oxidation of these alkaloids to diphenyl-5-5′-dicarboxylic acid (II. R = CH_3) is a very significant feature. Diphenyldicarboxylic acids were previously isolated from cocculidine[5] from *Cocculus luarifolius D.C.*, lycorenine[6] from *Lycoris radiata* Herb., Sinomenine[7] from *Sinomenium acutum* and acetyl thebaol[8] after a series of degradative reactions involving Hofmann degradation. These diphenyldicarboxylic acids possess at least one carboxyl group in one of the *ortho* positions of the diphenyl system.

The isolation of the diphenylcarboxylic acid (II. R = CH_3) is thus very significant and indicates

(1) K. V. J. Rao and L. R. Row, *J. Sci. Ind. Research (India)* **16B**, 156 (1957).

(2) (a) K. V. J. Rao and L. R. Row, *J. Sci. Ind. Research (India)* **18B**, 247 (1959).

(2) (b) A recent publication on the same topic by Anjaneyulu *et. al.* (*Chem. & Ind.*, June 6, p. 702, 1959) has prompted us to publish this paper. The information included in this paper has been delayed in publication as the investigation formed part of the D.Sc. thesis of one of us (K. V. J.) which is under preparation.

(3) I. R. C. Bick and A. R. Todd, *J. Chem. Soc.*, 1606 (1950).

(4) G. W. K. Cavill, *J. Soc. Chem. Ind.* **64**, 212 (1945); M. M. Marcel Paty and Raymond Quelet, *Compt. Rend.* **217**, 229 (1943).

(5) S. Yunusov, *J. Gen. Chem. U.S.S.R.*, **20**, 1514 (1950).

(6) H. Kondo and T. Ikeda, *Ber.*, **73**, 867 (1940).

(7) K. Goto, and H. Shishido, *Bull. Chem. Soc., Japan* **16**, 170 (1941).

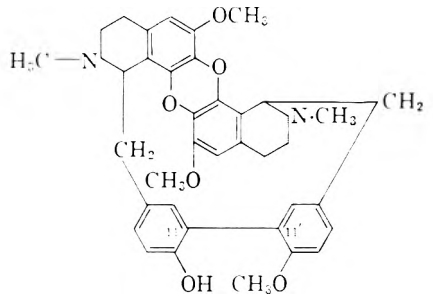
(8) K. W. Bentley and R. Robinson, *Experientia.* **6**, 353 (1950); K. W. Bentley and R. Robinson, *J. Chem. Soc.*, 947 (1952).

the 2,2′-dimethoxydiphenyl system (III. R = CH_3) in *O*-methyltiliacorine and *O,N*-dimethyltiliarine, with a probable attachment of the basic half (which should, of course, contain a dibenzo-*p*-dioxin system) at 5,5′-positions through two methylene groups. The absence of a carboxyl group in the 2- or 3′-positions rules out any phenanthridine structure for them.

Direct oxidation of the two alkaloids with 2% permanganate furnished a dicarboxylic acid different from the diphenyl dicarboxylic acid (II. R = CH_3). It was identified as 4-methoxyisophthalic acid (IV) by direct comparison with a synthetic sample which was secured by permanganate oxidation of 2-chloromethyl-anisaldehyde (V).[9] Obviously, the diphenyl system in the unmethylated alkaloids was getting oxidized. Such an oxidation is possible if the free hydroxyl in both the alkaloids were present in the diphenyl half. Then, on this consideration, tiliacorine and tiliarine may contain the hydroxy diphenyl system (III. R = H).

The position of the hydroxyl in the diphenyl system was further confirmed by ethylation of the alkaloids followed by oxidation. The dicarboxylic acid from *O*-ethyltiliacorine as well as from *O*-ethyl-*N*-methyltiliarine, gave a dimethyl ester different from the dimethyl ester of the carboxylic acid (II. R = CH_3). This confirms the 2′-position of the phenolic hydroxyl in the diphenyl half of tiliacorine and tiliarine, and their *O*-ethyl derivatives should have been oxidized to 2-methoxy-2′-ethoxydiphenyl-5-5′-dicarboxylic acid (II. R = C_2H_5).

Now, to suggest a structure for tiliacorine (or tiliarine) we have to accommodate (a) a 2-methoxy-2′-hydroxydiphenyl system[10] (III. R = H) and (b) a dibenzo-*p*-dioxin system which should also carry two isoquinoline units. Any attachment between the two systems could only be through the two methylene groups in the 5,5′-positions of the diphenyl system. While accommodating these two ring systems in a general structure of biscoclaurine type, it became clear to us that the older molecular formulas[1,2] for tiliacorine and tiliarine required modification. In this context, the methoxyl content could be a guiding factor. Thus in trilobine[11] there is one methoxyl in the dibenzo-*p*-dioxin system and in menisarine[12] two methoxyls. Analytical values for carbon, hydrogen, and nitrogen agree closely with menisarine type, necessitating the change from $C_{36}H_{36}O_6N_2$ to $C_{37}H_{38}O_6N_2$ for tiliacorine (which takes into account the diphenyl system). Anjaneyulu *et al.*[13,14] also suggested this formula for tiliacorine on the basis of oxidative degradation. The only disagreeing factor was the methoxyl content. Our experimental value for methoxyl was only 10.1% for tiliacorine instead of 15.1% on the basis of the new formula. It is well known that low methoxyl values are not unusual. A notable case in this connection, is that of aristolochic acid from *Aristolochia clematitis*.[15] From the foregoing, tiliacorine could be tentatively represented by VI and tiliarine is only a stereo isomer of nor-tiliacorine.



VI

Such a formulation is also supported by the Faltis theory.[16] Tiliacorine and tiliarine are unique examples of the bisbenzylisoquinoline type, having a 2′-hydroxy-2-methoxy diphenyl system in place of the 2-methoxy diphenyl ether system of menisarine.[12] Obviously, this is an intermolecular diphenyl link formed by dehydrogenation at 11 and 11′ positions in two coclaurine units. An intramolecular diphenyl link formation between the 8 and 10 positions is well known to be the basis of biogenetical formation of aporphine alkaloids[17] from a single laudanosine unit.

EXPERIMENTAL

o-Acetyltiliacorine. A 200-mg. sample of tiliacorine was refluxed with 5 ml. of acetic anhydride and 1.0 g. of freshly fused sodium acetate for 2 hr. and then poured into 30 ml. of water. The solution was neutralized with saturated sodium bicarbonate solution and extracted (3 × 20 ml.) with chloroform. *O*-acetyltiliacorine was crystallized three times from benzene–petroleum ether (1:1) when it came out as colorless needles; m.p. 233–236° dec., yield, 150 mg.

Anal. Calcd. for $C_{39}H_{40}O_7N_2$: C, 72.21; H, 6.17; N, 4.32; 1-AcO, 6.64. Found: C, 72.18; H, 6.58; N, 4.43; AcO, 6.74.

O-acetyltiliacorine was deacetylated with methanolic sulfuric acid (5%). The hydrolyzate gave on treatment with

(9) Raymond Quelet and Jean Allard, *Compt. Rend.* **205**, 238 (1937).

(10) It is very interesting to note that Y. Sugii (*J. Pharm. Soc. Japan*, **50**, 183, 1930) isolated a 2,2′-dihydroxy-5,5′-diallyldiphenyl from the bark of *Magnolia officinalis*, Rhed. et Wils and *Magnolia obovata* Thumb. He named it Magnolol. The presence of such a closely related diphenyl in a plant of Magnoliaceae which is also known to give rise to bisbenzylisoquinoline alkaloids, lends support to the structure of tiliacorine proposed in this paper.

(11) M. Tomita and C. Tani, *Chem. Abstr.* **45**, 4728, 4729 (1951).

(12) H. Kondo and M. Tomita, *Chem. Abstr.* **30**, 726 (1936); **33**, 626 (1939).

(13) B. Anjaneyulu, K. W. Gopinath, T. R. Govindachary, and B. R. Pai, *Chem. & Ind. (London)*, 702 (1959).

(14) B. Anjaneyulu, K. W. Gopinath, T. R. Govindachary, and B. R. Pai, *Chem. & Ind. (London)*, 1119 (1959).

(15) M. Pailer, L. Belohlov, and E. Sinomitsch, *Mh. Chemie*, **87**, 17 (1956); **88**, 367 (1957).

(16) F. Faltis, L. Holzinger, P. Ita, and R. Schwartz, *Ber.* **74B**, 79 (1941).

(17) R. Robinson, R. H. Manske and H. L. Holmes, *J. Chem. Soc.* **111**, 876 (1917); *The Alkaloids*, **Vol. IV**, Academic Press, Inc., New York p. 2 (1954).

base and crystallization from chloroform-acetone, rectangular prismatic needles, m.p. 260–261° dec. undepressed by admixture with tiliacorine.

Oxidation of tiliacorine. Isolation of 4-methoxyisophthalic acid (IV). A 2-g. sample of tiliacorine was dissolved in 100 ml. of 4% aqueous sulfuric acid and 500 ml. of 2% potassium permanganate was added dropwise at room temperature with continuous mechanical stirring. After 3 hr., the solution was brownish, turbid, and still purple, when it was saturated with sulfur dioxide. The resulting yellow solution was continuously extracted with ether in a liquid-liquid extractor. The ethereal extract was evaporated and the residue triturated with 25 ml. of 4% sodium bicarbonate solution. Acidification with hydrochloric acid of the bicarbonate extract gave no solid. It was, therefore, continuously extracted with ether for 4 hr. Removal of ether furnished a colorless crystalline solid which came out as colorless needles after three crystallizations from hot water; yield, 220 mg., m.p. 265–266° dec. undepressed by admixture with a synthetic sample of 4-methoxyisophthalic acid. It did not exhibit any blue color with a trace of nitric acid in concd. sulfuric acid.

Anal. Calcd. for $C_9H_8O_5$: C, 55.09; H, 4.08; 1-OCH_3, 15.8. Found: C, 54.65; H, 4.26; OCH_3, 16.32.

A 100-mg. sample of the acid in absolute ethanol was treated with excess diazomethane and kept at 0° for 20 hr. The dimethyl ester crystallized from methanol in the form of prismatic needles; m.p. 94–95°, alone or mixed with a synthetic sample of dimethyl 4-methoxy-isophthalate.

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.93; H, 5.35, 3-OCH_3, 41.53. Found: C, 58.48; H, 5.29; OCH_3, 42.09.

Oxidation of tiliarine: Isolation of 4-methoxyisophthalic acid (IV). A 3-g. sample of tiliarine was dissolved in 100 ml. of 4% aqueous sulfuric acid and oxidized with 700 ml. of 2% potassium permanganate at room temperature as in the case of tiliacorine and also worked up as before. The carboxylic acid after careful crystallization from hot water, came out as colorless needles, yield, 296 mg., m.p. 266–269°. It did not exhibit any positive dibenzo-*p*-dioxin color reaction.

The dimethyl ester (diazomethane) crystallized from ethanol in the form of prismatic needles, m.p. 93–95° not altered by dimethyl 4-methoxyisophthalate.

4-Methoxyisophthalic acid (IV) was obtained by the permanganate oxidation of 2-chloromethylanisaldehyde according to the method of Quelet and Allard.[9] The isophthalic acid was secured in good yield; but required four crystallizations from aqueous methanol to raise the melting point to 268–269°.

The methyl ester was obtained by esterification with ethereal diazomethane, m.p. 95–96°.

Oxidation of O-methyl tiliacorine dimethiodide. Isolation of 2,2′-dimethoxydiphenyl-5,5′-dicarboxylic acid (II. R = CH_3). A 2-g. sample of *O*-methyltiliacorine[2] dimethiodide in 300 ml. of water was stirred with freshly prepared silver oxide (from 3 g. of silver nitrate) for 3 hr. and filtered. The light brown filtrate was treated dropwise with 600 ml. of 2% potassium permanganate at room temperature (30°) during a period of 2 hr., until the purple permanganate color was permanent. A strong current of sulfur dioxide was passed through the turbid liquid until it was saturated. There was a considerable amount of pale yellow solid undissolved which was filtered off and the filtrate continuously extracted with ether. On evaporation, the ether extract left a pale yellow solid residue which was crystallized three times from methanol when colorless minute crystals were secured; yield 30 mg., m.p. 328–330°.

The yellow undissolved solid was shaken with 150 ml. of 4% sodium bicarbonate and filtered. On acidification, the filtrate deposited a colorless solid which after three crystallizations from ethanol came out as colorless crystalline material melting indefinitely between 328–332°. Two more crystallizations from methanol acetone (1:1) raised the melting point to 338–340° dec.; yield, 80 mg. identical with the sample obtained above in the filtrate. The carboxylic acid did not exhibit any color with sulfuric–nitric acid reagent.[3]

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.63; 2-OCH_3, 20.53. Found: C, 63.81; H, 4.89; OCH_3, 20.21.

The dicarboxylic acid was esterified with ethereal diazomethane. The dimethyl ester came out after two crystallizations from ethanol, as colorless rectangular plates, m.p. 171–173°, alone or mixed with a synthetic sample of dimethyl 2,2 -dimethoxydiphenyl-5,5′-dicarboxylate.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.46; H, 5.45; 4-OCH_3, 37.58. Found: C, 65.1; H, 5.58; OCH_3, 36.85.

Oxidation of O,N-dimethyl tiliarine dimethiodide. Isolation of 2,2′-dimethoxy-diphenyl-5,5′-dicarboxylic acid (II. R = Me). A 2-g. sample of *O,N*-dimethyltiliarine dimethiodide[2] was oxidized with 2% potassium permanganate as in the case of *O*-methyltiliacorine dimethiodide. The dicarboxylic acid was similarly isolated and crystallized twice from ethanol (and two more times from acetone) to give minute colorless crystals, m.p. 336–38°; yield, 85 mg., identical with the acid secured above.

The dimethyl ester (diazomethane) came out from ethanol as rectangular plates, m.p. 170–72°, undepressed by the dimethyl ester of 2,2′-dimethoxydiphenyl-5,5′-dicarboxylic acid.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.46; H, 5.46, 4-OCH_3, 37.58. Found: C, 65.58; H, 5.64; OCH_3, 37.05.

Methyl 3-bromo-4-methoxybenzoate (I). A solution of 5 g. of methyl 3-bromo-4-hydroxybenzoate[4] in 150 ml. of anhydrous acetone was refluxed with 3.15 g. of dimethyl sulfate and 7.5 g. of anhydrous potassium carbonate, on a water bath for 8 hr. The inorganic salts were filtered and washed with warm acetone. The residue from evaporation of the acetone filtrate, was shaken with 150 ml. of water and filtered. The solid was crystallized twice from methanol when methyl 3-bromoanisate[4] was secured in the form of colorless crystalline needles, m.p. 99–100°, yield, 5.1 g.

Dimethyl 2,2′-dimethoxydiphenyl-5,5′-dicarboxylate (II. R = CH_3). An intimate mixture of 5 g. of methyl 3-bromo-4-methoxybenzoate and 5 g. of copper bronze was heated at 240–250° in a sealed tube for 4 hr. The material was extracted repeatedly with ether and the extract evaporated. The residue was dissolved in benzene and run over a short column of chromatographic alumina. The colorless benzene eluate was evaporated and the colorless crystalline dimethyl ester crystallized twice from benzene–petroleum ether (b.p. 40–60°); yield, 238 mg., m.p. 171–173°. This agrees with the melting point described by Sugii[18] and by H. Gilman.[19]

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.46; H, 5.45; 4-OCH_3, 37.58. Found: C, 65.1; H, 5.58; OCH_3, 36.85.

A 500-mg. sample of the dimethyl ester was warmed on a water bath with 50 ml. of 4% sodium hydroxide till the solid went into solution. It was cooled and acidified with hydrochloric acid. The 2,2′-dimethoxydiphenyl-5,5′-dicarboxylic acid was crystallized from methanol, m.p. 338–340°, which agrees with the melting point given by Gilman.[19]

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.63. Found: C, 63.40; H, 4.80.

Oxidation of O-ethyltiliacorine dimethiodide. An aqueous solution of 3 g. of *O*-ethyltiliacorine dimethiodide[1] in 300 ml. of water was shaken for 2 hr. with silver oxide (freshly prepared from 3 g. of silver nitrate) and filtered. To the filtrate was added 900 ml. of 2% potassium permanganate at laboratory temperature dropwise wih mechanical stirring until the purple color persisted (2 hr.). A brisk current of sulfur dioxide was passed through the turbid solution. After saturation, it was filtered and the filtrate extracted continuously

(18) Y. Sugii, *J. Pharm. Soc. Japan*, **50**, 183 (1930); *Chem. Abstr.* **24**, 3505 (1930).

(19) H. Gilman, J. Swiss, and Lee C. Cheney, *J. Amer. Chem. Soc.* **62**, 1963 (1940).

with ether. Evaporation of the ether extract furnished only a very small residue.

The yellow undissolved solid was shaken with 125 ml. of 4% sodium bicarbonate for 30 min. and filtered. The filtrate was acidified and subjected to continuous extraction with ether. Removal of ether from the extract left a colorless residue which was mixed with the residue obtained above. To the total solid in absolute ethanol, excess diazomethane in ether was added and left at 0° overnight. The methyl ester was purified by two crystallizations from benzene–petroleum ether (1:1) when it came out as colorless prisms melting at 122–125°. Final purification was effected by sublimation at 0.5 mm. and the sublimate crystallized from benzene–petroleum ether (1:1), m.p. 124–125°, yield, 45 mg. The ester did not exhibit any blue color with sulfuric–nitric acid reagent.[3]

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.81; 3-OCH_3 and 1-OC_2H_5 as 4-OCH_3, 36.04. Found: C, 66.71; H, 6.05; OCH_3, 35.77.

Oxidation of O-ethyl-N-methyltiliarine dimethiodide. Two grams of *O*-ethyl-*N*-methyltiliarine dimethiodide[2] was oxidized following the procedure given above. The carboxylic acid was esterified with diazomethane and isolated as the dimethyl ester. The ester was purified by two crystallizations from benzene–petroleum ether (1:1) (solid, m.p. 122–125°) followed by vacuum sublimation at 0.5 mm. The sublimate was crystallized again from benzene–petroleum ether when the methyl ester was secured as colorless prisms, m.p. 123–125°, undepressed by the sample obtained similarly from *O*-ethyltiliacorine dimethiodide.

WALTAIR, INDIA

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Structures Related to Morphine. XIII.[1] 2-Alkyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphans and a More Direct Synthesis of the 2-Phenethyl Compound (NIH 7519)

J. HARRISON AGER AND EVERETTE L. MAY

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Starting from *p*-methoxybenzylmagnesium chloride and 1-alkyl-3,4-dimethylpyridinium iodides the 2-alkyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphane IIIb, IIIc, and IIId have been synthesized for neuropharmacological evaluation. Similarly the medically useful IIIf (NIH 7519) results from 3,4-dimethyl-1-phenethylpyridinium bromide or iodide. IIIb, IIId, and IIIe were also prepared from the known compound IIIa by standard reactions. This alternative synthesis confirms the constitution of the 2-alkyl compounds.

The potent (in mice) analgesic 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (IIIa)[1] has been found to be effective in blocking a conditioned response in mice and rats, a property not uncommon in morphine and morphine-like analgesics.[2] By varying the nitrogen substituent of III, one could expect to get a wide variation in analgesic activity which would permit to a limited extent a comparison of analgesic and other neuropharmacologic actions. We wish to report a few of the IIIa analogs studied in this connection along with a shorter synthesis for 2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (IIIf, NIH 7519.[1,3])

The most convenient route for the preparation of the 2-alkyl compounds was that described previously for IIIa.[4] *p*-Methoxybenzylmagnesium chloride and the appropriate 1-alkyl-(or aralkyl in the case of IIIf) 3,4-dimethylpyridinium iodide (I) were brought to reaction in dry ether. The resultant dihydropyridines (II) in dilute hydrochloric acid were hydrogenated to the corresponding 1,2,5,6-tetrahydro compounds, which were in turn cyclized and *O*-demethylated to III with hydrobromic acid, in 10–30% overall yields based on the starting pyridinium iodides. Because of low water solubility it was necessary to use aqueous alcoholic hydrochloric acid for the hydrogenation step in the preparation of IIIf. It is noteworthy that this synthesis for IIIf is some five steps shorter than that previously reported.[1]

The 2-ethyl (IIIb), 2-butyl (IIId), and 2-amyl (IIIe) compounds have been prepared also from IIIa by a route described earlier[1,3,5] which involves cyanogen bromide *N*-demethylation of the methyl ether of IIIa, acylation of the resultant secondary amine, reduction of the *N*-acyl derivative with ethereal lithium aluminum hydride and *O*-demethylation. This alternative synthesis provided sufficient proof of structure.

The 2-alkyl derivatives IIIb, IIIc, and IIId had no analgesic activity at sub-toxic doses. The *N*-amyl derivative (IIIe), on the other hand, was comparable to morphine in analgesic potency, somewhat more potent than IIIa. This is reasonably consistent with earlier findings[6] in the morphine series where the *N*-ethyl, -propyl, and -butyl homologs have less than one tenth the potency of morphine, and *N*-amylnormorphine is seven-tenths as effective as morphine.

(1) Communication XII, E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959).

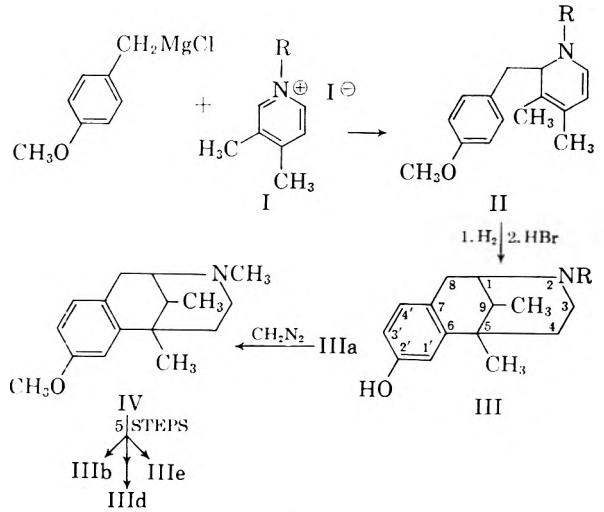
(2) Personal communication from Leonard Cook, Smith, Kline and French Laboratories.

(3) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294 (1959).

(4) (a) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957); (b) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

(5) E. L. May, *J. Org. Chem.*, **21**, 899 (1956).

(6) C. A. Winter, P. D. Orahovats, and E. G. Lehman, *Arch. Intern. Pharmacodynamie*, **110**, 186 (1957).



a) R = CH_3, b) R = C_2H_5, c) R = n-C_3H_7,
d) R = n-C_4H_9, e) R = n-C_5H_{11}, f) R = $CH_2CH_2C_6H_5$

EXPERIMENTAL

Melting points were taken by capillary using a Hershberg apparatus. Microanalyses are by Paula Parisius, Elizabeth Fath, and Byron Baer of the Institutes' service analytical laboratory, Dr. William C. Alford, Director.

1-Ethyl-3,4-dimethylpyridinium iodide (Ib). Ethyl iodide (4 ml.), 4 ml. of 3,4-lutidine,[7] 15 ml. of acetone and 15 ml. of benzene were refluxed for 2–4 hr., cooled to −5°, and filtered to give 9.4 g. (80%) of precipitate, m.p. 179–182° before and after a recrystallization from acetone.

Anal. Calcd. for $C_9H_{14}IN$: C, 41.08; H, 5.36. Found: C, 40.76; H, 5.42.

3,4-Dimethyl-1-propylpyridinium iodide (Ic). This compound was prepared from propyl iodide as described for the previous one; m.p. 104–106° (acetone-ether).

Anal. Calcd. for $C_{10}H_{16}IN$: C, 43.37; H, 5.82. Found: C, 43.00; H, 5.80.

1-Butyl-3,4-dimethylpyridinium iodide (Id). This iodide was prepared with butyl iodide as described above; m.p. 81–83.5° (acetone-ligroin, 30–60°).

Anal. Calcd. for $C_{11}H_{18}IN$: C, 45.37; H, 6.23. Found: C, 45.15; H, 6.19.

3,4-Dimethyl-1-phenethylpyridinium iodide (If). 2-Iodoethylbenzene (3.0 ml.), 2 ml. of 3,4-lutidine, 7 ml. of benzene, and 2 ml. of acetone, refluxed 3 hr. and cooled to 5° gave 4.9 g. (82%) of precipitate melting a 141–145°; plates (from acetone containing a trace of absolute alcohol) m.p. 142–144°.

Anal. Calcd. for $C_{15}H_{18}IN + 0.5H_2O$: C, 51.73; H, 5.50, H_2O: 2.36. Found: C, 51.46; H, 5.68; Loss in wt. (80°), 3.04.

The corresponding *bromide* prepared in a yield of 11.7 g. by refluxing together for 3 hr. 5 ml. of 3,4-lutidine, 9 g. of 2-bromoethylbenzene, and 15 ml. of absolute ethanol, evaporation to dryness *in vacuo* and trituration with acetone, melted at 175–176.5°; cubes from absolute ethanol-ethyl acetate.

Anal. Calcd. for $C_{15}H_{18}BrN$: C, 61.65; H, 6.21: Br, 27.35. Found: C, 61.34; H, 6.22; Br, 27.28.

2-Ethyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (IIIb). To a stirred suspension of 12.5 g. of Ib and 75 ml. of dry ether was added without cooling during 5–10 min., 200 ml. of 0.3*M* ethereal *p*-methoxybenzylmagnesium chloride.[8] After 1–2 hr. of stirring the two-layered mixture was poured into ice-ammonium chloride with vigorous stirring. After addition of a little aqueous ammonia, and brief shaking the ethereal layer was extracted thrice with excess, cold, dilute hydrochloric acid. These extracts were made alkaline with cold, aqueous ammonia, and the liberated base was dried in ether. Evaporation of the ether at the water pump left 6.9 g. of II (R = C_2H_5) which was dissolved quickly in 95 ml. of cold 1*N* hydrochloric acid. This solution with 3.0 g. of 5% palladium–barium sulfate absorbed 605 ml. (88%) of hydrogen during 4 hr., when uptake had almost stopped. The suction-filtered (through Super-Cel) solution was made alkaline with ice-cold, aqueous ammonia. The liberated base was shaken into ether. The extracts were dried over sodium sulfate and distilled at the water pump. The residue was molecularly distilled at 0.2 mm. (air-bath temperature 150–175°). The distillate and 50 ml. of 48% hydrobromic acid were kept at a bath temperature of 135–140° for 20 hr., poured onto ice and made basic with concd. ammonium hydroxide. The freed IIIb was shaken into chloroform. The dried extract was distilled at the water pump. The residue crystallized from a little methanol or acetone, giving 3.5 g. (30% based on Ib) of IIIb, m.p. 158–160°; prisms from methanol-water, m.p. 163–164°.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 77.90; H, 9.19.

The *hydrobromide* crystallized from acetone in needles of m.p. 230°, after sintering at 215°.

Anal. Calcd. for $C_{16}H_{24}BrNO$: C, 58.89; H, 7.41. Found: C, 58.74; H, 7.51.

2'-Hydroxy-5,9-dimethyl-2-propyl-6,7-benzomorphan (IIIc). Essentially as described in the preparation of IIIb, 12.5 g. of Ic, 75 ml. of dry ether, and 200 ml. of ethereal *p*-methoxybenzylmagnesium chloride gave, after molecular distillation (0.1 mm., 150°) of the crude IIIc from the chloroform extracts and crystallization of the distillate from a little acetone, 2.7 g. of IIIc, m.p. 165–170°. The analytical sample (from acetone) melted at 168–170°.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.71. Found: C, 78.56; H, 9.56.

The *hydrochloride* (prepared from the base in acetone with dry hydrogen chloride) crystallized from absolute ethanol-ether (charcoal) or absolute ethanol-acetone in white crystals of m.p. 240–242.5°. The analytical sample was dried for 5 hr. at 100°.

Anal. Calcd. for $C_{17}H_{26}ClNO$: C, 69.01; H, 8.86. Found: C, 68.75; H, 8.83.

2-Butyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (IIId). Essentially as described before except that the IIId from the chloroform extracts was molecularly distilled at 0.1 mm. (bath temperature 175–180°), this base was obtained in 15% yield from Id, after crystallization of the distillate from ether; plates from acetone, m.p. 152–153°.

Anal. Calcd. for $C_{18}H_{27}NO$: C, 79.08; H, 9.96. Found: C, 78.87; H, 9.83.

The *hydrobromide* crystallized from absolute ethanol-ether in needles, m.p. 211–212°.

Anal. Calcd. for $C_{18}H_{28}ClNO$: C, 61.02; H, 7.96. Found: C, 61.22; H, 7.78.

2'-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (IIIf).[1,3] To a stirred suspension of 10 g. of 3,4-dimethyl-1-phenethylpyridimium bromide[9] was added during 10–15 min. 130 ml. of 0.3*M* ethereal *p*-methoxybenzylmagnesium chloride. After 1–1.5 hr. the mixture was poured with vigorous stirring into ice-ammonium chloride solution, and a little ammonium hydroxide was added. The ethereal layer was extracted with three portions of cold 10% hydrochloric acid (in excess). The combined extracts were made alkaline

(7) Available from the Reilly Tar and Chemical Company, Indianapolis, Indiana.

(8) M. G. Van Campen, D. F. Meisner, and S. M. Parmerter, *J. Am. Chem. Soc.*, **70**, 2296 (1948).

(9) We are indebted to Dr. G. DeLaMater of the Mallinckrodt Chemical Works, Inc., for suggesting the bromide as a substitute for the iodide. The iodide crystallized as a hemihydrate and therefore required additional Grignard reagent.

with ice-cold ammonium hydroxide and the base extracted with ether. The dried (sodium sulfate) ethereal extracts gave, on evaporation to dryness at the water pump, 8.5–9.5 g. of amber-colored oil. This was treated with 80 ml. of cold 1*N* hydrochloric acid and just enough (30–40 ml.) 95% ethanol to effect complete solution of the oily material. The solution was transferred to a nitrogen-swept hydrogenation flask containing 1.2 g. of 10% palladium–barium sulfate and shaken under hydrogen. After 60–80 min. absorption had slowed from a maximum rate of 20 ml./min. to 2 ml./min. while a total of 90% of 1 molar equivalent was absorbed. Usually some oily material had separated. The mixture was filtered through Super-Cel (the flask and precipitate being washed with a little alcohol), made alkaline with cold ammonium hydroxide, and the base was shaken into ether. The combined ethereal extracts were washed with water and dried over sodium sulfate. The oil left after evaporation to dryness was molecularly distilled as rapidly as possible (boileezers, 0.1 mm., air-bath temperature 200–220°). The resultant distillate (4.7 g.), 20 ml. of 48% hydrobromic acid, and 10 ml. of 33% hydrogen bromide in acetic acid were kept at 145–150° (oil-bath temperature) for 20–24 hr., poured onto ice (in a separatory funnel), made alkaline with ammonium hydroxide and extracted with three portions of chloroform. The dried (sodium sulfate) extracts yielded (on evaporation of the chloroform *in vacuo*) a residue which was molecularly distilled as described above. The very viscous distillate crystallized from 6–8 ml. of acetone in a yield of 1.0–1.5 g. (m.p. 176–179°) after gradual cooling to −5°. The analytically pure material (from methanol) melted at 181–182° alone or in mixture with an authentic specimen.[1,3] The infrared spectra of the two were also identical.

The hydrobromide salt,[10] prepared by neutralizing the crude base (m.p. 176–179°) in acetone with 33% hydrobromic acid in acetic acid and adding an equal volume of ethyl acetate, melted at 167–171°; it gave an infrared spectrum identical with that of authentic hydrobromide.[1,3]

2-Ethyl-2′-methoxy-5,9-dimethyl-6,7-benzomorphan hydrobromide. IV (1.5 g.)[1,4b] in 10 ml. of dry chloroform was added (stirring) during 40 min. to 0.7 g. of cyanogen bromide in 5 ml. of chloroform. The solution was refluxed for 2–3 hr. and evaporated to dryness at the water pump. The residue and 20 ml. of 6% hydrochloric acid were refluxed overnight, cooled, made alkaline, and extracted with ether. The dried (sodium sulfate) ether extracts, on evaporation to dryness left 1.0 g. of crude 2′-methoxy-5,9-dimethyl-6,7-benzomorphan which was *N*-acetylated with 1 ml. of acetic anhydride (25°, 24 hr.). The mixture was shaken with ether and water, and the ethereal layer was washed with dilute hydrochloric acid, dried, and evaporated giving 1.0 g. of crude *N*-acetyl derivative. To this in 15 ml. of dry ether was added 10 ml. of 1.7*M* ethereal lithium aluminum hydride during 5–10 min. (stirring). The mixture was refluxed for 6 hr. and decomposed by careful addition of 5 ml. of water. The ethereal filtrate was dried and evaporated giving 0.9 g. of oily base which (in ether) was neutralized with 0.7 ml. of 33% hydrobromic acid in acetic acid; yield of hydrobromide 0.8 g. (45%), m.p. 232–237°; plates from acetone, m.p. 246–247°.

Anal. Calcd. for $C_{17}H_{26}BrNO$: C, 60.00; H, 7.70. Found: C, 59.81; H, 7.49.

O-Demethylation of 2-ethyl-2′-methoxy-5,9-dimethyl-6,7-benzomorphan to IIIb. By refluxing together for 30 min. 0.8 g. of this methyl ether and 5.0 ml. of 48% hydrobromic acid, evaporation to thorough dryness (*in vacuo*) and crystallization of the residue from alcohol-ether, 0.5 g. of IIIb hydrobromide identical with that prepared as described above was obtained. The free base melted at 163–164° alone or in mixture with that described above.

2-Butyl-2′-methoxy-5,9-dimethyl-6,7-benzomorphan hydrobromide. As described above, 1.0 g. of IV was *N*-demethylated with 0.5 g. of cyanogen bromide to give 0.7 g. of crude secondary amine. To this, 10 ml. of methanol, 2–3 ml. of water, and 1.0 g. of potassium carbonate, was added with stirring during 10 min., 0.5 ml. of butyryl chloride. The mixture was stirred for 2 hr., diluted with water and extracted thrice with ether. The combined extracts were washed with dilute hydrochloric acid, dried (sodium sulfate) and evaporated to dryness *in vacuo* giving 1 g. of crude butyramide derivative. It was dissolved in 10 ml. of dry ether and the solution treated gradually with 6–8 ml. of 1.3*M* ethereal lithium aluminum hydride. The mixture was refluxed overnight, treated carefully with 5 ml. of water and the ether was decanted, dried, and evaporated. This base (in dry ether) was acidified with hydrobromic-acetic acid giving a hydrobromide salt which crystallized from acetone-ether in a yield of 0.8 g.; plates, m.p. 224–225.5°.

Anal. Calcd. for $C_{19}H_{30}BrNO$: C, 62.19; H, 8.21. Found: C, 62.09; H, 7.95.

Demethylation to Id was effected as described above with boiling 48% hydrobromic acid. It was identical with the Id prepared as described above.

2-Amyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan (IIIc). The conversion of 2 g. of IV to 1.2 g. of hygroscopic 2-amyl-2′-methoxy-5,9-dimethyl-6,7-benzomorphan hydrobromide was carried out as described for the 2-butyl homolog, using valeryl chloride as the acylating agent. This hydrobromide (0.6 g.) and 3.0 ml. of 48% hydrobromic acid were refluxed for 15–20 min., cooled, and made alkaline with aqueous ammonia. The base was dried in ether and molecularly distilled at a bath temperature of 180° (0.1 mm.) giving 0.4 g. of IIIe which crystallized from ligroin (30–60°) in prisms, m.p. 142.5–144°.

Anal. Calcd. for $C_{19}H_{29}NO$: C, 79.40; H, 10.17. Found: C, 79.55; H, 10.35.

The *hydrochloride*, prepared by acidification of the base in ether with dry hydrogen chloride crystallized from absolute alcohol-ether in needles, m.p. 204–207°.

Anal. Calcd. for $C_{19}H_{30}ClNO$: C, 70.45; H, 9.34. Found: C, 70.64; H, 9.58.

Acknowledgment. We are indebted to the Smith, Kline and French Laboratories for conditioned-response testing and to Dr. Nathan B. Eddy and staff for data on analgesia.

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(10) This compound originally designated as NIH 7519 has been assigned the generic name phenazocine.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Nonsymmetrical Bimolecular Reduction: Structure of the So-Called "Hydroxycodeine"

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The so-called "hydroxycodeine" (II), obtained on reduction of 14-hydroxycodeinone (I) with zinc and acetic acid, is shown to have twice the molecular size of a simple reduction product of I. II is a trihydroxymonoketone, and consequently results from nonsymmetrical reductive coupling of two molecules of I. Structure VIII is proposed for II.

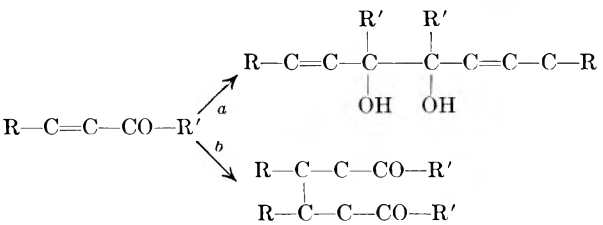
The reduction of 14-hydroxycodeinone (I) with zinc dust and acetic acid[1a] or with the zinc-copper couple and formic acid[1b] was first described by Freund and Speyer. From the reaction mixture they obtained a nonphenolic, high-melting compound (II), which they assumed to be 14-hydroxycodeine (III),[2] the secondary alcohol corresponding to I.

Subsequently, Lutz and Small[3] questioned this interpretation of Freund's compound as the normal reduction product of I: if it were correct, "dihydrohydroxycodeine A" (IV), obtained on catalytic reduction of II (platinum oxide in acetic acid), should be identical with one of the two authentic dihydrohydroxycodeines B and C (Va and b), which are formed on catalytic reduction (platinum oxide) of VI, the dihydro derivative of I. In reality, the chemical and pharmacological properties of IV differ widely from those of either Va or Vb. Hence, II can be neither III nor its 6-epimer, and Lutz and Small concluded that the zinc reduction of I had taken an irregular course; however, they did not attempt to establish the structure of II.

Further support for these doubts comes from the recent preparation[4] of authentic III, obviously different from II. The structure of III follows from the method used to prepare it (sodium borohydride reduction of I), and from the fact that it is reduced to Va,[4a] and reconverted to I by manganese dioxide.[4b] II is resistant to the latter reagent and hence should not be a *secondary* allylic alcohol.

In the course of marshalling together data relevant to the problems which the late Dr. Small[5] had under investigation, the question of the actual nature of II presented itself. That the substance might be a bimolecular species was suspected, since it is well known[6] that metal-acid reduction of ketones often results in the formation of such products. Furthermore, the melting points of II and IV (303–304° and 301–302°, respectively[3]) would be exceptionally high for simple codeine derivatives (*cf.* III, m.p. 156–157°; Va, 145°; Vb, 167°), but this would not be surprising if the compounds had twice the molecular weight. The first clue in support of this interpretation appeared as a result of a molecular weight determination (Signer) when a value *twice* that previously assigned was obtained (found, 627; calcd. for $C_{36}H_{40}N_2O_8$, 629).

In general, bimolecular reduction of α,β-unsaturated ketones[7] proceeds in a symmetrical way to yield[6] either an unsaturated 1,2-glycol (Reaction *a*) or a saturated 1,6-diketone (Reaction *b*).



In the present case, however, neither path is followed. Reaction *a* is excluded since the infrared spectrum of II shows a band at 5.78 μ (in potassium bromide), consistent with the presence of a nonconjugated carbonyl group. On the other hand, Reaction *b* seems unlikely, since the intensity of this carbonyl band, relative to other bands in the spectrum (*e.g.*, the one at 6.67 μ), is much lower than that of the corresponding band in authentic monomolecular ketones of the codeine series, *e.g.*, VI (5.8 μ). Consequently, II seemed to contain only *one* carbonyl group.

This last point was proven by the smooth formation from II of an *oxime* (in contrast to older state-

(1) (a) M. Freund and E. Speyer, *J. prakt. Chem.* (2) **94**, 135 (1916); (b) E. Speyer, S. Selig, and M. Heil, *Ann.* **430**, 1 (1923).

(2) Compound I was interpreted by Freund and Speyer as the 7-hydroxy derivative of codeinone as formulated on the basis of the Knorr-Hörlein structure for morphine: consequently they designated II as "7-hydroxycodeine." Their formulas and nomenclature have been modified to conform with modern usage.

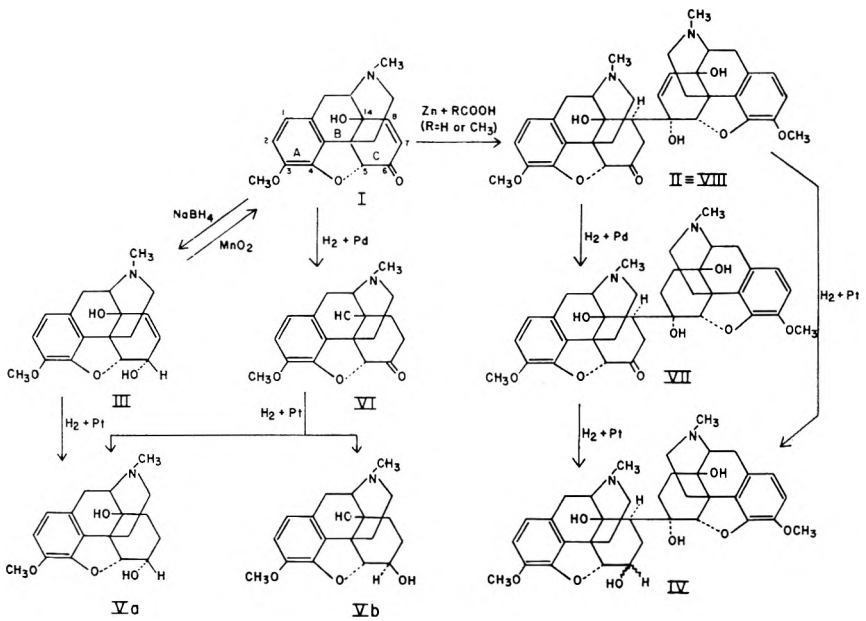
(3) R. E. Lutz and L. F. Small, *J. Org. Chem.* **4**, 220 (1939).

(4) (a) L. J. Sargent, L. H. Schwartzman, and L. F. Small, *J. Org. Chem.*, **23**, 1247 (1958); (b) U. Weiss, unpublished work.

(5) Deceased, June 1957.

(6) R. C. Fuson, *Record Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) **12**, 1 (1951).

(7) The conjugated system of I must be involved in the formation of II, since VI, the corresponding saturated ketone, is unaffected by zinc-acetic acid at 80–90°.[3]



ments[1b]). This derivative had the correct analysis for a *monoxime* of II.[7a] Furthermore, Zerewitinoff analysis of II showed *three* active hydrogen atoms per molecule $C_{36}H_{40}N_2O_8$. Two of these undoubtedly stem from the hydroxyl functions at C-14 originally present in I, while the third must be attributed to a hydroxyl group resulting from the reduction of the carbonyl in one of the two C_{18} moieties. II is therefore a trihydroxymonoketone.

According to Lutz and Small,[3] catalytic reduction of II over platinum oxide results in the slow uptake of *one* mole of hydrogen (per C_{18} unit) to give compound IV. Since this substance lacks the carbonyl band present in II and contains *four* active hydrogen atoms (based on a molecular weight of 629), the keto group of II has been reduced. However, the uptake of hydrogen found by Small actually corresponds to *two* moles per mole of II, $C_{36}H_{40}N_2O_8$, and consequently proves the presence of a second center of unsaturation. That this is a double bond was first indicated by the NMR spectrum,[8] which showed bands 3.62 and 4.58 p.p.m. lower in field than that of acetone, used as an internal reference (the corresponding values calculated relative to tetramethylsilane as reference are 5.7 and 6.7 p.p.m.). These bands can be ascribed to double bond and aromatic ring, respectively.

Conclusive proof for the presence of this double bond was obtained by catalytic reduction of II over palladium–barium sulfate, which proceeded with the uptake of *one* mole of hydrogen per molecular weight of 629 to give a new dihydro derivative (VII).[9] This compound retains the carbonyl group (band at 5.75 μ, *i.e.* in unaltered position). Further reduction of VII with platinum oxide as catalyst leads to IV.

On the other hand, it is also possible to reduce the carbonyl group specifically with sodium borohydride. This reaction seems to lead to the formation of two compounds in very unequal amounts; the two products are presumed to be epimers at C_6 (*cf.* the analogous hydride reduction of 8,14-dihydroxydihydrocodeinone,[4a] and the formation of much Va and little Vb on platinum-catalyzed hydrogenation of VI[3]). In the present case, neither the compounds themselves nor several of their salts were obtained crystalline, and the products were not investigated any further. However, the absence of carbonyl bands from the infrared spectra of both compounds showed that the desired reduction had taken place.

The data presented prove that II is formed from I by bimolecular reduction, that it contains a nonconjugated carbonyl, one reducible double bond, and three hydroxyls. Consequently, it must have been formed by a nonsymmetric reductive coupling of two molecules of I.

To account for these findings, we wish to propose formula VIII for II. This formulation seems in agreement with all observations made so far,[10,11]

(7a) NOTE ADDED IN PROOF: The infrared spectrum of this derivative (Nujol) lacked the characteristic carbonyl band at 5.8 μ.

(8) Kindly taken by Dr. E. D. Becker and Mr. R. B. Bradley of this Institute, using a Varian NMR spectrometer operating at 60 mc., and deuterium oxide plus hydrochloric acid as solvent.

(9) *Cf.*, however, the statement[1b] that II is not reduced by hydrogen-on-palladium.

(10) One apparent exception is the failure of II to give the pink color with *m*-dinitrobenzene and alkali characteristic of a methylene group activated by an adjacent carbonyl (von Bittó–Zimmermann reaction). However, this reaction is known to be negative for many compounds containing the grouping —CO—CH_2—, *e.g.*, the 6, 7, and 12-ketosteroids, (K. Kaziro and T. Shimada, *Z. physiol. Chem.*, *Hoppe-Seyler's* **249**, 220 (1937).

(11) The earlier literature[1b,3] contains references to various acetylated derivatives of II. These compounds have not been reinvestigated by us.

and formation of a substance of this constitution can be explained by a plausible mechanism. Structure VIII would result from reduction of the carbonyl of one molecule of I, followed by attack upon position 8 of another molecule by the intermediate reduced species, which could be either a carbanion or a free radical.[12] The susceptibility of position 8 in I and its analogs, particularly to nucleophilic attack, is well known.[13] Alternatively, conjugate reduction of one molecule of I with subsequent attack of the resulting carbanion upon the carbonyl carbon of another molecule would likewise yield VIII.

While formation of necessarily nonsymmetrical products by reductive coupling of two *different* substances is well known,[6,12a] reductive coupling of *like* molecules generally leads to symmetrical products.[6] Formation of a nonsymmetrical structure under the latter conditions seems to be quite uncommon, and we have been unable to find in the literature a case sufficiently close to the one described here to serve as a model for the reduction of I to II. Formation of compounds with nonsymmetrical structures has been observed by Fuson and coworkers[14] on reduction of *p*-anisyl duryl and mesityl ketones with sodium; however, neither course nor products of this reaction are analogous to ours. More closely related to the present case is an instance of heterogeneous bimolecular reduction: formation of compound IX either from the disodio salt of benzhydrol and benzalacetophenone, or from dipotassiobenzalacetophenone and benzophenone.[15] While here two *different* molecules are

$$(C_6H_5)_2\,CNa{-}ONa + C_6H_5CH{=}CHCOC_6H_5$$
$$\downarrow$$
$$(C_6H_5)_2\,C(OH)CH(C_6H_5)CH_2COC_6H_5 \quad IX$$
$$\uparrow$$
$$(C_6H_5)_2\,CO + C_6H_5CHKCHKCOC_6H_5$$

reductively combined in either case, the resulting product is a saturated γ-hydroxy ketone just like VIII, and it arises through a mechanism quite similar to the one postulated by us for the bimolecular reduction of I. We believe, therefore, that the formation of IX constitutes a valid analogy to that of VIII. Some other instances of nonsymmetric bimolecular reduction have been described which, while less closely related to our case, similarly proceed by attack of an intermediate reduced species upon the conjugated double bond of another molecule. Examples of such reactions are the reductive dimerization of α-nitroalkenes,[16a] and of α,β-unsaturated amides.[16b]

No direct experimental evidence is available on the stereochemistry of the juncture of the two moieties in VIII. However, either one of these moieties constitutes a very bulky substituent on ring C for the other one, and since the underside of this ring is very strongly hindered, it seems unlikely that the other ring system should have become attached to it from that side. Hence, we feel that the configuration can hardly be other than the one indicated in formula VIII.

EXPERIMENTAL[17]

"14-Hydroxycodeine" (II). Samples from Dr. L. F. Small's collection were used.

Anal. Calcd. for $C_{36}H_{40}N_2O_8$: Mol. wt. 629; active H, 3.0. Found: Mol. wt. 627 (Signer, in chloroform); active H, 3.0.

The test with diazotized sulfanilic acid was negative, confirming the older statements[1,3] that the compound is nonphenolic. It gives strong melting point depressions with IV and VII.

Oxime of II. A suspension of 0.19 g. of finely powdered II in a mixture of 73 ml. of 95% ethanol and 2 ml. of water was heated (reflux) for 20 hr. with 0.028 g. (1.3 equiv.) of hydroxylamine hydrochloride and 0.032 g. (1.3 equiv.) of fused sodium acetate. The clear solution was concentrated to small volume (*in vacuo*), diluted with 50 ml. of water and made basic with a slight excess of concd. ammonium hydroxide. The white precipitate was collected and recrystallized twice from 95% ethanol; small colorless prisms, m.p. 275–277° (evac. tube).

Anal. Calcd. for $C_{36}H_{41}N_3O_8$: C, 67.2; H, 6.42; N, 6.53. Found: C, 67.3; H, 6.44; N, 6.39.

Palladium-barium sulfate reduction of II to VII. A solution of 0.6 g. of II in 20 ml. of 10% acetic acid was shaken in hydrogen with 0.15 g. of 5% palladium on barium sulfate during 10 hr., (1 mole of hydrogen absorbed). The product was recovered from the filtered solution (chloroform/ammonium hydroxide) and obtained as a colorless foam which crystallized when triturated with a little warm ethanol. Recrystallization from this solvent afforded small rectangular plates, m.p. 307–309° dec. (evac. tube). Mixed melting points with both II and IV were strongly depressed. The infrared spectra of these three compounds are significantly different.

Anal. Calcd. for $C_{36}H_{42}N_2O_8$: C, 68.6, H, 6.71. Found: C, 68.3; H, 6.86. $[\alpha]_D^{20}$ −94.6° (c = 0.975, in 10% acetic acid).

Further reduction of VII to IV. A solution of 0.3 g. of VII in 8 ml. of 10% acetic acid absorbed 1.2 moles of hydrogen in 1 hr. when shaken with 25 mg. of platinum oxide. The product, isolated as above, was recrystallized from ethanol, m.p. 301–303° (evac. tube), undepressed when mixed with a sample prepared by Small directly from II.[3] A Zerewitinoff analysis showed *four* active hydrogens.

(12) (a) *Cf.* G. B. Bachman, M. Hamer, E. Dunning, and R. M. Schisla, *J. Org. Chem.*, **22**, 1296 (1957), and literature quoted there; (b) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 701.

(13) Examples, *inter alia:* addition of hydroxyl: S. P. Findlay and L. F. Small, *J. Am. Chem. Soc.*, **72**, 3247 (1950); **73**, 4001 (1951) (in *acidic* medium); U. Weiss, *J. Org. Chem.*, **22**, 1505 (1957) (in *alkaline* medium); of morpholine: U. Weiss, unpublished observations; of thioethyl D. E. Morris and L. Small, *J. Am. Chem. Soc.*, **56**, 2159 (1934).

(14) R. C. Fuson, G. W. Parshall, and E. H. Hess, *J. Am. Chem. Soc.*, **77**, 3776 (1955).

(15) P. J. Hamrick, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 493 (1959).

(16a) H. Shechter, D. E. Ley, and E. B. Roberson, Jr., *J. Am. Chem. Soc.*, **78**, 4984 (1956); (b) H. R. Snyder and R. E. Putnam, *J. Am. Chem. Soc.*, **76**, 33 (1954).

(17) Analyses are by the Analytical Service Laboratory of this Institute under the supervision of Dr. W. C. Alford. Melting points are corrected.

Hydride-reduction of II. A suspension of 0.6 g. sodium borohydride in 5 ml. methanol was added to 0.19 g. II suspended in 5 ml. methanol. After 20 hr. at room temperature, 10 ml. 10% aqueous sodium hydroxide was added to the slightly opalescent solution, and the mixture was heated over a free flame for 5 min. The milky liquid was cooled, diluted with water, and extracted six times with chloroform. The combined extracts were washed three times with small amounts of water, dried (sodium sulfate), and evaporated (*in vacuo*). The white residue was brought into solution by refluxing with six successive portions of hexane, which deposited noncrystalline solids on cooling. Additional material was obtained by evaporation of the filtrates. Infrared spectroscopy showed the presence of two different nonketonic products having very similar but definitely nonidentical spectra. One of these was present in the first three hexane filtrates, while all other fractions consisted of the other compound. All fractions were noncrystalline and melted over a wide temperature range (approx. 155–175°). Numerous attempts to convert the bases or a variety of their salts to well characterized, crystalline products were unsuccessful.

Treatment of II with manganese dioxide. Thirty milligrams of II, dissolved in 10 ml. chloroform, was stirred at room temperature with 100 mg. active manganese dioxide[18] for 20 min. The mixture was filtered with suction, and the dioxide was washed several times with chloroform. Evaporation of the combined filtrates left a residue which crystallized on treatment with a few drops of ethanol. The crystalline product did not depress the melting point of an authentic sample of II, and had the same infrared spectrum. Complete evaporation of the mother liquors gave an additional amount of this material.

Parallel treatment of 0.5 g. of III in 50 ml. chloroform with 1.5 g. of the same batch of manganese dioxide gave, after purification *via* the crystalline perchlorate, 0.35 g. (70%) of pure I, m.p. and mixed m.p. 272–273°.

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(18) T. Attenburrow *et al.*, *J. Chem. Soc.*, 1094 (1952).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

Synthesis of Several Fluorinated Cyclobutanes and Cyclobutenes

J. D. PARK, H. V. HOLLER,[1] AND J. R. LACHER

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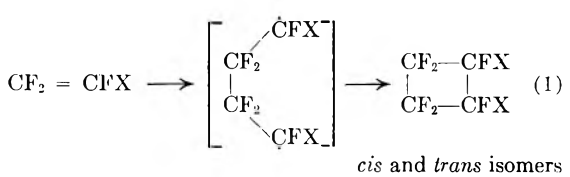
The synthesis of several fluorinated cyclobutanes by cyclization of $CF_2{=}CX_2$ olefins with themselves, and other olefins is reported. It appears that this cycloaddition takes place quite readily and easily only when X is halogen. The direction of addition of the unsymmetrical haloolefins can be rationalized and predicted by the assumption that in the product-determining transition state, the diradical of the lowest energy is preferentially formed with free (or nearly so) rotation about each single bond in the end positions (Equation 1). The physical properties of the fluorinated cyclobutanes and fluorinated cyclobutanes are described.

Many examples of the cyclization of $CF_2 = CX_2$-type olefins with themselves, alkenes and alkynes to form cyclobutanes and cyclobutenes are found in the literature. This cycloaddition appears to occur easily only when X is halogen.

Attempts to homocyclize trifluoroethylene, 2-bromo-1,1-difluoroethylene, and 2-chloro-1,1-difluoroethylene were unsuccessful. Propargyl chloride and tetrafluoroethylene also failed to cocyclize. Other studies have been carried out in this laboratory, but thus far all attempts to homocyclize fluoro-olefins of the type $CF_2 = CHX$ (where X is H, F, Cl, or Br) have been unsuccessful.

Recent work carried out in this laboratory has shown that chlorotrifluoroethylene dimerizes to give a product which is 50–50 (or nearly so) *cis-trans* 1,2-dichlorohexafluorocyclobutane. No differences in the distribution of the *cis-trans* isomers were observed when the dimerization reactions were carried out at temperatures ranging from 130 to 225°. This may be explained on the following basis. If the activated complex which forms when chlorotrifluoroethylene dimerizes has a rigid structure similar to the product molecules, then one would expect to get two parts of *cis* and one part of *trans*. The fact that the product is 50% of each suggests that the activated complex is a diradical with free (or nearly so) rotation, about each carbon single bond in the end position.

The direction of addition of unsymmetrical haloethylenes to themselves and to other unsymmetrical olefins can be rationalized and predicted by the assumption that in the product-determining transition state, the diradical of the lowest energy is preferentially formed. For example, in homocyclization:



(1)

cis and *trans* isomers

X = Cl, Br or I

The relative abilities of the halogens to stabilize free radicals appears to be: I>Br>Cl>F. The latter was determined by Haszeldine from the magnitudes of the bathochromic shifts in the ultraviolet spectra of halogenated alkyl iodides.[2]

The direction of cross-cyclization of haloethylenes with different alkenes or alkynes can likewise

(1) From the Ph.D. dissertation submitted to the University of Colorado, August, 1957.

(2) R. N. Haszeldine, *J. Chem. Soc.*, 1764 (1953).

TABLE I

THERMAL CYCLOADDITION REACTIONS

Reactants	G.	Time, Hr.	Temp.	Inhibitor	Product	G.	% Conversion
CH_2=$CHBr$ CF_2=CF_2	215 160	8	200	Terpene B[a]	CH_2—$CHBr$ CF_2—CF_2	40	12
CH_2=CH_2 CF_2=$CFCl$	126 685	9	200	Terpene B and hydroquinone	CH_2—CH_2 CF_2—$CFCl$	127	19.5
$(CH_2$=$CH)_2$ CF_2=$CFCl$	10 23	30	180	Terpene B and hydroquinone	CH_2—CH—CH=CH_2 CF_2—$CFCl$	24.6	78
C_2H_5C≡CH CF_2=CF_2	109 250	8	170	Terpene B	CH=C—C_2H_5 CF_2—CF_2	86	28
CF_2=$CFBr$	96	8	210	Terpene B	$CFBrCFBr$ CF_2—CF_2	24	25
CF_2=CBr_2	94	13	210	Terpene B and hydroquinone	CBr_2—CBr_2 CF_2—CF_2	26	28

[a] A terpene fraction, b.p. 176–196°, consisting primarily of dipentene and terpenolene.

be predicted. It is well known that the stability of alkyl free radicals stands in the order tertiary> secondary>primary. Unsaturation adjacent to a free radical is particularly effective in stabilizing that radical. Thus, with chlorotrifluoroethylene and butadiene the lowest energy diradical in the transition state would be ($CFCl—CF_2—CH_2—CH—CH=CH_2$), which leads to the product observed in the present work. The cycloaddition of chlorotrifluoroethylene with acrylonitrile leads to 3-cyano-2-chloro-1,1,2-trifluorocyclobutane[3] and with phenylacetylene leads to 1-phenyl-4-chloro-3,3,4-trifluorobutene.[4] These products can be rationalized assuming the most stable diradical intermediate. The cycloaddition of 1,1-dichloro-2,2-difluoroethylene to itself and other unsaturated materials leads to products predictable by assuming the lowest energy transitional diradical to be involved.

Similarly, the cyclobutanes formed by the cycloadditions of allenes[5] can also be rationalized by assuming the most stable intermediate diradical to be involved in the cyclization process.[6]

Cyclobutenes isomerize more or less readily to butadienes depending upon the position and nature of substituents.[7] The new cyclobutenes prepared in this work were thus brominated in order to determine chemically whether such an isomerization had occurred. In no case was this isomerization found. The surprising polymerization of 2,3,3-trifluorocyclobutene appears to be free radical in nature and could involve preliminary isomerization to the butadiene, but bromination data do not indicate this.

The thermal cyclization of tetrafluoroethylene, chlorotrifluoroethylene, 1,1-dichloro-2,2-difluoroethylene give 80 to 90% yields of the cyclobutanes. The cyclization of bromotrifluoroethylene, 1,1-dibromo-2,2-difluoroethylene, and trifluoroiodoethylene give only 25 to 30% yields of simple cyclic products.[8] In the latter reactions, quantities of heavy oils, presumably linear low molecular weight polymers, are formed. This may result from the lower carbon-halogen bond strengths for bromine and iodine and their greater ionic radii. The product of iodotrifluoroethylene cyclization is the cyclobutene. Bromine is spontaneously lost from 1,1,2,2-tetrabromotetrafluorocyclobutane above its melting point.

EXPERIMENTAL

The thermal cycloaddition reactions summarized in Table I were carried out generally following the procedures of Coffman *et al.*[9] The reactants were heated in an air-free stainless steel autoclave or a glass tube in the presence of a free radical inhibitor. The physical properties of these compounds are given in Table II. The following section is concerned with reactions carried out with the cycloaddition products.

3,3,4,4-Tetrafluorocyclobutene. Thirty-six grams of 3-bromo-1,1,2,2-tetrafluorocyclobutane was added dropwise to a slurry of 75 g. of powdered potassium hydroxide in mineral oil at room temperature. The reaction was completed by stirring 5 hr. at 80°. Volatile materials were removed under reduced pressure to obtain 4.0 g. of starting material and 8.0 g. (36% conversion) of 3,3,4,4-tetrafluorocyclobutane, b.p. 50.4–50.5° (634 mm.), n_D^{20} 1.3114, d_4^{20} 1.358. This latter material is shown to be pure by gas-liquid partition chromatography. Molecular weight was determined by gas density and found to be 130 (theory for $C_4H_2F_4$ 126). The molar refraction calculated for the 3,3,4,4-tetrafluorocyclobutene structure was 18.72; that found was 17.96.

Anal. Calcd. for $C_4H_2F_4$: C, 38.1; F, 60.3. Found: C, 37.7; F, 60.1.

(3) A. L. Barney and T. L Cairnes, *J. Am. Chem. Soc.*, **72**, 3193 (1950); F. J. Lorenzi-Thesis, University of Colorado, 1954.

(4) E. J. Smutny and J. D. Roberts, *J. Am. Chem. Soc.*, **77**, 3420 (1955).

(5) H. N. Cripps, J. R. Williams, and W. H. Sharkey, *J. Am. Chem. Soc.*, **80**, 751 (1958).

(6) W. H. Sharkey-Lecture, November 21, 1958, University of California, Berkeley, California.

(7) E. Vogel, *Ann.*, **615**, 14 (1958).

(8) R. J. Seffl, Thesis, University of Colorado (1950).

TABLE II

PHYSICAL PROPERTIES AND ANALYSES OF CYCLOADDITION PRODUCTS

Compound	B.P., °C./Mm. Hg	$n_D^{t°}$	$d_4^{t°}$	t_i, °C.	Molar Refraction		Analyses, %					
							Calcd.			Found		
					Calcd.	Found	Calcd.	Found	Other	Calcd.	Found	Other
$CH_2—CHBr$ | $CF_2—CF_2$	85.5/632	1.3787	1.777	20	26.90	26.90	23.2	36.7	Br, 38.6	23.4	36.3	Br, 36.6
$CH_2—CH_2$ | $CF_2—CFCl$	75/634	1.3597	1.347	20	23.93	23.66	33.2	39.4	H, 2.79 Cl, 24.5	33.3	39.8	H, 3.04 Cl, 24.4
$CH_2—CH—CH=CH_2$[a] | $CF_2—CFCl$	109/631	1.3927	1.344	25	32.75	32.70	42.3	33.4	H, 3.55 C, 20.8	42.5	33.2	H, 3.63 Cl, 20.7
$CH=CC_2H_5$ | $CF_2—CF_2$	55/100	1.3472	1.199	20	28.01	27.46	46.8	49.3		47.1	49.3	
$CFBrCFBr$ | $CF_2—CF_2$	90–90.5/638	1.3838		25								
$CBr_2—CBr_2$ | $CF_2—CF_2$	Melting Point 153–154°						10.83	17.1	Br, 72.0	10.95	15.9	Br, 72.0

[a] See ref. 10.

3,4-Dibromo-1,1,2,2-tetrafluorocyclobutane. A mixture of 5.0 g. of 3,3,4,4-tetrafluorocyclobutene and 8.0 g. of bromine was sealed in a pyrex tube and irradiated for 1 day with ultraviolet light. Distillation yielded 7.2 g. (63%) of 3,4-dibromo-1,1,2,2-tetrafluorocyclobutane, b.p. 63–64° (79 mm.), n_D^{20} = 1.4220, d_4^{20} 2.129. The molar refraction calculated for this cyclobutane structure was 34.62, found: 34.12.

Anal. Calcd. for $C_4H_2Br_2F_4$: Br, 55.9. Found: Br, 55.7.

2,3,3-Trifluorocyclobutene. Forty grams of 1-chloro-1,2,2-trifluorocyclobutane was added dropwise to a slurry of 100 g. of potassium hydroxide in mineral oil containing 0.1 g. each of *t*-butylcatechol and diphenylamine and the mixture was allowed to stir for 1 day at room temperature. Volatile materials were removed under reduced pressure to yield 8.6 g. (21%) of 2,3,3-trifluorocyclobutene, b.p. 26.8° (631 mm.), n_D^{25} = 1.3170, d_4^{25} 1.190. This cyclobutene polymerized to a white solid on standing in the absence of traces of *t*-butylcatechol. The molar refraction calculated for the 2,3,3-trifluorocyclobutene structure was 18.64; that found was 17.86. The calculated molecular weight was 108.1; that found by gas density was 109.7.

Anal. Calcd. for $C_4H_3F_3$: C, 44.5; F, 52.7. Found: C, 44.1; F, 52.4.

2,3-Dibromo-1,1,2-trifluorocyclobutane. A mixture of 5.7 g. of 2,3,3-trifluorocyclobutene and 8.6 g. of bromine was sealed in a glass tube at liquid nitrogen temperatures. The reaction was complete by the time the mixture warmed to room temperature and 7.5 g. (53%) of 2,3-dibromo-1,1,2-trifluorocyclobutane was obtained, b.p. 76° (59 mm.), n_D^{25} 1.4544, d_4^{25} 2.125. The molar refraction calculated for this structure was 34.54; that found was 34.17.

Anal. Calcd. for $C_4H_3Br_2F_3$: C, 17.9; H, 1.13; Br, 59.7; F, 21.3. Found: C, 18.2; H, 1.26; Br, 59.5; F, 21.8.

3-Vinyl-2-chloro-1,1,2-trifluorocyclobutane. About 10 g. (0.185 mole) of 1,3-butadiene, 23 g. (0.198 mole) of chlorotrifluoroethylene, 0.1 g. of hydroquinone, and 0.5 ml. of terpene B (see Table I, footnote a) inhibitor were sealed in an air-free, heavy-walled Pyrex combustion tube. The tube was heated for 36 hr. at 100°, 12 hr. at 120°, 24 hr. at 150°, and 30 hr. at 180°. The tube was then cooled and opened. Distillation of the reaction products yielded 24.6 g. (78%) of 3-vinyl-2-chloro-1,1,2-trifluorocyclobutane, b.p. 109° (631 mm.), n_D^{25} 1.3927, d_4^{25} 1.244. Barrick[10] reported a boiling point of 115° for the same adduct but did not characterize the nature of the adduct.

Anal. Calcd. for $C_6H_6ClF_3$: C, 42.25; H, 3.55; F, 33.42; Cl, 20.79. Found: C, 42.49; H, 3.63; F, 33.16; Cl, 20.70.

Ozonolysis of 3-vinyl-2-chloro-1,1,2-trifluorocyclobutane. A mixture of ozone and oxygen was passed through a solution of 14.2 g. of 3-vinyl-2-chloro-1,1,2-trifluorocyclobutane in 65 ml. of methylene chloride at −75° until ozone uptake ceased. After warming to room temperature, this ozonide solution was added dropwise to a stirred mixture of 27 g. of 30% hydrogen peroxide, 0.8 ml. sulfuric acid and 35 ml. of water. Cooling with an ice bath was necessary initially. Ultimately the methylene chloride was distilled from the above mixture and it was stirred at 60° overnight. The resulting acidic reaction mixture was ether extracted, the acidic components were in turn taken into aqueous base, and the latter solution acidified and ether extracted. From the final extract, 8.7 g. of acidic brown oil was obtained which slowly crystallized. These crystals were recrystallized twice from toluene to yield 2 g. of α,α-difluoroglutaric acid, m.p. 102–103°; neut. equiv. Calcd. for $HO_2CCF_2CH_2CO_2H$: 84.05. Found: 82.6. This acid was previously obtained from the hydrolysis of 3-cyano-2-chloro-1,1,2-trifluorocyclobutane and the melting point reported as 103–105°.[9]

Anal. Calcd. for $C_5H_6O_4F_2$: C, 35.7; H, 3.60. Found: C, 35.6; H, 3.85.

(9) D. D. Coffman, P. L. Barrick, R. D. Cramer, and M. S. Raasch, *J. Am. Chem. Soc.*, **71**, 490 (1949).

(10) P. L. Barrick, U. S. Patent **2,462,345** (1949).

Bromination of 1-ethyl-3,3,4,4-tetrafluorocyclobutene. About 9.90 g. (0.0642 mole) of 1-ethyl-3,3,4,4-tetrafluorocyclobutene, 10.27 g. (0.0643 mole) of bromine, and 0.2 ml. of a saturated aqueous solution of acetamide were sealed in an air-free pyrex tube. The tube was wrapped in foil and heated for 24 hr. at 100°. The entire amount of bromine was consumed. On opening the tube a large amount of hydrogen bromide escaped and 15.5 g. of crude products were obtained. Distillation yielded 1.2 g. of recovered starting material, 5 g. of an unsaturated monobromide, and more highly brominated products. The monobromide had the following properties: b.p. 73–74° (50 mm.), n_D^{25} 1.4171, d_4^{25} 1.687. The molar refraction calculated for an unsaturated monobromocyclic compound, $C_6H_5BrF_4$, was 35.73, while that observed was 34.74.

Anal. Calcd. for $C_6H_5BrF_4$: C, 30.9; H, 2.16; Br, 34.3. Found: C, 30.4; H, 2.42; Br, 33.8.

Tribromination. Nine grams (0.058 mole) of 1-ethyl-3,3,4,4-tetrafluorocyclobutane and 16 g. (0.10 mole) of bromine were refluxed and irradiated with ultraviolet light for 1 day. All the bromine was consumed, hydrogen bromide evolved, and 17 g. of crude products obtained. Distillation revealed a complex mixture of products from which 1.9 g. of an unsaturated tribromide b.p. 88–90° (6 mm.), n_D^{25} 1.5095, was isolated.

Anal. Calcd. for $C_6H_3BrF_4$: Br, 61.34. Found: Br, 61.75.

Attempted cyclization of propargyl chloride and tetrafluoroethylene. An equimolar mixture of propargyl chloride and tetrafluoroethylene was heated in an air-free stainless steel autoclave in the presence of terpene B inhibitor. While heating, the mixture detonated at about 150°.

Debromination of 1,2-dibromohexafluorocyclobutane. About 18.6 g. of 1,2-dibromohexafluorocyclobutane from bromotrifluoroethylene cyclization was added dropwise to a stirred slurry of 24 g. of zinc dust, activated previously by 0.5 ml. concd. hydrochloric acid, in 30 ml. of dibutoxytetraethylene glycol applying no heat. In an exothermic reaction, 8.0 g. (88%) of hexafluorocyclobutene boiled from the mixture. The product was identified as hexafluorocyclobutene by comparison of its spectrum with that of an authentic sample and by gas density molecular weight determination. This product had a molecular weight of 160 while that calculated for C_4F_6 is 162.

1,2-Dibromo-3,3,4,4-tetrafluorocyclobutene. About 0.0585 mole of activated zinc dust, prepared from 5.86 g. of 93% zinc dust plus 4 ml. of concd. hydrochloric acid, was added in small portions to a stirred solution of 26 g. (0.0585 mole) of 1,1,2,2 tetrabromotetrafluorocyclobutane in 80 ml. of ether at −80°. After zinc addition was complete, the mixture was stirred for 4 hr. at −80°, then was allowed to warm slowly, and was stirred for 1 day at room temperature. Volatile materials were removed from the reaction mixture under reduced pressure and distilled to yield 4 g. (24%) of 1,2-dibromo-3,3,4,4-tetrafluorocyclobutene, b.p. 92–94° (635 mm.), n_D^{25} 1.4222, d_4^{25} 2.112. The molar refraction calculated for 1,2-dibromo-3,3,4,4-tetrafluorocyclobutene structure was 34.14, while that observed was 34.17.

Anal. Calcd. for $C_4Br_2F_4$: C, 16.9; H, 0.0; Br, 56.3. Found: C, 16.9; H, 0.06; Br, 56.3.

Other attempted cycloadditions. Trifluoroethylene. Twenty-two grams of trifluoroethylene was treated for 30 hr. at 180° in an air-free Pyrex tube in the presence of hydroquinone and terpene B. From this reaction 86% of the trifluoroethylene was recovered and no 1,1,2,2,3,4-hexafluorocyclobutane formed. The latter is reported to boil at 27°.[11]

2-Chloro-1,1-difluoroethylene. Forty-two grams of 2-chloro-1,1-difluoroethylene was heated for 1 day at 180° and 1 day at 195° in the manner described above. No products boiling above room temperature were formed, but 86% of the starting material was recovered.

2-Bromo-1,1-difluoroethylene. Ninety-three grams of 2-bromo-1,1-difluoroethylene was heated for 1 day at 160° and 1 day at 180° as described above. No products boiling above room temperature were formed and 95% of the starting material was recovered.

Acknowledgment. We wish to express our appreciation to the Wright-Patterson Air Force Base, Ohio and to the Minnesota Mining and Manufacturing Company, St. Paul, Minnesota, for their support of this work.

BOULDER, COLO.

(11) R. N. Haszeldine and J. E. Osborne, *J. Chem. Soc.*, 61 (1956).

[CONTRIBUTION FROM THE SCIENTIFIC DEPARTMENT, ISRAEL MINISTRY OF DEFENCE]

Addition of Alcohols to Fluorinated Ethylenes

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The sodium alkoxide-catalyzed addition of primary alcohols to 1-bromo-2,2-difluoro-, 1,1-dibromo-2,2-difluoro-, and 1-bromo-1,2,2-trifluoroethylene has been studied. Properties of the products and infrared data are reported.

This paper parallels to some extent and supplements the recent publication of Park[1b] on the addition of ethanol to fluorobromoethylenes in the presence of alcoholic potassium hydroxide. It reports the addition of methyl, ethyl, and *n*-propyl alcohol to 1 - bromo - 2,2 - difluoro -, 1,1 - dibromo - 2,2-difluoro-, and 1-bromo-1,2,2-trifluoroethylene

$F_2C{=}CHBr$ $F_2C{=}CBr_2$ $F_2C{=}CFBr$

using the respective sodium alkoxides as catalyst.[2]

$RO{\cdot}CF_2{\cdot}CH_2Br$, $RO{\cdot}CF_2{\cdot}CHBr_2$, $RO{\cdot}CF_2{\cdot}CHBrF$

The physical properties and the analytical data for the compounds so obtained are summarized in Table I. The three ethoxy compounds (R = C_2H_5)

(1) (a) This paper forms part of the Ph.D. thesis, submitted by the author to the Hebrew University, Jerusalem.

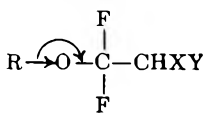
(1) (b) J. D. Park, H. J. Cummings, and J. R. Lacher, *J. Org. Chem.*, **23**, 1785 (1958).

(2) See W. T. Miller, E. W. Fager and P. H. Griswold, *J. Am. Chem. Soc.*, **70**, 431 (1948).

have previously been described by Swarts[3,4] who prepared them from 1,2-dibromo-1,1-difluoro-, 1,2,2-tribromo-1,1-difluoro-, and 1,2-dibromo-1,1,2-trifluoroethane, respectively, with sodium ethoxide or alcoholic potassium hydroxide. In these syntheses, too, the above three ethylenes are possibly formed as intermediates (by dehydrohalogenation).

The ethers derived from 1-bromo-2,2-difluoroethylene are stable in the presence of *large* quantities of water and still more stable in the presence of alkali; in contact with *small* quantities of water or humid air they decompose quickly and liberate hydrogen fluoride which appears to catalyze the decomposition, leading to the formation of bromoacetate or free bromoacetic acid. It was, thus, not possible to obtain satisfactory analyses for these ethers. The ethers derived from 1,1-dibromo-2,2-difluoroethylene showed this tendency to decompose in a much lesser degree, those derived from bromotrifluoroethylene not at all, with the exception of the propyl ether. The latter underwent far-reaching changes upon standing at room temperature in the presence of calcium chloride. The boiling point changed from 75.2° to 55–56° (at 130 mm.) and became unsharp, the density decreased from d^{15} 1.487 to 1.02 and the refractive index from n_D^{16} 1.3848 to 1.3825. Similar observations have been reported by Rapp[5] for the stability of (1,1,2-trifluoro-2-chloroethyl) *t*-butyl ether. The thermal stability of the ethers described shows the same sequence. The lower ethers derived from bromotrifluoroethylene distill without decomposition under atmospheric pressure, the propyl ether only under reduced pressure; those derived from 1,1-dibromo-2,2-difluoroethylene can only be distilled *in vacuo* (25–30 mm.), and those obtained from 1,1-difluoro-2-bromoethylene decompose upon prolonged heating in a column even under reduced pressure.

Tarrant[6] has suggested that the tendency of ethers of the type discussed here to form fluoride ions, depends essentially on the electron-donating power of the alkyl radical; the greater this power, the less stable the ether:



It appears that the number and negativity of electronegative elements in the [—CHXY group, too, influence the stability of the ethers. The more this group attracts electrons, the less tendency will be felt to form fluoride ions, and, therefore, the greater will be the stability of the ethers. One would thus expect the sequence

$$—CHFBr > —CHBr_2 > —CH_2Br$$

which is, indeed, the order of stability observed in the present experiments.

Table I shows that the atomic refraction of fluorine (calculated from the molecular refraction and the known equivalents of carbon, hydrogen, ether-oxygen and bromine) varies between 1.1 for the compounds containing three atoms of fluorine and 0.9 for those with only two fluorine atoms. A similar effect has been noted for the fluorobromoethanes and ethylenes.[7]

In Table II, the infrared spectra of some of the fluorinated ethers prepared, are summarized. A complete assignment of the infrared frequencies has not been successful. The CF_2 frequency is expected between 1200 and 1350 cm.$^{-1}$, in a region in which the asymmetric stretching frequency of the C—O—C group is also situated. The peak at about 1150 cm.$^{-1}$ can be ascribed to the C—F bond; the second (symmetric) C—O—C stretching frequency lies in *fluorinated* ethers at 1050 cm.$^{-1}$.[8]

EXPERIMENTAL

Starting materials. 1-Bromo-2,2-difluoro-, 1,1-dibromo-2,2-difluoro-, and *1-bromo-1,2,2-trifluoroethylene* were prepared from 1,2-dibromo-1,1-difluoroethane, 1,2,2-tribromo-1,1-difluoroethane and 1,2-dibromo-1,2,2-trifluoroethane, respectively, by treatment with aqueous potassium hydroxide. Details on these preparations will be published elsewhere.

General procedure for the addition reactions. A three necked flask, mounted with gas disperser, thermometer, stirrer and Y-tube carrying a reflux condenser and a thermometer to measure the temperature of the returning distillate, was used for the experiments; they were carried out in an atmosphere of dry and pure nitrogen. In the cases of bromotrifluoro- and bromodifluoroethylene the condenser was placed in a Dewar vessel filled with acetone–Dry Ice mixture; in the third case water was circulated through the condenser. The alcohols used were anhydrous in all experiments.

2-Bromo-1,1,2-trifluoroethyl methyl ether. The flask was cooled at −10° and a cold (−78°) solution of 18 g. of bromotrifluoroethylene in 25 ml. of methanol introduced. After adding dropwise a solution of 0.5 g. of sodium in 20 ml. of methanol, the temperature of the liquid was slowly raised to 16°. (From time to time, renewed cooling became necessary, as the reflux condenser became flooded.) The temperature of the returning distillate decreased to 3°; when it rose again to 16°, the flask was slowly heated to 60°. The product was then isolated by addition of water, dried with calcium chloride, and distilled. Thus 13.7 g. (63%) of the desired ether was obtained, b.p. 88.8°.

2-Bromo-1,1,2-trifluoroethyl ethyl ether. In the manner described above, 0.5 g. sodium in 20 ml. of ethanol was added to a solution of 21 g. of bromotrifluoroethylene in 25 ml. of ethanol at −15°. When the bath was removed, the temperature rose spontaneously to 55°, and the olefin began to boil. However, after some interval of time, the boiling

(3) F. Swarts, *Bull. Acad. Roy. Belges*, [3], **37**, 357 (1899).
(4) F. Swarts, *Bull. Acad. Roy. Belges*, 563 (1911).
(5) J. T. Baur and K. E. Rapp, *J. Am. Chem. Soc.*, **72**, 4480 (1950); K. E. Rapp, J. T. Barr, R. L. Pruett, C. T. Bahner, J. D. Gibson, and R. H. Lafferty, *J. Am. Chem. Soc.*, **74**, 749 (1952).
(6) P. Tarrant and H. C. Brown, *J. Am. Chem. Soc.*, **73**, 1781 (1951).
(7) Results to be published shortly.
(8) J. D. Park, C. M. Snow, and J. R. Lacher, *J. Am Chem. Soc.*, **73**, 862 (1951).

TABLE I

PHYSICAL PROPERTIES AND ANALYTICAL DATA OF ADDITION PRODUCTS

Compound	B.P. (°/mm.)	d_4^t	n_D^t	MR (found)	AR_F[b]	C		H		Br		F	
						Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
CH_3OCF_2CHFBr	88.8/760	1.721^{18}	1.3687^{18}	25.28	1.04	18.9	18.7	2.3	2.1	41.1	41.4	29.6	29.5
$C_2H_5OCF_2CHFBr$[a]	106/760	1.573^{20}	1.3744^{20}	30.08	1.10	23.5	23.2	2.9	2.9	38.9	38.6	27.6	27.5
n-$C_3H_7OCF_2CHFBr$	75.2/130	1.487^{15}	1.3848^{15}	34.81	1.13	26.7	27.2	4.0	3.7	36.6	36.2	25.8	25.8
$CH_3OCF_2CHBr_2$	55.8/130	2.101^{15}	1.4540^{15}	32.73	0.85	14.4	14.2	1.8	1.6	63.1	62.9	15.0	15.0
$C_2H_5OCF_2CHBr_2$	65/26	1.914^{15}	1.4472^{15}	37.41	0.88	17.9	17.9	2.4	2.3	60.0	59.7	14.3	14.2
n-$C_3H_7OCF_2CHBr_2$	72.2/23	1.794^{15}	1.4480^{15}	42.08	0.91	21.6	21.3	3.1	2.9	57.1	56.7	13.2	13.5
$CH_3OCF_2CH_2Br$	54.7/220	1.653^{18}	1.3898^{18}	25.08	0.91								
$C_2H_5OCF_2CH_2Br$[a]	70/175	1.527^{15}	1.3958^{15}	29.73	0.92								

[a] These compounds have been recently described by Park[1]: $C_2H_5OCF_2CH_2Br$: b.p. 55–56°/104 mm.; d_4^{25} 1.512, n_D^{25} 1.3980; $C_2H_5OCF_2CHFBr$: b.p. 62–62.5°/167 mm.; d_4^{25} 1.571; n_D^{25} 1.3710. [b] Calcd. from MR and the atomic refraction of carbon, hydrogen, bromine, and ether oxygen.

TABLE II

INFRARED SPECTRA OF THE FLUORINATED ETHERS

Substance															
CH_3OCF_2CHFBr	3015		1475		1370		1290	1220		1150	1055 (broad)	990		830	746	717
$C_2H_5OCF_2CHFBr$	3035		1460		1370		1285	1200			1055 (broad)		903	830	735 (broad)	
$C_3H_7OCF_2CHFBr$	3000		1480	1410	1370		1280	1195			1055 (broad)	980	955	848	750	727
$CH_3OCF_2CHBr_2$	3015	(3000)	1470				1282	1210		1136	1050 (broad)	990		823	741	700
$C_2H_5OCF_2CHBr_2$	3035	(3000)	1460		1390		1290	1190		1145	1030 (broad)		912	827	747	700
$C_3H_7OCF_2CHBr_2$	3000		1475	1410	1390	1360	1290	1230	1190	1150	1045 (broad)	975	955	844	746	700

ceased (no more refluxing liquid), and the desired ether could be isolated by addition of water; yield, 16.5 g. (61%); b.p. 106°.

2-Bromo-1,1,2-trifluoroethyl n-propyl ether. In the same manner, the reaction between 16 g. of bromotrifluoroethylene in 25 ml. of *n*-propyl alcohol and 0.5 g. of sodium in 20 ml. of propanol was carried out. The temperature rose spontaneously to 77°. The propanol was removed *in vacuo* and the product purified by distillation, b.p. 76° (130 mm.); yield, 16 g. (73%).

2,2-Dibromo-1,1-difluoroethyl methyl ether. In the manner described above, a few drops of a solution of 0.25 g. of sodium in 10 ml. of methanol were added to a solution of 25 g. of 1,1-dibromo-2,2-difluoroethylene in 30 ml. of methanol. A lively exothermic reaction took place. The balance of the sodium methoxide solution was added with cooling so that the temperature of the mixture did not exceed 40°. The ether was isolated by addition of water, dried and distilled, b.p. 55.8° (30 mm.); yield, 22 g. (77%).

2,2-Dibromo-1,1-difluoroethyl ethyl ether. To a solution of 24 g. of 1,1-dibromo-2,2-difluoroethylene in 30 ml. of alcohol, a solution of 0.5 g. of sodium in 20 ml. of ethanol was added, until further addition did not cause any more rise in temperature. Water was added and the ether dried over calcium chloride and distilled. It boiled at 65° (26 mm.); yield, 23 g. (79%).

2,2-Dibromo-1,1-difluoroethyl n-propyl ether. The reaction between 23 g. of 1,1-dibromo-2,2-difluoroethylene in 30 ml. of *n*-propyl alcohol and 0.5 g. of sodium in 20 ml. of the same solvent was carried out as in the foregoing case. The reaction was completed by heating the mixture at 90° for 30 min. and the excess *n*-propanol removed under reduced pressure. The product boiled at 72° (23 mm.); yield, 21 g. (72%).

With *isopropanol*, no reaction took place under the same operating conditions.

2-Bromo-1,1-difluoroethyl methyl ether. At −15°, a solution of 0.5 g. of sodium in 20 ml. of methanol was added to a solution of 20 g. of 1-bromo-2,2-difluoroethylene in 25 ml. of methanol. The mixture was slowly brought to room temperature and kept until the reflux ceased. As the product forms an azeotrope with methanol, it was precipitated by addition of water, dried and distilled; yield, 13.5 g. (61%). It boiled at 98° (760 mm.) or 58° (210 mm.). Upon standing for 4 days, it began to decompose and liberated hydrogen fluoride; at this stage, it had become impossible to distill the product without complete decomposition.

2-Bromo-1,1-difluoroethyl ethyl ether. In the same manner, the ethyl ether (b.p. 70° (175 mm.); yield, 12 g. (60%)) was obtained from 16.8 g. of 1-bromo-2,2-difluoro-ethylene in 25 ml. of alcohol and 0.5 g. of sodium in 20 ml. of ethanol. The product showed the same behavior as the methyl ether.

TEL-AVIV, ISRAEL

[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY OF THE DEPARTMENT OF SURGERY, UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE]

Derivatives of Fluorene. VIII. Fluorofluorenes. II[1]

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Further work is reported concerning ring-fluorinated 2-acetamidofluorene (a carcinogen), and related compounds. Improved preparation of the 4- and 5-fluoro isomers is described together with preparation of the new 1-fluoro and 8-fluoro-2-acetamidofluorenes. Monodemethylation of the $-N(CH_3)_2$ group is encountered in an attempted Schiemann decomposition. Some observations concerning the directive effect of substituent fluorine in nitration of the fluorene nucleus are noted.

This paper describes the preparation of further new *N*-2-(monofluorofluorenyl)acetamides[2] and related compounds, and better methods for some previously reported members of this series.

We have found the following method preferable for making *N*-2-(4-fluoro-fluorenyl)acetamide, a compound described in the previous paper in this series.[1] *m*-Nitroaniline was iodinated by modification of a known procedure.[3] The diazonium fluoborate of this substance gave the corresponding fluoro compound. The yield in this step was improved from very poor to above 40% by rapid heating (170°) in sand under aspirator vacuum. Lower temperatures and longer time, which had improved yields in some of our decompositions, led to greatly increased tar formation—perhaps because of the substituent iodine. An Ullmann reaction followed by hydrolysis, separation and cyclization gave 4-fluoro-2-nitrofluorenone. Reduction of the nitro group[1] and then of the 9-keto followed by acetylation, all as described in the Experimental section, yielded the desired product.

In an improved approach to the 2,5-isomer we began with 4-carboxyfluorenone[1] and, by way of the known acid chloride, azide and 4-aminofluorenone, obtained fluorenone-4-diazonium fluoborate. When this was decomposed in sand, 60% yields of 4-fluorofluorenone were recovered, but when heated in suspension in toluene (in this case at 60–65°), 70% yields were obtained with much greater convenience. Reduction gave the known 4-fluorofluorene.[1]

Use of a liquid medium in decomposing diazonium fluoborates is not new, but suspension in benzene, toluene, xylene,[4] chloro-, or bromo-

(1) This work was supported in part by a grant (C-1744) from the National Cancer Institute, U. S. Public Health Service. For the preceding paper in the fluorofluorene series see *J. Am. Chem. Soc.*, **81**, 1092 (1959).

(2) These compounds are being tested for carcinogenicity and in metabolic studies by Drs. J. A. and E. C. Miller at the McArdle Memorial Laboratory, The University of Wisconsin.

(3) M. P. Brenans and M. A. Haller, *Compt. rend.*, **138**, 1503 (1904).

(4) A. Roe and G. F. Hawkins, *J. Am. Chem. Soc.*, **71**, 1785 (1949). A. Roe, *Organic Reactions*, Vol. V, John Wiley and Sons, New York, N. Y., 1949, p. 211.

benzene[5] does not seem to have been used as extensively as the great convenience of the method would suggest. We have also used *o*-dichlorobenzene successfully with substances having a decomposition point too high for boiling xylene.

Nitration of 4-fluorofluorenone in 60–65% yield, reduction to the amine and carbonyl reduction with phosphorus and hydriodic acid gave the known[1] 5-fluoro-2-fluorenamine.

Preparation of the first of the new fluorinated 2-acetamidofluorenes to be described here started with nitration[6] of fluorene-1-carboxylic acid (obtained by oxidation of fluoranthene and reduction of the 9-oxofluorene-1-carboxylic acid with phosphorus and hydriodic acid[7]) to 7-nitrofluorene-1-carboxylic acid. A Schmidt reaction gave known 7-nitro-1-fluorenamine. The diazonium fluoborate of the latter, made in the presence of phosphoric acid[8] and decomposition in toluene, gave 1-fluoro-7-nitrofluorene, which was reduced[9] and acetylated to form *N*-2-(8-fluorofluorenyl)acetamide. Alternatively, we prepared 1-amino-fluorenone from 1-acetamidofluorenone.[10] A Schiemann reaction gave 1-fluorofluorenone, which was nitrated in the 7- position; this proved to be identical with the product obtained from oxidation of 1-fluoro-7-nitrofluorene with sodium dichromate. Reduction to the amine was followed by attempted reduction of the 9-carbonyl. This proved disappointing and the method was abandoned.

Trifluoroacetylation of 1-fluoro-7-fluorenamine, followed by nitration, led to a high yield of the 2-nitro derivative.[11] Mild alkaline hydrolysis and deamination gave 1-fluoro-2-nitrofluorene, which we reduced and acetylated to obtain *N*-2-(1-fluorofluorenyl)acetamide, identical (melting point, mixture melting point and infrared spectrum) with a by-product obtained in small yield from a reaction sequence which had given us the 3-fluoro-2-nitro- isomer.[12] The by-product, as is shown in the work cited, could only be from the alternate product of cyclodehydration, *i.e.*, the 1-fluoro-2-nitrofluorenone. Oxidation of 1-fluoro-2-nitrofluorene with sodium dichromate gave a fluorenone identical (infrared spectrum) with a compound described as 1-fluoro-2-nitrofluorenone.[13]

Observations of Bergmann *et al.*,[14] regarding the "unusually large reactivity of the *ortho*-position" (to fluorine) in electrophilic reactions of aromatic compounds, and of Allen *et al.*[15] concerning the "strong *para* directing influence of the fluorine substituent" (with fluoroindoles), are of interest in examining the results of nitration of fluorofluorenes (and 9-ones) and substituted fluorofluorenes. With only fluorine as a substituent, the unsubstituted ring is nitrated predominantly: 1-fluoro-, 2-fluoro-,[16] 3-fluoro-,[12] and 4-fluorofluorenone, and 2-fluorofluorene[17] all give the 7-nitro- derivative in high yield. When the non-fluoro-substituted ring is blocked with the 7-trifluoroacetamido- group (as above), nitration is mainly *ortho* to the 1-fluoro- substituent. However, 4-fluoro-7-trifluoroacetamidofluorene is nitrated *meta* to the fluorine in the 2-position (40%) and to a lesser extent (11%) in the 6-position. In reference[1] we assumed this was the 6-position, but in work described below, this is established beyond reasonable doubt: The known 7-acetamido-4-fluorofluorene was nitrated, presumably in the 6-position (2-acetamidofluorene is nitrated predominantly in the 3-(*ortho*)-position). Hydrolysis and trifluoroacetylation gave a substance identical with the 11% by-product above. In following papers in this series we expect to describe further directional effects in the nitration of fluorinated fluorene derivatives.

An attempt to confirm additionally the structure of the 2,1- isomer failed in its purpose, but gave interesting results. We diazotized 2-*N*,*N*-dimethylamino-1-fluorenamine[11] and carried out a Schiemann decomposition. The only product recovered (31%) was *N*-monomethyl-2-fluorenamine. It is possible that there was in the residual mixture a small amount of the desired 1-fluoro compound. A further instance of this type of monodemethylation is given in the next paper in this series.[12]

EXPERIMENTAL[18]

Improved procedure for N-2-(4-fluorofluorenyl)acetamide. 2-Fluoro-4-nitroiodobenzene. A slight molar excess of iodine monochloride (rather than with 3 molar equivalents[3]) was added dropwise at 80–82° (6 hr.) to *m*-nitroaniline. The reaction was kept at 80° for an additional 18 hr., yielding

(5) K. Inukai and Y. Maki, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **59**, 1162 (1956); *J. Chem. Soc. Japan, Pure Chem. Sect.*, **78**, 1305 (1957).

(6) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **21**, 1386 (1956).

(7) D. C. Morrison, *J. Org. Chem.*, **23**, 1772 (1958).

(8) H. A. Schoutissen, *J. Am. Chem. Soc.*, **55**, 4531 (1933).

(9) T. L. Fletcher and M. J. Namkung, *J. Org. Chem.*, **23**, 680 (1958).

(10) E. Sawicki and B. Chastain, *J. Org. Chem.*, **21**, 1028 (1956).

(11) M. J. Namkung and T. L. Fletcher, manuscript has been sent to this journal as Derivatives of Fluorene. VII.

(12) Work completed; manucript Fluorofluorenes. III to be submitted shortly.

(13) Dr. John H. Weisburger, National Cancer Institute, private communication and kind contribution of a copy of the infrared spectrum of his substance, m.p. 231–232° (see Experimental section).

(14) E. D. Bergmann, J. Blum, S. Butanaro, and A. Heller, *Tetrahedron Letters*, 15 (1959).

(15) F. L. Allen, P. Koch, and H. Suschitzky, *Tetrahedron*, **6**, 315 (1959).

(16) Unpublished data, this laboratory.

(17) J. A. Miller, R. B. Sandin, E. C. Miller, and H. P. Rusch, *Cancer Research*, **15**, 188 (1955).

(18) Melting points were taken on a Fisher-Johns apparatus and are corrected to standards. Microanalyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were run (potassium bromide discs) on a Beckman IR-5 instrument.

39–46% of the iodo compound, m.p. 160–161° (lit.,[3] m.p. 160.5°), yellow needles. This was stirred (47 g., 0.18 mole) into 160 ml. of 48–50% fluoboric acid in an ice-salt bath and diazotized with 12.5 g. (0.18 mole) of sodium nitrite in 28 ml. of water at 0–5°. The diazonium salt was filtered, washed with cold 5% fluoboric acid, methanol, and ether, and dried giving 59.2 g. (92.5%). This was decomposed in 20 g. batches and mixed with two volumes of sand, by heating at a bath temperature of 167–170° under aspirator vacuum for 30 min. After extraction with benzene and evaporation, the solid was recrystallized from methanol (Darco), giving 20.7 g. (44%) of the fluoro compound, m.p. 125–127.5°. Recrystallization from methanol gave an analytical sample, m.p. 128.5–129.5°.

Anal. Calcd. for $C_6H_3FINO_2$: C, 27.00; H, 1.13; N, 5.25. Found: C, 26.74; H, 1.16; N, 5.43.

4-Fluoro-2-nitro-9-oxofluorene. Activated copper powder (see ref. 1, footnote[16]), 60 g., with 19.4 g. (0.073 mole) of the above iodo-compound and 0.15 mole of either ethyl or methyl *o*-bromobenzoate in an Ullmann condensation, followed by the general procedures described in the previous fluorofluorene paper, gave 43% (7.6 g.) of yellow needles, m.p. 195.5–196.5°. With the methyl ester, reaction temperatures of 215–220° were required, 15–20° higher than with the ethyl ester, to obtain the same yields. Crystallization from a benzene-methanol mixture gave an analytical sample, m.p. 196–197°.

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49; N, 5.76. Found: C, 64.23; H, 2.58; N, 5.64.

4-Fluoro-9-oxo-2-fluorenamine. 2-Nitro-4-fluorofluorenone (0.95 g.) was mixed with stannous chloride dihydrate (4 g.), concd. hydrochloric acid (4 ml.), and 95% ethanol (3 ml.). The mixture was boiled with stirring for 15 min. then cooled to room temperature. The yellow precipitate was filtered, washed with 1% hydrochloric acid, and stirred in 2*N* sodium hydroxide (150 ml.). The amine was filtered, washed, and dried. Recrystallization from toluene gave dark purple needles, 0.8 g. (97%), m.p. 251–252°. One more crystallization gave an analytical sample, m.p. 251.5–252.5°.

Anal. Calcd. for $C_{13}H_8FNO$: C, 73.23; H, 3.78; N, 6.57; F, 8.91. Found: C, 73.48; H, 3.52; N, 6.39; F, 8.55.

4-Fluoro-2-fluorenamine. 2-Amino-4-fluorofluorenone (6.3 g., 0.03 mole) was mixed with 85% hydrazine hydrate (10.8 ml.) and sodium hydroxide (4.6 g.) dissolved in 2,2′-oxydiethanol (130 ml.). The mixture was refluxed at 178–180° (bath) for 2.5 hr. and at 210° (bath) for 3.5 hr., stirred into cold water, filtered, washed, and dried giving 5.3 g. (90%) of the crude product, m.p. 116–122°. One crystallization from benzene raised the melting point to 121–123.5°. There was no depression of the melting point when this was mixed with an authentic sample.[1]

2-Acetamido-4-fluorofluorene. Acetic anhydride (3 g.; 1.1 equivalents) was added to the crude product obtained above (5.3 g.) with rapid stirring. After thorough mixing, the solid mass was heated on a steam bath for 15 min. with frequent stirring, then dried in a desiccator under vacuum with moistened sodium hydroxide. Recrystallization from aqueous ethanol (Darco) gave 5.9 g. (93%); melting point and mixture melting point with authentic sample, 196–197.5°.

Improved procedure for N-2-(5-fluorofluorenyl)acetamide. 4-Fluorofluorenone. A mixture of 4-aminofluorenone (137 g., 0.7 mole), 48–50% fluoboric acid (420 ml.), and water (250 ml.) was warmed to effect solution, then cooled to 0–5°. Sodium nitrite (48.4 g.; 0.7 mole) in water (70 ml.) was added gradually. After further stirring (30 min.), the salt was filtered, washed with cold 5% fluoboric acid, methanol, and ether, and dried, giving 190–200 g. (93–98.5%).

(a) The diazonium fluoborate (42.7 g.) was mixed with three times its volume of dry sand and heated under reduced pressure (aspirator vacuum) at a bath temperature of 80–85° for 45 min. The mixture was extracted with acetone which was evaporated. The residue was recrystallized from methanol (Darco) giving 19.4 g. One crystallization from ethanol gave 16.7 g. melting at 159–161° (61% from the amine).

(b) The diazonium fluoborate (39.6 g.) was suspended in 1 l. of toluene which was heated slowly until evolution of gas commenced (internal temperature, 65°). The temperature was maintained at 60–65° until evolution of gas ceased. Then the reaction mixture was cautiously heated to boiling and the precipitate removed by filtration. The filtrate was treated with Darco and concentrated to obtain the product which was recrystallized from ethanol giving yellow needles (67% on the basis of the amine used), m.p. 161–162.5°.

Anal. Calcd. for $C_{13}H_7FO$: C, 78.78; H, 3.56; F, 9.59. Found C, 78.83; H, 3.44; F, 9.11.

Reduction of 4-fluorofluorenone. A mixture of 2 g. of 4-fluorofluorenone, 5 g. of red phosphorus, 6 ml. of 48–50% hydriodic acid and 50 ml. of acetic acid was refluxed 40 hr. and filtered hot. The filtrate was boiled almost to dryness and the resulting oil was extracted by boiling with petroleum ether (b.p. 30–60°). This was decanted and evaporated on the steam bath in a current of air. The residue amounted to 1.6 g. (86%), m.p. 38–39°. Recrystallization from cyclopentane (Darco) gave a substance identical with 4-fluorofluorene[1] (melting point and mixture melting point).

5-Fluoro-2-nitro-9-oxofluorene. The above ketone (16.6 g.) was slowly added with stirring to a mixture of glacial acetic acid (80 ml.) and fuming nitric acid (80 ml., d. 1.50) at 35°. Concentrated sulfuric acid (12 ml.) was then added slowly and the reaction temperature rose to 56°. After cooling to room temperature, the mixture was chilled in an ice bath. The yellow needles were filtered, washed with cold acetic acid, and dried giving 13.2 g. (65%), m.p. 211.5–213°.

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49; N, 5.76. Found: C, 63.97; H, 2.26; N, 5.92.

5-Fluoro-9-oxo-2-fluorenamine. A mixture of 5-fluoro-2-nitrofluorenone (50 g., 0.205 mole), stannous chloride dihydrate (200 g.), concd. hydrochloric acid (200 ml.), and 95% ethanol (125 ml.) was heated cautiously until the initial evolution of gas subsided. The pasty mixture was then boiled with stirring for 20 min. and cooled to room temperature. The solids were filtered and treated with 2*N* sodium hydroxide. The amine, after crystallization from toluene, melted at 204–205°, yielding 90–97° (39–42 g.).

Anal. Calcd. for $C_{13}H_8FNO$: N, 6.57. Found: N, 6.55.

N-2-(5-Fluoro-9-oxofluorenyl)acetamide. Acetylation of the preceding compound gave a substance, m.p. 245–246°.

Anal. Calcd. for $C_{15}H_{10}FNO_2$: C, 70.58; H, 3.95; N, 5.49. Found: C, 70.55; H, 4.00; N, 5.68.

5-Fluoro-2-fluorenamine. (a) Wolff-Kishner (Huang-Minlon) reduction of 5-fluoro-9-oxo-2-fluorenamine gave an oil which was acetylated to give the known amide[1] (49% in two steps).

(b) A mixture of 5-fluoro-9-oxo-2-fluorenamine (10 g., 0.047 mole), red phosphorus (22 g.), 47% hydriodic acid (30 ml.) and glacial acetic acid (250 ml.) was refluxed for 24 hr. As much acetic acid as possible was then distilled off, avoiding decomposition, and the remainder was diluted with water. The solution was filtered from the phosphorus and made alkaline with ammonium hydroxide. The oily precipitate was filtered, washed with ice water, and dried over phosphorus pentoxide (9.8 g.). This was extracted several times with 200 ml. portions of boiling *n*-hexane. The extract was concentrated until an oil began to separate. Then the mixture was chilled in ice water and white needles (4.5 g., 48%) were collected, m.p. 85–87°. A mixture melting point with the authentic compound showed no depression.

N-2-(5-Fluorofluorenyl)acetamide. Acetylation of the solid with acetic anhydride and one crystallization from aqueous ethanol (Darco) gave 87% of the known compound.

N-2-(8-Fluorofluorenyl)acetamide. 8-Fluoro-2-nitrofluorene. Diazotization of 2-nitro-8-fluorenamine (25.2 g.) in 270

ml. of 48–50% fluoboric acid and 270 ml. of 85% phosphoric acid with 17 g. of sodium nitrite in 100 ml. of water, with subsequent stirring at 0–5° for 1.5 hr., gave the salt, which was recovered and dried in the usual way. This was slowly added to boiling toluene (400 ml.). The mixture was gently boiled an additional hour with occasional addition of boiling toluene. Filtration and evaporation of the toluene followed by crystallization from ethanol (Darco) gave 75–80% yields of the substance, m.p. 141–142°. Recrystallization from ethanol gave an analytical sample, m.p. 143–143.5°.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52; N, 6.11. Found: C, 68.22; H, 3.51; N, 6.17.

8-Fluoro-2-fluorenamine. A solution of 12.0 g. of the above nitro compound in 500 ml. of toluene and 500 ml. of ethanol was reduced with 12 ml. of hydrazine hydrate and Raney nickel in the usual way.[9] The snow-white product, 9.9 g. (95%), melted at 138–139.5°. Recrystallization from ligroin gave an analytical sample, m.p. 139–139.5° (slight softening at 138°).

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.02; N, 7.03. Found: C, 78.63; H, 5.20; N, 7.01.

N-2-(8-Fluorofluorenyl)acetamide. To 10 g. of the amine in 50 ml. of benzene, 6 g. of acetic anhydride was added, and the mixture was warmed for 15 min. on the steam bath. The white precipitate was filtered and dried, 11.6 g., m.p. 189–190°. One crystallization from alcohol gave an analytical sample, m.p. 189–190°.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; N, 5.81; F, 7.88. Found: C, 74.97; H, 5.05; N, 6.23; F, 7.72.

1-Fluorofluorenone. A mixture of 4 g. of 1-aminofluorenone, 22 ml. of fluoboric acid, and 4 ml. of water was heated to aid salt formation, then cooled to 0°, and 1.5 g. of sodium nitrite in 6 ml. of water was added in the usual way for 10 min. and stirred for an additional 20 min. Filtration, followed by washing, gave 6.0 g. (100%), dec. ~140°.

The diazonium salt was decomposed in 100 ml. of boiling xylene, replenishing this as evaporation proceeded. After 1 hr. no more acidic fumes were apparent and the mixture was filtered and boiled down to near dryness. The yield was 3.2 g. (78.5%), m.p. 107–110°. Recrystallization from ligroin (d. 0.67–0.69), with Darco treatment gave 2.9 g., m.p. 110–111.5°. An analytical sample was obtained after one recrystallization from alcohol.

Anal. Calcd. for $C_{13}H_7FO$: C, 78.78; H, 3.56; F, 9.59. Found: C, 79.05; H, 3.46; F, 9.34.

1-Fluoro-7-nitro-9-oxofluorene. To a mixture of 15 ml. of acetic acid and 15 ml. of fuming nitric acid (d. 1.5) 3 g. of 1-fluorofluorenone was added at 35°. All the solids dissolved and the solution became dark. Upon addition of 3 ml. of concd. sulfuric acid, the temperature rose to 50° and gradually cooled to room temperature. The mixture was diluted with water and the resulting light yellow precipitate filtered off, washed, and dried to give 3.65 g. (99%), m.p. 196–202°. Recrystallization from benzene gave a first crop, m.p. 210–211°, of 2.7 g. (74%). Another crystallization (ethanol) did not raise the melting point.

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49; N, 5.76. Found: C, 64.12; H, 2.50; N, 6.08.

Oxidation of 1-fluoro-7-nitrofluorene. Sodium dichromate (3 g.) in glacial acetic acid was boiled for 10 min. with 1 g. of the compound. A near quantitative yield of product was recovered which, upon recrystallization from benzene (Darco), melted at 210–211°. A mixture melting point with the preceding compound showed no depression.

N-2-(8-Fluorofluorenyl)trifluoroacetamide. To a solution of 22.2 g. (0.072 mole) of 8-fluoro-2-fluorenamine in 200 ml. of hot benzene, a mixture of 20 g. (0.095 mole) of trifluoroacetic anhydride and 100 ml. of benzene was added slowly as a white precipitate formed. The mixture was boiled for 20 min. and cooled. A yield of 32.2 g. (98%) was obtained, m.p. 195–196°. One recrystallization from alcohol (Darco) gave an analytical sample, m.p. 195–195.5°.

Anal. Calcd. for $C_{15}H_9F_4NO$: N, 4.74. Found: N, 4.79.

N-2-(8-Fluoro-7-nitrofluorenyl)trifluoroacetamide. N-2-(8-Fluorofluorenyl)trifluoroacetamide (23 g.) was dissolved in 230 ml. of hot glacial acetic acid and cooled to 50°. Some precipitate formed. To the mixture, 23 ml. of nitric acid (d. 1.42) was added, while stirring and heating to 60°, at which point 3 ml. of concd. sulfuric acid was added with continuous thorough stirring. The solids dissolved, the temperature rose to 75° and a mass of yellow crystals formed. After cooling, the precipitate was filtered and washed with a little cold glacial acetic acid and then with alcohol and dried, giving 18.8 g. (71%), m.p. 242–245°. One recrystallization from toluene (Darco) gave an analytical sample 17.3 g., m.p. 245–245.5°.

Anal. Calcd. for $C_{15}H_8F_4N_2O_3$: N, 8.23. Found: N, 8.25.

By diluting the mother liquor with water, 5.6 g. of a second crop, m.p. 180–230° was obtained. This was recrystallized from alcohol and, in benzene solution, chromatographed through an alumina column, with benzene elution, giving 1.5 g. of *8-fluoro-7-nitro-2-fluorenamine*, m.p. 228–231°. A mixture melting point with the alkaline hydrolysis product (next paragraph) was not depressed.

8-Fluoro-7-nitro-2-fluorenamine. To a suspension of 12.3 g. (0.036 mole) of *N*-2-(8-fluoro-7-nitrofluorenyl)trifluoroacetamide in 1 l. of boiling alcohol, an aqueous solution (30 ml) of sodium hydroxide (5 g.) was added with stirring. The solution turned dark red and the solid dissolved. Upon boiling for 5 min., a red precipitate formed. The boiling was continued for 10 more min. and the mixture cooled. After filtration, drying, and recrystallization from alcohol (Darco), 8.3 g. (94.5%), m.p. 230–231°, was recovered. One further recrystallization from alcohol gave an analytical sample, m.p. 231–231.5°.

Anal. Calcd. for $C_{13}H_9FN_2O_2$: C, 63.93; H, 3.72. Found: C, 63.97; H, 3.78.

1-Fluoro-2-nitrofluorene. To a mixture of 160 ml. of concd. hydrochloric acid and 2.4 g. (0.035 mole) of sodium nitrite in 20 ml. of water at 0°, 4.7 g. (0.019 mole) of 8-fluoro-7-nitro-2-fluorenamine was added in small portions with stirring, over a period of 10 min. The mixture was stirred for an additional hour at 0° and 160 ml. of precooled 50% hypophosphorous acid was added. Gas was given off, copiously at first. This mixture was stirred for 3 hr. and stored at 3° for 36 hr., then placed in a water bath at 40° for 2 hr. with stirring and again kept at 3° overnight. The light tan precipitate was filtered and dried, giving 4.3 g. (99%), m.p. 152–170°. Recrystallization from toluene (Darco) and sublimation yielded 2.6 g. (60%) of light yellow crystals, m.p. 179–180°. One recrystallization from toluene gave an analytical sample, m.p. 181–181.5°.

Anal. Calcd. for $C_{13}H_8FNO_2$: N, 6.11. Found: N, 6.12.

1-Fluoro-2-fluorenamine. 1-Fluoro-2-nitrofluorene (2.4 g.) was reduced in the usual way[9] giving 2.0 g. (96%) of the amine, m.p. 110–113°. One recrystallization from alcohol gave an analytical sample, m.p. 113–114°.

Anal. Calcd. for $C_{13}H_{10}FN$: N, 7.03. Found: N, 7.29.

N-2-(1-Fluorofluorenyl)acetamide. To a solution of 1.9 g. of 1-fluoro-2-fluorenamine in 30 ml. of toluene, 1 g. of acetic anhydride was added and the mixture was warmed on a steam bath for 10 min. and then boiled to near dryness. After blowing off the residual toluene, the precipitate was recrystallized from alcohol, giving 2.2 g. (96%), m.p. 181–182°. One further recrystallization gave an analytical sample, m.p. 182–183°. A mixture melting point with the alternate Ullmann product mentioned above[12] showed no depression.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; F, 7.88; N, 5.81. Found: C, 74.86; H, 4.94; F, 7.84; N, 6.06.

1-Fluoro-2-nitrofluorenone. To a boiling solution of 1 g. of 1-fluoro-2-nitrofluorene in 30 ml. of glacial acetic acid, 3 g. of sodium dichromate (tech.) was added slowly with stirring. The mixture was boiled down to 5 ml., and 30 ml. of glacial acetic acid was added and then again it was boiled down to 5 ml. and cooled. The yellow precipitate was

filtered and washed with 2 ml. of cold glacial acetic acid and with alcohol and dried, giving 0.8 g. (75.5%), m.p. 241–242°. One recrystallization from toluene (Darco) gave an analytical sample, m.p. 243.5–244°.

Anal. Calcd. for $C_{13}H_6FNO_3$: F, 7.81; N, 5.76. Found: F, 8.00; N, 5.85.

The infrared spectrum of this compound was identical with the spectrum mentioned above,[13] although our melting point is somewhat higher.

N-2-(5-Fluoro-3-nitrofluorenyl)acetamide (7-acetamido-4 fluoro-6-nitrofluorene). To a solution of 1 g. of *N*-2-(5-fluorofluorenyl)acetamide in 10 ml. of glacial acetic acid at 50°, 1 ml. of nitric acid (d. 1.42) was added with stirring. The mixture was heated to 55°, then removed from the heat. The temperature rose to 60° and a yellow precipitate formed. After cooling, filtration, and washing with 2 ml. of cold glacial acetic acid and water, the product was dried, giving 1.0 g. (84.5%), m.p. 240–246° dec. One recrystallization from alcohol (Darco) gave an analytical sample, m.p. 241–246° slow dec.

Anal. Calcd. for $C_{12}H_{11}FN_2O_3$: C, 62.90; H, 3.87; N, 9.79. Found: C, 63.03; H, 4.21; N, 10.00.

5-Fluoro-3-nitro-2-fluorenamine. Hydrolysis of the above compound in refluxing concd. hydrochloric acid-alcohol for 15 hr. gave a yield of 88% of the amine, m.p. 233–235°. One recrystallization from alcohol gave an analytical sample, m.p. 238–239°.

Anal. Calcd. for $C_{13}H_9FN_2O_2$: N, 11.47. Found: N, 11.34.

N-2-(5-Fluoro-3-nitrofluorenyl)trifluoroacetamide (7-trifluoroacetamido-4-fluoro-6-nitrofluorene). Acylation with trifluoroacetic anhydride in benzene solution gave a quantitative yield, m.p. 201.5–202.5°. A mixture melting point with the lesser (11%) product of nitration of 4-fluoro-7-trifluoroacetamidofluorene[1] was not depressed, 201.5–202.5°.

Diazotization and Schiemann decomposition of 2-N,N-dimethylamino-1-fluorenamine. A mixture of 5 g. of 2-dimethylamino-1-fluoroenamine, 38 ml. of 50% fluoboric acid, and 15 ml. of water was heated to effect solution then cooled in an ice-salt bath. To this, an aqueous solution (5 ml.) of 1.75 g. of sodium nitrite was added with stirring at 0°. The brick-colored diazonium salt was filtered, washed with 5% fluoboric acid, methanol, and then ether, and dried, giving 7.2 g. (80%), dec. 110°. The salt (7.2 g.) was heated in 140 ml. of benzene at the boiling point, and gradual decomposition took place. After 30 min. no more white fumes were apparent and a small amount of dark material had formed. Darco treatment of the filtrate was followed by evaporation to dryness. Ammonium hydroxide (10 ml.) was added and the white precipitate was extracted with 100 ml. of toluene in several portions, and the toluene solution was dried with a little anhydrous sodium sulfate and boiled down to near dryness. The precipitate was recrystallized from petroleum ether (b.p. 30–60°, Darco), giving 1.35 g. (31% based on the starting compound) of 2-methylaminofluorene, m.p. 77.5–78°. One recrystallization from cyclopentane raised the melting point to 78–78.5°. A mixture melting point with authentic 2-methylaminofluorene was not depressed. Acetylation of this product gave authentic *N*-methyl-*N*-2-fluorenylacetamide[19] (melting point and mixture melting point).

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(19) T. L. Fletcher, M. E. Taylor, and A. W. Dahl, *J. Org. Chem.*, 20, 1021 (1955).

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, UNIVERSITY OF CHICAGO]

Organophosphorus Chemistry. Addition Reactions of Diethyl Phosphonate and the Oxidation of Triethyl Phosphite[1]

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The reactions of dialkyl phosphonates, with aldehydes and ketones to give dialkyl α-hydroxyalkylphosphonates, and with olefins to yield dialkyl alkylphosphonates are discussed. Trialkyl phosphites react smoothly and vigorously with hydroperoxides (oxidation-reduction) to yield the trialkyl phosphate and the corresponding alcohol. Cryoscopic molecular weight data reveal that the $\overset{+}{P}—\overset{-}{O}$ dipole readily enters into hydrogen-bonded associations with hydroxylic groups.

A series of stimulating lectures and discussions on newly discovered phosphorylation techniques[5] presented by Professor Alexander R. Todd in the autumn of 1948 led to the instant investigation of both heterolytic and homolytic reactions of phosphonic and phosphorous esters.[6]

Both chemical and physical evidence strongly support the existence of diethyl phosphonate as the keto structure (I) instead of the enol (II).[7]

$(C_2H_5O)_2P(O)H$ I $\qquad$ $(C_2H_5O)_2\ddot{P}OH$ II

(1) Presented before the Symposium on Organophosphorus Chemistry at the 134th meeting of the American Chemical Society in Chicago, Illinois, September 1958.

(2) Deceased, October 1957. This paper is presented as a memorial tribute to the pioneering efforts in organophosphorus chemistry of the late Professor Kharasch.

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(5) (a) F. R. Atherton, H. T. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 382, 660 (1945); (b) F. R. Atherton and A. R. Todd, *J. Chem. Soc.*, 674 (1947).

(6) (a) The work presented in this paper was performed in the period 1948–1950; (b) M. S. Kharasch and I. S. Bengelsdorf, *J. Org. Chem.*, 20, 1356 (1955).

(7) The latest physical evidence still corroborates these conclusions. See infrared analyses by L. W. Daasch, *J. Am. Chem. Soc.*, 80, 5301 (1958) and deuterium exchange studies by R. B. Fox and W. J. Bailey, Symposium on Organophosphorus Chemistry, 134th meeting of the American Chemical Society, Chicago, Illinois, September 1958, Abstracts, p. 70P.

TABLE I

PREPARATION OF DIETHYL α-HYDROXYPHOSPHONIC ESTERS, $(C_2H_5O)_2(O)PC(OH)RR'$

Formula	R	R'	Reaction Temp.	Reaction Time, hr.	Yield, %	B.P., °C/mm.	n_D^{20}	P,% Calcd., Found	C_2H_5O,% Calcd., Found
$C_5H_{13}O_4P$	H	H	85[a]	3	30	103–105/0.2	1.4342	18.4	53.5
								17.9	—
$C_6H_{15}O_4P$	CH_3	H	80	3	51	108–110/0.5	1.4348	17.0	49.5
								16.9	48.6
$C_8H_{19}O_4P$	n-C_3H_7	H	80	9	50	111–112/0.3	1.4378	14.7	42.8
								14.4	—
$C_8H_{19}O_4P$	i-C_3H_7	H	80–85	8	43[b]	96–97/0.3	1.4392	14.7	42.8
								14.5	42.8
$C_{11}H_{17}O_4P$	C_6H_5	H	100–110	8	54	83–83.2[c]	—	12.7	36.9
								12.5	—
$C_{13}H_{19}O_4P$	$C_6H_5CH{=}CH$	H	80–100	11	20	106.5–107[c,d]	—	11.5	33.3
								11.4	32.9
$C_7H_{17}O_4P$	CH_3	CH_3	160	10	17	80–100/0.2[e]	1.4320	15.8	45.9
								15.9	—

[a] As paraformaldehyde. [b] Same reaction for 12 hr. in a sealed tube gives rise to a non-volatile viscous oil which presumably arises by condensation of the α-hydroxy ester. [c] Melting points. [d] Absorbs bromine in carbon tetrachloride; other esters do not. [e] Molecular distillation bath temperature.

The physical and chemical properties of triethyl phosphite, however, are in agreement with a structure containing a trivalent-phosphorus atom which bears a free electron pair. The structures of these esters suggested that the phosphorus-hydrogen bond in the former may undergo both heterolytic and homolytic reactions. Most reactions of triethyl phosphite, however, are heterolytic in nature, *e.g.*, Arbuzov-Michaelis type, although free-radical reactions[8] recently have become recognized.

Thermal non-catalyzed addition of dieihyl phosphonate to carbonyl compounds. This reaction repre-

$$(C_2H_5O)_2(O)PH + R_2CO \text{ (R is H, alkyl, aryl)} \longrightarrow (C_2H_5O)_2PC(OH)R_2$$

sents a one-step synthesis of dialkyl α-hydroxy phosphonates.[9]

The esters are high-boiling liquids or crystalline solids whose water solubility decreases as the molecular weight increases. Table I summarizes the experimental data.

The most striking feature of the diethyl α-hydroxyphosphonates is their anomalous behavior in the cryoscopic determination of their molecular weights in benzene. The observed values indicate that the compounds are associated to a dimeric structure. Molecular weights determined in refluxing carbon tetrachloride (Swietoslawski ebullioscopic apparatus) are also indicative of associated structures; their persistence at the higher temperatures suggests strongly hydrogen-bonded structures involving intermolecular reactions between the hydroxyl group and the strong $\overset{+}{P}—\overset{-}{O}$ dipole.[10]

That the α-hydroxyl group is an integral and necessary requirement for the observed *inter*molecular association is supported by esterification studies. The α-acetoxyphosphonates are monomeric in benzene solution and possess lower boiling points than the parent hydroxylic esters. The molecular weight determinations are summarized in Tables IIa and IIb.

The saturated α-hydroxyphosphonic esters are readily hydrolyzed in 18% aqueous hydrochloric acid to the corresponding α-hydroxyphosphonic acids; the latter are crystalline solids. The first few members of the aliphatic series are very hygroscopic, however, and the crystalline salts formed with aromatic amines are useful in their characterization.[11] In strong alkali, however, the α-hydroxyphosphonates are not hydrolyzed, but quantitatively regenerate the starting aldehyde. The reaction, undoubtedly, proceeds by the removal of a proton by the base to yield the intermediate

(8) C. Walling and R. Rabinowitz, *J. Am. Chem. Soc.*, **81**, 1243 (1959) present a detailed review of this field.

(9) V. S. Abramov and co-workers, simultaneously and independently observed the base-catalyzed addition of dialkyl phosphonates to carbonyl compounds. Their first paper in a continuing series is *Doklady Akad. Nauk S.S.S.R.*, **73**, 487 (1950). Other reports on this reaction are by W. E. Craig and W. F. Hester, U. S. Pat. 2,485,573, 25 October 1949; *Chem. Abstr.*, **44**, 3005h (1950), A. R. Stiles, U. S. Pat. 2,593,213, April 15, 1952; *Chem. Abstr.*, **46**, 11228e (1952), and R. L. McConnell and H. W. Coover, Jr., *J. Am. Chem. Soc.*, **78**, 4450 (1956).

(10) The trimeric association of benzenephosphinic acid $C_6H_5PH(O)OH$ in benzene has been described by G. M. Kosolapoff and J. S. Powell, *J. Am. Chem. Soc.*, **72**, 4291 (1950). C. D. Miller, R. C. Miller, and W. Rogers, Jr., *J. Am. Chem. Soc.*, **80**, 1562 (1958) present evidence based upon infrared spectral band shifts that dialkyl α-hydroxyalkyl phosphonates show both *inter*- and *intra*molecular hydrogen bonding; molecular weight determinations are not described.

(11) (a) J. B. Conant and A. D. Macdonald, *J. Am. Chem. Soc.*, **42**, 2343 (1920); (b) I. S. Bengelsdorf and L. B. Barron, *J. Am. Chem. Soc.*, **77**, 2869 (1955).

TABLE II

MOLECULAR WEIGHT DATA

(a) DIETHYL α-HYDROXYPHOSPHONIC ESTERS $(C_2H_5O)_2$ OPC(OH)RR′

R	R′	Molecular Weight: Monomer Calcd.	Dimer Calcd.	Cryoscopic (C_6H_6)	Ebullioscopic (CCl_4)
H	H	168	336	352	355
CH_3	H	182	364	365	372
n-C_3H_7	H	210	420	393	330
i-C_3H_7	H	210	420	400	—
C_6H_5	H	244	488	536, 550	—
C_6H_5CH=CH	H	270	540	500	—
CH_3	CH_3	196	392	350	—

(b) DIETHYL α-ACETOXYPHOSPHONIC ESTERS $(C_2H_5O)_2OPCH(OCOCH_3)R$

R	Formula	B.p., °C/mm.	n_D^{20}	P,% Calcd.	P,% Found	Molecular Weight: Monomer Calcd.	Molecular Weight: Found (C_6H_6)
CH_3	$C_8H_{17}O_5P$	77–78/0.3	1.4268	13.8	13.7	224	229
n-C_3H_7	$C_{10}H_{21}O_5P$	80–81/0.3	1.4303	12.3	12.0	252	259
i-C_3H_7	$C_{10}H_{21}O_5P$	76–77/0.3	1.4310	12.3	12.0	252	261
C_6H_5CH=CH	$C_{15}H_{21}O_5P$	135–140/0.3[a]	—	9.9	9.8	—	—

[a] Molecular distillation.

TABLE III

ACIDIC HYDROLYSES OF DIETHYL α-HYDROXYPHOSPHONIC ESTERS[a]

$RCH(OH)P(O)(OH)_2$ R	Formula	M.P. °C.	P,% Calcd., Found	Remarks
H	CH_5O_4P	87–88	27.7 27.5	Anilinium salt (from ethanol), m.p. 167–168°. *Anal.* Calcd. for $C_7H_{12}NO_4P$: P, 15.1. Found: P, 15.0.
CH_3	$C_2H_7O_4P$	—	—	Acid isolated as oil which slowly crystallized. Attempts to purify unsuccessful. *Anal.* Calcd. for $C_2H_7O_4P$: Neut. equiv., 63; Found: Neut. equiv., 63.5. Anilinium salt, m.p. 168–169°. *Anal.* Calcd. for $C_8H_{14}NO_4P$: P, 14.1%. Found: P, 14.1.
n-C_3H_7	$C_4H_{11}O_4P$	154.5–155[b]	20.1 20.0	Shiny plates from benzene-glacial HOAc (2:1) mixture.
i-C_3H_7	$C_4H_{11}O_4P$	165–166	20.1 19.8	Same solvent as above.
C_6H_5	$C_7H_9O_4P$	167–168 dec.[c]	16.5 16.3	Same solvent as above.
$C_6H_5CH_2CH_2$	$C_9H_{13}O_4P$	173–173.5[d]	14.4 14.2	Attempted hydrolysis of original unsaturated ester from cinnamaldehyde only led to gummy materials. Hydrolysis proceeded smoothly after hydrogenation.

[a] All hydrolyses were conducted with 18% aqueous hydrochloric acid. [b] Fossek-Page method, acid m.p. 154.5–155°. [c] Fossek-Page method, acid m.p. 165–166°. [d] Fossek-Page method, acid m.p. 174.5–175°.

III; the latter undergoes phosphorus-carbon bond cleavage to yield the aldehyde.[12]

$$R{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}P(O)(OC_2H_5)_2 \xrightarrow{B:} BH^+ + R{-}\underset{\displaystyle -O}{\underset{|}{CH}}{-}P(O)(OC_2H_5)_2 \longrightarrow RCHO$$

III

Thus, diethyl α-hydroxy-*iso*-butylphosphonate, diethyl α-hydroxybenzylphosphonate, and diethyl α-hydroxy-γ-phenyl-2-propenylphosphonate give isobutyraldehyde (96.2%), benzaldehyde (99.3%), and cinnamaldehyde (94.5%), respectively, when treated with a 10% sodium hydroxide solution. The aldehydes were isolated as their 2,4-dinitrophenylhydrazone derivatives.

The acidic hydrolytic reactions of α-hydroxyphosphonates are described in Table III.

(12) If the R-group contains an appropriate leaving group, such as chlorine, or an electron-withdrawing group, such as carbonyl, one observes instead phosphorus-carbon bond cleavage with the formation of a phosphoric ester [*cf.* I. S. Bengelsdorf, *J. Org. Chem.*, **21**, 475 (1956); V. A. Kukhtin, V. S. Abramov, and K. M. Orekhova, *Doklady Akad. Nauk S.S.S.R.*, **128**, 1198 (1959)].

TABLE IV

FREE RADICAL ADDITION OF DIETHYL PHOSPHONATE TO 1-OCTENE

Initiator	Temp.	Time, hr.	1:1 Product[a] B.p.	n_D^{20}	Yield, %	2:1 Product[b] B.p.	n_D^{20}	Yield, %
Benzoyl peroxide[c]	85	4	105–106°/0.5	1.4354	43	150–153°/0.5	1.4472	28[d]
Azobisisobutyronitrile[e]	100	4	105–108°/0.5	1.4344	45	155°/0.5	1.4458	28[f]
Acetyl peroxide[g]	75–80	6	92°/0.5	1.4340	55	125–135/.001	1.4432	3[h]

[a] The 1:1 product is diethyl *n*-octylphosphonate. A typical analysis is *Anal.* Calcd. for $C_{12}H_{27}O_3P$: P, 12.4; mol. wt., 250; sapon. equiv., 250. Found. P, 12.4, 12.5; mol. wt., 255 (Benzene); sapon. equiv., 246, 256. [b] The 2:1 product is diethyl hexadecylphosphonate. The specific structure of the hexadecyl radical was not determined. *Anal.* Calcd. for $C_{20}H_{43}O_3P$: P, 8.5. Found: P, 8.2, 9.2. [c] 0.1 Mole ester to 0.1 mole olefin; 5 mole % initiator. [d] Also obtained 2.3 g. of non-volatile residue. [e] 0.19 Mole ester to 0.19 mole olefin; 4.75 mole % initiator. [f] Less than 1.0 g. non-volatile residue. [g] 0.36 Mole ester to 0.24 mole olefin; 5 mole % initiator. [h] Reaction was conducted in the presence of dimethyl fumarate (0.12 mole); residue is a clear, glassy, polymeric material consisting of diethyl phosphonate, 1-octene, and dimethyl fumarate units. *Anal.* Found: P 3.5; mol. wt., 847 (benzene); sapon. equiv., 136.

Free-radical initiated addition of diethyl phosphonate to olefins. The observation that phosphorus trichloride adds to olefins by homolytic cleavage of a phosphorus-chlorine bond[13] suggests that one may observe the homolytic cleavage of a phosphorus-hydrogen linkage as well.

This is indeed the case. The reaction of diethyl phosphonate with 1-octene in the presence of 5 mole % of benzoyl peroxide, acetyl peroxide, or azobisisobutyronitrile leads to synthesis of diethyl *n*-octylphosphonate as the primary product, (Table IV). This type of reaction has been described subsequently in the literature.[14]

Neither homolytic nor heterolytic fission of the phosphorus-chlorine bond in diethyl phosphorochloridate[15] was achieved, however, in the treatment of the latter with 1-octene, employing either benzoyl peroxide as the free radical initiator or aluminum chloride as the ionic catalyst. The starting 1-octene was recovered in the former case, whereas the latter experiment yielded monoethyl phosphate.

The reduction of hydroperoxides with triethyl phosphite. The smooth and vigorous reaction of triethyl phosphite with hydroperoxides leads to but two products, the alcohol derived from the reduction of the hydroperoxide, and triethyl phosphate from the simultaneous oxidation of the triethyl phosphite.

$$R(CH_3)_2C{-}OOH + (C_2H_5O)_3P: \longrightarrow R(CH_3)_2C{-}OH + (C_2H_5O)_3PO$$

Cryoscopic measurements in benzene solution indicated association between triethyl phosphate and α-cumyl alcohol (R = C_6H_5). In order to determine whether the association of triethyl phosphate and alcohols was a general phenomenon,[16] cryscopic molecular-weight determinations were performed on a series of triethyl phosphate–alcohol mixtures. The results are tabulated in Table V.

TABLE V

MOLECULAR WEIGHTS OF EQUIMOLAR MIXTURES OF TRIETHYL PHOSPHATE AND ALCOHOLS IN BENZENE

Alcohol	Molecular Weight Calcd.	Molecular Weight Found	Molecular Weight (Mixtures) Calcd.[a]	Molecular Weight (Mixtures) Found
None	182	188	—	—
Triphenylcarbinol	260	266	221	280
Isopropyl alcohol	60	85	121	171
1-Octanol	130	—	156	207
α,α-Dimethylbenzyl alcohol	136	148[b]	159	192

[a] Based upon the assumption that there is no association of the solute molecules. [b] M. S. Kharasch and A. C. Poshkus, unpublished work.

The data definitely indicate a degree of association of the triethyl phosphate molecule with that of the alcohol (*cf.* diethyl α-hydroxyalkylphosphonates above).

There is no definite evidence to determine whether the oxidation-reduction reaction proceeds *via* a homolytic or a heterolytic intermediate. The exothermicity and instantaneousness of the reaction, and the fact that it is not affected by the

(13) M. S. Kharasch, E. V. Jensen, and W. H. Urry, *J. Am. Chem. Soc.*, **67**, 1864 (1945).

(14) C. Walling, *Free Radicals in Solution*, John Wiley and Sons, Inc., New York, New York. 1957, p. 342–343 gives an excellent account of such research. More recent results are reported by A. R. Stiles, W. E. Vaughan, and F. F. Rust, *J. Am. Chem. Soc.*, **80**, 714 (1958), and L. A. Hamilton, Symposium on Organophosphorus Chemistry, 134th Meeting of the American Chemical Society, Chicago, Illinois, September 1958, Abstracts, p. 68P.

(15) F. R. Atherton, H. T. Howard, and A. R. Todd, *J. Chem. Soc.*, 1106 (1948).

(16) G. B. King and J. H. Walton, *J. Phys. Chem.* **35**, 1745 (1931) previously had observed "onium" addition compounds between phosphoric acid and oxygenated organic compounds.

presence of trinitrobenzene[8] an inhibitor of homolytic reactions, strongly suggest that the reaction of trialkyl phosphites with hydroperoxides chiefly occurs by an ionic mechanism. The trialkyl phosphite–hydroperoxide reaction should be useful as a quick nonaqueous analytical determination for either phosphites or hydroperoxides (volumetric or infrared). Triethyl phosphite can also serve to distinguish between hydroperoxidic and peroxidic content, as the former reacts at ambient temperatures while the latter requires heating.[8,17]

EXPERIMENTAL

Purification of materials. The diethyl phosphonate employed was prepared either by the interaction of phosphorus trichloride with ethanol,[18] or by purification of a generous sample supplied by the Victor Chemical Company (b.p. 77°/18 mm., n_D^{20} 1.4080). Aldehydes were distilled prior to use. The 1-octene was purified by distillation through a vacuum-jacketed column, b.p. 120–121°, n_D^{20} 1.4090. Acetyl peroxide was prepared in ether solution,[19] while azoisobutyronitrile (Rohm & Haas), benzoyl peroxide, and tank nitrogen were commercial products used without purification.

Triethyl phosphite was prepared by the interaction of phosphorus trichloride with ethanol in anhydrous ether in the presence of quinoline (b.p. 237°); this is a modification of the original method which employed pyridine.[20] The phosphite now is commercially available. It is a clear, mobile liquid with an obnoxious odor (b.p. 51–53°/13 mm., n_D^{20} 1.4138, 72% yield). Commercial (72%) α-cumyl hydroperoxide (Hercules Powder Company) was purified by precipitation as its sodium salt and its careful regeneration with acid.[21] The hydroperoxide, thus obtained, is of 98–99% purity (iodometric titration). Commercial *t*-butyl hydroperoxide was distilled through a vacuum-jacketed tantalum wire column, (b.p. 44°/27, 80% purity by iodometric titration).

Determination of phosphorus. The micro method described by Niederl and Niederl[22] was used, but sample weights were in the semimicro range. Ammonium phosphomolybdate was determined gravimetrically. Consistently low results for phosphorus were obtained for some compounds, *e.g.*, diethyl phosphonate, triethyl phosphate; the difficulty was eliminated by the use of a sulfuric-nitric acid wet combustion procedure followed by reflux with perchloric acid.

Diethyl α-hydroxyalkylphosphonates. Typical experimental procedures for the preparation, acetylation, acidic and basic hydrolyses, and proofs of structures are described below. Detailed information is in the tables (above).

Preparation: reaction of diethyl phosphonate with isobutyraldehyde. Diethyl phosphonate (20 g., 0.145 mole) and isobutyraldehyde (14.2 g., 0.197 mole) were placed in a 100-ml. two necked flask equipped with a gas inlet tube and a condenser fitted with a calcium chloride tube. The reagents were heated for 8 hr. at 80–85° (oil bath), under nitrogen. The diethyl α-hydroxyisobutylphosphonate distilled at 96–97°/0.3 mm. A distillation residue (4.7 g.) remained in the flask. Similar results can also be obtained if the two reagents are mixed, degassed, and sealed in glass reaction tubes (vacuum line) and heated in a cylindrical metal container in an oil bath.

Acetylation. Diethyl α-hydroxyethylphosphonate (5 g.) and acetic anhydride (10 g.) were refluxed for 4 hr. The dark-brown reaction product was distilled to give diethyl α-acetoxyethylphosphonate in 84% yield. The α-acetoxy derivatives give a positive qualitative hydroxamic acid test for carboxylic esters, whereas the original phosphonic esters react negatively.

Acidic hydrolysis. Diethyl α-hydroxy-*n*-butylphosphonate (1.0 g.) was refluxed with 18% aqueous hydrochloric acid. The α-hydroxy-*n*-butylphosphonic acid separated as shiny plates.

Basic hydrolysis. Ten milliliters of 10% sodium hydroxide were placed in a 100-ml. steam-distillation flask equipped with a dropping funnel. Steam passage was begun; a small flame under the flask prevented excessive dilution of the sodium hydroxide. A weighed sample of diethyl α-hydroxybenzylphosphonate, dissolved in 15 ml. of methanol, was slowly introduced into the flask (15 min.). Twenty milliliters of methanol was added to the 30–35 ml. distillate, followed by 10 ml. of 2,4-dinitrophenylhydrazine solution (2 g. of reagent in 5 ml. concd. sulfuric acid and 50 ml. methanol). After standing for 5 hr., 10 ml. of 6*N* sulfuric acid was added. The precipitate was collected the next day and washed with dilute methanolic sulfuric acid followed by 20% aqueous methanol. The hydrazone was dried to constant weight under reduced pressure over calcium chloride.[23]

Anal. Calcd. for 0.233 g. of ester: 0.273 g. hydrazone. Found: 0.271 g. hydrazone (aldehyde, 99.3%). The benzaldehyde 2,4-dinitrophenylhydrazone melted at 240–241° (lit., m.p. 237°). Other aldehydes and the melting points of their 2,4-dinitrophenylhydrazone derivatives are: isobutyraldehyde, 179–180° (lit. m.p. 182°, 187°); cinnamaldehyde, 245–246° (lit., m.p. 248°, 255°).

Proof of structure. The structure of an α-hydroxyalkylphosphonate was proved by its hydrolysis to the corresponding α-hydroxyalkylphosphonic acid and the demonstration that this acid was identical with an authentic sample prepared by the independent Fossek-Page method.[24] Thus, the reaction of *n*-butyraldehyde with phosphorus trichloride gave an acid which had the same phosphorus content (P, 20.1%) and did not depress the melting point of the acid obtained from the acidic hydrolysis of diethyl α-hydroxy-*n*-butylphosphonate.

Attempts to isolate an acid derivative from the hydrolysis of diethyl α-hydroxy-γ-phenyl-2-propenylphosphonate were unsuccessful. The ester (2.0 g.) was then hydrogenated in 60 ml. absolute ethanol (0.5–1.0 g. Raney nickel) under 30 lbs./sq. in. hydrogen pressure. The residual oil slowly crystallized on standing. It was washed with ligroin to give diethyl α-hydroxy-γ-phenylpropylphosphonate.

Anal. Calcd. for $C_{13}H_{21}O_4P$: P, 11.4. Found: P, 11.2.

The saturated ester (0.5 g., did not absorb bromine in carbon tetrachloride) was hydrolyzed to give shiny plates of α-hydroxy-γ-phenylpropylphosphonic acid (m.p. 173–173.5°). Dihydrocinnamaldehyde (b.p. 87–88°/8 mm.), prepared by the hydrogenation of cinnamaldehyde[25] (Raney nickel, absolute ethyl alcohol, room temperature), was treated with phosphorus trichloride to give α-hydroxy-γ-phenylpropylphosphonic acid. This acid had the same phosphorus content (P, 14.2%) and did not depress the melting point of the acid obtained from the acidic hydrolysis of the above hydrogenated ester.

(17) I. S. Bengelsdorf, unpublished work.

(18) P. Nylen, *Studien uber organische Phosphorverbindungen*, Almqvist and Wiksells, Uppsala, Sweden, (Thesis), 1930.

(19) H. Friedlander, Ph. D. Dissertation, Dept. of Chemistry, University of Chicago, 1947.

(20) T. Milobedzki and A. Sachnowski, *Chem. Polski*, **15**, 34 (1917); *Chem. Abstr.* **13**, 2865 (1919).

(21) M. S. Kharasch, A. Fono, and W. Nudenberg, *J. Org. Chem.*, **15**, 763 (1950).

(22) J. B. Niederl and V. Niederl, *Micromethods of Quantitative Organic Analysis*, John Wiley and Sons, New York, 1942, p. 199.

(23) M. S. Kharasch and J. H. Cooper, *J. Org. Chem.*, **10**, 48 (1945).

(24) (a) W. Fossek, *Monatsh.*, **5**, 636 (1884); (b) H. J. Page, *J. Chem. Soc.*, **101**, 423 (1912).

(25) H. A. Weidlich and M. Meyer-Delius, *Ber.*, **74B**, 1195 (1941).

High-boiling residues from the diethyl phosphonate-aldehyde reactions. The experimental data concerning the residues remaining after the distillation of the α-hydroxyphosphonates are summarized in Table VI.

TABLE VI

HIGH-BOILING RESIDUES FROM $(C_2H_5O)_2P(O)H$—RCHO REACTIONS[a]

RCHO R	P, %	C_2H_5O, %	Mol. wt.
H	19.0	—	—
CH_3	21.3	33.3	—
n-C_3H_7	18.3	31.4	747
i-C_3H_7[b]	15.7,[c] 19.3[d]	38.0,[c] 32.3[d]	528,[c] 717[d]

[a] All of the residues are viscous, colorless oils which are hydrolyzable with 18% hydrochloric acid to give α-hydroxyalkylphosphonic acids identical with those obtained from the acidic hydrolyses of the distillable diethyl α-hydroxyphosphonates. [b] Residue is major product if reaction time is prolonged (12 hr.). [c] Sealed tube reaction. [d] Flask reaction.

Preparation of diethyl n-octylphosphonate. The free-radical reactions of diethyl phosphonate with 1-octene were conducted in a 125-ml. three necked round bottomed flask equipped with a gas inlet tube, and a reflux condenser fitted with a calcium chloride tube. An atmosphere of nitrogen was maintained during the reaction period. The reaction with azoisobutyronitrile serves as a typical experimental procedure (further details and analyses are in Table IV).

A solution of azoisbutyronitrile (1.6 g., 0.009 mole) in a mixture of diethyl phosphonate (12.9 g.) and 1-octene (10.4 g.) was slowly added over a 3-hr. period to a mixture of diethyl phosphonate (13.8 g., 0.19 mole total) and 1-octene (11.2 g., 0.19 mole total) maintained at 97°. After heating for an additional hour at 100° the unchanged 1-octene (10.3 g.) and diethyl phosphonate (14.7 g., b.p. 45°/0.5 mm.) were removed at reduced pressure. The residue was distilled to give the following fractions: Fraction 1: Diethyl *n*-octylphosphonate (1:1 addition product), Fraction 2: Diethyl hexadecylphosphonate (2:1 addition product), Fraction 3: A residue (1.0 g.) which did not distill.

Similar results are obtained in the use of benzoyl peroxide or acetyl peroxide as the free radical initiator.

Identification of the 1:1 addition product as diethyl-n-octylphosphonate. Triethyl phosphite (5 g., 0.03 mole) and *n*-octyl bromide (5.84 g., 0.03 mole) were heated for 7 hr. at 150° (Arbuzov-Michaelis reaction).[26] The liberated ethyl bromide was collected in a trap (3.0 g.) and diethyl *n*-octylphosphonate was recovered by distillation (b.p. 91.8°/0.3 mm., n_D^{20} 1.4361, 65% yield).

Anal. Calcd. for $C_{12}H_{27}O_3P$: P, 12.4%; Found: P, 12.4%.

Hydrolysis with 18% aqueous hydrochloric acid gave *n*-octylphosphonic acid (m.p. 102–102.5°), which did not depress the melting point of the alkylphosphonic acid obtained from a similar acidic hydrolysis of the product obtained from the free radical addition of diethyl phosphonate to 1-octene.

The latter sample of *n*-octylphosphonic acid was crystallized as small white platelets from 65°-petroleum ether (m.p. 101.8–102.8°).

Anal. Calcd. for $C_8H_{19}O_3P$: P, 15.9. Found: P, 15.6.

Treatment of an ethereal solution of the acid with aniline gave the monoanilinium salt of *n*-octylphosphonic acid. It was recrystallized from water (m.p. 143–145°).

Anal. Calcd. for $C_{14}H_{26}O_3NP$: P, 10.8. Found: P, 10.7.

The monocyclohexylaminium salt of *n*-octylphosphonic acid was prepared in a similar manner (m.p. 187–188°).

Anal. Calcd. for $C_{14}H_{32}O_3NP$: P, 10.5. Found: P, 10.5.

(26) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).

Reaction of diethyl phosphorochloridate with 1-octene in the presence of aluminum chloride. Diethyl phosphorochloridate was prepared by the interaction of diethyl phosphonate with sulfuryl chloride[15] in 71% yield (b.p. 72–73°/8 mm.). It was characterized by its reaction with aniline to give diethyl anilinophosphate (m.p. 95–96°).[27]

Anal. Calcd. for $C_{10}H_{16}O_3NP$: P, 13.4. Found: P, 13.4.

Aluminum chloride (2.1 g., 0.016 mole) was added to diethyl phosphorochloridate (9 g., 0.052 mole) and 1-octene (5.86 g., 0.052 mole) at room temperature. The reaction mixture was then heated for 4 hr. at 90°. The liquid decantate was distilled to give a volatile material (presumably ethyl chloride) and unchanged 1-octene (5.3 g.).

The residual solid was washed with an 18% aqueous hydrochloric acid solution. Concentration of the aqueous solution and treatment of the residue with aniline gave a gelled solid. The latter was extracted with ethanol to yield the monoanilinium salt of monoethyl phosphate (m.p. 163–164°).

Anal. Calcd. for $C_8H_{14}O_4NP$: P, 14.1. Found: P, 13.9, 14.2. This salt was prepared in an independent manner by treating an alcoholic suspension of barium monoethyl phosphate[28] with the calculated amount of sulfuric acid. The barium sulfate was collected and the treatment of the ethanolic filtrate with aniline precipitated monoanilinium monoethyl phosphate. This salt had the same phosphorus content (P, 14.1%) and did not depress the melting point of the salt obtained from the above aluminum chloride reaction.

Reaction of triethyl phosphite with α-cumyl hydroperoxide. The reaction was conducted in a 500-ml. three necked round bottomed flask fitted with a mechanical stirrer, dropping funnel, and reflux condenser. A solution of α-cumyl hydroperoxide (49.2 g., 0.323 mole) in 98 ml. of toluene was slowly added over a 1-hr. period to a solution of triethyl phosphite (53.7 g., 0.323 mole) in 100 ml. toluene. A cooling bath maintained the temperature at 25–30°. The toluene was removed at reduced pressure and the residue was distilled as an equimolar mixture of triethyl phosphate and α-cumyl(α,α-dimethylbenzyl) alcohol (b.p. 47–50°/.01 mm., n_D^{20} 1.4571).

Anal. Calcd. for $C_9H_{12}O{\cdot}C_6H_{15}O_4P$: C, 56.6; H, 8.5; P, 9.7; sapon. equiv., 318; mol. wt., 159. Found: C, 56.6; H, 8.6; P, 9.6; sapon. equiv., 324; mol. wt., 206, 216.

Identification of the α-cumyl hydroperoxide-triethyl phosphite product. The presence of α-cumyl alcohol was shown when the above mixture (3 g.) was heated for 7 hr. with a mixture of thioglycolic acid (3 g.) and 24 ml. of 2*N* hydrochloric acid to give a quantitative yield of long white needles of α-cumylmercaptoacetic acid (m.p. 69–70° from benzene-ligroin).[29] This acid did not depress the melting point of α-cumylmercaptoacetic acid prepared by the reaction of thioglycolic acid with α-methylstyrene.

The presence of triethyl phosphate was not primarily verified (see below), but the product of the reaction was compared with a synthetic mixture of α-cumyl alcohol (0.68 g., 0.005 mole) and triethyl phosphate (0.91 g., 0.005 mole), as follows: Reaction product: n_D^{20} 1.4571; sapon. equiv., 324. Synthetic mixture: n_D^{20} 1.4573; sapon. equiv., 324.

Reaction of triethyl phosphite with t-butyl hydroperoxide. A solution of triethyl phosphite (23.5 g., 0.142 mole) in 50 ml. of toluene was treated with a solution of *t*-butyl hydroperoxide (16.4 g., 0.141 mole) in 50 ml. of toluene in the manner described for the α-cumyl hydroperoxide reaction.

A mixture of *t*-butyl alcohol and toluene was removed at reduced pressure. The residue was distilled to give triethyl

(27) H. McCombie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 380 (1945).

(28) A sample was kindly supplied by Prof. F. H. Westheimer and Dr. W. W. Butcher.

(29) B. Holmberg, *J. prakt. Chem.*, **141**, 93 (1934).

phosphate (b.p. 46–47°/0.3 mm., n_D^{20} 1.4058, quantitative yield).

Anal: Calcd. for $C_6H_{15}O_4P$: P, 17.0%; Found: P, 17.0%.

The *t*-butyl alcohol was identified as the 3,5-dinitrobenzoate ester (melting point and mixture melting point 139.5–140.0°).

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CHICAGO, ILL.

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Intermolecular-Intramolecular Polymerization of 2,6-Diphenylheptadiene-1,6

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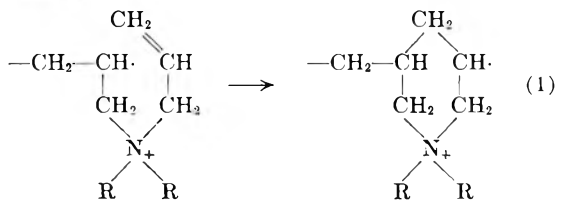
The synthesis of 2,6-diphenylheptadiene-1,6 from 1,3-dibenzoylpropane was accomplished in good yield utilizing the Wittig reaction. It was polymerized using free radical, cationic, anionic, and Ziegler-type initiation to give in all cases soluble polymers of essentially the same structure with few or no double bonds detectable in the infrared spectrum. This is the first example of a diene on which all known general types of initiation have led to intermolecular-intramolecular polymerization.

In order to explain the solubility of polymers obtained from diallyl quaternary ammonium salts, Butler and Angelo[1] proposed an intermolecular-intramolecular propagation mechanism in the free radical polymerization, the intramolecular step producing piperidinium units:

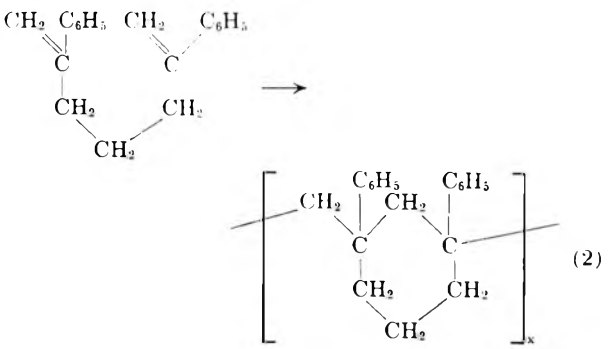


(1)

Strong evidence for this mode of polymerization is seen in Marvel's results on the polymerizations of 2,6-dicarboxyheptadiene-1,6 and its esters.[2] High molecular weight soluble polymers with no detectable residual unsaturation were obtained. For example, 2,6-dicarbomethoxyheptadiene-1,6 was polymerized using free radical initiation in an emulsion system to give polymer with an intrinsic viscosity in chloroform of 0.73. It was soluble in a number of organic solvents and showed no carbon-carbon double bonds in the infrared spectrum.

A number of examples of intermolecular-intramolecular polymerization have since appeared. These include, in addition to the free radical variety discussed above, Ziegler-type,[3] anionic,[4] and cationic.[5]

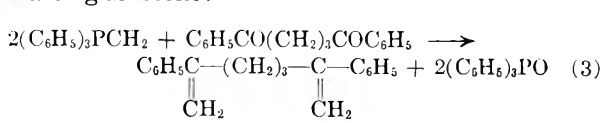
This paper reports the preparation of 2,6-diphenylheptadiene-1,6 and its polymerization. All the known general types of initiation mentioned above were employed and resulted only in intermolecular-intramolecular polymerization. To our knowledge, this is the first example of a diene which responds in this fashion:



(2)

DISCUSSION

Monomer synthesis. A powerful synthetic tool for unequivocal olefin formation is the Wittig reaction[6] in which a carbonyl group is converted to an ethylenic group via the action of a triphenylphosphinemethylene. *The ethylenic linkage is reported to form only at the point* where the carbonyl group existed originally. This reaction was conducted by us on 1,3-dibenzoylpropane to give 2,6-diphenylheptadiene-1,6 in 65% yield based on starting diketone:



(3)

The structure of the diene was confirmed by oxidation to the starting diene in 76% yield using sodium periodate and osmium tetroxide.[7]

(1) G. B. Butler and R. J. Angelo, *J. Am. Chem. Soc.*, **79**, 3128 (1957).

(2) C. S. Marvel and R. D. Vest, *J. Am. Chem. Soc.*, **79**, 5771 (1957).

(3) C. S. Marvel and J. K. Stille, *J. Am. Chem. Soc.*, **80**, 1740 (1958).

(4) J. F. Jones, *J. Polymer Sci.*, **33**, 7 (1958).

(5) J. F. Jones, *J. Polymer Sci.*, **33**, 513 (1958).

(6) G. Wittig and E. Schollkopf, *Ber.*, **87**, 1308 (1954).

(7) R. Pappo, D. S. Allen, R. V. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

In general, the reaction was conducted in two steps. The ylide was prepared by adding a solution of phenyllithium or butyllithium in diethyl ether to a suspension of triphenylmethylphosphonium bromide in an appropriate medium. This step was followed by the addition of the dione. In the course of a number of synthetic attempts, glycol dimethyl ether (Ansul) was found to give good results as the reaction medium. It served as an excellent solvent for the large concentrations of ylide prepared and permitted a higher reaction temperature than could be obtained by using diethyl ether in conventional equipment.[8]

The main shortcoming in the use of glycol dimethyl ether in the reaction was the problem of separating the triphenylphosphine oxide formed. This was overcome by replacing the solvent with diethyl ether in which triphenylphosphine oxide–lithium bromide complex is insoluble.[6] Use of phenyllithium instead of butyllithium in the ylide-forming step gave better yields of crude diene but added a purification difficulty in the removal of biphenyl by-product probably formed in the preparation of the phenyllithium.

Polymerization. The monomer was polymerized using radical, cationic, anionic and Ziegler-type initiators. In all cases the polymers obtained were soluble in a number of solvents. Infrared spectra were run on polymers representing each mode of polymerization and found to be essentially the same. Only the lower molecular weight polymers (having low polymer melt temperatures[9]) showed a slight absorption in the carbon-carbon double bond region.

Thermal polymerizations without initiator were run at 100° and 180°. Only the latter temperature afforded any appreciable polymer. The reaction was slow and the highest inherent viscosity, ηinh, $\left(\frac{\ln \eta\text{rel.}}{\text{concn.}} \text{ at } 0.5\% \text{ concentration at } 30.0°\right)$ in benzene was 0.23. When cumene hydroperoxide was used as a free radical initiator, polymerization at 100° was slow, five days being required to give a 35% yield of polymer with an inherent viscosity of 0.35 and polymer melt temperature of 265°.

Cationic polymerizations were run in a number of solvents. When boron trifluoride was used as the initiator in hexane or carbon disulfide, the polymers could be prepared either in high conversion and low molecular weight or low conversion and high molecular weight. On the other hand, in methylene chloride, conditions leading both to high and low conversions gave polymers having the same polymer melt temperatures (~250°). Boron trifluoride etherate as initiator led only to very low molecular weight polymers (polymer melt temperatures ~125°).

Polymerization with a Ziegler-type catalyst from aluminum triisobutyl and titanium tetrachloride proceeded slowly, four days being required to give a 71% yield of polymer with a polymer melt temperature of 140°. An increase in the ratio of monomer to catalyst by a factor of about 50 gave a polymer with a somewhat higher molecular weight, the polymer melt temperature rising to 190°.

The best method for obtaining both high conversion and high molecular weight polymer was anionic polymerization. Lithium naphthalene was used as the initiator and tetrahydrofuran as the solvent. In the best case, an 80% yield of polymer with an inherent viscosity in benzene of 0.49 and a polymer melt temperature of 300° was obtained. In an attempt to obtain this result consistently, polymerizations were run using tetrahydrofuran which had been distilled from lithium naphthalene, nitrogen which had been scrubbed with lithium naphthalene in tetrahydrofuran solution, and in one case treating the monomer with Girard's reagent to remove traces of ketonic material. Attempts to raise the molecular weight by increasing the ratio of monomer to initiator failed. In many cases, lithium metal had to be present as well as lithium naphthalene. In some cases the reaction would not proceed unless a large excess of naphthalene were deliberately added.

Polymer properties. All of the polymers prepared were soluble in tetrahydrofuran, chloroform, and benzene. Clear films were cast from these solvents but these and melt-pressed films prepared in the Carver press were all brittle. Brittle fibers could be drawn from the polymer melts. The most interesting feature of the polymer was its excellent thermal stability. Melts could be held at 300° open to the air for at least a minute without any sign of discoloration, gelation, or depolymerization. This is in marked contrast to the noncyclic analog, poly-α-methylstyrene, which readily depolymerizes under these conditions. By extrapolation of inherent viscosities, the limiting polymer melt temperature of the polymer appears to be about 300°. This high value is interesting in that the polymer does not contain any polar groups and presumably results from a stiff chain structure. This was confirmed by the construction of molecular models which showed little capacity for free rotation.

EXPERIMENTAL

1,3-Dibenzoylpropane. This intermediate was prepared following the procedure of Japp and Mitchie.[10] The synthesis is a two-step one involving the reaction of ethyl benzoyl-

(8) Wittig's preparations use diethyl ether as the solvent in pressure equipment at temperatures around 65°.

(9) The temperature at which a wet streak is left on a hot metal bar on pressing a sample with a spatula. In any homologous series, the melting point increases with molecular weight to a limiting value. In this study, the polymer melt temperature was used as a relative measure of molecular weight (though it is understood that branching would affect such a relationship).

(10) F. R. Japp and A. C. Mitchie, *J. Chem. Soc.*, **79**, 1016 (1901).

acetate and formaldehyde in the presence of piperidine to give diethyl α,α'-dibenzoylglutarate followed by hydrolysis and decarboxylation to give the dione.

Triphenylmethylphosphonium bromide. In a 1-l. 3-necked flask equipped with thermometer, stirrer, and Dry Ice-acetone condenser, 200 g. (0.76 mole) of triphenylphosphine was dissolved in 400 ml. of dry benzene. To the stirred solution held at −5°, 100 g. (1.06 moles) of methyl bromide was added all at once and the mixture was stirred overnight at room temperature. The cake which formed was broken up, filtered, and washed a number of times with benzene. The yield was 257 g. (95%) and the product, which melted at 233.5–234°, was sufficiently pure for further use.

2,6-Diphenylheptadiene-1,6. In a 2-l., 3-necked flask equipped with a stirrer, dropping funnel, condenser, and nitrogen cover, 120.8 g. (0.338 mole) of triphenylmethylphosphonium bromide was dispersed in 500 ml. of dry glycol dimethyl ether. Over a period of 3/4 hr., a solution of 0.369 mole of phenyllithium in diethyl ether was added. Almost all of the solid appeared to go into solution. A solution of 40 g. (0.158 mole) of 1,3-dibenzoylpropane in 200 ml. of dry glycol dimethyl ether was added dropwise over 1 hr. The solution was then refluxed for 20 hr., following which the solvent was removed under vacuum to near dryness. About 700 ml. of dry diethyl ether was added and the precipitate which formed was separated by filtration. Treatment of the precipitated triphenylphosphine oxide–lithium bromide complex with water gave a 94% yield of triphenylphosphine oxide.

The diethyl ether filtrate was evaporated to about 200 ml., washed with water until free of alkali, dried over sodium sulfate, and evaporated to dryness to give 39 g. of a dark yellow oil. After the addition of 0.1 g. of di-*t*-butyl-*p*-cresol, the oil was distilled through a Vigreux column at around 0.1 mm. A small amount of solid forecut identified as biphenyl came over followed by product; yield 25.9 g. (65%).

Carefully distilled monomer is a water-white liquid and has the following properties: b.p. 108°/ca. 0.03 mm., n_D^{25} 1.5801, d_4^{25} 0.998.

Anal. Calcd. for $C_{19}H_{20}$: C, 91.9; H, 8.1. Found: C, 91.8; H, 7.8.

Oxidation of 2,6-diphenylheptadiene-1,6. The method used was essentially that of Pappo, *et al.*[7] A mixture of diethyl ether and water containing 0.62 g. (0.0025 mole) of diene, approximately 0.1 g. osmium tetroxide, and excess sodium metaperiodate was stirred for 3 days. The ether layer was dried over sodium sulfate and the black osmium-containing material was removed from the ether solution by passage through an alumina column. Ether and chloroform were used as eluants. Evaporation gave 0.48 g. (76%) of dione, m.p. 64.5–66.5° (lit.,[10] m.p. 67°). A mixed melting point with known dione showed no depression. The dioxime was prepared, m.p. 162–164° (lit.,[11] m.p. 165–166°). A mixed melting point with the dioxime of the known dione showed no depression.

Polymerization. Polymerization procedures typical of the different types of initiation follow below.

Thermal. One milliliter of monomer was sealed off under nitrogen in a 5-ml. test tube and kept in refluxing *o*-dichlorobenzene for 4 days. The gelled, clear product was dissolved in chloroform and precipitated by pouring the solution into methanol; yield 41%, PMT[9] 280°, ηinh (benzene) 0.23.

Anal. Calcd. for $C_{19}H_{20}$: C, 91.9; H, 8.1. Found: C, 91.5; H, 8.0.

Free radical initiation. One milliliter of monomer containing approximately 40 mg. of cumene hydroperoxide was sealed off under nitrogen in a 5-ml. test tube and kept in boiling water for 5 days. The product was precipitated twice from chloroform into methanol. Yield 36%, PMT 265°, ηinh (benzene) 0.35.

Cationic. In a 50-ml. flask equipped with a stirrer, nitrogen cover, and stopper, boron trifluoride gas was introduced over a solution of 1 ml. of monomer in 5 ml. of methylene chloride maintained at Dry Ice-acetone temperature. An almost immediate viscosity increase occurred. Precipitation with methanol gave a 94% yield of polymer with PMT 255° and ηinh 0.19.

Anionic. In a nitrogen blanketed 50-ml. flask equipped with stirrer and stopper, a small flattened piece of lithium metal was stirred with 5 mg. of naphthalene in 10 ml. of tetrahydrofuran until a faint green color began to appear. At this point, one ml. of monomer was introduced. The color promptly discharged and after a few seconds turned red. The polymer was precipitated into methanol; yield 80%, PMT 300°, ηinh 0.49.

Ziegler-Type. In a 50-ml. flask equipped with a magnetic stirrer, 0.6 ml. titanium tetrachloride (0.001*M* in Decalin[12] decahydronaphthalene solvent) was dissolved in 6 ml. of Decalin under a nitrogen blanket. One milliliter of 0.001*M* aluminum triisobutyl in Decalin was added with stirring to give an immediate brown-black precipitate. After 10 min., 1.5 ml. of monomer was added. The closed flask was stirred for 4 days and the contents precipitated into ethanol; yield 71%, PMT ~140°.

Acknowledgment. The author is indebted to Dr. R. Zbinden for interpretation of the infrared spectra.

WILMINGTON, DEL.

(11) M. Milone and G. Venturello, *Gazz. chim. ital.*, 66, 808 (1936).

(12) Registered du Pont trade-mark.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION OF DAINIPPON PRINTING INK MFG. CO., LTD.]

New Reactions of Organic Isocyanates. I. Reaction with Alkylene Carbonates

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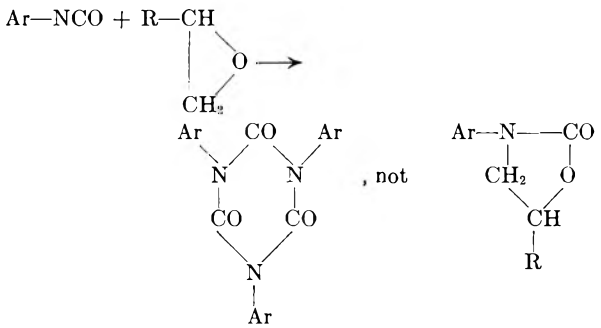
Phenyl isocyanate and ethylene carbonate in the presence of a tertiary amine as catalyst give a crystalline product on heating at 70°. If the reaction is carried out at 130°, 3-phenyloxazolidone-2 is obtained in good yield with elimination of carbon dioxide. A molecular complex of triphenylisocyanurate and ethylene carbonate is proposed for the structure of the former product. Chemical behavior of this complex is discussed in comparison with that of triphenylisocyanurate. Other combinations of various isocyanates and carbonates were also examined.

In recent years, Jones and Savill[1] tried to prepare *N*-substituted oxazolidones by condensation of epoxides with aromatic isocyanates in the presence of basic catalyst, and found that the trimerization of isocyanate alone proceeded smoothly contrary to their expectation.

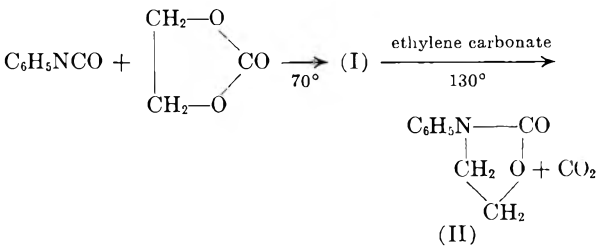


In the course of a study on polyurethane coating material using diisocyanate, we found, independently of Jones's work, that the mixture of tolylene diisocyanate and epichlorohydrine was polymerized at room temperature by adding a small amount of tertiary amine, to produce an insoluble and infusible resinous product. Succeeding experiments have revealed that this polymerization was based on base-catalyzed trimerization of the NCO- group, greatly accelerated in the presence of 1,2-epoxides.

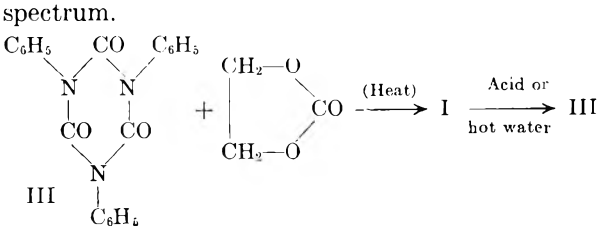
This unexpected phenomenon has led us to extend the research to a wider scope, not only with epoxy compounds but also with other types of reactive cyclic compounds. As a result we have found a series of interesting new reactions of organic isocyanates, and in this paper we report the reaction with alkylene carbonates.

The reaction between isocyanates and alkylene carbonates has not yet been reported in the literature. No change was observed when these two were mixed in the absence of catalyst, but an apparent reaction was observed on adding a trace of tertiary amine. For example, if a few drops of *N*-methylmorpholine was introduced to the mixture of tolylene diisocyanate and ethylene carbonate, the viscosity gradually increased with considerable heat evolution, and finally a transparent, brittle, resinous product was formed, while the addition of catalyst to tolylene diisocyanate without ethylene carbonate did not show any reaction at all under similar conditions. The high polymer thus formed, when heated at 130° or above, began to decompose with a large amount of carbon dioxide evolution and finally a highly viscous substance was left.

In order to investigate this polymer formation and decomposition reaction, we used a model experiment of monofunctional isocyanates. When phenyl isocyanate, ethylene carbonate, and a trace of *N*-methylmorpholine were heated at 70° for a few hours, a crystalline mass was formed and after further heating for about an hour the irritating odor of isocyanate completely disappeared. This crystalline product (I) can be recrystallized from various organic solvents and has a melting point of 222°. I, when heated above 130°, preferably in the presence of excess carbonate, began to decompose with evolution of carbon dioxide, and 3-phenyloxazolidone-2 (II) was isolated in excellent yield from the residue. The amount of carbon dioxide evolved was also almost quantitative (one mole of carbon dioxide from one mole of phenyl isocyanate). These processes can be shown as follows:



Analytical data of I agree with the formula $3(C_6H_5NCO)\cdot(C_3H_4O_3)$. If treated with dilute mineral acid or hot water, I gave triphenylisocyanurate (III). On the other hand, on heating III and ethylene carbonate in an inert solvent, a crystalline product was obtained which was shown to be I by its melting point and by its infrared absorption spectrum.



(1) J. I. Jones and N. G. Savill, *J. Chem. Soc.*, 4392 (1957).

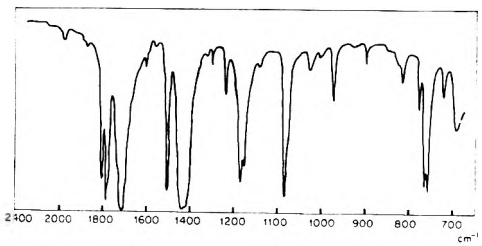
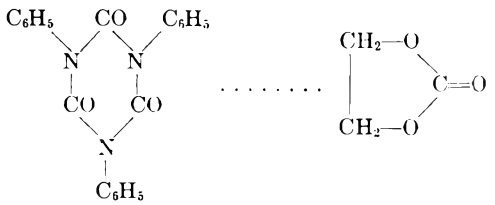


Fig. 1. Infrared spectrum of I (solid in KBr)

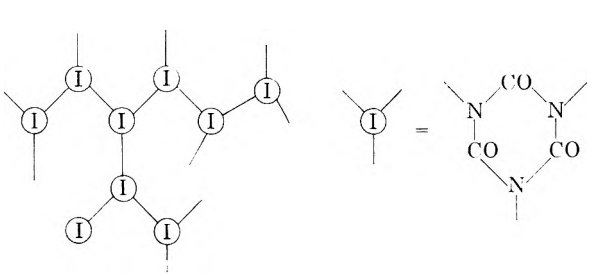
The infrared spectrum of I contains almost all the principal bands of III and ethylene carbonate and no new peak of appreciable strength appears. Molecular weight of I determined by Rast's method was 230, about half the value of that calculated for the formula $3(C_6H_5NCO)\cdot C_3H_4O_3$. I gives a clear x-ray diffraction pattern, which is quite different from those of III and ethylene carbonate. From the facts described above, I is best represented, we think, as an equimolar molecular complex of III and ethylene carbonate. The difference between the calculated and observed values of molecular weight might be explained by complete dissociation of the complex to the separate parts under the conditions of the molecular weight determination.



Direct evidence is not presented in this paper to the effect that I is really a molecular complex. Interaction forces between the components and effects of substituents will be discussed later.

From these model experiments it is clear that the base-catalyzed trimerization of the NCO- group is exceedingly accelerated by the presence of ethylene carbonate, and the trimer formed a molecular complex with ethylene carbonate.

In the case of diisocyanate a three-dimensional polymer is thus formed, which has a network structure knotted by an isocyanurate ring. We think these polymers should be called "Polyisocyanurate."



An isocyanate trimer, unlike its dimer, is known to be very stable toward various reagents.[2] To our surprise, I reacted with certain reagents ineffective with the corresponding isocyanate trimer. For instance, heating with aniline at 160° converted I to diphenylurea in good yield, whereas trimer was recovered unchanged under the same conditions. Lower alcohols did not attack I at refluxing temperature, but a higher one, for example octanol, gave its carbanilate almost quantitatively on heating at 170°. In this case also, carbanilate formation did not proceed at all with trimer alone.

$$I + 3\ C_6H_5NH_2 \longrightarrow 3\ C_6H_5NHCONHC_6H_5$$

$$I + 3\ C_8H_{17}OH \longrightarrow 3\ C_6H_5NHCOOC_8H_{17}$$

Aliphatic isocyanates reacted with alkylene carbonates in a similar way, but more slowly, to produce corresponding trimers, and here the formation of oxazolidone with elimination of carbon dioxide seemed rather difficult. Hexamethylene diisocyanate, for example, after heating at 120° for one and a half hours gave a light-colored, transparent resin, which was difficult to decompose at higher temperatures. When the mixture of *n*-butylisocyanate and ethylene carbonate was heated in the presence of catalyst at 120–130°, isocyanate was entirely consumed after a few hours, and two oily layers separated on cooling. They were recognized to be tri-*n*-butylisocyanurate and ethylene carbonate, respectively. Isolation of a molecular complex of the type described above was unsuccessful in this case.

Various *para*-substituted phenyl isocyanates and some alkylene carbonates were also examined. Results are listed in Table I.

In case of dichloroethylene carbonate and vinylene carbonate, side reactions (decomposition and polymerization of carbonate) proceeded predominantly to produce dark substances, and neither complex nor oxazolidone could be obtained.

EXPERIMENTAL

Nacconate-65 (National Aniline Division, Allied Chemical Corp.) was used as tolylene diisocyanate, with distillation before use. Various monoisocyanates were prepared from the corresponding amines by phosgenation in the usual way. Their boiling points were: phenyl, 64–65° (23 mm.); *p*-chlorophenyl, 96° (21 mm.); *p*-tolyl, 79–81° (20 mm.); *p*-ethoxyphenyl, 124° (21 mm.); *n*-butyl, 114–116°, respectively. Triarylisocyanurates were obtained from the corresponding monomers by standing overnight with about an equal amount of epoxide, for example epichlorohydrine, and a small amount of tertiary amine. They usually separated almost quantitatively as big crystals. After filtering and washing, they were pure enough for most purposes.

(2) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Revs.*, **57**, 47 (1956).

(3) M. S. Newman and R. W. Addor, *J. Am. Chem. Soc.*, **77**, 3789 (1955).

TABLE I

REACTION PRODUCTS FROM ISOCYANATES AND ALKYLENE CARBONATES

Isocyanate	M.P. of Trimer, °C.	Carbonate	Complex M.P., °C.	Complex Yield, %	Oxazolidone M.P., °C.	Oxazolidone Yield, %
Phenyl-	273	Ethylene-	220–222	98	117–119	92
p-Cl-Phenyl-	322	Ethylene-	240 (dec.)	59	116–117	70
p-CH_3-Phenyl-	263	Ethylene-	Not isolated		90	63
p-C_3H_5O-Phenyl-	246	Ethylene-	Not isolated		95–96	78
2,4-Tolylenedi-	350<	Ethylene-	Resin		Not isolated	
n-Butyl-	b_2: 148–149	Ethylene-	Not isolated		—	—
Hexamethylenedi-	350<	Ethylene-	Resin		—	—
Phenyl-	273	Propylene-[a]	*ca.* 140 (dec.)[b]	55	81–82	94[c]
Phenyl-	273	Chloroethylene-	*ca.* 155 (dec.)[b]	75	Not isolated[d]	

[a] Five-membered methyl ethylene carbonate. [b] Showed indistinct decomposition points. [c] 3-Phenyl-5-methyl-oxazolidone-2 was obtained. [d] On heating, violent gas evolution was observed, and a dark, resinous substance was left.

Chloroethylene carbonate was synthesized by chlorinating ethylene carbonate by Newman's method,[3] b.p. 115–116° (16.5 mm.).

Reaction of tolylenediisocyanate with ethylene carbonate. To a mixture of tolylenediisocyanate, 17.4 g., and ethylene carbonate, 35.2 g., was added a few drops of *N*-methylmorpholine. The temperature began to rise within a few minutes and the viscosity also increased gradually. After about an hour it could not be poured and finally a light yellow, transparent resin was formed. If too much catalyst is present, the reaction proceeds so violently that the resin is often partly charred. The polymer thus formed, when heated over 130°, began to melt again with the evolution of a large amount of carbon dioxide. The final product, after complete gas generation, was highly viscous. Isolation of the corresponding bisoxazolidone was unsuccessful. If the resin was finely powdered and was subjected to decomposition at 160°, 1 hr. was enough for complete degradation.

Reaction of phenylisocyanate with ethylene carbonate to form I. A 12.0-g. sample of phenyl isocyanate, 13.2 g. of ethylene carbonate, and a few drops of *N*-methylmorpholine were heated at 70° for several hours. A crystalline mass was formed, suddenly in most cases, and after further heating for about an hour the irritating odor of phenyl isocyanate completely disappeared, and then the reaction was complete. After cooling, the product was filtered and washed with cold benzene two or three times to remove excess carbonate. Crude I, m.p. 215–218°, weighed 14.5 g. (98% yield). By recrystallization from dry benzene, the melting point was raised to 220–222°.

Anal. Calcd. for $C_{24}H_{19}O_5N_3$ (445): C, 64.71%; H, 4.30%; N, 9.43%. Found: C, 64.73%; H, 4.55%; N, 9.64%. Mol. wt. (Rast), 225 and 235 (average 230).

Reaction of phenylisocyanate dimer with ethylene carbonate. Dimer was obtained from monomer and pyridine by Blair's method.[4] A 1.2-g. sample of dimer (m.p., 175°) and 0.9 g. of ethylene carbonate in dry benzene were heated to reflux with a trace of *N*-methylmorpholine. On cooling the clear solution I separated as white needles, m.p. 220°.

Formation of I *from triphenylisocyanurate and ethylene carbonate.* A 3.0-g. sample of triphenylisocyanurate and 1.0 g. of ethylene carbonate were heated in 10 cc. of dry benzene. Triphenylisocyanurate gradually dissolved, and after distilling the solvent and recrystallizing from benzene there was obtained 2.6 g. of I, which was identified by melting point and infrared spectrum.

3-Phenyloxazolidone-2. A 14.8-g. sample of I, 12.0 g. of ethylene carbonate, and a few drops of *N*-methylmorpholine were heated at 160°. Gas evolution was observed immediately, and the reaction was complete after a few hours. The mixture solidified on cooling, and on washing with cold mixture of petroleum ether–ethyl acetate (1:1) there was obtained 15.0 g. (92% yield) of crude I product. Repeated recrystallization from ethanol raised the melting point to 117–119°. It was shown to be 3-phenyloxazolidone-2 by comparing infrared spectrum with an authentic sample. Similar results were also obtained when phenyl isocyanate and ethylene carbonate were heated at 160° from the beginning.

Reaction of I *with aniline.* A 4.5-g. sample of I and 8.0 g. of aniline were heated at 160° with a small amount of *N*-methylmorpholine. After about 3 hr. fine needles separated, which was shown to be *N,N'*-diphenylurea, m.p. 234–235°, yield 5.1 g. (80%). In the case of aniline and triphenylisocyanurate (III) instead of I, most of the starting material was recovered unchanged after a longer heating period.

Reaction of I *with 2-ethylhexanol.* A mixture of 5.0 g. of I, 20 g. of 2-ethylhexanol [b.p. 84–86° (15 mm.)], and a small amount of *N*-methylmorpholine was heated at 170–180° for 7 hr. After about 0.5 hr. I was completely dissolved. After distilling the excess alcohol, 8.3 g. (99%) of a colorless liquid was obtained, b.p. 160–175° (5 mm.). After rectification it was shown to be 2-ethylhexyl carbanilate, from a comparison of the infrared spectrum with an authentic sample, b.p. 157–159° (3 mm.). On heating triphenylisocyanurate (III), 2-ethylhexanol, and a trace of *N*-methylmorpholine under the same condition, (III) was recovered entirely unchanged.

Reaction of n-butylisocyanate and ethylene carbonate. A 29.7-g. sample of *n*-butylisocyanate and 26.4 g. of ethylene carbonate were heated with 0.5 g. of *N*-methylmorpholine at 120–130° for 5 hr. The isocyanate was then completely consumed and two oily layers separated on cooling. In the case where ethylene carbonate was not present, most of the isocyanate was recovered unchanged after refluxing for 36 hr. in a bath of 140°. Distillation of the reaction mixture under reduced pressure gave 24 g. of a colorless liquid, b.p. 149–152° (1.5 mm.). It was identified as tri-*n*-butylisocyanurate, by comparing infrared spectrum with an authentic sample. The authentic sample was prepared from *n*-butylisocyanate by the action of sodium methylate, b.p. 149–150° (2 mm.).

Anal. Calcd. for $C_{15}H_{27}O_3N_3$: N, 14.13%. Found: N, 14.40%. Mol. wt., calcd. for $C_{15}H_{27}O_3N_3$, 297. Found (cryoscopic method, nitrobenzene), 304 (average of two determinations.

Various isocyanates and carbonates. From mixtures of isocyanates and carbonates other than those described above, were obtained the corresponding complexes and oxazolidones which are listed in Table I. They were identified by melting point, analysis, and infrared spectra.

(4) J. S. Blair and G. E. Smith, *J. Am. Chem. Soc.*, **56**, 907 (1934).

Acknowledgment. The authors wish to thank the Dainippon Printing Ink Mfg. Co., Ltd., for permission to publish this work. The helpful counsel and advice of Professor Hiroshi Sobue, Tokyo University, are especially appreciated. Thanks are also due to Mr. Tokuji Saito, the head of this laboratory, for his encouragement throughout the study. The authors also express their appreciation to Mr. Shigeyoshi Yoshioka for the infrared spectral analyses and their interpretation.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Maleamic and Citraconamic Acids, Methyl Esters, and Imides

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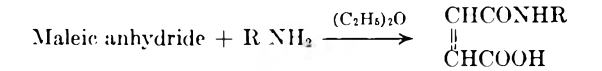
Received November 30, 1959

A series of maleamic and citraconamic acids has been made by the reaction of primary and secondary aliphatic and heterocyclic amines with maleic and citraconic anhydrides. Methyl esters have been prepared from several of these acids. It has been found possible to prepare *N*-alkylmaleimides and citraconimides by cyclization of the *N*-alkylmaleamic and citraconamic acids under much milder reaction conditions than had formerly been used.

The preparation of numerous maleamic and citraconamic acids, their methyl esters, and their imides was undertaken because these substances were needed as intermediates for various other projects. Except for a few primary amines[1-4] the reaction of aliphatic amines with maleic anhydride had not been investigated. A few maleamic acids have been mentioned but not well characterized in recent patents.[5,6] The reaction of amines with citraconic anhydride has not been reported. Although considerable work has been described both in the literature and in patents on *N*-arylmaleamic acids and imides,[7] little investigation has been devoted to the synthesis of *N*-alkylmaleimides and citraconimides. Only the *N*-methyl- and *N*-ethylmaleimides[2,8,9] have been reported in the early literature. One or two other *N*-alkylmaleimides have been referred to in some recent patents, but no descriptions of the method of preparation or characterization of the products was given. *N*-Phenylcitraconimide has been reported by Reissert.[10]

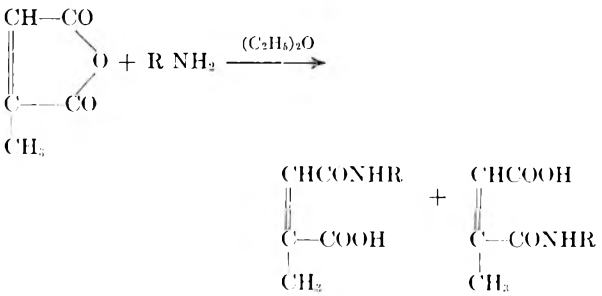
The presentation of the material of the current work has been subdivided, for convenience, according to the types of compounds involved.

I. *Maleamic and citraconamic acids.* A. *Maleamic acids* (Table I A). Maleic anhydride reacted with a variety of primary and secondary aliphatic and heterocyclic amines, equimolar amounts of the reactants being used in cold dilute ether solution.



Excellent yields of the crystalline maleamic acids resulted in most cases. In a few instances, as with some of the heterocyclic amines, the yields of the maleamic acids were poorer. The amine salt of the maleamic acid was obtained as a side product in some of these runs. A few of these have been isolated and characterized (see Experimental section).

B. *Citraconamic acids* (Table I B). Several representative amines reacted with citraconic anhydride under conditions similar to those described above. In these reactions primary amines invariably gave a mixture of two *isomeric* amide



acids in excellent yields. These mixtures of isomers could usually be separated by their differential solubilities in suitable solvents. When secondary amines were used in this reaction only a single product was isolated. The latter result is consistent

(1) R. Anschütz, *Ber.*, **20**, 3214 (1887).
(2) A. Piutti and E. Giustiniani, *Gazz. chim. ital.*, **26** I 431 (1896).
(3) Y. Liwschitz, Y. Edlitz-Pfeffermann, and Y. Lapidoth, *J. Am. Chem. Soc.*, **78**, 307 (1956).
(4) L. E. Coleman, Jr., J. F. Bork, and H. Dunn, Jr., *J. Org. Chem.*, **24**, 135 (1959).
(5) J. M. Weiss and R. P. Weiss, U. S. Patent **2,306,918**, Dec. 29, 1942.
(6) J. J. Giammaria, U. S. Patent **2,727,862**, Dec. 20, 1955.
(7) N. E. Searle, U. S. Patent **2,444,536**, July 6, 1948. This single patent is cited, since it is directly related to the current work.
(8) E. Giustiniani, *Gazz. chim. ital.*, **22** I, 169 (1892).
(9) A. Piutti, *Gazz. chim. ital.*, **18**, 483 (1888).
(10) A. Reissert and F. Tiemann, *Ber.*, **19**, 623 (1886).

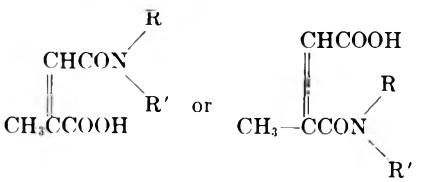
TABLE I

A. *N*-Substituted Maleamic Acids

HOOCCH=CHCONRR′

No.	R / N \ R′	M.P.°	Yield, %	Crystn. solvent[a]	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	CH_3NH[j]	167–168	75	Ac	$C_5H_7NO_3$	46.5	46.5	5.4	5.2
2	C_2H_5NH	123	90	M	$C_6H_9NO_3$	50.4	50.5	6.3	6.4
3	n-C_3H_7NH	98–99	95	M	$C_7H_{11}NO_3$	53.5	53.7	7.0	7.1
4	n-C_4H_9NH	85	90	M	$C_8H_{13}NO_3$	56.2	56.3	7.6	7.5
5	n-$C_6H_{13}NH$	78	95	Ac·E	$C_{10}H_{17}NO_3$	60.3	60.6	8.6	8.5
6	n-$C_8H_{17}NH$	84–85	90	M	$C_{12}H_{21}NO_3$	63.5	63.3	9.3	9.1
7	$C_6H_{11}NH$[b]	150	80	Ch·E	$C_{10}H_{15}NO_3$	60.9	61.0	7.6	7.5
8	$C_6H_5CH_2NH$[c,j]	142	95	M	$C_{11}H_{11}NO_3$	64.4	64.2	5.4	5.7
9	$C_6H_5CH_2CH_2NH$[j]	136–137	90	Ac	$C_{12}H_{13}NO_3$	65.8	65.9	6.0	5.9
10	$(C_2H_5)_2N$[d]	41	80	Ac·E	$C_8H_{13}NO_3$	56.2	56.0	7.6	7.2
11	$(n$-$C_6H_{13})_2N$	130	60	B·E	$C_{16}H_{29}NO_3 \cdot H_2O$	63.7	63.4	10.2	9.7
12	$(CH_2)_4N$[e]	95	80	M·E	$C_8H_{11}NO_3$	56.8	56.1	6.5	6.2
13	$(CH_2)_5N$[f]	80–81	60	Ac·E	$C_9H_{13}NO_3$	59.0	59.1	7.1	7.0
14	$O(C_2H_4)_2N$[g]	120–121	95	Ac·E	$C_8H_{11}NO_4$	51.9	52.1	6.0	6.0
15	$CH_3N(C_2H_4)_2N$[h]	196	95	M	$C_9H_{14}NO_3 \cdot H_2O$	50.4	50.6	7.4	7.5

B. *N*-Substituted Citraconamic Acids



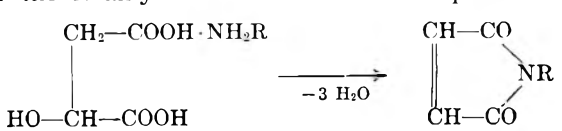
16	n-C_3H_7NH	α[i] 140	60	A	$C_8H_{13}NO_3$	56.1	55.8	7.6	7.0
		β 122	35	Æ			56.7		7.4
17	$C_6H_5CH_2NH$	α 132	60	A	$C_{12}H_{13}NO_3$	65.7	65.8	5.9	5.4
		β 142	35	Æ			65.7		5.7
18	C_6H_5NH	α 172	65	A	$C_{11}H_{11}NO_3$	64.4	64.9	5.4	5.4
		β 184	30	Æ			64.3		5.2
19	$(CH_2)_4N$[e]	α 110	95	A	$C_9H_{13}NO_3$	59.1	59.0	7.1	7.4

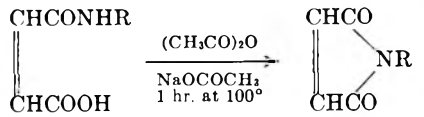
[a] A = ethanol; Ac = acetone; Æ = ethylacetate; B = benzene; Ch = chloroform; E = ether; M = methanol. [b] C_6H_{11} = cyclohexyl. [c] Reported by M. Frankel *et al. J. Am. Chem. Soc.*, **75**, 330 (1953). [d] Reported by M. L. Stein *et al. Ricerca Sci.*, **22**, 1007 (1952); *Chem. Abstr.*, **47**, 6872 (1953). [e] Pyrrolidino. [f] Piperidino. [g] Morpholino. [h] *N*′-Methylpiperazino. [i] The α and β designations have been used arbitrarily to specify the different isomers. The α symbol was used for the isomer which was less soluble in alcohol and which was obtained in larger amount. No assignment of specific structures of the two isomers has been attempted so far. [j] Kjeldahl nitrogen analyses were obtained for the following compounds: No. 1: Calcd.: 10.7% N; Found: 10.5. No. 8: Calcd.: 6.8% N; Found: 6.6. No. 9: Calcd.: 6.6% N; Found: 6.3.

with the findings of other investigators[11] who showed that the reaction of secondary amines with camphoric anhydride gave only one product.

II. *Methyl esters of the acids* (Table II). Methyl esters of several of the maleamic and citraconamic acids were prepared by refluxing an acetone suspension of the dry potassium salt of the acids with excess methyl iodide for a period of six to twelve hours.

III. *Maleimides and citraconimides* (Table III). Only the *N*-methyl- and N-ethylmaleimides[2,8,9] were reported in the older literature and these were made by a rather drastic pyrolytic decomposition of the alkylammonium salts of malic acid or of the *N*-alkylmaleamic acids. These procedures entailed elevated reaction temperatures and yields were not high. Even the more recent procedure reported by Coleman and co-workers[4] used high temperatures and called for heating maleamic acids for two or more hours at 180°. Yields were poor and accompanied by considerable polymer formation. Repetition of Coleman's[4] method in these laboratories led to similar findings. It has now been found that the milder reaction conditions used by Searle[7] for the preparation of *N*-aryl maleimides worked very well for the cyclization of *N*-alkylmaleamic acids to *N*-alkylmaleimides also, and yields of 50–70% were readily obtained.





(11) K. Auwers and H. Schnell, *Ber.*, 26, 1524 (1893).

TABLE II

METHYL ESTERS OF MALEAMIC ACIDS

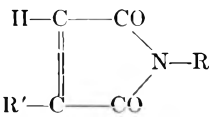
$CH_3OOCCH{=}CHCONRR'$

No.	NRR'	M.P.-B.P.°	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
20	*n*-Propylamino[a]	122/1 μ	60	$C_9H_{15}NO_3$	58.4	58.7	8.1	7.6
21	*n*-Butylamino	85/1 μ	75	$C_9H_{15}NO_3$	58.4	58.1	8.1	7.7
22	*n*-Amylamino	110/10 μ	60	$C_{10}H_{17}NO_3$	60.3	60.4	8.5	8.5
23	*n*-Hexylamino	53	60	$C_{11}H_{19}NO_3$	61.9	62.2	8.9	8.8
24	*n*-Octylamino	64	90	$C_{13}H_{23}NO_3$	64.7	64.7	9.6	9.4
25	Benzylamino	132/4 μ	70	$C_{12}H_{13}NO_2$	65.7	65.7	6.0	6.3
26	Dimethylamino	60/2 μ	70	$C_7H_{11}NO_3$	53.4	53.5	7.0	6.5
27	Diethylamino[b]	124/2 μ	60	$C_8H_{13}NO_3$	56.2	56.1	7.6	7.5
28	Piperidino[c]	56	85	$C_{10}H_{15}NO_3$	60.9	61.0	7.6	8.0

[a] Citraconic methyl ester obtained from the *alpha* isomer, m.p. 140°. [b] See Ref. (d) Table I (A). [c] Crystallized from ether/pentane.

TABLE III

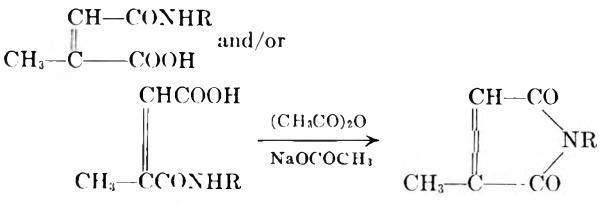
N-SUBSTITUTED MALEIMIDES AND CITRACONIMIDES



No.	R	R'	M.P.-B.P.°	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
29	Methyl[a,b]	H	96	60	$C_5H_5NO_2$	54.1	54.3	4.5	4.7
30	*n*-Propyl[a]	H	80	60	$C_7H_9NO_2$	60.4	60.1	6.4	5.9
31	*n*-Butyl	H	97/8 mm.	60	$C_8H_{11}NO_2$	62.7	62.4	7.2	7.2
32	*n*-Hexyl	H	115/5 mm.	50	$C_{10}H_{15}NO_2$	66.3	65.7	8.3	8.5
33	*n*-Octyl	H	142/5 mm.	60	$C_{12}H_{19}NO_2$	68.9	68.9	9.1	9.2
34	Benzyl[a]	H	93	70	$C_{11}H_9NO_2$	70.6	70.6	4.8	4.9
35	Phenyl[a,c]	CH_3	98	60	$C_{11}H_9NO_2$	70.6	70.8	4.8	4.9
36	Benzyl[a]	CH_3	29	60	$C_{12}H_{11}NO_2$	71.5	71.3	5.5	5.6

[a] Crystallized from ether. [b] Reported in references 2 and 8. It was prepared there by a different procedure. [c] Ref. 10.

The method of Searle[7] worked equally well for the conversion of *N*-alkylcitraconamic acids to *N*-alkylcitraconimides. The same *N*-alkylcitraconimide was obtained by the cyclization of either of the two isomeric *N*-alkylcitraconamic acids or of a crude mixture of the two.



EXPERIMENTAL[12]

Only a few typical procedures are described here in detail. The chemical and physical properties and analyses of the products are collected in Tables I–III.

N-n-Propylmaleamic acid. A solution of 6 g. (0.1 mole) of freshly distilled *n*-propylamine in 100 cc. of anhydrous ether was added dropwise over 0.5 hr. to a well stirred solution of 10 g. (0.1 mole) of maleic anhydride in 300 cc. of anhydrous ether at 0°. A white precipitate of *N-n*-propylmaleamic acid was formed immediately upon addition of the amine. The reaction mixture was stirred for 1 hr. longer. The precipitate was collected, washed with ether, and recrystallized from a methanol-ether mixture. The purified sample melted at 99° and was obtained in 95% yield.

N-n-Propylcitraconamic acids (α and β isomers). When 0.1 mole quantities of *n*-propylamine and freshly distilled citraconic anhydride were combined according to the method described above, a 95% yield of a crude mixture of amide–acid isomers was obtained. A solution of 16.5 g. of the crude mixture in 150 cc. of boiling absolute ethanol gave, on cooling, 8 g. of thick needle crystals melting at 140° (*alpha* isomer). Concentration of the filtrates gave 2.5 g. of a mixture of the isomeric acids. The mother liquors were evaporated to dryness and the residue upon recrystallization from ethyl acetate gave 5.5 g. of prisms melting at 122° (*beta* isomer).

Mono(N'-methylpiperazinoamide) of maleic acid. By the procedure described above 0.1 mole amounts of maleic anhydride and *N*-methylpiperazine gave 19.5 g. (98–100%) of the corresponding amide acid. This product was recrystallized from methanol-ether mixtures and the monohydrate melted at 196°.

Monopiperidinoamide of maleic acid. In a similar reaction maleic anhydride and piperidine reacted to give the corresponding amide acid. This was isolated and purified by recrystallization from mixtures of acetone, ether, and hexane. The purified sample melted at 80–81° and was obtained in 50–60% yield.

In this case and a few others, unusual difficulty was encountered in obtaining a pure product in high yield. In several of these cases formation of the amine salt of the amide acid appeared to be a complicating factor. It is not understood why this should have been true in only a very few of all

(12) All melting and boiling points are uncorrected.

the compounds made of this type. Several examples of the amine salts of the amide acids, which were obtained in a relatively pure state, are given below.

N-Ethylmaleamic acid ethylammonium salt. This byproduct was obtained in 15% yield from the mother liquors of *N*-ethylmaleamic acid and was recrystallized from a methanol/ether mixture; m.p. 235°. It was soluble in water and decolorized permanganate readily.

Anal. Calcd. for $C_8H_{16}N_2O_3$: C, 51.4; H, 8.03. Found: C, 51.3; H, 8.14.

N-Cyclohexylmaleamic acid cyclohexylammonium salt. The mother liquor from the crystallization of the *N*-cyclohexylmaleamic acid from methanol yielded the byproduct on addition of anhydrous ether. Recrystallized from methanol/ether; m.p. 181°.

Anal. Calcd. for $C_{16}H_{27}N_2O_3$: C, 65.3; H, 8.83. Found: C, 65.4; H, 8.73.

N-n-Octylmaleamic acid methyl ester. A solution of 12 g. (0.05 mole) of *N*-*n*-octylmaleamic acid and 2.8 g. (0.05 mole) of potassium hydroxide in 100 cc. of absolute alcohol was evaporated to dryness *in vacuo*. A suspension of the dry potassium salt in 150 cc. of dry acetone containing 20 cc. of methyl iodide was refluxed for 6 hr. The precipitated potassium iodide was removed and the filtrate evaporated. The ester was taken up in ether, washed with 5% sodium bicarbonate solution, and dried over anhydrous potassium carbonate. On evaporation to a small volume and cooling, the ester separated as a waxy solid melting at 64°. The yield was 90%.

N-n-Butylmaleimide. A mixture of 34 g. (0.2 mole) of *N*-*n*-butylmaleamic acid, 100 cc. of acetic anhydride, and 10 g. of sodium acetate was heated on a steam bath (at 100°) for 1 hr. This reaction mixture was poured into 300 cc. of ice water and stirred for 2 hr. The aqueous mixture was extracted with ether and the ether layer was dried over anhydrous sodium sulfate. The ether was evaporated and the residue was distilled *in vacuo*. The product, *N*-*n*-butylmaleimide, boiled at 97–99°, at 8 mm. and a yield of 17 g. (55–60%) was obtained.

The distillation residue from this preparation gave 3 g. of a solid. After recrystallization from ethanol 1–2 g. of crystals was obtained which melted at 270–272°. This substance was insoluble in water or dilute sodium bicarbonate solution, and decolorized dilute potassium permanganate solution instantly. On the basis of these results and the analytical data given below this compound seemed to be *N,N'*-di-*n*-butylfumaramide. The *trans* configuration about the double bond was confirmed by an infrared peak at 10.2 mμ.[13]

Anal. Calcd. for $C_{12}H_{22}N_2O_2$: C, 63.8; H, 9.7. Found: C, 64.0; H, 9.6.

The alcohol filtrates from the above diamide upon concentration gave 1 g. of another solid. This was recrystallized from mixtures of alcohol, ether, and hexane and melted at 198–199°. It was insoluble in water, but soluble in dilute sodium bicarbonate and in alcohol, and it decolorized dilute potassium permanganate solution instantly. Infrared spectra showed this, too, has a *trans* (10.2 mμ peak)[13] configuration about the double bond. This would be then the *trans* isomer of the starting (*cis*) maleamic acid.

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.2; H, 7.6. Found: C, 56.1; H, 7.5.

Similarly the distillation residues from the work up of the cyclization of several other maleamic acids gave products analogous to those obtained with the *N*-*n*-butyl compound.

N,N'-di-n-Hexylfumaramide. This product melted at 241–242° after recrystallizations from ethanol. It decolorized dilute potassium permanganate solution rapidly and had the characteristic *trans* infrared peak at 10.3 mμ.[13]

Anal. Calcd. for $C_{16}H_{30}N_2O_2$: C, 68.2; H, 10.9. Found: C, 67.8; H, 11.1.

Small amounts of the *trans* amide acid seemed to be present in this run, too, but were not obtained in analytically pure form.

N,N'-di-n-Octylfumaramide. This product crystallized from ethanol, melted at 230–231°, and had the *trans* infrared peak at 10.2 mμ.

Anal. Calcd. for $C_{20}H_{38}N_2O_2$: C, 71.0; H, 11.3. Found: C, 71.0; H, 11.5.

N-Benzylcitraconimide. A mixture of 22 g. (0.1 mole) of the mixture of isomeric *N*-benzylcitraconamic acids, 6 g. of anhydrous sodium acetate, and 100 cc. of acetic anhydride was heated with stirring until the internal temperature reached 60–70°. Heating and stirring were maintained for 1 hr. This reaction was mildly exothermal. After cooling, the reaction mixture was poured into ice water and stirred for 4 hr. Free acid was neutralized with sodium carbonate and the product was extracted with ether. After washing with sodium bicarbonate and drying over potassium carbonate, evaporation of the ether layer gave the *N*-benzylcitraconimide. The dark product was recrystallized from methanol, after treating with Darco, and gave colorless crystals melting at 29° and boiling at 189–190° at 26 mm.

Acknowledgment. We wish to thank Mr. Charles K. Marr for the microanalyses reported in this work.

TUCKAHOE, N. Y.

(13) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., (1954) p. 8.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

Ultraviolet Spectra of Substituted Acetophenones and Benzoic Acids

W. J. HORTON AND DONALD E. ROBERTSON[1]

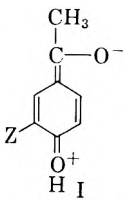
Received December 17, 1959

An empirical calculation of the maxima of 2,5-disubstituted acetophenones and benzoic acids is compared with the experimentally found values. A simple additive relationship holds since the steric factor of the substituent is contained in the constants used and since no strongly coupling (*ortho-para vs. meta*) substituents have been included.

In a previous article[2] the empirical method of Cram[3] was employed to calculate the maxima of the first primary and the secondary band of 2,3- and 2,5-hydroxy-, methoxy- or methyl-substituted acetophenones. In the present work these and similar calculations for other acetophenones are compared with the experimentally obtained values (Table I).

The excellent correlation between such calculated values and experimental values suggests a constant contribution by the substituents to each band, with the exception of two cases. Certain features inherent in the examples in Table I are responsible for such a simple treatment.

(a) No substituents are located at the position *para* to the electronegative acetyl group. Such *ortho-para vs. meta* directing groups are reported to couple strongly and give rise to $\Delta m\mu$'s which are products of the individual contributions rather than the sum.[4] Further, it has been proposed[5]



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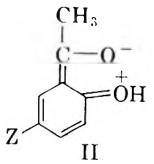
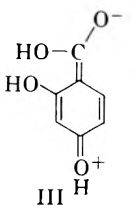


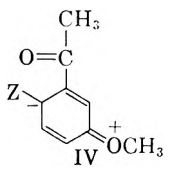
II

that chromophores from strong coupling (I or II) explain the similarity of the trisubstituted benzene (I.Z = *ortho-para* directing group) spectra to that of the disubstituted benzene (I.Z = H).

(b) No examples in Table I involve 2,3-substituents. Such cases show hypsochromic effects due to distortion of the substituents out of the plane of the benzene ring.[2] The steric effects in the monosubstituted acetophenones (Table I) may be seen by comparing (in each band) the bathochromic shifts in the *meta* isomer relative to the *ortho* isomer. *o*-Hydroxyacetophenone is the exception and hydrogen bonding is no doubt responsible. Such steric effects in monosubstituted acetophenones are contained in the individual $\Delta m\mu$'s used to calculate the maxima of the 2,5-disubstituted acetophenones. It seems obvious from Table I that no interaction occurs between the 2- and 5-substituents so as to alter the steric portion of the increment ascribed to the *ortho* group. In the more widely deviating secondary band[6] of 2-halo-5-methyl- (or methoxy) acetophenones, the lack of agreement is directionally correct for an increased carbon-halogen bond distance due to the 5-substituent. Further, the deviation is greater with 2-halo-5-methoxy-[7] than with 2-halo-5-methylacetophenones. Such changes (III) in double bond character in the excited state resulting in changed steric conditions have been suggested.[8] A form such as IV (Z = halogen) might give rise to a greater carbon-halogen bond distance and a resulting hypsochromic effect.



III



IV

(c) No 2,5-substituents are available in Table I which oppose *ortho-para-* and *meta*-directing groups. Such cases ought to give rise to strong coupling and nonadditivity of the individual contributions.[4]

An examination of the data in Table I suggests assignment, for these cases, of the first primary band to transitions to excited states analogous to I,[8] with the secondary band arising from transitions to states such as V. Substituent groups influence the positions of both bands by their influence on the π-electrons of the benzene ring. The *ortho* and *meta* halogens (Table I) raise the excited state

(1) A part of the Doctoral Dissertation of Donald E. Robertson, 1959.

(2) W. J. Horton and J. T. Spence, *J. Am. Chem. Soc.*, **80**, 2453 (1958).

(3) D. J. Cram and F. W. Crantz, *J. Am. Chem. Soc.*, **72**, 595 (1950).

(4) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947).

(5) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **77**, 4535 (1955).

(6) In our hands, wide steric deviations in 2,3-disubstituted acetophenones are seen in the secondary band.[2]

(7) There is some uncertainty about the experimental values found for 2-bromo-5-methoxyacetophenone due to the lack of supporting analytical data. The identity of the compound is assured by the method of synthesis and an analysis of the crystalline oxime.

(8) W. F. Forbes and W. A. Mueller, *Can. J. Chem.*, **34**, 1340 (1956).

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA OF SUBSTITUTED ACETOPHENONES[a]

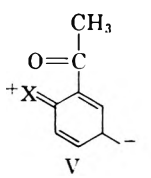
	Primary Band			Secondary Band		
	mμ	$\epsilon \times 10^{-3}$	$\Delta m\mu$[b]	mμ	$\epsilon \times 10^{-3}$	$\Delta m\mu$[b]
Acetophenone[c]	244	12.0	...	278	1.15	..
2-Fluoro	237	9.72	−7	282.5	1.55	4
3-Fluoro	238.5	8.91	−5	283.5	1.45	5
4-Fluoro[d]	242	11.5	−2	...		..
2-Chloro	239	5.65	−5	284	0.802	6
3-Chloro	239	4.98	−5	288	0.605	10
4-Chloro[d]	249	16.0	5	...		..
2-Bromo	~235.5[e]	4.61	−8	285	0.844	7
3-Bromo	242.5	9.02	−1	289.5	1.08	11
4-Bromo[d]	253	16.0	9	...		..
2-Iodo	~245[e]	4.79	1	294.5	1.02	16
4-Iodo[d]	262	16.0	18	...		..
2-Methyl[f]	242	8.5	−2	283	1.25	5
3-Methyl[c]	249	10.0	5	289	1.20	11
4-Methyl[f]	252	15.0	8	~278[e]	0.850	0
2-Methoxy[g]	246	11.0	2	305	3.8	27
3-Methoxy[c]	249	7.9	5	307	2.4	29
4-Methoxy[h]	276.5	15.5	33	...		..
2-Hydroxy[g]	251.5	9.3	7	327	3.2	49
3-Hydroxy[i]	252.5	10.0	8	311	5.0	33
4-Hydroxy[g]	276	13.0	32	...		..

2,5-DISUBSTITUTED ACETOPHENONES

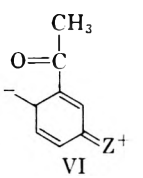
	Calcd. mμ	Experimental, mμ	$\epsilon \times 10^{-3}$	Deviation, mμ	Calcd. mμ	Experimental mμ	$\epsilon \times 10^{-3}$	Deviation, mμ
2-Cl-5-CH_3	244	243	5.25	−1	295	290	0.904	−5
2-Cl-5-CH_3O[j]	244	~240.5	4.97	−4	313	302.5	1.80	−11
2-Br-5-CH_3	240	~239	5.25	−1	296	291	0.10	−5
2-Br-5-CH_3O[k]	241	~242	5.26	1	314	298	1.63	−16
2,5-$(CH_3)_2$[l]	247	245	9.90		294	296	1.80	2
		251	8.70	−1 (mean)				
2-CH_3O-5-F	241	243	7.09	2	310	315	4.20	5
2-CH_3O-5-Cl	241	244	7.25	3	315	317	3.28	2
2-CH_3O-5-Br	243	239	7.59	−4	316	316	2.87	0
2-CH_3O-5-CH_3[c]	251	251	7.80	0	316	318	3.50	2
2,5-$(CH_3O)_2$[c]	251	250	6.30	−1	334	336	3.90	2
2-HO-5-F	246	248.5	8.44	2	332	335	4.20	3
2-HO-5-Cl	246	248	6.94	3	337	338	3.49	1
2-HO-5-Br	250	246	7.45	−4	338	339.5	3.30	1
2-HO-5-CH_3[c]	256	255	11.0	−1	338	338	3.50	0
2-HO-5-CH_3O[c]	256	256	7.4	0	356	355	3.8	−1
2,5-$(HO)_2$	259	256.5	6.88	−2	360	364	3.92	4

[a] The solvent was 95% ethanol unless otherwise noted. Other ultraviolet data on these acetophenones appears in the literature. Attention is directed here only to the Ref. under d below. [b] $\Delta m\mu$ = wave length of substituted acetophenone − corresponding wave length of acetophenone (244 or 278 mμ). Half mμ have been dropped. [c] Ref. 2, in 1:1 (vol.) ethanol-water; the acetophenone values 243 and 279 mμ (ethanol) are given by E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3757 (1955). [d] W. F. Forbes and W. A. Mueller, *Can. J. Chem.*, **35**, 488 (1957). [e] Indicates an inflection. [f] In hexane or ethanol, E. A. Braude, F. Sondheimer, and W. F. Forbes, *Nature*, **173**, 117 (1954). [g] R. A. Morton and A. L. Stubbs, *J. Chem. Soc.*, 1347 (1940). [h] In 0.1*N* hydrochloric acid, maximum 2% methanol; band also at 219.5 mμ (ε, 1060). [i] N. A. Valyashko and A. E. Lutsky, *J. Gen. Chem. U.S.S.R.*, **21**, 1029 (1951). [j] Also λ_{max} 219 mμ, ε, 18500. [k] Repeated attempts failed to yield acceptable analytical values for carbon, hydrogen, and bromine. [l] E. A. Braude and F. Sondheimer, Ref. c.

(primary band) relative to acetophenone itself but lower the excited state that is responsible



V



VI

for the secondary band. The inductive effect of the halogens, F>Cl>Br>I, is in the order of the $\Delta m\mu$'s (Table I) of the *ortho* increments for the primary band (-7, -5, -1, 1) and similarly of the *meta* increments (-5, -5, -1, --). Such an order is the inverse of that expected on the basis of size and consequent steric interaction with the acetyl group. The comparison of even *ortho*-fluoro- *vs.* *meta*-fluoroacetophenone indicates some steric effects in the *ortho*

TABLE II[a]

ULTRAVIOLET ABSORPTION SPECTRA OF SUBSTITUTED BENZOIC ACIDS

	Primary Band				Secondary Band			
	mμ	ε × 10⁻³	log ε	Δmμ	mμ	ε × 10⁻³	log ε	Δmμ
Benzoic acid[b]	228		4.02	...	273		2.94	..
o-Fluoro	224	9.27		−4	275	1.51		2
m-Fluoro	225.5	10.4		−2	275.5	1.60		2
p-Fluoro	228.5	10.2		0	...			..
o-Chloro	~229	5.00[d]		1	278		2.88[c]	5
m-Chloro	229	8.98		1	280.5	0.975		7
p-Chloro[d]	234	15.0		6	...			..
o-Bromo	~222	7.61		−6	280	0.867		7
m-Bromo	222	9.11		−6	281	0.888		8
p-Bromo[d]	238.5	16.0		10	...			..
o-Iodo	233[d,e]	7.00		5	288	1.24		15
m-Iodo	...				286	1.09		13
p-Iodo	252[d]	17.0		24	...			..
o-Methyl[d]	228	5.00		0	279		2.86[c]	6
m-Methyl[d]	232	9.00		4	279		3.01[c]	6
p-Methyl[d]	236	14.0		8	...			..
o-Methoxy[d]	230	6.00		2	291		3.43[c]	18
m-Methoxy[d]	230	7.00		2	293		3.39[c]	20
p-Methoxy[d]	249	14.0		21	...			..
o-Hydroxy[d]	236	7.50		8	307		3.57[c]	34
m-Hydroxy[d]	236	6.00		8	301		3.39[c]	28
p-Hydroxy[d]	251	12.5		23	...			..

2,5-DISUBSTITUTED BENZOIC ACIDS

	Calcd.	Experimental	ε × 10⁻³	Deviation	Calcd.	Experimental	ε × 10⁻³	Deviation
2-F-5-CH_3O	...	...		...	295	299.5	2.99	4
2-Cl-5-CH_3	...	...		...	284	285	1.11	1
2-Cl-5-CH_3O	231	233	9.03	2	298	298.5	2.05	0
2-Br-5-CH_3	226	~228	8.26	2	286	287	1.12	1
2-Br-5-CH_3O	224	~232	8.84	8	300	298	1.93	−2
2-Br-5-HO	230	~230	7.81	0	308	300	1.96	−8
2-CH_3O-5-F	228	229	6.13	1	293	301	3.62	8
2-CH_3O-5-Cl	231	232	9.01	1	298	304	2.93	6
2-CH_3O-5-Br	224	231	9.64	7	299	304.5	2.66	5
2-HO-5-F	234	231	6.29	−3	309	312	4.39	3
2-HO-5-Cl	237	232.5	7.52	−4	314	314	3.64	0
2-HO-5-Br	230	230.5	8.05	0	315	314	3.40	−1

[a] The solvent was 95% ethanol unless otherwise noted. [b] H. E. Ungnade, E. E. Pickett, L. Rubin, and E. Youse, *J. Org. Chem.*, **16**, 1318 (1951). [c] C. M. Moser and A. T. Kohlenberg, *J. Chem. Soc.*, 804 (1951). [d] In absolute ethanol, W. F. Forbes and M. B. Sheratte, *Can. J. Chem.*, **33**, 1829 (1955). [e] Missing in our examination of the spectra.

compound. The primary band Δmμ's for the other substituents (Table I) at the *ortho* and *meta* positions reflect their influence on the π-electrons, giving rise to slightly bathochromic Δmμ's.

The increments in the secondary band (a) are positive with respect to acetophenone itself (b) increase when the substituent is shifted from the *ortho* to the *meta* position (c) are large, relative to the corresponding Δmμ for the primary band and (d) appear, in the case of the *para* isomer to be shifted onto the primary band. A comparison of the respective *meta*-secondary-Δmμ's *vs.* *para*-primary-Δmμ's (F, 5, −2; Cl, 10, 5; Br, 11, 9; CH_3, 11, 8; CH_3O, 29, 33; HO, 33, 32) seems to indicate that the chromophore to which the secondary band is mainly ascribed (such as VI) has been shifted onto the 1,4-axis (such as I.Z = H) to which the primary band is assigned. The zero increment in the secondary band for *p*-methylacetophenone is similarly accounted for on this basis. It should also be noted that a secondary band reappears in 4-methoxyacetophenones which contain an additional methoxy group (2,4-dimethoxy-, 302.5 mμ, ε-8190; 3,4-dimethoxy-, 302.5 mμ, ε, 8100 and 2,4,5, trimethoxyacetophenone, 327 mμ, ε, 8380).[9]

In a similar treatment of benzoic acids (Table II) several divergent cases arise. These cases of non-additivity of the 2- and 5-substituent -Δmμ's (such as 2-bromo-5-hydroxybenzoic acid) give rise to large negative deviations in the secondary band which suggest the similar behavior of this type of compound in the acetophenone (secondary band).

The secondary band positive deviations in the case of 2-methoxy-5-halobenzoic acids have their

(9) Unpublished data by W. J Horton.

TABLE III

ACETOPHENONES

Acetophenone	Yield, %[a]	B.P. °(mm.) Found	B.P. °(mm.) Reported	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2-F	41	94.5 (34.5)	80–85 (16)[b]					
3-F	40	190 (630.0)	81 (9)[c]					
Oxime, m.p.	43.6–44.5			C_8H_8NOF	62.74	5.27	62.98	5.31
2-Cl	71	119–120 (26)	85–87.5 (5.5)[d]					
Oxime, m.p.	104–105		105–106[d]					
3-Cl	37	120 (27)	80 (2.5)[e]					
Oxime, m.p.	85.5–88		88–89[f]					
2-Br	54	136 (28)	131–135 (20)[g]					
Oxime, m.p.	127.5–129		129[h]					
3-Br	49	155 (47)	102–106 (4)[g]					
Oxime, m.p.	100.6–101.6			C_9H_8NOBr	44.88	3.77	44.87	3.85
2-I	70	103 (1.5)	112 (4)[i]					
Oxime, m.p.	129.5–136		130–132[i]					
2-Cl-5-CH_3	42	67 (0.65)	245.8–246 (760.1)[j]					
Oxime, m.p.	115.8–117.4		100–101[k]	$C_9H_{10}NOCl$	58.86	5.49	59.13	5.48
2-Cl-5-CH_3O	63	116 (3)		$C_9H_9O_2Cl$	58.55	4.91	58.61	4.99
Oxime, m.p.	114.4–117.2			$C_9H_{10}NO_2Cl$	54.14	5.05	54.26	5.08
2-Br-5-CH_3	54	83 (0.45)		C_9H_9OBr	50.73	4.26	51.24	4.48
Oxime, m.p.	128.8–131.5			$C_9H_{10}NOBr$	47.39	4.42	47.38	4.58
2-Br-5-CH_3O	60	105 (0.65)		$C_9H_9O_2Br$	47.19	3.96	47.49	4.16
Oxime, m.p.	130.8–132.2			$C_9H_{10}NO_2Br$	44.28	4.13	44.38	4.17
2-CH_3O-5-F	30[l]	135 (23.5)	128 (15)[m]					
2-CH_3O-5-Cl	67[l]	162 (25)	108 (2)[n]					
Oxime, m.p.	157.9–159.3			$C_9H_{10}NO_2Cl$	54.14	5.05	54.16	5.05
2-CH_3O-5-Br	44	128.5 (2.2)		$C_9H_9O_2Br$	47.18	3.96	46.10	4.06
Oxime, m.p.	159.6–161.8			$C_9H_{10}NO_2Br$	44.28	4.13	43.98	4.22
2-HO-5-F	59[m] m.p.	56.4–57.6	57[m]					
2-HO-5-Cl	96[o] m.p.	52.2–53.6	54[p]					
2-HO-5-Br	44[q] m.p.	57.4–59.2	56[p]					
2,5-$(HO)_2$	59 m.p.	204.6–205.4	202–203[r]					

[a] From the benzoic acid according to Ref. 11. [b] W. Borsche and M. Wagner-Roemmich, *Ann.*, **546**, 273 (1941). [c] D. P. Evans, V. G. Morgan, and H. B. Watson, *J. Chem. Soc.*, 1167 (1935). [d] H. G. Walker and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 1386 (1946). [e] N. J. Leonard and J. N. Boyd, Jr., *J. Org. Chem.*, **11**, 405 (1946). [f] A. B. Sen and D. D. Mukerji, *J. Indian Chem. Soc.*, **28**, 161 (1951); *Chem. Abstr.*, **46**, 935a (1952). [g] R. L. Lutz *et al.*, *J. Org. Chem.* **12**, 617 (1947). [h] W. Borsche and W. Scriba, *Ann.*, **541**, 283 (1939). [i] W. S. Rapson and R. G. Shuttleworth, *J. Chem. Soc.*, 487 (1941). [j] C. F. H. Allen and M. P. Bridgess, *J. Am. Chem. Soc.*, **49**, 1846 (1927). [k] F. Mayer and W. Freund *Ber.* **55**, 2049 (1922). [l] By methylation (methyl sulfate) of the corresponding hydroxy compound. [m] Ng. Ph. Bua-Hoï, D. Levit and Ng. D. Xuong *J. Org. Chem.*, **19**, 1617 (1954). [n] A. B. Sen and P. M. Bhargava, *J. Indian Chem. Soc.*, **26**, 287 (1949), *Chem. Abstr.*, **44**, 3197i (1950). [o] By Fries Rearrangement of the corresponding phenol acetate. [p] K. Kindley and H. Oelschlager, *Chem. Ber.*, **87**, 194 (1954). [q] By bromination of *o*-hydroxyacetophenone. [r] G. C. Amin and N. M. Shah, *Org. Syntheses*, **Coll. Vol. III**, 280 (1955).

counterpart in 2-methoxy-5-fluoroacetophenone (and decrease in 2-methoxy-5-chloro- or 2-methoxy-5-bromoacetophenone so as to be inconspicuous). All of these secondary band deviations suggest interaction between 2,5-substituents resulting in changed bond distances and consequent nonadditivity due particularly to the group at the 2-position.

In the primary band, the positive deviation of 2-methoxy-5-bromobenzoic acid is consistent with the above discussion; however, the positive primary deviation of 2-bromo-5-methoxybenzoic acid is not explained.

In summary, the benzoic acids follow the pattern of the acetophenones but are less regular in their agreement with prediction.

EXPERIMENTAL[10]

The ultraviolet absorption maxima were obtained on a Beckman Model DU Spectrophotometer; the material used was that submitted for analysis for carbon and hydrogen in the case of unreported compounds or material submitted to a similar regimen in the case of a known compound. The acetophenones were obtained from the corresponding benzoic acid *via* the acid chloride and sodio malonic ester[11] except for several cases, noted in Table III.

(10) The melting points of materials prepared for the determination of spectra or for ultimate analysis are corrected.

(11) A. L. Wilds and L. W. Beck, *J. Am. Chem. Soc.*, **66**, 1692 (1944).

TABLE IV

BENZOIC ACIDS

Benzoic Acid	Yield,[a] %	Melting Point, Found (corrected)	Melting Point, Reported	Formula	Analyses, Calcd. C	Analyses, Calcd. H	Analyses, Found C	Analyses, Found H
o-F	55[b]	124.4–125.3	126.5[c]					
m-F	55[b]	122.4–124.4	124[c]					
p-F	50	185.4–187.2	186[d]					
m-Cl	46	155.8–156.8	154.25[e]					
o-Br	32	149.1–150.3	148[f]					
m-Br	50	154.9–157.3	152–153[g]					
o-I	[h]	161.6–163.0	162.5–163[i]					
m-I	15[j]	186.8–188.4	187–188[k]					
2-F-5-CH_3O	36[l]	146.3–148.3		$C_8H_7O_3F$	56.47	4.15	56.56	4.18
Amide		122.4–125.0		$C_8H_8NO_2F$	56.80	4.77	56.96	4.66
2-Cl-5-CH_3	75[m]	148.5–149.7		$C_8H_7O_2Cl$	56.32	4.14	56.88	4.06
Amide		186.8–187.6		C_8H_8NOCl	56.65	4.75	56.95	4.85
2-Cl-5-CH_3O	21	173.4–174.9	172.5–173[n]					
2-Br-5-CH_3	81[m]	137.6–139	135[o]					
Amide		197.9–198.5		C_8H_8NOBr	44.88	3.77	45.09	3.84
2-Br5-CH_3O	89[p]	159.4–160.1	160[n]					
2-Br-5-HO	[q]	184.2–185.6	185 (dec.)[r]					
Benzoate		198.7–199.9		$C_{14}H_9O_4Br$	52.36	2.83	52.67	3.08
2-CH_3O-5-F	78[s]	88.0–89.0	89[s]					
2-CH_3O-5-Cl	36[t]	97.6–98.8	96.2–97.2[u]					
2-CH_3O-5-Br	72[v]	119.8–121	120.0–120.8[u]					
2-HO-5-F	83[w]	178.8–180.4	180[s]					
2-HO-5-Cl	[h]	173.8–175.1	173–174[x]					
2-HO-5-Br	[h]	167.5–169.5	165.4–166.2[u]					

[a] By potassium permanganate oxidation of the appropriate methyl compound, except for those cases which are noted. [b] By Schiemann reaction from the ethyl aminobenzoate. [c] J. F. J. Dippy and F. R. Williams, *J. Chem. Soc.*, 1466 (1934). [d] G. Schiemann and W. Winkelmüller, *Org. Syntheses*, **Coll. Vol. II**, 299 (1943). [e] D. H. Andrews, G. Lynn, and J. Johnston. *J. Am. Chem. Soc.*, **48**, 1286 (1926). [f] J. Meisenheimer, P. Zimmermann, and U. V. Kummer, *Ann.*, **446**, 213 (1926). [g] B. Flürscheim and E. L. Holmes, *J. Chem. Soc.*, **131**, 474 (1928). [h] Eastman Kodak Company material recrystallized repeatedly. [i] H. G. Rule, W. Hay, A. N. Numbers, and T. R. Paterson, *J. Chem. Soc.*, **131**, 183 (1928). [j] Overall, by diazotization of *m*-toluidine and permanganate oxidation. [k] V. H. Wallingford and P. A. Krueger, *Org. Syntheses*, **Coll. Vol. II**, 353 (1943). [l] The necessary *4-fluoro-3-methylanisole*, b.p. 169.5–170° (633.3 mm.), *Anal.* Calcd. for C_8H_9OF: C, 68.55; H, 6.47. Found: C, 68.71; H, 6.53, was prepared in 30% yield *via* the Schiemann reaction from 4-methoxy-2-methylaniline. [m] By diazotization of 2-amino-5-methylbenzoic acid. [n] G. B. Bachman and G. M. Picha, *J. Am. Chem. Soc.*, **68**, 1599 (1946). [o] W. Borsche and A. Herbert, *Ann.*, **546**, 277 (1941). [p] By permanganate oxidation of the corresponding aldehyde. [q] By chromic acid–acetic acid oxidation (25% yield) of the benzoate of the aldehyde followed by saponification (75% yield). [r] P. H. Beyer, *Rec. trav. chim.*, **40**, 621 (1921). [s] By sodium hypobromite oxidation of the corresponding acetophenone as reported; Ng. Ph. Buu-Hoï, D. Levit, and Ng. D. Xuong, *J. Org. Chem.*, **19**, 1617 (1954). [t] By permanganate oxidation of the corresponding acetophenone. [u] A. S. Hussey and I. J. Wilk, *J. Am. Chem. Soc.*, **72**, 830 (1950). [v] By permanganate oxidation of the corresponding aldehyde. [w] By demethylation as in footnote s. [x] G. Wittig, *Ber.*, **57**, 88 (1924).

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Some 2,3-Disubstituted Glycidamides and Related Compounds[1]

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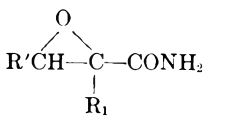
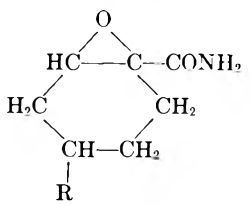
Several 2,3-disubstituted glycidamides have been prepared by the epoxidation of the unsaturated amides by means of monoperphthalic acid. The glycidamides containing alkyl groups of two to four carbon atoms show a useful degree of hypnotic or sedative action. A number of other related compounds prepared in the course of the work were also screened but showed little if any depressant action.

The sedative and hypnotic properties of many types of amides are well known. However, the depressant properties of analogs of glycidamide, I, have been studied but little. Billeter and coworkers[3] studied a group of 3-substituted and 3,3-disubstituted compounds. A large number of 2,3-disubstituted glycidamides have been prepared in our laboratories by B. R. Harriman.[4] Some of these were found to have a brief sedative action but of such slight degree as to be of little value.

We have now prepared a series of 2,3-disubstituted glycidamides, II, and two alicyclic epoxy amides, III:



I. R = R_1 = H
II. R = C_2H_5, C_3H_7, C_6H_5
R_1 = C_2H_5, C_3H_7, C_4H_9



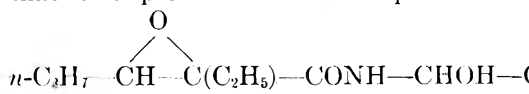
III. R = H, CH_3

These were prepared by the action of monoperphthalic acid on the unsaturated amide in anhydrous media. 2-Ethyl-3-propylglycidureide was prepared in the same way.

To determine the effect of a second amide group on the depressant activity, 2-carbamyl-3,3-diethylglycidamide (IV) was prepared. 2-Cyano-3-ethyl-2-pentenamide, from diethyl ketone and cyanoacetamide, was treated with alkaline hydrogen peroxide in acetone[5] to give IV directly in one step. While this particular reaction of an α-carbamyl-α,β-unsaturated nitrile appears not to have been previously reported, it is, of course, analogous to the preparation of α-phenyl glycidamides from α-phenyl-α,β-unsaturated nitriles.[6]

In connection with our study of the most interesting of the glycidamides reported here—2-ethyl-3-propylglycidamide (V)—it was desirable to have the 2,3-dihydroxy amide resulting from hydrolytic cleavage of the epoxy group. This epoxide proved to be surprisingly resistant to acid hydrolysis. After refluxing an acidified aqueous solution of the amide V for 48 hours, 20% unchanged amide was recovered and about a 50% yield of the desired product, 2,3-dihydroxy-2-ethylhexanamide, was obtained.

Finally, chloral was condensed with V. Numerous chloral derivatives of amides are reported in the literature, in which the products have the structure R—CONH-CHOH-CCl_3. However, in the case of the product from V, the chloral might possibly undergo reaction with the epoxide ring to give 2-trichloromethyl-4-ethyl-4-carbamyl-5-*n*-propyl-1,3-dioxolane. To prove that this was not the case and that the product did indeed have the structure resulting from condensation of chloral with the amide function, infrared spectra were used. 2-Ethylhexanamide[7] (VI) and its condensation product with chloral, *n*-C_4H_9-$CH(C_2H_5)$-CONH-CHOH-CCl_3[8] (VII), were prepared. The infrared spectra of V and VI showed the single absorption maximum at 1650–1670 cm.$^{-1}$, characteristic of *N*-unsubstituted amides, whereas the spectra from VII and the condensation product from V and chloral showed the twin maxima at 1665–1700 and 1500–1525 cm.$^{-1}$ characteristic of *N*-monosubstituted amides.[9] Thus, evidence was obtained that this product had the expected structure,



Pharmacological testing was carried out in rabbits, using the intravenous route of administration, or in rats, using the intraperitoneal route. All of the dialkyl-substituted glycidamides reported here show sedative or hypnotic activity in

(1) Presented in part before the Medicinal Chemistry Division at the 124th National Meeting of the American Chemical Society, Chicago, Sept. 6–11, 1953.

(2) Present address, Cutter Laboratories, Berkeley, California.

(3) (a) J. R. Billeter, Thesis, University of Paris, 1935. (b) E. Fourneau, J. R. Billeter, and D. Bovet, *J. Pharm. Chim.* **19**, 49 (1934).

(4) Unpublished work. Present address, Ansco, Binghamton, N. Y.

(5) B. Radziszewski, *Ber.* **18**, 355 (1885).

(6) J. V. Murray and J. B. Cloke, *J. Am. Chem. Soc.* **56**, 2749 (1934).

(7) F. F. Blicke and A. P. Centolella, *J. Am. Chem. Soc.* **60**, 2924 (1938).

(8) J. P. Larocca, J. M. Leonard, and W. E. Weaver, *J. Org. Chem.* **16**, 47 (1951).

(9) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, New York, 1954, pp. 180–185.

TABLE I

α,β-UNSATURATED AMIDES

$$R-CH=C(R^1)-CONH_2$$

R	R^1	M.P.	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
C_2H_5	C_2H_5	75–90[a]	$C_7H_{13}NO$	66.09	65.70	10.30	10.01	11.01	10.80
n-C_3H_7	C_2H_5	67–68[b]	$C_8H_{15}NO$						
C_2H_5	n-C_3H_7	72–86[c]	$C_8H_{15}NO$						
n-C_3H_7	n-C_3H_7	55–65	$C_9H_{17}NO$	69.64	69.67	11.04	10.81	9.02	8.86
n-C_3H_7	n-C_4H_9	92–94[d]	$C_{10}H_{19}NO$	70.95	70.97	11.31	11.01	8.27	8.09
n-C_3H_7	n-C_4H_9	76–77[d]	$C_{10}H_{19}NO$	70.95	70.88	11.31	11.08	8.27	7.97
C_6H_5	C_2H_5	126.5–127[e]	$C_{11}H_{13}NO$						
$-CH_2CH_2CH_2CH_2-$		128–130[f]	$C_7H_{11}NO$						
$-CH_2CH(CH_3)CH_2CH_2-$		139.5–141[g]	$C_8H_{13}NO$						

[a] This material is apparently a mixture of *cis-trans* isomers; reported[12] m.p. 117°. [b] Reported[13] m.p. 67–68°. [c] A mixture of isomers; Macq[14] reports two isomers, melting at 89° and 115.5°. [d] Fractionally crystallized from petroleum ether (b.p. 40–60°). [e] Reported[17] m.p. 135–137°. [f] Reported[18] m.p. 129–130.5°. [g] Reported[19] m.p. 140°.

these animals with little or no toxicity. The other compounds reported here show little or no such activity. A detailed study of 2-ethyl-3-propylglycidamide has been published.[10] Clinically it is being used as a tranquillizing agent.

EXPERIMENTAL[11]

α,β-Unsaturated amides. The unsaturated amides from which the glycidamides were prepared are listed in Table I These amides were prepared by one of three standard methods: 1) from the corresponding unsaturated acid by treatment of the acid with thionyl chloride, followed by treatment of the acid chloride with ammonia; 2) by heating the appropriate α-bromoamide with an excess of *N,N*-dimethylaniline for several hours at 130–140°; or 3) by hydrolysis of the corresponding α,β-unsaturated nitrile. The cyclohexene amides were prepared by method 3. 2-*n*-Propyl-2-pentenamide and the two isomeric 2-*n*-butyl-2-hexenamides were prepared by method 2, from 2-bromo-2-propylvaleramide[15] and 2-bromo-2-*n*-butylhexanamide,[16] respectively. The remaining unsaturated amides were prepared from the unsaturated acids. The acids were prepared in turn by dehydration and hydrolysis of β-hydroxy esters obtained from the Reformatsky reaction, or by oxidation of commercially available 2-ethyl-2-hexenaldehyde to give 2-ethyl-2-hexenoic acid.

The Reformatsky reaction of *n*-butyraldehyde with ethyl 2-bromovalerate gave *ethyl 2-n-propyl-3-hydroxycaproate,* b.p. 115–140°/18 mm., in 48% yield. Treatment of this ester with thionyl chloride and then with alcoholic potassium hydroxide gave *2-n-propyl-2-hexenoic acid,* b.p. 135–140°/15 mm., in 25% overall yield.

Anal. Calcd. for $C_9H_{16}O_2$: Neut. equiv. 156.2. Found: Neut. equiv. 155.5.

All of the remaining intermediates are known compounds. In the preparation of 4-methyl-1-cyclohexene-1-carboxamide,[19] the intermediate 1-cyano-4-methyl-1-cyclohexene was found to boil at 97–103°/34 mm., which is more in line with the anticipated boiling point than is the value of 98–100°/5 mm. previously reported.[19]

2,3-Disubstituted glycidamides. The unsaturated amide was dissolved in an ether solution of monoperphthalic acid[20] sufficient to provide about three moles of peracid per mole of unsaturated amide. A little anhydrous magnesium sulfate was added and the solution was stored in a refrigerator at 5°. The content of peracid was determined at intervals. The solution was allowed to stand until slightly more than the calculated amount of peracid had disappeared. Reaction time varied between 6 and 38 days. Water was added to destroy the excess peracid and the filtered solution was evaporated to dryness *in vacuo.* The residue was treated with chloroform, in which the desired glycidamide is soluble and the by-product phthalic acid is but slightly soluble. The chloroform extract was washed with dilute sodium bicarbonate solution to remove traces of phthalic acid, dried, and evaporated. The residue of crude glycidamide was recrystallized to constant melting point from petroleum ether (b.p. 75–90°). Yields of crude product were very good, but in some cases purification involved considerable loss.

Physical properties and yields of the glycidamides prepared are listed in Table II. The high- and low-melting isomers of 2-*n*-butyl-3-*n*-propylglycidamide were obtained from the high- and low-melting isomers of the unsaturated amides, respectively.

2-Ethyl-3-n-propylglycidureide. 2-Ethyl-2-hexenoic acid[21] was converted to the acid chloride, b.p. 89–92°/22 mm.,

(10) M. R. Warren, C. R. Thompson, and H. W. Werner, *J. Pharmacol. Exptl. Therap.* **96,** 209 (1949). Oxanamide is the generic name of 2-ethyl-3-*n*-propylglycidamide. Quiactin is the registered trade-mark of The Wm. S. Merrell Co. for its brand of oxanamide.

(11) Microanalyses by Micro-Tech Laboratories, Skokie, Ill. All melting and boiling points are uncorrected.

(12) H. Sutter, F. Rottmayr, and H. Porsch, *Ann.* **521,** 189 (1936).

(13) C. Mannich and E. Kniss, *Ber.* **74B,** 1637 (1941).

(14) A. Macq, *Bull. sci. acad. roy. Belg.* [5] **12,** 753 (1926).

(15) G. Fuchs, *Z. Angew. Chem.* **17,** 1508 (1904).

(16) M. Tiffeneau, *Bull. soc. Chim.* [4] **33,** 188 (1923).

(17) W. A. Lott and W. G. Christiansen, *J. Am. Pharm. Assoc.* **23,** 788 (1934).

(18) J. Kenner and R. L. Wain, *Ber.* **72B,** 456 (1939).

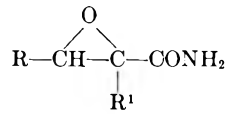
(19) M. Qudrat-i-Khuda and S. K. Ghosh, *J. Indian Chem. Soc.* **17,** 19 (1940).

(20) H. Böhme, *Org. Syntheses* **20,** 70 (1940). The batch size was doubled and only two ether extractions were used to give a more concentrated solution. Yields varied and the solution used contained from 0.20 to 0.52 mole of monoperphthalic acid per liter of ether solution.

(21) J. Lichtenberger and M. Naftali, *Bull. soc. Chim.* [5] **4,** 325 (1937).

TABLE II

2,3-DISUBSTITUTED GLYCIDAMIDES



R	R^1	Yield, %	M.P.	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
C_2H_5	C_2H_5	6.5	91–93	$C_7H_{13}NO_2$	58.74	59.17	9.15	9.18	9.78	9.65
n-C_3H_7	C_2H_5	69	90–91	$C_8H_{15}NO_2$	61.13	60.96	9.62	9.59	8.91	8.80
C_2H_5	n-C_3H_7	43	99–100	$C_8H_{15}NO_2$	61.13	60.95	9.62	9.67	8.91	8.74
n-C_3H_7	n-C_3H_7	15	103.5–105	$C_9H_{17}NO_2$	63.11	63.22	10.01	9.98	8.18	7.96
n-C_3H_7	n-C_4H_9	30	93–95	$C_{10}H_{19}NO_2$	64.82	64.85	10.34	10.20	7.56	7.53
n-C_3H_7	n-C_4H_9	38	107–109	$C_{10}H_{19}NO_2$	64.82	64.57	10.34	10.03	7.56	7.37
C_6H_5	C_2H_5	—	144–150	$C_{11}H_{13}NO_2$	69.10	68.85	6.85	6.90	7.32	6.94
$-CH_2CH_2CH_2CH_2-$		50	107.5–108	$C_7H_{11}NO_2$	59.57	59.47	7.85	8.01	9.92	9.70
$-CH_2-CHCH_2CH_2-$ (CH$_3$ on CH)		60	141.5–142	$C_8H_{13}NO_2$	61.93	62.15	8.44	8.44	9.03	8.92

which was heated with an excess of dry powdered urea for 6 hr. at 130–160°. The crude product was recrystallized from 50% aqueous ethanol and then from a 2:1 mixture of petroleum ether and absolute ethanol to give a 27% yield of *2-ethyl-2-hexenoylurea*, m.p. 151–153°.

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.68; H, 8.74; N, 15.21. Found: C, 58.71; H, 8.59; N, 15.26.

This ureide was reported by Lott and Christiansen[17] but without melting point or analysis.

A solution of the unsaturated ureide with monoperphthalic acid in absolute ether and dioxane, kept at 5° for 21 days, gave a 48% yield of the glycidureide, m.p. 146–150°, after two recrystallizations from petroleum ether (b.p. 75–90°).

Anal. Calcd. for $C_9H_{16}N_2O_3$: C, 54.00; H, 8.06; N, 14.00. Found: C, 54.02; H, 7.79; N, 13.87.

2-Carbamyl-3,3-diethylglycidamide. Diethyl ketone and cyanoacetamide were condensed by the procedure of Cope *et al.*[22] to give *2-cyano-3-ethyl-2-pentenamide*, b.p. 115–116°/0.8 mm., m.p. 34–36°, in 45% yield.

Anal. Calcd. for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.91; H, 8.17; N, 18.58.

Twenty grams (0.131 mole) of this nitrile was treated with 200 ml. of 15% aqueous hydrogen peroxide and 50 ml. acetone. Slow addition of 10 ml. of 10% aqueous sodium carbonate solution caused a highly exothermic reaction, requiring ice cooling. After the mixture stood overnight at room temperature, the precipitate was collected, washed with water, and dried. The crude product weighed 22.3 g. (91% yield) and melted at 240–240.5°. The melting point was not changed by recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.05. Found: C, 51.83; H, 7.62; N, 15.01.

(22) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.* **63**, 3452 (1941).

2,3-Dihydroxy-2-ethylhexanamide. A mixture of 20 g. of 2-ethyl-3-*n*-propylglycidamide, 5 drops of concd. sulfuric acid, and 50 ml. of water was refluxed for 48 hr. The water was removed *in vacuo* and the residue was recrystallized from a 6:1 mixture of petroleum ether (b.p. 75–90°) and absolute ethanol to give 11.2 g. of white needles, m.p. 110–112°. The analytical sample melted at 111–112° after another crystallization.

Anal. Calcd. for $C_8H_{17}NO_3$: C, 54.85; H, 9.78; N, 7.99. Found: C, 55.05; H, 9.55; N, 7.94.

From the filtrate of the original crystallization there was isolated 4 g. of unchanged glycidamide.

2-Ethyl-3-n-propyl-N-(1-hydroxy-2,2,2-trichloroethyl)glycidamide. A mixture of 31 g. (0.2 mole) of 2-ethyl-3-*n*-propylglycidamide and 44 g. (0.3 mole) of chloral was heated on a steam bath for 4 hr. The cooled solution was diluted with 100 ml. of ether and washed successively with water, sodium bisulfite solution, and water. The dried solution was evaporated and the viscous colorless oil remaining was put under a slight vacuum and seeded with a few crystals from an earlier preparation, whereupon the oil slowly crystallized. The crude material was recrystallized twice from petroleum ether (b.p. 30–60°) to give 11.5 g. (19% yield) of white crystals, m.p. 84.5–85.5°.

Anal. Calcd. for $C_{10}H_{16}Cl_3NO_3$: C, 39.42; H, 5.30. Found: C, 39.81; H, 5.52.

When the crude material was heated moderately under a vacuum of 0.2 mm. it decomposed into the starting amide and chloral.

Acknowledgment. The authors are indebted to Mr. Jay K. Seyler for technical assistance in a portion of this work and to Mr. William F. Boyd for the infrared spectra.

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[Contribution from The Chemistry Department, Faculty of Science, Cairo University]

Bromination and Iodination of Some *p*-Alkylbenzoic Acids

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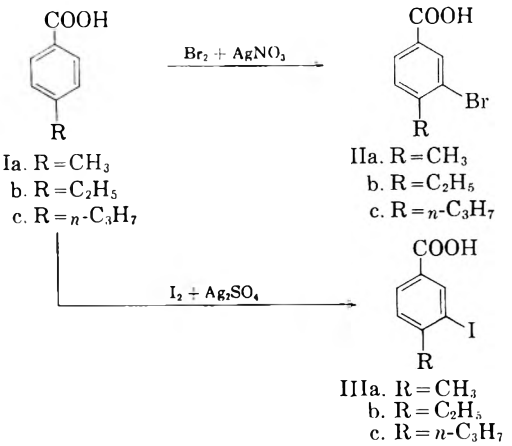
Bromination and iodination of some *p*-alkylbenzoic acids may be effected in almost quantitative yields. Bromination of the *p*-alkylbenzoic acids (Ia–c) with bromine in the presence of silver nitrate in acidic medium (*cf.* Derbyshire and Waters[1]) gives 3-bromo-4-alkylbenzoic acids (IIa–c).

Iodination of the *p*-alkylbenzoic acids (Ia–c) with iodine in the presence of silver sulfate in concentrated sulfuric acid (cf. Derbyshire and Waters[2]) affords 3-iodo-4-alkylbenzoic acids (IIIa–c):



Ia. R = CH_3
b. R = C_2H_5
c. R = n-C_3H_7

IIa. R = CH_3
b. R = C_2H_5
c. R = n-C_3H_7

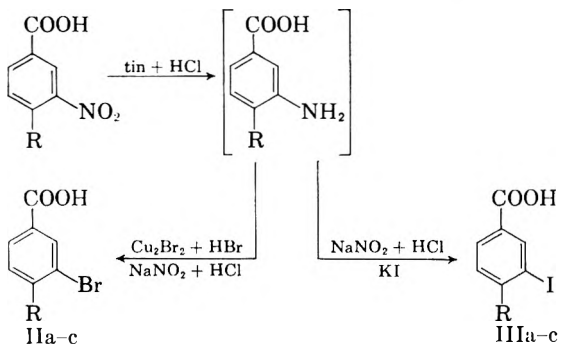
IIIa. R = CH_3
b. R = C_2H_5
c. R = n-C_3H_7

Scheme A

Authentic specimens of IIa–c and IIIa–c were prepared from the corresponding 4-alkyl-3-nitrobenzoic acids (*cf.* Fahim and Fleifel[3]) which were reduced with tin and hydrochloric acid to give 3-amino-4-alkylbenzoic acids. These were subjected without isolation to Sandmeyer's reaction to give samples of 3-bromo-4-alkylbenzoic acids or 3-iodo-4-alkylbenzoic acids (*cf.* Kloeppel[4]) which were found to be identical with IIa–c and IIIa–c, respectively (Scheme B).

An authentic specimen of IIa was also prepared by another route, starting with *p*-nitrotoluene (*cf.* Claus and Kunath,[5] and Higginbottom *et al.*[6]).

The preceding facts indicate that the halonium ion aromatic substitution is aided by the *ortho* activating alkyl group in the 4-position. The *meta*



IIa–c IIIa–c

Scheme B

directing in the 1-position is deactivating. It only allows substitution in the 3-position; it does not aid it as in fact the alkyl group does.

EXPERIMENTAL

General procedure. (a) *Bromination of p-alkylbenzoic acids.* The *p*-alkylbenzoic acid (Ia–c) (0.1 mole) (prepared according to Fahim and Fleifel[3]) was mixed with nitric acid (66 ml.; *d.*, 1.40), distilled water (50 ml.), glacial acetic acid (300 ml.), and bromine (17.6 g.; 0.11 mole) in a 3-necked ground-joint flask provided with a mechanical stirrer, a reflux condenser, and a tap funnel. An aqueous solution of silver nitrate (17 g.; 0.1 mole) in distilled water (50 ml.) was added dropwise during $^1/_2$ hr. with vigorous stirring and the reaction mixture was stirred for 2 hr. longer at room temperature (25°). It was then poured into ice-cold water and the precipitate collected. The solid product, which consisted of the organic acid and silver bromide, was digested with sodium carbonate and filtered off. The carbonate extract was boiled with charcoal, filtered, cooled, and acidified (a little amount of sodium bisulfite being added). The precipitated acid was collected, dried, and crystallized.

(b) *Iodination of p-alkylbenzoic acids.* Finely powdered iodine (26 g.; 0.11 mole) was added portionwise during $^1/_2$ hr. to the mixture of *p*-alkylbenzoic acid (Ia–c) (0.1 mole), silver sulfate (16 g.; 0.05 mole) in conc. sulfuric acid (240 ml.) and a little distilled water (30 ml.) on the boiling water bath with efficient stirring. The reaction mixture was refluxed for Ia, 0.5 hr., Ib, 2.5 hr., Ic, 5 hr. with vigorous stirring. It was then poured into ice-cold water and worked up as mentioned before. The iodo acids (IIIa–c) obtained on acidification of the sodium carbonate extract were filtered, dried, and crystallized.

Authentic specimens of IIa–c *and* IIIa–c. 4-Alkyl-3-nitrobenzoic acid (0.1 mole) (prepared as recommended by Fahim and Fleifel[3]) was refluxed with tin foil (25 g.) and concd. hydrochloric acid (100 ml.) on a steam bath for 5 hr. The product was decanted from any unchanged tin, cooled, and then diazotized with a solution of sodium nitrite (6.9 g.; 0.1 mole) in water (30 ml.). The diazonium solution was treated either with cuprous bromide (29 g.; 0.1 mole) in

(1) D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.*, 573 (1950).
(2) D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.*, 3694 (1950).
(3) H. A. Fahim and A. M. Fleifel, *J. Chem. Soc.*, 4519 (1952).
(4) E. Kloeppel, *Ber.*, 26, 1733 (1893).
(5) Ad. Claus and H. Kunath, *J. prakt. Chem.*, 39, 487 (1889).
(6) A. Higginbottom, P. Hill, and W. F. Short, *J. Chem. Soc.*, 264 (1937).

TABLE I

3-BROMO-4-ALKYL- AND 3-IODO-4-ALKYL-BENZOIC ACIDS

Compound	Solvent	M.P.,°	Yield, %	Formula	Carbon, % Caled.	Carbon, % Found	Hydrogen, % Caled.	Hydrogen, % Found	Bromine, % Caled.	Bromine, % Found
IIa	C_2H_5OH	204	100	$C_8H_7O_2Br$[4]	44.65	44.25	3.20	3.10	37.20	36.80
IIb	C_2H_5OH	165	100	$C_9H_9O_2Br$	47.16	46.89	3.93	3.75	34.93	34.87
IIc	Benzene-ligroin	89–90	95	$C_{10}H_{11}O_2Br$	49.38	48.97	4.52	4.41	32.92	32.50
									Iodine, % Caled.	Iodine, % Found
IIIa	C_2H_5OH	205–206	100	$C_8H_7O_2I$[5]	36.64	36.85	2.67	2.50	48.47	48.15
IIIb	C_6H_6	191–192	100	$C_9H_9O_2I$	39.13	38.86	3.26	3.38	46.08	45.42
IIIc	C_2H_5OH	232–233	100	$C_{10}H_{11}O_2I$	41.37	41.0	3.79	3.58	43.79	43.40

hydrobromic acid (100 ml.; 48%) or with an aqueous solution of potassium iodide (18 g.; 0.11 mole). The reaction mixture was stirred for 1 hr. at room temperature, a little sodium bisulfite added, the precipitated acids collected after acidification and crystallized. Mixed melting point determination was carried out between the bromo- acids and IIa–c, and between the iodo- acids and IIIa–c, respectively, and in each case no depression was observed.

An authentic specimen of IIa was also prepared by a series of already known reactions starting with *p*-nitrotoluene (*cf.*[5,6]) which was brominated according to procedure (a) to give 2-bromo-4-nitrotoluene in 100% yield (*cf.*[6]). The latter was converted to the corresponding nitrile which on hydrolysis gave 3-bromo-4-methylbenzoic acid (2-bromo-*p*-toluic acid), m.p. 204°, undepressed when mixed with IIa. The 3-bromo-4-alkyl- and 3-iodo-4-alkyl-benzoic acids are listed in Table I.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Reactions of Furan Compounds. XVIII. Nuclear Acetoxylation[1]

G. FRANK D'ALELIO, CARL J. WILLIAMS, JR.,[2] AND CHRISTOPHER L. WILSON

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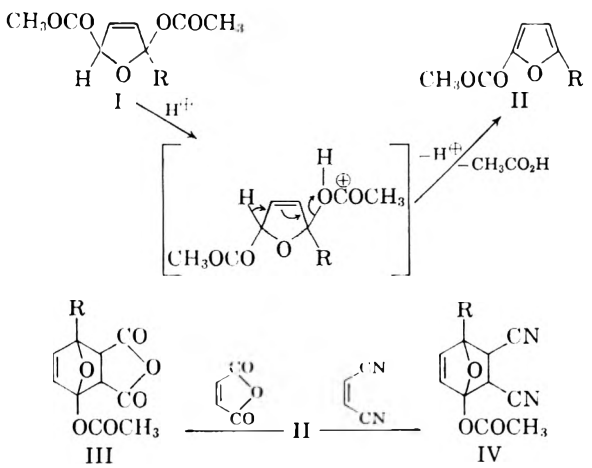
The acid-catalyzed pyrolysis of 2,5-diacetoxy-2,5-dihydrofuran resulting in the elimination of acetic acid and the formation of 2-acetoxyfuran and γ-crotonolactone has been studied further. Lactone formation is believed to involve further pyrolysis of 2-acetoxyfuran in the presence of acetic acid to give the lactone and acetic anhydride. The syntheses of diacetoxylated α-substituted furans by the action of bromine and potassium acetate in acetic acid acetic anhydride on α-substituted furans did not yield the expected products. However, their unstable formation is suspected because of the isolation of 2-acetoxy-5-methylfuran, anemonin, 2-oxo-5-acetoxymethylene-2,5-dihydrofuran, and 2-oxo-5-methoxymethylene-2,5-dihydrofuran from 2-methylfuran, furfuryl acetate, furfural diacetate, and furfuryl methyl ether, respectively.

The synthesis of 2-acetoxyfuran has been previously described; vapor-phase pyrolysis of 2,5-diacetoxy-2,5-dihydrofuran (I. R = −H) at 400–450° gave 7–40% 2-acetoxyfuran (II. R = −H) and varying amounts of a by-product, γ-crotonolactone (V).[3] Milder acid-catalyzed liquid-phase pyrolysis (100°) in the presence of a high-boiling diluent was subsequently reported to give much-improved yields (80%) of 2-acetoxyfuran.[4] The pyrolysis failed in the presence of a basic substance such as sodium acetate, and it was reasoned that the production of 2-acetoxyfuran was an acid-catalyzed



elimination of acetic acid. Pyrolysis in the absence of acid was attributed to traces of residual acid and/or by-products of the pyrolysis itself (*e.g.*, acetic

(1) Abstracted from a portion of the Ph.D. dissertation of C. J. Williams, University of Notre Dame, 1958. Part XVII, *J. Am. Chem. Soc.*, **81**, 2440 (1959).

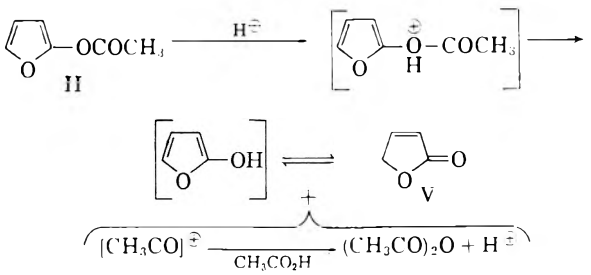
(2) Present address: Research Laboratories, Eastman Kodak Co.

(3) N. Clauson-Kaas and N. Elming, *Acta Chem. Scand.*, 6, 560 (1952).

(4) C. L. Wilson, M. P. Cava, and C. J. Williams, Jr., *J. Am. Chem. Soc.*, **78**, 2306 (1956).

acid, acetic anhydride). Such a reaction scheme may be denoted by the equation I→II,

It has now been shown that liquid-phase pyrolysis in the absence of a high-boiling diluent gives only γ-crotonolactone in poor yield because of extensive resinification. It seemed reasonable that this product might arise from further acid-catalyzed acetic acid elimination from 2-acetoxyfuran as shown by the equation



The truth of this proposal was established by subjecting an equimolar mixture of 2-acetoxyfuran and acetic acid to the conditions of pyrolysis. Acetic anhydride (68%) and γ-crotonolactone (V. 48%) were obtained, while the 2-acetoxyfuran was consumed in the reaction. Analogous results were reported when 2-acetoxyfuran was treated with bromine in carbon tetrachloride at a low temperature; the products were 2-bromo-5-oxo-2,5-dihydrofuran and acetyl bromide.[5] Further, the action of the oxidizing reagents (bromine and potassium acetate in acetic acid and acetic anhydride) on 2-acetoxyfuran has now been shown to give 2-oxo-5-acetoxy-2,5-dihydrofuran, the same lactone as that resulting from the action of lead tetraacetate on 2-acetoxyfuran.[5]

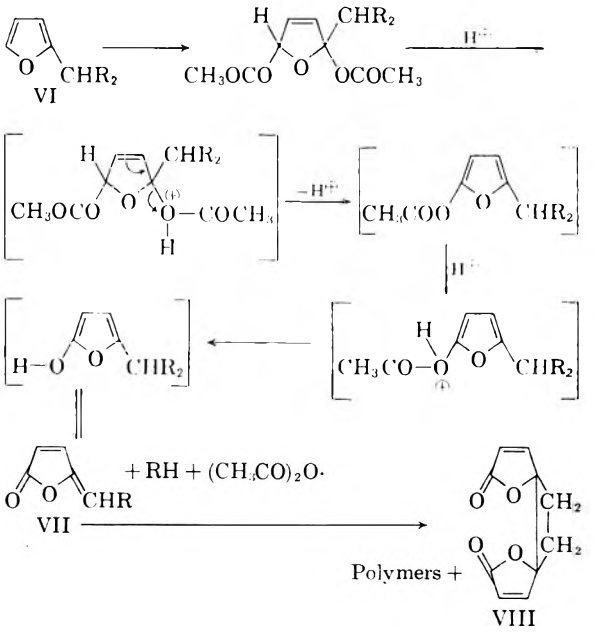
The action of the oxidizing reagents on α-substituted furans such as 2-methylfuran, furfuryl acetate, furfuryl diacetate, furoic acid, and ethyl furoate has not in the past given the predicted nuclear oxidation.[6,7] Among the possible causes of failure are resinification promoted by acidic impurities and by-products, deactivation of the substituted furan nucleus to bromine addition, and oxidation of side-chain substituents.

Renewed interest has been directed to the diacetoxylation of 2-methylfuran; rapid bromine decoloration on addition of the 2-methylfuran to the diacetoxylation mixture at −20° indicated that addition had occurred. Subsequent vacuum distillation of the reaction residues, however, resulted in virtually complete resinification. In one instance, however, a small yield (6.1%) of 2-acetoxy-5-methylfuran (II. R = CH_3) was isolated; thus the instability of the diacetoxylated intermediate was again evidenced. The new ester readily formed Diels-Alder adducts with maleic anhydride and fumaronitrile, their melting points being quite apart from the corresponding adducts with the isomeric furfuryl acetate.

Subjection of a series of α-substituted furans to the diacetoxylation reagents furnished additional evidence for the instability of the diacetoxylated intermediates, the products being analogous to γ-crotonolactone. Furfuryl acetate (VI. R_2 = H, $OCOCH_3$) gave furfural diacetate (VI. R_2 = $(OCOCH_3)_2$, 1.6%) and protoanemonin (VII. R = H), an unstable monomeric lactone which rapidly polymerized to anemonin (VIII, 4.9%) and amorphous polymer.

Furfural diacetate with the oxidation reagents yielded, on attempted vacuum distillation of the residues with or without acid-catalysis, a clear, colorless liquid which solidified on cooling. From analytical and experimental data, this compound was identified as 2-oxo-5-acetoxymethylene-2,5-dihydrofuran (VII. R = $OCOCH_3$). The only analytically pure compound isolated from the action of the oxidizing reagents on furfuryl methyl ether satisfied the elemental requirements for the analogous 2-oxo-5-methoxymethylene-2,5-dihydrofuran (VII. R = OCH_3). The production of these lactones possibly resulted from concurrent substitution and addition followed by elimination; such a reaction would be analogous to that by which furfural diacetate was obtained from furfurylacetate.

The initial reaction in the sequences described above probably involved addition to the furan ring with varying amounts of side-chain substitution. The instability of the diacetoxydihydrofuran intermediates and substituted acetoxyfurans in the presence of traces of hydrogen bromide and acidic by-products facilitated elimination to give the various lactones. Such reaction paths may be denoted by the general equation VI→VII,



(5) N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.*, **6**, 565 (1952).

(6) N. Clauson-Kaas, F. Limborg, and J. Fakstorp, *Acta. Chem. Scand.* **2**, 109–116 (1948).

(7) N. Clauson-Kaas, F. Limborg, and J. Fakstorp, *Acta. Chem. Scand.*, **6**, 569 (1952).

The various reaction paths proposed above again exemplify the multiplicity of furan reactivity. It is possible that addition, substitution, elimination, and ring-cleavage reactions all occurred to some extent, as the substituted furans exhibited the behavior of a resonance-stabilized conjugated diene and vinyl ether.

EXPERIMENTAL

γ-Crotonolactone (V). A mixture of 2,5-diacetoxy-2,5-dihydrofuran (92 g., 0.49 mole) and β-naphthalenesulfonic acid (0.200 g.) was immersed in an oil bath preheated to 105°. Instantaneous pyrolysis gave 36.5 g. of clear colorless distillate and 52.7 g. of solid black residue (representing 57.3% of the starting material). Distillation of the clear product gave γ-crotonolactone (3.7 g., 0.044 mole, 9%, boiling range 85–95°/12 mm., n_D^{25} = 1.4666) (lit.[3], b.p. 88–89°/mm., n_D^{25} = 1.4662, 19%).

Origin of γ-crotonolactone. A mixture of 2-acetoxyfuran (12.6 g., 0.1 mole), acetic acid (6.0 g., 0.1 mole), and β-naphthalenesulfonic acid (0.01 g.) was heated at 100° for 30 min., the color of the mixture turning dark amber. Distillation yielded a 10.6-g. fore-run of acidic material, boiling-range 31–53°/20 mm., γ-crotonolactone (4.0 g., 0.048 mole, 48%, boiling-range 56–70°/4 mm., n_D^{20} = 1.4680), and 3.2 g. of black solid residue. Fractional distillation of the acidic fore-run gave acetic acid (2.2 g., 0.03 mole, boiling range 49–62°/70 mm., n_D^{20} = 1.3732) and acetic anhydride (6.9 g., 0.068 mole, boiling-range 62°/70 mm. −30°/10 mm., n_D^{20} = 1.3892). No 2-acetoxyfuran (b.p. 59–60°/15 mm., n_D^{20} = 1.4467) was recovered.

2-Oxo-5-acetoxy-2,5-dihydrofuran. To a well-stirred slurry of bromine (40 g., 0.25 mole) and potassium acetate (51 g., 0.51 mole) in acetic acid (100 ml.) and acetic anhydride (150 ml.) at −20°, 2-acetoxyfuran (II. R = H) (40 g., 0.32 mole) was added. A momentary temperature rise to 10° was noted, but the bromine color persisted after stirring 1 hr. at 0°. On heating to 80°, the mixture turned white within 3 min., and potassium bromide was precipitated during 10 min. stirring at 80°. Salt removal (filtration) and solvent removal (at 70°/10–15 mm.) left a black viscous residue to which 100 ml. of ether was added. Salt and solvent removal gave a dark purple solution which, when distilled from a flask coated with potassium acetate, gave 2-oxo-5-acetoxy-2,5-dihydrofuran (23.0 g., 0.16 mole, 64%, b.p. 92–96°/3 mm., n_D^{20} = 1.4596) (lit.,[5] n_D^{25} = 1.4593).

2-Acetoxy-5-methylfuran (II. R = CH_3). The addition of 2-methylfuran (82 g., 1 mole) to a well-stirred slurry of bromine (160 g., 1 mole), potassium acetate (205 g., 2.09 moles) in acetic acid (400 ml.), and acetic anhydride (600 ml.) at −20° gave a colorless mixture in seconds. Subsequent stirring at 0°, 80°, and salt and solvent removal, all as described above, gave a black viscous residue to which 200 ml. of ether was added. Following the removal of precipitated salts, the ether filtrate was divided into four equal parts, each one being distilled from a flask coated with potassium acetate (attempted distillation in bulk resulted in complete resinification). The high-boiling fractions were diluted with 100 ml. of ether and washed successively with water, aqueous bicarbonate, and water. Fractional distillation of the dried ether solution gave 2-acetoxy-5-methylfuran (8.5 g., 0.061 mole, 6.1%, b.p. 72–73°/10 mm.).

Anal. Calcd. for $C_7H_8O_3$: C, 59.99; H, 5.75. Found:[8] C, 59.78; 59.85; H, 5.98, 6.07.

3-Acetoxy-6-methyl-3,6-epoxy-Δ⁴-tetrahydrophthalic anhydride (III). To 2-acetoxy-5-methylfuran (0.648 g., 0.0046 mole) was added maleic anhydride (0.450 g., 0.0046 mole). The addition of benzene-petroleum ether (9:1) produced in 5 min. fine white needles of 3-acetoxy-6-methyl-3,6-epoxy-Δ⁴-tetrahydrophthalic anhydride, m.p. 149.8–150°.

Anal. Calcd. for $C_{11}H_8O_6$: C, 55.46; H, 4.23. Found: C, 56.06, 56.04; H, 4.24, 4.11.

3-Acetoxy-6-methyl-3,6-epoxy-Δ⁴-tetrahydrophthalonitrile (IV). To 2-acetoxy-5-methylfuran (0.54 g., 0.0039 mole) was added fumaronitrile (0.3 g., 0.0038 mole). Gentle heating followed by the addition of 1 ml. of benzene-petroleum ether (9:1) induced the precipitation of fine white needles, m.p. 130.0–130.4°.

Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.11, H, 3.73. Found, C, 60.81, H, 3.36.

Anemonin (VIII). The addition of furfuryl acetate (VI. R_2 = H, $OCOCH_3$) (114 g., 1.02 moles) to a well-stirred slurry of bromine (160 g., 1 mole), potassium acetate (205 g., 2.09 moles) in acetic acid (400 ml.), and acetic anhydride (600 ml.) at −20° produced instant decolorization. Subsequent stirring at 0° and 80° and salt and solvent removal, all as described above, gave a black vicous residue to which was added 200 ml. of ether. Following the removal of precipitated salts and ether, the black viscous residue was fractionally distilled from a 1-l. flask coated with potassium acetate. These fractions on refrigeration slowly deposited solid material from which furfural diacetate (VI. R = $OCOCH_3$) (3.2 g., 1.6%, m.p. 48.0–48.4) and anemonin (VIII) (4.7 g., m.p. 142.–142.5°, 4.9%) were isolated and identified, 16.7 g. of insoluble and infusible amorphous polymer was also obtained. Neither the anemonin[9] nor the furfural diacetate depressed the melting point of authentic samples, and the furfural diacetate readily formed a maleic anhydride adduct, m.p. 127–130° (lit.[10] m.p. 126.5–27° C.).

2-Oxo-5-acetoxymethylene-2,5-dihydrofuran (VII. R = $OCOCH_3$). The addition of furfural diacetate[11] (VI. R = $OCOCH_3$) (50 g., 0.25 mole, in 50 ml. acetic anhydride) to a well-stirred slurry of bromine (80 g., 0.5 mole), potassium acetate (100 g., 1 mole) in acetic acid (400 ml.), and acetic anhydride (600 ml.) at −17° produced a temperature rise to 0° but no color change. Following a 30 min. stirring period at 0°, the mixture was heated to 80° for 1 hr., during which time progressive decolorization from orange to light tan occurred. Salt and solvent removal as described above gave a black viscous residue to which 100 ml. of ether was added. Precipitated salts were removed, and after alkaline washing and drying, ether removal left a black viscous residue. Fractional distillation (with or without acid catalysis) gave a clear, white acidic distillate which deposited solid material on standing at room temperature. This solid was characterized in the following manner: Attempts to prepare a maleic anhydride adduct, a bromine adduct, or an analytically pure dinitrophenylhydrazone were unsuccessful, although a positive Fehling's test was noted, the compound dissolved slowly in either acidic or basic aqueous media, yielding a dark violet alkaline solution and an amber acidic solution—no isolable solid was obtained from either solution; following Gilman's procedure,[12] the solid (1 g.) was suspended in 40 ml. of acetic acid, and 4 g. of chromic anhydride was added. The exothermic reaction mixture was cooled to room temperature and stirred for 24 hr. The acetic acid was removed by distillation under reduced pressure, and the residues were extracted with two 25-ml. portions of ether. The addition of aniline (0.5 ml.) to this extract produced, on standing, maleic anhydride dianilide (m.p. 186–188°). A mixed melting-point with maleic anhydride dianilide (m.p. 186–188°) showed no depression. The compound which best seems to fit the analytical data and these experimental observations

(8) Analyses by Midwest Microlab. Inc., Indianapolis, Ind.

(9) C. Grundemann and E. Kober, *J. Am. Chem. Soc.*, **77**, 2333 (1955).

(10) M. G. Van Campen, Jr., and J. R. Johnson, *J. Am. Chem. Soc.*, **55**, 430 (1933).

(11) H. E. Burdick and J. Adkins, *J. Am. Chem. Soc.*, **56**, 438 (1934).

(12) H. Gilman, R. A. Franz, A. P. Hewlett, and G. F. Wright, *J. Am. Chem. Soc.*, **72**, 3 (1950).

is 2-oxo-5-acetoxymethylene-2,5-dihydrofuran; the yields of 8–9.7 g. of sublimed material represented 21–24%.

Anal. Calcd. for $C_7H_6O_4$: C, 54.55; H, 3.92. Found: C, 54.39, 54.65; H, 3.77, 4.07.

2-Oxo-5-methoxymethylene-2,5-dihydrofuran (VII. R = OCH_3). The addition of furfuryl methyl ether (VI. R_2 = H, OCH_3) (28 g., 0.25 mole) to a well stirred slurry of bromine (40 g., 0.25 mole) and potassium acetate (51.5 g., 0.52 mole) in acetic anhydride (150 ml.) at −17° produced instantaneous decolorization and a temperature rise to 4°. Stirring at 0° and 80° followed by salt and solvent removal, all as described above, gave a dark-brown viscous residue. Removal of salts precipitated by the addition of ether (100 ml.) and subsequent ether removal gave a black viscous residue which was distilled from a flask coated with potassium acetate. The high-boiling distillate (12.6 g., boiling-range 60–107°/2–3 mm.) was immediately washed with dilute aqueous cold carbonate and quickly extracted with ether. Fractional distillation of the ether extract yielded 2 g. (0.012 mole, 6.4%) of a colorless liquid, b.p. 51–52°/3 mm., n_D^{25} = 1.4743; microanalysis, the formation of a purple color with phosphoric acid and the immediate hydrolysis with sulfuric acid to a product which gives a dinitrophenylhydrazone derivative support the identification of this material as 2-oxo-5-methoxymethylene-2,5-dihydrofuran.

Anal. Calcd. for $C_6H_6O_3$: C, 57.20; H, 4.76. Found: C, 56.72, 56.97; H, 4.96, 4.71.

Repetition of this reaction sequence on a molar scale gave inconclusive results; unstable higher-boiling materials of nonanalytical purity were obtained.

Acknowledgment. We wish to thank the University of Notre Dame and the E. I. du Pont de Nemours and Company for their support of this work.

NOTRE DAME, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Reactions of Furan Compounds. XIX. Synthesis of 2-Methoxyfuran and its 5-Methyl- and 5-Methoxymethyl Derivatives[1]

G. FRANK D'ALELIO, CARL J. WILLIAMS, JR.,[2] AND CHRISTOPER L. WILSON

Received December 8, 1959

Modification of the acid-catalyzed pyrolysis of 2,5-dimethoxy-2,5-dihydrofuran has given an improved yield of 2-methoxyfuran. Similar pyrolyses of 2,5-dimethoxy-2,5-dihydro-2-methylfuran and 2,5-dimethoxy-2,5-dihydro-2-furfuryl methyl ether have given 2-methoxy-5-methylfuran and 2-methoxy-5-furfuryl methyl ether, respectively. Diels-Alder adducts of these new substituted methoxyfurans with maleic anhydride are reported, as well as the synthesis of 3-methoxy-6-methyl phthalic anhydride by the aromatization of 3-methoxy-6-methyl-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride.

The synthesis of 2-methoxyfuran (II. R = H) has been previously reported by two different routes: the reaction of 5-bromo-2-furoic ester with sodium methoxide followed by saponification and decarboxylation (10–36%),[3] and the acid-catalyzed pyrolysis of 2,5-dimethoxy-2,5-dihydrofuran (11%).[4]

The pyrolytic technique has been improved by the dropwise introduction of 2,5-dimethoxy-2,5-dihydrofuran (I. R = H) into a preheated (220–250°) mixture of β-naphthalenesulfonic acid and high-boiling diluent. Resinification was minimized by maintaining the rate of intermediate addition, as accurately as possible, equal to that of product distillation. Once this condition was established, the pyrolysis proceeded with relative smoothness, and 51% of 2-methoxyfuran (II. R = H) was obtained.

The general applicability of this acid-catalyzed elimination of methanol has now been demonstrated. The intermediates, 2,5-dimethoxy-2,5-dihydro-2-methylfuran (I. R = $-CH_3$) and 2,5-dimethoxy-2,5-dihydro-2-furfuryl methyl ether (I. R = $-CH_2OCH_3$), were prepared by electrolytic oxidation of 2-methyl furan and furfuryl methyl ether respectively.[5]

The dropwise introduction of 2,5-dimethoxy-2,5-dihydro-2-methylfuran into a mixture of β-naphthalenesulfonic acid and high-boiling diluent gave no elimination; the intermediate was recovered unchanged. The addition of a few drops of glacial acetic acid to the pyrolysis flask provided sufficient acidity for elimination, and 2-methoxy-5-methylfuran (II. R = $-CH_3$, 28%) was obtained. Analytical results indicated a sensitivity of 2-methoxy-5-methylfuran to atmospheric oxygen; redistillation and storage under nitrogen at 5° gave an analytically stable sample. Oxidation of 2-methoxy-5-methylfuran by potassium ferricyanide to recognizable products failed.

The pyrolysis of 2,5-dimethoxy-2,5-dihydro-2-furfuryl methyl ether (I. R = $-CH_2OCH_3$) required even more stringent acidic conditions. The intermediate was recovered in good yield from successive treatments with β-naphthalenesulfonic acid, glacial acetic acid, or *o*-phosphoric acid in the pyrolysis flask at 250°. Partially pyrolysis, induced by mixing *o*-phosphoric acid with the intermediate be-

(1) Abstracted from a portion of the Ph.D. dissertation of C. J. Williams, University of Notre Dame, 1958.

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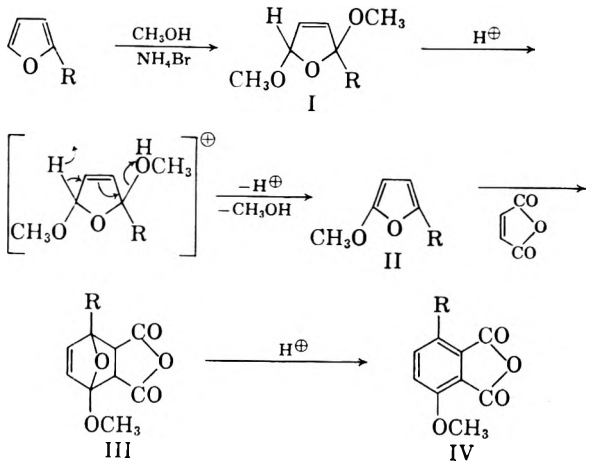
(3) E. K. Amstutz and R. J. Petfield, *J. Org. Chem.*, 19, 1944 (1954).

(4) C. L. Wilson, M. P. Cava, and C. J. Williams, Jr., *Chem. and Ind.*, 1955, 17.

(5) N. Clauson-Kaas *et al.*, *Acta Chem. Scand.*, 6, 545, 556 (1952).

fore addition to the pyrolysis flask which also contained *o*-phosphoric acid, gave 2-methoxy-5-furfuryl methyl ether (II. R = $-CH_2OCH_3$, 23%).

The pyrolysis of dialkoxydihydrofurans seems clearly an acid-catalyzed process which may be denoted by the following equation, I → II,



The substituted dialkoxydihydrofurans exhibited greater stability to acid-catalyzed pyrolysis than the analogous substituted 2,5-diacetoxy-2,5-dihydrofurans, which defy isolation and purification in the presence of traces of acid impurities.[6]

The Diels-Alder reactivity of the two new furan ethers was exemplified by their addition to maleic anhydride. Thus 2-methoxy-5-methylfuran and 2-methoxy-5-methyl furfuryl ether gave 3-methoxy-6-methyl-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride (III. R = $-CH_3$) and 3-methoxy-6-methoxymethyl-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride (III. R = $-CH_2OCH_3$), respectively.

In a manner analogous to the facile aromatization of the furan–maleic anhydride adduct (3,6-epoxy-Δ^4-tetrahydrophthalic anhydride) by various dehydrating agents, a new positional isomer, 2-methyl-6-methoxyphthalic anhydride (IV. R = $-CH_3$, 20%) was synthesized by aromatization of 3-methoxy-6-methyl-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride (III. R = $-CH_3$) in polyphosphoric acid. Simple recrystallization of the adduct (III. R = $-CH_3$) from warm methanol gave identical material (IV. R = $-CH_3$, 75%), demonstrating the ease of this aromatization.

EXPERIMENTAL[7]

2,5-Dimethoxy-2,5-dihydrofuran (I. R = H). A solution of ammonium bromide (1.2 g., 0.012 mole), furan (17.3 g., 0.25 mole), and methanol (60 ml., 1.87 moles) was placed in the electrolysis cell. The electrolysis cell employed in this and subsequent preparations consisted of a hollow brass cylindrical cathode (14 × 1.5 in.) and a hollow graphite cylindrical anode (16 × 0.5 in.) held longitudinally within and insulated by rubber stoppers. A thermometer was suspended inside the graphite cylinder which had numerous holes throughout its length to permit flow of the electrolytic mixture with the brass tube. Current was applied by a commercial battery-charger capable of an output of 6 amperes at 30 volts. The average current was 2.6 amperes; the average cell temperature, 12°.

The cell was placed in an ice bath and 19 amp. hr. (140% of theory) was passed through the mixture. Neutralization of the yellow mixture by pouring it into 20 ml. of methanol containing 1.0 g. of sodium, removal of methanol by distillation, and filtration of sodium bromide left a residue which on distillation gave 2,5-dimethoxy-2,5-dihydrofuran (23.4 g., 0.18 mole, 72%, b.p. 159–165°, n_D^{20} = 1.4316) (lit.,[8] b.p. 160–162°, n_D^{25} = 1.4323).

2-Methoxyfuran (II. R = H). To a mixture of dibutyl phthalate (25 ml.) and β-naphthalenesulfonic acid, preheated to 220–250°, was added 2,5-dimethoxy-2,5-dihydrofuran (99 g., 0.76 mole), dropwise, in such a manner as to minimize accumulation of material in the pyrolysis flask, which consisted of standard-taper dropping-funnel, flask, Claisen-head column, condensor, and receiving flask. The distillate (82.2 g., b.p. 60–140°) was washed with 100 ml. of saturated calcium chloride and extracted with two 75-ml. portions of ether. Distillation of the dried ether extract yielded 2-methoxyfuran (37.8 g., 0.385 mole, 50.8%, b.p. 92–110°, n_D^{20} = 1.4522) (lit.,[3] b.p. 108–109°).

2,5-Dimethoxy-2,5-dihydro-2-methylfuran (I. R = $-CH_3$). A solution of ammonium bromide (2.2 g., 0.022 mole), 2-methylfuran (29.5 g., 0.36 mole) and methanol (48 ml., 1.5 moles) was electrolyzed as described above by the passage of 16 amp.-hr. (80% of theory) at an average current of 3 amperes. Neutralization, removal of solvent and precipitated salt, and distillation gave 2,5-dimethoxy-2,5-dihydro-2-methylfuran (25.2 g., 0.175 mole, 49%), b.p. 86–91°/55 mm., n_D^{20} = 1.4304) (lit.,[4] n_D^{25} = 1.4262, 70%).

2-Methoxy-5-methylfuran (II. R—OCH_3). A mixture of 2,5-dimethoxy-2,5-dihydro-2-methylfuran (25 g., 0.175 mole), β-naphthalenesulfonic acid (0.100 g.), and acetic acid (0.2 g.) was added dropwise to dioctyl phthalate (25 ml.) in such a manner as to minimize accumulation of material in the pyrolysis flask (heated by an open flame). The distillate (22.2 g., b.p. 125°/750 mm.) was washed with 100 ml. of saturated calcium chloride and extracted with two 75-ml. portions of ether; the ether extracts were in turn washed with 100 ml. of dilute sodium carbonate, and dried. Ether removal and fractional distillation gave 2-methoxy-5-methylfuran (5.3 g., 0.48 mole, 28%, b.p. 137–144°, n_D^{20} = 1.4600), and 2,5-dimethoxy-2,5-dihydro-2-methylfuran (7.2 g., 0.051 mole, n_D^{20} = 1.4323). The 2-methoxy-5-methylfuran appeared unstable to atmospheric oxygen.

Anal. Calcd. for $C_6H_8O_3$: C, 64.27; H, 7.19. Found: C, 64.50, 62.90, 60.23, 59.23; H, 7.66, 7.42, 7.14, 7.10.

Redistilled 2-methoxy-5-methylfuran, (b.p. 136–137/750 mm.) stored under nitrogen at 5°, remained clear and colorless.

Anal. Found C, 63.29, 63.27; H, 7.32, 7.27.

3-Methoxy-6-methyl-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride (III. R = $-CH_3$). Maleic anhydride (0.5 g., 0.05 mole) was dissolved in 2-methoxy-5-methylfuran (0.6 g., 0.05 mole). Benzene (3 ml.) was added to the resulting warm, bright orange mixture, followed by petroleum ether until a slight turbidity was induced. Fine white needles of 3-methoxy-6-methyl-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride were precipitated, which, when washed with benzene and filtered, gave 0.65 g., 62% 0.031 mole, m.p. 133–135°. This distinguished 2-methoxy-5-methylfuran from the isomeric furfuryl methyl ether (maleic anhydride adduct, m.p. 97°).[9]

(6) N. Clauson-Kaas, *et al.*, *Acta. Chem. Scand.*, **2**, 109–116 (1948); **4**, 1233 (1952).

(7) Analyses were performed by Midwest Microlab., Inc., Indianapolis, Indiana.

(8) N. Clauson-Kaas *et al.*, *Acta. Chem. Scand.*, **6**, 531, 962 (1954).

(9) M. G. Van Campen, Jr., and J. R. Johnson, *J. Am. Chem. Soc.*, **55**, 430 (1933).

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 5 7.14; H, 4.76. *Found:* C, 57.02, 57.23; H, 4.81, 4.72.

3-Methoxy-6-methylphthalic anhydride (IV. R = $-CH_3$). Methanol (2 ml.) was added to 3-methoxy-6-methyl-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride (0.50 g., 0.024 mole) and the mixture was warmed gently for 15 min. to effect solution. On standing overnight at 5°, fine white needles of 3-methoxy-6-methylphthalic anhydride (0.34 g., 0.018 mole, 75%) were precipitated, m.p. 186–187° (closed-tube). The melting point was unchanged by sublimation, and could be duplicated by cooling and remelting the sample.

An alternate aromatization was performed by suspending 3-methoxy-6-methyl-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride (0.10 g., 0.005 mole) in 3 ml. of *o*-phosphoric acid at 25° and stirring vigorously for 10 min. The white precipitate obtained on pouring this mixture into ice water (10 ml.), when filtered, washed with cold water, and dried, gave 3-methoxy-6-methylphthalic anhydride (0.02 g., 0.001 mole, 20%), m.p. 186–188°. A mixed melting-point with the above sample aromatized in methanol showed no depression.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.20. *Found:* C, 62.72, 62.41; H, 4.31, 4.19.

2,5-Dimethoxy-2,5-dihydro-2-furfuryl methyl ether (I. R = $-CH_2OCH_3$). A solution of ammonium bromide (1.2 g., 0.012 mole), furfuryl methyl ether (28 g., 0.25 mole) and methanol (48 ml. 1.5 moles) was electrolyzed as above at an average current of 3 amp. for 16 amp.-hr. Neutralization, solvent and salt removal, and distillation gave 2,5-dimethoxy-2,5-dihydro-2-furfuryl methyl ether (31.4 g., 0.18 mole, 72%, b.p. 90–94°/9 mm., $n_D^{18} = 1.4412$) (Lit.,[4] $n_D^{18} = 1.4384$, 83%).

2-Methoxy-5-furfuryl methyl ether (II. R = $-CH_2OCH_3$). A mixture of 2,5-dimethoxy-2,5-dihydro-2-furfuryl methyl ether (23.3 g., 0.13 mole) and *o*-phosphoric acid (0.5 g.) was added dropwise to a preheated (230°) mixture of dioctyl phthalate (11 g.) and *o*-phosphoric acid (0.25 g.), the addition being such as to minimize accumulation of material in the pyrolysis flask. The distillate (17.1 g., b.p. 60–105°) was added to 100 ml. of saturated calcium chloride and the resulting mixture was extracted with two 75-ml. portions of ether. The combined ether extracts were washed with aqueous dilute bicarbonate and dried; ether removal and fractional distillation of the residue gave 2-methoxy-5-furfuryl methyl ether (4 g., 0.03 mole, 23%, b.p. 93–100°/60 mm., $n_D^{21} = 1.4620$).

Anal. Calcd. for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.01, 59.28; H, 6.77, 6.97.

3-Methoxy-6-methoxymethyl-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride (III. R = $-CH_2OCH_3$). Maleic anhydride (0.5 g., 0.05 mole) was mixed with 2-methoxy-5-furfuryl methyl ether; gentle heating gave a deep purple solution. Benzene (3 ml.) was added followed by petroleum ether until a slight turbidity existed; on standing overnight at 5°, precipitation occurred. Filtration and washing with cold benzene yielded 3-methoxy-6-methoxymethyl-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride (0.12 g., 0.005 mole, 14%, m.p. 95–97°).

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 54.90; H, 5.00.

Acknowledgment. We wish to thank The University of Notre Dame and the E. I. du Pont de Nemours and Co. for their support of this work.

NOTRE DAME, IND.

Notes

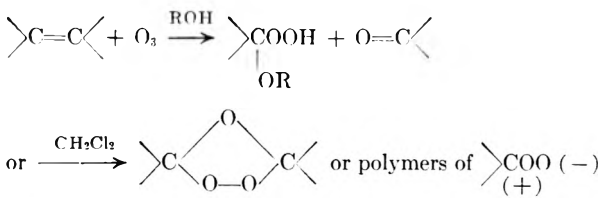
A department for short papers of immediate interest.

A Convenient Method for Reduction of Hydroperoxidic Ozonation Products

W. S. KNOWLES AND Q. E. THOMPSON

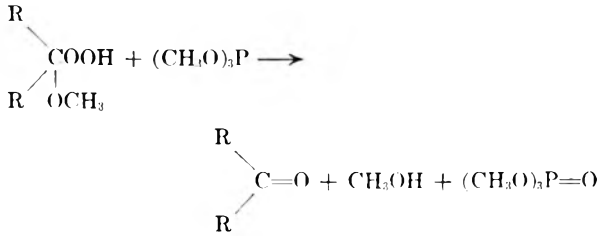
Received November 12, 1959

Criegee and co-workers[1] have shown that, in general, the ozonolysis of olefins in hydroxylic solvents gives rise to hydroperoxides plus a carbonyl fragment, whereas use of inert (nonparticipating) solvents results in the formation of ozonides and polymeric peroxides.



Many reducing agents[2] and procedural variations have been employed for converting the products of ozonolysis (usually without regard to their structure) to neutral carbonyl fragments. In general, catalytic hydrogenation, reduction with metal-acid combinations and with acidified iodide ion have been most widely utilized.

Experience in this laboratory has indicated that aldehydic and ketonic materials are best obtained by effecting ozonolysis at low temperatures (−40° or below) in a hydroxylic solvent, usually methanol, followed immediately by reduction at the lowest possible temperature. One of the principle failings of present reduction methods has been insufficient activity at low temperatures.[3] The lower trialkyl phosphite esters rapidly reduce the hydroperoxidic[4] ozonation products to the corresponding carbonyl compounds at temperatures around −40°



In addition to rapidity and convenience, this procedure has wide applicability and has, in our hands, generally proved equal or superior to older methods It is well suited for characterization purposes. One may obtain derivatives of the carbonyl fragments merely by adding the appropriate reagent to the methanol solution following completion of the low temperature ozonolysis and reduction steps. The trialkyl phosphate formed as the coproduct is relatively inert and does not interfere with the formation of carbonyl derivatives Results obtained when this technique was applied to a number of readily available laboratory olefins are shown in Table I. Generally the yields compare favorably with those obtained using other methods, although the yield of benzaldehyde from *trans*-stilbene was inferior to that (93%) previously reported.[5,6]

On the other hand, 1,4-butyndiol diacetate was converted to the corresponding dione diacetate in somewhat better yield than the 35% reported by Criegee and Lederer.[7]

The phosphite reduction method was less advantageous when isolation of the free carbonyl compounds was required, as it was necessary to choose a phosphite ester with physical properties such that neither it nor its corresponding phosphate would interfere in the isolation procedure. Trimethyl phosphite was used most often in the present investigation. Reduction of cyclohexene-methanol ozonation products with triethyl, triisopropyl, and tri-*n*-butyl phosphites proceeded equally well.

In order to ascertain something of the reactivity of trimethyl phosphite with various other peroxidic materials obtained by ozonolysis of olefins, reaction with the intermediates obtained from the ozonolysis of phenanthrene in methanol was investigated. The structures of these intermediate

(1) (a) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958); (b) R. Criegee, *Record of Chemical Progress*, **18**, 111 (1957) for excellent discussion of this work.

(2) See reference 1a and an earlier review by L. Long, *Chem. Rev.*, **27**, 437 (1940) for a more complete enumeration of these reducing agents.

(3) R. H. Perry, *J. Org. Chem.*, **24**, 829 (1959).

(4) Reduction of simple *tert*-alkyl hydroperoxides by triethyl phosphite has been previously observed by I. S. Bengelsdorf *et al.*, Abstr. 134th Meeting American Chemical Society, Chicago, Illinois, 1958, paper No. 115, p. 69P and by C. Walling, Abstr. 16th National Organic Symposium, Seattle, Washington, 1959, p. 88. See also D. B. Denney, W. F. Goodyear, and B. Goldstein, *J. Am. Chem. Soc.*, **82**, 1393 (1960) and references cited therein.

(5) A. Maggiolo, *Organic Ozone Reactions and Techniques*, The Welsbach Corporation, Ozone Process Division, Philadelphia, Pa., 1957.

(6) L. A. Subluskey, G. C. Harris, A. Maggiolo, and A. Tumolo, paper presented at International Ozone Conference, Chicago, Illinois, November 28–30, 1956; *Advances in Chem. Ser.*, **21**, 149 (1958).

(7) R. Criegee and M. Lederer, *Ann.*, **583**, 29 (1953).

TABLE I

REDUCTION OF OZONATION HYDROPEROXIDES WITH TRIMETHYL PHOSPHITE

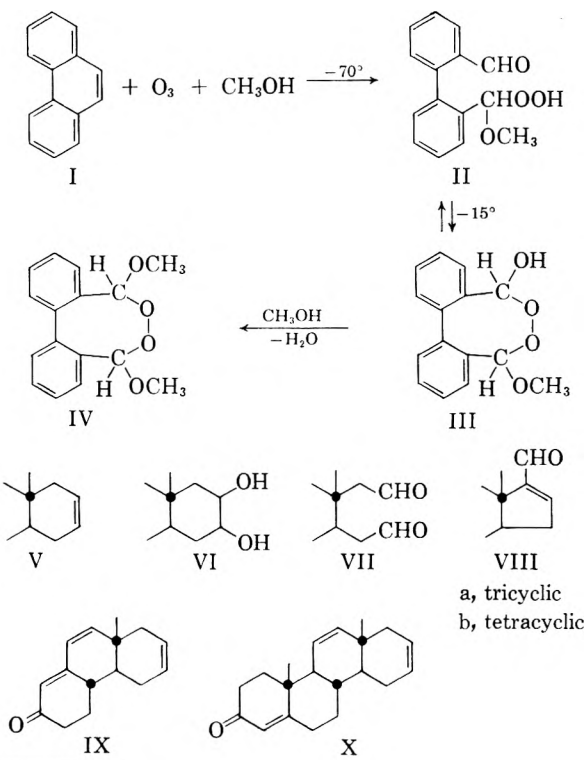
Olefin	Carbonyl product	Yield (%)	Isolated as	M.P.
Cyclohexene	Adipaldehyde	85	Disemicarbazone	193–195°[a]
3-Methylcyclohexene	3-Methyladipaldehyde	77	Di-*p*-nitrophenylhydrazone	163–164°[b]
trans-Stilbene	Benzaldehyde	84	Semicarbazone	220–222°[c]
Indene	Homophthalaldehyde	65	Di-*p*-nitrophenylhydrazone	218–220°[d]
Phenanthrene	2,2′-Diphenyldicarboxaldehyde	100	Di-*p*-nitrophenylhydrazone	265–266° dec.[e]
Dibutyl maleate	Butyl glyoxylate	78	Semicarbazone	220–222°[f]
Cinnamic acid	Benzaldehyde	86	Semicarbazone	220–222°[c]
	Glyoxylic acid	30	Semicarbazone	209–210°[g]
Phenylacetylene	Phenylglyoxal	40	Di-*p*-nitrophenylhydrazone	310–312°[h]
1,4-Butynediol acetate	1,4-Diacetoxy-1,2-butanedione	65	Di-*p*-nitrophenylhydrazone	290–310° dec.[i]

[a] A. Wohl and H. Schweitzer, *Ber.*, **39**, 895 (1906) have reported 206°. [b] *Anal.* Calcd. for $C_{19}H_{22}N_6O_4$: C, 57.28; H, 5.57; N, 21.1. Found: C, 57.25; H, 5.57; N, 21.0. [c] F. J. Wilson, I. M. Heilbron, M. M. J. Sutherland, *J. Chem. Soc.*, **1914**, 2905 give m.p. 221° dec. [d] J. L. Warnell and R. L. Shriner, *J. Am. Chem. Soc.*, **79**, 3165 (1957) report 220–221°. [e] *Anal.* Calcd. for $C_{26}H_{20}N_6O_4$: C, 64.99; H, 4.20; N, 17.49. Found: C, 64.83; H, 4.31; N, 17.46. [f] *Anal.* Calcd. for $C_7H_{13}N_3O_3$: C, 44.91; H, 7.00; N, 22.45. Found: C, 44.78; H, 6.84; N, 22.69. [g] E. Muller, *Ber.*, **47**, 3021 (1914) has reported m.p. 207°. [h] F. Straus reports 310–311°, *Ann.*, **393**, 292 (1912). [i] *Anal.* Calcd. for $C_{20}H_{20}N_6O_8$: C, 50.85; H, 4.27; N, 17.79. Found: C, 51.10; H, 4.45; N, 18.00.

products have been elucidated by Bailey[8] and by Wibaut.[9] Presumably, the first material in the low temperature ozonolysis is the open hydroperoxide II. At about −15°, however, the cyclic hemiacetal III appears to be the principle product. On standing in methanol at room temperature, III is converted to the peracetal IV.

When the clear phenanthrene ozonation solution at −70° was treated with trimethyl phosphite, vigorous reduction occurred and a quantitative yield of the dialdehyde was obtained as its di-*p*-nitrophenylhydrazone. Identical results were obtained when ozonolysis was carried out at −15°. On the other hand, IV was found to be stable for many days in trimethylphosphite at room temperature. As it is likely that III was in equilibrium with the open form, these results indicate that probably only the hydroperoxy function (—OOH) is effectively reduced by the phosphite. This assumption was further supported by the observation that cyclohexene ozonized at −60° using inert solvents (methylene chloride-acetonitrile) gave an ozonolysis mixture which was attacked only slightly by trimethylphosphite, even at room temperature.

The contraction of a six-membered ring D cyclohexene to the corresponding cyclopentene carboxaldehyde was a cardinal feature of Woodward's classical steroid synthesis.[10] Whether this ring contraction was carried out on tricyclic[10,11] or tetracyclic[12] intermediates, the path was multi-step and laborious, as it required hydroxylation of V (osmium tetroxide[10] or silver acetate-iodine[11,12]) to VI, protection of the glycol (except in one case[12]), and finally cleavage with periodic acid and cyclization of the dialdehyde (VII) to VIII. At best, the over-all yield from V to VIII did not exceed 35%. Attempts in this laboratory to prepare dialdehydes of type VII by ozonolysis of V using standard workup methods were only nominally successful.[13] However, low temperature selective



(8) P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956).

(9) J. P. Wibaut and T. J. DeBoer, *Rec. trav. chim.*, **78**, 183 (1959).

(10) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(11) L. B. Barkley, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *J. Am. Chem. Soc.*, **78**, 4111 (1956).

(12) L. B. Barkley, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *J. Am. Chem. Soc.*, **76**, 5014 (1954).

(13) In U. S. Patent **2,854,459** (1958) to W. S. Knowles and B. S. Wildi, the maximum over-all yields for the ring contraction steps were about 25%.

ozonolysis of the tricyclic and tetracyclic ketones IX and X in methanol followed by reduction with trimethyl phosphite yielded, after cyclization, the corresponding 5-membered ring D aldehydes (VIIIa,b) in 54% and 57% over-all yields, respectively with marked saving of time and labor over previous methods.

EXPERIMENTAL[14]

Apparatus. A Welsbach T-23 laboratory ozonizer was used. The ozone-oxygen stream was monitored by a Welsbach model C ozone meter. The ozone was delivered to an Ace Glass Mini-Lab Reactor assembly cat. No. 10104. With appropriate flow meters and potassium iodide traps, the amount of ozone delivered to a reaction mixture and the amount absorbed in a given time could be readily determined by titration of the iodine liberated by the off-gas stream.

General procedure for preparation and reduction of hydroperoxide ozonation cleavage products. Twenty-five millimoles of the olefin was dissolved in about 50 ml. of dry[15] methanol. If low temperature insolubility were encountered, an additional 50 ml. of methylene chloride[15] was also added. The solution was cooled to −65° to −70° in a Dry Ice bath and treated with a 3–4% oxygen-ozone stream until the calculated amount of ozone had been absorbed. A slow nitrogen stream was then bubbled through the cold solution and 5 ml. (about 40 mmoles) of trimethyl phosphite was added. Reduction was usually very rapid and accompanied by a marked temperature rise to around −20° even with strong cooling. Within 5 min. the reduction was complete and the solution was allowed to come to room temperature. Preparation of the carbonyl derivative was effected by addition of about 50–55 mmoles[16] of *p*-nitrophenylhydrazine or semicarbazide in methanol or other appropriate solvent, followed by heating for a short time on a steam bath.

In the case of cinnamic acid, the crude semicarbazones were collected and stirred for 30 min. with 50 ml. of cold 0.5*M* sodium hydroxide solution in order to dissolve out glyoxylic acid semicarbazone. Filtration and acidification served to isolate the latter from benzaldehyde semicarbazone.

l-(−)-anti-trans-3a,7,8,9,9a,9b-Hexahydro-3a-methyl-7-oxo-(1H)-benz[e]indene-3-carboxaldehyde (VIIIa). A solution of 2.14 g. (10 mmoles) of IX[17] was dissolved in 30 ml. of methylene chloride and diluted with 30 ml. of methanol. A standardized ozone-oxygen stream delivering 0.70 mmole of ozone per min. was added at −60° until 10 mmoles of ozone had been absorbed (14.5 min.). Addition of ozone was terminated and 3.0 ml. of trimethyl phosphite was added. A slight temperature rise was noted and the reaction mixture was allowed to come to room temperature over 1 hr. The solvents were removed *in vacuo* on a rotating drier. The clear oily residue was then heated at 60–80° at 0.5 mm. to remove phosphate esters. This crude dialdehyde was then cyclized in benzene using the piperidine-acetic acid method of Woodward.[10] A total of 1.635 g. of crude VIIIa was obtained which yielded sticky crystals on scratching. The crude product was dissolved in ether and was put through a short column of alumina. A total of 1.233 g. (54%) of almost colorless crystals, m.p. 118–123°, was obtained. Two recrystallizations from ether gave the analytical sample, m.p. 124.5–126°.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.91; H, 7.06. Found: C, 79.14; H, 7.25.

(+)-Δ-9(11),16-Bisdehydro-21-norprogesterone (VIIIb). One gram (3.55 mmoles) of the (−) tetracyclic ketone X[12] was dissolved in 50 ml. of methylene chloride to which was then added 50 ml. of methanol. The solution was treated for 5.1 min. with ozone at −60° as in the previous experiment. Reduction was effected by addition of 2 ml. of trimethyl phosphite. Subsequent workup and cyclization was also effected as previously described. A first crop of 465 mg., m.p. 154–156°, of essentially pure VIIIb was obtained. Infrared assay of material in mother liquors indicated the presence of another 131 mg. The total yield of useful product amounted to 57%. Recrystallization of first crop material from isopropyl alcohol gave pure material, m.p. 160–161°, showing no melting point depression with authentic material.[12]

In an identical experiment, but with the ozonolysis carried out at 0° instead of −65°, the total yield of VIIIb was only 28%.

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(14) Melting points are uncorrected.

(15) The use of reasonably dry solvents is indicated because of sensitivity of trialkyl phosphites to water. This did not appear to be a stringent requirement, however, as solvents of reagent grade were found to be quite satisfactory.

(16) It is known that carbonyl reagents such as phenylhydrazine, *p*-nitrophenylhydrazine, or hydroxylamine will itself reduce certain ozonation products. See P. S. Bailey, *Ber.*, **87**, 993 (1954), J. P. Wibaut and J. van Dijls, *Rec. trav. chim.*, **64**, 413 (1946), L. W. F. Kampschmidt and J. p. Wibaut, *Rec. trav. chim.*, **73**, 431 (1954), P. W. Haaijman and J. P. Wibaut, *Rec. trav. chim.*, **60**, 842 (1941) and p. H. Bergman and K. DeJong, *Rec. trav. chim.*, **78**, 275 (1959) for examples of this reaction. The relatively high yields of derivative obtained using essentially no excess of reagent indicate that the carbonyl compound is not acting as a reducing agent in the present case.

(17) Q. E. Thompson, *J. Org. Chem.*, **23**, 622 (1958).

Alkylation of Amines by Esters and Lithium Aluminum Hydride

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Ethyl acetate has often been recommended[1] as a reagent for the decomposition of excess lithium aluminum hydride in lithium aluminum hydride reductions. During the preparation of 1,2-propanediamine derivatives as intermediates for our analgesic program,[2] we encountered difficulties which indicated that this reagent should be used with caution in the preparation of amines, since the addition of an ester to a mixture of an amine and lithium aluminum hydride may result in alkylation of the amine.[3]

(1) (a) W. G. Brown, *Organic Reactions*, John Wiley and Sons, Inc., New York, N. Y., 1951, VI, p. 488; (b) M. D. Banus, *Chem. Eng. News*, **32**, 2424 (1954); (c) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, Inc., New York, N. Y., 1956, p. 1010.

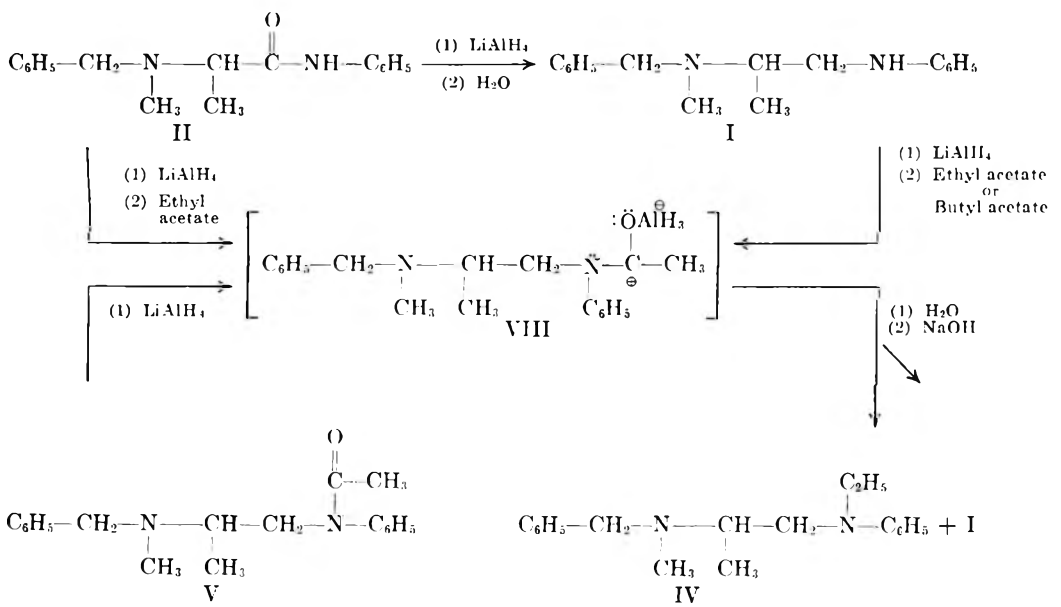
(2) (a) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959); (b) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., 135th National Meeting of The American Chemical Society, Boston, April 1959.

An excellent yield of N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine (I) was obtained when 2-(benzylmethylamino)propionanilide (II) was reduced with lithium aluminum hydride in tetrahydrofuran and the excess lithium aluminum hydride was decomposed with water. Reaction of I with propionic anhydride resulted in an almost quantitative yield of *N*-(2-benzylmethylaminopropyl)propionanilide (III), isolated as the hydrochloride. On the other hand, when II was reduced in the same manner but ethyl acetate was used for the decomposition, I was less pure as evidenced by the lower yield, lower index of refraction, and failure of the product to crystallize completely; reaction of this product with propionic anhydride gave a lower yield of III which was less easily purified.

When the mother liquor from the isolation of III in this latter reaction was made basic and the oil was extracted into ether and distilled, a second product was obtained which had an elemental analysis and an infrared absorption spectrum in agreement with the structure N^2-benzyl-N^1-ethyl-N^2 - methyl - N^1 - phenyl - 1,2 - propanediamine (IV). Additional evidence for the identity of IV was afforded when this same compound was obtained in 20% yield by the lithium aluminum hydride reduction of *N*-(2-benzylmethylaminopropyl)-acetanilide (V). The major product in this reduction was I, formed by the reductive decomposition of V. This combination of products is to be expected in the lithium aluminum hydride reduction of hindered tertiary amides.[4]

Compound IV was also isolated in about 20% yield when a mixture of I and lithium aluminum hydride in tetrahydrofuran was treated with ethyl acetate or butyl acetate. When ethyl butyrate was used in the final step, N^2-benzyl-N^1-butyl-N^2-methyl-N^1-phenyl-1,2-propanediamine (VI) was obtained. This latter compound was identical with that isolated in low yield when *N*-(2-benzylmethylaminopropyl)butyranilide (VII) was reduced. The crude products from these experiments were examined by gas chromatography. The butyl analog (VI) was not found in the product from the butyl acetate reaction and the ethyl analog (IV) was not found in the product from the ethyl butyrate reaction. These results may be considered as proof that the entering alkyl group was derived from the acyl portion of the ester.

All of these reactions may be explained on the basis of an intermediate state (VIII) as pictured in Chart I. Gaylor[5] has postulated such an intermediate in lithium aluminum hydride reductions of amides and has described the mechanism for conversion to reduction or decomposition products.



EXPERIMENTAL

Chromatography. Crude reaction mixtures were separated by partition chromatography using a heptane-dimethylformamide solvent system and a Celite column. Per cent transmission was measured at 249 mμ and yields were calculated by comparison with pure standards. Gas chromatography was carried out using a Perkin-Elmer vapofractometer, Model 154C, equipped with a Craig polyester-succinate column.

2-(Benzylmethylamino)propionanilide (II). A mixture of 228 g. (1.0 mole) of 2-bromopropionanilide,[6] 242 g. (2.0 moles) of benzylmethylamine and 1200 ml. of benzene was heated at reflux for 4 hr. and then filtered to remove benzylmethylamine hydrobromide. The filtrate was concentrated

(3) Experiments, to be reported in a later publication, indicate that the one-step alkylation of secondary amines by esters and lithium aluminum hydride may be used as a preparative method, often resulting in good to excellent yields of tertiary amines.

(4) (a) V. M. Micović and M. L. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953); (b) A. W. Burgstahler, *J. Am. Chem. Soc.*, **73**, 3021 (1951); (c) K. Banholzer, T. W. Campbell, and H. Schmid, *Helv. Chim. Acta*, **35**, 1577 (1952).

(5) N. G. Gaylord, *Experientia* **10**, 166, 423 (1954).

(6) A. Tigerstedt, *Ber.* **25**, 2919 (1892).

to remove the benzene and the residue was recrystallized from ethanol. The yield of 2-(benzylmethylamino)propionanilide, m.p. 71–72°, was 80%.

Reduction of 2-(benzylmethylamino)propionalilide (II). *Method A. Decomposition with water.* A solution of 268 g. (1.0 mole) of 2-(benzylmethylamino)propionanilide in 1 l. of tetrahydrofuran was added dropwise, under a nitrogen atmosphere, to a cooled solution of 76 g. (2.0 moles) of lithium aluminum hydride in 2 l. of tetrahydrofuran. The reaction mixture was heated at reflux for 5 hr., allowed to stand overnight, and then treated successively with 76 ml. of water, 228 ml. of 15% sodium hydroxide, and 228 ml. of water. The insoluble portion was filtered and washed with tetrahydrofuran, and the combined filtrates were dried over magnesium sulfate and distilled. The yield of N^2-benzyl-N^2methyl-N^1-phenyl-1,2-propanediamine, b.p. 145–150°/0.3 mm. and n_D^{25} 1.5700, was 221 g. (87%).

Anal. Calcd. for $C_{17}H_{22}N_2$: C, 80.3; H, 8.7; N, 11.0. Found: C, 80.0; H, 8.5; N, 11.0.

This product completely crystallized on standing. A sample recrystallized from ethanol melted at 41–42°.

Method B. Decomposition with ethyl acetate. One mole of 2-(benzylmethylamino)propionanilide was reduced as described above, but 150 ml. of ethyl acetate was added prior to the water and sodium hydroxide. The yield of impure product b.p. 148–164°/0.3 mm. and n_D^{25} 1.5673, was 79%. This material only partly crystallized on standing.

N-(2-Benzylmethylaminopropyl)propionanilide hydrochloride (III). *A. From pure N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine*(I). A mixture of 50.8 g. (0.2 mole) of N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine, prepared by Method A, and 75 ml. of propionic anhydride was heated on a steam bath for 2 hr. and concentrated to remove the propionic acid and excess propionic anhydride. The residue was dissolved in 330 ml. of ether and treated with 110 ml. of 2*N* ethanolic hydrogen chloride. The reaction mixture was cooled overnight and filtered, and the product was washed with a mixture of ethanol and ether. The yield of *N*-(2-benzylmethylmethylaminopropyl)propionanilide hydrochloride, m.p. 150–152°, was 45.4 g. (65%). Concentration of the mother liquors followed by addition of ether resulted in an additional 14.5 g. (79% total), m.p. 149–151°. Recrystallization from acetone or from ethanol by addition of ether, raised the melting point to 151–152°.

Anal. Calcd. for $C_{20}H_{27}ClN_2O$: C, 69.2; H, 7.8; Cl, 10.2; N, 8.1. Found: C, 69.3; H, 7.9; Cl, 10.4; N, 8.3.

The mother liquor from the filtration of the recovered salt was concentrated to a sirup, treated with aqueous sodium hydroxide, and extracted with ether. The ether layer was concentrated and the residue distilled, b.p. 150–160°/0.1 mm. and n_D^{25} 1.5522. The infrared absorption spectrum of this material was almost identical with that of *N*-(2-benzylmethylaminopropyl)propionanilide, b.p. 146–148°/0.1 mm. and n_D^{25} 1.5491, prepared from the purified hydrochloride. The pure base crystallized on standing and melted at 51–52° after recrystallization from hexane.

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.4; H, 8.4; N, 9.0. Found: C, 77.0; H, 8.5; N, 9.0.

In an alternate reaction the product was not converted to the salt but the base was distilled, b.p. 166–170°/0.3 mm., n_D^{25} 1.5491, and yield 90%.

B. From impure N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine (I). A mixture of 100 g. (0.38 mole) of impure diamine, prepared by Method B, and 130 ml. of propionic anhydride was heated on a steam bath for 3 hr. and concentrated to remove the propionic acid and excess propionic anhydride. The residue was dissolved in 550 ml. of ether and 180 ml. of 2.3*N* ethanolic hydrogen chloride was added. Crystallization was slow and the reaction mixture was allowed to stand for 5 days before filtration. The yield, including recoveries, of *N*-(2-benzylmethylaminopropyl)-propionanilide hydrochloride, m.p. 148–151°, was 60%.

N^2-Benzyl-N^1-ethyl-N^2-methyl-N^1-phenyl-1,2-propanediamine (IV). *A. From impure N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine* (I). The mother liquor from the filtration of the above salt was concentrated to remove the solvent, treated with dilute sodium hydroxide, and the oil was extracted into ether and fractionally distilled. The fraction with b.p. 133–136°/0.06 mm., n_D^{25} 1.5591, weighed 11.5 g. An infrared absorption spectrum showed a weak carbonyl band but indicated that most of the propionanilide had been removed. This material was further purified by partition chromatography and pure N^2-benzyl-N^1-ethyl-N^2-methyl-1,2-propanediamine, n_D^{25} 1.5635 and b.p. 136–140°/0.3 mm., was obtained.

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.8; H, 9.3; N, 9.9; mol. wt., 282. Found: C, 80.5; H, 9.4; N, 9.7; neut. equiv., 279.

The dipicrate was prepared and recrystallized from ethanol, m.p. 89–91°.

Anal. Calcd. for $C_{31}H_{32}N_8O_{14}$: C, 50.3; H, 4.4; N, 15.1. Found: C, 50.7; H, 4.9; N, 14.7.

B. From N-(2-benzylmethylaminopropyl)acetanilide (V). A solution of 14.8 g. (0.05 mole) of *N*-(2-benzylmethylaminopropyl)acetanilide in 50 ml. of tetrahydrofuran was added dropwise, under a nitrogen atmosphere, to a solution of 4.0 g. (0.01 mole) of lithium aluminum hydride in 300 ml. of tetrahydrofuran. The reaction mixture was heated at reflux for 3 hr. and then treated successively with 4 ml. of water, 12 ml. of 15% sodium hydroxide, and 12 ml. of water. The precipitate was filtered and washed with tetrahydrofuran and the filtrates were dried over magnesium sulfate and distilled. The yield of crude products, b.p. 136–140°/0.2 mm. and n_D^{25} 1.5670, was 10.1 g. Partition chromatography indicated a ratio of 72% N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine to 28% N^2-benzyl-N^1-ethyl-N^2-methyl-N^1-phenyl-1,2-propanediamine. The products were identical with those obtained by the reduction of 2-(benzylmethylamino)propionanilide using ethyl acetate decomposition, described above, or the reaction of N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine with lithium aluminum hydride and ethyl acetate or butyl acetate, described below.

C. From N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine (I), *lithium aluminum hydride and ethyl acetate or butyl acetate.* A solution of 5.1 g. (0.02 mole) of N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine in 20 ml. of tetrahydrofuran was added to a solution of 2.0 g. (0.05 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran. The mixture was heated at reflux for 15 min. and a solution of 0.12 mole of freshly distilled ethyl acetate in 30 ml. of tetrahydrofuran was added. The reaction mixture was allowed to reflux for 1 hr. and was then treated successively with 2 ml. of water, 2 ml. of 15% sodium hydroxide, and 6 ml. of water. The solid was filtered and washed with tetrahydrofuran. The filtrates were concentrated to remove the solvent. Partition chromatography on the residue indicated a ratio of 79% N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine to 21% N^2-benzyl-N^1-ethyl-N^2-methyl-N^1-phenyl-1,2-propanediamine.

When butyl acetate was substituted for ethyl acetate in the above procedure, the ratio was 81% to 18%, respectively, of the same products.

N^2-Benzyl-N^1-butyl-N^2-methyl-N^1-phenyl-1,2-propanediamine (VI). *A. From N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine* (I), *lithium aluminum hydride and ethyl butyrate.* When ethyl butyrate was substituted for ethyl acetate in the above procedure, the crude product contained N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine and N^2-benzyl-N^1-butyl-N^2-methyl-N^1-phenyl-1,2-propanediamine in a ratio of 83% to 17%.

B. From N-(2-benzylmethylaminopropyl)butyranilide (VII). The lithium aluminum hydride reduction of 9.8 g. of *N*-(2-benzylmethylaminopropyl)butyranilide resulted in 6.6 g. of crude oil which largely crystallized on standing. Partition chromatography indicated a ratio of 93% to 7%, respectively, of the same products obtained above.

When a mixture of 4.1 g. of the crude product and 2.5 ml. of ethanol was cooled and filtered, 3.1 g. of N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine, m.p. 40–41°, was

obtained. The mother liquor was concentrated and the products separated by chromatography. The yield of N^2-benzyl-N^1-butyl-N^2-methyl-N^1-phenyl-1,2-propanediamine, n_D^{25} 1.5497, was 420 mg. The infrared absorption spectrum had a more intense alkyl band than the analogous N^1-ethyl compound and lacked a CO or NH band.

Anal. Calcd. for $C_{21}H_{30}N_2$: C, 81.2; H, 9.7; N, 9.0. Found: C, 80.3; H, 9.8; N, 9.0.

The dipicrate was prepared and recrystallized from ethanol, m.p. 99–100°.

Anal. Calcd. for $C_{33}H_{36}N_8O_{14}$: C, 51.4; H, 4.7; N, 14.6. Found: C, 51.5; H, 5.2; N, 14.4.

N-(2-Benzylmethylaminopropyl)acetanilide (V). This compound was prepared by the reaction of N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine with acetic anhydride. The yield of *N*-(2-benzylmethylaminopropyl)acetanilide, b.p. 150–156°/0.1 mm. and n_D^{25} 1.5552, was 86%.

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 77.0; H, 8.2; N, 9.4. Found: C, 76.7; H, 8.2; N, 9.3.

N-(2-Benzylmethylaminopropyl)butyranilide (VII). This compound, b.p. 165–167°/0.2 mm. and n_D^{25} 1.5446, was obtained in 80% yield by the reaction of N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine with butyric anhydride.

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.7; H, 8.7; N, 8.6. Found: C, 77.6; H, 9.0; N, 8.6.

Acknowledgment. We are indebted to Dr. J. H. Clark and associates and to Mr. H. J. Brabander for the preparation of some of the intermediates, to Mr. C. Pidacks and co-workers for the chromatography, and to Mr. L. Brancone and Mr. W. Fulmor and associates for the microanalyses and infrared absorption spectra.

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The Nitration of 4-Nitro-o-iodotoluene

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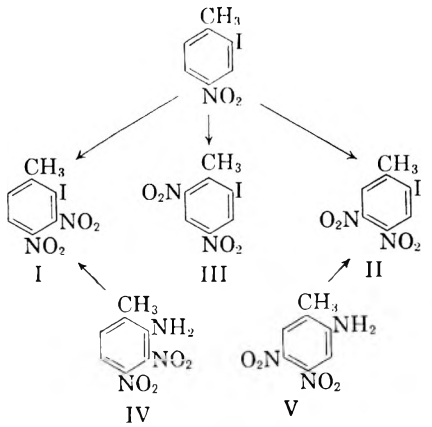
Dinitroiodo compounds have received little attention, as only a few of them are described in the literature. During a program of research on nitration of some iodo[2,3] compounds in this laboratory, nitration of 4-nitro-*o*-iodotoluene was undertaken for detailed investigation. The reaction can be expected to give three dinitro isomers, *viz.*, 3,4-(I); 4, 5-(II) and 4,6-(III) dinitro-*o*-iodotoluenes.

Only two isomers, *i.e.*, 4,5-dinitro-(II) and 4,6-dinitro-*o*-iodotoluene (III), were isolated from the reaction mixture. The identity of 4,5-dinitro-*o*-iodotoluene (II) was confirmed by an unequivocal synthesis from 4,5-dinitro-*o*-toluidine[4] (V) by Sandmeyer's reaction. Attempts to prepare 4,6-dinitro-*o*-iodotoluene (III) from 4,6-dinitro-*o*-toluidine[5] failed. 3,4-Dinitro-*o*-iodotoluene (I) has also been synthesized from 3,4-dinitro-*o*-toluidine[4] (IV). 4,5-Dinitro-*o*-iodotoluene (II) behaves normally with hydrazine hydrate giving 2-nitro-5-iodo-*p*-tolylhydrazine as the main product. The structure is assigned by analogy with other hydrazine preparations.[2]



The various dinitroiodo isomers prepared above can be distinguished readily, by taking advantage of their color reactions in acetone solution with aqueous sodium hydroxide, in which colors ranging from light red to intense green are produced.

EXPERIMENTAL[6]

Nitration of 4-nitro-o-iodotoluene. To a suspension of 4-nitro-*o*-iodotoluene (10 g.) in concd. sulfuric acid (42 ml., d. 1.8), fuming nitric acid (14 ml., d. 1.5) was added dropwise with vigorous shaking. It was then heated on a water bath for about 2 hr. and poured on crushed ice. The yellow crystalline material which separated was repeatedly crystallized successively from ethanol and methanol to give 4,5-dinitro-*o*-iodotoluene (5.2 g.) as yellow flakes, m.p. 97°.

Anal. Calcd. for $C_7H_5O_4N_2I$: I, 41.2. Found: I, 41.0.

The mother-liquor on standing deposited crystals of 4,6-dinitro-*o*-iodotoluene (1 g.) which crystallized from ethanol as pale yellow needles, m.p. 178°.

Anal. Calcd. for $C_7H_5O_4N_2I$: I, 41.2. Found: I, 40.8.

There remained an oil (1.5 g.) which could not be induced to crystallize.

3,4- and 4,5-Dinitro-o-toluidines[4] were prepared according to the method described previously.

4,5-Dinitro-o-iodotoluene. 4,5-Dinitro-*o*-toluidine (0.5 g.) dissolved in concd. sulfuric acid (5 g.) containing a little water was diazotized at 0° with sodium nitrite (0.4 g.). After 0.5 hr. the mixture was treated with a solution of potassium iodide (5 g.) in water. The 4,5-dinitro-*o*-iodotoluene formed was isolated in the usual manner and recrystallized from ethanol as yellow flakes (0.4 g.), m.p. 96°; mixed melting point with a sample of 4,5-dinitro-*o*-iodotoluene obtained by nitration of 4-nitro-*o*-iodotoluene remained undepressed.

3,4-Dinitro-o-iodotoluene was prepared by adopting a procedure, similar to that described above, from 3,4-dinitro-*o*-toluidine as pale yellow needles, m.p. 117°.

Anal. Calcd. for $C_7H_5O_4N_2I$: I, 41.2. Found: I, 40.7.

2-Nitro-5-iodo-p-tolylhydrazine. To a solution of 4,5-dinitro-*o*-iodotoluene (5 g.) in ethanol twice the equivalent

(1) Present address: Central Drug Research Institute, Lucknow (India).

(2) R. S. Kapil, *J. Chem. Soc.*, **24**, 4127 (1959).

(3) R. S. Kapil, *J. Org. Chem.*, in press.

(4) O. L. Brady and P. N. Williams, *J. Chem. Soc.*, **117**, 1137 (1920).

(5) R. S. Kapil, *J. Indian Chem. Soc.*, in press.

(6) All melting points are uncorrected.

quantity of hydrazine hydrate was added dropwise with vigorous shaking. It was kept for about an hour, when the 2-nitro-5-iodo-*p*-tolylhydrazine which precipitated was filtered, washed well with water, dried, and recrystallized from ethanol–ethyl acetate mixture as orange red needles (2.8 g.) m.p. 163°.

Anal. Calcd. for $C_7H_8O_2N_3I$: I, 43.3. Found: I, 42.8.

The *acetyl* derivative was crystallized from ethanol as lemon yellow needles, m.p. 217°.

Anal. Calcd. for $C_9H_{10}O_3N_3I$: I, 37.9. Found: I, 37.7.

The *benzoyl* derivative was crystallized from ethanol as pale yellow needles, m.p. 199°.

Anal. Calcd. for $C_{14}H_{12}O_3N_3I$: I, 31.9. Found: I, 31.6.

Color reactions in acetone solution with aqueous sodium hydroxide were performed as described earlier.[7]

The various characteristic colors produced are recorded below:

o-Iodotoluenes	Colors Produced
3,4-Dinitro-	Intense green
4,5-Dinitro-	Light red
4,6-Dinitro-	Violet

Acknowledgment. The author's thanks are due to Dr. S. S. Joshi, D.Sc., Principal, Meerut College, Meerut (India) for his kind interest in this work.

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(7) G. T. Morgan and H. D. K. Drew, *J. Chem. Soc.*, **117**, 784 (1920).

Nitration of 1,3,5-Trihalobenzenes

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The nitration of 1,3,5-tribromobenzene by mixed acid has previously been hindered by decomposition and the migration of the bromine atoms to other positions on the ring under the conditions of nitration employed.[1] We have reinvestigated the nitration of symmetrical trihalobenzenes and have developed a procedure for the nitration of 1,3,5-tribromobenzene which has greatly reduced bromine migration and decomposition of the starting material and extended it to 1,3,5-trichlorobenzene and other sterically hindered compounds. By nitrating 1,3,5-tribromo-2,4-dinitro- or 1,3,5-trichlorobenzene in a solution of potassium nitrate in fuming sulfuric acid good yields of the corresponding trinitro compounds were obtained, compared with 20–30% over-all yields by previous methods.[1] The method was found to be useful for nitrating other aromatic compounds such as 2,4,2′,4′-tetranitrobibenzyl which previously had been converted to the hexanitro compound in low yield.[2]

The nitration of tribromobenzene was carried out in two steps. Because the singular position of the bromine atoms *ortho*, *ortho*, *para* to the three open positions on the ring should enhance ring reactivity only mild conditions were used for the dinitration of 1,3,5-tribromobenzene in contrast to prolonged reaction periods at reflux temperature in earlier work.[3] This compound was easily nitrated in nearly quantitative yield at 25–60° by mixed fuming nitric acid and commercial concentrated sulfuric acid in less than an hour. However if the nitration mixture were held at this temperature after nitration was complete bromine evolution occurred.

The nitration of the sixth position required more drastic conditions because of the intense deactivation effect of the nitro groups and steric hindrance of the bromine atoms *ortho* to the open position. Because of the low yields and extensive decomposition encountered by previous workers in nitrating with mixed acids this method of nitration was not further investigated. Instead nitration of 1,3,5-tribromo-2,4-dinitrobenzene by a solution of potassium nitrate dissolved in fuming sulfuric acid gave yields up to 74% without excessive bromine migration or decomposition.[4] Some 1,2,3,5-tetrabromo-4,6-dinitrobenzene was found in the reaction products, as well as some unidentified low melting by-products which were not separable by the usual means. An investigation of reaction conditions showed that the optimum rate of nitration was obtained at a ratio of four moles of nitrate to one of dinitrotribromobenzene. The rate of nitration was also sharply affected by the reaction temperature. At temperatures below 120° long reaction periods were necessary, but at 130° and above, extensive decomposition began to occur and the formation of the side reaction product, 1,2,3,5-tetrabromo-4,6-dinitrobenzene, was favored. Optimum reaction was obtained at 125–127° for a reaction period of eight to nine hours. The optimum concentration of potassium nitrate relative to fuming sulfuric acid was not determined other than to assume complete utilization of the nitrate to give NO_2^+ ions. Millen and others[5] have given evidence that twelve weight per cent nitric acid in 35% fuming sulfuric acid produces $(NO_2^+)(HS_2O_7^-)$ as the only solute, a concentration of nitrating agent nearly equivalent to that used in this study.

Although the two step nitration procedure produced *sym*-trinitrotrichlorobenzene in good yield, it was found that 1,3,5-trichlorobenzene could be trinitrated in 73% yield in one step by the fuming sulfuric acid–potassium nitrate solution. Optimum reaction was obtained by using a molar ratio of

(1) (a) C. L. Jackson and J. F. Wing, *Am. Chem. J.*, **10**, 283 (1888). (b) C. L. Jackson and J. F. Wing, *Am. Chem. J.*, **12**, 7, 167 (1890).

(2) K. G. Shipp, Private Communication.

(3) H. J. Backer and S. J. Van der Baan, *Rec. trav. chim.*, **56**, 1175 (1937).

(4) C. Weygand, *Organic Preparation*, Interscience Publishers, Inc., New York, N. Y., 1945, p. 279.

(5) D. J. Millen, *J. Chem. Soc.*, 2589 (1950).

trichlorobenzene to potassium nitrate and sulfur trioxide of one to eight to twenty for eighteen hours at 135°.

EXPERIMENTAL

1,3,5-Tribromo-2,4-dinitrobenzene. 1,3,5-Tribromobenzene (31.5 g., 0.1 mole) was added portionwise to a solution of 155 g. of commercial white fuming nitric acid, assay 95%, in 62 g. of concd. sulfuric acid at room temperature, allowing the autogenous temperature to rise no higher than 60°. Within 10 min. after the addition was complete the reaction mixture was cooled and the solid collected, washed, and dried. 1,3,5-Tribromo-2,4-dinitrobenzene was obtained in 98% yield, m.p. 191°; recrystallized, m.p. 192°.

Anal.[6] Calcd. for $C_6H\ Br_3N_2O_4$: C, 17.80; H, 0.25; Br, 59.22. Found: C, 17.91; H, 0.22; Br, 59.08.

1,3,5-Trichloro-2,4,6-trinitrobenzene. Potassium nitrate (40.4 g., 0.4 mole) was added to 266.5 ml. (1.0 mole) of 30% oleum at 65° with external cooling to maintain this temperature. The resulting mixture of potassium salts and nitration solution was then heated to 110°, becoming clear at 95°. 1,3,5-Trichlorobenzene (9.0 g., 0.005 mole) was added with stirring. The temperature was raised to 130–135° and held for 18 hr. After cooling to room temperature the viscous mixture was slowly poured onto three times its volume of flaked ice. The solid which separated was collected, washed free of acid, dried, and recrystallized from chloroform. 1,3,5-Trichloro-2,4,6-trinitrobenzene was obtained in 73% yield, m.p. 190°.

Anal. Calcd. for $C_6Cl_3N_3O_6$: C, 22.75; Cl, 33.65; N, 13.27. Found: C, 22.72; Cl, 33.62; N, 12.81.

1,3,5-Tribromo-2,4,6-trinitrobenzene. The above procedure was also used for nitration of 0.12 mole (48.5 g.) of 1,3,5-tribromo-2,4-dinitrobenzene employing instead 0.54 mole (54.5 g.) of potassium nitrate dissolved in 320 g. of 30% fuming sulfuric acid (1.2 moles of sulfur trioxide), heated at 125 ±1° for 9 hr. There was obtained after recrystallization from chloroform a 74% yield of 1,3,5-tribromo-2,4,6-trinitrobenzene, m.p. 297°, and 6% of 1,2,3,5-tetrabromo-4,6-dinitrobenzene, m.p. 232°.

Anal. Calcd. for $C_6Br_3N_3O_6$: C, 16.02; Br, 53.30; N, 9.34. Found: C, 16.30; Br, 53.45; N 9.16. Calcd. for $C_6Br_4N_2O_4$: C, 14.90; Br, 66.09; N, 5.79. Found: C, 15.02; Br, 65.81; N, 5.87.

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(6) Analyses by Oakwold Laboratories, Alexandria, Va.

Reactions of Dinitrogen Tetroxide with Alicyclic Sulfides

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The reactions of dinitrogen tetroxide with 1,4-dithiane and 1,3,5-trithiane have been investigated in connection with a general study of addition compounds of dinitrogen tetroxide with organic sulfides. Bell and Bennett[1] made a slight reference to the oxidation of 1,4-dithiane in ether solution by nitrous fumes to give predominantly 1,4-dithiane α-disulfoxide [*trans* isomer] and a little 1,4-dithiane β-disulfoxide [*cis* isomer], but they gave few experimental details. The results reported here shed some light on the intermediates formed in the course of the reaction. More especially, we would like to call attention to an unexpected isomerization of 1,4-dithiane α-disulfoxide to 1,4-dithiane monosulfone.

Dinitrogen tetroxide is known to oxidize alkyl sulfides to the corresponding sulfoxides.[2] Methyl phenyl sulfide has also been oxidized to methyl phenyl sulfoxide by means of dinitrogen tetroxide.[3] Addison and Sheldon[2] have shown also that dinitrogen tetroxide forms molecular addition compounds with alkyl sulfoxides. They suggested that the formation of such addition compounds may inhibit further oxidation of the sulfur by dinitrogen tetroxide and explain why the sulfoxides rather than sulfones are produced.

EXPERIMENTAL

1,4-Dithiane was prepared by the method of Masson,[4] which involves the reaction between potassium sulfide and ethylene dibromide in ethanol solution. The product which we obtained by this procedure melted at 111–112°[5] (lit.[4] 111°). Commercial nitrogen dioxide was dried by passing it through a glass tube filled with phosphorus (V) oxide and sand. Solid dinitrogen tetroxide (m.p. −11.5°, lit.,[6] m.p. −11.2°) was then collected in a trap cooled with Dry Ice and stored in a refrigerator until needed. Eastman White Label 1,3,5-trithiane (m.p. 216–218°, lit.[7] m.p. 216°) was used without further purification.

About 1 g. of 1,4-dithiane was dissolved in a few ml. of chloroform. A large excess of dinitrogen tetroxide was distilled into this solution and the entire mixture held at 0° for about 12 hr. At the end of this time, the system was composed of a deep blue solution with a white precipitate on the bottom of the container. The excess oxides of nitrogen were removed with an aspirator, at room temperature, and the white solid residue were collected and stored over Drierite in a desiccator. After this treatment, the white solid was odorless and decomposed at 225–230°. This same product was obtained by mixing 1,4-dithiane and dinitrogen tetroxide in the absence of a solvent. When this white, solid product (prepared by either method) was recrystallized from 95% ethanol, it produced a mixture of 1,4-dithiane α-disulfoxide (m.p. 263–265° dec., lit.[1] m.p. 263°) and 1,4-dithiane β-disulfoxide (m.p. 242–243° dec., lit.,[1] m.p. 235–250°). The isomers were separated by the fractional crystallization method described by Bell and Bennett.[1] The mixture was composed of 93–94% of the α-disulfoxide and 6–7% of the β-disulfoxide. The yield of the combined α- and β-disulfoxides was quantitative based upon the amount of 1,4-dithiane used.

Anal. Calcd. for $C_4H_8S_2O_2$ (α- or β-form): C, 31.6%; H, 5.3%. Found: for the α-isomer, C, 31.7%; H, 5.5%; for the β-isomer, C, 31.6%; H, 5.3%.[8]

Decomposition points of mixtures of these products with

(1) E. Bell and G. Bennett, *J. Chem. Soc.*, 1798 (1927).

(2) C. Addison and C. Sheldon, *J. Chem. Soc.*, 2705 (1956).

(3) Von L. Horner and F. Hubenett, *Ann.*, **597**, 193 (1953).

(4) O. Masson, *J. Chem. Soc.*, **49**, 233 (1886).

(5) All melting and decomposition points are uncorrected.

(6) W. Giauque and J. Kemp, *J. Chem. Phys.*, **6**, 40 (1938).

(7) A. Hofmann, *Ber.*, **3**, 584 (1870).

(8) Analyses performed by Galbraith Microanalytical Laboratories, Knoxville, Tennessee.

authentic reference samples of the disulfoxides confirmed their identities. The reference samples of the disulfoxides were prepared by the oxidation of 1,4-dithiane in glacial acetic acid with hydrogen peroxide by the method of Bell and Bennett.[1]

Addition of excess dinitrogen tetroxide to some of the 1,4-dithiane α-disulfoxide, at 0° for 12 hr., followed by removal of the excess dinitrogen tetroxide, gave a white, solid, addition compound which decomposed at 225–230°. The composition of the addition product was variable, presumably because of incomplete reaction resulting from heterogeneity of the process. The pure addition compound is believed to have a 1:1 dinitrogen tetroxide to sulfoxide mole ratio. When this solid addition compound was heated to 150–190°, it was found that 1,4-dithiane monosulfone (m.p. 205–207°, lit.,[9,10] m.p. 200°, 203°) sublimed out of the solid.

Anal. Calcd. for $C_4H_8S_2O_2$: C, 31.6%; H, 5.3%. Found: C, 31.7%; H, 5.4%.[8]

The yield of the monosulfone was 39% of theory based upon the amount of 1,4-dithiane α-disulfoxide used.

When 1,4-dithiane β-disulfoxide was treated with dinitrogen tetroxide in the same manner as described for the α-disulfoxide, a white, solid, addition product was obtained. The composition of this product as obtained was variable. The substance began to decompose at 125°, and no sublimation product was observed.

Dinitrogen tetroxide reacts rapidly with 1,3,5-trithiane at 0° to cleave the trithiane ring and to yield sulfur-containing, volatile products and a yellow, solid residue which was insoluble in a variety of organic solvents.

The oxidation of 1,4-dithiane by dinitrogen tetroxide to 1,4-dithiane α-disulfoxide and a small amount of 1,4-dithiane β-disulfoxide was to be expected from earlier work.[1,2,3]

Because dinitrogen tetroxide could be added to pure 1,4-dithiane α-disulfoxide to produce the white solid which decomposed at 225–230°, and by simple recrystallization of this solid the 1,4-dithiane α-disulfoxide could be recovered, no molecular rearrangement occurs at room temperature when the disulfoxide unites with the dinitrogen tetroxide. Such behavior is characteristic of a rather stable Lewis acid-base type addition compound. The production of 1,4-dithiane monosulfone as a sublimation product of this white solid was unexpected, as no analogous reaction has previously been reported. The yield of the monosulfone is not higher than it is perhaps because heterogeneity of the reactions system prevents the completely quantitative formation of the dinitrogen tetroxide-α-sulfoxide addition compound. The failure of the addition compound between dinitrogen tetroxide and 1,4-dithiane β-disulfoxide to give the monosulfone upon sublimation is also interesting.

Because Lewis acids like aluminum chloride in benzene[11] and chlorine water[12] are known to cleave the 1,3,5-trithiane ring, it is not surprising that dinitrogen tetroxide produces a similar result.

The oxidation of 1,4-dithiane to 1,4-dithiane α-disulfoxide and 1,4-dithiane β-disulfoxide provides a method for the synthesis of these products which is superior to the hydrogen peroxide method. The dinitrogen tetroxide procedure gives a quantitative yield of the disulfoxides. A slight excess of hydrogen peroxide is likely to cause further oxidation to the trioxide of disulfone. Furthermore, the dinitrogen tetroxide procedure is faster and involves simple laboratory manipulations.

(9) E. Fromm and B. Ungar, *Ber.*, **56**, 2286 (1923).

(10) E. Bell and G. Bennett, *J. Chem. Soc.*, 86 (1928).

(11) S. Lee and G. Dougherty, *J. Org. Chem.*, **4**, 48 (1939).

(12) S. Lee and G. Dougherty, *J. Org. Chem.*, **5**, 81 (1940).

Acknowledgment. Appreciation is expressed to Miss Geraldine Westmoreland, who assisted with some of the laboratory operations.

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Reduction of Bromonitro Compounds with Zinc. An Amplification

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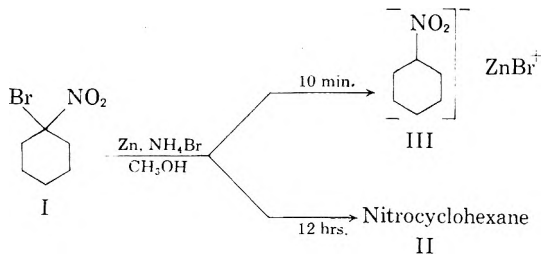
In 1955 Klager[1] reported the reduction of methyl 4-nitro-4-chloropentanoate and of 1-bromo-1-nitrocyclohexane with zinc. Under the conditions employed, a white precipitate formed which could not be adequately characterized because of its insolubility. Analyses on the precipitate obtained directly from the reaction mixture gave variable results. Subsequent treatment of this precipitate with aqueous hydrochloric acid afforded the corresponding ketones, methyl 4-ketopentanoate and cyclohexanone. Klager postulated the structure of this precipitate to be a zinc complex of the ketoxime. The object of the present work was to elucidate the course of this reduction and, if possible, to shed some light on the structure of the precipitate.

It was decided to use 1-bromo-1-nitrocyclohexane as a model compound and to make one change in the reaction–substitution of ammonium bromide for ammonium chloride. In this way any possible ambiguity in the halogen analyses is eliminated. In Klager's work the variability of analysis of the precipitate indicated the possibility that this solid was a transient species and, while the appearance of the reaction mixture was unchanged after the initial solid formation, that actually a change in composition of the solid was occurring.

The reduction of 1-bromo-1-nitrocyclohexane (I) was then repeated. In this case however, the mixture of zinc, ammonium bromide, and 1-bromo-1-nitrocyclohexane in methanol was allowed to reflux for twelve hours instead of ten minutes. Two products were isolated, an insoluble white solid which proved to be inorganic, and nitrocyclohexane (II). On the basis of this information and that obtained by Klager, one may postulate a structure for the organic precipitate (III) isolated by Klager. This zinc salt of the nitroparaffin would be expected to undergo a Nef-type reaction[2] when treated with aqueous acid to yield cyclohexanone. And upon further refluxing in methanol the zinc salt might be expected to abstract a proton from methanol to form nitrocyclohexane.

(1) K. Klager, *J. Org. Chem.*, **20**, 1348 (1955).

(2) H. B. Hass and E. F. Riley, *Chem. Revs.*, **32**, 373 (1943).



Reduction of 1-bromo-1-nitrocyclohexane (I) was then studied using an excess of zinc and ammonium bromide. In this case the only product isolated was cyclohexylamine hydrobromide (IV). When nitrocyclohexane is reduced under the same conditions cyclohexylamine hydrobromide is also formed. When, however, the reaction is stopped after only one hour, *N*-cyclohexylhydroxylamine (V) is formed as is reported in the literature.[2,3] The structure of the hydrobromide was confirmed by treatment with aqueous alkali and preparation of *N*-cyclohexylbenzamide (VI) from the resulting free amine.

EXPERIMENTAL

1-Bromo-1-nitrocyclohexane was prepared in 60% yield according to the procedure of Iffland and Criner.[4] Melting points and boiling points are uncorrected. Analyses by Mr. E. M. Hubbard and associates and by Galbraith Laboratories, Knoxville, Tenn.

Zinc reduction of 1-bromo-1-nitrocyclohexane (I), (a) To nitrocyclohexane (II). 1-Bromo-1-nitrocyclohexane (20.8 g., 0.10 mole) was mixed with 250 ml. of methanol and 17.6 g. (0.18 mole) of ammonium bromide, 11.6 g. of 90% zinc dust (0.16 mole) added and heating of the mixture begun. As in Klager's experiment, a white precipitate formed almost immediately with concomitant disappearance of the zinc dust. However, the reaction was not stopped at this point but allowed to reflux for 12 hr. further. At the end of the reaction a white solid was still present. After cooling, this solid was removed by filtration, washed with methanol, dried (Abderhalden), and analyzed.

Anal. Found: C, 0.70, 1.08; H, 2.46, 2.76; N, 9.35, 9.65; Br, 56.36, 56.53; Zn, 27.57, 27.87.

The filtrate was evaporated to small volume and the residue partitioned between ether and water. The ether solution was washed once with water, dried over sodium sulfate and evaporated to small volume. The residue was distilled yielding 5.7 g. (44.1%) of nitrocyclohexane, b.p. 16 mm. 88–90°, $n_D^{25°}$ 1.4612.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.79; H, 8.58. Found: C, 56.09; H, 8.69.

(*b*) *To cyclohexylamine hydrobromide* (IV). To a mixture of 14.5 g. (0.07 mole) of 1-bromo-1-nitrocyclohexane and 34 g. (0.35 mole) of ammonium bromide in 400 ml. of methanol was added 23.3 g. (0.32 mole) of 90% zinc dust in small portions. After the initial reaction had subsided, the mixture was heated at reflux for 16 hr. The mixture was filtered and the solvent evaporated. The residue was dissolved in cold methanol and filtered. Crystallization from ether-methanol afforded 3.0 g. (24%) of cyclohexylamine hydrobromide. Evaporation of the mother liquor afforded another 5.0 g. of crude material. A benzamide prepared in the usual way from the free amine[5] had a melting point of 148.5–149.3°, mixed melting point with an authentic sample of *N*-cyclohexylbenzamide, 148.5–149.2°.

Reduction of nitrocyclohexane. (*a*) *To N-cyclohexylhydroxylamine* (V). To a solution of 12.9 g. (0.10 mole) of nitrocyclohexane in 250 ml. of methanol was added 39.2 g. (0.40 mole) of ammonium bromide and 21.8 g. (0.30 mole) of 90% zinc dust. After the initial exothermic reaction had subsided the mixture was heated at reflux for 1 hr. The mixture was then filtered and the filtrate evaporated to dryness. The residue was dissolved in ether-methanol, the solution was filtered and crystallization effected from methanol-hexane. The crystals were filtered, washed with hexane and air dried yielding 7.0 g. (60.8%) of *N*-cyclohexylhydroxylamine, m.p. 136.5–138° with sublimation (lit.,[6] m.p. 137°).

(*b*) *To cyclohexylamine hydrobromide* (IV). To a solution of 6.45 g. (0.05 mole) of nitrocyclohexane in 150 ml. of methanol was added 29.4 g. (0.30 mole) of ammonium bromide and 13.1 g. (0.18 mole) of 90% zinc dust. After the initial exothermic reaction had subsided, the mixture was heated at reflux for 16 hr. The mixture was then filtered and the filtrate evaporated to dryness. The residue was redissolved in cold methanol, the solution filtered, and ether added to the filtrate. The resulting crystals were filtered, washed with ether and air dried yielding 4.12 g. (46%) of cyclohexylamine hydrobromide. The benzamide prepared from a portion of this sample had a melting point of 148–149° and when mixed with authentic *N*-cyclohexylbenzamide, a melting point of 148.2–149.2°.

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(3) J. Scheiber, *Ann.*, **365**, 215 (1909).

(4) D. C. Iffland and G. X. Criner, *J. Am. Chem. Soc.*, **75**, 4047 (1953).

(5) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, 3rd Ed., New York (1948), p. 177.

(6) G. F. Bloomfield and G. A. Jeffrey, *J. Chem. Soc.*, 120 (1944).

Syntheses of 1-Benzylnaphthalenes

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Received September 14, 1959

The syntheses of substituted 1-benzylnaphthalenes may be effected by the action of benzylmagnesium chloride solution on the corresponding tetralones. The tertiary alcohols, which, are the initial reaction products, are easily dehydrated by distillation in vacuum during purification to olefins (IIa–g), 3,4-dihydro-1-benzylnaphthalenes and/or the double bond isomers, 1-benzal-1,2,3,4-tetrahydronaphthalenes (*cf.* Howell and Robertson[1]). These may be dehydrogenated with sulfur to the corresponding 1-benzylnaphthalenes (IIIa–g) as shown in the following scheme:

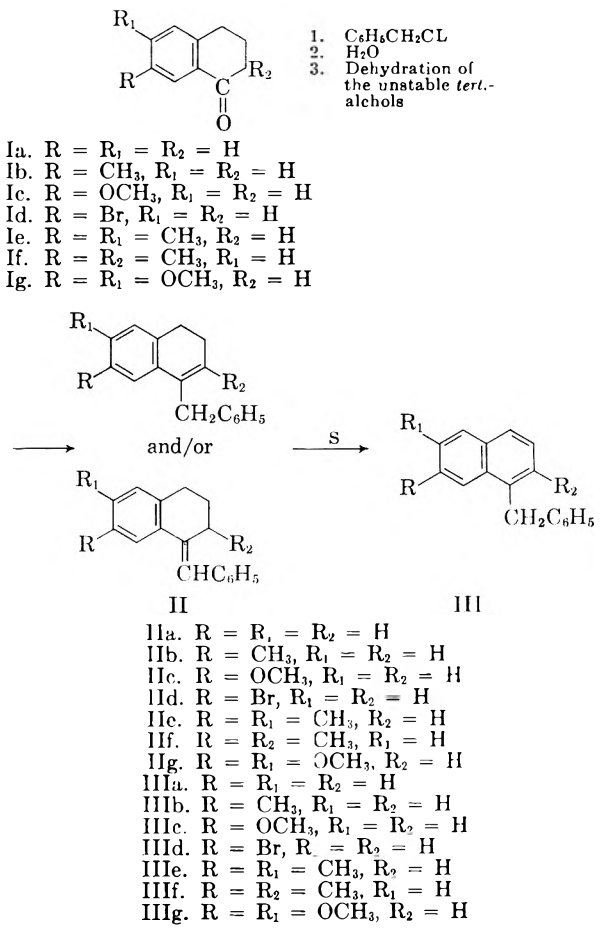
(1) W. N. Howell and A. Robertson, *J. Chem. Soc.*, 587 (1936).

TABLE I

SUBSTITUTED 1-BENZYL-3,4-DIHYDRO- AND 1-BENZYL-NAPHTHALENES

Starting Material	Product	B.P.	M.P.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ia[a]	IIa	181/183/8 mm.		70	$C_{17}H_{16}$	92.72	91.96	7.27	7.09
	IIIa	200–202/8 mm.	58	50	—	—	—	—	—
Ib[b]	IIb	190–192/8 mm.		51	$C_{18}H_{18}$	92.30	91.85	7.69	7.75
	IIIb	208–210/10 mm.	58–59	47	$C_{18}H_{16}$	93.10	92.50	6.89	6.80
Ic[c]	IIc	180–183/10 mm.		45	$C_{18}H_{18}O$	86.4	86.47	7.20	7.08
	IIIc	200–210/10 mm.	56–57	82	$C_{18}H_{16}O$	87.09	86.68	6.45	6.16
Id[d]	IId	218–220/10 mm.		65	$C_{17}H_{15}Br$[e]	68.22	68.80	5.01	4.87
	IIId	226–227/10 mm.	109–110	30	$C_{17}H_{13}Br$[f]	68.68	69.01	4.37	4.75
Ie[b]	IIe	200–202/10 mm.		48	$C_{19}H_{20}$	91.93	91.25	8.06	7.86
	IIIe	210–212/10 mm.	78–79	70	$C_{19}H_{18}$	92.68	91.85	7.31	7.24
If[g]	IIf	200–203/10 mm.		55	$C_{19}H_{20}$	91.93	91.15	8.06	7.85
	IIIf	208–210/10 mm.	96–97	75	$C_{19}H_{18}$	92.68	91.95	7.31	7.09
Ig[h]	IIg	206–207/10 mm.		65	$C_{19}H_{20}O_2$	81.43	80.95	7.14	7.11
	IIIg	245–247/10 mm.	94–95	80	$C_{19}H_{18}O_2$	82.01	81.79	6.47	6.25

[a] Ia, E. L. Martin and L. F. Fieser, *Org. Syntheses*, Coll. Vol. II, 569 (1950). [b] Ib, Ie, E. De Barry Barnett and F. G. Sanders, *J. Chem. Soc.*, 436 (1933). [c] Ic, P. C. Mitter and L. K. De, *J. Indian Chem. Soc.*, *16*, 35 (1939). [d] Id, L. F. Fieser and A. M. Seligman, *J. Am. Chem. Soc.*, *60*, 170 (1938). [e] Calcd.: Br, 26.75; Found: 26.2. [f] Calcd.: Br, 26.96; Found: 27.32. [g] If, (*cf.* ref. 3). [h] Ig, R. D. Haworth and C. R. Mavin, *J. Chem. Soc.*, 1485 (1932).



Ia. R = R_1 = R_2 = H
Ib. R = CH_3, R_1 = R_2 = H
Ic. R = OCH_3, R_1 = R_2 = H
Id. R = Br, R_1 = R_2 = H
Ie. R = R_1 = CH_3, R_2 = H
If. R = R_2 = CH_3, R_1 = H
Ig. R = R_1 = OCH_3, R_2 = H

II III

IIa. R = R_1 = R_2 = H
IIb. R = CH_3, R_1 = R_2 = H
IIc. R = OCH_3, R_1 = R_2 = H
IId. R = Br, R_1 = R_2 = H
IIe. R = R_1 = CH_3, R_2 = H
IIf. R = R_2 = CH_3, R_1 = H
IIg. R = R_1 = OCH_3, R_2 = H
IIIa. R = R_1 = R_2 = H
IIIb. R = CH_3, R_1 = R_2 = H
IIIc. R = OCH_3, R_1 = R_2 = H
IIId. R = Br, R_1 = R_2 = H
IIIe. R = R_1 = CH_3, R_2 = H
IIIf. R = R_2 = CH_3, R_1 = H
IIIg. R = R_1 = OCH_3, R_2 = H

An authentic specimen of IIIa was prepared by the Friedel-Crafts reaction, when naphthalene was allowed to react with benzyl chloride in the presence of anhydrous aluminum chloride as recommended by Nenitzescu *et al.*[2]

(2) C. D. Nenitzescu, D. A. Isăcescu, and C. N. Ionescu, *Ann.*, **491**, 217 (1931).

The products of the Grignard reaction (IIa–g) and substituted 1-benzylnaphthalenes (IIIa–g) are listed in Table I.

EXPERIMENTAL

General procedure. A solution of the tetralone (Ia–g, 0.1 mole) in dry thiophene-free benzene (25 ml.) was added to the Grignard solution of benzylmagnesium chloride (from benzyl chloride, 0.3 mole, magnesium metal, 0.4 g. 1.2 g.-atoms and dry ether 30 ml.). The mixture was refluxed on a steam bath for 3–5 hr. (Ia–e, Ig); (in the case of If, reflux period was 20 hr.) (*cf.* Baddar *et al.*[3]).

It was decomposed with cold dilute sulfuric acid, extracted with ether, dried over anhydrous sodium sulfate, the ether removed, and the product fractionally distilled in vacuum. The olefins (IIa–g) were oily materials which did not solidify and hence were purified by vacuum distillation (twice) in a ground-joint apparatus prior to analysis.[3]

Dehydrogenation. The olefin (IIa–g, 1 g.) was heated with sulfur (0.3 g.; 1.2 g.-atom) in a nitrobenzene bath (205–210°) for 5 hr. (except IId, 1 hr.) until hydrogen sulfide ceased to be evolved. The product was extracted with ether, filtered, dried, and the solvent evaporated. The residual oil was purified by distillation in vacuum and the solid obtained on cooling (IIIa–g) was crystallized from methanol.

Authentic 1-benzylnaphthalene (IIIa).[4] This was prepared according to Nenitzescu *et al.*[2] A mixture of naphthalene (20 g.) and benzyl chloride (6 g.) was treated portionwise with aluminum chloride (22 g.) until hydrogen chloride ceased to be evolved. The product was decomposed with 6*N* hydrochloric acid and steam distilled. The residue was taken up in ether, dried, distilled in vacuum at 200–202°/8 mm., and crystallized from ethanol, m.p. 58°, undepressed when mixed with IIIa.

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(3) F. G. Baddar, H. A. Fahim, and A. M. Fleifel, *J. Chem. Soc.*, 3302 (1955).

(4) I. I. Lapkin and A. V. Lyubimova, *J. Gen. Chem.*, **19**, 707 (1949), gave m.p. 58° for 1-benzylnaphthalene which they prepared by Clemmensen reduction of 1-naphthylphenyl ketone.

Preparation of Vinylene Carbonate

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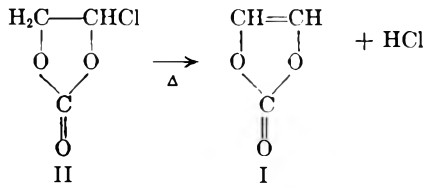
Vinylene carbonate (I), a novel monomer and dienophile, has been previously prepared by the dehydrochlorination of monochloroethylene carbonate (II) with triethylamine or from *sym*-dichloroethylene carbonate by the action of zinc dust.[2,3] We wish to report that chloroethylene carbonate can be thermally dehydrohalogenated to yield vinylene carbonate.



This method has the advantage of being less time consuming and eliminates the use of ether and the amine.

The pyrolysis can be carried out at atmospheric or subatmospheric pressure, with or without a diluent of vaporized hydrocarbon or inert carrier gas. Materials which have been successfully used as column packings are granular anhydrous calcium sulfate (Drierite), granular anhydrous calcium chloride, and glass Raschig rings. Granular activated charcoal and granular activated alumina yielded only gaseous products under a variety of experimental conditions. The most suitable column packing found in our brief study was 8-mesh calcium sulfate (Drierite). The activity of this bed decreases rapidly with use as shown by yields of 44.5%, 21%, and 5% of vinylene carbonate on successive one mole runs under identical conditions. The activity of the bed may be restored to its original level by heating the system to about 500° and slowly passing air over the bed. Maximum conversions (35–40%) and maximum yields (40–45%) for one mole runs with a Drierite bed are obtained at 250° at reduced pressure (50–60 mm of Hg). Higher or lower temperatures lower both conversion and yield. A low yield and conversion to vinylene carbonate results when chloroethylene carbonate is pyrolyzed over glass Raschig rings at 400–425°. Attempts to obtain I by pyrolysis of *sym*-dichloroethylene carbonate have failed.

EXPERIMENTAL

Apparatus and Procedure. The pyrolysis was carried out by passing the compound or a mixture of the compound and a diluent through a 25 mm. o.d. Pyrex tube packed for a distance of 90 cm. and heated to the desired temperature by means of an electrically controlled furnace. The reactants were added dropwise to the reaction zone from a dropping funnel, and the pyrolyzate was collected in a receiver cooled in a Dry Ice bath. A water pump served as a source of reduced pressure.

Pyrolysis. A. Monochloroethylene carbonate over Drierite. The chloro carbonate (122.5 g.; 1 mole) in 100 ml. of dry toluene was added dropwise during a period of 90 min. to the reaction zone packed with 8-mesh Drierite and heated at 250–260°. The system was maintained at 50–60 mm. during the run. The pyrolyzate was neutralized by the addition of solid potassium acetate, was filtered, and distilled. There was obtained 5 g. of material, b.p. 29–30° (25 mm.) followed by 28 g. of vinylene carbonate, b.p. 63–65° (18 mm.), n_D^{25} 1.4190, and 13 g. of recovered monochloroethylene carbonate, b.p. 114–119° (18 mm.). The conversion to vinylene carbonate was 32%, and the yield was 36%.

The low boiling material [b.p. 29–30° (25 mm.)] was a mixture of compounds containing large quantities of chloroacetaldehyde. It reacted with ethanol saturated with hydrogen chloride to furnish chloroacetal, which was identified by comparison of its infrared spectra with that of an authentic sample.

The bed was regenerated for the following run by heating the system to 500° and slowly passing air over the bed for a period of about two hours.

B. Monochloroethylene carbonate over glass Raschig rings. The column described above was packed with Pyrex glass Raschig rings (6 × 6 mm.). The system was heated at 400–425° at 60–80 mm. while adding monochloroethylene carbonate (122.5 g.; 1 mole) in 100 ml. of dry toluene for thirty minutes. The pyrolyzate was distilled and furnished 5 g. of impure vinylene carbonate [b.p. 60–62° (18 mm.), n_D^{25} 1.4220] and 62 g. of recovered monochloroethylene carbonate.

The material collected at 60–62° (18 mm.) was shown to be composed largely of vinylene carbonate as it reacted with hexachlorocyclopentadiene to give a high yield of the adduct, m.p. 233–234° (dec.) [reported[3] m.p. 241–242.8° (corr.)].

Anal. Calcd. for $C_8H_2O_3Cl_6$: C, 26.77; H, 0.56; Cl, 59.28. Found: C, 26.97; H, 0.74; Cl, 59.37.

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(2) M. S. Newman and R. W. Addor, *J. Am. Chem. Soc.*, **75**, 1263 (1953).

(3) M. S. Newman and R. W. Addor, *J. Am. Chem. Soc.*, **77**, 3789 (1955).

A Simplified Procedure for Preparing 9,12-Dioxo-*trans*-10-octadecenoic Acid

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In a recent paper,[1] the preparation of 9,12-dioxo-*trans*-10-octadecenoic acid by the chromic acid oxidation of 12-oxo-*cis*-9-octadecenoic acid was re-

(1) J. Nichols and E. Schipper, *J. Am. Chem. Soc.*, **80**, 5705 (1958).

ported. An earlier publication[2] reported the preparation of 12-oxo-*cis*-9-octadecenoic acid by the rapid chromic acid oxidation of ricinoleic acid. The high melting by product reported by Ellis[3] from the chromic acid oxidation of ricinoleic acid was characterized as 9,12-dioxo-*trans*-10-octadecenoic acid.[1]

A method was developed for preparing 9,12-dioxo-*trans*-10-octadecenoic acid from ricinoleic acid in fair yield in a single step. The method consists of running the chromic acid oxidation under a controlled set of conditions so that both keto groups are introduced without decomposition. This development may be of economic importance for industrial preparations. Advantages of the single-step procedure are that considerably less handling of reactants and smaller quantities of raw materials are involved. Furthermore, problems of isolation and storage of the oxygen sensitive intermediate, 12-oxo-*cis*-9-octadecenoic acid, are completely eliminated.

EXPERIMENTAL

Hydrolysis of castor oil. Crude ricinoleic acid was prepared by refluxing 180 ml. of castor oil with a solution containing 350 ml. of ethanol, 53 ml. of water, and 71 g. of potassium hydroxide for a period of 5 min. After cooling, the reaction mixture was acidified with 4*N* hydrochloric acid. The oil layer was removed, washed three times with water, and dried over sodium sulfate. Yield was 146 g. of a pale yellow oil containing approximately 80% of ricinoleic acid.

9,12-Dioxo-trans-10-octadecenoic acid. To a vigorously stirred solution of 146 g. of crude ricinoleic acid in 1.6 l. of glacial acetic acid was added all at once an oxidizing solution composed of 107 g. of sodium dichromate dihydrate, 132 ml. of water, 57.5 ml. of concd. sulfuric acid, and 950 ml. of glacial acetic acid. The temperature of the mixture rose spontaneously to 54°. After about 2 min., the temperature began to drop. When the temperature had fallen to 45°, a fresh oxidizing solution composed of 120 g. of sodium dichromate dihydrate, 600 ml. of water, 60 ml. of concd. sulfuric acid, and 300 ml. of glacial acetic acid was poured in all at once. Vigorous agitation was continued, and the temperature of the reaction mixture was maintained at 40–45° by external heating for a period of 55 min. At the end of this time, the reaction was terminated by pouring in 4 l. of ice and water. This brought down the crude acid as a crystalline precipitate. The precipitated crude acid was collected by vacuum filtration and washed with water until free of chromous salts. The crude product was air dried and recrystallized from 300 ml. of ethanol (3A formulation). Yield was 32 g. (28.6%) of a white, crystalline product having an uncorrected melting point of 111–112°. (Lit.,[1] m.p. 112–113°). Upon comparison of this material with a sample of 9,12-dioxo-*trans*-10-octadecenoic acid prepared by the procedure of Nichols and Schipper,[1] it was found that the two products had identical melting points and infrared absorption. Mixed melting point of the two products was 111–112° (uncorrected).

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(2) J. Nichols, U. S. Patent **2,623,888** (1952).
(3) G. W. Ellis, *J. Chem. Soc.*, 9 (1950).

Cyanamide Derivatives. LVI.[1] On the Isomers of Trimethylmelamine[2]

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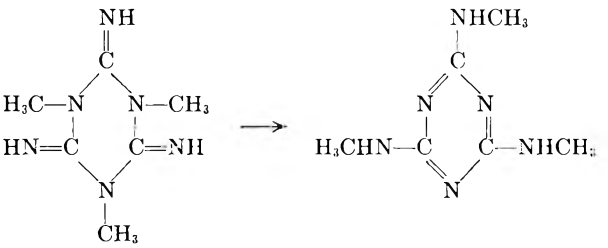
Received August 11, 1959

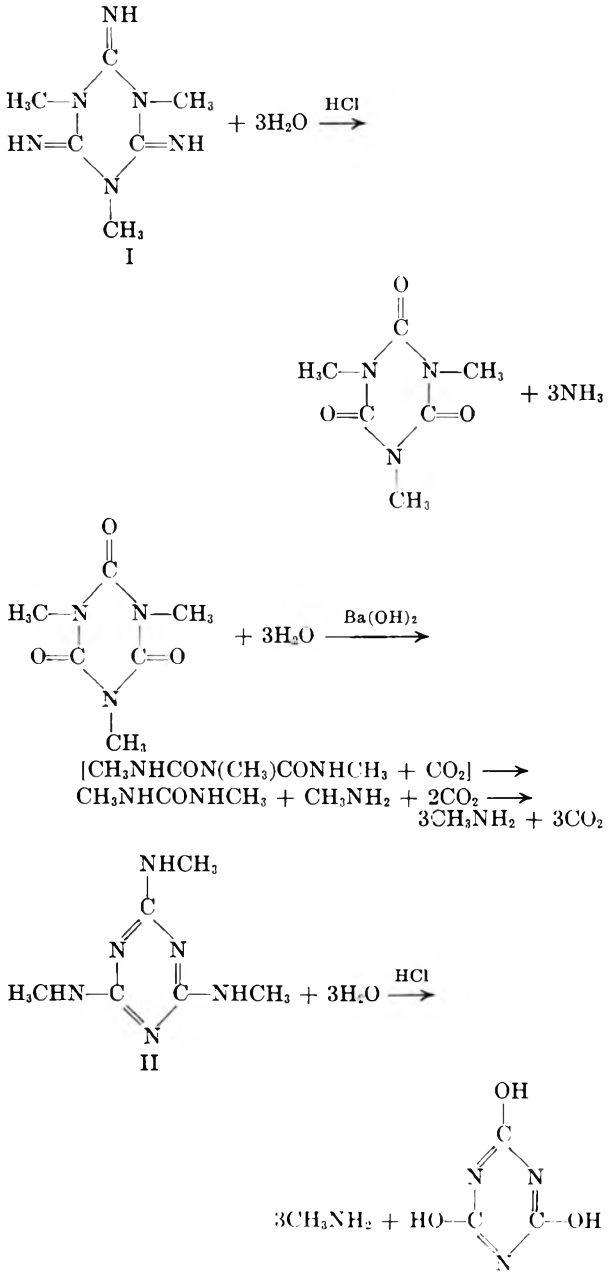
We have indicated in a previous paper[3] that monomethylcyanamide was first obtained in a pure state as a liquid solidified at −40 −50°. In order to learn more about this compound, we have further investigated and reported[4] the reactions of monomethylcyanamide. The present report concerns the results of new observations on the transformation of trimethylisomelamine into its isomer by simple heating.



I II

It is a well known fact that the polymerization of monomethylcyanamide occurs very readily and produces trimethylisomelamine (I). In the course of our studies on this compound, it was found that trimethylisomelamine could be transformed into normal trimethylmelamine[5] (II) by heating it above its melting point for two to three hours. The properties of nor-trimethylmelamine are quite different from those of its isomer. Although it solidified as a resinous substance, it could be purified by distillation. It is easily soluble in water and alcohol but not its isomer. The difference in structure of the two isomers has been verified by the identification of their hydrolytic products and the absorption characteristics in ultraviolet and infrared spectrum. The hydrolysis of these compounds took place as follows:

(1) Part LIV, *J. Org. Chem.*, **23**, 100 (1958), LV: *J. Electrochem. Soc.*, **105**, 598 (1958).
(2) This paper was prepared for delivery before the annual meeting of the Chemical Society of Japan held in April 1956.
(3) R. Kitawaki, M. Yamashita, and K. Sugino, *J. Chem. Soc. Japan (Pure Chem. Sect.)*, **78**, 567 (1957), (Part L of this series).
(4) R. Kitawaki, *J. Chem. Soc. Japan (Pure Chem. Sect.)*, **78**, 1435, 1439 (1957), (Part LI and LII of this series).
(5) A. W. Hofmann, *Ber.*, **18**, 2755 (1885).



EXPERIMENTAL

Monomethylcyanamide. Because of the careful attention required for the preparation of pure monomethylcyanamide without formation of *sym*-dimethylguanidine and trimethylisomelamine, we shall repeat the description of the procedure we took.

A solution of perfectly dried cyanogen bromide, 26.5 g., in 200 cc. absolute ether cooled at −3−−7° was first placed in a four-necked flask fitted with stirrer, thermometer, gas inlet and outlet, and dry methylamine gas was bubbled in slowly with stirring. This resulted in the separation of methylamine hydrobromide. The bubbling was continued for 2 hr., keeping the reaction temperature at −3−−7° by cooling. At the end of the reaction the evolution of heat ceased; then the flow of methylamine gas was slowed and finally cut off entirely when the *p*H of the mixture reached about 7. The amount of methylamine used was about 100% of the theoretical. The resulting mixture was filtered with a glass filter and the ether removed below 5° without light to leave a liquid. This liquid was purified by dissolving it again in 30 cc. absolute ether, followed by filtration and evaporation of the solvent. The yield was 11.5 g.

Anal.[6] Calcd. for $C_2H_4N_2$: N, 49.97. Found: N, 49.27.

Monomethylcyanamide is a colorless liquid which melts at −40−−50° and may be preserved as crystals in a vessel containing Dry Ice.

Trimethylisomelamine. A solution containing 10 g. of methylcyanamide in 200 cc. of water was made alkaline by adding ammonia, heated on a water bath for 1 hr., and cooled to room temperature. The crystals were filtered and recrystallized from hot water, m.p. 178°.

Anal. Calcd. for $C_6H_{12}N_6$: N, 49.97. Found: N, 49.83.

Rearrangement of trimethylisomelamine to nor-trimethylmelamine. Five grams of completely dried trimethylisomelamine was placed in a test tube and heated gradually in an oil bath. It melted at 178° and formed a clear liquid. After keeping this liquid at 180° for 2 hr., it was allowed to cool, forming a resinous solid. A small heat evolution was seen in the heating curve 40 min. after the heating was started. An evolution of a small amount of ammonia was then witnessed and a weight loss of 0.102 g. (2.04%) was recorded. Four grams of the crude product was then purified by distillation. A fraction, b.p. 310–320°, was collected to give 2.5 g. of a product which was also a resinous solid at room temperature.

Anal. Calcd. for $C_6H_{12}N_6$: N, 49.97. Found: N, 49.87.

An oxalate was formed which was recrystallized from 70–80% alcohol, m.p. 223–224°.

Anal. Calcd. for $C_8H_{14}N_6O_4$: N, 32.55. Found: N, 33.13.

Hydrolysis of trimethylisomelamine. This was carried out in accordance with the direction provided by Hofmann.[7] A 7-cc. sample of concd. hydrochloric acid was gradually added to a mixture of 1.68 g. of trimethylisomelamine in 7 cc. of water, resulting in the formation of a clear solution. It was then heated at 140° for 5 hr. in a sealed tube and allowed to cool in order to separate trimethylisocyanuric acid crystals. The crystals (1.15 g., 67%) were collected and recrystallized from hot water, m.p. 175–176°.

Anal. Calcd. for $C_6H_9N_3O_3$: N, 24.55. Found: N, 24.20.

The filtrate was then diluted to 500 cc. and to it was added sodium hydroxide to form a 1*N* alkali solution; ammonia was distilled into 0.1*N* hydrochloric acid with steam. The hydrochloric acid solution was evaporated to dryness leaving 1.83 g. crude ammonium chloride. It was then purified by extraction with butanol to remove methylamine hydrochloride; yield, 1.38 g. (84%), m.p. above 300°. It gave a very clear reaction to Nessler's test.

Anal. Calcd. for NH_4Cl: N, 26.18. Found: N, 26.05.

Hydrolysis of trimethylisocyanuric acid. For the purpose of further identification, the hydrolysis of trimethylisocyanuric acid was carried out as follows:

A 1.71-g. sample of trimethylisocyanuric acid was dissolved in 100 cc. of water free from carbon dioxide and a clear solution of 9.4 g. barium hydroxide in 400 cc. of water was added to it. A precipitate of barium carbonate was immediately formed. The reaction mixture was subjected to distillation with steam and the distillate (350 cc.) was caught in 0.1*N* hydrochloric acid. This was evaporated to dryness leaving 0.70 g. methylamine hydrochloride, m.p. 225–226° after recrystallization from absolute butanol. The Nessler's test for ammonia proved completely negative. Identity was further confirmed by converting it to methylguanidine hydrochloride by treating it with cyanamide. The picrate derived from the hydrochloride melted at 199°.

The residue from steam distillation was filtered in order to separate barium carbonate. The yield was 4.45 g. The mother liquor, after removal of excess barium hydroxide.

(6) 0.7% Bromide was involved as a contaminant.

(7) A. W. Hofmann, *Ber.*, **18**, 2781 (1885).

was concentrated at diminished pressure to obtain 0.40 g. of solid matter. This was treated with 5 cc. water and after removal of unchanged trimethylisocyanuric acid by filtration, the solution was again concentrated to dryness at diminished pressure leaving *sym*-dimethylurea, m.p. 80°. It formed a characteristic nitroso compound melted at 97–98°. It showed no depression of the melting point on admixture with the authentic sample.

Hydrolysis of trimethylmelamine. A 10-cc. sample of concd. hydrochloric acid was added to a solution of 2.20 g. of distilled trimethylmelamine in 10 cc. water, and the mixture was heated at 150–160° for 5 hr. in a sealed tube. The resulting solution was allowed to cool to room temperature resulting in the separation of cyanuric acid needle crystals. The crystals were filtered, dried, and weighed 1.32 g., 79%, m.p. above 350°.

Anal. Calcd. for $C_3H_3N_3O_3$: N, 32.55. Found: N, 32.23.

Identity was further confirmed by converting them to cyanuric chloride. It melted at 145° and gave no melting point depression with the authentic sample.

The filtrate was then diluted to 300 cc; made alkaline and subjected to steam distillation. The distillate was caught into 0.1*N* hydrochloric acid. The hydrochloric acid solution was evaporated to dryness leaving 2.46 g. methylamine hydrochloride, m.p. 225–226° after recrystallization from butanol. The Nessler's test for ammonia was completely negative. Identity was further confirmed by converting it to methylguanidine hydrochloride by treating it with cyanamide. The picrate derived from the hydrochloride melted at 199°.

Ultraviolet and infrared spectrums. The ultraviolet absorption spectrum of trimethylisomelamine indicated no maxima from 250 mμ to 280 mμ. On the other hand, that of trimethylmelamine showed a weak maxima at about 235 mμ which might have been due to the conjugated double bond.

The infrared absorption spectrum of trimethylmelamine[8] indicated a very distinct absorption at 12.25 μ, pointing to the presence of triazine ring.[9] Trimethylisomelamine[10] had no absorption at the same region.

The infrared absorption spectrum of cyanuric acids[11] derived from melamine and trimethylamine was also measured. They showed the same spectrum indicating the same identity and had an absorption at 12.80 μ.

Acknowledgment. This investigation was promoted by a grant for fundamental scientific research from the Ministry of Education of Japan and also a grant from Nippon (Japan) Carbide Industries Inc., for which the authors wish to express their deep appreciation. Our gratitude goes to Dr. Motoji Yamashita[12] of our laboratory for his valuable help. We also wish to thank Mr. Hiroshi Kobayashi of the laboratory of Inorganic Chemistry of the Institute and Mr. Yoshiki Matsui of Research Laboratory of Shionogi Pharmaceutical Co. for the ultraviolet and infrared work, respectively.

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(8) Film from ether.

(9) Same result was obtained by W. M. Padgett and W. F. Hamner, *J. Am. Chem. Soc.*, **80**, 803 (1958), for trimethylmelamine.

(10) In Nujol.

(11) Pressed into a potassium bromide disk.

(12) Present address, Nippon (Japan) Carbide Industries Inc., Uozu City, Toyama-Pref. Japan.

Cyanamide Derivatives. LVII.[1] New Route for Preparation of Biguanide[2]

KOZO SHIRAI AND KIICHIRO SUGINO

Received August 11, 1959

O-alkylisuorea is a substance quantitatively obtainable from crystalline cyanamide on a commercial basis.

We have discovered that biguanide can be obtained in a pure state and good yield by treating *O*-alkylisourea with guanidine in ethanol.

The reactions are indicated schematically as follows:

$$NH_2C(NH)OR + NH_2C(NH)NH_2 \longrightarrow NH_2C(NH)NHC(NH)NH_2 + ROH$$

$$NH_2C(NH)NHC(NH)NH_2 + NH_2C(NH)NH_2\cdot HCl \longrightarrow NH_2C(NH)NHC(NH)NH_2\cdot HCl + NH_2C(NH)NH_2$$

Melamine was a main by-product resulting from the reaction of *O*-alkylisourea with biguanide as well as other reactions of the former.[3] A small amount of dicyandiamide was also formed.

Although we have been able to obtain the biguanide salt by treating dicyandiamide with the ammonium salt in the fused state,[4] we do not consider it a convenient method to prepare biguanide because of the low yield and complexity of purification. Therefore, this method offers a practical route for the preparation of biguanide.

EXPERIMENTAL

A 500-cc. sample of an ethanolic solution[5] of 88.1 g. of *O*-ethylisourea, 59.1 g. of guanidine, and 191 g. of guanidine hydrochloride was placed in a four necked flask fitted with a condenser, stirrer, thermometer, and a sodium hydroxide tube. The solution was heated at 60°–65° with stirring and a precipitate formed after 2 hr. Heating was continued for 3 hr. and then allowed to cool overnight. The separated crystals were filtered and washed with ethanol, dried, and weighed 64.2 g. They were dissolved in 200 cc. of cold water and the insoluble residues were filtered. Evaporation of the filtrate at diminished pressure gave 57.0 g. of pure biguanide monohydrochloride, m.p. 224°–225°. The melting points of free base, mononitrate, and monopicrate derived from the monohydrochloride were 130°,[6] 202°,[7] and 232°,[7] respectively. The yield was 54% based on

(1) Part LVI, *J. Org. Chem.*, **25**, 1043 (1960).

(2) This paper was prepared for delivery before the annual meeting of the Chemical Society of Japan held on April 1957.

(3) K. Sugino and K. Shirai, unpublished results. U. S. patent application, Serial No. 782675, Dec. 24, 1958.

(4) For example, K. Sugino, *J. Chem. Soc. Japan*, **60**, 351 (1939), (Part VII of this series).

(5) This solution was prepared in the following manner: Free guanidine ethanolic solution was first prepared from a solution of guanidine hydrochloride in ethanol by removing the acid with metallic sodium. It was concentrated at diminished pressure to a concentration of 3–5*N*. A quantity of *O*-ethylisourea and guanidine hydrochloride crystals was added to a certain volume of the solution and diluted to a certain concentration by ethanol.

reacted *O*-ethylisourea.[8] The insoluble residue consisted of melamine whose melting point was 349°. The yield was 6.2 g., 19% based on reacted *O*-ethylisourea. Both yields based on guanidine were almost quantitative.

Anal. (Biguanide monohydrochloride). Calcd. for $C_2H_8N_5Cl$: N, 50.91, Cl, 25.77. Found: N, 51.13, Cl, 25.53.

To the mother liquor were added 67.0 g. of *O*-ethylisourea and 39.6 g. of guanidine hydrochloride and the resulting solution was heated for 3 hr. at 60°–65° and worked up as described above. As a result, 71.1 g. of pure biguanide monohydrochloride and 6.7 g. melamine were obtained. The yields were 58% and 12%, respectively, based on reacted *O*-ethylisourea.

Another run was carried out using 400 cc. of a methanolic solution of 74.1 g. of *O*-methylisourea, 59.1 g. of guanidine, and 191 g. of guanidine hydrochloride. The solution was heated at 60°–65° for 3 hr. and worked up as described above. As a result, 54.5 g. of pure biguanide monohydrochloride, melting at 224°–225°, and 6.0 g. of melamine, melting at 349°, were obtained. The yields were 54% and 19%, respectively, based on *O*-methylisourea consumed. To the mother liquor were added 55.0 g. of *O*-methylisourea and 38.0 g. of guanidine hydrochloride; the reaction was again carried out in the same manner as described above. As a result, 69.0 g. of pure biguanide monohydrochloride and 6.5 g. of melamine were obtained. The yields were 56% and 17%, respectively, based on *O*-methylisourea consumed. Both yields based on guanidine were almost quantitative.

Acknowledgment. This investigation was promoted by a grant for fundamental scientific research from the Ministry of Education of Japan and also a grant from Nippon (Japan) Carbide Industries, Inc., for which the authors wish to express their deep appreciation. Thanks also go to Dr. Keijiro Odo for his valuable help.

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(6) K. Rackman, *Ann.* **376**, 171 (1910); K. Sugino and M. Ogawa, *J. Electrochem. Assoc. Japan*, **6**, 294 (1938), (Part IV of this series).

(7) K. Sugino, *J. Chem. Soc. Japan*, **60**, 359 (1939).

(8) This was calculated as follows: The total alkalinity of the solution was determined by titration with 0.1*N* hydrochloric acid using methylorange as the indicator. The concentration of *O*-alkylisourea was then calculated by subtracting the amount of guanidine from the amount of total base.

Cyanamide Derivatives. LVIII.[1] Formation of Formoguanamine and Guanidine Salt by the Reaction of Formamidine Salt with Dicyandiamide[2]

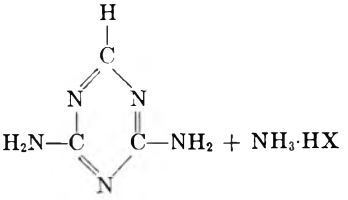
KOZO SHIRAI AND KICHIRO SUGINO

Received August 11, 1959

We discovered that the reaction of formamidine with dicyandiamide gave good yields of formoguanamine and guanidine salt.

(1) Part LVII, *J. Org. Chem.*, **25**, 1045 (1960).

$$NH_2CH{=}NH\cdot HX + NH_2C(NH)NHCN \longrightarrow$$



$$0.5\ NH_2C(NH)NHCN + NH_3\cdot HX \longrightarrow NH_2C(NH)NH_2\cdot HX$$

As a simple method for the preparation of formamidine has been devised by us,[3] we have obtained a convenient route to prepare pure formoguanamine.

EXPERIMENTAL

A sample of 4.03 g. of formamidine hydrochloride and 6.30 g. of dicyandiamide was thoroughly mixed and heated in an oil bath at 150°–160° for 1.5 hr. The mixture melted at 70° and heat evolution was observed at about 160°. Therefore, attention is required to keep the reaction temperature at the desired region by a suitable method. Crystals of the products began to separate during the reaction and a solidification of the total mixture was observed at the end. The reaction products were pulverized, extracted with 30 cc. of water, and filtered. After the residue was washed with 5 cc. of ethanol and dried, it was recrystallized from hot water. A 4.90-g. sample (88%) of formoguanamine was obtained, m.p. 316°. It showed no depression on admixture with an authentic sample.[4] Melting point of the picrate[4] was 247°.

The water extract, combined with ethanol wash, was concentrated to dryness and then extracted with 20 cc. of ethanol.[5] Evaporation of the extract gave 3.71 g., 78% of guanidine hydrochloride, m.p. 184°; m.p. of picrate, 315°.

Better results were obtained by using phenol as a solvent. Here is an example.

An 8.05-g. sample of formamidine hydrochloride and 12.60 g. of dicyandiamide were mixed with 20 g. of phenol and the mixture was heated in an oil bath at 200° for 1 hr. After the reaction, the solvent was removed by distillation and the residue was worked up as described above. A 10.28-g. sample, 93%, of formoguanamine and 8.40 g., 89%, of guanidine hydrochloride were obtained.

Acknowledgment. This investigation was promoted by a grant for fundamental scientific research from the Ministry of Education of Japan and also a grant from Nippon (Japan) Carbide Industries, Inc., for which the authors wish to express their deep appreciation. Thanks go also to Dr. Keijiro Odo for his valuable help.

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(2) Synthesis of *sym*-triazine system, I. This paper was prepared for delivery before the annual meeting of the Chemical Society of Japan on April 1958.

(3) K. Odo, E. Ichikawa, K. Shirai, and K. Sugino, *J. Org. Chem.*, **22**, 1715 (1957).

(4) M. Yamashita, *J. Chem. Soc. Japan (Ind. Chem. Sec.)*, **54**, 786 (1951), (Part XL of this series).

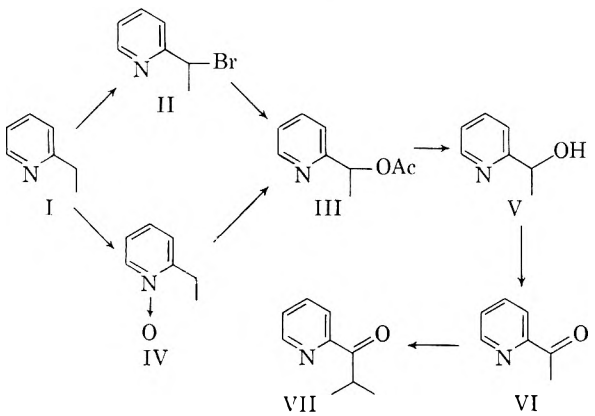
(5) If a salt other than hydrochloride is used, the solvent should be changed accordingly.

2-Pyridyl Alkyl Ketones

B. H. WALKER[1]

Received December 17, 1959

The formation of 2-pyridyl alkyl ketones from 2-alkylpyridines was of interest in the synthesis of Muscopyridine.[2] Using the scheme shown, 2-ethylpyridine (I) was transformed into 2-pyridyl methyl ketone (VI) and then to 2-pyridyl isopropyl ketone (VII).



The preparation of 2-(α-acetoxyethyl)pyridine (III) by rearrangement of 2-ethylpyridine oxide (IV) in acetic anhydride has been described.[3-5] Buu-Hoï[6] has reported that 2-picoline is brominated on the side chain, but experimental elaboration of this is lacking. We have found that radical bromination of 2-ethylpyridine produced 2-(α-bromoethyl)pyridine (II) in 75% yield. Treatment of II with silver acetate in acetic acid led to 2-(α-acetoxyethyl)pyridine (III) in 90% yield. This was shown to be identical with 2-(α-acetoxyethyl)pyridine (III) produced by rearrangement of 2-ethylpyridine oxide (IV) by comparison of their infrared spectra. Alkaline hydrolysis of III gave 2-(α-hydroxyethyl)pyridine (V) in 91% yield. The oxidation of 2-(α-hydroxyethyl)pyridine (V) to the corresponding ketone with dichromate sulfuric has been accomplished in low yield by Kuhn and Muzing.[7] Oxidation with chromium trioxide in pyridine likewise gave a low yield of the ketone.[8] A superior oxidizing agent was found in *N*-bromosuccinimide. Oxidation of 2-(α-hydroxyethyl)pyridine (V) using *N*-bromosuccinimide as the oxidizing agent was rather slow but occurred under very mild conditions, yielding 65% of pure 2-pyridyl methyl ketone.

The purpose of this study was to determine whether this sequence of reactions would be applicable to the synthesis of Muscopyridine.[2] Since this was the case, we were not interested in obtaining a specific methylation product but in obtaining a homogeneous one in reasonably good yield.

The alkylation of 2-pyridyl methyl ketone (VI) to a homogeneous substitution product was expected to be difficult due to a number of potential side reactions. Indeed, when VI was allowed to react with an equivalent amount of potassium *t*-butoxide and methyl iodide over an extended period, a 15% yield of 2-pyridyl isopropyl ketone (VII) was obtained along with a large amount of nonvolatile material. However alkylation reactions of this type are known to proceed more rapidly under the proper conditions.[9] The conditions selected, excess methyl iodide and potassium *t*-butoxide and five minute reaction time, resulted in a 48% yield of 2-pyridyl isopropyl ketone (VII).

EXPERIMENTAL[10-12]

2(α-Bromoethyl)pyridine (II). To 30.0 g. (0.28 mole) of 2-ethylpyridine in 830 ml. of carbon tetrachloride was added 50 g. (0.28 mole) of *N*-bromosuccinimide and 50 mg. of benzoyl peroxide. The solution was heated under reflux using an infrared lamp until no more *N*-bromosuccinimide remained on the bottom of the flask (2 hr.). After cooling the solution for 1 hr. in an ice bath, the succinimide was removed by filtration and washed with cold carbon tetrachloride. The filtrate was concentrated under reduced pressure and the product distilled. The yield of 2-(α-bromoethyl)-pyridine was 39.22 g. (75.5%); this material was a red unstable oil, b.p. 89.5–90.5° (7 mm.) n_D^{25} 1.5550–1.5561.[13] The sample prepared for analysis deposited a film on the sides of the flask immediately after distillation and was therefore not analyzed.

2-(α-Acetoxyethyl)pyridine (III). In a flask covered with aluminum foil was placed 39.22 g. (0.211 mole) of 2-(α-bromoethyl)pyridine, 300 ml. of glacial acetic acid, and 38.6 g. (0.232 mole) of silver acetate. The mixture was

(1) Present address: The Upjohn Company, Kalamazoo, Mich.

(2) K. Bieman, G. Büchi, and B. H. Walker, *J. Am. Chem. Soc.*, **79**, 5558 (1957).

(3) G. Kobayashi and S. Furukawa, *Pharm. Bull.*, **1**, 347 (1953).

(4) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

(5) O. H. Bullitt and J. T. Maynard, *J. Am. Chem. Soc.*, **76**, 1370 (1954).

(6) N. P. Buu-Hoï, *Ann.*, **556**, 1 (1944).

(7) E. Kuhn and W. Muzing, *Ber.*, **85**, 29 (1952).

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

(9) R. M. Lukes, G. I. Poos, R. E. Beyler, W. F. Johns, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 1707 (1953).

(10) Boiling points and melting points are uncorrected.

(11) All of the distillations were performed through a modified Podbielniak column constructed according to J. Cason and H. Rapoport, in *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y. 1950, p. 232.

(12) We are indebted to Dr. S. M. Nagy and his associates for analyses and for the infrared spectra, which were determined in 10% solution or 1% in potassium bromide, unless otherwise indicated, with a Baird Double Beam Infrared Recording Spectrometer, Model B, fitted with a sodium chloride prism.

(13) It was noticed that all of the pyridines reported here tended to react with carbon dioxide and/or water during the measurement of the index of refraction. The value always became lower as a consequence of this. In one case the value for the index of refraction dropped by 0.0042 on opening the refractometer for one minute.

immediately placed in an ice bath and cooled until the acetic acid commenced to crystallize. The cooling bath was then removed and the solution stirred (magnetically) for 9 hr. at room temperature, heated to reflux and left at room temperature overnight. The silver bromide was separated by filtration of the cooled solution and the filtrate was distilled under reduced pressure. After distillation of the acetic acid there was obtained 31.5 g. (90.5%) of 2-(α-acetoxyethyl)pyridine, b.p. 112–113° (12 mm.), [reported[4] b.p. 109–111° (16 mm.)].[14]

The infrared spectrum (pure liquid) of the acetate prepared by this route was identical with the infrared spectrum of the acetate prepared by rearrangement of 2-ethylpyridine oxide (IV).

2-(α-Hydroxyethyl)pyridine (V). To 9.0 g. (0.225 mole) of sodium hydroxide, 83 ml. of water and 57 ml. of methanol under a nitrogen atmosphere was added 31.5 g. (0.191 mole) of 2-(α-acetoxyethyl)pyridine. The solution was heated under reflux for 11.5 hr., transferred to a continuous extractor, diluted with 300 ml. of saturated sodium chloride solution and continuously extracted with benzene for 25 hr. Distillation of the extract yielded 21.37 g. (91%) of 2-(α-hydroxyethyl)pyridine, b.p. 93.5–94.0° (7 mm.) n_D^{25} 1.5223 (reported[5] b.p. 85–89° (5 mm.) n_D^{25} 1.5253).[15] The picrolonate, recrystallized from ethanol, melted at 184–186° dec.[15]

2-Pyridyl methyl ketone (VI). To a solution of 105 g. of *N*-bromosuccinimide, 1200 ml. of acetone, and 120 ml. of water was added 31.64 g. (0.257 mole) of 2-(α-hydroxyethyl)-pyridine and 2 ml. of glacial acetic acid. The pale yellow solution turned red within 12 hr. and pale yellow again after a total of 20.5 hr.[16] The reaction mixture was allowed to stand for a total of 48 hr. before being neutralized with solid sodium carbonate. A sodium thiosulfate solution was added to the lacrimatory mixture until a drop of the mixture failed to produce a blue color when placed on a piece of acidified starch iodide paper. The lacrimatory properties of the two phase system disappeared at this time. The cooled solution was filtered and the filtrate made acidic with hydrochloric acid (*p*H 1). After removal of the acetone by distillation, the residue was made basic (*p*H 9) and the aqueous solution distilled. The 1.0 l. of distillate was continuously extracted with benzene for 36 hr. Distillation of the extract yielded 20.00 g. (65%) of 2-pyridyl methyl ketone, b.p. 82–83.5° (13–15 mm.) n_D^{25} 1.5153 [reported[17] b.p. 78° (12 mm.)].

The phenylhydrazone recrystallized from methanol-water melted at 156–158° (reported[17] m.p. 155.5–156°).

2-Pyridyl isopropyl ketone[18] (VII). To a solution prepared from 4.5 g. (0.116 mole) of potassium and 230 ml. of *t*-butyl alcohol (distilled from 3 g. of sodium), 300 ml. of sodium-dried benzene was added. To the stirred refluxing solution under a nitrogen atmosphere was added, as fast as possible, 7.0 g. (0.058 mole) of 2-pyridyl methyl ketone. This addition was followed immediately by the addition, during 1 min., of 24.6 g. (0.174 mole) of methyl iodide in 5 ml. of dry benzene. The solution was maintained at reflux for an additional 4 min., then quenched with 50 ml. of ice water. After the addition of 25 ml. of concd. hydrochloric acid, the solution was concentrated under reduced pressure. The residue was made basic by the addition of 20 g. of potassium hydroxide (*p*H 11). After saturating the solution with solid sodium chloride, it was extracted with eight portions of ether. The combined ether solutions were filtered through and dried over sodium sulfate, concentrated under reduced pressure, and distilled. There was obtained a forerun of 1.37 g., b.p. 73.5–87.5° (7 mm.) n_D^{25} 1.5084–1.5053, followed by 4.15 g. (48%) of 2-pyridyl isopropyl ketone, b.p. 87.5–88.5° (7 mm.) n_D^{25} 1.5000–1.4989 (reported[19] 107–108° (25 mm.) n_D^{25} 1.5028). The pot residue amounted to 1.0 g.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H 7.43. Found: C, 72.56; H 7.69.

The 2,4-dinitrophenylhydrazone after one recrystallization from ethyl acetate melted at 180.0–181.6°. The analytical sample melted at 181.0–181.4° (reported[19] m.p. 181.0–181.5°).

Anal. Calcd. for $C_{15}H_{15}N_5O_4$: C, 54.61; H, 4.59. Found: C, 54.46; H, 4.70.

When equimolar quantities of potassium, methyl iodide, and methyl 2-pyridyl ketone were used, the same product was obtained in 15% yield. The infrared spectrum was identical with that of the ketone prepared above, and a mixture melting point of the 2,4-dinitrophenylhydrazones was undepressed.

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(14) We have repeated the preparation of 2-(α-acetoxyethyl)pyridine using the procedure of Boekelheide and Linn[4] and obtained a 67% yield of the acetate. b.p. 105–110° (9–10 mm.) n_D^{25} 1.4893–1.4923 (reported[5] n_D^{25} 1.4913).

(15) Hydrolysis of the acetate produced *via* the *N*-oxide route[4] yielded the alcohol in 75% yield, b.p. 93.5–94.5° (7 mm.) n_D^{25} 1.5220–1.5230.

Anal. Calcd. for C_7H_9ON: C, 68.27; H, 7.37. Found: C, 68.49; H, 7.65.

The ultraviolet absorption spectrum in ethanol showed: $\lambda_{max.}$ 256 mμ log ε 3.48, $\lambda_{max.}$ 261 mμ log ε 3.55, $\lambda_{max.}$ 267.5 mμ log ε 3.23.

The picrolonate prepared from this material was recrystallized from ethanol and melted at 183.0–185.6° dec.

Anal. Calcd. for $C_{17}H_{17}N_5O_6$: C, 52.71; H, 4.42. Found: C, 52.93; H, 4.79.

(16) B. C. Anderson, Ph.D. thesis, Massachusetts Institute of Technology, 1955.

(17) P. C. Teague, A. R. Ballentine, and G. L. Rushton, *J. Am. Chem. Soc.*, **75**, 3429 (1953).

(18) S. Bertucat, *Compt. Rend.*, **232**, 1758 (1951), has claimed the synthesis of this compound and three of its derivatives; however, no physical properties were reported for the compound and we have been unable to prepare any of the recorded derivatives.

(19) H. R. Henze and M. B. Knowles, *J. Org. Chem.*, **19**, 1127 (1954).

Cyclizations Leading to 2-Acylpyrroles and 2-Pyrrolecarboxylic Esters[1,2]

GEORGE G. KLEINSPEHN AND ALSOPH H. CORWIN

Received December 21, 1959

Prior to the outset of this investigation, the reductive condensation of certain β-diketones and β-ketoaldehydes with ethyl α-oximinoacetoacetate[3–5]

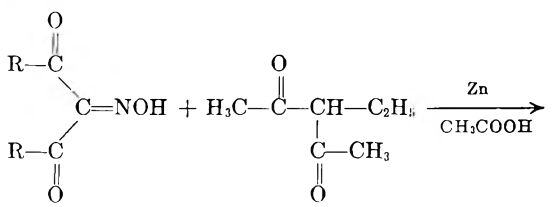
(1) Studies in the Pyrrole Series, XXIX. Paper XXVIII, B. Harrell and A. H. Corwin, *J. Am. Chem. Soc.*, **78**, 3135 (1956).

(2) This work was supported by a research grant (NSF-G 1195) from the National Science Foundation.

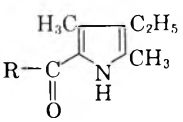
(3) H. Fischer and E. Fink, *Z. physiol. Chem.*, **280**, 123 (1944).

and diethyl oximinomalonate[6] on the one hand and with ethyl oximinocyanoacetate[6] on the other had been shown to give 2-pyrrolecarboxylic esters[3-6] and 2-pyrrolecarbonitriles,[6] respectively. More recently two further publications[7,8] have described additional condensations of this same general type which lead to other 2-pyrrolecarboxylic esters[7,8] and even to tetraalkylpyrroles.[8] In every case cyclization is accompanied by the loss of an acyl or an alkoxycarbonyl group which was initially present in the oximino moiety.

In order to determine whether an adaptation of this cyclization reaction might constitute a useful synthetic route to 2-acylpyrroles,[9] the reductive condensation of each of two α-oximino-β-diketones with 3-ethyl-2,4-pentanedione (III) was investigated. The reaction of 3-oximino-2,4-pentanedione (I) with III in the presence of zinc dust and acetic acid provided 2-acetyl-4-ethyl-3,5-dimethylpyrrole (IV) in 16% yield. Under similar conditions 2-oximino-1,3-diphenyl-1,3-propanedione (II) and III afforded an 11% yield of 2-benzoyl-4-ethyl-3,5-dimethylpyrrole (V). Pyrroles IV and V had been previously prepared by other investigators *via* the acylation[10,11] of 3-ethyl-2,4-dimethylpyrrole. This appears to be the first reported instance in which an α-oximino-β-diketone has participated in a pyrrole ring synthesis involving scission of one of its acyl groups. The presence of the 3-ethyl group in III apparently precludes the usual Knorr condensation. It has long been known that an aminomethyl monoketone may occasionally take part in a similar cyclization[12,13] so that a 2-acylpyrrole



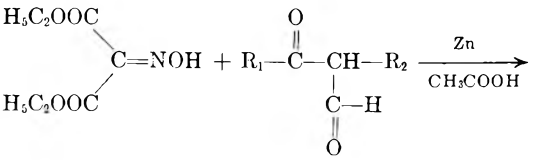
I. R = CH_3
II. R = C_6H_5



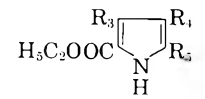
IV. R = CH_3
V. R = C_6H_5

by-product sometimes accompanies the expected product of a Knorr condensation.

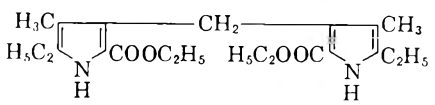
In connection with a synthetic program in progress in this laboratory, it was desirable to develop a convenient synthesis for ethyl 3-ethyl-4-methyl-2-pyrrolecarboxylate (X). Our previous synthesis[6] of ethyl 3,4-dimethyl-2-pyrrolecarboxylate (IX) from 2-methyl-3-oxobutyraldehyde (VII) and diethyl oximinomalonate (VI) led us to attempt the synthesis of X *via* reductive condensation of VI with 2-methyl-3-oxovaleraldehyde (VIII). Surprisingly, condensation proceeded in the opposite sense to provide ethyl 5-ethyl-4-methyl-2-pyrrolecarboxylate (XI), an isomer of X, in a yield of only 2%. As the reported melting points of pyrrolecarboxylic esters X[11,14] and XI[4] lie within 4° of one another, unequivocal identification of the product was achieved through conversion to the corresponding dipyrrylmethane (XII)[4] in 65% yield. The isolation of XI from this cyclization reaction



VI VII. $R_1 = R_2 = CH_3$
VIII. $R_1 = C_2H_5$, $R_2 = CH_3$



IX. $R_3 = R_4 = CH_3$, $R_5 = H$
X. $R_3 = C_2H_5$, $R_4 = CH_3$, $R_5 = H$
XI. $R_3 = H$, $R_4 = CH_3$, $R_5 = C_2H_5$



XII

parallels the experience of Fischer and Fink,[4] who obtained XI and ethyl 4,5-dimethyl-2-pyrrolecarboxylate from the reductive condensation of ethyl α-oximinoacetoacetate with VIII and VII, respectively.

In an earlier communication[6] we reported the synthesis of ethyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate (XIV) in 65% yield from the reaction of diethyl oximinomalonate (VI) with 3-ethyl-2,4-pentanedione (III) in the presence of zinc and acetic acid. In the course of this work the analogous reductive condensation of ethyl α-oximinoacetoacetate (XIII) and III was carried out to give this same pyrrole (XIV) in 47% yield. A number of very closely related pyrrole syntheses from α-oximinoacetoacetic esters and 3-substituted 2,4-pentanediones have been reported recently.[7,8]

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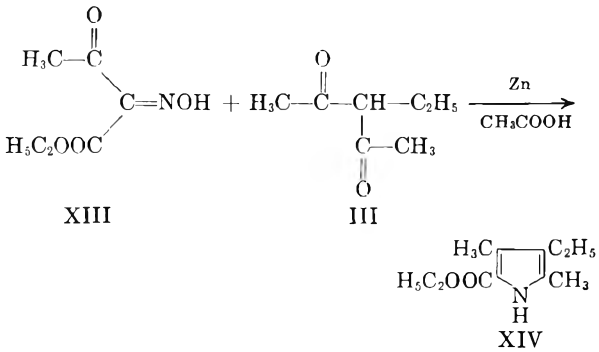

XIII III

XIV

EXPERIMENTAL[15]

2-Acetyl-4-ethyl-3,5-dimethylpyrrole (IV). The reductive condensation of 50 mmol. of 3-oximino-2,4-pentanedione[16,17] with 50 mmol. of 3-ethyl-2,4-pentanedione[18,19] was carried out in the presence of zinc dust, sodium acetate, and aqueous acetic acid using the procedure[6] described for the preparation of 2-carbethoxy-3,5-dimethylpyrrole from diethyl oximinomalonate and 2,4-pentanedione. Yield of crude product, 1.3 g. or 16%. A product melting at 112–114.5° was obtained after a single recrystallization from methanol. Additional recrystallization from aqueous methanol and from isooctane afforded an analytically pure sample of m.p. 114.5–115.5°; lit.,[10,11] m.p. 114–115°, 111–112°.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.36; H, 9.09.

2-Benzoyl-4-ethyl-3,5-dimethylpyrrole (V). The procedure was essentially that employed for the preparation of IV with a few minor modifications. In this instance 25 mmol. each of 3-ethyl-2,4-pentanedione[18,19] and of 2-oximino-1,3-diphenyl-1,3-propanedione[20] were employed. Zinc dust was removed from the brown viscous, semisolid product by filtration of its solution in hot benzene-methanol. Evaporation of the filtrate to a sirupy, semicrystalline residue and trituration of this residue with a little ether produced a viscous slurry of the crystalline product, which was collected on the filter. Yield of crude product, 0.3 g. or 11%; m.p. 132–139°. Recrystallization from aqueous methanol gave a purer product of m.p. 140.5–141.5°; lit.,[11] m.p. 143°.

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54. Found: C, 79.13; H, 7.63.

Isolation and identification of ethyl 5-ethyl-4-methyl-2-pyrrolecarboxylate (XI) *from the reductive condensation of diethyl oximinomalonate* (VI) *with 2-methyl-3-oxovaleraldehyde* (VIII). To 30 ml. of glacial acetic acid previously heated to 85° was added with stirring 1) 7.9 g. of anhydrous sodium acetate, 2) a solution of 7.7 g. (57 mmol.) of the sodium salt of 2-methyl-3-oxovaleraldehyde in 10 ml. of water and 5 ml. of acetic acid, and 3) a solution of 9.5 g. (50 mmol.) of diethyl oximinomalonate in 7 ml. of acetic acid. Addition of 11 g. of zinc dust was then begun at such a rate that the temperature rose to and remained in the range 100–106°. When all of the zinc dust had been introduced with vigorous stirring, the reaction mixture was heated 15 min. longer, then poured into 150 ml. of ice water. An oil containing some solid separated upon refrigeration. This was extracted with ether, and the residue remaining after evaporation of the ether was distilled under reduced pressure in order to separate the pyrrole from less volatile materials. A broad fraction of b.p. 80–155° at 16–20 mm. was collected, treated with aqueous sodium hydroxide, then extracted with ether. Recrystallization from ethanol of the oily crystalline solid obtained upon evaporation of this ether extract gave 170 mg. or 2% yield of pyrrole XI, m.p. 72–77°; lit.,[3] m.p. 79°.

Since the isomeric ethyl 3-ethyl-4-methyl-2-pyrrolecarboxylate (X)[11,14] is reported to melt at 75° or 76°, the identification of our pyrrolecarboxylic ester product of m.p. 72–77° was achieved through conversion to diethyl 3,3′-methylenebis(5-ethyl-4-methyl-2-pyrrolecarboxylate) (XII). Crude XII was obtained in 65% yield by heating our product with formaldehyde in aqueous ethanol in the presence of a small amount of concd. hydrochloric acid. Recrystallization from ethanol afforded a pure product of m.p. 193–196°; lit.,[4] m.p. 190°. The isomeric diethyl 5,5′-methylenebis(3-ethyl-4-methyl-2-pyrrolecarboxylate)[21] is reported to melt at 148°.

Anal. Calcd. for $C_{21}H_{30}N_2O_4$: C, 67.35; H, 8.07. Found: C, 67.28; H, 8.30.

Ethyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate (XIV). The preparative procedure was the same as that employed in the preparation of IV except that the zinc dust rather than the oximino compound was added gradually to the other reactants. Condensation of 30 mmol. each of ethyl α-oximinoacetoacetate and of 3-ethyl-2,4-pentanedione in this manner gave 2.75 g. or 47% yield of product of m.p. 89–90°; lit.,[6] m.p. 90–91°.

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.46; H, 8.94.

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(15) All melting points were determined on the Fisher-Johns melting point apparatus.

(16) L. Wolff, P. Bock, G. Lorentz, and P. Trappe, *Ann.*, **325**, 139 (1902).

(17) The authors wish to thank Mr. Peter M. Eller for the preparation of this intermediate.

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(19) The authors wish to thank Mr. Wilford L. Mendelson for the preparation of this intermediate.

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Substituted Aminobenzoquinolines

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This communication deals with the preparation of a number of substituted 1-amino-3-methylbenzo[*f*]quinolines and 4-amino-2-methylbenzo[*h*]quinolines for trials against *E. histolytica*.

The compounds were prepared by the action of 1-chloro-3-methylbenzo[*f*]quinoline or 4-chloro-2-methylbenzo[*h*]quinoline on the appropriate amine in boiling ethanol (Method I). Benzylamine, 2-phenylethylamine, 4-phenoxybutylamine, and 3-diethylaminopropylamine did not react under these conditions; in these cases, the reaction was carried out by heating the reactants in phenol (Method II) and the products isolated as the salicylate.

The condensation of 1-naphthylamine and ethyl acetoacetate in the presence of iodine and subsequent cyclization of the resulting anil in hot liquid paraffin yielded 4-hydroxy-2-methylbenzo[*h*]quinoline which on treatment with phosphorus oxychloride gave the intermediate 4-chloro-2-methylbenzo[*h*]quinoline; a similar procedure with 2-naphthylamine yielded 1-chloro-3-methylbenzo[*f*]quinoline.[1]

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TABLE I

SUBSTITUTED 1-AMINO-3-METHYLBENZO[*f*]QUINOLINES AND 4-AMINO-2-METHYLBENZO[*h*]QUINOLINES

Ser. No	Base	M.P.[a]	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Water, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	1-*p*-Chloroanilino-3-methylbenzo[*f*]quinoline	208	$C_{20}H_{15}N_2Cl$	75.35	75.47	4.71	5.09	8.79	8.71	—	—
2	1-*m*-Chloroanilino-3-methylbenzo[*f*]quinoline	220	$C_{20}H_{15}N_2Cl$	75.35	75.22	4.71	4.94	8.79	8.82	—	—
3	1-*p*-Bromoanilino-3-methylbenzo[*f*]quinoline	208	$C_{20}H_{15}N_2Br$	66.12	65.99	4.13	4.31	7.71	7.75	—	—
4	1-*m*-Bromoanilino-3-methylbenzo[*f*]quinoline	223	$C_{20}H_{15}N_2Br$	66.12	66.32	4.13	4.19	7.71	7.65	—	—
5	1-Anilino-3-methylbenzo[*f*]quinoline	221	$C_{20}H_{16}N_2$	84.51	84.38	5.63	5.74	9.86	9.90	—	—
6	1-*p*-Iodoanilino-3-methylbenzo[*f*]quinoline	207	$C_{20}H_{15}N_2I\cdot{}^1/_4H_2O$	57.90	57.69	3.74	4.04	6.76	6.76	1.09	1.23
7	1-*m*-Iodoanilino-3-methylbenzo[*f*]quinoline	218	$C_{20}H_{15}N_2I\cdot{}^1/_4H_2O$	57.90	58.12	3.74	3.96	6.76	6.80	1.09	1.19
8	1-*p*-Anisidino-3-methylbenzo[*f*]quinoline	218	$C_{21}H_{18}N_2O\cdot{}^1/_4H_2O$	79.12	79.31	5.81	6.05	8.79	8.83	1.41	1.45
9	1-*p*-Toluidino-3-methylbenzo[*f*]quinoline	196	$C_{21}H_{18}N_2\cdot{}^1/_4H_2O$	83.31	83.15	6.12	6.22	9.26	9.30	1.49	1.48
10	1-*m*-Toluidino-3-methylbenzo[*f*]quinoline	234	$C_{21}H_{18}N_2\cdot{}^1/_2H_2O$	82.08	82.23	6.19	6.19	9.12	9.10	2.93	3.12
11	1-*p*-Carboxyanilino-3-methylbenzo[*f*]quinoline	266	$C_{21}H_{16}N_2O_2\cdot 1^1/_4H_2O$	71.90	72.12	5.28	5.47	7.99	7.82	6.42	6.46
12	1-Benzylamino-3-methylbenzo[*f*]quinoline salicylate	248	$C_{21}H_{18}N_2,C_7H_6O_3\cdot{}^1/_2H_2O$[b]	75.41	75.43	5.62	5.71	6.29	6.33	2.02	2.12
13	1-(2-Phenylethyl)amino-3-methylbenzo[*f*]quinoline salicylate	227	$C_{22}H_{20}N_2,C_7H_6O_3\cdot H_2O$	74.36	74.27	5.98	5.79	5.98	6.09	3.85	3.88
14	1-(4-Phenoxybutyl)amino-3-methylbenzo[*f*]quinoline salicylate	178	$C_{24}H_{24}N_2O,C_7H_6O_3\cdot{}^1/_2H_2O$	73.96	73.74	6.16	6.63	5.57	5.59	1.79	1.84
15	1-(3-Diethylaminopropyl)amino-3-methylbenzo[*f*]-quinoline salicylate	230	$C_{21}H_{27}N_3,3C_7H_6O_3\cdot{}^1/_2H_2O$	67.74	67.67	6.18	6.14	5.65	5.68	1.21	1.25
16	4-*p*-Chloroanilino-2-methylbenzo[*h*]quinoline	161	$C_{20}H_{15}N_2Cl\cdot{}^1/_3H_2O$	73.96	73.94	4.83	4.89	8.63	8.58	1.85	1.95
17	4-*m*-Chloroanilino-2-methylbenzo[*h*]quinoline	92	$C_{20}H_{15}N_2Cl\cdot 1^1/_2H_2O$	69.47	69.54	5.21	5.35	8.10	8.10	7.81	7.85
18	4-*p*-Bromoanilino-2-methylbenzo[*h*]quinoline	181	$C_{20}H_{15}N_2Br\cdot{}^2/_3H_2O$	64.00	64.06	4.35	4.05	7.47	7.48	3.20	3.10
19	4-*m*-Bromoanilino-2-methylbenzo[*h*]quinoline	133	$C_{20}H_{15}N_2Br\cdot H_2O$	62.99	62.85	4.46	4.75	7.35	7.38	4.72	4.85
20	4-Anilino-2-methylbenzo[*h*]quinoline	140	$C_{20}H_{16}N_2\cdot{}^1/_2H_2O$	81.91	81.61	5.80	5.83	9.56	9.50	3.08	3.12
21	4-*p*-Iodoanilino-2-methylbenzo[*h*]quinoline	174	$C_{20}H_{15}N_2I\cdot H_2O$	56.07	56.26	3.97	3.97	6.54	6.58	4.21	4.23
22	4-*m*-Iodoanilino-2-methylbenzo[*h*]quinoline	156	$C_{20}H_{15}N_2I\cdot{}^1/_2H_2O$	57.28	57.12	3.82	4.01	6.68	6.75	2.15	2.30
23	4-*p*-Anisidino-2-methylbenzo[*h*]quinoline	168	$C_{21}H_{18}N_2O\cdot{}^1/_2H_2O$	78.02	77.92	5.88	6.15	8.67	8.55	2.79	2.68
24	4-*p*-Toluidino-2-methylbenzo[*h*]quinoline	176	$C_{21}H_{18}N_2\cdot{}^1/_3H_2O$	82.90	82.84	6.14	6.40	9.21	9.00	1.97	2.10
25	4-*m*-Toluidino-2-methylbenzo[*h*]quinoline picrate	216	$C_{21}H_{18}N_2\cdot C_6H_3N_3O_7$[c]	61.48	61.66	3.98	4.24	13.28	13.25	—	—
26	4-(2-Phenylethyl)amino-2-methylbenzo[*h*]quinoline salicylate	232	$C_{22}H_{20}N_2\cdot C_7H_6O_3$	77.33	77.44	5.78	5.98	6.22	6.12	—	—

[a] Melting points are uncorrected. [b] $C_7H_6O_3$ = salicylic acid. [c] $C_6H_3N_3O_7$ = picric acid; the base was an oil and was converted into the picrate and crystallized from ethanol.

EXPERIMENTAL

Method I. 1-Chloro-3-methylbenzo[*f*]quinoline (0.005 mole) and an equivalent amount of the appropriate amine were dissolved in 90% ethanol and boiled under reflux for 5 to 10 hr. The hydrochloride of the base crystallized during this period and was filtered and washed with ethanol. It was dissolved in hot dilute acetic acid, and the solution neutralized with ammonia to precipitate the base. It was filtered, washed with water, and crystallized from 90% ethanol.

The 4-amino-2-methylbenzo[*h*]quinoline derivatives were prepared in the same way as above, by boiling under reflux for 40 hr.

Method II. A mixture of 0.005 mole of 1-chloro-3-methylbenzo[*f*]quinoline or 4-chloro-2-methylbenzo[*h*]quinoline and a slight excess of thea ppropriate amine was heated in phenol in an oil bath at 130–140° for 30 hr. The reaction mixture was poured into an excess of a solution of sodium hydroxide. The base was obtained as a sticky precipitate which solidified in a day. It was dried in the desiccator, dissolved in ether, and after filtration, the ether solution was treated with a solution of salicylic acid in ether. The salicylate of the base which precipitated was filtered, washed with ether, and crystallized from 90% ethanol.

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Reactions of Pyrones Catalyzed by Trifluoroacetic Acid

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Previous experiments[2,3] with pyrones have shown that trifluoroacetic acid catalyzes the reaction of acyl halides with pyrones to form either mono or diacylated products. These reactions have indicated that the activated complex of a 2- or 4-pyrone with trifluoroacetic acid is a carbanion.

It was therefore decided to try the reaction of pyrones with nitriles and with substituted acrylic acids such as cinnamic acid and crotonic acid.

In every instance in which condensation between a pyrone and a nitrile was attempted, experimental evidence indicated that a reaction had taken place.

The resulting imides are characterized in the I_{A-F} series given in Table I. Compound I_F is a ketone formed from the easily hydrolyzed imide. As Compound I_E represents the simplest molecule, it was selected as representative of the group for hydrolysis to the ketone and thus to the malononitrile derivative (IV). Malononitrile has been demonstrated[3,4] to indicate the presence of the pyrone carbonyl as well as the ketonic carbonyl.

Table II describes the three instances in which the authors were able to isolate the condensation product from the reaction of pyrones with substituted acrylic acids. The *p*-bromophenacyl bromide derivative (V) of II_A was prepared to characterize the acid because it was representative of the group and had the simplest molecule.

The compounds of the III_{A-C} series in Table III represent the nearest approach of a continuing search over a period of several years for a method by which pyrones may be carboxylated. However, every attempt to hydrolyze the carbethoxy compounds was a failure.

In the face of such limited data and so few cases one can only speculate that the position of the carboxyl or carboxyls on the pyrone ring of the carbethoxy compound is such that in the presence of boiling mineral acids the substances rapidly decarboxylate.

EXPERIMENTAL[5]

Compounds I_{A-F} *series.* A mixture of 0.1 mole of the pyrone and 0.1 mole of the nitrile in 20 ml. of trifluoroacetic acid was refluxed for at least 90 min. The cooled solution was diluted with 200 ml. of water and chilled in the freezing compartment of the refrigerator. The precipitate was dried in air and recrystallized twice from absolute ethanol to give the analytical sample.

Compounds of II_{A-C} *series.* One tenth mole of cinnamic or crotonic acid was mixed with 0.1 mole of the pyrone in 15 ml. trifluoroacetic acid and the mixture refluxed for a minimum of 15 hr. At the termination of the reflux period, 100 ml. of water was added to the mixture. The material was cooled somewhat and then filtered. The residue was dried in air and the analytical samples were obtained by recrystallizing the crude compounds twice from boiling heptane.

Compounds of III_{A-C} *series.* To a mixture consisting of 0.1 mole of the pyrone and 30 ml. of trifluoroacetic acid, thoroughly shaken, was added, all at once, either 0.1 mole or 0.2 mole of ethyl chloroformate. The solution was heated under reflux in an all-glass refluxing assembly in the hood for 2 hr. or for a sufficiently longer time that hydrogen chloride vapors were no longer evolved.

At the termination of the reaction period the mixture was poured into 200 ml. distilled water, chilled, and filtered. The air dried precipitate was recrystallized twice from heptane. Compounds of this series are listed in Table III.

Preparation of compound IV. A 5.0-g. sample of compound of I_E was refluxed in a mixture of 90 ml. distilled water and 10 ml. concd. hydrochloric acid for several hours. The solution was filtered while hot and the residue remaining on the paper was dried, then refluxed with 2.5 g. of malononitrile in 15 ml. of acetic anhydride for 1 hr. The solution was poured into water and the light brown precipitate when recrystallized several times from absolute ethanol melted at 122°.

Anal. Calcd. for $C_{21}H_{13}N_5O_3$: N, 18.26. Found: N, 18.27.

p-Bromophenacyl derivative of II_A (V). Two and seven tenths grams (0.01 mole) of II_A was mixed with 0.8 g. of sodium bicarbonate in 8 ml. of water. After the effervescence had subsided, 40 ml. of ethanol and 0.01 mole of *p*-bromophenacyl bromide (2.7 g.) was added. The mixture was

(1) The person to whom correspondence regarding the contribution should be addressed.

(2) L. L. Woods and P. A. Dix, *J. Org. Chem.*, **24**, 1126 (1959).

(3) L. L. Woods, *J. Org. Chem.*, **24**, 1804 (1959).

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(5) All analyses were performed by Dr. Carl Tiedcke and all melting points were determined on a Fisher-Johns melting point assembly.

TABLE I

REACTIONS OF PYRONES WITH NITRILES

No.	Pyrone	Nitrile	M.P., °	Yield, %	Empirical Formula	Analyses, Calcd. (Found) Carbon	Hydrogen	Nitrogen
I_A	Kojic acid	*p*-Nitrophenylacetonitrile	167.5–168	70	$C_{14}H_{12}N_2O_6$	55.26 55.10	3.97 4.24	9.20 9.04
I_B	α-Chloro-α-deoxy kojic acid	*p*-Nitrophenylacetonitrile	118–120	86	$C_{14}H_{11}N_2ClO_5$	52.10 52.39	3.43 3.58	8.68 8.44
I_C	2-Hydroxymethyl-5-methoxy-4-pyrone	*p*-Nitrophenylacetonitrile	140	94	$C_{15}H_{14}N_2O_6$	56.60 56.41 60.23	4.43 4.29 3.49	8.80 8.86 5.40
I_D	Comenic acid	Benzonitrile	Sublimes above 200, discolors above 270	66	$C_{13}H_9NO_5$	60.51	4.70	5.12
I_E	2,6-Dimethyl-4-pyrone	*p*-Nitrophenylacetonitrile	115.5–116.5	76	$C_{15}H_{14}N_2O_4$	62.93 62.42	4.92 4.55	9.78 10.12
I_F	α-Chloro-α-deoxy kojic acid	Cyanoacetic acid	162–163	54	$C_9H_7ClO_6$[a]	43.83 44.10	2.86 3.11	—

[a] As hydrolysis of the compound failed to change the melting point and composition, the original product was the ketone and not the imide.

TABLE II

REACTIONS OF PYRONES WITH SUBSTITUTED ACRYLIC ACIDS

No.	Pyrone	Unsaturated Acid	Yield, %	M.P.	Formula	Analyses, Calcd. (Found) Carbon	Hydrogen	Chlorine
II_A	2,6-Dimethyl-4-pyrone	Cinnamic acid	98	128–129	$C_{16}H_{16}O_4$	70.59 70.91	5.92 5.70	
II_B	Coumarin	Cinnamic acid	61	142.5–143.5	$C_{18}H_{14}O_4$	73.45 73.19	4.79 4.59	
II_C	α-Chloro-α-deoxy-kojic acid	Crotonic acid	29	145–146	$C_{10}H_{11}O_5Cl$	48.69 48.52	4.49 4.29	14.37 14.19

TABLE III

CARBETHOXY DERIVATIVES OF PYRONES

No.	Pyrone	Moles of Ethyl Chlorocarbonate per Mole Pyrone	M.P.	Formula	Yield, %	Analyses, Calcd. (Found) Carbon	Hydrogen
III_A	Kojic acid	1	162–163	$C_9H_{10}O_6$	41	50.23 50.41	4.68 4.41
III_B	α-Chloro-α-deoxykojic acid	2	140–141	$C_{12}H_{13}ClO_7$	32	47.30 47.54	4.30 4.14
III_D	6-Nitrocoumarin	2	160–161.5	$C_{12}H_{13}NO_8$	51	53.73 53.48	3.90 3.68

refluxed for 90 min. and then poured into 400 ml. of water. Ten milliliters of concd. hydrochloric acid and 1 g. of aluminum chloride was then added; the resulting precipitate was filtered and dried in air, yield 2.5 g. Recrystallization of the precipitate twice from ethanol produced crystals melting at 155°.

Anal. Calcd. for $C_{24}H_{21}BrO_5$: C, 61.41; H, 4.51; Br, 17.02. Found: C, 61.02; H, 4.23; Br, 17.45.

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Coenzyme Q. XIV. Reactions of Ethyl Cyanoacetate with Dimethoxybenzoquinones

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A sensitive color reaction[1] for certain quinones, has been modified so that it is applicable to co-

(1) R. Craven, *J. Chem. Soc.*, 1605 (1931).

enzyme Q_{10} (I) and other dimethoxybenzoquinones. We find that tetrasubstituted dimethoxybenzoquinones give a positive test contrary to the early concept.[1]

Craven[1] reported an intense bluish-violet coloration, changing to blue, green, and finally reddish brown when certain quinones are treated with ethyl cyanoacetate and excess alcoholic ammonia. He stated that the reaction requires the presence of a labile hydrogen or halogen atom adjacent to a carbonyl group of the quinone.

When structure studies on coenzyme Q[2,3] first indicated that it is a dimethoxybenzoquinone containing one or two alkyl substituents, it was thought that Craven's test might indicate a tri- or a tetrasubstituted benzoquinone. It appeared that coenzyme Q_{10} is not a tetrasubstituted benzoquinone, since no color was produced in the test; however, coenzyme Q_{10} is not soluble in alcoholic aqueous ammonia. When the test was modified by dissolving coenzyme Q_{10} and ethyl cyanoacetate in absolute ethanol and then adding gaseous ammonia, a blue color developed which reached maximum intensity in about five minutes. After about thirty minutes, the color had changed to green; after twenty hours, a tan color had developed.

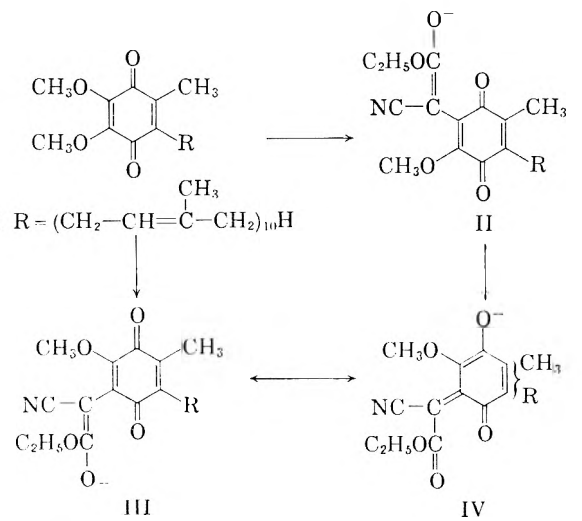
All three of the possible dimethoxydimethylbenzoquinones (2,3-dimethoxy-5,6-dimethyl-, 2,5-dimethoxy-3,6-dimethyl-, and 2,6-dimethoxy-3,5-dimethylbenzoquinone) gave positive tests. The blue color given by 2,5-dimethoxy-3,6-dimethylbenzoquinone was very persistent, and lasted for twenty-four hours. The blue colors formed by the other two compounds had changed to green after about one-half hour. Therefore, the test could not exclude a tetrasubstituted benzoquinone for the structure of coenzyme Q_{10} and did indicate that it is not a 2,5-dimethoxy-3,6-dialkylbenzoquinone.

Jeffreys[4] recently reported that the methoxy group of methoxybenzoquinone could be displaced by the anion of ethyl cyanoacetate. Previous investigators[5] had shown that methoxy groups in benzoquinones were readily displaced. Therefore, the blue color produced from coenzyme Q_{10} with ethyl cyanoacetate in the presence of ammonia is probably due to the reaction of one or both of the methoxy groups with the formation of ions represented by II, III, and IV. Although it is likely that only one of the methoxy groups is reactive under these conditions, one cannot tell without further studies whether just one or both methoxy groups participate; thus, two orientations are possible.

TABLE I

COLOR CHANGES FROM REACTION OF ETHYL CYANOACETATE WITH VARIOUS BENZOQUINONES

Benzoquinone	Color after 5 Min.	30 Min.	24 Hr.
Coenzyme Q_{10}	Blue	Green	Tan
2,3-Dimethoxy-5,6-dimethylbenzoquinone	Blue	Green	Tan
2,5-Dimethoxy-3,6-dimethylbenzoquinone	Blue	Blue	Blue
2,6-Dimethoxy-3,5-dimethylbenzoquinone	Blue	Green	Tan
2,5-Dimethoxybenzoquinone	Blue	Blue	Blue
2,6-Dimethoxybenzoquinone	Blue	Green	Tan
2,3-Dimethoxybenzoquinone	Blue	Green	Tan
2,5-Dihydroxybenzoquinone	Pink color with separation of pink crystals		
Diethoxy homolog of coenzyme Q_{10}	Light blue	Light green	Light tan
Duroquinone	Colorless	Colorless	Colorless



An ethoxy group is displaced with greater difficulty since the diethoxy homolog of coenzyme Q_{10}[6] gives a much weaker color.

Morton and co-workers[7] have reported that ubiquinone (coenzyme Q_{10}) and aurantiogliocladin (2,3-dimethoxy-5,6-dimethylbenzoquinone) give a blue color only slowly with ethyl cyanoacetate in ammonia-ethanol.

The blue color produced by the action of potassium hydroxide on an ethanolic solution of coenzyme Q_{10} and ethyl cyanoacetate has been de-

(2) R. L. Lester, F. L. Crane, and Y. Hatefi, *J. Am. Chem. Soc.*, **80**, 4751 (1958).

(3) D. E. Wolf, C. H. Hoffman, N. R. Trenner, B. H. Arison, C. H. Shunk, B. O. Linn, J. F. McPherson, and K. Folkers, *J. Am. Chem. Soc.*, **80**, 4752 (1958).

(4) J. A. D. Jeffreys, *J. Chem. Soc.*, 2153 (1959).

(5) D. Buckley, H. B. Henbest, and P. Slade, *J. Chem. Soc.*, 4891 (1957).

(6) B. O. Linn, N. R. Trenner, C. H. Shunk, and K. Folkers, *J. Am. Chem. Soc.*, **81**, 1263 (1959).

(7) R. A. Morton, U. Gloor, O. Schindler, G. M. Wilson, L. H. Chopard-dit-Jean, F. W. Hemming, O. Isler, W. M. F. Leat, J. F. Pennock, R. Rüegg, U. Schwieter, and O. Wiss, *Helv. Chim. Acta.*, **41**, 2343 (1958).

veloped into a quantitative determination of coenzyme Q_{10} in urine.[8]

EXPERIMENTAL

About 1 mg. of a substituted benzoquinone was dissolved in 2 ml. of absolute ethanol, if necessary, with warming. The solution was cooled to room temperature, 2 drops of ethyl cyanoacetate was added, and then anhydrous ammonia was absorbed in the solution for 1–2 min. The colors formed by various substituted benzoquinones are listed in Table I.

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(8) F. R. Koniuszy, P. H. Gale, A. C. Page, Jr., and K. Folkers, *Arch. Biochem. and Biophys., in press.*

The Preparation of C^{14}-Labeled Spermine and C^{14}-Labeled Spermidine

E. L. JACKSON AND S. M. ROSENTHAL

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The reaction of acrylonitrile with putrescine to produce *N,N'*-bis(2-cyanoethyl)putrescine (I) and catalytic reduction of this nitrile to yield spermine (II) has been reported by Schultz.[1] Spermidine (III) was not obtained in this process by Schultz. The method has been adapted by us to the small-scale preparation, in one operation, of both C^{14}-labeled spermine and C^{14}-labeled spermidine. The cyanoethylation of putrescine-1-C^{14} with the use of nonisotopic acrylonitrile was carried out in ethanol solution. Reduction of the products, without isolation, by Raney nickel and hydrogen at 136–142° and 4700 p.s.i. yielded spermine and spermidine labeled with C^{14} in the putrescine moiety. The spermine and spermidine were separated chromatographically. Application of the procedure to the products of the cyanoethylation of nonisotopic putrescine by acrylonitrile-1-C^{14} afforded spermine and spermidine labeled with C^{14} in the propylamine moiety. The production of spermidine in this way may be due to the presence of its parent nitrile[2] (IV) among the products of the cyanoethylation of putrescine. As the reaction of acrylonitrile with amines is reversible,[3] the spermidine also could owe its origin to the partial dissociation of *N,N'*-bis-(2-cyanoethyl)putrescine to form IV; such a dissociation would be promoted by the elevated reduction temperature.

$$NC(CH_2)_2NH(CH_2)_4NH(CH_2)_2CN \quad (I)$$

$$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2 \quad (II)$$

$$H_2N(CH_2)_4NH(CH_2)_3NH_2 \quad (III)$$

$$H_2N(CH_2)_4NH(CH_2)_2CN \quad (IV)$$

EXPERIMENTAL

Spermine and spermidine from putrescine-1-C^{14} and acrylonitrile. To a suspension of 223 mg. of putrescine-1-C^{14} dihydrochloride[4] (1.38 mmoles) in 2 ml. of absolute ethanol was added 1.44 ml. of 1.92*N* sodium hydroxide which gave a solution of putrescine-1-C^{14} base. A solution of 164 mg. of nonisotopic acrylonitrile (3.09 mmoles) in 2 ml. of absolute ethanol was mixed with the putrescine-1-C^{14} solution. After being shaken for 5 min., the solution was kept at room temperature for 18 hr. It was diluted with 1 ml. of absolute ethanol, then refluxed for 1 hr. and kept at room temperature for 2 hr. The solution was transferred to a hydrogenation bomb and mixed with *ca.* 0.3 g. of Raney nickel catalyst and 20 ml. of absolute ethanol which had been saturated with ammonia at 20–23°. The mixture was shaken with hydrogen at 136–142° and 4700 p.s.i. for 30 min. The catalyst was filtered and washed thoroughly with absolute ethanol. Nearly all of the solvent was evaporated, with the use of a column, on the steam bath and the residue was neutralized to *p*H 7.0 with hydrochloric acid. Chromatographic separation of the spermidine and spermine was carried out upon Dowex 50 resin (2% cross linked, 100–200 mesh) in the hydrogen form. A column 24 × 1.5 cm. inside diameter was employed with gradient chromatography[4] using 300 ml. of water in the mixing flask and 2.5*N* hydrochloric acid in the reservoir. Spermidine appeared in the eluate between 344 and 468 ml. Spermine was eluted between 484 and 650 ml. These fractions were evaporated to dryness *in vacuo* over potassium hydroxide, and each was subjected to a second chromatography. The yields were 115 mg. (0.45 mmole) of spermidine trihydrochloride (0.034 μc per μ mole) and 114 mg. (0.33 mmole) of spermine tetrahydrochloride (0.034 μc per μ mole). The specific activity of the starting putrescine-1-C^{14} dihydrochloride was 0.034 μc per μ mole.

The above radioactive spermidine trihydrochloride and spermine tetrahydrochloride were found to be contaminated with small amounts of unknown material, and required further purification. An aliquot of the spermidine hydrochloride was recrystallized by dissolving it in a minimum quantity of absolute methanol, acidifying the solution with ethanolic hydrochloric acid, adding an equal volume of ethanol, and then adding ethyl acetate dropwise until precipitation occurred. After standing overnight at 5°, the precipitate was collected by centrifugation. The spermine was recrystallized by dissolving the hydrochloride in 1 ml. of water and adding a slight excess of 1*M* sodium phosphate solution of *p*H 7.2. On standing overnight at 5° spermine phosphate crystallized.

For identification of spermidine and spermine, the compounds were prepared as described with the use of nonisotopic putrescine dihydrochloride and acrylonitrile. An aqueous solution of the spermidine trihydrochloride from the column was treated with a few drops of 37% hydrochloric acid, then concentrated to a small volume and diluted with ethanol to start crystallization; m.p. 257–258° (uncorr.). The crystals showed an infrared spectrum identical with that of authentic spermidine trihydrochloride.

Anal. Calcd. for $C_7H_{22}Cl_3N_3$: C, 33.01; H, 8.71; Cl, 41.77; N, 16.50. Found (dried at 100° *in vacuo*): C, 33.30; H, 8.60; Cl, 41.85; N, 16.78.

The spermine tetrahydrochloride was thrice recrystallized from a mixture of 12% hydrochloric acid and ethanol. The infrared spectrum of these crystals was identical with that of authentic spermine tetrahydrochloride.

(1) H. P. Schultz, *J. Am. Chem. Soc.*, **70**, 2666 (1948).
(2) See O. Bayer, *Angew. Chem.*, **61**, 235 (1949).
(3) F. C. Whitmore, *et al.*, *J. Am. Chem. Soc.*, **66**, 725 (1944).
(4) H. Tabor, S. M. Rosenthal, and C. W. Tabor, *J. Biol. Chem.*, **233**, 907 (1958).

Anal. Calcd. for $C_{10}H_{30}Cl_4N_4$: C, 34.49; H, 8.68; Cl, 40.73; N, 16.09. Found (dried at 100° *in vacuo*): C, 34.50; H, 8.68; Cl, 40.56; N, 16.11.

Spermine and spermidine from putrescine and acrylonitrile-1-C^{14}. In a 25-ml. flask were mixed 278 mg. of nonisotopic putrescine dihydrochloride (1.7 mmoles), 5 ml. of absolute ethanol, and 1.59 ml. of 2.17*N* sodium hydroxide solution. Into this mixture was distilled, under high vacuum at room temperature, 204 mg. (3.8 mmoles) of acrylonitrile-1-C^{14}; the flask then was sealed under vacuum.[5] After *ca.* 44 hr. the solution was refluxed and treated by the above described procedure for the preparation of radioactive spermidine and spermine from putrescine-1-C^{14}. The yields were 116 mg. (0.46 mmole) of spermidine trihydrochloride showing 0.30 μc per μ mole and 221 mg. (0.64 mmole) of spermine tetrahydrochloride showing 0.60 μc per μ mole. These compounds contained small amounts of unknown material and were purified further as described for the products obtained from putrescine-1-C^{14}.

Acknowledgement. We express our thanks to Dr. H. Tabor for the gift of the putrescine-1-C^{14}, to Dr. W. C. Alford and his associates for the microanalyses, and to Mr. William Jones and Mr. H. K. Miller for the infrared spectra.

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(5) The acrylonitrile-1-C^{14} was prepared and mixed immediately after synthesis with the putrescine solution by Dr. S. Rothschild of Tracerlab, Inc., Boston, Massachusetts. The specific activity was approximately 0.26 μc per mmole.

Steroids. CXLIV.[1] Synthesis of Some 6α,17α-Dihaloprogesterones[2]

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Recent work in our laboratory[3] has demonstrated the potentiating effect upon progestational activity when a 6α-halogen atom is introduced into the progesterone molecule, notably of 17α-acetoxyprogesterone. As Engel and Jahnke[4] had observed that 17α-bromoprogesterone has about double the progestational activity of progesterone, it appeared of interest to synthesize certain progesterone analogs possessing halogen atoms at C-6 as well as C-17 and to subject them to biological assay.

For the synthesis of 6α-fluoro-17α-bromoprogesterone (VI) we selected a route patterned closely after the earlier described[5] preparation of 6α-fluoroprogesterone. 17α-Bromo-Δ^5-pregnen-3β-ol-20-one (II)[4,6] was transformed into its 5α,6α-epoxide III, which was opened to the fluorohydrin IV through the intervention of boron trifluoride.[5,7] Oxidation at C-3 by means of chromium trixide in acetone solution[8] afforded the ketone V, whose dehydration with inversion at C-6 to 6α-fluoro-17α-bromoprogesterone (VI) was accomplished with hydrogen chloride in acetic acid.

The synthesis of 6α-chloro-17α-bromoprogesterone (XI) commenced with 17α-bromo-Δ^5-pregnen-3β-ol-20-one acetate (I),[6] which was chlorinated in carbon tetrachloride solution to the 3β-acetoxy-5α,6β-dichloride, VII. The acetoxy group was removed by exposure to hydrochloric acid and the 3β-hydroxy-5α,6β-dichloride (VIII) was oxidized[8] to 5α,6β-dichloro-17α-bromopregnane-3,20-dione (IX). Heating with ethanolic sodium acetate solution caused dehydrochlorination without inversion at C-6 to yield 6β-chloro-17α-bromoprogesterone (X), while the desired 6α-chloro-17α-bromoprogesterone (XI) was obtained by treatment of IX with hydrogen chloride in acetic acid solution.

A closely related reaction sequence was employed for 6α,17α-dichloroprogesterone (XVII). The enol diacetate XII[9] of Δ^5-pregnen-3β-ol-20-one was chlorinated to 5α,6β,17α-trichloropregnan-3β-ol-20-one acetate (XIII),[10] the 3-acetoxy group removed and the 3β-ol XIV oxidized with chromium trioxide.[8] Treatment of the resulting 5α,6β,17α-trichloropregnane-3,20-dione (XV) with sodium acetate led to 6β,17α-dichloroprogesterone (XVI), while exposure of XV to hydrogen chloride in acetic acid furnished directly the required 6α,17α-dichloroprogesterone (XVII).

Bioassays[11] in the rabbit showed that 6α-chloro-17α-bromoprogesterone (XI) and 6α,17α-dichloroprogesterone (XVII) possessed approximately 20% the oral progestational activity of Norlutin[12] (19-nor-17α-ethynyltestosterone).

(1) Paper CXLIII, A. Bowers and E. Denot, *J. Am. Chem. Soc.*, in press.

(2) Taken from the professional thesis of O. Candiani, submitted to the Instituto Politécnico Nacional, Mexico, D.F.

(3) H. J. Ringold, E. Batres, A. Bowers, J. Edwards, and J. Zderic, *J. Am. Chem. Soc.*, **81**, 3485 (1959).

(4) Ch. R. Engel and H. Jahnke, *Can. J. Biochem. and Physiol.*, **35**, 1047 (1957).

(5) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958).

(6) P. L. Julian and W. J. Karpel, *J. Am. Chem. Soc.*, **72**, 362 (1950).

(7) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4765 (1957).

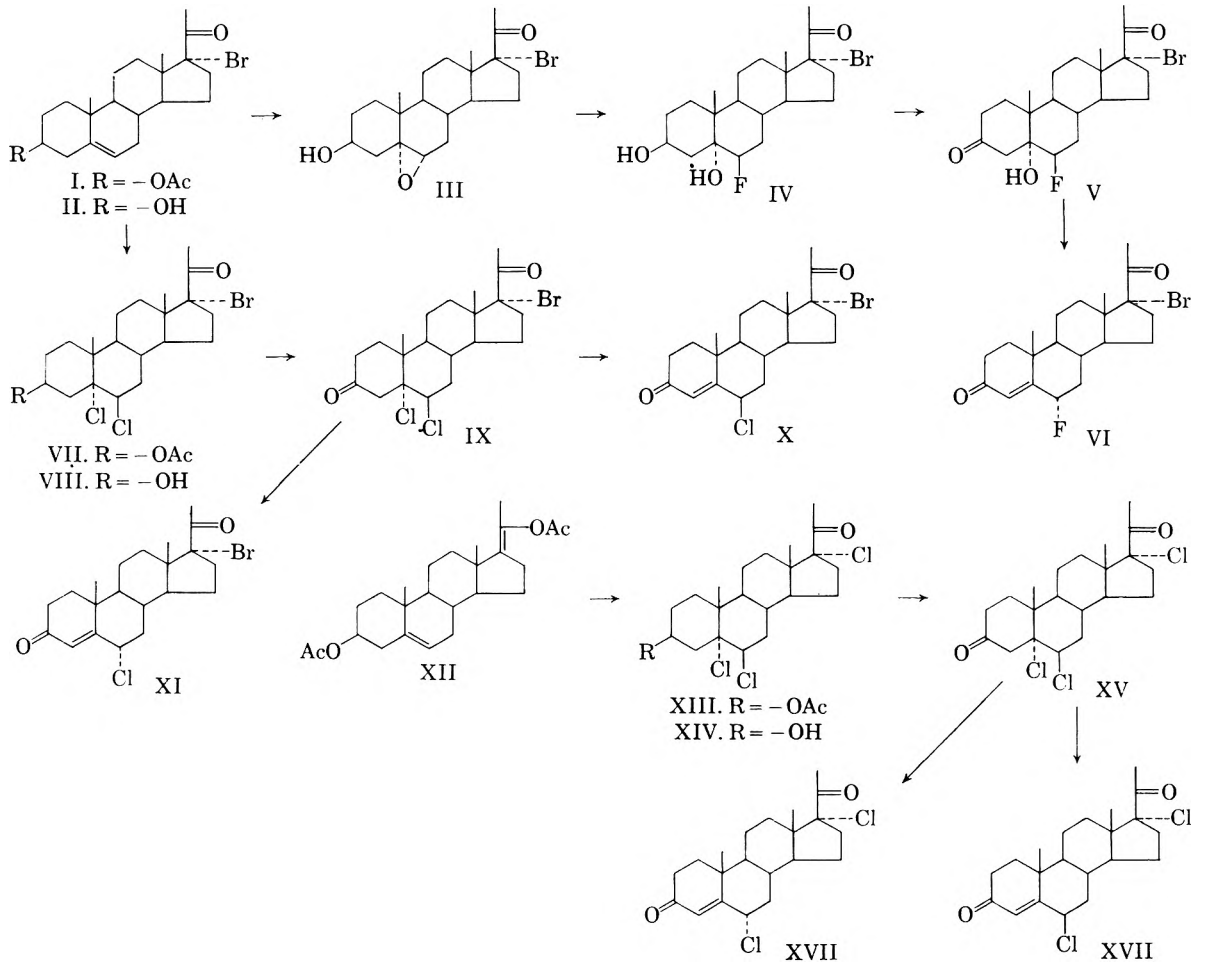
(8) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(9) L. F. Fieser and Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 1840 (1949).

(10) The 17α orientation of the chlorine atom is confirmed by the negative Cotton effect of its rotatory dispersion curve (see C. Djerassi, I. Fornaguera, and O. Mancera, *J. Am. Chem. Soc.*, **81**, 2383 (1959).

(11) Assays by Endocrine Laboratories, Madison, Wisconsin.

(12) See D. A. McGinty and C. Djerassi, *Ann. N. Y. Acad. Sci.*, **71**, 500 (1958).



EXPERIMENTAL[13]

5α,6α-Oxido-17α-bromopregnan-3β-ol-20-one (III). 17α-Bromo-Δ⁵-pregnen-3β-ol 20-one (II)[4] (17 g.) in chloroform (140 cc.) was treated at −50° with a solution of perphthalic acid in ether (89 cc. · 1.16*N*). After 2 hr. at this temperature the mixture was kept for 16 hr. at 0°. The solution was diluted with chloroform and washed with water, aqueous sodium carbonate, and again with water, dried, and evaporated. Crystallization from acetone-hexane gave 6.3 g. of the epoxide III, m.p. 163–166°. The analytical sample melted at 170–171°, $[\alpha]_D$ −92°.

Anal. Calcd. for $C_{21}H_{31}BrO_3$: C, 61.29; H, 7.59; Br, 19.43; O, 11.66. Found: C, 61.25; H, 7.84; Br, 19.49; O, 11.75.

6β-Fluoro-17α-bromopregnane-3β,5α-diol-20-one (IV). The preceding epoxide (3 g.) in dry ether-benzene (1:1; 300 cc.) was treated with boron trifluoride etherate (3 cc.) at room temperature for 20 hr. The solution was washed with aqueous sodium carbonate solution and water, dried, and evaporated and the resulting oil chromatographed on 90 g. of alumina. Elution with ether afforded the fluorohydrin (IV) which was crystallized from acetone-hexane, m.p. 176–177° (600 mg.). The analytical sample melted at 182–183°, $[\alpha]_D$ −57°.

Anal. Calcd. for $C_{21}H_{32}BrFO_3$: C, 58.46; H, 7.47; Br, 18.52; F, 4.40. Found: C, 58.48; H, 7.55; Br, 18.68; F, 4.24.

(13) Melting points are uncorrected and were determined on the Fisher Johns block. All physical measurements were performed under the direction of Dr. L. Throop. The microanalyses are due to Dr. A. Bernhardt, Mülheim, Germany. All rotations were measured in chloroform solution.

6α-Fluoro-17α-bromoprogesterone (VI). The fluorohydrin (IV; 600 mg.) in acetone (15 cc.) was treated dropwise with a slight excess of 8*N* chromium trioxide–sulfuric acid solution[8] at 0° and the product precipitated with ice water and filtered to give 570 mg. of crude V, m.p. 186–188°. This was dissolved in glacial acetic acid (25 cc.) and the solution was saturated with dry hydrogen chloride gas at 10°. After 6 hr. at this temperature the solution was poured into aqueous sodium acetate solution and filtered to give 380 mg. of crude 6α-fluoro-17α-bromoprogesterone (VI) with $\lambda_{max}^{C_2H_5OH}$ 236 mμ, log ε 4.13. Two crystallizations from aqueous acetone afforded an analytical sample, m.p. 180–181°, $[\alpha]_D$ +12°, $\lambda_{max}^{C_2H_5OH}$ 236 mμ, log ε 4.20.

Anal. Calcd. for $C_{21}H_{28}BrFO_2$: C, 61.31; H, 6.85; Br, 19.43. Found: C, 61.61; H, 7.22; Br, 19.70.

5α,6β-Dichloro-17α-bromopregnan-3β-ol-20-one acetate (VII). To a solution of 17α-bromo-Δ⁵-pregnen-3β-ol-20-one acetate (I)[6] (3.5 g.) in carbon tetrachloride (50 ml.) and pyridine (1 ml.) cooled in Dry Ice–ethanol was added a solution of chlorine in carbon tetrachloride (10 ml.; 6.8%, 1.1 equiv.). When the color had disappeared, the solution was evaporated to dryness *in vacuo* and the resulting oil crystallized from methylene chloride–methanol to yield VII (2.5 g.), m.p. 173–178°. Recrystallization from the same solvents and from acetone-hexane afforded an analytical sample, m.p. 185–186°, $[\alpha]_D$ −79°.

Anal. Calcd. for $C_{23}H_{33}BrCl_2O_3$: C, 54.34; H, 6.54; Br, 15.72; Cl, 13.45; O, 9.44. Found: C, 53.94; H, 6.43; Br, 16.15; Cl, 14.09; O, 9.84.

5α,6β-Dichloro-17α-bromopregnan-3β-ol-20-one (VIII). The preceding compound (3.75 g.), dissolved in dioxane-methanol (1:1; 120 ml.), was treated with concd. hydrochloric acid (4.5 ml.) and the solution allowed to stand at room

temperature for 20 hr. The product was precipitated with water, filtered, and crystallized from methanol to give (VIII) (2.6 g.), m.p. 100–115° (bubbling). The analytical sample melted at 114–116° (after drying *in vacuo*) $[\alpha]_D$ −74°.

Anal. Calcd. for $C_{21}H_{31}BrCl_2O_2$: C, 54.09; H, 6.70; Br, 17.14; Cl, 15.21. Found: C, 53.98; H, 6.76; Br, 17.91; Cl, 14.68.

5α,6β-Dichloro-17α-bromopregnane-3,20-dione (IX). The preceding compound (2.26 g.) in acetone (60 ml.) was treated at 0° with a slight excess of 8*N* chromium trioxide–sulfuric acid solution and the product precipitated by the addition of ice water. Crystallization from methanol gave the 3-ketone (IX) (1.6 g.), m.p. 158–161°. The analytical sample melted at 161–162°, $[\alpha]_D$ −85°.

Anal. Calcd. for $C_{21}H_{29}BrCl_2O_2$: C, 54.32; H, 6.29; Br, 17.21; Cl, 15.27; O, 6.89. Found: C, 54.71; H, 6.09; Br, 17.29; Cl, 15.40; O, 6.75.

6β-Chloro-17α-bromoprogesterone (X). The preceding compound (500 mg.) in absolute ethanol (40 ml.) was refluxed with fused sodium acetate (1.2 g.) for 1.5 hr. Part of the solvent was evaporated and the product precipitated with ice water. Crystallization from aqueous acetone gave 6β-chloro-17α-bromoprogesterone (X) (103 mg.), m.p. 145–148°. The analytical sample melted at 154–155°, $[\alpha]_D$ −48°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ, log ε 4.12.

Anal. Calcd. for $C_{21}H_{28}BrClO_2$: C, 58.91; H, 6.59; Br, 18.66; Cl, 8.24; O, 7.48. Found: C, 58.85; H, 6.69; Br, 18.41; Cl, 8.04; O, 7.61.

6α Chloro-17α-bromoprogesterone (XI). 5α,6β-Dichloro-17α-bromopregnane-3,20-dione (IX) (400 mg.) in glacial acetic acid (25 ml.) was treated with dry hydrogen chloride gas at 10° for 2 hr. Precipitation with water and filtration gave 320 mg. of crude product, $\lambda_{max}^{C_2H_5OH}$ 236–238 mμ, log ε 4.13. Crystallization from aqueous acetone gave an analytical sample of 6α-chloro-17α-bromoprogesterone, m.p. 157–158°, $[\alpha]_D$ +14°, $\lambda_{max}^{C_2H_5OH}$ 236 mμ, log ε 4.16.

Anal. Calcd. for $C_{21}H_{28}BrClO_2$: C, 58.91; H, 6.59; Br, 18.66; Cl, 8.24; O, 7.48. Found: C, 58.65; H, 6.44; Br, 18.38; Cl, 7.81; O, 7.34.

5α,6β,17α-Trichloropregnan-3β-ol-20-one acetate (XIII). To a solution of the crude enol acetate XII[3] (3 g.) in carbon tetrachloride (15 ml.) at 0° was added a solution of chlorine in carbon tetrachloride (1%; 120 ml.) during 5 min. After a further 10 min., the solution was washed with cold 5% sodium carbonate solution and water, dried, and evaporated *in vacuo*. The resulting oil was chromatographed on 90 g. of neutral alumina. Elution with hexane-benzene (1:1) gave material which on crystallization from methylene chloride–methanol afforded 5α,6β,17α-trichloropregnan-3β-ol-20-one acetate (XIII) (711 mg.), m.p. 175–180°. Recrystallization gave an analytical sample, m.p. 194–195°, $[\alpha]_D$ −70°.

Anal. Calcd. for $C_{23}H_{33}Cl_3O_3$: C, 59.54; H, 7.17; Cl, 22.95; O, 10.34. Found: C, 58.97; H, 7.26; Cl, 23.22; O, 10.46.

5α,6β,17α-Trichloropregnan-3β-ol-20-one (XIV). The trichloroacetate XIII (2.6 g.) dissolved in dioxane-methanol (1:1; 50 ml.) was treated with concd. hydrochloric acid (4 ml.) and allowed to stand at 25°, for 24 hr. The product was precipitated with ice water, filtered, and crystallized from methylene chloride–methanol, yielding the trichloroalcohol XIV (2.15 g.), double m.p. 92° and 152–156°. The analytical sample melted at 92° and 164–165°, $[\alpha]_D$ −67°.

Anal. Calcd. for $C_{21}H_{31}Cl_3O_2$: C, 59.78; H, 7.41; Cl, 25.23. Found: C, 60.28; H, 7.47; Cl, 25.30.

5α,6β,17α-Trichloropregnane-3,20-dione (XV). The foregoing compound (1.2 g.) in acetone (30 ml.) was treated at 0° with a slight excess of 8*N* chromium trioxide–sulfuric acid. The product started to crystallize and ice water was added and the material filtered to yield the 3-ketone XV (1 g.), m.p. 161–163°. Recrystallization from aqueous acetone gave the analytical sample, m.p. 171–172°, $[\alpha]_L$ −60.5°.

Anal. Calcd. for $C_{21}H_{29}Cl_3O_2$: C, 60.08; H, 6.76; O, 7.62. Found: C, 59.90; H, 6.98; O, 7.46.

6β,17α-Dichloroprogesterone (XVI). 5α,6β,17α-Trichloropregnane-3,20-dione (500 mg.) was refluxed in absolute ethanol (40 ml.) with fused sodium acetate (1.2 g.) for 90 min. Precipitation with water and filtration gave an amorphous material with $\lambda_{max}^{C_2H_5OH}$ 240 mμ, log ε 3.90, which was chromatographed on 15 g. of neutral alumina. Elution with benzene and crystallization from aqueous acetone gave 6β,17α-dichloroprogesterone (180 mg.), m.p. 182–185°. Two further crystallizations gave material of m.p. 192–193°, $[\alpha]_D$ −30°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ, log ε 4.12.

Anal. Calcd. for $C_{21}H_{28}Cl_2O_2$: C, 65.79; H, 7.36; Cl, 18.50; O, 8.35. Found, C, 65.46; H, 7.50, Cl, 18.62; O, 8.54.

6α,17α-Dichloroprogesterone (XVII). 5α,6β,17α-Trichloropregnane-3,20-dione (700 mg.) in glacial acetic acid (50 ml.) was treated at 0° with a stream of dry hydrogen chloride gas for 2 hr. The product was precipitated with ice-water and collected. Chromatography over 20 g. of alumina elution with benzene, and crystallization from aqueous acetone yielded 6α,17α-dichloroprogesterone (310 mg.), m.p. 160–162°. Recrystallization gave material of m.p. 165–166°, $[\alpha]_D$ +29°, $\lambda_{max}^{C_2H_5OH}$ 236 mμ, log ε 4.16.

Anal. Calcd. for $C_{21}H_{28}Cl_2O_2$: C, 65.79; H, 7.36; Cl, 18.50; O, 8.35. Found: C, 65.80; H, 7.46; Cl, 18.31, O, 8.26.

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The Preparation of 19-Nortestosterone-17-propionate

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Received December 9, 1959

Among the various esters of 19-nortestosterone (I) the 17-propionate (II) has been proved to be biologically the most efficient.[1,2] It has been shown previously that attempts to prepare II with propionyl chloride or propionic anhydride gave mixtures of mono and di (enol) propionates *even at room temperature*.[3] In contrast, the preparation of II was recorded in a patent[4] by first heating a solution of I in pyridine and propionic anhydride for three hours at 75° and then for sixteen hours at room temperature. In another patent[5] the preparation of II was mentioned using propionic anhydride and pyridine without giving any physical constants of II. However, a suitable method has been worked out in these laboratories to prepare II in excellent

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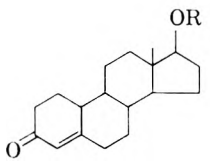
(3) A. L. Wilds and Norman A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

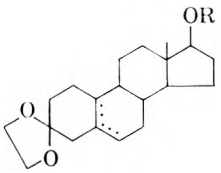
(4) R. A. Donis and A. C. Ott, U. S. Patent **2,798,879**; *Chem. Abstr.*, **51**, 15621a (1957).

(5) C. Djerassi, F. Sondheimer, and G. Rosenkranz, U. S. Patent **2,756,244**; *Chem. Abstr.*, **51**, 5852g (1957).

yield. The enolizable 3-keto function in 19-nortestosterone was first protected by the formation of 3-ethylenedioxy derivative (III).[6] The ethylenedioxy derivative (III) without further purification was treated with pyridine and propionic anhydride at room temperature to give 3-ethylenedioxy-19-nortestosterone-17-propionate (IV). The ethylenedioxy group from IV was then removed by acid-catalyzed exchange with acetone to give 19-nortestosterone-17-propionate (II). The overall yield of II without isolating the intermediates is 90–95%.



I. R = H
II. R = $OC.CH_2CH_3$



III. R = H
IV. R = $OC.CH_2CH_3$

EXPERIMENTAL

3-Ethylenedioxy-19-nortestosterone-17-propionate (III). A mixture of 19-nortestosterone (7 g.) benzene (525 ml.) ethylene glycol (52 ml.) and *p*-toluenesulfonic acid monohydrate (0.35 g.) was heated under reflux with stirring in a modified Dean-Stark phase separator until no more water phase separated (*ca.* 20–24 hr.). At the completion of this step the solution was washed with aqueous sodium bicarbonate, and then with water until neutral, and the solvent was then removed under reduced pressure under a stream of nitrogen. 3-Ethylenedioxy-19-nortestosterone (III) (8.3 g.) was obtained as a gum. Without further purification this was dissolved in pyridine (20 ml.) and propionic anhydride (8 ml.) was added and kept at room temperature for 18 hr. The excess pyridine was then removed under reduced pressure in a stream of nitrogen and the residue was dissolved in ether. The ether extract was washed with sodium bicarbonate solution, and then with water until neutral, and dried over sodium sulfate. After evaporating the solvent 3-ethylenedioxy-19-nortestosterone-17-propionate (IV) (10 g.) was obtained as a solid and no further purification was attempted.

19-Nortestosterone-17-propionate (II). The above solid (10 g.) was dissolved in anhydrous acetone (150 ml.) and *p*-toluenesulfonic acid monohydrate (0.4 g.) was added and the contents heated under reflux for 14 hr. After this time the reaction mixture was concentrated to a small volume (20 ml.) and then diluted with water. The precipitated 19-nortestosterone-17-propionate (8.3 g.) was filtered and washed with sodium bicarbonate solution and then with water until the washings were neutral.

This product melted at 60–65°. On further recrystallization from aqueous methanol, II was obtained with water of crystallization and melted at 71–73°. A sample dried in high vacuum over phosphorus pentoxide for 20 hr. at 35° melted at 50–51° and still contained half a molecule of water of crystallization. $[\alpha]_D^{23.5}$ +58.0° (in chloroform): $\lambda_{max}^{methanol}$ 240 mμ, ϵ = 17,280; ν_{max}^{KBr} 1727, 1668, and 1613 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{30}O_3$,$^1/_2H_2O$ (339.45): C, 74.29; H, 9.20. Found: C, 74.56; H, 9.09.

Acknowledgment. I wish to express my appreciation to Dr. L. R. Axelrod for his interest and encouragement throughout this investigation. This work was supported by a Grant from the Wyeth Laboratories.

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(6) J. A. Zderic, D. C. Limon, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, 81, 3120 (1959).

Bisammonium Salts Related to 1,10-Decamethylenebisatropinium Diiodide[1,2]

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Received August 17, 1959

Studies concerned with the preparation of synthetic muscle paralyzing agents have often focused on structures in which two quaternary nitrogens are approximately 15 Å apart.[5,6] This distance corresponds to a methylene chain containing ten carbon atoms.

One of the more interesting compounds resulting from this approach is 1,10-decamethylenebisatropinium diiodide[7] (ID) which, in the rabbit, exhibited curariform activity twice that of *d*-tubocurarine (DTC) with a greater margin of safety. Unfortunately, this compound also possessed atropine-like activity greater than that of atropine itself and thus was unsatisfactory as a muscle paralyzing agent.

The potential pharmacological interest of this type of compound prompted an investigation into possible structural modifications which involved: 1) the removal of the two-carbon bridge between atoms 1 and 5 of the tropane ring system (Table I) to give the simpler piperidine system (Table II); 2) the substitution on the nitrogen atom; and 3) variations in the substituents on carbon 4 of the piperidine ring

The tropane series. (Table I). Except for homatropine, which was commercially available, the tropane derivatives were obtained through the intermediate tropinone[8] which was prepared by

(1) Presented in part at the 129th Meeting of the American Chemical Society, Dallas, April 1956.

(2) Taken in part from a dissertation submitted by Samuel I. Trotz in partial fulfillment of requirements for the degree of Doctor of Philosophy, Saint Louis University, 1956. Supported in part by Grant #44 from the American Medical Association Council on Pharmacy and Chemistry.

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(6) W. D. M. Paton and E. J. Zaimis, *Nature*, 162, 810 (1949).

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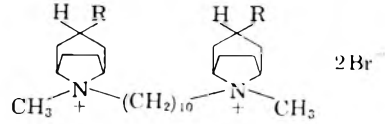
TABLE I

BISQUATERNARY AMMONIUM DERIVATIVES IN THE TROPANE SERIES

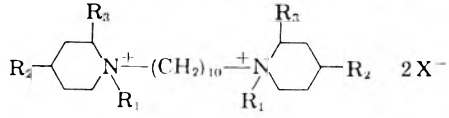


Compd.	R	Method	Reaction Time, Hr.	M.P.°	Yield, %	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Bromine Calcd.	Bromine Found	Frog, MPD[a] Mg./kg.
IA	OH	A	4	277–277.5	60	$C_{26}H_{50}Br_2N_2O_2$	53.61	53.89	8.65	8.52	27.4	27.1	60
IB	C_6H_5CO	B	1.5	272	50	$C_{40}H_{58}Br_2N_2O_4$	60.76	60.67	7.39	7.64	20.2	20.0	15
IC	$C_6H_5CHOHCO_2$	B	1.5	222	21	$C_{42}H_{62}Br_2N_2O_6$	59.29	59.23	7.35	7.15	18.8	18.7	20
ID[b]	$C_6H_5CH(CH_2OH)CO_2$												8
d-Tubocurarine (DTC)													2

[a] MPD—minimum paralyzing dose (lymph-sac injection). [b] 1,10-Decamethylenebisatropinium diiodide, Ref. 7.

TABLE II

DIQUATERNARY AMMONIUM DERIVATIVES IN THE PIPERIDINE SERIES



Compd.	R_1	R_2	R_3	X	Method	Reaction Time, Hr.	M.P.°	Yield, %	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found	Frog, MPD[a] Mg./kg.
IIA	CH_3	H	H	Br	A	22	252–254	76	$C_{22}H_{46}Br_2N_2$	53.01	53.19	9.30	9.21	32.1	31.8	60
IIB	C_2H_5	H	H	Br	A	24	243	80	$C_{24}H_{50}Br_2N_2$	54.75	55.09	9.57	9.68	30.4	30.4	80
IIC	$C_6H_5CH_2$	H	H	I	A	24	195	16	$C_{34}H_{54}I_2N_2$	54.84	55.08	7.31	7.40	34.1	33.7	9
IID	CH_3	H	CH_3	I	C	17	258–259	75	$C_{24}H_{50}I_2N_2$	46.46	46.47	8.12	7.90	40.9	40.6	80
IIE	CH_3	H	C_2H_5	I	C	22	250–250.5	70	$C_{26}H_{54}I_2N_2$	48.15	48.39	8.39	8.36	39.1	39.1	60
IIF	CH_3	OH	H	Br	B	14	246	75	$C_{22}H_{46}Br_2N_2O_2$	49.81	49.95	8.74	8.79	30.1	30.1	80
IIG	$C_6H_5CH_2$	OH	H	I	A	24	203.5–204.5	40	$C_{34}H_{54}I_2N_2O_2$	52.58	52.69	7.01	7.19	32.7	32.2	20
IIH	CH_3	$C_6H_5CO_2$	H	Br	A	17	235–236.5	75	$C_{36}H_{54}Br_2N_2O_4$	58.53	58.98	7.37	7.31	21.6	21.5	10
1,10-Decamethylenebisatrophinium diiodide (IID)[b]																8
d-Tubocurarine (DTC)																2

[a] MPD—minimum paralyzing dose (lymph-sac injection). [b] Ref. 7.

the alkaline condensation of succinaldehyde, methyl amine, and acetonedicarboxylic acid. Tropinone was reduced catalytically to tropine.[8] Benzoyltropine hydrochloride[9] was prepared by the reaction of tropine and benzoyl chloride. Bistropinium derivatives were synthesized by the reaction of 1,10-dibromodecane with the appropriately substituted tropane derivative both in the presence and absence of solvent.

The Piperidine Series. (Table II). The *N*-alkyl substituted piperidines were readily available and 2-alkyl piperidines were prepared by catalytic hydrogenation of the corresponding pyridine analogs. 4-Hydroxy-1-methyl piperidine was prepared by decarboxylation and reduction of *N*-methylchelidamic acid (from chelidonic acid and methylamine) according to the method of Mills.[10] 4-Hydroxy-1-benzyl piperidine[11] was prepared by the base catalyzed self-condensation of benzyldi(β-carbethoxyethyl)-amine to *N*-benzyl-3-carbethoxy piperidone-4, followed by hydrolysis, decarboxylation and reduction. 1-Methyl-4-piperidyl benzoate was prepared by treating 4-hydroxy-1-methyl piperidine hydrochloride[12] with benzoyl chloride and liberating the free base with sodium carbonate.

The diammonium compounds of this series were prepared by the reaction of tertiary heterocyclic amines with a 1,10-dihalodecane in the presence (Method A) or absence of solvent (Method B) or by formation of an intermediate 1,10-dipiperidino decane (from 1,10-dibromodecane and a secondary heterocyclic amine) followed by quaternization with an alkyl halide (Method C).

The yields of the crude quaternary ammonium compounds were satisfactory except in the cases of the *N*-benzyl substituted compounds. The products were usually recrystallized from ethanol-ether solutions although a few compounds were isolated more readily from methanol-ether or isopropanol-ether solutions. The products were high melting, soluble in water and alcohols and insoluble in ether. Many were hygroscopic in crude form, but were usually easy to handle when pure. Attempts to synthesize the diquaternary salt of 1-benzyl-4-piperidyl benzoate were unsuccessful.

Pradhan and co-workers[13] have published on the curariform potency of three of the bisammonium compounds (IIA, IIB, and IIC) in the dog. In each case, however, different halide salts than those used here were reported.

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(12) N. W. Bolyard and S. M. McElvain, *J. Am. Chem. Soc.*, **51**, 922 (1929).

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PHARMACOLOGICAL RESULTS

All quaternary ammonium salts were screened for paralyzing activity in frogs (*Rana pipiens*) by lymph sac injections to obtain the minimum paralyzing dose (MPD). Paralyzed frogs were checked for specificity of muscle paralysis at the neuromyal junction by direct and indirect stimulation of the sciatic nerve. The MPD of the compounds tested varied from 9 to 80 mg./kg.

The ethylene bridge of the atropine moiety did not contribute significantly to curariform activity. Little change in activity was noted in comparing compounds which differed only by the presence or absence of the bridge; *i.e.*, IA and IIF or IB and IIH. An open model of the tropane ring, IIE, had the same activity as the unsubstituted piperidine ring, IIA.

Variation of the alkyl substituents on the nitrogen atoms had little effect except when the benzyl group was attached. The benzyl group imparted a large increase in activity to similar structures; *i.e.*, IIA and IIC or IIF and IIG.

The ester group on carbon atom 4 of the piperidine nucleus appeared to contribute in large measure to curare-like activity in these series. A complete pharmacological report will be presented elsewhere.

EXPERIMENTAL[14]

N-Alkylpiperidines. *N*-Methyl piperidine was prepared by the reaction of formaldehyde and formic acid with piperidine.[15] *N*-Ethyl piperidine was purchased from Distillation Products Industries. *N*-Benzyl piperidine[16] was prepared by treating benzyl chloride with piperidine.

2-Alkylpiperidines. Both 2-methyl- and 2-ethylpiperidine were prepared by the low pressure hydrogenation[17] of the corresponding commercially available pyridines.

1,10-Di(2-alkylpiperidino)decanes. In a 50-ml. round-bottom flask 3 g. (0.01 mole) of 1,10-dibromodecane was mixed with 0.06 mole of the appropriate 2-alkylpiperidine and 10 ml. of reagent grade benzene. The mixture was refluxed on a steam bath until no more hydrobromide of the substituted piperidine appeared to form. All solid material was filtered off and the excess starting compounds were removed by vacuum distillation. The residual oils would not solidify or yield solid hydrochlorides and were identified as their methiodides, IID and IIE.

1,10-Diquaternary salts. The diquaternary salts of the appropriately substituted 1,10-dipiperidinodecanes and the 1,10-decamethylenebistropines were prepared in one of three ways.

Method A. In 10 ml. of absolute ethanol, 0.025 mole of an *N*-alkyl substituted heterocyclic amine and 0.11 mole of a 1,10-dihalodecane were refluxed for 4 to 24 hr. Crystallization of the product usually occurred as the solvent was removed under reduced pressure.

(14) Analyses for carbon and hydrogen were determined by Clark Microanalytical Laboratories, Urbana, Ill. All melting points are corrected.

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Method B. The *N*-alkyl substituted heterocyclic amine (0.01 mole) was mixed with 0.005 mole of a 1,10-dihalodecane and heated on a steam bath without solvent for from 1.5 to 14 hr. The solid which resulted was recrystallized from absolute alcohol.

Method C. The appropriately substituted 1,10-dipiperidinodecane (0.005 mole) was refluxed with 0.1 mole of methyl iodide in 10 ml. of absolute ethanol for from 17 to 22 hr. The solids produced were recrystallized from ethanol or isopropyl alcohol to a constant melting point.

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Formation of Isomaltulose in Enzymatic Dextran Synthesis

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During a study of the formation of dextran from sucrose, using enzyme preparations from the bacterium *Leuconostoc mesenteroides* (NRRL B-512F), two new sugars were isolated as by-products of the reaction. One of these, the crystalline disaccharide leucrose, was briefly described in a preliminary note[2] in 1952 and later shown[3] to be 5-*O*-α-D-glucopyranosyl - D - fructose. From the leucrose mother liquors a small amount of another disaccharide was obtained analytically and chromatographically pure, although not crystalline. It could easily be distinguished from isomaltose by paper chromatography, but its phenylosotriazole was identical with that of isomaltose, thereby essentially establishing its structure as isomaltulose, 6-*O*-α-D-glucopyranosyl-D-fructose. This conclusion was reported[4] at the 1954 Symposium on Carbohydrates in Relation to Biology and Medicine, where the rotation of the sugar was given as +98°. Because of the pressure of other work, publication of the details of these studies was delayed. In the meantime, an elegant method for the 90% conversion of sucrose into crystalline isomaltulose by the action of *Enterobacteriaceae* was reported by Weidenhagen and Lorenz in 1957.[5,6] Their product with an optical rotation of $[\alpha]_D^{20} = 97.2°$ was given the trivial name palatinose. Seeding a water-methanol solution of our lyophilized isomaltulose with crystals supplied by Dr. Weidenhagen resulted in complete conversion of our product to crystalline isomaltulose having an x-ray diffraction pattern identical with that of the Weidenhagen sample. In the present paper we wish to complete our studies on the by-products of the enzymatic dextran synthesis by reporting the details of this work on isomaltulose.

EXPERIMENTAL

Isolation of isomaltulose. In work already described,[3] 600 g. of sucrose was enzymatically converted to a mixture of products from which were separated 213.3 g. of dextran, 60.4 g. of crude crystalline leucrose, 33.4 g. of tri-, tetra- and higher oligosaccharides, and 32.9 g. of a disaccharide mixture (in the mother liquor from the leucrose crystallization). Aliquots (250 mg.) of this latter mixture were separated on a cellulose powder column (3 × 118 cm.), using 3:2:1.5 butanol:pyridine:water[7] as eluant. Isolation of the various fractions showed the 32.9 g.-mixture to consist of 19.1 g. leucrose, 4.3 g. isomaltose, and 9.5 g. of a disaccharide later shown to be isomaltulose.

Final purification of the isomaltulose was accomplished by applying 150 mg. of the fairly pure material obtained from the cellulose column to large sheets ($18^1/_4'' \times 22^1/_2''$) of heavy filter paper (Whatman No. 3)[8] and by employing the butanol:pyridine:water mixture again as the developing solvent. The 100 mg. of disaccharide obtained by water elution of the proper area was shown by further paper chromatography to be a single substance. $[\alpha]_D^{25}$ + 103° (c 1.9; water). No mutarotation was observed in 4 hr.; this result is in accord with the report of Weidenhagen and Lorenz.[5,6]

Anal. Calcd. for $C_{12}H_{22}O_{11}$: C, 42.12; H, 6.45. Found: C, 42.22; H, 6.52.

Properties of isomaltulose. The lyophilized isomaltulose obtained in our work crystallized completely in wet methanol on seeding with a sample provided by Dr. Weidenhagen. X-ray diffraction patterns showed the two crystalline compounds to be identical.

By the Somogyi method,[9] the sugar showed 50% of the reducing power of fructose on a molar basis. Subjected to paper chromatography (butanol:pyridine:water) it moved just ahead of maltose in a position approximately one-third of the distance between maltose and sucrose. When sprayed with urea-phosphoric acid reagent, chromatograms of isomaltulose gave the greenish-blue spot characteristic of fructose disaccharides.

Determination of fructose in isomaltulose by the anthrone method of Wise *et al.*[10] gave an unusually high result (121% of theory). This yield was accounted for when further studies showed that the new sugar produced hydroxymethylfurfural at a more rapid rate than either fructose or sucrose.

Attempts to establish the ketose nature of the reducing moiety by the Willstätter-Schudel alkaline hypoiodite oxidation were unsatisfactory. The 0.346 mole of iodine consumed was much higher than would be expected of a ketose. This behavior was explained when it was demonstrated that isomaltulose can be readily transformed by alkali into compounds chromatographically indistinguishable from isomaltose, glucose, fructose, and possibly mannose. A disaccharide spot believed to be the 2-epimer of isomaltose is also evident.

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(2) F. H. Stodola, H. J. Koepsell, and E. S. Sharpe, *J. Am. Chem. Soc.*, **74**, 3202 (1952).

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(7) A. Jeanes, C. S. Wise, and R. J. Dimler, *Anal. Chem.*, **23**, 415 (1951).

(8) The mention of products does not imply endorsement over others of the same quality.

(9) M. Somogyi, *J. Biol. Chem.*, **160**, 61 (1945).

(10) C. S. Wise, R. J. Dimler, H. A. Davis, and C. E. Rist, *Anal. Chem.*, **27**, 33 (1955).

Structural Studies. Isomaltulose was hydrolyzed by heating for 1 hr. in 0.25*N* hydrochloric acid. Paper chromatography showed approximately equal amounts of glucose and fructose.

Isomaltulose (68 mg.) was converted to 63 mg. of the phenylosazone, which, when crystallized from wet ethyl acetate, melted at 203–204° (cor.). The phenylosazone of isomaltose was found to melt at 201–202° (cor.). Both osazones were cleaved with sodium periodate to yield the crystalline 1,2-bisphenylhydrazone of mesoxalaldehyde. Oxidation of the phenylosazone of isomaltulose with copper sulfate gave 23 mg. of a phenylosotriazole [m.p. 179–180° (cor.)], shown by mixed melting-point test and x-ray diffraction patterns to be identical with the phenylosotriazole prepared from pure isomaltose.

Acknowledgments. The authors wish to thank Mr. Henry Zobel for x-ray diffraction patterns, Drs. R. J. Dimler and J. W. Van Cleve for advice, Dr. Allene Jeanes for samples of isomaltose, and Professor R. Weidenhagen for the crystalline isomaltulose.

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Synthesis of 4-(2,3-Epoxypropoxy)phenyltrimethylsilane

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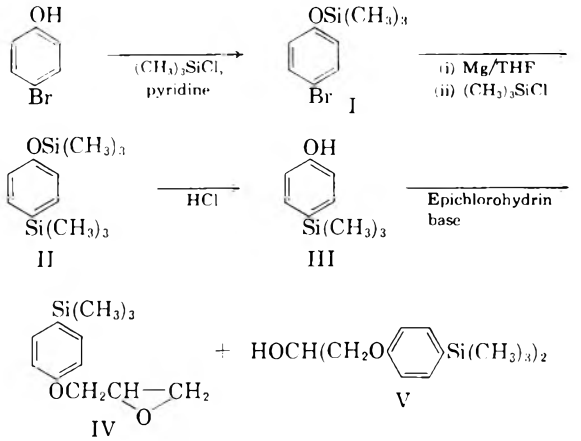
Organosilicon compounds containing epoxide groups are of quite recent origin. Martin[1] reported the preparation of glycidyl silicon ethers by reaction of glycidol with chlorosilanes in the presence of a hydrogen chloride acceptor (*e.g.*, triethylamine). About the same time, Andrianov and Dubrovina[2] reported the synthesis of alkylacetoxyepoxysilanes; and Brynolf[3] prepared 3,4-epoxybutyltrimethylsilane by the reaction of trimethylsilylmethylmagnesium bromide with epichlorohydrin followed by treatment with base. Very recently, Plueddemann and Fanger[4] reported an interesting series of epoxyorganosiloxanes formed either by peracetic acid epoxidation of olefinic organosilicon compounds, or by addition of silicon hydrides across the olefinic bond of unsaturated epoxy compounds.

Evidently silicon analogs of commercial epoxy (Epon) resins have not been described. In this paper we wish to report the synthesis of 4-(2,3-epoxypropoxy)phenyltrimethylsilane, IV, a silicon analog of the well known phenyl glycidyl ether.[5,6]

This new type of epoxysilane was synthesized using the following sequence of reactions:



Compounds I, II, and III have been reported previously,[7–10] although modifications of the published procedures were employed in the present work. Reaction of 4-trimethylsilylphenol (III) with epichlorohydrin in basic solution at room temperature (20°) was found to proceed readily, the optimum yield of IV being obtained at about a 1:3 molar ratio of III with epichlorohydrin. The use of less epichlorohydrin resulted in the formation of larger amounts of the secondary product, 1,3-bis(4-trimethylsilylphenoxy)-2-propanol, V, by reaction of IV with III.

EXPERIMENTAL

4-Bromophenoxytrimethylsilane. I. A mixture of 4-bromophenol (865 g., 5.0 moles), anhydrous benzene (900 ml.), and pyridine (395 g., 5.0 moles) was cooled in an ice bath at 0–5°; then trimethylchlorosilane (542.5 g., 5.0 moles) in benzene (500 ml.) was added dropwise with stirring. Throughout the addition care was taken to maintain the temperature in the range 5–20°. After stirring for 3 hr., and standing overnight, the precipitated pyridinium chloride was filtered. The filtrate was distilled at atmospheric pressure to remove most of the benzene, and the residue was distilled *in vacuo*, the fraction of b.p. 120–130°/20–30 mm. being collected. Refractionation gave pure I of b.p. 122°/20 mm., in good agreement with the literature value.[7,9] The yield was 882 g. (72%).

It should be noted that specimens of this compound partially decomposed to 4-bromophenol on standing for several weeks in tightly-stoppered Pyrex glass bottles. The infrared spectrum of freshly prepared I showed no bands due to hydroxyl. These developed gradually and it was considered inadvisable to use specimens of I older than about 1 month for Grignard syntheses.

4-Trimethylsilylphenoxytrimethylsilane. II. A modification of the synthesis of Frisch and Shroff[9] was employed using tetrahydrofuran rather than ether as solvent. This was

(1) R. W. Martin, U. S. Patent 2,730,532 (1956).
(2) K. A. Andrianov and V. G. Dubrovina, *Doklady Akad. Nauk S.S.S.R.*, 108, 83 (1956).
(3) S. Brynolf, *Acta Chem. Scand.*, 10 (5), 883 (1956).
(4) E. P. Plueddemann and G. Fanger, *J. Am. Chem. Soc.*, 81, 2632 (1959).
(5) T. Lindeman, *Ber.*, 24, 2145 (1891).
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(7) J. L. Speier, *J. Am. Chem. Soc.*, 74, 1003 (1952).
(8) J. L. Speier, U. S. Patents 2,611,776, 2,611,777 (1952); 2,645,630 (1953).
(9) K. C. Frisch and P. D. Shroff, *J. Am. Chem. Soc.*, 75, 1249 (1953).
(10) K. C. Frisch, U. S. Patent 2,711,417 (1955).

significant in view of the fact that the time for Grignard formation was 2 hr. instead of 18 hr. with ether.

In a 5-l. three-necked flask, fitted with motor-driven stirrer, thermometer, and dropping funnel, were placed the following reactants: magnesium turnings (27 g., 1.1 g.-atoms), sodium-dried tetrahydrofuran (tetrahydrofuran, distilled free from hydroquinone, 50 ml.), and methyl iodide (5 ml.). The mixture was gently warmed on the water bath until methylmagnesium iodide had formed. Tetrahydrofuran (150 ml.) was added and the mixture heated to gentle reflux. 4-Bromophenoxytrimethylsilane (245 g., 1.0 mole) in tetrahydrofuran (400 ml.) was added dropwise with vigorous stirring over a 1-hr. period, after which the mixture was refluxed a further hour then cooled to 10°. Trimethylchlorosilane (120 g., 1.1 moles) was added with stirring, the mixture was then brought to reflux for 1 hr., and allowed to cool overnight. The crystallized magnesium salts were dissolved in water (500 ml.), the tetrahydrofuran layer separated, washed four times with water, dried over anhydrous sodium sulfate, and distilled. The colorless liquid fraction of b.p. 132–135°/22–44 mm. was collected in 184 g. (77.4%) yield. Refractionation yielded a liquid of b.p. 132–133°/25 mm., in agreement with the literature[7] value.

4-Trimethylsilylphenol. III. 4-Trimethylsilylphenoxytrimethylsilane (48.0 g., 0.2 mole) in 95% ethyl alcohol (15 ml.) was acidified with *one* drop of concd. hydrochloric acid then diluted with water (6 ml.). After shaking for 5 min., the mixture was diluted to turbidity with more water and then allowed to stand for 15 min. The lower aqueous layer was discarded and the organic layer was washed twice with 50-ml. aliquots of water. The organic layer was transferred to a large dish and the alcohol allowed to evaporate in the air. 4-Trimethylsilylphenol rapidly crystallized in theoretical yield, m.p. 74°, in agreement with the published values.[7,9]

As difficulty was initially encountered in the preparation of this compound it is important to emphasize the following precautions to be taken in its synthesis. Only 1 very small drop of concd. acid is required to cleave the trimethylsiloxy group to the phenol, and the temperature must be kept below 25°. The use of more acid, or heating, results in some cleavage of the 4-trimethylsilyl group to phenol itself. The preparation of Frisch and Shroff,[9] in which II is refluxed in dilute ethanolic acid, could not be reproduced in this laboratory. The atmosphere of the laboratory was found to be sufficiently acidic to cause some cleavage of III to phenol when specimens were exposed in open dishes for about 1 week. The silylphenol could be stored in tightly capped bottles, or as the sodium salt.

4-(2,3-Epoxypropoxy)phenyltrimethylsilane. IV. 4-Trimethylsilylphenol (166 g., 1.0 mole) was dissolved in a solution of sodium hydroxide (50 g., 1.25 moles) in water (500 ml.) and isopropyl alcohol (50 ml.). Epichlorohydrin (277 g., 3.0 moles) was then added, the whole stoppered and shaken vigorously for 15 min. and allowed to stand at room temperature for 20 hr. A pale yellow organic layer floating on a dark brown aqueous phase resulted. The mixture was extracted with ether, washed twice with water, dried over anhydrous potassium carbonate, and distilled to remove most of the ether. The residue was distilled *in vacuo* and the fraction of b.p. 145–185°/20 mm. was collected as a colorless liquid in 152 g. (68.5%) yield. The main fraction distilled at 170–172°/20 mm. Redistillation gave 117 g. of colorless oil, b.p. 170°/20 mm.

Anal. Calcd. for $C_{12}H_{18}O_2Si$: C, 64.80; H, 8.16. Found: C, 64.84; H, 8.11.

1,3-Bis(4-trimethylsilylphenoxy)-2-propanol. V. The residue remaining after distillation of IV was recrystallized from isopropyl alcohol and a white crystalline solid, m.p. 74°, was obtained. The infrared spectrum showed strong absorption in the hydroxyl region together with three strong bands due to the trimethylsilyl group at 1248, 838, and 759 cm.$^{-1}$.[11,12]

In the preparation of phenyl glycidyl ether[6] under similar conditions 1,3-diphenoxy-2-propanol is formed as a by-product. By analogy, this compound was concluded to be 1,3-bis(4-trimethylsilylphenoxy)-2-propanol.

Anal. Calcd. for $C_{21}H_{32}O_3Si_2$: C, 64.87; H, 8.31. Found: C, 64.70; H, 8.34.

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A New Synthesis of Organothiosilanes

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Compounds containing the silicon-sulfur linkage have been prepared by the reactions of silicon (IV) sulfide with alkyl silicates,[1] silylamines with hydrogen sulfide or thiphenols,[2,3] silyl iodide with mercury (II) sulfide,[4] silicon tetrachloride with hydrogen sulfide,[5] silicon tetrachloride with sodium hydrosulfide,[6] and $Pb(SR)_4$ types with silicon tetrachloride.[7a,b]

Solutions of triphenylsilyllithium[8] in tetrahydrofuran react smoothly with sulfur to give the lithium salt of triphenylsilanethiol (I):

$$(C_6H_5)_3SiLi + S \longrightarrow \underset{\text{I}}{(C_6H_5)_3SiSLi} \xrightarrow{RX} (C_6H_5)_3SiSR$$

R = —CH_3 (II), —$CH_2C_6H_5$ (III), —COC_6H_5 (IV)

Subsequent reaction of intermediate I with methyl iodide, benzyl chlorde, or benzoyl chloride gives rise to (methylthio)triphenylsilane (II), (benzylthio)triphenylsilane (III), and (benzoylthio)triphenylsilane(IV), respectively, in good yields. To our knowledge, the latter compound (IV), is the first reported to contain the Si—S—CO— linkage.

(1) L. Malatesta, *Gazz. chim. ital.*, **78**, 753 (1948).

(2) E. Larsson and R. E. I. Marin, Swedish Patent **138,357**, Dec. 9, 1952 [*Chem. Abstr.*, **48**, 2761 (1954)].

(3) E. Larsson and R. E. I. Marin, *Acta Chem. Scand.*, **5**, 964 (1951).

(4) H. J. Emeleus, A. G. MacDiarmio, and A. G. Maddock, *J. Inorg. & Nuclear Chem.*, **1**, 194 (1955).

(5) W. C. Schumb and W. J. Bernard, *J. Am. Chem. Soc.*, **77**, 862 (1955).

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(8) H. Gilman and G. D. Lichtenwalter, *J. Am. Chem. Soc.*, **80**, 608 (1958).

(Methylthio)triphenylsilane(II) is cleaved by phenyllithium to give tetraphenylsilane in a reaction analogous to the well-known cleavages of siloxanes by organometallic reagents.

$$(C_6H_5)_3SiSCH_3 + C_6H_5Li \longrightarrow (C_6H_5)_4Si + CH_3SLi$$

No observable reaction was noted between the lithium salt of triphenylsilanethiol (I) and iodobenzene, chlorotrimethylsilane, or chlorotriphenylsilane.

EXPERIMENTAL[9]

Preparation of the intermediate lithium salt of triphenylsilanethiol (I). To a stirred suspension of 0.62 g. (0.0193 g.-atom) of sulfur in 25 ml. of tetrahydrofuran was added 50 ml. of a tetrahydrofuran solution of triphenylsilyllithium[8] prepared by the cleavage of 5.0 g. (0.00965 mole) of hexaphenyldisilane with excess lithium. During the addition, some heat was given off, and the solution became almost black in appearance. When the addition was complete, Color Test I[10] was negative, indicating that the triphenylsilyllithium had reacted completely.

Solutions of I prepared in this manner were used in the following three reactions.

Reactions of intermediate I. A. With methyl iodide. Excess methyl iodide was added to a solution of I prepared in the manner described. The dark color of the solution was discharged, and heat was evolved. The tetrahydrofuran was strip distilled. The resulting oil was fractionated to give 4.05 g. (76%) of crude (methylthio)triphenylsilane, b.p. 145–150° (0.06 mm.), which solidified on standing. Recrystallization from petroleum ether (b.p. 60–70°) gave 3.07 g. (52%) of pure product, m.p. 83–84°.

Anal. Calcd. for $C_{19}H_{18}SSi$: Si, 9.15. Found: Si, 9.33, 9.28.

B. With benzyl chloride. To a solution of I prepared in the manner described was added excess benzyl chloride. The dark color of the solution was discharged over a period of about 30 min. The tetrahydrofuran was stripped off. Distillation of the residual oil gave 3.33 g. (45%) of crude (benzylthio)triphenylsilane (III), b.p. 172–177° (0.015 mm.). Two recrystallizations from petroleum ether (b.p. 60–70°) gave 2.7 g. (36%) of crystals, m.p. 92–94°.

Anal. Calcd. for $C_{25}H_{22}SSi$: Si, 7.33. Found: Si, 7.08, 7.27.

C. With benzoyl chloride. Addition of 3.05 g. (0.0217 mole) of benzoyl chloride to a solution of I, prepared in the manner described, resulted in a fast exothermic reaction. The tetrahydrofuran was stripped off the almost clear solution. The resulting oil was distilled to give 4.48 g. (59%) of crude (benzoylthio)triphenylsilane (IV), b.p. 183–189° (0.01 mm.). Recrystallization from anhydrous petroleum ether (b.p. 60–70°) gave 2.75 g. (36%) of yellow needles, m.p. 128–129°. The infrared spectrum of the product showed a normal carbonyl absorption peak at 5.9 μ.

Anal. Calcd. for $C_{25}H_{20}OSSi$: Si, 7.08. Found: Si, 7.10, 6.87.

Cleavage of (methylthio)triphenylsilane (II) *by phenyllithium.* To a stirred solution of 2.0 g. (0.00653 mole) of II in 20 ml. of ether was added 32 ml. of an ethereal solution containing 0.00978 mole of phenyllithium. The reaction mixture was hydrolyzed with water and filtered to give 1.97 g. (89%) of tetraphenylsilane, m.p. 233–235°, identified by a mixed melting point with an authentic specimen. The filtrate smelled strongly of a sulfur compound, presumably methyl mercaptan.

(9) Reactions were carried out under an atmosphere of dry, oxygen-free nitrogen. Temperatures are uncorrected.

(10) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, 47, 2002 (1925).

Acknowledgment. This research was supported in part by the United States Air Force under Contract AF 33(616)-3510 monitored by Materials Laboratory, Directorate of Laboratories, Wright Air Development Center, Wright-Patterson AFB, Ohio. Infrared analyses were obtained through the courtesy of the Institute for Atomic Research, Iowa State College, and special acknowledgment is made to Dr. V. A. Fassell and Mr. R. Kniseley for obtaining the spectra.

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Consecutive Rate Constants for Saponification of the Isomeric Diethyl Phthalates

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In our recent publication[2] the saponification and acid-catalyzed hydrolysis of the diethyl phthalates and methoxyphthalates were reported. The rates of saponification of the individual ester groups in diethyl 2- and 5-methoxyisophthalates were calculated by the method of Frost and Schwemer.[3] Unfortunately, the tables in the Frost and Schwemer publication did not include time ratios for values of k_1/k_2 greater than 10.0, where k_1 and k_2 are, respectively, the rate constants for the consecutive saponification of first one and then the remaining carbethoxyl group of the diester molecule. This made it necessary to obtain by tedious calculation and interpolation the value of k_1/k_2 for diethyl 5-methoxyisophthalate which is greater than 10.0.

A computer program has been written[4] to extend broadly the tables of Frost and Schwemer, and thereby greatly facilitate the calculation of the consecutive or separate rate constants from a much wider range of experimental data. By using the new extended tables obtained from the computer program together with our previous experimental results,[2] it has been possible to calculate k_1 and k_2 for the saponification of the diethyl esters of the isomeric phthalic acids, and to recalculate those for 2- and 5-methoxyisophthalic acids. The recalculation of k_1 and k_2 for the latter two methoxy compounds has revealed that the constants initially reported[2] are one-half the true values.

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(2) C. A. Burkhard and R. E. Burnett, *J. Am. Chem. Soc.*, 80, 341 (1958).

(3) A. A. Frost and W. C. Schwemer, *J. Am. Chem. Soc.*, 74, 1268 (1952).

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The new and recalculated values for separate rate constants, and the ratio of k_1/k_2, for the saponification of the five esters are given in Table I.

TABLE I

RATES OF SAPONIFICATION OF DIETHYL ESTERS, 25°. INITIAL CONCENTRATION = 0.025 mole/l.

Diethyl ester	$k_1 \times 10^4$ l. mole^{-1} sec.$^{-1}$	$k_2 \times 10^4$ l. mole^{-1} sec.$^{-1}$	k_1/k_2
2-Methoxyisophthalate, Run 1	45.6	9.31	4.90
Run 2	46.4	9.46	4.90
5-Methoxyisophthalate	89.7	7.40	12.11
Phthalate	13.2	2.65	4.97
Isophthalate, Run 1	82.2	6.07	13.55
Run 2	79.7	5.88	13.55
Terephthalate,[a] Run 1	153	7.10	21.72
Run 2	157	7.20	21.72

[a] Crystals separated from the reaction mixture.

In a previously reported study[5] of the rate of saponification of diethyl phthalate in 91% ethanol a value of $k_1/k_2 = 2.5$ was obtained at 40.° Wegscheider[6] reported a ratio of about 2 for k_1/k_2 at 25°. In the present work the ratio (4.97) was found to be about double those originally reported. As has been noted[7] already the rate of saponification for the isomeric phthalates increases in the order diethyl phthalate, diethyl isophthalate, and diethyl terephthalate, the last being the fastest. The major increase is evidenced in the rate for the saponification of the first ester group, k_1. While attack on the first ester linkage in all five diesters, Table I, is enhanced, to varying extents through the influence of the second ester group, the much lower value of k_1 for the phthalate ester suggests a shielding effect brought about by the proximity of the bulky ethyl group. In the acid-catalyzed hydrolysis of these same esters,[2] the overall k for diethyl phthalate is again noticeably lower than the others.

In the aliphatic series,[3] *e.g.*, in the saponification of diethyl adipate in dilute aqueous solution at room temperature, the values of k_1/k_2 indicate that the second ester group saponifies at a rate several times slower than the first group. Westheimer[8] attributes such effect to the electrostatic repulsion between the attacking hydroxyl ion and the monoethyl adipate anion. Since, under the conditions of saponification presently used (Table I) the rate constant for the saponification of ethyl benzoate was found[2] to be 6.3×10^{-4} l. mole^{-1} sec.$^{-1}$, which is close to the k_2 values in Table I, the electrostatic repulsion effect of the monoethyl phthalate anions would seem to be of lesser importance than the accelerating influence of the second ester group previously mentioned (indicated by the high k_1 values).

The position effect of the methoxyl groups in the substituted isophthalates on the saponification rate of the first ester linkage appears to be normal. The values for k_1 in Table I agree with the previously observed structural relations in that saponification is slightly faster when the methoxyl is *meta* and slower when *ortho* to the ester groups.

With the exception of the references cited for phthalate, the k_1 and k_2 values, and their ratios, for the isomeric esters had hitherto not been reported.

EXPERIMENTAL

The diethyl esters were purified by distillation in a Podbielniak spinning-band column or by recrystallization: diethyl phthalate, n_D^{20} 1.5021; diethyl isophthalate, n_D^{20} 1.5071; and diethyl terephthalate, m.p. 44°.

Saponification procedure. Reaction mixtures (100 ml.) containing 0.05 equiv. per l. of ethyl ester and of sodium hydroxide in 85% by weight ethanol were prepared. In each case 0.005 equiv. of ester and 40.6 ± 0.2 g. of aqueous ethanol (85% by weight ethanol) were weighed in 250-ml. glass-stoppered flasks and placed in a water bath maintained at 25 ± 0.1°. At the start of a reaction 50 ml. of 0.1*N* alcoholic sodium hydroxide (85% by weight ethanol), also adjusted to 25°, was added by pipet to the ester solution. To effect solution the flask was swirled in the bath for about 2 min. Zero time was taken at half the delivery time of the 50-ml. pipet. During a run at least five 10-ml. aliquots of reaction mixture were taken out at intervals and added to 15 ml. of 0.1*N* aqueous hydrochloric acid which had been cooled in ice to stop the reaction. Sampling time was taken when half the aliquot had been delivered into the acid. The resulting acid solution was promptly titrated with 0.1*N* aqueous sodium hydroxide to a greenish-blue end-point with bromothymol blue. It was established by direct titration of each of the five dibasic acids under consideration that in all cases both carboxyl groups are determined quantitatively under the analytical conditions employed. Duplicate saponification runs gave satisfactory checks.

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(5) G. Semerans, *Gazz. chim. ital.*, **65**, 252 (1935).

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Electronic Effects in the Gomberg Reaction[1]

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When benzene competes with chlorobenzene or nitrobenzene for phenyl radicals in a Gomberg reaction the substituted benzene reacts more rapidly.[2] If the phenyl radical is substituted by an electron

(1) Presented at the 135th Meeting of the American Chemical Society at Boston, Mass., April 1959, Abstr., p. 47-0.

(2) D. R. Augood, D. H. Hey, and G. H. Williams, *J. Chem. Soc.*, 2994 (1952).

withdrawing group the relative rate ratio $(C_6H_5X/C_6H_6)K$ is decreased.[3] This decrease in $(C_6H_5X/C_6H_6)K$ is explained by assuming that as the radical nucleus becomes more electron deficient it becomes more difficult for it to react with the already electron deficient substituted benzene. The reverse, of course, is true if one of the substituents either on the benzene or the phenyl radical is electron donating and the other electron withdrawing.[4]

However, an examination of the examples of this phenomena compiled by Augood and Williams[4] suggests that as the substituents on the phenyl radical become more electron withdrawing the $(C_6H_5X/C_6H_6)K$ ratio may approach unity as a limit, rather than decreasing indefinitely: the lowest $(C_6H_5X/C_6H_6)K$ value reported was 0.94 for the competition of nitrobenzene and benzene for *p*-nitrophenyl radicals. This rate ratio we feel is within error of unity. If the $(C_6H_5X/C_6H_6)K$ values are approaching unity (or a related number) as a limit an explanation quite different from the one offered above would be required.

We felt the problem could be resolved by determining the $(C_6H_5Cl/C_6H_6)K$ for 3,4-dichlorophenyl radicals. Since the competitive reaction of benzene and chlorobenzene for phenyl radicals[2] yields a $(C_6H_5Cl/C_6H_6)K$ of 1.4 and for *p*-chlorophenyl radicals[3] a value of 1.0, we expected 3,4-dichlorophenyl radicals to fall below unity, confirming the original explanation, or remain at unity, The results of our experiments are recorded in Fig. 1.

The competitive reaction with phenyl radicals was carried out to compare our method of analysis, principally vapor phase chromatography, with those of previous investigators. The $(C_6H_5Cl/C_6H_6)K$ value obtained agrees within error with those previously reported. Competition of benzene and chlorobenzene for 3,4-dichlorophenyl radicals yields a $(C_6H_5Cl/C_6H_6)K$ of 0.73 ± .03 thus confirming the original explanation.

We believe the $(C_6H_5Cl/C_6H_6)K$ of 0.73 represents the first unequivocal example of a substituted benzene reacting more slowly than benzene in a simple Gomberg reaction[5] as a result of electronic influences.[6]

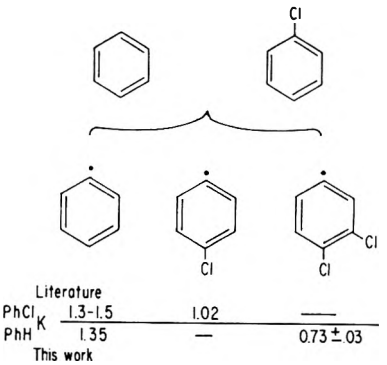

Fig. 1. Competition of benzene and chlorobenzene for various phenyl radicals

EXPERIMENTAL

Competitive reaction with phenyl radicals. Benzene diazonium chloride (0.1 mole) was prepared in the usual way[7] and the aqueous solution was then stirred vigorously with a mixture of 156 g. (2.0 moles) of benzene and 225 g. (2.0 moles) of chlorobenzene the temperature being maintained between 0° and 10°. To this mixture was rapidly added a solution of sodium acetate trihydrate, 50 g. dissolved in a minimum of water. The reaction mixture was allowed to come to room temperature and the reaction was followed by measuring the nitrogen evolved. Eighty per cent of the theoretical nitrogen was evolved in 12 hr. at room temperature. The temperature was gradually raised to 70° and kept there until nitrogen evolution ceased (total evolved nitrogen, 95%). The organic phase was washed with water, dried over magnesium sulfate and the mixed solvent removed through a 3 ft. Todd distilling apparatus. The biphenyl and chlorinated biphenyl mixture was then distilled from residue through a simple Claisen head, b.p. 115–125°/3 mm., yield 30% (based on analysis of product). The distillate was analyzed directly by vapor phase chromatography.[8] Analysis of the chromatograms indicated a $(C_6H_5Cl/C_6H_6)K$ of 1.35.

Competitive reaction with 3,4-dichlorophenyl radicals. 3,4-Dichlorobenzene diazonium chloride (0.1 mole) was treated exactly as described above. After removal of the mixed solvent the chlorinated biphenyl mixture was distilled from the residue, b.p. 130–170°/3 mm., yield 55% (based on analysis of product).

Analysis: Run No. 1, $(C_6H_5Cl/C_6H_6)K$ (from % C) 0.70, (from % Cl) 0.74, (from V.P.C.) 0.76; Run No. 2, $(C_6H_5Cl/C_6H_6)K$ (from V.P.C.) 0.75, Average equals 0.73±.03.

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(7) D. F. DeTar and Abdul A. Kazimi, *J. Am. Chem. Soc.*, **77**, 3843 (1955).

(8) Vapor phase chromatograms were obtained with a Perkin Elmer model 154 Vapor Fractometer, using a 1.5 meter 10% silicone impregnated firebrick column at temperatures between 170° and 200°. Areas under the chromatographic peaks were measured with an Ott compensating planimeter.

Fluorinated Diuretic Agents

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The exceptional diuretic potency of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide[2] and

of its 3,4-dihydro derivative[3] prompted us to synthesize the corresponding 6-fluoro compounds. Treatment of *m*-fluoroaniline with chlorosulfonic acid in the presence of sodium chloride gave the amorphous 1,3-bissulfonylchloride which on treatment with ammonia yielded crystalline 6-amino-4-fluorobenzene-1,3-disulfonamide (I) Cyclization with boiling formic acid[2] produced 6-fluoro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (II) reduced[3] by sodium borohydride to 6-fluoro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (III). I, II, and III were potent diuretic agents in the saline-loaded female dog.[4]

EXPERIMENTAL[5]

6-Amino-4-fluorobenzene-1,3-disulfonamide (I). *m*-Fluoroaniline (28.2 g.) was added slowly to a cooled suspension of 0.5 g. sodium chloride in chlorosulfonic acid (50 g.) and the mixture then heated for 2.5 hr. by means of an oil bath held at 150–160°. The solution was cooled and poured with stirring into a mixture of ice and water. The gummy bissulfonyl chloride (9 g.) was collected by filtration, washed, dried, and added to 80 ml. of 30% ammonium hydroxide. The solution was heated for 1 hr. at 90°, concentrated at atmospheric pressure to a small volume and cooled yielding 4.65 g. of I, m.p. 220–223°. Recrystallization from water gave the analytical specimen, m.p. 233–235°, λ_{max} 261, 301 mμ, log ε 4.32, 3.53.

Anal. Calcd. for $C_6H_8FN_3O_4S_2$: C, 26.79; H, 2.99; F, 7.05; S, 23.78; N, 15.62. Found: C, 26.71; H, 2.88; F, 6.80; N, 15.16; S, 23.27.

6-Fluoro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (II). A mixture of I (4.47 g.) and 85% formic acid (100 ml.) was boiled for 2 hr. and then concentrated to dryness *in vacuo*. The residue was taken up in hot water and a small amount of insoluble material removed. Concentration of the solution and cooling yielded 3.23 g. of II, m.p. 285–290°. Further recrystallization from water raised the melting point to 309–310°, λ_{max} 271 mμ, log ε 4.08.

Anal. Calcd. for $C_7H_6FN_3O_4S_2$: C, 30.11; H, 2.16; F, 6.80; N, 15.05; S, 22.96. Found: C, 30.24; H, 2.30; F, 6.26; N, 14.83; S, 22.85.

6-Fluoro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (III). A solution of 1.4 g. of II in 200 ml. of methanol was cooled to 0° and treated with a cold solution of sodium borohydride (3 g.) in 30 ml. of water. After standing for 1 hr. at 0° and for 14 hr. at 10° the solution was treated dropwise with acetic acid to destroy the excess hydride and then concentrated *in vacuo*. Extraction with ethyl acetate gave crude III which was crystallized from water yielding 0.67 g. of 3,4-dihydro compound, m.p. 218–220°. Pure III melted at 218–221°, λ_{max} 266, 305 mμ, log ε 4.35, 3.56.

Anal. Calcd. for $C_7H_8FN_3O_4S_2$: C, 29.89; H, 2.87; F, 6.75; N, 14.94; S, 22.80. Found: C, 30.03; H, 2.88; F, 6.32; N, 14.62; S, 22.39.

6-Propionylamino-4-fluorobenzene-1,3-dipropionylsulfonamide (IV). A solution of 0.81 g. of I in 100 ml. of propionic anhydride was boiled for 2 hr. The solvent was removed *in vacuo* and the residue crystallized from methanol yielding 0.58 g. of tripropionate (IV), m.p. 238–240°, λ_{max} 222, 268 mμ, log ε 4.21, 4.13.

Anal. Calcd. for $C_{15}H_{20}FN_3O_4S_2$: C, 41.18; H, 4.60; F, 4.34; N, 9.60; S, 14.66. Found: C, 41.58; H, 4.53; F, 4.10; N, 9.40; S, 14.39.

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(1) This material represents part of the professional thesis submitted by Srta. Carmen Pelayo to the Facultad de Química, Universidad Nacional Autónoma de México.

(2) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, **79**, 2028 (1957).

(3) G. De Stevens, *Experientia*, **14**, 463 (1958).

(4) We wish to thank Mr. R. H. Tust of the Pharmacology Dept. of Eli Lilly for these assays.

(5) Melting points are uncorrected and ultraviolet absorption spectra were determined in 96% ethanol.

Preparation of Fluorocarbon α-Olefins

R. N. GRIFFIN AND M. I. BRO

Received December 21, 1959

Previous workers have shown that thermal decomposition of the alkali metal salts of perfluorocarboxylic acids produces high yields of olefins containing one less carbon atom.[1] When small

$$R_fCF_2—CF_2CO_2M \longrightarrow R_f—CF=CF_2 + MF + CO_2$$

amounts of the salt are used, α-olefin of high (≥ 90%) isomeric purity is obtained. As the bed depth of the salt is increased, the isomeric purity of the olefinic product decreases. The α-olefin of highest purity is produced early in the pyrolysis, and as the reaction progresses the product contains larger amounts of isomeric internal olefins. Since their boiling points generally differ by only a few degrees, the separation of the terminal and internal olefins is tedious.

Contrary to previous reports,[2] perfluorocarboxylic acids also undergo a similar general reaction to yield fluorocarbon olefins having one less carbon.

$$R_f—CF_2—CF_2—CO_2H \xrightarrow[\Delta]{} R_f—CF=CF_2 + CO_2 + HF$$

We have prepared olefins in good yield from linear and branched aliphatic perfluorocarboxylic acids, as well as linear ω-hydroperfluorocarboxylic acids.

The reaction is carried out by passing an anhydrous mixture of the acid and an inert gaseous diluent through a heated tube at temperatures of 400–650°. The flow rate of the inert gas is adjusted so that residence time of the acid in the hot zone of the tube is about five seconds. Decarboxylation appears to occur most readily when the acids are in vaporized form. Little or no isomerization of terminal to internal olefin is observed in the pyrolysis. This may be due to differences in catalytic activity of hydrogen fluoride and alkali metal fluorides, or to the low concentration of fluoride in the hot reaction zone, or both.

(1) J. D. LaZerte, U. S. Patent **2,601,536** issued June 24, 1952; L. J. Hals, T. S. Reid, and G. H. Smith, U. S. Patent **2,668,864,** issued Feb. 9, 1954; J. D. LaZerte, L. J. Hals, T. S. Reid, and G. H. Smith, *J. Am. Chem. Soc.* **75,** 4525 (1953).

(2) T. S. Reid, G. H. Smith, and W. H. Pearlson, U. S. Patent **2,746,997,** issued May 22, 1956.

EXPERIMENTAL

Pyrolysis of perfluoropropionic acid. Perfluoropropionic acid (16.4 g., 0.10 mole) was passed through a quartz tube heated to 650° using nitrogen as carrier gas. The residence time in the tube was about 3 seconds. The products contained 85–90% tetrafluoroethylene, about 10% of pentafluoroethane, and traces of hexafluoropropylene and perfluorocyclobutane; all determined by mass spectrographic analysis. In other experiments, Monel tubes with either nitrogen or carbon dioxide as the carrier were used with similar results.

Pyrolysis of perfluorobutyric acid. Perfluorobutyric acid (21.4 g., 0.10 mole) was passed through a Monel tube under the same conditions as those used with perfluoropropionic acid. The product contained 86% hexafluoropropylene, about 10% hexafluoroethane, and 4% octafluoropropane.

Pyrolysis of ω-hydroperfluorononanoic acid. Dropping 20 g. ω-hydroperfluorononanoic acid through a Vycor tube at 586–613° produced 12 g. of nearly pure ω-hydroperfluorooctene-1 as well as an undetermined amount of unchanged acid.

Pyrolysis of perfluorooctanoic acid. Perfluorooctanoic acid (3.4 g., 0.0082 mole) was dropped through a Vycor tube at 620° with a residence time of about 5 seconds, using carbon dioxide as a carrier. The yield of olefin was 89%. Since the starting material was a mixture of isomers, no attempt was made to determine the isomeric purity of the products.

Acknowledgment. The authors wish to thank Dr. R. E. Brooks for his guidance in the early stages of the work.

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Inner Complexes. I. Copper and Beryllium Chelates of 4-Acetyl-5-ketohexanoic Esters

RUDOLPH W. KLUIBER, FREDERICK G. OBERENDER, AND CARL J. ROSSI

Received November 23, 1959

Although the properties of inner complexes depend largely on the nature of the ring system, such physical constants as solubility and melting point can be modified by varying the substituents attached to the chelate ring. In a study of these effects and potential commercial uses of inner complexes, we have prepared a series of metal derivatives of various esters of 4-acetyl-5-ketohexanoic acid (I). The ethyl and methyl esters and their copper derivatives have previously been reported by March[1] who prepared them by basic condensation of the corresponding β-chloropropionic ester and 2,4-pentanedione. Because of the availability of various acrylic esters, their monoaddition to 2,4-pentanedione presented a potentially more attractive synthesis. Analogous Michael reactions have been reported with malonic esters[2,3] and β-keto esters,[3,4] but no work has been reported on the monoaddition of acrylic esters to the active methylene of a β-diketone system.

$$CH_2 = CH—COOR + CH_3COCH_2COCH_3 \longrightarrow (CH_3CO)_2CHCH_2CH_2COOR$$
I

Ethyl 4-acetyl-5-ketohexanoate has now been prepared in 83% yield from ethyl acrylate and an excess of 2,4-pentanedione using a stoichiometric amount of sodium ethoxide in ethanol. This was converted to the copper chelate using ammoniacal copper sulfate and to the beryllium chelate using a sodium acetate–buffered beryllium nitrate solution. The use of a buffered solution eliminates the neutralization step and decreases the contamination of the product with beryllium oxide. In preparing the metal derivatives from the other esters, the distillation of the intermediate ester diketone was omitted and only the yields for the over-all conversion to the pure chelate were recorded. The solubility of these chelates in aliphatic and aromatic hydrocarbons increases with increasing chain branching. For the straight chain ester copper chelates the solubility rises to a maximum and decreases as the chain length increases. The solubility of *bis*(2,4-pentanediono) copper II in benzene was found to be 1.0 mg./ml. at 27°, whereas for the copper chelates of the *n*-alkyl 5-keto-4-acetyl hexanoates, the solubility was: ethyl, 2.0 mg./ml.; butyl, >7 mg./ml.; lauryl, 2.3 mg./ml. These are given in Table I along with other characterization data.

In three cases, the *n*-decyl, lauryl, and isoamyl esters, about 10% of a crystalline *bis*-adduct separated from the crude Michael addition product. These 4,4-diacetylpimelic esters are characterized in Table II.

EXPERIMENTAL

Alkyl 4-acetyl-5-keto-hexanoate. The following preparation of the ethyl ester illustrates the general procedure used in the preparation of the other alkyl esters. However, except for the ethyl ester, the crude residual product was converted directly to the metal derivatives. Metallic sodium (12 g., 0.52 mole) was dissolved in approximately 250 ml. of commercial absolute ethanol in a 500 ml. three necked flask equipped with a stirrer and a dropping funnel. 2,4-Pentanedione (100 g., 1.0 mole) was added to the stirred sodium ethoxide solution cooled by an ice bath. Ethyl acrylate 50 g. (0.5 mole) was added dropwise with stirring to the cooled reaction mixture, and the stirring was continued approximately 16 hr. at room temperature. The reaction was quenched with an excess of glacial acetic acid and the clear solution (*p*H 4–5) was evaporated under reduced pressure. The semisolid residue was treated with 20 ml. of water and extracted with four 100-ml. portions of ether. After drying the extracts over anhydrous magnesium sulfate, the ether was removed under reduced pressure and the residual product distilled, yielding 83 g. (83%) of a light yellow liquid, b.p. 124–128° (3 mm.) (reported[1] 154–155°, 15 mm.).

(1) F. March, *Ann. Chim. Phys.*, **726**, 331 (1902).

(2) C. S. Marvel and M. P. Stoddard, *J. Org. Chem.*, **3**, 198 (1938).

(3) E. H. Riddle, *Monomeric Acrylic Esters*, Reinhold Publishing Corp., New York, 1954, pp. 172–185.

(4) L. Ruzicka, *Helv. Chim. Acta*, **2**, 144 (1919).

TABLE I[5]

CHARACTERIZATION OF R—OOCCH$_2$CH$_2$—C(CH$_3$)=C(O)—M—O—C(CH$_3$)=C(O)—CH$_2$CH$_2$COOR

R	M	Empirical Formula	% Yield, Over-all	M.P., °	% Calculated C	% Calculated H	% Found C	% Found H
Methyl	Cu	$C_{18}H_{26}O_8Cu$	35	200 dec.[a]	—	—	—	—
Ethyl	Cu	$C_{20}H_{30}O_8Cu$	60	205 dec.[b]	—	—	—	—
Ethyl	Be	$C_{20}H_{30}O_8Be$	62	113–114	58.94	7.42	58.65	7.67
Allyl	Cu	$C_{22}H_{30}O_8Cu$	20	174–175	54.35	6.22	54.18	6.31
Allyl	Be	$C_{22}H_{30}O_8Be$	25	88.1–88.8	61.22	7.01	61.39	7.09
Butyl	Cu	$C_{24}H_{38}O_8Cu$	32	157–159	55.66	7.39	55.69	7.74
n-Amyl	Cu	$C_{26}H_{42}O_8Cu$	20	148.5–152	57.18	7.75	57.51	7.90
i-Amyl	Cu	$C_{26}H_{42}O_8Cu$	25	151.5–152	57.18	7.75	57.45	7.63
2-Octyl	Cu	$C_{32}H_{54}O_8Cu$	27	121.5–122.5	60.97	8.64	60.41	8.86
n-Decyl	Cu	$C_{36}H_{62}O_8Cu$	24	123–124	62.99	9.11	62.99	8.96
Lauryl	Cu	$C_{40}H_{70}O_8Cu$	33	122–123.5	64.70	9.50	64.45	9.58
Lauryl	Be	$C_{40}H_{70}O_8Be$	20	50–52	69.92	10.25	70.04	10.16

[a] Reported m.p. 220.[1] [b] Reported m.p. 209.[1]

TABLE II[5]

CHARACTERIZATION OF $(CH_3CO)_2C(CH_2CH_2COOR)_2$

R	M.P., °	Empirical Formula	% Calculated C	% Calculated H	% Found C	% Found H
i-Amyl	54–54.5	$C_{21}H_{36}O_6$	65.59	9.44	65.85	9.62
n-Decyl	56.5–57	$C_{31}H_{56}O_6$	70.95	10.76	71.21	10.81
Lauryl	65–65.5	$C_{35}H_{64}O_6$	72.37	11.11	72.13	10.91

Bis[*3-(2'-carbethoxyethyl)-2,4-pentanediono*]*beryllium* (II). Beryllium nitrate trihydrate (20 g., 0.1 mole) was dissolved in a minimum amount of water in a 500 ml. three necked flask equipped with an efficient stirrer. This solution was buffered to approximately *p*H 5 by the addition of 150 ml. of saturated sodium acetate. Ethyl 5-keto-4-acetylhexanoate (40 g., 0.2 mole) was added and the resultant reaction mixture was stirred vigorously for 2 hr. (precipitation of the product began after 10 min.). The reaction mixture was cooled in an ice bath, and the white product collected by suction filtration, yielding, after being washed with 150 ml. of ice water and dried overnight in vacuo at 50°, 35 g. (87%) of crude beryllium chelate of ethyl 5-keto-4-acetylhexanoate, m.p. 115–118°. Recrystallization from benzene–petroleum ether yielded 31 g. (76%) of white crystalline product, m.p. 113–114°. The infrared spectrum of the compound pressed in potassium bromide contained only a single peak at 6.30 in the 6.25–6.75 μ region, confirming the absence of a hydrogen attached directly to the ring.[6]

The other beryllium compounds were analogously prepared.

Bis[*3-(2'-carbalkoxyethyl)-2,4-pentanediono*]*copper* (II). The crude diketo ester (0.2 mole) was shaken overnight with 100 ml. of aqueous ammoniacal copper sulfate (0.1 mole). The precipitated solid was removed by filtration and crystallized from benzene–petroleum ether. In the 6.25–6.75 μ region of the infrared, these compounds absorbed strongly only at 6.34 μ.

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(5) All melting points are corrected. Analyses by the laboratory of Drs. Weiler and Strauss, Oxford, England.

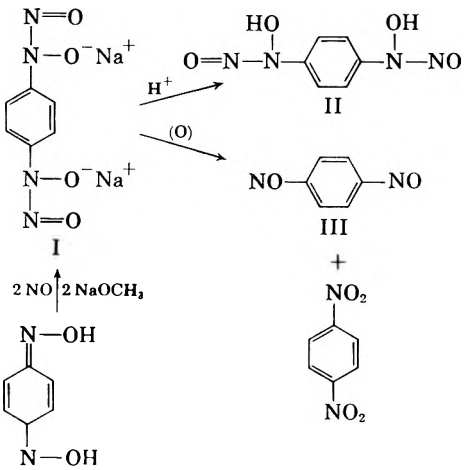
(6) R. P. Dryden and A. Winston, *J. Phys. Chem.*, 62, 635 (1958).

Communications TO THE EDITOR

New Reaction of Oximes and Nitric Oxide

Sir:

We wish to report a new reaction of oximes with nitric oxide. When *p*-benzoquinone dioxime was dissolved in a methanolic solution of sodium methoxide, and treated with oxygen-free nitric oxide at pressures ranging from atmospheric to 100 p.s.i., disodium - di - *N* - nitroso - *p* - phenylenedihydroxylamine (I) was obtained in 98% yield. (*Anal.* Calcd. for $C_6H_4N_4Na_2O_4$: C, 29.76; H, 1.66; N, 23.14; Na, 19.4. Found: C, 29.57; H, 1.74; N, 22.88; Na, 19.36[1]; neut. equiv., 121 ± 2).

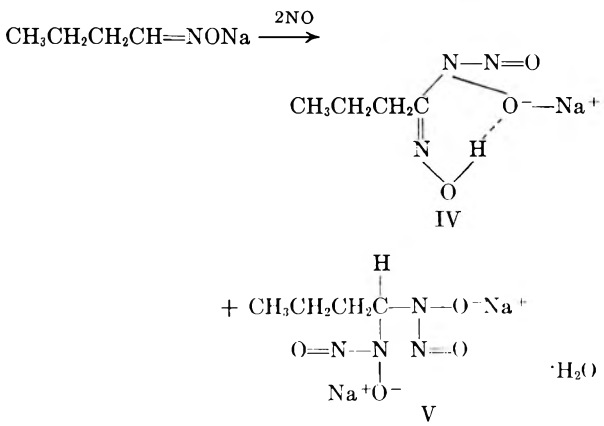


A positive Liebermann test was obtained from I, or the *aci* form II. Upon mild hypochlorite oxidation of I, *p*-dinitrosobenzene (III) was obtained; use of an excess of oxidizing agent gave only *p*-dinitrobenzene. Acidic decomposition of II liberated oxides of nitrogen and III; II is considerably unstable and liberates oxides of nitrogen slowly at room temperature.

This compound is structurally analogous with *N*-nitrosophenylhydroxylamine (Cupferon), and by using similar methods metal cations may be precipitated. The lead salt was prepared. (*Anal.* Calcd. for $C_6H_4O_4Pb$: Pb, 51.3. Found: Pb, 51.1). Organic basis may be substituted for the metal cation by replacing sodium methoxide. The following examples are cited: piperazino salt (*Anal.* Calcd. for $C_{10}H_{16}N_6O_4$: C, 42.3; H, 5.6; N, 29.6. Found: C, 42.3; H, 5.65; N, 29.5), dipiperidino salt (*Anal.* Calcd. for $C_{16}H_{28}N_6O_4$: C, 52.3; H, 7.66; N, 22.4. Found: C, 52.36; H, 7.63; N, 22.91).

Similar products were obtained from *o*-benzoquinonedioxime. (*Anal.* Calcd. for $C_6H_4Ag_2N_4O_4$: Ag, 52.9. Found: Ag, 53.3), 9,10-phenanthraquinonedioxime (*Anal.* Calcd. for $C_{14}H_8N_4Na_2O_4$: Na, 13.5. Found: Na, 13.03), 9,10-anthraquinonedioxime (*Anal.* Calcd. for $C_{14}H_8N_4Na_2O_4$: Na, 13.5. Found: 13.46), thymolquinonedioxime (*Anal.* Calcd. for $C_{10}H_{12}Ag_2N_4O_4$: Ag, 46.1. Found: Ag, 46.0).

Reaction of nitric oxide on sodio-*n*-butyraldoxime in methanol gave *syn*-1-oximino-1-*N*-nitrosohydroxylaminobutane (IV). (*Anal.* Calcd. for $C_4H_8N_3NaO_3$: C, 28.4; H, 4.73; N, 24.9. Found: C, 28.37; H, 4.51; N, 24.4) and smaller amounts of an anti-adduct hydrate (V) (*Anal.* Calcd. for $C_4H_{10}N_4O_5$: C, 20.00; H, 4.17; N, 25.3; Na, 19.17. Found: C, 19.90; H, 4.68; N, 23.9; Na, 19.16). The infrared absorption showed a broad band at 2340 cm.$^{-1}$ for a bonded OH in IV, and in V absorption occurred at 3500–3300 cm.$^{-1}$ (free OH). The remainder of the spectrum is similar.



Using hexane as a solvent in a heterogeneous reaction between the sodium salt of the oxime and nitric oxide, IV was obtained in 88% yield. On acidic decomposition *n*-butyraldoxime was recovered, and basic hydrolysis afforded butyric acid. Analogous products were obtained from isobutyraldoxime (*Anal.* Calcd. for $C_4H_8N_3NaO_3$: C, 28.41; H, 4.73; N, 24.9. Found: C, 27.34; H, 4.62; N, 24.9), benzaldoxime (*Anal.* Calcd for $C_7H_6N_3NaO_3$: C, 41.4; H, 2.95; N, 20.7; Na 11.38. Found: C, 41.35; H, 3.07; N, 20.1; Na, 11.03), cinnamaldoxime (*Anal.* Calcd. for $C_9H_8N_3NaO_3$: N, 18.3; Na, 10.04. Found: N, 17.75; Na, 10.11), 2-thiophenaldoxime (*Anal.* Calcd. for $C_5H_4N_3NaO_3S$: C, 28.70; H, 1.93; N, 20.09; Na, 10.99. Found: C, 28.32; H, 2.38; N, 19.99; Na, 10.56), *p*-chlorobenzaldoxime (*Anal.* Calcd. for $C_7H_4ClN_3NaO_2$: C, 35.37; H, 2.12; N, 17.68; Na 9.67; Cl, 14.95. Found: C, 35.16; H, 1.98; N, 16.72; Na, 9.88; Cl, 15.18).

Extension of the reaction to ketoximes resulted in

(1) Difficulty was encountered in obtaining accurate analyses because of the explosive character and the light sensitivity of some of these compounds.

the absorption of two moles of nitric oxide; however, the products obtained are unstable.

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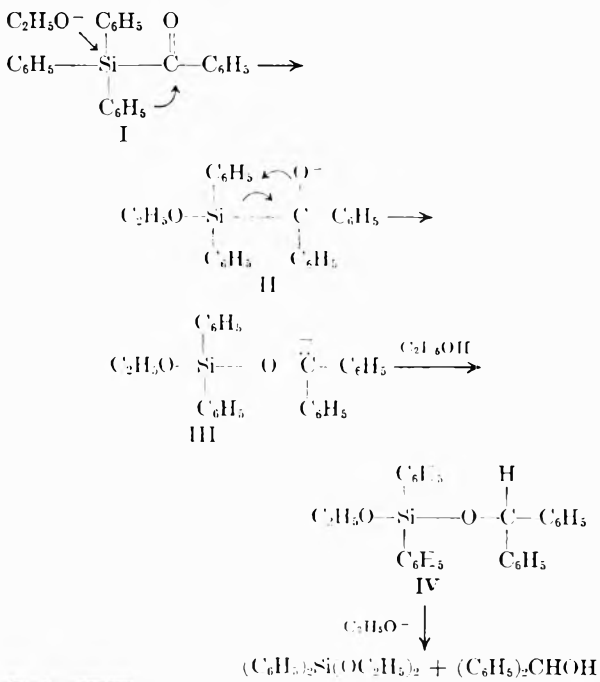
Received March 22, 1960

Alkoxide-Catalyzed Rearrangements of Benzoyltriphenylsilane

Sir:

It has been reported that benzoyltriphenylsilane (I) decomposes in dilute aqueous sodium hydroxide solution at room temperature to triphenylsilanol and benzaldehyde.[1] An even more interesting reaction occurs when the ketone is treated with sodium ethoxide. The major product isolated is benzhydryloxyethoxydiphenylsilane (IV), obtained in 61% yield along with small quantities of benzhydrol and diphenyldiethoxysilane, shown to be formed by subsequent reaction of ethoxide ion with IV.

Evidently nucleophilic attack by ethoxide ion on silicon results in the displacement of a phenyl group from silicon to the carbonyl-carbon atom, the formation of a bond between silicon and the carbonyl-oxygen, and the cleavage of the silicon carbonyl—carbon bond. The result of these 1,2-rearrangements, probably proceeding *via* anion II, is the carbanion III, leading to the final product by reaction with the solvent. A similar result was obtained using sodium methoxide.



(1) A. G. Brook, *J. Am. Chem. Soc.*, 79, 4373 (1957).

The reaction may be presumed to occur in two steps, both of which have been observed before. The migration of an aryl group from silicon to an *alpha* carbon has been reported by Eaborn and Jeffrey[2] under similar conditions, and bond formation between silicon and an oxygen atom once removed is observed in the rearrangement of α-silylcarbinols to their isomeric ethers.[3] The distinctive feature of the present reaction is the occurrence of two successive rearrangements. Further work is in progress.

Treatment of 5.0 g. (0.0137 mole) of benzoyltriphenylsilane in 50 ml. of benzene with the sodium ethoxide from approximately 0.1 g. of sodium in 25 ml. of ethanol for 6 hr. at room temperature, during which time the yellow color faded, followed by hydrolysis in dilute acid led to the isolation of a total of 3.24 g. (61%) of benzyhydroxyethoxydiphenylsilane (IV), m.p. 77–78.5° from ethanol (*Anal.* Calcd. for $C_{27}H_{26}O_2Si$: C, 79.0: H, 6.38. Found: C, 78.8: H, 6.38). The mother liquors on distillation at 126°/1 mm. gave partially crystalline material from which was isolated 0.20 g. (8%) of benzhydrol, m.p. 67–68°, and 0.3 g. (8%) of diphenyldiethoxysilane, b.p. 130°/2 mm., n_D^{20} 1.5303. The infrared spectra of all compounds were consistent with the proposed structures; the latter two compounds were compared with authentic samples.

Treatment of IV in ethanol with hot dilute aqueous sodium hydroxide for 1 hr. gave 73% diphenylsilanediol, m.p. 163–166°, and 68% benzhydrol, m.p. 66–68°, both identified by infrared spectra and mixed melting point. Treatment of IV with one equivalent of sodium ethoxide over 22 hr. at room temperature gave 90% benzhydrol, m.p. 66–68°, a trace of diphenylsilanediol, and 30% of diphenyldiethoxysilane, b.p. 131°/2 mm., n_D^{20} 1.5281.

Similar treatment of I with sodium methoxide gave 20% of benzhydryloxymethoxydiphenylsilane, m.p. 45–47.5° from methanol. *Anal.* Calcd. for $C_{26}H_{24}O_2Si$: C, 78.8: H, 6.06. Found: C, 78.8: H, 6.03. In addition benzhydrol (31%) and diphenyldimethoxysilane (15%), b.p. 108°/0.5 mm., n_D^{20} 1.550 were obtained, and were identified by comparison with authentic samples. All compounds had infrared spectra consistent with the proposed structures.

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(2) C. Eaborn and J. C. Jeffrey, *J. Chem. Soc.*, 137 (1957).

(3) A. G. Brook, *J. Am. Chem. Soc.*, **80**, 1886 (1958); A. G. Brook, C. M. Warner and M. McGriskin, *J. Am Chem. Soc.*, **81**, 981 (1959).