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1-Methyl-7-halo-2-naphthalenecarboxylic Acid Derivatives

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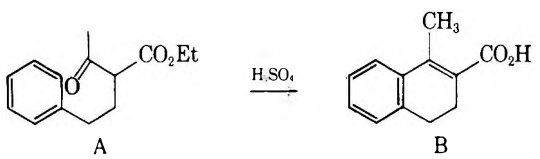
β-(*p*-Bromo and *p*-chlorophenyl)ethyl acetoacetic esters (**6**) were cyclized with cold concentrated sulfuric acid affording the respective 1-methyl-2-carboxy-7-halo-3,4-dihydronaphthalenes (**7**) which were esterified and then aromatized with bromine to the naphthalene compound. Studies of the condition of the ring-closure reaction are reported. Reduction of the naphthalene ester and subsequent treatment with phosphorous tribromide afforded 1-methyl-7-halo-2-bromomethylnaphthalenes (**11**). 7-Bromo-1-tetralone (**12**) was converted to the corresponding 2-carboxylic acid (**13**) and 2-carboethoxy ester (**16**), but attempts to introduce the 1-methyl group failed.

One difficulty in the preparation of polyfunctional naphthalenes from naphthalene and mono- and disubstituted naphthalenes is the myriad of possible products with similar properties which may be formed. The more acute problem arises in those cases where a *particular isomer* cannot be readily synthesized in good yield and a high degree of purity by using any combination of simple, available naphthalene starting materials and employing known reaction sequences.[2] This is the situation for the 1-methyl-7-halo-2-naphthalenecarboxylic acids and their derivatives.

The key step in the present ten-step syntheses is a modification of the van Auwers[3] ring closure of β-



A B

phenethylacetoacetic ester (A), which affords 1-methyl-3,4-dihydronaphthalene-2-carboxylic acid (B). The conditions and variables for the reaction have been studied here; the yields have been substantially increased. The reactions were initially carried out using the β-(*p*-chlorophenyl) compound, but, when the prepared material had been consumed, we turned to the synthesis of the corresponding bromo isomers. Finally, a carboxyl group was introduced into the 2-position of 7-bromo-1-tetralone; however, further transformations did not appear promising and the ring-closure reactions are preferred for obtaining the desired 1,2,7-trisubstitution pattern.

Synthesis of 7-Bromo- and 7-Chloro-3,4-dihydronaphthalene-2-carboxylic Acids (I).— *p*-Bromobenzyl bromide (**1** Br) and *p*-chloroacetonitrile (**2** Cl) are the commercially available starting materials for these two sequences. Compounds **2** Br, **3**, **4**, and **5** were prepared in good to excellent yields by slight modifications of standard procedures. An attempt to prepare bromide **5** using phosphorous tribromide led to lower yields of less pure product. The alkylation reaction (**5** → **6**) in the bromo series was modified from run to run (see Experimental), but the product was consistently obtained in only 45–55% yield.

The conditions of the sulfuric acid ring-closure reaction were critical in terms of obtaining maximum yields. A study of the various factors is set forth in Tables I and II for the chloro and the bromo series. Several attempts to use polyphosphoric acid failed. Even the maximum yield shown for the chloro compound (expt. 43) surely does not reflect the optimum conditions which might be found; our later experience with the bromo series indicates the use of still longer reaction times. When the reactants (ester **6** and concentrated sulfuric acid) are mixed at low temperature, there is formed an immediate yellow, orange, or red color, and, in general, the higher the ratio of sulfuric acid, the lighter the initial color. In all cases where it was sought, at least some starting material was recovered, although often only a few tenths of a per cent. This ester could be subjected again to the conditions of the cyclization reaction and additional acid obtained. Aromatic sulfonation is a slow competitive reaction which

(1) (a) To whom inquiries may be directed at the University of California; (b) National Science Foundation Undergraduate Research Participants, summer, 1962.

(2) For example, see the excellent discussion of naphthalene and tetralone chemistry by E. H. Rodd and J. Van Alpher ("Chemistry of Carbon Compounds," Vol. IIIB, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1956, Chapter XX, pp. 1273–1348) and by N. Donaldson ("The Chemistry and Technology of Naphthalene Compounds," E. Arnold Publishers, Ltd., London, 1958).

(3) (a) K. van Auwers and K. Müller, *J. prakt. Chem.*, **104**, 124 (1925). (b) For the formation of cyclic ketones from acids see W. S. Johnson, *Org. Reactions*, **2**, 114 (1944).

TABLE I

CYCLIZATION CONDITIONS FOR 1-METHYL-7-CHLORO-3,4-DIHYDRONAPHTHALENE-2-CARBOXYLIC ACID (7 Cl)

Expt. no.	Ratio H_2SO_4–ester (6)	% yield	Recovered ester (6), g.	% conversion	Comments
20	10.0	0	*a*		1 hr. at 0°
25	8.1	1	9.2		1 hr. at 0°
26	8.2	8	7.0	33	6 → 15° on mixing, cooled to 6°; total, 30 min.
27	7.9	52	2.6	83	4 → 13° on mixing, cooled to 10°, and allowed to warm to room temperature; total, 30 min.
30	8.0	55	0.7	65	25 → 40° on mixing; total, 30 min. at ambient temperatures
39	8.0	1	0.2	15	85 → 105° on mixing, stirred at 87° on steam bath for 30 min.
40	7.7	38	1.8	90	4 → 14° on mixing, cooled to 10°, and allowed to warm to room temperature; total, 30 min.
41	8.0	39	11.5	91	Same as 40
42A	8.0	31	10.4[b]	66[b]	Same as 40
42B	8.7	20	34.0	78	Same as 40
42C	8.8	40	18.8	89	Same as 40 except 1-hr. total
43	7.3	61	10.0	91	Same as 40 except 2-hr. total

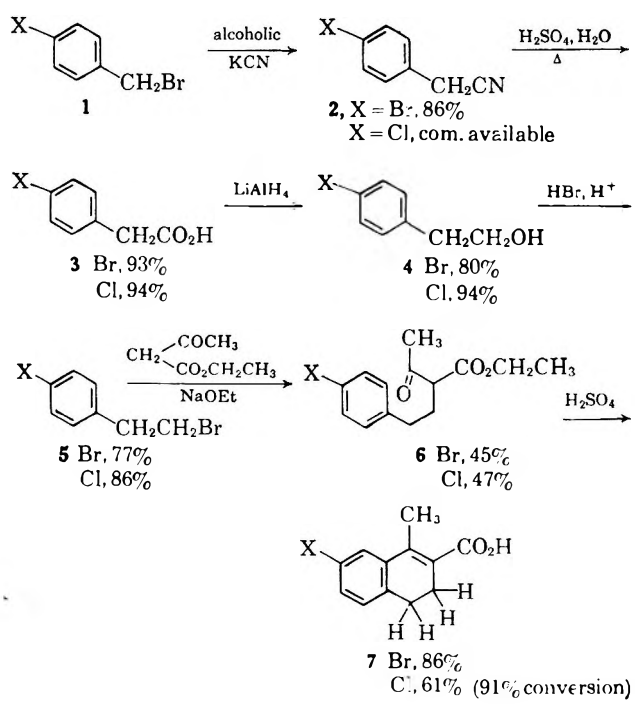
[a] No attempted isolation. [b] Represents minimum, some loss by spillage.

TABLE II

CYCLIZATION CONDITIONS FOR 1-METHYL-7-BROMO-3,4-DIHYDRONAPHTHALENE-2-CARBOXYLIC ACID (7 Br)

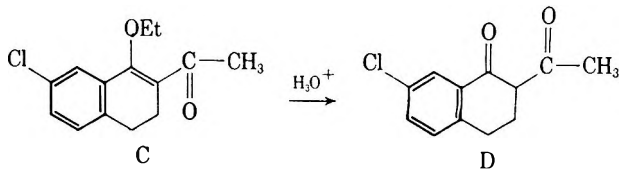
Expt. no.	Ratio H_2SO_4–ester (6)	Time, hr.	% yield	Recovered ester (6), g.	% conversion
42[a]	9.2	2.0	49	1.2	55
55[a]	10.2	1.0	17	16.6	58
56[a]	10.2	1.0	7	8.9	15
63	9.2	1.0	28	2.9	59
69	18.3	19.5	70	0.3	73
71	20.0	37.5	54	0.8	56
73	20.0	24.0	62	1.1	65
103	20.2	18.0	86	*b*	
115	9.2	19.5	68	0.3	72
119A	27.5	19.5	76	0.3	80
119B	37.6	19.5	73	0.1	75
125	27.6	19.5	77		

[a] These were early experiments carried out by one investigator; the remainder was performed by another. [b] No attempted isolation.

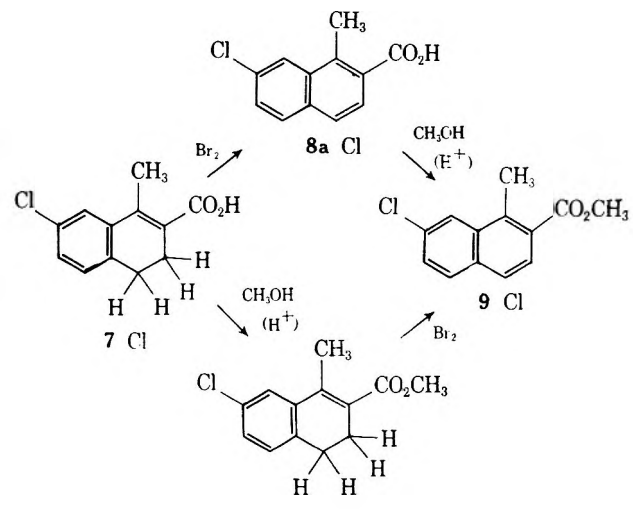


may account, at least in part, for the loss of material. Although the yield has been significantly reduced between 18 and 19.5 hr. (expt. 103 and 69), the optimum yield might be obtained after shorter reaction times.

In addition to the analytical and spectral evidence (see Experimental) which has been obtained for the structure of acid **7**, it was shown that the product did not contain sulfur, thus ruling out sulfonic acids. Further, a negative iodoform test indicates that it is not the compound which would be obtained by ring closure of the ester carbonyl (C), nor its subsequent hydrolysis product, diketone D.

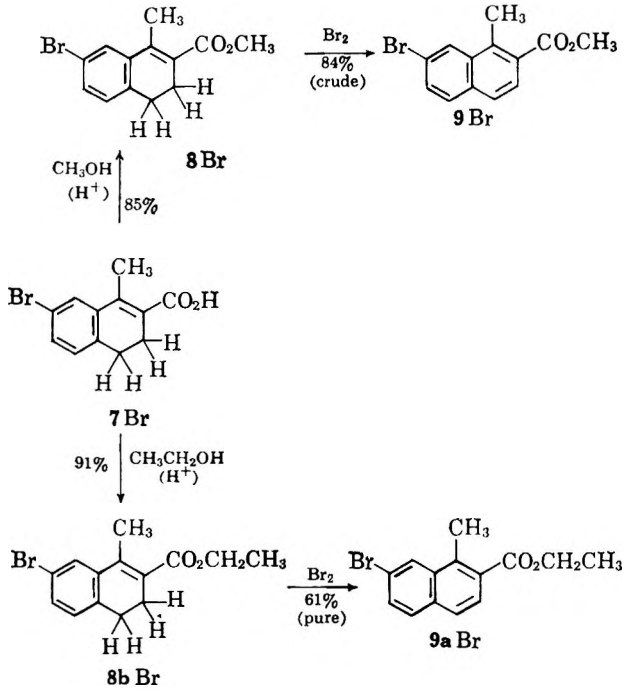


Aromatization and Naphthalene Derivatives.—The oxidation of the 3,4-dihydronaphthalenes was accomplished by treating a warm solution of the compound with bromine in carbon tetrachloride. In the chloro series, this was carried out both with the acid (**7** Cl) and

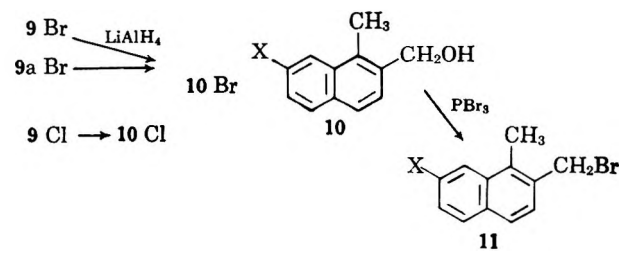


with the corresponding methyl ester (**8** Cl). Acid **7** Cl was extremely insoluble in carbon tetrachloride; however, ester **8** Cl was quite soluble and readily underwent aromatization. The compounds (**9** Cl) prepared by these two routes were identical.

Having established that the aromatization could be readily effected using the ester, both the methyl (**8** Br) and the ethyl esters (**8b** Br) were prepared in the bromo series and were smoothly aromatized. The higher melting 3,4-dihydroethyl ester (**8b** Br) was more readily purified and is to be preferred. Neither of these aromatized compounds, however, gave completely satisfactory elemental analyses despite repeated attempts at purification. Spectral data were consistent with these structures and further chemical transformations (*vide infra*) served to establish the structures.



The naphthalene esters in both series were reduced to the corresponding hydroxymethyl compounds (**10**) with lithium aluminum hydride and subsequently converted with phosphorous tribromide to the respective 1-methyl-2-bromomethyl-7-halonaphthalene (**11**). In the bromo series, reduction of the methyl and of the ethyl esters afforded products which were identical.

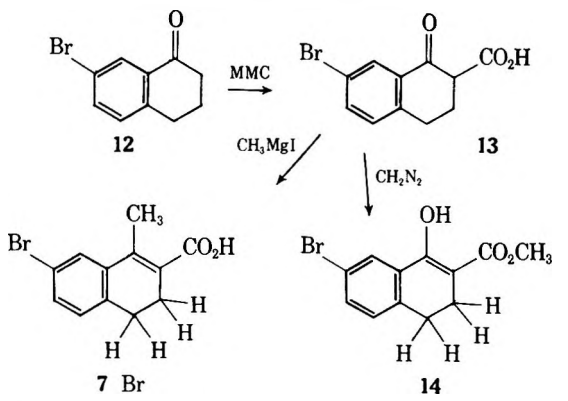


Attempts *via* 7-Bromo-1-tetralone (12).—Introduction of a carboxyl group into the 2-position of 7-bromo-1-tetralone (**12**) may be accomplished by at least two direct methods which utilize the activated methylene of 1-tetralones: (a) the use of methylmagnesium carbonate,[4] and (b) the alkylation with diethyl oxalate, followed by decarbonylation.[5] Both methods have been successful in our hands, and a few Grignard reactions of these compounds were attempted.

7-Bromo-1-tetralone (**12**) has been synthesized by the succinoylation of bromobenzene, followed by Clemmensen reduction and subsequent ring closure, using improved modifications of the procedures described previously.[6] The over-all yield has been increased to 50% employing a direct ring closure of the acid.

The conditions of this polyphosphoric acid (PPA) ring closure were most critical[7,8] and, consequently, were studied in some detail in order to obtain maximum yields of ketone **12**. The best yield in these experiments was obtained by mixing the starting material with PPA at 40° and maintaining the temperature at 75° for 35 min. (63% yield), but this was nearly the same as starting at 40°, maintaining the mixture at 70° for 10 min., and finally at 80° for 20 min. (61% yield). The lowest yield (39%) was obtained by heating the mixture at 80° for 7 min.

Ketone **12** was added to a solution of methylmagnesium carbonate (MMC) in dimethylformamide (DMF) and β-keto acid **13** was obtained in 27–57% yields (40% average). The compound is *extremely* susceptible to decarboxylation not only on storage in a dry atmosphere but especially in solution (*vide infra*). Preparation of



methyl ester **14**, using diazomethane in cold ether, proceeded in poor yield (31%), and a considerable amount of starting ketone **12** was obtained as a result of decarboxylation. However, the methyl ester was stable and easily handled.

Treatment of acid **13** with methylmagnesium iodide led to the isolation of only traces of 1-methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (**7** Br), and, again, considerable quantities of ketone **12** were produced. The instability of acid **13** and the poor yields of acid **7** Br dictated the route employing diethyl oxalate.

The glyoxalyl derivative **15** was prepared in yields of 50–70% using diethyl oxalate and sodium ethoxide. The bright yellow, α,γ-diketo ester **15** was stable and underwent a ready decarbonyation over soft glass at 180–185° in 85–90% yields. The n.m.r. spectrum indicates that β-keto ester **16** exists predominantly in the enol form under these conditions ($CDCl_3$) and the enol

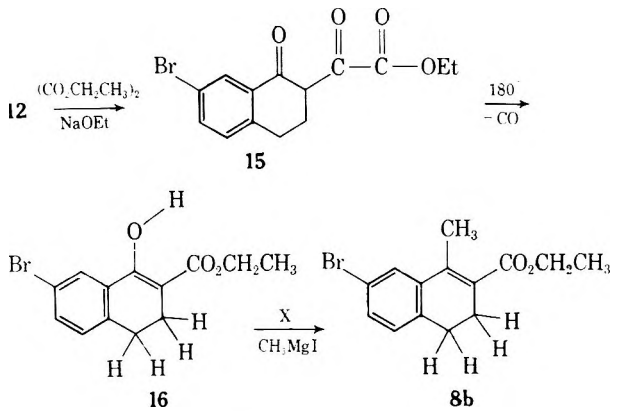
(4) M. Stiles, *J. Am. Chem. Soc.*, **81**, 2598 (1959).

(5) For a general discussion, see C. R. Hauser, F. W. Swamer and J. T. Adams, *Org. Reactions*, **8**, 116 (1954). For a specific example, see H. R. Snyder, L. A. Brooks and S. H. Shapiro, "Organic Syntheses," Coll. Vol. II John Wiley and Sons, Inc., New York, N. Y., 1943, p. 251.

(6) L. F. Fieser and A. M. Seligman, *J. Am. Chem. Soc.*, **60**, 170 (1938)

(7) J. Koo, *ibid.*, **75**, 1891 (1953).

(8) H. R. Snyder and F. X. Werber, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 798.



proton is found at τ −2.45 at 60 Mc.[9] Treatment of ester **16** with methylmagnesium iodide (inverse addition) gave immediate gas evolution and afforded none of the desired 3,4-dihydronaphthalene **8b** Br; 77% of the starting material was recovered unchanged.

Experimental[10]

The Chloro Series. *p*-Chlorophenylacetic Acid (3 Cl).—This is a modification of the hydrolysis of phenylacetonitrile.[11] A mixture of 210 ml. of concentrated sulfuric acid, 280 ml. of water, and 226.7 g. (1.49 moles) of *p*-chlorophenylacetonitrile (Eastman Kodak, No. P-6947, m.p. *ca.* 28–30°) was heated under reflux with stirring for 3 hr. The reaction mixture was poured with stirring into 1 l. of cold water and the entire suspension was treated with sufficient ether to dissolve the solids. The aqueous layer was repeatedly extracted with ether and the combined organic layer was dried and evaporated affording 243.9 g. of *p*-chlorophenylacetic acid (96% yield) as white crystals, m.p. 102–106°. A small sample was recrystallized twice from ether–petroleum ether (b.p. 30–60°), raising the melting point to 106–107° (lit.[12] m.p. 104–105°).

2-(*p*-Chlorophenyl)ethanol (4 Cl).—A solution of 107.4 g. (0.614 mole) of *p*-chlorophenylacetic acid (**3** Cl) in 400 ml. of dry ether (distilled from *n*-butylmagnesium bromide) was added dropwise over a period of 2 hr. to a stirred mixture of lithium aluminum hydride (38 g., 1.0 mole) in 800 ml. of dry ether. Refluxing was continued for 1 hr., the mixture was cooled to room temperature, and the excess hydride was decomposed by the dropwise addition of methanol. Ice and dilute hydrochloric acid were then added, the layers were separated, and the aqueous layer was extracted several times with ether. The combined ether extracts were washed with water, dried, and evaporated.

The remaining oil was distilled at reduced pressure affording 93.2 g. (94% yield) of colorless 2-(*p*-chlorophenyl)ethanol in those fractions which distilled at 144–153° at 30–34 mm. (lit.[13] 166° at 47.2 mm.).

The reaction was run several times and the yields were generally about 90%. Other values were obtained for the distilling range: 163–165° at 44.5 mm. and 127–129° at 9 mm.

2-(*p*-Chlorophenyl)bromoethane (5 Cl).—To a stirred mixture of 60 ml. of 48% hydrobromic acid and 15 ml. of concentrated sulfuric acid was added over a period of 5 min. 58.9 g. (0.376 mole) of 2-(*p*-chlorophenyl)ethanol (**4** Cl). An additional 10 ml. of concentrated sulfuric acid was added and the mixture was heated under reflux for 3 hr. The mixture was cooled to room temperature and poured over ice. The layers were separated and the aqueous solution was extracted with several portions of ether. The combined ether extracts were successively washed with water, dilute sodium bicarbonate, and water, and then dried and evaporated.

The resulting oil was distilled at reduced pressure and the fractions collected at 114–123° at 7 mm. afforded 70.7 g. (86% yield) of 2-(*p*-chlorophenyl)-1-bromoethane (**5** Cl) as a colorless oil, (b.p. 133° at 15 mm.).

Anal. Calcd. for C_8H_8BrCl: C, 43.77; H, 3.67; total halogen, 52.55. Found: C, 43.94; H, 3.79; total halogen, 52.38.

The yield in this reaction was generally 70–80%; however, treatment of the alcohol with phosphorus tribromide afforded the corresponding bromide in only 50–55% yield.

3-Carbethoxy-5-(*p*-chlorophenyl)pentanone-2 (6 Cl).—To a stirred solution of sodium ethoxide (prepared from 17 g. (0.74 g.-atom) of sodium in 400 ml. of absolute ethanol) was added 97 g. (0.745 mole) of ethyl acetoacetate followed by the dropwise addition of 134.5 g. (0.613 mole) of 2-(*p*-chlorophenyl)-1-bromoethane (**5** Cl). The mixture was heated under reflux for 6 hr. and then allowed to stand at room temperature with stirring for *ca.* 30 hr. Water and dilute hydrochloric acid were added, the layers were separated, and the aqueous layer was washed with ether. The combined ether portion was successively washed with water, dilute sodium bicarbonate, and water. (Acidification of the bicarbonate washings gave a negligible precipitate.) The ether was dried and removed and the resulting oil was distilled at reduced pressure.

The fraction distilling at 140–160° (most at 155°) and 1.5 mm. was collected and represents 164.5 g. (47% yield) of 3-carbethoxy-5-(*p*-chlorophenyl)pentanone-2. The material was redistilled twice (138.5–139° at 0.5–0.7 mm. and 139.5–140° at 0.8 mm.). The infrared spectrum (CCl_4) showed peaks at 5.77 and 5.70 (shoulder) μ (C=O).

Anal. Calcd. for $C_{14}H_{17}ClO_3$: C, 62.57; H, 6.38; Cl, 13.19. Found: C, 62.70; H, 6.19; Cl, 13.21.

1-Methyl-2-carboxy-7-chloro-3,4-dihydronaphthalene (7 Cl).—This reaction was carried out many times (see Table I) and these directions represent the case of maximum yield (expt. 43), although not necessarily the optimum conditions.

Concentrated sulfuric acid (240 g.) and 33.29 g. (0.124 mole) of 2-carbethoxy-5-(*p*-chlorophenyl)pentanone-2 (**6** Cl) were separately cooled to 4° and the ester was then added to the sulfuric acid. Although the temperature rose, the mixture was swirled in the ice bath until the temperature had dropped to 10°. The flask was removed from the bath and allowed to come to room temperature. After 2-hr. total reaction time, the mixture was poured onto ice, ether was added, the layers were separated, and the aqueous portion was extracted with ether. The combined organic layer was washed with water and subsequently with 10% sodium hydroxide.

The sodium hydroxide layer was acidified with dilute hydrochloric acid and extracted with several portions of ether. The dried ether was evaporated, affording 16.94 g. (61% yield) of 1-methyl-2-carboxy-7-chloro-3,4-dihydronaphthalene (**7** Cl) as a white solid.

A sample was recrystallized successively twice from benzene–petroleum ether, once from ether–petroleum ether, and twice from benzene, affording white crystals, m.p. 212–212.5°.

Anal. Calcd. for $C_{12}H_{11}ClO_2$: C, 64.73; H, 4.98; Cl, 15.92. Found: C, 64.74; H, 4.64; Cl, 15.721.

The ether solution which had been extracted with base was dried and evaporated affording 9.96 g. of an oil, whose infrared spectrum was identical with that of starting material. This represents a 91% conversion to the dihydronaphthalene compound. The oils thus recovered were cyclized with sulfuric acid affording additional product: $\lambda_{max}^{95\%\ EtOH}$ 228 (log ϵ 4.31), 278 (4.05), and 304 (shoulder) mμ (3.77).

1-Methyl-2-carbomethoxy-7-chloro-3,4-dihydronaphthalene (7 Cl).—A mixture of 10.79 g. (0.49 mole) of 1-methyl-2-carboxy-7-chloro-3,4-dihydronaphthalene (**7** Cl), 300 ml. of absolute

(9) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," International Series Monographs on Organic Chemistry, Vol. V, Pergamon Press, London, 1959, p. 71.

(10) Melting points are uncorrected and were taken at 1°/min. (or less) on a Fischer-Johns apparatus. The spectra were recorded as follows: infrared, Perkin-Elmer Model 21, fitted with sodium chloride optics, and Perkin-Elmer Infracord; ultraviolet, Cary recording spectrophotometer and with the Perkin-Elmer Model 202; n.m.r., Varian Associates Model A-60, usually as a dilute solution in chloroform-*d* and tetramethylsilane (TMS) (internal standard). It has been our standard practice to distil tetrahydrofuran (THF) twice from lithium aluminum hydride (pre-drying over anhydrous calcium chloride if necessary). The second distillation is usually carried out under an atmosphere of dry nitrogen. Solvents for infrared and n.m.r. spectral determinations are always dried immediately before use by passing them through a capillary dropping tube containing a few grams of alumina, usually Woelm, activity grade I. The addition of decolorizing charcoal to organic solutions of crude compounds still containing a drying agent greatly aids later purification by distillation or crystallization. Anhydrous magnesium sulfate was used throughout as the drying agent.

(11) R. Adams and A. F. Thal, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 436.

(12) F. Beilstein and A. Kuhlberg, *Ann.*, **147**, 346 (1868).

(13) R. R. Dreisbach and S. A. Shroder, *Ind. Eng. Chem.*, **41**, 2879 (1948).

methanol, and 6 ml. of concentrated sulfuric acid was heated under reflux for 8 hr. and allowed to stand overnight at room temperature. Water was added and the mixture was extracted with several portions of ether. The combined ether extracts were washed successively with water, 10% sodium hydroxide, water, 5% hydrochloric acid, and water, and then dried. The ether was taken to dryness affording 10.56 g. (93% yield) of 1-methyl-2-carbomethoxy-7-chloro-3,4-dihydronaphthalene (8 Cl) as a white solid, m.p. 50–51.5° after recrystallization from petroleum ether.

An analytical sample was successively recrystallized once from *n*-hexane, once from ether, and three times from petroleum ether. The sample melted at 51–52°.

Anal. Calcd. for $C_{13}H_{13}ClO_2$: C, 65.96; H, 5.54; Cl, 14.98. Found: C, 65.81; H, 5.73; Cl, 14.86.

This ester was also prepared from diazomethane in lower yields. The infrared spectra of the methyl esters prepared by these two methods were identical.

1-Methyl-2-carbomethoxy-7-chloronaphthalene (9 Cl) *via* the 3,4-Dihydronaphthalene Ester (8 Cl).—To a boiling solution of 7.51 g. (0.032 mole) of 1-methyl-2-carbomethoxy-7-chloro-3,4-dihydronaphthalene (8 Cl) in 100 ml. of carbon tetrachloride was added slowly 10 ml. of carbon tetrachloride solution containing 0.045 mole (6 ml.) of bromine. After the addition, the solvent was removed *in vacuo* and the resulting solid was recrystallized several times from ether–petroleum ether and again from methanol affording 1-methyl-2-carbomethoxy-7-chloronaphthalene (9 Cl) as white crystals, m.p. 86–87.5°. The following spectral properties were found: infrared (CCl_4), 5.81 μ (C=O); ultraviolet, $\lambda_{max}^{95\%\ EtOH}$ 233 (log ϵ 4.74), 243 (4.69, shoulder), 274 (3.90), 284 (3.91), and 295 mμ (3.72); n.m.r. (CCl_4), C_1–CH_3, τ 7.23 (singlet), $-CO_2CH_3$, τ 6.12 (singlet), Ar-C_8-H, τ 2.00 (singlet), and other Ar-H at τ 2.31–2.65 (complex multiplet, maximum at τ 2.47).

Anal. Calcd. for $C_{13}H_{11}ClO_2$: C, 66.53; H, 4.73; Cl, 15.11. Found: C, 66.13; H, 4.58; Cl, 14.87.

1-Methyl-2-carboxy-7-chloronaphthalene (8a Cl).—To a boiling slurry of 10.33 g. (0.046 mole) of 1-methyl-2-carboxy-7-chloro-3,4-dihydronaphthalene (7 Cl) in 300 ml. of carbon tetrachloride was added 11 ml. of a carbon tetrachloride solution containing 0.050 mole of bromine. Fumes of HBr were evolved. The mixture was cooled in an ice bath and filtered affording a solid, m.p. 210–230° after recrystallization several times from toluene.

A portion of this solid was refluxed with 100 ml. of 10% sodium hydroxide for 4 hr., acidified with hydrochloric acid, and filtered. The solid was recrystallized several times from toluene and from benzene–toluene, affording 1-methyl-2-carboxy-7-chloronaphthalene (8 Cl) as a white solid, m.p. 242.5–244°.

Anal. Calcd. for $C_{12}H_9ClO_2$: C, 65.32; H, 4.11; Cl, 16.07. Found: C, 65.25; H, 4.41; Cl, 15.77.

1-Methyl-2-carbomethoxy-7-chloronaphthalene (9 Cl) *via* the Naphthoic Acid (8a Cl).—A mixture of 640 mg. (2.9 mmoles) of 1-methyl-2-carboxy-7-chloronaphthalene (8a Cl), 20 ml. of absolute methanol, and 0.5 ml. of concentrated sulfuric acid was heated under reflux for 6 hr. and allowed to stand overnight at room temperature. Crystals had formed in the flask and these were collected and recrystallized from ether affording 1-methyl-2-carbomethoxy-7-chloronaphthalane, m.p. 85–86.5°. Mixture melting point with a sample of the ester (m.p. 86–87.5°) prepared *via* the 3,4-dihydronaphthalene was 85.5–87°.

1-Methyl-2-hydroxymethyl-7-chloronaphthalene (10 Cl).—To a mixture of 1.2 g. (0.0316 mole) of lithium aluminum hydride in 75 ml. of dry ether (distilled from *n*-butylmagnesium bromide) which had been refluxed for 1 hr. was added, dropwise over a period of 0.5 hr., a solution of 5.91 g. (0.0251 mole) of 1-methyl-2-carbomethoxy-7-chloronaphthalene (9 Cl) dissolved in 150 ml. of dry ether. The mixture was refluxed for 8 hr., allowed to cool to room temperature, and successively treated with ethyl acetate, methanol, ice, and sufficient 1:1 hydrochloric acid to dissolve the solids. The layers were separated and the aqueous portion was saturated with sodium chloride and extracted with ether. The combined organic portion was washed with saturated sodium chloride solution, dried, treated with charcoal, and taken to dryness, affording a white solid which gave 2.88 g. (55% yield) of 1-methyl-2-hydroxymethyl-7-chloronaphthalene (10 Cl) after recrystallization from ether–petroleum ether. Two crystalline modifications were obtained depending on the conditions of the crystallization: rosettes, m.p. 96.5–97°, and flat needles which first melted at 83.5°, solidified, and remelted at 96.5–97°. The former were usually obtained from solutions which had been cooled overnight in the freezing compartment of a refrigerator; the latter precipitated from solution at room temperature. Further, a sample melting at 85° was allowed to stand in the cold and reverted to the 97° form.

A sample consisting of both crystalline forms was submitted for analysis and showed the following spectral properties: infrared (CCl_4), 2.78 μ (–OH); ultraviolet, $\lambda_{max}^{CH_3OH}$ 232.5 (log ϵ 4.93) and 278 mμ (3.71, broad); n.m.r. (CCl_4), C_1–CH_3, τ 7.52 (singlet), $-C_2$–CH_2–, τ 5.14 (doublet, $J \sim 7$ c.p.s.), $-C_2$–CH_2–OH, τ 6.65 (broad multiplet), Ar-C_8-H, τ 2.97 (singlet), and other Ar-H at τ 2.1–2.75 (complex multiplet, maximum peak at τ 2.38).

Anal. Calcd. for $C_{12}H_{11}ClO$: C, 69.74; H, 5.37; Cl, 17.16. Found: C, 69.45; H, 5.33; Cl, 17.28.

1-Methyl-2-bromomethyl-7-chloronaphthalene (11 Cl).—A mixture of 1.988 g. (0.0097 mole) of 1-methyl-2-hydroxymethyl-7-chloronaphthalene (10 Cl) and 8 g. (0.0295 mole) of phosphorous tribromide in 24 ml. of dry carbon tetrachloride was refluxed 6 hr. and then allowed to stand at room temperature for 24 hr. The solution was decanted from the small amount of acid (H_3PO_3) and poured into an equal volume of ice–water. The layers were separated and the organic portion was washed several times with ice–water, dried, filtered, and taken to dryness. The residue was recrystallized from ether–petroleum ether (charcoal) affording a total of 0.682 g. (26% yield) of 1-methyl-2-bromomethyl-7-chloronaphthalene (11 Cl), m.p. 92–93°.

A sample was further recrystallized to m.p. 92.5–93°, submitted for analysis, and showed the following spectrum: n.m.r. (CCl_4), C_1–CH_3, τ 7.46 (singlet), $-C_2$–CH_2–Br, τ 5.45 (singlet), Ar-C_8-H, τ 2.12 (singlet), and other Ar-H at τ 2.30–2.87 (complex multiplet, maximum at τ 2.66).

Anal. Calcd. for $C_{12}H_{10}ClBr$: C, 53.46; H, 3.74; Cl, Br, 42.79. Found: C, 53.29; H, 3.85; Cl, Br, 42.90.

The Bromo Series. *p*-Bromobenzyl Cyanide (2 Br).—A mixture of 16.3 g. (0.251 mole) of potassium cyanide in 150 ml. of 95% ethanol and 65 ml. of water was heated to reflux and 49 g. (0.195 mole) of solid *p*-bromobenzyl bromide (1 Br) was added in portions through the condensor over a period of 0.5 hr. An additional 50 ml. of 95% ethanol was used to wash the condensor. The mixture was refluxed for 30 min., 500 ml. of water was added, and the yellow oil, which solidified, was removed and recrystallized from 75 ml. of 95% ethanol (charcoal). After standing in the freezing compartment of a refrigerator overnight, 33 g. (86% yield) of *p*-bromobenzyl cyanide (2 Br) was obtained (two crops), m.p. 47.5–48.5° (lit.[14] m.p. 50°). Many additional runs with a 45-min. reflux period were carried out on larger scale (250 g. of *p*-bromobenzyl bromide) and the *p*-bromobenzyl cyanide was consistently obtained in good yield (79–81%) and in high purity (m.p. *ca.* 47–49°).

***p*-Bromophenylacetic Acid (3 Br).**—A stirred mixture of 599.4 g. (3.06 moles) of *p*-bromobenzyl cyanide (2 Br) in 650 ml. of concentrated sulfuric acid and 860 ml. of water was heated under reflux for 3 hr. and poured into 2.55 kg. of ice–water; the resulting white solid was collected by suction filtration, washed with fresh ice–water, and sucked for several hours at the water pump. The granular solids were dissolved in 2.5 l. of ether, dried (charcoal), filtered, concentrated to 1 l., diluted with 800 ml. of petroleum ether, swirled, and allowed to stand for 1 hr. in an ice–water bath. The solid was collected, washed with a little fresh cold solvent, air-dried for several hours, and finally dried overnight in a vacuum desiccator (P_2O_5). There was obtained 609.3 g. (92.5% yield) of *p*-bromophenylacetic acid (3 Br) in two crops (593 g., 16.3 g.), each melting at 115.5–116° (lit.[14] m.p. 114°). On a smaller scale this reaction afforded similar yields, although the first crop was often more pure (*i.e.*, one melting at 117–118°).

2-(*p*-Bromophenyl)ethanol (4 Br.).—To a stirred mixture of 19 g. (0.50 mole) of lithium aluminum hydride in 350 ml. of dry ether (distilled from *n*-butylmagnesium bromide) was added dropwise, over a period of 75 min., a solution of 68.9 g. (0.31 mole) of *p*-bromophenylacetic acid (3 Br) in 250 ml. of dry ether. The mixture was refluxed for 1 hr. and cooled in an ice–water bath; methanol was *cautiously* added dropwise until the visible evolution of hydrogen had ceased. Ice and dilute hydrochloric acid were added, the layers were separated, and the aqueous portion was extracted several times with ether. The combined ether extracts were washed with water, dried (Norit), and filtered. The ether was removed and the remaining colorless oil was fractionally distilled affording 50.78 g. (80% yield) of 2-(*p*-bromophenyl)-

(14) J. Frederick, *J. Chem. Soc.*, 161 (1934).

ethanol (4 Br) as a colorless, viscous oil, distilling in the range 149–154° at 17–19 mm. (lit.[15] 143–150° at 7 mm.).

A portion was redistilled and the fraction collected at 154–155° at 18.5 mm. was submitted for analysis.

Anal. Calcd. for C_8H_8BrO: C, 47.79; H, 4.51; Br, 39.74. Found: C, 47.67; H, 4.60; Br, 39.71.

The yields were about 75–80% when the reaction was carried out on 250–350 g. of *p*-bromophenylacetic acid. Material distilling in the range of 148–154° at 13–15 mm. was collected and used directly in the following reaction, and had $n^{25}D$ 1.5700, infrared (CCl_4), 2.80 μ (–OH), and ultraviolet, $\lambda_{max}^{95\%\ EtOH}$ 221 mμ (log ε 4.00).

2-(*p*-Bromophenyl)bromoethane (5 Br.)—To a stirred mixture of 142 ml. (1.23 mole) of 48% HBr (b.p. 125°, colorless, distilled from anhydrous barium bromide), 41.4 ml. of concentrated sulfuric acid, and 179.7 g. (0.895 mole) of 2-(*p*-bromophenyl)-ethanol (4 Br) was added an additional 25.2 ml. of concentrated sulfuric acid (dropwise). The mixture was refluxed with stirring for 3 hr. and then poured onto 500 g. of ice. (In some experiments, a cream-colored solid precipitated at this point; however, the product usually separated as an oil.) The layers (or solid) were separated, and the aqueous solution was extracted with ether. The combined organic portion (solid dissolved) was washed successively with water, 5% sodium bicarbonate, water, and saturated sodium chloride. The yellow ethereal solution was then dried (Norit) and concentrated *in vacuo* affording 208.9 g. (88% crude yield) of a yellow oil. Distillation of the oil at reduced pressure afforded 183.3 g. (77% yield) 2-(*p*-bromophenyl)-bromoethane (5 Br) as a colorless, viscous oil distilling in the range 144–148.5° at 13–13.5 mm. (The main fraction often solidified, m.p. *ca.* 17°.)

A redistilled sample, collected in the range 124.5–125.5° at 5–5.5 mm., was submitted for analysis, and had $n^{25}D$ 1.5929 and ultraviolet, $\lambda_{max}^{95\%\ EtOH}$ 222 mμ (log ε 4.13).

Anal. Calcd. for $C_8H_8Br_2$: C, 36.40; H, 3.06; Br, 60.55. Found: C, 36.68; H, 3.12; Br, 60.37.

3-Carbethoxy-5-(*p*-bromophenyl)pentanone-2 (6 Br).—Into a three-necked 500-ml. round-bottomed flask equipped with a mechanical stirrer, dropping funnel, and condenser (calcium chloride drying tube) was added with stirring 90 ml. of absolute ethanol and 3.01 g. (0.131 g.-atom) of freshly cut sodium metal. When the sodium had reacted, 17.03 g. (0.131 mole) of ethyl acetoacetate (freshly distilled, b.p. 43–46° at 3 mm.) was added, followed by the dropwise addition (10 min.) of 34.5 g. (0.131 mole) of 2-(*p*-bromophenyl)bromoethane (5 Br). The temperature was gradually increased and a white solid (sodium bromide) separated from the pale green solution. The mixture was refluxed for 5 hr., allowed to stand at room temperature overnight, and then further refluxed for 30 min. The solution was transferred to a separatory funnel and treated with 4:1 hydrochloric acid; the lower layer (organic) was drawn off. The aqueous layer was treated with saturated sodium chloride and extracted with ether; the combined organic portion was successively washed with water, 5% hydrochloric acid, and water. The ethereal solution was dried (charcoal), filtered, and taken to dryness *in vacuo* affording 40.9 g. of a straw-colored oil which was fractionally distilled at reduced pressure: (a) 45–48° at 1 mm., 3.21 g. of ethyl acetoacetate; (b) 98–107° at 1.5 mm., 2.77 g. of 2-(*p*-bromophenyl)-bromoethane (5 Br); (c) 142–155° at 1.5 mm., 18.22 g. of 3-carbethoxy-5-(*p*-bromophenyl)pentanone-2 (6 Br); and (d) residue of 10.45 g. Fraction c represents 45% yield (48% yield based on recovered starting materials).

Redistillation afforded a clear, liquid sample [b.p. 149–150° at 1.5 mm.; $n^{25}D$ 1.5215; infrared (neat), 5.78 and 5.85 μ (C=O)] which was submitted for analysis.

Anal. Calcd. for $C_{14}H_{17}BrO_3$: C, 53.69; H, 5.47; Br, 25.52. Found: C, 53.91; H, 5.57; Br, 25.40.

Several attempts were made to increase the yield in this reaction by taking extreme precautions, such as baking the apparatus overnight under nitrogen and carrying out the reaction under nitrogen which had been passed over copper at 500°, or by scrupulously drying the ethanol by the ethyl succinate method [16] The yields, however, remained in the 48–55% range.

1-Methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (7 Br).—The reaction was carried out repeatedly and this procedure represents the experiment of maximum yield. Concentrated sulfuric acid (350 g.) and 17.26 g. (0.0530 mole) of 3-carboxy-5-(*p*-bromophenyl)-pentanone-2 (6 Br) were each cooled to 3°. The ester was then added to the sulfuric acid dropwise with swirling at a rate such that the temperature did not rise above 5–6°. The mixture became yellow-orange almost immediately and after the addition had been completed the mixture was allowed to stand at room temperature for 18 hr. The red-orange solution was poured with stirring onto 1 kg. of ice and a white solid precipitated immediately. This was collected, washed, and dried *in vacuo* affording 12.7 g. (86% yield) of 1-methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (7 Br), m.p. 205–207°.

A sample [m.p. 215–215.5°[17]; infrared (KBr), 6.05 μ (–COOH); ultraviolet, $\lambda_{max}^{CH_3OH}$ 228 (log ε 4.51), 275 (4.23), and 296 mμ (3.77, shoulder)] was recrystallized several times from ether–petroleum ether and submitted for analysis.

Anal. Calcd. for $C_{12}H_{11}BrO_2$: C, 53.95; H, 4.15; Br, 29.92. Found: C, 53.84; H, 4.34; Br, 29.86.

1-Methyl-2-carboxymethyl-7-bromo-3,4-dihydronaphthalene (8 Br.)—A mixture of 150 ml. of methanol, 3 ml. of concentrated sulfuric acid, and 4.87 g. (0.0182 mole) of 1-methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (7 Br) was refluxed for 12 hr., cooled to room temperature, diluted with water, and extracted with ether. The combined ethereal extract was successively washed with water, saturated sodium bicarbonate, 5% hydrochloric acid, and finally water. The ether was dried (charcoal) and taken to dryness affording 4.31 g. (85% yield) of 1-methyl-2-carboxymethyl-7-bromo-3,4-dihydronaphthalene (8 Br) as a clear oil, which solidified on standing. A sample [m.p. 29–30°; infrared (CCl_4), 5.83 μ (C=O); ultraviolet, $\lambda_{max}^{CH_3OH}$ 231 (log ε 4.45), 248 (small shoulder), 280 (4.06), and 310 mμ (3.67, broad)] was submitted for analysis after several recrystallizations from petroleum ether.

Anal. Calcd. for $C_{13}H_{13}BrO_2$: C, 55.53; H, 4.66; Br, 28.42. Found: C, 55.65; H, 4.42; Br, 28.39.

1-Methyl-2-carbomethoxy-7-bromonaphthalene (9 Br).—A solution of 2.81 g. (0.010 mole) of 1-methyl-2-carboxymethyl-7-bromonaphthalene (8 Br) in 10 ml. of dry carbon tetrachloride was warmed and treated with a solution of bromine in carbon tetrachloride (0.001 mole/ml.) with intermittent warming and swirling. The bromine solution was added in small portions (*ca.* 1 ml.) and after a short induction period (2–3 min.), the bromine color was discharged fairly rapidly with the evolution of hydrogen bromide (total reaction time *ca.* 15–20 min.). The first 9 ml. (theoretical, 10 ml.) of bromine solution was taken up in a reasonable time (above) and the mixture was allowed to stand at room temperature for 0.5 hr. with an additional 0.5 ml. (9.5 ml. total) at which time the bromine color was still apparent.

The mixture was diluted with an equal volume of carbon tetrachloride, washed successively with water, 1% sodium bisulfite, 1% sodium bicarbonate, and finally dried (Nuchar). The filtered solution was taken to dryness *in vacuo*, affording 2.35 g. (84% yield) of 1-methyl-2-carboxymethyl-7-bromonaphthalene (9 Br) as a white solid, m.p. 70.5–77°, softening at 69°.

Several samples [all with m.p. 81.5–82°; infrared (CCl_4), 5.79 μ (C=O); ultraviolet, $\lambda_{max}^{CH_3OH}$ 234.5 (log ε 4.70), 247.5 (3.78), 284.5 (3.80), and 295 mμ (3.60); n.m.r. (CCl_4), C_1–CH_3, τ 7.12 (singlet), $-CO_2CH_3$, τ 6.05 (singlet), Ar-C_8-H, τ 1.65 (singlet), other Ar-H at τ 2.00–2.48 (complex multiplet, maximum peak at τ 2.32)] were submitted for analysis after various recrystallizations from petroleum ether.

Anal. Calcd. for $C_{13}H_{11}BrO_2$: C, 55.93; H, 3.97; Br, 28.63. Found: C, 55.90, 55.83, 55.21; H, 3.99, 3.76, 3.89; Br, 30.80, —, 30.38.

1-Methyl-2-carboxyethyl-7-bromo-3,4-dihydronaphthalene (8b Br).—A mixture of 250 ml. of absolute ethanol, 35 ml. of dry benzene, 10 ml. of concentrated sulfuric acid, and 10.04 g. (0.0375 mole) of 1-methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (7 Br) was refluxed for 24 hr. in a flask fitted with a Dean–Stark trap and condensor (calcium chloride drying tube). The solution was cooled to room temperature, diluted with 800 ml. of cold water, and extracted with ether. The combined organic extracts were washed successively with water, half-saturated sodium bicarbonate, water, and saturated sodium chloride, and then dried (Nuchar). The filtered light yellow solution was taken to dryness affording 10.08 g. (91% crude yield) of 1-methyl-2-carboxyethyl-

(15) L. Thielen and C. Dornfeld (to G. D. Searle and Co.), U. S. Patent 2,862,971 (Dec. 2, 1958). A mixture contaminated with undetermined amounts of *meta* and *ortho* isomers is reported to distil at 144.5–145° at 15 mm.: D. Sontag, *Ann. chim.*, [11]1, 359 (1934); *Chem. Abstr.*, **28**, 4717 (1934).

(16) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd Ed., Longmans, London, 1957, p. 168.

(17) See also the preparation discussed under Tetralone Reactions.

7-bromo-3,4-dihydronaphthalene (**8b** Br) as a white solid (small amount of an adhering yellow oil). Recrystallization from 50 ml. of *n*-hexane (charcoal) afforded 7.06 g. (64% yield) of white crystals, m.p. 65–66°. Further recrystallizations from *n*-hexane afforded a sample [m.p. 66.5–67°; infrared (CCl_4, 5.84 μ (C=O)] which was submitted for analysis.

Anal. Calcd. for $C_{11}H_{13}BrO_2$: C, 56.96; H, 5.12; Br, 27.07. Found: C, 57.20; H, 4.97; Br, 26.92.

1-Methyl-2-carboxyethyl-7-bromonaphthalene (**9a Br**).—To a warm (not boiling) solution of 7.06 g. (0.0239 mole) of 1-methyl-2-carboxyethyl-7-bromo-3,4-dihydronaphthalene (**8b** Br) in 24 ml. of dry carbon tetrachloride was added (in 2-ml. portions) 24 ml. of 1 *M* bromine in carbon tetrachloride. The bromine color was discharged almost instantly and copious fumes of hydrogen bromide were evolved. The solution was cooled to room temperature, diluted with an equal volume of carbon tetrachloride, and successively washed with ice-cold water, 1% sodium bisulfite, 1% sodium bicarbonate, and water, and finally dried (Nuchar).

The solution was taken to dryness affording 7.04 g. (100% crude yield) of 1-methyl-2-carboxyethyl-7-bromonaphthalene (**9a** Br) as a yellow-white solid. One recrystallization from 40 ml. of *n*-hexane afforded 4.27 g. (61% yield) of the compound as white prisms, m.p. 75–79.5°.

Further recrystallizations from *n*-hexane and from *n*-hexane–benzene–methanol afforded samples which were submitted for analysis: sample A, m.p. 78–79°, and sample B (duplicate determination), m.p. 78–79.5°. Infrared absorption (CCl_4) showed a peak at 580 μ (C=O); ultraviolet, $\lambda_{max}^{CH_3OH}$ 234.5 (log ϵ 4.69), 275 (3.76), 284.5 (3.77), and 295 mμ (3.57).

Anal. Calcd. for $C_{14}H_{15}O_2Br$: C, 57.36; H, 4.47; Br, 27.26. Found: C, 57.88, 57.25, 57.48; H, 4.47, 4.15, 4.48; Br, 28.54, 27.88, 29.35.

1-Methyl-2-hydroxymethyl-7-bromonaphthalene (**10 Br**) ***via* the Methyl Ester** (**9 Br**).—To a solution of 100 mg. (2.63 mmoles) of lithium aluminum hydride in 20 ml. of dry tetrahydrofuran which had been refluxed for 15 min. was added dropwise over a period of 5 min. a solution of 1.251 g. (4.48 mmoles) of 1-methyl-2-carbomethoxy-7-bromonaphthalene (**9** Br) in 10 ml. of dry tetrahydrofuran. The mixture was refluxed for 1.5 hr., cooled to room temperature, and treated with 1 ml. of ethyl acetate and then 1 ml. of methanol (no visible gas evolution). A few pieces of ice were added, followed by 5 ml. of 1:1 hydrochloric acid. The clear solution was then treated with 5 ml. of saturated sodium chloride solution, the layers were separated, and the aqueous portion was extracted with ether. The combined organic portion was successively washed with water, 2.5% sodium bicarbonate solution, water, and saturated sodium chloride, and dried (Nuchar). The filtered ether solution was taken to dryness *in vacuo* affording 1.04 g. (93% crude yield) of 1-methyl-2-hydroxymethyl-7-bromonaphthalene (**10** Br) as a white solid, which gave 0.817 g. (73% yield) of the compound, m.p. 110–110.5°, softening at 82.5°, after recrystallization from 1:1 benzene–*n*-hexane.

Further recrystallization from *n*-hexane–benzene and from 60:6:1 *n*-hexane–benzene–methanol afforded a sample which was submitted for analysis: m.p. 110.5–111°; infrared absorption (CCl_4), 2.77 μ (—OH); ultraviolet, $\lambda_{max}^{CH_3OH}$ 235.5 (log ϵ 4.91) and broad 285 mμ (3.72); n.m.r., C_1–CH_3, τ 7.48 (singlet), C_2–CH_2–OH, τ 5.24 (singlet), –C_2–CH_2–O*H*, τ 7.87 (singlet), Ar–C_8–H, τ 1.90 (singlet) and other Ar-H at τ 2.22–2.76 (complex multiplet, maximum at τ 2.48).

Anal. Calcd. for $C_{12}H_{11}OBr$: C, 57.39; H, 4.42; Br, 31.82. Found: C, 57.40; H, 4.86; Br, 31.82.

1-Methyl-2-hydroxymethyl-7-bromonaphthalene (**10 Br**) ***via* the Ethyl Ester** (**9a Br**).—To a solution of 300 mg. (7.89 mmoles) of lithium aluminum hydride in 35 ml. of tetrahydrofuran, which had been refluxed for 15 min., was added portionwise (*ca.* 2 ml./min.) a solution of 2.93 g. (10.0 mmoles) of 1-methyl-2-carboxyethyl-7-bromonaphthalene (**9a** Br) in 25 ml. of dry tetrahydrofuran. The mixture was refluxed for 1 hr., cooled to room temperature, and isolated as before.

The crude alcohol (2.10 g., 84% yield—represents minimum, some lost by spillage) was recrystallized from 30:7:3 *n*-hexane–benzene–methanol, affording white crystals, m.p. 110–111°, m.m.p. 110–110.5° with alcohol (m.p. 110.5–111°) from methyl ester procedure. The infrared spectra were identical.

1-Methyl-2-bromomethyl-7-bromonaphthalene (**11 Br**).—To a warm solution of 581 mg. (2.31 mmoles) of 1-methyl-2-hydroxymethyl-7-bromonaphthalene (**10** Br) in 10 ml. of dry carbon tetrachloride was added a solution of 600 mg. (2.22 mmoles) of phosphorus tribromide in 10 ml. of dry carbon tetrachloride. The cloudy mixture was refluxed for 1 hr. and allowed to stand at room temperature for 24 hr.; the solution was decanted from the yellow semisolid (H_3PO_3), which was washed with a little fresh cold carbon tetrachloride. The combined organic portion was washed with water, dried, and taken to dryness *in vacuo* affording 0.607 mg. (94% crude yield) of 1-methyl-2-bromomethyl-7-bromonaphthalene (**11** Br) as a light yellow solid, m.p. 87–91° after two recrystallizations from chloroform–*n*-hexane (charcoal). Further recrystallizations from *n*-hexane afforded a white sample [m.p. 92–93°, ultraviolet peaks at $\lambda_{max}^{CH_3OH}$ 242.5 (log ϵ 4.78) and broad 284 mμ (3.76)] which was submitted for analysis.

Anal. Calcd. for $C_{12}H_{10}Br_2$: C, 45.89; H, 3.21; Br, 50.90. Found: C, 46.06; H, 3.00; Br, 50.48.

Tetralone Reactions. β-(*p*-Bromobenzoyl)propionic Acid.—This compound was prepared in 90% yield (average 67%, from several runs) from purified bromobenzene[18] and freshly recrystallized succinic anhydride (acetic anhydride) using slight modifications of the published procedure.[6] Several recrystallizations from water afforded colorless plates, m.p. 146.5–147° (lit.[6] m.p. 148–149°). It is essential that the commercial anhydrous aluminum chloride be fresh and *white* and that the initial reaction mixture be kept stirred at 0–5° during the slow addition of dilute mineral acid, in order to avoid the formation of very stable foams, from which the product can be isolated only with difficulty in poor yields.

γ-(*p*-Bromophenyl)butyric Acid.—Clemmensen reduction of the succinoylation product afforded a 60% yield of the reduced acid as colorless crystals, m.p. 70–70.5° (lit.[6] m.p. 71–72°) after two recrystallizations from ether–petroleum ether. Unlike the published distillation procedure,[3] the isolation used here was a slow crystallization of the crude yellow oil from ether–petroleum ether at 0–5°. Distillation of the initial crude material afforded lower yields of the acid, whose melting point was raised only after at least four recrystallizations.

7-Bromo-1-tetralone (**12**).—Many PPA cyclizations were carried out, starting with the conditions suggested for γ-phenylbutyric acid.[4,5] Only the optimum conditions are described here.

A mixture of 150 g. of PPA and 36.86 g. (0.152 mole) of γ-(*p*-bromophenyl)butyric acid, initially at room temperature, was heated on a steam bath with stirring for 10 min., at which time the temperature had risen to 80°. It was maintained at this temperature for 45 min., becoming rust colored after only 15 min., and then 200 ml. of ice–water was added.

The suspension was treated with ether, the yellow solid dissolved, and the layers were separated. The ether was washed successively with water, 5% sodium hydroxide, water, 3% acetic acid, 5% sodium bicarbonate, and finally with water. The organic layer was dried and evaporated, affording 24.20 g. (85% crude yield) of a light yellow solid. The product was chromatographed on 200 g. of Merck alumina using first benzene–petroleum ether and then benzene for elution. The solid was recrystallized from ether (Norit) affording 18.31 g. (64% yield) of 7-bromo-1-tetralone (**12**): m.p. 77–78.5° (lit.[3] m.p. 76–77°); infrared (CCl_4), 5.87 μ (C=O).

2-Carboxy-7-bromo-1-tetralone (**13**).—Methylmagnesium carbonate was prepared from 35 g. (0.64 mole) of magnesium methoxide and 33.6 g. (0.84 mole) of "bone-dry" carbon dioxide in 500 ml. of DMF (spectroscopic grade) as previously described.[2] Tetralone **12** (11.1 g., 0.049 mole) was added, and the mixture was stirred and heated at 120–130° for 1.5 hr., then cooled to room temperature, and finally treated with ice and ice–hydrochloric acid mixture. The solid was collected, reprecipitated from 5% sodium bicarbonate (which had been extracted with ether), collected, and dried over phosphous pentoxide. The white solid (6.93 g.), m.p. 103.5–108° (with gas evolution, remelts at 74–75°), was obtained in 52% yield; infrared (KBr), 3.5–4.6 (–CO_2H, broad) and 6.21, 6.30, and 6.44 μ (C=C).

Anal. Calcd. for $C_{11}H_9BrO_3$: C, 49.09; H, 3.37. Found: C, 49.25; H, 3.37.

2-Carbomethoxy-7-bromo-1-tetralone (**14**).—Diazomethane was prepared from DuPont EXR-101[19] and the ethereal solution (in excess) was added to a cold ether solution of 2.51 g. (0.093 mole) of acid **13**. After standing at room temperature overnight, the yellow mixture was treated with a few milliliters of water and allowed to stand several hours. The colorless ether solution

(18) The commercial product was washed successively with 5% sodium hydroxide, 5% hydrochloric acid, water, and saturated sodium chloride, dried over anhydrous sodium sulfate, and then distilled.

(19) N,N'-Dinitroso-N,N'-dimethylterephthalamide.

was washed with 5% sodium bicarbonate, dried, and evaporated *in vacuo*. The oil crystallized on standing in an ice bath, affording 0.83 g. (31% yield) of methyl ester **14**. Recrystallization from petroleum ether afforded colorless crystals: m.p. 49–50° (raised to 52–53.5° by repeated crystallization); infrared (CCl_4), 5.69, 5.87, and a doublet at 6.00 and 6.14 μ. See the corresponding ethyl ester **16** described below.

Anal. Calcd. for $C_{12}H_{11}O_3Br$: C, 50.90; H, 3.92; Br, 28.23. Found: C, 51.31; H, 4.43; Br, 26.87.

1-Methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (7 Br).—To an ice-cold solution of methylmagnesium iodide, prepared from 1.87 g. (0.078 g.-atom) of magnesium and 14.63 ml. (0.234 mole) of iodomethane in dry tetrahydrofuran (THF), was added a cold solution of keto acid **13** in dry THF. The mixture was stirred for 2 hr. at 0°, allowed to warm to room temperature over a period of 3 hr., and then refluxed for 45 min. The mixture was cooled to 0–3°, decomposed with cold, dilute hydrochloric acid, and the THF was removed by distillation (maximum distillate b.p. *ca.* 100°). The resulting aqueous solution was extracted with ether which in turn was washed with 5% sodium bicarbonate. After acidification of these bicarbonate washings, the acidic products were obtained by extraction with ether which was dried (Norit) and evaporated *in vacuo*. The resulting solid was recrystallized from benzene, affording minute quantities (*ca.* 3–5 mg.) of white needles, m.p. 214.5–215° (evolution of gas).[20]

Ethyl 7-Bromo-1-tetralone-2-glyoxalate (15).—To a cold, fresh solution of sodium ethoxide (prepared from 3.4 g. (0.147 g.-atom) of sodium in *ca.* 30 ml. of dry ethanol) was added over a period of 15 min. with stirring, a warm solution of 24.8 g. (0.110 mole) of 7-bromo-1-tetralone (**12**) and 16.4 g. (0.112 mole) of diethyl oxalate in 30 ml. of dry ethanol. The mixture was stirred in an ice–water bath for 1 hr. and for an additional 6 hr. at room temperature. Cold, dilute sulfuric acid was then added and the mixture was allowed to stand overnight. The dark, tacky solid was collected, dissolved in ether (Norit), dried, and concentrated, affording 26.70 g. (72.5% yield) of oxalyl ester **15** as bright yellow crystals: m.p. 63–65°[21]; infrared (CCl_4), 5.75 (C=O), and 6.11, 6.28, and 6.50 μ (C=C).[22]

Anal. Calcd. for $C_{14}H_{13}O_4Br$: C, 51.71; H, 4.03; Br, 24.58. Found: C, 51.67; H, 4.15; Br, 24.33.

Ethyl 7-Bromo-1-tetralone-2-carboxylate (16).—The decarbonylation was carried out by heating 25.43 g. (0.078 mole) of oxalyl ester **15** with 2 g. of powdered soft glass at 180–185° at 40 mm. When the vigorous evolution had ceased (*ca.* 30 min.) the pressure was lowered to 0.75 mm. and the fraction distilling at 155–170° was collected, affording 20.35 g. (88% yield) of ethyl 7-bromo-1-tetralone-2-carboxylate (**16**). This was recrystallized from 95% ethanol affording colorless crystals, m.p. 63–66.5°.[23]

Anal. Calcd. for $C_{13}H_{13}O_3Br$: C, 52.54; H, 4.41; Br, 26.89. Found: C, 52.87, 52.62; H, 4.41, 4.71; Br, 27.33, 26.63.

The infrared spectra of **16** (CCl_4) had peaks at 5.77, 5.93, and a doublet at 6.08 and 6.17 μ,. Ethyl 1-tetralone-2-carboxylate is reported also to absorb at 5.77, 5.89, and 6.08 μ, corresponding to the ester carbonyl, the unsaturated keto carbonyl, and the chelated ester, respectively.[24] The methyl ester shows similar absorption (*vide supra*). N.m.r. ($CDCl_3$) showed peaks at τ −2.45 (singlet, enol-OH), τ 2.03 (singlet C_8-H),[25] τ 2.53–3.02 (complex multiplet, Ar-H), τ 5.67 (quartet, $-CO_2CH_2CH_3$), τ 7.32 (unresolved multiplet, may be doublet or triplet, $-CH_2-CH_2-$), and τ 8.63 (triplet, $-CO_2CH_2-CH_3$).

Attempted Preparation of 1-Methyl-2-carbethoxy-7-bromo-3,4-dihydronaphthalene (8b Br).—Methylmagnesium iodide in dry ether was added to a solution of β-keto ester **16** in cold ether. Gas evolution was apparent immediately, and careful work-up in the usual manner afforded 2.28 g. (77% recovery) of starting material. No further attempts were made to effect this conversion.

(20) A sample of this α,β-unsaturated acid prepared by the lengthy independent synthesis above melts at 215–215.5° with *no observable gas evolution*. It is believed that the procedure here affords a compound containing an appreciable amount of the original keto acid.

(21) Attempts were made to prepare the *p*-nitrophenylhydrazine derivative, but elemental analyses could not be reconciled with a reasonable structure for the red solid, m.p. 178–179°. The approximate formulation is $C_{22}H_{18}BrN_5O_6$.

(22) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 142.

(23) This compound crystallized from ether in both rods and plates, but these were shown to be identical by mixture melting point. This appears to be solely a nucleation phenomenon.

(24) L. J. Bellamy and R. F. Brance, *J. Chem. Soc.*, 4487 (1954).

(25) In the n.m.r. spectra of all naphthalene compounds containing a *peri*-hydrogen *ortho* to a halogen atom, we find a distinct separation of this proton from the remainder of the aromatic ones.

The Synthesis of 4-Aminoisoxazolo[5,4-*d*]pyrimidines[1]

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A number of derivatives of isoxazolo[5,4-*d*]pyrimidine have been prepared as potential purine antagonists. Condensation of hydroxylamine with methylethoxymethylenemalononitrile, ethylethoxymethylenemalononitrile, and phenylmethoxymethylenemalononitrile gave a series of 3-substituted 4-cyano-5-aminoisoxazoles which, upon reaction with ethyl orthoformate–acetic anhydride, followed by an amine, gave 4-amino- and substituted aminoisoxazolo[5,4-*d*]pyrimidines. The structures of several of the 4-substituted amino derivatives were confirmed through independent synthesis by heating the 4-amino derivative with a mixture of the alkyl amine and its hydrochloride salt. Catalytic reduction of the 4-aminoisoxazolo[5,4-*d*]pyrimidines resulted in cleavage of the O–N bond; hydrolysis of the resulting imine then gave 4-amino-5-acetyl- and 5-benzoyl-6-hydroxypyrimidines. Several derivatives of the pyrido[2,3-*d*]pyrimidine ring system were prepared by subsequent reaction with malononitrile.

There is continuing interest in the preparation of potential purine antagonists for studies in cancer chemotherapy, since many of the currently active purine derivatives and analogs exhibit excessive toxicity and are unsuited for clinical use. One may cite as an example 4-aminopyrazolo[3,4-*d*]pyrimidine, which, although active as a purine antimetabolite, shows signs of hepatotoxicity in man.[2] Many derivatives of 4-aminopyrazolo[3,4-*d*]pyrimidine (and related purine analogs) have been prepared in an attempt to improve the antitumor activity and reduce the toxicity of the parent compound.[3] We wish to describe in this paper the synthesis and chemical properties of some derivatives of the little-known, structurally related isoxazolo[5,4-*d*]pyrimidine ring system.

The preparation of a bicyclic ring system, such as the desired isoxazolo[5,4-*d*]pyrimidine system, can be approached from either of two directions; that is, the

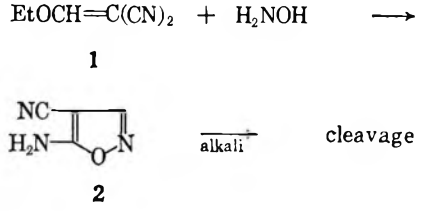
(1) This work was supported by a research grant (CY-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) R. K. Shaw, R. N. Shulman, J. D. Davidson, D. P. Rall, and E. Frei, *Cancer*, **13**, 482 (1960).

(3) See E. Y. Sutcliffe, K. Y. Zee-Cheng, C. C. Cheng, and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 588 (1962), and preceding papers cited therein.

pyrimidine ring can be formed first and the isoxazole ring closed in the terminal step of the synthetic sequence, or the isoxazole ring can be prepared initially and the pyrimidine ring attached in the terminal stages. We chose the latter approach because of prior experience in the cyclization of *o*-aminonitriles to condensed 4-aminopyrimidine systems. This work has been described in detail elsewhere.[4]

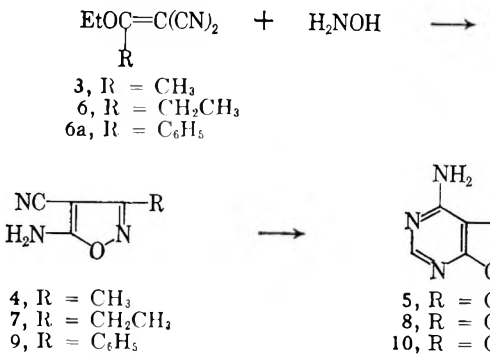
An attractive intermediate for this synthetic sequence would be 5-amino-4-cyanoisoxazole (**2**) which has been described[5] and is readily accessible by the reaction of ethoxymethylenemalononitrile (**1**) with hydroxylamine. However, attempted cyclization of **2** with formamidine acetate[6] in ethanol or 2-ethoxyethanol, a procedure which is successful with other *o*-aminonitriles and leads, in these latter cases, directly



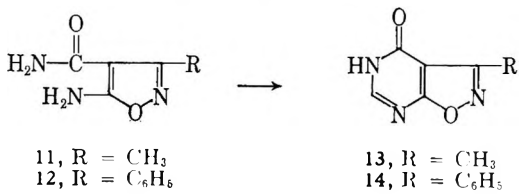
to fused 4-aminopyrimidine heterocycles, was unsuccessful, since **2** proved to be unstable in the presence of alkali. This is not unexpected, for the presence of an unsubstituted 3-position in isoxazole derivatives is known to lead to alkali instability *via* ring cleavage.[7] Evidently replacement of the acidic proton in the 3-position would be a necessary preliminary step if such 5-amino-4-cyanoisoxazole intermediates were to be useful in the synthesis of the desired bicyclic derivatives.

We therefore prepared 5-amino-4-cyano-3-methylisoxazole (**4**) by the reaction of hydroxylamine with methylethoxymethylenemalononitrile (**3**).[8] As expected, compound **4** was stable to alkali, and reaction with formamidine acetate in 2-ethoxyethanol yielded the desired bicyclic compound, 4-amino-3-methylisoxazolo[5,4-*d*]pyrimidine (**5**). The yield in this direct pyrimidine-annulation reaction was disappointingly low, however, and it was found that a two-step sequence involving preliminary treatment of **4** with a mixture of ethyl orthoformate and acetic anhydride, followed by treatment with ethanolic ammonia, led to compound **5** in 77% yield.

Several related 5-amino-4-cyanoisoxazoles then were prepared by the reaction of hydroxylamine with ethylethoxymethylenemalononitrile (**6**) and phenylmethoxymethylenemalononitrile (**6a**)[9] to give the 3-ethyl and 3-phenyl derivatives of 5-amino-4-cyanoisoxazole (**7** and **9**, respectively). Treatment of these aminonitriles with ethyl orthoformate and acetic anhydride followed by ammonia, as described above, led in high yield to the 3-substituted 4-aminoisoxazolopyrimidines **8** and **10**. Compound **9** was a previously known intermediate, having been prepared by Dornow and Teckenburg[10] by an alternative route.



Several 4-hydroxy derivatives of the isoxazolo[5,4-*d*]-pyrimidine system were prepared by conversion of the aminonitriles **4** and **9** by treatment with concentrated sulfuric acid to the carboxamides **11** and **12**, followed by cyclization with a mixture of ethyl orthoformate and acetic anhydride to give 3-methylisoxazolo[5,4-*d*]-pyrimidin-4(5*H*)-one (**13**) and the corresponding 3-phenyl derivative (**14**). The structure of **13** was confirmed by an independent synthesis from **5** by treatment with dilute hydrochloric acid and sodium nitrite.



A similar conversion of compound **10** to **14** was not successful because of the extreme insolubility of **10** in acid solution. Attempts to carry out the conversion of **10** to **14** with nitrosyl sulfuric acid led to extensive decomposition.

We have previously demonstrated[4] with other *o*-aminonitriles that treatment with ethyl orthoformate and acetic anhydride to give the ethoxymethyleneamino derivative, followed by treatment with primary amines, leads *via* the intermediate formation of a formamidine, followed by intramolecular addition to the nitrile group and a subsequent base-catalyzed ring opening–ring closure sequence, to 4-substituted aminopyrimidine heterocycles in good yield. By application of this reaction sequence to the *o*-aminonitriles **4** and **9** and by employing methylamine, 3-dimethylaminopropylamine, and 3-diethylaminopropylamine, the appropriately substituted isoxazolopyrimidines **17**–**22** were readily prepared in good yield.

Since it was conceivable, although not probable, that all of these final products might have been 5-substituted 4-imino rather than the rearranged 4-substituted amino compounds, it was thought desirable to confirm this structural assignment by an independent synthesis of some of these derivatives. By treatment of 4-amino-3-methylisoxazolo[5,4-*d*]pyrimidine (**5**) with a mixture of 3-diethylaminopropylamine and its hy-

(4) For examples and leading references, see E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).

(5) H. Kano, Y. Makisumi, and K. Ogata, *Chem. Pharm. Bull.* (Tokyo), **6**, 105 (1958).

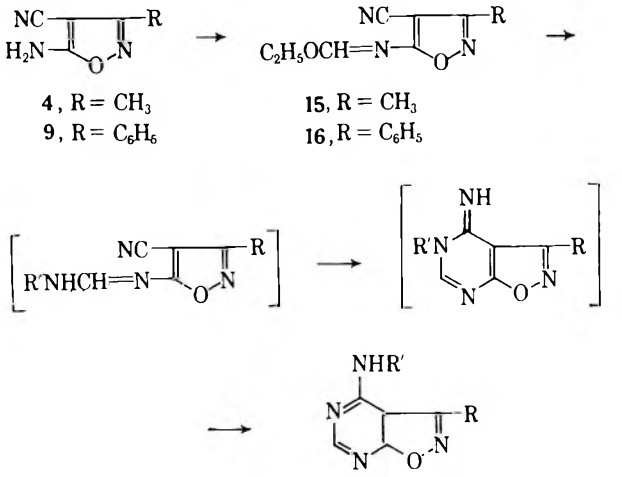
(6) E. C. Taylor and W. A. Ehrhart, *J. Am. Chem. Soc.*, **82**, 3138 (1960).

(7) See (a) R. A. Barnes, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 465; (b) A. Quilico, "The Chemistry of Heterocyclic Compounds. Five- and Six-Membered Compounds with Oxygen and Nitrogen," R. H. Wiley, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, p. 45.

(8) W. Huber and H. A. Hölscher, *Ber.*, **71B**, 99 (1938); Y. Urushibara and M. Takebayashi, *Bull. Chem. Soc. Japan*, **11**, 557 (1936).

(9) A. Dornow and F. Schleese, *Ber.*, **91**, 1830 (1958).

(10) A. Dornow and H. Teckenburg, *ibid.*, **93**, 1103 (1960).



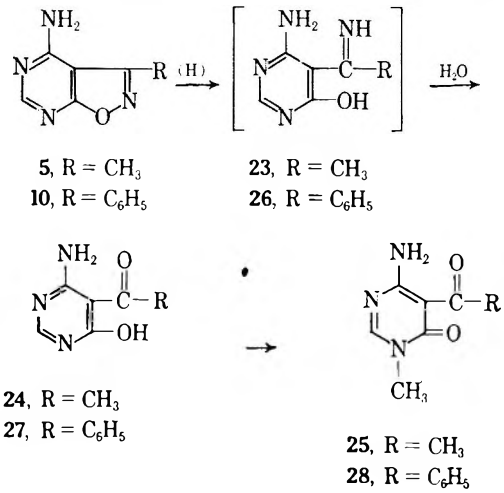
4, R = CH_3
9, R = C_6H_5

15, R = CH_3
16, R = C_6H_5

17, R = CH_3; R′ = CH_3
18, R = CH_3; R′ = $CH_2CH_2CH_2N(CH_3)_2$
19, R = CH_3; R′ = $CH_2CH_2CH_2N(CH_2CH_3)_2$
20, R = C_6H_5, R′ = CH_3
21, R = C_6H_5; R′ = $CH_2CH_2CH_2N(CH_3)_2$
22, R = C_6H_5; R′ = $CH_2CH_2CH_2N(CH_2CH_3)_2$

responding hydrochloride,[11] compound **19** was formed in 24% yield, and it proved to be identical in every respect with the product formed by the ethyl orthoformate–acetic anhydride–amine sequence described above. Similarly, treatment of **10** with 3-diethylaminopropylamine and its hydrochloride gave **22** in 30% yield. Since the ultraviolet spectra of all of the above described 4-substituted amino derivatives in each series (*i.e.*, 3-methyl and 3-phenyl) were essentially identical, we feel confident in assigning the above structures.

It is well known that isoxazole rings are readily cleaved by hydrogenation,[12-15] and it was thought that useful pyrimidine intermediates suitable for further cyclization to condensed pyrimidine heterocycles might be available by reductive cleavage of the isoxazole ring in these bicyclic purine analogs. Thus, catalytic reduction of **5** followed by treatment with water gave 5-acetyl-4-amino-6-hydroxypyrimidine (**24**) in 91% yield. The intermediate imine (**23**), presumably formed as the initial product of the reductive cleavage, proved to be too unstable for characterization. Attempted recrystallization resulted in every case in loss of ammonia, and unsatisfactory analyses were the inevitable result. Attempted capture of the imine **22** by various reagents designed to give a pyrimidopyrimidine were also unpromising because of concomitant hydrolysis. Methylation of **24** with dimethyl sulfate gave **25**, which was readily characterized by the formation of a 2,4-dinitrophenylhydrazone. Similar reductive cleavage of **10** under the same conditions resulted in the rapid uptake of 1 mole of hydrogen, and treatment of the reduction mixture with water then gave 4-amino-5-benzoyl-6-hydroxypyrimidine (**27**), which was also characterized as its monomethyl derivative **28**. The position of methylation in **24** and **27** is assumed to be on N-1 as shown by analogy with the known methylation of 4-amino-6-hydroxypyrimidine to 4-amino-1-methylpyrimidin-6(1*H*)-one and by the observation that both methyl derivatives (**25** and **28**) are stable to alkali.[16]



5, R = CH_3
10, R = C_6H_5

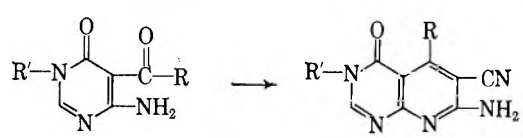
23, R = CH_3
26, R = C_6H_5

24, R = CH_3
27, R = C_6H_5

25, R = CH_3
28, R = C_6H_5

The unreactivity of the ketone grouping in **27** is worthy of note. It proved to be extremely difficult to characterize **27** in the form of its carbonyl derivatives, for the benzoyl grouping was unreactive towards such reagents as phenylhydrazine and hydroxylamine (although it slowly formed a 2,4-dinitrophenylhydrazone). The decreased carbonyl reactivity of **27** compared with **24** is probably due to the increase in steric hindrance in the former compound. It should be noted that 5-acyl derivatives of 4,6-disubstituted pyrimidines are notably unreactive towards carbonyl reagents.[17]

Several experiments were carried out which serve to illustrate the potential usefulness of these 5-aroyl and 5-acyl 6-aminopyrimidines as intermediates for the preparation of condensed pyrimidine heterocycles. For example, the reaction of **24** with malononitrile in pyridine led in 54% yield to the pyridopyrimidine **29**. Similarly, **28** reacted with malononitrile in pyridine to give the pyridopyrimidine **30** in 22% yield. Presumably the lower yield in the latter case was also the result of steric hindrance at the carbonyl group. However, less reactive methylene derivatives, such as phenylacetonitrile, ethyl cyanoacetate, and cyanoacetamide, failed to react.



24, R = CH_3; R′ = H
28, R = C_6H_5; R′ = CH_3

29, R = CH_3; R′ = H
30, R = C_6H_5; R′ = CH_3

Experimental[18]

5-Amino-4-cyano-3-methylisoxazole (**4**).—To 14 g. (0.2 mole) of hydroxylamine hydrochloride dissolved in 80 ml. of 10% sodium hydroxide was added, with vigorous stirring, 27.2 g. (0.2 mole) of methylethoxymethylenemalononitrile (prepared according to the method of Huber and Hölscher[8]). The tempera-

(11) For examples of acid-catalyzed amidine exchange reactions of this type, see C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **82**, 3973 (1960).
(12) G. Shaw, *J. Chem. Soc.*, 720 (1950).
(13) G. Stagno D'Alcontres, *Gazz. chim. ital.*, **80**, 441 (1950).
(14) L. Panizzi, *ibid.*, **76**, 44 (1946).
(15) G. N. Walker, *J. Org. Chem.*, **27**, 1929 (1962).
(16) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1298 (1961).
(17) W. Pfleiderer and G. Strauss, *Ann.*, **612**, 178 (1958).
(18) All melting points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. All ultraviolet spectra were determined in ethanol.

ture was kept below 50° by making this addition slowly and by addition of small amounts of ice. After stirring for an additional 1.5 hr. at approximately 20°, the colorless solid was filtered, washed with water, and recrystallized from aqueous ethanol to give white needles, m.p. 222–224° dec., yield 17.2 g. (71%).

Anal. Calcd. for $C_5H_5N_3O$: C, 48.78; H, 4.10; N, 34.14. Found: C, 48.59; H, 4.17; N, 34.18.

Ethylethoxymethylenemalononitrile (6).—A solution of 15 g. (0.22 mole) of malononitrile in a mixture of 47.5 g. (0.27 mole) of triethyl orthopropionate and 75 ml. of acetic anhydride was refluxed for 9.5 hr. After removal of the excess reagents *in vacuo*, distillation gave 27.3 g. (82%) of yellow liquid, b.p. 118–120° (2.7 mm.).[19] This substance was used immediately after its preparation.

5-Amino-4-cyano-3-ethylisoxazole (7).—This compound was prepared from ethylethoxymethylenemalononitrile in the same manner as compound **4**. The crude product was recrystallized from ethanol–petroleum ether (b.p. 60–70°) to give white crystals, m.p. 139–140°, 82% yield.

Anal. Calcd. for $C_6H_7N_3O$: C, 52.54; H, 5.15; N, 30.64. Found: C, 52.49; H, 5.01; N, 30.74.

5-Amino-4-cyano-3-phenylisoxazole (9) was prepared according to the directions of Dornow and Teckenburg.[10] The phenylmethoxymethylenemalononitrile required in this preparation was generously donated by Smith Kline and French Laboratories, Philadelphia, Pa.

4-Cyano-5-ethoxymethyleneamino-3-methylisoxazole (15).—A solution of 10 g. (0.081 mole) of 5-amino-4-cyano-3-methylisoxazole (**4**) in 25 ml. of acetic anhydride and 37 ml. of triethyl orthoformate was refluxed for 4 hr. while protected against moisture with a calcium chloride tube. Concentration *in vacuo* (0.1 mm.) gave a brown oil which crystallized upon immersion in ice. Recrystallization from petroleum ether (b.p. 60–70°) gave 12.3 g. (84%) of white needles, m.p. 33–34°. A small amount of higher melting solid insoluble in petroleum ether was removed by filtration and discarded.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.42; H, 5.50; N, 23.20.

4-Amino-3-methylisoxazolo[5,4-*d*]pyrimidine (5). A.—A solution of 10 g. (0.081 mole) of 5-amino-4-cyano-3-methylisoxazole (**4**) in an equimolar mixture of 25 ml. of acetic anhydride and 37 ml. of triethyl orthoformate was refluxed for 4 hr. After concentration *in vacuo* the residual oil was poured into 100 ml. of ethanolic ammonia. Precipitation occurred immediately. After 2 hr. of stirring at room temperature the mixture was refrigerated. Filtration, washing with water, and vacuum drying gave 8.9 g. of white solid, m.p. 303–305° dec. An additional 0.6 g. of product separated from the filtrate upon standing: yield 9.5 g. (77%). Recrystallization from aqueous ethanol (large volume) or dimethylformamide–ethanol gave colorless crystals, m.p. 303–305° dec.; λ_{max} 249, 273 mμ ($\epsilon \times 10^3$ 7.7, 5.7).

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.77; H, 4.00; N, 37.05.

B.—The addition of 10 g. (0.056 mole) of recrystallized 4-cyano-5-ethoxymethyleneamino-3-methylisoxazole to approximately 100 ml. of ethanolic ammonia, followed by stirring at room temperature for 1 hr., gave 7.0 g. (83%) of white crystals, m.p. 300–302° dec., identical with the product prepared by method A.

4-Amino-3-ethylisoxazolo[5,4-*d*]pyrimidine (8) was prepared in the same manner as described above for compound **5** except that 10 g. of 5-amino-4-cyano-3-ethylisoxazole (**7**) was employed. The yield was 9.0 g. (75%) of white solid, m.p. 219–221°. Recrystallization from a large volume of ethanol yielded small, white needles, m.p. 221–222°; λ_{max} 249, 272 mμ ($\epsilon \times 10^3$ 10.6, 7.8).

Anal. Calcd. for $C_7H_5N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.22; H, 4.90; N, 34.16.

4-Cyano-5-ethoxymethyleneamino-3-phenylisoxazole (16).—A solution of 10 g. (0.054 mole) of 5-amino-4-cyano-3-phenylisoxazole (**9**) in 25 ml. of acetic anhydride and 37 ml. of triethyl orthoformate was refluxed for 4 hr. Upon cooling to room temperature, long white needles separated. Filtration and concentration of the filtrate gave 12 g. (92%) of product, m.p. 110–112°, which upon recrystallization from ethanol melted at 111–112°.

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60. Found: C, 64.45; H, 4.71.

4-Amino-3-phenylisoxazolo[5,4-*d*]pyrimidine (10).—Anhydrous ammonia was bubbled through a stirred suspension of 10 g. (0.042 mole) of 4-cyano-5-ethoxymethyleneamino-3-phenylisoxazole (**16**) in 150 ml. of ethanol at room temperature for 2 hr. Initially a viscous yellow-green mixture formed, but, as more ammonia was added, the alcohol became warm and a more fluid suspension resulted. After cooling, filtration, and concentration of the filtrate to a small volume, 7.5 g. (84%) of white solid was obtained. Recrystallization from aqueous ethanol yielded shiny white plates, m.p. 211–212°; λ_{max} 244, 276 mμ ($\epsilon \times 10^3$ 12.4, 8.2).

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.26; H, 3.77; N, 26.41. Found: C, 62.34; H, 3.96; N, 26.36.

5-Amino-3-methylisoxazole-4-carboxamide (11).—To 35 ml. of concentrated sulfuric acid was added slowly with stirring 5.0 g. (0.04 mole) of 5-amino-4-cyano-3-methylisoxazole (**4**). The temperature reached 55° during the addition. The solution, still stirred, was heated at 50–55° for 1 hr. and then left at room temperature for an additional hour. Cautious addition to crushed ice yielded a white solid which slowly dissolved as the stirred mixture was allowed to warm to room temperature. Concentrated ammonium hydroxide was carefully added, with ice cooling, to pH 9 and the resulting suspension was refrigerated overnight to give 3.8 g. (68%) of a crystalline white solid. Recrystallization from ethanol–petroleum ether gave small, white crystalline rods, m.p. 190–193° dec.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.79; H, 4.54; N, 29.80.

5-Amino-3-phenylisoxazole-4-carboxamide (12.)—Using a similar procedure, 5.0 g. (0.027 mole) of 5-amino-4-cyano-3-phenylisoxazole (**9**) gave 4.6 g. (83%) of product (the addition of ammonium hydroxide in this reaction was made directly to the suspension 1 hr. after the mixture was poured onto ice). Recrystallization from water yielded white needles, m.p. 178–180°.

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46. Found: C, 59.19; H, 4.39.

3-Methylisoxazolo[5,4-*d*]pyrimidin-4(5*H*)-one (13.)—A solution of 2.0 g. (0.014 mole) of 5-amino-3-methylisoxazole-4-carboxamide (**11**) in 15 ml. of acetic anhydride and 15 ml. of triethyl orthoformate was refluxed for 3 hr. The resulting orange solution was concentrated to dryness *in vacuo*, and the residue was dissolved in ammonium hydroxide (Norit), filtered, and acidified with acetic acid. After refrigeration for 2 hr., filtration, and vacuum drying, 1.4 g. of product, m.p. 214–218° dec., was obtained. Recrystallization from ethanol gave white needles, m.p. 219–221° dec. For analysis a sample was recrystallized from ethanol–petroleum ether (b.p. 60–70°); λ_{max} 235, 242 (sh), 267 mμ ($\epsilon \times 10^3$ 6.4, 6.0, 5.4).

Anal. Calcd. for $C_6H_5N_3O_2$: C, 47.68; H, 3.34; N, 27.81. Found: C, 47.65; H, 3.55; N, 27.56.

Diazotization of 4-amino-3-methylisoxazolo[5,4-*d*]pyrimidine (**5**) with sodium nitrite in dilute hydrochloric acid at 0°, followed by stirring at room temperature overnight, gave a product, m.p. 218–219° dec., which was identical in every respect (mixture melting point and infrared spectrum) with that obtained by cyclization of the amide.

3-Phenylisoxazolo[5,4-*d*]pyrimidin-4(5*H*)-one (14) was prepared in 75% yield from 5-amino-3-phenylisoxazole-4-carboxamide (**12**) by a procedure analogous to that described above for the preparation of **13**. The crude product, m.p. 237–239° dec., was recrystallized from ethanol–petroleum ether (b.p. 60–70°) to give colorless platelets, m.p. 239–241° dec.; λ_{max} 249 mμ ($\epsilon \times 10^3$ 15.7).

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 62.29; H, 3.32; N, 19.85.

3-Methyl-4-methylaminoisoxazolo[5,4-*d*]pyrimidine (17).—Anhydrous methylamine was bubbled through a solution of 2.0 g. (0.011 mole) of 4-cyano-5-ethoxymethyleneamino-3-methylisoxazole (**15**) in 30 ml. of ethanol for approximately 1.5 hr., with gentle heating. Solid separated from the reaction mixture after 0.5 hr. Cooling and filtering gave 1.4 g. of a white crystalline solid; the filtrate upon standing gave an additional 0.1 g. of product; the total yield was 1.5 g. (83%). Recrystallization from 1-butanol yielded clusters of white crystals, m.p. 237–238°; λ_{max} 252, 283 mμ ($\epsilon \times 10^3$ 9.8, 9.1).

Anal. Calcd. for $C_7H_9N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.37; H, 4.86; N, 34.18.

3-Methyl-4-(3′-dimethylaminopropylamino)isoxazolo[5,4-*d*]-pyrimidine (18).—A solution of 5.4 g. (0.03 mole) of 4-cyano-5-

(19) This compound previously has been reported [C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **78**, 5296 (1956)] to have b.p. 142° (7 mm.).

ethoxymethyleneamino-3-methylisoxazole (**15**) and 3.2 g. (slight molar excess) of 3-dimethylaminopropylamine in 50 ml. of ethanol was refluxed for 3 hr. Upon cooling to room temperature, a white crystalline solid precipitated. Filtration and vacuum drying yielded 5.5 g. (78%) of product, m.p. 165–168°. Concentration of the filtrate gave 0.8 g. of uncyclized solid. Recrystallization of the cyclized product from ethanol gave white needles, m.p. 168–169°; λ_{max} 253, 284 mμ (ε × 10^3 10.3, 9.5).

Anal. Calcd. for $C_{11}H_{17}N_3O$: C, 56.15; H, 7.28; N, 29.77. Found: C, 56.45; H, 7.41; N, 29.40.

3-Methyl-4-(3′-diethylaminopropylamino)isoxazolo[5,4-*d*]pyrimidine (19). A.—An ethanolic solution (20 ml.) containing 1.8 g. (0.01 mole) of 4-cyano-5-ethoxymethyleneamino-3-methylisoxazole (**15**) and 1.3 g. (0.01 mole) of 3-diethylaminopropylamine was refluxed for 3 hr. The ethanol was removed *in vacuo*, and the residue was suspended in *n*-heptane and filtered, yielding 2.3 g. (88%). Recrystallization from *n*-heptane gave white plates, m.p. 93–94°; λ_{max} 253, 284 mμ (ε × 10^3 10.8, 19.1).

Anal. Calcd. for $C_{13}H_{21}N_5O$: C, 59.29; H, 8.04; N, 26.60. Found: C, 59.34; H, 7.97; N, 26.50.

B.—A mixture of 1.5 g. (0.01 mole) of 4-amino-3-methylisoxazolo[5,4-*d*]pyrimidine (**5**), 5 ml. of 3-diethylaminopropylamine, and 2.0 g. of its hydrochloride was heated for 3 hr. at 145–155°. Repeated extraction of the resulting dark viscous oil with hot *n*-heptane followed by removal of the solvent under reduced pressure gave 0.65 g. (24%) of a yellow solid. Recrystallization from *n*-heptane yielded white crystals, m.p. 91–93°, identical in every respect (infrared and mixture melting point) with the product obtained by method A.

4-Methylamino-3-phenylisoxazolo[5,4-*d*]pyrimidine (20).—To a saturated solution of anhydrous methylamine in 40 ml. of ethanol was added 2.0 g. (0.008 mole) of 4-cyano-5-ethoxymethyleneamino-3-phenylisoxazole (**16**). After stirring for 4 hr. at room temperature, the mixture was refrigerated. Filtration and concentration of the filtrate to a small volume gave 0.9 g. (50%) of white crystals which were recrystallized from dimethylformamide–ethanol to give large white crystalline plates, m.p. 222–224°; λ_{max} 240, 290 mμ (ε × 10^3 11.0, 8.1).

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.62; H, 4.43; N, 24.88.

3-Phenyl-4-(3′-dimethylaminopropylamino)isoxazolo[5,4-*d*]pyrimidine (21).—A solution of 2.8 g. (0.12 mole) of 4-cyano-5-ethoxymethyleneamino-3-phenylisoxazole (**16**) and 1.1 g. (slight molar excess) of 3-dimethylaminopropylamine in 80 ml. of ethanol was refluxed for 4 hr. and filtered to remove a small amount of undissolved solid; the filtrate was evaporated to dryness under reduced pressure. The residual oil which solidified upon being swirled with a little *n*-heptane was filtered to yield 2.6 g. (74%) of product. Evaporation of the filtrate to dryness gave uncyclized material as shown by the presence of nitrile absorption in the infrared. Recrystallization of the product from *n*-heptane yielded white needles, m.p. 79–80°; λ_{max} 238, 291 mμ (ε × 10^3 12.4, 8.9).

Anal. Calcd. for $C_{16}H_{19}N_5O$: C, 64.62; H, 6.44; N, 23.55. Found: C, 64.69; H, 6.46; N, 23.26.

3-Phenyl-4-(3′-diethylaminopropylamino)isoxazolo[5,4-*d*]pyrimidine (22). A.—A mixture of 2.1 g. (0.01 mole) of 4-amino-3-phenylisoxazolo[5,4-*d*]pyrimidine (**10**), 5 ml. of 3-diethylaminopropylamine, and 2.0 g. of its hydrochloride was heated for 3 hr. at 140–145°. The dark brown oil was covered with 15 ml. of water and the flask was shaken vigorously. Filtration gave a sticky, pale green solid. Recrystallization from *n*-heptane (Norit) yielded 1.0 g. (30%) of white crystals, m.p. 85–87°; λ_{max} 238, 291 mμ (ε × 10^3 12.0, 9.1).

Anal. Calcd. for $C_{18}H_{23}N_5O$: C, 66.44; H, 7.12; N, 21.52. Found: C, 66.46; H, 7.05; N, 21.61.

B.—A solution of 2.4 g. (0.01 mole) of 4-cyano-5-ethoxymethyleneamino-3-phenylisoxazole (**16**) in 70 ml. of hot ethanol was treated with 1.3 g. (0.01 mole) of 3-diethylaminopropylamine and refluxed for 3 hr. After cooling to room temperature, filtration removed a trace amount of undissolved solid. Removal of the solvent under reduced pressure gave an oil which crystallized to 2.6 g. (80%) of a white solid, m.p. 81–84° upon trituration with *n*-heptane. This was identical in every respect with the product obtained by method A.

5-Acetyl-4-amino-6-hydroxypyrimidine (24).—A solution of 3.0 g. (0.02 mole) of 4-amino-3-methylisoxazolo[5,4-*d*]pyrimidine (**5**) in 180 ml. of dimethylformamide was hydrogenated with 0.4 g. of 10% palladium on charcoal, with magnetic stirring, at room temperature (22°) and atmospheric pressure. Reduction ceased after 1 mole of hydrogen was absorbed. After removing the catalyst by filtration, the clear filtrate was distilled to dryness at 22° (1 mm.). The residual white solid was covered with 100 ml. of water, boiled for 30 min. with magnetic stirring (ammonia evolved), and then dissolved by the addition of 10% sodium hydroxide. After standing at room temperature for 1.5 hr., acidification with glacial acetic acid gave 2.8 g. (91%) of white solid, m.p. 308–310° dec. This substance gave a positive haloform test. Recrystallization from water yielded small clusters of white needles, m.p. 310–311° dec.

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.05; H, 4.61. Found: C, 47.21; H, 4.40.

5-Acetyl-4-amino-1-methylpyrimidin-6(1*H*)-one (25).—A solution of 2.0 g. (0.013 mole) of 5-acetyl-4-amino-6-hydroxypyrimidine (**24**) in 15 ml. of *ca.* 7% sodium hydroxide was treated with 3 ml. of dimethyl sulfate and stirred for 1.5 hr. at room temperature. Filtration gave 1.4 g. (63%) of a white solid, m.p. 210–215°. Recrystallization from ethanol yielded white needles, m.p. 214–215°; infrared, $\lambda_{max}^{CHCl_3}$ 5.98 μ (–C(=O)–CH$_3$).

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43. Found: C, 50.51; H, 5.41.

A 2,4-dinitrophenylydhrazone was prepared in methanol.

Anal. Calcd. for $C_{13}H_{13}N_7O_5$: N, 28.27. Found: N, 28.58.

4-Amino-5-benzoyl-6-hydroxypyrimidine (27) was prepared in 72% yield from 4-amino-3-phenylisoxazolo[5,4-*d*]pyrimidine (**10**) in the manner described above for the preparation of **24** from **5**. Recrystallization of the crude product, m.p. 290–292° dec., from dimethylformamide–ethanol gave small, white glistening crystals, m.p. 292–294° dec.

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22. Found: C, 61.42; H, 4.18.

4-Amino-5-benzoyl-1-methylpyrimidin-6(1*H*)-one (28).—A solution of 3.0 g. (0.014 mole) of 4-amino-5-benzoyl-6-hydroxypyrimidine (**27**) in 17 ml. of 10% sodium hydroxide was treated with 5 ml. of dimethyl sulfate and stirred for 1.25 hr. at room temperature. The resulting white solid was filtered, washed with a little water, and dried *in vacuo*, yielding 2.8 g. (89%). Recrystallization from ethanol gave shiny white platelets, m.p. 225–227°; infrared, $\lambda_{max}^{CHCl_3}$ 5.99 μ (–C(=O)–C$_6$H$_5$).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.57; H, 5.03; N, 18.20.

7-Amino-6-cyano-5-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (29).—A solution of 1.0 g. (0.0065 mole) of 5-acetyl-4-amino-6-hydroxypyrimidine (**24**) and 0.5 g. (0.007 mole) of malononitrile in 70 ml. of pyridine was heated under reflux with stirring. Solid started to separate from the reaction mixture after 0.5 hr. After 18 hr. of refluxing, the mixture was filtered hot to give 0.7 g. (54%) of a yellow solid, m.p. >340°. Unchanged starting material was recovered by cooling of the filtrate. The product was prepared for analysis by vacuum sublimation (290° at 0.25 mm.); infrared, λ_{max}^{Nujol} 4.51 μ (–CN).

Anal. Calcd. for $C_9H_7N_5O$: C, 53.73; H, 3.51; N, 34.81. Found: C, 53.68; H, 3.46; N, 34.92.

7-Amino-6-cyano-3-methyl-5-phenylpyrido[2,3-*d*]pyrimidin-4(3H)-one (30).—A solution of 0.9 g. (0.004 mole) of 4-amino-5-benzoyl-1-methylpyrimidin-6(1*H*)-one (**28**) and 0.35 g. (0.005 mole) of malononitrile in 15 ml. of pyridine was heated under reflux for 18 hr. The solvent was removed by evaporation under reduced pressure and the residue was triturated with water and filtered. Extraction of the solid with chloroform and filtration gave 0.25 g. (22%) of yellow product, m.p. >340°, which was recrystallized from dimethylformamide for analysis; infrared, λ_{max}^{Nujol} 4.53 μ (–CN).

Anal. Calcd. for $C_{15}H_{11}N_5O$: C, 64.97; H, 4.00. Found: C, 64.58; H, 4.06.

Synthesis of Some [1,2,3]Thiadiazolo[5,4-*d*]pyrimidines and Pyrimido[4,5-*b*][1,4]thiazines[1]

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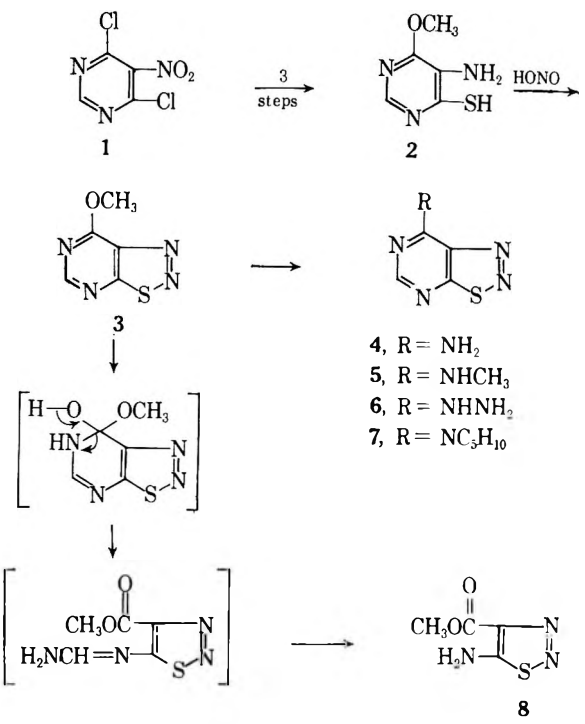
A number of 7-substituted [1,2,3]thiadiazolo[5,4-*d*]pyrimidines and 4-substituted pyrimido[4,5-*b*][1,4]thiazines have been prepared. Diazotization of 5-amino-4-mercapto-6-methoxypyrimidine gave 7-methoxy[1,2,3]-thiadiazolo[5,4-*d*]pyrimidine, which underwent facile nucleophilic displacement of the 7-methoxy group when treated with amines, and pyrimidine ring cleavage to methyl 5-amino-1,2,3-thiadiazole-4-carboxylate when heated with acid. Catalytic reduction of 4-carboxymethylthio-6-methoxy-5-nitropyrimidine gave 4-methoxy-7*H*-pyrimido[4,5-*b*][1,4]thiazin-6(5*H*)-one. Treatment of 5-amino-4-mercapto-6-methoxypyrimidine with phenacyl chloride in alkali yielded 4-methoxy-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine.

As a part of our continuing program directed towards the synthesis of potential purine and pteridine analogs as antimitotic agents, we wish to describe the preparation of a number of [1,2,3]thiadiazolo[5,4-*d*]pyrimidines and pyrimido[4,5-*b*][1,4]thiazines.

4,6-Dichloro-5-nitropyrimidine (**1**) was converted by a three-step sequence[2] to 5-amino-4-mercapto-6-methoxypyrimidine (**2**), which served as the starting material for many of the syntheses to be described. Thus, diazotization of **2** at 0° in dilute hydrochloric acid gave a pale yellow solid which upon vacuum sublimation yielded a white, crystalline material. Microanalysis and the absence of diazo absorption in the infrared spectrum of the material established its structure as 7-methoxy[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**3**).[3] A series of 7-substituted derivatives was then readily prepared from **3** by nucleophilic displacement of the extremely labile methoxy group.[4] Thus, treatment of **3** with ethanolic ammonia gave 7-amino-[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**4**). Similar treatment of **3** with methylamine, hydrazine, and piperidine gave the corresponding 7-substituted derivatives **5**, **6**, and **7** (Scheme I).

SCHEME I



An attempt to effect hydrolysis of the methoxy group in **3** to give the corresponding 7-hydroxy derivative led to an unexpected cleavage reaction. Heating **3** with 2.5 *N* hydrochloric acid for approximately 10 min. followed by cooling resulted in the separation of a white, crystalline solid which exhibited bands at 2.94, 3.06, and 5.89 μ in the infrared, and whose microanalysis indicated the loss of a nitrogen atom but probable retention of the methoxy group. Such a result could only be compatible with hydrolytic cleavage of the pyrimidine ring to give methyl 5-amino-1,2,3-thiadiazole-4-carboxylate (**8**), which probably occurs as shown. There is ample precedent for pyrimidine cleavage reactions at the N-3–C-4 position occurring under similar conditions. For example, Albert[5] showed that acid hydrolysis of 4-methylpteridine (**9**) gave N′-(3-acetyl-2-pyrazinyl)formamidine (**10**); pteridine (**11**) under the same conditions gave 2-aminopyrazine-3-carboxaldehyde (**12**). In a similar type of cleavage reaction, 4-methylmercaptopyrimido-[4,5-*d*]pyrimidine (**13**), when dissolved at room temperature in dilute acetic acid, gave after 24 hr. a 63% yield of 4-formylamino-6-methylmercaptopyrimidine-5-carboxaldehyde (**14**).[6] Likewise, 4-amino- and 4-substituted aminopyrimido[4,5-*d*]pyrimidines (**15**) upon hydrolysis with 0.5 *N* hydrochloric acid were shown to give 4,6-diaminopyrimidine-5-carboxaldehydes (**16**), presumably *via* the hydrolytic pathway shown in Scheme II.[6] Finally, Shealy and Clayton[7] recently have shown that basic reagents under mild conditions cleave the pyrimidine ring of [1,2,5]thiadiazolo[3,4-*d*]-pyrimidin-7(6*H*)-one (**17**) to give derivatives of 4-amino-1,2,5-thiadiazole-3-carboxylic acid (**18**).

Confirmation for the assigned structure **8** for the hydrolysis product of **3** was obtained in the following manner. Treatment of **8** with an excess of formamidine acetate in 2-ethoxyethanol gave [1,2,3]thiadi-

(1) This work was supported by a research grant (CY-2551) to Princeton University from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) E. C. Taylor, J. W. Barton, and W. W. Paudler, *J. Org. Chem.*, **26**, 4961 (1961).

(3) The only previously described derivatives of this ring system appear to be the 7-amino [M. Ishidate and H. Yuki, *Chem. Pharm. Bull.* (Tokyo), **8**, 131 (1960)], the 5-amino-7-methyl [F. L. Rose, *J. Chem. Soc.*, 3448 (1952)], and the 5-mercapto-7-methyl [R. S. Karlinskaya, N. V. Kromov-Borisov, *Zh. Obshch. Khim.*, **32**, 1847 (1962)] derivatives.

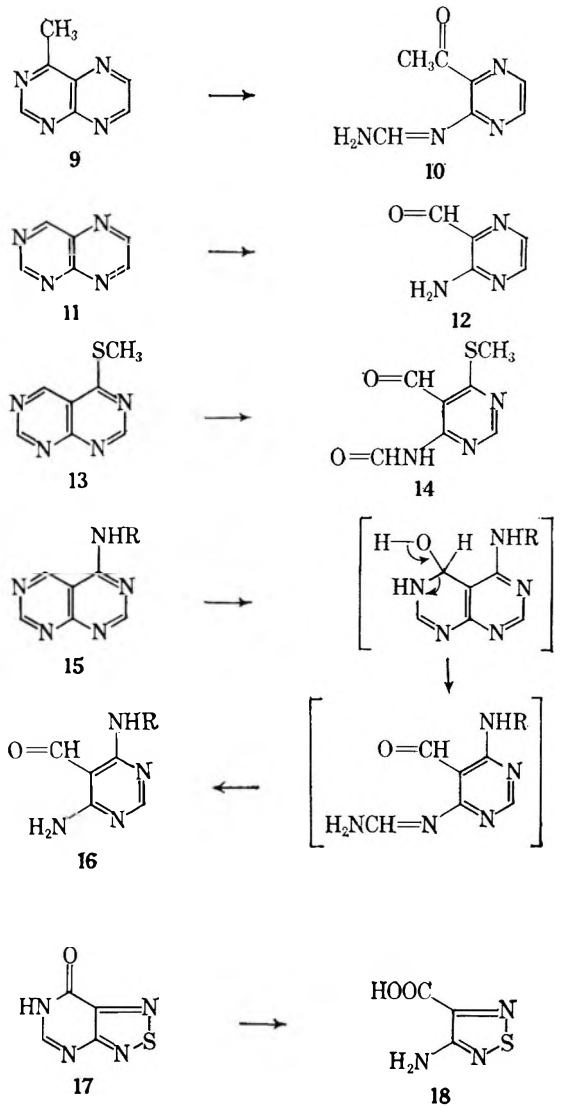
(4) Facile nucleophilic displacement reactions at position 7 in [1,2,5]-thiadiazolo[3,4-*d*]pyrimidine derivatives have been reported by Y. F. Shealy, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.*, **27**, 2154 (1962).

(5) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2063 (1956).

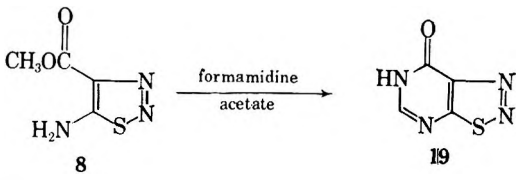
(6) E. C. Taylor and W. A. Ehrhart, unpublished observations.

(7) Y. F. Shealy and J. D. Clayton, *J. Org. Chem.*, **28**, 1491 (1963).

SCHEME II



azolo[5,4-*d*]pyrimidin-7(6*H*)-one (**19**), which was identical in physical properties with a sample of the same material prepared by a different route by workers at the Southern Research Institute.[8]



Unexpectedly, all attempts to convert the ester **8** to the corresponding carboxamide were unsuccessful.

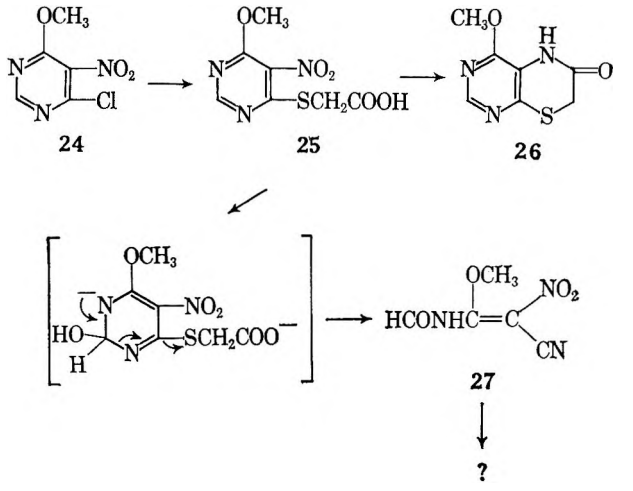
A further derivative of the [1,2,3]thiadiazolo[5,4-*d*]-pyrimidine ring system was prepared from 5-amino-uracil by treatment with phosphorus pentasulfide in refluxing pyridine to give 5-amino-4-thiouracil (**20**) followed by diazotization to give **21**.

(8) Courtesy of Dr. J. A. Montgomery.

One modification of the pteridine ring system which might give rise to biologically active compounds would be the replacement of one of the nitrogen atoms in the pyrazine ring by sulfur. Recently, Schroeder and Dodson[9] have described the preparation of a number of derivatives of pyrimido[5,4-*b*][1,4]thiazine (**22**);

we wish to describe at this time the synthesis of several derivatives of the isomeric system **23**. Reaction of 4-chloro-6-methoxy-5-nitropyrimidine (**24**), one of the intermediates in the conversion of **1** to **2**, with mercaptoacetic acid at 0° in alkaline solution, followed by acidification, gave 4-carboxymethylthio-6-methoxy-5-nitropyrimidine (**25**) (Scheme III). Catalytic reduction of **25** then gave directly the ring-closed product,

SCHEME III



4-methoxy-7*H*-pyrimido[4,5-*b*][1,4]thiazin-6(5*H*)-one (**26**).[10] In contrast to the behavior of the methoxy derivative **3**, compound **26** proved to be inert towards displacement reactions; only starting material could be obtained upon heating **26**, even under very vigorous conditions, with a variety of amines and hydrazine.

The reaction of **24** with mercaptoacetic acid in alkaline solution proved to be very sensitive to temperature. When the reaction was carried out at room temperature rather than at 0°, none of the desired product **25** was formed; the only product obtained was an impure solid which exhibited strong $-NH_2$ bands and a $-CN$ band in the infrared. It thus seems probable that, under the alkaline condition employed, ring opening of **25** had taken place to give **27**. Analogous ring cleavages of mercapto-substituted pyrimidine heterocycles in alkaline solution previously have been observed[11]; the cleavage of 4-mercaptopteridine (**28**) to 2-amino-3-cyanopyrazine (**29**) upon

(9) E. F. Schroeder and R. M. Dodson, *J. Am. Chem. Soc.*, **84**, 1904 (1962).

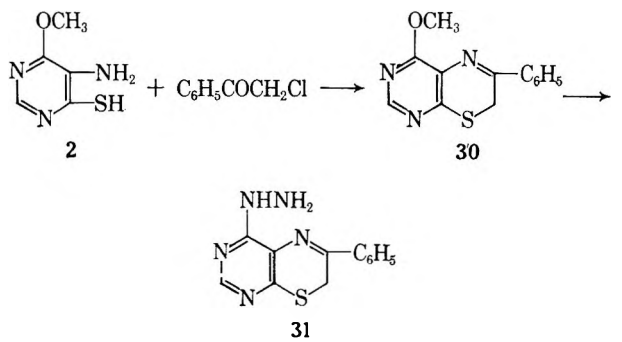
(10) Previously prepared derivatives of this system appear to be the 2-amino-4-methyl [F. L. Rose, *J. Chem. Soc.*, 3448 (1952)] and the 4-amino and 4-carboxymethylthio [M. Ishidate and H. Yuki, *Chem. Pharm. Bull.* (Tokyo), **8**, 131 (1960)] derivatives.

(11) E. C. Taylor, R. J. Knopf, J. A. Cogliano, J. W. Barton, and W. Pfleiderer, *J. Am. Chem. Soc.*, **82**, 6058 (1960).

28 29

treatment with chloroacetic acid and alkali is illustrative.

An alternative route to derivatives of the pyrimido-[4,5-*b*][1,4]thiazine ring system (**23**) involved treatment of 5-amino-6-mercapto-4-methoxypyrimidine (**2**) in alkaline solution with phenacyl chloride. 4-Methoxy-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine (**30**) was formed directly in 62% yield. Here again the methoxy group proved surprisingly unreactive towards nucleophilic displacement reactions; for example, only starting material could be recovered from an attempted reaction of **30** with alcoholic ammonia. Treatment of **30** with hydrazine hydrate in refluxing ethanol, however, led to the 4-hydrazino derivative (**31**) in good yield.



2 30

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Experimental[12]

5-Amino-4-mercapto-6-methoxypyrimidine (**2**).—Compound **2** was prepared according to the procedure of Taylor, *et al.*,[2] using 4,6-dichloro-5-nitropyrimidine purchased from Aldrich Chemical Co.

7-Methoxy [1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**3**).—To 6.0 g. (0.038 mole) of 5-amino-4-mercapto-6-methoxypyrimidine (**2**) dissolved in a mixture of 40 ml. of concentrated hydrochloric acid and 350 ml. of water, and cooled to 0°, was added with stirring a solution of 3.1 g. (excess) of sodium nitrite in 15 ml. of water. During the addition, which was made portionwise over 15 min., a solid formed. After stirring for an additional 2 hr. at 0–5°, filtration and vacuum drying gave 5.0 g. of a pale yellow solid. Vacuum sublimation at 115–125° (0.5 mm.) yielded 4.3 g. (67%) of white crystals, m.p. 151–152°; λ_{max} 234 (sh), 261, 280 mμ ($\epsilon \times 10^3$ 5.4, 6.7, 5.0).

Anal. Calcd. for $C_5H_4N_4OS$: C, 35.72; H, 2.40; N, 33.33. Found: C, 35.68; H, 2.54; N, 33.30.

7-Amino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**4**).—Anhydrous ammonia was bubbled through a solution of 1.6 g. of 7-methoxy-[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**3**) in 120 ml. of hot ethanol for 0.5 hr. During this period the solution was heated on a hot plate. A solid separated almost immediately. Filtration and washing with hot ethanol gave 1.3 g. (86%) of a white solid, m.p. >270° dec. (slow). For analysis a sample was sublimed at 155–165° (0.5–0.7 mm.). This compound is reported[3] to melt with decomposition above 250°; λ_{max} 244, 263 (sh), 272 (sh), 313 mμ ($\epsilon \times 10^3$ 6.2, 3.2, 2.9, 4.9).

Anal. Calcd. for $C_4H_3N_5S$: C, 31.38; H, 1.98; N, 45.75; S, 20.89. Found: C, 31.41; H, 2.29; N, 45.75; S, 20.62.

7-Methylamino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**5**).—Anhydrous methylamine was bubbled for 1.5 hr. through a solution of 1.0 g. of 7-methoxy[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**3**) dissolved in 35 ml. of dioxane. The solution was heated on a steam bath during the initial 0.5 hr. of the reaction. Filtration and concentration of the filtrate yielded 0.9 g. (90%) of a slightly yellow solid, m.p. 217–219° dec. Two sublimations at 125° (0.5 mm.) gave white crystals, m.p. 219° dec.; λ_{max} 247, 267 (sh), 274 (sh), 325 mμ ($\epsilon \times 10^3$ 8.1, 3.7, 3.5, 5.9).

Anal. Calcd. for $C_5H_5N_5S$: C, 35.93; H, 3.02; N, 41.91; S, 19.15. Found: C, 35.94; H, 3.34; N, 42.00; S, 19.27.

7-Hydrazino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**6**).—A hot solution of 0.4 g. (0.0024 mole) of 7-methoxy[1,2,3]thiadiazolo-[5,4-*d*] pyrimidine (**3**) in 25 ml. of ethanol was treated with 0.2 g. (excess) of 85% hydrazine. Instantaneously a feathery, yellow solid precipitated. The mixture was then heated for 5 min. on a hot plate and then allowed to stand at room temperature for 10 min. Filtration gave 0.3 g. (75%) of product, m.p. 204–206° dec. For analysis the solid was recrystallized from a large volume of ethanol and had m.p. 208–209° dec.; λ_{max} 247, 275 (sh), 328 mμ ($\epsilon \times 10^3$ 7.7, 3.8, 6.9).

Anal. Calcd. for $C_4H_4N_6S$: C, 28.57; H, 2.40; N, 49.99. Found: C, 28.54; H, 2.41; N, 49.70.

7-Piperidino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**7**).—A solution of 1.0 g. (0.006 mole) of 7-methoxy[1,2,3]thiadiazolo[5,4-*d*]-pyrimidine (**3**) in 40 ml. of boiling ethanol was treated with 0.8 g. (excess) of piperidine and refluxed for 5 hr. Concentration of the resultant yellow-green solution produced a white solid, which after washing with water and drying weighed 1.1 g., m.p. 81–83°. Recrystallization from petroleum ether (60–70°) gave 0.95 g. (73%) of microneedles, m.p. 84–85°.

Anal. Calcd. for $C_9H_{11}N_5S$: C, 48.86; H, 5.01; N, 31.66. Found: C, 48.80; H, 5.14; N, 31.47.

Methyl 5-Amino-1,2,3-thiadiazole-4-carboxylate (**8**).—A suspension of 3.0 g. (0.018 mole) of 7-methoxy[1,2,3]thiadiazolo-[5,4-*d*]pyrimidine (**3**) in 45 ml. of 2.5 *N* hydrochloric acid was heated to boiling, whereupon solution occurred. In several minutes the originally clear solution became cloudy. After a total of 10 min. of boiling, the mixture was quickly filtered; the filtrate was refrigerated for 1 hr. The white solid which separated was filtered, washed with a little cold water, and dried *in vacuo* to give 1.8 g. (62%), m.p. 170–171° dec. For analysis the product was purified by sublimation at 135–140° (0.7 mm.); λ_{max} 267, 285 (sh) mμ ($\epsilon \times 10^3$ 8.5, 6.6); infrared,[13] λ_{max}^{Nujol} 2.94, 3.06, 3.16, 5.89, 6.20, 6.64, 7.25, 7.55, 8.05, 9.00, 10.40, 11.20, 12.08, 12.89 μ (medium and strong absorptions).

Anal. Calcd. for $C_4H_5N_3O_2S$: C, 30.19; H, 3.17; N, 26.41. Found: C, 30.47; H, 3.34; N, 26.64.

Methyl 5-Acetylamino-1,2,3-thiadiazole-4-carboxylate.—A solution of 0.5 g. (0.0031 mole) of methyl 5-amino-1,2,3-thiadiazole-4-carboxylate (**8**), 8 ml. of acetic anhydride, and 20 ml. of benzene was refluxed for 40 hr. The precipitated solid was filtered, washed with water, and sublimed at 140° (1.5 mm.). The first fraction to sublime appeared to be starting material, m.p. 170–171°. The second fraction obtained at 160° (2 mm.) was a white crystalline solid, m.p. 245–246° dec.

Anal. Calcd. for $C_6H_7N_3O_3S$: C, 35.83; H, 3.51. Found: C, 36.14; H, 3.59.

[1,2,3]Thiadiazolo[5,4-*d*]pyrimidin-7(6*H*)-one (**19**).—A solution of 0.65 g. (0.004 mole) of methyl 5-amino-1,2,3-thiadiazole-4-carboxylate (**8**) and 1.0 g. (excess) of formamidine acetate in 10 ml. of 2-ethoxyethanol was refluxed for 40 min. Concentration to dryness at reduced pressure gave a brown solid which was covered with 10 ml. of water and filtered. Recrystallization of the solid so obtained from ethanol (Norit) yielded 0.3 g. (45%) of white crystals, m.p. 230–231° dec.; $\lambda_{max}^{0.1\ N\ HCl}$ 233, 286 mμ ($\epsilon \times 10^3$ 6.9, 5.3); $\lambda_{max}^{0.1\ N\ NaOH}$ 237, 258 (sh), 310 mμ ($\epsilon \times 10^3$ 7.4, 6.3).

Anal. Calcd. for $C_4H_2N_4OS$: C, 31.16; H, 1.31; N, 36.35; S, 20.81. Found: C, 31.52; H, 1.46; N, 36.38; S, 20.70.

5-Amino-4-thiouracil (**20**).—A mixture of 20 g. (0.016 mole) of 5-aminouracil (Eastman, White Label), 60 g. (large excess) of phosphorus pentasulfide (Monsanto), and 700 ml. of reagent grade pyridine were heated, with stirring, at reflux for approximately 2 hr. The resultant green-black suspension was evaporated to dryness under reduced pressure, and the residue was covered with 400 ml. of water and heated to boiling for 1 hr.

(12) Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. All ultraviolets pectra were determined in ethanol unless otherwise specified.

(13) Infrared and ultraviolet spectra of some 5-substituted amino-1,2,3-thiadiazoles have been reported by E. Lieber, N. Calvanico, and C. N. R. Rao, *J. Org. Chem.*, **28**, 257 (1963).

After overnight refrigeration, filtration gave 16.5 g. of a greenish solid. Two recrystallizations from 10% sulfuric acid (Norit) yielded yellow crystals, which melted slowly with decomposition above 185°. Refrigeration of the filtrate gave a small amount of additional solid, total yield 14.8 g. (*ca.* 50%). The product appeared to be a sulfate salt on the basis of microanalysis.

Anal. Calcd. for $C_4H_5N_3OS \cdot 0.5H_2SO_4$: C, 25.00; H, 3.14; N, 21.88; S, 25.00. Found: C, 24.51; H, 3.31; N, 21.91; S, 24.81.

[1,2,3]Thiadiazolo[5,4-*d*]pyrimidin-5(4*H*)-one (21).—To 5.0 g. (*ca.* 0.026 mole) of the sulfuric acid salt of 5-amino-4-thiouracil (**20**) dissolved in 170 ml. of 2.5 *N* hydrochloric acid and cooled to 0° was added, with stirring, 2.3 g. (excess) of sodium nitrite in 15 ml. of water during 15 min. After an additional 1.5 hr. at 0–5°, the solid was filtered, washed with a little cold water, and oven-dried to yield 3.1 g. (77%) of yellow solid, m.p. 239° (effervescence). Two recrystallizations from a large volume of ethanol gave a pale cream-colored solid, m.p. 239° dec.; λ_{max} 236, 287 mμ ($\epsilon \times 10^3$ 3.7, 8.2).

Anal. Calcd. for $C_4H_2N_4OS$: C, 31.16; H, 1.31; N, 36.35; S, 20.81. Found: C, 31.20; H, 1.65; N, 36.30; S, 20.80.

4-Carboxymethylthio-6-methoxy-5-nitropyrimidine (25). To a suspension of 9.0 g. (0.047 mole) of 4-chloro-6-methoxy-5-nitropyrimidine in 125 ml. of water immersed in ice, there was added 4.3 g. (0.047 mole) of mercaptoacetic acid (Fisher). At 0° and with vigorous stirring a solution of 3.8 g. (0.095 mole) of sodium hydroxide in 30 ml. of water was added over 20 min. During this addition, color changes of yellow to green to brown were observed. After stirring for an additional 4.5 hr. at 0–5°, the now blue solution was filtered to remove 0.75 g. of starting material, and the ice-cooled filtrate was acidified with concentrated hydrochloric acid. After standing for 5 min. at room temperature the precipitated blue-purple solid was filtered and dissolved in a large volume of ethanol. Three treatments with Norit gave a yellow-green solution which was concentrated to a small volume, treated with a little water and refrigerated. Filtration and vacuum drying (80°) yielded 6.4 g. (55%) of yellow-green crystals, m.p. 136–138°, with preliminary shrinking about 120°. One additional recrystallization from ethanol brought the melting point to 138–139°.

Anal. Calcd. for $C_7H_7N_3O_5S$: C, 34.29; H, 2.88; N, 17.14; S, 13.06. Found: C, 34.49; H, 2.77; N, 16.92; S, 12.77.

4-Methoxy-7*H*-pyrimido[4,5-*b*][1,4]thiazine-6(5*H*)-one (26).—A solution of 2.5 g. (0.01 mole) of 4-carboxymethylthio-6-methoxy-5-nitropyrimidine (**25**) in 70 ml. of methanol was treated with 0.5 g. of platinum oxide and hydrogenated in a Parr apparatus (*ca.* 2 atm.). After 2 hr., the catalyst was filtered off and the filtrate was concentrated to dryness to give a red oily solid. Two treatments with 25-ml. portions of ethyl acetate followed by evaporation of solvent gave 1.8 g. of brown solid. Two recrystallizations from ethanol–petroleum ether (b.p. 60–70°) yielded white crystals, 1.4 g. (70%), m.p. 190–191°; λ_{max} 236, 246 (sh), 283 (sh), 295 mμ ($\epsilon \times 10^3$ 15.0, 13.5, 5.0, 5.5).

Anal. Calcd. for $C_7H_7N_3O_2S$: C, 42.64; H, 3.58; N, 21.32; S, 16.14. Found: C, 42.68; H, 3.48; N, 21.39; S, 16.11.

4-Methoxy-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine (30).—A solution of 4.9 g. (0.031 mole) of 5-amino-6-mercapto-4-methoxypyrimidine (**2**) in 40 ml. of 10% sodium hydroxide was treated with 4.9 g. (0.031 mole) of phenacyl chloride and stirred for 24 hr. at room temperature. After filtering and washing with a little ether, the resultant tan solid, m.p. 175–180°, weighed 5.8 g. Two recrystallizations from ethanol–benzene gave 5.0 g. (62%) of pale yellow needles, m.p. 177–179° (does not form a clear melt); λ_{max} 233, 268, 295, 344 mμ ($\epsilon \times 10^3$ 13.6, 20.0, 6.4, 8.4).

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.60; H, 4.63; N, 16.29.

4-Hydrazino-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine (31).—A solution of 0.5 g. (0.002 mole) of 4-methoxy-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine (**30**) in 10 ml. of ethanol was treated with 2 ml. of 85% hydrazine and refluxed for 5 hr. The solution was filtered hot. Cooling of the filtrate then gave 0.35 g. (70%) of long, yellow needles, m.p. 198–202°. The analytical sample was recrystallized from ethanol to give deep orange needles, m.p. 198–200°; λ_{max} 276, 378 (broad) mμ ($\epsilon \times 10^3$ 21.0, 7.5).

Anal. Calcd. for $C_{12}H_{11}N_5S$: C, 56.02; H, 4.31; N, 27.23; S, 12.44. Found: C, 56.01; H, 4.33; N, 27.01; S, 12.35.

Heterocyclic Studies. XII. The Base-Catalyzed Deuterium Exchange and Rearrangement of 2,3-Dihydro-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one to α-Aminopyridines[1,2]

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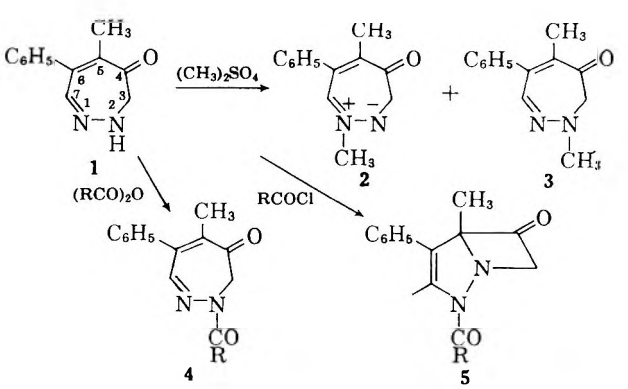
Deuterium exchange of the diazepinone **1** in basic solution was determined by n.m.r. spectra and found to occur at C-3 and more slowly at C-7 to give the 3,3,7-d_3 compound by deuteration of the anions **6** and **7**. Rearrangement of **1** in basic solution gives 2- and 6-amino-3-hydroxy-4-methyl-5-phenylpyridines in approximately equal amounts. The 2-methyldiazepinone **3** gives the 2-methylaminopyridine **11**. A suggested mechanism for the rearrangement is cleavage to the acyclic intermediate **14** and recyclization.

In previous papers we have described the formation of and structural evidence for the diazepinone **1**.[3,4] Electrophilic reagents attack **1** at both nitrogen atoms; with methyl sulfate in alkaline solution, equal amounts of the 1- and 2-methyl derivatives **2** and **3** are produced. Acylation with acid chlorides in pyridine solution occurs at N-1; in this case the substitution is accompanied by bridging to give the bicyclic ketone **5**.[5] With acid anhydrides the 2-acyl derivatives **4** are obtained.

The factors governing the position of attack of **1** with various reagents are not yet fully understood;



some of these products have been assumed to arise by participation of the anion **6** and others from the neutral molecule.[4] The ketone **1** is soluble in dilute aqueous alkali, and this acidic character has been attributed to

(1) Supported in part by Grant No. DA-CML-18-108-61-6-24 from the Army Chemical Corps.

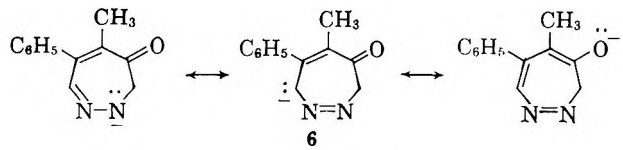
(2) Paper XI: J. A. Moore and C. L. Habraken, *J. Am. Chem. Soc.*, **86**, 1456 (1964).

(3) J. A. Moore and R. W. Medeiros, *ibid.*, **81**, 6026 (1959).

(4) J. A. Moore and J. Binkert, *ibid.*, **81**, 6029 (1959).

(5) J. A. Moore, F. J. Marascia, R. W. Medeiros, and E. Wyss, *ibid.*, **84**, 3022 (1962).

the delocalization of negative charge in **6**. The NH group is clearly the most acidic center in the molecule, and, since no alkylation or acylation products involving attack at the potentially enolizable C-3–C-4 system have been encountered, the possible role of the enolate anion **7** in reactions of **1** has not been considered. In connection with studies on the aldol condensation of **1**,



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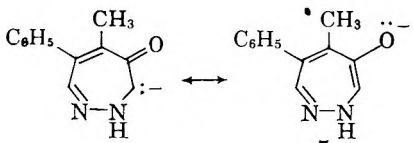

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described in the following paper,[6] it was of interest to examine this possibility by means of deuterium exchange studies. This work has established that enolization at C-3 is in fact rapid, and has also revealed a new rearrangement pathway of this highly reactive molecule.

The deuterium exchange of **1** was carried out in 2.5 *N* sodium deuterioxide–deuterium oxide solution at room temperature. The extent and position of exchange was determined by observing the changes in the n.m.r. spectrum at 60 Mc., both in the D_2O solution directly and also of the diazepinone **1** recovered from the exchange in $CDCl_3$ (tetramethylsilane) solution. In $CDCl_3$, and also dimethyl sulfoxide, the singlet (δ = 7.03 p.p.m.) from the C-7 proton of **1** was clearly separated (upfield) from the phenyl–NH multiplet at 7.08–7.50 p.p.m. (Fig. 1A), although not far enough for independent integration. The multiplet from 7.03–7.50 p.p.m. corresponded to seven protons, C_6H_5, C-7 *H*, and N*H*. In aqueous sodium hydroxide or sodium deuterioxide (Fig. 1C) the C-7 proton signal was again separated from the phenyl peak, but was now downfield. The phenyl signal in this case was a single peak without fine structure. (Peak positions in the D_2O spectra cannot be given since no internal standard was present.) That the separate peak was due to the C-7 proton in both cases follows from the exchange results described below. The signals from the C*H*$_3$ and C*H*$_2$ groups (1.88 and 3.86 p.p.m., respectively, in $CDCl_3$) corresponded exactly to three and two protons both in $CDCl_3$ and H_2O–NaOH solutions. The CH_2 peak in the $CDCl_3$ spectrum was a doublet (J = 3 c.p.s.) due to spin coupling with the N*H*; this splitting was absent in the spectrum of the 2-methyldiazepinone **3**.

Twenty-two spectra of a solution of **1** in D_2O–NaOD were recorded and integrated at intervals over an extended period; values for the areas of the CH_3, CH_2, combined phenyl–C-7, and water peaks during the first 4 days are given in Table I. The area of the methyl peak was used as a reference in calculating the loss in protons from the C-3 and C-7 positions. In the first spectrum, integrated 15 min. after the solution was prepared, the CH_2 peak area corresponded to 1.4 protons; after 3 days this peak was no longer detectable, indicating complete exchange at this position. The peak due

(6) R. K. Bly, E. C. Zoll, and J. A. Moore, *J. Org. Chem.*, **29**, 2128 (1964).

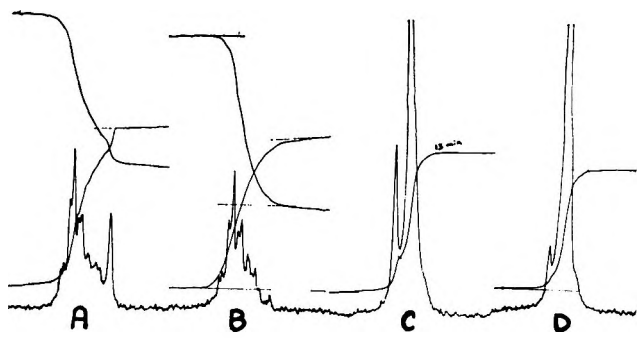


Fig. 1.—Phenyl–C-7 peaks of n.m.r. spectra of compound **1**: A, $CDCl_3$ solution before exchange; B, $CDCl_3$ solution after 96-hr. exchange; C, D_2O–NaOD solution after 13 min.; D, D_2O–NaOD solution after 72 hr.

to the C-7 proton diminished more slowly and had not disappeared completely until the tenth day; the change during 72 hr. is indicated in Fig. 1C and 1D. The area of the combined phenyl–C-7 peak dropped from an initial value of 6.3 protons (theoretical value 6.0, since NH exchange is very rapid) to a minimum corresponding to about 5.1 protons after 4 days. The area of the water peak increased during this period, but the integration was too erratic to permit correlation with the number of protons lost as water by exchange at C-3 and C-7. No loss of protons from the methyl and phenyl groups was apparent. The ratio of the phenyl–C-7 peak to the total integral fluctuated after the fourth day, but there was no consistent drift.

TABLE I

INTEGRATION OF N.M.R. SPECTRUM OF **1** IN D_2O–NaOD

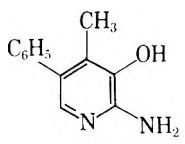
Time, hr.	Peak area[a]				Number of protons[b]	
	CH_3	CH_2	H_2O	Phenyl–C-7	CH_2	Phenyl–C-7
0.25	6.9	3.2	9.1	14.6	1.4	6.3
0.5	6.9	3.1			1.35	
1.6	7.0	1.8	10.3	14.8	0.8	6.3
3.6	7.2	1.0	10.3	14.5	0.4	6.1
7.2	7.3	0.8	10.9	14.5	0.3	5.9
25	7.3	0.4	11.8	13.8	0.15	5.6
72	6.9	0	11.4	12.7	0	5.5
96	7.2		11.9	12.4		5.1

[a] In units of 0.5 cm. on integration curve. [b] Three times peak area/methyl area.

Another solution of **1** in sodium deuterioxide was acidified after 4 days and the precipitated diazepinone was purified by recrystallization. The n.m.r. spectrum (Fig. 1B) contained no discernible peaks for the C-3 or C-7 protons; the ratio of phenyl–NH to methyl peaks was 6.0:3.0, although this agreement is probably fortuitous. These data demonstrate that the deuterated product is the 3,3,7-d_3 compound, exchange at C-3 arising by deuteration of anion **7** and at C-7 by deuteration of **6**. The fact that exchange at C-7 is slower than at C-3, even though **6** is presumably present in much larger concentration, may be due to a low negative charge density at C-7 or possibly shielding by the adjacent phenyl group.

In the course of these exchange experiments it became evident from the n.m.r. data and isolation of the deuterated compound that solutions of **1** in alkali were not, as earlier believed,[4] stable on prolonged standing. The material recovered from the exchange solution after 4 days contained an appreciable impurity and, on

refluxing an alkaline solution of **1** for a few hours, a colorless amphoteric product was isolated which was identified as 2-amino-3-hydroxy-4-methyl-5-phenylpyridine (**8**) by comparison with an authentic sample.[7] This structure, coupled with n.m.r. evidence discussed below, prompted a search for the isomeric 6-aminohydroxymethylphenylpyridine (**9**), and this was isolated in smaller amount after chromatography on cellulose. Neither of the pyridines was obtained in pure form, but both compounds were characterized by conversion to derivatives and comparison with previously prepared specimens.[7]



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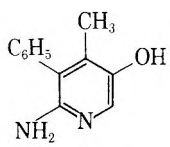

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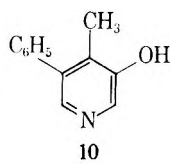

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Concurrent with the isolation of these pyridines, independent evidence of the rearrangement was obtained from the n.m.r. spectra of the D_2O solution discussed above. Two peaks, displaced downfield from the methyl resonance of **1**, became visible after 3 days and steadily increased in intensity until, after 46 days, the three methyl peaks were of comparable area, with the two new peaks separated by 9 and 22 c.p.s. from the methyl peak of **1**. It was apparent that these new peaks arose from the methyl groups of **8** and **9**, and the assignment of the higher field signal to **9** and the lower to **8** was made by comparison with the shifts of the methyl peaks of authentic samples of the pyridines in alkaline D_2O solution. The n.m.r. data for **8** and **9** and two related pyridines are given in Table II. To permit the assignment of the peaks in the exchange spectrum,

TABLE II

N.M.R. PEAKS[a] OF AMINO-3-HYDROXY-4-METHYL-5-PHENYLPYRIDINES IN D_2O–NaOD[c]

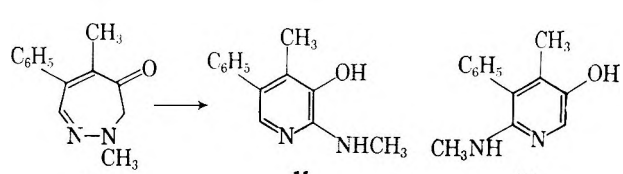
Compound	Methyl	Phenyl	2- or 6-H	Other
8	122	444	426	
9	109	448	[b]	
11	123	443	431	N-CH_3, 177
10	122	438	448, 472	

[a] Peak positions in c.p.s. relative to methyl peak of **1** taken as 100. [b] Peak could not be identified.

the diazepinone **1** was used as an internal reference; the methyl peak of **1** was assigned an arbitrary shift value of 100 c.p.s. The δ-values of 22 and 9 c.p.s. for **8** and **9**, respectively, coincide precisely with those observed in the spectrum of **1**. It is of interest that the position of the methyl peak of **8** corresponds exactly to that of the methyl peak of the desamino pyridine **10**, showing no effect of the 2-amino group, while the presence of the 6-amino group in **9** causes a diamagnetic shift of the methyl signal of 13 c.p.s.

In the isolation of the pyridines **8** and **9** on a preparative scale, the 2-amino isomer **8** appeared to be present in larger amount, but the yields on isolation are a poor measure since the compounds are extremely sensitive to oxidation and can be purified only with substantial losses. The yield of the crude pyridine mixture was 39% but only a few per cent of the purified separate isomers was obtained. A better indication of the yields was provided by the relative areas of the methyl peaks in the n.m.r. spectrum. Within the limits of error of the integration (about 10%), the ratio of the area of the methyl peaks to the total integral (all protons in the solution) remained constant (20.5 to 23%) throughout the entire series of spectra, indicating no significant deuterium exchange of methyl protons, either in **1** or in the pyridines. In the later spectra, a small peak or peaks, evidently due to methyl groups in unidentified decomposition products, became apparent upfield from the methyl peaks of **1**, **8**, and **9**. In the spectrum after 46 days, the pyridines comprised about 45% of the total methyl integral, about 35% appeared to be due to unreacted **1**, and the remainder to other species. Moreover, the relative areas of the two pyridine peaks differed by no more than 10%; if either was in excess, it appeared to be **9** rather than **8**. From these data it can be concluded that the yields of **8** and **9** are in the range of 25%.

The isolation of the pyridines **8** and **9** from the reaction of **1** with base suggested the identity of an amphoteric product that had been obtained previously in the attempted alkoxide-catalyzed aldol condensation of the 2-methyldiazepinone **3**.[6] By analogy with the reaction of **1**, it was clear that this compound was either 2- or 6-methylamino-3-hydroxy-4-methyl-5-phenylpyridine (**11** or **12**). Accordingly, the reaction of **3** with base was repeated in aqueous methanolic alkali and a product was isolated (94% of crude crystalline material) which had the composition $C_{13}H_{14}N_2O$ and whose properties corresponded in all respects with those expected for **11**. Treatment with acetic anhydride–pyridine furnished a diacetyl derivative. The pK_A values and ultraviolet spectra in neutral, acid, and basic solutions of the rearrangement product were very similar to those of **8**, but these properties do not distinguish between **8** and **9**,[7] and did not rule out the 6-methylamino structure **12**. A distinction between **11** and **12** was possible, however, from the n.m.r. spectrum in alkaline D_2O (Table II). Two three-proton peaks were present 23 and 77 c.p.s. downfield from the methyl peak of **1**, corresponding to the C-methyl and N-methyl peaks, respectively; the shift of 23 c.p.s. may be compared to those of 22 and 9 c.p.s. for the 2- and 6-amino derivatives, and provides conclusive proof of the 2-methylamino structure **11** for the rearrangement product. The other peaks in the spectrum are consistent with this structure but do not distinguish between the 2- and 6-isomers.

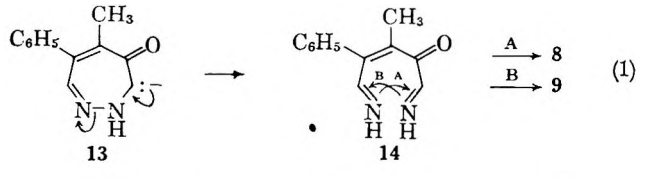


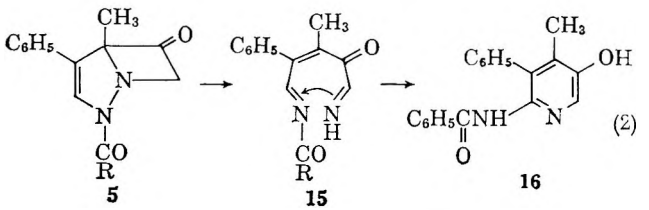
3 **11** **12**

The over-all path of the rearrangements of **1** and **3** to the amino pyridines is quite obvious; barring an implausible series of changes, N-2 of the diazepinone ring is extruded in the formation of the 2-amino compounds **8** and **11**, and N-1 is extruded in the formation of the 6-aminopyridine **9**. The formation of two isomers in the case of **1** and of a single isomer from **3** is inevitable from these structural changes, and shows only that alkyl migration does not occur. The ring contraction is al-

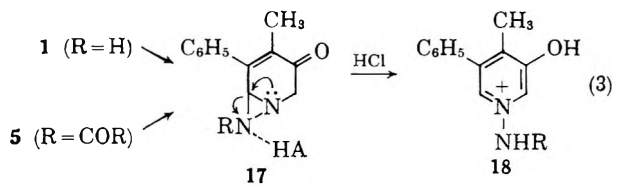
(7) J. A. Moore and F. J. Marascia, *J. Org. Chem.*, **81**, 6049 (1959).

most certainly a consequence of enolate formation at C-3, and a mechanism which suggests itself is the cleavage of this anion (**13**) by β-elimination to give an acyclic precursor **14** which can cyclize in two ways to give **8** and **9**. In the case of **3**, only path A would lead to product. A very similar intermediate (**15**) has been suggested previously as the precursor of the 6-benzamidopyridine (**16**) formed by solvolysis of the bicyclic ketone **5**[5]; in this case only path B is operative.

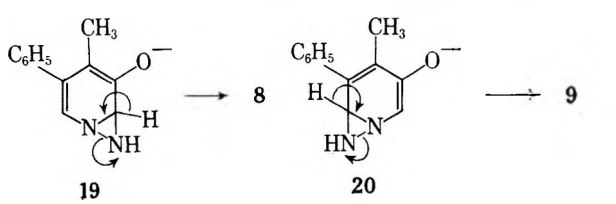




The ring contraction of **1** to **8** and **9** completes a set of four rearrangements that have been observed with **1** and the tautomeric benzoyldiazabicyclo[3.2.0]heptenone **5**. The α-aminopyridines **8**, **9**, **11**, and **16** are obtained from the diazepine and bicyclic systems in basic and neutral conditions, respectively (eq. 1 and 2), and in both systems mineral acid leads to 1-aminopyridinium salts **18** (eq. 3).[4,5] These acid-catalyzed rearrangements in both series have been suggested to occur by way of a 1,7-diazabicyclo[4.1.0]heptenone (**17**). A similar mechanism has been proposed for the ring contraction which accompanies acylation of an anilinoazepine to give *o*-phenylenediamine derivatives.[8]



A similar pathway, involving the bicyclic anions **19** and **20**, might be considered also for the formation of **8** and **9**. This appears very unlikely, however, since it requires that the diazabicyclo[4.1.0]heptane systems in



17 and **20** collapse to give exclusively **18** in acid and **9** in base. A careful search for the presence of **18** (R = H) in the base reaction was not made, but the yield of **18** isolated in the acid reaction was as high as 95%, with no indication of the presence of **9**. Furthermore, it is attractive to view the formation of the 6-aminopyridines from both **1** and **5** as proceeding by a common mechanism (acyclic intermediates **14** and **15**, eq. 1 and 2). Although **15** is not definitely established as the precursor of **16**, it is extremely improbable that **16** arises from the intermediate **18** (R = C_6H_5CO).[5] If parallel behavior of the two systems is assumed, an acyclic route to the α-aminopyridine products and a bicyclic route to the 1-aminopyridinium products presents the most consistent pattern available at present for all four rearrangements.

(8) R. Huisgen, D. Vossius, and R. Appl, *Chem. Ber.*, **91**, 1 (1958).

Experimental

Deuterium Exchange of 1.—Freshly cut sodium (115 mg.) was added to 2 ml. of deuterium oxide (<99%) while a slow stream of dry nitrogen was passed over the surface. To 1 ml. of this solution was added 200 mg. of **1** and the solution was sealed in a Varian n.m.r. sample tube.

The n.m.r. spectra were recorded on a Varian A-60 instrument with these settings throughout the series: filter band width, 1; radiofrequency field, 0.16; sweep time, 250 sec.; spectrum amplitude, 4.0; integral amplitude, 8.0. The total integral curve recorded on 22 spectra over a 46-day period varied from 15.6 to 17.7 cm. in height.

A solution of 200 mg. of **1** in 1 ml. of the above sodium deuterioxide solution was allowed to stand for 4 days and was then acidified by the addition of a solution of 310 mg. of phosphorus pentoxide in 1 ml. of deuterium oxide. The yellow precipitate, 193 mg. after drying in *vacuo*, was recrystallized from methylene chloride–ether to give orange needles, m.p. 150°.

Rearrangement of 2,3-Dihydro-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one (1).—A solution of 500 mg. of **1** in 5 ml. of 5% aqueous sodium hydroxide was refluxed for 3 hr. under a stream of nitrogen. The dark solution was cooled and acidified with hydrochloric acid; a small amount of tar was removed by filtration. The resulting yellow solution was treated with charcoal, which removed some of the color, and then brought to pH 7 with base. A total of 195 mg. of greenish white solid, m.p. 170–190° dec., was collected in several crops.

A 34-mg. portion of the first crop was sublimed twice at 0.1 mm. to give white crystals, m.p. 200–204° dec., pK_A 6.0 and 10.1, λ_{max}^{EtOH} 312 mμ (ε 5900), $\lambda_{max}^{EtOH,HCl}$ 322 mμ (7300), $\lambda_{max}^{EtOH,NaOH}$ 324 mμ (6400). The infrared spectrum was identical with that of authentic 2-amino-3-hydroxy-4-methyl-5-phenylpyridine (**8**).[7]

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.31; H, 6.29; N, 13.83.

A solution of 120 mg. of the crude solid material from above in 2 ml. of methanol was then placed on a column of Ecteola cellulose powder (10 g.) and eluted with pH 7.8 phosphate buffer. Fractions (5 ml.) were collected and aliquots were spotted on coated paper. The paper strips were developed with phosphate buffer and the pyridine components were visualized with ultraviolet light. The earlier fractions contained mainly the 2-amino-5-hydroxypyridine **9**. These were combined and extracted with several portions of methylene chloride. The dried extracts were evaporated to give 25 mg. of pale yellow residue which crystallized from ethyl acetate–ether to give a white powder, m.p. 193–195°; infrared spectrum was nearly identical with that of authentic **9**.

Later fractions eluted with buffer and with methanol contained the 2-amino-3-hydroxypyridine **8**. Extraction with methylene chloride and crystallization gave a very small amount of white solid, m.p. 200–205° dec. The infrared spectrum was the same as that from sublimed material.

For further characterization, 25 mg. of the crude 2-amino-3-hydroxy isomer from the original solid before chromatography was dissolved in methanol containing 15 mg. of sodium and treated with 50 mg. of picryl. After heating for 10 min. and dilution with water, a red precipitate was obtained which was recrystallized to give 15 mg. of 7,9-dinitro-4-methyl-3-phenyl-10*H*-pyrido[3,2-*b*][1,4]benzoxazine, m.p. 196°, undepressed on mixture with authentic sample.[7]

A sample of the other aminohydroxypyridine isomer obtained from the earlier fractions of the cellulose chromatography was treated with benzoyl chloride and pyridine at 70°. After isolation in the usual manner colorless crystals of 2-benzamido-5-benzoyloxy-4-methyl-3-phenylpyridine, m.p. 198–200°, were obtained. The infrared spectrum, λ^{KBr} 3.10, 5.74, and 6.08 μ, was identical with that of a sample previously prepared from authentic **9**.

Rearrangement of 2,3-Dihydro-2,5-dimethyl-6-phenyl-4*H*-1,2-diazepin-4-one (3).—A solution of 604 mg. of **3** in 3 ml. of methanol and 2.5 ml. of aqueous 5% sodium hydroxide was refluxed (70°) for 3 hr. under a stream of nitrogen. The solution was cooled then and neutralized with dilute hydrochloric acid. A white precipitate, total of 570 mg. in several crops, was collected, washed with water, and dried. The material could not be sublimed without extensive decomposition. Recrystallization was finally accomplished with extensive loss from a very small volume of methanol to give colorless crystals of 3-hydroxy-4-methyl-2-methylamino-5-phenylpyridine (**11**), m.p. 200° dec., pK_A 5.7 and 9.7 (50% MeOH), λ_{max}^{MeOH} 276 (infl.) and 310 mμ (ε 10,000), $\lambda_{max}^{MeOH,\ HCl}$ 258 and 313 mμ (11,000), $\lambda_{max}^{Me_2SO}$ 319 mμ (12,800).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.11; H, 6.67; N, 12.99.

A solution of 37 mg. of the base in 1 ml. of methanol was treated with 0.5 ml. of concentrated hydrochloric acid. Evaporation of the methanol gave a crystalline mass which was collected and washed with a very small volume of iced water. Recrystallization from methanol–ether gave colorless needles of the **hydrochloride**, m.p. 235–240° dec.

Anal. Calcd. for $C_{13}H_{14}N_2O \cdot HCl$: C, 62.27; H, 6.03. Found: C, 62.45; H, 6.08.

3-Acetoxy-4-methyl-2-methylacetamido-5-phenylpyridine.—A solution of 300 mg. of the above base in 1.8 ml. of acetic anhydride and 3 ml. of pyridine was allowed to stand overnight at 25° and then was concentrated at reduced pressure to about one-third volume. Methanol was added, the solution was again evaporated, the residue was then dissolved in ether, and the solution was washed with dilute aqueous acid, base, and water and then evaporated to give 228 mg. of colorless solid. Recrystallization from acetone–ether gave colorless prisms, m.p. 135–136°, λ^{KBr} 3.32, 5.69, and 6.04 μ.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.39; H, 6.24; N, 9.21.

Acknowledgment.—We wish to thank Miss Barbara Garland for obtaining the n.m.r. data, and Dr. John M. Vandenbelt and Mrs. Carola Henrich Spurlock, Parke, Davis and Company, for the pK_A and ultraviolet data.

Heterocyclic Studies. XIII. The Aldol Condensation of 2,3-Dihydro-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one and Rearrangement to a Pyridazine[1]

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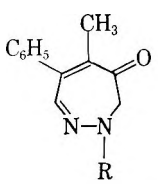
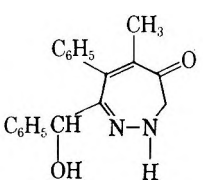
Received November 18, 1963

The aldol condensation of the diazepinone **1a** with benzaldehyde gives the 3α-hydroxybenzyl compound **3**, which is dehydrated to the 2-acetyl-3-benzylidene derivative **7** with acetic anhydride. Rearrangement of **7** to benzyl 3-(4-methyl-5-phenylpyridazinyl) ketone **8** occurs on hydrolysis. The structure **8** was based on degradation to the pyridazine carboxylic acid **12**, the pyridazine **13**, and the dicarboxylic acid **15a**. By carrying out the sequence of reactions with **1a** labeled at C-3 with C^{14} it was shown that C-3 is extruded in the ring contraction to **8**. The mechanisms of the aldol condensation and rearrangement and the instability of diazatropone and diazatropilidene derivatives are discussed.

One of the reactions of the diazepinone **1a** mentioned in the first report[2] of the compound was the base-catalyzed condensation with benzaldehyde to give an aldol product considered to be **2**.[3] Physical data and evidence from a degradative sequence now require revision to structure **3**.



1a, R = H
b, R = CH_3



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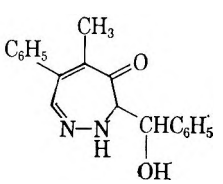


3

The infrared and ultraviolet spectra of the aldol, which were very similar to those of **1a**, did not clearly distinguish between **2** and **3**, but the n.m.r. spectrum, obtained after chemical evidence for **3** was in hand, was consistent only with this structure. In $CDCl_3$ solution (TMS) containing D_2O the C-3 and benzyl protons formed a pair of doublets (C-3, δ = 3.35 and 3.47 p.p.m.; benzyl, δ = 5.18 and 5.30 p.p.m.; J_{AB} = 7.5 c.p.s.) in addition to the single peaks at 1.92 and 6.99 p.p.m. due to methyl and C-7 protons, respectively, and phenyl multiplet at 7.2–7.7 p.p.m. Without D_2O, peaks due to N–H at 6.87 p.p.m. and OH at 4.0–4.2 p.p.m. (doublet, position concentration dependent) were also present, and the peak due to the benzyl proton was further split into a complex multiplet at 5.2–5.5 p.p.m.

The aldol product was remarkably resistant to acid-catalyzed dehydration and was recovered unchanged from acid treatment sufficient to cause the rearrangement of **1a** to the 1-aminopyridine.[4] Treatment with thionyl chloride in pyridine gave a dark tar. With polyphosphoric acid a small amount of the parent ketone **1a** was isolated. In contrast to **1a**, neither an oxime nor semicarbazone could be prepared from the aldol. Mixtures of unstable products which could not be characterized were obtained with dimethyl sulfate.

The formation of **3** can be viewed as a simple aldol condensation of the C-3 enolate of **1a** with benzaldehyde. It has been shown by n.m.r. studies[5] that the protons at both C-3 and C-7 in **1a** exchange with deuterium in NaOD. This work also revealed that ring contraction of **1a** and **1b** to α-aminopyridines occurs in alkaline solution, presumably by cleavage of the C-3 enolate anion. A point that must be accounted for in formulating the conversion of **1a** to **3** is the fact that the 2-methyldiazepinone **1b** does not undergo an analogous condensation; under a variety of conditions only the 2-methylaminopyridine was obtained. The product was isolated as a complex of unknown nature, and the pyridine structure was not established until the completion of the work described in the preceding paper.[5]

(1) Supported in part by a grant from the Geschickter Fund for Medical Research.

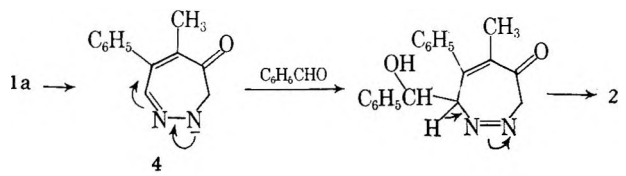
(2) J. A. Moore, *J. Am. Chem. Soc.*, **77**, 3417 (1955).

(3) The structure originally proposed[2] was based on an enolic formula for **1a**.

(4) J. A. Moore and J. Binkert, *J. Am. Chem. Soc.*, **81**, 6029 (1959).

(5) J. A. Moore and E. C. Zoll, *J. Org. Chem.*, **29**, 2124 (1964).

The contrasting behavior of **1a** and **1b** was originally accounted for by formulating the condensation of **1a** as a reaction of the C-7 enolate **4**, leading to **2**. but, with the establishment of **3** as the aldol, another explanation is required.



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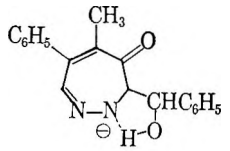
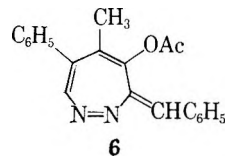
The failure of **1b** to undergo aldol condensation may simply be due to the loss of the enolate anion in the cleavage reaction, which is irreversible, at the expense of the aldol product, whose formation is readily reversible. That cleavage does not similarly occur to the exclusion of aldol formation in the case of **1a** must be due to the presence of the acidic proton at N-2 in **3**. The predominant anion **5** would be further stabilized by hydrogen bonding from the hydroxyl group, as in the familiar enhancement of the acidity of benzoic acid by *ortho*-hydroxyl groups.[6] Both reversal of the aldol condensation and the dehydration of **3** would thus be suppressed in comparison to the corresponding condensation of **1b**, although reversal of **3** does occur in aqueous alkali.



5

The only transformation product that has been obtained from the aldol **3** is an orange compound formed with acetic anhydride and pyridine whose formula corresponded to an *anhydro*-acetyl derivative. The color suggested a seven-membered ring to accomodate the chromophore, although the visible spectrum contained only strong end absorption ($\epsilon_{400\ m\mu}$ 2500), and no maximum at 408 mμ as in **1** and **3**. The infrared spectrum (CCl_4 solution) contained sharp bands at 1760, 1680, and 1630 cm.$^{-1}$, displaced to slightly lower frequencies (1750, 1660, and 1630) in KBr. The n.m.r. spectrum contained methyl peaks at δ = 1.70 and 2.45 p.p.m. a peak at 6.60 p.p.m. presumably due to C_6H_5—CH=, and the aryl C-7 multiplet at 7.3–8.0 p.p.m.

This compound was originally assigned[2] an O-acetyl structure based on the C-7 aldol structure **2**; structures **6** and **7** can be considered on the basis of the aldol **3**. The n.m.r. spectrum is not decisive in this case since so few protons are visualized; the shift upfield of the C-5 methyl peak from the position at 1.92 p.p.m. in **1a**, **1b**, and **3** indicates an appreciable change in magnetic shielding. Although the 1760-cm.$^{-1}$ carbonyl band is suggestive of an enolic acetate, structure **6** contains no carbonyl group which could give rise to the strong 1680-cm.$^{-1}$ band, and the infrared data clearly establish the N-acetyl structure **7**. The usual carbonyl frequency for an N,N-disubstituted amide is in the vicinity of 1660 cm.$^{-1}$, and the position is 1690 cm.$^{-1}$ for the acetyl group in the N-acetyl derivative of **1a**.[4] Much higher frequencies are observed, however, in acetyl derivatives of electronegative heterocyclic systems. Staab[7] has observed the parallel increase in rate of hydrolysis and carbonyl stretching frequency of the acetyl derivatives of pyrrole (1732 cm.$^{-1}$), imidazole (1747), 1,2,4-triazole (1750), and tetrazole (1779) which is due to the increased double bond character and force constant. The 1750-cm.$^{-1}$ band in the solid state spectrum of **7** may also be compared with the value (KBr spectrum) of 1740 cm.$^{-1}$ for 1-acetyl-3(5)-methyl-4-phenylpyrazole.[8]



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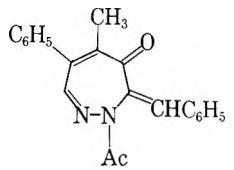


7

The benzylidene ketone **7** was a stable solid, unaffected by heat or air; no reaction was observed with semicarbazide nor with maleic anhydride in refluxing benzene. In keeping with the "active acetyl" character indicated by the infrared data, however, hydrolysis occured very readily with a trace of base or, more cleanly, on brief warming with methanolic hydrochloric acid.

The hydrolysis product, obtained in 60% yield, was a colorless neutral substance, $C_{19}H_{16}ON_2$, corresponding to loss of the acetyl group (or loss of water from **3**). The infrared spectrum of this compound contained a single carbonyl band at 1700 cm.$^{-1}$; the ultraviolet spectrum had λ_{max} 250 mμ (ϵ 9000), with marked change on addition of alkali. It was obvious from the change in color that a rearrangement, presumably ring contraction to a heteroaromatic system, had accompanied the hydrolysis. The compound formed a 2,4-dinitrophenylhydrazone and was reduced by sodium borohydride to a carbinol which was distinctly basic. It was slowly oxidized by silver oxide, but the fuschin test was negative and the general behavior suggested a readily enolized ketone rather than an aldehyde. This premise was confirmed by oxidation, with either permanganate or alkaline hydrogen peroxide, to a mixture of benzoic acid and an acid $C_{12}H_{10}O_2N_2$, both in yields greater than 50%. This demonstrated that a C-11 heterocyclic unit and the phenyl group originating from benzaldehyde were attached through a $-CH_2CO-$ bridge. Direct evidence on this point was obtained by oxidation with selenium dioxide to an α-diketone, characterized by conversion to a quinoxaline with *o*-phenylenediamine.

Decarboxylation of the heterocyclic acid occurred very readily to give a basic oil which was identified as 4-methyl-5-phenylpyridazine (**13**) by comparison of the crystalline picrate with an authentic sample prepared from methylphenylmaleic anhydride *via* the 3,6-dichloro derivative and hydrogenolysis, thus defining the structure of the acid as **12** or the 6-isomer. (See Chart I.)

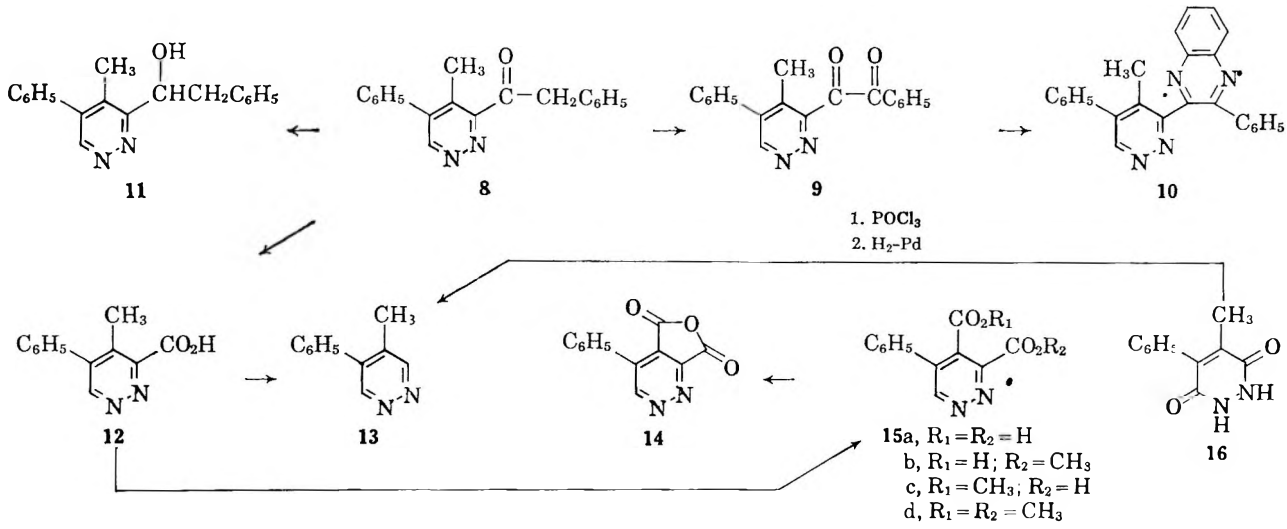
The two structural questions remaining were the placement of the C-8 side chain in **13** and the location of the carbonyl group in the two-carbon bridge. The point of attachment of the C-8 chain was approached by

(6) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp. 210, 211.

(7) H. A. Staab, *Chem. Ber.*, **89**, 1927 (1956); W. Otting, *ibid.*, **89**, 1940 (1956).

(8) C. L. Habraken and J. A. Moore, *J. Org. Chem.*, in press.

CHART I



further oxidation of the pyridazine acid with hot permanganate to a diacid which was obtained as a hydrate and characterized as the dimethyl ester. One of the two possible diacids, 5-pyridazine-3,4-dicarboxylic acid (**15**), had been previously reported as a hydrate[9]; several salts were also described, but not the ester. The melting point of our hydrated diacid was unsharp and was accompanied by decomposition, but the literature values was duplicated by using a preheated block. Proof for structure **15a** was obtained by conversion of the diacid to a cyclic anhydride. On heating with thionyl chloride or acetic anhydride, a substance was obtained which was isolated by sublimation, pointing to a monomeric composition. The infrared spectrum had bands at 5.34 and 5.60 μ, consistent with structure **14**, but brief exposure to air generated the diacid, and analytical evidence was not obtained. The very rapid hydrolysis of anhydrides derived from azine-*o*-dicarboxylic acids has been observed on several occasions.[10] To further characterize the substance as an anhydride, a freshly prepared sample was treated with methanol and two products, evidently the isomeric monomethyl esters, were obtained. By fractional crytallization one of these products was obtained in pure form; a negative color test with ferrous sulfate[11] indicated that this was the 3-carbomethoxy-4-carboxylic acid **15b**, which would be expected to predominate in the ring opening of **14**. The other isomer gave a pink color with ferrous sulfate, expected for **15c**, with a carboxyl group adjacent to the hetero atom. Both monomethyl esters on treatment with diazomethane gave the diester **15d**, also obtained from **15a**.

With the establishment of structure **12**, it remained to decide between the benzyl pyridazinyl ketone and phenyl pyridazinemethyl ketone structures. Since a crystalline oxime could not be obtained for Beckmann rearrangement, the Baeyer–Villiger oxidation was employed. Treatment of the ketone with perbenzoic acid gave a product containing an additional oxygen atom, but the infrared carbonyl stretching frequency was unchanged and the compound could not be saponified, indicating that N-oxide formation had occurred rather than the desired ketone cleavage. Oxidation was then carried out with persulfuric acid in benzene solution. The concentrated sulfuric acid layer contained the pyridazine acid **12**, and no benzoic acid. After concentration of the benzene layer, the sweet smelling oily residue was distilled to give a clear oil with an infrared spectrum identical with that of authentic diphenylmethane. The findings are consistent with the conversion of **8** to the benzyl ester of **12**, followed by alkylation of solvent benzene in the presence of concentrated sulfuric acid.[12]

These experiments unequivocally established structure **8** for the rearrangement product, as well as structure **11** for the derived carbinol. Several attempts to characterize the $-CHOHCH_2-$ system of **11** by dehydration produced no trace of the disubstituted ethylene. The carbinol was recovered unchanged after prolonged refluxing with concentrated hydrochloric acid; refluxing acetic anhydride gave the acetate. Similar difficulty in the dehydration of 1-(2- or 4-pyridyl)-1-ethanol has been reported[13–15] and variously attributed to inductive[13,14] and resonance[15] effects imparted by the hetero atom. The same influences apparently operate to prevent dehydration in **11** and also account for the marked depression of the basicity of the ketone **8**.

The ketone structure **8** provided strong support for the C-3 attachment of the benzyl group in the diazepine precursors, but, to rule out the possibility of rearrangement of the C-5–N-2 chain during the ring contraction, the reaction sequence was carried out with **1a** labeled at C-3 with C^{14}. Some modification in the standard preparative procedure for **1a** was required to introduce C^{14} selectively at C-3. Both C-3 and C-7 are derived from diazomethane,[16] and, although the diazo ketone **17** has been isolated,[17] much better over-all yields of **1a** are obtained by use of large excess of diazomethane to convert α-methylcinnamoyl chloride to a mixture of **17**

(9) R. Stoermer and H. Fincke, *Ber.*, **42**, 3128 (1909).

(10) *Inter alia*, E. Täuber, *ibid.*, **28**, 451 (1895); O. Mumm and H. Hünecke, *ibid.*, **50**, 1577 (1917).

(11) F. Feigl, "Spot Test in Organic Analysis," Elsevier, New York, N. Y., 1956, p. 287.

(12) O. Meister, *Ber.*, **6**, 963 (1873).

(13) G. B. Bachmann and D. Micucci, *J. Am. Chem. Soc.*, **70**, 2381 (1948).

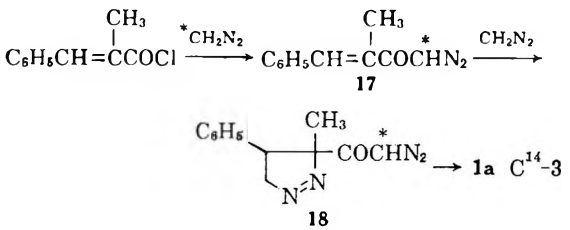
(14) C. S. Marvel, E. L. Coleman, and G. P. Scott, *J. Org. Chem.*, **20**, 1785 (1955).

(15) W. R. Boehme and J. Koo, *ibid.*, **26**, 3589 (1961).

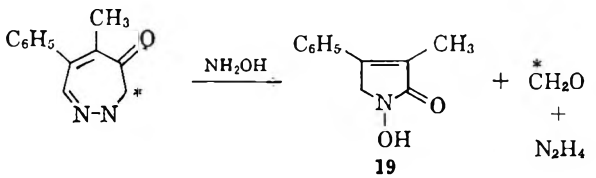
(16) J. A. Moore and R. W. Medeiros, *J. Am. Chem. Soc.*, **81**, 6026 (1959).

(17) J. A. Moore, *J. Org. Chem.*, **20**, 1607 (1955).

and **18**. For the present purposes it was necessary to work out optimum conditions for the preparation of **17** using the minimum amount of diazomethane, both to conserve labeled material and minimize contamination of **17** with the pyrazoline **18** which would be labeled at the diazepine position. An attempt was made to eliminate the wasteful use of one-half of the diazomethane as a base in the initial reaction with acid chloride by adding pyridine or triethylamine,[18] but the only product obtained was the hitherto unknown α-methylcinnamic anhydride. In the conditions finally selected, the diazomethane-C^{14}, obtained in 71% yield from N-methyl-C^{14}-N-nitroso-*p*-toluenesulfonamide, was used in 2.15:1 molar ratio to give **17** in 60% total yield. Subsequent operations followed the usual procedures,[16] and the diazepinone-C-3[14] was diluted to a specific activity of 1.27×10^3 d.p.s./mmole for subsequent reactions. In order to determine the extent of labeling at C-7, **1a** C^{14} was subjected to a degradation which selectively removes C-3; namely, cleavage with hydroxylamine to **19**, formaldehyde, and hydrazine.[7] The formaldehyde, isolated as the dimedon derivative, contained 94.5% of the C^{14} activity, and the hydroxamic acid **19**, 6.4%.



The sequence **1a** → **3** → **7** → **8** → **12** → **13** was then carried out with labeled material after optimizing the reaction conditions for each step.

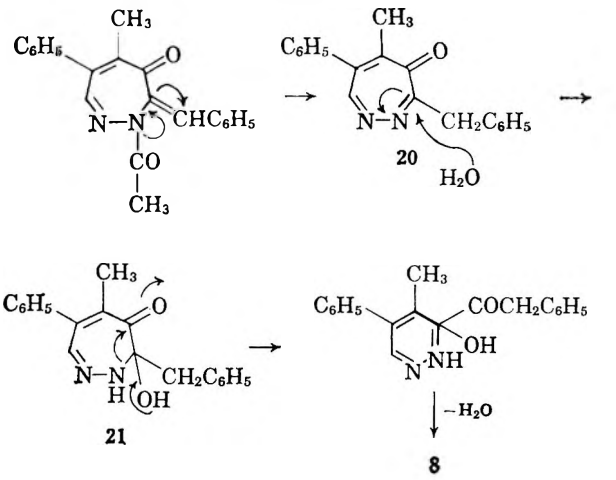


Final decarboxylation gave carbon dioxide containing 95.4% of the C^{14} with 6.7% found in the picrate of the pyridazine **13**. These results agree well with those of the hydroxylamine cleavage, and provide a firm link between the diazepine and pyridazine structures.

The details of the ring contraction whereby C-3 is extruded can be represented by a very simple sequence (Chart II). Hydrolysis of **7** with concomitant tautomerization leads to the intermediate diazatropone **20** which undergoes addition of water. The resulting carbinolamine **21** could then revert to an acyclic aminodiketone followed by recyclization, or, more simply, the ring contraction may be viewed as an example of the general α-oxo alcohol rearrangement[19] as illustrated in **21**. The stage is apparently set for the rearrangement when C-3 becomes trigonal, and it may be predicted that, if the direct dehydration of the aldol **3** could be effected, ring contraction to **8** would follow spontaneously, although this has not been observed.

The rearrangement of **7** to **8** represents an additional example of a general type of heterocyclic rearrangement

CHART II



involving the disruption of the ring by solvolytic attack at a hetero atom and re-establishment of a new heterocyclic or carbocyclic system by participation of a neighboring reactive center. These may occur with ring contraction as in the present case, ring expansion as in the formation of pyridines from α-aminomethyldimethoxydihydrofurans,[20] or without change in ring size as in the conversion of acyl-1,3,5-triazines to aminopyrimidines[21] or pyrylium salts to benzenes,[22] to cite a few typical examples. Ring contractions occurring by this process are particularly common among unsaturated seven-membered heterocycles,[7,23-25] since there is usually a strong driving force in the formation of an aromatic system.

It is noteworthy that the rearrangement of **7** must involve at some stage, such as **20**, a heterocyclic counterpart of the aromatic tropone system.[26] Very few examples of azepines or diazepines at this oxidation level are known. There has been considerable speculation about the degree of aromatic character that may be present, although there is very little evidence of stabilization in these systems, from either experimental or theoretical standpoints.[25,27] A remarkable exception to this generalization appears to be the azatropone **23** recently reported, without experimental details, by Johnson and co-workers.[28] The facile ring cleavage of

(18) M. S. Newman and P. Beal, *J. Am. Chem. Soc.*, **71**, 1506 (1949).

(19) S. Selman and J. F. Eastham, *Quart. Rev.* (London), **14**, 221 (1960).

(20) N. Clauson-Kaas, N. Elming, and Z. Tyle, *Acta Chem. Scand.*, **9**, 1 (1955).

(21) D. R. Osborne and R. Levine, *J. Org. Chem.*, **27**, 2933 (1963).

(22) K. Dimroth in "Neuere Methoden der Praparativen Organischen Chemie," W. Foerst, Ed., Verlag Chemie, Weinheim/Bergstr., 1961, p. 239.

(23) R. Huisgen, D. Vossius, and M. Appl, *Chem. Ber.*, **91**, 1 (1958).

(24) E. Schmitz and R. Ohme, *ibid.*, **95**, 2012 (1962).

(25) (a) J. A. Barltrop, C. G. Richards, D. M. Russel, and G. Ryback, *J. Chem. Soc.*, 1132 (1959); (b) L. N. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *J. Org. Chem.*, **29**, 332 (1964).

(26) T. Nozoe in "Non-Benzenoid Aromatic Compounds," D. Ginsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, p. 399.

(27) R. W. Schmid, *Helv. Chim. Acta*, **45**, 1992 (1962).

(28) (a) E. Bullock, B. Gregory, and A. W. Johnson, *J. Am. Chem. Soc.*, **84**, 2260 (1962). (b) NOTE ADDED IN PROOF.—A revision of the azatropone structure **23** to a furopyridine has now been made: E. Bullock, B. Gregory, and A. W. Johnson, *J. Chem. Soc.*, 1632 (1964).

the enolic diazatropilidene structure, **22**,[5] and the rearrangement of the diazatroponoid structure **20** provide additional indications of the lack of aromatic stability in these aza analogs.

Experimental[29]

2,3-Dihydro-3-(α-hydroxybenzyl)-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one (3).—A solution of 7.0 g. of diazepine **1a** and 13 ml. of freshly distilled benzaldehyde in 150 ml. of 0.2 *N* sodium ethoxide in ethanol was allowed to stand at room temperature for 4 days. About half of the ethanol was removed at reduced pressure; the solution was then acidified with 1 *N* hydrochloric acid and the remaining alcohol was removed. More water was then added and the suspension was extracted with ether; the ether solution was dried and concentrated and the benzaldehyde was then removed at 1.0 mm. The dark red sirup crystallized on addition of ether to give 4.8 g. (45%) of yellow solid, m.p. 134–137°. Recrystallization from ether and then methanol–water gave a mass of pale lemon-yellow filaments, m.p. 145–146°; λ_{max}^{EtOH} 245 (infl.), 309 (ε 5200), 395 mμ (2700); $\lambda_{max}^{0.1\ N\ NaOH}$ 243 (ε 26,000), 344 (2700), 412 mμ (5400); λ^{KBr} 3.09, 6.10 μ.

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.59, 74.39; H, 6.06, 5.94; N, 9.33.

The compound was freely soluble in 10% aqueous alkali, and separated unchanged on prompt acidification. On standing overnight the solution developed a strong benzaldehyde odor. For preparative reversal of the condensation, 100 mg. of **3** in 0.2 *N* sodium ethoxide solution was stored for 5 days, acidified with dilute hydrochloric acid, and extracted with ether. After evaporation, the orange residue crystallized on addition of a drop of methanol. A total of 30 mg. of orange prisms of **1a**, m.p. 130–145°, was obtained in three crops. Recrystallization gave dark yellow prisms, m.p. and m.m.p. (with authentic **1a**) 145–148°.

After treatment of 306 mg. of **3** with methanolic semicarbazide acetate for 3 days, a total of 302 mg. of unreacted starting material, m.p. 143–145°, was recovered. Under the same conditions, **1a** gave a crystalline semicarbazone after 1 hr.

Sodium Borohydride Reduction of 3.—A solution of 40 mg. of sodium borohydride in 2 ml. of 50% ethanol was added during 15 min. to a suspension of 616 mg. (2 mmoles) of the aldol **3** in 10 ml. of ethanol. The resulting pale yellow solution was kept at room temperature for an additional 15 min. The excess hydride was decomposed with a few drops of acetic acid and the solvent evaporated under reduced pressure. The residue was washed with water and a small amount of ethanol, and then dissolved in ethanol, filtered, and slowly precipitated with ether in several crops. The over-all yield of crystalline product was 437 mg. (71%), m.p. 160–165°. Recrystallization from ethanol–ether raised the melting point to 174–175°.

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 73.93; H, 6.75; N, 8,96,

2,3-Dihydro-3-(α-hydroxy-*p*-chlorobenzyl)-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one.—A solution of 350 mg. of **1a** and 910 mg. of recrystallized *p*-chlorobenzaldehyde in 7 ml. of 0.2 *N* sodium ethoxide was stored for 2 days at room temperature. The solution was then concentrated, diluted with water, acidified, and extracted with ether. Evaporation of the dried ether solution gave 227 mg. (39%) of bright yellow crystals. Recrystallization from methylene chloride–ether and then ethanol–water gave yellow blades, m.p. 148–150°.

Anal. Calcd. for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.08. Found: C 66.84; H, 4.96.

Reaction of 2-Methyldiazepinone Ib with Benzaldehyde and Sodium Ethoxide.—A solution of 1.0 g. of **1b** and 1.80 ml. of benzaldehyde in 50 ml. of 0.1 *N* ethanolic sodium ethoxide was stored at room temperature for 4 days. After dilution with 30 ml. of water and chilling, the solution was just neutralized with hydrochloric acid and extracted with five 20-ml. portions of methylene chloride. After drying and evaporation, the crystalline residue was collected and recrystallized from a mixture of ethyl acetate and ether to give 775 mg. (78%) of nearly colorless crystals, m.p. 197–200° dec. The compound darkened rapidly on attempted recrystallization from methanol or ethanol. Recrystallization from ether–benzene gave white needles, m.p. 202–204° dec.; λ_{max}^{EtOH} 275, 310 mμ (ε 12,400); $\lambda_{max}^{EtOH\ +\ HCl}$ 259, 313 mμ (ε 13,500); $\lambda_{max}^{EtOH\ +\ NaOH}$ 319 mμ (ε 15,500); pK_A (50% MeOH) 6.0 and 9.8; estimated mol. wt., 261.

Anal. Calcd. for $C_{16}H_{18}N_2O$ ($C_{13}H_{11}N_2O_2 \cdot C_3H_7O$) (mol. wt., 270.2): C, 71.09; H, 6.71; N, 10.36. Found (Bly): C, 71.34; H, 6.38; N, 10.31. Found (Zoll): C, 70.89; H, 6.54; N, 10,32; (N)-CH_3, 5.71 (calcd. for one (N)-CH_3: 5.65).

These analyses were obtained on different samples—one recrystallized from ethyl acetate and one from benzene–ether, both dried at 100°, one sample prepared a year after the other. The same product, with essentially the same infrared spectrum (not well resolved—few sharp bands), was obtained when the reaction was carried out in methanolic solution with benzaldehyde, in ethanolic solution with *p*-chlorobenzaldehyde, and *no* aldehyde in a nitrogen atmosphere (without nitrogen or aldehyde, which apparently served as an antioxidant, the yield was very low). The n.m.r. spectrum in D_2O plus a trace of NaOD contained small impurity peaks, a triplet and quartet upfield and downfield, respectively, from two methyl singlets.

This substance was eventually shown to be a solvated form of 2-methyl amino-2-hydroxy-4-methyl-5-phenylpyridine by conversion to an acetylation product identical with the diacetate described in the preceding paper.[5] The nature of the persistent C_3O_4 fragment is completely unknown. Material with correct analytical values for the pyridine was eventually obtained[3] by avoiding all contact with any organic compounds or solvents except methanol, from which it was recovered with substantial losses.

2-Acetyl-2,3-dihydro-3-benzylidene-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one (7).—A solution of 2.40 g. of **3** in 4 ml. of pyridine and 7 ml. of acetic anhydride was allowed to stand at room temperature overnight and was then concentrated at reduced pressure (70°). The residue was treated with water and the resulting orange gum crystallized on addition of a little methanol. The solid was collected and washed with cold methanol to give 1.7 g. (66%) of orange prisms, m.p. 166–169°. These were recrystallized from methanol–ether and ethanol–hexane mixtures, m.p. 169–170°; λ_{max}^{EtOH} 227 (ε 18,300), 304 (23,600), 335 mμ (infl.), strong end absorption; infrared, see discussion.

Anal. Calcd. for $C_{21}H_{18}N_2O_2$: C 76.34; H, 5.49; N 8.48. Found: C 76.55; H, 5.40; N, 8.42.

The compound was recovered unchanged from treatment with semicarbazide acetate under the conditions described for **3**.

2-Acetyl-2,3-dihydro-3-*p*-chlorobenzylidene-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one.—A solution of 120 mg. of the 3-(α-hydroxy-*p*-chlorobenzyl)diazepinone described above and 0.9 ml. of acetic anhydride in 1 ml. of pyridine was stored at room temperature for 24 hr. After addition of water the product was extracted with methylene chloride and the extract was washed, dried, and evaporated to give an orange oil which crystallized on addition of methanol and water. A total of 83 mg. of crystals was obtained; after recrystallization from methanol and then ether–pentane, the melting point was 163–164°; λ^{KBr} 5.70, 6.10, 6.20 μ.

Anal. Calcd. for $C_{21}H_{17}O_2N_2Cl$: C, 69.13; H, 4.70. Found: C 69.12; H, 4.73.

Benzyl 3-(4-Methyl-5-phenylpyridazinyl) Ketone (8).—To a solution of 3.3 g. of the acetate **7** in 300 ml. of methanol was added 75 ml. of 10% hydrochloric acid and 150 ml. of a 1:4 mixture of concentrated hydrochloric acid and methanol. The solution was heated at 40° for 30 min.; the color gradually changed from orange to pale yellow. The solution was concentrated under reduced pressure to about half of its original volume, and cooled in an ice bath; 120 ml. of 10% potassium hydroxide was added. The pale yellow precipitate was collected and washed with a small amount of chilled ether, giving 1.60 g. of white plates, m.p. 123–125°. The aqueous filtrate was extracted with ether and the extract was combined with the ether washings of the first crop. The combined ether extract was washed with water, 1 *N* sodium bicarbonate, and again with water. The ether was dried and evaporated under reduced pressure. The oily residue was seeded with some of the previously obtained crystalline product and a small amount of ether was added. The crystals were filtered and washed with ether as before to give an additional 0.27 g. of product. The combined yield was 1.87 g. (65%). Recrystallization from chloroform–hexane gave 1.63 g. of colorless material, m.p. 125–126°; λ_{max}^{EtOH} 250 (ε 9000), 310 mμ (about 900); $\lambda_{max}^{0.2\ N\ NaOH}$ 291 (ε 14,600), 345 mμ (6100); λ^{KBr} 5.89 μ.

(29) Melting points were taken on a Fisher-Johns block with a calibrated thermometer. Infrared spectra were obtained in KBr pellets except where otherwise noted. Ether and methylene chloride solutions were dried with anhydrous sodium sulfate.

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.15; H, 5.80; N, 9.78.

The product was insoluble in aqueous 1 *N* hydrochloric acid or 1 *N* sodium hydroxide. However, addition of sodium hydroxide to 2 *N* ethanol solution gave a bright yellow color and enhanced the solubility in this solvent.

The **2,4-dinitrophenylhydrazone of 8** was prepared in the usual way from 30 mg. of **8**. An amorphous solid separated which was redissolved in ethanol and precipitated as an oil by addition of water. This oil was then triturated with water to give crystals, m.p. 97–100°. After crystals were obtained, repeated crystallization from methanol and ethanol gave yellow prisms, m.p. 160–161°. On repeating the preparation, oily material and then solid, m.p. 97–100°, were always obtained initially even when high melting seed was available.

Anal. Calcd. for $C_{25}H_{20}N_6O_4$: C, 64.09; H, 4.30; N, 17.94. Found: C, 64.06; H, 4.43; N, 18.03.

2-Phenyl-1-[3-(4-methyl-5-phenylpyridazyl)]-1-ethanol (11).—To a suspension of 145 mg. (0.5 mmole) of **8** in 5 ml. of ethanol was added dropwise a solution of 20 mg. of sodium borohydride 2 ml. of 50% ethanol. Gradually the starting material dissolved and the initial bright yellow color disappeared. The solution was allowed to stand at room temperature for 20 min.; the excess hydride was then decomposed with a few drops of acetic acid and the solution was concentrated to a 2-ml. volume. Water (10 ml.) was added and the resulting suspension was extracted with ether. Evaporation of the ether under reduced pressure gave 143 mg. (98%) of pale yellow crystals, m.p. 106–109°. Recrystallization from methanol–water and treatment with charcoal gave white plates, m.p. 111–112°; λ_{max}^{EtOH} 251 mμ (ε 8100); $\lambda_{max}^{0.1\ N\ HCl}$ (infl.) 251 (ε 6400), 301 mμ (5000).

Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.67; H, 6.46; N, 9.37.

The alcohol was insoluble in aqueous 1 *N* sodium hydroxide but dissolved readily in 1 *N* hydrochloric acid. Addition of sodium hydroxide to an ethanolic solution failed to give the bright yellow color observed with the ketone.

Acetate of 11.—A solution of 100 mg. of the alcohol in 1 ml. of pyridine and 4 ml. of acetic anhydride was heated at 70° for 10 min. The solution was cooled in an ice bath and treated with water to decompose the excess acetic anhydride. The aqueous solution was decanted and the gummy residue was dissolved in ether and dried with anhydrous sodium sulfate. Evaporation of the ether gave 105 mg. of a pale yellow oil which crystallized slowly when a small amount of methanol was added. One recrystallization from methanol–water followed by two recrystallizations from ether gave white needles, m.p. 93°.

Anal. Calcd. for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07. Found: C, 76.04; H, 6.38.

4-Methyl-5-phenylpyridazine-3-carboxylic Acid (12). A. Permanganate Oxidation.—To a stirred solution of 500 mg. (1.72 mmoles) of the ketone **8** in 2 ml. of acetone was added in small portions during 2 hr. 515 mg. (3.26 mmoles) of potassium permanganate. The mixture was stirred at room temperature for an additional 30 min. A few drops of ethanol were added to decompose any unchanged permanganate and the precipitated manganese dioxide was filtered and washed with 0.5 *N* sodium hydroxide and with acetone. The washings were combined with the filtrate and most of the acetone evaporated under reduced pressure. The remaining alkaline solution was diluted with water to about 30 ml., saturated with salt, and washed with ether to remove a trace of nonacidic products. The solution was then acidified with hydrochloric acid and extracted first with two 15- and 20-ml. portions of ether and then with three 15- to 20-ml. portions of chloroform. The ether and the chloroform extracts were dried separately and evaporated under reduced pressure. The chloroform extract gave 120 mg. of crystalline material, m.p. 130–134°. The ether extract gave 400 mg. of a semioily residue which upon recrystallization from benzene gave 90 mg. of a crystalline product, m.p. 132–135°. This was combined with the material obtained from the chloroform extract to give a total of 210 mg. (61%) of the pyridazine carboxylic acid **12**. The benzene mother liquor was evaporated under reduced pressure and the residue sublimed to give 163 mg. (79%) of benzoic acid, m.p. and m.m.p. 120–122°.

The acid **12** was recrystallized from chloroform, giving colorless prisms, m.p. 135–136° dec.; λ_{max}^{EtOH} 255 mμ (ε 7100); $\lambda_{max}^{0.2\ N\ KOH}$ 246 mμ (ε 7400); λ^{KBr} 3.05, 4.17, 4.45, 5.15, 5.90 μ.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.38; H, 4.64; N, 13.15. Found: C, 67.28; H, 4.71; N, 13.08.

Occasionally this acid precipitated in a different crystalline form which melted at about 80°; when the melt was seeded with the higher melting crystals, it solidified and then melted at 135°.

The acid reacted with diazomethane to give a **methyl ester**, m.p. 104, λ^{KBr} 5.81 μ.

B. Hydrogen Peroxide Oxidation.—To a solution of 73 mg. (0.25 mmole) of the ketone **8** in 2 ml. of methanol and 0.25 ml. of 1 *N* sodium hydroxide was added dropwise at 10-min. intervals 30% hydrogen peroxide. The solution changed from dark yellow to a pale straw color. About 5 ml. of water was added and the alkaline solution was extracted with ether. Evaporation of the ether extract gave 20 mg. of a light brown oil which was not identified. The aqueous solution was acidified and extracted with two 3-ml. portions of ether and three 5-ml. portions of chloroform. Both extracts were dried and evaporated under reduced pressure. The residue from the ether extract was a mixture of benzoic acid and the pyridazine carboxylic acid **12**, which were separated by washing with a small amount of ether to give 18 mg. (65%) of benzoic acid. The acid **12** from the two extracts was combined to give 33 mg. (61%).

4-Methyl-5-phenylpyridazine (13). A. From 12.—Fifty milligrams of the acid **12** was placed in a sublimator and heated under vacuum to 140°. The acid melted with rapid gas evolution and a colorless liquid collected on the cold finger. The distillate was dissolved in 2 ml. of ethanol and an equal volume of a saturated solution of picric acid in ethanol was added. The precipitate which formed after a few minutes was filtered and washed with methanol to give 63 mg. (59%) of yellow needles of the **picrate**, m.p. 133–135°. Recrystallization from methanol gave raised m.p. 136–137°, m.m.p. (with authentic picrate from B) 136–137°. The infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{17}H_{13}N_5O_7$: C, 51.13; H, 3.28; N, 17.54. Found: C, 51.20; H, 3.41; N, 17.33.

B. From 16. 4-Methyl-5-phenylpyridazine-3,6-dione (16).—**16** was prepared by refluxing a solution of 2.4 g. of 3-methyl-4-phenylmaleic anhydride,[30] m.p. 94–95°, and 1.7 g. of hydrazine sulfate in 15 ml. of water and 25 ml. of acetic acid for about 3 hr. The solution was then evaporated to small volume and diluted with water. The resulting gelatinous precipitate was collected and refluxed in acetone to remove unchanged anhydride. A total of 740 mg. of white powder was obtained, m.p. 322–326° (sealed capillary); λ_{max}^{EtOH} 257 (ε 4700), 313 mμ (3400); $\lambda_{max}^{EtOH + NaOH}$ 339 mμ (ε 2800).

3,6-Dichloro-4-methyl-5-phenylpyridazine.—A solution of 300 mg. of the above dione in 3.5 ml. of phosphorus oxychloride was refluxed for 30 min. The amber solution was then concentrated at reduced pressure and the dark brown residue was treated with water, then made slightly alkaline, and extracted with ether. The dried ether solution was evaporated to give a semicrystalline residue which was recrystallized from methanol–water to give 116 mg. of cream-colored prisms, m.p. 112–116°. Further recrystallization from methanol–water gave shiny colorless cubes, m.p. 120–122°; λ_{max}^{EtOH} 260 mμ (ε 4000) (no change with acid or base).

Anal. Calcd. for $C_{11}H_8Cl_2N_2$: C, 55.25; H, 3.37; N, 11.72. Found: C, 55.35; H, 3.44; N, 12.14, 12.01.

4-Methyl-5-phenylpyridazine.—A solution of 112 mg. of the above dichloropyridazine in 8 ml. of ethanol was stirred in a hydrogen atmosphere with 200 mg. of 10% palladium–charcoal for 20 hr. The solution was then filtered and evaporated, and the residue was taken up in 10 ml. of water. A small amount of oily material was extracted with ether, the clear aqueous solution was made basic with potassium hydroxide, and the oil was extracted with ether. Evaporation of the ether solution gave 47 mg. of pale yellow oil which was distilled at 50° in a short-path still to give 36 mg. of colorless mobile oil, pK_A 3.3, λ_{max}^{EtOH} 245 mμ, $\lambda_{max}^{0.1\ N\ HCl}$ 297 mμ (ε 2000).

Anal. Calcd. for $C_{11}H_{10}N_2$: N, 16.46. Found: N, 16.45.

Solutions of 16 mg. of the above base in ether and 22 mg. of picric acid in ether containing a few drops of ethanol were combined and an oil separated. The supernatant solution was decanted, and the oil was crystallized from 0.2 ml. of ethanol at 0°. A total of 6.0 mg. of yellow prisms of the picrate was obtained, m.p. 137–138° after drying at 0.1 mm.

(30) J. A. Moore and F. J. Marascia, *J. Am. Chem. Soc.*, **81**, 6049 (1959); the material used in the present work was from the same sample described in this reference, obtained by bromination and dehydrobromination of 3-methyl-4-phenylsuccinic acid.

1-Phenyl-2-[3-(4-Methyl-5-phenylpyridazinyl]ethanedione (9).—One hundred milligrams (0.35 mmole) of the ketone **8** was added to a solution of 38 mg. (0.35 mmole) of selenium dioxide in 2 ml. of dioxane and 0.01 ml. of water and heated at 80–85° for 3.5 hr. The precipitated selenium was filtered and the dioxane was evaporated under reduced pressure. Addition of a small amount of methanol to the oily residue gave 51 mg. (47%) of pale yellow crystals, m.p. 128–132°. The product was treated with charcoal and recrystallized from ether. Several recrystallizations and filtrations through a fine filter were required to remove finely dispersed selenium. The recrystallized product melted at 134–135°; λ_{max}^{EtOH} 250 mμ (ε 16,800), inflection at about 390 mμ (ε 103); λ^{KBr} 5.88, 6.00 μ. An analytically pure sample could not be obtained because of the difficulties in removing the last traces of selenium and the instability of the product in solution.

The **quinoxaline 10** was prepared by treatment of 20 mg. (0.065 mmole) of crude diketone with 7.6 mg. (0.070 mmole) of *o*-phenylenediamine in acetic acid for 40 min. at 80°. The acetic acid was evaporated under reduced pressure and the residue was recrystallized several times from ethanol to give 4 mg. of pale yellow crystals, double m.p. 178° and 187–190°. The infrared spectrum of this derivative no longer showed the two peaks in the carbonyl region (5.88 and 6.00 μ) which occurred in the spectrum of the starting diketone.

Anal. Calcd. for $C_{25}H_{18}N_4$: C, 80.19; H, 4.85; N, 14.96. Found: C, 79.75; H, 5.03; N, 15.06.

Hydrogen Peroxide Cleavage of 1-Phenyl-2-[3-(4-methyl-5-phenylpyridazinyl)]ethanedione.—A solution of 30 mg. (0.098 mmole) of the diketone **9** in 1.5 ml. of 30% hydrogen peroxide was allowed to stand at 5° overnight. The solution was diluted with 5 ml. of water, made alkaline, washed with three 5-ml. portions of ether, acidified, and then extracted with one 8-ml. portion of ether and three 5-ml. portions of chloroform. Both the ether and the chloroform extract were dried and evaporated under reduced pressure. The residue from the ether extract was heated with 5 ml. of hexane and filtered. The hexane was evaporated and the residue sublimed to give 11 mg. (92%) of benzoic acid, m.p. and m.m.p. 120–122°. Evaporation of the chloroform extract gave 14 mg. of crystalline residue. This was combined with the hexane-insoluble material obtained from the ether extract to give a total of 17 mg. (81%) of the pyridazine carboxylic acid **12**, m.p. 129–133°. After recrystallization from chloroform, the acid melted at 135–137° and gave no mixture melting point depression with a sample of the acid **12** obtained previously from compound **8**.

5-Phenylpyridazine-3,4-dicarboxylic Acid (15a).—A solution of 100 mg. (0.46 mmole) of the acid **12** in 5 ml. of 1 *N* sodium hydroxide was heated to 70°, and 150 mg. (0.95 mmole) of potassium permanganate was added in small portions during 40 min. The reaction mixture was heated at reflux for an additional 30 min., cooled to room temperature, and filtered. Acidification of the filtrate with 6 *N* hydrochloric acid gave 109 mg. (96%) of white needles. The product began to decompose above 160° and melted with decomposition at about 214–227°; when placed on the block at 200°, it melted at 225–227°. The melting point remained unchanged after recrystallization from ethanol–water; λ^{KBr} 2.84, 2.95, 3.63, 4.25, 4.39, 5.20, 5.82–5.95 μ.

Anal. Calcd. for $C_{12}H_8N_2O_4 \cdot H_2O$: C, 54.96; H, 3.84; N, 10.68. Found: C, 55.55; H, 3.98; N, 10.79.

The **dimethyl ester 15d** was prepared by treatment of the diacid with excess diazomethane in ether. Recrystallization from ether and sublimation gave white crystals, m.p. 131–132°; λ^{KBr} 5.75, 5.80 μ.

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.91; H, 4.59; N, 10.46.

5-Phenylpyridazine-3,4-dicarboxylic Acid Anhydride (14).—A suspension of 100 mg. of the dicarboxylic acid in 2 ml. of acetic anhydride was heated at 100–110° until all of the acid dissolved. The acetic anhydride was removed *in vacuo*, and the dark residue was washed with a small amount of anhydrous ether. Sublimation gave 62 mg. of a pale yellow crystalline product which began to decompose at about 150° and melted with further decomposition at 177–185°. In contrast to the starting material the product was fairly soluble in chloroform or benzene. Recrystallization from benzene–ether gave colorless crystals, m.p. 182–185° (preheated block); λ^{KBr} 5.34, 5.60 μ. After standing, the bands corresponding to the acid began to appear in the infrared spectrum. The analysis indicates complete conversion to the nonhydrated acid **15a**.

Anal. Calcd. for $C_{12}H_8O_4$: C, 59.02; H, 3.30. Found: C, 59.17; H, 3.66.

Similar material was obtained when the acid was refluxed with thionyl chloride in benzene solution.

The Monomethyl Esters of 5-Phenylpyridazine-3,4-dicarboxylic Acid.—The anhydride (**14**) was prepared from 105 mg. of the dicarboxylic acid as described above and immediately dissolved in 5 ml. of absolute methanol. After standing for a short time at room temperature, the pale yellow solution became colorless and was then evaporated under reduced pressure to give 93 mg. of crystalline residue, m.p. 110–145° dec. The product was boiled with 10 ml. of ether and filtered, and the ether was evaporated. The ether-insoluble fraction was recrystallized from chloroform–hexane, giving 29 mg. of white crystals of the **3-monomethyl ester 15b**, m.p. 158–170°. Further recrystallization of the first crop gave a material which melted at 178–180° and gave a negative ferrous sulfate test; λ^{KBr} 2.90, 3.59, 3.81, 4.03, 5.21, 5.70–5.94 μ (broad peak).

Anal. Calcd. for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.90. Found: C, 60.78; H, 4.37.

Two additional crops of crystals were obtained from the first chloroform–hexane mother liquor by concentration, until the solution became cloudy, and subsequent cooling in ice. The second crop was combined with the residue obtained from the ether extract to give a total of 35 mg. of material which melted at 105–120°. Several recrystallizations from ether gave a small amount of the **4-monomethyl ester 15c**, m.p. 105–112°, pink color with ferrous sulfate solution; λ^{KBr} 2.95, 4.16, 4.50, 5.17, 5.76, 5.89 μ.

Treatment of both the higher and the lower melting material with diazomethane gave the same product, identical in melting point, mixture melting point, and infrared spectrum with the 5-phenylpyridazyl-3,4-dicarboxylic acid dimethyl ester **15d** prepared by treatment of the diacid with diazomethane.

Perbenzoic Acid Oxidation of Benzyl 3-(4-Methyl-5-phenylpyridazinyl) Ketone.—A solution of 150 mg. (0.52 mmole) of **8** in a 0.038 *N* solution of perbenzoic acid in chloroform was allowed to stand at 5° for 10 days. The solution was extracted with 1 *N* sodium bicarbonate and with water until it gave a negative potassium iodide test, dried, and evaporated under reduced pressure. The residue was warmed with a 50:50 ether–hexane mixture and filtered to give 115 mg. of crystalline product, m.p. 142–144°. Concentration of the filtrate gave an additional 13 mg. of crystals, m.p. 139–144°. After recrystallization from chloroform–ether the product had m.p. 148–149°, λ^{KBr} 5.87 μ.

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 75.30; H, 5.36; N, 8.98.

Persulfuric Acid Cleavage of Benzyl 3-(4-Methyl-5-phenylpyridazinyl) Ketone.—To a cooled slurry of 1.60 g. of potassium persulfate in 4.00 g. of concentrated sulfuric acid and 0.74 ml. of water was added a solution of 200 mg. (0.69 mmole) of **8** in 5 ml. of benzene. The reaction mixture was allowed to warm to room temperature and was then stirred for 20 min. The benzene layer was decanted and the acid layer was washed with two 3-ml. portions of benzene. The combined benzene solution was washed with sodium bicarbonate and water and dried. The solvent was removed through a Vigreux column, and the dark, sweet-smelling residue distilled under vacuum to give 25 mg. (22%) of diphenylmethane, identical in infrared spectrum with an authentic sample. The sulfuric acid layer was cooled in ice, carefully diluted with 20 ml. of water, and extracted with chloroform. The chloroform solution was washed with water and extracted with 1 *N* sodium hydroxide. The alkaline solution was acidified and again extracted with chloroform. The chloroform extract was dried and evaporated to give 58 mg. (39%) of the pyridazine carboxylic acid **12**, m.p. 130–134°. After recrystallization from chloroform the product melted at 135–137° and gave no mixture melting point depression with the acid obtained in previous experiments.

α-Methylcinnamic Anhydride.—To a stirred ether solution of 0.07 mole of diazomethane was added 9.7 ml. (0.07 mole) of triethylamine; standing overnight a white solid, presumably triethylamine hydrochloride, separated. This material was redissolved in ether and the solution was washed thoroughly with aqueous sodium bicarbonate. After drying and concentrating, the ether solution deposited long colorless needles, m.p. 82–83°; λ^{KBr} 5.70, 5.94 μ.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.74; H, 6.23.

Radioactivity Measurements.—All C^{14} counting was done with a Packard-Tri-Carb liquid scintillation counter, Model 314X. The scintillation mixture contained 4 g. of 2,5-diphenyloxazole and 0.1 g. of 1,4-bis-2-(phenyloxazolyl)benzene/l. of toluene. For compounds **1a**, **3**, and **7**, all of which have strong absorption at 400 mμ, counting efficiency was too low to permit direct counting. In these cases samples were oxidized to carbon dioxide by a standard chromic acid wet combustion technique, and barium carbonate was counted in a thixotropic scintillation gel. For all other compounds, weighed samples were counted directly in the scintillation solution. All samples were counted five times, usually for 10 min., and for each sample the efficiency was determined by adding a benzoic acid-C^{14}-1 standard; efficiencies ranged from 44–58%. The specific activities reported below are corrected for background and counting loss.

1-Diazo-3-methyl-4-phenyl-3-buten-2-one C^{14}-1 (17).—Diazomethane-C^{14} was prepared by the standard procedure[31] from 21.5 g. (0.2 moles) of N-methyl-C^{14}-N-nitroso-*p*-toluenesulfonamide[32] containing 0.1 mc. of C^{14} activity. The yield by titration was 71%. To this diazomethane was added a solution of 5.90 g. of freshly crystallized α-methylcinnamoyl chloride. After standing at room temperature for 5 hr., the solution was evaporated at reduced pressure and the diazo ketone was collected in three crops, total yield 4.1 g. (61%), m.p. 85–89°; specific activity 9.33×10^4 d.p.s./mmole.

This diazo ketone was converted to the pyrazoline **18** with nonradioactive diazomethane in 48% yield by the usual procedure; **18** had m.p. 92–95°. This product was then diluted with unlabeled **18** to give 3.9 g., m.p. 92–93°; specific activity 2.30×10^4 d.p.s./mmole. The radioactive pyrazoline was converted to **1a** in 70% yield, and the product was again diluted with unlabeled material to give 7.7 g. of **1a**, m.p. 151–152°; specific activity 1.27×10^3 d.p.s./mmole.

Subsequent steps were then carried out by the procedures described above without further dilutions of radioactivity. Compounds **3**, **7**, **8**, and **12** had specific activities ranging from 100–103% of that of **1a**. In the decarboxylation of **12**, a slow stream of nitrogen was bled into the sublimer and the entrained carbon dioxide was absorbed in sodium hydroxide solution and then precipitated by addition of barium chloride. The barium carbonate had specific activity 1.21×10^3 d.p.s./mmole; the picrate of **13** had specific activity 85 d.p.s./mmoles.

(31) T. J. deBoer and H. J. Backer, *Org. Syn.*, **36**, 16 (1956).

(32) Obtained from New England Nuclear Corp.

Acknowledgment.—We wish to thank Dr. J. M. Vandenbelt and Mrs. Carola Henrich Spurlock, Parke, Davis and Company, for the pK_A and ultraviolet data.

Thiadiazoles. III. Amino-Group Exchange and Ring-Cleavage Reactions of 7-Amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidines[1]

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Displacement of the amino group of 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (I) by secondary amines was shown to occur with the formation of 7-(disubstituted amino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidines (V–VIII). Primary amines were likewise shown to effect displacement of the amino group, but cleavage of the pyrimidine ring to a 1,2,5-thiadiazole may ensue. The structure of the amino-group exchange product from I and butylamine was shown to be 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine, rather than the 6-butyl derivative, by reduction to 4,5-diamino-6-(butylamino)pyrimidine and by independent synthesis. Products of ring cleavage of I were shown to be *N*-substituted amidines, *e.g.*, 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV). The formation of the thiadiazolopyrimidines resulting from exchange of amino groups could be favored over the formation of 1,2,5-thiadiazoles by limiting the reaction time. Exchange of one mono- or disubstituted amino group for another and the reversibility of this type of reaction were also demonstrated. Evidence that these amine-exchange reactions are influenced by the relative basicities of the attacking and departing amines and by steric effects was obtained. It is suggested that the exchange of amino groups occurs by direct displacement and that ring cleavage is an independent process.

Facile nucleophilic displacement from position 7 of substituents commonly subject to expulsion from heterocyclic rings was observed during the course of investigations on the synthesis of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines.[2] These displacements were effected by aniline generated during the formation of the thiadiazole ring by *N*-sulfinylaniline (III). Evidence was subsequently obtained that trace amounts of 7-anilino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (IV) may be formed during the preparation of 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (I) from 4,5,6-triaminopyrimidine (II, $R_1 = R_2 =$ H) and *N*-sulfinylaniline. Moreover, cleavage of the pyrimidine ring of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines bearing oxygen functions was found to proceed under comparatively mild conditions.[3] These reactions indicate an unusual lability of the pyrimidine ring that is probably ascribable to electron localization at the hetero atoms. The lability of the ring system suggested that additional studies of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines might contribute to further elucidation of the course of amino-group exchange and ring-opening reactions of fused pyrimidine heterocycles.

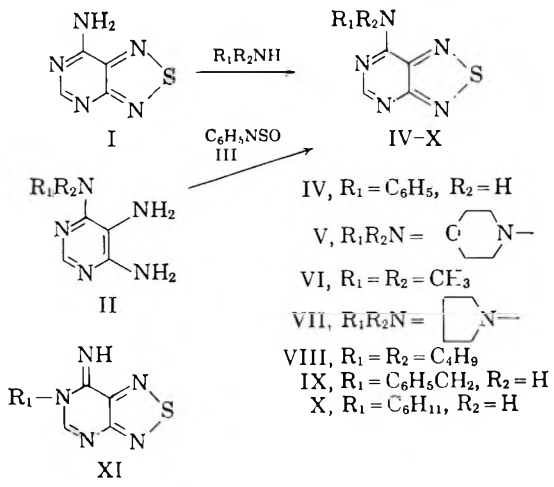
Paper chromatographic evidence for the formation of trace amounts of the 7-anilino derivative (IV) during the preparation of the 7-amino derivative (I) was confirmed by showing that a small amount of the 7-anilino derivative (IV) could be isolated by greatly prolonging the reaction time. Interaction of pure I and refluxing aniline afforded IV in low yield. From reactions of I with refluxing morpholine and with dimethylamine at 100°, 7-morpholino[1,2,5]thiadiazolo-[3,4-*d*]pyrimidine (V) and 7-(dimethylamino)[1,2,5]-thiadiazolo[3,4-*d*]pyrimidine (VI) were isolated and were shown to be identical with specimens of these compounds that had been prepared[2] from reactions of the appropriate 6-substituted 4,5-diaminopyrimidines (II) and N-sulfinylaniline (III). Similarly, reactions of I with pyrrolidine, with dibutylamine, and with certain primary amines gave the 7-(substituted amino) derivatives VII–X (Chart I).

(1) This investigation was supported by the C. F. Kettering Foundation and by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740.

(2) Y. F. Shealy, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.*, **27**, 2154 (1962).

(3) (a) Y. F. Shealy and J. D. Clayton, *ibid.*, **28**, 1491 (1963); (b) Y. F. Shealy and J. D. Clayton, *ibid.*, **29**, 2141 (1964).

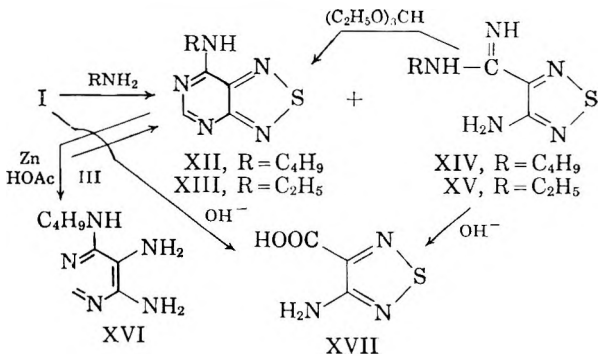
CHART I



The structural assignments (VII–X) for the products of these reactions are based on their composition, characteristic ultraviolet spectra, and analogy to V–VI. However, if amino-group exchange proceeds by a ring-opening and reclosure mechanism,[4,5] 6-substituted 7-imino[1,2,5]thiadiazolo[3,4-*d*]pyrimidines (XI) are possible products of exchange by primary amines. During studies of the interaction of benzylamine and of cyclohexylamine with the 7-amino derivative (I), the ultraviolet long-wave-length absorption maximum of [1,2,5]-thiadiazolo[3,4-*d*]pyrimidines was observed to move hypsochromically, during long-term reactions, toward that of certain 1,2,5-thiadiazoles.[3a] Both the possibility of pyrimidine ring cleavage and the structure of products of exchange with primary amines were investigated more fully by employing butylamine as the nucleophile.

Two compounds were detected in and isolated from crude products of reactions of 7-amino[1,2,5]thiadiazolo-[3,4-*d*]pyrimidine (I) with refluxing butylamine that were allowed to proceed for 1–2 days. The higher-melting product had the composition of 7-(butylamino)-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII) and exhibited ultraviolet absorption consistent with this structure. The second, lower-melting product had the composition of 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV) and, like other derivatives[3a] of 4-amino-1,2,5-thiadiazole-3-carboxylic acid, showed an absorption maximum near 320 mμ. In contrast to 4-amino-1,2,5-thiadiazole-3-carboxamide,[3a] but, in accord with the presence of the basic amidine group, the second product formed a stable hydrochloride. Reduction of the higher-melting compound with zinc and acetic acid[6] gave 4,5-diamino-6-(butylamino)pyrimidine (XVI), identical with a specimen prepared by reducing 4-amino-6-butylamino-5-nitropyrimidine. The higher-melting compound was synthesized by treating 4,5-diamino-6-(butylamino)pyrimidine (prepared from the 5-nitropyrimidine) with *N*-sulfinylaniline. These interconversions excluded 6-butyl-6,7-dihydro-7-imino-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XI, $R_1 = C_4H_9$), a potential product of opening and subsequent reclosure of the pyrimidine ring, and they confirmed the structure (XII) assigned to the higher-melting product. The structure (XIV) assigned to the second, lower-melting product was confirmed by the following reactions: (1) basic hydrolysis gave 4-amino-1,2,5-thiadiazole-3-carboxylic acid[3a] (XVII); and (2) an acid-catalyzed reaction with triethyl orthoformate reclosed the pyrimidine ring, giving 7-(butylamino)[1,2,5]thiadiazolo-[3,4-*d*]pyrimidine (XII). Further studies of the interaction of I and butylamine showed that XII could be obtained in 84% crude yield by limiting the reaction time to 7 hr.; 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV) could be isolated free of XII in 40–50% yield by prolonging the reaction time to 90–120 hr. (Chart II).

CHART II



Reactions of I with ethylamine gave analogous results. The structural assignments for the higher-melting thiadiazolopyrimidine (XIII) and the lower-melting thiadiazole (XV) are based on elemental analyses, analogy to the products formed by butylamine, and ultraviolet spectra. The formation of XIII was also favored by reaction periods shorter than those that afforded the best yields of the thiadiazole (XV). The 1,2,5-thiadiazoles obtained from I are closely related to those isolated from reactions of [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one with amines, hydrazine, or aqueous base.[3a] Ring opening also resulted from the action of aqueous base on I; the final product of a prolonged reaction at room temperature was 4-amino-1,2,5-thiadiazole-3-carboxylic acid (XVII). An analogous ring opening is the cleavage of 4-aminopteridine by hydrazine and by aqueous base[8]; other examples of the formation of ring-cleavage products from variously substituted heterocycles have been cited previously.[3a] Compound XVII might be the hydrolysis product of an intermediate thiadiazole formed by ring opening of I, or I might first be hydrolyzed to the 7(6*H*)-one, which can be cleaved to XVII by aqueous base.[3a] Evidence has been presented by Brown and Jacobsen[9] that both of these pathways are followed, depending on reaction conditions, in the alkaline cleavage of an *N*-

(4) E. C. Taylor, Jr., and C. K. Cain, *J. Am. Chem. Soc.*, **73**, 4384 (1951).

(5) E. C. Taylor, Jr., *ibid.*, **74**, 1648 (1952).

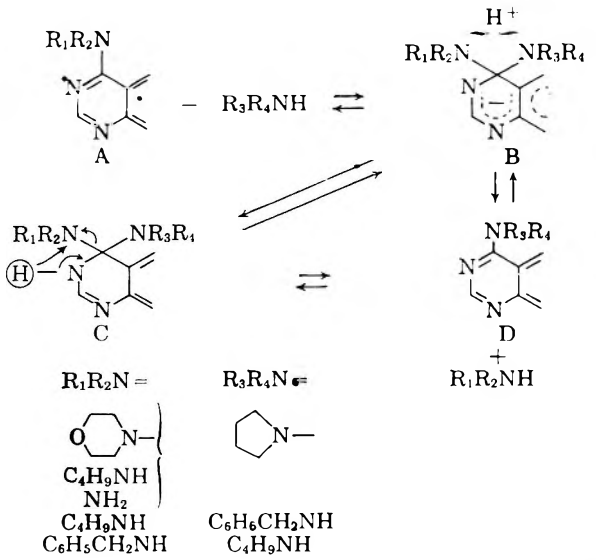
(6) The reduction of XII is another example of reductive cleavage, by a different reagent, of the thiadiazole ring of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines.[3a] D. C. Sen [*J. Indian Chem. Soc.*, **15**, 537 (1938)] reported the reduction of bornylene-1,2,5-thiadiazole to bornylene-2,3-diamine by zinc and acetic acid. 2,1,3-Benzothiadiazoles are reduced to *o*-phenylenediamines by tin or zinc in acidic media. Iron and acetic acid or sodium dithionite reduce certain nitro- and phenylazo-2,1,3-benzothiadiazoles to amino derivatives without cleaving the thiadiazole ring. See V. G. Pesin, A. M. Khaletskii, and V. A. Sergeev, *Zh. Obshch. Khim.*, **32**, 181 (Eng. transl.,[7] p. 177) (1962), and preceding publications.

(7) *J. Gen. Chem. USSR*, Consultants Bureau Enterprises, Inc., New York, N. Y.

(8) R. M. Evans, P. G. Jones, P. J. Palmer, and F. F. Stephens, *J. Chem. Soc.*, 4106 (1956).

(9) D. J. Brown and N. W. Jacobsen, *ibid.*, 1978 (1960).

CHART III



substituted pteridine, 1,4-dihydro-4-imino-1-methylpteridine; 4-aminopteridine has been hydrolyzed by aqueous base to 4-hydroxypteridine.[10]

Because of its relatively strong basic properties, pyrrolidine was chosen for a study of exchange of substituted amino groups. Reactions of pyrrolidine with 7-morpholino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (V) and with 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII) both gave 7-pyrrolidino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (VII) at the temperature of refluxing pyrrolidine. Thus, a secondary amine effected displacement, as summarized in Chart III, of ammonia, a primary amine, and another secondary amine. In addition, exchange of one primary amine for another[11] was demonstrated by the isolation in low yield of 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII) from a reaction of the 7-benzylamino derivative (IX) with butylamine. Considerable IX (52%) was recovered, and chromatographic evidence of slight ring opening to XIV was obtained. The reversibility of these exchange reactions was shown by reversing the roles of benzylamine and butylamine. A small quantity of the 7-benzylamino derivative (IX) was isolated by treating the 7-butylamino derivative (XII) with benzylamine. However, when the roles of pyrrolidine and morpholine were reversed by treating the 7-pyrrolidino derivative (VII) with morpholine, the 7-pyrrolidino derivative (VII) was recovered[12] after a much longer reaction period than that required at the same temperature for the formation of the 7-pyrrolidino derivative (VII) in high yield from the 7-morpholino derivative (V).

The basicity[13] (in water) of the four bases involved in reactions of pyrrolidine with the three thiadiazolopyrimidines (Chart III) increases in the order morpholine < ammonia < butylamine < pyrrolidine. The rate of formation of VII in relation to the basicity of the amine displaced would be expected to decrease in the order morpholine > ammonia > butylamine. The butylamino group was displaced by pyrrolidine much less readily than the morpholino and amino groups, both of which were displaced almost quantitatively after reaction periods of 1–2 hr. Our observations of shifts of the long-wave-length ultraviolet absorption maximum during the formation of VII do not show a clear distinction between displaceability of the amino and morpholino groups by pyrrolidine; steric effects or volatilization of the displaced ammonia may have counteracted the difference in base strength. The failure of morpholine (pK_a 8.36) to effect any appreciable displacement of pyrrolidine (pK_a 11.27) from VII under comparable conditions is consistent with the difference in base strength of the two amines. Reactions of I with pyrrolidine, morpholine, and dibutylamine represent a variation of the attacking amine. The 7-pyrrolidino derivative (VII) was formed more rapidly than the 7-morpholino derivative (V), even though the temperature of the morpholine reaction was higher. This difference may be due to either steric or basic effects, but steric effects must be responsible for the fact that the dibutylamino derivative (VIII) formed more slowly than either V or VII, even though the attacking amine is comparable in basicity[13] to pyrrolidine.[14] Although these observations are qualitative, they are consistent with the expectation that, other factors being equal, diplaceability of amino groups by amines depends on both steric effects and the relative basicities (or nucleophilicities) of the attacking and departing amines.

Amino-group exchange reactions, some of which were acid catalyzed, of 2,4-diaminopteridines[4,5,15,16] and 2,4-diaminoquinazolines,[17] as well as 2,4-disubstituted pteridines[4,16] and quinazolines[18] having one amino substituent, have been described. In addition, acid-catalyzed exchange of amino groups of pyrimidines[19,20] and of purines[19,21] has been reported. Most of these reactions were conducted at temperatures of 130–200°, whereas exchange of amino groups at position 7 of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines was effected without acid catalysis and frequently at temperatures below 100°; for example, the benzylamino derivative (IX) was obtained from I in 88% yield after a 16-hr. reaction at 80–85° and the pyrrolidino derivative (VII) was obtained in nearly quantitative yields from either I or V after approximately 2 hr. at 85–90°. Taylor[4,5] proposed a mechanism based on ring opening and subsequent reclosure for amino-group exchange reactions of 2,4-disubstituted pteridines. A similar course had been proposed by Leonard and co-workers[22] for amine exchange involving a ring-nitrogen atom of

(10) A. Albert, D. J. Brown, and G. Cheeseman, *J. Am. Chem. Soc.*, 474 (1951).

(11) Exchange of one primary amine for another has been previously observed with certain bifunctional pteridines,[4] quinazolines,[17] and pyrimidines.[19]

(12) A trace amount of the 7-morpholino derivative (V) was detected chromatographically in the recovered VII (*cf.* ref. 42).

(13) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957), and references cited therein.

(14) Diisopropylamine failed to displace chlorine from a 6-chloropurine nucleoside, although a number of other primary and secondary amines effected this displacement: see L. Goldman and J. W. Marsico, *J. Med. Chem.*, **6**, 413 (1963).

(15) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *J. Am. Chem. Soc.*, **73**, 2864 (1951).

(16) M. D. Potter and T. Henshall, *J. Chem. Soc.*, 2000 (1956).

(17) F. H. S. Curd, E. Hoggarth, J. H. Landquist, and F. L. Rose, *ibid.*, 1766 (1948).

(18) R. J. Grout and M. W. Partridge, *ibid.*, 3540 (1960).

(19) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **82**, 3971 (1960).

(20) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **28**, 2672 (1963).

(21) N. J. Leonard and J. A. Deyrup, *J. Am. Chem. Soc.*, **84**, 2148 (1962).

(22) N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, **11**, 341 (1946); N. J. Leonard, W. V. Ruyle, and L. C. Bannister, *ibid.*, **13**, 617 (1948); N. J. Leonard and W. V. Ruyle, *ibid.*, **13**, 903 (1948).

4-quinazolones. Likewise, base-catalyzed rearrangements of certain purines,[23-27] pyrazolopyrimidines,[27,28] pteridines,[29,30] quinazolines,[18,31] and pyrimidines[9,32,33] in which an alkyl or aryl group appears to migrate from a ring-nitrogen atom to an exocyclic nitrogen or in which an amino group and another substituent appear to exchange positions have been explained[26-28,31,34] by sequences consisting of ring opening and recyclization. This course has been validated for a pyrimidine by the use of an N^{15}-label,[35] and a ring-opened intermediate has been isolated from a "normal" hydrolytic replacement of chlorine from the purine ring.[36]

The apparent relationship between amino-group exchange and ring opening may be questioned on the basis of the facts (1) that reactions of I with butylamine and ethylamine resulted in both displacement of an amino group and ring opening by the same reagent under the same conditions except for reaction time and (2) that one secondary amine (pyrrolidine) displaced another (morpholine).[37] The fact that the thiadiazoles (XIV XV) were most easily isolated after reaction periods much longer than those that favored the formation of the corresponding 7-(substituted amino)-[1,2,5]thiadiazolo[3,4-*d*]pyrimidines (XII–XIII) indicated that the thiadiazoles must have been formed chiefly, if not entirely, from the 7-(substituted amino)-[1,2,5]thiadiazolo[3,4-*d*]pyrimidines and, consequently, that the *isolated* products of ring opening were formed *after* amino-group exchange had already occurred. Evidence in support of this conclusion was furnished by ultraviolet spectra of aliquots from reactions of I with butylamine. The observed long-wave-length absorption maximum shifted from the position of maximum absorption of I (340 mμ at pH 7) to approximately that of XII (357 mμ), and then it broadened and moved near that of the thiadiazole (XIV) at 320 mμ. Exchange of the 7-morpholino group for a 7-pyrrolidino group would be possible either by direct displacement at position 7 (Chart III) or by ring opening at position 5 (E from A) and subsequent reclosure (F), but not by ring opening at position 7. On the premise that ring opening as a prerequisite of amine exchange would proceed by fission of the N-6–C-7 bond,[38]

E F

the exchange of one secondary amine for another argues for direct displacement rather than ring opening and reclosure. In addition, the influence of basicity and steric factors on the exchange of amino groups of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines is reminiscent of aromatic nucleophilic substitution,[39] and acid catalysis[5,17,19] of other amino-group exchange reactions is also reminiscent of acid-catalyzed displacement of halogens from certain heterocycles.[40] In the absence of knowledge of the rate-controlling processes, it is not possible to exclude ring opening (E), amidine exchange, and reclosure (F) as the basis for exchange of amino groups, but it is suggested that amino-group exchange occurs by direct nucleophilic displacement (Chart III) and that ring opening is an independent process.

Experimental[41]

7-Anilino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (IV).—A solution of 200 mg. of 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (I) in 10 ml. of redistilled aniline was heated at the reflux temperature for 1.5 hr., concentrated to about 3 ml., diluted with 1 *N* hydrochloric acid to approximately pH 2, and extracted continuously with benzene. Concentration of the benzene extract to dryness gave 84 mg. (28%) of crude IV (m.p. 168–169°). Recrystallization of this material from benzene–cyclohexane gave a 12% yield of pure IV, which was identical by melting point (179–180°), ultraviolet spectra, and paper chromatography with specimens prepared from other starting materials.[2]

7-Anilino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (IV) was also isolated in 12% yield from a reaction of 4,5,6-triaminopyrimidine and *N*-sulfinylaniline that was allowed to proceed for 50 hr. in refluxing pyridine. Yields of crude I as high as 95% are obtained by this method after a reaction period of 4–5 hr. at 110°. Trace amounts of IV detectable by paper chromatography may be present in crude specimens of I. (IV has been easily detected chromatographically by its bright yellow fluorescence in ultraviolet light in synthetic mixtures of IV and I containing 1% of IV.)

7-Morpholino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (V).—A reaction solution consisting of 500 mg. of I and 60 ml. of redistilled morpholine was heated, in an atmosphere of nitrogen and with the exclusion of moisture, for 24 hr. at the reflux temperature. Ultraviolet spectra of aliquots removed from the reaction mixture showed that the observed long-wave-length maximum at pH 7 had shifted from that of I (340 mμ) to 357 and to 363 mμ after 5 hr. and 6.5 hr., respectively, and to that of V (369–370 mμ) after 24 hr. The yellow solid remaining after the solvent had been evaporated under reduced pressure was washed well with water and dried *in vacuo* at 55°: wt. 600 mg. (82%), m.p. 154–155°. The yellow crystalline product (58% yield) obtained by recrystallizing the crude product from water melted at 155–156°; its infrared and ultraviolet absorption spectra were identical with those of a specimen[2] of V prepared from 4,5-diamino-6-morpholinopyrimidine.

(23) E. Fischer, *Ber.*, **31**, 542 (1898).
(24) G. B. Elion, *J. Org. Chem.*, **27**, 2478 (1962).
(25) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 539 (1960).
(26) H. G. Windmueller and N. O. Kaplan, *J. Biol. Chem.*, **236**, 2716 (1961).
(27) E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).
(28) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **24**, 1570 (1959).
(29) W. V. Curran and R. B. Angier, *J. Am. Chem. Soc.*, **80**, 6095 (1958); R. B. Angier and W. V. Curran, *J. Org. Chem.*, **27**, 892 (1962); R. B. Angier, *ibid.*, **28**, 1509 (1963).
(30) W. Pfleiderer, E. Liedek, R. Lohrmann and M. Rukwied, *Chem. Ber.*, **93**, 2015 (1960).
(31) E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.*, **27**, 2622 (1962).
(32) H. C. Carrington, F. H. S. Curd, and D. N. Richardson, *J. Chem. Soc.*, 1858 (1955).
(33) D. J. Brown, E. Hoerger, and S. F. Mason, *ibid.*, 4035 (1955); D. J. Brown and J. S. Harper, *ibid.*, 1298 (1961); D. J. Brown, *J. Appl. Chem.*, **9**, 203 (1959).
(34) E. C. Taylor and M. J. Thompson, *J. Org. Chem.*, **26**, 5224 (1961).
(35) D. J. Brown, *Nature*, **189**, 828 (1961); J. Goerdeler and W. Roth, *Chem. Ber.*, **96**, 531 (1963).
(36) E. Shaw, *J. Org. Chem.*, **27**, 883 (1962).
(37) Exchange of one secondary amine for another does not appear to have been reported previously.
(38) Mechanisms proposed for ring opening of variously substituted fused pyrimidine heterocycles at the position corresponding to 7 of V have been based on rupture of the C–N bond corresponding to the N-6–C-7 bond of V; see ref. 4, 5, 22, 23–28, 31, 34, 36.
(39) J. F. Bunnett, *Quart. Rev.* (London), **12**, 1 (1958); J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).
(40) For example: C. K. Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944); J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.*, 1014 (1949); N. B. Chapman and C. W. Rees, *ibid.*, 1190 (1954); N. B. Chapman and D. Q. Russell-Hill, *ibid.*, 1563 (1956).
(41) Melting points, infrared and ultraviolet spectra, and paper chromatographic data were determined by methods outlined previously.[3a] Paper chromatography was performed by Miss Kathleen Hewson, Miss Mary Broadaway, and Mrs. Dottye Searcy. Microanalyses and spectral determinations were by Drs. W. J. Barrett, W. C. Coburn, Jr., and P. D. Sternglanz, and associates of the Analytical Section of this institute. Some of the elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

7-(Dimethylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (VI).—A solution of 500 mg. of I and 50 ml. of an anhydrous dimethylamine–pyridine solution, containing a large excess of dimethylamine, was heated in a 100-ml. stainless steel bomb at 125° for 24 hr. The reaction mixture was freed of volatile components under reduced pressure. Recrystallization of the residual yellow solid (588 mg.) from water gave 300 mg. (51%) of 7-(dimethylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine, identical according to its melting point (172–173°), paper chromatograms, and infrared and ultraviolet spectra with a specimen prepared[2] from 4,5-diamino-6-(dimethylamino)pyrimidine.

7-(Dibutylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (VIII) was isolated in 55% yield by recrystallizing (from 50% aqueous ethanol) the crude product obtained from a reaction of refluxing dibutylamine (redistilled) with I for 55 hr. The bathochromic shift of the long-wave-length maximum corresponding to the conversion of I to VIII was incomplete at 32 hr. and complete at 55 hr. Recrystallization of a specimen from 50% aqueous ethanol gave the analytical sample: m.p. 86–87°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 229 (12.9), 265 (4.7), 355 (17.0) in 0.1 *N* hydrochloric acid; 235 (15.7), 275 (3.9), 285 (sh), 374 (11.9) at pH 7; 235 (15.8), 276 (4.0), 285 (sh), 374 (12.0) in 0.1 *N* sodium hydroxide; 234 (16.2), 277 (4.5), 287 (3.2), 378 (11.7) in ethanol.

Anal. Calcd. for $C_{12}H_{19}N_5S$: C, 54.30; H, 7.22; N, 26.39; S, 12.08. Found: C, 54.23; H, 7.34; N, 26.43; S, 12.05.

7-Pyrrolidino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (VII).—A solution of 4.93 g. of I and 150 ml. of redistilled pyrrolidine was heated at the reflux temperature for 4.5 hr. The mixture, which contained yellow needles after it had been allowed to stand at room temperature overnight, was cooled in an ice bath and filtered. The precipitate was analytically pure after it had been washed with water and dried *in vacuo* at 50°: wt. 3.25 g. (49%), m.p. 179°. An additional portion (m.p. 178–179°) amounting to 1.75 g. (26%) was isolated by evaporating the solvent from the filtrate and slurrying the residue with water. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 227 (13.3), 265–270 (4.3, plateau), 347 (17.1) in 0.1 *N* hydrochloric acid; 234 (16.9), 275 (4.0), 285 (sh), 368 (12.6) at pH 7; 234 (17.1), 275 (4.1) 285 (sh), 368 (12.6) in 0.1 *N* sodium hydroxide.

Anal. Calcd. for $C_9H_9N_5S$: C, 46.35; H, 4.35; N, 33.78; S, 15.45. Found: C, 46.20; H, 4.36; N, 33.87; S, 15.55.

In order to compare displaceability of amino groups, I was treated with dry pyrrolidine by the exact procedure described below for the reaction of V with pyrrolidine. The observed long-wave-length maximum at pH 7 shifted from 340 (I) to 368 mμ (VII) within 1–1.5 hr. (Reaction was incomplete after 0.5 hr.) The product obtained after 1.5 hr. amounted to a 97% yield, m.p. 177–178°. Recrystallization from ethanol–water gave VII (72%), pure by melting point and ultraviolet data.

7-(Benzylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (IX).—A solution of 6.0 g. of I in 120 ml. of redistilled benzylamine was heated at 80–85° for 16 hr., cooled to room temperature, and added dropwise to 275 ml. of phosphate buffer (pH 7). The pale yellow crystalline solid that formed was separated by filtration, washed with water, and dried *in vacuo* at 60°: yield 8.37 g. (88%), m.p. 202–203°. A specimen was recrystallized from aqueous ethanol. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 219 (16.0), 264 (5.0), 342 (18.6) in 0.1 *N* hydrochloric acid; 222 (16.8), 272 (5.1), 280 (sh), 353 (12.3) at pH 7; 265–70 (sh), 280 (sh), 358 (9.8) in 0.1 *N* sodium hydroxide; 223 (16.8), 274 (5.4), 282 (sh), 360 (11.8) in ethanol.

Anal. Calcd. for $C_{11}H_9N_5S$: C, 54.29; H, 3.74; N, 28.78; S, 13.18. Found: C, 54.43; H, 3.95; N, 28.91; S, 13.25.

During a preliminary experiment at 80° for 78 hr., a decrease in the ultraviolet absorption at 355–360 and an increase at 320–330 mμ, suggestive of thiadiazole formation,[3a] was noted. A small amount of IX was isolated.

7-(Cyclohexylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (X).—A solution of 1.0 g. of I in 50 ml. of redistilled cyclohexylamine was heated at 90° for 30 hr. Half of the reaction solution was removed and concentrated *in vacuo* to an oil that solidified after several portions of water were added and evaporated. Recrystallization of the solid from aqueous ethanol gave yellow crystals: yield 35%, m.p. 164°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 222 (12.2), 263 (4.3), 270 (sh), 344 (16.9) in 0.1 *N* hydrochloric acid; 226 (13.7), 272 (4.6), 280 (sh), 359 (11.7) at pH 7; 272 (4.4), 280 (sh), 360 (11.1) in 0.1 *N* sodium hydroxide; 225 (13.8), 274 (4.8), 283 (4.0), 363 (11.0) in ethanol.

Anal. Calcd. for $C_{10}H_{13}N_5S$: C, 51.03; H, 5.57; N, 29.74; S, 13.63. Found: C, 50.73; H, 5.34; N, 29.66; S, 13.6.

Continued heating of the second half of the reaction mixture at 90–100° for several days caused the observed long-wave-length ultraviolet absorption maximum to approach that of certain 1,2,5-thiadiazoles.[3a]

Interaction of Butylamine and I.—From several reactions of refluxing butylamine with I for periods of 20–32 hr. both the 7-butylamino derivative (XII) and the thiadiazole XIV were obtained and were separated by subliming XIV from the mixture at 100° under reduced pressure (0.5 mm.). The residue was essentially pure XII and was obtained in 50–60% yields from the shorter reactions. At higher temperatures some of XII, as well as XIV, sublimed. In order to define more exactly the conditions favoring amino-group exchange and those favoring 1,2,5-thiadiazole formation, the following experiments were performed.

Interaction of 6.5 g. of I and 200 ml. of refluxing butylamine (freshly distilled, but not otherwise dried) was allowed to proceed for 120 hr., and the butylamine was evaporated *in vacuo*. A solution of the residual oil in 150 ml. of 50% aqueous ethanol yielded two crops of yellow solid (m.p. 52–55°) amounting to 4.7 g. and 1.96 g. Recrystallization of the first crop from 50% aqueous ethanol gave 3.15 g. of crystals, m.p. 58–59°. Sublimation of the second crop and recrystallization of the sublimate from 50% aqueous ethanol gave an additional 900 mg., m.p. 59–60°, total yield 49%. The analytical sample of **4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV)** was prepared by recrystallizing a crude specimen from 50% aqueous ethanol and subliming the resulting precipitate. The white sublimate melted at 60–61°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 215 (9.5), 320 (6.2) in 0.1 *N* hydrochloric acid; 215 (9.4), 320 (6.2) at pH 7; 317 (8.5) in 0.1 *N* sodium hydroxide; 260–280 (2.9 plateau), 325 (9.6) in ethanol.

Anal. Calcd. for $C_7H_{13}N_5S$: C, 42.19; H, 6.57; N, 35.16; S, 16.08. Found: C, 42.37; H, 6.50; N, 34.90; S, 16.24.

A pure hydrochloride of XIV was prepared by introducing hydrogen chloride into an ethanol solution of XIV, evaporating the ethanol, adding ether to the residual oil, chilling, and reprecipitating the resulting solid from ethanol with a large volume of ether. λ_{max} was 322 mμ (ϵ 6400) in ethanol.

Anal. Calcd. for $C_7H_{13}N_5S \cdot HCl$: C, 35.66; H, 5.99; S, 13.61; Cl, 15.04. Found: C, 35.68; H, 5.70; S, 13.7; Cl, 15.1.

Interaction, under a nitrogen atmosphere and with the exclusion of atmospheric moisture, of 500 mg. of I and 25 ml. of refluxing, dry butylamine (twice distilled from and stored over calcium hydride) was followed by determining the ultraviolet absorption of aliquot residues. The observed long-wave-length maximum at pH 7 shifted from that of I (340 mμ) to that of XII (357 mμ after 6–8 hr.), broadened and moved hypsochromically (338 mμ at 50 hr.), and gradually approached (325 mμ after 90 hr.) that of XIV. Ring opening appeared to be somewhat faster than in the 120-hr. reaction, which had also been followed spectroscopically. The isolated yield of XIV after 90 hr. was 43%. An identical experiment was discontinued after 7 hr. (Ultraviolet absorption reached a maximum at 357 mμ within 6 hr.) The residue remaining after the butylamine had been evaporated *in vacuo* was slurried with water and dried. The yellow crystalline solid, which amounted to 563 mg. (84%) and melted at 138–140°, was **7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]-pyrimidine (XII)** containing, according to paper chromatography, a trace amount of thiadiazole (XIV). Recrystallization of the solid from aqueous ethanol gave pure XII (66% yield): m.p. 142–143°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 222 (12.8), 264 (4.3), 270 (sh), 342 (16.5) in 0.1 *N* hydrochloric acid; 223 (13.7), 272 (4.9), 280 (sh), 357 (11.4) at pH 7; 272 (4.7), 280 (sh), 357 (10.7) in 0.1 *N* sodium hydroxide; 224 (13.7), 274 (5.1), 283 (4.3), 362 (10.9) in ethanol.

Anal. Calcd. for $C_8H_{11}N_5S$: C, 45.91; H, 5.29; N, 33.47; S, 15.32. Found: C, 45.98; H, 5.22; N, 33.47; S, 15.25.

Reduction of 7-(Butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII).—To a stirred solution that was composed of 860 mg. of the 7-butylamino derivative (XII), 30 ml. of ethanol, 30 ml. of water, and 3 ml. of glacial acetic acid and that was maintained under a nitrogen atmosphere at 70° was added, during 1 hr., 3.13 g. of zinc dust. The reaction mixture was kept under these conditions for an additional 2 hr., filtered to remove unreacted zinc, and made basic to pH 9 with 6 *N* sodium hydroxide. The precipitated zinc hydroxide was removed by filtration, the solvents were evaporated *in vacuo* from the filtrate, and the residual solid was leached with three 25-ml. portions of hot ethyl acetate. A first crop of crude product (m.p. 138–139°) amount-

ing to 520 mg. (70%) crystallized from the combined and concentrated ethyl acetate extracts. Recrystallization of a portion of the crude product gave a 78% recovery of crystals identical by melting point (141–142°), infrared spectrum, and ultraviolet spectra with 4,5-diamino-6-(butylamino)pyrimidine (XVI) prepared from 4-amino-6-butylamino-5-nitropyrimidine.

7-(Butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII) from 4,5-Diamino-6-(butylamino)pyrimidine.—A solution of 500 mg. of 4,5-diamino-6-(butylamino)pyrimidine (prepared from 4-amino-6-butylamino-5-nitropyrimidine), 1.15 g. of *N*-sulfinylaniline, and 50 ml. of anhydrous pyridine was heated at 90–95° for 3.5 hr. Pyridine was evaporated under reduced pressure; water (25 ml.) was added to the residue and its volume was reduced by one-half under reduced pressure; and yellow crystals were collected by filtration, washed with water, and dried *in vacuo* at 56°: yield 560 mg. (97%), m.p. 142°. Recrystallization from 2:1 water–ethanol gave material having a melting point (143°), ultraviolet and infrared spectra, and R_f values identical with those of XII obtained from I.

4-Amino-6-butylamino-5-nitropyrimidine.—A mixture of 3.0 g. of 4-amino-6-chloro-5-nitropyrimidine, 6 ml. of butylamine, and 312 ml. of ethyl acetate was stirred at room temperature overnight. A precipitate was separated by filtration, the filtrate was concentrated to dryness, and the residue was washed with ethyl acetate and combined with the first crop. Washing the combined portions of solid several times with water left 3.22 g. (89%) of yellow solid. A 50% aqueous ethanol solution yielded 2.82 g. (78%) of pale yellow crystals. Specimens of both the crude and recrystallized samples melted principally at 140°, but some crystals persisted to 170°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 241 (24.1), 294 (3.6), 342 (7.1) in 0.1 *N* hydrochloric acid; 342 (9.5) at pH 7; 344 (9.6) in 0.1 *N* sodium hydroxide; 340 (9.9) in ethanol.

Anal. Calcd. for $C_9H_{13}N_5O_2$: C, 45.49; H, 6.20; N, 33.16. Found: C, 45.53; H, 6.19; N, 33.09.

4,5-Diamino-6-(butylamino)pyrimidine (XVI).—4-Amino-6-(butylamino)-5-nitropyrimidine (2.57 g.) in 225 ml. of ethyl acetate was reduced with hydrogen and about 1 g. of Raney nickel catalyst. When the consumption of hydrogen ceased, additional catalyst was added to complete the hydrogenation. The ethyl acetate filtrate, after having been concentrated, deposited 1.53 g. (69%) of crystals, m.p. 139–140°. Recrystallization of 1 g. of this material from ethyl acetate gave 320 mg. of XVI: m.p. 143°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 222 (20.5), 283 (11.1) in 0.1 *N* hydrochloric acid; 218 (28.2), 279 (10.8) at pH 7; 279 (10.5) in 0.1 *N* sodium hydroxide; 218 (29.4), 283 (10.5) in ethanol.

Anal. Calcd. for $C_9H_{15}N_5$: C, 53.01; H, 8.34; N, 38.64. Found: C, 53.14; H, 8.18; N, 38.37.

Hydrolysis of 4-Amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV).—A mixture of 500 mg. of XIV and 65 ml. of 1 *N* sodium hydroxide was heated at the reflux temperature for 2.5 hr., cooled, acidified to pH 2, concentrated to approximately one-half the original volume, and refrigerated. The precipitate, which contained inorganic salts, was washed well with water and dried: 64% yield of white crystals, m.p. 220–221° (sublimation). The ultraviolet spectra, R_f values, and melting point of this material were identical with those of 4-amino-1,2,5-thiadiazole-3-carboxylic acid (XVII) obtained by ring cleavage of [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one.[38]

Cyclization of 4-Amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV to XII).—A solution of 199 mg. of XIV, 10 ml. of triethyl orthoformate, and a small crystal of *p*-toluenesulfonic acid monohydrate was heated at the reflux temperature for 4 hr.; the reaction mixture was concentrated to dryness *in vacuo*; and the yellow crystalline residue was triturated with water. Pure 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII), identical by melting point (142–143°) and by infrared and ultraviolet spectra with specimens prepared from I and from 4,5-diamino-6-(butylamino)pyrimidine (XVI), was obtained in 63% yield by recrystallizing the crude product (84% yield, m.p. 137–138°) from 50% aqueous ethanol.

7-(Ethylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XIII).—Several experiments indicated that both 7-(ethylamino)[1,2,5]-thiadiazolo[3,4-*d*]pyrimidine (XIII) and 4-amino-*N*-ethyl-1,2,5-thiadiazole-3-carboxamidine (XV) were formed from I and ethylamine in proportions depending on the reaction time and the concentration of I. The following procedure favored the formation and isolation of XIII. A mixture consisting of 1.0 g. of I, 20 ml. of ethylamine, and 20 ml. of methanol was heated in a 100-ml. stainless steel bomb at 80° for 12.5 hr. Yellow crystals were filtered from the reaction mixture and washed with ethanol: wt. 450 mg. (38%), m.p. 202–203°. Purification of additional crops from the filtrate gave 385 mg. (32%) with the same melting point. Pale yellow needles of the 7-ethylamino derivative (XIII) crystallized from ethanol or from 75% ethanol: m.p. 202–203°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 220 (13.1), 263 (4.4), 270 (sh), 339 (16.1) in 0.1 *N* hydrochloric acid; 224 (13.5), 272 (4.9), 280 (sh), 355 (11.0) at pH 7; 224 (13.9), 274 (5.1), 283 (4.4), 360 (10.5) in ethanol.

Anal. Calcd. for $C_6H_7N_5S$: C, 39.75; H, 3.90; N, 38.64; S, 17.69. Found: C, 39.93; H, 3.82; N, 38.45; S, 17.6.

4-Amino-*N*-ethyl-1,2,5-thiadiazole-2-carboxamidine (XV).—The procedure used to prepare XIII was repeated except that the reaction time was 48 hr. The dark gum remaining after volatile components had been evaporated *in vacuo* was dissolved in 40% aqueous ethanol. The ethanol solution, after treatment with a small quantity of activated carbon, deposited 355 mg. (36%) of crystals with a melting point of 80–82°. A second crop (175 mg., m.p. 85–140°) was a mixture of XV and XIII according to paper chromatography. Recrystallization of the first crop from 40% ethanol gave white needles: m.p. 83°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 321 (6.0) in 0.1 *N* hydrochloric acid; 321 (6.1) in pH 7 buffer; 318 (8.1) in 0.1 *N* sodium hydroxide; 265 (2.5), 325 (9.1) in ethanol.

Anal. Calcd. for $C_5H_9N_5S$: C, 35.12; H, 5.30; N, 40.89; S, 18.72. Found: C, 35.49; H, 5.20; N, 40.85; S, 18.8.

4-Amino-1,2,5-thiadiazole-3-carboxylic Acid from I.—A solution of 500 mg. of I in 65 ml. of 0.2 *N* sodium hydroxide (4 equiv.) was stirred at room temperature for 18 days. Crude XVII, identified by its infrared spectrum, was obtained in 55% yield by the isolation procedure used in the hydrolysis of XIV. Recrystallization from water gave a 79% recovery: m.p. 220° (sublimation), neut. equiv. 148 (calcd. 145.2).

Displacement of Substituted Amino Groups. A. Morpholino by Pyrrolidine.—A solution (protected from atmospheric moisture with a tube of calcium sulfate) of 300 mg. of 7-morpholino-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine[42] (V) in 15 ml. of dry pyrrolidine (twice distilled from and stored over calcium hydride) was heated at the reflux temperature for 2.5 hr. Reaction was incomplete after 0.75 hr. and appeared, as judged by ultraviolet spectra of aliquots determined in 0.1 *N* hydrochloric acid, to be essentially complete within 1–2 hr. Concentration of the reaction mixture to dryness *in vacuo* left a yellow crystalline solid: m.p. 178°, yield 270 mg. (98%). (A small amount of product was lost in aliquots removed from the reaction mixture for ultraviolet examination.) Paper chromatography of this material showed that it was 7-pyrrolidino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (VII) containing a trace amount of the 7-morpholino derivative (V). Recrystallization of the crude product from aqueous ethanol gave an 82% recovery of crystals with melting point of 178° and infrared and ultraviolet spectra identical with those of the 7-pyrrolidino derivative (VII) prepared from I.

B. Butylamino by Pyrrolidine.—A solution of 344 mg. of 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine[42] (XII) in 18 ml. of pyrrolidine (distilled from sodium hydroxide and dried with calcium hydride) was heated at the reflux temperature with the exclusion of atmospheric moisture. The observed long-wavelength ultraviolet absorption maximum at pH 7 displayed a slow bathochromic shift from that of the 7-butylamino derivative (357 mμ), but it did not reach the maximum of VII (368 mμ) within 13.5 hr. The reaction mixture was cooled, and a precipitate of VII, identified by melting point and ultraviolet spectra, was collected by filtration: yield 75 mg. (23%). Fractions, totaling 242 mg., from the filtrate were shown by paper chromatography to contain additional VII, unreacted 7-butylamino derivative (XII), and an unidentified compound.

C. Attempted Displacement of the Pyrrolidino Group by Morpholine.—The procedure described above for the conversion of the 7-morpholino derivative (V) to the 7-pyrrolidino derivative (VII) was employed in heating a solution of 400 mg. of VII in 20 ml. of dry morpholine at 85° for 72 hr. The infrared spectrum of the yellow solid (352 mg., 88% recovery, m.p. 178°) was identical with that of pure VII. The recovery of VII was not quantitative owing to losses in aliquots (an estimated 4.5%) removed during

(42) The specimens of V, VII, IX, and XII used as starting materials for exchange of substituted amino groups were prepared from I, but they contained no I detectable by paper chromatography. If any I had been present as a contaminant, it would have reacted with the attacking amine to form the corresponding 7-(substituted amino)[1,2,5]thiadiazolo[3,4-*d*]-pyrimidine.

the course of the attempted reaction and in water washings. The 7-pyrrolidino and 7-morpholino derivatives may be separated by paper chromatography in pH 6.7 acetate buffer and detected as blue fluorescent spots by ultraviolet light.[2,3a] A paper chromatogram of the recovered material and of pure specimens of V and VII for reference showed VII together with a very weak spot corresponding to V.[42]

D. Butylamino by Benzylamine.—Heating a solution of 400 mg. of the 7-butylamino derivative[42] (XII) in 10 ml. of redistilled benzylamine at 80–85° for 74 hr. and isolation and purification of the product, as described for IX from I, gave a 16% yield of material identical by infrared spectrum and melting point (202°) with the 7-benzylamino derivative (IX) obtained from I.

E. Benzylamino by Butylamine.—A solution of 500 mg. of the 7-benzylamino derivative[42] (IX) in 25 ml. of butylamine (distilled from and stored over calcium hydride) was heated for 6 hr. at the reflux temperature with the exclusion of atmospheric moisture. The residue obtained by evaporating the butylamine was heated in a sublimation apparatus at 125° (0.1 mm.). The principal (solid) fraction (175 mg.) was resublimed in the same way. A small, oily forerun was collected from both sublimations; paper chromatograms of the oily forerun from the second sublimation had a weak spot (in addition to a spot that was either IX or XII) corresponding to 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV). The residue (260 mg.) from the first sublimation was shown by its melting point (200–202°) and infrared spectrum to be the starting material (IX). Recrystallization of the second sublimate from aqueous ethanol gave 43 mg. (10%) of 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII), identical by melting point and infrared spectrum with specimens obtained from I, from XVI, and XIV.

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Thiadiazoles. IV. 4-Ureido- and 4-Amino-1,2,5-thiadiazole-3-carboxylic Acid Derivatives from [1,2,5]Thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-diones[1]

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4-Ureido-1,2,5-thiadiazole-3-carboxylic acid is formed from [1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (III) by the action of aqueous base, and *N*-methyl-4-(methylamino)-1,2,5-thiadiazole-3-carboxamide is similarly obtained from 4,6-dimethyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione. Either 4-ureido-, 4-(3-benzylureido)-, or 4-amino-*N*-benzyl-1,2,5-thiadiazole-3-carboxamide may be obtained by interaction of III and benzylamine. Similarly, these three types of thiadiazole derivatives were isolated, depending on reaction conditions, from reactions of III with other alkylamines or with hydrazine. The isolation of 4-ureido derivatives unsubstituted on the ureido group provides proof of one of two alternative courses for the formation of *o*-amino-carboxylic acid derivatives from fused pyrimidine heterocycles of type III. 4-Ureido-*N*-butyl-1,2,5-thiadiazole-3-carboxamide was shown to be easily hydrolyzed by base to 4-ureido-1,2,5-thiadiazole-3-carboxylic acid, and evidence that III is an intermediate in this facile hydrolysis is presented.

The formation of 1,2,5-thiadiazole derivatives by cleavage of the pyrimidine ring of [1,2,5]thiadiazolo-[3,4-*d*]pyrimidines bearing amino[2] or oxygen[3] functions at position 7 has been described previously. We have extended the investigation of this method for the preparation of 1,2,5-thiadiazoles by employing [1,2,5]thiadiazolo[3,4-*d*]pyrimidines having oxygen functions at both positions 5 and 7. The previously observed ease of nucleophilic attack on this thiadiazolopyrimidine ring system suggested that mild conditions might be employed to isolate intermediates that would provide proof for the course of ring opening of this type of disubstituted pyrimidine heterocycles.

Treatment of 4,6-dimethyl[1,2,5]thiadiazolo[3,4-*d*]-pyrimidine-5,7(4*H*,6*H*)-dione (I, 8-thiatheophylline) with 0.1 *N* potassium hydroxide solution gave *N*-methyl-4-(methylamino)-1,2,5-thiadiazole-3-carboxamide (II). This reaction is analogous to the cleavage of theophylline to *N*-methyl-5- (or 4-) (methylamino)-imidazole-4- (or 5-) carboxamide[4] and of 1,3-dimethylpteridine-2,4(1*H*,3*H*)-diones to *N*-methyl-3-(methylamino)pyrazinamides.[5] [1,2,5]Thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (III) was cleaved by boiling 1 *N* sodium hydroxide solution to a compound with the composition, after acidification, of 4-ureido-1,2,5-thiadiazole-3-carboxylic acid (IV). A second compound formed in small quantity from this reaction was subsequently identified as 4-amino-1,2,5-thiadiazole-3-carboxylic acid[3] (V). Reaction of III with concentrated aqueous ammonia in a sealed vessel at 100–110° afforded a better yield (91%) of the ureido acid (IV). Subsequently it was shown, as explained below, that III is cleaved by dilute aqueous base at room temperature. Pteridine-2,4(1*H*,3*H*)-diones have been cleaved by aqueous alkali at higher temperatures, usually 170° or above, to 3-aminopyrazinoic acids,[6] and *vic*-triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione has been cleaved to an amino amide, 5-amino-*vic*-triazole-4-carboxamide, under similar conditions by concentrated aqueous ammonia[7] and to the corresponding acid by refluxing aqueous alkali.[7a]

Alkaline degradation of certain purine-2,6(1*H*,3*H*)-diones with methyl groups on the ring-nitrogen atoms has been reported[8] to yield carbamic acid derivatives

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH-43-64-51, and by the C. F. Kettering Foundation.

(2) Y. F. Shealy and C. A. O'Dell, *J. Org. Chem.*, **29**, 2135 (1964).

(3) Y. F. Shealy and J. D. Clayton, *ibid.*, **28**, 1491 (1963).

(4) H. Auterhoff and M. F. Hebler, *Arzneimittel-Forsch.*, **9**, 621 (1959).

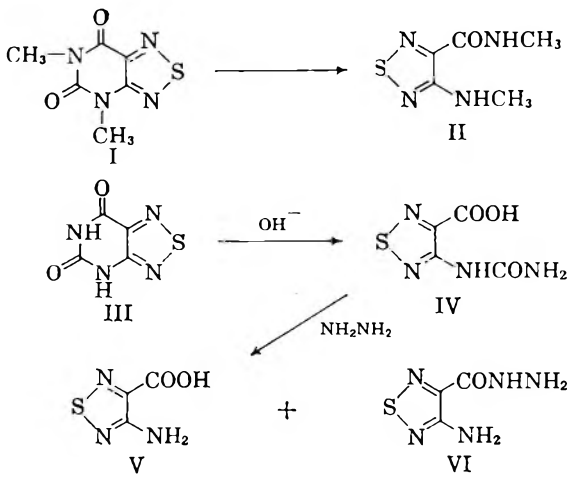
(5) (a) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956); (b) G. P. G. Dick, H. C. S. Wood, and W. R. Logan, *ibid.*, 2131 (1956); (c) E. C. Taylor, Jr., C. K. Cain, and H. M. Loux, *J. Am. Chem. Soc.*, **76**, 1874 (1954); (d) E. C. Taylor, Jr., H. M. Loux, E. A. Falco, and G. H. Hitchings, *ibid.*, **77**, 2243 (1955); (e) R. B. Angier and W. V. Curran, *J. Org. Chem.*, **27**, 892, 1366 (1962).

(6) J. Weijlard, M. Tishler, and A. E. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945); R. C. Ellingson, R. L. Henry, and F. G. McDonald, *ibid.*, **67**, 1711 (1945); *cf.* Ref. 5c and d.

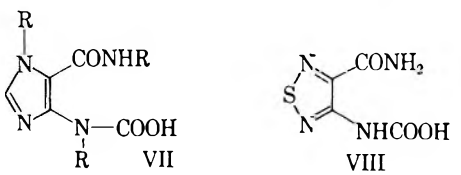
(7) (a) J. S. Webb and A. S. Tomcufcik, U. S. Patent 2,714,110. (July 26, 1955); (b) L. L. Bennett, Jr., and H. T. Baker, *J. Org. Chem.*, **22**, 707 (1957).

(8) R. Maly and R. Andreasch, *Monatsh. Chem.*, **4**, 369 (1883); E. Fischer and O. Bromberg, *Ber.*, **30**, 219 (1897); H. Biltz and H. Rakett, *ibid.*, **61**, 1409 (1928); A. Einhorn and F. Baumeister, *ibid.*, **31**, 1138 (1898).

(VII) sufficiently stable to be isolated; warming these imidazoles in water caused decarboxylation to the amino carboxamides. The carbamic acid VIII, which would have the same composition as the ureido acid (IV), is analogous to the imidazole derivatives



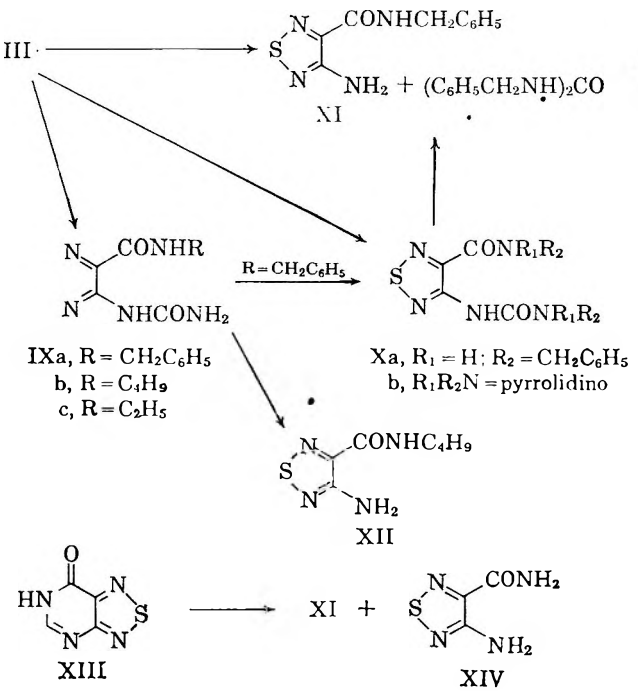
(VII). When the thiadiazole obtained from the alkaline cleavage of III was heated in boiling water for 2 hr., 86% of the compound was recovered. This result supports the ureido acid structure (IV) rather than the carbamic acid structure (VIII). In addition, treatment of the ureido acid with hydrazine afforded 4-



amino-1,2,5-thiadiazole-3-carboxylic acid (V), which must have been formed by cleavage of the ureido group, and 4-amino-1,2,5-thiadiazole-3-carboxylic acid hydrazide (VI), which could have arisen by reaction of hydrazine at both the ureido and the carboxyl carbon atoms.

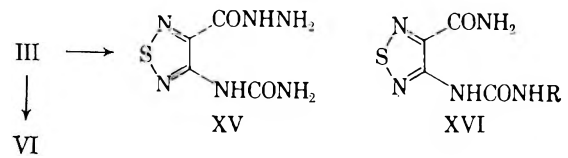
Three thiadiazoles were isolated, depending on reaction conditions, from reactions of III with benzylamine. Treatment of III with refluxing benzylamine for 6.5 hr. resulted in the formation of 4-amino-*N*-benzyl-1,2,5-thiadiazole-3-carboxamide (XI); the by-product, *N*,*N*′-dibenzylurea, was also isolated in high yield. *N*-Benzyl-4-(3-benzylureido)-1,2,5-thiadiazole-3-carboxamide (Xa) was isolated following interaction of III and refluxing benzylamine for 1 hr., and, finally, *N*-benzyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXa) was obtained by treating III with benzylamine at 75–80°. The reaction conditions that produced the 4-benzylureido derivative (Xa) from III also gave this compound from the 4-ureido derivative (IXa), and the 4-benzylureido derivative, in turn, yielded the 4-amino derivative (XI) under the conditions that effected the formation of XI from III.

4-Amino-*N*-benzyl-1,2,5-thiadiazole-3-carboxamide (XI) was identical with a specimen obtained by treating [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (XIII) with benzylamine. 4-Amino-1,2,5-thiadiazole-3-carboxamide (XIV) was isolated as a second product of the interaction of XIII and benzylamine; this reaction,



therefore, parallels reactions[3] of XIII with butylamine and with methylamine, both of which gave XIV plus the appropriate *N*-alkyl amide.

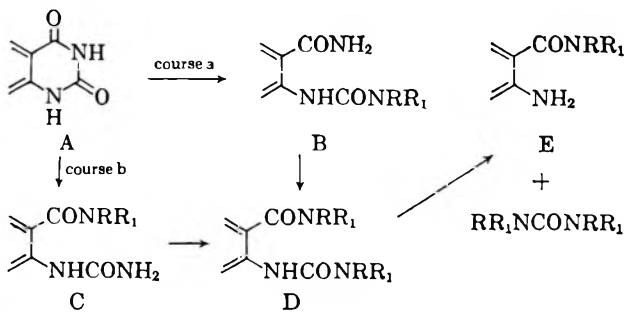
Other amino compounds gave results similar to those obtained with benzylamine. Reactions of III with boiling butylamine and with ethylamine at 50–60° afforded, respectively, *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXb) in 79% yield and *N*-ethyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXc) in 89% yield. Further treatment of the *N*-butyl derivative with butylamine under more strenuous conditions gave 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamide[3] (XII). Xb was isolated from a reaction of III with pyrrolidine; no attempt was made to obtain derivatives analogous to IX or XI. Either 4-ureido-1,2,5-thiadiazole-3-carboxylic acid hydrazide (XV) or 4-amino-1,2,5-thiadiazole-3-carboxylic acid hydrazide (VI) could be obtained from reactions of III with hydrazine. The ureido derivative was formed at 50–60°; the amino derivative was isolated by employing a higher temperature.



The ureido thiadiazoles obtained as initial products of ring opening of III were assigned structures IXa–c and XV, rather than the isomeric structures represented by XVI, by analogy to the structure of the ureido acid (IV). The formation of Xa and XII from the initially formed ureido thiadiazoles does not confirm structure IX because Xa might be formed by reaction of benzylamine at the amide group of XVI (R = $CH_2C_6H_5$) and XII might result from attack by butylamine at both the amide and the ureido groups of XVI (R = C_4H_9). Confirmation of the assigned structures (IX and XV) was obtained by preparing a representative of XVI. 4-(3-Ethylureido)-1,2,5-

thiadiazole-3-carboxamide (XVI, R = C_2H_5), prepared from the amino amide XIV and refluxing ethyl isocyanate, was shown to be different from the product (IXc) obtained from III and ethylamine.

The action of amines on pteridine-2,4(1*H*,3*H*)-diones gave either 3-aminopyrazinamides (pyrazine corresponding to E) or 3-(3-substituted ureido)pyrazinamides (pyrazine corresponding to D), and further treatment of the 3-substituted ureido derivatives with the appropriate amine gave the amino derivatives.[9] Taylor[9a] proposed two pathways, designated as courses a and b, between pteridine-2,4(1*H*,2*H*)-diones and 3-aminopyrazinamides and cited evidence in support of course b, although intermediates of type C were not isolated and could not be prepared.[10] The isolation of 4-ureido-1,2,5-thiadiazole-3-carboxylic acid (IV) and its derivatives (IXa–c and XV) represents the isolation of intermediates of type C; the sequence III → IXa → Xa → XI, found in the reactions of III with benzylamine, exemplifies course b.



It was observed that *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXb) is unstable in dilute aqueous base. The product isolated, in 90% yield, from a solution of IXb in 0.1 *N* sodium hydroxide at room temperature was 4-ureido-1,2,5-thiadiazole-3-carboxylic acid (IV), but closer examination of this facile conversion revealed that it is not a simple hydrolysis of an *N*-alkylamide to a carboxylic acid. Changes in the ultraviolet absorption of a 0.1 *N* sodium hydroxide solution of IXb indicated that it cyclized to III with the elimination of butylamine and that IV then formed from III. (See the Experimental for details.) A re-examination of the reaction of III with aqueous base under similar conditions showed, as mentioned above, that IV is formed in high yield at room temperature. Finally, additional evidence for this course was obtained by quenching the reaction by acidifying a 0.1 *N* sodium hydroxide solution of IXb and lyophilizing. Paper chromatograms of the crude product obtained after 0.5 hr. showed spots with R_f values, in four solvent systems, corresponding to III and IXb. Quenching after 70 min. gave a mixture in which III, IXb, and a small amount of IV were detected chromatographically. From this mixture a specimen of III was isolated and identified by its infrared spectrum.

Experimental

Melting temperatures, infrared and ultraviolet spectra, and paper chromatographic data were determined by methods outlined previously.[3] Principal infrared absorption bands are listed only in the 1700–1400- and 900–650-cm.$^{-1}$ regions. In contrast to the usual blue or violet fluorescence of spots of 4-amino-1,2,5-thiadiazole-3-carboxylic acid derivatives[3] and of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines,[11] all of the ureido carboxamides (IX, X, and XVI) appeared on paper chromatograms as yellow or orange fluorescent spots under 254-mμ light, the ureido acid (IV) as bluish yellow spots, and the ureido acid hydrazide (XV) as a dull reddish orange fluorescence. These ureido derivatives were not detectable with 365-mμ light. XV was apparently degraded partly to blue fluorescent materials in the 2-propanol–ammonia and the acetate buffer (pH 6.7) solvent systems.

***N*-Methyl-4-(methylamino)-1,2,5-thiadiazole-3-carboxamide (II).**—A mixture of 396 mg. of 4,6-dimethyl[1,2,5]thiadiazolo-[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (I) and 40 ml. of 0.1 *N* potassium hydroxide solution was heated in a boiling water bath for 3 hr. Chilling the reaction mixture at 5° overnight produced a crop of 145 mg. of white needles: m.p. 96° (with sublimation). A second crop of 58 mg. (m.p. 95°) of product (total yield 59%) was obtained by concentrating the filtrate. The compound may be purified by recrystallization from water or by sublimation: m.p. 96° (with sublimation). λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 219 (11.9), 345 (5.9) in 0.1 *N* hydrochloric acid and at pH 7; 344 (5.9) in 0.1 *N* sodium hydroxide. ν in cm.$^{-1}$ was 1670 s, 1570 ms, 1550 s, 1480 m, 1415 ms; 895 m, 855 m, 810 ms, 795 mw, 750 w.

Anal. Calcd. for $C_5H_8N_4OS$: C, 34.87; H, 4.68; N, 32.54; S, 18.62. Found: C, 35.12; H, 4.83; N, 32.49; S, 18.66.

4-Ureido-1,2,5-thiadiazole-3-carboxylic Acid (IV).—In initial experiments on the cleavage of [1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione[11] (III) with aqueous base, reaction temperatures near 100° were applied. From a reaction of III with 1 *N* sodium hydroxide in a boiling water bath for 2 hr., a 41% yield of IV was obtained. A second crop of solid (18% yield) from this reaction was shown by its infrared and ultraviolet spectra to be principally 4-amino-1,2,5-thiadiazole-3-carboxylic acid[3] (V). Heating III and 15 *N* aqueous ammonia in a bomb at 100–110° for 5 hr. yielded 91% of the calculated amount of IV. After evidence was obtained, as described below, that the mild alkaline hydrolysis of *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXb) proceeds by way of III, the following experiment was performed.

A solution of 340 mg. (2 mmoles) of III in 125 ml. of 0.1 *N* sodium hydroxide was stirred at 23–24° for 8.5 hr. and then acidified with 7 ml. of 2 *N* hydrochloric acid. The precipitated solid was collected by filtration, washed twice with water, and dried *in vacuo* at 78° over phosphorus pentoxide: yield 327 mg. (87%), m.p. 234–235° dec. A sample for analysis was recrystallized from a 1:1 mixture of dimethylformamide and water. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 220 (sh), 231 (12.3), 302 (7.2) in 0.1 *N* hydrochloric acid; 224 (13.6), 297 (8.2) at pH 7 and in 0.1 *N* sodium hydroxide. ν in cm.$^{-1}$ was 1680 s, 1640 s, 1560 s, 1530 sh, 1505 s, 1450 m, 1400 ms; 860 m, 815 m, 800 mw, 760 mw, 730 ms, 700 w, 675 w.

Anal. Calcd. for $C_4H_4N_4O_3S$: C, 25.52; H, 2.14; N, 29.78; S, 17.04. Found: C, 25.74; H, 2.21; N, 29.59; S, 16.75.

A solution of the ureido acid (IV) in water was boiled under reflux for 2 hr. in order to determine whether decarboxylation would occur. The ureido acid was recovered in 86% yield and identified by its infrared and ultraviolet spectra.

Cleavage of the Ureido Group of IV with Hydrazine.—A solution of 565 mg. of 4-ureido-1,2,5-thiadiazole-3-carboxylic acid (IV) and 10 ml. of hydrazine was heated at the reflux temperature for 5.25 hr. Water (10 ml.) was added to the solid remaining after the hydrazine had been evaporated *in vacuo*. The insoluble portion was separated by filtration, washed with water, and dried at 78° *in vacuo*: wt. 190 mg. (40% yield). The ultraviolet and infrared spectra and the melting point of this material were the same as those of 4-amino-1,2,5-thiadiazole-3-carboxylic acid

(9) (a) E. C. Taylor, Jr., *J. Am. Chem. Soc.*, **74**, 1651 (1952); (b) E. C. Taylor, Jr., J. A. Carbon, and D. R. Hoff, *ibid.*, **75**, 1904 (1953); (c) G. P. G. Dick, D. Livingston, and H. C. S. Wood, *J. Chem. Soc.*, 3730 (1958).

(10) Under the conditions used to obtain certain pyrazines of types D and E from pteridinediones (A), a 3-aminopyrazinamide[9a] (E, R = R_1 = H) and an *N*-methyl-3-(methylamino)pyrazinamide[9c] failed to undergo amine exchange at the amide group. These failures have been cited[9a,c] as evidence to exclude course a, but this type of evidence is not unequivocal. Amine exchange at the amide group of an *o*-aminocarboxamide (E) may require more drastic conditions, because of the electron-donating *o*-amino group, than the exchange represented by B → D.

(11) Y. F. Shealy, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.*, **27**, 2154 (1962).

hydrazide (VI) obtained from III (below) and from [1,2,5-thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one.[3]

The aqueous filtrate was acidified to pH 1 and evaporated to a solid residue. A 10-ml. water solution of this residue, after filtration and chilling, deposited 134 mg. (31%) of crystals that were identified by their infrared and ultraviolet spectra and by paper chromatography as 4-amino-1,2,5-thiadiazole-3-carboxylic acid[3] (V).

N-**Benzyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXa).**—A solution consisting of 5.10 g. of [1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7-(4*H*,6*H*)-dione and 200 ml. of benzylamine (distilled from and dried over calcium hydride) was heated at 75–80° for 4 hr. The starting material and the apparatus were thoroughly dried before being used, and the reaction mixture was protected from atmospheric moisture with a tube of calcium sulfate. The solid remaining after the benzylamine had been evaporated *in vacuo* was slurried with ethanol (100 ml.), removed by filtration, washed with ethanol, and dried *in vacuo*: wt. 7.92 g. Although the melting point (177–179°) indicated that this material was essentially pure, paper chromatograms showed the presence of some of the starting material. Paper chromatograms of the residual oil from the filtrate showed that it contained III, IXa, and Xa. The crude solid was recrystallized twice from ethanol, an ethanol-insoluble fraction being removed each time. The yield of purified IXa was 4.35 g. (52%). A sample for analysis was recrystallized from benzene: m.p. 179°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 233 (16.0), 305 (8.7) in 0.1 *N* hydrochloric acid; 233 (16.7), 304 (8.8) at pH 7. $\bar{\nu}$ in cm.$^{-1}$ was 1700 s, 1640 s, 1575 ms, 1540 ms, 1520 m, 1490 m, 1450 w, 1435 m, 1400 ms; 840 m, 815 m, 795 w, 755 ms, 725 m, 700 ms, 650 w.

Anal. Calcd. for $C_{11}H_{11}N_5O_2S$: C, 47.64; H, 4.00; N, 25.26; S, 11.56. Found: C, 47.88; H, 4.09; N, 25.17; S, 11.7.

N-**Benzyl-4-(3-benzylureido)-1,2,5-thiadiazole-3-carboxamide (Xa).** A. **From III.**—The procedure used in the preparation of IXa was duplicated with 510 mg. of III except that the reaction time was 1 hr. and the reaction temperature was that of the refluxing solution. The sirup remaining from the evaporation of the solvent was slurried with toluene, and a crop of 656 mg. of crystals was filtered from the chilled mixture and washed with hexane. Trituration of the syrupy residue from the filtrate with ethanol yielded a second crop of 115 mg. of crystals. Two recrystallizations of the combined crops from ethanol gave 340 mg. (31%): m.p. 147–148°. A yield of 51% of analytically pure Xa was obtained, after several recrystallizations, from a larger scale preparation in which no special precautions, other than the use of freshly distilled benzylamine, were taken to exclude moisture. Specimens of Xa recrystallized from ethanol–hexane mixtures were observed to melt at 143–144°; the molten material resolidified and remelted at 147–148° when seeded with the higher melting crystals. Solid-state infrared spectra of the two crystal forms were similar although they displayed some differences. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 232 (20.2), 311 (8.4) in ethanol. $\bar{\nu}$ in cm.$^{-1}$ (higher melting form) was 1680 s, 1660 sh, 1640 vs, 1590 w, 1560 s, 1515 s, 1500 w, 1455 m, 1440 w, 1410 m; 890 w, 850 w, 825 m, 800 w, 765 w, 740 m, 720 m, 700 ms, 670 w.

Anal. Calcd. for $C_{18}H_{17}N_5O_2S$: C, 58.83; H, 4.67; N, 19.06; S, 8.73. Found: C, 58.92; H, 4.49; N, 19.36; S, 8.74.

B. **From IXa.**—Treatment of 555 mg. of *N*-benzyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXa) with benzylamine by the same procedure gave, after purification, 160 mg. (22%) of Xa. The infrared spectrum and melting point behavior (143–144° and 147–148°) were the same as those of specimens obtained from III.

4-Amino-*N*-benzyl-1,2,5-thiadiazole-3-carboxamide (XI). A. **From III.**—A solution consisting of 1.02 g. of the 5,7(4*H*,6*H*)-dione (III) and 20 ml. of benzylamine (redistilled and dried over calcium hydride) was heated at the reflux temperature for 6.5 hr. The reactants and apparatus were thoroughly dried prior to being used, and the reaction mixture was protected from atmospheric moisture with a tube of calcium sulfate. The reaction solution was diluted with 20 ml. of toluene, chilled in an ice bath, and filtered to remove 1.23 g. of white crystals: m.p. 167–172°. A second crop of 152 mg. (m.p. 165–170°) was obtained by further chilling the combined filtrate and toluene washings (5 ml.). The two crops of crystals were crude *N*,*N*′-dibenzylurea (total yield 95%). A sample that gave satisfactory analytical data for carbon, hydrogen, and nitrogen and that melted at 171.5–172° was obtained by recrystallizing a specimen of crude material from 50% aqueous ethanol.

The filtrate, combined with the solvent washings, from the second crop of dibenzylurea was evaporated *in vacuo* to a sirup. Crude XI (959 mg., m.p. 76–81°) crystallized in two crops from a solution of the syrup in 2 ml. of toluene and 8 ml. of cyclohexane and was recrystallized from an isopentyl acetate–cyclohexane (1:3) solution. A crop of 409 mg. of crystals (m.p. 79–81°) was obtained, and recrystallization of the filtrate residue from an ethyl acetate–cyclohexane solution furnished an additional 180 mg. (m.p. 80–82°). The crystals from a second isopentyl acetate–cyclohexane recrystallization of the combined crops were dissolved in ethyl acetate and cyclohexane, a small crop of amorphous solid was filtered from the cooled solution, and the residue from this filtrate was recrystallized from ethyl acetate–cyclohexane (1:10). The white crystals melted at 80–81°. (Difficulties were experienced in raising the melting point of crude XI to this value regardless of the starting material used.) λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 225 (slight shoulder), 326 (7.2) in 0.1 *N* hydrochloric acid, pH 7 phosphate buffer, and 0.1 *N* sodium hydroxide solution. $\bar{\nu}$ in cm.$^{-1}$ was 1660 s, 1600 s, 1530 s, 1450 m, 1420 mw; 860 m, 810 m, 800 w, 755 m, 730 m, 720 m, 695 m, 670 w.

Anal. Calcd. for $C_{10}H_{10}N_4OS$: C, 51.25; H, 4.30; N, 23.92; S, 13.69. Found: C, 51.60; H, 4.37; N, 23.51; S, 13.7.

B. **From Xa.**—The procedure used in the conversion of III to XI was applied to a solution of 735 mg. of *N*-benzyl-4-(3-benzylureido)-1,2,5-thiadiazole-3-carboxamide (Xa) in 15 ml. of dry benzylamine. The benzylamine was evaporated *in vacuo* until crystallization began, toluene was added, and the white crystalline *N*,*N*′-dibenzylurea (85% yield) was removed by filtration. The yellow oil obtained by evaporating the filtrate was dissolved in hot toluene, the solution was diluted with cyclohexane and seeded with XI, and crystals (278 mg., m.p. 75–80°) were filtered from the chilled mixture and recrystallized from cyclohexane: m.p. 79°. The infrared and ultraviolet spectra were identical with those of the analytical sample of XI prepared from III.

The Reaction of [1,2,5]Thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (XIII) with Benzylamine.—A solution of 925 mg. of XIII and 15 ml. of redistilled benzylamine (dried with calcium hydride) was heated at 80° for 3.5 hr. and then concentrated *in vacuo* to a syrup. Trituration of the syrup with 8 ml. of xylene caused the crystallization of 214 mg. (25%) of crude **4-amino-1,2,5-thiadiazole-3-carboxamide (XIV)**: m.p. 165–168°. Recrystallization from ethanol–hexane (1:1) gave crystals with melting point (170°) and infrared spectrum identical with specimens obtained previously.[3]

The xylene filtrate and washings from the crude XIV were concentrated to a syrup. Dissolution of this material in a mixture of 2 ml. of toluene, 2 ml. of ethyl acetate, and 8 ml. of cyclohexane and seeding of the solution with the product obtained from III gave 512 mg. (36%) of crude **4-amino-*N*-benzyl-1,2,5-thiadiazole-3-carboxamide** (m.p. 70–75°). Recrystallization of this material from ethyl acetate–cyclohexane solution and from a large volume of hexane gave white crystals (m.p. 77–79°) having an infrared spectrum identical with that of the pure specimen of XI obtained from III.

***N*-Butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXb).**—A mixture of 1.02 g. of III and 40 ml. of redistilled *n*-butylamine was heated at the reflux temperature for 200 min. The reaction mixture became homogeneous during the heating period. Evaporation of the butylamine left a crystalline solid that was recrystallized from aqueous ethanol: yield 1.15 g. (79%), m.p. 151°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 217 (sh), 232 (14.9), 304 (8.3) in 0.1 *N* hydrochloric acid and at pH 7. $\bar{\nu}$ in cm.$^{-1}$ was 1695 s, 1650 s, 1605 ms, 1550 s, 1520 sh, 1500 m, 1460 w, 1400 ms; 860 m, 830 m, 790 m, 740 w, 710 w, 650 w.

Anal. Calcd. for $C_8H_{11}N_5O_2S$: C, 39.49; H, 5.38; N, 28.78; S, 13.18. Found: C, 39.56; H, 5.39; N, 28.79; S, 13.39.

4-Amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamide (XII) from IXb.—A solution of 500 mg. of *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXb) and 50 ml. of redistilled butylamine was heated in a stainless steel bomb at 200° for 14 hr. Concentration of the reaction mixture gave a yellow oil that crystallized when it was chilled. The crystalline residue, which was probably a mixture of XII and the urea by-product, was slurried with 15 ml. of water, collected by filtration, and dried *in vacuo* at 56°: wt. 660 mg., m.p. 63–77°. Two recrystallizations from hexane gave 226 mg. (55%) of crystals identical by melting point (82–83°, oil bath), mixture melting point, and infrared and ultraviolet spectra with 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carbox-

amide[3] obtained from [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one.

***N*-Ethyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXc).**—A suspension of 510 mg. of III in 40 ml. of anhydrous 1-butanol and 30 ml. of commercial, anhydrous, liquid ethylamine was heated at 50–60° for 37.5 hr. The mixture was homogeneous after about 28 hr. A condenser supplied with solid carbon dioxide was used to contain the ethylamine in the reaction mixture. The reaction mixture, which deposited white needles upon cooling to room temperature, was reduced in volume to 15 ml. *in vacuo* and stored at 5°. The crystals were collected by filtration, washed with 10 ml. of 9:1 hexane–ethanol, and dried *in vacuo* at 56°: wt. 578 mg. (89%), m.p. 192–194°. Two recrystallizations from ethanol gave 367 mg. (57%), m.p. 196°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 218 (sh), 232 (14.6), 304 (8.1) in 0.1 *N* hydrochloric acid and at pH 7. $\bar{\nu}$ in cm.$^{-1}$ was 1690 ms, 1640 s, 1610 s, 1545 ms, 1510 ms, 1440 m, 1400 ms; 890 w, 860 m, 820 m, 800 w, 775 mw, 740 mw, 730 mw, 695 w, 670 w.

Anal. Calcd. for $C_6H_9N_5O_2S$: C, 33.48; H, 4.22; N, 32.54; S, 14.90. Found: C, 33.48; H, 4.39; N, 32.62; S, 14.8.

***N*-(4-Pyrrolidinocarbonyl-1,2,5-thiadiazolyl)-1-pyrrolidinecarboxamide (Xb)** was isolated from a reaction of III with pyrrolidine at 75–80° for 10 days and was obtained pure in 18% yield by recrystallization from cyclohexane: m.p. 150–151°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 242 (14.4), 298 (6.9) in 0.1 *N* hydrochloric acid and at pH 7. $\bar{\nu}$ in cm.$^{-1}$ was 1690 s, 1620 ms, 1540 s, 1490 w, 1455 ms; 885 w, 850 w, 820 m, 790 m, 750 w, 730 w, 715 m, 680 w.

Anal. Calcd. for $C_{12}H_{17}N_5O_2S$: C, 48.79; H, 5.80; N, 23.71; S, 10.85. Found: C, 48.83; H, 5.80; N, 23.72; S, 10.5.

4-Ureido-1,2,5-thiadiazole-3-carboxylic Acid Hydrazide (XV).—A solution of 5.1 g. of the 5,7(4*H*,6*H*)-dione (III) in 150 ml. of hydrazine was heated at 50° for 20 hr. Evaporation of the hydrazine *in vacuo* at 30–35° left a solid that was triturated with ethanol and then recrystallized from acetic acid. The fine white crystals were collected in two crops totaling 3.11 g. (51%), m.p. 245° dec. A specimen for analysis was recrystallized from water: m.p. 246–247° dec. (The decomposition temperature was variable; the readings reported here were made by sprinkling a specimen along the surface of a Kofler Heizbank melting point apparatus.). λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 235 (14.7), 306 (7.9) in 0.1 *N* hydrochloric acid; 232 (13.5), 305 (7.9) at pH 7; 235 (slight shoulder), 315 (7.6) in 0.1 *N* sodium hydroxide. $\bar{\nu}$ in cm.$^{-1}$ was 1720 s, 1680 ms, 1630 s, 1600 ms, 1510 s, 1490 m; 870 ms, 830 m, 800 m, 775 m, 720 w, 690 m.

Anal. Calcd. for $C_4H_6N_6O_2S$: C, 23.76; H, 2.99; N, 41.57; S, 15.86. Found: C, 23.74; H, 2.92; N, 41.39; S, 15.95.

4-Amino-1,2,5-thiadiazole-3-carboxylic Acid Hydrazide (VI).—A solution of 5.10 g. of the 5,7(4*H*,6*H*)-dione and 30 ml. of hydrazine was heated at 90° for 3 hr. and then diluted with 50 ml. of warm water. A crystalline solid was removed by filtration, washed with water, and dried *in vacuo* at 56°: wt. 4.31 g., m.p. 202–212°. Sublimation of the crude product at 0.3 mm. (130–150°) gave 2.61 g. (55%) of white sublimate: m.p. 204–206°. The infrared and ultraviolet spectra were identical with those of VI obtained from [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7-(6*H*)-one.[3]

4-(3-Ethylureido)-1,2,5-thiadiazole-3-carboxamide (XVI, R = C_2H_5).—A suspension of 288 mg. of 4-amino-1,2,5-thiadiazole-3-carboxamide[3] (XIV) in 15 ml. of ethyl isocyanate was heated, with stirring, for 66.5 hr. at the reflux temperature and then filtered, and the solid residue was washed with toluene. Recrystallization of the solid (340 mg.) from ethyl acetate gave 244 mg. (57%) of white needles; the melting point (192°) was unchanged after a second recrystallization. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 221 (sh), 234 (16.6), 307 (7.4) in 0.1 *N* hydrochloric acid and at pH 7; unstable in 0.1 *N* sodium hydroxide. $\bar{\nu}$ in cm.$^{-1}$ was 1690 m, 1660 vs, 1560 ms, 1515 s, 1450 m; 845 m, 820 m, 810 sh, 780 w, 755 mw, 705 m, 655 w.

Anal. Calcd. for $C_6H_9N_5O_2S$: C, 33.48; H, 4.22; N, 32.54; S, 14.90. Found: C, 33.53; H, 4.34; N, 32.62; S, 15.1.

The melting point of a mixture of this compound with the product (IXc), of the same composition, obtained from III was depressed (160–164°), and the infrared spectra of the two compounds differed.

Basic Hydrolysis of *N*-Butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXb).—An attempt to determine the ultraviolet spectrum of IXb in 0.1 *N* sodium hydroxide solution revealed that it was unstable in base. A solution of 243 mg. (1 mmole) of *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide in 5 ml. of ethanol and 25 ml. of 0.12 *N* aqueous sodium hydroxide (3 mmoles) was then stirred at room temperature for 22 hr. The solution was acidified to pH 1 with 1 *N* hydrochloric acid and concentrated *in vacuo* to a volume of 10 ml. The white crystalline precipitate was collected by filtration, washed with 5 ml. of water, and dried *in vacuo* at 56° over phosphorus pentoxide: yield 169 mg. (90%), m.p. 231–233° dec. Ultraviolet spectra at pH 1, 7, and 13, R_f values in four solvent systems, and the infrared spectrum were identical with those of the ureido acid (IV) obtained from the 5,7(4*H*,6*H*)-dione (III).

Further examination of the behavior of IXb in base indicated that the facile formation of IV was not a simple hydrolysis of an amide to an acid. The spectrum of a freshly prepared solution of IXb (4.4×10^{-5} *M*) in 0.1 *N* sodium hydroxide showed absorption maxima at 253 and at 337 and a minimum at 287 mμ. In 0.1 *N* sodium hydroxide the spectrum of the ureido acid (IV) has maxima at 224 and at 297 and a minimum at 253 mμ; and the spectrum of the 5,7(4*H*,6*H*)-dione (III) has maxima at 226, 283, and 356 and minima at 257 and 308 mμ. Observation of the spectral changes occurring at room temperature in a 0.1 *N* sodium hydroxide solution of IXb showed that, as the maximum at 253 mμ decreased in intensity, a shoulder near 240 mμ shifted toward and then appeared as a maximum at 225 mμ. This latter maximum might have been due to either III or IV, but subsequent intensity changes, correlated with changes in the 290–360-mμ region, suggested that initially it was due chiefly to the 5,7(4*H*,6*H*)-dione (III). Simultaneously, the long-wave-length maximum at 337 shifted to a maximum at 355 mμ, ascribable to the 5,7(4*H*,6*H*)-dione, and a new maximum began to appear at 295–300 mμ. After approximately 0.75 hr., maxima or shoulders near 225, 250–255, 295–300, and 350–355 mμ were consistent with the postulate that IXb, III, and IV were present; and after approximately 1.5 hr. the observed spectrum could be explained by assuming that only III and the ureido acid were present. As the maximum at 355 mμ decreased, the maximum at 297 mμ increased, and the spectrum was essentially that of the ureido acid (IV) after 7–8 hr.

These spectral changes strongly suggested that the amide (IXb) initially cyclizes in base to the 5,7(4*H*,6*H*)-dione (III) and that the ureido acid (IV) is then formed from III. Further evidence for this course was obtained from the following experiments. After a solution of *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (1 mmole) in 0.1 *N* sodium hydroxide (3 mmoles) had stood at 24° for 30 min., it was acidified to pH 2 and the mixture was lyophilized. Paper chromatograms of the residue developed in four solvent systems showed two spots corresponding to IXb and III. The total residue obtained in the same manner from an identical solution after 70 min. at 28° showed a small amount of the ureido acid (IV) on chromatograms in addition to the strongly fluorescing spots of IXb and III. The organic components were leached from this residue with acetonitrile, and a small amount of III was isolated by precipitating its potassium salt from an ethanol solution and acidifying an aqueous solution of the salt. The infrared spectrum of the isolated specimen was identical with that of an authentic specimen of III. In addition, it was shown that the higher temperatures previously used to prepare IV from III were not required. An experiment, already described above, showed that IV could be obtained from III under conditions similar to those prevailing during the spectroscopically observed formation of IV from *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide. (The proportion of base was much higher in the spectroscopically observed formation of IV from IXb than in the other experiments in which IV was formed from III or IXb.)

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4-Thiazoline-2-thiones. I. The Structure of Intermediate 4-Hydoxythiazolidine-2-thiones

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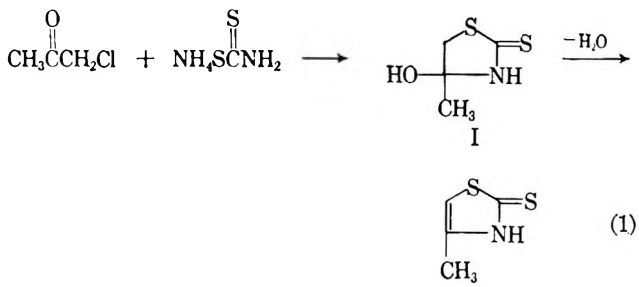
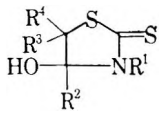
Intermediate products of the reaction of ammonium dithiocarbamate and α-halo aldehydes or ketones, formerly presumed to be substituted dithiocarbamates, have been determined to be 4-hydroxythiazolidine-2-thiones. They are compared with 4-hydroxy-3-methylthiazolidine-2-thiones obtained from reaction of α-halo ketones, carbon disulfide, and methylamine and with substituted dithiocarbamates obtained from the reaction of α-halo ketones, carbon disulfide, and dimethylamine.

A general method for preparing 4-thiazoline-2-thiones employs the reaction of ammonium dithiocarbamate and α-halo aldehydes or ketones. When the reaction is conducted for a short time with cooling, intermediate products can be isolated. These intermediates have been presumed to be acyclic.[1,2] They are referred to as substituted dithiocarbamates or dithiourethanes, which cyclize readily on standing or on being heated to form 4-thiazoline-2-thiones. Substituted dithiocarbamates have been described from the reactions of ammonium dithiocarbamate and chloroacetaldehyde,[3] chloroacetone,[4] ethyl α- and γ-chloroacetoacetate,[4-6] and phenacyl bromide.[5,5] Results of instrumental analyses and chemical evidence now reveal that these intermediates are actually 4-hydroxythiazolidine-2-thiones. The latter yield 4-thiazoline-2-thiones by dehydration.

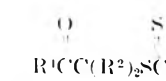


(1)

Determination of which of the two types of intermediates is isolated can be aided by comparison of the prepared series of 4-hydroxythiazolidine-2-thiones and substituted dithiocarbamates, I–VI.



I, $R^1 = R^3 = R^4 = H$; $R^2 = CH_3$
II, $R^1 = R^2 = CH_3$; $R^3 = R^4 = H$
IV, $R^1 = H$; $R^2 = R^3 = R^4 = CH_3$
V, $R^1 = R^2 = R^3 = R^4 = CH_3$
VII, $R^1 = R^3 = R^4 = H$; $R^2 = C_6H_5$
VIII, $R^1 = CH_3$; $R^2 = C_6H_5$; $R^3 = R^4 = H$
X, $R^1 = H$; $R^2 = C_6H_5$; $R^3 = R^4 = CH_3$
XI, $R^1 = CH_3$; $R^2 = C_6H_5$; $R^3 = R^4 = CH_3$
XIII, $R^1 = R^2 = R^3 = R^4 = H$
XIV, $R^1 = R^3 = H$; $R^2 = CH_3$; $R^4 = CO_2C_2H_5$
XV, $R^1 = R^3 = R^4 = H$; $R^2 = CH_2CO_2C_2H_5$



III, $R^1 = CH_3$; $R^2 = H$
VI, $R^1 = R^2 = CH_3$
IX, $R^1 = C_6H_5$; $R^2 = H$
XII, $R^1 = C_6H_5$; $R^2 = CH_3$

The infrared absorption spectrum of the intermediate isolated from reaction of ammonium dithiocarbamate and chloroacetone does not support a dithiocarbamate structure. Absorption bands expected in the 5.8- and 8-μ regions attributed to a ketone C=O group are missing. A band near 3.00 μ indicates the presence of the OH group, however, required by structure I. Disappearance of the C=O band of an intermediate dithiocarbamate was assumed earlier to be due to an enolized form or an overlapping with a C=N band, created in double enolization involving the methylene and amino groups. Hirano has suggested, based on infrared analysis, that intermediates formed from the reaction of α-halo ketones, primary amines, and carbon disulfide are 3-alkyl-4-hydroxythiazolidine-2-thiones rather than dithiocarbamates.[7] The intermediate isolated from reaction of chloroacetone, methylamine, and carbon disulfide fails to show C=O, NH stretching, and NHC=S out-of-plane deformation bands expected of a dithiocarbamate, but the OH band required by structure II is present. Use of dimethylamine in the reaction forms a dithiocarbamate (III) which cannot cyclize to a thiazolidine. Strong bands in the infrared spectrum of this substance attributed to a C=O group are apparent. The ultraviolet spectrum of the dithiocarbamate III has two major peaks at 246 and 274 mμ, contrasting with that of II or that of thiazolidine-2-thione which are similar and have one peak at 273 mμ. Results of examination of polarographic data, additionally, are consistent with the presence of a reducible C=O in compound III, and the absence of C=O in compound II. The dithiocarbamate III forms an oxime and a 2,4-dinitrophenylhydrazone, but compounds I and II do not. For further comparison, the series includes the corresponding reaction products, IV, V, and VI, derived from 3-bromo-3-methyl-2-butanone. Substitution of the methylene group of a dithiocarbamate by methyl groups would preclude cyclization *via* enolization.[2] The infrared spectra of 5,5-dimethylthiazolidines (IV and V) show OH absorption, but not C=O absorption which is shown by VI. The NH bands are apparent as required by IV. They are absent in V but would be required by a dithiocarbamate.

A related series of compounds bearing phenyl substitution is obtained by similar reactions of phenacyl bromide and α-bromoisobutyrophenone. From an

(1) J. M. Sprague and A. H. Lane, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, Chapter 8, p. 558.

(2) R. H. Wiley, *Org. Reactions*, **6**, 375 (1951).

(3) R. A. Mathes and A. J. Beber, *J. Am. Chem. Soc.*, **70**, 1451 (1948).

(4) T. G. Levi, *Gazz. chim. ital.*, **61**, 719 (1931).

(5) I. Ubaldini and A. Fiorenza, *ibid.*, **73**, 169 (1943).

(6) J. J. D'Amico and M. W. Harman, *J. Am. Chem. Soc.*, **77**, 476 (1955).

(7) H. Hirano, *J. Pharm. Soc. Japan*, **75**, 244 (1955); *Chem. Abstr.*, **50**, 1850^b (1956).

TABLE I

PREPARATIVE DATA OF 4-HYDROXYTHIAZOLIDINE-2-THIONES AND SUBSTITUTED DITHIOCARBAMATES

No.	Yield,[c] %	M.p., °C.[b]	Recrystn. solvent[c]	Formula	Calcd., % C	H	N	S	Found, % C	H	N	S
I	7	104 (80–82)[d]	Ether	$C_4H_7NOS_2$	32.2	4.7	9.4	43.0	32.0	4.6	9.2	43.1
II	84	83	Ether–ligroin	$C_5H_9NOS_2$	36.8	5.6	8.6	39.3	37.0	5.7	8.3	39.0
III	97	53	Methanol–water	$C_6H_{11}NOS_2$	40.6	6.3	7.9	36.2	40.3	6.1	7.7	36.4
III oxime		101–102	Methylene chloride–ligroin	$C_6H_{12}N_2OS_2$			14.6				14.2	
III 2,4-DNP		157.5	Ethanol	$C_{12}H_{15}N_5O_4S_2$			19.6				19.5	
IV	86	117	Benzene	$C_6H_{11}NOS_2$	40.6	6.3	7.9	36.2	40.7	6.1	7.8	35.9
V	96	64	Methanol–water	$C_7H_{13}NOS_2$	43.9	6.9	7.3	33.5	44.2	7.0	7.4	33.9
VI	97	63–64	Ethanol	$C_{11}H_{13}NOS_2$	55.2	5.5	5.9	26.8	54.8	5.7	5.6	27.0
VII	10	101–102.5 (100–103)[d]										
VIII	97	132–133	Methylene chloride–ligroin	$C_{10}H_{10}NOS_2$	53.5	4.5	6.3	28.6	53.3	4.9	5.9	28.8
IX	97	111–112	Ethanol	$C_{11}H_{13}NOS_2$	55.2	5.5	5.9	26.8	54.8	5.7	5.6	27.0
IX oxime		113–114	Methylene chloride–ligroin	$C_{11}H_{14}N_2OS_2$			11.0				10.7	
IX 2,4-DNP		199–200	Ethyl acetate	$C_{17}H_{17}N_5O_4S_2$			16.7				16.4	
X	97	154	Methanol	$C_{11}H_{13}NOS_2$	55.2	5.5	5.9	26.8	55.5	5.5	5.7	26.9
XI	75[e]	184	Methanol	$C_{12}H_{15}NOS_2$	56.9	6.0	5.5	25.4	56.9	6.2	5.4	25.6
XII	91	114	Ether	$C_{13}H_{17}NOS_2$	58.4	6.4	5.2	24.0	58.3	6.4	5.1	23.7
XIII	20	112 (110)[f]										
XIV[g]	83	128	Ether	$C_7H_{11}NO_3S_2$	38.0	5.0	6.3	29.0	37.9	4.8	6.2	28.8
XV	80	90 (74–75)[h]	Ether	$C_7H_{11}NO_3S_2$	38.0	5.0	6.3	29.0	37.7	4.8	6.1	28.7

[a] Based on crude product. [b] Determined after recrystallization. [c] The ligroin used is a hydrocarbon solvent, b.p. 35–60°. [d] Ref. 4. [e] Recrystallized. [f] Ref. 3. [g] Reported in ref. 5 without properties. [h] Ref. 6.

examination of properties, the products of these reactions can be concluded to have corresponding structures, VII–XII.

Intermediate products isolated from reaction of chloroacetaldehyde, ethyl α-chloroacetoacetate, or ethyl γ-chloroacetoacetate and ammonium dithiocarbamate are found upon similar examination to be the 4-hydroxythiazolidines XIII–XV, respectively. Preparative and comparative analytical data related to the thiazolidines and dithiocarbamates (I-XV) are summarized in Tables I and II.

The reactivity of 4-hydroxythiazolidine-2-thiones towards dehydration varies depending on substitution. Storage at room temperature for a few hours results in conversion of intermediates I and VII to corresponding 4-thiazoline-2-thiones. Analyses must be made immediately after preparation. However, intermediates XIII and XV may be kept for several days without change. Dehydration generally occurs in boiling water over 1–2 hr. For this reason recrystallization of the intermediates from water as reported earlier is not recommended. Dehydration is complete in a few minutes in boiling dilute hydrochloric acid. Progress of this reaction can be observed conveniently by ultraviolet spectra analyses since the thiazolidine-2-thiones studied are characterized by λ_{max} 273–279 mμ, and the 4-thiazoline-2-thiones formed, by λ_{max} 315–340 mμ. 5-Carbethoxy-4-methyl-4-thiazoline-2-thione absorbs at the higher wave length. Substitution at the 5-position appears to result in this shift. 5-Acetyl-4-methyl-4-thiazoline-2-thione[8] and the oxime have λ_{max} 353 mμ (ε 19,000) and 339 mμ (ε 19,800). In contrast, 4-carbethoxy- and 4-carboxy-4-thiazoline-2-thione[8] are characterized by λ_{max} 302 mμ (ε 12,800) and 305 mμ (ε 12,800).

TABLE II

No.	Major characteristic infrared wave lengths, λ_{max}, μ[a,b]	Ultraviolet absorption spectra[c] λ_{max}^{MeOH}, mμ	ε	λ_{max}^{MeOH}, mμ	ε
	4-Hydroxythiazolidine-2-thiones				
I	3.03, 3.16, 14.00	245	7150	276	16500
II	3.07	252 sh	9150	272	15600
IV	3.00, 3.20, 13.85	248	6470	274	17400
V	2.92	255 sh	9300	274	16600
VII	3.05, 3.27, 13.78	245	14400	273	7600
VIII	3.02	253 sh	10100	275	16100
X	2.90, 3.07, 13.73	247	7560	279	17900
XI	3.00	250 sh	8600	274	17700
XIII	3.07, 3.15, 14.08	244	6600	277	15500
XIV	2.92, 3.17, 5.80, 8.60, 13.77	244	5530	277	13900
XV	2.90, 3.19, 5.82, 8.56	244	6830	277	15700
	Substituted Dithiocarbamates				
III	5.80, 7.97	246	9020	274	10100
VI	5.85, 8.00	248	9150	278	9370
IX	5.90, 8.03	245	21700	272	10800
XII	6.00, 8.00	246	16700	277	10400

[a] Recorded on a Baird-Atomic Model NK-1 spectrophotometer with sodium chloride optics. [b] Assignment: 2.90–3.07, stretching OH; 3.07–3.27, stretching NH; 5.80–6.00, stretching C=O; 7.97–8.03, aliphatic ketone; 8.56–8.60, stretching ester O—C=O; 13.77–14.08, out-of-plane deformation NHC=S. [c] Recorded on a Cary Model 11MS spectrophotometer.

Experimental

Melting points were determined in open, soft-glass capillary tubes; melting points below 200° are corrected.

Materials.—Chloroacetone, phenacyl bromide, and ethyl α-chloroacetoacetate were used as obtained commercially (Eastman Kodak Co.); α-bromoisobutyrophenone (Aldrich Chemical Co.) was redistilled, b.p. 126° (13 mm.), $n^{25}D$ 1.5543. 3-Bromo-3-methyl-2-butanone was obtained by bromination,[9] b.p. 59° (40

(8) J. J. D'Amico, *J. Am. Chem. Soc.*, **75**, 102 (1953).

(9) A. Favorskii, *J. prakt. Chem.*, [2]**88**, 641 (1913).

mm.), $n^{25}D$ 1.4562. Solid ammonium dithiocarbamate[10] was used without purification.

4-Hydroxythiazolidine-2-thiones (I, VII, and XIII).—These substances were found to be the intermediate products isolated from the reactions of ammonium dithiocarbamate with chloroacetone, phenacyl bromide, and chloroacetaldehyde, respectively, under the conditions of procedures previously described.[3,4]

4-Hydroxythiazolidine-2-thiones (IV, X, XIV, and XV).—In a typical preparation, 27.9 g. (0.253 mole, 10% excess) of freshly prepared ammonium dithiocarbamate was suspended in 250 ml. of acetone in a 1-l. suction flask and stirred, with cooling, in an ice–brine bath. A solution of 37.9 g. (0.23 mole) of ethyl γ-chloroacetoacetate in 100 ml. of acetone was added dropwise over a 30-min. period, the temperature of the reaction mixture being kept below 10°. After the solution had been stirred for 45 min. longer, the minimum volume of water to cause solution was added and the cold solution was stirred for 15 min. longer. Removal of acetone *in vacuo* without letting the reaction mixture become warm resulted in separation of a colorless oil. Crystallization was induced by stirring a small portion of the oil in a little ether. Crude 4-carbethoxymethyl-4-hydroxythiazolidine-2-thione (XV) amounted to 45.0 g. and melted at 90°.

4-Hydroxy-3-methylthiazolidine-2-thiones (II, V, VIII, and XI).—An example of the general procedure used to prepare these compounds is the synthesis of 4-hydroxy-3,4,5,5-tetramethylthiazolidine-2-thione (V). Potassium acetate (43.2 g., 0.44 mole) was dissolved in 250 ml. of methanol. The solution was cooled in an ice–brine bath, and 34.2 g. (0.44 mole) of 40% methylamine was added. The temperature was maintained below 10° throughout the remainder of the reaction. To the stirred solution was added dropwise 26.5 ml. (0.44 mole) of carbon disulfide mixed with an equal volume of methanol during 15 min. The resulting solution stood for 2.5 hr. A solution of 36.3 g. (0.22 mole) of 3-bromo-3-methyl-2-butanone in 50 ml. of methanol was added over 15 min., with stirring. After standing for 3 hr., 150 ml. of water was added. To isolate the product, methanol was removed *in vacuo*, the reaction mixture being kept cold. Crude product separated as a white solid weighing 27.3 g., m.p. 96°.

Substituted Dithiocarbamates (III, VI, IX, and XII).—In a typical synthesis employing largely the method just described, a solution of 20.2 g. (0.206 mole) of potassium acetate, 37.1 g. (0.206 mole) of 25% dimethylamine and 12.4 ml. (0.206 mole) of carbon disulfide in 175 ml. of methanol was treated with 23.4 g. (0.103 mole) of α-bromoisobutyrophenone in 50 ml. of methanol. Standing overnight at room temperature afforded glistening, white crystals. After the solids had been collected by filtration and washed with cold water to separate a little potassium chloride, the crude α-(N,N-dimethylthiocarbamoylthio)isobutyrophenone (XII) amounted to 25 g., m.p. 113–114°.

An oxime and 2,4-dinitrophenylhydrazone of III and IX were made (see Table I). The hindered ketones VI and XII failed to form these carbonyl derivatives under similar conditions.

4-Thiazoline-2-thiones.—The 4-hydroxythiazolidine-2-thiones were dehydrated readily either by boiling in water for 1–2 hr. or in 0.5% hydrochloric acid for a few minutes. Methanol can be added to aid solution and then boiled off. In this way there was obtained the known derivative, 4-thiazoline-2-thione, λ_{max} 313 mμ (ε 12,500), m.p. 79–80°, lit.[3] m.p. 79–80°. Also afforded were the 4-methyl, λ_{max} mμ 318 (ε 15,700), m.p. 87.5–88.5°, lit.[4] m.p. 87°; 3,4-dimethyl, 315 mμ (ε 15,000), m.p. 117°, lit.[11] m.p. 119°; 4 phenyl, 236 and 318 mμ (ε 16,800 and 14,300), m.p. 173–174°, lit.[12] m.p. 173–174°; and 5 carbethoxy-4-methyl, 340 mμ (ε 21,800), m.p. 144–145°, lit.[8] m.p. 143–144°, homologs.

3-Methyl-4-phenyl-4-thiazoline-2-thione.—This substance was obtained essentially quantitatively, m.p. 131–132°, by boiling 4-hydroxy-3-methyl-4-phenylthiazolidine-2-thione (VIII) in a solution of methanol and 0.5% hydrochloric acid. Recrystallization from ethanol gave white plates, m.p. 131–132°, λ_{max} 316 mμ (ε 15,600).

Anal. Calcd. for $C_{10}H_9NS_2$: C, 57.9; H, 4.4; N, 6.8; S, 30.9. Found: C, 57.7; H, 4.3; N, 6.9; S, 30.6.

2,2′-Dithiobis(4-phenylthiazole).—Oxidation of 4-phenyl-4-thiazoline-2-thione by the method using iodine[13] yielded the new disulfide in approximately quantitative yield, m.p. 158–159°. Recrystallization from chloroform–ethanol gave fine, white needles, m.p. 159.5–160.5°, λ_{max} 235 and 258 mμ (ε 33,800 and 30,700).

Anal. Calcd. for $C_{18}H_{12}N_2S_4$: C, 56.2; H, 3.2; N, 7.3; S, 33.3. Found: C, 55.9; H, 3.0; N, 6.9; S, 33.3.

5-Acetyl-4-methyl-4-thiazoline-2-thione Oxime.—Recrystallized from 80% ethanol, this derivative gave pale yellow needles, m.p. 215° dec.

Anal. Calcd. for $C_6H_8N_2OS_2$: C, 38.3; H, 4.3; N, 14.9. Found: C, 38.1; H, 4.5; N, 14.8.

(10) R. A. Mathes, *Inorg. Syn.*, **3**, 48 (1950).

(11) J. D. Kendall and H. G. Suggate, *J. Chem. Soc.*, 1503 (1949).

(12) W. S. Emerson and T. M. Patrick, Jr., *J. Org. Chem.*, **13**, 722 (1948).

(13) E. M. Gibbs and F. A. Robinson, *J. Chem. Soc.*, 925 (1945).

4-Thiazoline-2-thiones. II. Preparation of 4-Alkylsulfonylmethyl Derivatives

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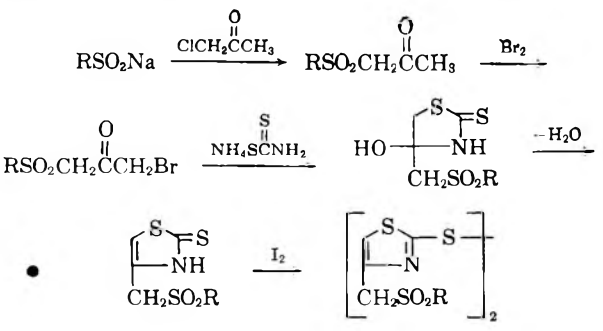
Syntheses and properties are described of the homologous series of 4-alkylsulfonylmethyl-4-thiazoline-2-thiones and disulfide derivatives obtained through intermediate 1-alkylsulfonyl-2-propanones, 1-alkylsulfonyl-3-bromo-2-propanones, and 4-alkylsulfonylmethyl-4-hydroxythiazolidine-2-thiones.

A series of 4-alkylsulfonylmethyl derivatives of 4-thiazoline-2-thiones has been obtained by reaction of ammonium dithiocarbamate and 1-alkylsulfonyl-3-bromo-2-propanones. This type of synthesis proceeds through an intermediate product which can be isolated and has been shown to be a substituted 4-hydroxythiazolidine-2-thione.[1] In a subsequent step, dehydration forms a 4-thiazoline ring. Required 1-alkylsulfonyl-3-bromo-2-propanones were obtained by reactions in the over-all scheme of synthesis, at the left. Use of these methods afforded the 1-alkylsulfonyl-2-propanones described in Table I. These ketones are characterized by 2,4-dinitrophenylhydrazones. Bromination of 1-butylsulfonyl-2-propanone in acetic acid has been reported to occur at C-3, and the site of reaction has been determined by unequivocal synthesis.[2]



(1) Part I: W. J. Humphlett and R. W. Lamon, *J. Org. Chem.*, **29**, 2146 (1964).

(2) Y. Yamamoto, *J. Pharm. Soc. Japan*, **73**, 934 (1953); *Chem. Abstr.*, **48**, 10,738° (1954).

TABLE I

ALKYLSULFONYL-2-PROPANONES

$CH_3(CH_2)_nSO_2CH_2COCH_3$

n	Yield, %	B.p., °C. (mm.)	$n^{25}D$	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H	2,4-Dinitrophenylhydrazones[a] M.p., °C.	Formula	Calcd., % N	Found, % N
1	23	152–154 (11)	1.4630	$C_5H_{10}O_3S$	40.0	6.7	39.9	6.6	134–135	$C_{11}H_{14}N_4O_6S$	17.0	16.7
2	28	146–147 (10)	1.4618	$C_6H_{12}O_3S$	43.9	7.3	43.8	7.4	148–149	$C_{12}H_{16}N_4O_6S$	16.3	16.0
3		146–147[b] (6)	1.4628						143–144	$C_{13}H_{18}N_4O_6S$	15.6	15.4
4	43	165–167 (7)	1.4633	$C_8H_{18}O_3S$	50.0	8.4	49.7	8.4	149–150	$C_{14}H_{20}N_4O_6S$	15.1	14.9
5	34	121–123 (0.5)	1.4623	$C_9H_{18}O_3S$	52.4	8.8	52.1	9.0	118–119	$C_{15}H_{22}N_4O_6S$	14.5	14.3
6	50	121–122 (0.1)	1.4616	$C_{10}H_{20}O_3S$	54.5	9.2	54.6	9.3	90–91	$C_{16}H_{24}N_4O_6S$	14.0	13.9

[a] Recrystallized from ethanol. [b] Lit.[4] b.p. 147–150° (7 mm.).

TABLE II

1-ALKYLSULFONYL-3-BROMO-2-PROPANONES

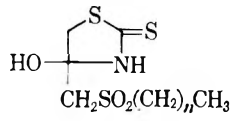
$CH_3(CH_2)_nSO_2CH_2COCH_2Br$

n	Yield, %	M.p., °C.[a]	Formula	Calcd., % C	Calcd., % H	Calcd., % Br	Found, % C	Found, % H	Found, % Br
1	87	84–85	$C_5H_9BrO_3S$	26.2	4.0	34.9	26.3	4.0	34.8
2	89	112–113	$C_6H_{11}BrO_3S$	29.6	4.6	32.9	29.7	4.6	33.1
3		119–120[b]							
4	100	116–117	$C_8H_{15}BrO_3S$	35.4	5.6	29.5	35.4	5.7	29.8
5	86	108–109	$C_9H_{17}BrO_3S$	37.9	6.0	28.0	38.0	6.0	28.1
6	95	99–100	$C_{10}H_{19}BrO_3S$	40.1	6.4	26.8	39.9	6.4	27.0

[a] Recrystallized from ethanol. [b] Lit.[2] m.p. 119°.

TABLE III

4-ALKYLSULFONYLMETHYL-4-HYDROXYTHIAZOLIDINE-2-THIONES[a]



n[b]	Yield, %	M.p., °C.	Recrystn. solvent	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
2	98	128–129	Chloroform–ethanol–petr. ether	$C_5H_{13}NO_3S_3$	32.9	5.1	33.1	5.3
3	94	119	Ether	$C_6H_{15}NO_3S_3$	35.7	5.6	35.3	5.5
4	89	128–129	Chloroform–ethanol	$C_9H_{17}NO_3S_3$	38.1	6.1	38.1	6.2
5	94	138–139	Chloroform–ethanol	$C_{10}H_{19}NO_3S_3$	40.6	6.4	40.6	6.4
6	89	141–142	Chloroform–ethanol–petr. ether	$C_{11}H_{21}NO_3S_3$	42.4	6.8	42.3	6.9

[a] Generally very soluble in alcohol or acetone, slightly soluble in ether, insoluble in water. [b] Attempts to isolate the pure homolog, $n = 1$, were unsuccessful.

Bromination in acetic acid of the ketones listed in Table I yielded the corresponding 1-alkylsulfonyl-3-bromo-2-propanones (Table II). Reaction of ammonium dithiocarbamate with the α-bromo ketones produced the 4-alkylsulfonylmethyl-4-hydroxythiazolidine-2-thiones listed in Table III.

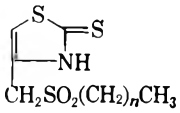
When 4-hydroxythiazolidine-2-thione was substituted by a 4-methyl group, the product became more reactive towards dehydration and was unstable at room temperature.[1] Substitution by a 4-alkylsulfonylmethyl group, however, resulted in increased stability. 4-Butylsulfonylmethyl-4-hydroxythiazolidine-2-thione was unchanged, for example, after storage for 18 months at room temperature. Infrared absorption spectra of the hydroxy intermediates showed major characteristic absorption bands near 3.0 (OH), 3.2 (NH), 14.2 (NHC=S), and 7.7 and 8.8 μ (SO_2). These hydroxy intermediates were dehydrated readily by boiling in water for 1 hr., forming 4-thiazoline-2-thiones (Table IV). The 4-alkylsulfonylmethyl-4-hydroxythiazolidine-2-thiones were characterized by ultraviolet absorption spectra having λ_{max} 245 and 277 mμ, whereas the 4-thiazoline-2-thiones absorbed at λ_{max} 319 mμ. Oxidation of the 4-thiazoline-2-thiones to disulfides (Table V) resulted in a shift in the ultraviolet spectra to a shorter wave length, λ_{max} 270 mμ.

Experimental

Melting points were determined in open, soft-glass capillaries and are corrected; boiling points are uncorrected. Infrared spectra were recorded on a Baird-Atomic spectrophotometer,

TABLE IV

4-ALKYLSULFONYLMETHYL-4-THIAZOLINE-2-THIONES[a]

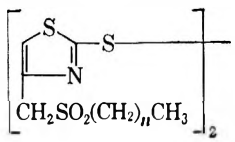


n	Yield, %	M.p., °C.	Formula	Calcd., % C	H	N	Found, % C	H	N	λ_{max}^{EtOH} mμ	ε
1	100	183–184	$C_6H_9NO_2S_3$	32.3	4.1	6.3	32.0	4.0	6.2	319	14,700
2	91	153–154	$C_7H_{11}NO_2S_3$	35.4	4.7	5.9	35.6	4.6	5.9	319	13,400
3	89	164–165	$C_8H_{13}NO_2S_3$	38.2	5.2	5.6	38.4	5.3	5.6	319	12,600
4	74	164–165	$C_9H_{15}NO_2S_3$	40.7	5.8	5.3	40.6	5.7	5.2	319	15,200
5	62	160–161	$C_{10}H_{17}NO_2S_3$	43.0	6.1	5.0	42.8	6.3	5.0	319	14,500
6	24	152–153	$C_{11}H_{19}NO_2S_3$	45.0	6.5	4.8	44.8	6.3	4.6	318	14,000

[a] Generally insoluble in chloroform or ether; slightly soluble in hot water; soluble in hot ethanol, crystallizing on cooling as yellow needles.

TABLE V

2,2′-DITHIOBIS(4-ALKYLSULFONYLMETHYL)THIAZOLES[a]



n	Yield, %	M.p., °C.	Formula	Calcd., % N	S	Found, % N	S	$\lambda_{max.}^{CHCl_3}$ mμ	ε
1	83	160–161	$C_{12}H_{16}N_2O_4S_5$[b]	6.3		6.0		270	8600
2	84	159–160	$C_{14}H_{20}N_2O_4S_6$	5.9	40.7	5.6	40.8	270	11,000
3	97	169	$C_{16}H_{24}N_2O_4S_6$	5.6	38.4	5.8	38.1	270	9100
4	100	182	$C_{18}H_{28}N_2O_4S_6$[c]	5.3		5.0		270	9200
5	99	182–183	$C_{20}H_{32}N_2O_4S_6$	5.0	34.5	4.9	34.3	270	9200
6	100	169–171	$C_{22}H_{36}N_2O_4S_6$	4.8	32.9	4.6	32.8	270	9100

[a] Recrystallized from chloroform; soluble in pyridine; insoluble in alcohol, acetone, ethyl acetate, or water. [b] Calcd.: C, 32.4; H, 3.6. Found: C, 32.3; H, 3.6. [c] Calcd.: C, 40.9; H, 5.3. Found: C, 40.9; H, 5.5.

Model NK-1, with sodium chloride optics. Ultraviolet spectra were recorded on a Cary spectrophotometer, Model 11 MS.

Alkylsulfonyl-2-propanones (Table I).—Butylsulfonyl-2-propanone and higher homologs were prepared by a known method by reaction of sodium alkanesulfinates[3] with chloroacetone.[4]

Propylsulfonyl-2-propanone was prepared by the following modification. Gaseous sulfur dioxide was bubbled into a solution of 1 mole of propylmagnesium bromide in 800 ml. of ether, with cooling and stirring, until precipitation of magnesium propanesulfinate was complete. The suspension was stirred into 1500 g. of ice and water, heated under water-pump vacuum to remove ether, and filtered. To the filtrate was added 212 g. of sodium carbonate, and the mixture was boiled for a few minutes. After evaporation to dryness, the resulting solid was extracted by boiling and stirring with 2.3 l. of ethanol. Evaporation of the extract gave a weight of a white solid about equal to the theoretical yield of sodium propanesulfinate. The salt was used without further purification. A solution was made of 95 g. of crude sodium propanesulfinate and 67.7 g. (0.73 mole) of chloroacetone in 550 ml. of ethanol, and refluxed for 3 hr. Concentrated *in vacuo* and diluted with water, the separated organic layer was collected, and the residue was extracted with ether. The combined organic phases were dried over anhydrous sodium sulfate and fractionated through a 20-cm. column packed with glass helices, yielding 24 g. of product. Recovered chloroacetone amounted to 19 g.

Ethylsulfonyl-2-propanone was prepared similarly except that crude, solid sodium ethanesulfinate was used, without purification by extraction with alcohol.

1-Alkylsulfonyl-3-bromo-2-propanones (Table II).—All bromo ketones of this series were afforded by a known procedure[2] by bromination of alkylsulfonyl-2-propanones in acetic acid solution.

4-Alkylsulfonylmethyl-4-hydroxythiazolidine-2-thiones (Table III).—Preparation of 4-butylsulfonylmethyl-4-hydroxythiazolidine-2-thione by a procedure similar to that used to make 4-hydroxythiazolidine-2-thiones described in part I of this series[1] is typical of syntheses of compounds of Table III. Thus, 15.0 g. (0.058 mole) of 1-bromo-3-butylsulfonyl-2-propanone in an equal volume of acetone was added over 15 min. to a stirred suspension of 7.0 g. (0.064 mole, 10% excess) of ammonium dithiocarbamate in 150 ml. of acetone, cooled to 10°. After the mixture had been cooled and stirred for 45 min. longer, the crude product was isolated by adding 50 ml. of water and the acetone was removed *in vacuo* without allowing the product to become warm. The yield was 18 g. of white crystals, m.p. 119°. Recrystallization did not alter the melting point. Characteristic bands in the infrared spectrum appeared at 2.93 (OH), 3.18 (NH), 7.68 and 8.82 (SO_2), and 14.3 μ (NHC=S).

4-Alkylsulfonylmethyl-4-thiazoline-2-thiones (Table IV).—As an example of the general method of dehydration to form compounds of this class, a mixture of 13.5 g. (0.05 mole) of 4-butylsulfonylmethyl-4-hydroxythiazolidine-2-thione and 500 ml. of water was boiled for 1 hr. On cooling, crystals formed which were collected by filtration. The yield of crude 4-butylsulfonylmethyl-4-thiazoline-2-thione amounted to 11.2 g., m.p. 164–165°. After recrystallization from water or ethanol, the melting point remained unchanged.

Ethanol may be added to the reaction mixture to increase the solubility of higher homologs.

2,2′-Dithiobis(4-alkylsulfonylmethyl)thiazoles (Table V).—Oxidation of 4-alkylsulfonylmethyl-4-thiazoline-2-thiones by the method using iodine[5] gave the disulfides of this series.

(3) P. Allen, Jr., *J. Org. Chem.*, **7**, 23 (1942).

(4) A. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 237 (1949).

(5) E. M. Gibbs and F. A. Robinson, *J. Chem. Soc.*, 925 (1945).

5,6-Dihydro-4*H*-1,3,4-oxadiazines. III. *cis–trans* Isomerism[1]

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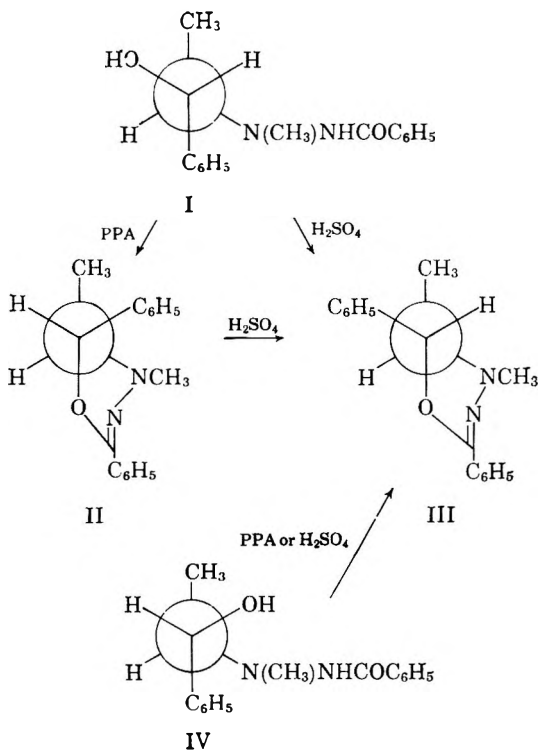
cis- and *trans*-5,6-dihydro-4*H*-1,3,4-oxadiazines have been synthesized. *cis* isomers have been converted into *trans* isomers. Conformation of the isomers is postulated on the basis of n.m.r. measurements. A proposed mechanism for the formation of *cis* and *trans* isomers is discussed.

We reported[2,3] that sulfuric acid dehydration of certain 2-(β-hydroxyalkyl) acid hydrazides is accompanied by neighboring group participation with the formation of a 5,6-dihydro-4*H*-1,3,4-oxadiazine; and that for effective neighboring group participation the hydroxyl group should be either tertiary or benzyl, and the acyl moiety should be aromatic, heterocyclic, or bulky aliphatic. Even when both the hydroxyl group and the acyl moiety are the most favorable structural types for effective participation, a competing reaction, hydrolysis of the hydrazide linkage, occurs to a significant extent.

In an attempt to retard this competing reaction, cyclodehydration of certain 2-(β-hydroxyalkyl) acid hydrazides was carried out with polyphosphoric acid (PPA) instead of sulfuric acid. Polyphosphoric acid did not increase the yield of 5,6-dihydro-4*H*-1,3,4-oxadiazine, but it did produce an interesting change in the course of the reaction. Cyclodehydration of N-benzoylamino-*l*-ephedrine (I)[4] with PPA gave *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (II), whereas cyclodehydration of I with sulfuric acid gave *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (III). Cyclodehydration of N-benzoylamino-*d*-pseudoephedrine (IV) with either polyphosphoric acid or sulfuric acid gave III. Treatment of II with concentrated sulfuric acid at 25° converted it to III. Treatment of II with PPA at 25° for 24 hr. produced no change. However, treatment of II with PPA at 65° for 1 hr. gave a mixture of 57% II and 22% III.



Cyclodehydration of a series of N-acylamino-*l*-ephedrines[2] with sulfuric acid gave exclusively the *trans* isomer in every instance. In contrast, polyphosphoric acid cyclodehydration gave either the *cis* or the *trans* isomer or a mixture of both. In fact, cyclodehydration of I with polyphosphoric acid on one occasion gave the *cis* isomer and later, under the same reaction conditions (1 hr. at 60°), yielded the *trans* isomer. In these experiments, a mixture of *cis* and *trans* isomers of varying composition was formed. Higher reaction temperatures (60–70°) gave mixtures richer in *trans* isomer, and a lower reaction temperature (25°) gave mixtures richer in *cis* isomer. The isomers were separated by fractional crystallization from isopropyl alcohol. The *cis* isomers were less soluble.

The best method of synthesis of the *cis* isomer of a 5,6-dihydro-4*H*-1,3,4-oxadiazine was one in which an appropriate N-acylamino-*l*-ephedrine was stirred with excess polyphosphoric acid for 18 hr., unchanged N-acylamino-*l*-ephedrine was removed by adsorption onto alumina, and the mixture of *cis* and *trans* (mostly *cis*) isomers was separated by careful crystallization from a dilute solution at room temperature.

Cyclodehydration of N-benzoylamino-*l*-ephedrine (I) with phosphorus pentoxide in refluxing toluene gave *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (II). The *cis*- and *trans*-5,6-dihydro-4*H*-1,3,4-oxadiazines are listed in Table I.

The 4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazines, II and III, were designated *cis* and *trans*, respectively, on the basis of n.m.r. data (see Table II). Both II and III exhibit essentially the same chemical shifts regarding their protons—one sharp line (−7.29 for II and −7.30 p.p.m. for III) due to a phenyl group attached to an "ordinary" tetrahedral carbon (C-6), and two structured groups (−7.83 and −7.25 for II and −7.77 and −7.24 p.p.m. for III) caused by a phenyl group with a carboxyl-type substituent (C-2). The N-methyl groups (N-4), having essentially identical shifts (−2.80 for II and −2.81 p.p.m. for III), must be structurally and chemically quite similar. The system $-OCH(C_6H_5)CH(CH_3)-$ is seen in both II and III, but their shifts and couplings differ. Assuming the ring takes the likely half-chair form of cyclohexene,

(1) Presented in part before the Division of Organic Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

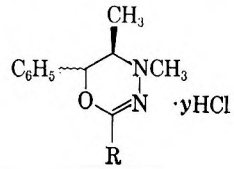
(2) D. L. Trepanier, V. Sprancmanis, and K. G. Wiggs, *J. Org. Chem.*, **29**, 668 (1964).

(3) D. L. Trepanier and V. Sprancmanis, *ibid.*, **29**, 673 (1964).

(4) We have selected Newman projection formulae I and IV to represent the preferred conformations of N-benzoylamino-*l*-ephedrine and N-benzoylamino-*d*-pseudoephedrine on the basis of reports by L. H. Welsh [*J. Am. Chem. Soc.*, **71**, 3500 (1949)], W. J. Close [*J. Org. Chem.*, **15**, 1131 (1950)], and J. B. Hyne [*J. Am. Chem. Soc.*, **81**, 6058 (1959)].

TABLE I

2-SUBSTITUTED 4,5-DIMETHYL-6-PHENYL-5,6-DIHYDRO-4*H*-1,3,4-OXADIAZINES[a]

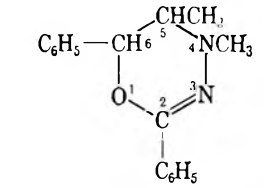


R	*y*	Configuration at C-5 and C-6	M.p., °C.	Method[b] of prepn.	% yield[c]	Recrystn. solvent	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	$[\alpha]^{28}D$ (*c*, solvent)[d]
C_6H_5	0	*trans*	142–143	H_2SO_4, 25°, 18 hr.	46	*i*-PrOH	76.66	6.81	10.52	76.41	7.02	10.10	+213 ± 2° (3.99, C_6H_6)
				PPA, 60°, 1 hr.	49								
C_6H_5	0	*cis*	101–102	PPA, 60°, 1 hr.	32	*i*-PrOH	76.66	6.81	10.52	76.63	6.81	10.62	−239 ± 2° (4.17, C_6H_6)
				PPA, 25°, 24 hr.	67[e]								
				P_2O_5, 110°, 18 hr.	44								
4-$CH_3OC_6H_4$	1	*trans*	159–161		95[f]	2-Butanone–ether	64.95	6.36	8.42	65.59	6.48	8.65	+34.8 ± 2° (4.02, $CHCl_3$)
4-$CH_3OC_6H_4$	1	*cis*	164.5–165.5[g]	PPA, 25°, 18 hr.[h]	50	2-Butanone	64.95	6.36	8.42	64.19	6.31	9.00	−78 ± 3° (4.22, $CHCl_3$)
4-$C_2H_5OC_6H_4$	0	*trans*	101–102	H_2SO_4, 25°, 18 hr.	57	*i*-PrOH	73.52	7.15	9.03	73.62	7.36	9.17	+176 ± 2° (4.10, C_6H_6)
4-$C_2H_5OC_6H_4$	0	*cis*	88–89	PPA, 60°, 1 hr.	25	*i*-PrOH	73.52	7.15		74.12	7.30		−164 ± 2° (4.02, $CHCl_3$)
4-$CH_3OC_6H_4$	0	*trans*	123.5–124.5	H_2SO_4, 25°, 18 hr.	55	*i*-PrOH	72.95	6.80		72.93	6.92		+190 ± 2° (4.11, C_6H_6)
				PPA, 60°, 1 hr.	94								

[a] Compounds listed in Table I were prepared from N-acylamino-*l*-ephedrines and not from diastereoisomeric N-acylamino-*d*-pseudoephedrines. [b] See Experimental section. [c] No attempt was made to obtain optimum yields. [d] Rudolph Laboratory Polarimeter Model No. 62. [e] Also isolated 6.1% yield of the *trans* isomer. [f] Prepared by treating the free base with ethereal hydrogen chloride. [g] A mixture of *cis*- and *trans*-4,5-dimethyl-2-(*p*-methoxyphenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine hydrochlorides melted at 132–148°. [h] Free base purified by chromatography on Merck acid-washed alumina (No. 71695). Hydrochloride prepared by treating free base with ethereal hydrogen chloride.

TABLE II

N.M.R. DATA OF *cis*- AND *trans*-4,5-DIMETHYL-2,6-DIPHENYL-5,6-DIHYDRO-4*H*-1,3,4-OXADIAZINES[a]



Substituents	—Chemical shifts, – p.p.m.— *cis* isomer	*trans* isomer
2-C_6H_5, *o*-H's	7.83	7.77
m- and *p*-H's	7.25	7.24
4-CH_3	2.80	2.81
5-H	3.23	2.61
6-H	5.40	4.95
5-CH_3	0.75	1.02
6-C_6H_5	7.29	7.30
	Coupling constants, c.p.s.	
J (H-5–H-6)	2.9$_0$	7.54
J (H-5–CH_3)	6.3$_7$	6.58
J (H-6–CH_3)	0	0

[a] Proton n.m.r. analyses were obtained at 60 Mc., with a Varian Associates A-60 analytical n.m.r. spectrometer, for 10% w./v. CCl_4 solutions containing a trace of tetramethylsilane (TMS) as internal reference. The chemical shifts are given as the negative values of the shielding in parts per million relative to TMS at 0.00 p.p.m., and pertinent coupling constants, *J*, are given in cycles per second.

a value of 2.9$_0$ c.p.s. for *J* (H-5–H-6) indicates the dihedral angle between the C–H bonds is approximately 60° and the 5- and 6-protons are gauche. Thus II is the *cis* isomer. The 5-CH_3 and 6-C_6H_5 substituents are axial–equatorial either way with rapid interchange possible, although one might expect the form with 6-C_6H_5 equatorial to be preferred. The *trans* isomer (III) has a coupling constant of 7.54 c.p.s. for *J* (H-5–H-6) indicative of 5- and 6- protons *trans* axial–axial with a dihedral angle approaching 180°, and the 5-CH_3 and 6-C_6H_5 groups always equatorial.

The infrared spectra of *cis*- and *trans*-2-substituted-5,6-dihydro-4*H*-1,3,4-oxadiazines exhibit a difference in the 1350–1400-cm.$^{-1}$ region (see Fig. 1). The *trans* isomers exhibit bands at 1383 (vs) and 1368 (w), and *cis* isomers exhibit bands at 1380 (s) and 1354 (vs). This consistent difference in infrared absorption provides a basis for easy differentiation of *cis* and *trans* isomers in this series of compounds.

The ultraviolet absorption of *cis*- and *trans*-2-substituted 5,6-dihydro-4*H*-1,3,4-oxadiazines are practically identical. For example, *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (II) exhibits $\lambda_{max}^{CHCl_3}$ 240 mμ (ε 4840) and 296 mμ (ε 9740), and *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (III) exhibits $\lambda_{max}^{CHCl_3}$ 240 mμ (ε 4640) and 294 mμ (ε 9080).

cis- and *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazines (II and III) behaved differently when subjected to acid hydrolysis. The *cis* isomer (II) readily yielded N-benzoylamino-*l*-ephedrine. The *trans* isomer (III) was more difficult to hydrolyze[5] and gave benzoic acid as the only identified product.

The experimental results show that sulfuric acid dehydration gives exclusively the thermodynamically more stable *trans* isomer regardless of whether the starting 2-(β-hydroxyalkyl) acid hydrazide has the *threo* or *erythro* configuration. PPA at 25° gives mainly the kinetically controlled product, whose configuration is determined by the configuration of the starting 2-(β-hydroxyalkyl) acid hydrazide. N-(acylamino)ephedrines give mainly *cis* isomer contaminated with a small amount of *trans* isomer. N-acylaminopseudoephedrines give exclusively *trans* isomer with PPA because this is both the kinetically controlled and the thermodynamically more stable product. As the reaction temperature is elevated to 60–70°, PPA cyclodehydration of N-(acylamino) ephedrines gives a mixture of *cis* and *trans* isomers much richer in *trans* isomer, so much so that it may be the predominant isomer in the mixture.

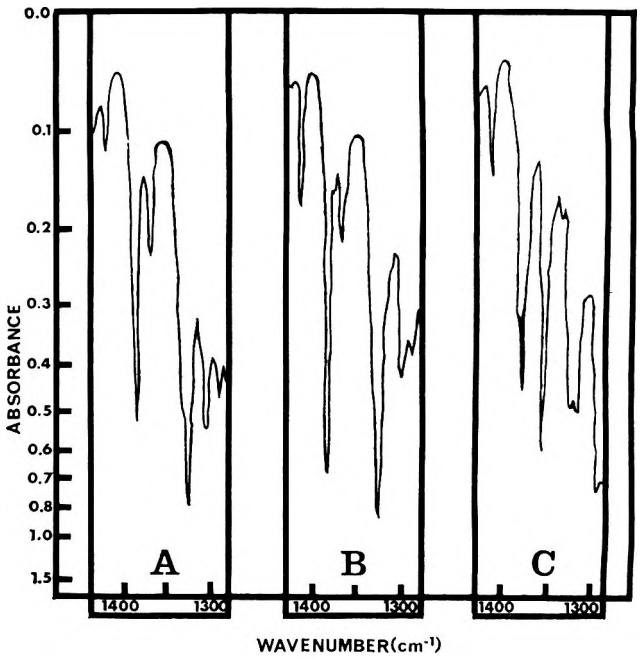


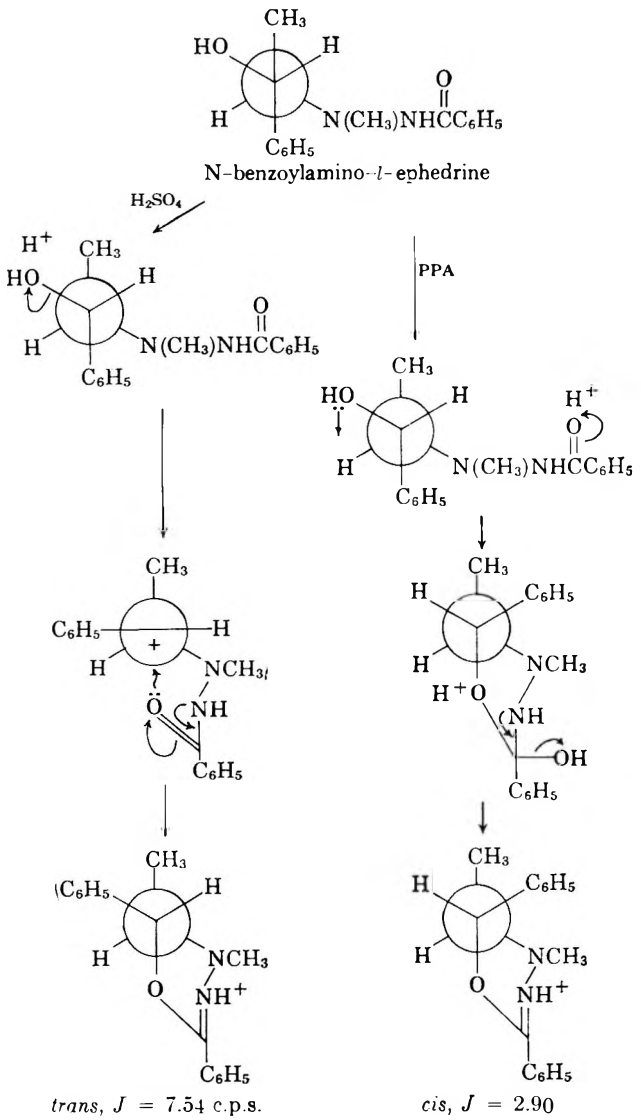
Fig. 1.—Portion of infrared spectra of *trans*-4,5-dimethyl-2-(*o*-methoxyphenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (A), *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (B), and *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (C).

We propose the following mechanism (see Scheme I) to account for the different results obtained with sulfuric and polyphosphoric acids. Sulfuric acid protonates the hydroxyl group of the 2-(β-hydroxyalkyl) acid hydrazide and this then dissociates into a water molecule and a carbonium ion. Formation of a trigonal carbonium ion destroys the asymmetry of the hydroxyl-bearing carbon atom and allows the phenyl and hydrogen to assume the most stable configuration. N-benzoylamino-*l*-ephedrine and N-benzoylamino-*d*-pseudoephedrine form the same intermediate carbonium ion because they differ only in configuration about the hydroxyl-bearing carbon atom. The carbonium carbon is attacked by the nucleophilic oxygen of the hydrazide carbonyl giving the conjugate acid of the *trans*-oxadiazine.

Polyphosphoric acid at 25° cyclodehydrates mainly with retention of configuration, and thus either produces no inversion or an equal number of inversions. A reasonable pathway requiring no inversion is one in which PPA protonates the carbonyl oxygen, and this is followed by attack of the hydroxylic oxygen atom upon

(5) Hydrolysis was repeated using either hydrochloric, hydrobromic, or sulfuric acids.

SCHEME I



the carbonyl carbon and subsequent loss of water, giving the conjugate acid of either the *cis*- or *trans*-oxadiazine depending upon the configuration about the hydroxyl-bearing carbon of the starting 2-(β-hydroxyalkyl) acid hydrazide.

Alternatively, both sulfuric acid and PPA may initially cyclodehydrate with retention of configuration followed, in the case of sulfuric acid, by a very rapid isomerization to the more stable *trans* form, and, in the case of PPA, by a slow isomerization to the *trans* form.

Additional work is planned to gain a better understanding of the mechanism and scope of this cyclodehydration reaction.

Experimental[6]

General Procedures for the Preparation of the Compounds Listed in Table I. Sulfuric Acid Method.—The N-acylamino-*l*-ephedrine was added, portionwise, with swirling, to five times its weight of concentrated sulfuric acid. After 18 hr., the mixture was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform solution was evaporated *in vacuo*, and the residue was crystallized from an appropriate solvent.

Polyphosphoric Acid Method.—A mixture of the N-acylamino-*l*-ephedrine and twenty times its weight of polyphosphoric acid was kept either at 60° for 1 hr. or at 25° for 18–24 hr. (see Table I). The cooled mixture was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo*, and the residue was crystallized from an appropriate solvent.

Phosphorus Pentoxide Method.—A stirred mixture of 6.0 g. N-benzoylamino-*l*-ephedrine, 3.0 g. phosphorus pentoxide, and 150 ml. toluene was refluxed for 18 hr. The cooled mixture was washed (sodium carbonate, water), dried (magnesium sulfate), and evaporated *in vacuo*. The residue was crystallized from an appropriate solvent.

Conversion of *cis*-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (II) to *trans*-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (III).—A mixture of 1.0 g. of II and 20 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 24 hr. and then was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo*, and the residue was recrystallized from isopropyl alcohol: m.p. 142–143°, yield 0.83 g. (83%).

Conversion of *cis*-4,5-Dimethyl-2-(*p*-methoxyphenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine to *trans*-4,5-Dimethyl-2-(*p*-methoxyphenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine.—A mixture of 1.0 g. of *cis*-4,5-dimethyl-2-(*p*-methoxyphenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine hydrochloride and 25 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 2 hr. and then was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform solution was evaporated *in vacuo*, and the residue recrystallized from isopropyl alcohol gave 1.1 g. (63%) of *trans*-4,5-dimethyl-2-(*p*-methoxyphenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, m.p. 123–124.5°.

Treatment of N-Benzoylamino-*d*-pseudoephedrine Hydrochloride with Sulfuric Acid.—N-Benzoylamino-*d*-pseudoephedrine hydrochloride[7] (2.0 g.) was added, portionwise, with swirling, to 10 ml. of concentrated sulfuric acid. After standing at 25° for 18 hr., the mixture was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo*. The residue was crystallized from isopropyl alcohol to give 1.1 g. (65%) of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine which melted at 142–143.5°, $[\alpha]^{28}D$ +211 ± 2° (c 4.07, C_6H_6).

Treatment of N-Benzoylamino-*d*-pseudoephedrine Hydrochloride with Polyphosphoric Acid.—A mixture of 1.0 g. of N-benzoylamino-*d*-pseudoephedrine hydrochloride[7] and 30 g. of polyphosphoric acid was stirred for 15 min. and then allowed to stand at room temperature for 18 hr.[8] The mixture was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform solution was evaporated *in vacuo*, and the residue recrystallized twice from isopropyl alcohol gave 0.53 g. (64%) of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, m.p. 142–143°, $[\alpha]^{28}D$ +210 ± 2° (c 4.12, C_6H_6).

Acid Hydrolysis of *cis*-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine.—A mixture of 1.0 g. of *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, 10 ml. of ethanol, and 4 ml. of concentrated hydrochloric acid was refluxed for 20 hr., cooled, treated with 30 ml. of water, extracted with ether, basified with sodium hydroxide solution, and extracted with ether. The ether extract of the alkaline aqueous mixture was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The residue recrystallized from isopropyl alcohol gave 0.42 g. (40%) of N-benzoylamino-*l*-ephedrine (I), m.p. 168–170°, identical in its melting point and infrared spectrum with authentic I.

Acid Hydrolysis of *trans*-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine.—A mixture of 1.0 g. of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, 30 ml. of

(6) The melting points were obtained in a capillary tube with a Thomas–Hoover Uni-Melt apparatus and are corrected. The elemental analyses were done by Midwest Microlab, Inc., Indianapolis, Ind. Ultraviolet absorption spectra were obtained on a Beckman DU spectrophotometer.

(7) The same results were obtained when this experiment was repeated with the free base.

(8) Heating at 75° for 1 hr. gave the same result.

concentrated hydrochloric acid,[9] and 30 ml. of water was refluxed for 20 hr. The hot mixture was treated with charcoal and filtered. The cooled filtrate deposited 0.23 g. of benzoic acid, m.p. 121–122°.

Treatment of *cis*-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine with PPA. A. Ambient Temperature.—A mixture of 3.0 g. of *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine and 50 g. of PPA was allowed to stand, with occasional stirring, at room temperature for 24 hr. The mixture was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform solution was evaporated *in vacuo*, and the residue was recrystallized from isopropyl alcohol to give 2.5 g. (83%) of *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, m.p. 97.5–101.5°.

B. At 65°.—The reaction was repeated as above, except that the mixture was heated at 65° for 1 hr. instead of being kept at 25° for 24 hr. There was obtained 0.66 g. (22%) of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine which melted at 141–142°, and 1.7 g. (57%) of the unchanged *cis* isomer, m.p. 100–101°.

(9) Sulfuric and hydrobromic acids gave benzoic acid as the only identified product.

Acknowledgment.—The authors express their appreciation to Drs. W. J. Potts and J. Heeschen for recording and interpreting infrared and n.m.r. data, respectively.

Reactions of N-Benzylthieno[3,2-*b*]pyrrole. I. Metalation and an Electrophilic Substitution[1]

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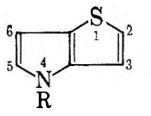
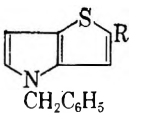
Treatment of N-benzylthieno[3,2-*b*]pyrrole (Ib) with a slight excess of *n*-butyllithium yielded the 2-lithium compound, IIa, which was converted to the 2-carbomethoxy derivative, IIb. The structure of IIb was shown by nuclear magnetic resonance spectroscopy and by unequivocal chemical evidence. The reaction of Ib with *n*-butyllithium in large excess, followed by carbonation and esterification, afforded a tricarbomethoxy derivative believed to be III. The action of acetyl chloride and stannic chloride on Ib in benzene at 0° led to the 5-acetyl derivative, VIII.

A practical synthesis of thieno[3,2-*b*]pyrrole (Ia) was developed by Matteson and Snyder,[2] but investigations of the chemistry of this compound were severely restricted by its instability. The stability of the ring system of Ia can be increased, however, by placing a benzyl group on the nitrogen atom, and the resulting compound, N-benzylthieno[3,2-*b*]pyrrole (Ib), has been prepared.[3] The chemistry of Ib has not been explored previously; its behavior toward *n*-butyllithium and under Friedel–Crafts acetylation conditions is now described.



Ia, R = H
b, R = $CH_2C_6H_5$



IIa, R = Li
b, R = CO_2Me

When N-benzylthieno[3,2-*b*]pyrrole (Ib) was allowed to react with *n*-butyllithium, 4-benzylthieno[3,2-*b*]-pyrrole-2-lithium (IIa) evidently was formed. The reaction of this lithium derivative with acetyl chloride at −78° led to uncharacterizable products, but carbonation of IIa followed by treatment with diazomethane afforded 2-carbomethoxy-4-benzylthieno[3,2-*b*]pyrrole (IIb) in 70% yield, based on Ib. The lithium compound IIa is the first derivative prepared by direct substitution of N-benzylthieno[3,2-*b*]pyrrole.

The structure of IIb was initially deduced from its nuclear magnetic resonance (n.m.r.) spectrum. The n.m.r. spectrum of N-benzylthieno[3,2-*b*]pyrrole (Ib) has been examined,[4] and the new data obtained in this work are tabulated in Table I.[5] Spin–spin interactions are observed between the α- and β-thiophene protons, and between the α- and β-pyrrole protons. In addition, long-range spin–spin couplings between the α-thiophene and α-pyrrole protons, and between the β-thiophene and β-pyrrole protons, are observed. The former interaction is large enough to be clearly visible, but the latter, being of a magnitude close to the limit of resolution of the instrument, hitherto has been observed only once.[4]

The n.m.r. spectrum of IIb showed a multiplet centered at τ 2.77 (benzene ring protons), a singlet at 4.85 (benzyl methylene protons), and a singlet at 6.19 (carbomethoxy protons). It also had doublets at τ 2.98 and 3.61 (J = 3.0 c.p.s.), and a singlet at 2.47, each having an area corresponding to one proton. Because of the field strengths at which they appeared and the magnitude of their coupling constant, the doublets were assigned to the α- and β-pyrrole protons, respectively. The absence of evidence of interaction between an α-thiophene proton and the α-pyrrole proton indicated that the former proton was missing. The remaining singlet at τ 2.47 was therefore assigned to the β-thiophene proton.

The lowering of the field strength at which the β-thiophene proton in IIb absorbs is not surprising. Gale[6] noted a shift of 0.80 τ-unit to lower field in the position of absorption of the β-thiophene proton in going from 5-carbethoxythieno[3,2-*b*]pyrrole to 2,5-dicarbethoxy-

(1) Supported by a grant (C 3969) from the U. S. Public Health Service.

(2) D. S. Matteson and H. R. Snyder, *J. Am. Chem. Soc.*, **79**, 3610 (1957); *J. Org. Chem.*, **22**, 1500 (1957).

(3) A. D. Josey, R. J. Tuite, and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 1597 (1960).

(4) R. J. Tuite, H. R. Snyder, A. L. Porte, and H. S. Gutowsky, *J. Phys. Chem.*, **65**, 187 (1961).

(5) Proton magnetic resonance spectra were obtained by Mr. D. H. Johnson and his associates with a Varian Associates A-60 spectrometer. Tetramethylsilane was employed as an internal standard. Chemical shifts are expressed in τ-units as defined by G. V. D. Tiers [*ibid.*, **62**, 1151 (1958)].

(6) W. W. Gale, Thesis, Doctor of Philosophy, University of Illinois, Urbana, Ill., 1961.

TABLE I

N.M.R. DATA

Compound	Chemical shift, τ (peak multiplicity),[a] and couplings, c.p.s.	Assignment
Ib[b]	2.77 (m)	Benzene ring protons
	3.01 (q)	α-Thiophene proton
	3.15 (q)	α-Pyrrole proton
	3.27 (d)	β-Thiophene proton
	3.58 (d)	β-Pyrrole proton
	4.87 (s)	Benzyl methylene protons
	$J_{2,3} = 5.3$	
	$J_{5,6} = 3.0$	
	$J_{2,5} = 1.0$	
IIb	2.47 (s)	β-Thiophene proton
	2.77 (m)	Benzene ring protons
	2.98 (d)	α-Pyrrole proton
	3.61 (d)	β-Pyrrole proton
	4.85 (s)	Benzyl methylene protons
	6.19 (s)	Carbomethoxy protons
	$J_{5,6} = 3.0$	
III	2.46 (s)	β-Thiophene proton
	2.62 (s)	Benzene ring protons
	2.67 (s)	β-Pyrrole proton
	3.16 (s)	Benzyl methylene proton
	6.12 (s)	Carbomethoxy protons
	6.16 (s)	Carbomethoxy protons
	6.21 (s)	Carbomethoxy protons
VI	2.75 (m)	Benzene ring protons
	3.29 (m)	5-Pyrrole proton
	3.80 (m)	4-Pyrrole proton
	3.97 (m)	3-Pyrrole proton
	4.89 (s)	Benzyl methylene protons
	6.32 (s)	Carbomethoxy protons
	7.2 (m) 7.4 (m)	Propionate methylene protons
VIII	2.79 (d)	α-Thiophene proton
	2.92 (m)	Benzene ring protons and β-pyrrole proton
	3.29 (d)	β-Thiophene proton
	4.34 (s)	Benzyl methylene protons
	7.58 (s)	Acetyl group protons
	$J_{2,3} = 5.5$	

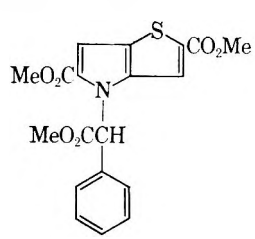
[a] s = singlet, d = doublet, q = quartet, m = multiplet. [b] The τ-values and coupling constants tabulated here differ slightly from those previously reported.[4]

thieno[3,2-*b*]pyrrole. Gronowitz and Hoffman[7] have also noted the deshielding effect of a carbomethoxy group in the 2- or 3-position of thiophene on the adjacent ring proton.

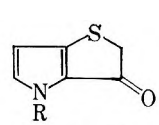
The metalation of Ib in the 2-position parallels the behavior of thiophene,[8] N-substituted pyrroles[9] and indoles,[10] and thianaphthene,[11] all of which undergo metalation α to the hetero atom. This general behavior of heterocycles toward organolithium reagents has been explained by a mechanism involving incipient coordination of the metal atom with an electron pair on the hetero atom, followed by abstraction of a proton from the carbon atom adjacent to the hetero atom by the organic portion of the reagent.[12,13] It is also possible that the α-position is attacked merely because the electron-withdrawing effect of the hetero atom renders the α-proton more acidic than its neighbors. If any 4-benzylthieno[3,2-*b*]pyrrole-5-lithium was formed, the corresponding carbonation product was apparently lost in the work-up. It appears, however, that metalation at the 2-position is favored, possibly because the anion resulting from abstraction of the 2-proton can be stabilized by $p\pi$–$d\pi$ interaction with the sulfur atom. No such stabilization of a 5-anion is possible.

In an attempt to prepare the dilithium derivative of N-benzylthieno[3,2-*b*]pyrrole, the latter substance was allowed to react with a severalfold excess of *n*-butyllithium. Upon carbonation of the resulting lithium derivative an acidic compound was obtained, which had a melting range higher than that of the acid derived from IIa. The new acid was treated with an excess of diazomethane to esterify all carboxyl groups present.

The n.m.r. spectrum of the esterified compound showed singlets, each having an area equivalent to one proton, at τ 2.46, 2.67, and 3.16. Other singlets were observed at τ 2.62 (five protons) and 6.12, 6.16, and 6.21 (each three protons). These last three peaks, of equal area and in almost the same position, indicate the presence of three carbomethoxy groups. By analogy with IIb, the peak at τ 2.46 is assigned to the β-thiophene proton. It was expected that the second lithium atom should enter the thienopyrrole nucleus in the 5-position, and that a carbomethoxy group in this position should deshield the β-pyrrole proton. The position of absorption of the β-thiophene proton was 0.80 τ-unit lower in the spectrum of IIb than in that of Ib. If the peak at τ 2.67 is assigned to the β-pyrrole proton, it denotes a downfield shift of 0.91 τ-unit from the corresponding position in the spectrum of Ib. The area of the peak at τ 2.62 indicates that the third carbomethoxy group is not located in the benzene ring. This conclusion is also suggested by the observation that *n*-butyllithium metalates benzene in only 5% yield.[14] The absence of a peak between τ 4 and 5 indicates that the benzyl methylene group has been attacked, and the peak at τ 3.16 is assigned to the remaining benzyl methylene proton. This interpretation is in accord with the observation that toluene is metalated (in very low yield, however) at the methyl group,[15] and with the postulated[12,13] initial coordination of the organometallic reagent at the hetero atom. The product is therefore designated as 4-(α-carbomethoxybenzyl)-2,5-dicarbomethoxythieno[3,2-*b*]pyrrole (III).



III



IVa, R=H

b, R=$CH_2C_6H_5$

The infrared spectrum of III revealed carbonyl absorption bands centered at 1750 cm.$^{-1}$ and 1700 cm.$^{-1}$,

(7) S. Gronowitz and R. A. Hoffman, *Arkiv. Kemi*, **16**, 539 (1960) and references cited therein.

(8) H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, **71**, 1870 (1949).

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

(10) D. A. Shirley and P. A. Roussel, *J. Am. Chem. Soc.*, **75**, 375 (1953).

(11) D. A. Shirley and M. D. Cameron, *ibid.*, **72**, 2788 (1950).

(12) H. Gilman and J. W. Morton, Jr., *Org. Reactions*, **8**, 261 (1954).

(13) H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience Publishers, Inc., New York, N. Y., 1954, p. 14.

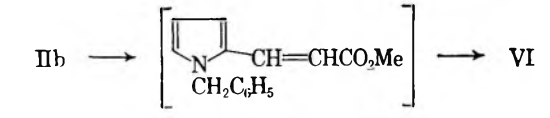
(14) H. Gilman and J. W. Morton, Jr., *Org. Reactions*, **8**, 265 (1954).

(15) H. Gilman, H. A. Pacevitz, and O. Baine, *J. Am. Chem. Soc.*, **62**, 1514 (1940).

indicating that there are carbomethoxy groups in more than one type of environment. The band at 1700 cm.$^{-1}$ is assigned to the groups in the 2- and 5-positions, by analogy with the corresponding absorptions in IIb (1695 cm.$^{-1}$) and in 2-carbethoxy- and 2,5-dicarbethoxythieno[3,2-*b*]pyrrole (each about 1690 cm.$^{-1}$).[6] The band at 1750 cm.$^{-1}$ is several wave numbers higher than the carbonyl absorption in methyl benzoate (1724 cm.$^{-1}$).[16]

In order to verify the interpretation of the n.m.r. spectrum of the 2-carbomethoxy derivative IIb, the structure of this compound was proved chemically. 2H,3H-Thieno[3,2-*b*]pyrrol-3-one (IVa) and its N-benzyl analog IVb have been desulfurized to give 2-acetylpyrrole[2] and 1-benzyl-2-acetylpyrrole,[3] respectively. The 2-carbomethoxy derivative IIb was desulfurized similarly to convert it to a suitable derivative of the known[17] compound, 1-benzyl-2-pyrrolepropionic acid (V). This derivative then was synthesized from N-benzylpyrrole by a route analogous to that employed by Kutcher and Klamerth[18] in the synthesis of 2-pyrrolepropionic acid.

Treatment of IIb with T-1 Raney nickel[19] gave an oil, which proved to be 1-benzyl-2-pyrrolepropionic acid methyl ester (VI), in 86% yield. The n.m.r. spectrum of VI showed a multiplet at τ 2.75 due to the benzene ring protons, a singlet at 4.89 due to the benzyl methylene protons, and a singlet at 6.32 due to the carbomethoxy protons. In addition, multiplets were observed at τ 3.29, 3.80, and 3.97; these were assigned to the 5-, 4-, and 3-protons, respectively, of the pyrrole ring. These absorptions were closely analogous in position and general shape to those of the corresponding protons in 2-methyl-[20,21] and 2-ethylpyrrole.[22] The spectrum also showed complex multiplets centered at τ 7.2 and 7.4, of the type which can arise from an A_2B_2 system in which the chemical shift (δ) between the A and B protons is comparable to their coupling constant (J_{AB}).[23] The presence of these multiplets, which were assigned to the propionate methylene protons, indicated that the α,β-unsaturated ester intermediate VII was smoothly hydrogenated by hydrogen present in the nickel catalyst. The infrared spectrum of the desulfurization product showed no N–H absorption, indicating that no catalytic hydrogenolysis of the benzyl group occurred, and no C=C absorption in the vicinity of 1600 cm.$^{-1}$, indicating that none of the intermediate VII survived.

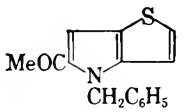


VII

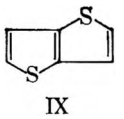
The procedure of Kutcher and Klamerth[18] was readily adapted to the synthesis of 1-benzyl-2-pyrrolepropionic acid methyl ester. N-Benzylpyrrole, prepared according to the method of Josey, Tuite, and Snyder,[3] was converted to 1-benzyl-2-formylpyrrole in 66% yield *via* the Vilsmeier formylation reaction. Treatment of the formyl compound with diethyl malonate and piperidine in refluxing absolute ethanol gave the condensation product, 2-(1-benzylpyrrolyl)methylenemalonic ester, which was subsequently hydrogenated at atmospheric pressure over Raney nickel. The hydrogenation product, 2-(1-benzylpyrrolylmethyl)-malonic ester, was saponified in methanolic potassium hydroxide. It was found that the diacid could be decarboxylated by heating above 140° under reduced pressure. The addition of copper–bronze powder did not appear to facilitate the decarboxylation. Much resinification occurred, and sublimation of the mixture proved to be the best method of isolating the 1-benzyl-2-pyrrolepropionic acid (V). The pure acid, obtained by resublimation, was converted to its methyl ester (VI) by treatment with diazomethane. The n.m.r. and infrared spectra of this ester were identical with those of the desulfurization product of 2-carbomethoxy-4-benzylthieno[3,2-*b*]pyrrole (IIb).

N-Benzylthieno[3,2-*b*]pyrrole (Ib) was exposed to several reagents in attempts to discover the position of attack by electrophiles. Treatment of Ib with bromine at temperatures as low as −60° produced a complex mixture of resinous substances. Several attempts to form the mono- and dinitro derivatives of Ib by treating it with cupric nitrate in acetic anhydride[24] met a similar fate. The reaction of ethyl diazoacetate and Ib led only to mixtures of Ib and one or more substitution products which could not be isolated or characterized.

The action of stannic chloride on a solution of Ib and acetyl chloride in benzene at 0° afforded an oily white crystalline material which corresponded to a 12% yield of a monoacetyl derivative. The infrared spectrum of this material had a carbonyl absorption band at 1638 cm.$^{-1}$. Upon examination of its n.m.r. spectrum, the compound was designated as 4-benzyl-5-acetylthieno[3,2-*b*]pyrrole (VIII). The oil present in the product could not be removed, and it may represent a trace amount of a position isomer of VIII.



VIII



IX

The n.m.r. spectrum of VIII has a multiplet, centered at τ 2.92, having an area equivalent to at least six protons. Part of this absorption is undoubtedly due to the benzene ring protons. Singlets at τ 4.34 (two protons) and 7.58 (three protons) are assigned to the benzyl methylene protons and the acetyl group protons, respectively. The spectrum also shows doublets at τ

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 179, 182.

(17) O. Cervinka, K. Pelz, and I. Jirkovsky, *Collection Czech. Chem. Commun.*, **26**, 3116 (1961).

(18) W. Kutcher and O. Klamerth, *Z. Physiol. Chem.*, **289**, 229 (1952).

(19) X. A. Dominguez, I. C. Lopez, and R. Franco, *J. Org. Chem.*, **26**, 1625 (1961).

(20) R. Abraham and H. Bernstein, *Can. J. Chem.*, **37**, 1056 (1959).

(21) S. Gronowitz, A. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Arkiv. Kemi*, **18**, 133 (1961).

(22) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, spectrum no. 130.

(23) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 89–95.

(24) For examples of the use of these reagents as a nitrating medium, see A. G. Anderson, Jr., J. A. Nelson, and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4980 (1953); H. W. Moore and H. R. Snyder, *J. Org. Chem.*, **29**, 97 (1964).

2.79 and 3.29 (J = 5.5 c.p.s.). Because of their position and the magnitude of their coupling constant, these doublets are assigned, respectively, to the α- and β-thiophene protons. The doublet at τ 2.79 shows no further splitting, denoting no interaction between the α-thiophene proton and an α-pyrrole proton, and indicating that the acetyl group occupies the α-pyrrole position. It is expected[7] that such an acetyl group would deshield the β-pyrrole proton. The absorption due to this proton, which appears at τ 3.58 in Ib, is probably obscured beneath the benzene ring multiplet. It is also noteworthy that the α-thiophene proton of VIII absorbs at slightly lower field than that in Ib. In view of the interaction between the α-thiophene and α-pyrrole protons in Ib, it is not surprising that the deshielding effects of an electron-withdrawing group in the 5-position should manifest itself in the 2-position. Gronowitz and Hoffman[7] have observed that the 5-position in 2-acetylthiophene experiences this type of deshielding. The shifts of the absorption bands of the benzene ring protons and the benzyl methylene protons away from their usual values may also be a manifestation of the diamagnetic anisotropy of a carbonyl group in the 5-position. Comparison of the benzyl methylene proton bands of N-benzylpyrrole and N-benzyl-2-formylpyrrole, obtained during the synthesis of V, shows a downfield shift of 0.58 τ-unit between the former compound and the latter.

When the portion of the spectrum of VIII between τ 2.0 and 3.5 was recorded at a sweep width of 100 c.p.s., the fine structure of the doublet centered τ 3.29 was observed. Each peak of this doublet was resolved into a doublet whose coupling constant was 0.6 c.p.s. Since these peaks are assigned to the β-thiophene proton, this fine structure is probably due to spin–spin coupling between the β-thiophene and β-pyrrole protons. Although this interaction is not normally visible in routine spectra of thienopyrrole derivatives, it has been shown to exist.[4]

The position of the carbonyl absorption band in the infrared spectrum of VIII cannot be used as supporting evidence for its structure. Although its frequency coincides exactly with that of 2-acetylpyrrole (1638 cm.$^{-1}$),[25] it is also very close to the value reported for the 2-acetyl carbonyl absorption in 3-acetoxy-2,4-diacetylthieno[3,2-*b*]pyrrole (1637 cm.$^{-1}$).[25]

In attempts to increase the yield of VIII, N-benzylthieno[3,2-*b*]pyrrole was treated with acetyl chloride and stannic chloride in carbon disulfide at −78°, with acetic anhydride and orthophosphoric acid at 60°, and with acetyl chloride and the nitromethane–aluminum chloride adduct in nitromethane at −30°. None of these experiments gave a crystalline product.

In view of the poor yield of VIII, no definitive statement on the relative reactivities of the various ring positions in Ib can be made. If any electrophilic substitution occurred at the 2-, 3-, or 6-positions of Ib, the products evidently were lost. Since the thieno[3,2-*b*]pyrrole nucleus is isosteric with indole, some substitution in the 6-position of IIb, which corresponds to the reactive 3-position of indole,[26] might be expected. However, the formation of VIII indicates that the behavior of Ib resembles that of thieno[3,2-*b*]thiophene (IX), which is known to undergo electrophilic substitution α to the hetero atom.[27]

(25) R. J. Tuite, A. D. Josey, and H. R. Snyder, *J. Org. Chem.*, **82**, 4360 (1960).

(26) V. Schomaker and L. Pauling, *ibid.*, **61**, 1779 (1939).

Experimental[28]

Preparation of N-Benzylthieno[3,2-*b*]pyrrole (Ib).—This compound was prepared by the method of Josey, Tuite, and Snyder.[3] When Ib was prepared in this way, its infrared spectrum revealed a weak band at 1650 cm.$^{-1}$, due to carbonyl absorption of unchanged 4-benzyl-2H,3H-thieno[3,2-*b*]pyrrol-3-one. Even when the ketone, IVb, was swamped with nearly four times the amount of sodium borohydride previously used,[3] the carbonyl absorption was still visible. The N-benzylthieno[3,2-*b*]pyrrole was isolated as a brown oil which crystallized upon refrigeration and was used without further purification.

Reaction of N-Benzylthieno[3,2-*b*]pyrrole (Ib) with *n*-Butyllithium.—A pentane–heptane solution of *n*-butyllithium, obtained from the Foote Mineral Company, was employed. Its concentration was determined by titration according to the method of Gilman and Haubein.[29]

The N-benzylthieno[3,2-*b*]pyrrole was prepared and isolated as an oil in the usual manner.[3] This oil was dried over phosphorus pentoxide at room temperature (0.1 mm.) for 24 hr. The apparatus used was oven-dried, assembled while hot, and flushed with a stream of dry nitrogen as it cooled. The nitrogen atmosphere was maintained throughout the reaction.

To a solution of 1.45 g. (6.8 mmoles) of Ib in 80 ml. of anhydrous ether was added 8.4 mmoles of *n*-butyllithium in pentane–heptane solution (6.5 ml. of solution) dropwise with magnetic stirring at room temperature over a 30-min. period. The solution turned brown during this time. The solution was stirred at room temperature for 15 hr. longer, and then was poured onto an excess of Dry Ice under anhydrous ether. When the solid carbon dioxide had disappeared and the dark brown reaction mixture had warmed to room temperature, 70 ml. of water was added. The organic phase was separated and extracted with two 20-ml. portions of 2% aqueous sodium hydroxide. The aqueous solutions were combined, chilled in ice, and acidified with concentrated hydrochloric acid. When pH 4 was reached, a flocculent brown solid appeared. Acidification was continued until precipitation was complete. The crude 2-carboxy-4-benzylthieno[3,2-*b*]pyrrole weighed 1.52 g. (87%). A small portion of this acid was recrystallized twice from methanol–water, and recovered as tan microcrystals, m.p. 192–196° dec. An infrared spectrum of the recrystallized compound (in a potassium bromide pellet) revealed a broad band centered at 1670 cm.$^{-1}$ (carbonyl absorption).

The crude acid was suspended in 50 ml. of ether and treated with an ethereal solution of diazomethane, prepared from 1.5 g. of nitrosomethylurea.[30] Nitrogen evolution occurred as the diazomethane solution was added. The reaction mixture, which contained a finely divided tan solid, was allowed to stand at room temperature for several hours. The ether was then removed *in vacuo* to give 1.28 g. (80%, based on the crude acid) of crude 2-carbomethoxy-4-benzylthieno[3,2-*b*]pyrrole (IIa). Four recrystallizations from cyclohexane afforded an analytical sample, m.p. 95–96°.

An infrared spectrum of the compound in a potassium bromide pellet had a peak at 1695 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.38; H, 4.96; N, 4.80.

Reaction of N-Benzylthieno[3,2-*b*]pyrrole (Ib) with Excess *n*-Butyllithium.—The antimoisture precautions observed here were identical with those taken in the preparation of Ia. To a solution of 2.29 g. (10.7 mmoles) of Ib in 100 ml. of anhydrous ether under an atmosphere of dry nitrogen was added 42.9 mmoles of *n*-butyl-

(27) H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience Publishers, Inc., New York, N. Y., 1954, p. 10.

(28) All melting points were determined on a Kofler hot stage and are uncorrected. Microanalyses were performed by Mr. Josef Nemeth and his associates. Infrared spectra were determined by Mr. D. H. Johnson and his associates with a Perkin-Elmer Model 21 infrared spectrophotometer equipped with sodium chloride optics. Solvent evaporations carried out *in vacuo* were done with a rotary evaporator under water pump pressure.

(29) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).

(30) F. Arndt, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 166.

lithium in a pentane–heptane solution dropwise with stirring over a 30-min. period. After the addition was completed, the dark brown reaction mixture was stirred for 14 hr. under the nitrogen atmosphere, then was poured onto an excess of Dry Ice under anhydrous ether. When the excess Dry Ice had sublimed and the mixture had warmed to room temperature, 20 ml. of water was added. The ether layer was removed and extracted with four 20-ml. portions of 2% aqueous sodium hydroxide. The aqueous extracts were added to the original water layer. The aqueous solution was chilled in an ice bath, and carefully acidified to pH 5 with hydrochloric acid, whereupon a dark tarry mass appeared. The solution was filtered, the tarry residue was discarded, and the filtrate was acidified further. At pH 4 a tan flocculent precipitate appeared. Acidification was continued until no more solid appeared upon addition of acid. The crude triacid weighed 2.51 g. (68%), and melted at 210–225° dec. An infrared spectrum of the crude acid in a potassium bromide pellet had a very broad band centered at 1685 cm.$^{-1}$ (carbonyl absorption).

To a suspension of 2.51 g. (7.27 mmoles) of the crude triacid in 150 ml. of ether was added an ethereal solution of diazomethane prepared from 3 g. of nitrosomethylurea.[30] The reaction mixture was stirred for 90 min., and the solvent was removed *in vacuo* to give 2.39 g. (85%) of 4-(α-carbomethoxybenzyl)-2,5-dicarbomethoxythieno[3,2-*b*]pyrrole (III). Two successive recrystallizations from 95% ethanol, followed by sublimation at 130° (0.04 mm.), afforded an analytical sample, m.p. 168.5–169.5°.

An infrared spectrum of a 10% solution of the compound in chloroform had a broad band centered at 1700 cm.$^{-1}$ and a narrower band at 1750 cm.$^{-1}$ (carbonyl absorptions).

Anal. Calcd. for $C_{13}H_{12}NO_6S$: C, 58.80; H, 4.43; N, 3.62. Found: C, 58.72; H, 4.40; N, 3.38.

Desulfurization of 2-Carbomethoxy-4-benzylthieno[3,2-*b*]pyrrole (IIb).—Two hundred milligrams (0.74 mmole) of IIb was mixed with 2.0–2.5 g. of T-1 Raney nickel[19] in 25 ml. of 95% ethanol. The mixture was refluxed for 5 hr., allowed to cool, and the nickel was filtered and was washed with a little 95% ethanol which was added to the clear mother liquor. The ethanol then was removed *in vacuo* to give 154 mg. (86%) of methyl 1-benzyl-2-pyrrolepropionate (VI) as a clear yellow oil, which could not be induced to crystallize.

An infrared spectrum of a 10% solution of this oil in chloroform revealed a peak at 1730 cm.$^{-1}$ (carbonyl absorption).

Preparation of 1-Benzyl-2-formylpyrrole.—A 200-ml. three-necked round-bottom flask fitted with a magnetic stirrer, reflux condenser, and dropping funnel was placed in an ice bath and charged with 5.11 g. (0.0699 mole) of dimethylformamide. To this was added, with stirring over a 15-min. period, 10.74 g. (0.0699 mole) of phosphorus oxychloride. The ice bath was removed, and the phosphorus oxychloride–dimethylformamide complex was stirred for 15 min. The ice bath was replaced, and 15 ml. of ethylene dichloride was added to the complex. After the resulting solution had been allowed to chill, a solution of 10.0 g. (0.06 mole) of freshly distilled N-benzylpyrrole in 15 ml. of ethylene dichloride was added dropwise with stirring over a 1-hr. period. The ice bath was replaced with a heating mantle, and the orange solution was refluxed for 25 min. The solution was allowed to cool, and about 50 g. (0.37 mole) of sodium acetate trihydrate in 60 ml. of water was added. The orange mixture was stirred at room temperature for 80 min., then refluxed for 20 min. The cooled mixture was poured into a separatory funnel. The orange organic phase was separated and washed with two 7-ml. portions of a saturated sodium carbonate solution (the washings were alkaline). The ethylene dichloride solution was dried over anhydrous sodium carbonate and, after the filtered solution was concentrated *in vacuo*, 12.6 g. of a red oil was obtained.

The oil was distilled *in vacuo*. Only one fraction was collected, b.p. about 130° (0.9 mm.). The colorless distillate weighed 8.08 g. (69%). It was stored in a brown bottle in the refrigerator. An infrared spectrum of a 10% solution of the compound in chloroform had a peak at 1660 cm.$^{-1}$ (carbonyl absorption).

Reaction of 1-Benzyl-2-formylpyrrole with Diethyl Malonate.—A solution of 3.63 g. (0.0196 mole) of 1-benzyl-2-formylpyrrole, 3.2 g. (0.0200 mole) of diethyl malonate, and 0.1 ml. of piperidine in 10 ml. of absolute ethanol was refluxed for 14 hr. Upon cooling, white platelets precipitated from the yellow solution. These crystals were removed by filtration, and the mother liquor was concentrated *in vacuo*. Upon chilling, the concentrated solution yielded a small quantity of white platelets, which were combined with the first crop to give 3.92 g. (61%) of 2-(1-benzylpyrrolyl)methylenemalonic ester, m.p. 92–98°. This product was used without further purification.

An infrared spectrum of the compound in a potassium bromide pellet had a doublet with maxima at 1720 and 1700 cm.$^{-1}$ (carbonyl absorption), and a band at 1610 cm.$^{-1}$ (conjugated C=C absorption).

Hydrogenation of 2-(1-Benzylpyrrolyl)methylenemalonic Ester.—A suspension of 4 g. of T-1 Raney nickel[19] in about 20 ml. of 95% ethanol was placed in an atmospheric pressure hydrogenation apparatus, and to it was added 2.00 g. (0.0061 mole) of 2-(1-benzylpyrrolyl)methylenemalonic ester dissolved in the minimum amount of warm 95% ethanol. The resulting mixture was stirred under hydrogen for about 27 hr., or until hydrogen uptake was complete. The nickel then was removed by filtration and washed once with a little 95% ethanol which was added to the mother liquor. Removal of the solvent *in vacuo* afforded 1.76 g. (88%) of 2-(1-benzylpyrrolylmethyl)malonic ester as a clear oil, which was used without further purification.

An infrared spectrum of a film of this oil had a doublet with maxima at 1720 and 1710 cm.$^{-1}$ (carbonyl absorption). It showed no N–H stretching absorption, and only slight C=C stretch at 1600 cm.$^{-1}$.

Saponification and Decarboxylation of 2-(1-Benzylpyrrolylmethyl)malonic Ester.—A solution of 2.14 g. (0.0065 mole) of 2-(1-benzylpyrrolylmethyl)malonic ester in 25 ml. of 50% methanolic potassium hydroxide was refluxed 5 hr. After cooling, the reaction mixture was quenched with 20 ml. of water. The methanol was removed from the mixture *in vacuo* to give an aqueous suspension of fine white platelets. These platelets were collected and dissolved in the minimum amount of water, and the resulting solution was chilled in ice and carefully acidified to pH 4 with hydrochloric acid. At pH 5, the diacid began precipitating from the solution as fine white plates. The dried product weighed 1.14 g. (64%) and had m.p. 136–138° dec.

A mixture of 679 mg. (2.48 mmoles) of the diacid and a pinch of copper–bronze powder was heated under reduced pressure (laboratory vacuum line) at temperatures up to 160° for 90 min. Gas evolution was observed above 135°. The product, a black tarry material, was placed in a microsublimator and heated to 135° (0.11 mm.) for 18 hr. The monoacid sublimed as fine white needles which weighed 107 mg. The residue in the sublimator was heated to 195° (0.11 mm.) for 24 hr., affording an additional 47 mg. of pale yellow sublimate. The total yield of 1-benzyl-2-pyrrolepropionic acid (V) was 154 mg. (27%). A portion of the first crop of sublimed monoacid was placed in the microsublimator and heated to 100° (0.11 mm.) to give the analytical sample of fine white needles, m.p. 139–143°, lit.[17] m.p. 141–142°.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.32; H, 6.59; N, 6.11. Found: C, 73.60; H, 6.77; N, 6.08.

To a suspension of 100 mg. (0.44 mmole) of 1-benzyl-2-pyrrolepropionic acid in 1 ml. of ether was added an ethereal solution of diazomethane until gas evolution ceased and the yellow diazomethane color persisted. Removal of the solvent *in vacuo* afforded 97 mg. (90%) of methyl 1-benzyl-2-pyrrolepropionate (VI) as a tan oil. The infrared and n.m.r. spectra of this oil were identical in every respect with those of the methyl 1-benzyl-2-pyrrolepropionate obtained by desulfurization of IIb.

Preparation of 4-Benzyl-5-acetylthieno[3,2-*b*]pyrrole (VIII).—A solution of 2.69 g. (0.0126 mole) of N-benzylthieno[3,2-*b*]pyrrole (Ib) and 0.990 g. (0.0126 mole) of acetyl chloride in 80 ml. of benzene was chilled to 0° in an ice bath. To this solution was added a solution of 3.28 g. (0.0126 mole) of stannic chloride in 20 ml. of benzene dropwise over a 30-min. period with manual swirling. As the first drops of stannic chloride solution were added, the reaction mixture became deep purple, and soon the addition product began to precipitate as a gummy purple solid. After the addition was completed, the reaction mixture was allowed to stand at room temperature for 1 hr. Then it was treated with a solution of 6 ml. of concentrated hydrochloric acid in 80 ml. of water. The resulting mixture was stirred for 18 hr., or until almost all of the purple gum had dissolved. During this period, 80 ml. of benzene was added. At the end of the 18-hr. period, methylene chloride was added to aid the dissolution of the remaining gum and to facilitate the separation of the aqueous and nonaqueous phases. The mixture was filtered to remove interfacial debris, and the dark red organic phase was separated

and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* afforded 2.36 g. of a dark tar.

This tar was dissolved in the minimum amount of chloroform and introduced onto a column of neutral alumina. During elution with chloroform a broad yellow band, and above it a broad rust-colored band, developed on the column. The eluate collected before the yellow band reached the bottom of the column was concentrated *in vacuo* to give 0.658 g. of brown oil, which crystallized upon standing in the refrigerator. The yellow and rust-colored bands were eluted, and the eluates were concentrated to give brown oils which did not crystallize upon chilling. They were discarded.

The brown crystals were placed in a sublimator and heated to 110° (0.025 mm.). The product sublimed as oily white crystals, which weighed 0.268 g. (12%). Since a sample of this sublimate darkened when allowed to stand in the air at room temperature, the remainder was kept refrigerated. A portion of this sublimate was rinsed with several drops of ether in an attempt to remove the oily material. Then it was sublimed at 80° (0.025 mm.). As soon as the oily sublimate began to crystallize, the sublimation was interrupted and the cold finger was cleaned. Sublimation then was resumed at 80° (0.025 mm.). This fractional sublimation did not effect removal of the oily material. One additional sublimation at 100° (0.025 mm.) gave slightly oily white crystals, m.p. 107–117° with previous softening, which were submitted for analysis.

An infrared spectrum of the compound in a potassium bromide pellet had a band at 1638 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_{15}H_{13}NOS$: C, 70.57; H, 5.13; N, 5.48. Found: C, 70.35; H, 5.10; N, 5.53.

Preparation and Reactions of 5-Carbethoxythieno[3,2-*b*]pyrrole and Some of Its Derivatives[1,2]

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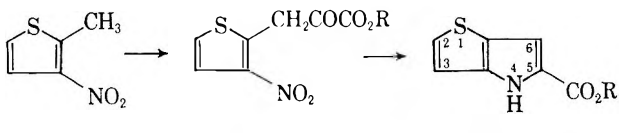
The preparation of 5-carbethoxythieno[3,2-*b*]pyrrole (IIIb) is accomplished by condensation of 2-methyl-3-nitrothiophene (I) with diethyl oxalate followed by stannous chloride reduction of the product, ethyl 3-nitro-2-thienylpyruvate (IIb), in an over-all yield of 47%. A similar procedure gives rise to 2,5-dicarbethoxythieno-[3,2-*b*]pyrrole (XIV) from 2-methyl-3-nitro-5-carbethoxythiophene (XII) in an over-all yield of 38%. Some typical electrophilic, aromatic reactions are carried out on these two thieno[3,2-*b*]pyrrole derivatives. Structures of the various substances are proposed on the basis of chemical and spectral data.

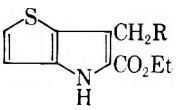
Although thieno[3,2-*b*]pyrrole and several of its derivatives have been synthesized,[4-9] there remained a need for additional synthetic pathways, and especially for routes leading to compounds having substituents of unambiguous orientation. In the earliest preparation of the parent heterocycle,[4] the pyruvic acid IIa was prepared *via* an azlactone in several steps from 2-methyl-3-nitrothiophene (I), since the condensation of I with diethyl oxalate was thought to be unsuccessful.[10] Compound IIa was then reduced to yield 5-carboxythieno-[3,2-*b*]pyrrole (IIIa), which was decarboxylated thermally.[4]

The preparation of 5-carbethoxythieno[3,2-*b*]pyrrole (IIIb) now has been accomplished by reaction of 2-methyl-3-nitrothiophene (I) and diethyl oxalate followed by reduction of the product, ethyl 3-nitro-2-thienylpyruvate (IIb), with stannous chloride. The over-all yield of this sequence was 47%. The structure of IIIb was confirmed by its hydrolysis to 5-carboxythieno[3,2-*b*]pyrrole (IIIa), a known compound,[4] with which it was identical in all respects. Nuclear magnetic resonance data for IIIb are shown in Table I. The coupling constant, $J_{2,3}$ = 5.3 c.p.s., is the same as that for N-benzylthieno[3,2-*b*] pyrrole.[11] The spectrum of IIIb exhibits a long-range splitting ($J_{3,6}$ = 0.7 c.p.s.), an effect which also has been observed in N-benzylthieno[3,2-*b*]pyrrole.[11]



I IIa, R = H; b, R = Et IIIa, R = H; b, R = Et

When IIIb was treated with dimethylamine and formaldehyde, 6-dimethylaminomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVa) was isolated in good yield.



IVa, R = $N(CH_3)_2$
b, R = $N(CH_2)_5$
c, R = H
d, R = CN

The structure of IVa was indicated by its n.m.r. spectrum, which contained two equally split doublets, J = 5.7 c.p.s., in the aromatic region. These were assigned to the thiophene protons. The reaction of piperidine, formaldehyde, and IIIb afforded the 6-piperidinomethyl compound IVb, which gave an n.m.r. spectrum similar in the aromatic region to that of IVa.

Chemical proof for the position of the aminomethyl group was obtained through the conversion of IVb in a modified Sommelet reaction[12] to 6-formyl-5-carbethoxythieno[3,2-*b*]pyrrole (V), from which, by treatment with

(1) Abstracted from portions of the theses submitted by W. W. Gale (June, 1961) and A. N. Scott (June, 1964) to the Graduate College of the University of Illinois in partial fulfillment of the requirements for degrees of Doctor of Philosophy.

(2) This investigation was supported in part by a grant [3969 Bio] from the National Cancer Institute, U. S. Public Health Service.

(3) University Fellow, June–August, 1959; Phillips Petroleum Co. Fellow, 1959–1960.

(4) H. R. Snyder, L. A. Carpino, J. F. Mills, and J. F. Zack, *J. Am. Chem. Soc.*, **79**, 2556 (1957).

(5) D. S. Matteson and H. R. Snyder, *J. Org. Chem.*, **22**, 1500 (1957).

(6) W. Carpenter and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 2592 (1960).

(7) R. J. Tuite, A. D. Josey, and H. R. Snyder, *ibid.*, **82**, 4360 (1960).

(8) R. J. Tuite and H. R. Snyder, *ibid.*, **82**, 4364 (1960).

(9) J. Witt, Jr., Thesis, Doctor of Philosophy, University of Illinois, 1961.

(10) L. A. Carpino, Thesis, Doctor of Philosophy, University of Illinois, 1953.

(11) R. J. Tuite, H. R. Snyder, A. L. Porte, and H. S. Gutowsky, *J. Phys. Chem.*, **65**, 187 (1961).

(12) H. R. Snyder, S. Swaminathan, and H. J. Sims, *J. Am. Chem. Soc.*, **74**, 5110 (1952).

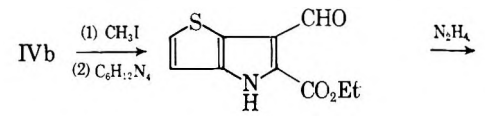
TABLE I

N.M.R. DATA[a]

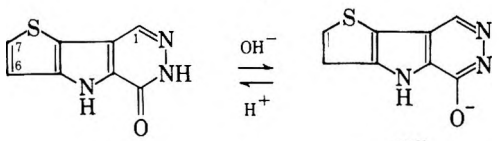
Compound	Chemical shifts (δ) of aromatic protons, p.p.m.	Assignment of protons, ring position numbers	Couplings, c.p.s.
IIIb[b]	7.4	2	$J_{2,3} = 5.3$
	7.0	3	$J_{3,6} = 0.7$
	7.2	6	$J_{4,6} = 2.0$
IVa[c]	7.3	2	$J_{2,3} = 5.7$
	6.8	3	
IVb[c]	7.3	2	$J_{2,3} = 5.7$
	6.9	3	
IVc[d]	7.4	2	$J_{2,3} = 5.7$
	6.9	3	
IVd[d]	7.5	2	$J_{2,3} = 5.7$
	6.9	3	
V[e]	7.7	2	$J_{2,3} = 5.3$
	7.1	3	
VI[e]	8.6	1	$J_{6,7} = 5.3$
	7.3	6	
	7.8	7	
VIII[d]	7.2	2	...
IXa[d]	7.8	3	
	7.2	6	$J_{4,6} = 1.9$
IXb[d]	7.6	3	
	7.1	6	$J_{4,6} = 1.6$
IXc[d]	8.0	3	
	7.2	6	$J_{4,6} = 1.7$
XII[d]	7.7	3	
	7.2	6	$J_{4,6} = 1.6$
XIII[d]	7.8	3	...
XIV[d]	7.6	3	...

[a] Spectra obtained on Varian Associates spectrometers, Models V-4300-B or A-60, by Mr. O. W. Norton and Mr. D. H. Johnson. [b] 25% solution in acetone. [c] 20% in deuteriochloroform. [d] 20% in dimethyl sulfoxide. [e] 5% in dimethyl sulfoxide.

hydrazine under suitable conditions,[13] the pyridazinone VI was prepared. The formation of a new ring which joins positions 5 and 6 of thienopyrrole clearly establishes that aminomethylation of IIIb occurred in the pyrrole ring, in contrast to monoacylations (discussed below) in which the thiophene ring is attacked.



V



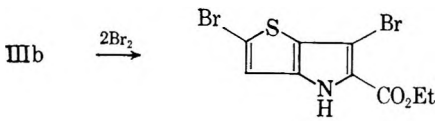
VI VII

The pyridazinone VI, although ketonic in the solid state, dissolves reversibly in aqueous alkali to form the anion VII, which contains an aromatic pyridazine ring.

The methiodide of IVa could be reduced by sodium borohydride to give 6-methyl-5-carbethoxythieno[3,2-*b*]-pyrrole (IVc) in 64% yield. The n.m.r. spectrum of IVc was entirely consistent with the assigned structure. In addition, the methosulfate of IVa was used to alkylate potassium cyanide. The product, 6-cyanomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVd) was isolated in only 17% yield.

(13) N. N. Suvorov, Z. D. Ovchinnikova, and Y. N. Sheinker, *J. Gen. Chem. USSR*, **31**, 2174 (1961).

When 5-carbethoxythieno[3,2-*b*]pyrrole (IIIb) was treated with 1 molar equiv. of bromine, a mixture of IIIb and a dibromo derivative of IIIb was obtained. All attempts to isolate a monobromo compound were unsuccessful even at temperatures below 0°. The dibromo compound, 2,6-dibromo-5-carbethoxythieno[3,2-*b*]pyrrole (VIII), was obtained in 96% yield when IIIb was treated with 2 molar equiv. of bromine. The n.m.r. spectrum of VIII contained one peak, a singlet, in the aromatic region. The absence of splitting in this peak indicated that position 6 had been substituted in VIII. The fact that VIII did not yield a Mannich base even at a temperature of 100° for a period of 2 weeks also furnished evidence that VIII was not the 2,3-disubstituted derivative. The 2,6- rather than the 3,6-dibromo structure was implied by the position of the aromatic singlet in the n.m.r. spectrum (Table I). A bromine atom in the 3-position of thiophene has been found to lower the magnetic field at which the 2-proton resonance appears.[14] The fact that the resonance of the aromatic proton in VIII appeared at a higher field than the resonance of the 2-proton in IIIb gave evidence that VIII was not the 3,6-disubstituted isomer.

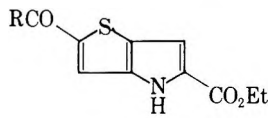


VIII

Under the same mild conditions which led to the dibromo derivative VIII, 3 molar equiv. of bromine afforded, 2,3,6-tribromo-5-carbethoxythieno[3,2-*b*]pyrrole. The n.m.r. spectrum of this compound contained no aromatic peaks.

The behavior of IIIb shows that positions 2 and 6 are similar in reactivity toward bromine, while position 3 is only slightly less reactive. From the Mannich reactions, in which the attacking electrophiles appear to be more selective, only the 6-aminomethyl compounds have been isolated.

The reaction of 5-carbethoxythieno[3,2-*b*]pyrrole (IIIb) with acetyl chloride and aluminum chloride produced 2-acetyl-5-carbethoxythieno[3,2-*b*]pyrrole (IXa) in 71% yield. The structure of IXa was indicated by its n.m.r. spectrum which contained a singlet at δ = 7.8 and a doublet at 7.2 p.p.m. The doublet had a coupling constant of 1.9 c.p.s. and was assigned to the 6-proton resonance. It is known that an acetyl group in the 2-position of thiophene greatly lowers the magnetic field at which resonance of the 3-proton appears.[14] Chemical proof for the position of the acetyl group was furnished by the oxidation of IXa to 2-carboxy-5-



IXa, R=CH3
b, R=OH
c, R=H

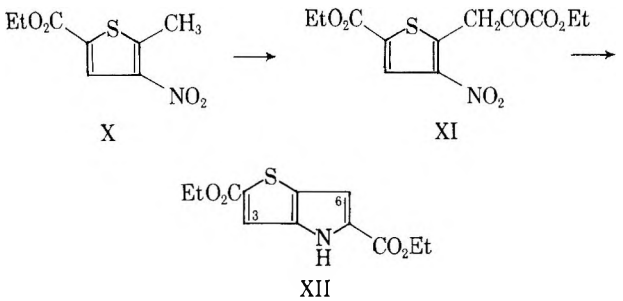
IX

carbethoxythieno[3,2-*b*]pyrrole (Xb) with alkaline permanganate. The oxidation product was identical in all respects with an authentic sample of Xb prepared by the condensation of 2-methyl-3-nitro-5-thenoic acid followed by reductive cyclization.

(14) S. Gronowitz and R. A. Hoffman, *Arkiv. Kemi*, **13**, 279 (1958).

Direct formylation of IIIb also occurred at the 2-position; reaction of IIIb with phosphorus oxychloride and dimethylformamide furnished 2-formyl-5-carbethoxythieno[3,2-*b*]pyrrole (IXc) in 66% yield. The 2-formyl compound gave infrared and n.m.r. spectra distinctly different from those of its 6-formyl isomer V. Through oxidation, the 2-formyl derivative was converted to the 2-carboxy compound IXb.

2,5-Dicarbethoxythieno[3,2-*b*]pyrrole (XII) was synthesized in essentially the same way as was IIIb. Condensation of 2-methyl-3-nitro-5-carbethoxythiophene (X) with diethyl oxalate afforded ethyl 5-carbethoxy-3-nitro-2-thienylpyruvate (XI), which, when reduced with stannous chloride, gave XII. A doublet at $\delta = 7.2$ ($J = 1.6$ c.p.s.) and a singlet at 7.7 p.p.m. were assigned to the resonances of the 6- and 3-protons, respectively. The fact that XII could be synthesized in a manner similar to that of IIIb indicates the general utility of the method for the synthesis of substituted thieno[3,2-*b*]pyrrole derivatives.



Bromination of XII yielded a monobromo derivative even in the presence of excess bromine. The structure of the product was 6-bromo-2,5-dicarbethoxythieno-[3,2-*b*]pyrrole (XIII) on the basis of its n.m.r. spectrum, which showed one singlet in the aromatic region at $\delta = 7.8$ p.p.m. This peak could only be due to the resonance of the 3-proton because of its position and lack of splitting.

When XII was treated with dimethylamine and formaldehyde, 6-dimethylaminomethyl-2,5-dicarbethoxythieno[3,2-*b*]pyrrole (XIV) was isolated in 79% yield. The structure of XIV was indicated by its n.m.r. spectrum, which revealed a singlet at $\delta = 7.6$ p.p.m., too low in field for a 6-proton.

The formation of a 6-substituted product in the bromination of XII demonstrated the deactivating influence of a 2-carbethoxyl group on the 3-position. The fact that the Mannich reaction and the bromination of XII were carried out under identical conditions with those employed in the same reactions of 5-carbethoxythieno[3,2-*b*]pyrrole indicated that an electron-withdrawing group in the 2-position did not reduce the reactivity of the 6-position.

Experimental[15]

Ethyl 3-Nitro-2-thienylpyruvate (IIb).—This preparation was carried out under strictly anhydrous conditions. A slow, steady stream of dry nitrogen was passed over 180 ml. of absolute ethanol, while 8.30 g. (0.36 g.-atom) of sodium metal was added. After the addition of the sodium was completed, the mixture was stirred and the ethanol was brought to gentle reflux. A solution of 22.8 g. (0.16 mole) of 2-methyl-3-nitrothiophene,[4] 72.0 g. (0.49 mole) of diethyl oxalate, and 180 ml. of absolute ethanol was added all at once to the gently refluxing solution of sodium ethoxide. Almost immediately there appeared a deep purple precipitate in the reaction mixture. The mixture was kept at reflux for 15 min. The reaction was quenched by the addition of the mixture to 2 l. of water which contained 75 ml. of concentrated hydrochloric acid, and a tan solid was precipitated. The tan solid was collected and dried in the air. The dried product was dissolved in boiling benzene, and the solution was treated with Darco and filtered while still hot. The filtrate was placed in the refrigerator overnight. The yellow crystals which had formed were collected and dried. The yield of ethyl 3-nitro-2-thienylpyruvate was 35.9 g. (93%), m.p. 101–102°. Two additional recrystallizations from methylcyclohexane afforded the analytical sample, m.p. 101.5–102°.

An infrared spectrum of a 10% chloroform solution of the compound indicated peaks at 3430 (enol hydroxyl), 1700 and a shoulder at 1730 (carbonyl absorptions), and 1350 and 1530 cm.$^{-1}$ (nitro group).

Anal. Calcd. for $C_9H_9NO_5S$: C, 44.44; H, 3.73; N, 5.76. Found: C, 44.61; H, 3.70; N, 5.59.

5-Carbethoxythieno[3,2-*b*]pyrrole (IIIb).—To a solution of 10.0 g. (0.04 mole) of ethyl 3-nitro-2-thienylpyruvate in 110 ml. of absolute ethanol was added slowly with stirring a solution containing 74 g. of stannous chloride dihydrate in 125 ml. of concentrated hydrochloric acid. During the addition, the temperature of the mixture was kept below 30° by means of external cooling. Initially much of the pyruvate precipitated. The mixture was stirred for 3 hr., during which time it became homogeneous and its temperature spontaneously rose to 35–40° owing to the heat of reaction, and then fell gradually. If the temperature exceeded 40°, a cooling bath was applied. By the end of the reaction period, the solution was red and usually homogeneous, but occasionally part of the product had crystallized. The acidic reaction mixture was extracted three times with chloroform. The combined chloroform extracts were washed successively with hydrochloric acid, water, and aqueous sodium chloride solution, and were dried over anhydrous sodium sulfate. Evaporation of the chloroform gave the crude thienopyrrole, which was purified by elution with benzene on a chromatographic column of acid washed alumina. The nearly white crystals thus obtained weighed 4.4 g. (55% yield), m.p. 122–130°. One recrystallization from cyclohexane–benzene afforded a product which melted 129–130.5°. An analytical sample was prepared by one recrystallization from methylcyclohexane, m.p. 132.5–133°.

An infrared spectrum (10% in chloroform) contained peaks at 3450 and 3300 (pyrrole NH, free and bonded), and 1690 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_9H_9NO_2S$: C, 55.37; H, 4.65; N, 7.17. Found: C, 55.26; H, 4.69; N, 7.13.

6-Dimethylaminomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVa).—To 3.5 ml. of glacial acetic acid were added 170 mg. (3.78 mmoles) of dimethylamine (as a 40% aqueous solution), 110 mg. (3.67 mmoles) of formaldehyde (as a 37% aqueous solution), and 700 mg. (3.59 mmoles) of 5-carbethoxythieno[3,2-*b*]pyrrole. The temperature was kept between 0–5° while the components were added. The reaction mixture was heated on the steam bath for 1 hr. and then allowed to stand at room temperature for 12 hr. The mixture was poured onto 10 g. of ice, and it was brought to pH 10 by the careful addition of 10% sodium hydroxide. The temperature was not allowed to exceed 10° while the base was added. The gummy, white substance which precipitated could not be enticed to solidify; therefore, it was taken up in 50 ml. of ether. The ether solution was extracted with three 10-ml. portions of 10% hydrochloric acid. The hydrochloric acid extracts were combined and brought to pH 10 by the careful addition of 10% sodium hydroxide while the temperature was kept below 10°. The gummy, white substance which precipitated, solidified when stored in the refrigerator overnight. The solid was collected and dried in a vacuum desiccator for 36 hr. over phosphorus pentoxide. It was recrystallized from petroleum ether (30–60°) to yield 840 mg. (93%) of a white solid, m.p. 90–93°. The analytical sample was prepared by three recrystallizations from petroleum ether (30–60°) and was crushed in a mortar and dried in the air, m.p. 95–96°.

An infrared spectrum of a 10% chloroform solution of the product revealed peaks at 3450 and 3300 (pyrrole N–H and hydrogen-bonded pyrrole N–H), and 1675 cm.$^{-1}$ (carbonyl absorption).

(15) Melting points are uncorrected. Microanalyses were performed by Mr. Josef Nemeth and his associates, University of Illinois. Infrared spectra were obtained from a Perkin-Elmer Model 21 spectrophotometer by Mr. D. H. Johnson and associates.

Anal. Calcd. for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10. Found: C, 57.37; H, 6.55; N, 10.82.

6-Piperidinomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVb).—Piperidine (5.1 ml.), 37% aqueous formaldehyde (4.0 ml.), and 5-carbethoxythieno[3,2-*b*]pyrrole (10.0 g., 0.051 mole) were mixed in that order into 20 ml. of glacial acetic acid with cooling in an ice–water bath. The mixture was heated on a steam bath for 0.5 hr. and was allowed to stand at room temperature for 12 hr. After dilution with an equal volume of water, the mixture was extracted with ether to remove unchanged ester. The aqueous solution was brought to pH 8 by slow addition of excess potassium carbonate solution, during which the Mannich base separated as an oil or a white solid. The product was extracted into ether. After the ethereal solution was dried over sodium sulfate, most of the ether was evaporated. The residue was crystallized from hexane.

Another crystallization from cyclohexane afforded a first crop of 7.6 g., m.p. 126–136°, and a second crop of 1.0 g. From the ether extract of the acidic reaction mixture, 1.67 g. of unchanged ester was recovered. The yield of aminomethylated product, corrected for recovered ester, was 69%. Two recrystallizations of the product from petroleum ether (30–60°) afforded analytically pure 6-piperidinomethyl-5-carbethoxythieno[3,2-*b*]pyrrole, m.p. 127.5–136°.

An infrared spectrum of a 10% chloroform solution of the product revealed peaks at 3450 and 3300 (pyrrole N–H and hydrogen-bonded pyrrole N–H), and 1675 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_{15}H_{20}N_2O_2S$: C, 61.61; H, 6.89; N, 9.58. Found: C, 61.43; H, 6.84; N, 9.57.

6-Piperidinomethyl-5-carbethoxythieno[3,2-*b*]pyrrole Methiodide.—A solution of 540 mg. of 6-piperidinomethyl-5-carbethoxythienopyrrole in about 15 ml. of ether was added dropwise to 10 ml. of methyl iodide with stirring. The mixture was refrigerated for 24 hr. The solid was collected and washed with ether, yielding 803 mg. (96%), m.p. 175–183° dec.

6-Formyl-5-carbethoxythieno[3,2-*b*]pyrrole (V).—The methiodide salt of 6-piperidinomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (870 mg., 2.0 mmoles) was dissolved with warming in 8 ml. of propionic acid–water (2 to 1 by volume). The solution was cooled and 550 mg. of hexamethylenetetramine was added and dissolved with swirling. This solution was added over a 1-hr. period in an atmosphere of nitrogen to a boiling solution of 116 mg. of hexamethylenetetramine in 0.56 ml. of the same solvent. After the addition was complete, boiling was continued for 1.5 hr. under nitrogen. Then the light yellow solution was cooled and poured into 32 ml. of water. The solid product began to separate immediately. After the mixture had been stored in the refrigerator overnight, the solid was collected and washed with ice–water. The material weighed 270 mg. after drying *in vacuo* over potassium hydroxide. For purification the crude material was sublimed at 110–120° (10 μ), in a cold-finger sublimator and recrystallized from benzene–absolute ethanol. A yield over 50% of theoretical was obtained, m.p. 214–220° dec. An analytical sample was prepared by two recrystallizations from benzene-ethanol, m.p. 217–221° dec. The substance absorbed in the infrared (KBr pellet) at 1705 (ester carbonyl) and 1635 cm.$^{-1}$ (aldehyde carbonyl). The unpurified dinitrophenylhydrazone of the aldehyde ester melted at 306–309°.

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.81; H, 4.07; N, 6.27. Found: C, 53.54; H, 4.19; N, 6.53.

3H,4H,5H-Thieno[3′,2′:2,3]pyrrolo[4,5-*d*]pyridazin-4-one (VI).—The following procedure was similar to that of Suvorov, *et al.*,[13] for the conversion of 3-formyl-2-carbethoxyindole to the corresponding indolopyridazinone. 6-Formyl-5-carbethoxythieno-[3,2-*b*]pyrrole (68 mg.) was dissolved with warming in 6.5 ml. of redistilled ethyl cellosolve (b.p. 134–135°). A solution containing 0.20 ml. of 100% hydrazine hydrate in 0.68 ml. of ethyl cellosolve was also prepared. While the hydrazine solution was refluxed under nitrogen, the aldehyde solution was added dropwise during a 2-hr. period. The combined solution was boiled for 1 hr. more. About 4 ml. of solvent was removed by distillation. As the remaining solution slowly cooled, the product crystallized. After the mixture had been refrigerated for several hours, the product was collected and washed with ethyl cellosolve and with diethyl ether. The white, needle-like crystals of pyridazinone weighed 42 mg., decomposition above 300°. The material is poorly soluble in common organic solvents, but dissolves readily in alkali.

For purification the product was dissolved in warm 10% sodium hydroxide solution, filtered, and precipitated with excess dilute hydrochloric acid. The precipitate was washed with boiling acetone and with ether. The analytical sample thus prepared was slightly yellow, apparently owing to some decomposition of the compound while in anionic form. An infrared spectrum of a potassium bromide pellet of the compound revealed a carbonyl absorption at 1655 cm.$^{-1}$.

Anal. Calcd. for $C_8H_5N_3OS$: C, 50.25; H, 2.64. Found: C, 49.71; H, 2.60.

6-Methyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVc).—To 700 mg. (2.78 mmoles) of 6-dimethylaminomethyl-5-carbethoxythieno[3,2-*b*]pyrrole was added 3 ml. of methyl iodide. The mixture was stoppered and allowed to stand at room temperature for 1 hr., and then the methyl iodide was removed. The resulting methiodide salt was dissolved in 10 ml. of absolute methanol. To this solution was carefully added 2.5 g. of sodium borohydride in small portions. After the addition of sodium borohydride was completed, the reaction mixture was diluted to a volume of 50 ml. by the addition of 3 *N* hydrochloric acid. The mixture was stored in the refrigerator overnight, and then the gray-blue precipitate which had formed was collected and dried. The precipitate was dissolved in boiling methylcyclohexane, and the solution was treated with Darco and filtered. The filtrate was stored in the refrigerator for several hours. The white crystals which had formed were collected and dried. The yield of 6-methyl-5-carbethoxythieno[3,2-*b*]pyrrole was 372 mg. (64%), m.p. 140–143.5°. Two additional recrystallizations from methylcyclohexane afforded the analytical sample, m.p. 144–145°. An infrared spectrum of a 10% chloroform solution of the product revealed peaks at 3450 and 3300 (pyrrole N–H and hydrogen-bonded pyrrole N–H), and 1685 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.30; N, 6.69. Found: C, 57.49; H, 5.23; N, 6.75.

6-Cyanomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVd).—The methosulfate salt prepared from 700 mg. (2.78 mmoles) of 6-dimethylaminomethyl-5-carbethoxythieno[3,2-*b*]pyrrole was dissolved in 30 ml. of water which contained 490 mg. (10.0 mmoles) of potassium cyanide. The reaction mixture was stirred at room temperature for a period of 60 hr. Trimethylamine was evolved during the course of this reaction as indicated by a litmus test. At the end of 60 hr. a brown semisolid had precipitated. The reaction mixture was transferred to a separatory funnel and extracted several times with ethyl acetate. Only a small amount of the brown gum appeared to dissolve in this solvent. The ethyl acetate extracts were combined, dried over sodium sulfate, and filtered to remove the drying agent. The filtrate was concentrated to dryness on a rotary evaporator, and the residue was recrystallized from benzene–methylcyclohexane. Two additional recrystallizations from this solvent afforded 110 mg. (17%, based on 6-dimethylaminomethyl-5-carbethoxythieno[3,2-*b*]pyrrole) of analytically pure 6-cyanomethyl-5-carbethoxythieno[3,2-*b*]pyrrole, m.p. 133.4–133.8°.

An infrared spectrum of a potassium bromide pellet of the product revealed peaks at 3250 (pyrrole N–H), 2245 (nitrile group), and 1670 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96. Found: C, 56.44; H, 4.36; N, 11.60.

2,6-Dibromo-5-carbethoxythieno[3,2-*b*]pyrrole (VIII).—To a solution of 195 mg. (1.0 mmole) of 5-carbethoxythieno[3,2-*b*]-pyrrole in 30 ml. of chloroform was added 160 mg. (2.0 mmoles) of bromine. The solution was stirred for 2 hr. The evolution of hydrogen bromide was shown by a test with a piece of moistened litmus paper. At the end of 2 hr. the reaction mixture was evaporated to dryness on a rotary evaporator. A solid residue was obtained which was recrystallized once from an ethanol-water mixture to yield 339 mg. (96%) of 2,6-dibromo-5-carbethoxythieno[3,2-*b*]pyrrole, m.p. 160–162°. An analytical sample was prepared by sublimation of the once recrystallized material at 120° (0.05 mm.). The melting point of the analytical sample was 163.5°.

The infrared spectrum of a 5% chloroform solution of the product revealed peaks at 3450 and 3300 (pyrrole N–H and hydrogen-bonded pyrrole N–H) and 1690 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_9H_7Br_2NO_2S$: C, 30.62; H, 2.00; N, 3.97. Found: C, 30.49; H, 1.89; N, 3.77.

2,3,6-Tribromo-5-carbethoxythieno[3,2-*b*]pyrrole.—To a solution of 195 mg. (1.0 mmole) of 5-carbethoxythieno[3,2-*b*]pyrrole in 50 ml. of chloroform was added 240 mg. (3.0 mmoles) of bromine. The reaction mixture was stirred for 2 hr., and then the chloroform was removed on a rotary evaporator to yield an off-white solid. This solid was dissolved in boiling 95% ethanol, and the solution was treated with a small amount of Darco and

filtered. The filtrate was allowed to cool in the refrigerator for several hours to yield 375 mg. (87%) of the tribromo compound, m.p. 198–204°. The analytical sample was prepared by sublimation of the once recrystallized material at 145° (0.05 mm.), m.p. 205.2–206.5°. An infrared spectrum of a potassium bromide pellet of the product revealed peaks at 3280 (pyrrole N–H) and 1690 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_9H_6Br_3NO_2S$: C, 25.08; H, 1.40; N, 3.25. Found: C, 25.35; H, 1.51; N, 3.43.

2-Acetyl-5-carbethoxythieno[3,2-*b*]pyrrole (IXa).—To a suspension of 1.068 g. (8.0 mmoles) of anhydrous aluminum chloride in 25 ml. of carbon disulfide was added slowly 627 mg. (8.0 mmoles) of acetyl chloride. The mixture which resulted was stirred while a solution of 780 mg. (4.0 mmoles) of 5-carbethoxythieno[3,2-*b*]pyrrole in 60 ml. of carbon disulfide was added rapidly. A green color appeared almost immediately; and, after a short time, a black gum deposited on the bottom of the flask. After the mixture was stirred for 1 hr., the carbon disulfide was poured into 50 ml. of ice-cold 3 *N* hydrochloric acid. The black gum remained in the reaction flask. The carbon disulfide and acid mixture was transferred to a separatory funnel, and the aqueous layer was separated and discarded. The carbon disulfide layer was washed with 25 ml. of 10% sodium bicarbonate and subsequently with 25 ml. of water. The carbon disulfide layer was then collected and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the filtrate was evaporated to dryness. The residue weighed 43 mg., m.p. 158–162°.

To the black gum was added 50 ml. of ice-cold 3 *N* hydrochloric acid. After the gum had been scratched for some time, it was completely converted into a yellow solid which was filtered. The yellow solid weighed 680 mg. after drying, m.p. 162–163°, and it was combined with the residue obtained from the carbon disulfide layer. Two recrystallizations of this material from benzene–petroleum ether (60–90°) afforded 670 mg. (71%) of analytically pure 2-acetyl-5-carbethoxythieno[3,2-*b*]pyrrole, m.p. 163–163.5°. An infrared spectrum of a potassium bromide pellet of the product revealed peaks at 3250 (pyrrole N–H) and 1695 and 1650 cm.$^{-1}$ (carbonyl absorptions).

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.87; H, 4.71; N, 6.01.

2-Carboxy-5-carbethoxythieno[3,2-*b*]pyrrole (IXb).—This reaction was carried out under strictly anhydrous conditions. A slow, steady stream of dry nitrogen was passed over 30 ml. of absolute ethanol while 1.38 g. (0.06 mole) of sodium metal was added. After the addition of the sodium was completed, the sodium ethoxide solution was brought to reflux. A solution of 8.8 g. (0.06 mole) of diethyl oxalate, 5.00 g. (0.027 mole) of 2-methyl-3-nitro-5-thenoic acid, and 30 ml. of absolute ethanol was added to the sodium ethoxide solution. A deep purple precipitate formed almost immediately. The mixture was heated for 5 min., and 50 ml. of water was added to dissolve the precipitate and quench the reaction. After the solution was cooled, 13.9 g. of sodium hydrosulfite was added in portions of 2 g. while the temperature was kept below 60°. The mixture was stirred for 5 hr., and then the golden yellow solution was acidified to pH 1 by the careful addition of 6 *N* hydrochloric acid. The acidified solution was then extracted with several portions of ether. The ether extracts were combined and extracted several times with 10% sodium bicarbonate. Acidification of the combined bicarbonate extracts to pH 1 yielded a fine, yellow precipitate which was collected and dried. Three recrystallizations of this solid from an acetone–water mixture afforded the analytical sample. The yield of analytically pure 2-carboxy-5-carbethoxythieno-[3,2-*b*]pyrrole was 765 mg. (12%), m.p. 278–280° dec.

An infrared spectrum of a potassium bromide pellet of the compound revealed peaks at 3250 (pyrrole N–H) and at 1690 and 1660 cm.$^{-1}$ (carbonyl absorptions).

Anal. Calcd. for $C_{10}H_9NO_4S$: C, 50.19; H, 3.79; N, 5.85. Found: C, 50.27; H, 3.95; N, 5.74.

2-Formyl-5-carbethoxythieno[3,2-*b*]pyrrole (IXc).—To 5 ml. of dimethylformamide was added slowly 1.534 g. (10.0 mmoles) of phosphorus oxychloride while the temperature was kept at 0°. To this mixture was added a solution of 975 mg. (5.0 mmoles) of 5-carbethoxythieno[3,2-*b*]pyrrole in 5 ml. of dimethylformamide which had been previously cooled to 0°. The reaction mixture was allowed to warm slowly, and it was stirred for 24 hr. while the temperature was maintained between 40–50°. At the end of this time the mixture was cherry red. It was then poured into a mixture of 50 g. of ice and 50 ml. of water. The solution which resulted was neutralized with 10% sodium hydroxide, and a tan precipitate was obtained. This tan solid was collected and dried in the air to a weight of 982 mg. It was then dissolved in approximately 3 ml. of chloroform and chromatographed on 50 g. of alumina with chloroform as the eluent. Two bands appeared after a short time: one, a brown band which did not appear to move; the other, a yellow band which moved quite rapidly. The first fraction was colorless and yielded upon evaporation to dryness 142 mg. of white crystals, m.p. 131–132°. A mixture melting point with 5-carbethoxythieno[3,2-*b*]pyrrole yielded no depression. The chromatography was carried out until the yellow band was completely removed. The fractions containing the yellow material were combined and evaporated to dryness to yield 710 mg. of a yellow solid, m.p. 174–178°. Two recrystallizations of this material from benzene afforded 623 mg. (66%, based on the amount of 5-carbethoxythieno[3,2-*b*]pyrrole consumed) of analytically pure 2-formyl-5-carbethoxythieno[3,2-*b*]-pyrrole, m.p. 181–181.8°. An infrared spectrum of a potassium bromide pellet of the product revealed peaks at 3250 (pyrrole N–H), 2800 (aldehydic C–H stretch), and 1690 and 1660 cm.$^{-1}$ (carbonyl absorptions).

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.81; H, 4.07; N, 6.27. Found: C, 53.82; H, 4.16; N, 6.30.

5-Carboxythieno[3,2-*b*]pyrrole (IIIa).—A solution of 250 mg. of 5-carbethoxythieno[3,2-*b*]pyrrole, 15 ml. of 5% sodium hydroxide, and 5 ml. of 95% ethanol was refluxed for 12 hr. The light red solution was treated with Darco, filtered, and the filtrate was acidified to pH 1 with concentrated hydrochloric acid. A gray solid was precipitated. The mixture was cooled in the refrigerator for several hours, and the solid was collected and dried. The crude material was dissolved in a boiling ethanol–water mixture, and the solution was treated with Darco and then filtered. The filtrate was placed in the refrigerator overnight, and the glistening white crystals which had formed were collected and dried. One additional recrystallization from ethanol–water afforded 129 mg. (60%) of 5-carboxythieno[3,2-*b*]pyrrole, m.p. 204–205° dec.

An infrared spectrum of a Nujol mull of the product revealed peaks at 3290 (pyrrole N–H) and 1690 cm.$^{-1}$ (carbonyl absorption).

2-Methyl-3-nitro-5-carbethoxythiophene (X).—To a solution of 37.4 g. (0.2 mole) of 2-methyl-3-nitro-5-thenoic acid[4] in 600 ml. of absolute ethanol was carefully added 35 ml. of concentrated sulfuric acid. The mixture was then heated at reflux for 18 hr. and allowed to cool. The reaction mixture was concentrated *in vacuo* to a volume of approximately 100 ml. The concentrated solution was brought to pH 8 by the careful addition of 10% sodium bicarbonate. The mixture was then transferred to a separatory funnel and was extracted with four 50-ml. portions of ether. The ether extracts were combined and washed with 100 ml. of 10% sodium bicarbonate. The ether layer was dried over sodium sulfate and then filtered to remove the drying agent. The filtrate was concentrated *in vacuo* to remove the solvent, and the residue was distilled at diminished pressure. The material which boiled between 120–130° (1.6 mm.) was collected. The yield of almost water-white liquid was 34.6 g. (81%). One additional distillation afforded the analytical sample, b.p. 122° (1.6 mm.).

An infrared spectrum of a 10% chloroform solution of the product revealed peaks at 1550 and 1350 (nitro group) and 1710 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_8H_9NO_4S$: C, 44.44; H, 4.20; N, 6.48. Found: C, 44.58; H, 4.06; N, 6.33.

Ethyl 5-Carbethoxy-3-nitro-2-thienylpyruvate (XI).—This preparation was carried out under strictly anhydrous conditions. A slow, steady stream of dry nitrogen was passed over 60 ml. of absolute ethanol while 2.08 g. (0.027 mole) of 2-methyl-3-nitro-5-carbethoxythiophene, 18 g. (0.122 mole) of diethyl oxalate, and 60 ml. of absolute ethanol was added all at once. Immediately, a deep red-brown color appeared. The solution was kept at reflux for 15 min., and then was added to 1 l. of water which contained 30 ml. of concentrated hydrochloric acid. A black, gummy material was deposited. This gum was converted to a red-brown solid when it was scratched. The solid was collected and air-dried. The crude material was then dissolved in 600 ml. of boiling methylcyclohexane, and the solution was treated with Darco and filtered. The filtrate was allowed to cool in the refrigerator for several hours. The yield of ethyl 5-carbethoxy-3-nitro-2-thienylpyruvate was 7.44 g. (59%), m.p. 137–142°. Three additional recrystallizations from methylcyclohexane af-

forded the analytical sample, m.p. 142.8–143.7°. An infrared spectrum of a 10% chloroform solution of the product revealed peaks at 3400 (enolic O–H) and 1700–1725 cm.$^{-1}$ (broad, due to three carbonyl absorptions).

Anal. Calcd. for $C_{12}H_{13}NO_7S$: C, 45.71; H, 4.15; N, 4.44. Found: C, 45.58; H, 4.02; N, 4.23.

2,5-Dicarbethoxythieno[3,2-*b*]pyrrole (XII).—To a solution containing 18 g. of stannous chloride dihydrate, 150 ml. of 95% ethanol, and 50 ml. of concentrated hydrochloric acid was added 3.15 g. (0.01 mole) of ethyl 5-carbethoxy-3-nitro-2-thienylpyruvate. The mixture was stirred for 8 hr. while the temperature was kept between 40–50°. The deep red reaction mixture was placed in a dropping funnel and was slowly added to 150 ml. of 50% potassium hydroxide. The temperature of the strongly alkaline solution was not allowed to exceed 10°. After the addition was completed, the mixture which contained a yellow precipitate was extracted with several portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, and filtered to remove the drying agent. The solvent was removed from the filtrate to yield a solid residue. The residue was dissolved in a boiling methylcyclohexane–benzene mixture, and the solution was treated with Darco and filtered. The filtrate was allowed to cool in the refrigerator for several hours. The slightly yellow crystals which had precipitated were collected and dried. The yield of 2,5-dicarbethoxythieno[3,2-*b*]pyrrole was 1.70 g. (64%), m.p. 156–158°. Two additional recrystallizations from benzene–methylcyclohexane afforded the analytical sample, m.p. 158.3–159°. An infrared spectrum of a 5% chloroform solution of the product revealed peaks at 3430 and 3280 (pyrrole N–H and hydrogen-bonded pyrrole N–H) and 1680–1705 cm.$^{-1}$ (broad, carbonyl absorption).

Anal. Calcd. for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found: C, 53.72; H, 4.81; N, 5.18.

6-Bromo-2,5-dicarbethoxythieno[3,2-*b*]pyrrole (XIII).—To a solution of 267 mg. (1.0 mmole) of 2,5-dicarbethoxythieno[3,2-*b*]-pyrrole in 30 ml. of chloroform was added 160 mg. (2.0 mmoles) of bromine. At the end of 3 hr. the reaction mixture was concentrated to dryness on a rotary evaporator. A solid residue was obtained which was dissolved in a boiling mixture of methylcyclohexane–benzene, and the solution was treated with Darco and filtered. The filtrate was stored in the refrigerator overnight. The white crystals which had formed were collected and dried. The yield of 6-bromo-2,5-dicarbethoxythieno[3,2-*b*]pyrrole was 306 mg. (88%), m.p. 178.7–179.8°. One additional recrystallization from benzene–methylcyclohexane afforded the analytical sample, m.p. 179.1–179.9°.

An infrared spectrum of a 5% chloroform solution of the product revealed peaks at 3450 and 3300 (pyrrole N–H and hydrogen-bonded pyrrole N–H) and 1690–1705 cm.$^{-1}$ (broad, carbonyl absorption).

Anal. Calcd. for $C_{12}H_{12}NO_4S$: C, 41.63; H, 3.50; N, 4.05. Found: C, 41.32; H, 3.37; N, 3.86.

6-Dimethylaminomethyl-2,5-dicarbethoxythieno[3,2-*b*]pyrrole (XIV).—To 3.0 ml. of glacial acetic acid were added 85 mg. (1.89 mmoles) of dimethylamine (as a 40% aqueous solution) and 470 mg. (1.76 mmoles) of 2,5-dicarbethoxythieno[3,2-*b*]pyrrole. The temperature was kept between 0–5° while the components were added. The reaction mixture was heated on the steam bath for 1 hr. and then allowed to stand at room temperature for 12 hr. The mixture was poured into 25 ml. of ice–water, and the resulting solution was brought to pH 10 by the slow addition of 10% sodium hydroxide. The temperature was not allowed to exceed 10° while the base was added. The white solid which precipitated was filtered and washed freely with ice–water. The solid was dried *in vacuo* over anhydrous calcium sulfate for 24 hr. The yield of the crude Mannich base was 518 mg. (89%), m.p. 120–123°. The material was dissolved in a boiling mixture of benzene–methylcyclohexane, and the solution was treated with Darco and filtered. The filtrate was allowed to cool overnight in the refrigerator. The white crystals which had formed were collected and dried. The yield of 6-dimethylaminomethyl-2,5-dicarbethoxythieno[3,2-*b*]pyrrole was 460 mg. (79%), m.p. 124.3–124.9°. An analytical sample was prepared by one recrystallization from benzene–methylcyclohexane, m.p. 124.3–124.9°. An infrared spectrum of a 5% chloroform solution of the product revealed peaks at 3470 and 3330 (pyrrole N–H and hydrogen-bonded pyrrole N–H) and 1680–1720 cm.$^{-1}$ (broad, carbonyl absorptions).

Anal. Calcd. for $C_{15}H_{20}N_2O_4S$: C, 55.53; H, 6.21; N, 8.64. Found: C, 55.41; H, 6.20; N, 8.69.

Preparation and Reductive Cyclization of Some Carbon-Alkylated Derivatives of Ethyl 3-Nitro-2-thienylpyruvate[1]

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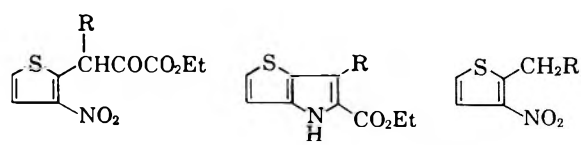
Alkylation reactions of the ambident anion of ethyl 3-nitro-2-thienylpyruvate were studied. The C-allyl and C-benzyl derivatives were prepared and converted in poor yields to the corresponding 6-alkylated 5-carbethoxythieno[3,2-*b*]pyrroles.

Condensation of 2-methyl-3-nitrothiophene (IIIa) with diethyl oxalate affords ethyl 3-nitro-2-thienylpyruvate (Ia), which can be reduced and cyclized to 5-carbethoxythieno[3,2-*b*]pyrrole (IIa).[3] In this paper we described the behavior of the pyruvic ester Ia toward certain alkylating agents; reductive cyclization of carbon-alkylated derivatives of Ia offers one route to 6-substituted 5-carbethoxythieno[3,2-*b*]pyrroles of type II. These studies were part of a program directed toward synthesis of 6-substituted thieno[3,2-*b*]pyrroles analogous to biologically active indole compounds.



Ia, R = H
b, R = $CH_2CH{=}CH_2$
c, R = $CH_2C_6H_5$
d, R = Br

IIa, R = H
b, R = $CH_2CH{=}CH_2$
c, R = $CH_2C_6H_5$

IIIa, R = H
b, R = CH_3
c, R = $CH_2C_6H_4NO_2$-*p*
d, R = CH_2CN
e, R = $CH_2CH{=}CH_2$

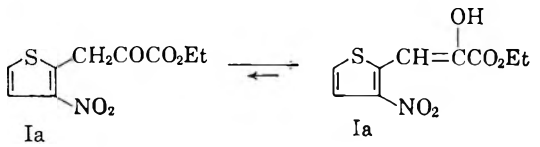
In the solid state and in fresh solutions the pyruvate Ia exists predominantly as the enol, as indicated by strong infrared peaks at 3400 cm.$^{-1}$ for the enolic hydroxyl absorption, and at 1700 cm.$^{-1}$ for the hydrogen-bonded ester carbonyl absorption. In the nuclear magnetic resonance (n.m.r.) spectrum of Ia in chloroform,

(1) (a) Supported in part by a grant (C3969-Bio) from the National Cancer Institute, U. S. Public Health Service; (b) abstracted in part from the thesis submitted by A. N. Scott, to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1964.

(2) National Science Foundation Summer Fellow, 1962.

(3) W. W. Gale, A. N. Scott, and H. R. Snyder, *J. Org. Chem.*, **29**, 2160 (1964).

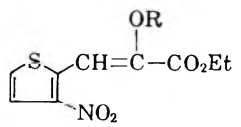
only peaks due to the enol form are detectable. Undoubtedly the enol owes its stability to its extended π-conjugated system. A similarly high degree of enolization has been noted in methyl 2-thienylpyruvate and methyl phenylpyruvate.[4]



Ia Ia

Pyruvate Ia readily loses a proton to form an intensely red anion, the negative charge of which is shared by the enol oxygen, the carbon adjacent to the ring, and the nitro oxygens. Alkylation could conceivably occur at any of these three sites, but only carbon alkylation would afford a pyruvate of type I which might be converted to a 6-alkylated thienopyrrole.

Through reactions of Ia, alkyl bromides, and alkali metal carbonates in refluxing acetone, two carbon-alkylated pyruvates were prepared: the allyl compound Ib (93% yield), and the benzyl compound Ic (*ca.* 45% yield). No oxygen alkylation was detected with allyl bromide, but in certain experiments using benzyl bromide some benzyl enol ether (IVa) was produced along with the C-benzyl derivative. In many other attempts, carbon alkylated pyruvates could not be isolated. For example, reaction of Ia with methyl iodide and potassium carbonate in acetone afforded only the O-methyl derivative IVb (24% yield) and a trace of 2-ethyl-3-nitrothiophene (IIIb). Similarly, alkylation with *p*-



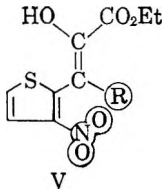
IVa, R = $CH_2C_6H_5$
b, R = CH_3
c, R = $CH_2C_6H_4NO_2$-*p*

nitrobenzyl chloride in ethanolic sodium ethoxide gave principally the ether IVc and in smaller yield the deacetylated product IIIc. A small amount of 3-(3-nitro-2-thienyl)propionitrile (IIId) was obtained from reaction with chloroacetonitrile. Knoevenagel condensations with aromatic aldehydes and Michael addition to electrophilic olefins did not occur.

Although the alkali metal enolate was readily soluble in acetone, its poor solubility in ethanol, *t*-butyl alcohol, and tetrahydrofuran impeded alkylations attempted in these solvents.

The structures of the alkylated pyruvates were deduced chiefly from n.m.r. spectra.[5] The carbon-alkylated pyruvates Ib and Ic were predominantly ketonic oils. The internal methylene of the allyl group and the benzyl methylene appeared as multiplets at δ = 2.8 and *ca.* 3.3 p.p.m., respectively. The multiplicity of the benzyl methylene peak may be attributed to the asymmetry of an adjacent carbon and to conformational effects.[6] The benzyl methylene of the ether IVa and O-methyl group of IVb gave n.m.r. singlets at 5.2 and 4.0 p.p.m., respectively. The proton at the tertiary carbon of Ic produced a triplet (apparently a coalesced quartet) at 5.9 p.p.m. In Ib this resonance appeared at 5.7 p.p.m. Triplets in this region did not appear in the spectra of the ethers IVa and IVb, but a singlet at 8.1 p.p.m. in each spectrum was assigned to the proton on the carbon adjacent to the ring. The main product from reaction of Ia with *p*-nitrobenzyl chloride was thought to be the enol ether IVc because of infrared peaks at 1708 (α,β-unsaturated ester carbonyl), and 1620 and 1605 cm.$^{-1}$ (doublet due to enol carbon–carbon double bond[7]). Thiophenes of type III were assigned structures on the basis of infrared spectra.

Steric hindrance is probably responsible, at least in part, for the ketonic character of the C-alkylated pyru-



V

vates, Ib and Ic. Molecular models of V show that when R is hydrogen, coplanarity and therefore π-interaction are possible between the atoms of the nitrothienyl group and the appropriate atoms of the enolic side chain. Because of the many resonance possibilities afforded by enolization, the keto–enol equilibrium shifts in favor of the enol form. When R is alkyl as in Ib and Ic such coplanarity is prohibited by the crowding between R and the nitro group. Conjugation is not greatly extended through enolization and the molecule tends to be ketonic.

The products of type III probably arose through basic cleavage of C-alkylpyruvates. Attack of base at the 2-keto group of a type I molecule could lead to two cleavage fragments, an oxalic acid derivative and a resonance-stabilized anion of III. When the weak base, sodium bicarbonate, was employed in the alkylation with allyl bromide, little or no cleavage occurred, but with potassium carbonate, a stronger base, there was extensive cleavage of the desired product Ib to IIIe. In the reaction of Ia, benzyl bromide and lithium carbonate, the yield of C-benzylpyruvate probably suffered owing to cleavage. The facile cleavage of C-alkylpyruvates stands in contrast to the relative stability to base of the simple pyruvate Ia. In the C-alkylated compounds, the steric crowding that suppresses enolization is relieved through cleavage. The simple pyruvate, on the other hand, tends to form the stable enolate ion, which is safe from destruction by base.

From our limited data, little can be said concerning the factors that influence the ratio of carbon to enolic oxygen alkylation (C–O ratio) in Ia. Of the alkylating agents examined, only allyl and benzyl bromide produced C–O ratios greater than one. These halides are known to effect carbon alkylation of phenoxides more readily than do saturated halides.[8] It also has been noted that under some conditions a smaller cation will associate in solution with the oxygen of phenoxide, thus

(4) A. M. Stock, W. E. Donahue, and E. D. Amstutz, *J. Org. Chem.*, **23**, 1840 (1958).

(5) Chemical shifts are expressed in units of δ, parts per million downfield from internal tetramethylsilane. The spectra were obtained by Mr. D. H. Johnson and associates on a Varian A-60 n.m.r. spectrometer.

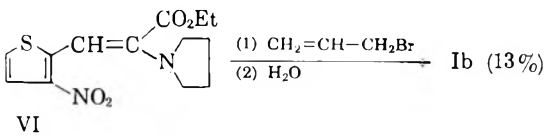
(6) H. S. Gutowsky, *J. Chem. Phys.*, **37**, 2196 (1962); *Pure Appl. Chem.*, **7**, 93 (1963).

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 41.

(8) D. Y. Curtin, R. J. Crawford, and M. Wilhelm, *J. Am. Chem. Soc.*, **80**, 1391 (1958).

blocking O-alkylation and promoting C-alkylation, while a larger cation will tend to dissociate from the anion and expose it to O-alkylation.[8,9] In reactions of Ia and benzyl bromide in acetone we obtained a C–O ratio of 3:1 with sodium bicarbonate and at least 10:1 (from n.m.r. data) with lithium carbonate.

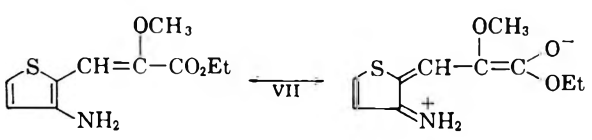
The Stork enamine method for the α-alkylation of ketones[10] was investigated as a possible route to C-alkylated derivatives of Ia. In this method a ketone is converted to a tertiary enamine, which is treated with an electrophilic alkylating agent in the absence of catalyst. Acid hydrolysis of the alkylated enamine affords the α-alkylated ketone. If this method could be applied to Ia, enol ethers could not form and the product would not be exposed to cleavage by base. Although Ia was converted by pyrrolidine to the enamine VI, alkylations of this enamine proved difficult. The allyl compound Ib was obtained under forcing



VI

conditions in only 13% yield. Attempted alkylations of VI with ethyl bromoacetate and acrylonitrile failed completely and Ia was recovered as the result of hydrolysis of VI during the work-up.

Stannous chloride in hydrochloric acid converted Ia to IIa in 55% yield.[3] The same reductant mainly gave resinous materials from the C-alkylpyruvates Ib and Ic; the 6-allylthienopyrrole IIb was obtained in yields up to 7% while the 6-benzylthienopyrrole IIc was formed in 11% yield. The yields were not improved by conducting the reactions under nitrogen. These poor results may be due to steric hindrance to cyclization. Also, the intermediate amines from the predominantly ketonic pyruvates may undergo rapid resinification if they, too, are ketonic. Free aminothiophenes, if not stabilized by electron-withdrawing groups, rapidly polymerize under normal conditions.[11] It is of interest in this connection that a stable free amine (VII) was obtained from the stannous chloride reduction of the methyl enol ether IVb. The satisfactory conversion of Ia to IIa may depend upon similar stabilization of the intermediate enolic amine.



Ethyl 3-nitro-2-thienylbrompyruvate (Id) was prepared by the action of bromine on Ia. When Id was reduced in the usual way[3] with stannous bromide in hydrobromic acid, the only product was 5-carbethoxythieno[3,2,-*b*]pyrrole, unsubstituted in position 6. The facile reduction of the carbon–bromine bond in Id also was exemplified by the immediate release of iodine upon treatment of Id with potassium iodide.

(9) N. Kornblum, R. Seltzer, and P. Haberfield, *J. Am. Chem. Soc.*, **85**, 1148 (1963).

(10) G. Stork, A. Brizzolara, A. Landesman, H. Szmuszkovicz, and R. Terrel, *ibid.*, **85**, 207 (1963).

(11) H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 233; S. Gronowitz, "Advances in Heterocyclic Chemistry," A. R. Katritzky, Ed., Associated Publishers, New York, N. Y., 1963, p. 85.

Experimental[12]

Ethyl 2-Keto-3-(3-nitro-2-thienyl)-5-hexenoate (Ib).—Ethyl 3-nitro-2-thienylpyruvate[3] (4.86 g., 0.020 mole), 10 ml. of allyl bromide, and 1.85 g. (0.22 mole) of sodium bicarbonate in 40 ml. of acetone were heated together under reflux for 14 hr. The mixture was diluted with ether, filtered to remove inorganic salts, and dried over sodium sulfate. The solvent and excess allyl bromide were removed *in vacuo*. There remained 5.29 g. (93%) of dark orange oil which, according to spectra, was relatively pure hexenoate. An analytical sample, prepared by chromatography on alumina and molecular distillation, was a yellow oil which darkened on standing.

An infrared spectrum of a liquid film of the compound revealed a peak at 1730 with a shoulder at 1700 (carbonyl groups) and a peak at 1640 cm.$^{-1}$ (olefinic carbon–carbon double bond). A very weak band appeared at 3450 cm.$^{-1}$ (enolic hydroxyl).

Anal. Calcd. for $C_{12}H_{13}NO_4S$: C, 50.87; H, 4.62; N, 4.94. Found: C, 50.89; H, 4.60; N, 5.03.

6-Allyl-5-carbethoxythieno[3,2-*b*]pyrrole (IIb).—Ethyl 2-keto-3-(3-nitro-2-thienyl)-5-hexenoate (500 mg.) dissolved in 6 ml. of absolute ethanol was added slowly with cooling to a solution of 4 g. of stannous chloride dihydrate in 6 ml. of concentrated hydrochloric acid. As the mixture was stirred without external temperature control, the temperature rose spontaneously to 35°. After being stirred for 75 min., the mixture was cooled and was added slowly to a mixture of 20 ml. of saturated aqueous potassium carbonate solution, 10 ml. of water, and 20 ml. of ether, with swirling in an ice bath. The ether layer was decanted and the aqueous layer was extracted twice with ether. The combined ether solution was washed with aqueous potassium carbonate and with saturated potassium chloride solution, then was filtered and dried over sodium sulfate. The red oil which remained upon removal of the ether was placed on a 2 × 2 in. chromatographic column of acid-washed alumina and eluted with benzene–cyclohexane (2:1). The second and third liters of eluent contained 31 mg. (7%) of the allylcarbethoxythienopyrrole, m.p. 80–94°. Two recrystallizations from petroleum ether (40–60°) afforded an analytical sample of white prisms, m.p. 97–98°.

An infrared spectrum of a 5% chloroform solution of the compound contained a carbonyl absorption at 1690 and a pyrrole N–H absorption at 3500 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.26; H, 5.57; N, 5.95. Found: C, 60.84; H, 5.49; N, 5.90.

Ethyl 2-Keto-3-(3-nitro-2-thienyl)-4-phenylbutyrate (Ic).—A mixture of 1.944 g. (0.008 mole) of ethyl 3-nitro-2-thienylpyruvate, 1.370 g. (0.008 mole) of benzyl bromide, and 0.296 g. (0.004 mole) of lithium carbonate in 10 ml. of acetone was heated under reflux for 38 hr. A dark, viscous oil remained after removal of the solvent. The oil was chromatographed on silica gel with cyclohexane as eluent. The first band to be eluted contained 1.21 g. of orange oil, mainly the C-benzylated pyruvate (45%) according to n.m.r. and infrared spectra. The material was employed without further purification in the synthesis of 6-benzyl-5-carbethoxythieno[3,2-*b*]pyrrole.

6-Benzyl-5-carbethoxythieno[3,2-*b*]pyrrole (IIc).—Ethyl 2-keto-3-(3-nitro-2-thienyl)-4-phenylbutyrate (1.00 g., 0.003 mole) was dissolved in 9 ml. of ethanol and treated under nitrogen with a solution of 5.5 g. of stannous chloride dihydrate in 9 ml. of concentrated hydrochloric acid. The procedure was that outlined above for the preparation of 6-allyl-5-carbethoxythienopyrrole. A nearly white product weighing 76 mg. (11% yield) was obtained by chromatography and recrystallization from hexane–benzene. Three more crystallizations from hexane–benzene gave analytically pure 6-benzyl-5-carbethoxythienopyrrole as white needles, m.p. 126–129°. An infrared spectrum of the product in chloroform showed peaks at 1690 (carbonyl), 3300 and 3450 cm.$^{-1}$ (bonded and free N–H).

Anal. Calcd. for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91. Found: C, 67.47; H, 5.38; N, 4.89.

(12) Melting points are uncorrected. Microanalyses were performed by Mr. Josef Nemeth and his associates, University of Illinois. Infrared spectra were obtained from a Perkin-Elmer Model 21 spectrophotometer by Mr. D. H. Johnson and associates.

Methylation of Ethyl 3-Nitro-2-thienylpyruvate.—A mixture of 4.24 g. (0.017 mole) of ethyl 3-nitro-2-thienylpyruvate, 2.60 g. of anhydrous potassium carbonate, 15 ml. of methyl iodide, and 300 ml. of acetone was heated at reflux for 12 hr. During the reflux period, the initially red mixture became light orange. The mixture then was cooled and filtered to remove inorganic salts. After removal of the acetone, the residual oil was chromatographed on alumina with benzene as eluent. The first band to be eluted contained 3.58 g. of an oil which slowly crystallized. Recrystallization from ethanol–water afforded 1.66 g. (24%) of the enol methyl ether, ethyl 2-methoxy-3-(3-nitro-2-thienyl)acrylate (IVb). A second recrystallization gave an analytical sample of yellow needles, m.p. 74.5–75.5°. The material failed to give a ferric chloride test for enols. An infrared spectrum (KBr pellet) contained peaks at 1725 (ester carbonyl) and 1612 cm.$^{-1}$ (enol C=C).

Anal. Calcd. for $C_{10}H_{11}NO_5S$: C, 46.70; H, 4.28; N, 5.45. Found: C, 46.67; H, 4.36; N, 5.30.

The filtrate from the first recrystallization of IVb was evaporated and again chromatographed on alumina. Fractionation of the benzene eluent afforded a trace of crystalline solid, m.p. 40–42°, which was assigned the structure of 2-ethyl-3-nitrothiophene (IIIb) on the basis of infrared spectra.

Reduction of Ethyl 2-Methoxy-3-(3-nitro-2-thienyl)acrylate (IVb).—Reduction of IVb under conditions employed for the reductive cyclization of Ib to IIb, afforded ethyl 2-methoxy-3-(3-amino-2-thienyl)acrylate (VII), a yellow solid, which was purified by recrystallization from benzene–petroleum ether (30–60°), m.p. 89.5–90.5°.

Anal. Calcd. for $C_{10}H_{13}NO_3S$: C, 52.91; H, 5.73; N, 6.17. Found: C, 52.75; H, 5.88; N, 5.97.

Reaction of Ethyl 3-Nitro-2-thienylpyruvate with *p*-Nitrobenzyl Chloride.—To a stirred solution of 0.1 g. (0.0043 g.-atom) of sodium metal in 15 ml. of absolute ethanol was added a solution of 1.0 g. (0.0041 mole) of the pyruvate Ia in 25 ml. of ethanol. The mixture was brought to reflux temperature and a solution of 0.71 g. (0.0041 mole) of *p*-nitrobenzyl chloride in 20 ml. of ethanol then was added over a 10-min. period. The resulting mixture was refluxed for 19 hr. Most of the ethanol was evaporated, and the solution was diluted with water and acidified with hydrochloric acid. The brown solid which precipitated was collected, dried, and recrystallized from absolute ethanol. A yellow solid, 0.354 g. (24%), which separated from the solution was identified through analysis and infrared spectroscopy as ethyl 2-(*p*-nitrobenzoxy)-3-(3-nitro-2-thienyl)acrylate (IVc). Another recrystallization from ethanol provided an analytical sample, m.p. 168.5–169°.

Anal. Calcd. for $C_{16}H_{14}N_2O_7S$: C, 50.80; H, 3.73; N, 7.40. Found: C, 50.98; H, 3.69; N, 7.44.

The filtrate from the first recrystallization of IVc yielded 0.185 g. (12%) of another yellow solid identified as 1-(3-nitro-2-thienyl)-2-(*p*-nitrophenyl)ethane (IIIc). An analytical sample from ethanol–water melted at 120–121°.

Anal. Calcd. for $C_{12}H_{10}N_2O_4S$: C, 51.80; H, 3.62; N, 10.08. Found: C, 51.63; H, 3.61; N, 10.35.

Cyanomethylation of Ethyl 3-Nitro-2-thienylpyruvate.—The pyruvate Ia (0.50 g.), sodium iodide (0.31 g.), and chloroacetonitrite (0.156 g.) were dissolved in 25 ml. of absolute ethanol. To this solution at reflux temperature was added a solution of sodium metal (0.051 g.) in 25 ml. of absolute ethanol. The mixture was heated at reflux for 24 hr., then reduced in volume, acidified with dilute hydrochloric acid, and extracted with ether. An oil which remained after removal of the ether was taken up in cyclohexane, treated with Darco, filtered, and chilled. 3-(3-Nitro-2-thienyl)propionitrile (IIId) was obtained in 15% yield as white needles, m.p. 77.5–78.3°. In the infrared (KBr pellet) the material does not absorb in the carbonyl region but exhibits a nitrile absorption at 2240 cm.$^{-1}$.

Anal. Calcd. for $C_7H_6N_2O_2S$: C, 46.20; H, 3.32; N, 15.40. Found: C, 45.94; H, 3.12; N, 15.18.

Ethyl 1-Pyrrolidino-2-(3-nitro-2-thienyl)acrylate (VI).—In a two-necked 100-ml. flask were placed 55 ml. of dry benzene, 2.00 g. (0.0082 mole) of ethyl 3-nitro-2-thienylpyruvate, 0.62 g. (0.0088 mole) of dry redistilled pyrrolidine, and 40 mg. of *p*-toluenesulfonic acid monohydrate. The flask was fitted with a nitrogen inlet and with a Soxhlet extractor containing a thimble filled with molecular sieve, as recommended by Stork[9] for the efficient removal of water in conversions of ketones to enamines. The mixture was refluxed vigorously under nitrogen. After 12 hr., the reaction was shown to be complete by infrared analysis. The mixture absorbed strongly at 1730 (ester carbonyl of enamine), while peaks due to unchanged pyruvate at 1700 (bonded ester carbonyl) and 3400 cm.$^{-1}$ (enolic hydroxyl) were weak or absent. Removal of the benzene and excess pyrrolidine *in vacuo* afforded a viscous, dark red oil, principally the enamine, which was used directly in attempted alkylations.

When the sulfonic acid catalyst was omitted, considerable cleavage of the pyruvate to 2-methyl-3-nitrothiophene occurred.

Ethyl 3-Nitro-2-thienylbromopyruvate (Id).—A solution of 3.35 g. (0.021 mole) of bromine in 80 ml. of chloroform was added slowly to a stirred solution of 5.00 g. (0.020 mole) of ethyl 3-nitro-2-thienylpyruvate in 100 ml. of chloroform. The temperature of the reaction mixture was held between −5 and −10° with an ice–salt bath. Moist litmus paper indicated the evolution of hydrogen bromide. When the addition was complete, the chloroform was removed *in vacuo*. The residue was dissolved in ethyl ether and treated with Darco. The ether solution was reduced in volume and hot petroleum ether (b.p. 30–60°) was added to effect crystallization. A yield of 5.4 g. (82%) of light yellow crystals was obtained, m.p. 66–68°. For analysis, the material was recrystallized twice from ethyl ether–petroleum ether (b.p. 30–60°), m.p. 67–68°.

An infrared spectrum of a 10% chloroform solution of the product exhibited a carbonyl absorption at 1730 cm.$^{-1}$. There was no band for enolic hydroxyl in the region 3200–4000 cm.$^{-1}$.

Anal. Calcd. for $C_9H_8BrNO_5S$: C, 33.55; H, 2.50; N, 4.35. Found: C, 33.44; H, 2.48; N, 4.38.

Arylboronic Acids. VII. Some Reactions of *o*-Formylbenzeneboronic Acid[1]

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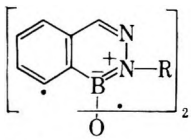
The behavior of *o*-formylbenzeneboronic acid towards various aldehyde reagents is described. Reaction with secondary diamines, malononitrile, sodium bisulfite, and Girard's reagent T provides the usual products, while the 2,4-dinitrophenylhydrazone is isolated as the diethyl boronate ester. The boronic acid function participates in condensation reactions with semicarbazide and *p*-carboxyphenylhydrazine hydrochlorides to give the corresponding 4-hydroxyborazaroisoquinolines. α-Substituted boronophthalides are formed with isopropylidene malonate, nitromethane, and sodium cyanide.

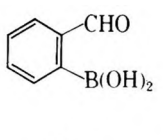
The formation of the stable boron-containing compounds, bis(4,3-borazaro-4-isoquinolinyl) ether (Ia) and bis(3-phenyl-4,3-borazaro-4-isoquinolinyl) ether (Ib), from the reaction of *o*-formylbenzeneboronic acid (II) with hydrazine and phenylhydrazine hydrochloride, respectively, was recently reported by Dewar.[2] Although II also reacted with hydroxylamine to form a cyclic derivative (III), the aldehyde appeared to be

(1) This work was supported by a grant [AT(11-1)-314] from the Atomic Energy Commission; report COO-314-8.

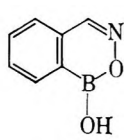
(2) M. J. S. Dewar and R. C. Dougherty, *J. Am. Chem. Soc.*, **84**, 2648 (1962); **86**, 433 (1964).



Ia, R = H
b, R = C_6H_5
c, R = $CONH_2$



II

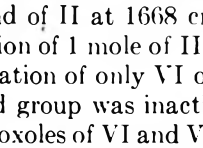


III

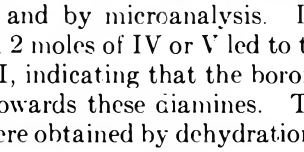
less reactive than its *para* isomer, presumably owing to interaction of the formyl and boronic acid groups.[3]

The purpose of the present investigation was the further study of the behavior of II towards aldehyde reagents to determine whether any uncyclized derivatives could be obtained, and also to see if the boronic acid function were capable of entering into any of the reactions to produce novel structures.

When II reacted with methanolic solutions of N,N'-diphenylethylene diamine[4] (IV) and 1,5-diazacyclooctane[5] (V), the respective products, 1,3-diphenyl-2-(*o*-boronophenyl)tetrahydroimidazole (VI) and 9-(*o*-boronophenyl)-1,5-diazabicyclo[3.3.1]nonane (VII), were obtained. The structures of VI and VII were indicated by the disappearance of the infrared carbonyl band of II at 1668 cm.$^{-1}$ and by microanalysis. Reaction of 1 mole of II with 2 moles of IV or V led to the isolation of only VI or VII, indicating that the boronic acid group was inactive towards these diamines. The boroxoles of VI and VII were obtained by dehydration.



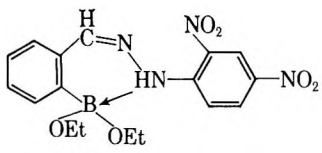
VI



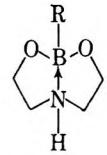
VII

o-Formylbenzeneboronic acid reacted with sodium bisulfite to provide the expected addition product, sodium α-hydroxy(*o*-borono)benzylsulfonate (VIII). The α-hydroxy group of VIII could not be made to form a lactone with the boronic acid function by means of vacuum desiccation at elevated temperatures, however. The condensation of II with malononitrile in dimethyl sulfoxide or dimethylformamide provided *o*-boronobenzalmalononitrile (IX). The presence of a conjugated structure rather than a lactone was indicated by the infrared spectrum of IX, which revealed a band at 2235 cm.$^{-1}$ (conjugated dinitrile),[6] and by the absence of strong bands near 1000 (C–O stretch)[7] and 1100 cm.$^{-1}$ (cyclic ether).[8]

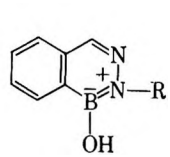
Although Girard's reagent T (betaine hydrazide hydrochloride) gave the normal hydrazone with II, the 2,4-dinitrophenylhydrazone, prepared in ethanol and phosphoric acid according to the method of Fieser,[9] was isolated as its diethyl boronate ester (X), as shown by microanalysis and infrared and nuclear magnetic resonance spectra. The hydrolytic stability of this ester was sufficient to enable it to resist atmospheric moisture over a period of weeks, which was unexpected for an ethyl ester of an arylboronic acid[10,11] and might be due to boron–nitrogen coordination similar to that reported for the thiosemicarbazone and isonicotinylhydrazone of II.[12] Evidence for such an interaction was provided by the infrared spectrum of X, which revealed that the N–H stretching bands had been lowered in frequency to 3250 and 3090 cm.$^{-1}$, similar to the observation made by Serafinowa and Makosza.[12] Although the electron-withdrawing effect of the 2,4-dinitrophenyl group would be expected to negate a large part of the donor ability of the nitrogen atom, comparison with the properties of the boronic acid esters (XI) of diethanolamine, which are stable to neutral hydrolysis because of boron–nitrogen coordination,[13] seems to require the structure X.



X



XI



XII

a, R = *p*-$C_6H_4CO_2H$
b, R = $CONH_2$

Evidence of the participation of the boronic acid group in condensation reactions of the aldehyde II was provided by the isolation of 3-(*p*-carboxyphenyl)-4-hydroxy-4,3-borazaroisoquinoline (XIIa) from the reaction of II with *p*-carboxyphenylhydrazine hydrochloride. Similarly, semicarbazide hydrochloride gave 3-formamido-4-hydroxy-4,3-borazaroisoquinoline (XIIb), which was converted to bis(3-formamido-4,3-borazaro-4-isoquinolinyl) ether (Ic) by extended dehydration. The structures of XIIa, XIIb, and Ic were supported by microanalyses in conjunction with molecular weight determinations. These three compounds resisted deboronation by concentrated hydrochloric acid at room temperature for 24 hr.

The ability of the boronic acid group of II to incorporate itself into a heterocycle was also manifested in the reaction of isopropylidene malonate[14] with II in dioxane. Instead of the expected *o*-boronocinnamic acid, there was obtained a product (XIIIa) whose infrared spectrum revealed a strong carbonyl band at 1743 cm.$^{-1}$, indicative of an unsaturated aliphatic acid, and strong bands at 1091 and 1002 cm.$^{-1}$, characteristic of the boronophthalide structure. A partial nuclear magnetic resonance spectrum of XIIIa in dimethyl sulfoxide also favored the assignment to boronophthalidylacetic acid.[15] This compound was also produced by the reaction of malonic acid with II in dioxane.

A similar structure, α-(nitromethyl)boronophthalide (XIIIb), was formed in the reaction of II with nitromethane, as evidenced by the presence of boronophthalide bands (see Table I) in the infrared spectrum. The nuclear magnetic resonance spectrum of XIIIb

(3) H. R. Snyder, A. J. Reedy, and W. J. Lennarz, *J. Am. Chem. Soc.*, **80**, 835 (1958).
(4) H. W. Wanzlick and W. Löchel, *Chem. Ber.*, **86**, 1463 (1953).
(5) J. H. Billman and L. C. Dorman, *J. Org. Chem.*, **27**, 2419 (1962).
(6) R. E. Kitson and N. E. Griffith, *Anal. Chem.*, **24**, 334 (1952).
(7) W. J. Lennarz and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 2172 (1960).
(8) W. J. Dale and J. E. Rush, *J. Org. Chem.*, **27**, 2598 (1962).
(9) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1957, p. 316.
(10) M. F. Lappert, *Chem. Rev.*, **56**, 998 (1956).
(11) W. Gerrard, "The Organic Chemistry of Boron," Academic Press, New York, N. Y., 1961, p. 71.
(12) B. Serafinowa and M. Makosza, *Roczniki Chem.*, **35**, 937 (1961).
(13) R. L. Letsinger and J. R. Nazy, *J. Org. Chem.*, **24**, 93 (1959).
(14) J. A. Hedge, C. W. Kruse, and H. R. Snyder, *ibid.*, **26**, 3166 (1961).
(15) Based on the analogous phthalidyl radical, *o*-C_6H_4COOCH: *Chem. Abstr.*, **51** (Subject Index), 11R (1957).

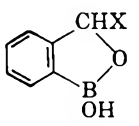
TABLE I

SELECTED INFRARED BANDS OF α-SUBSTITUTED BORONOPHTHALIDES[a]

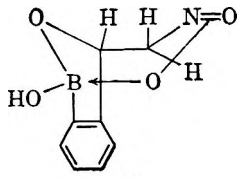
α-Substituent	Infrared bands, cm.⁻¹ B–O stretch[b]	Cyclic ether	C–O stretch
$-CH_2CO_2H$	1397–1358	1091	1002
$-CH_2NO_2$	1386–1356	1096	1015
$-CN$	1330	1076	978
$-CO_2H$	1340	1090	970

[a] All infrared spectra were obtained in KBr disks by the staff of the Spectroscopy Laboratory of the Department of Chemistry and Chemical Engineering of the University of Illinois, using a Perkin-Elmer Model 21 infrared spectrophotometer (equipped with sodium chloride optics). [b] L. J. Bellamy, W. Gerrard, M. F. Lappert, and R. L. Williams, *J. Chem. Soc.*, 2412 (1958).

in dimethyl sulfoxide (containing single proton quartets at τ 4.07, 4.57, and 5.38) revealed that the nitromethyl protons were nonequivalent. The unusually low τ-value of 0.31 for the BO–H proton (normally found at 1.9 to 2.4 for boronophthalides),[16] in conjunction with a single nitro stretching band[17] at 1551 cm.$^{-1}$ and a lowered BO–H stretch at 3175 cm.$^{-1}$ (3250–3440 cm.$^{-1}$ is the normal range)[7] found in the infrared spectrum of XIIIb, suggest the existence of a coordinated structure like XIV for this compound.



XIIIa, X = CH_2CO_2H
b, X = CH_2NO_2
c, X = CN
d, X = CO_2H
e, X = CH_3
f, X = CH_2Br



XIV

Sodium cyanide reacted with II to produce *o*-boronomandelonitrile, which lost water to form α-cyanoboronophthalide (XIIIc) when heated to 65°. This boronolactone was quantitatively hydrolyzed by concentrated hydrochloric acid to α-carboxyboronophthalide (XIIId). The α-substituted boronophthalides mentioned were not deboronated when allowed to stand in concentrated hydrochloric acid for 24 hr., which was not unexpected in view of the unusual stability of the boronophthalide ring.[7]

Previous to this study, the only α-substituted boronophthalides on record have been those of Dale,[8] who prepared α-methylboronophthalide (XIIIe) and α-(bromomethyl)boronophthalide (XIIIf) by dehydrobromination of *o*-(1-bromoethyl)benzeneboronic anhydride and *o*-(1,2-dibromoethyl)benzeneboronic anhydride, respectively. Although the aromatic ring of boronophthalide has been nitrated in the 3- and 5-positions,[7,18] the protons of the methylene group of boronophthalide and its benzene ring-substituted derivatives have proven resistant to substitution,[7,18,19] presumably because of the deactivating influence of the adjacent ether linkage.

(16) R. T. Hawkins, W. J. Lennarz, and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 3053 (1960).

(17) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1960 p. 297.

(18) R. R. Haynes, Ph.D. Thesis, University of Illinois, 1963.

(19) R. K. Kurz, Ph.D. Thesis, University of Illinois, 1961.

Experimental[20]

Preparation of *o*-Formylbenzeneboronic Acid.—This reaction was run *in the hood*. From a magnetically stirred solution of 23.6 g. (66.7 mmoles) of *o*-toueneboronic anhydride in 550 ml. of carbon tetrachloride in a 1000-ml., one-necked round-bottomed flask (equipped with a Claisen head, a condenser, and receiver protected by a drying tube), was distilled 50 ml. of carbon tetrachloride to insure the absence of water from the solution. The distillation apparatus was then removed and (while the solution was still boiling) in its place was quickly fitted a parallel side-arm connecting tube equipped with a 150-ml. pressure-equalizing addition funnel and a reflux condenser (protected with a drying tube). Bromine (64.2 g., 401 mmoles) was diluted with 100 ml. of dry carbon tetrachloride and placed in the addition funnel, and a 150-w. tungsten light bulb was situated a few inches from the flask. The bromine solution was added dropwise over a period of 2–2.5 hr. to the boronic anhydride solution, which was vigorously stirred and maintained at a gentle reflux during the addition. The pale yellow dibromide solution thus obtained was then stripped of solvent and any unchanged bromine *in vacuo*. To the cream-colored residue were then added 300 ml. of carbon tetrachloride and 100 ml. of water, and the resulting mixture was placed in a cold water bath (5–10°) and magnetically stirred. To this cooled slurry was added dropwise cold 15% aqueous sodium hydroxide until all the dibromide was dissolved in the aqueous layer (*ca.* pH 10). After filtration and separation, the yellow aqueous layer (maintained at 10–15°) was acidified with concentrated hydrochloric acid until a pH of 4 was reached. The precipitate resulting from the acidification was filtered and dried *in vacuo* over calcium chloride and weighed 25.6 g. (88% yield). The product was treated with Darco in water, resulting in 23.1 g. of white needles, which were observed to lose water at 110–120° and to resolidify at 125–130° before melting with decomposition at 163–165°. An analytical sample was prepared by recrystallizing the aldehyde twice from water and drying *in vacuo* for 24 hr. over calcium chloride.

Anal. Calcd. for $C_7H_7BO_3$: C, 56.07; H, 4.70. Found: C, 56.11; H, 4.79.

Earlier reports[3,21] have placed the melting point of this compound at 115–123°, which was the range in which the crystals were observed under the microscope to dissolve in the water resulting from the formation of *o*-formylbenzeneboronic anhydride; the figure of 163–165° reported here actually represented the melting point of the boroxin.

Preparation of *o*-Formylbenzeneboronic Anhydride.—To 150 ml. of dry benzene in a 200-ml. one-necked flask equipped with a heating mantle, magnetic stirrer, Dean–Stark water separator, condenser, and drying tube was added 1.50 g. (10 mmoles) of *o*-formylbenzeneboronic acid. The stirred suspension was refluxed for 24 hr., during which time *ca.* 0.20 ml. of water had accumulated in the trap. The benzene was removed *in vacuo* to yield 1.31 g. of a white hygroscopic powder (m.p. 165–166° dec.), representing a virtually quantitative yield of pure *o*-formylbenzeneboronic anhydride.

Anal. Calcd. for $C_7H_5BO_2$: C, 63.71; H, 3.82; mol. wt., 396. Found: C, 63.44; H, 3.78; mol. wt. (in benzene), 401.

Preparation of 1,3-Diphenyl-2-(*o*-boronophenyl)tetrahydroimidazole.—To a solution of 0.53 g. (23 mmoles) of N,N′-diphenylethylenediamine monohydrate in 5 ml. of absolute methanol in a 25-ml. beaker was added with stirring, in one portion, a solution of 0.33 g. (22 mmoles) of *o*-formylbenzeneboronic acid in 1 ml. of absolute methanol. A white crystalline precipitate appeared after a few seconds of continued stirring. After standing in the refrigerator for an hour, the reaction mixture was filtered and air-dried. The product was then washed with 1 ml. of water and again air-dried to yield 0.749 g. (99% yield) of white crystals, m.p. 144–146°, with dehydration at 105–115°. One recrystallization from chloroform–benzene raised the melting point to 146–148°.

An analytical sample was prepared by recrystallizing once more from chloroform–benzene.

Anal. Calcd. for $C_{21}H_{21}BN_2O_2$: C, 73.27; H, 6.15; N, 8.14; mol. wt., 344. Found: C, 73.36; H, 6.26; N, 8.03; mol. wt. (in chloroform), 320.

(20) Microanalyses and molecular weight determinations (using a Mechrolab Model 301A vapor pressure osmometer) were performed by Mr. Josef Nemeth and his associates. All melting points were taken on a Kofler hot stage microscope and are uncorrected.

(21) K. Torssell, *Arkiv Kemi*, **10**, 507 (1957).

The anhydride, m.p. 146–148° was prepared by drying a sample of the acid at 110° *in vacuo* overnight.

Anal. Calcd. for $C_{21}H_{19}BN_2O$: C, 77.32; H, 5.87; N, 8.59. Found: C, 77.18; H, 5.99; N, 8.71.

Preparation of 9-(*o*-Boronophenyl)-1,5-diazabicyclo[3.3.1]nonane.—A warmed, agitated suspension of 293 mg. (7.33 mmoles) of sodium hydroxide and 1.00 g. (3.62 mmoles) of 1,5-diazacyclooctane dihydrobromide in 4 ml. of methanol was treated with several drops of water until the neutralization reaction was completed. This solution was filtered into a solution of 542 mg. (3.62 mmoles) of *o*-formylbenzeneboronic acid in 1 ml. of methanol. After being thoroughly mixed, the resulting solution was placed on a steam bath and allowed to evaporate overnight. The residue was washed with 5 ml. of 50% aqueous methanol, filtered, and air-dried to yield 0.75 g. (84% yield) of white crystals, m.p. 294–298°, with loss of water at 105–110°. Recrystallization from 75% methanol resulted in 0.58 g. (65% yield) of purified product, m.p. 297–299°.

An analytical sample was obtained by another recrystallization from 75% methanol, followed by drying at 110° *in vacuo* overnight, to give the anhydride.

Anal. Calcd. for $C_{13}H_{17}BN_2O$: C, 68.45; H, 7.52; N, 12.28. Found: C, 68.28; H, 7.34; N, 12.46.

Preparation of Sodium α-Hydroxy(*o*-borono)benzylsulfonate.—To 450 mg. (3 mmoles) of *o*-formylbenzeneboronic acid was added 1.0 ml. of a freshly prepared 3.1 *M* solution of sodium bisulfite, resulting in a rapid exothermic dissolution of the aldehyde. The water was removed *in vacuo* and the residue was extracted with two 10-ml. portions of boiling absolute ethanol. The filtrate was evaporated *in vacuo*, and to the glassy residue was added 2 ml. of water, and the resulting solution was concentrated under reduced pressure. In this manner a yield of 665 mg. (87% yield) of slightly hygroscopic crystals, m.p. 275–287° dec., was obtained.

A sample was purified for analysis by extracting with cold absolute ethanol, evaporating the filtrate, adding water to the residue, re-evaporating, and finally drying over phosphorus pentoxide for 24 hr. *in vacuo*.

Anal. Calcd. for $C_7H_8SBO_6Na$: C, 33.10; H, 3.17. Found C, 33.35; H, 3.26.

Preparation of *o*-Boronobenzalmalononitrile.—A solution of 450 mg. (3 mmoles) of *o*-formylbenzeneboronic acid, 198 mg. (3 mmoles) of freshly distilled malononitrile, and a drop of pyridine in 2 ml. of dimethyl sulfoxide was heated on a steam bath for 24 hr. in a 5-ml. flask equipped with a reflux condenser protected by a drying tube. The reaction mixture was then cooled to room temperature, triturated with 20 ml. of water, and placed in the refrigerator overnight. After filtering, washing with 5 ml. of water, and air-drying, a yield of 783 mg. (98% yield) of white crystals, m.p. 208–212° dec. with dehydration at 110–115°, was obtained. Two recrystallizations from water provided a product melting at 217–219° dec.

A sample of analytical purity was obtained by recrystallizing twice more from water.

Anal. Calcd. for $C_{10}H_7BN_2O_2$: C, 60.66; H, 3.56; N, 14.15. Found: C, 60.88; H, 3.83; N, 14.14.

The anhydride, m.p. 217–219° dec., was obtained by dehydrating at 110° for 48 hr. over phosphorus pentoxide *in vacuo*.

Anal. Calcd. for $C_{10}H_5BN_2O$: C, 66.72; H, 2.80; N, 15.56. Found: C, 66.44; H, 3.03; N, 15.83.

The substitution of dimethylformamide for dimethyl sulfoxide in this reaction provided an 89% yield of product which showed no change in melting point when mixed with the dicyanide prepared in dimethyl sulfoxide.

Preparation of *o*-Formylbenzeneboronic Acid (Carboxymethyl)-trimethylammonium Chloride Hydrazone.—To 5 ml. of 95% ethanol in a 10-ml. flask equipped with a reflux condenser were added 765 mg. (5.1 mmoles) of *o*-formylbenzeneboronic acid and 838 mg. of Girard's reagent T, followed by a drop of glacial acetic acid. The resulting solution was refluxed for 1 hr., and then cast into 50 ml. of ether. After standing in the refrigerator for 1 hr., the solution was filtered. The precipitate obtained was dried, dissolved in ethanol, treated with Darco, and reprecipitated with ether. The resulting white crystals were dissolved in 1 ml. of water and the solution was evaporated *in vacuo* to give 1.38 g. (87% yield) of white crystals, m.p. 198–202° dec., with dehydration at 95–105°.

An analytical sample was prepared by twice repeating the above ethanol–ethyl ether–water treatment, and was dried *in vacuo* over calcium chloride. Inasmuch as the elemental composition of a sample prepared in this manner was found to be consistent with the monohydrate of the expected compound, a more severe dehydration (110° for 48 hr. at 0.05 mm. over phosphorus pentoxide) was used, providing a hygroscopic white solid, m.p. 202–203° dec., of the expected composition.

Anal. Calcd. for $C_{12}H_{19}N_3BClO_3$: C, 48.11; H, 6.39; N, 14.03. Found: C, 48.44; H, 6.10; N, 13.99.

Preparation of the Diethyl Ester of *o*-Formylbenzeneboronic Acid 2,4-Dinitrophenylhydrazone.—To a solution of 450 mg. (3 mmoles) of *o*-formylbenzeneboronic acid in 10 ml. of 95% ethanol was added dropwise with stirring 12.5 ml. of 0.25 *M* (3.12 mmoles) 2,4-dinitrophenylhydrazine (prepared by the method of Fieser[9]), and the reaction mixture was chilled in the refrigerator for an hour. After filtration and air-drying, there was obtained 1.12 g. of orange crystals, m.p. 247–249° dec., 97% yield. Recrystallization from ethanol raised the melting point to 249–250° dec.

The analytical sample was obtained by three further recrystallizations from ethanol and subsequent drying over calcium chloride.

Anal. Calcd. for $C_{17}H_{19}BN_4O_6$: C, 52.87; H, 4.96; N, 14.51. Found: C, 52.70; H, 4.87; N, 14.64.

The ester was hydrolyzed with hot water to provide the acid form of the 2,4-dinitrophenylhydrazone, m.p. 226–227° dec.

Anal. Calcd. for $C_{13}H_{11}BN_4O_6$: C, 47.30; H, 3.36; N, 16.98. Found: C, 47.51; H, 3.24; N, 16.78.

Preparation of 3-(*o*-Carboxyphenyl)-4-hydroxy-4,3-borazaroisoquinoline.—To a solution of 450 mg. (3 mmoles) of *o*-formylbenzeneboronic acid in 10 ml. of 50% ethanol was added dropwise with agitation 12.5 ml. of 0.25 *M* (3.12 mmoles) *p*-carboxyphenylhydrazine hydrochloride in water. After cooling in the refrigerator for 1 hr., the tan-colored product was filtered and washed with 5 ml. of water and air-dried. After recrystallization from ethanol–water, a yield of 712 mg. (89%) of tan crystals, m.p. 288–289° dec., was obtained.

The analytical sample was obtained by twice recrystallizing from water–ethanol and drying over calcium chloride *in vacuo*.

Anal. Calcd. for $C_{14}H_{11}BN_2O_3$: C, 63.19; H, 4.17; N, 10.53; mol. wt., 266. Found: C, 62.86; H, 4.25; N, 10.80; mol. wt. (in acetone), 257.

Preparation of 3-Formamido-4-hydroxy-4,3-borazaroisoquinoline.—To a solution of 450 mg. (3 mmoles) of *o*-formylbenzeneboronic acid in 10 ml. of 50% ethanol was added dropwise with agitation 12.5 ml. of 0.25 *M* semicarbazide hydrochloride in water. After being chilled in the refrigerator for an hour, the reaction mixture was filtered, and the product was washed with 5 ml. of water and air-dried. The white crystals were recrystallized from ethanol–water, resulting in 571 mg. (92% yield) of product, m.p. 295–299° dec., with sintering at 275–290°.

An analytical sample was prepared by two further recrystallizations from ethanol–water, followed by drying over calcium chloride *in vacuo*.

Anal. Calcd. for $C_8H_8BN_3O_2$: C, 50.84; H, 4.27; N, 22.23; mol. wt., 189. Found: C, 51.27; H, 4.25; N, 22.54; mol. wt. (in dioxane), 201.

Dehydration of this compound (140° at 0.25 mm. over phosphorus pentoxide for 48 hr.) provided bis(3-formamido-4,3-borazaro-4-isoquinolinyl) ether.

Anal. Calcd. for $C_{16}H_{14}B_2N_6O_3$: C, 53.39; H, 3.92; N, 23.35; mol. wt., 360. Found: C, 53.19; H, 4.09; N, 23.12; mol. wt. (in acetone), 347.

Preparation of Boronophthalidylacetic Acid.—To a 10-ml. flask equipped with a reflux condenser and a drying tube were added 750 mg. (5 mmoles) of *o*-formylbenzeneboronic acid, 865 mg. (6 mmoles) of isopropylidene malonate, 5 ml. of reagent dioxane, and a drop of pyridine. The solution was heated on a steam bath for 24 hr. and then evaporated *in vacuo*. The resulting yellow glass was treated with Darco in water, and the aqueous solution obtained from this treatment was concentrated under reduced pressure to a thick sirup, which was then triturated with benzene to yield 308 mg. (32%) of white crystals, m.p. 127–130°.

Two recrystallizations from chloroform provided an analytical sample, m.p. 129–130°.

Anal. Calcd. for $C_9H_9BO_4$: C, 56.30; H, 4.73. Found: C, 56.31; H, 4.69.

Substitution of malonic acid for isopropylidene malonate in this reaction provided a 17% yield of boronophthalidylacetic acid.

Preparation of α-(Nitromethyl)boronophthalide.—To a magnetically stirred, cooled (15–20°) solution of 850 mg. (21 mmoles)

of sodium hydroxide in water was added 3.00 g. (20 mmoles) of *o*-formylbenzeneboronic acid. After the solution was stirred for 5 min., there was added dropwise 1.09 ml. (1.22 g., 20 mmoles) of nitromethane. This solution was stirred for 15 min., after which time it was cooled to 5° while 20% hydrochloric acid was added dropwise until a pH of 3 was attained. After standing in the refrigerator for an hour, the reaction mixture was filtered. The precipitate, upon air-drying, provided 3.72 g. (96% yield) of product, m.p. 110–114°. Treatment with Darco in water gave white needles, m.p. 117–119°.

Two more recrystallizations from water provided a sample of analytical purity.

Anal. Calcd. for $C_8H_8BNO_4$: C, 49.78; H, 4.18; N, 7.26. Found: C, 49.81; H, 4.28; N, 7.09.

Preparation of α-Cyanoboronophthalide.—To a magnetically stirred, cooled (15–20°) solution of 1.04 g. (20 mmoles) of 95% sodium cyanide in water was added 3.00 g. (20 mmoles) of *o*-formylbenzeneboronic acid. After stirring for 15 min., the solution was cooled to 5° and acidified with concentrated hydrochloric acid to a pH of 5. The white precipitate thus formed was removed by filtration, and the filtrate was further acidified with 10% acid until no more precipitate formed. The two crops thus obtained were found to weigh 3.52 g. (99+% yield) upon air-drying. A recrystallization from water provided 2.81 g. (88% yield) of purified *o*-boronomandelonitrile (dehydration range, 60–65°). Dehydration of this material either by heating to 65° or by vacuum desiccation was found sufficient to cause lactone formation.

The analytical sample of the lactone (m.p. 107–109°) was prepared by twice recrystallizing from water, followed by drying over phosphorus pentoxide for 24 hr. *in vacuo*.

Anal. Calcd. for $C_8H_6BNO_2$: C, 60.43; H, 3.80; N, 8.81; mol. wt., 159. Found: C, 60.26; H, 3.79. N, 8.75; mol. wt. (in benzene), 160.

Preparation of α-Carboxyboronophthalide.—To a 15-ml. beaker containing 10 ml. of concentrated hydrochloric acid was added 159 mg. (1 mmole) of α-cyanoboronophthalide, and the mixture was allowed to stand for 24 hr. in the hood. The white crystalline product was separated by filtration, washed with two 10-ml. portions of acid, and dried, to provide 175 mg. (98% yield) of α-carboxyboronophthalide (m.p. 141–142°), which proved to be analytically pure.

Anal. Calcd. for $C_8H_7BO_4$: C, 53.99; H, 3.96; mol. wt., 178. Found: C, 53.76; H, 4.08; mol. wt. (in dioxane), 171.

The Interconversion of 2-Substituted 2-Oxazolines and 2-Thiazolines

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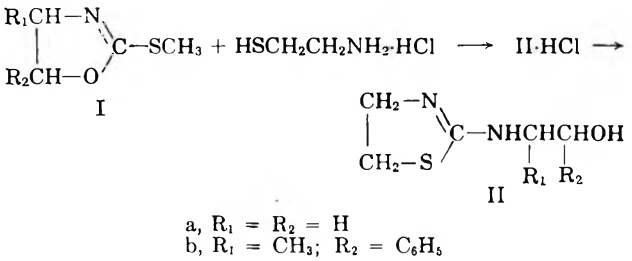
The anomalous products obtained from the reaction of two 2-methylthio-2-oxazolines with 2-mercaptoethylamine hydrochloride were identified as 2-(2-hydroxyethylamino)-2-thiazolines. On standing in solution, the latter compounds undergo rearrangement to 2-(2-mercaptoethylamino)-2-oxazolines, isolated as the disulfides. The interconversion of 2-oxazolines containing a 2-mercaptoethylamino side chain and 2-thiazolines containing a 2-hydroxyethylamino side chain, possibly through a bicyclic intermediate, is thus demonstrated.

In a previous paper[1] we have reported that products with anomalous properties are obtained from the reaction of 2-mercaptoethylamine hydrochloride with both 2-methylthio-2-oxazoline (Ia) and 2-methylthio-4-methyl-5-phenyl-2-oxazoline (Ib). The crystalline bases, IIa and IIb, afforded by these reactions have empirical formulas of $C_5H_{10}N_2OS$ and $C_{12}H_{16}N_2OS$. We have now demonstrated that these compounds are 2-(2-hydroxyethylamino)-2-thiazoline and 2-(2-hydroxy-1-methyl-2-phenylethylamino)-2-thiazoline, respectively, as shown.



I

II

a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = C_6H_5$

As reported previously,[1] the nuclear magnetic resonance spectrum of IIb contained a single sharp band that represented two protons at a frequency assignable to NH. This observation had suggested the possibility that a spiran such as V had been isolated, although the infrared spectrum strongly indicated that an unsaturated heterocyclic ring was present. The n.m.r. spectrum of the unsubstituted base, IIa, has been found to contain an analogous sharp signal with an intensity corresponding to two protons. In both cases, this band shifted to higher field as a single sharp peak on dilution. However, in the n.m.r. spectrum of 2-ethylaminoethanol,[2] the NH and OH protons are assigned to a single band, presumably as a result of rapid proton exchange.[3] We have found that the singularity of the NH–OH signal in 2-ethylaminoethanol is maintained over a wide range of concentrations and temperatures. Thus these two-proton signals in the spectra of IIa and IIb could arise from NH and OH rather than from two NH groups.

The infrared spectrum of IIb in chloroform had failed to show the presence of hydroxyl,[1] possibly, as previously suggested, because of hydrogen bonding. In dilute carbon tetrachloride solution it was indeed possible to observe a rather weak, though definite, free OH band at 2.76 μ. That both IIa and IIb contained an OH group was clearly demonstrated by near-infrared spectroscopy. The near-infrared spectra of the compounds showed the first overtone bands of both OH and NH.[4,5]

Additional evidence for the presence of hydroxyl in IIa and IIb was obtained by acetylation with acetic anhydride and pyridine. In both cases the spectrum of

(1) R. C. Clapp, L. Long, Jr., and T. Hasselstrom, *J. Org. Chem.*, **28**, 1308 (1963).

(2) "Varian N.M.R. Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, no. 92.

(3) Other systems in which OH and amine NH protons undergo rapid proton exchange and give a single signal are discussed by J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 440 and 455.

(4) W. Kaye, *Spectrochim. Acta*, **6**, 281 (1954).

(5) K. Whetsel, W. E. Roberson, and M. W. Krell, *Anal. Chem.*, **29**, 1006 (1957).

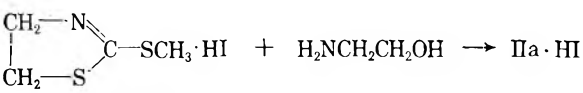
the acetylated product contained an ester carbonyl absorption at 5.75 μ and indicated that O-acetylation had taken place.

With the identification of a hydroxyl group in the structures of IIa and IIb, the strong absorption in the infrared at 6.16 μ can reasonably be assigned to the unsaturation in the 2-thiazoline ring.[6,7] In the spectrum of the disulfide of 2-(2-mercaptoethylamino)-2-thiazoline,[8] a similarly substituted 2-amino-2-thiazoline, the comparable band is identically located.

Interesting confirmatory evidence that the phenyl group is located in the side chain in IIb was provided by n.m.r. spectra. In the spectrum of IIb the proton bound to the carbon containing the phenyl group gave a doublet at τ 5.19. On acetylation, this signal was displaced to τ 4.02, a displacement to lower field of the predicted magnitude for the α-proton of a secondary alcohol on acylation.[9] In the spectra of 4-methyl-5-phenyl-2-thiooxazolidone and 2-methylthio-4-methyl-5-phenyl-2-oxazoline,[1] this doublet is at τ 3.99 and 4.28, respectively, electron-withdrawal effects apparently producing a similar displacement to lower field.

A distinction between the side-chain and ring locations of this CH–phenyl proton is indicated by the coupling constants of the doublet. For IIb and its acetyl derivative, the values of the constants are 3 and 3.5 c.p.s., whereas for the cyclic compounds, 4-methyl-5-phenyl-2-thiooxazolidone and 2-methylthio-4-methyl-5-phenyl-2-oxazoline, the values are 8.5 and 9.5 c.p.s., respectively. Also, in the spectrum of IIb, the signal assigned to the methylene group adjacent to the sulfur atom is centered at τ 6.67, comparable to its position (τ 6.60) in the cyclic 2-methylthio-2-thiazoline[10] rather than to the position (τ 7.06) of the acyclic methylene in the disulfide of 2-(2-mercaptoethylamino)-2-oxazoline.[1]

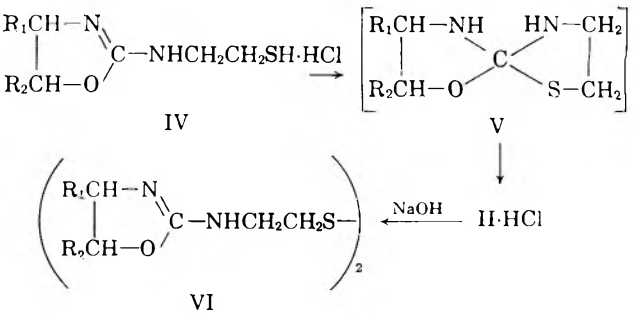
Finally, we have obtained IIa in 50–60% yield from the reaction of 2-methylthio-2-thiazoline hydroiodide (III) and 2-aminoethanol. From the properties of the



III

compounds and this alternate synthesis, the formulation of IIa and IIb as 2-(2-hydroxyethylamino)-2-thiazoline and 2-(2-hydroxy-1-methyl-2-phenylethylamino)-2-thiazoline is established.

It can be presumed that 2-(2-mercaptoethylamino)-2-oxazoline hydrochlorides (IV) are formed initially in the reaction of the 2-methylthio-2-oxazolines (I) with 2-mercaptoethylamine hydrochloride. Rearrangement to the stable 2-(2-hydroxyethylamino)-2-thiazoline hydrochlorides (II·HCl) may then take place through such a bicyclic intermediate as V. This intermediate corresponds to the intermediate previously proposed for the reactions of transthiazolination[8] and transoxazolination.[1] It is analogous to the cyclic intermediate



IV V

VI

postulated by Doherty, *et al.*,[11] for the conversion of 2-(2-aminoethyl)-2-thiopseudourea (AET) to 2-mercaptoethylguanidine and similar rearrangements.

As previously reported,[1] the 2-(2-hydroxyethylamino)-2-thiazolines (IIa and IIb) undergo conversion to the 2-(2-mercaptoethylamino)-2-oxazolines, isolated as the disulfides (VI), on standing in solution in the air. This rearrangement, which proceeds more rapidly in alkaline solution, can be readily followed by the shift of the strong infrared band at 6.16 to a wave length of 6.00 μ, characteristic of oxazolines of type VI. It can again take place through the intermediate V. Removal of the initially formed mercaptan from the system by oxidation to the disulfide, catalyzed by base, apparently effects complete conversion to the disulfide.

The reactions involved in the rearrangements demonstrate the interconvertibility, under the proper conditions, of 2-oxazolines with 2-mercaptoethylamino side chains and 2-thiazolines with 2-hydroxyethylamino side chains.

Experimental

N.m.r. Spectra.—Spectra were determined in deuteriochloroform at 60 Mc. with a Varian Model A-60 spectrometer.

Spectra were run on 20-, 40-, 80-, 160-, and 320-mg. samples of 2-ethylaminoethanol, each diluted with 1 ml. of deuteriochloroform, and on the neat liquid. The NH–OH signal shifted progressively from τ 6.0 to 7.4. When spectra were recorded on the 80-mg. solution at temperatures from −40 to 60°, this signal shifted from τ 5.5 to 7.4.

Infrared Spectra.—The near-infrared spectra were taken in carbon tetrachloride in a Cary Model 14 spectrophotometer. Both 2-(2-hydroxyethylamino)-2-thiazoline (IIa) and 2-(2-hydroxy-1-methyl-2-phenylethylamino)-2-thiazoline (IIb) gave bands at 1.41 (OH) and 1.48 μ (NH). Comparative spectra were run on 2-ethylaminoethanol and benzyl alcohol. The former showed bands at 1.41 (OH) and 1.54 μ (NH)[12]; the first OH overtone in benzyl alcohol is at 1.41 μ.

The infrared spectrum of IIb showed the characteristic strong N=C—N absorption at 6.16 μ in the solid state (potassium bromide pellet) as well as in solution, indicating that no rapid alteration has accompanied solution. In the hydrobromide of IIb this band was at 6.10 μ (potassium bromide). The hydrobromide, which was not previously described, was obtained by treatment of IIb with an equivalent of anhydrous hydrogen bromide and melted at 129.5–131.5°.

Anal. Calcd. for $C_{12}H_{17}BrN_2OS$: C, 45.43; H, 5.40; S, 10.11. Found: C, 45.46; H, 5.36; S, 10.20.

2-(2-Hydroxyethylamino)-2-thiazoline (IIa).—The hydrochloride of IIa, obtained from 2-methylthio-2-oxazoline and 2-mercaptoethylamine hydrochloride,[1] was converted to the free base by treatment with sodium bicarbonate. To a solution of 530 mg. (2.9 mmoles) of the hydrochloride in 12 ml. of water was added 1.2 g. (14.3 mmoles) of sodium bicarbonate. The solid residue remaining after concentration of this solution under reduced pressure at 25–30° was extracted successively with 6-ml. and

(6) M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4699 (1950).

(7) L. Long, Jr., R. C. Clapp, F. H. Bissett, and T. Hasselstrom, *J. Org. Chem.*, **26**, 85 (1961).

(8) R. C. Clapp, L. Long, Jr., and T. Hasselstrom, *ibid.*, **26**, 1666 (1961).

(9) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p. 55.

(10) A. F. McKay, D. J. Whittingham, and M-E. Kreling, *J. Am. Chem. Soc.*, **80**, 3339 (1958).

(11) D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *ibid.*, **79**, 5667 (1957).

(12) The lower wave length for NH in IIa and b reflects the adjacent unsaturation.

two 3-ml. portions of absolute ethanol. The extracts were concentrated, and the concentrate was extracted with 6-ml. and 2-ml. portions of boiling ethyl acetate. From these extracts there was obtained 319 mg. (75%) of colorless crystals, m.p. 95–97°. Recrystallization from ethyl acetate afforded colorless flat crystals, m.p. 96–97.5°; $\lambda_{max}^{CHCl_3}$ 2.89 (NH), 6.16 (N=C—N), and 6.66 μ.

Anal. Calcd. for $C_5H_{10}N_2OS$: C, 41.07; H, 6.89; S, 21.93. Found: C, 41.33; H, 6.90; S, 21.74.

The ultraviolet spectrum in aqueous solution gave a maximum at 211–212 mμ (ϵ 11,170); the spectrum of 2-amino-2-thiazoline[11,13] contained a maximum at 202–203 mμ (ϵ 8,470). For a solution of 54 mg. in 1 ml., the NH–OH band in the n.m.r. spectrum was at τ 4.67; at one-half this concentration it was at τ 5.00.

2-(2-Acetoxy-1-methyl-2-phenylethylamino)-2-thiazoline Picrate.—A solution of 300 mg. of 2-(2-hydroxy-1-methyl-2-phenylethylamino)-2-thiazoline (IIb)[1] in 7 ml. of pyridine and 7 ml. of acetic anhydride was allowed to stand at room temperature in an atmosphere of nitrogen for 17 hr. The solvent was removed under reduced pressure at a bath temperature of 40–50°. After the viscous concentrate had been washed with water, it was treated with ethanolic picric acid solution. Crystallization of the resulting crude picrate from ethanol gave 417 mg. of crystalline solid that melted from 192–197°. Recrystallization from ethanol yielded 366 mg. (57%) of fine yellow needles, m.p. 207–209°, λ_{max}^{KBr} 5.7 (s) and 6.15 (s) μ.

Anal. Calcd. for $C_{20}H_{21}N_5O_9S$: C, 47.33; H, 4.17; S, 6.32. Found: C, 47.41; H, 4.04; S, 6.28.

2-(2-Acetoxy-1-methyl-2-phenylethylamino)-2-thiazoline.—A solution of 611 mg. of the picrate in 30 ml. of chloroform was shaken twice with 10-ml. portions of cold 0.5 *N* sodium hydroxide solution. After it had been washed with water, the dried (anhydrous sodium sulfate) chloroform solution was concentrated to an oil. Addition of hexane to a solution of the oil in benzene yielded 281 mg. (84%) of nearly colorless crystals, m.p. 126–127.5°. Recrystallization from benzene–hexane gave colorless crystals, m.p. 126.5–128°; $\lambda_{max}^{CHCl_3}$ 2.90 (NH), 5.75 (ester C=O), and 6.14 μ (N=C—N).

Anal. Calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.40; H, 6.52; N, 10.07. Found: C, 60.58; H, 6.43; N, 10.02.

Acid hydrolysis (1.5 *N* hydrochloric acid on steam bath for 1 hr.) afforded the hydroxy compound, IIb. On treatment with alkali, the rearranged disulfide (VI, $R_1 = CH_3$; $R_2 = C_6H_5$) was obtained.

The acetyl derivative could not be obtained directly from the acetylation reaction; isolation required purification through the picrate.

(13) G. W. Raiziss and L. W. Clemence, *J. Am. Chem. Soc.*, **63**, 3124 (1941).

2-(2-Acetoxyethylamino)-2-thiazoline Picrate.—A solution of 800 mg. of 2-(2-hydroxyethylamino)-2-thiazoline hydrochloride (IIa·HCl) in 40 ml. of pyridine and 40 ml. of acetic anhydride was allowed to stand at room temperature in an atmosphere of nitrogen for 16 hr. After the solvent had been removed under reduced pressure, ethanolic picric acid solution was added. The crude picrate that precipitated crystallized from ethanol as yellow needles, 1.14 g. (62%), m.p. 145–147°, λ_{max}^{KBr} 5.7 (ester C=O) and 6.15 μ (N=C—N).

Anal. Calcd. for $C_{13}H_{15}N_5O_9S$: C, 37.41; H, 3.62; N, 16.78. Found: C, 37.66; H, 3.64; N, 16.70.

When a solution of the picrate in chloroform was treated with cold dilute sodium hydroxide, the base was obtained as an oil that failed to solidify. However, its infrared spectrum in chloroform showed the appropriate bands for O-acetylated IIa.

Alternate Synthesis of 2-(2-Hydroxyethylamino)-2-thiazoline (IIa).—A solution of 1.52 g. (5.82 mmoles) of 2-methylthio-2-thiazoline hydroiodide (III)[10] and 356 mg. (5.83 mmoles) of 2-aminoethanol in 60 ml. of absolute ethanol was refluxed for 21 hr. Removal of the solvent under reduced pressure gave 1.70 g. of viscous concentrate. Water was added to a 1.55-g. portion of the concentrate, and a little insoluble oil was removed by shaking with ether. Treatment of a 10-ml. portion of the resulting 30 ml. of aqueous solution with ethanolic picric acid solution yielded 402 mg. (60%) of crystalline picrate, m.p. 140–143°. Recrystallization from ethyl acetate afforded yellow crystals, m.p. 142.5–144.5°, that were identical with the previously obtained[1] picrate of 2-(2-hydroxyethylamino)-2-thiazoline by mixture melting point and infrared spectrum.

The remaining 20 ml. of aqueous solution was made strongly alkaline with sodium hydroxide and aerated for about 14 hr. After concentration, 172 mg. (33%) of white solid, m.p. 130.5–133°, precipitated. Crystallization from ethyl acetate gave white crystals, m.p. 133–135°, of the disulfide of 2-(2-mercaptoethylamino)-2-oxazoline (VI, $R_1 = R_2 = H$). Identity was established by mixture melting point and infrared spectrum.

When 2-methylthio-2-thiazoline, 2-aminoethanol, and an equivalent of anhydrous hydrogen chloride were refluxed in absolute ethanol, crude IIa hydrochloride was obtained. However, the crude hydrochloride was somewhat hygroscopic and could not be efficiently purified.

Attempts to obtain IIb from the reaction of 2-methylthio-2-thiazoline and α-(1-aminoethyl)benzyl alcohol (norephedrine) hydrochloride were unsuccessful. After prolonged refluxing in ethanol, the starting materials were recovered.

Acknowledgment.—We are indebted to Frank H. Bissett for the n.m.r. spectra, to John A. Sousa and Dr. Julius Weinstein for the infrared spectra, and to Carmine DiPietro for the microanalyses. We also thank Dr. Martin G. Ettlinger of Rice University and Dr. M. Kent Wilson of Tufts University for helpful discussions.

1,1′-Diacetyl-1,1′-dihydro-4,4′-bipyridine and the Yellow and Colorless Modifications of 1,1′-Diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine. The 1,1′-Diacetyl-4,4′-bipyridine Radical Cation

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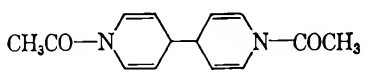
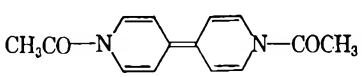
The properties of the yellow and colorless modifications of 1,1′-diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (I) have been carefully examined. The colorless form is shown to be pure I, and the yellow form (I-y), a mixture of I and 3–5% of 1,1′-diacetyl-1,1′-dihydro-4,4′-bipyridine (II). The existence of 1-acetylpyridinyl radicals (V) in samples of the yellow form, postulated by other workers, has been disproved by magnetic susceptibility and e.s.r. spectrum measurements on I-y. Evidence affirming structures I and II is presented. The n.m.r. spectrum of I indicates much double bond character in the amide C–N bond. Chemical behavior of II has been studied including its facile oxidation to 4,4′-bipyridine. The 1,1′-diacetyl-4,4′-bipyridine radical cation (XIV, green), an unstable intermediate in this oxidation process, has been prepared in solution and characterized by its visible and e.s.r. spectra.

1,1′-Diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (I) is described as a product of reductive coupling and acetylation of pyridine with zinc dust and acetic anhydride.[3–5] The reaction, discovered by Dimroth and



I

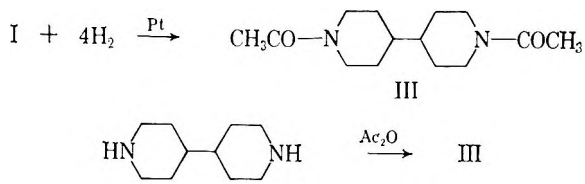
Heene,[3] leads to bright yellow crystals (I-y) having the molecular formula of I, $C_{14}H_{16}N_2O_2$. By crystallization of I-y from dilute methanolic potassium hydroxide solution,[3] a colorless modification is obtained having the same melting point and molecular formula. There is general agreement[3–6] that the colorless form is I, although its structure has not been rigorously established. The reason for the yellow color of I-y has been investigated by various workers.[3–6] It has been suggested that I-y is a mixture of I and pyridinyl radicals[6] or some colored diamagnetic impurity[3–5]; another suggestion is that I-y exists as a structural isomer of I.[3,6] We have carefully re-examined the problem and find that I-y contains no free radicals but is a mixture of I and small amounts of 1,1′-diacetyl-1,1′-dihydro-4,4′-bipyridine (II). Chemical behavior confirming structure assignments I and II is presented.



II

We have repeated the preparation of I-y according to the procedures of Dimroth and Heene[3] and Wibaut and Arens[5] and obtained yields similar to those reported previously (25–40%). Improved yields (45–47%) have been achieved by employing modifications in the procedure including a somewhat larger excess of zinc, a nitrogen atmosphere, and longer reaction time. Samples prepared by different procedures all appear to have closely similar properties. The colorless form (I) may be prepared by recrystallization of I-y in the manner described[3,5] in 70–82% yields, lit.[5] 73.5%.

Evidence presented previously[3–6] in support of structure I for the colorless form was found to be incomplete. Hydrogenation of I was reported to yield 1,1′-diacetyl-4,4′-bipiperidine (III)[6,7] by uniform absorption of 4 mole equiv. of hydrogen. By preparing an authentic sample of III by acetylation of 4,4′-bipiperidine and comparing it with the hydrogenation product obtained from I, we have now established this fact.



III

Since the location of double bonds in I had not previously been established, we have carefully examined the spectral properties of this substance. The infrared spectrum (potassium bromide) shows no O–H or N–H stretching bands, but strong amide C=O and olefinic C=C stretching bands at 1660 and 1620 cm.$^{-1}$, respectively. The ultraviolet spectrum (95% ethanol) reveals a broad band with maximum at 263 mμ (ϵ_{max} 24,000).[8] Structure I should have a spectrum roughly equivalent to two independently absorbing N-acetyl-1,4-dihydropyridine molecules. Published data on unsubstituted materials of this type appear to be lacking, but a reasonable model would be N-acetyl-9,10-dihydroacridine; its ultraviolet spectrum has the appearance of a broad band envelope with small protruding maxima of nearly equal intensity at *ca.* 252 and 258 mμ (ϵ_{max} ~19,000).[9]

The proton n.m.r. spectrum of I (*ca.* 20% in deuteriochloroform solution) is in agreement with structure I. The effect of rotational restriction about the amide C–N bond is observed in a large splitting of the

(1) U. S. Naval Ordnance Test Station, China Lake, Calif.

(2) Esso Research and Engineering Co., Linden, N. J.

(3) O. Dimroth and R. Heene, *Ber.*, **54**, 2934 (1921).

(4) O. Dimroth and F. Frister, *ibid.*, **55**, 1223 (1922).

(5) J. P. Wibaut and J. F. Arens, *Rec. trav. chim.*, **60**, 119 (1941).

(6) R. L. Frank, F. Pelletier, and F. W. Starks, *J. Am. Chem. Soc.*, **70**, 1767 (1948).

(7) B. Emmert and A. Wolpert, *Ber.*, **74**, 1015 (1941).

(8) The ultraviolet spectrum of I previously reported[6] [λ_{max} 239 mμ (ϵ_{max} 5400) in 95% ethanol] would indicate that some oxidation to 4,4′-bipyridine had occurred; we find for 4,4′-bipyridine λ_{max} 239 mμ (ϵ_{max} 11,000) in the same solvent. In our hands ethanolic solutions of I, in a stoppered flask, were found to be quite stable (2% decrease in absorbance intensity at 263 mμ after 18 hr.).

(9) E. R. Blout and R. S. Corley, *J. Am. Chem. Soc.*, **69**, 763 (1947); measurement was made in 95% ethanol. Numbers, taken from a curve, are approximate.

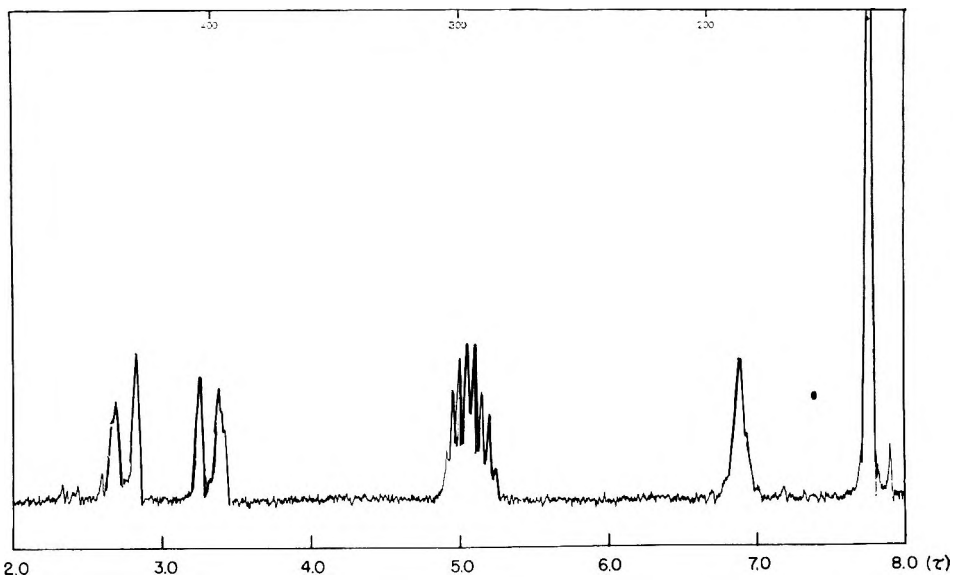
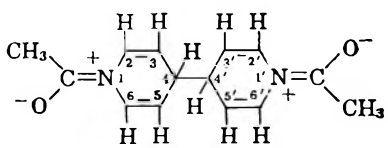


Fig. 1.—Proton n.m.r. spectrum of 1,1′-diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (I) in deuteriochloroform at 10°: 60 Mc., tetramethylsilane internal reference.

adjacent ring proton signals indicating much p-orbital content of this C–N bond (contribution from resonance structures such as I′). Figure 1 shows the n.m.r.



I′

spectrum obtained at 10° with a Varian A-60 spectrometer. The group of four olefinic proton peaks which appear as doublets centered at τ 2.77 and 3.32 represent the protons in 2(2′)- and 6(6′)-positions.[10] [The chemical shift difference of 0.55 p.p.m. (33 c.p.s.) is much larger than the corresponding separation of *N*-methyl signals observed for dimethyl formamide (0.09 p.p.m.; chloroform).] The narrower 8-c.p.s. splitting of these two signals represents a *cis*-ethylenic coupling to adjacent ring protons in the 3(3′)- and 5(5′)-positions. These protons in turn appear as a complex multiplet at τ 5.08, in which the effects of rotational asymmetry as well as spin-coupling interactions contribute to the fine structure. A poorly resolved multiplet at τ 6.90 is assigned to the 4(4′)-position protons and appears to be broadened by spin coupling to all eight of the remaining ring protons. A sharp single acetyl methyl peak found at τ 7.78 completes the spectrum. Areas under the peaks correspond to the appropriate number of protons. Proton n.m.r. spectra of N-alkyl- and N-aryl-1,4-dihydropyridines have been reported.[11–13] These, however, do not show the peak splitting of the 2,6-olefinic protons observed in I.

To confirm the assumption that rotational restriction accounted for the doubling of ring-proton spectra, a series of spectra were determined at 10° intervals from 10 to 60°. The four-line group assigned to 2(2′)- and 6(6′)-protons showed the expected effect of increasing exchange rate, a steady line broadening that first obliterated the spin splitting near 50° followed by coalescence of the two remaining broad peaks above 60°. The fine structure of the multiplet assigned to the 3(3′)- and 5(5′)-protons behaved similarly, with line broadening at lower temperatures leaving two broad peaks about 7 c.p.s. apart which coalesced above 50°.

Further confirmation of restricted rotation appeared in the behavior of this material in other solvents. The n.m.r. spectrum observed for I in dimethylformamide showed the splitting of 2(2′)- and 6(6′)-protons reduced to 14 c.p.s., less than half that observed for a comparable deuteriochloroform solution. Gradual dilution of the deuteriochloroform solution with dimethylformamide resulted in intermediate reductions of the anisotropy splitting. This type of solvent dependence has been noted in n.m.r. spectra of amide solutions and correlated with associative interactions between the amide and the solvent.[14]

The properties of yellow I-y, except for the color, appear superficially to be identical with those of colorless I. Both substances have the same elemental analysis and melting point.[3,5,15] As with I, 1,4-diacetyl-4,4′-bipiperidine (III) is readily formed on hydrogenation with absorption of 4 mole equiv. of hydrogen at a uniform rate.[6] Only minor differences are noted in the spectra of I and I-y (infrared,[6] ultraviolet, and n.m.r.) and these suggest that I-y contains impurities. Thus the possibility is excluded that I-y exists as a double bond isomer of I.

(10) The molecule I is symmetrical and the protons of the two halves have identical n.m.r. peaks. A closely similar olefinic proton spectrum has been observed for 1,4-diacetyl-1,4-dihydropyridine oxime,[7] indicating that the observed doubling of ring proton signals is not related to the bicyclic structure of I (unpublished results, this laboratory). A similar splitting of vinyl ring protons (quartet, τ 6.81–7.35) is observed with 2,6-di-*t*-butylbenzoquinone-4-oxime methyl ether: L. A. Cohen and W. M. Jones, *J. Am. Chem. Soc.*, **85**, 3397 (1963).

(11) R. F. Hutton and F. H. Westheimer, *Tetrahedron*, **3**, 73 (1958).

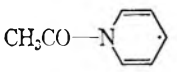
(12) E. M. Kosower and T. S. Sorensen, *J. Org. Chem.*, **27**, 3764 (1963).

(13) M. Saunders and E. H. Gold, *ibid.*, **27**, 1439 (1963).

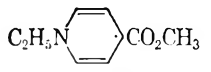
(14) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **5**, 139 (1962).

(15) The melting points of I and I-y occur with some decomposition and depend on the rate of heating. Capillary melting points reported for I-y are 124–125°[3] and 130–131°.[5] We find melting ranges from 122–125° to 128–132° on various samples from different preparations. For colorless I melting points reported were 123–125°,[3] 130–131°,[6] and 132–132.8°[5]; our samples melted over the range 123–129°. Before melting, the colorless form is observed to turn yellow.

The suggestion has been made that I-y is yellow owing to the presence of 1-acetylpyridinyl radicals (V) as I-y was found to be paramagnetic while I was not.[6] The radical V probably has a certain stability[16] and a



V



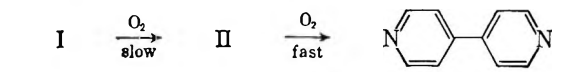
VI (green)

recent report[17] of the isolation of the 4-carbomethoxy-1-ethylpyridinyl radical (VI) as an emerald green liquid supports this idea. However, VI is extremely sensitive to oxygen and it appeared unlikely to us that V could exist as a trapped impurity in I for prolonged periods. We therefore repeated the magnetic susceptibility measurements on I-y ($K = -0.405 \times 10^{-6}$ g.$^{-1}$) and I ($K = -1.013 \times 10^{-6}$ g.$^{-1}$) and, contrary to the original report[6], found both substances to be diamagnetic.[18] Also, I-y showed no e.s.r. signal indicating absence of significant amounts of free radicals (calculated radical concentration less than 10^{-15} M). Thus the color of I-y must be due to some colored impurity other than radicals.

The presence of 1,1′-diacetyl-1,1′-dihydro-4,4′-bipyridine (II) as an impurity in I-y was suggested earlier.[3-5] The suggestion rested tentatively on the demonstration that low yields of II could be obtained by air oxidation of I in hot acetic anhydride solution.[3,4] Direct evidence of the presence of II in I-y has now been obtained by trituration of I-y with cold chloroform, in which I is very soluble but II is only slightly soluble; a 4.5% recovery of II (6% of material assaying 75% II by ultraviolet spectroscopy) was obtained in this manner. Also, the characteristic visible spectrum of II having a maximum at 428 mμ (95% ethanol) is found in I-y, but not in I. By comparison of absorbances at 428 mμ (calculated at zero time by extrapolation) it is estimated that I-y contains *ca.* 3–5% II. The maximum in the ultraviolet spectrum at 263 mμ in I (ϵ_{max} 24,000) is also found in I-y but of slightly lowered extinction coefficient (ϵ_{max} 23,200 after the rapid conversion of II to 4,4′-bipyridine VII[4] is complete). By correcting for the absorbance of VII at 263 mμ, the amount of II present in I-y is calculated to be 4.6%. The infrared spectrum of I-y suggests very small amounts of II to be present, but no significant amounts of other impurities except possible trace amounts of VII. However, an accurate assay cannot be made from the appropriate characteristic infrared absorbances because of the low concentrations of impurities. It is concluded that samples of I-y contain II as the major (and only colored) impurity and 93–97% I.

Structure II was established by its hydrogenation to 1,4-diacetyl-4,4′-bipiperidine (III) (platinum catalyst, 1 atm., ethanol, 25°), 5 mole equiv. of hydrogen being rapidly and uniformly absorbed.

4,4′-Bipyridine (VII) has been obtained by air oxidation of I or II[3,4,19] in various solvents, the oxidation of II occurring quite rapidly.[4] Oxidation of I to II has been demonstrated,[3,4] and in our opinion is the cause, rather than radical formation,[6] for color changes observed with I in solution. The appearance of a yellow color when ethanolic solutions of I (colorless) are warmed in a stoppered flask and the disappearance of the yellow color on exposure to air[6] are believed due to rapid oxidation of II (yellow in solution) to VII (colorless). The intermediate steps in the oxidation, II → VII, are discussed below. (Dilute solutions of I in

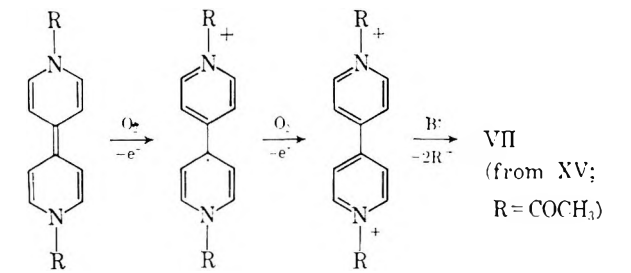


VII

ethanol are much more stable[8] than those of II.) The rate of conversion of II to VII has been followed spectrophotometrically in 95% ethanol solution by observing the decrease in intensity of absorption at 428 mμ (by extrapolation to zero time, ϵ_{max} 32,500). Excellent first-order plots of log A (absorbance) against time are obtained, $k = 2.8 \times 10^{-3}$ sec.$^{-1}$ at 25°. The band at 428 mμ found in I-y due to presence of II disappears at the same average rate, although the range of rate constant values is larger. The disappearance of the 428-mμ band is accompanied by the appearance of a strong 4,4′-bipyridine band at 239 mμ in the ultraviolet region (ϵ_{max} 10,300 after destruction of II is 98% ocmplete; 4,4′-bipyridine ϵ_{max} 11.000 at 239 mμ). The rate of disappearance of II in ethanol solution is more rapid in the presence of dilute sodium hydroxide and is also hastened by exposure to strong incandescent light.

The chemical behavior of I and II finds close analogy in that of colorless 1,1′-dibenzyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (VIII), m.p. 83–87°, and the corresponding brown dihydro compound (IX), m.p. 140° with decomposition.[20] Compound VIII in solution is oxidized to IX by air and becomes yellow-brown as its melting point is approached. 1,1′-Dibenzyl-4,4′-bipiperidine is formed by hydrogenation of VIII and IX (4 and 5 mole equiv. of hydrogen absorbed, respectively).[21]

Another property to be predicted for II, which is characteristic of IX, is its one-electron oxidation to a deeply colored radical cation (XIV, R = $COCH_3$). This radical is an intermediate in the oxidation process leading to 4,4′-bipyridine (II → VII). Radical X (R = $CH_2C_6H_5$) and XI (R = H, derived from 4,4′-bi-



II, IX, XII X, XI (blue) XIII, XIV (green) XV, XVI, XVII, XVIII

XI, XVIII, R = H
IX, X, XVI, R = $CH_2C_6H_5$

II, XIV, XV, R = $COCH_3$
XII, XIII, XVII, R = C_6H_5

(16) Arguments have been advanced explaining the stability of V; *cf.* R. A. Barnes in "Pyridine and Its Derivatives," Part I, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 56.

(17) E. M. Kosower and E. J. Poziomek, *J. Am. Chem. Soc.*, **85**, 2035 (1963).

(18) Compound II is also diamagnetic ($K = -0.298 \times 10^{-6}$ g.$^{-1}$). Measurements were performed by Mr. Kenneth Kneip, Tulane University.

(19) A. E. Arbuzov, *Bull. acad. sci. URSS Classe sci. chim.*, 451 (1945); *Chem. Abstr.*, **42**, 5912 (1948).

(20) R. Weitz, T. König, and L. V. Wistinghausen, *Ber.*, **57**, 153 (1924).

(21) R. Weitz, *Angew. Chem.*, **66**, 658 (1954).

pyridine itself) are blue,[21-24] and XIII (R = C_6H_5) from 1,1′-diphenyl-1,1′-dihydro-4,4′-bipyridine (XII) is green.[21] A dilute chloroform solution of II, to which trifluoroacetic acid had been added, was oxidized immediately upon exposure to air or treatment with iodine to a deep green substance (blue-green in concentrated solutions), λ_{max} 637 and 707 mμ, assigned the radical cation structure XIV (R = $COCH_3$). The visible spectrum of XIV resembles that of 1-carbomethoxy-4-ethylpyridinyl radical (VI, $\lambda_{max}^{CH_3CN}$ 632.5, shoulders at 690 and 775 mμ).[17] The e.s.r. spectrum of XIV was determined at −15° in degassed chloroform solution containing a few drops of trifluoroacetic acid (1% solution of II). At this temperature the green color persisted for 45 min. A single sharp line centered at 2.003 gauss, width ~7–10 gauss between inflection points, was obtained. By double integration of the spectrum curve area, the conversion to radical is calculated to be very high (roughly quantitative), and would suggest the narrow single-line spectrum without resolved hyperfine structure to be due to exchange narrowing due to high radical concentration.[25] Attempts to observe hyperfine structure by decreasing concentration failed because solutions were unstable.

Further oxidation of XIV occurs rapidly in air leading to a light yellow solution presumed to contain the dication XV, analogous to known dications XVI, XVII, and XVIII derived from X, XI, and XIII, respectively. Addition of II to the solution of XV regenerates the green color. Deacylation of XV (by treatment with water or other base) produces 4,4′-bipyridine (VII).

Experimental[26]

1,1′-Diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (Yellow Modification, I-y).—The original procedure of Dimroth and Heene[1] was followed with certain modifications. To a mixture of 200 ml. (194 g., 2.46 moles) of pure pyridine, 1 l. of acetic anhydride, 20 ml. of acetic acid, and 1.0 g. of ferric chloride contained in a 3-l. three-necked flask was added, with vigorous stirring, a 75-g. portion of powdered zinc (99.9% assay). The mixture was stirred vigorously until a temperature rise to 40° occurred (0.5–1.5 hr.).[27] The temperature was then maintained at 30–40° by occasional ice-bath cooling and nitrogen was passed through the system; zinc (265 g. more, total 340 g.) was added in *ca.* 30-g. portions at regular intervals during 4.5–5 hr. Vigorous stirring was continued for 15 hr. (25–30°) after addition of the zinc was complete (nitrogen atmosphere maintained). The flask was then surrounded by a large container of boiling water to heat the stirred mixture to 90° within 5 min. The mixture was then filtered immediately through a Büchner funnel and the filter cake was washed three times with acetic anhydride (100-ml. portions). The clear yellow filtrate was chilled immediately in an ice bath and kept at 0–5° for 4 hr while shaking and stirring vigorously at intervals. The bright yellow crystals were filtered and washed first with acetic anhydride and then several times with water and finally dried in a vacuum desiccator over sodium hydroxide; yield 135–140 g. (45–47%), m.p. 125–128°.[15,26] Alternatively, the acetic anhydride filtrate may be poured directly into a large amount of ice and water and filtered (47% yield). When the procedure of Dimroth and Heene[3] was followed on the above scale (90% assay zinc, air atmosphere), yields of 23–34% were obtained; m.p. 122–127° to 128–132° on different runs, lit. m.p. 124–125°[3] and 130–131°.[5]

1,1′-Diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (Colorless Modification, I).—A 50.0-g. sample of the yellow form I-y was dissolved in 500 ml. of hot methanol. A solution of 2 g. of potassium hydroxide in 20 ml. of methanol was added and the mixture was heated to boiling for 5–10 min. After filtering, the filtrate was chilled quickly in an ice bath and shaken vigorously. The crystals were filtered immediately and washed with ice-cold methanol to yield 35–41 g. (70–82%) of colorless I, m.p. 126–129°,[15,26] lit. m.p. 123–125°[3] and 132–132.8°.[5] The melting point depends on the rate of heating and values determined on a Kofler hot stage were 5–10° lower.[26] As observed previously[6] samples of I and I-y when exposed to air at room temperature occasionally decompose spontaneously, and rapidly form a viscous brown oil. Samples placed in a well-sealed container in a refrigerator have never been observed to decompose after storage for periods of several months.

1,1′-Diacetyl-1,1′-dihydro-4,4′-bipyridine (II) was prepared according to the procedure of Dimroth and Frister[4] by heating equivalent amounts of I and 4,4′-bipyridine in acetic anhydride under nitrogen on the steam bath for 30 min. The crude product was recrystallized from hot acetic acid as bright orange leaflets (30% yield), m.p. 260–264° dec.,[26] lit. m.p. 248°[3] and 284°[4]; the melting point depends on the rate of heating. The substance has very limited solubility in all solvents tested and a suitable n.m.r. spectrum could not be obtained. The infrared spectrum (Nujol) showed split carbonyl absorption at 1660 and 1640 and a C=C stretching band at 1560 cm.$^{-1}$ (absent in I but present in 4,4′-bipyridine at 1580 cm.$^{-1}$); strong bands at 893 and 750 present in I and at 815 cm.$^{-1}$ present in 4,4′-bipyridine were absent.

The ultraviolet spectrum was determined in 95% ethanol solution (c 2.1 × 10^{-4} M) using a Cary Model 11 MS recording spectrophotometer. Absorbance of the yellow solution (λ_{max} 428, shoulder 415 mμ) decreased with time and absorbance readings were taken at intervals at 428 mμ: 429 sec., A 1.95; 520, 1.48; 611, 1.11; 756, 0.71; 847, 0.55; 942, 0.43. By plotting log A against time the points were found to lie on a straight line and extrapolation to zero time gave A = 6.8 (ϵ_{max} 32,400). From the slope a first-order rate constant could be calculated, k = 2.93 × 10^{-3} sec.$^{-1}$. Values obtained in another run were ϵ_{max} 32,600 and k = 2.72 × 10^{-3} sec.$^{-1}$; average 2.8 × 10^{-3} sec.$^{-1}$ ϵ_{max} 32,500 (for shoulder at 415 mμ, ϵ 28,200, calculated in the same manner). The disappearance of the band at 428 mμ is accompanied by an increase in intensity of a band at 239 mμ in the ultraviolet region: 540 sec., A 1.90; 780, 2.05; 899, 2.08; 1238, 2.17; 1490, 2.20. At 1490 sec., ϵ_{max} was 10,300 at 239 mμ and 560 at 428 mμ (when destruction of II is 98% complete). The band at 239 mμ is believed to be that of 4,4′-bipyridine which was found to have an absorption maximum at this wave length (ϵ_{max}^{239} 11,000), lit.[28] λ_{max} 237 mμ (ϵ_{max} 13,000) in hexane.

Addition of dilute sodium hydroxide to saturated ethanolic solutions of II (100 ml. in volumetric flask) hastened the transformation to a colorless solution (25°); 1.0 ml. of 1.0 N aqueous sodium hydroxide caused decolorization in 45 min. and 0.1 ml. caused decolorization in 80 min. A control solution containing no additives was decolorized in 200 min. Exposure of ethanolic solutions of II to ultraviolet or incandescent lamps hastens destruction of the yellow color two- to threefold.

1,1′-Diacetyl-4,4′-bipyridine Radical Cation (XIV).—Saturated solutions of II in chloroform (*ca.* 0.7 g./100 ml., deep yellow) when treated with a few drops of trifluoroacetic acid produced a deep blue-green color when shaken in air (λ_{max} 637 and 707 mμ). Within a few minutes the solution became light yellow in color; addition of more II regenerated the green color. The transformation could also be carried out with iodine (nitrogen atmos-

(22) E. Müller and K. A. Bruhn, *Ber.*, **86**, 1122 (1953).

(23) F. Bruin, F. W. Heineken, M. Bruin, and A. Zahlan, *J. Chem. Phys.*, **36**, 2783 (1962).

(24) The deep blue color produced by prolonged heating of ethanolic solutions of I was shown by Dimroth[2] to arise from the 4,4,-bipyridine formed by decomposition. Later,[23] the blue color was shown to be that of the cation radical XI (R = H).

(25) R. L. Ward and S. I. Weissman, *J. Am. Chem. Soc.*, **79**, 2086 (1957).

(26) Melting points reported for I-y, I, and II were determined in capillary tubes, others on a Kofler hot stage.

(27) An induction period of 0.5–1.5 hr. was noted before a temperature rise and the appearance of a bright yellow-green color occurred. Maintenance of an air atmosphere during this time (rather than nitrogen) and the additions of acetic acid and a small amount of ferric chloride were found to shorten this induction period.

(28) C. W. F. Spiers and J. P. Wibaut, *Rec. trav. chim.*, **56**, 573 (1937). The lower value of ϵ_{max} found in 95% ethanol (compared with hexane) may be due to formation of pyridinium ions. P. Krumholz [*J. Am. Chem. Soc.*, **73**, 3487 (1951)] reported for VII λ_{max} *ca.* 238 mμ (ϵ_{max} 15,000) in methanol containing ammonia (0.02 M); numbers taken from published curve are approximate. At low concentrations such as those employed here (1.4 × 10^{-4} M anhydrous VII) some 4,4,-bipyridinium mono ion may be produced (λ_{max} 256 mμ) causing a broadening of the band envelope and lowering of ϵ_{max}.

phere), traces of which produced a deep green color while an excess produced a light yellow solution. The green solutions were stable in air for only a few minutes and stable under nitrogen for only slightly longer periods. By careful addition of glycerol as a floating layer over the chloroform solutions,[23] the green color remained for 15–20 min. The green solutions, believed to contain 1,1'-diacetyl-4,4'-bipyridyl radical cation (XIV) could also be prepared in acetonitrile and less readily in benzene, ethanol, acetone, or acetic acid; solutions of XIV prepared in these solvents were much less stable than the chloroform solutions.

The e.s.r. spectrum of the radical cation XIV was obtained with a Strand Model 600 x-band spectrometer and a Harvey Wells L-128 magnet. The magnetic field (nominally 3400 gauss) was calibrated by monitoring the frequency of a Harvey Wells F-502 NMR oscillator with a Hewlett Packard HP-524C frequency counter. Field sweep rates of 1 gauss/min. were used. Microwave power was kept low, although no saturation was observed up to 10 mw. of klystron power.

Solutions were prepared in pure chloroform in quartz e.s.r. tubes equipped with Teflon stopcocks and then degassed using the triple freeze-thaw technique.[29] The stopcock was opened briefly to allow the addition of a few drops of trifluoroacetic acid to generate the radical. All spectra were obtained at −15° using a glass flow cryostat. At this temperature the green color was found to persist for *ca.* 45 min. if degassed chloroform and fresh trifluoroacetic acid were used. On a 1% solution (0.1 g./10 ml.) a single sharp line was obtained, centered at 2.003 gauss (width ~7–10 gauss measured between inflection points). Attempts to observe hyperfine structure by decreasing concentration failed because solutions were unstable. The lowest stable concentration was *ca.* 0.1% with spectrum parameters the same as for the 1% solution.

Radical concentrations were measured by using a chromium-doped ruby crystal mounted within the microwave cavity as an internal standard.[30] The crystal was oriented in such a manner as to give a single line well resolved from the radical signal. The two signals thus obtained were compared on the basis of a double integration of the area under each curve. The intensity of the ruby signal was calibrated with a series of diphenylpicrylhydrazide–asphaltene standards. The estimated radical concentration of the 1% solution (containing *ca.* 2.5×10^{19} molecules/ml.) was 5×10^{18}/ml. In a single line spectrum of the type observed, intensity measurements are reliable to about one order of magnitude. Thus the conversion to radical is roughly quantitative.

Properties of Yellow Modification I-y.—The infrared spectrum (potassium bromide) was practically identical with that of I; no OH or NH bands but strong amide C=O and olefinic C=C stretching bands at 1660 and 1620 cm.$^{-1}$, respectively. Slight lowering of intensities of certain bands present in I and absent in II (893 and 750 cm.$^{-1}$) was noted. Also present was a very weak band near 810 cm.$^{-1}$, absent in I and II but present in 4,4'-bipyridine (813 cm.$^{-1}$) as a very strong broad band.

The visible spectrum was determined in 95% ethanol by the procedure described for II, the characteristic maximum at 428 mμ and shoulder at 415 mμ were observed. A 1.95×10^{-3} *M* solution (employing mol. wt. 244.3) had an absorbance of 2.0 at zero time at 428 mμ (ϵ_{max} 1030) corresponding to 3.2% II another sample contained 4.3% II. The decrease in absorbance at 428 mμ was followed as with pure II and plots of log *A* against time gave a straight line from which rate constants could be calculated from the slopes; values of 1.23, 2.26, and 3.55×10^{-3} sec.$^{-1}$ were observed with different samples (rate for pure II, 2.8×10^{-3} sec.$^{-1}$). The variation in rates may possibly be attributed to variable amounts of trace impurities present in each sample.

In the ultraviolet spectrum a broad band was observed at 262 mμ (ϵ_{max} 23,200 after solution became colorless in spectrophotometer, *ca.* 30 min.); after standing 18 hr., ϵ_{max}^{262} was 22,800 (employing mol. wt. 244.3). The measurement at 30 min. was determined after the impurity II had been completely converted into 4,4'-bipyridine (VII). At 262 mμ, VII has ϵ 5900 and, assuming no impurity other than VII to be present, the amount of VII is calculated to be 4.4% from the equation $\epsilon_{obsd} = \epsilon^{I}(1 - c) + \epsilon^{VII}c$, where ϵ^{I} and ϵ^{VII} are the extinction coefficients of I and VII at 262 mμ, *i.e.*, 24,000 and 5900, respectively, and c is the fraction of VII in the mixture. Since VII arises quantitatively from II, the amount of VII originally present in I-y is probably very small (<1%).

The n.m.r. spectrum of I-y in deuteriochloroform solution was practically indistinguishable from that of I.

The e.s.r. spectrum of I-y showed no signal. In various runs the spectrometer setting was varied such that line widths up to 100 gauss would have been detected if the spin concentration were greater than 10^{-15} *M*. In all cases, the results were negative. The absence of an e.s.r. signal is not conclusive proof that the material is diamagnetic, but this point was covered by the magnetic susceptibility measurements. Compounds I and II and substance I-y were all found to be diamagnetic[18]; see discussion for numerical values.

Trituration of a 4.0-g. sample of yellow I-y with 10 ml. of chloroform produced an orange solid which was filtered and washed with water to yield orange crystals, 0.24 g., m.p. 176–180° dec. A 2.06×10^{-4} *M* solution (employing mol. wt. 242.3) of this substance in 95% ethanol was calculated to have ϵ_{max} 24,300 at 428 mμ by extrapolation to zero time as described above, corresponding to 75% II in the crude product. The recovery of pure II corresponds to 4.5%. The decrease in absorbance at 428 mμ occurred uniformly as with pure II, $k = 2.54 \times 10^{-3}$ sec.$^{-1}$. The loss of II due to solubility in the concentrated solution of I is believed to be small since the solubility of II would be less in such a solution than in pure chloroform where it is only *ca.* 1.0–0.7 g./100 ml. at 25°.

4,4'-Bipiperidine.—A 1.56-g. sample of 4,4'-bipyridine (anhydrous, m.p. 111–112°) in 50 ml. of absolute ethanol was hydrogenated with 1.0 g. of 10% palladium–charcoal catalyst at 50 p.s.i. and 25° in a Parr apparatus until hydrogen uptake ceased (6 mole equiv. absorbed after 60 hr.). The catalyst was filtered and the filtrate was concentrated and triturated with acetone to yield 1.39 g. (83%) of 4,4'-bipiperidine, m.p. 168–170°[26]; recrystallization from acetone did not change the melting point; lit. m.p. 170–171°[31] and 171–172°.[32] The substance readily absorbs water and carbon dioxide from the atmosphere. When the hydrogenation procedure employed with I and II (see below) was applied to 4,4'-bipyridine (700 mm., 25°, platinum catalyst), essentially no hydrogen uptake was observed after 19 hr.

1,1'-Diacetyl-4,4'-bipiperidine (III). A. From 4,4'-bipiperidine.—A 0.9-g. sample of 4,4'-bipiperidine in 15 ml. of acetic anhydride was heated under reflux for 2 hr.; concentration of the mixture to near dryness followed by addition of acetone led to 0.19 g. of crude 1,1'-diacetyl-4,4'-bipiperidine, m.p. 174–175° after recrystallization from acetone (lit.[7] m.p. 174°); infrared spectrum (potassium bromide) had a strong amide carbonyl band at 1640 cm.$^{-1}$, NH and OH bands absent.

B. From II by Hydrogenation.—A 0.0798-g. sample of 1,1'-diacetyl-1,1'-dihydro-4,4'-bipyridine (II) partly suspended in 10 ml. of acetic acid was hydrogenated in the presence of platinum oxide catalyst (10 mg.) at 702 mm., 25°, until hydrogen uptake essentially ceased (2.3 hr., 5.0 mole equiv. of hydrogen absorbed uniformly); near the end of the reaction the deep yellow color of the solution changed to colorless. The platinum was filtered and the filtrate was concentrated to dryness *in vacuo* to yield 0.08 g. of material, m.p. 158–159°; recrystallization from acetone raised the melting point to 174.5–175.5°; when mixed with the authentic sample (m.p. 174–175°) the melting point was not depressed; infrared spectrum (potassium bromide) identical with that of the authentic sample.

C. From I by Hydrogenation.—The procedure employed above with II was applied to 1,1'-diacetyl-1,1',4,4'-tetrahydro-4,4'-bipyridine (I) dissolved in ethanol. Four mole equivalents of hydrogen were absorbed uniformly before uptake ceased (1.5 hr.). The product was isolated as above in 78% yield, m.p. 169–174°; recrystallization from dioxane gave m.p. 174°; when mixed with an authentic sample the melting point was not depressed; infrared spectrum was identical with authentic sample.

Anal. Calcd. for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10; mol. wt., 252.35; sapon. equiv., 126.17. Found: C, 66.93; H, 9.84; N, 11.10; mol. wt., 257; sapon. equiv., 126.

Acknowledgment.—The authors are indebted to Professor Hans B. Jonassen for assistance in securing the magnetic susceptibility and e.s.r. measurements and for helpful discussions.

(29) G. W. Nederbragt and C. A. Reilly, *J. Chem. Phys.*, **24**, 1110 (1956).
(30) L. S. Singer, *J. Appl. Phys.*, **30**, 1463 (1959).
(31) E. Meixner, *Ber.*, **62**, 1732 (1929).
(32) E. P. Hart, *J. Chem. Soc.*, 3872 (1953).

12-Pyridylbenz[*a*]anthracenes[1,2]

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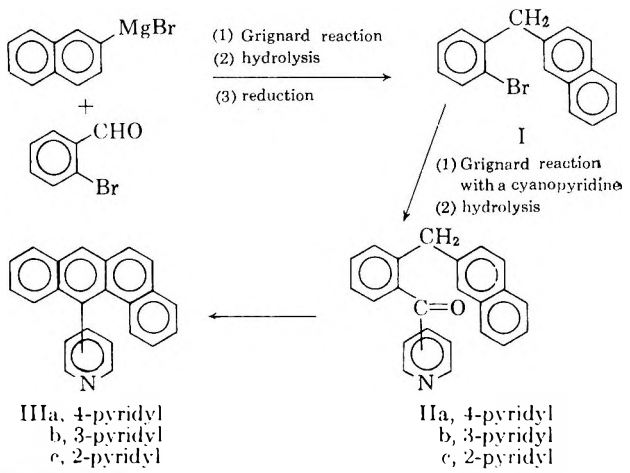
Five new ketones and one ketimine have been prepared and ring closed to their corresponding 12-pyridylbenz[*a*]anthracenes which were then studied in dehydrogenation reactions.

As part of our continuing effort to aid in the study of air pollution problems, we recently published a synthesis of alkyl dibenzopyrenes[5] which utilized the dehydrogenation of 12-phenylbenz[*a*]anthracenes as the last step in the synthetic route. In view of the known carcinogenicity of polynuclear aromatic compounds containing ring nitrogen, it appeared useful to attempt to extend the dehydrogenation reaction to the 12-pyridylbenz[*a*]anthracenes and thus have azadibenzopyrenes available for testing purposes. In order to make the desired compounds using a reaction route similar to the one which was successful in the hydrocarbon series,[6] it was necessary to prepare the three isomeric 2-(2-naphthylmethyl)phenyl pyridyl ketones and or the three isomeric 1-(2-benzyl)naphthyl pyridyl ketones. Either of these series of ketones should, on aromatic cyclodehydration,[7] lead to the desired 12-pyridylbenz[*a*]anthracenes. The cyclodehydrogenation of these new structures was also studied and led to rather unusual results.

The synthetic route shown in Chart I was first adopted as the most feasible approach to the 12-pyridylbenz[*a*]anthracenes.

When 2-naphthylmagnesium bromide[8] was allowed to react with 2-bromobenzaldehyde[9] and the resulting adduct was hydrolyzed, a mixture of 2-naphthyl-2-bromophenylmethane and 2-naphthyl-2-bromophenyl ketone was obtained instead of the expected secondary alcohol, 2-naphthyl-2-bromophenylcarbinol. We are currently investigating this reaction further. The mixture was reduced in excellent yield with lithium aluminum hydride and aluminum chloride according to the method of Blackwell and Hickinbottom.[10]

CHART I



IIIa, 4-pyridyl
b, 3-pyridyl
c, 2-pyridyl

IIa, 4-pyridyl
b, 3-pyridyl
c, 2-pyridyl

The three isomeric 2-(2-naphthylmethyl)phenyl pyridyl ketones (IIa–IIc) were prepared from the Grignard reagent of I and the appropriate cyanopyridine. The yields were as follows: the 4-isomer (IIa), 50%; the 2-isomer (IIc), 45%; and the 3-isomer (IIb), 35%). That the 3-isomer gives the lowest per cent yield has also been observed in related work in the preparation of 2-benzylphenyl pyridyl ketones[11] and 2-(1-naphthylmethyl)phenyl pyridyl ketones.[12] The ketones were isolated as very viscous oils which distilled above 200° (0.20 mm.) and which gave satisfactory carbon, hydrogen, and nitrogen analyses. The ketones exhibited strong absorption at 5.9–6.0 μ, which is consistent with a diaryl ketone and is further evidence for the structures assigned (IIa–IIc).

In view of the difficulties encountered in preparing the 2-(2-naphthylmethyl)phenyl pyridyl ketones and since the isomeric 1-(2-benzyl)naphthyl pyridyl ketones (VIa–VIc) would presumably give the desired 12-pyridylbenz[*a*]anthracenes when subjected to an aromatic cyclodehydration reaction,[7] we sought to prepare these compounds using the reactions shown in Chart II.

The nuclear bromination of 2-methylnaphthalene was effected in 80% yield according to the improved method of Hall and Mitchell,[13] and the side-chain bromination to give 1-bromo-2-bromomethylnaphthalene (IV) was achieved in 70% yield according to the method of Newman and Kosak.[14] A recently devised Grignard reagent cross-coupling procedure[15] was used to cross couple 1-bromo-2-bromonaphthalene with phenylmagnesium bromide to give a 71% yield of 1-bromo-2-benzylnaphthalene. An interesting side product, tentatively designated as 1,2-bis-2,2′-(1-bromonaphthyl)ethane, was isolated in 13% yield.

The Grignard reagent of V was prepared in ether. When the Grignard reagent was formed, the ether was replaced with benzene and the cyanopyridines were added, dissolved in benzene. From these reactions after the usual hydrolysis, there was obtained a 65% yield of the 4-isomer (VIa) and a 63% yield of the 3-

(1) Presented in part before a joint meeting of the Division of Water and Waste Chemistry and the Division of Analytical Chemistry at the 140th National Meeting of the American Chemical Society, Chicago, Ill. Sept., 1961.

(2) This investigation was supported by a research grant (AP-0008-06) from the Division of Air Pollution, Bureau of State Services, U. S. Public Health Service.

(3) Allied Chemical Corp. Fellow, 1960–1961.

(4) This paper has been taken from the Doctorate Thesis of T. J. Delia presented to the Virginia Polytechnic Institute in 1961.

(5) F. A. Vingiello and W. W. Zajac, *J. Org. Chem.*, **26**, 2228 (1961).

(6) F. A. Vingiello and A. Borkovec, *J. Am. Chem. Soc.*, **78**, 1240 (1956).

(7) C. K. Bradsher, *ibid.*, **62**, 486 (1940).

(8) Prepared by the method of F. A. Vingiello, T. J. Delia, P. Polss, and D. Farrier [*J. Chem. Educ.*, **40**, 544 (1963)].

(9) Prepared by the general method of H. B. Hass and M. L. Bender [*Org. Syn.*, **30**, 99 (1950)].

(10) J. Blackwell and W. J. Hickinbottom, *J. Chem. Soc.*, 1405 (1961).

(11) F. A. Vingiello and M. M. Schlechter, *J. Org. Chem.*, **28**, 2448 (1963).

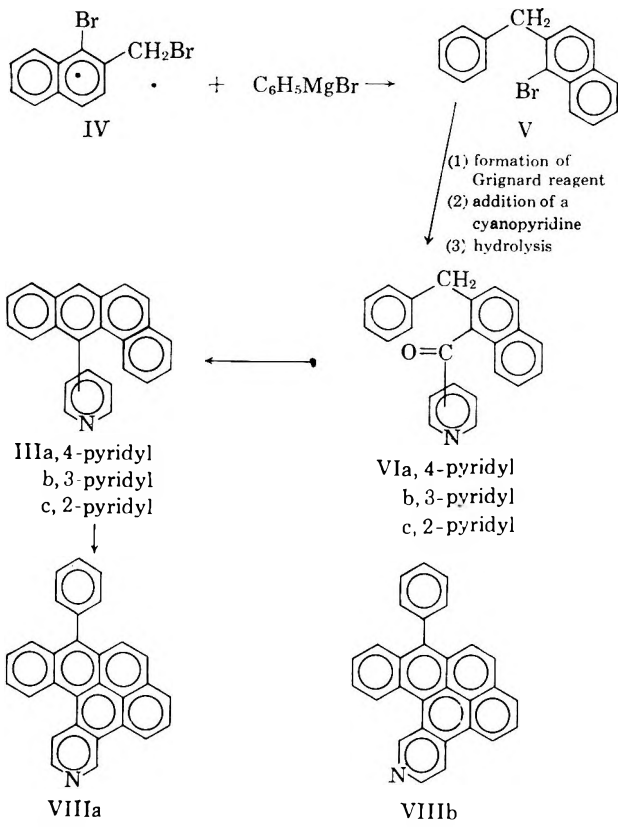
(12) F. A. Vingiello, E. B. Ellerbe, T. J. Delia, and J. Yanez, *J. Med. Chem.*, **7**, 121 (1964).

(13) D. M. Hall and R. K. Mitchell, *J. Chem. Soc.*, 1375 (1951).

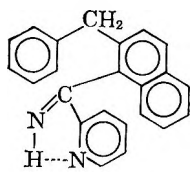
(14) M. S. Newman and A. I. Kosak, *J. Org. Chem.*, **14**, 375 (1949).

(15) F. A. Vingiello, S-G. Quo, and J. Sheridan, *ibid.*, **26**, 3202 (1961).

CHART II



isomer (VIb). However, none of the 2-isomer (VIc) was ever isolated. There was obtained instead a 94% yield of the corresponding ketimine (VII). Several attempts to hydrolyze this to the ketone failed and finally, under quite vigorous conditions, it was cyclized to 12-(2-pyridyl)benz[a]anthracene. This resistance to hydrolysis may be understood by examining the



VII

structure of VII. Two factors are at once clear: first, a five-membered hydrogen-bonded structure is favored; second, the back side of the ketimine group is well protected by the adjacent naphthyl group. It is interesting to note that the infrared spectrum of VII shows no N–H peak. The ketones VIa and VIb exhibited strong absorption at 6.0 μ and formed 1:1 adducts with picric acid.

All three isomeric 2-(2-naphthylmethyl)phenyl pyridyl ketones (IIa–IIc) were converted to their corresponding 12-pyridylbenz[a]anthracenes (IIIa–IIIc) using an acid-catalyzed aromatic cyclodehydration reaction.[7] In a similar way the two isomeric 1-(2-benzyl)-naphthyl pyridyl ketones VIa and VIb and the ketimine VII were converted to IIIa–IIIc. As expected, more vigorous conditions were needed to cyclize VIa, VIb, and VII than were needed to cyclize IIa, IIb, and IIc, since ring closure is effected into the less reactive phenyl ring rather than a naphthyl ring. The products obtained by either route were identical as shown by melting points and ultraviolet spectral patterns, and subsequent dehydrogenation reactions.

Attempts to convert the pyridylbenz[a]anthracenes (IIIa–IIIc) to their corresponding N-oxides using the method of Boekelheide and Linn[16] met with success only in the case of the 4-isomer, IIIa.

A study of the cyclodehydrogenation of the 12-pyridylbenz[a]anthracenes was undertaken using known dehydrogenation catalysts.[5,17] Thirty-seven reactions were run using various catalysts and reaction conditions. Under none of the conditions tried could simple dehydrogenation to an azadibenzopyrene be accomplished. Only when benzene was used as a solvent was dehydrogenation observed, and in each case it was accompanied by phenylation. In the best examples, the 4-isomer (IIIa) gave 14% of a compound tentatively considered to be 3-aza-10-phenyldibenzo[*def*,*p*]chrysene (VIIIa); the 3-isomer (IIIb) gave 6% of a compound tentatively considered to be 2-aza-10-phenyldibenzo[*def*,*p*]chrysene (VIIIb); the 2-isomer (IIIc) did not give a dibenzochrysene. The assigned structures are consistent with ultraviolet absorption data, elemental analysis, and molecular weight determinations.

The yields of dehydrogenation products may be rationalized if one looks carefully at the respective molecular models. Addition of $AlCl_3$ to the nitrogen atom of IIIc gives a structure which cannot assume a planar configuration. It seems reasonable that this would prevent dehydrogenation. The analogous salt of IIIb can assume a planar structure when the nitrogen atom is away from the "a" ring of the benz[a]anthracene moiety but not when it is adjacent to it. The analogous salt of IIIa poses no steric interference between the attached $AlCl_3$ and the benz[a]anthracene moiety. It should be mentioned that a yield of 14% for this type of reaction is not low.

Dual dehydrogenation–phenylation reactions have been reported by Zander.[18] In the present series it appears that the nitrogen atom favors phenylation since it does not occur in the similar carbocyclic series.[5] The conditions under which the reactions were run suggest the possibility of a free-radical reaction. The phenylation might then be expected to occur at the deactivated 10-position since it is known that other deactivating groups (*e.g.*, nitro) facilitate phenylation.[19] The suggestion that phenylation occurs at the 10-position is further supported by the work of Roitt and Waters.[20] In studying the attack of free radicals on polynuclear aromatic hydrocarbons, they find that only the *meso* positions of anthracene, benz[a]anthracene, and benz[a]pyrene are attacked. They also report that the 12-position of benz[a]anthracene is not attacked because attack of the radical occurs by approaching in the same plane as the polynuclear system and only a completely exposed position would undergo such an attack.

(16) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).
(17) E. Clar, *Ber.*, **63**, 112 (1930).
(18) M. Zander, *ibid.*, **92**, 2749 (1959).
(19) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 722.
(20) I. N. Roitt and W. A. Waters, *J. Chem. Soc.*, 2695 (1952).

Experimental[21-24]

2-Bromobenzaldehyde.—A solution of 18 g. (0.80 g.-atom) of sodium dissolved in 800 ml. of absolute ethanol was added to a 2-l. three-necked, round-bottomed flask equipped with a stirrer, reflux condenser, and separatory funnel. To this solution was added 74 g. (0.83 mole) of 2-nitropropane followed by 300 g. (0.80 mole) of 2-bromobenzyl bromide.[25] The mixture was stirred for 15 hr., filtered, and the filtrate was concentrated. The residue was dissolved in a solution of 320 ml. of ether and 480 ml. of water. The two layers were separated and the water layer was extracted with ether. The combined ether layers were washed twice with 75-ml. portions of 10% sodium hydroxide, once with an equal volume of water, dried over magnesium sulfate, concentrated, and distilled at 12 mm. The fraction distilling at 115–118°, lit.[26] b.p. 118–119° (12 mm.), weighed 97 g. (66%).

2-(2-Naphthylmethyl)bromobenzene (I).—A Grignard reagent was prepared, in ether, from 103 g. (0.50 mole) of 2-bromonaphthalene[8] and 12 g. (0.50 g.-atom) of magnesium. A solution of 80.2 g. (0.430 mole) of 2-bromobenzaldehyde in ether was added to the Grignard reagent. The solution was heated under reflux for 2 hr. and hydrolyzed with concentrated hydrochloric acid. The usual work-up produced a yellow, viscous oil which distilled at 188–193° (0.50 mm.), yield 64 g. An infrared spectrum of the mixture revealed a carbonyl function having a peak at 6 μ but no hydroxyl function.

This mixture was not purified further. A solution of 148 g. of the mixture in ether was added slowly to a slurry of 222 g. of aluminum chloride and 31 g. of lithium aluminum hydride in ether. The mixture was heated under reflux for 2 hr., decomposed with ethyl acetate, and worked up in the usual way. The product was collected as a colorless oil at 155–175° (0.15 mm.), yield 120 g. The product solidified on standing, m.p. 49.0–50.5°.

Anal. Calcd. for $C_{17}H_{13}Br$: C, 68.70; H, 4.41; Br, 26.89. Found: C, 68.72; H, 4.59; Br, 26.68.

2-(2-Naphthylmethyl)phenyl 4-Pyridyl Ketone (IIa).—A Grignard reagent was prepared from 18.2 g. (0.06 mole) of 2-(2-naphthylmethyl)bromobenzene and 1.50 g. (0.06 g.-atom) of magnesium turnings in 75 ml. of dry ether. When almost all of the magnesium had reacted, 6.40 g. (0.06 mole) of 4-cyanopyridine dissolved in 75 ml. of dry ether and 25 ml. of dry benzene was added over a period of 1 hr. The complex precipitated and the mixture was heated under reflux for 12 hr. After cooling, the mixture was decomposed with 40 ml. of 20% ammonium chloride solution and 10 ml. of concentrated hydrochloric acid and heated under reflux for 10 hr. The mixture was cooled, the organic layer was separated, and the aqueous layer was neutralized with sodium carbonate solution. The neutral solution was extracted with an ether–benzene mixture, the organic solutions were combined, dried, and concentrated. The residual oil was distilled under reduced pressure and the product was collected as an extremely viscous, dark red oil, b.p. 229–256° (0.90 mm.), 10.3 g. (52%). Redistillation gave an analytical sample, b.p. 207–209° (0.20 mm.).

Anal. Calcd. for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.15; H, 5.15; N, 4.20.

2-(2-Naphthylmethyl)phenyl 3-Pyridyl Ketone (IIb).—This compound was prepared essentially as the 4-isomer. Using 30.0 g. (0.10 mole) of 2-(2-naphthylmethyl)bromobenzene, 2.40 g. (0.10 g.-atom) of magnesium, and 15.0 g. (0.14 mole) of 3-cyanopyridine dissolved in dry benzene, there was obtained an extremely viscous, dark red oil, b.p. 237–247° (0.60 mm.), 12.8 g. (40%). Redistillation gave an analytical sample, b.p. 207–208° (0.10 mm.).

Anal. Calcd. for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.74; H, 5.36; N, 4.61.

2-(2-Naphthylmethyl)phenyl 2-Pyridyl Ketone (IIc).—This compound was prepared essentially as the 4-isomer. Using 28.0 g. (0.09 mole) of 2-(2-naphthylmethyl)bromobenzene, 2.30 g. (0.09 g.-atom) of magnesium, and 9.40 g. (0.09 mole) of 2-cyanopyridine in dry ether, there was obtained an extremely viscous, dark red oil, b.p. 230–298° (1.5 mm.), 13.8 g. (48%). Redistillation gave an analytical sample, b.p. 212–214° (0.12 mm.).

Anal. Calcd. for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.39; H, 5.38; N, 4.50.

1-Bromo-2-benzylnaphthalene (V) and 1,2-Bis-2,2′-(1-bromonaphthyl)ethane.—A Grignard reagent was prepared from 157 g. (1.0 mole) of bromobenzene and 24.3 g. (1.0 g.-atom) of magnesium turnings in 400 ml. of dry ether. When most of the magnesium had reacted, the ether was replaced with benzene and 150 g. (0.50 mole) of 1-bromo-2-bromomethylnaphthalene in 400 ml. of benzene was added. The mixture was refluxed for 12 hr. and worked up essentially as was described for IIa above. The product distilled at 150–179° (0.14 mm.), lit.[27] b.p. 136–138° (10^{-4} mm.), 104.5 g. (71%).

The residue on trituration with acetone gave 13.2 g. of tan solid assumed to be a dimerization product, m.p. 173–184°. Recrystallization from benzene gave white prisms, m.p. 190.5–191°.

Anal. Calcd. for $C_{22}H_{16}Br_2$: C, 60.03; H, 3.66. Found: C, 60.25; H, 4.21.

1-(2-Benzyl)naphthyl 4-Pyridyl Ketone (VIa).—A Grignard reagent was prepared from 29.7 g. (0.10 mole) of 1-bromo-2-benzylnaphthalene and 2.43 g. (0.10 g.-atom) of magnesium turnings in dry ether. Most of the ether was replaced with benzene so that the boiling point of the solution was 72°. A solution of 10.0 g. (0.096 mole) of 4-cyanopyridine in dry benzene was added during 30 min. The mixture was heated for 10 hr. and worked up essentially as has been described for IIa. The product, a viscous, red oil, distilled at 234–250° (0.8 mm.), 20 g. (65%). The oil crystallized on standing and was recrystallized from ethanol to give near-white, plate-like crystals, m.p. 106–107°.

Anal. Calcd. for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.42; H, 5.33; N, 4.23.

A picrate was prepared in ethanol and had m.p. 193–195°.

Anal. Calcd. for $C_{29}H_{20}N_4O_8$: C, 63.04; H, 3.65; N, 10.14. Found: C, 62.90; H, 4.13; N, 9.66.

1-(2-Benzyl)naphthyl 3-Pyridyl Ketone (VIb).—This compound was prepared essentially as the 4-isomer. Using 29.7 g. (0.10 mole) of 1-bromo-2-benzylnaphthalene, and 2.43 g. (0.10 g.-atom) of magnesium turnings, and 9.8 g. (0.094 mole) of 3-cyanopyridine, there was obtained an extremely viscous, red oil, b.p. 227–247° (0.70 mm.), 19.3 g. (64%). Redistillation gave an analytical sample, b.p. 212–219° (0.60 mm.).

Anal. Calcd. for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.21; H, 5.57; N, 4.42.

A picrate was prepared in ethanol and had m.p. 145–147°.

Anal. Calcd. for $C_{29}H_{20}N_4O_8$: C, 63.04; H, 3.65; N, 10.14. Found: C, 62.46; H, 3.72; N, 10.24.

1-(2-Benzyl)naphthyl 2-Pyridyl Ketimine (VII).—A Grignard reagent was prepared from 29.7 g. (0.10 mole) of 1-bromo-2-benzylnaphthalene and 2.43 g. (0.10 g.-atom) of magnesium turnings in dry ether. When most of the magnesium had reacted, 9.00 g. (0.086 mole) of 2-cyanopyridine dissolved in dry benzene was added, and the mixture was refluxed for 30 min. It was then decomposed with 100 ml. of 10% sodium hydroxide, refluxed for 1 hr., and made acidic with dilute hydrochloric acid. The organic layer was separated and, on standing, large, light green, cubic crystals formed, 17.2 g., m.p. 59–68°. Concentration of the filtrate gave an additional 9.00 g.; total yield, 26.2 g. (94%). Recrystallization from benzene gave large, white cubic crystals, m.p. 61–68°.

Anal. Calcd. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.06; H, 5.63; N, 9.35.

12-(4-Pyridyl)benz[*a*]anthracene (IIIa). A. From 2-(2-Naphthylmethyl)phenyl 4-Pyridyl Ketone (IIa).—A mixture of 6.1 g. of IIa, 20 ml. of 48% hydrobromic acid, and 40 ml. of glacial acetic acid was heated under reflux for 18 hr. The mixture was poured onto ice, the solution was neutralized with sodium carbonate solution, and the product was extracted with benzene. The solution was concentrated and cooled, yielding crystals, m.p. 215–216.5°, 4.8 g. (83%). Recrystallization from benzene gave fine, white needles, m.p. 220–221°.

(21) All boiling points are uncorrected. All melting points were taken on a Fisher-Johns melting apparatus and are corrected.

(22) All analyses were carried out by Geller Laboratories, Bardonia, N. Y.

(23) The infrared data were taken on a Beckman Model IR-5 spectrophotometer in CCl_4 solution. The ultraviolet data were taken on a Model 3000 Perkin-Elmer Spectracord using a 1-cm. quartz cell and ethanol as the solvent.

(24) The chromatography column used in this investigation was 18 mm. × 370 mm. packed with Fisher's basic alumina, Brockman activity I, 80–200 mesh. The petroleum ether had a 30–60° boiling range.

(25) R. L. Letsinger and I. H. Skoog, *J. Am. Chem. Soc.*, **77**, 5176 (1955).

(26) I. Heilbrons, "Dictionary of Organic Compounds," Vol. I., Oxford University Press, New York, N. Y., 1946, p. 273.

(27) E. A. Evans, *J. Chem. Soc.*, 2790 (1957).

Anal. Calcd. for $C_{23}H_{15}N$: C, 90.46; H, 4.95; N, 4.59. Found: C, 90.36; H, 5.13; N, 4.69.

The wave-length maxima for IIIa are λ 368, 358, 350, 342, 335, 329, 288, 277, 267, 256, and 232 mμ.

B. From 1-(2-benzyl)naphthyl 4-Pyridyl Ketone (VIa).—A mixture of 3.85 g. of VIa, 50 ml. of 48% hydrobromic acid, and 100 ml. of glacial acetic acid was heated under reflux for 47 hr. and then worked up as was IIa in A. The product weighed 3.15 g. (87%), m.p. 218–221°.

12-(3-Pyridyl)benz[*a*]anthracene (IIIb). A. From 2-(2-Naphthylmethylphenyl 3-Pyridyl Ketone (IIb).—A mixture of 4.4 g. of IIb, 20 ml. of 48% hydrobromic acid, and 40 ml. of glacial acetic acid was heated under reflux for 18 hr. and then worked up as was IIIa in A. The product, 2.0 g. (48%), was recrystallized from ethanol giving pale yellow needles, m.p. 169–170°.

Anal. Calcd. for $C_{23}H_{15}N$: C, 90.46; H, 4.95; N, 4.59. Found: C, 90.14; H, 4.93; N, 4.78.

The wave-length maxima for IIIb are λ 366, 360, 350, 343, 335, 289, 278, 269, 253, and 232 mμ.

B. From 1-(2-Benzyl)naphthyl 3-Pyridyl Ketone (VIb).—A mixture of 2.7 g. of VIb, 25 ml. of 48% hydrobromic acid, and 50 ml. of glacial acetic acid was sealed in a Carius tube and heated for 9 hr. at 180° and then worked up as was IIIa in A. The product, 1.7 g. (67%), on recrystallization from ethanol gave pale yellow needles, m.p. 169–170°. The same reaction conducted at reflux temperature for 48 hr. gave only 42% of IIIb.

12-(2-Pyridyl)benz[*a*]anthracene (IIIc). A. From 2-(2-Naphthylmethyl)phenyl 2-Pyridyl Ketone (IIc).—A mixture of 0.40 g. of IIc, 20 ml. of 48% hydrobromic acid, and 40 ml. of glacial acetic acid was heated under reflux for 13 hr. and worked up as was IIIa in A. The product, 0.17 g. (45%), was recrystallized from absolute ethanol giving white plate-like crystals, m.p. 131.5–132.5°.

Anal. Calcd. for $C_{23}H_{15}N$: C, 90.46; H, 4.95; N, 4.59. Found: C, 90.30; H, 4.93; N, 4.69.

The wave-length maxima for IIIc are λ 366, 368, 349, 342, 335, 288, 278, 268, 254, and 232 mμ.

B. From 1-(2-Benzyl)naphthyl 2-Pyridyl Ketimine (VII).—A mixture of 1.0 g. of VII, 15 ml. of 48% hydrobromic acid, and 30 ml. of glacial acetic acid was placed in a Carius tube and heated for 24 hr. at 180°. The product was chromatographed[24] giving 0.13 g. (14%) of IIIc.

12-(4-Pyridine N-oxide)benz[*a*]anthracene.—A solution of 1.0 g. of 12-(4-pyridyl)benz[*a*]anthracene in glacial acetic acid was oxidized with 30% hydrogen peroxide using the method of Boekelheide and Linn.[16] The product, 0.60 g. (57%), was recrystallized from ethanol giving white needles, m.p. 276.0–278.5° dec.

Anal. Calcd. for $C_{23}H_{15}NO$: C, 85.96; H, 4.70; N, 4.36. Found: C, 86.31; H, 4.77; N, 4.28.

The wave-length maxima for the N-oxide are λ 370, 360, 351, 343, 336, 288, 277, 268, 254, and 233 mμ.

3-Aza-10-Phenyldibenzo[*def*,*p*]chrysene (VIIIa).[28]—A solution of 0.50 g. of 12-(4-pyridyl)benz[*a*]anthracene in 75 ml. of benzene was heated under reflux, 1 g. of $AlCl_3$ was added, and the mixture was heated for 5 min The mixture was cooled, decomposed with dilute hydrochloric acid, and neutralized. The aqueous layer was separated and extracted with benzene–acetone, and the organic solutions were combined, washed with water, and dried over calcium sulfate. The solution was concentrated to *ca.* 5 ml. and chromatographed on alumina using a mixture of benzene and petroleum ether (1:1) as the eluent. A colorless, blue fluorescent band was removed from which no pure material could be obtained. The remaining yellow band was removed using benzene as the eluant. Upon concentration and cooling there was obtained a yellow solid, m.p. 281–282°, yield 0.87 g. (14%).

The analytical sample was obtained by recrystallization from benzene as fine, yellow needles, m.p. 282–283°.

Anal. Calcd. for $C_{29}H_{17}N$: C, 91.79; H, 4.52; N, 3.69; mol. wt., 379. Found: C, 91.51; H, 4.42; N, 3.91. mol. wt. (Rast), 399 and 400.

The wave-length maxima for VIIIa are λ 331, 316, 300, 289, 265, 255, and 248 mμ.

2-Aza-10-phenyldibenzo[*def*,*p*]chrysene (VIIIb).—This product was obtained essentially as was compound VIIIa. One-half gram of 12-(3-pyridyl)benz[*a*]anthracene yielded 0.039 g. (6%) of fine, yellow needles, m.p. 258.0–259.5°.

Anal. Calcd. for $C_{29}H_{17}N$: C, 91.79; H, 4.52; N, 3.69. Found: C, 91.92; H, 4.78; N, 3.74.

The wave-length maxima for VIIIb are λ 331, 316, 300, 289, 258, 243, and 232 mμ.

(28) This is the best of 37 experiments.

The Chemistry of Pyridine. III. Substitution of 1-Alkoxy, 1-Acyloxy-, and 1-Sulfonyloxypyridinium Salts by Mercaptans

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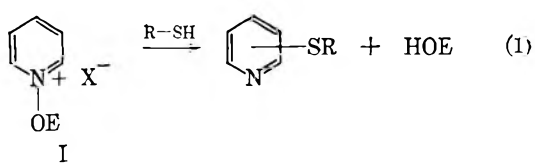
The substitution of pyridine N-oxide *via* N-alkoxy-, N-alkoxy-, N-acyloxy-, and N-sulfonyloxypyridinium salts with 1-butanethiol produced mixtures of 2-, 3-, and 4-butylmercaptopyridine. The yield of these sulfides and the distribution of the isomers depended on the reaction conditions and the nature of the departing substituent from the ring nitrogen of the pyridinium moiety. The mode of formation of the diverse products is discussed.

It had previously been shown[1,2] that N-alkoxypyridinium salts were substituted by mercaptans to form a mixture of alkylmercaptopyridines according to eq. 1.



I (1)

It was of interest to ascertain the course of this reaction when groups of different electronic disposition were attached to the ring nitrogen of I. This paper describes the reaction expressed by eq. 1 when E was ethyl, acetyl, benzoyl, and arenesulfonyl. It was found that a change of E from alkyl to acyl or sulfonyl resulted in different mixtures of alkylmercaptopyridines.

Before studying the substitution of the various pyridinium salts it was essential to establish if pyridine N-oxide itself would be substituted by mercaptide ion. When the N-oxide was treated with 1-butanethiol in the presence of sodium *n*-butylmercaptide, it was recovered partly, and no alkyl pyridyl sulfides could be detected.[3] Therefore it seemed essential to convert pyridine N-oxide first to a salt of type I before substitution by mercaptans could take place. The most available salts are the crystalline N-alkoxypyridinium salts (I, E is alkyl), which are readily formed when

(1) L. Bauer and L. A. Gardella, *J. Org. Chem.*, **28**, 1320 (1963).

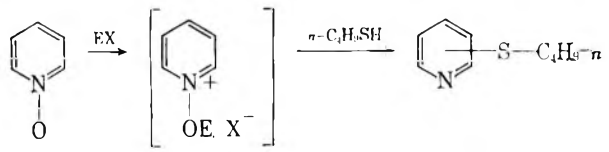
(2) L. Bauer and L. A. Gardella, *ibid.*, **28**, 1323 (1963).

(3) In conducting this experiment, cognizance was taken of the reduction of N-oxides with mercaptans described by D. I. Relyea, P. O. Tawney, and A. R. Williams [*ibid.*, **27**, 477 (1962)]. However, our experiment was performed in the presence of the sodium mercaptide.

pyridine N-oxide is treated with an alkyl halide, sulfate, or sulfonate. Attempts to isolate crystalline salts from pyridine N-oxide with acyl and sulfonyl halides met with little success, the products being labile hygroscopic solids or temperamental gums.[4] Hence, these salts were prepared *in situ* prior to reaction with mercaptan.

In our previous study,[1] it was shown that 1-ethoxypyridinium ethyl sulfate reacted with *n*-propylmercaptide ion to yield pyridine and a mixture of 3- and 4-propylmercaptopyridines. In a cognate experiment, the 1-ethoxypyridinium cation was attacked by *n*-butylmercaptide ion to furnish a mixture of 2-, 3-, and 4-butylmercaptopyridines in the ratio 4:15:6 (Table I). The three sulfides were separated

TABLE I



EX	Yield of sulfides, %	% of butylmercaptopyridine in sulfide mixture 2-	3-	4-	Method[a]
$(C_2H_5)_2SO_4$	15	16	60	24	F
p-$CH_3C_6H_4SO_3C_2H_5$	11	11	74	15	G
$(CH_3CO)_2O$	67	61	39		D
CH_3COCl	10	89	9	2	E
C_6H_5COCl	19	81	18	1	A
C_6H_5COCl	16	81	15	4	B
$C_6H_5SO_2Cl$	32	50	50		C

[a] See Experimental section.

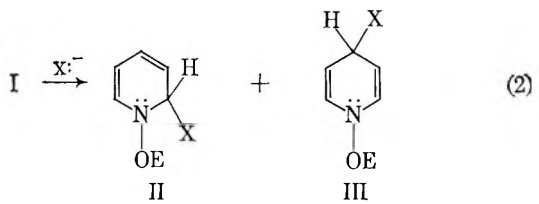
by chromatography on alumina and identified (as throughout this work) by comparing their infrared and n.m.r. spectra with those of authentic specimens. There was little variation in yield and isomer distribution of sulfides when the N-ethoxypyridinium moiety was accompanied by either the ethyl sulfate or *p*-toluenesulfonate anion (Table I). However, it was essential to conduct these experiments in the presence of sodium *n*-butylmercaptide, since no substitution was noted when this strong base was omitted. This point is relevant since, in the experiments with pyridinium salts carrying an electron-attracting group on the ring nitrogen, the reaction proceeded very well in 1-butanethiol alone.

The addition of 1-benzoyloxypyridinium chloride to a suspension of sodium *n*-butylmercaptide in excess mercaptan furnished a mixture of 2-, 3-, and 4-butylmercaptopyridines in a ratio of 20:4:1, in contrast to the predominance of the 3-isomer with the alkoxypyridinium salts. The total yield of mercaptopyridines and the isomer ratio, were not significantly different when the sodium mercaptide was omitted; in these experiments, 3-pyridyl benzoate was also produced. In similar fashion, the reaction of 1-benzenesulfonyloxypyridinium chloride with 1-butanethiol produced an equal mixture of 2- and 3-butylmercaptopyridines devoid of the multitude of products obtained when pyridine 1-oxide was heated with arenesulfonyl chloride.[5]

(4) V. J. Traynelis, A. I. Gallagher, and R. F. Martello [*J. Org. Chem.*, **26**, 4365 (1961)] managed to crystallize 1-acetoxy-2-picolinium picrate from the reaction of 2-picoline 1-oxide with picryl acetate.

The above experiments were conducted in a large excess of 1-butanethiol. In a different vein, the substitution of pyridine 1-oxide by 1-butanethiol was examined in a large excess of acetic anhydride.[6] There was formed a good yield of 2- and 3-butylmercaptopyridine (61:39), again free from the 4-isomer. The products were accompanied by 2-, 3-, and 4-pyridinols (after hydrolysis), the 3-isomer being the major product.[6] In contrast to the excellent yield of sulfides from the reaction in excess acetic anhydride, the reaction of 1-acetoxypyridinium chloride with 1-butanethiol in the presence of sodium *n*-butylmercaptide afforded a poor yield of product.

No simple mechanism can be advanced to explain the observed α-, β-, and γ-substitution of salts of type I by mercaptans (*viz.*, mercaptide ion). There are described in the literature mechanisms to account for α- and γ- as distinct from β-substitution of I.[7] For α- and γ-substitution of I it was postulated that attack by a nucleophile present in the medium ($X:^-$) neutralizes the positive charge to form 1,2- and 1,4-dihydropyridines (II and III) as illustrated in eq. 2. Aromatization



(2)

of these intermediates, by the elimination of HOE, leads to the formation of 2- and 4-substituted pyridines. The general question now arises on the pathway of elimination of HOE. In intermediates II and III where the α- and γ-hydrogens are acidic enough, the first step may be removal of such hydrogens by base to form an anion which then loses OE^-. Such a sequence of events is shown in eq. 3 (for II only),[8] p. 2185.

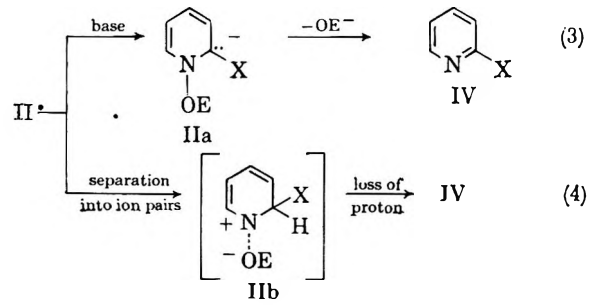
When abstraction of a proton from the α- or γ-position is not encouraged (*e.g.*, when X is SR), an alternate mechanism is suggested for the aromatization. This route calls for the separation of OE from II or III into ion pairs as the first step. For the 1,2-dihydropyridine, the loss of a proton from IIb creates the 2-substituted

(5) A recent paper by H. J. den Hertog, D. J. Buurman, and P. A. de Villiers [*Rec. trav. chim.*, **80**, 325 (1961)] summarized the products obtained from the reaction of pyridine N-oxide with *p*-toluenesulfonyl chloride at 160°. There was obtained pyridine, 2,3′-dipyridyl ether, 3-pyridyl *p*-toluenesulfonate, 1-(2′-pyridyl)-2-pyridone, as well as 1-(2′-pyridyl)-3- and -5-chloro-2-pyridones. The last three products can be explained if 2-chloropyridine is an intermediate in that reaction. It has been shown by F. Ramirez and P. W. von Ostwalden [*J. Am. Chem. Soc.*, **81**, 156 (1959)] that the reaction of 2-bromopyridine with pyridine N-oxide produced 1-(2′-pyridyl)-2-pyridone and its 3- and 5-bromo substitution products.

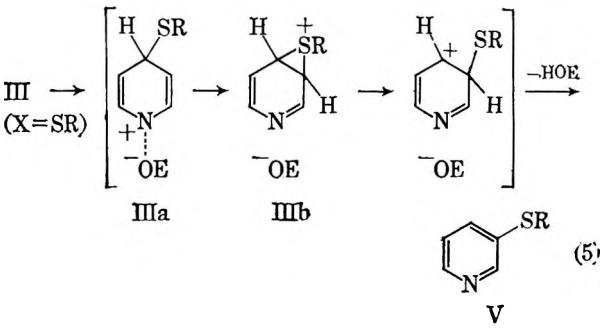
(6) The formation of 3-pyridinol in this reaction is surprising since the well-known substitution of pyridine N-oxide by acetic anhydride yielded only 2-pyridinol [see J. H. Markgraf, H. B. Brown, S. C. Mohr, and R. G. Peterson, *ibid.*, **85**, 958 (1963)]. We inspected the infrared spectrum of the pyridinol fraction from pyridine N-oxide and acetic anhydride and found no bands assignable to 3- or 4-pyridinol.

(7) The literature up to 1962 was summarized in ref. 1. More recently published substitution of pyridinium salts type I were reported by M. Hamana and his co-workers [*J. Pharm. Soc. Japan*, **82**, 519 (1962); *Chem. Pharm. Bull.* (Tokyo), **11**, 415, 1331 (1963)].

(8) Such a path has been suggested by H. Tani [*ibid.*, **7**, 930 (1959)] and W. E. Feely and E. M. Beaver [*J. Am. Chem. Soc.*, **81**, 4004 (1959)] for the reaction of 1-alkoxypyridinium salts (I, E is alkyl) with cyanide ion (X = CN) to form 2- and 4-pyridinecarbonitriles.



pyridines (eq. 4).[9] This mechanism is most apt to apply when the departing groups are acetate, benzoate, or sulfonate ions. This might explain the abundance of 2-butylmercaptopyridine in the products (Table I) in the substitution of 1-acetyloxy-, 1-benzoyloxy-, and 1-arenesulfonyloxypyridinium salts in contrast to the 1-alkoxyyridinium salts (Table I). However, the puzzling feature is the formation of the 3-butylmercaptopyridines. In the reaction in which an electron-attracting group is attached to nitrogen, 4-substitution is conspicuously small while 3-substitution is more pronounced. It is suggested that substitution at position 3 arises from the 1,4-dihydropyridine (III).



Separation of the latter into ion pairs (IIIa) creates a potential electrophilic center at the β-positions. Such polarization could induce migration of the nucleophilic thioether group *via* an episulfonium ion[10] (IIIb) to lead to V as indicated in eq. 5.[11]

The unexpected β-substitution of I by acyloxy ions in several of the reactions cannot be explained satisfactorily at present.[12] Further experiments are planned to investigate these reactions and their mechanisms in greater detail.

A number of investigators have searched for evidence for free-radical mechanism in the substitution of I, but thus far the reactions are better explained *via* ionic intermediates. In order to test if a free-radical mechanism was involved for the substitution of I by mercaptans, the following experiments were carried out. When 1-ethoxypyridinium ethyl sulfate was treated with 1-butanethiol and sodium *n*-butylmercaptide (as in F, Experimental section) in the presence of benzoyl peroxide, the same yield and isomer ratio of butylmercaptopyridines were obtained as when the peroxide was omitted. Also, the reaction of 1-ethoxypyridinium ethyl sulfate with 1-butanethiol in boiling carbon tetrachloride (24 hr.) in the presence of benzoyl peroxide did not furnish any 2-, 3-, or 4-butylmercaptopyridines. Again, the reaction of pyridine N-oxide with 1-butanethiol and benzoyl chloride (in the absence of sodium *n*-butylmercaptide) in carbon tetrachloride in the presence of benzoyl peroxide gave rise to the same mixture of thioethers as in A. These experiments tend to rule out a free-radical mechanism as the major pathway of these reactions.

Experimental[13]

Materials.—Pyridine N-oxide was obtained from Reilly Tar and Chemical Co.; 2- and 3-pyridinol, 2-pyridinethiol, and 4-chloropyridine from Aldrich Chemical Co.; 4-pyridinol from Winthrop Labs. The generous gifts of 1-butanethiol from Pennsalt Chemical Co. and Phillips Petroleum Co. are gratefully acknowledged. Petroleum ether used in this work refers to that fraction, b.p. 30–60°. Activated alumina used throughout this investigation was purchased from Alcoa (Grade F-20). Sodium hydride used in subsequent experiments was in the form of a 53% dispersion in mineral oil, available from Metal Hydrides, Inc.

Synthesis of Reference Compounds. 2-Butylmercaptopyridine.—A solution of 2-pyridinethiol (5.6 g., 0.05 mole) in 10% sodium hydroxide solution (50 ml.) was stirred with 1-bromobutane (7.0 g., 0.05 mole) first at 25° for 1.5 hr., then at 70° for 1 hr. After the usual work-up,[14] the **sulfide** (2.25 g., 27%) was distilled, b.p. 71° at 1 mm.

Anal. Calcd. for $C_9H_{13}NS$: C, 64.62; H, 7.83; N, 8.37. Found: C, 64.59; H, 7.72; N, 8.45.

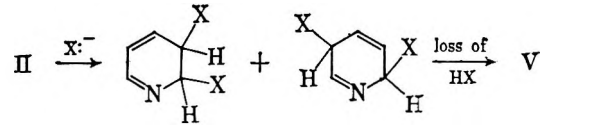
3-Butylmercaptopyridine.—A solution of 3-pyridinethiol hexachlorostannate[15] (6.66 g., 0.015 mole) in 10% sodium hydroxide solution (100 ml.) was stirred with 1-bromobutane (4.11 g., 0.03 mole) for 5 hr. at 25°. The mixture was extracted with ether. The ether layer was shaken with 10% hydrochloric acid. The **sulfide** was isolated from the acidic aqueous phase in the usual manner[14] and distilled *in vacuo*. Since the product was found to be impure, it was chromatographed on alumina (30 g.). It was eluted with petroleum ether–ether (9:1). Distillation furnished the pure sulfide (1.49 g., 30%), b.p. 141° at 31 mm.

Anal. Calcd. for $C_9H_{13}NS$ (as above). Found: C, 64.74; H, 7.73; N, 8.42.

(9) Such a mechanism may be responsible for the substitutions when pyridine N-oxide is treated with acid halides and anhydrides to form 2- and 4-substituted pyridines.[7] Few of these reactions have been examined in detail to discover their mechanism. A notable exception is the reaction of pyridine N-oxide with acetic anhydride to form 2-acetoxypyridine[6] which is postulated to proceed by means of the 1-acetoxypyridinium cation.

(10) Migration of a sulfide group to a potentially electrophilic center *via* episulfonium intermediates is a well-known phenomenon. For a recent summary, see K. D. Gundermann, *Angew. Chem.*, **75**, 1194 (1963).

(11) Another mechanism has been proposed to explain β-substitution; for a summary, see S. Oae, T. Kitao, and Y. Kitaoka, *Tetrahedron*, **19**, 827 (1963). It has been suggested that, in intermediates II or III, the group OE is displaced by nucleophilic attack at one of the β-positions to form yet another dihydropyridine. This is illustrated for II. Aromatization to



form V is achieved when the elements HX are eliminated. In a basic medium, the most acidic proton in the new dihydropyridines are those at the β-position and this might account for the formation of the 3-substituted pyridine by such a path.

(12) Intermolecular rearrangement of II and III (X = OCOR) analogous to the one suggested in eq. 5 presents a possible mechanism. However, the role of mercaptan, if any, in this substitution is not understood at present.

(13) All melting and boiling points are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., and by Dr. Kurt Eder, Geneva, Switzerland. Some of the nitrogen analyses were obtained using a Coleman nitrogen analyzer, Model 29.

(14) The procedure used to isolate the basic thioethers was as follows. If the reaction medium were basic, it was acidified with hydrochloric acid and extracted with ether or a mixture of ether–benzene (1:1) to remove neutral and acidic products. The aqueous phase was then made alkaline with 20% sodium hydroxide and the bases were extracted into methylene chloride. The methylene chloride solution was dried (sodium sulfate) and fractionally distilled.

(15) N. Steiger, *Chem. Abstr.*, **44**, 8380 (1950).

4-Butylmercaptopyridine.—This was prepared in 25% yield from 4-chloropyridine and 1-butanethiol as described for the synthesis of 2-propylmercaptopyridine.[1] The sulfide was distilled, placed on alumina, eluted by petroleum ether, and redistilled, b.p. 145–147° at 19 mm.

Anal. Calcd. for $C_9H_{13}NS$ (as above). Found: C, 64.43; H, 7.67; N, 8.60.

Reaction of Pyridine N-Oxide with 1-Butanethiol. A. In the Presence of Benzoyl Chloride.—Benzoyl chloride (14.1 g., 0.1 mole) was added dropwise, over a period of 40 min., to an ice-cold solution of pyridine N-oxide(9.5 g., 0.1 mole) in 1-butanethiol (100 ml.). During that time, a chalk-white suspension was formed. The mixture was then warmed on the steam bath for 0.5 hr., after which it was quenched by 15% hydrochloric acid (50 ml.). The two layers were separated and the organic phase was extracted once more with 15% hydrochloric acid (25 ml.). The combined acid layers were extracted once with an ether–benzene solution (1:1, 50 ml.) and worked up for pyridines as shown below. No attempt was made in this experiment to isolate neutral or acidic products.

The hydrochloric acid solution containing the pyridines was boiled under reflux for 2 hr. (This was necessary to hydrolyze pyridyl benzoates present. It was also found that the butylmercaptopyridines were stable to such a hydrolysis.). On cooling, the acid fraction was extracted once more with ether–benzene (1:1, 75 ml.) and then made alkaline with 20% sodium hydroxide and extracted with methylene chloride (five 50-ml. portions). Distillation of the extract afforded the mixture of butylmercaptopyridines (3.50 g., b.p. 140–146° at 25 mm.).

The butylmercaptopyridines were separated by column chromatography on alumina (70 g.). 2-Butylmercaptopyridine (2.57 g.) was eluted by petroleum ether (700 ml.) and by petroleum ether–benzene (9:1, 200 ml.); 3-butylmercaptopyridine (0.57 g.), by petroleum ether–benzene (1:1, 100 ml.) and benzene (400 ml.); and 4-butylmercaptopyridine (0.04 g.), by benzene–ether (9:1, 100 ml.) and ether (100 ml.). The combined yield of pure sulfides was 3.18 g. This represents a 19% yield based on 0.1 mole of pyridine N-oxide or 36% if the recovered pyridine N-oxide (see below) is taken into account.

The basic solution from above was neutralized with hydrochloric acid and evaporated *in vacuo*. The dry residue was extracted with 2-propanol (100 ml.) and that solvent was removed *in vacuo*. The residue (5.15 g.) was boiled down with benzene to remove the last traces of 2-propanol before placing it onto activated alumina (50 g.). Elution with methylene chloride (1200 ml.) and methylene chloride–ethanol (3:1, 50 ml.) afforded pyridine N-oxide (4.43 g., 47%). Further elution with methylene chloride–ethanol (3:1, 300 ml.) gave 3-pyridinol (0.24 g., 3% based on 0.1 mole), m.p. and m.m.p. 127°.

The pyridine N-oxide and pyridinol fractions were examined carefully for the presence of 2- and 4-pyridinol (infrared spectroscopy), but neither could be detected.

Several experiments with some modification to A are briefly mentioned here. When the reaction of pyridine N-oxide (0.1 mole) with 1-butanethiol (0.3 mole) was carried out in benzene (100 ml.) instead of excess mercaptan, there was isolated the same mixture of 2- and 3-butylmercaptopyridines (3.4 g.), b.p. 140–160° at 35 mm. Further distillation furnished a thick oil (2.71 g.), b.p. 129–140° at 0.5 mm., which set to a semisolid on cooling. Its infrared spectrum was identical with 3-pyridyl benzoate which was prepared from 3-pyridinol and benzoyl chloride.[16] The ester was characterized by a picrate, m.p. 155–156° (from ethanol), undepressed on admixture of the known[17] picrate. Hydrolysis of the ester isolated in this reaction gave 3-pyridinol, m.p. and m.m.p. 127°.

In a similar experiment as above but using carbon tetrachloride (100 ml.), benzoyl peroxide (1 g., 0.004 mole) was added in portions to the boiling solution (over a period of 8 hr.). This experiment yielded the same mixture of sulfides (2.2 g.) and 3-pyridyl benzoate (2.3 g.).

B. Reaction of 1-Benzoyloxypyridinium Chloride with Sodium *n*-Butylmercaptide.—Benzoyl chloride (14.1 g., 0.1 mole) was added dropwise to freshly distilled pyridine N-oxide (9.5 g., 0.1 mole). The mixture became warm and turned into a paste which finally set into a dry, mobile powder. This powder was used immediately in the next step without further treatment.

Sodium hydride (9.1 g. of a 53% suspension in mineral oil, 0.2 mole) was added in three portions to 1-butanethiol (125 ml.) at 0° with stirring. Sodium *n*-butylmercaptide separated as a fine suspension in excess mercaptan. To this stirred mixture was added 1-benzoyloxypyridinium chloride and the mixture was heated at 100° for 2 hr.

The reaction was then quenched with ice-cold 10% hydrochloric acid and the basic fraction was isolated as usual.[14] Distillation of the bases afforded a mixture of butylmercaptopyridines (3.13 g.), b.p. 142–145 (24 mm.), which were separated on alumina as described above. The yield and isomer ratios are contained in Table I.

In these experiments, no 3-pyridyl benzoate was isolated after the sulfides had distilled. Hence, no attempts were made to examine the aqueous phase (after the sulfides were extracted) for pyridinols or to isolate unchanged pyridine N-oxide.

C. In the Presence of Benzenesulfonyl Chloride.—To an ice-cold solution of pyridine N-oxide in 1-butanethiol (9.5 g., 0.1 mole in 100 ml.) was added benzenesulfonyl chloride (17.7 g., 0.1 mole) as described in A. A fine white suspension resulted and the mixture was heated on the steam bath for 0.5 hr., during which time a colorless gum separated from the colorless solution. The reaction was quenched by 15% hydrochloric acid (50 ml.) and the reaction mixture was worked up for butylmercaptopyridines, pyridinols, and unchanged pyridine N-oxide as described under A. The sulfides were again separated by chromatography on alumina, and their yields and isomer distribution are listed in Table I.

All attempts to find pyridinols (in the hydrolyzed aqueous basic fraction) failed. This fraction contained only pyridine N-oxide (3.81 g., 40%, after chromatography on alumina).

In an attempt to carry out this reaction in the presence of sodium *n*-butylmercaptide, benzenesulfonyl chloride was added to a suspension of sodium *n*-butylmercaptide in a solution of pyridine N-oxide in excess 1-butanethiol. However, unlike C, only 0.24 g. of butylmercaptopyridines (1%) was obtained. In earlier experiments attempts to prepare solid N-arenesulfonyloxypyridinium salts by mixing pyridine N-oxide and benzene and *p*-toluenesulfonyl chloride neat, in a manner analogous to the preparation of N-benzoyloxypyridinium chloride (see B), were not successful.

D. In the Presence of Acetic Anhydride.—A solution of pyridine N-oxide (9.5 g., 0.1 mole) and 1-butanethiol (32 ml., 0.3 mole) in acetic anhydride (100 ml.) was boiled under reflux for 2 hr. The solution was concentrated *in vacuo* (at 17 mm.) and then boiled with 25 ml. of 15% hydrochloric acid for 0.5 hr. (to hydrolyze esters). The acid solution was extracted with 1:1 ether–benzene, and concentrated to half its volume several times to remove acetic acid since it interferes with work-up for pyridinols. It was then made alkaline with 20% sodium hydroxide. The basic fraction was extracted with methylene chloride (five 50-ml. portions). Distillation of this extract afforded a fraction (11.16 g.), b.p. 136–143° at 28 mm.

Part of this fraction (2.79 g.) was placed on alumina (60 g.) and the isomers were eluted as follows: 2-butylmercaptopyridine (1.69 g.) by petroleum ether (600 ml.) and petroleum ether–benzene (19:1, 100 ml.), and the 3-isomer (1.1 g.) by petroleum ether–benzene (1:1, 100 ml.) and benzene (300 ml.).

The basic aqueous solution was neutralized and evaporated to dryness. The residue was extracted by 2-propanol, that solvent was removed *in vacuo*, and the residue was extracted with hot benzene. On cooling, 3-pyridinol (0.44 g.) was obtained which was identified by its melting point and infrared spectrum.

E. As 1-Acetoxypyridinium Chloride, and in the Presence of Sodium *n*-Butylmercaptide.—The salt from pyridine N-oxide and acetyl chloride was difficult to isolate, and hence the following procedure was adopted. Acetyl chloride (7.8 g., 0.1 mole) was added dropwise to a solution of pyridine N-oxide (9.5 g., 0.1 mole) in 50 ml. of benzene. A white suspension was formed which was added to a suspension of sodium *n*-butylmercaptide in 1-butanethiol (prepared as in B). After the mixture was heated at 100° for 2 hr., it was worked up as in A. The sulfides were separated as usual and are listed in Table I.

F. As 1-Ethoxypyridinium Ethyl Sulfate.—Ethoxypyridinium ethyl sulfate was prepared and used as described previously.[1]

(16) C. J. Cavallito and T. H. Haskell, *J. Am. Chem. Soc.*, **66**, 1166 (1944).

(17) H. Bojarska-Dahlig and T. Urbanski, *Chem. Abstr.*, **48**, 1338 (1954).

The addition of 1-ethoxypyridinium ethyl sulfate to sodium *n*-butylmercaptide in 1-butanethiol and subsequent reaction at 100° for 0.5 hr. gave, after the usual work-up (see A), butylmercaptopyridines listed in Table I.

G. **As 1-Ethoxypyridinium *p*-Toluenesulfonate.**—Pyridine N-oxide (4.75 g., 0.05 mole) was heated with ethyl *p*-toluenesulfonate (10.0 g., 0.05 mole) at 100° for 1.5 hr. The sirup was washed with ether and the resultant salt was added to a suspension of sodium *n*-butylmercaptide in excess 1-butanethiol as in B. Work-up according to the general method (see A) gave the sulfides listed in Table I.

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Steroids. CCXL.[1,2] The Reaction of Steroidal Alcohols with 2-Chloro-1,1,2-trifluorotriethylamine

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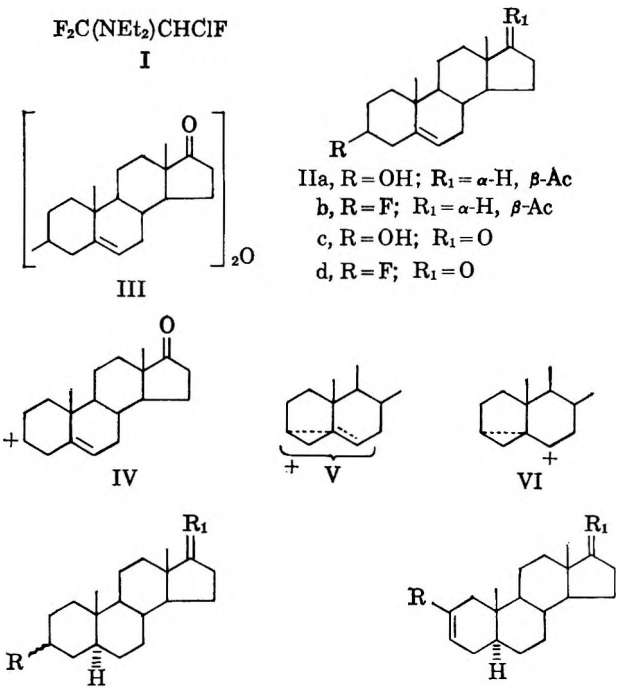
The reaction of 2-chloro-1,1,2-trifluorotriethylamine (I) with steroidal alcohols is described. Primary and secondary hydroxy steroids generally yield products resulting from replacement of hydroxyl by fluorine, ester formation, simple dehydration, dehydration accompanied by rearrangement, and ether formation. Tertiary alcohols undergo dehydration with or without concomitant rearrangement. The dependence of product formation on the nature of the steroidal alcohol, solvent, and reaction temperature is discussed. Nuclear magnetic resonance spectral data are analyzed for the various alcohols and reaction products.

The remarkable enhancement of biological activity in steroid hormones resulting from introduction of fluorine at various sites in the steroid molecule is well documented in the chemical literature.[3] During the past decade a number of synthetic routes to fluoro steroids have been developed in pursuit of further derivatives.[4] The recent observation of Yarovenko and Raksha that 2-chloro-1,1,2-trifluorotriethylamine (I) reacts readily under mild conditions with primary aliphatic alcohols to give replacement of hydroxyl by fluorine,[5] prompted us to investigate the utility of this reagent for the preparation of fluoro steroids.[2] Ayer, in a preliminary communication, has recently described a similar investigation of the reactions of the amine I with steroidal alcohols.[6]

When 3β-hydroxypregn-5-en-20-one (IIa) was treated with the fluorinating reagent I in dry tetrahydrofuran, there was obtained the 3β-fluoro derivative IIb.[3,7] Reaction proceeded with over-all retention of configuration. However, when a mixture of 3β-hydroxyandrost-5-en-17-one (IIc), 1.5 molar equiv. of the reagent I, and dry methylene chloride were refluxed briefly, two products could be isolated by chromatography on Florisil.[8] The less polar product consisted of the known 3β-fluoro derivative IId[6,7] (58%). The more polar product proved to be the ether III (4.8%), the structure of which was established by elementary analysis, n.m.r. spectroscopy, and mass spectrometry.[9] Ayer,[6] using different reaction conditions, obtained only



(1) Steroids CCXXXIX: L. H. Knox, E. Velarde, and A. D. Cross *J. Am. Chem. Soc.*, **85**, 2533 (1963). The present paper also constitutes Spectra and Stereochemistry, part X; part IX, A. D. Cross and P. Crabbé, *ibid.*, **86**, 1221 (1964).

(2) A preliminary account of this work was published by L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *Tetrahedron Letters*, 1249 (1962).

(3) For leading references, see A. Bowers, P. G. Holton, E. Denot, M. C. Loza, and R. Urquiza, *J. Am. Chem. Soc.*, **84**, 1050 (1962).

(4) For a review of methods currently available for the introduction of fluorine into the steroid system, see J. W. Chamberlin, "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, p. 155.

(5) N. N. Yarovenko and M. A. Raksha, *Zh. Obshch. Khim.*, **29**, 2159 (1959); *cf. Chem. Abstr.*, **54**, 9724*h* (1960).

(6) D. E. Ayer, *Tetrahedron Letters*, 1065 (1962).

(7) (a) T. N. Jacobsen and E. V. Jensen, *Chem. Ind.* (London), 172, (1957); (b) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 4813 (1957).

(8) Florisil is a magnesium silicate marketed by the Floridin Co., Hancock, W. Va.

(9) Determinations carried out on a C.E.C. 21-1036 mass spectrometer equipped with a "direct inlet" system [see J. F. Lynch, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *Experientia*, **19**, 211 (1963)].

TABLE I

N.M.R. SPECTRAL DATA FOR SOME STEROID ALCOHOLS, DEHYDRATION PRODUCTS, RELATED FLUORO STEROIDS, AND OTHER DERIVATIVES[a]

Compound	18-H	19-H	Other protons
IIa[b,c]	38.3	60.8	127.5 (21-H), 322 (6-H), 210 (h.b.w.[d] 20) (3α-H)
IIb	38.8	62.2	127.3 (21-H), *ca.* 325 (6-H), *ca.* 237 and *ca.* 287 (h.b.w. *ca.* 23) (3α-H), J_{HF} = *ca.* 50
IIc[e,f]	52.8	62.0	328 (6-H), 211 (3α-H)
IId	53.5	64.9	327 (6-H), 238 and 289 (h.b.w. *ca.* 22) (3α-H), J_{HF} = 51
III	52.9	61.8	320 (6-H), 193 (h.b.w. *ca.* 23) (3α-H)
VIIa[g]	51.3	50.1	215 (h.b.w. 23) (3α-H)
VIIb	51.3	48.7	265 and 313 (h.b.w. 7) (3β-H), J_{HF} = 48
VIIc	52.9	52.9	293 (h.b.w. 22) (3α-H), 349.9 and 400.6 ($O_2CCHClF$), J_{HF} = 50.7
VIId	52.9	49.8	118.8 (Nac), 250 (h.b.w. 16) (3β-H), 494 (NH)
VIIf	47.6	49.1	119.2 (NAc), 122.4 (OAc), 250 (h.b.w. 14) (3β-H), 277 (17α-H), 355 (NH).
VIIh	47.5	47.5	117.4 (NAc), 121.5 (OAc), 225 (h.b.w. 25) (3α-H), 276 (17α-H), 324 (NH).
VIIj[h]	51.9	48.8	243 (h.b.w. 7) (3βH)
IX	46.5	52.8	57.8 (2α- and 2β-Me), 121.4 (OAc)
Xa	47.7	40.0	121.6 (OAc), 96.3 (vinylic Me)
Xb	47.4	43.6	122.1 (OAc), 98 (h.b.w. 5) (vinylic Me), 317 (2-H), 277 (17α-H)
XI	46.5 and	44.2	71.2 (3β-Me), 121.1 (OAc), 276 (17αH)
XVIId[i-k]	47.6	72.0	344 (h.b.w. 3.1) (4-H)
XVIIe	38.8, 40.9 J_{HF} = 2.1	70.6	344 (4-H), 239.5 and 294.7 (17βH), J_{HF} = 55.2
XVIIf	52.9	71.7	344.5 (h.b.w. 3.4) (4-H), 352.0 and 402.8 ($O_2CCHClF$), J_{HF} = 50.8
XVIIg	42.8	71.9	222.2, 228.0 (17βH), $J_{16\beta,17\beta}$ = 5.8, 344 (4-H)
XVIIh	49.8	71.3	344 (h.b.w. 3.0) (4-H), 295.0 and 301.2 (17β-H), $J_{17\beta,16\beta}$ = 6.2, 350.3 and 401.4 ($O_2CCHClF$), J_{HF} = 51.1
XVIIj[l,m]	54.9	73.0	73.0 (17α-Me), 345 (h.b.w. 3.4) (4-H)
XIXb	53.5	75.7, 80.2 J_{HF} = 4.5	123.0 (OAc), 268 and 318 (6-H), J_{HF} = 50, 326 (h.b.w. 21) (3α-H)
XXIIa		69.9	55.0 and 61.6 (17β-Me), $J_{apparent}$ = 6.6, 344 (4-H)
XXIIb[n]		70.5	58 (allylic methyls)
XXIIb[n] (4,5-dihydro)		58.4	58.4 (alylic methyls)
XXIII		70.5	55.3 and 61.0 (17β-Me), $J_{apparent}$ = 5.7, 344 (4-H)
XXVa	47.0		227.3 (OMe)
XXVb	40.8, 42.6 J_{HF} = 1.8		226.5 (OMe)
XXVc	51.8		226.2 (OMe), 294 (17α-H), 351.6 and 402.6 ($O_2CCHClF$), J_{HF} = 51
XXVI			226.3 (OMe), 57.5 and 63.0 (17β-Me), $J_{apparent}$ = 5.5
XXVII	47.3	44.2	121.3 (OAc), 334 (3-H), 223 (=C—CH_2—O)

[a] See ref. 10. For comparison with various data reported in the literature the following chemical shift values have been employed: $\nu_{benzene} - \nu_{TMS}$ = 384 c.p.s.; $\nu_{H2O} - \nu_{TMS}$ = 282; $\nu_{cyclohexane} - \nu_{TMS}$ = 86 c.p.s. Where necessary, resonances recorded elsewhere at 40 Mc.p.s. have been multiplied by 3/2 for the same reason. [b] J. N. Shoolery and M. T. Rogers [*J. Am. Chem. Soc.* **80**, 5121 (1958)] give $\nu_{18\text{-H}}$ 39 and $\nu_{19\text{-H}}$ 61.5. [c] R. F. Zürcher [*Helv. Chim. Acta*, **44**, 1380 (1961)] gives $\nu_{19\text{-H}}$ 60.5. [d] h.b.w. = half-band width; values in c.p.s. [e] Lit.[b] $\nu_{18\text{-H}}$ 54 and $\nu_{19\text{-H}}$ 61.5. [f] W. R. Nes and U. H. Kim [*Steroids*, **1**, 594 (1963)] report $\nu_{18\text{-H}}$ 52.2 and $\nu_{19\text{-H}}$ 62.4. [g] Lit.[b] $\nu_{18\text{-H}}$ and $\nu_{19\text{-H}}$ 52.5. [h] Lit.[b] $\nu_{18\text{-H}}$ 52.5, $\nu_{19\text{-H}}$ 49.5, and $\nu_{3\beta\text{-H}}$ 249; lit.[c] $\nu_{19\text{-H}}$ 48.4. [i] Lit.[b] $\nu_{18\text{-H}}$ 48, $\nu_{19\text{-H}}$ 72, and $\nu_{4\text{-H}}$ 343.5; lit.[c] $\nu_{19\text{-H}}$ 71.9. [j] T. Okamoto and Y. Kawazoe [*Chem. Pharm. Bull.* (Tokyo), 11, 643 (1963)] give $\nu_{18\text{-H}}$ 48.8. [k] T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold [*J. Am. Chem. Soc.*, **85**, 1699 (1963)] give $\nu_{4\text{-H}}$ 344 (h.b.w. 3.4). [l] Lit.[b] $\nu_{18\text{-H}}$ 54, $\nu_{19\text{-H}}$ 72, and $\nu_{4\text{-H}}$ 343.5; lit.[c] $\nu_{19\text{-H}}$ 72.9. [m] E. Caspi and D. M. Piatak [*Can. J. Chem.*, **41**, 2294 (1963)] give $\nu_{18\text{-H}}$ 54.0, $\nu_{19\text{-H}}$ 70.8, $\nu_{17\alpha\text{ Me}}$ 70.8, and $\nu_{4\text{-H}}$ 342.6. [n] Lit.[m] $\nu_{19\text{-H}}$ 70.2, $\nu_{\text{allylic Me}}$ 57.0, and $\nu_{4\text{-H}}$ 345.

the fluoro derivative IId. In the n.m.r. spectrum[10] (see Table I) the ether showed only two resonances attributable to angular methyl groups which is indicative of symmetry of substitution about the ether link. Moreover, both protons in the environment —CH—O—CH— resonated at the same frequency (180–210 c.p.s., broad multiplet, half-band width *ca.* 20 c.p.s.) and both must therefore be *axially* oriented. Structure III, involving ether formation with retention of configuration, is in accord with our interpretation of the mechanism of action of the reagent (*vide infra*). The mass spectrum of the ether III showed a small peak for the molecular ion at 558 but very few other peaks with m/e ratios greater than 271. The primary fission occurs therefore at a homoallylic C–O bond to give an m/e peak at 271 (IV, strongest peak in the spectrum). The charged species IV would be expected to achieve stabilization through charge delocalization (IV ↔ V ↔ VI).[11]

The marked influence of solvent and temperature on product composition in these reactions is illustrated by results obtained with 3β-hydroxy-5α-androst-17-one (VIIa) where the products arise by (1) elimination, with formation of the Δ^2-derivative VIIIa,[2,6,12] (2) substitution of hydroxyl by fluorine with inversion

(10) N.m.r. spectra were recorded on a Varian A-60 spectrometer using 5% w. v. solutions in deuteriochloroform containing tetramethylsilane (TMS) as an internal reference. Chemical shifts, ν, are quoted as c.p.s. downfield from the TMS reference (0.0 c.p.s.) and are accurate to ±1 c.p.s. Coupling constants, J, also expressed in c.p.s. units are accurate to ±0.5 c.p.s. A.D.C. thanks the Universidad Nacional Autonoma de México for time on the spectrometer.

(11) For a general discussion of the mass spectra of ethers, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 3.

(12) (a) R. E. Marker, O. Kamm, D. M. Jones, and L. W. Mixon, *J. Am. Chem. Soc.*, **59**, 1363 (1937); (b) A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada, and E. Denot, *J. Med. Chem.*, **6**, 156 (1963); (c) V. Prelog, L. Ruzicka, P. Meister, and P. Wieland, *Helv. Chim. Acta*, **28**, 618 (1945).

to form VIIb,[2,6] (3) formation of the chlorofluoroacetate ester VIIc, and (4), in one case, formation of the amide VIId. In all cases the variety of reaction product is easily rationalized in terms of a common reaction mechanism (*vide infra*). The structures of the products VIIb–d were elucidated by n.m.r. spectroscopy and further supported by analyses and infrared spectral examination (see Experimental section). Low-field resonance (below 200 c.p.s.) in the spectrum of the fluoro steroid VIIb was limited to one proton only and this appeared as a pair of multiplets, each with a half-band width of 7 c.p.s. This resonance is interpreted as being due to an equatorial 3β-proton coupled to an axial 3α-fluorine, J_{HF} = 48 c.p.s. The ester VIIc showed a characteristic broad multiplet at 293 c.p.s. with a half-band width *ca.* 22 c.p.s. for the axial 3α-proton, and a pair of sharp singlet resonances at 349.9 and 400.6 c.p.s. for the single proton of the chlorofluoroacetate group strongly coupled to the fluorine on the same carbon atom, J_{HF} = 50.7 c.p.s. This easily detected, widely split, low-field doublet proved of great utility in the recognition of chlorofluoroacetate esters. An extra singlet resonance for three protons at 118.8 c.p.s. was surprisingly observed in the fourth reaction product VIId, which was formed only where acetonitrile was employed as solvent for the reaction. It appeared likely therefore that the solvent had participated in the reaction leading to an acetamido steroid. Infrared absorption bands at 3280, 1650, and 1545 cm.$^{-1}$ for a secondary amide group supported this conclusion. A multiplet resonance at 494 c.p.s. for NH and a multiplet resonance at 250 c.p.s. for an equatorial 3β-proton provided further evidence. The latter resonance was broader (half-band width 16 c.p.s.) than is usually observed for equatorial 3β-protons owing to coupling with the adjacent proton on nitrogen. Proof of structure came from reduction of the amide VIId with sodium borohydride to 3α-acetamido-5α-androstan-17β-ol (VIIe)[13a] followed by acetylation to the known 3α-acetamido-5α-androstan-17β-ol acetate (VIIf)[13a] which was identified by comparison with an authentic sample.[13b]

When 1 molar equiv. of the reagent I was added to a solution of 3α-hydroxy-(5α)-androstan-17-one (VIIj) in tetrahydrofuran (Table II) and the mixture was immediately evaporated *in vacuo*, an essentially quantitative yield of the Δ²-derivative VIIIa was obtained. Ayer[6] obtained also a little of the 3β-fluoro derivative. Under similar conditions, reaction of the amine I with 2,2-dimethylandrostane-3β,17β-diol 17-acetate (IX), prepared by sodium borohydride reduction of the corresponding 3-ketone,[14] yielded 2,3-dimethylandrost-2-en-17β-ol acetate (Xa) which, as reported earlier,[2] was identified by n.m.r. spectroscopy (see Table I). In tetrahydrofuran 3β-methylandrostane-3α,17β-diol 17-acetate (XI)[15] apparently failed to react with 1 molar equiv. of the reagent I after refluxing for 10 min. When 2 molar equiv. of I were employed and the reflux period extended to 1 hr., the dehydration product Xb[15] was isolated in 62% yield. N.m.r. spectral data (Table I) were consistent with the assigned structure.

Having discussed the multitude of products which arise from various steroidal 3-alcohols it is pertinent to consider next the mechanism of action of the reagent to facilitate discussion of reactions at other centers. The amine I is suitably constructed to undergo an

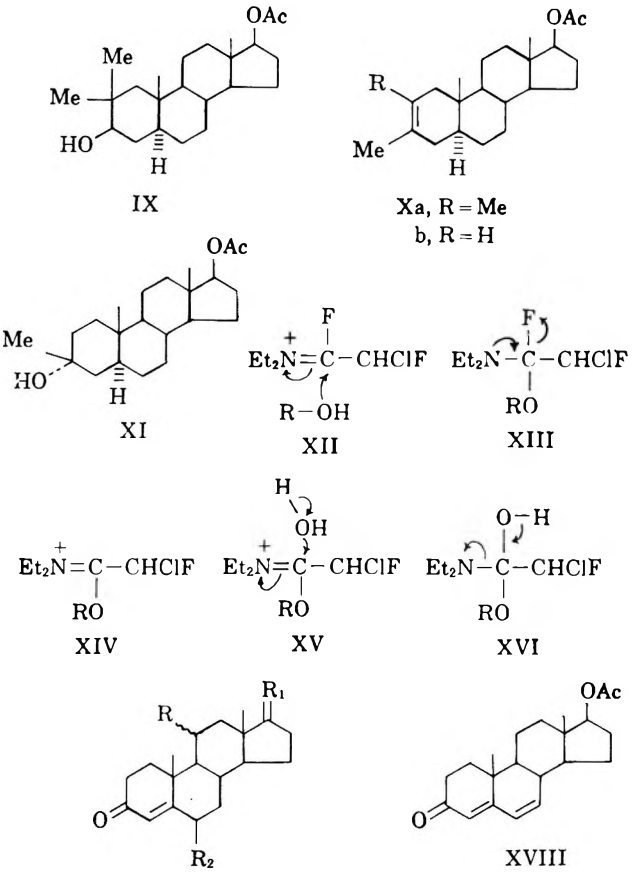


TABLE II

EFFECT OF REACTION CONDITIONS ON PRODUCT COMPOSITION IN THE TREATMENT OF 3β-HYDROXY-5α-ANDROSTAN-17-ONE (VIIa, 6 MMOLES) WITH THE REAGENT I (9 MMOLES)[a]

Reaction conditions			Products isolated, % yield			
Solvent	Temp., °C.	Time, hr.	Δ²- (VIIIa)	3α-F (VIIb)	Ester (VIIc)	Amide (VIId)
CH_2Cl_2	0	16	34	42	3	0
CH_3CN	0	16	23	0	3	21
Tetrahydrofuran	0	16	19	18	17	0
Tetrahydrofuran	25	0.1	63	0	0	0

[a] In 25 ml. of solvent.

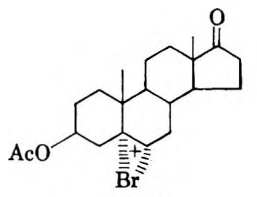
(13) (a) M. M. Janot, Q. Khuong-Hun, and R. Goutarel, *Bull. soc. chim. France*, 1640 (1960). (b) We wish to thank Dr. J. Schmitt, Etablissements Clin-Byla, Paris, for a sample of the amino alcohol VIIg which proved identical with the 3α-amino compound obtained by us from hydrogenation of 4,5-dihydrotestosterone oxime. Both samples of this amino alcohol VIIg on acetylation gave the same O,N-diacetyl derivative VIIf, indistinguishable from the derivative VIIf arrived at from the fluoramine reaction product (see Experimental section). The 3β-amino isomer which was also formed by hydrogenation of the oxime was converted to the 3β-acetamido derivative VIIh.

(14) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959).

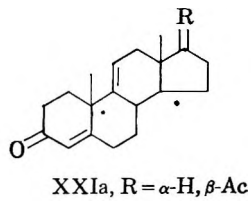
(15) B. Pelc, *Collection Czech. Chem. Commun.*, **25**, 1624 (1960).

internal displacement of fluorine and the resultant charged ammonium species XII adds to any alcohol as illustrated (I → XII, + alcohol → XIII). Further internal displacement of fluoride leads to another charged species XIV.[2,6,16] According to the nature and substitution of R, the species XIV can react further by SN1 or SN2 reactions with liberation of a stable neutral amide, N,N-diethyl chlorofluoroacetamide. Thus, an SN2 displacement by fluoride ion leads to substitution with inversion (*e.g.*, VIIa → VIIb), while a suitable solvent can similarly intervene [*e.g.*, VIIa (as XIV) + CH_3CN → VIId]. For Δ^5-3-alcohols internal displacement at C-3 with formation of the more stable *i*-steroid nonclassical carbonium ion, leading to over-all substitution with retention of configuration, is expected and observed (IIa → IIb). Formation of the ether III constitutes a special case of this reaction with a second molecule of steroid acting in place of fluoride ion. For these alcohols the possibility of 3β-fluoro Δ^5-steroid formation by an SNi-type substitution reaction (four-centered cyclic intermediate from XIV) cannot be excluded on the basis of the available evidence. Where water is present in the reaction mixture as a contaminant, then the chlorofluoroacetate esters are formed (XV → XVI) with expulsion of diethylamino ion. A further possible mode of collapse of an incipient or developed carbonium ion is loss of a proton either before or subsequent to a carbon skeleton rearrangement (*e.g.*, VIIa → VIII, and IX → X). Similar examples have been described elsewhere.[1]

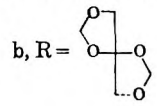
Two C-6 alcohols were examined. Brief warming with the amine I in tetrahydrofuran did not affect 6β-hydroxytestosterone acetate[17] (XVIIa), but in diglyme, under reflux, dehydration occurred with formation of the dienone (XVIII).[18,19] Another case of substitution with retention of configuration was discovered when 5α-bromo-3β,6β-dihydroxyandrostan-17-one 3-acetate (XIXa)[20] was treated with the amine I. The product was quickly identified as the 6β-fluoro derivative XIXb since the resonance of the 19-protons was split by long-range coupling, $J_{19\text{-H},6\beta\text{-F}} = 4.5$ c.p.s. The latter phenomenon is known to occur only when a certain steric relationship of the 19-protons and fluorine atom is maintained,[21] and this condition is fulfilled by 6β-, but not 6α-fluoro steroids. It is apparent that the action of the amine I on the 6β-hydroxy steroid XIXa leads to a charged species (*cf.* XV) which can undergo internal displacement of the amide moiety by bromine leading to the bromonium ion XX. Fluoride ion attack then leads to the 6β-fluoro steroid XIXb.

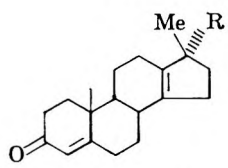


XX

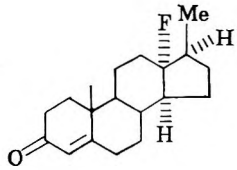


XXIa, R = α-H, β-Ac

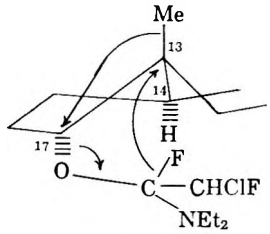




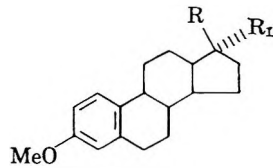
XXIIa, R = H
b, R = Me



XXIII



XXIV



XXVa, R = OH; R1 = H
b, R = H; R1 = F
c, R = O2CCHClF; R1 = H

A significant difference in the reactivity of 11α- and 11β-alcohols was observed. While 11α-hydroxypregn-4-ene-3,20-dione (XVIIb)[22] reacted with the amine I in methylene chloride at 0° to give the $\Delta^{4,9(11)}$-derivative XXIa[23] in 86% yield, hydrocortisone bismethylenedioxy derivative XVIIc,[24] under the same conditions, was recovered quantitatively. When the latter was refluxed for 1 hr. with the reagent I in methylene chloride, the dehydration product XXIb[25] could be isolated in 82% yield based on unrecovered starting material.[26]

Without exception, 17β-secondary alcohols gave three products, these being the dehydration product with migration of the 13β-methyl group, the 17α-fluoro derivative, and the 17β-chlorofluoroacetate. Thus, testosterone XVIId reacted with the amine I in tetrahydrofuran at room temperature with formation of 17β-methyl-18-norandrosta-4,13-dien-3-one (XXIIa), 17α-fluoroandrost-4-en-3-one (XVIIe),[2,6] and testosterone chlorofluoroacetate (XVIIf) in crude yields of 25, 18, and 26%, respectively. The structure of the dehydration product XXIIa was demonstrated by elementary and n.m.r. spectral analyses (see Table I). The absence of any signal in the vinyl region excluded the alternative structure containing a Δ^{12}-double bond.

During the course of our work, a synthesis of the 17α-fluoro derivative XVIIe was described by Henbest and Jackson[27] which involved a nucleophilic displacement reaction with testosterone *p*-toluenesulfonate

(16) The electrons of both nitrogen and oxygen of XIII assist the expulsion of fluoride ion. Although the resultant positive charge is placed on nitrogen in XIV, the oxygen atom obviously also bears partial charge which facilitates carbonium ion formation.

(17) J. Romo, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954).

(18) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

(19) Using different experimental conditions Ayer[6] was able to convert 6β,11α-dihydroxypregn-4-ene-3,20-dione to 6α-fluoropregna-4,9(11)-diene-3,20-dione in low yield.

(20) V. Grenville, D. K. Patel, V. Petrow, J. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4105 (1957).

(21) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 1736, 3784 (1962); see also L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, P. W. Landis, and A. D. Cross, *ibid.*, **85**, 1851 (1963), footnote 29.

(22) D. H. Peterson, H. C. Murray, S. H. Epstein, L. M. Reineke, A. Weinstraub, P. D. Meister, and H. M. Leigh, *ibid.*, **74**, 5933 (1952).

(23) C. W. Shoppee and I. Reichstein, *Helv. Chim. Acta*, **24**, 351 (1941).

(24) R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

(25) R. E. Beyler and L. H. Sarett, U. S. Patent 2,888,457 (1959).

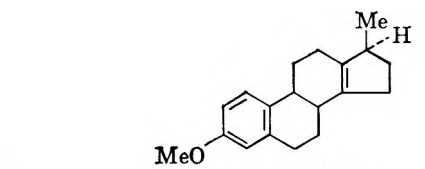
(26) Ayer[6] was able to isolate also a little of the 11β-fluoro derivative from 11α-hydroxyprogesterone.

(27) H. B. Henbest and W. A. Jackson, *J. Chem. Soc.*, 954 (1962).

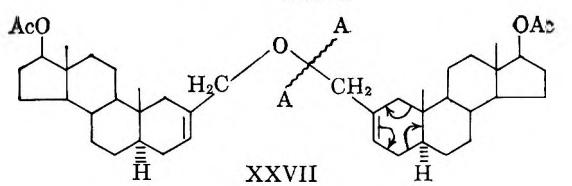
and tetrabutylammonium fluoride. The chlorofluoroacetate XVIIf, in common with similar esters isolated in this study, showed a characteristic strong band at *ca.* 1770 cm.$^{-1}$ in the infrared spectrum and was readily hydrolyzed to testosterone. In the n.m.r. spectrum the highly characteristic doublet, J_{HF} = *ca.* 50 c.p.s., for the lone proton in the chlorofluoroacetate ester group was clearly visible. Epitestosterone (XVIIg) under similar conditions afforded the 18-norsteroid XXIIa (80%, identified by mixture melting point and comparative spectra with a sample obtained from testosterone), the chlorofluoroacetate XVIIh (2%), and a third product for which we propose structure XXIII (7%). This last compound shows no proton resonance, other than that for the C-4 proton, at low fields thus excluding protons in the environment H–C–F. Since analysis shows the presence of one fluorine substituent, this has to be attached to quaternary carbon. Structure XXIII is suggested by consideration of the stereochemically favored mechanism (*cf.* XXIV) in which the 13β-methyl group migrates to the 17β-position as the 17α-carbon–oxygen bond polarizes. Simultaneously, the developing fluoride ion can attack C-13 from the α-face. Other structures (*e.g.*, 13α-H, 14ξ-fluoro) involving hydride ion migration 14$\alpha \rightarrow$ 13α) cannot be excluded, but are less attractive possibilities. The presence of the 17β-methyl group is supported by proton resonance for three methyl protons as a doublet, $J_{apparent}$ = 5.7 c.p.s.,[28] with each arm of the doublet broadened by long-range coupling, probably with fluorine. These results are in contrast to certain acid-catalyzed dehydrations of 17β- and 17α-ols which are reported to give Δ^{16}- and $\Delta^{13(17)}$-derivatives, respectively.[29] Estradiol-3-methyl ether (XXVa) reacted with the amine I in tetrahydrofuran at room temperature with formation of the 18-norsteroid XXVI, the 17α-fluoro derivative XXVb, and the chlorofluoroacetate XXVc in crude yields of 47, 26, and 9%, respectively. Chemical shift data for these and other compounds described above, which support the assigned structures, are summarized in Table I.

Under relatively mild conditions, and in a variety of solvents, tertiary steroidal alcohols are inert to the amine I (*vide supra*). At elevated temperatures, however, tertiary alcohols yield exclusively, and in high yield, products resulting from dehydration, with or without rearrangement. When 17α-methyltestosterone (XVIIj) was briefly refluxed in acetonitrile with the amine (I), 17,17-dimethyl-18-norandrosta-4,13-dien-3-one (XXIIb)[30] was obtained. The structure of XXIIb was established by n.m.r. and elemental analyses. Several other examples of rearrangement with 13β-methyl migration to C-17 have been reported in the recent literature, with structure determinations by the n.m.r. method.[30,31] In each case the diagnostic changes are the disappearance of the 18-proton resonance and the appearance of a new methyl resonance at higher frequencies as either a doublet or singlet dependent upon the secondary or tertiary nature of the original C-17 alcohol. In a further example, 17α-methyldihydrotestosterone (XVIIj, 4,5-dihydro) was treated with the reagent I to obtain the analogous 17,17-dimethyl derivative (XXIIb, 4,5-dihydro).

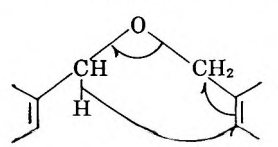
We reported earlier[2] that the fluorinating reagent I converted 2-hydroxymethylandrost-2-en-17β-ol acetate (VIIIb)[32] into 2-fluoromethylandrost-2-en-17β-ol acetate (VIIIc), identical with a sample of the same fluoromethyl compound prepared by an alternative route.[33] Further studies of the n.m.r. spectra of several preparations of this product reveal that it is in fact an inseparable mixture of the 2-fluoromethyl compound VIIIc and the 3β-fluoro-2-methylene isomer.[34] The mixture shows melting point and chromatographic behavior of a pure compound. A second product from the reaction of the allylic alcohol VIIIb with the reagent I was shown to be the ether XXVII. In the n.m.r. spectrum only two angular methyl proton resonance singlets were observed which suggested symmetry of structure about the ether link. Resonance for the two C-3 olefinic protons occurred at 334 c.p.s., while there was no sign of *exo*-methylene proton resonances. The allylic methylenes attached to ethereal oxygen gave a broad (half-band width 6 c.p.s.) 'singlet' resonance at 223 c.p.s. In the mass spectrum[9] the molecular ion was detected as m/e = 674. As with the other ether III examined, it was apparent that the primary cleavages take place at the ether link since there were only a few low intensity peaks above m/e = 330. A peak



XXVI



XXVII



XXVIIa

at m/e = 330 corresponds to the charged specie remaining after cleavage (fission at AA in XXVII) and transfer of a hydrogen (XXVIIa). Other peaks may arise from a breakdown of ring A in the ether or derived primary fission particles by the cyclic electron shift mechanism shown in XXVII. Very recently a report has appeared describing mass spectral patterns

(28) An important paper by F. A. L. Anet [*Can. J. Chem.*, **39**, 2262 (1961)] has drawn attention to the fact that for many methyl groups the observed splitting is not the true magnitude of the coupling constant.

(29) *Cf.* L. F. Fieser and M. Fieser, "Steroids," Rheinhold Publishing Corp., New York, N. Y., 1959, p. 529.

(30) E. Capsi and D. M. Piatak, *Can. J. Chem.*, **41**, 2294 (1963).

(31) *Inter alia*, (a) A. D. Cross, H. Carpio, and H. J. Ringold, *J. Med. Chem.*, **6**, 198 (1963); (b) A. J. Mason, *et al.*, *ibid.*, **6**, 1 (1963); (c) R. Kirdani, R. I. Dorfman, and W. R. Nes, *Steroids*, **1**, 219 (1963); (d) W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961); (e) E. Caspi and D. M. Piatak, *Chem. Ind.* (London), 1984 (1962); (f) V. Tortorella, G. Lucente, and A. Romeo, *Ann. chim.*, **50**, 1198 (1960); *cf. Varian Tech. Info. Bull.*, **3**, No. 2 (1961).

(32) J. C. Orr, *et al.*, *J. Med. Chem.*, **6**, 166 (1963).

(33) J. A. Edwards, *et al.*, *ibid.*, **6**, 174 (1963).

(34) A. D. Cross and P. W. Landis, forthcoming publication.

for other types of Δ^2-steroids for which the same mechanism of ring A fission is proposed.[35]

There are a number of features concerning the n.m.r. data which merit comment. First, by using standard values for the chemical shifts of the angular methyl protons in 5α-androstane ($\nu_{18\text{-H}}$ = 41.5 c.p.s. and $\nu_{19\text{-H}}$ = 47.5 c.p.s.[36]), it is possible to calculate the shifts of each of these frequencies owing to substituent groups at various points in the steroid nucleus. In Table III

TABLE III

N.M.R. SPECTRAL DATA[10] FOR 5α,14α-ANDROSTANE AND SOME SIMPLE DERIVATIVES[a]

Compound	$\nu_{18\text{-H}}$	$\nu_{19\text{-H}}$	Other protons
5α,14α-Androstane	41.5 (41.5)	47.5 (47.5)	
5α-Androstan-3-one	43.5	61.1	
5α-Androstan-3α-ol	41.7	47.3	243, h.b.w.[b] 7 (3β-H)
5α-Androstan-3β-ol	41.9	48.8	215, h.b.w. 24 (3α-H)

[a] Values are given in c.p.s.; values in parentheses are those of Zürcher (ref. 37b). [b] h.b.w. = half-band width; values are in c.p.s.

are collected angular methyl proton resonance frequency data for 5α,14α-androstane and three 3-substituted derivatives. From this information the frequency shifts due to each functional group were calculated. These values are assembled in Table IV. With knowledge of these frequency shifts it was possible, by simple additions and subtractions, to calculate the frequency shifts due to other substituents in the compounds studied.[38,39] These data are also collected in Table IV.

From Table IV it is seen that in almost no case did the shifts calculated in this work differ by more than 0.5 c.p.s. from the values found by Zürcher. This agreement lends further support to the principle of shift additivity since the observed differences are well within experimental error.

The resonance patterns of the 17-proton in 17-monosubstituted 16-unsubstituted steroids offer a simple means of assigning the stereochemistry of the substituent (*cf.* Table I). For 17β-substituted steroids

TABLE IV

FREQUENCY SHIFTS OF ANGULAR METHYL PROTON RESONANCES DUE TO SUBSTITUENT GROUPS[a-c]

Substituent group	$\Delta\nu_{18\text{-H}}$	$\Delta\nu_{19\text{-H}}$
3-C=O*	2 (2.5)	13.5 (14.5)
3α-OH*	0 (0.5)	0 (0)
3β-OH*	0.5 (0.5)	1.5 (2.0)
3α-F	0	0
3β-F	1	3.5
3α-AcNH*	1.5	1.5
3β-AcNH*	1.5	0
3β-O_2CCHClF*	1.5	4.5
3-Methyl-Δ^2-*	1.0	4.0
2,3-Dimethyl-Δ^2-	1.0	−7.5
Δ^4-3-C=O[d]	4.0 (4.5)	24.5 (25.0)
3-Methoxy-$\Delta^{1,3,5(10)}$[e]	4.0	
17-C=O	10.0 (10.0)	0.5 (1.0)
17β-OAc*	4.5 (5.0)	0 (0)
17α-OH*	−3	0
17α-F*	−5.5	−1.5
17β-O_2CCHClF*	7	0
17α-O_2CCHClF*	4	−0.5
17α-Me, 17β-OH*	9 (9)	1 (0.5)

[a] Shifts are relative to values for 5α,14α-androstane and are quoted to the nearest 0.5 c.p.s. Zürcher's values[37b] are given in parentheses. All values are for 8β,9α,14α stereochemistry, and 5α where applicable. [b] Data marked by an asterisk in this table are derived from a consideration of only one example of each functional group and hence must be considered less reliable than Zürcher's data where the latter were compiled from numerous examples. [c] Positive values of $\Delta\nu$ indicate a downfield shift. [d] Calculated using Zürcher's values of $\Delta\nu_{18\text{-H}}$ = 2 and $\Delta\nu_{19\text{-H}}$ = 0 for the 17β-OH function. [e] This value is calculated making the assumption that an aromatic ring A does not alter the conformation of ring D relative to nonaromatic ring A steroids.

the 17α-proton appears as a characteristic ill-resolved triplet.[41] However, the 17β-proton resonance in the epimeric 17α compounds is an apparent doublet, J = *ca.* 6 c.p.s. (*cf.* XVIIg and XVIIh). The reason for this is clear from models[42] which demonstrate that the angle subtended by the adjacent 17β- and 16α-C–H bonds is close to 90° and coupling between 17β- and 16α-protons is therefore predictably very small.[43] Conversely, the 17β-C–H to 16β-C–H subtended angle is less than 20° and strong coupling will occur, the magnitude being dependent upon numerous factors.[44]

An interesting situation occurs with Δ^2-steroids where an inspection of models[42] reveals that the 10β-angular methyl group during rotation brings the 19-protons near to the shielding cone of the double bond. From Tables III and IV and Zürcher's[37b] value of $\Delta\nu_{19\text{-H}}$ = 0 for a Δ^2-double bond, it may be noted that progressive substitution of the double bond by methyl groups results in an upfield shift of $\nu_{19\text{-H}}$ by *ca.* 4 c.p.s. per methyl group.[45]

Experimental[46]

2-chloro-1,1-2-trifluorotriethylamine (I) was prepared essentially as described by Yarovenko and Raksha.[6] Chlorotrifluoro-

(35) H. Audier, M. Fétizon, and W. Vetter, *Bull. soc. chim. France*, 1971 (1963).

(36) Zürcher reported earlier[37a] a value of 46.5 c.p.s. for $\nu_{19\text{-H}}$ of 5α-androstane. During our studies it became apparent that this figure required revision to 47.5 c.p.s. It is most important to note that many previously published $\Delta\nu_{19\text{-H}}$ shift values due to substituents on the steroid nucleus which were based on the earlier reference frequency of 46.5 c.p.s. must now be revised and reduced by 1 c.p.s. Zürcher subsequently revised his value of $\nu_{19\text{-H}}$ to 47.5 c.p.s.[37b] and, in fact, his new reference values for both $\nu_{18\text{-H}}$ and $\nu_{19\text{-H}}$ are in excellent agreement with those recorded by us (Table III). Much of the task of retabulating additivity shifts of angular methyl frequencies has been performed by Zürcher.[37b]

(37) (a) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961); (b) **46**, 2054 (1963).

(38) The concept of frequency shift additivities is of considerable importance in alicyclic chemistry. However considerable care must be exercised in its application. Several cases have been reported where the additivity principle is no longer valid because of conformational distortion.[37,39] It appears unlikely, for example, that widespread use of this rule will be possible with ring-D 16,17-disubstituted steroids since this ring can readily adopt any one of three conformations to relieve strain.[40] Table IV contains only data which have been derived from studies of steroids where marked conformational distortions are unlikely.

(39) K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961); A. D. Cross, *ibid.*, **84**, 3206 (1962); A. D. Cross and I. T. Harrison, *ibid.*, **85**, 3223 (1963); T. Okamoto and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **11**, 643 (1963).

(40) F. V. Brutcher, Jr. and W. Bauer, Jr., *J. Am. Chem. Soc.*, **84**, 2236 (1963); A. D. Cross and P. Crabbe, *ibid.*, **86**, 1221 (1964); C. Beard and A. D. Cross, unpublished observations.

(41) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

(42) A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(43) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(44) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963); *cf.*, also, part IX in the series, Spectra and Stereochemistry.

(45) A 2-methyl substituent has a similar effect (A. D. Cross, unpublished observations).

(46) Melting points are uncorrected. Optical rotations were determined in chloroform solutions and ultraviolet spectra were measured in 95% ethanol. Infrared spectra, determined in potassium bromide disks on a Perkin-Elmer Model 21 spectrometer equipped with sodium chloride optics, were recorded by Dr. Matthews and his staff.

ethylene was bubbled for 8 hr. into diethylamine (50.0 g.) maintained at −5 to −10°. Distillation *in vacuo* afforded 48.0 g. (44%) of the reagent I, b.p. 28–30° (8 mm.), lit.[5] b.p. 32–33° (6 mm.).

3β-Fluoropregn-5-en-20-one (IIb).—A solution of 1.9 g. (6 mmoles) of 3α-hydroxypregn-5-en-20-one (IIa) and 1.1 g. (6 mmoles) of the amine I in dry tetrahydrofuran (20 ml.) was kept at room temperature for 10 min. and then evaporated to dryness *in vacuo* at steam bath temperature. Recrystallization of the solid residue from methanol gave the fluoro derivative IIb (0.97 g. 52%), m.p. 155–160°, which was identical by infrared comparison and mixture melting point with a sample prepared by an alternative route.[3]

Reaction of 3β-Hydroxyandrost-5-en-17-one (IIc) with the Amine I.—A mixture of 3β-hydroxyandrost-5-en-17-one (2.9 g., 10 mmoles), the amine I (2.85 g., 15 mmoles), and dry methylene chloride (25 ml.) was heated under reflux for 15 min. and then evaporated *in vacuo* on the steam bath. The residue was adsorbed from hexane containing a little benzene onto Florisil (90 g.). The crystalline fractions eluted with hexane and hexane–ether (4:1) were combined (2.43 g.) and recrystallized from hexane yielding 1.67 g. (57.5%) of 3β-fluoroandrost-5-en-17-one (IId),[6,7] m.p. 155–157°, raised to 157–158° by recrystallization from hexane; $[\alpha]_D$ −13°; ν_{max} 1743 cm.$^{-1}$ (17-ketone).

Anal. Calcd. for $C_{19}H_{27}FO$: C, 78.57; H, 9.37; F, 6.54. Found: C, 78.61; H, 9.49; F, 6.53.

Further elution with ether afforded the ether III (0.27 g., 4.6%), m.p. 276–278°, raised to 278–280° by recrystallization from acetone; $[\alpha]_D$ −5°; ν_{max} 1745 and 1100 cm.$^{-1}$.

Anal. Calcd. for $C_{38}H_{54}O$: C, 81.67; H, 9.74. Found: C, 81.38; H, 9.78.

Reaction of 3β-Hydroxy-5α-androstan-17-one (VIIa) with the Amine I. A.—A solution of 1.7 g. (6 mmoles) of 3β-hydroxy-5α-androstan-17-one and 1.7 g. (9 mmoles) of the reagent I in dry methylene chloride (25 ml.) was kept at 0° for 16 hr. Solvent was removed by evaporation *in vacuo* at room temperature and the residual oil was adsorbed from hexane onto Florisil (100 g.) The first crystalline fractions eluted with hexane–ether (9:1) consisted of androst-2-en-17-one (VIIIa, 0.55 g., 33.7%), m.p. 105–107° after recrystallization from hexane, and identical by mixture melting point and infrared spectral comparison with an authentic sample.[12] Further elution with the same solvent system afforded 3α-fluoroandrostan-17-one (VIIb, 0.73 g., 41.7%), m.p. 118–119°, $[\alpha]_D$ +95°, ν_{max} 1745 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{29}FO$: C, 78.03; H, 9.97; F, 6.49. Found: C, 78.10; H, 10.19; F, 6.10.

Finally, elution with hexane–ether (1:1) and ether yielded the chlorofluoroacetate VIIc (0.07 g., 3.0%), m.p. 149–151° after recrystallization from methanol; $[\alpha]_D$ +52°; ν_{max} 1740 (17-ketone), 1205, and 1770 cm.$^{-1}$ (chlorofluoroacetate ester).

Anal. Calcd. for $C_{21}H_{30}FO_3Cl$: C, 65.52; H, 7.85; Cl, 9.21; F, 4.93. Found: C, 65.52; H, 7.58; Cl, 9.47; F, 4.40.

B.—The above procedure was repeated at 0 and 25°, substituting dry tetrahydrofuran for methylene chloride, with the results shown in Table II.

C.—When dry acetonitrile was substituted for methylene chloride in procedure A, chromatography afforded, in addition to androst-2-en-17-one (VIIIa) and the ester VIIc, the amide VIId (370 mg., 21%), m.p. 246–248° after recrystallization from acetone; $[\alpha]_D$ +107°; ν_{max} 3280, 1650, and 1545 (secondary amide), and 1745 cm.$^{-1}$ (17-ketone).

Anal. Calcd. for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.23; O, 9.65. Found: C, 75.95; H, 10.04; N, 4.09; O, 9.82.

3α-Acetamido-5α-androstan-17β-ol (VIIe).—To a solution of the amido ketone VIId (150 mg.) in dioxane (2 ml.) there was added a solution of sodium borohydride (75 mg.) in a mixture of dioxane (1 ml.) and water (0.5 ml.). The mixture was stirred at room temperature for 1 hr., neutralized with acetic acid, and the crude product (m.p. 255–257°) was isolated in the usual manner. A sample recrystallized from acetone afforded pure 3α-acetamido-5α-androstan-17β-ol (VIIe), m.p. 258–260°, $[\alpha]_D$ +34°; lit.[13a] m.p. 250°, $[\alpha]_D$ +33°.

Anal. Calcd. for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20. Found: C, 75.49; H, 10.56; N, 4.58.

3α-Acetamido-5α-androstan-17β-ol 17-Acetate (VIIf).—Acetylation of the alcohol (VIIe, 100 mg.) obtained above in a pyridine–acetic anhydride mixture yielded the O,N-diacetylated derivative VIIf which was recrystallized from acetone, m.p. 199–200°, $[\alpha]_D$ +29°; lit.[13a] m.p. 185°, $[\alpha]_D$ +32°. The melting point was undepressed on admixture with an authentic sample obtained by acetylation of the corresponding amino alcohol VIIg (*vide infra*).[13b] Infrared spectra were indistinguishable.

Anal. Calcd. for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.31; H, 9.88, N, 3.90.

3α-Amino-5α-androstan-17β-ol (VIIg).—3-Oximino-5α-androstan-17β-ol was first prepared as described by Janot.[13a] After recrystallization from acetone the sample had m.p. 220–222°, $[\alpha]_D$ +22°, lit.[13a] m.p. 215°.

Anal. Calcd. for $C_{19}H_{31}NO_2$: N, 4.59. Found: N, 4.58.

Hydrogenation of this oxime (3.0 g.) in acetic acid (30 ml.) over platinum oxide (600 mg.) overnight at an initial hydrogen pressure of 50 p.s.i. and isolation of the product by filtration and distillation of the solvent under reduced pressure afforded the 3α-amino derivative contaminated with a small amount of the 3β-isomer (3.0 g.), m.p. 187–193°. Two crystallizations of a 100-mg. sample from methanol afforded the pure 3α-isomer, m.p. 190–192°. A mixture melting point with an authentic sample[13b] showed no depression, and infrared spectra of the two specimens were identical.

Anal. Calcd. for $C_{19}H_{33}NO$: C, 78.29; H, 11.41; N, 4.70. Found: C, 78.34; H, 11.62; N, 4.58.

3α- and 3β-Acetamido-5α-androstan-17β-ol 17-Acetates (VIIf and VIIh).—The mixture of amino alcohols obtained above (2.9 g.) was acetylated in a pyridine–acetic anhydride mixture. The crude product, m.p. 185–187°, on recrystallization from methanol afforded the 3β-isomer (VIIh, 0.43 g.), m.p. 274–276°, raised to 277–279° by a second recrystallization from methanol (lit.[13a] m.p. 278°).

Anal. Calcd. for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93, N, 3.73. Found: C, 73.65; H, 9.89; N, 3.85.

From the mother liquors there was obtained the 3α-isomer which, after two crystallizations from acetone, amounted to 1.3 g., m.p. 198–200°. This was identical by mixture melting point and infrared spectral comparison with 3α-acetamido-5α-androstan-17β-ol acetate (VIIf) prepared from VIId (*vide supra*).

Reaction of 3α-Hydroxy-5α-androstan-17-one (VIIj) with the Reagent I.—To a solution of 1.48 g. (5 mmoles) of the alcohol VIIj in dry methylene chloride (9 ml.) at room temperature, there was added 0.95 g. (5 mmoles) of the reagent I, and the mixture was evaporated to dryness *in vacuo*. The residue was adsorbed from hexane onto neutral alumina (50 g.). The crystalline fractions eluted with hexane consisted of androst-2-en-17-one[12] (VIIIa, 1.15 g.), m.p. 97–100° after crystallization from hexane. Further elution with hexane–ether (1:1) afforded unchanged alcohol VIIf (0.30 g.), m.p. 188–189°. Based on unrecovered starting material, the yield of the olefin VIIIa was essentially quantitative.

2,2-Dimethyl-5α-androstane-3β,17β-diol 17-Acetate (IX).—To a solution of 2,2-dimethyl-17β-hydroxy-5α-androstan-3-one acetate[14] (2.2 g.) in dioxane (20 ml.) there was added dropwise with stirring a solution of sodium borohydride (1.0 g.) in a mixture of dioxane (25 ml.) and water (2 ml.). Stirring was continued for 1 hr. and the product was isolated by dilution with cold water and filtration. Recrystallization from methanol afforded the 3β-alcohol IX (1.53 g., 69.0%), m.p. 174–175°, raised to 177–178° by a further recrystallization from methanol; $[\alpha]_D$ +18°; ν_{max} 3480 (OH) and 1735 cm.$^{-1}$ (acetate).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.46; H, 10.56.

Reaction of the Alcohol IX with the Reagent I.—A solution of 1.17 g. (3.2 mmoles) of the above alcohol IX and 0.75 g. (4 mmoles) of the reagent I in dry tetrahydrofuran (8 ml.) was warmed briefly (10 min.) on the steam bath and then evaporated *in vacuo*. The crude product was adsorbed from hexane onto Florisil (50 g.). The crystalline fractions eluted with hexane consisted of 2,3-dimethylandrost-2-en-17β-ol acetate (Xa, 0.540 g., 50%), m.p. 130–131°. Recrystallization from methanol afforded a pure sample, m.p. 141–143°, $[\alpha]_D$ +36°, ν_{max} 1735 and 1255 cm.$^{-1}$ (acetate).

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.39; H, 10.89.

3-Methyl-5α-androst-2-en-17β-ol Acetate (Xb).—A solution of 3β-methylandrostane-3α,17β-diol 17-acetate[15] (1.56 g., 4 mmoles) and the reagent I (1.56 g., 8 mmoles) in tetrahydrofuran (25 ml.) was refluxed for 1 hr. Evaporation to dryness and recrystallization of the crude residue from methanol afforded 0.63 g. of 3-methyl-5α-androst-2-en-17β-ol acetate (Xb), m.p. 95–97°. Chromatography of the mother liquors on Florisil gave an additional 0.19 g. of this product, m.p. 97–98°, raising the yield to 0.82 g. (62%). Recrystallization from methanol afforded a

pure sample, m.p. 99–100°, $[\alpha]_D$ +51° (lit.[15] m.p. 105–107°, $[\alpha]_D$ +47°), ν_{max} 1738 and 1250 cm.$^{-1}$ (acetate).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.13; H, 10.42.

Reaction of 6β-Hydroxytestosterone 17-Acetate (XVIIa) with the Reagent I.—A mixture of 340 mg. (1.04 mmoles) of the 6β-hydroxy steroid XVIIa,[17] 400 mg. (2.2 mmoles) of the reagent I, and diglyme (10 ml.) was heated under reflux for 1 hr. The product was isolated by dilution with water and filtration, and then was adsorbed from hexane onto Florisil (25 g.). Crystalline fractions eluted with hexane–ether (1:1) were combined (150 mg., 44%) and recrystallized from acetone affording 6-dehydrotestosterone acetate (XVIII), m.p. 145–147°, $[\alpha]_D$ +45°, λ_{max} 282–284 mμ (log ε 4.28); lit.[18] m.p. 143–144°, $[\alpha]_D$ +36° (chloroform), λ_{max} 284 mμ (log ε 4.53). Identification was further established by infrared spectral comparison with an authentic sample.

When tetrahydrofuran was employed as solvent in place of diglyme, the alcohol XVIIa was recovered.

5α-Bromo-6β-fluoro-3β-hydroxyandrostan-17-one 3-Acetate (XIXb).[47]—To a solution of 250 mg. of 3β,6β-dihydroxy-5α-bromoandrostan-17-one 3-acetate[20] in 40 ml. of dry methylene chloride was added 0.4 ml. of the reagent I and the solution was allowed to stand at room temperature for 24 hr. Evaporation of the solvent and chromatography of the residue on alumina gave, after crystallization of the product from methylene chloride–hexane, 5α-bromo-6β-fluoro-3β-hydroxyandrostan-17-one acetate (60 mg.), m.p. 186–188°, $[\alpha]_D$ ±0°, λ_{max} 278–282 mμ (log ε 1.63), ν_{max} 1744 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}BrFO_3$: C, 58.70; H, 7.03. Found: C, 59.02; H, 7.31.

Reaction of 11α-Hydroxypregn-4-ene-3,20-dione (XVIIb) with the Reagent I.—A mixture of 2.0 g. (6 mmoles) of the 11α-alcohol XVIIb,[22] 1.70 g. (9 mmoles) of the reagent I, and dry methylene chloride (25 ml.) was kept at 0° for 16 hr. The mixture was evaporated and the residue was crystallized from methanol yielding 1.35 g. of pregna-4,9(11)-diene-3,20-dione (XXIa), m.p. 123–125°. Chromatography of the mother liquors on Florisil afforded an additional 200 mg. of XXIa, raising the yield to 1.55 g. (86.0%).

Reaction of 11β-Hydroxy-17,20,20-21-methylenedioxypregn-4-en-3-one (XVIIc) with the Reagent I.—A solution of 2.30 g. (6 mmoles) of the 11β-alcohol XVIIc[24] and 1.70 g. (9 mmoles) of the reagent I in methylene chloride (25 ml.) was heated under reflux for 1 hr. Solvent was evaporated under reduced pressure and the residue was recrystallized from acetone yielding the $\Delta^{9(11)}$-derivative XXIb[25] (1.62 g.), m.p. 235–236°, identical with an authentic sample by infrared comparison. The mother liquor was adsorbed from benzene onto Florisil (50 g.). The first crystalline fractions eluted with benzene–ether (4:1) consisted of the dehydration product XXIb (0.15 g.). Further elution with the same solvent system yielded unchanged alcohol XVIIc (0.18 g.). Based on unrecovered starting material, the yield of XXIb amounted to 82.4%.

A similar reaction using methylene chloride solvent, but at reaction temperature of 0°, afforded only unchanged starting material.

Reaction of Testosterone (XVIId) with the Reagent I.—A mixture of 1.72 g. (6 mmoles) of testosterone, 1.71 g. (9 mmoles) of the reagent I, and dry acetonitrile (20 ml.) was kept at room temperature for 30 min. and then evaporated *in vacuo* at room temperature. The residue was adsorbed from hexane onto Florisil (100 g.). The partially crystalline fraction eluted with hexane consisted of 17β-methylandrosta-4,13-dien-3-one (XXIIa, 0.40 g., 24.7%), m.p. 112–113° after recrystallization from hexane, $[\alpha]_D$ +69°, λ_{max} 238–240 mμ (log ε 4.23), ν_{max} 1680 and 1620 cm.$^{-1}$ (enone).

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69; O, 5.92. Found: C, 83.97; H, 9.82; O, 6.38.

Further elution with hexane–ether (9:1) afforded 0.31 g. (18.0%) of 17α-fluoroandrost-4-en-3-one (XVIIe), m.p. 100–105°, raised to 146–148° after recrystallization from methanol; $[\alpha]_D$ +96°; λ_{max} 240–242 mμ (log ε 4.23); ν_{max} 1685 and 1615 cm.$^{-1}$ (enone).

Anal. Calcd. for $C_{19}H_{27}FO$: C, 78.57; H, 9.37. Found: C, 78.09; H, 9.01.

Further elution with hexane–ether (1:1) gave 0.61 g. (26.5%) of testosterone chlorofluoroacetate (XVIIf), m.p. 177–179° after recrystallization from methanol; $[\alpha]_D$ +81°; λ_{max} 240–242 mμ (log ε 4.21); ν_{max} 1660 and 1615 (enone), 1775 and 1205 cm.$^{-1}$ (chlorofluoroacetate ester).

Anal. Calcd. for $C_{21}H_{28}ClFO_3$: C, 65.86; H, 7.36; Cl, 9.26; F, 4.96. Found: C, 66.08; H, 7.45; Cl, 9.05; F, 5.36.

Finally, elution with ether afforded 0.11 g. of testosterone.

Reaction of 17α-Hydroxyandrost-4-en-3-one (Epitestosterone) (XVIIg) with the Reagent I.—A mixture of 8.7 g. (30 mmoles) of epitestosterone, 8.5 g. (45 mmoles) of the reagent I, and dry tetrahydrofuran (100 ml.) was stirred at room temperature overnight (14 hr.). Solvent was removed by evaporation *in vacuo*, and the residue was adsorbed onto Florisil (400 g.). The partially crystalline fractions eluted with hexane–ether (9:1, 250-ml. fractions) consisted of the dehydration product XXIIa (6.45 g., 79.6%), m.p. 110–112°, identical by infrared comparison with a sample obtained by similar treatment of testosterone (*vide supra*). Further elution with the same solvent system afforded 0.59 g. (7.0%) of a product considered to be 13α-fluoro-17β-methylandrost-4-en-3-one (XXIII), m.p. 118–119° after recrystallization from methanol, $[\alpha]_D$ +101°, λ_{max} 240–242 mμ (log ε 4.34), ν_{max} 1670 and 1615 cm.$^{-1}$ (enone).

Anal. Calcd. for $C_{19}H_{27}FO$: C, 78.57; H, 9.37; F, 6.54. Found: C, 78.79; H, 9.51; F, 6.49.

Continued elution with the same solvent system yielded epitestosterone chlorofluoroacetate (XVIIh, 0.21 g., 1.8%), m.p. 155–156° after recrystallization from methanol; $[\alpha]_D$ +70°; λ_{max} 240 mμ (log ε 4.26); ν_{max} 1680 and 1620 (enone), and 1770 and 1208 cm.$^{-1}$ (chlorofluoroacetate ester).

Anal. Calcd. for $C_{21}H_{29}ClF$: C, 65.88; H, 7.37; Cl, 9.26; F, 4.96. Found: C, 66.04; H, 7.52; Cl, 9.36; F, 5.58.

Reaction of Estradiol-3-methyl Ether (XXVa) with the Reagent I.—A solution of-8.58 g. (30 mmoles) of estradiol-3-methyl ether and 8.50 g. (45 mmoles) of the reagent I in dry tetrahydrofuran (100 ml.) was kept at room temperature for 30 min. Solvent was removed by evaporation *in vacuo* at room temperature, and the residual oil was adsorbed from hexane onto Florisil (300 g.). The first crystalline fractions eluted with hexane consisted of 3-hydroxy-17β-methylgona-1,3,5(10),13-tetraene-3-methyl ether (XXVI, 3.79 g., 47.1%), m.p. 65–75°. Two crystallizations from methanol afforded the analytical sample, m.p. 107–108°; $[\alpha]_D$ +42°; λ_{max} 280 mμ (log ε 3.30) and 287 mμ (log ε 3.20); ν_{max} 1615, 1575, 1507, 810, and 782 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 84.92; H, 9.10.

The latter crystalline fractions eluted with hexane consisted of the 17α-fluoro derivative XXVb (2.35 g., 26.0%), m.p. 96–98° after recrystallization from methanol; $[\alpha]_D$ +62°; λ_{max} 278–280 mμ (log ε 3.31) and 287 mμ (log ε 3.27); ν_{max} 1612, 1580, and 1505 cm.$^{-1}$ (benzene ring).

Anal. Calcd. for $C_{19}H_{25}FO$: C, 79.47; H, 8.74. F, 6.58. Found: 79.37; H, 8.67; F, 7.04.

The final crystalline fractions eluted with hexane–ether (9:1) consisted of the chlorofluoroacetate XXVc (1.0 g., 8.7%), m.p. 145–147° after recrystallization from methanol; $[\alpha]_D$ +41°; λ_{max} 278 mμ (log ε 3.35) and 287 mμ (log ε 3.29); ν_{max} 1780 and 1215 (chlorofluoroacetate ester), 1618, 1585, and 1510 cm.$^{-1}$ (aromatic ring).

Anal. Calcd. for $C_{21}H_{26}ClFO_3$: C, 66.22; H, 6.88; Cl, 9.31; F, 4.99. Found: C, 66.62; H, 6.96; Cl, 8.93; F, 5.30.

Reaction of 17β-Hydroxy-17α-methylandrostan-3-one (XVIIi, 4,5-dihydro) with the Reagent I.—A solution of 1.80 g. (6 mmoles) of the alcohol (XVIIj, 4,5-dihydro) and 2.26 g. (12 mmoles) of the reagent I in tetrahydrofuran (40 ml.) was heated under reflux for 10 min. Recrystallization of the crude product from methanol afforded 0.38 g. of 17,17-dimethyl-18-norandrost-13-en-3-one (XXIIb, 4,5-dihydro), m.p. 140–141°. Chromatography of the mother liquors on Florisil gave an additional 0.56 g. of this product, m.p. 140–141°, for a total yield of 55.4%. Recrystallization from methanol gave the analytical sample, m.p. 142–143°, $[\alpha]_D$ ±0°, ν_{max} 1712 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{30}O$ C, 83.86; H, 10.56. Found: C, 83.36; H, 10.62.

Reaction of 17α-Methylandrost-4-en-17β-ol-3-one (XVIIj) with the Reagent I.—A mixture of 1.8 g. (6 mmoles) of XVIIj, 2.3 g. (12 mmoles) of the reagent I, and dry acetonitrile (25 ml.) was heated under reflux for 5 min. Solvent was distilled on the steam bath under reduced pressure and the residual oil was chromatographed on Florisil (100 g.). The crystalline fractions eluted with hexane–ether (4:1) consisted of 17,17-dimethyl-18-norandrostane-4,13-dien-3-one (XXIIb), 700 mg. (41.4%), m.p.

(47) This reaction was carried out by Dr. I. T. Harrison of these laboratories.

68.70°. Recrystallization from methanol furnished the analytical sample, m.p. 74–75°, $[\alpha]D$ +58°.

Anal. Calcd. for $C_{20}H_{28}O$: C, 84.85; H, 9.92. Found: C, 84.73; H, 9.90.

Reaction of 2-Hydroxymethyl-5α-androst-2-en-17β-ol 17-Acetate (VIIIb) with the Reagent I.—A solution of 1.73 g. (5 mmoles of 2-hydroxymethyl-5α-androst-2-en-17β-ol acetate (VIIIb, 1.0 g., 5 mmoles) of the reagent I, and dry tetrahydrofuran (20 ml.) was warmed gently on the steam bath for 10 min. Solvent was removed by evaporation under reduced pressure and the residual oil was adsorbed from hexane onto Florisil (100 g.). Elution with hexane–ether (9:1) afforded the mixed fluorinated products (see Discussion) (1.13 g., 65%), m.p. 110–117°, m.p. 115–117° after recrystallization from methanol, $[\alpha]D$ +40°. Further elution with the same solvent system yielded the ether XXVII (0.59 g., 38%), m.p. 180–183°, raised to 203–205° by recrystallization from ethyl acetate; $[\alpha]D$ +61°; ν_{max} 1738 and 1255 cm.$^{-1}$ (acetate).

Anal. Calcd. for $C_{44}H_{66}O_5$: C, 78.31; H, 10.16. Found: C, 78.45; H, 10.05.

Acknowledgment.—The authors are indebted to Professor C. Djerassi for the mass spectra and for consultations on their significance.

Steroids. CCLVII.[1] 5,10-Disubstituted Estranes

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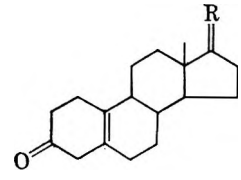
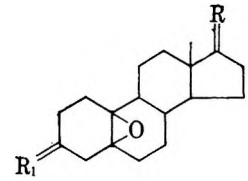
Epoxidations of various 3,17-disubstituted estr-5(10)-enes have been effected. Additions to the 5β,10β-epoxides, with ring opening, gave a variety of 5,10-disubstituted estranes including some stereoisomeric 3,5,10,17-tetrols and their derivatives. Assignment of configuration in estran-3α-ol 5β,10β-epoxide 3-acetates was facilitated by the occurrence of an intramolecular acetylation to give 5α-acetates.

Although strenuous efforts have been directed to the synthesis of 19-norsteroids bearing a 10β-hydrogen,[2] relatively little has been reported concering 19-norsteroids derived by electrophilic addition to estr-5(10)-enes. Rapala and Farkas described the hydrogenation of the latter compounds[3] and, with co-workers, converted a series of estr-5(10)-en-3-ones to estra-4,9-dien-3-ones by addition of bromine across the 5(10)-double bond followed by dehydrohalogenation.[4] An earlier communication from the Syntex laboratories revealed the conversion of 17β-hydroxyestr-5(10)-en-3-one (Ia) to the corresponding 5β,10β-epoxide (IIa).[5] Isomerization of the latter (IIa) with base afforded 10β-hydroxy-19-nortestosterone (IIIa), whose stereochemical identity had been established previously by optical rotatory dispersion studies.[6] Cleavage of the epoxide (IIa) by boron trifluoride led to the corresponding 5α-fluoro-10β-hydroxy derivative.[5] β-Addition of osmium tetroxide to the estra-5(10)-ene (Ia) is described in the patent literature, but no constants are given for the product.[7] Another patent claims that peracid oxidation of estr-5(10)-ene-3,17-dione (Ib) leads to a mixture of 10α- and 10β-hydroxyestr-4-ene-3,17-dione.[8] No firm evidence for the formation of the 10α-hydroxy compound is provided.

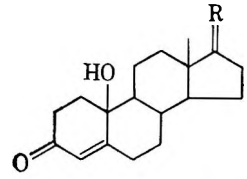
In view of the pre-eminent position occupied by estrane derivatives in the realm of ovulation inhibition by oral administration, we continued researches into electrophilic additions to nonconjugated 5(10)-double bonds.[9]



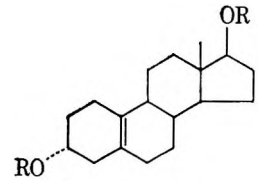
Ia, R = α-H, β-OH
b, R = O



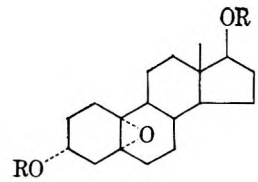
IIa, R = α-H, β-OH; R$_1$ = O
b, R = R$_1$ = O
c, R = R$_1$ = α-H, β-OH
d, R = α-H, β-OH; R$_1$ = α-OH, β-H
e, R = α-H, β-OAc; R$_1$ = α-OAc, β-H
f, R = R$_1$ = α-H, β-OAc
g, R = O; R$_1$ = α-OH, β-H



IIIa, R = αH, βOH
b, R = O



IVa, R=H
b, R=Ac



Va, R=H
b, R=Ac

Peracid oxidation of estr-5(10)-ene-3,17-dione (Ib) afforded the corresponding 5β,10β-epoxide (IIb).[11]

(1) Steroids CCLVI: I. T. Harrison, *Proc. Chem. Soc.*, 110 (1964).

(2) For reviews see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, Chapter 18; F. J. Kakis, "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, Chapter 6; A. Bowers, *Drug Trade News*, 39 (Sept. 16, 1963).

(3) R. T. Rapala and E. Farkas, *J. Org. Chem.*, **23**, 1404 (1958).

(4) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Am. Chem. Soc.*, **82**, 2402 (1960).

(5) J. Pérez Ruelas, J. Iriarte, F. A. Kincl, and C. Djerassi, *J. Org. Chem.*, **23**, 1744 (1958).

(6) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956).

(7) R. L. Pederson and J. C. Babcock, U.S. Patent 2,806,862 (1957).

(8) F. B. Colton, U. S. Patent 2,729,654 (1956).

(9) During the final stages of our work, we became aware of independent and simultaneous studies by Dr. S. G. Levine in this field. Very few of our results overlap with his and, generally, the two separate studies utilized different substituents at C-17. We wish to acknowledge a most friendly exchange of information with Dr. Levine and express thanks for a copy of his recent communication[10] prior to publication.

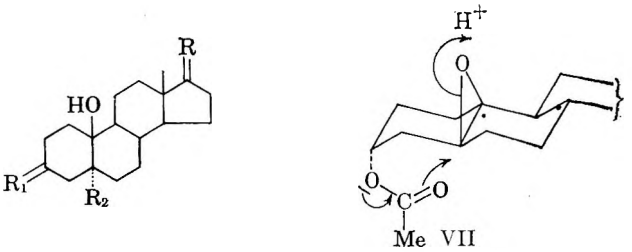
(10) S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Letters*, 1517 (1963).

(11) After completion of our work (1962), R. Gardi, C. Pedrali, and A. Ercoli [*Gazz. chim. ital.*, **93**, 1503 (1963)] reported bromination and epoxidation of estr-5(10)-enes.

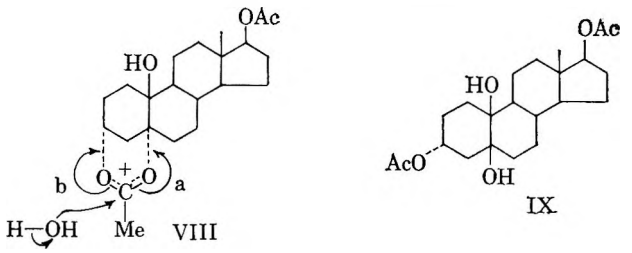
Sodium borohydride reduction of the latter furnished estrane-3β,17β-diol 5β,10β-epoxide (IIc), also obtained by borohydride reduction of the related 3-ketone IIa.[5] A 3β-orientation of the hydroxyl is expected since the β-epoxide function should hinder β-face approach of the reagent to the 3-keto group. When estr-5(10)-ene-3,17-dione or the monoketone Ia[5] was first reduced to a diol (shown in the sequel to be IVa) then subjected to peracid oxidation, estrane-3α,17β-diol 5β,10β-epoxide (IId) was obtained. The derived diacetate IIe was different from that (IIf) prepared from the first diol epoxide IIc. Alkaline hydrolysis of the 3α,17β-diacetate IIe regenerated the diol IId, thus demonstrating the stability of the 3α-hydroxy 5β,10β-epoxide system to mild base treatment. In a further structural correlation estr-5(10)-ene-3α,17β-diol (IVa) was converted to the diacetate IVb and epoxidation carried out to yield the same 5β,10β-epoxide 3α,17β-diacetate IIe as was obtained by the alternative reaction sequence outlined above.

This additional correlation was deemed advisable since, although additions to 5(10)-double bonds normally proceed predominantly from the β-face[5,10] to give products containing the anti-5,9,10-backbone, a homoallylic 3α-hydroxyl might lead to a stereochemically controlled α-face epoxidation,[12] in which case the corresponding 3α-acetate would be expected to give a different epoxide though being a much less effective stereochemically controlling neighboring group.[13] Moreover, the epoxide resulting from oxidation of the 3α,17β-diacetate IVb proved to be different from estrane-3α,17β-diol 5α,10α-epoxide diacetate (Vb) described later in this work. Further chemical proof of the β-orientation of the epoxide in both diols IIc and IId stemmed from conversion (*vide infra*) of each to 10β-hydroxyestr-4-en-3-one derivatives. The epoxide configuration being established, the only possible structural difference rested in the orientation of the 3-hydroxyl group formed by reduction of 5β,10β-epoxy 3-ketones (II) and $\Delta^{5(10)}$-3-ketones (I), respectively. The formation of a 3α-hydroxyl in borohydride[16] reduction of the latter system I was proven convincingly by the following series of reactions.

Treatment of estrane-3α,17β-diol 5β,10β-epoxide (IId) with 2 *N* sulfuric acid–ether two-phase system at room temperature (1.5 hr.) led to the expected tetrol VIa which was converted by chromic acid reagent[17] to the corresponding dione VIb (ν_{max} 1740 and 1705 cm.$^{-1}$). Methanolic potassium hydroxide effected dehydration of this 5α-hydroxy 3-ketone VIb with formation of 10β-hydroxyestr-4-ene-3,17-dione[8,11] (IIIb) which was indistinguishable from an authentic sample.[6,8] In striking contrast exposure of estrane-3α,17β-diol 5β,10β-epoxide diacetate (IIe) to the same two-phase acid reagent furnished the expected estrane-3α,5α,10β-17β-tetrol 3α,17β-diacetate (VIc) as the minor product and a second diactate in abundance. The unknown diacetate was identified as estrane-3α,5α,10β,17β-tetrol 5α,17β-diacetate (VId) by virtue of its chemical properties and from the nuclear magnetic resonance (n.m.r.) spectrum[18] of the ketone VIe which was formed by oxidation of VId with chromic acid reagent.[17] The ketone VIe showed singlet resonances at 49.5 (13β-methyl) and 120.6 c.p.s. (two acetates). However, at lower fields resonance was observable at *ca.* 277 c.p.s., equivalent to only *one* proton in the environment H–C–OAc, and this had the ill-resolved triplet pattern typical of a 17α-proton in steroid 17β-acetates.[19] This information, when coupled with the fact that the ketone VIe underwent facile β-elimination of an acetate with concomitant generation of the 10β-hydroxy-4-en-3-one chromophore, as in III (λ_{max} 236–238 mμ), established that acid treatment of the epoxy diacetate IIe induced acyl migration (3$\alpha \rightarrow$ 5α) leaving an oxidizable 3-hydroxyl group. An indication of the existence of 1,3-diaxially oriented hydroxyl and acetate group was derived from the infrared spectrum of the diacetate VId which shows acetate carbonyl stretching absorption frequencies at 1730 and 1755 cm.$^{-1}$. The latter frequency must arise from the 5α-acetate where the alcoholic oxygen is hydrogen bonded to 3α-hydroxyl leaving the carbonyl with more double bond character. Consideration of the mechanics of this reaction suggests that only when the acetate is oriented 3α does internal participation of the acetate in acid-catalyzed



VIa, R = α-H, β-OH; R_1 = α-OH, β-H; R_2 = OH
b, R = R = O; R_2 = OH
c, R = α-H, β-OAc; R_1 = α-OAc, β-H; R_2 = OH
d, R = α-H, β-OAc; R_1 = α-OH, β-H; R_2 = OAc
e, R = α-H, β-OAc; R_1 = O, R_2 = OAc
f, R = R_1 = α-H, β-OAc; R_2 = OH
g, R = R_1 = α-H, β-OH; R_2 = Me
h, R = R_1 = O; R_2 = Me
j, R = α-H, β-OAc; R_1 = α-OAc, β-H; R_2 = Me



(12) Henbest and Wilson have demonstrated stereochemical control of epoxidation by allylic hydroxyl,[13] but absence of such an effect with certain homoallylic alcohols.[14] However, cases have been reported where homoallylic hydroxyls can exercise stereochemical control in electrophilic additions to the proximate double bond (*e.g.*, Simmons–Smith reaction[15]).

(13) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

(14) H. B. Henbest and B. Nicholls, *ibid.*, 4608 (1957).

(15) S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **81**, 3235 (1961).

(16) Levine and collaborators[9] reported reduction of the 3-keto group in the system I by tritertiarybutoxy aluminum hydride to give a 3α-hydroxyl group whose orientation was established in a different manner from that reported here.

(17) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

(18) N.m.r. spectra were recorded at 60 Mc. for 5–8% w./v. solutions in deuteriochloroform containing a little tetramethylsilane as an internal reference standard. Chemical shifts, ν, are quoted as c.p.s. from the reference and are accurate to ± 1 c.p.s. Coupling constants, J, also expressed in c.p.s., are accurate to ± 0.5 c.p.s. We thank the Universidad Nacional Autónoma de México for time on the Varian A-60 spectrometer.

(19) *Cf.* N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution N.M.R. Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 353.

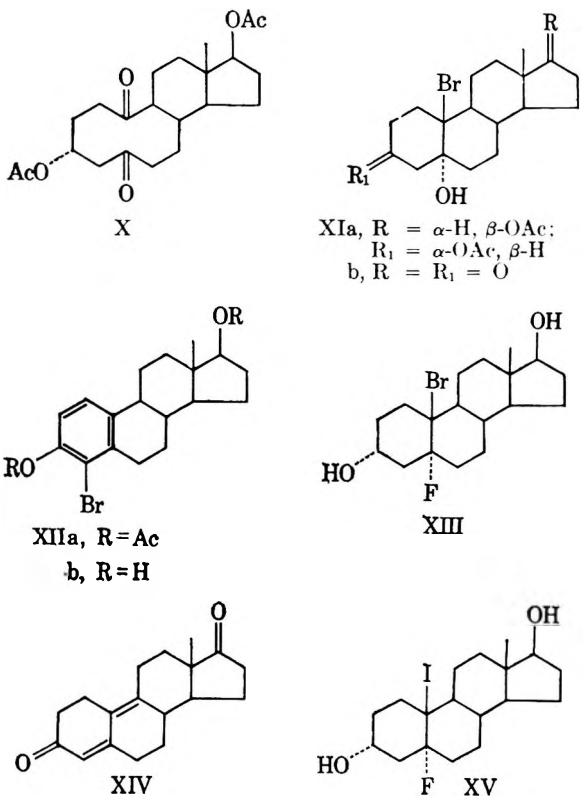
5β,10β-epoxide opening become feasible. Thus, with acid the epoxy diacetate (IIe = VII) affords a charged species VIII which can collapse through the intervention of solvent water, routes a and b, to yield *two* diacetates, VIc and VId, respectively.[20] It was established in a separate experiment that androstane-3α,17β-diol diacetate is insensitive to the mild acid conditions employed in the rearrangement. With lithium aluminum hydride the diacetate VId gave the tetrol Ia (*vide supra*) which was also arrived at by a similar reduction of the disecondary diacetate VIc. Subsequently, acetyl migration followed by oxidation to give VIe was wrought upon the epoxy diacetate IIe in one reaction through the medium of a two-phase chromic acid oxidative system.[21] Alkaline treatment of VIe led to the development of an ultraviolet absorption maximum at 236–238 mμ. The 17-ketone IIIb derived from IIIa by chromic acid oxidation[17] was indistinguishable from a specimen obtained by alkaline treatment of the epoxydione IIb.

When estrane-3β,17β-diol 5β,10β-epoxide diacetate (IIf) was subjected to dilute acid in a water–ether two-phase system, the sole isolable product was estrane-3β,5α,10β-17β-tetrol 3β,17β-diacetate (VIf), resistant to attack by chromic acid reagent.[17] Thus no internal acyl migration was effected in this case, as was expected for the 3β-oriented ester group.

Osmium tetroxide oxidation of estr-5(10)-ene-3α,-17β-diol diacetate (IVb) led to a new tetrol diacetate which we formulate as the 5β,10β-diol IX. Lead tetraacetate cleavage then gave the 5,10-seco-5,10-dione X.

Attention was turned next to the action of methyl Grignard reagent upon the 5β,10β-epoxides. Such treatment of estrane-3β,17β-diol 5β,10β-epoxide (IIc), followed by acetylation, furnished an oily product which was hydrolyzed to the crystalline triol VIg. Oxidation led to the diketone VIh in which a new angular methyl group was disclosed by a second three-proton singlet at 74.4 c.p.s. in the n.m.r. spectrum,[16] in addition to that at 53.0 c.p.s. for the 13β-methyl. Analyses were in agreement with a C-19 structure. The corresponding 3α-alcohol IId afforded with methyl Grignard and then acetylation a triol diacetate VIj which showed three-proton singlet resonances[16] at 48.4 and 68.8 c.p.s., equivalent to *two* methyl groups attached to quaternary carbon as well as acetate proton resonance at 121.8 c.p.s. (two acetates). Accordingly, we formulate this Grignard reaction product at the 5α-methyl-10β-hydroxy derivative VIj. Insufficient material was obtained for further investigation. The 5α-methyl structures are favored since the products then possess the most stable stereochemistry of rings A, B, and C.

Various 10-bromo analogs were prepared and studied. Additions to the 5(10)-double bond are considered to proceed by β-face attack of a positively charged species.[5] Over-all *trans* diaxial addition is then expected to give 5α,10β-adducts. Estr-5(10)-ene-3α,17β-diol diacetate (IVb) readily added hypobromous acid leading to the 10β-bromo derivative XIa. The bromohydrin XIa on exposure to methanolic sodium methoxide underwent an internal displacement of bromide with formation of the 5α,10α-epoxide Va, purified through the diacetate Vb. Similarly estr-5(10)-ene-3,17-dione (Ib) was converted to the crude bromohydrin XIb. However, reaction of the latter with methoxide and chromatography of the product over silica gel led to only a small amount of solid showing strong ultraviolet absorption at 232–234 mμ, tentatively considered to be 10β-bromoestr-4-ene-3,17-dione. Hydrochloric acid–acetic acid reagent promoted dehydration of this unsaturated ketone to afford estrone. In an attempt to obtain more of the α-epoxide Va, oily impure fractions containing some bromohydrin XIa were subjected to methoxide ion. Chromatography of the crude product over silica gel led to an amorphous solid. Acetylation of the latter furnished a new crystalline compound giving a positive Beilstein reaction. Formulation of this compound as 4-bromoestradiol diacetate (XIIa) stems primarily from spectral analyses and is supported by elemental analyses of both the diacetate and the derived diol XIIb. Both the diacetate and diol showed ultraviolet and infrared spectral characteristics of a nonconjugated aromatic ring. In the n.m.r. spectrum the diacetate XIIa showed three-proton resonance singlets at 48 (13β-methyl), 122 (17β-acetate), and 139 c.p.s. (phenolic acetate), and an AB quartet centered at 426 c.p.s. ($\Delta\nu$ 24 c.p.s., J = 8.5 c.p.s.) for the adjacent C-1 and C-2 protons. Since no further aromatic proton resonance was visible, the compound is substituted at both C-3 and C-4. Mechanistically, 4-bromoestradiol derivatives may arise from the bromohydrin XI by hydrolysis and dehydration to a Δ^4-steroid followed by further addition of hypobromous acid to furnish a 4β,10β-dibromo-3α,5α,17β-triol. Elimination of quaternary bromine and hydroxyl would lead to a sensitive diene which requires only oxidation to give 4-bromoestradiol.



(20) Excellent evidence for the existence of charged intermediates such as VIII was reported very recently by J. W. Blunt, M. P. Hartshorn, and D. N. Kirk [*Chem. Ind.* (London), 1955 (1963)] who isolated the perchlorate salt of such an ion in the cholestane series.

(21) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

N-Bromoacetamide–hydrofluoric acid halogenated the 5(10)-double bond of the diol IVa to yield the 10β-bromo-5α-fluoro derivative XIII. The latter was oxidized with chromic acid[17] to the corresponding 3,17-dione which, without purification, was dehydrohalogenated through the agency of sodium methoxide in methanol to obtain estra-4,9-diene-3,17-dione (XIV).

Finally, the 5(10)-enediol (IVa) was converted to the 5α-fluoro-10β-iodo derivative XV by means of N-iodosuccinimide–hydrofluoric acid.

Levine and co-workers[9] have already discussed the conformational factors which lead to a predominance of 3α-alcohol in the reduction of estr-5(10)-en-3-ones (I).

Experimental[22]

Estrane-3,17-dione 5β,10β-Epoxide (IIb).—To an ice-cold solution of estr-5(10)-ene-3,17-dione (Ib, 6 g.) in methylene dichloride (100 ml.) was added cold ethereal 3.6 *N* monoperphthalic acid (100 ml.), and the whole was stored at 0° for 16 hr. After being diluted with ethanol, the solution was extracted with 10% aqueous sodium bicarbonate, washed with water, dried, and evaporated. Crystallization of the residual solid from acetone–hexane yielded the the 5β,10β-epoxide (5.5 g.). A pure sample showed m.p. 145–147°, $[\alpha]_D$ +39°, ν_{max} 1712 and 1740 cm.$^{-1}$; lit.[11] m.p. 155–156° for a sample recrystallized from methanol, $[\alpha]_D$ +39°.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; O, 16.64. Found: C, 75.05; H, 8.54; O, 16.52.

Estrane-3β,17β-diol 5β,10β-Epoxide (IIc).—Reduction of the above dione epoxide IIb (1 g.) dissolved in methanol (70 ml.) with a methanolic solution of sodium borohydride (400 mg. in 17 ml.) during 0.75 hr. at room temperature and work-up in the normal manner gave the diol IIc (340 mg.), recrystallized from acetone–hexane to obtain a pure specimen, m.p. 149–150°, $[\alpha]_D$ +89°.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65; O, 16.42. Found: C, 73.89; H, 9.46; O, 16.28.

The diacetate epoxide IIf was obtained by treatment of the above diol IIc with cold acetic anhydride–pyridine followed by work-up in the usual manner. A sample recrystallized from methylene chloride–hexane showed m.p. 108–110°, $[\alpha]_D$ −11°, ν_{max} 1740 and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; O, 21.25. Found: C, 69.81; H, 8.67; O, 21.31.

Estr-5(10)-ene-3α,17β-diol (IVa).—A suspension of estr-5(10)-ene-3,17-dione (Ib, 8 g.) in methanol (300 ml.) was mixed with a solution of sodium borohydride (8 g.) in the same solvent (150 ml.) and kept at room temperature for 0.75 hr. Dilution with water precipitated a solid which was collected (7.1 g.) and crystallized from methanol–acetone to furnish the diol IVa (5 g.), m.p. 203–208°. Further recrystallizations gave the analytical sample, m.p. 210–212°, $[\alpha]_D$ +178° (ethanol), ν_{max} 3210 cm.$^{-1}$; lit.[23] m.p. 208–209°, $[\alpha]_D$ + 122.5° (chloroform).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21; O, 11.58. Found: C, 78.19; H, 10.28; O, 11.56.

The corresponding diacetate IVb was prepared by exposure of the diol IVa to warm acetic anhydride–pyridine and work-up in the normal manner. Crystallizations of the product from methylene chloride–methanol afforded a pure specimen, m.p. 119–120°, $[\alpha]_D$ +130°, ν_{max} 1740 and 1245 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; O, 17.75. Found: C, 73.39; H, 9.07; O, 17.74.

Estrane-3α,17β-diol 5β,10β-Epoxide (IId).—Peracid oxidation of estr-5(10)-ene-3,17β-diol (IVa) by the procedure described above led to the corresponding 5β,10β-epoxide IId, m.p. 159–161°, $[\alpha]_D$ +79°, after crystallization from acetone–hexane; lit.[11] m.p. 154–155°, $[\alpha]_D$ +78°.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65; O, 16.42. Found: C, 73.62; H, 9.78; O, 16.75.

Estrane-3α,17β-diol 5β,10β-Epoxide Diacetate (IIe). A.—Acetylation of the above diol epoxide (IId) with acetic anhydride–pyridine and work-up in the normal manner afforded the diacetate derivative IIe which, after chromatography over silica and recrystallization from methylene dichloride–hexane, had m.p. 173–174°, $[\alpha]_D$ +54°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; O, 21.25. Found: C, 70.29; H, 8.41; O, 21.11.

B.—Peracid oxidation of estr-5(10)-ene-3α,17β-diol diacetate (IVb) by the procedure described above led to the 5β,10β-epoxide IIe, purified by recrystallization from methylene dichloride–hexane to furnish a sample, m.p. 172–174°, indistinguishable from that prepared by the above alternative route on the basis of comparative infrared spectra and mixture melting point (no depression).

The epoxide diacetate IIe (1.2 g.) was dissolved in methanol (50 ml.) containing potassium hydroxide (2 g.), and the soluton was kept under reflux during 1 hr. Neutralization was then effected by adding acetic acid. To the residue remaining after evaporation to dryness was added water, and the insoluble material (820 mg.) was filtered off and recrystallized from acetone–hexane to give the above diol IId, m.p. 99–101° and 159–161°, $[\alpha]_D$ +80°.

Estrane-3α,5α,10β,17-tetrol (VIa).—A solution of estrane-3α,17β-diol 5β,10β-epoxide (IId, 380 mg.) in ether (75 ml.) was stirred vigorously at room temperature with 3.5% aqueous sulfuric acid (3 ml.) for 2 hr. After dilution with water the two-phase system was extracted with ethyl acetate. The extracts were washed with water to neutrality and dried (Na_2SO_4), and the residue was crystallized from acetone–hexane and acetone–methanol to yield the tetrol VIa (70 mg.), m.p. 243–244°, $[\alpha]_D$ −11° (in ethanol), ν_{max} 3330 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74; O, 20.62. Found: C, 69.35; H, 9.92; O, 20.46.

5α,10β-Dihydroxyestrane-3,17-dione (VIb).—The tetrol VIa (50 mg.) in cold acetone (5 ml.) was treated dropwise with chromic acid reagent[17] until an excess of oxidant was present. Care was taken to maintain the reaction temperature at or below 10°. Addition of water caused precipitation of a solid which was collected and recrystallized from ether–hexane, thereby affording the diketone VIb (25 mg.), m.p. 223–225°; $[\alpha]_D$ +118° (in ethanol); ν_{max} 3480, 3550, 1740, and 1705 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.13; O, 21.31. Found: C, 70.58; H, 8.41; O, 21.39.

A small sample of the dione VIb in alkaline methanol developed strong ultraviolet absorption at 238–240 mμ indicative of formation of 10β-hydroxyestr-4-ene-3,17-dione (IIIb). On a larger scale, dilution of the alkaline alcoholic solution with water and filtration yielded a crystalline solid which, after purification, proved to be identical with authentic specimen of the enone IIIb.[6,8]

Acid-Catalyzed Rearrangement of Estrane-3α,17β-diol 5β,10β-Epoxide Diacetate (IIe).—A solution of the 3α,17β-diacetate 5β,10β-epoxide IIe (450 mg.) in ether (100 ml.) was stirred vigorously with 3.5% aqueous sulfuric acid (4 ml.) at room temperature for 2 hr. Work-up of the reaction mixture as outlined above furnished a solid (430 mg.) from which was obtained by several crystallizations from methylene chloride–hexane a pure sample of estrane-3α,5α,10β,17β-tetrol 5α,17β-diacetate (VId), m.p. 229–232°; $[\alpha]_D$ +27° (in dioxane); ν_{max} 3460, 1755 (5α-OAc), 1730 (17β-OAc), and 1245 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.33. Found: C, 67.35; H, 8.76; O, 23.98.

From the mother liquors of the diacetate VId was isolated, by chromatography over silica, an isomeric product. Several crystallizations from methylene chloride–hexane gave a pure specimen of estrane-3α,5α,10β,17β-tetrol 3α,17β-diacetate (VIc), m.p. 191–192°; $[\alpha]_D$ −28°; ν_{max} 3630, 3550, 1740, and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.33. Found: C, 67.25; H, 8.75; O, 24.08.

Reduction of the tetrol 5α,17β-diacetate VId (140 mg.) in tetrahydrofuran (30 ml.) at reflux for 2 hr. with lithium aluminum hydride (100 mg.) and work-up in the usual manner led to the 3α,5α,10β,17β-tetrol VIa (120 mg.), m.p. 243–245°, undepressed by admixture with the sample described above.

Reduction of the tetrol 3α,17β-diacetate VIc (60 mg.) by the same procedure led to the same product VIa (25 mg.).

(22) Except where stated otherwise, melting points are uncorrected, optical rotations are for chloroform solutions, ultraviolet spectra were obtained with ethanol solutions, and infrared spectra were run with potassium bromide disks. Microanalyses were performed either by Mid-West Micro Laboratories, Indianapolis 20, Ind., or by Dr. A. Bernhardt, Mulheim (Ruhr), Germany.

(23) J. A. Hartman [*J. Am. Chem. Soc.*, **77**, 5451 (1955)] obtained this compound but assigned the incorrect[16] stereochemistry at C-3.

5α,10β,17β-Trihydroxyestran-3-one 5α,17β-Diacetate (VIe). A.—Estrane-3α,17β-diol 5β,10β-epoxide diacetate (IIe, 150 mg.) was dissolved in ether (50 ml.). A solution of chromic acid (134 mg. of sodium chromate in 0.6 ml. of 35% aqueous sulfuric acid) was added and the two-phase system[21] was stirred for 2 hr. at room temperature then diluted with water and ether. The ether layer was washed with aqueous bicarbonate and with water to neutrality, dried, and evaporated to yield a solid residue, m.p. 160–170° (85 mg.). Recrystallization from methylene chloride–hexane furnished an analytical specimen of 5α,10β,17β-trihydroxyestran-3-one 5α,17β-diacetate (VIe), m.p. 178–183°; $[\alpha]_D$ +29°; ν_{max} 3430, 1738, 1712, and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.29; H, 8.48.

B.—Estrane-3α,5α,10β,17β-tetrol 5α,17β-diacetate (VId, 50 mg.) in cold acetone (10 ml.) solution was treated dropwise with chromic acid solution[17] until an excess of reagent was apparent. Dilution with water caused precipitation of a solid (35 mg.), m.p. 170–178°, from which was obtained by crystallizations from methylene chloride–hexane a sample of the 3-ketone VIe, indistinguishable from that described above.

With acid or alkali the 5α-acetoxy 3-ketone VIe developed strong ultraviolet absorption at 236–238 mμ.

Action of Ether–Aqueous Acid on Androstane-3α,17β-diol Diacetate.—To a solution of androstane-3α,17β-diol diacetate (30 mg.) in ether (30 ml.) was added aqueous sulfuric acid (0.3 ml. of 35%) and the whole was stirred at room temperature for 4 hr. Dilution with water and extraction with ether led, by evaporation of the washed ether extracts, to recovered starting material. Examination of the mother liquors from crystallization revealed only traces of by-products.

Acid-Catalyzed Hydration of Estrane-3β,17β-diol 5β,10β-Epoxide Diacetate (IIf).—A solution of the 5β,10β-epoxide 3β,17β-diacetate IIf (1 g.) in ether (50 ml.) was treated with aqueous sulfuric acid (1 ml. of 35%) by the method previously outlined. There resulted an amorphous solid (800 mg.) from which was obtained by chromatography over silica gel (100 g.) and elution with hexane–ether estrane-3β,5α,10β,17β-tetrol 3β,17β-diacetate (VIf, 200 mg.). Recrystallization from acetone–hexane gave a pure sample, m.p. 233–235°; $[\alpha]_D$ −15°; ν_{max} 3510, 1730, and 1255 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.33. Found: C, 67.42; H, 8.59; O, 24.28.

A solution of this diacetate VIf in acetone did not decolorize Jones reagent.[17]

Estrane-3α,5β,10β,17β-tetrol 3α,17β-Diacetate (IX).—Osmium tetroxide (1.0 g.) was added to a solution of estr-5(10)-ene-3α,17β-diol diacetate (IVb, 1.0 g.) in a mixture of chloroform (30 ml.) and pyridine (30 ml.). After 6 days at room temperature, the reaction mixture was diluted with ethyl acetate (75 ml.). Hydrogen sulfide was then bubbled through the solution for 30 min. when the insoluble salts were removed by filtration over Celite. Removal of the solvent gave a product which was adsorbed from benzene onto alumina (50 g.). Elution with benzene–ether (70:30, 600 ml.) afforded estrane-3α,5β,10β,17β-tetrol 3α,17β-diacetate (IX, 330 mg.), m.p. 165–172° raised by crystallizations from acetone–hexane to 187–189°, $[\alpha]_D$ +31°.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.34. Found: C, 67.31; H, 8.70; O, 23.95.

3α,17β-Dihydroxy-5,10-secoestrane-5,10-Dione Diacetate (X).—Lead tetraacetate (1.46 g.) was added with stirring to a solution of estrane-3α,10β,5β,17β-tetrol 3α,17β-diacetate (IX, 1.0 g.) in dry benzene (85 ml.) and glacial acetic acid (85 ml.) at room temperature. After 15 min. the reaction mixture was poured into ice–water and the product was isolated by extraction with benzene. The combined benzene solutions were washed several times with water and dried over sodium sulfate. Removal of the solvent and crystallization from acetone–hexane gave 3α,17β-dihydroxy-5,10-secoestrane-5,10-dione acetate (X, 810 mg.), m.p. 139–142° raised by several crystallizations from the same solvent mixture to 147–149°, $[\alpha]_D$ −43°.

Anal. Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22; O, 24.46. Found: C, 67.27; H, 8.13; O, 24.25.

5α-Methylestrane-3β,10β,17β-triol (VIg).—A solution of estrane-3β,17β-diol 5β,10β-epoxide (IIc, 1 g.) in benzene (50 ml.) was treated with methyl Grignard reagent (20 ml. of a 3 *N* ethereal solution) at reflux during 18 hr. under a nitrogen atmosphere. The cooled reaction mixture was then treated with ammonium chloride and extracted with ethyl acetate, washing with 2% aqueous sulfuric acid and with water to neutrality. Evaporation of the dried (Na_2SO_4) solution yielded an amorphous solid (960 mg.) which was promptly acetylated with acetic anhydride (2 ml.) and pyridine (10 ml.) at 0° in the normal manner. There was obtained a solid acetylated derivative which was chromatographed over silica. Elution with hexane–ether (90:10) afforded 550 mg. of a solid. This material was treated under reflux for 1 hr. with methanolic potassium carbonate (200 mg. in 20 ml.). Dilution with water, extraction with ethyl acetate as usual, and recrystallization of the resultant solid (170 mg.) from acetone–hexane gave a product considered to be 5α-methylestrane-3β,-10β-17β-triol (VIg, 110 mg.), m.p. 237–240°, $[\alpha]_D$ +29° (in ethanol), ν_{max} 3280 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46; O, 15.56. Found: C, 73.76; H, 10.48; O, 15.60.

5α-Methyl-10β-hydroxyestrane-3,17-dione (VIh).—Oxidation of the above 3β,10β,17β-triol (VIg, 2 g.) in acetone (200 ml.) with chromic acid reagent[15] in the normal way yielded, after isolation of the product (1.8 g.), chromatography, and recrystallization from methylene chloride, a pure sample of the 3,17-dione VIh, m.p. 218–219°; $[\alpha]_D$ +128°; ν_{max} 3450, 1740, and 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27; O, 15.77. Found: C, 74.78; H, 9.29; O, 15.86.

5α-Methylestrane-3α,10β,17β-triol 3α,17β-Diacetate (VIj).—Treatment of estrane-3α,17β-diol 5β,10β-epoxide (IId, 920 mg.) in benzene (75 ml.) with ethereal methyl magnesium bromide (50 ml. of 3 *N*) by the procedure described above furnished crude amorphous 5α-methylestrane-3α,10β,17β-triol (VIk, 918 mg.). By acetylation in the usual manner there could be isolated the corresponding diacetate VIj (835 mg.) which was chromatographed over silica (100 g.). A pure specimen separated as prisms from acetone–hexane and had m.p. 233–234°; $[\alpha]_D$ −12°; ν_{max} 3520, 1735, 1710, 1250, and 1265 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25; O, 20.38. Found: C, 70.58; H, 9.39; O, 20.50.

10β-Bromoestrane-3α,15α,17β-triol 3α,17β-Diacetate (XIa).—A solution of estr-5(10)-ene-3α,17β-diol diacetate (IV, 1.37 g.) in dioxane (12 ml.) was treated with aqueous perchloric acid (1.8 ml. of 70%) and N-bromosuccinimide (700 mg.) at 10° with stirring during 0.75 hr. The precipitate which formed on dilution with water was collected and washed with water. This product, 820 mg., m.p. 98–105°, was placed on a column of silica (100 g.) and subjected to chromatographic separation, whereupon the 10β-bromo diacetate XIa (230 mg.) was obtained. A sample recrystallized from acetone–ether showed m.p. 157–159°; $[\alpha]_D$ −34°; ν_{max} 3560, 1740, and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{33}BrO_5$: C, 57.76; H, 7.27; Br, 17.47; O, 17.49. Found: C, 58.02; H, 6.99; Br, 17.78; O, 17.77.

Estrane-3α,17β-diol 5α,10α-Epoxide Diacetate (Vb).—The bromohydrin XIa (615 mg.) was dissolved in a mixture of methylene chloride and methanol (50 ml. of 1:5) and treated at 10° with a solution of methanolic sodium methoxide (3 ml. of 1 *N*) during 15 min. The mixture was then concentrated *in vacuo* to one-third its original volume and water was added. Ethyl acetate extracted the precipitated solid and this solution was washed with water to neutrality, dried (Na_2SO_4), and evaporated to leave estrane-3α,17β-diol 5α,10α-epoxide (Va) as an amorphous solid. Acetylation of the diol Va in the usual way with acetic anhydride–pyridine reagent led to the corresponding diacetate Vb. This was chromatographed over alumina and crystallized from methylene chloride–hexane giving 380 mg. of product, m.p. 117–122°. The pure specimen separated from methanol–water as prisms and had m.p. 124–125°, $[\alpha]_D$ +71°, ν_{max} 1735 and 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; O, 21.75. Found: C, 70.2; H, 8.72; O, 21.66.

Conversion of Estr-5(10)-ene-3,17-dione to Estrone.—A solution of estr-5(10)-ene-3,17-dione (Ib, 1.59 g.) in dioxane (15 ml.) was treated with aqueous perchloric acid (12.1 ml. of 0.6 *N*) and N-bromoacetamide (345 mg.) at −5° as outlined above to form 10β-bromo-5α-hydroxyestrane-3,17-dione (XIb). The crude product (1.04 g.) was exposed to methanolic sodium methoxide (50 ml. of 1 *N*) during 15 min. at 10°, and worked up as described above. Thereby was obtained a small quantity of a product considered to be 10β-bromoestr-4-ene-3,17-dione. After recrystallization from methylene chloride–ether the crystals totaled 50 mg., m.p. 188–195°, λ_{max} 232–234 mμ (log ε 4.12). This supposed 10β-bromo-4-en-3-one (20 mg.) in acetic acid (2 ml.) was treated with hydrogen chloride gas and kept at room temperature during 18 hr. Dilution with water caused formation of a precipitate. The latter was collected and crystal-

lized from methylene chloride–hexane to afford estrone (5 mg.), m.p. 242–252°, showing an ultraviolet absorption maximum at 280–282 mμ (log ε 3.30) and an infrared spectrum essentially identical with that of authentic estrone.

4-Bromoestra-1,3,5(10)-triene-3,17β-diol Diacetate (XIIa).—Oily fractions totaling 1.2 g. containing the bromohydrin XIa were obtained from the column chromatography of this bromohydrin (*vide supra*) and from recrystallization of the mother liquors. Treatment with methanolic sodium methoxide (50 ml. of 1 *N*) during 15 min. at 10°, followed by work-up as described above, then acetylation in the normal manner (Ac_2O–pyridine) yielded an oily product (700 mg.), where solid 5α,10α-epoxide Vb had been obtained earlier. The oil was placed on a column of silica (100 g.) and elution with benzene–hexane (40:60) gave a new product (310 mg.), less polar than epoxy diacetate Vb which was eluted in later fractions. Recrystallization of this new product from methylene chloride–hexane gave 4-bromoestra-1,3,5(10)-triene-3,17β-diol diacetate (XIIa), the analytical specimen of which showed m.p. 171–173°; $[\alpha]D$ +24°; ν_{max} 1770 and 1200 (phenolic acetate), 1735, and 1255 cm.$^{-1}$ (acetate); λ_{max} 268–270 (log ε 2.59) and 277 mμ (log ε 2.56); λ_{max} (for alkaline ethanol solution) 244 (log ε 3.86) and 304 mμ (log ε 3.87).

Anal. Calcd. for $C_{22}H_{27}BrO_4$: C, 60.68; H, 6.39; Br, 18.36; O, 14.70. Found: C, 60.31; H, 6.41; Br, 18.68; O, 14.60.

4-Bromoestra-1,3,5(10)-triene-3,17β-diol (XIIb).—Potassium carbonate (400 mg.) was added to a mixture of the above diacetate XIIa (160 mg.) and methanol (20 ml.), and the whole was maintained at reflux during 0.75 hr. before being neutralized with acetic acid. Concentration *in vacuo* to 3–4-ml. volume was followed by dilution with water (50 ml.). The resultant precipitate was collected and washed with water, giving 110 mg. of the diol XIIb, m.p. 160–190°. Chromatographic purification over alumina followed by one crystallization from methylene chloride–hexane afforded a crystalline solid (40 mg.), m.p. 203–215°, further purified by recrystallization to m.p. 209–212°; $[\alpha]D$ +41° (in ethanol); ν_{max} 3580, 3300, 1615, 1565, and 1495 cm.$^{-1}$; λ_{max} 284 mμ (log ε 3.26); λ_{max} (for alkaline ethanol solution) 244 (log ε 3.88) and 314 mμ (log ε 3.51).

Anal. Calcd. for $C_{18}H_{23}BrO_2$: C, 61.53; H, 6.59; Br, 22.75; O, 9.10. Found: C, 61.52; H, 6.96; Br, 23.16; O, 9.36.

10β-Bromo-5α-fluoroestrane-3α,17β-diol (XIII).—A precooled (*ca.* −80°) suspension of estr-5(10)-ene-3α,17β-diol (IVa, 500 mg.) and N-bromoacetamide (270 mg.) in dry methylene dichloride (20 ml.) was added with stirring to a solution of anhydrous hydrogen fluoride (3.41 g.) in tetrahydrofuran (5.98 g.) at *ca.* −80° (acetone–Dry Ice). After stirring at −80° for 1 hr. and then at 0° for a further 16 hr., the reaction mixture was added to an excess of ice-cold sodium bicarbonate solution. Isolation with methylene dichloride and crystallization of the product from methanol afforded 10β-bromo-5α-fluoroestrane-3α,17β-diol (XIII, 330 mg.), m.p. 157–161° raised by several crystallizations from methanol to 169–171° dec., $[\alpha]D$ 0°.

Anal. Calcd. for $C_{18}H_{28}BrFO_2$: C, 57.62; H, 7.55; Br, 21.29; F, 5.06. Found: C, 57.48; H, 7.48; Br, 22.28; F, 4.88.

Estra-4,9-diene-3,17-dione (XIV).—An excess of 8 *N* chromic acid (permanent orange coloration) was added to a solution of 10β-bromo-5α-fluoroestrane-3α,17β-diol (XIII, 500 mg.) in acetone (80-ml.) at 0°. After a further 2 min. at 0°, addition of water and isolation with methylene chloride afforded the crude oxidation product which was immediately heated under reflux for 3 hr. in methanol solution (150 ml.) containing sodium acetate (1.5 g.). Addition of ice–water and filtration gave a solid product which was adsorbed from hexane–benzene (1:1) onto alumina (25 g.). Elution with hexane–benzene (30:70, 500 ml.) and crystallization from acetone–hexane afforded estra-4,9-diene-3,17-dione (XIV, 120 mg.), m.p. 139–141° raised by crystallizations from the same solvent mixture to 141–143°, $[\alpha]D$ −152°, λ_{max} 300–302 mμ (log ε 4.34), lit.[4] m.p. 130–131°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20; O, 11.84. Found: C, 80.24; H, 8.29; O, 11.61.

5α-Fluoro-10β-iodoestrane-3α,17β-diol (XV).—A precooled (*ca.* −80°) suspension of estr-5(10)-ene-3α,17β-diol (IVa, 500 mg.) and N-iodosuccinimide (384 mg.) in methylene chloride (50 ml.) was added to a solution of anhydrous hydrogen fluoride (10.0 g.) in tetrahydrofuran (17.6 g.) at *ca.* −80° (acetone–Dry Ice). After stirring at −80 for 1.5 hr. and then at 0° for a further 16 hr., the reaction mixture was added to an excess of ice-cold sodium bicarbonate solution. Isolation with methylene chloride and crystallization from methylene chloride–hexane afforded 5α-fluoro-10β-iodoestrane-3α,17β-diol (XV), m.p. 128–130° dec., unchanged after several crystallizations from the same solvent mixture.

Anal. Calcd. for $C_{18}H_{28}FIO_2$: C, 51.2; H, 6.68; F, 4.50; I, 30.05. Found: C, 51.23; H, 6.84; F, 4.78; I, 30.23.

The Photochemical Reaction of Nitrobenzene and Tolane

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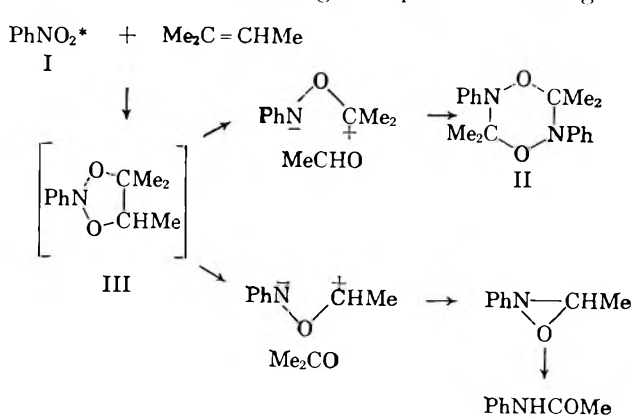
Products arising from the photochemical reaction of nitrobenzene and diphenylacetylene have been identified. Diphenylketene is postulated as an intermediate in the formation of benzophenone anil (V), carbon dioxide, and the β-lactam of β-anilinotetraphenylpropionic acid (VIII). Mechanistic pathways are discussed to account for the formation of dibenzanilide (VI) and other products. The photochemical rearrangements of N-phenylphenylbenzoyl nitrone (XVII) to dibenzanilide and of triphenyl nitrone to N,N-diphenylbenzamide are reported.

Büchi and Ayer[2] found that photochemically excited nitrobenzene (I) can effect cleavage of an olefinic double bond in a manner analogous to that of ozone. On irradiation of nitrobenzene with 2-methyl-2-butene, they obtained acetaldehyde, acetone, acetanilide, and a dimer (II). They postulated a 1,3,2-dioxazolidine intermediate (III), which is an analog of a primary ozonide.

The present paper is concerned with the action of photochemically excited nitrobenzene on tolane (IV). A petroleum ether (b.p. 38.7–57.9°) solution of tolane and nitrobenzene was irradiated for 3 days under an atmosphere of nitrogen with a mercury arc lamp (Hanovia Type A). A Pyrex filter was employed to remove the lower wave lengths capable of exciting to-



(1) Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, Zurich, Switzerland.

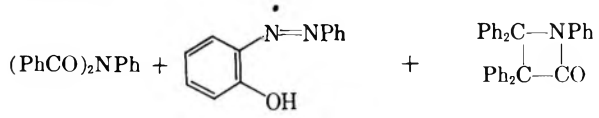
(2) G. Büchi and D. E. Ayer, *J. Am. Chem. Soc.*, **78**, 689 (1956).

lane.[3] Tolane, itself, is known to undergo photochemical transformations.[4]

The products of the photochemical reaction of nitrobenzene and tolane are benzophenone–anil (V), carbon dioxide, nitrosobenzene, dibenzanilide (VI), 2-hydroxyazobenzene (VII), and the β-lactam of N-phenyl-β-aminotetraphenylpropionic acid (VIII). Recovered starting materials and tars were also obtained.

$$\underset{\text{I}}{\underset{0.10\text{ mole}}{PhNO_2^*}} + \underset{\text{IV}}{\underset{0.10\text{ mole}}{PhC{\equiv}CPh}} \longrightarrow$$

$$\underset{12\text{ mmoles}}{Ph_2C{=}NPh} + \underset{20\text{ mmoles}}{CO_2} + \underset{3.2\text{ mmoles}}{PhNO} +$$



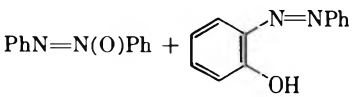
$$\underset{18\text{ mmoles}}{\text{VI}} \qquad \underset{0.4\text{ mmole}}{\text{VII}} \qquad \underset{0.9\text{ mmole}}{\text{VIII}}$$

When the photolysis is carried out in aqueous dioxane, the products are diphenylacetic acid (IX), dibenzanilide, benzil, azoxybenzene, and 2-hydroxyazobenzene. Recovered tolane (16 mmoles) and some intractable material were also isolated.

$$\underset{\text{excess}}{PhNO_2^*} + \underset{50\text{ mmoles}}{PhC{\equiv}CPh} + \underset{\text{excess}}{H_2O} \longrightarrow$$

$$\underset{\text{IX}}{Ph_2CHCOOH} + PhN(COPh)_2 + PhCOCOPh +$$

$$\underset{3.2\text{ mmoles}}{} \qquad \underset{20\text{ mmoles}}{} \qquad \underset{6.3\text{ mmoles}}{}$$

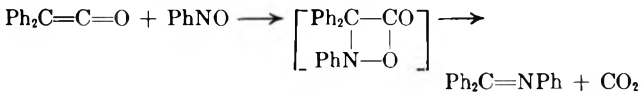


$$\underset{5.5\text{ mmoles}}{} \qquad \underset{0.5\text{ mmole}}{}$$

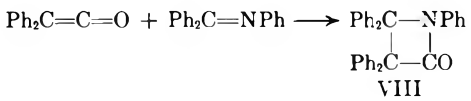
Diphenylketene as an Intermediate.—The reaction probably proceeds through the intermediacy of diphenylketene (X). Diphenylketene can be formed by transfer of an oxygen atom from nitrogen to acetylenic carbon, followed by cleavage of nitrosobenzene and migration of a phenyl group.

$$PhNO_2^* + PhC{\equiv}CPh \longrightarrow PhNO + \underset{\text{X}}{Ph_2C{=}C{=}O}$$

The formation of benzophenone anil and carbon dioxide can be explained by the reaction of diphenylketene with nitrosobenzene, first observed by Staudinger and Jelagin.[5]



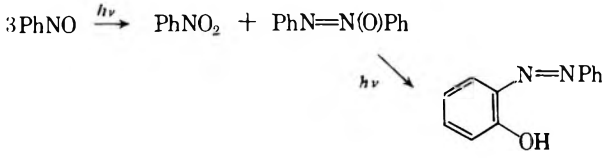
The β-lactam (VIII) can form by condensation of diphenylketene and benzophenone anil. This condensation is, in fact, a method for preparing the β-lactam (VIII).[5]



When the irradiation of tolane and nitrobenzene is carried out in aqueous dioxane, then benzophenone anil, carbon dioxide, and the β-lactam (VIII) are absent in the products, since diphenylketene is rapidly hydrolyzed to diphenylacetic acid.

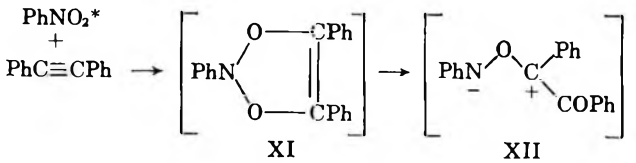
$$Ph_2C{=}C{=}O + H_2O \longrightarrow Ph_2CHCOOH$$

2-Hydroxyazobenzene.—The isolation of 2-hydroxyazobenzene (VII) is not surprising since this compound is a known product of the photochemical disproportionation of nitrosobenzene.[6] It can be prepared by the photochemical rearrangement of azoxybenzene.[7]



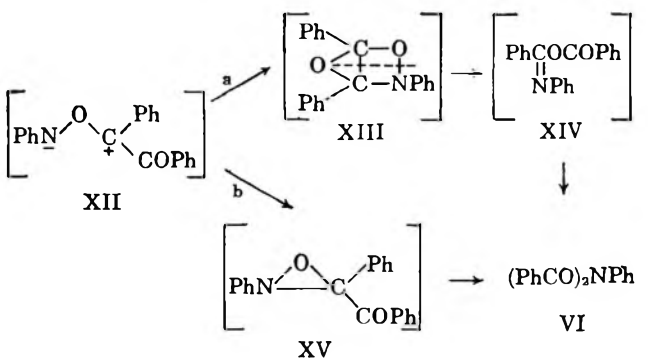
VII

Dibenzanilide.—As in the photochemical reaction of nitrobenzene and olefins, an analogy to ozonolysis can be postulated for the reaction with diphenylacetylene. Nitrobenzene and tolane can form an unstable 1,3,2-dioxazole (XI), analogous to an acetylenic primary ozonide.[8] This intermediate can cleave at one of the weak O–N bonds to form the zwitterion XII. The



XI XII

zwitterion is then capable of rearranging to dibenzanilide (VI). One possible pathway (a) involves the strained intermediate XIII, which would be expected to cleave at its weakest bonds to form XIV, the mixed anhydride of benzoic acid and benzanilide. The intermediate XIV would not be isolated because it can rearrange to the more stable dibenzanilide VI. Attempts to prepare XIV have led to the formation of dibenzanilide.[9] The questionable intermediate XIII casts some doubt on this mechanism. A more likely pathway (b) would proceed through the oxazirane intermediate XV, which could undergo benzoyl migration to dibenzanilide.



XII XIII XIV XV VI

(3) For ultraviolet spectra of tolane and nitrobenzene, respectively, see (a) H. H. Schlubach and V. Franzen, *Ann.*, **573**, 110 (1951); and (b) D. W. Sherwood and M. Calvin, *J. Am. Chem. Soc.*, **64**, 1351 (1942).

(4) G. Büchi, C. W. Perry, and E. W. Roff, *J. Org. Chem.*, **27**, 4106 (1962).

(5) H. Staudinger and S. Jelagin, *Ber.*, **44**, 373 (1911).

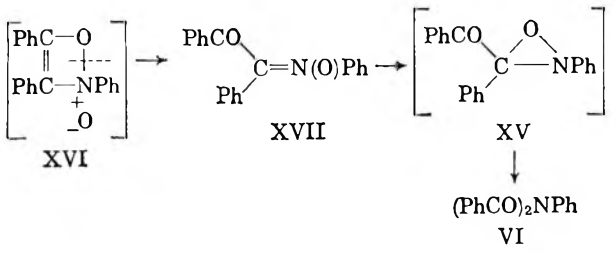
(6) E. Bamberger, *ibid.*, **35**, 1610 (1902).

(7) W. M. Cumming and G. S. Ferrier, *J. Chem. Soc.*, **127**, 2374 (1925).

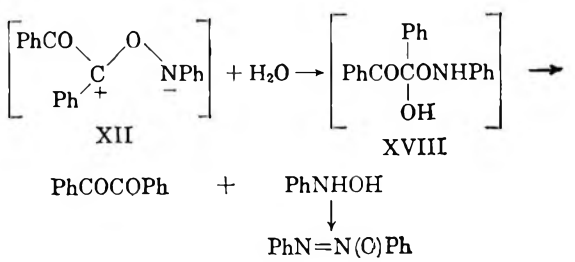
(8) R. Criegee and M. Lederer, *Ann.*, **583**, 29 (1953).

(9) (a) O. Mumm, *Ber.*, **43**, 889 (1910); (b) H. C. Wheeler and T. B. Johnson, *Am. Chem. J.*, **30**, 34 (1903).

Another mechanistic possibility is the participation of a four-membered ring intermediate (XVI), rather than the 1,3,2-dioxazole. This intermediate could cleave to N-phenylphenylbenzoylnitrone (XVII), which is indeed photochemically rearranged to dibenzanilide, probably through the intermediacy of the oxazirane (XV).[10]



Benzil and Azoxybenzene.—In aqueous dioxane, the zwitterionic intermediate XII may be converted to the hydrated intermediate XVIII, which could subsequently cleave to benzil and N-phenylhydroxylamine. N-Phenylhydroxylamine would not be isolated as such under the conditions of the work-up, but rather as the more stable azoxybenzene. Azoxybenzene is a common degradation product of N-phenylhydroxylamine.[11]



The formation of benzil and azoxybenzene in aqueous dioxane calls into question the participation of N-phenylphenylbenzoylnitrone (XVII) in the photochemical reaction of nitrobenzene and tolane, since the nitrone is not at all hydrolyzed to benzil under these conditions, but converted completely to dibenzanilide.

Experimental

Materials.—Tolane (diphenylacetylene) was purchased from Pilot, m.p. 63°. Nitrobenzene (Eastman) was redistilled before use. Airco Prepurified nitrogen was employed. Petroleum ether refers to Fischer Certified Reagent petroleum ether, b.p. 38.7–57.9°.

Photochemical Apparatus.—Irradiations were carried out employing a 550-w., high pressure mercury arc lamp (Hanovia, Type A), with a water-cooled, quartz immersion well (Hanovia, Cat. No. 19434) and a Pyrex filter sleeve. Photochemical reactions were run under nitrogen with magnetic stirring.

Photochemical Reaction of Nitrobenzene and Tolane.—A mixture of 17.8 g. (0.1 mole) of tolane and 12.3 g. (0.1 mole) of nitrobenzene dissolved in petroleum ether was irradiated for 3 days. During the course of the irradiation the exhaust nitrogen was passed through a known volume of 1 *N* carbonate-free sodium hydroxide solution. At the completion of the irradiation the alkaline solution was treated with excess barium chloride. Carbon dioxide could be estimated by standard volumetric or gravimetric procedures. The yield of carbon dioxide was about 20 mmoles.

A. Steam Distillation of the Reaction Mixture.—The early fractions of the steam distillate exhibited a green color. The green fractions were combined, dried over sodium sulfate, and chromatographed on a Perkin-Elmer vapor fractometer Model 154, employing a C-column. The components of the mixture were identified as nitrosobenzene and nitrobenzene. Nitrosobenzene was assayed colorimetrically by virtue of its absorption peak at 770 mμ (ε 45). The yield was 3.2 mmoles.

After removal of the unchanged nitrobenzene, the residue from the steam distillation was extracted with ether, dried over sodium sulfate, and evaporated to dryness. The residue was extracted with cold petroleum ether.

B. Chromatography of the Petroleum Ether Extract.—The petroleum ether extract was chromatographed on a column of Florisil. The first fractions obtained with petroleum ether elution contained recovered tolane (9.0 g.), a 51% recovery. On further elution with petroleum ether, 80 mg. (0.4 mmole) of 2-hydroxyazobenzene (red-orange needles, m.p. 83°) was obtained. The compound was identical with a known sample of 2-hydroxyazobenzene[7] by mixture melting point and ultraviolet, infrared, and n.m.r. spectral comparisons.[12] Immediately following the 2-hydroxyazobenzene band, another orange band was obtained. Rechromatography of the material on Florisil with petroleum ether elution afforded 3.08 g. of yellow needles, m.p. 110°. The material was identified by comparison with a known sample of benzophenone anil.[13] The yield of benzophenone anil was 12%.

C. Chromatography of the Petroleum Ether Insoluble Residue.—The residue from petroleum ether extraction was dissolved in a few milliliters of benzene and charged to a column of Florisil packed in carbon tetrachloride. Elution with benzene afforded 0.41 g. (1.8% yield) of the β-lactam (VIII). The compound was identified by its elementary analysis, infrared spectrum (5.76 μ in chloroform), and comparison with a known sample prepared according to Staudinger and Jelagin.[5]

With ether as the eluent, 5.41 g. (18% yield) of dibenzanilide was obtained. The material was identical in spectral and melting point properties with dibenzanilide prepared by the method of Freundler.[14] Further elution afforded intractable material.

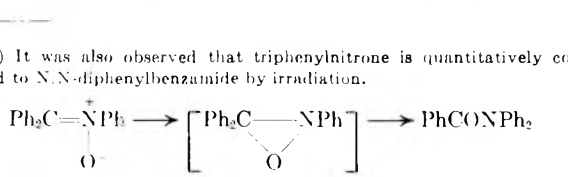
Irradiation of Tolane and Nitrobenzene in Aqueous Dioxane.—A solution of 8.90 g. (50 mmoles) of tolane, 25 ml. of nitrobenzene, 150 ml. of dioxane, and 10 ml. of distilled water was irradiated for 27 hr. No carbon dioxide was observed. The dioxane and nitrobenzene were removed by steam distillation. No nitrosobenzene was detected. The residue was extracted with 10% aqueous potassium bicarbonate solution. Acidification of the bicarbonate extract afforded 0.69 g. (6.4% yield based on tolane) of diphenylacetic acid, identical with an authentic sample.

The residue was chromatographed on Florisil with petroleum ether elution. A total of 2.83 g. (32%) of tolane was recovered, and 0.10 g. (0.5 mmole) of 2-hydroxyazobenzene was isolated. A white solid (1.01 g., m.p. 33°) was obtained with spectra identical with that of azoxybenzene. A mixture melting point with authentic azoxybenzene was undepressed. Further elution provided 0.90 g. of a yellow solid, m.p. 92–94°. The material was identified as benzil by spectral and melting point studies; the yield was 12.5%. Elution with benzene afforded 6.19 g. (40% yield) of dibenzanilide. With more polar solvents, only intractable material was obtained.

Irradiation of N-Phenylphenylbenzoylnitrone.—N-Phenylphenylbenzoylnitrone (XVII), m.p. 156°, was prepared by the procedure of Krőhnke.[15] A solution of 1.0 g. of the nitrone (XVII) in 50 ml. of dioxane was irradiated for 24 hr. The dioxane was evaporated leaving a solid, m.p. 157–160°. The compound was indentified as dibenzanilide by its infrared spectrum and undepressed mixture melting point. Similar results were obtained when the irradiation was carried out in aqueous dioxane.

Irradiation of Triphenylnitrone.[10]—A solution of 0.55 g. of

(10) It was also observed that triphenylnitrone is quantitatively converted to N,N-diphenylbenzamide by irradiation.



(11) (a) E. Bamberger, *Ber.*, **33**, 131 (1900); (b) E. Bamberger and F. Tschirner, *ibid.*, **32**, 342 (1899); (c) R. Willstätter and S. Dorogi, *ibid.*, **42**, 2167 (1909).

(12) The n.m.r. spectrum of 2-hydroxyazobenzene exhibits a sharp singlet of area 1 at τ −2.7.

(13) G. Reddelien, *Ber.*, **42**, 4760 (1909).

(14) P. Freundler, *Compt. rend.*, **137**, 712 (1903).

(15) F. Krőhnke, *Ber.*, **72B**, 534 (1939).

triphenylnitrone[16] in 5 ml. of dioxane was irradiated for 2 days. Removal of the solvent afforded a white solid, m.p. 178–180°, identical with N,N-diphenylbenzamide, in essentially quantitative yield.

(16) H. Rupe and R. Wittwer, *Helv. Chim. Acta*, **5**, 220 (1922).

Acknowledgment.—The author thanks the National Science Foundation and the National Institutes of Health for research fellowships and expresses gratitude to Professor Robert Burns Woodward for supervision of the work.

The Synthesis of L-1,4-Thiazane-3-carboxylic Acid 1-Oxide[1]

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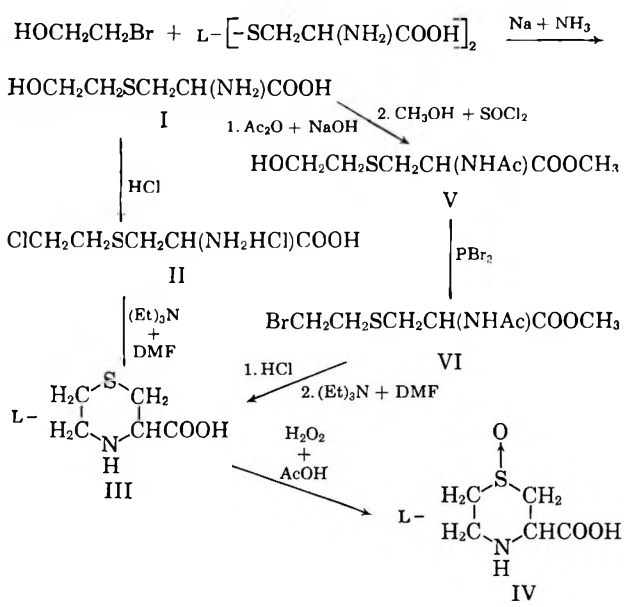
S-(2-Hydroxyethyl)-L-cysteine (I) has been converted to S-(2-chloroethyl)-L-cysteine hydrochloride (II). Cyclization of this compound in dimethylformamide containing triethylamine yielded L-1,4-thiazane-3-carboxylic acid (III, reduced "chondrine"). Oxidation yielded a mixture of diastereoisomeric sulfoxides from which (+)-L-1,4-thiazane-3-carboxylic acid 1-oxide (IV, "chondrine") was obtained.

Kuriyama, *et al.*,[3] isolated the sulfoxide amino acid "chondrine" (L-1,4-thiazane-3-carboxylic acid 1-oxide, IV) from the red alga *Chondria crassicaulis*. More recently, this compound has been isolated from a brown alga *Undaria pinnatifida*.[4] This compound was of interest to us because of its relation to the other known cyclic sulfoxide amino acid "cycloalliin" (L-5-methyl-1,4-thiazane-3-carboxylic acid 1-oxide) obtained from onions.[5] We have synthesized L-1,4-thiazane-3-carboxylic acid (III), which Kuriyama[3] obtained by hydriodic acid reduction of "chondrine." The DL-amino acid was also synthesized. Oxidation of III with hydrogen peroxide in acetic acid yielded a mixture of diastereoisomeric sulfoxides from which the dextrorotatory isomer was obtained by fractional crystallization, $[\alpha]^{26}D$ +19.0.



The identity of the intermediate (III) with the reduced "chondrine" obtained by Kuriyama was established by analysis and specific rotation; the structure was confirmed for the DL-compound by Raney nickel desulfurization which yielded the expected N-ethyl-DL-alanine. Reduced "chondrine" (III) was also characterized by the preparation of a crystalline hydrochloride and a cyclohexylamine salt of the N-2,4-dinitrophenyl derivative.

Bromoethanol and L-cystine were condensed with sodium in liquid ammonia to give S-(2-hydroxyethyl)-L-cysteine (I, 94%). This compound on heating in reagent hydrochloric acid (38%) gave S-(2-chloroethyl)-L-cysteine hydrochloride (II, 70–90%). Finally, the chloride was cyclized in dimethylformamide–triethylamine to give III in an 80% yield. The corresponding DL-compound was also prepared in a similar manner from S-(2-chloroethyl)-D,L-cysteine hydrochloride. This intermediate was prepared by addition of β-mercaptoethanol to α-acetamidoacrylic acid[6] to give S-(2-hydroxyethyl)-N-acetyl-DL-cysteine as an oil which, on heating with 38% hydrochloric acid, yielded the DL-chloride (II).

In a modification of this general procedure, I was acetylated and methylated to yield the crystalline S-(2-hydroxyethyl)-N-acetyl-L-cysteine methyl ester (V) which was converted to the bromide (VI). When VI was hydrolyzed with 38% hydrochloric acid at 90–95° and cyclized as before, III was obtained in good yield. However, when VI was hydrolyzed by refluxing in 2.5–3.0 *N* hydrochloric acid for 18 hr., extensive decomposition occurred and further reaction with triethylamine–dimethylformamide produced a complex mixture of products. The thiazane carboxylic acid could then be obtained in maximum yields of only 7% by ion-exchange chromatography. These results are similar to the findings of Welti and Whittaker[7] who observed that refluxing β-hydroxyethyl sulfides in dilute hydrochloric acid yielded a mixture of decomposition products in contrast with heating in concentrated acid, in which case high yields of β-chloroethyl sulfides were obtained.

When cyclization was attempted in aqueous base (barium hydroxide or sodium carbonate at pH 8–10), no

(1) Presented before the Division of Biological Chemistry at the 135th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(3) M. Kuriyama, M. Takagi, and K. Murata, *Hokkaido Daigaku Suisan Gakubu Kenkyu Iho* (*Faculty of Fisheries Bulletin, Hokkaido University*), **11**, 58 (1960).

(4) F. Tominaga and K. Oka, *J. Biochem.* (Tokyo), **54**, 222 (1963).

(5) A. I. Virtanen and E. J. Matikkala, *Acta Chem. Scand.*, **13**, 623 (1959).

(6) A. Schöberl and A. Wagner, *Chem. Ber.*, **80**, 379 (1947); D. McHale, P. Mamalis, and J. Green, *J. Chem. Soc.*, 2847 (1960).

(7) D. Welti and D. Whittaker, *ibid.*, 3955 (1962).

thiazane derivative could be detected and the major product was 2-hydroxyethyl cysteine. Ogston, *et al.*,[8] found that the hydroxyl ion is more nucleophilic toward the intermediate ethylene–sulfonium ion of mustard gas than methylamine. The competition factors in water at 25° for β,β′-dichloroethyl sulfide were found to be 8000 for OH^- as compared with 390 for methylamine. Apparently, in our cyclization reaction the entropy advantage of cyclization over reaction with a second molecule is not sufficient to enable the amino group to compete successfully with hydroxyl ion in attacking the presumed intermediate sulfonium ion.

Experimental

S-(2-Hydroxyethyl)-L-cysteine (I).—To a solution of 10.4 g. of sodium in 1000 ml. of liquid ammonia, 24 g. (0.1 mole) of L-cystine was added in small portions to the first permanent discharge of blue. Bromoethanol (35.0 g., 0.28 mole) was added cautiously, in very small portions, over a period of an hour. After spontaneous evaporation of the ammonia, the solid was dissolved in 300 ml. of water and passed through a column of Dowex 50 (H^+) (56 × 300 mm.). The resin was washed with 3.5 l. of water and the amino acid was then eluted with 3 l. of normal ammonium hydroxide. Concentration *in vacuo* yielded a crystalline solid which, upon solution in 50 ml. of water and addition of 500 ml. of ethanol, yielded 31 g. (94%) of product free of cystine. Recrystallization from 440 ml. of 92% ethanol yielded 29 g. (88%) of the pure compound, m.p. 189–189.5°,[9] $[\alpha]^{20}D$ −53.3 (*c* 2, water).

Anal. Calcd. for $C_5H_{11}NO_3S$: C, 36.35; H, 6.71; S, 19.41. Found: C, 36.4; H, 6.61; S, 19.7.

S-(2-Chloroethyl)-L-cysteine Hydrochloride (II).—A solution of 5.0 g. (0.030 mole) of I in 200 ml. of 38% reagent hydrochloric acid was heated for 7 hr. in a hot water bath at 92–95° and then concentrated *in vacuo* to a white solid. Crystallization from 175 ml. of isopropyl alcohol at 0° yielded 5.3 g. of white micaceous plates. Additional material was obtained from the mother liquor to give a total yield of 6.19 g. (91%). Recrystallization from isopropyl alcohol yielded the pure compound (70%), m.p. 181.5–182° dec. (preheat 170°).[10]

Anal. Calcd. for $C_5H_{11}Cl_2NO_2S$: C, 27.28; H, 5.04; Cl, 32.21; N, 6.36. Found: C, 27.6; H, 5.05; Cl, 32.07; N, 6.40.

L-2,4-Thiazane-3-carboxylic Acid (III).—To a solution of 6.0 g. (0.0273 mole) of S-(2-chloroethyl)-L-cysteine hydrochloride in 450 ml. of anhydrous dimethylformamide, there was added 50 ml. of anhydrous triethylamine. A white solid precipitated. The mixture was stirred and heated, under anhydrous conditions, for 2.5 hr. in a water bath at 90–94° and was then concentrated *in vacuo* to a light brown solid. This was dissolved in 75 ml. of water and passed through a column of Dowex 50 (H^+) (260 cm.[3]) which was then washed with 2 l. of water and finally with 1.5 l. of 1.5 *N* ammonium hydroxide. The ammoniacal eluate was concentrated *in vacuo* to 400 ml. and added to 100 ml. of Amberlite IRC-50 (H^+) and allowed to stand overnight. This treatment removed most of the color. On concentration to 30 ml. and refrigeration, the solution yielded 1.91 g. of white crystalline product. An additional 1.31 g. was obtained when the mother liquor was reduced to 5 ml., and 15 ml. of acetone was added (combined yield 80%). Both fractions were chromatographically homogeneous with butanol–acetic acid–water (52:13:35) and collidine–lutidine (1:3) saturated with water. Recrystallization from 30 parts of water–acetone (1:2) yielded the pure amino acid as tiny white needles, m.p. 270–271° dec. (sealed tube), $[\alpha]^{25.5}D$ −54.03 (*c* 1.6, water) and −31.18 (*c* 1.5, 2 *N* HCl). Kuriyama,[3] *et al.*, report the values $[\alpha]^{13}D$ −52.94 (water) and −26.38 (6 *N* HCl) and a decomposition point of 262–263° (sealed tube).

The compound had a relative R_f with respect to alanine at 25° of 1.23 in butanol–acetic acid–water (52:13:35) and 1.42 in collidine–lutidine (1:3) saturated with water.

Anal. Calcd. for $C_5H_9NO_2S$: C, 40.80; H, 6.16; N, 9.52. Found: C, 40.8; H, 6.15; N, 9.47.

The hydrochloride was prepared by dissolving 1 g. of the amino acid in 50 ml. of normal hydrochloric acid and concentration *in vacuo* to a crystalline solid. Recrystallization from 1.5 ml. water to which was added 30 ml. of acetone yielded 0.95 g. of the hydrochloride as tiny dense needles, m.p. 201–204° dec.

Anal. Calcd. for $C_5H_{10}ClNO_2S$: C, 32.70; H, 5.49; Cl, 19.30; N, 7.63. Found: C, 32.7; H, 5.42; Cl, 19.3; N, 7.76.

S-(2-Chloroethyl)-DL-cysteine Hydrochloride (II).—A solution of 8.5 g. (0.066 mole) of acetamidoacrylic acid, 7.0 g. (0.09 mole) of β-mercaptoethanol, and 7.0 g. of potassium carbonate in 250 ml. of water was stirred for 3.5 hr., under nitrogen, in a water bath at 90 ± 3°. The cooled solution was freed of potassium ion by passing through a column of Dowex 50 (H^+) and the solution was then concentrated *in vacuo* to yield 12 g. of S-(2-hydroxyethyl) N-acetyl-DL-cysteine as a pale yellow oil.

The oil was heated with 350 ml. of reagent concentrated hydrochloric acid in a water bath at 95–97° for 9 hr. Concentration *in vacuo* to a dry solid and crystallization from isopropyl alcohol yielded 8.8 g. (61% based on acetamidoacrylic acid) of S-(2-chloroethyl)-DL-cysteine hydrochloride, m.p. 157° dec. (preheat 150°). This compound was more difficult to crystallize than the corresponding L-compound and tended to separate as a gel on recrystallization. Elemental analyses were generally unsatisfactory with low values for chloride.

Anal. Calcd. for $C_5H_{11}Cl_2NO_2S$: C, 27.28; H, 5.04; Cl, 32.21. Found: C, 27.1; H, 5.19; Cl, 31.5.

DL-1,4-Thiazane-3-carboxylic Acid.—S-(2-Chloroethyl)-DL-cysteine hydrochloride was cyclized and the product was isolated by the same procedure as for the corresponding L-compound. Crystallization from aqueous acetone yielded the substance as small prisms (63%), m.p. 263–264° dec. (sealed tube).

Anal. Calcd. for $C_5H_9NO_2S$: C, 40.80; H, 6.16; N, 9.52. Found: C, 40.8; H, 6.15; N, 9.47.

S-(2-Hydroxyethyl)-N-acetyl-L-cysteine Methyl Ester (V).—To a solution of 21.5 g. (0.130 mole) of III in 100 ml. of 1.5 *N* sodium hydroxide at 0° there was added 27 g. (0.27 mole) of acetic anhyride and 325 ml. of 1.5 *N* sodium hydroxide in small portions over a 3-hr. period. Sodium ion was removed by passage through Dowex 50 (H^+) and the filtrate was concentrated *in vacuo* to give a quantitative yield of the N-acetyl derivative as a colorless oil.

To prepare the methyl ester, the N-acetyl amino acid (39.4 g., 0.19 mole) was dissolved in 750 ml. of absolute methanol at −5° to which 10 ml. of thionyl chloride was added dropwise with continuous stirring over a 1-hr. period. The solution was kept at −20° for 20 hr. and at 0° for an additional 20 hr. and it was then concentrated *in vacuo* to 200 ml. The solution was diluted with methanol to 500 ml., stirred for 4 hr. with 350 ml. of a weak acid exchanger [Duolite A-4 (NH_2)], and filtered; the resin was washed with 800 ml. of methanol. The filtrate was concentrated *in vacuo* to a pale amber oil. Crystallization from ethyl acetate yielded 31.9 g. (75.6%) of coarse, sugar-like granular crystals, m.p. 49–50°, $[\alpha]^{25}D$ −75.3 (*c* 1, methanol).

Anal. Calcd. for $C_8H_{15}NO_4S$: C, 43.42; H, 6.83; N, 6.33. Found: C, 43.2; H, 6.84; N, 6.32.

S-(2-Bromoethyl)-N-acetyl-L-cysteine Methyl Ester (VI).—To a solution of 14 g. (0.063 mole) of V in 300 ml. of dry methylene chloride, there was added dropwise over a 2-hr. period a solution of 8 g. (0.030 mole) of phosphorus tribromide in 300 ml. of methylene chloride. During the addition, the solution was stirred at room temperature under anhydrous conditions. After standing overnight, the solution was washed with 150 ml. of water, dried with sodium sulfate, and concentrated *in vacuo* to 100 ml. Addition of 500 ml. of hexane precipitated an oil which crystallized at 0°. The crude product was obtained as fibrous needles, 16.8 g. (93%). Recrystallization from methylene chloride–hexane yielded the pure compound, 15.3 g. (85%), m.p. 72–73°.

Anal. Calcd. for $C_8H_{14}NO_3BrS$: C, 33.81; H, 4.97; Br, 28.12; S, 11.28. Found: C, 34.0; H, 5.0; Br, 28.5; S, 11.4.

L-1,4-Thiazane-3-carboxylic Acid (III). Alternate Synthesis.—A solution of 6.0 g. (0.021 mole) of bromide VI in 225 ml. of 37% reagent hydrochloric acid was heated under reflux for 8 hr. in a water bath kept at 100°. Removal of solvent *in vacuo* yielded a white crystalline solid which was cyclized in dimethylformamide–triethylamine as previously described to yield 2.09 g. (67% based on VI) of the cyclic amino acid (III) identical with the previous preparation.

(8) A. G. Ogston, E. R. Holiday, J. S. L. Philpot, and L. A. Stocken, *Trans. Faraday Soc.*, **44**, 45 (1948).

(9) A. Zilkha and S. Rappoport [*J. Org. Chem.*, **28**, 1105 (1963)] report the synthesis of this compound with m.p. 210° by reaction of ethylene oxide with cysteine in the presence of triethylamine.

(10) T. A. Connors and W. C. Ross [*Chem. Ind.* (London), 366 (1958)] report a melting point of 186–188° for this compound.

Raney Nickel Desulfurization of DL-III.—A solution of 0.80 g. of DL-1,4-thiazane-3-carboxylic acid in 250 ml. of 80% ethanol containing 20 ml. of Raney nickel suspension[11] was refluxed for 6 hr. It was then filtered through a layer of filter aid and the filter cake was washed with 600 ml. of 1:10 aqueous ammonia. After removal of ammonia *in vacuo* and precipitation of nickel with hydrogen sulfide, the final solution was concentrated *in vacuo* to an oil which was dissolved in 85% ethanol. Evaporation of the solution yielded 100 mg. of N-ethyl-D,L-alanine as small plates. Paper chromatography with butanol–acetic acid–water and collidine–lutidine gave the same R_f as for the authentic synthetic compound. The infrared spectrum (potassium bromide disk) was identical with that of a synthetic specimen.

Cyclohexylamine Salt of N-2,4-Dinitrophenyl-L-1,4-thiazane-3-carboxylic Acid.—The dinitrophenyl derivative was prepared as previously described[12] from 0.5 g. of the amino acid. After abortive attempts to crystallize, the compound was converted to the cyclohexylamine salt[12] which was crystallized from acetone as long yellow needles (0.98 g.), m.p. 185° dec., $[\alpha]^{25}D$ −135.8 (*c* 2, acetic acid).

Anal. Calcd. for $C_{17}H_{24}N_4O_6S$: C, 49.50; H, 5.86; S, 7.77. Found: C, 49.2; H, 5.83; S, 7.89.

(+)-L-1,4-Thiazane-3-carboxylic Acid 1-Oxide (Chondrine, IV).—To a suspension of 2.344 g. (0.0159 mole) of L-1,4-thiazane-3-carboxylic acid (III) in 35 ml. of acetic acid, 1.2 ml. of 30% hydrogen peroxide was added in 0.2-ml. portions over a period of 3 hr. with continuous stirring at 25°. The solution was allowed to stand overnight at room temperature and was then concentrated *in vacuo* to an oil. Crystallization from a mixture of 40 ml. of water and 140 ml. of acetone yielded 1.78 g. of product, $[\alpha]^{25}D$ +9.57. A second crop was obtained, 0.656 g., $[\alpha]^{15}D$ +2.35. Infrared (potassium bromide disk) showed typical sulfoxide absorption at 9.7–9.8 μ and no sulfone absorption for each fraction. Paper chromatography with two solvent systems showed only one ninhydrin-active spot. Five recrystallizations of the more dextrorotatory fraction from a combination of 20 parts of water and 40–50 parts of ethanol at 0° yielded 160 mg. (least soluble fraction) of (+)-L-1,4-thiazane-3-carboxylic acid 1-oxide, m.p. 252° dec. (sealed capillary), $[\alpha]^{26}D$ +19.0 (*c* 1, water).[13]

Anal. Calcd. for $C_5H_9NO_3S$: C, 36.81; H, 5.52; N, 8.59; S, 19.63. Found: C, 36.5; H, 5.64; N, 8.45; S, 19.6.

Paper chromatography with collidine–lutidine (1:3, saturated with water) at 25° gave a relative R_f with respect to alanine of 1.36. With butanol–acetic acid–water (52:13:35), the relative R_f was 0.80.

Acknowledgment.—We are indebted to L. M. White and Geraldine Secor for elemental analyses.

(11) R. Mozingo, *Org. Syn.*, **21**, 15 (1941).

(12) J. F. Carson and F. F. Wong, *J. Org. Chem.*, **26**, 4997 (1961).

(13) Kuriyama, *et al.* (ref. 3), report $[\alpha]^{16}D$ +20.91 (water) for the naturally occurring sulfoxide "chondrine."

The Multicentered Reactivity of Pseudoxazolones

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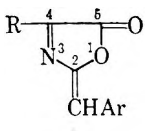
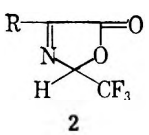
Received December 2, 1963

2-Arylidene pseudoxazolones possess several reactive sites for nucleophilic attack. The hydrolysis, aminolysis, and catalytic hydrogenation of these compounds are discussed and their behavior toward lithium aluminum hydride, phenylmagnesium bromide, and benzene under Friedel–Crafts conditions is reported. The attempted preparation of the linearly conjugated 2-benzylidene-4-benzyl-5(2H)-oxazolone gives instead the cross-conjugated 2-benzyl-4-benzylidene-5(4H)-oxazolone.

In recent years, there has been considerable impetus in the study of pseudoxazolones,[2] the 5(2H) isomers of the familiar 5(4H)-oxazolones or azlactones. Two classes of pseudoxazolones have been investigated,[3] the 2-arylidene type (**1**), the subject of this paper, and the 2-trifluoromethyl compounds (**2**), which Weygand and co-workers[4] have examined for the synthesis of α-keto acids and peptides.

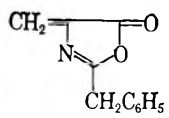


1



2

The only member of the 2-arylidene series to receive much attention has been 2-benzylidene-4-methyl-5-(2H)-oxazolone (**1a**, R = CH_3; Ar = C_6H_5). It is conveniently prepared by ring closure of either 2-phenylacetamido-3-bromopropionic acid[5] or N-(α-halophenylacetyl)alanine.[6,7] Recently, we have shown[8] that this pseudoxazolone, when exposed to light, slowly forms a dimer having a cyclobutane structure. Although the ultraviolet spectrum of **1a** supports the 5(2H) formulation rather than the isomeric 5(4H) form (**3**), the chemical evidence has been indecisive.[7] The formation of the photodimer now provides support for the 5(2H) structure.



3

Since the pseudoxazolones possess several potential sites for chemical attack, we have explored the chemistry of these compounds in order to shed further light on their reactivity.

Discussion and Results

While the 2-arylidene linkage is the reactive center for photodimerization and for attack by weak nucleo-

(1) Abstracted from the Ph.D. Thesis of E. J. Piasek, June, 1962.

(2) The *Chemical Abstracts* nomenclature for this system is 3-oxazolin-5-one.

(3) For a detailed discussion of pseudoxazolones, see R. Filler, "Advances in Heterocyclic Chemistry," Vol. IV, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1964, in press.

(4) F. Weygand and U. Glockler, *Chem. Ber.*, **89**, 653 (1956); F. Weygand and W. Steglich, *Angew. Chem.*, **73**, 433 (1961); F. Weygand, W. Steglich, and H. Tanner, *Ann.*, **658**, 128 (1962); F. Weygand, A. Prox, L. Schmidhammer, and W. Konig, *Angew. Chem., Intern. Ed. Engl.*, **2**, 183 (1963).

(5) I. L. Knunyants and V. V. Shokina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 409 (1955).

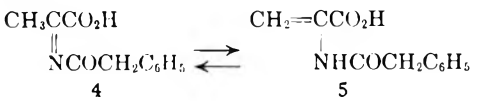
(6) M. Bergmann and F. Stern, *Ann.*, **448**, 20 (1926).

(7) J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, **72**, 833 (1950).

(8) R. Filler and E. J. Piasek, *J. Org. Chem.*, **28**, 221 (1963).

philes,[9] the principal sites of attack by most nucleophiles are the 4- and 5-positions. Reaction at the lactone carbonyl leads to open-chain acids and their derivatives. Addition to the >C=N linkage, as well as ring opening may occur, and occasionally, fragmentation at the carbon-nitrogen bond is also observed.

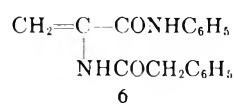
Hydrolysis.—Compound **1a** is hydrolyzed rapidly in acidic, basic, or neutral media to form pyruvic acid and phenylacetamide (or phenylacetic acid). Even atmospheric moisture is sufficient to cause some hydrolysis after several weeks (as well as dimerization[8]). The precursor of these products undoubtedly is the imido acid (**4**), which probably exhibits triad prototropy with 2-phenylacetamidoacrylic acid (**5**). In dilute sodium hydroxide solution, a small amount of **5** accompanies the products of >C=N cleavage.[10]



With the 4-unsubstituted pseudoxazolone[11] (**1b**, Ar = C_6H_5; R = H), prepared from N-(α-bromophenylacetyl)glycine, such prototropic shifts cannot occur. The instability of this compound is characterized by formation of a dark, resinous material with dilute sodium hydroxide and decomposition to a charred mass on brief exposure to air. With hydrochloric acid, an acidic substance[12] is obtained.

Aminolysis.—It has been reported[11] that **1a** reacts with benzylamine to form a product by addition of two molecules of amine, but no experimental data were presented. In our hands, this reaction gave phenylacetamide (79%) and a small amount of material, believed to be pyruvic benzylamide, isolated as its 2,4-dinitrophenylhydrazone. These products apparently arise by hydrolytic cleavage of the imidoamide, perhaps from traces of water.

The reports[11,13a] that **1a** fails to react with aniline in boiling xylene seemed to us most surprising, although it was found[11] that reaction proceeds in methanol (containing N-ethylpiperidine) to give methyl 2-anilino-2-phenylacetamidopropionate.[13b] We have observed that **1a** does, indeed, react with aniline in refluxing benzene to give, in 45% yield, a product which absorbs bromine without evolution of HBr and whose analytical data and infrared spectrum are compatible with the anilide structure (**6**).[14]

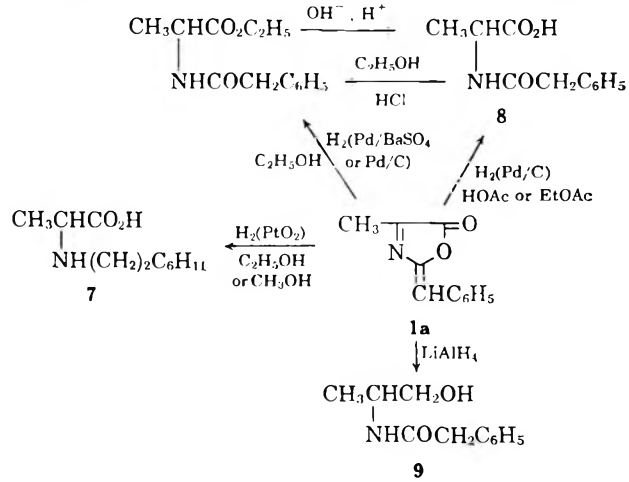


Hydrogenation.—The results of our studies on the reduction of **1a** are summarized in Scheme I. The pseudoxazolone is hydrogenated under catalytic conditions, but the 2-benzyl-4-methyl-5(4H)-oxazolone formed initially[15] is solvolyzed readily to open-chain reduction products. Of particular interest is compound **7**, obtained with platinum oxide catalyst.

In methanol and ethanol, the system (including the aromatic ring) is completely reduced to the α-amino acid, which shows the expected amphoteric properties (acid–base solubility and infrared spectra).

SCHEME I

REDUCTION OF 2-BENZYLIDENE-4-METHYL-5(2H)-OXAZOLONE



Attempts to prepare the azlactone by cyclization of **8** resulted in an oil of complex composition, but a prominent band at 1800 cm.$^{-1}$ is indicative of the presence of oxazolone.

The reaction of **1a** with lithium aluminum hydride is attended by reduction at both the >C=N and lactone >C=O groups with formation of the amido alcohol (**9**).

Reaction with Grignard Reagent.—Phenylmagnesium bromide and phenyl lithium attack the carbonyl group of **1a**. The structure of the product has not been clearly established, although its infrared spectrum suggests the presence of –OH, –NH, and aryl ketone groups. Further studies on this reaction are in progress.

Reaction with Benzene (Aluminum Chloride).—The reaction of **1a** with benzene under Friedel–Crafts conditions was complex and failed to yield any identifiable product. From **1b**, however, the acylamino ketone (**10**) was isolated. Two molecules of benzene are incorpo-

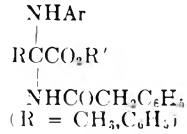
(9) O. V. Kil'disheva, M. G. Lin'kova, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 719 (1957).

(10) King and McMillan (ref. 7) were also able to isolate compound **5** after hydrolysis with 5% sodium carbonate solution or with dilute ammonia. We obtained only cleavage products with sodium carbonate.

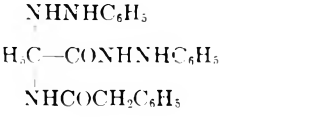
(11) "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, pp. 739–741.

(12) We have not established the structure of this substance. On alkaline hydrolysis, phenylacetamide was obtained.

(13) (a) M. Brenner and K. Rüfenacht, *Helv. Chim. Acta*, **37**, 203 (1954). (b) NOTE ADDED IN PROOF.—It has been reported very recently [A. Mustafa, M. K. Hilmy, A. E. Sammour, and M. M. N. Eldeen, *Tetrahedron*, **20**, 1063 (1964)] that **1a** and its 4-phenyl analog react with aryl amines in alcohols to give compounds of the following type.



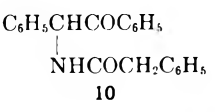
The phenyl analog and excess phenylhydrazine gave a product for which structure A has been proposed.



(14) Brenner and Rüfenacht[13a] reported the isolation of **6**, m.p. 139–142°, in 9% yield and **1a** as the major product in the reaction of **5** with ethyl chloroformate and aniline. Our product had m.p. 112–115°.

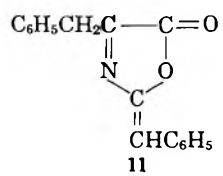
(15) Reduction in the presence of Raney nickel and ethyl acetate solvent gave the 5(4H)-oxazolone.[11] In methanol, methyl 2-phenylacetamidopropionate was isolated. This oxazolone could be formed by hydrogenation of either the >C=C< or >C=N— bonds, followed by a 1,3-proton shift.

rated and it is reasonable to postulate the 1,4-addition of benzene to the >C=N—C=C— chain, followed by acylation of the 2-benzyl-4-phenyl-5(4H)-oxazolone formed initially. Azlactones *acrylate* benzene readily under these conditions.[3,16,17]

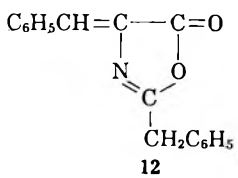


10

5(2H)–5(4H) Equilibrium.—While the possibility of a rapid equilibrium between the 5(2H)- and 5(4H)-oxazolones cannot be excluded, Knunyants[9] has concluded that the preferred structure is the one which permits the most extended conjugation. The evidence cited earlier in the present paper in favor of the 5(2H) structure for **1a** tends to support Knunyants' postulate. In this connection, it seemed desirable to investigate the isomeric pair, **11** and **12**.



11



12

The pseudoxazolone contains a linear conjugated chain of three double bonds and a terminal aromatic ring. The azlactone also possesses these features, but in a cross-conjugated arrangement. The structures may be differentiated by positions of maxima in the ultraviolet region. Compound **11** should absorb near 355 mμ and **12**, near 330 mμ.[18]

Compound **12** was obtained from benzaldehyde and phenaceturic acid.[19] In an attempt to prepare **11** by cyclization of N-(α-chlorophenylacetyl)phenylalanine in acetic anhydride–pyridine, only **12**, λ_{max}^{EtOH} 331 mμ, was obtained. Compound **12** is readily solvolyzed in ethanol to the open-chain ester, λ_{max}^{EtOH} 282 mμ, a behavior typical of the 5(4H)-oxazolones.[18]

We conclude, therefore, that the cross-conjugated oxazolone **12** is the thermodynamically stable isomer.

Experimental[20]

2-Benzylidene-4-methyl-5(2H)-oxazolone (1a).—This compound was prepared according to a procedure described previously.[8]

Hydrolysis of Pseudoxazolone (1a). 1. With Sodium Hydroxide.—One gram (5.3 mmoles) of **1a** in 20 ml. of 1.5% sodium hydroxide was allowed to stand for 40 min. with occasional shaking to yield, after filtration, 0.06 g. (8.3%) of phenylacetamide, m.p. 156°. Acidification of the filtrate and concentration by air blowing gave 0.04 g. (3.6%) of α-phenylacetamidoacrylic acid, m.p. 168° (lit.[7] m.p. 166°); ν^{CHCl_3} 3310, 1710, 1675, and 1630 cm.$^{-1}$. The filtrate reacted with 2,4-dinitrophenylhydrazine to give pyruvic acid 2,4-dinitrophenylhydrazone, m.p. 215°.

With 10% NaOH, a 41% yield of phenylacetamide, m.p. 157–158°, was obtained. When the reaction was allowed to proceed for 36 hr. and the solution acidified with 20% HCl, phenylacetic acid, m.p. 76–77°, was isolated in 41.2% yield and pyruvic acid was recovered from the filtrate as its 2,4-dinitrophenylhydrazone.

2. With Sodium Carbonate.—Reaction of **1a** with 5% Na_2CO_3 solution at room temperature for 10 hr. gave phenylacetamide in 57% yield.

3. With Water.—The pseudoxazolone was heated on a steam bath with water for 10 hr. After cooling, a 41% yield of phenylacetamide was obtained.

4. With Hydrochloric Acid.—Reaction of the pseudoxazolone with 10% HCl at room temperature for 24 hr. furnished phenylacetic acid in 40% yield.

5. In Air.—Pseudoxazolone was exposed to the atmosphere for 1 month. A white solid, m.p. 140–185°, formed. One gram of this solid in 20 ml. of benzene was chromatographed on an alumina column. Pseudoxazolone and its dimer[8] were eluted with a large excess of benzene. From the methanol eluate, 60 mg. of phenylacetamide was obtained.

Hydrogenation of 1a.—A solution of **1a** in 95% ethanol was hydrogenated for 48 hr. at 40 p.s.i. in the presence of 10% palladium-on-charcoal catalyst to give an oil (ν 3300, 1745, and 1685 cm.$^{-1}$) believed to be ethyl α-phenylacetamidopropionate. The oil was allowed to stand overnight at room temperature with 10% sodium hydroxide solution. The solution was acidified with 10% HCl and the resulting solid crystallized from ethyl acetate–methanol to give α-phenylacetamidopropionic acid, m.p. 150°. Similar results were obtained with palladium ($BaSO_4$) catalyst in ethanol.

When reduction was carried out in glacial acetic acid, α-phenylacetamidopropionic acid (m.p. 153–154°; ν^{KBr} 3200, 1715, and 1650 cm.$^{-1}$) was isolated in 35% yield.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32. Found: C, 63.75; H, 6.50.

This acid was converted to the ethyl ester (*vide supra*) on treatment with ethanol and dry hydrogen chloride.

The reduction of **1a** in ethanol or methanol in the presence of platinum oxide catalyst furnished the amino acid **7**. This amorphous solid was purified by dissolving it in a large volume of ethanol at room temperature and reducing the volume by evaporation under vacuum, yield 24%, m.p. 268–270°, ν^{KBr} 2950 and 1585 cm.$^{-1}$, soluble in acid and base.

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.43; H, 10.54; N, 7.25.

Reduction of 1a with Lithium Aluminum Hydride.—A slurry of 1.64 g. (0.0432 mole) of lithium aluminum hydride in 125 ml. of anhydrous ether was agitated and heated under reflux for 45 min. Pseudoxazolone (4 g., 0.021 mole) in 250 ml. of anhydrous ether was added cautiously during a 15 min. period. The reaction mixture was refluxed for 2.5 hr., then decomposed with 50 ml. of wet ether, followed by 5 ml. of water. The white suspension was filtered under suction and the filter cake washed with 30 ml. of ether. The ether solution, dried over anhydrous magnesium sulfate, was evaporated by air blowing to an amorphous residue, $\nu^{CH_2Cl_2}$ 3300 and 1600 cm.$^{-1}$, which was dried at 80° (1 mm.) for 1.5 hr. The residue was treated with 8 ml. of phenyl isocyanate and heated on a hot plate at 80° for 5–10 min. The solution was placed in a freezer overnight and a white solid separated. It was filtered under suction, washed with ethyl acetate, and air-dried. A solid, m.p. 160–180°, was obtained, which when crystallized twice from ethyl acetate gave 2.0 g. (30%) of the urethan of **9**, m.p. 142–144°; ν^{KBr} 3250, 1700, and 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 69.21; H, 6.45. Found: C, 69.18; H, 6.56.

Reaction of 1a with Benzylamine.—A solution of 1 g. (5.25 mmoles) of pseudoxazolone in 13 ml. of dry benzene, containing 1 ml. of benzylamine, was refluxed for 1 hr. A white solid (0.30 g.), m.p. 158–160°, separated as the mixture cooled. The volume of filtrate was brought up to 13 ml. with benzene and refluxed for 2 hr. to yield an additional 0.26 g. of solid. Thus, 0.56 g. (79%) of product was obtained. It crystallized from ethyl acetate as transparent platelets, m.p. 160–161°; ν^{KBr} 3200, 3070, and 1640 cm.$^{-1}$.

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71. Found: C, 71.42; H, 6.74.

No depression in melting point was observed upon admixture of the product with an authentic sample of phenylacetamide.

The filtrate was dissolved in a large volume of ether and extracted with 17 ml. of 5% hydrochloric acid, followed by water. A droplet of oil separated at the ether–acid interface, but the addition of several milliliters of methanol dissolved the oil. The

(16) E. Ciorănescu, L. Birladeanu, and R. Sternberg, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 144 (1961).

(17) R. Filler and Y. S. Rao, *J. Org. Chem.*, **27**, 2403 (1962), and references therein.

(18) R. Filler and H. Novar, *ibid.*, **25**, 663 (1960), and references therein.

(19) E. Erlenmeyer, *Chem. Ber.*, **31**, 2239 (1898).

(20) Melting points are corrected and boiling points uncorrected. Analyses were conducted by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were measured on a Perkin-Elmer 21 spectrophotometer using sodium chloride optics and ultraviolet spectra were determined on a Beckman DK-2 spectrophotometer.

ether solution was dried over anhydrous magnesium sulfate and concentrated by evaporation to an amorphous residue, which was dissolved in ethanol and treated with 2,4-dinitrophenylhydrazine. A small amount of orange solid (*ca.* 20 mg.), m.p. 210–240°, precipitated.

Two crystallizations from benzene gave several milligrams of solid, m.p. 245–247°, believed to be pyruvic benzylamide 2,4-dinitrophenylhydrazone.

Reaction of 1a with Aniline.—To 1 ml. of aniline (freshly distilled) in 5 ml. of dry benzene was added 0.5 g. (2.67 mmoles) of pseudoxazolone and the solution refluxed for 0.5 hr. Evaporation of the solution under vacuum gave an oil, which solidified to a yellow-green amorphous solid. Suspension of the solid in petroleum ether (b.p. 40–60°) and suction filtration gave a cream-colored solid, m.p. 80–110°. The product was crystallized from ethanol to yield white crystals, m.p. 114–118°. A second crystallization gave 0.34 g. (45%) of anilide 6, m.p. 112–115°; ν^{KBr} 3355, 1687, 1635, and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75. Found: C, 73.19; H, 6.46.

The product was insoluble in alkali and decolorized a solution of bromine in carbon tetrachloride.

Grignard Reaction of 1a.—The Grignard reagent was prepared from 1.08 g. (0.045 mole) of magnesium and 4.72 ml. (0.045 mole) of bromobenzene in 100 ml. of anhydrous ether. To this reagent was added a suspension of 2.8 g. (0.015 mole) of pseudoxazolone in 100 ml. of anhydrous ether over a 15-min. period. When approximately one-half of the suspension had been added, a tan-colored solid separated from the reaction mixture. The mixture was refluxed and stirred for 30 hr., but the solid did not dissolve. This mixture was hydrolyzed with 18% hydrochloric acid; the ether layer separated, was washed with several portions of water, and dried over anhydrous magnesium sulfate. Evaporation of the ether gave an amorphous product, which dissolved in chloroform and precipitated with petroleum ether to yield 2.2 g. of solid, m.p. 90–95°. The product was soluble in most organic solvents and could only be purified by repeated chloroform–petroleum ether precipitations until a constant melting product, m.p. 104–106°, was obtained; λ_{max}^{EtOH} end absorption; $\nu^{CH_2Cl_2}$ 3450, 3310, and 1695 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 73.06; H, 6.03; N, 4.79.

Attempts to prepare a 3,5-dinitrobenzoate, oxime, and urethan derivative were unsuccessful. 2,4-Dinitrophenylhydrazine gave a crude, dark brown solid, m.p. 158–170°, which could not be purified.

The same product was obtained when tetrahydrofuran replaced ether, or when inverse addition was employed. With phenyllithium, the yield of this product was lower.

N-(α-Chlorophenylacetyl)phenylalanine.—To a solution of 2.5 g. (0.062 mole) of sodium hydroxide in 150 ml. of water was added 5 g. (0.03 mole) of *dl*-phenylalanine. The suspension was stirred magnetically and when the amino acid had dissolved cooled to 8°, α-chlorophenylacetyl chloride (5.7 g., 0.03 mole) was added dropwise, the clear solution extracted with 20 ml. of ether, and the aqueous layer acidified with 300 ml. of chloroform. The chloroform solution was washed with two 100-ml. portions of water, dried over anhydrous magnesium sulfate, and evaporated on a steam bath until the volume was reduced by one-fourth. After refrigeration for several hours, a white solid was obtained, which was washed with chloroform and air-dried. N-Substituted phenylalanine (4.13 g., 42%), m.p. 123–150°, was obtained. Two crystallizations of the solid from chloroform gave a product, m.p. 142–162°.

Anal. Calcd. for $C_{17}H_{16}ClNO_3$: C, 64.25; H, 5.08. Found: C, 64.45; H, 5.50.

2-Benzyl-4-benzylidene-5(4H)-oxazolone (12).—One-gram of the substituted alanine was dissolved in a solution of 2.5 ml. of pyridine and 12 ml. of acetic anhyride. After 25 min. the deep red solution was poured over ice. A dense oily layer with occluded solid formed on the bottom of the flask. The aqueous layer was decanted and the residue treated with enough ethanol (50%) to dissolve the oil and to yield 0.62 g. (44%) of yellow solid, m.p. 108–111°. Crystallization from carbon tetrachloride gave white needles, m.p. 109–112° (lit.[19] m.p. 105°); λ_{max}^{EtOH} 331 mμ (after several days, 282 mμ, ε 19,300); ν^{KBr} 1784, 1800 sh, and 1655 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98. Found: C, 77.74; H, 5.11.

Sublimation of the oxazolone at 90° (1 mm.) for 24 hr. gave a long-needled, transparent solid, m.p. 110–112°, ν^{KBr} 1784 and 1800 sh cm.$^{-1}$.

Phenaceturic Acid.—The N-substituted glycine was prepared by dropwise addition of 4.14 g. of phenacetyl chloride to an alkaline solution (2.14 g. of sodium hydroxide in 40 ml. of water) of glycine (2 g.), maintained at 10°. The reaction mixture, after extraction with ether, was acidified with 10 ml. of 18% hydrochloric acid. A white solid (2.68 g., 52%), m.p. 148–150° (lit.[21] m.p. 143° for phenaceturic acid), was collected on a Büchner funnel and had ν^{KBr} 3378, 1725, and 1608 cm.$^{-1}$.

2-Benzyl-4-benzylidene-5(4H)-oxazolone from Phenaceturic Acid.—Two grams of the acid were added to 1.1 ml. of benzaldehyde in 2.2 ml. of acetic anhydride, containing 0.8 g. of sodium acetate. The mixture was heated on a steam bath for 1 hr. Ice was added and an amorphous solid settled to the bottom of the flask. The aqueous solution was decanted and several milliliters of ethanol was added to the residue. The mixture was filtered under suction; the filter cake was washed with several milliliters of ethanol. Colorless crystals were obtained, m.p. 108–111°, which did not depress the melting point of the product prepared by the Bergmann synthesis.

2-Benzylidene-5(2H)-oxazolone (1b).—This pseudoxazolone was prepared by cyclization of N-(α-chlorophenylacetyl)glycine according to a procedure described previously.[11]

Hydrolysis of 1b.—To 250 mg. of pseudoxazolone was added 19 ml. of 0.1 *N* sodium hydroxide. After 10 min., the solution had turned deep red. Acidification gave an emulsion which was extracted with 1-butanol. Evaporation of the solvent yielded a dark viscous residue.

Reaction of 1b under Friedel–Crafts Conditions.—One gram of 1b in 25 ml. of dry benzene was added dropwise to a stirred slurry of 2.32 g. of anhydrous aluminum chloride in 50 ml. of dry benzene. After the solution had been stirred for 30 min., 12 ml. of 18% hydrochloric acid was added. The mixture was filtered under suction to yield 0.30 g. of product, m.p. 137–160°. Two crystallizations from ethanol gave the acylamino ketone 10, m.p. 142–143.5°; ν^{KBr} 3300, 1690, and 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81. Found: C, 79.84; H, 6.06.

Acknowledgment.—This investigation was supported by Public Health Service Research Grant No. CA-04532-05 from the National Cancer Institute.

(21) E. Salkowski and H. Salkowski, *Chem. Ber.*, **12**, 653 (1879).

The Synthesis of 1,4-Dichlorobicyclo[2.2.1]heptane[1]

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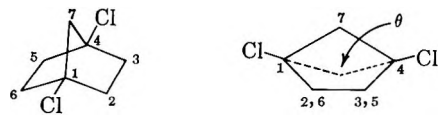
1,4-Dichlorobicyclo[2.2.1]heptane has been prepared by several routes and its structure has been established rigorously.

There has appeared recently a scheme for calculating internuclear distances and dipole moments of bicyclo[1.1.1]pentane, bicyclo[2.2.1]hexane, and bicyclo[2.2.1]-heptane derivatives.[3] Because of the widespread interest in these bicyclic systems, any refinement of the method or numerical values would be of great practical value. An excellent starting point for checking and improving the method would be the unknown 1,4-dichlorobicyclo[2.2.1]heptane (I), since its dipole moment is extremely sensitive to the angle of intersection of the C–Cl bond vectors. This paper describes the preparation of I and its structure proof. A subsequent paper will report the dipole moment of I and related compounds.



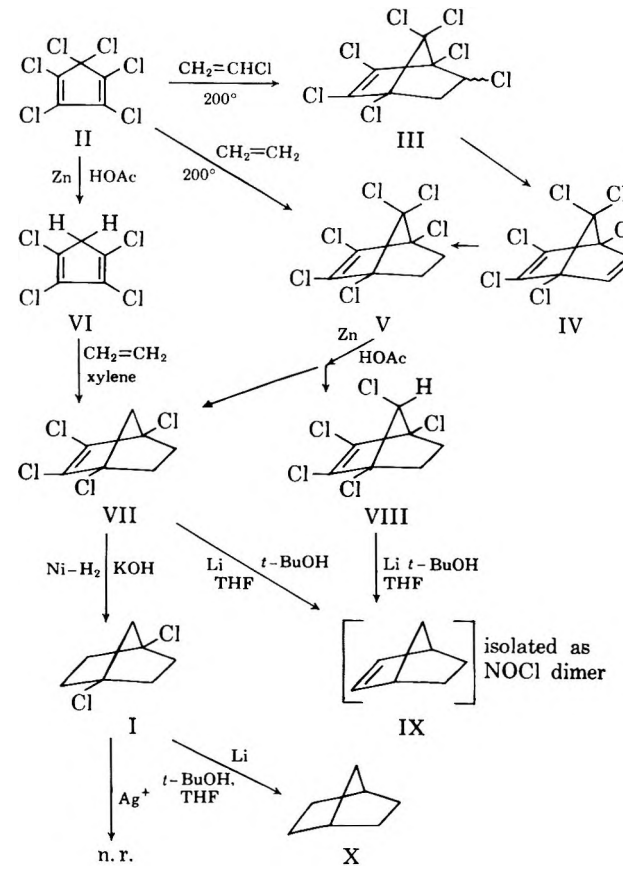
I

Preparation of 1,4-Dichlorobicyclo[2.2.1]heptane (I).—The general plan for the preparation of the dichloride (I) was to prepare a polychlorinated derivative of norbornane from which all but the bridgehead chlorines would be removed by taking advantage of the low relative reactivity of bridgehead halogens. As it developed 1,2,3,4-tetrachlorobicycloheptene-2 (VII, see Chart I) could be converted into the desired dichloride in one simple step so that the synthetic problem was reduced to finding a practical synthesis of VII. The preparation of VII was carried out by several routes from the readily available hexachlorocyclopentadiene (II) as outlined in Chart I.

One of these routes was to remove two chlorines from II to give the known 1,2,3,4-tetrachlorocyclopentadiene (VI),[4] which was then converted to the desired tetrachloride (VII) in 20% yield by bubbling ethylene through a solution of VI in refluxing xylene. The structure of VII follows in part from its mode of preparation and correct analysis. Corroborative evidence is provided by removal of all four of the chlorines using the Winstein reduction procedure[5] to give bicycloheptene (isolated as its nitrosyl chloride dimer). Further evidence for the structure of VII is provided by synthesis of it from other known compounds as shown in Chart I and described below.

Another route to VII was by way of the known heptachloride[6,7] III which was converted into the previously described hexachloride IV by the procedure outlined by

CHART I



Kleinman[6] followed by catalytic reduction to V. The over-all yield of V for these three steps was 49%.

An alternate preparation of I suggested by the work of Schmerling[8] and Hoch[9] was to bubble ethylene for 24 hr. into II that was maintained at 200°. In this manner 94% yields of pure V could be prepared on a large scale with simple apparatus.

The two bridge chlorines of V were removed by treatment with zinc and acetic acid[10] to give a low yield (29%) of the desired intermediate VII. In addition to VII a compound containing five chlorines was isolated in 40% yield. The structure of the pentachloro compound was assigned as VIII by the following evidence. First, it was established that the bicycloheptane skeleton was present by conversion of VIII into the same nitrosyl chloride dimer that had been obtained previously from VII. An infrared spectrum of VIII

(1) This work was supported by the National Science Foundation.

(2) Taken from the dissertation submitted by J. G. Zajacek to Cornell University for the Ph.D. degree, Sept., 1962.

(3) C. F. Wilcox, Jr., *J. Am. Chem. Soc.*, **82**, 414 (1960); see also H. Krieger, *Suomen Kemistilehti*, **B31**, 348 (1958).

(4) A. Roedig and L. Hornig, *Ber.*, **88**, 2003 (1955); A. A. Danish, M. Silverman, and Y. A. Tajiima, *J. Am. Chem. Soc.*, **76**, 6144 (1954).

(5) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind.* (London), 405 (1960).

(6) U. S. Patent 2,655,513 (Oct. 13, 1953); M. Kleinman, *Chem. Abstr.*, **48**, 10,773 (1954); U. S. Patent 2,736,730 (Feb. 28, 1956); M. Kleinman *Chem. Abstr.*, **50**, 10,780 (1956).

(7) U. S. Patent 2,717,851 (Sept. 13, 1955); R. E. Lidov, *Chem. Abstr.*, **50**, 2914 (1956).

(8) U. S. Patent 2,881,223 (April 7, 1959); L. Schmerling, *Chem. Abstr.*, **53**, 17,013 (1959).

(9) P. E. Hoch, *J. Org. Chem.*, **26**, 2066 (1961).

(10) S. B. Soloway, A. M. Daniana, J. W. Sims, H. Bluestone, and R. E. Lidov, *J. Am. Chem. Soc.*, **82**, 5377 (1960).

showed a band at 6.35 μ, which is characteristic of a structural unit containing two chlorines on a double bond.[10] This same band was present in compounds III, IV, V, and VII, and absent in I. The integrated n.m.r. spectrum indicated that VIII had a lone hydrogen on a carbon bearing a chlorine and that VIII had four other hydrogens arranged to give a characteristic A_2B_2 pattern. The *syn* relationship of the chlorine at C-7 was assigned primarily because VIII failed to be reduced over Adams catalyst. A similar inertness to reduction was observed for V, which also has a chlorine *syn* to the Cl—C=C—Cl group; compound VII without the blocking Cl is readily reduced over Adams catalyst. The *syn* assignment is considered tentative until a detailed n.m.r. analysis, in progress, has been completed.

Compound VII was converted to the dichloride (I) in 82% yield by reduction with Raney nickel in the presence of excess base. This reaction probably proceeds by a consecutive series of reductions and eliminations. The structure of I was established in the following manner. Reduction of I with lithium and *t*-butyl alcohol, in tetrahydrofuran, gave norbornane, thereby establishing the skeleton of I. Analytical data indicated the presence of two chlorine atoms. The lack of reactivity of I when heated with alcoholic $AgNO_3$ at 100° for 30 hr. showed that these chlorines were in bridgehead (inert) positions. An n.m.r. spectrum of I showed two peaks in a 1:4 ratio in the methylene region and no peaks for tertiary hydrogens or hydrogens adjacent to a chlorine atom.

Conclusions

1,4-Dichlorobicyclo[2.2.1]heptane can be prepared by several synthetic sequences. The preferred route to the dichloride is the sequence II → V → VII → I. These reactions can be run on a large scale and only one careful distillation is required. The over-all yield of I from II is 22%.

Experimental

1,2,3,4,5,7,7-Heptachlorobicyclo[2.2.1]heptane-2 (III).—Compound III was prepared from hexachlorocyclopentadiene and vinyl chloride following the procedure of Kleinman[6] modified only by passing in the vinyl chloride for 24 hr. instead of the specified 14 hr. After the unreacted hexachlorocyclopentadiene had been removed by distillation, the product in the distillation pot solidified on cooling. It was purified by sublimation at 100° and 2.5 mm. to give a 71% yield of III, m.p. 147.5–162.5°, lit.[6] m.p. 125–136°.

1,2,3,4,7,7-Hexachlorobicyclo[2.2.1]heptadiene-2,5 (IV).—Compound IV was prepared by a procedure closely related to that of Kleinman.[6] A solution of 432 g. (1.27 moles) of heptachloride III and 73.7 g. (1.31 moles) of potassium hydroxide (85%) in 1300 ml. of absolute ethanol was heated under reflux for 3 hr. The ethanol was removed by distillation through a 30-cm. glass helix packed column. To the residue was added 250 ml. of pentane. The salts that precipitated were collected by filtration and washed with pentane until the washings were colorless (*ca.* 500 ml.). The combined filtrate and washings were dried over magnesium sulfate and the pentane was removed by distillation through a 30-cm. column packed with glass helices. The residue was distilled through a 30-cm. Vigreux column to give 255 g. (67%) of IV, b.p. 111–116° at 4.5 mm., lit.[6] b.p. 128–130° at 7 mm.

1,2,3,4,7,7-Hexachlorobicyclo[2.2.1]heptane-2 (V). Method A.—To 200 ml. of ethyl acetate and 0.3 g. of platinum dioxide was added 217 g. (0.73 mole) of diene IV. The mixture was reduced on a Parr hydrogenation apparatus until hydrogen uptake ceased (0.74 mole). The catalyst was removed by filtration and the ethyl acetate was removed by distillation through a 30-cm. Vigreux column. The distillation was continued to give 175 g. (80%) of V, b.p. 112–116° at 4.2 mm.

Method B.—Ethylene was bubbled for 24 hr. through 2538 g. (9.4 moles) of hexachlorocyclopentadiene that was maintained at 200°. The ethylene uptake was 244 g. Unreacted hexachlorocyclopentadiene was removed by distillation through a 90-cm. tantalum wire column, b.p. 123–135° at 20 mm. Continued distillation at lower pressure gave 2630 g. (94%) of product V, b.p. 113° at 2–3 mm. The product solidified on standing, m.p. 37.5–39°, lit.[8] b.p. 111° at 3 mm., m.p. 38°.

1,2,3,4-Tetrachlorobicyclo[2.2.1]heptene-2 (VII). Method A.—To an efficiently stirred solution of 203 g. (0.681 mole) of V in 1100 ml. of glacial acetic acid heated under reflux was added over 0.5-hr. period 250 g. (3.8 moles) of zinc dust (90% technical). The mixture was heated under reflux for an additional 8 hr., then cooled to room temperature. The unreacted zinc was removed by filtration through glass wool. The filtrate was poured into 2 l. of cold water, and the organic layer was extracted with a total of 900 ml. of pentane. The extract was washed successively with water, 10% sodium carbonate solution, and finally with water until the wash was neutral. The solution was dried over magnesium sulfate and the pentane was removed by distillation through a 30-cm. glass helix-packed column. The residue was distilled under nitrogen through a 90-cm. column packed with a stainless steel sponge. The first fraction gave 43.8 g. (29%) of compound VII, b.p. 74–77° at 3 mm., which solidified on standing, m.p. 38–40°.

Anal. Calcd. for $C_7H_6Cl_4$: C, 36.24; H, 2.61; Cl, 61.15. Found: C, 36.49; H, 2.72; Cl, 61.10.

Later fractions contained compound VIII, which was isolated as described below. This reaction also was carried out several times at twice this scale with essentially identical yield.

Method B.—1,2,3,4-Tetrachlorocyclopentadiene (VI) was prepared by reduction of hexachloride II with zinc dust and acetic acid according to the procedure of Roedig.[4] Ethylene was bubbled rapidly for 24 hr. through a solution of 40 g. (0.2 mole) of compound VI in 200 ml. of xylene. The reaction temperature was maintained at 120–125° by an oil bath during the addition of ethylene. The xylene was removed by distillation at atmospheric pressure through a 90-cm. tantalum wire column. The residue was distilled to give 9 g. (20%) of compound VII, b.p. 70–72° at 3 mm. The liquid distillate crystallized on seeding and cooling and melted at 37–38.5° after crystallization from pentane and sublimation. The infrared spectrum of this sample was identical with the spectrum of compound VII prepared by method A above.

1,2,3,4,7-Pentachlorobicyclo[2.2.1]heptene-2 (VIII).—The distillation of the products of the reaction of zinc and acetic acid with V was usually discontinued after the tetrachloride VII had been collected. However, in one run with 100 g. of V, continued distillation gave 35 g. of XI (*ca.* 40%), b.p. 94–97° at 3 mm., which solidified on standing. The solid had m.p. 59.2–59.8° after three crystallizations from methanol.

Anal. Calcd. for $C_7H_5Cl_5$: C, 31.18; H, 1.89; Cl, 66.55. Found: C, 31.26; H, 1.89; Cl, 66.71.

1,4-Dichlorobicyclo[2.2.1]heptane (I).—A solution of 25 g. (0.11 mole) of compound VII and 17 g. (0.26 mole) of potassium hydroxide (85%) in 200 ml. of absolute methanol was shaken on a Parr hydrogenation apparatus at room temperature with 25 g. of Raney nickel. Hydrogen absorption was complete in less than 2 hr. The solution was filtered to remove the catalyst and then poured into 500 ml. of ice–water. The organic material was extracted three times with a total of 300 ml. of pentane and the combined extracts were dried over magnesium sulfate. Most of the solvent was removed by distillation through a 30-cm. column packed with glass helices. When the distillation flask was cooled the product separated as a solid, which was collected by filtration to give 15 g. (82%) of compound I, m.p. 78–79°. The solid was purified further by sublimation at 50°.

Anal. Calcd. for $C_7H_{10}Cl_2$: C, 50.95; H, 6.11; Cl, 42.96. Found: C, 50.90; H, 6.20; Cl, 42.90.

Conversion of I to Norbornane (X).—To a solution of 5 g. (0.03 mole) of compound I and 9.2 g. (0.12 mole) of *t*-butyl alcohol in 80 ml. of dry tetrahydrofuran was added 2 g. (0.28 g.-atom) of cut lithium ribbon. In 10–15 min., a vigorous exothermic reaction began and external cooling was necessary. After the initial reaction had subsided, the reaction mixture was heated under

reflux for 2 hr. It was then cooled, poured onto 1000 g. of ice, and extracted three times with a total of 200 ml. of pentane. The pentane solution was washed with water and dried over magnesium sulfate. The pentane was removed by distillation through a 30-cm. column packed with glass helices and the residue was analyzed by gas–liquid chromatography using a silicone oil on Chromosorb-P column. The retention time of the main peak (small solvent peaks were present also) was identical with that of an authentic norbornane sample. The infrared spectrum of a collected sample of the main peak was identical with the spectrum of norbornane.

Treatment of Compound I with Silver Nitrate.—A solution of compound XVI in saturated ethanolic silver nitrate was sealed in a test tube and heated at 100° for 30 hr. A shiny film formed on the walls of the tube dissolved completely on addition of 1:1 nitric acid and no nitric acid-insoluble material was formed in the reaction.

Acknowledgment.—The authors wish to thank the National Science Foundation for support of this research.

Reactions of Enol Ethers with Carbenes. III.[1] Vinyl Sulfides and Δ^3-Dihydrothiapyran[2]

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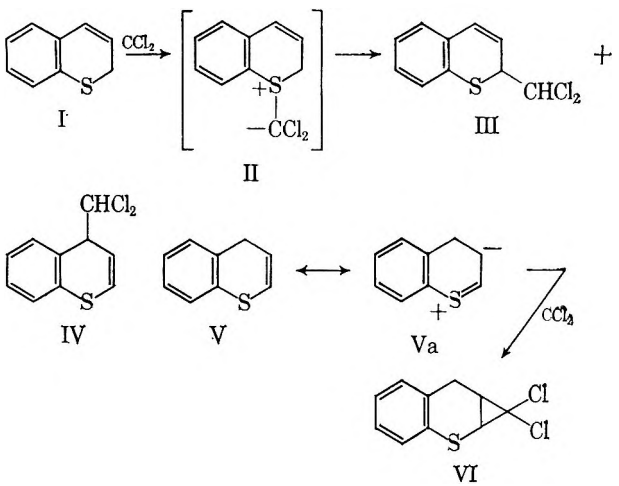
The reactions of cyclic and noncyclic vinyl sulfides with ethyl trichloroacetate and sodium methoxide lead to the formation of cyclopropanes in high yields (60–77%). The reaction of cyclic allyl sulfides with these reagents leads to the formation of unsaturated insertion products.

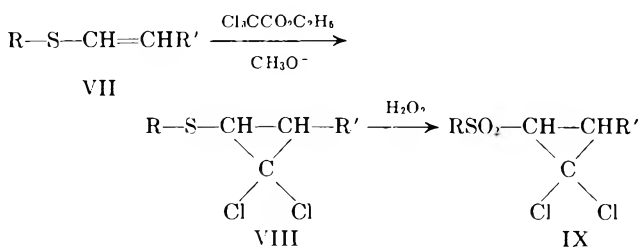
In a previous study[5] we observed that the reaction of 2H-1-benzothiapyran (I) with dichloroearbene[6] produced the insertion products III and IV, while reaction of the isomeric 4H-1-benzothiapyran (V), under identical conditions, produced only the cyclopropane VI.



The remarkable difference in behavior of these two isomeric olefins was attributed to the difference in nucleophilic character of the two double bonds (*i.e.*, V ↔ Va) relative to sulfur, and it was suggested that the reaction with I may involve the "ylid" intermediate II. Evidence was cited to indicate the carbanion derived directly from I or V was not an intermediate in either reaction.

In order to learn more about the generality and mechanism of these interesting transformations, an investigation of the reaction of saturated sulfides, and the reaction of α,β-, β,γ-, and γ,δ-unsaturated sulfides, with dichlorocarbene precursors was undertaken. This paper describes our preliminary findings with vinyl sulfides and the isomeric Δ^2- and Δ^3-dihydrothiapyrans.

The reactions of the α,β-unsaturated sulfides VIIa–d (1 mole) with ethyl trichloroacetate (1.1–1.6 moles)



VIIa, R = C_6H_5; R′ = H
b, R = C_6H_5; R′ = CH_3, *cis–trans*
c, R = *n*-C_4H_9; R′ = CH_3, *cis–trans*
d, R = *t*-C_4H_9; R′ = CH_3, *cis–trans*

and sodium methoxide (1.3–2.0 moles) was carried out in olefin-free petroleum ether (b.p. 30–60°) using conditions previously described for other olefins.[6] In each case high yields of the corresponding cyclopropanes VIII (60–77%) were obtained.[7] The dichlorocyclopropanes were characterized by their composition and spectra (infrared, ultraviolet, and n.m.r., see Experimental), and by conversion to the corresponding sulfones IX. The olefins VIIb–d were mixtures of *cis* and *trans* isomers, prepared by isomerization[8] of the corresponding allyl sulfides; the corresponding cyclopropanes VIIIb–d were, as expected, mixtures of *cis* and *trans* isomers (by n.m.r. and v.p.c.).

(1) For the proceeding article in this series, see W. E. Parham and M. O. Bhasvar, *J. Org. Chem.*, **29**, 1575 (1964).

(2) Supported in part by a grant (No. GP 159) from the National Science Foundation.

(3) In part from the Master's Thesis of L. Christensen, University of Minnesota, 1962.

(4) In part from the dissertation of S. H. Groen, University of Groningen, The Netherlands. O.E.C.D. Postgraduate Travel Grant awarded by Netherlands Organization for the Advancement of Pure Research (Z.W.O.).

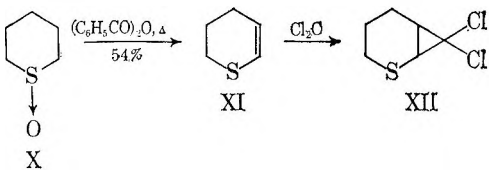
(5) W. E. Parham and R. Koncos, *J. Am. Chem. Soc.*, **83**, 4034 (1961).

(6) The reaction was carried out with ethyl trichloroacetate and sodium methoxide and is assumed to involve formation of trichloromethyl anion, dichlorocarbene, and methyl ethyl carbonate. *Cf.* W. E. Parham and E. Schweizer, *J. Org. Chem.*, **24**, 1733 (1959).

(7) Subsequent to the completion of our work E. P. Prilezhaeva, N. P. Petukhova, and M. F. Shostakovskii [*Dokl. Akad. Nauk SSSR*, **144**, 1059 (1962); *Chem. Abstr.*, **57**, 13,632 (1962)] described the preparation of the 1,1-dichlorocyclopropanes from ethyl vinyl sulfide and phenyl vinyl sulfide in 40 and 25.9% yield, respectively, by reaction with chloroform and potassium *t*-butylate. These authors also describe the sulfoxide and sulfone derivatives of the cyclopropyl adducts.

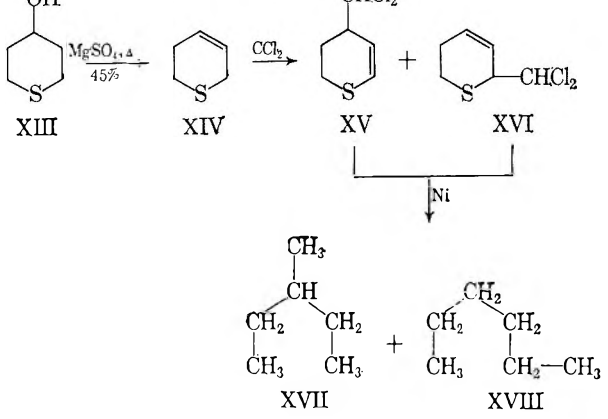
(8) D. S. Tarbell and M. A. McCall, *J. Am. Chem. Soc.*, **74**, 48 (1952).

A study of the reactions of the isomeric olefins Δ^2-dihydrothiapyran (XI) and Δ^3-dihydrothiapyran (XIV) with dichlorocarbene was of particular interest in view of the structural relationship of these olefins with the benzthiapyrans I and V. Δ^2-Dihydrothiapyran (XI) had previously been prepared by reaction of hydrogen sulfide with dihydropyran over activated alumina at 425°.[9] In our hands this procedure gave a product in variable yields and of questionable purity. A product of higher purity and stability was prepared from tetrahydrothiapyran 1-oxide (X) as shown in the accompanying equation. The usual procedure of using



acetic anhydride in the Pummerer reaction[1,10] gave unsatisfactory results since the product was contaminated with acetic anhydride and acetic acid, and was more difficult to purify; use of benzoic anhydride proved to be preferable for preparation of this olefin. The olefin reacted readily with ethyl trichloroacetate and sodium methoxide to give the expected 7,7-dichloro-2-thia[4.1.0]heptane (XII) in 70% yield. There was no evidence for the formation of unsaturated insertion products.

Δ^3-Dihydrothiapyran (XIV) was prepared from tetrahydrothiapyran-4-ol (XIII), and the infrared, ultraviolet, and nuclear magnetic resonance spectra



of this product were all consistent with the assigned structure. Reaction of the olefin XIV with ethyl trichloroacetate and sodium methoxide gave an unstable oil which showed considerable unsaturation. A distilled sample of the product had composition in close agreement with that calculated for the insertion products XV and or XVI, and spectral data (see Experimental) suggested that the product was a mixture of XV and XVI. While their instability precluded separation of XV and XVI, further evidence relative to the composition of the mixture was obtained by desulfurization with Raney nickel. The reaction was effected in alcohol solvent, and the volatile hydrocarbons were analyzed by vapor phase chromatography. 3-Methylpentane and *n*-hexane were found in approximately equal amounts, data consistent for the presence of both XV and XVI. A third component (one-fourth the intensity of *n*-hexane) was also present. The latter material was not identified; however, it was shown not to be 2-methylpentane.

It can be concluded, therefore, that the reaction of ethyl trichloroacetate and sodium methoxide with α,β-unsaturated sulfides leads generally to the corresponding 1,1-dichlorocyclopropanes, while reactions involving cyclic β,γ-unsaturated sulfides leads to insertion products.

Experimental

Vinyl Sulfides (VIIa–d).—Phenyl vinyl sulfide (VIIa, b.p. 84–86° at 12 mm., n^{20}D 1.5882, 74% yield; lit.[11] 83.7%, b.p. 94–97° at 25 mm.) was prepared as previously described[11] from β-chloroethyl phenyl sulfide; $\lambda_{max}^{95\%\ alc}$ 247 mμ (ϵ 8020), 264 mμ (ϵ 7740). ***cis,trans*-Phenyl propenyl sulfide** (VIIb, b.p. 48–51° at 0.5 mm., n^{20}D 1.5870, 79% yield; lit.[8] b.p. 61–69° at 1.3 mm., n^{20}D 1.5860, 95%) was prepared as previously described[8]; $\lambda_{max}^{95\%\ alc}$ 248 mμ (ϵ 10,180), 264.5 mμ (ϵ 10,800). ***cis,trans*-*n*-Butyl propenyl sulfide** (VIIc, 72% yield, b.p. 78.5–79.5° at 26 mm., n^{25}D 1.4742) was prepared by a procedure similar to that described[12] for the preparation of *t*-butyl propenyl sulfide. The vinyl sulfide VIIc showed $\lambda_{max}^{95\%\ alc}$ 225 mμ (ϵ 6340), 244 mμ (shoulder) (ϵ 3480); ν^{neat} C=C (1610 cm.$^{-1}$), *trans* CH=CH- (940 cm.$^{-1}$); n.m.r. spectrum[13] (20% in CCl_4): —CH= (multiplet between 279–338 c.p.s., weight 2.0), S-CH_2 (multiplet, 133–154 c.p.s., weight 1.9), =C—CH_3 and —CH_2— (complex 68–103 c.p.s., weight 6.9), CH_3—CH_2— (multiplet, 45–85 c.p.s., weight 3.1).

Anal. Calcd. for $C_7H_{14}S$: C, 64.54; H, 10.83. Found: C, 64.30; H, 10.95.

***cis*- and *trans*-*t*-butyl propenyl sulfide** (VIId, 23% yield, n^{27}D 1.4647, b.p. 140–142°; lit.[12] 66% yield, b.p. 139.1–140.8, n^{20}D 1.4700) was prepared as previously described[12] and showed $\lambda_{max}^{95\%\ alc}$ 249 mμ (ϵ 3260), 226 mμ (ϵ 3390); ν^{neat} C=C (1610 cm.$^{-1}$), *trans* —CH=CH— (940 cm.$^{-1}$); n.m.r. spectrum[13] (20% in CCl_4): —CH= (multiplet, 299–347 c.p.s., weight 2.0), *cis* and *trans* —CH_3 (multiplet, 85–96 c.p.s., weight 3.1), *cis* and *trans* $(CH_3)_3C$— (two nearly superimposed singlets, 66 and 68 c.p.s., weight ~9).

1,1-Dichlorocyclopropanes VIIIa–d. 1,1-Dichloro-2-phenylmercaptocyclopropane (VIIIa).—A 500-ml. flask was equipped with a nitrogen-inlet tube and a condenser equipped with a calcium chloride tube. Dry methanol (150 ml.) was added to the flask and sodium (6.5 g., 0.28 g.-atom) was added in small pieces. Nitrogen gas was admitted to the flask during the entire course of the reaction. When the sodium had dissolved, the excess methanol was removed from the stirred solution, and the residual solid was heated at 100° (12 mm.) for 30 min. Dry thiophene-free benzene (100 ml.) was added to the solid, and most of the benzene was evaporated. Olefin-free petroleum ether (200 ml., b.p. 30–60°) and phenyl vinyl sulfide (Ia, 29.5 g., 0.217 mole) were added; the resulting mixture was cooled in an ice bath and ethyl trichloroacetate (46.0 g., 0.240 mole) was added dropwise over a 30-min. period. The mixture was stirred under a nitrogen atmosphere for 6 hr. at ice-bath temperature, and then was allowed to warm to room temperature overnight. Water (80 ml.) was added to the reaction mixture, the organic layer was separated, and the aqueous phase was extracted with petroleum ether (50 ml., b.p. 30–60°). The combined organic extracts were dried ($MgSO_4$) and concentrated in a rotatory evaporator. Distillation of the residue through a 3-in. Vigreux column gave (a) recovered Ia, 3.0 g., and (b) the cyclopropane VIIIa, 29.0 g. (61% yield, b.p. 95–99° at 1 mm., n^{20}D 1.5905).

A sample of VIIIa was redistilled (b.p. 86–87° at 0.4 mm., n^{20}D 1.5915, m.p. 24–24.5°) for analysis; $\lambda_{max}^{95\%\ alc}$ 240 mμ (ϵ 7640),

(9) (a) R. F. Naylor, *J. Chem. Soc.*, 2749 (1949); (b) Yu K. Yur'ev, T. B. Dubrovina, and E. P. Tregribov, *J. Gen. Chem. USSR* (Engl. Trans.), **16**, 843 (1946); *Chem. Abstr.*, **41**, 1654 (1947).

(10) W. E. Parham and M. D. Bhavsar, *J. Org. Chem.*, **28**, 2686 (1963).

(11) F. Montanari, *Boll. sci. fac. chim. ind. Bologna*, **14**, 55 (1956); *Chem. Abstr.*, **51**, 5723 (1957).

(12) D. S. Tarbell and W. E. Lovett, *J. Am. Chem. Soc.*, **78**, 2259 (1956).

(13) The n.m.r. spectra were determined on a Varian V 4302 at 56.44 Mc. (reference, tetramethylsilane). Weights are estimates obtained by using a planimeter.

250 mμ (ε 7300); n.m.r. spectrum[14] (pure liquid): aromatic H (multiplet, 419–445 c.p.s., weight 5), —S—CH (quartet, 157, 164, 167, and 174 c.p.s., weight 1.0), (*cis*)H—C—H(*trans*) [(part of an ABX system in which second-order effects are apparent in intensities), H (*cis*) (quartet, 94, 101, 104, and 111 c.p.s., weight 1), H (*trans*) (triplet, 68, 76, and 83 c.p.s., weight 1), *J* (*gem*) = *J* (*trans*) = 7.3 c.p.s., *J* (*cis*) = 10.1 c.p.s.].[15]

Anal. Calcd. for $C_9H_8Cl_2S$: C, 49.33; H, 3.68; Cl, 32.36; S, 14.63. Found: C, 49.21; H, 3.71; Cl, 32.26; S, 14.75.

cis- and *trans*-**1,1-Dichloro-2-phenylmercapto-3-methylcyclopropane** (**VIIIb**).—The reaction was carried out as described for VIIIa using sodium (3.0 g., 0.13 g.-atom), phenyl propenyl sulfide (13.0 g., 0.087 mole), ethyl trichloroacetate (23.0 g., 0.120 mole), and olefin-free petroleum ether (100 ml., b.p. 30–60°). The yield of VIIIb (b.p. 95–105° at 0.6 mm., $n^{20}D$ 1.5844) was 15.5 g. (77%). The sample was redistilled for analysis; b.p. 90–91.5° (0.3 mm.); $n^{20}D$ 1.5852 (12.0 g., 59% yield); $\lambda_{max}^{95\% \text{ alc}}$ 240 mμ (ε 8030), 251 mμ (ε 8270); n.m.r. spectrum[14] (pure liquid) of *cis*- and *trans*-VIIIb: aromatic H (multiplet, 417–440 c.p.s., weight 5), —S—CH (doublet, 173 and 163 c.p.s., *J* (*cis*) = 10 c.p.s., and doublet, 135 and 142 c.p.s., *J* (*trans*) = 7.0 c.p.s., combined weight 1), $CHCH_3$ (multiplet, 77–127 c.p.s., weight 1), $CHCH_3$ [doublets (?), 63, 65, 69, 71 c.p.s., weight 2.8]; v.p.c. of *cis*-*trans*-VIIIb: one peak with shoulder (8.9% Reoplex on Chromosorb 60–80 M at 200°).

Anal. Calcd. for $C_{10}H_{10}Cl_2S$: C, 51.51; H, 4.32; Cl, 30.42; S, 13.75. Found: C, 51.45; H, 4.40; Cl, 30.10; S, 13.75.

1,1-Dichloro-2-*n*-butylmercapto-3-methylcyclopropane (**VIIIc**).—The procedure was essentially that described for VIIIa except commercial sodium methoxide was employed. From *n*-butyl propenyl sulfide (10.0 g., 0.077 mole), ethyl trichloroacetate (19.1 g., 0.100 mole), sodium methoxide (7.0 g., 0.13 mole, weighed in a drybox), and petroleum ether (100 ml.) there was obtained 9.8 g. (60% yield) of VIIIc (b.p. 74–76° at 1.6 mm., $n^{25}D$ 1.4967); $\lambda_{sh}^{95\% \text{ alc}}$ 226 mμ (ε 260). The n.m.r. spectrum[13] of *cis*- and *trans*-VIIIc (20% in CCl_4) showed no absorption above 162 c.p.s. (no unsaturation).

Anal. Calcd. for $C_8H_{14}Cl_2S$: C, 45.07; H, 6.62. Found: C, 44.79; H, 6.67.

1,1-Dichloro-2-*t*-butylmercapto-3-methylcyclopropane (**VIIId**).—The reaction of *t*-butyl propenyl sulfide (6.0 g., 0.046 mole), ethyl trichloroacetate (14.0 g., 0.073 mole), commercial sodium methoxide (5.0 g., 0.093 mole) and petroleum ether (50 ml.) was carried out as described for VIIIc, and gave 6.5 g. (66% yield) of VIIId (b.p. 62–67° at 1.5 mm., $n^{25}D$ 1.4943). A sample was redistilled (b.p. 56–57° at 1.0 mm., $n^{25}D$ 1.4935) for analysis; $\lambda_{sh}^{95\% \text{ alc}}$ 225 mμ (ε 440); n.m.r. spectrum[13] (20% in CCl_4) showed no peaks above 152 c.p.s. (no unsaturation).

Anal. Calcd. for $C_8H_{14}Cl_2S$: C, 45.07; H, 6.62. Found: C, 44.87; H, 6.40.

Preparation of the Sulfones IXa–d. 1,1-Dichloro-2-phenylsulfonylcyclopropane (**IXa**).—A stirred mixture of sulfide VIIIa (3.0 g., 0.014 mole), acetic acid (20 ml.), and hydrogen peroxide (6 ml., 30%) was heated at 100° for 3 hr. The mixture was cooled and water (100 ml.) was added. The solid obtained (3.3 g., 94% yield) melted at 87–88° when crystallized from water–ethanol.

Anal. Calcd. for $C_9H_8Cl_2O_2S$: C, 43.04; H, 3.21. Found: C, 43.04; H, 3.29.

cis- and *trans*-**1,1-Dichloro-2-phenylsulfonyl-3-methylcyclopropane** (**IXb**).—The procedure used for oxidation of VIIIb was essentially that described for IXa. The oil obtained subsequent to addition of water was extracted with ether and the ether extract was washed with saturated sodium carbonate and finally with water. The oily mixture of *cis*- and *trans*-IXa (3.2 g., 92% yield) obtained from the dried ether was crystallized by cooling (−70°) a solution prepared by dissolving the mixture in ethanol (two parts)–petroleum ether (one part). The mixture melted at 67–77°.

Anal. Calcd. for $C_{10}H_{10}Cl_2O_2S$: C, 45.29; H, 3.80. Found: C, 45.10; H, 4.01.

cis- and *trans*-**1,1-Dichloro-2-*n*-butylsulfonyl-3-methylcyclopropane** (**IXc**).—*cis*,*trans*-Sulfone IXc was obtained from VIIIc as an oil (2.4 g., 83% yield). The infrared spectrum of the crude product was essentially identical with that of a sample obtained by redistillation (1.4 g., 46% yield, $n^{26}D$ 1.4930, b.p. 81–82.5° at 0.05 mm.).

Anal. Calcd. for $C_8H_{14}Cl_2O_2S$: C, 39.19; H, 5.75. Found: C, 39.04; H, 5.76.

cis- and *trans*-**1,1-Dichloro-2-*t*-butylsulfonyl-3-methylcyclopropane** (**IXd**).—The product was obtained as a solid, 94% yield, m.p. 106–112° (from ethanol).

Anal. Calcd. for $C_8H_{14}Cl_2O_2S$: C, 39.19; H, 5.75. Found: C, 39.29; H, 5.82.

The sample used for analysis (m.p. 106–112°) was recrystallized three times from ethanol; the melting point was raised to 134–137°.

Anal. Found: C, 39.19; H, 5.72.

Δ²-Dihydrothiapyran (**XI**).—A mixture of tetrahydrothiapyran 1-oxide (52.7 g., 0.45 mole), prepared in 92% yield by oxidation of tetrahydrothiapyran with 30% hydrogen peroxide in absence of solvent,[16] and benzoic anhydride (117 g., 0.52 mole) in dry benzene (75 ml.) was heated at the reflux temperature for 14 hr. The benzene was removed by distillation at atmospheric pressure using an oil-bath temperature of 100–110°. When all of the benzene had been removed, the pressure was reduced, and the product XI was distilled rapidly at 66–69° (55–60 mm.). The product was redistilled through a small spiral wire column to give pure Δ²-dihydrothiapyran (24.5 g., 54% yield, b.p. 66° at 57 mm., $n^{26}D$ 1.5363; lit.[9b] b.p. 143.6–144.2°, $n^{20}D$ 1.5328); $\lambda_{max}^{95\% \text{ alc}}$ 229 mμ (ε 5420), 249 mμ (ε 2810); ν^{neat} C=C (1604 cm.$^{-1}$).

Anal. Calcd. for C_5H_8S: C, 59.95; H, 8.05. Found: 59.93; H, 8.35.

Tetrahydrothiapyran-4-one.—Several procedures and combinations of procedures previously described[17] were employed; however, yields were inconsistent and varied from 0–39%. Methyl thiodipropionate[18] (103 g., 0.50 mole) was added dropwise over a period of 1 hr. to a cold (0–5°) stirred (magnetic) suspension of fresh commercial sodium methoxide (60 g., 1.11 mole, weighed in a drybox) in dry ether (400 ml.). The mixture was kept cold for 6–8 hr. and then allowed to stir at room temperature for 20–22 hr. Sulfuric acid (15%, 1 l.) was then added, the ether was distilled, and the resulting mixture was heated with stirring at the reflux temperature for 12 hr. The mixture was cooled and extracted with three 300-ml. portions of ether. The ether was washed free of acid with strong aqueous bicarbonate, and the ether extract was dried ($MgSO_4$) and concentrated. The yellow oil crystallized when cooled and was recrystallized from ether–petroleum ether (b.p. 30–60°) to give the ketone as a white solid (23 g., 39%, m.p. 62–65°, lit.[17b] m.p. 64–66°).

Tetrahydrothiapyran-4-ol (**XIII**).—Tetrahydrothiapyran-4-one (24.0 g., 0.21 mole) was reduced with sodium borohydride (4.0 g., 0.11 mole) in 95% ethanol (100 ml.). The hydride was added at room temperature over a 2-hr. period, and the resulting mixture was heated at reflux for 4 hr. The cooled mixture was neutralized (litmus) with dilute hydrochloric acid, and the resulting mixture was dried (K_2CO_3) and distilled. Tetrahydrothiapyran-4-ol (XIII, 18 g., 73% yield, b.p. 72° at 1 mm.; lit.[19] b.p. 84–85° at 1.8 mm., m.p. 49°) was obtained as a liquid which solidified in the receiver.

Δ³-Dihydrothiapyran (**XIV**).—Crushed tetrahydrothiapyran-4-ol (10.0 g., 0.085 mole) and anhydrous magnesium sulfate (100 g., 0.84 mole) were heated in a nitrogen atmosphere at 200° for 4 hr. in a flask equipped with a condenser. The olefin, containing some water, was distilled from the magnesium sulfate. The olefin from three runs was dissolved in ether, dried with magnesium sulfate, and distilled. Δ³-Dihydrothiapyran (11.5 g., 45% yield) was obtained as a clear liquid (b.p. 75° at 58 mm., $n^{21.5}D$ 1.5305; lit.[9a] b.p. 35–36° at 12 mm., $n^{20}D$ 1.5328); $\lambda^{95\% \text{ alc}}$ no absorption above 220 mμ; ν^{neat} C=C (1652 cm.$^{-1}$).

Anal. Calcd. for C_5H_8S: C, 59.95; H, 8.05. Found: C, 59.92; H, 8.16.

7,7-Dichloro-2-thiabicyclo[4.1.0]heptane (**XII**).—The reaction of Δ²-dihydrothiapyran (XI, 12.86 g., 0.13 mole), ethyl trichloroacetate (47.69 g., 0.25 mole), and commercial sodium methoxide (14.0 g., 0.26 mole) in olefin-free petroleum ether was carried out as described for the other vinyl sulfides. 7,7-Dichloro-2-thia-

(14) Taken on a Varian A60 at 60 Mc. (reference, tetramethylsilane). Weights were obtained by use of an integrator.

(15) Compare T. D. Graham and M. T. Rogers, *J. Am. Chem. Soc.*, **84**, 2249 (1962).

(16) D. S. Tarbell and C. Weaver, *ibid.*, **63**, 2939 (1941).

(17) (a) C. Barkenbus, V. C. Midkiff, and R. M. Newman, *J. Org. Chem.*, **16**, 232 (1951); (b) C. M. Bennett and L. V. D. Scorah, *J. Chem. Soc.*, 199 (1927).

(18) L. L. Gershbein and C. D. Hurd, *J. Am. Chem. Soc.*, **69**, 241 (1947).

(19) M. Protiva and E. Adlerova, *Chimia* (Aarau), **12**, 145 (1958).

bicyclo[4.1.0]heptane (XII, 16.35 g., 70% yield, b.p. 71° at 0.75 mm., $n^{25}D$ 1.5604) was distilled through a spiral-wire column.

The infrared and n.m.r. spectrum of XII were consistent with the assigned structure and showed absence of any unsaturation (no insertion detected).

Anal. Calcd. for $C_6H_9Cl_2S$: C, 39.36; H, 4.40. Found: C, 39.53; H, 4.76.

Reaction of Δ^3-Dihydrothiapyran (XIV) with Dichlorocarbene.—The reaction of XIV (6.64 g., 0.066 mole) with ethyl trichloroacetate (25.24 g., 0.13 mole) and commercial sodium methoxide (7.5 g., 0.14 mole) was carried out by a procedure identical with that employed with XI. The product was distilled rapidly (b.p. 65–110° at 0.25 mm., 4.3 g., 35% calcd. as XV or XVI) without use of a fractionating column. The black tarry residue was not further processed. The distillate was fractionated through a spiral-wire column to give (a) 1.0 g., b.p. 52–64° (0.4 mm.), $n^{25}D$ 1.5717, yellow oil which rapidly turned brown; (b) 1.87 g., clear, b.p. 64–68° (0.4 mm.), $n^{25}D$ 1.5700; and (c) 1.28 g., mostly hold up in column, $n^{25}D$ 1.5899. The infrared spectra of all of these fractions showed the presence of considerable unsaturation in the 1608–1680-cm.$^{-1}$ region.

Fraction b showed $\lambda_{max}^{95\% \text{ etc}}$ 233 mμ (ε 4970), 248 mμ (ε 4330); ν^{neat} C=C (1608 s and 1665 w cm.$^{-1}$); n.m.r. spectrum[13]: strong broad absorption in the region τ 3.6–4.6 (317–362 c.p.s.), consistent with the unsaturated insertion products XV and XVI.

Anal. Calcd. for $C_6H_8Cl_2S$: C, 39.36; H, 4.40. Found: C, 39.62; H, 4.37.

Desulfurization Reactions. A. XV and XVI.—The mixture of XV and XVI (1.4 g., fraction b, above) in 75% ethanol–water (100 ml.) and Raney nickel (about 6 g.)[5] was heated at the reflux temperature for 1.5 hr. Water (25 ml.) was added, and the resulting mixture was distilled. The distillate was diluted with water and then was extracted with ether (5 ml.).

Vapor phase chromatography of the ether extract using a diisodecyl phthalate column (set at 55°, carrier gas helium, flow 15 p.s.i.) showed the presence of three components in addition to solvents. Two of the compounds were identified as *n*-hexane and 3-methylpentane (approximately equal amounts). The other product (approximately 0.25 peak intensity of *n*-hexane) was not identified; however, it was shown not to be 2-methylpentane.

B. XII.—Reaction of XII (1.7 g.) with Raney nickel (~6.0 g.) was carried out as described in A, above. Analysis of the ether solution by v.p.c. (same conditions as above) showed *n*-hexane and 2-methylpentane to be present in the approximate ratio, 3:1.

Reaction of Enol Ethers with Carbenes. IV.[1] Allyl Sulfides and Saturated Sulfides[2]

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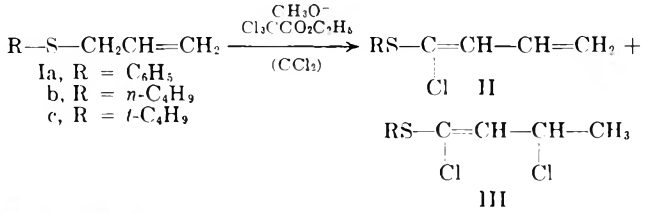
The reaction of ethyl trichloroacetate and sodium methoxide with noncyclic allyl sulfides leads to the formation of 1-chloro 1-substituted mercaptobutadienes in high yields, together with some olefins derived by addition of hydrogen chloride to the butadienes. The course of these reactions is discussed, and additional data concerning reaction of saturated sulfides with ethyl trichloroacetate and sodium methoxide is presented. It is shown that saturated sulfides inhibit the formation of dichlorocyclopropyl adducts from olefins such as cyclohexene. Evidence is also presented for a minor chlorination process in reactions involving ethyl trichloroacetate and sodium methoxide.

In previous reports we have described evidence which shows that dichlorocarbene, generated from ethyl trichloroacetate and sodium methoxide,[4] reacts with vinyl sulfides to give cyclopropanes,[1] and with cyclic allyl sulfides[1,5] to give insertion products. This paper describes reactions of open-chain allyl sulfides with dichlorocarbene precursors, and presents preliminary data concerning reactions of dichlorocarbene with saturated sulfides.

The reaction of the allyl sulfides (I, 1 mole) with ethyl trichloroacetate (1–1.5 moles) and sodium methoxide (1–2 moles) were carried out at ice-bath temperature, and the reaction mixtures were allowed to warm to room temperature overnight. The allyl sulfides studied were allyl phenyl sulfide (Ia), allyl *n*-butyl sulfide (Ib), and allyl *t*-butyl sulfide (Ic); evidence will be presented showing that the principal reaction in each case is properly summarized by the equation I → II + III.



A. Reaction of Allyl Phenyl Sulfide.—The reaction of allyl phenyl sulfide (Ia) with ethyl trichloroacetate and sodium methoxide afforded as a principal product a liquid A (IIa) in 46–60% yield with the empirical formula $C_{10}H_9ClS$. Vapor phase chromatography of this product on Reoplex and on Carbowax columns showed only one peak.

The infrared spectrum of the product showed no alkyl hydrogen, but did show olefinic absorption at 1610, 900–910, 980, and 1835 cm.$^{-1}$ characteristic of the —CH=CH_2 grouping. The ultraviolet spectrum of IIa (95% alcohol) showed λ_{max} 244 mμ (ε 16,370), (shoulder), 274 mμ (ε 8680); the n.m.r. spectrum[6] (neat) was complex but showed =CH_2 (complex 282–312 c.p.s., weight 2.0), —CH= (complex 363–405 c.p.s., weight 1.9), and aromatic H (complex 408–430 c.p.s., weight 5.4).

The product gave a colorless polymeric sulfone when treated with hydrogen peroxide in acetone, or with 1 equiv. of perbenzoic acid in benzene or chloroform; however, a solid derivative (m.p. 143–144°, >40%

(1) For the preceeding article in this series, see W. E. Parham, L. Christensen, S. H. Groen, and R. M. Dodson, *J. Org. Chem.*, **29**, 2211 (1964).

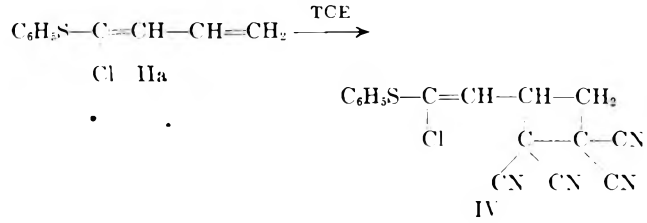
(2) Supported in part by a grant (no. GP-159) from the National Science Foundation, and by a grant from the U. S. Army Research Office (Durham), Contract No. DA-ORD-31-124-61-GB.

(3) From the dissertation of S. H. Groen, the University of Groningen, The Netherlands. O.E.C.D. Postgraduate Travel Grant awarded by the Netherlands Organization for the Advancement of Pure Research (Z.W.O.).

(4) W. E. Parham and E. E. Schweizer, *J. Org. Chem.*, **24**, 1733 (1959).

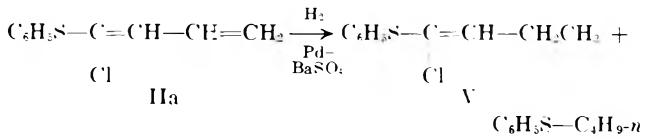
(5) W. E. Parham and R. Koncos, *J. Am. Chem. Soc.*, **83**, 4034 (1961).

(6) The n.m.r. spectra were taken on Varian A60 at 60 Mc. (reference tetramethylsilane). Weights were obtained by integration.



yield) was formed with tetracyanoethylene.[7] The tetracyanoethylene (TCE) adduct was assigned structure IV[8] on the basis of the following evidence: empirical formula, $C_{16}H_9ClN_4S$; infrared spectrum (halo carbon–Nujol mull): C=C (1600 cm.$^{-1}$), CN (2252 cm.$^{-1}$), absence of $CH=CH_2$ absorption; ultraviolet spectrum (95% alcohol): λ_{max} 215 mμ (ε 33,510), 246 mμ (ε 19,590); n.m.r. spectrum[9] (<1% in $DCCl_3$): aromatic H (near 423 c.p.s.), $=CH-CH-C(CN)_2$ (multiplet, 232–265 c.p.s.), $=CH-CH$ (doublet, 315 and 323 c.p.s.), CH_2 (multiplet, 150–190 c.p.s.); n.m.r. spectrum[9] (25% in acetone): aromatic H (complex near 422 c.p.s., weight ~5.3), $=CH-$ (doublet, 353 and 360 c.p.s., weight ~1.0, J = 7.2 c.p.s.), $=CH-CH$ (multiplet, 248–280 c.p.s., weight ~1.1), CH_2 (near solvent absorption). Compound IV gave a red product in boiling methanol[7] which was not further investigated.

Confirmation of the structure of the diene as IIa was achieved by its reduction, with hydrogen in the presence of excess black 5% palladium on barium sulfate, to V. The olefin was obtained in 60–68% yield and structure V was assigned on the basis of the

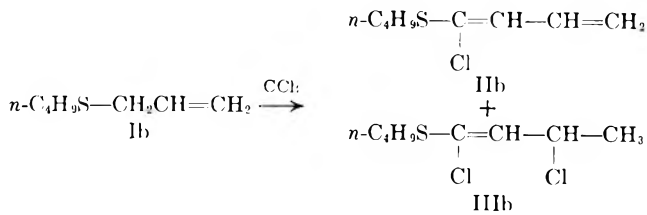


following evidence: empirical formula, $C_{10}H_{11}ClS$; ultraviolet spectrum (95% alcohol): λ_{max} 213 mμ (ε 14,590), (shoulder) 221 mμ (ε 8070), 248 mμ (ε 10,250); infrared spectrum: CH_2 (2932 cm.$^{-1}$), CH_3 (2970, 2875, and 1370 cm.$^{-1}$), C=C (1600 cm.$^{-1}$), trisubstituted olefin (840 cm.$^{-1}$); n.m.r. spectrum[9] (20% in CCl_4): aromatic H (near 408 c.p.s., weight ~4.9), $=CH-$ (triplet, 343, 350, 357 c.p.s., J = 6.9 c.p.s., weight ~1.0), $-CH_2-$ (multiplet, 112–147 c.p.s., weight ~2.0), CH_3 (triplet, 49, 57, 65 c.p.s., J = 7.7 c.p.s., weight ~3.1). The n.m.r. spectrum is exactly that expected for V and is incompatable with any alternative position isomer. 1-Chloro-1-phenylmercaptobutene-1 was further characterized by oxidation (H_2O_2) to 1-chloro-1-phenylsulfonylbutene-1 (m.p. 31–32.5°). The infrared and nuclear magnetic resonance spectra of the sulfone are consistent with the assigned structure and are reported in the Experimental section.

n-Butyl phenyl sulfide was also isolated from the reduction products of IIa, and was identified by comparison of its infrared spectrum and its palladious chloride complex with those of authentic samples.

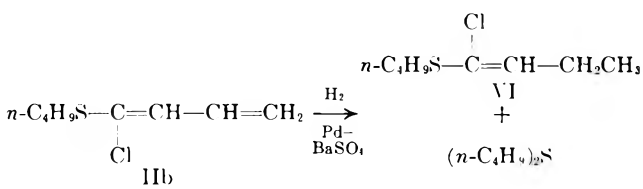
The reaction of allyl phenyl sulfide with the dichlorocarbene precursors produced, in addition to the major product IIa, a small amount of higher boiling liquid which eliminated hydrogen chloride upon distillation. When 2 equiv. of base were employed in the reaction, the higher boiling product was not detected, and the diene IIa was isolated pure in 60% yield. The structure IIIa was assigned to this second product by analogy (see IIIb, below) and is thought to form by addition of hydrogen chloride to the diene IIa.

B. Reaction of Allyl *n*-Butyl Sulfide.—Two products were isolated from the reaction of allyl *n*-butyl sulfide and the dichlorocarbene precursors: a liquid A, identified as *cis* and *trans* IIb, and a liquid B, identified as *cis* and *trans* IIIb.



It was evident from the empirical formula and infrared, ultraviolet, and n.m.r. spectra (see Experimental) that the major product (A, IIb, 68% yield) was structurally related to 1-chloro-1-phenylmercaptobutadiene (IIa). Further evidence for both *cis* and *trans* IIb was the appearance of two close peaks when analytically pure diene was chromatographed (v.p.c.) on Carbowax, and one peak with a shoulder when chromatographed on silicone grease.

Additional evidence for the structure of A as 1-*n*-butylmercapto-1-chlorobutadiene (IIb) was obtained by its reduction, with hydrogen in the presence of excess palladium on barium sulfate, to VI.



The reduction did not proceed as selectively as did that of IIa; a total of 45% by weight of product was recovered which was composed of (1) di-*n*-butyl sulfide (proved by infrared and by vapor phase chromatography), approximately 25%; (2) recovered IIb, a minor component (by v.p.c.); and (3) the olefin VI (principal product by v.p.c.), which was characterized by elemental and spectral (infrared, ultraviolet, and n.m.r.) analysis (see Experimental).

In some runs involving reaction of allyl *n*-butyl sulfide with ethyl trichloroacetate and sodium methoxide a higher boiling liquid was obtained. This product was not obtained analytically pure since it evolved some hydrogen chloride upon distillation. The composition of this product was, however, in agreement with the molecular formula, $C_8H_{14}Cl_2S$. This formula corresponds to two products which could logically be expected from the reaction: (1) the insertion product VIII, IX, or XVIII; or (2) the product IIIb formed by addition of hydrogen chloride to the diene IIb. The

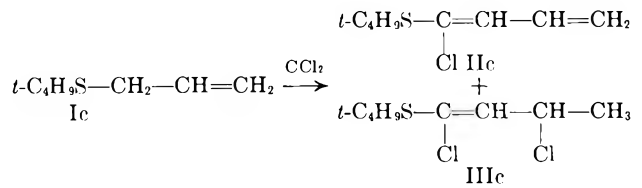
(7) For discussion of reactions of olefins with tetracyanoethylene, see J. K. Williams, D. W. Wiley, and B. C. McKusick, *J. Am. Chem. Soc.*, **84**, 2210 (1962); **84**, 2216 (1962).

(8) The 1,4 Diels–Alder adduct seems less probable since vinyl hydrogen absorption in the n.m.r. spectrum would not be expected near 250 c.p.s. for such a product.

(9) The n.m.r. spectra were taken on Varian V 4302 at 56.44 Mc. (reference, tetramethylsilane). Weights are estimates obtained by using a planimeter.

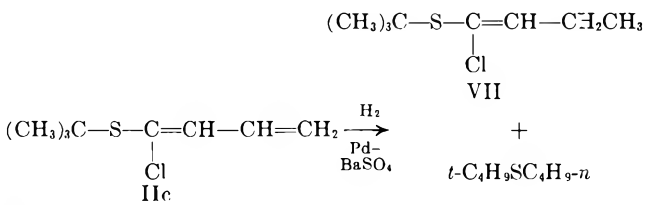
infrared, ultraviolet, and n.m.r. spectra (see Experimental) were consistent with those expected for the diene–HCl addition product IIIb, but not for the insertion products VIII, IX, and XVIII. The structure of this material was shown to be IIIb by its independent synthesis by reaction of 1-*n*-butylmercapto-1-chlorobutadiene (IIb) with anhydrous hydrogen chloride.

C. Reaction of Allyl *t*-Butyl Sulfide.—The principal product (66% yield) obtained by reaction of allyl *t*-butyl sulfide (Ic) with ethyl trichloroacetate and sodium methoxide was established, by processes similar to those described in A and B, above, to be 1-*t*-butylmercapto-1-chlorobutadiene (IIc). The minor component was identified as *cis* and *trans* IIIc.



The major compound showed one main peak, together with one small peak or shoulder, upon vapor phase chromatography using Reoplex, and only one peak using a silicone grease column as well as with two other columns employed. Whether a single isomer of IIc was formed predominantly, or whether the *cis* and *trans* isomers were not well resolved during chromatography, was not established. The diene IIc had the composition calculated for $C_8H_{13}ClS$. The ultraviolet, infrared, and nuclear magnetic resonance spectra (see Experimental) are comparable with those observed for IIa and IIb, and are consistent with the assigned structure IIc.

Reduction of IIc with brown 5% palladium on barium sulfate gave a 30% by weight recovery of product which was shown to be composed of VII and



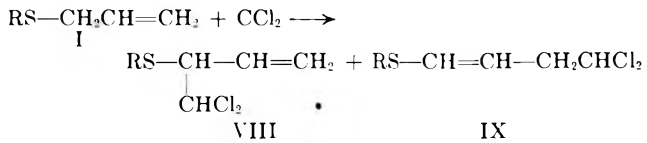
t-butyl *n*-butyl sulfide in the approximate ratio 4 to 1. The principal reduction product was assigned the structure *cis* and *trans* VII on the basis of elemental and spectral (ultraviolet, infrared, n.m.r.) analysis which are discussed in the Experimental section.

The n.m.r. spectrum of VII provided convincing evidence for both *cis* and *trans* isomers. Further evidence for *cis* and *trans* isomers of VII was provided by oxidation to the corresponding mixed sulfones. The n.m.r. spectrum of the mixture of *cis*- and *trans*-sulfone showed a split peak for the *cis* and *trans* $(CH_3)_3$-C—S groups, nearly identical triplets for the *cis* and *trans* CH_3 groups, and the —CH= group changed from four peaks (two superimposed triplets, two peaks in common) in the sulfide to five peaks (two superimposed triplets, one peak in common).

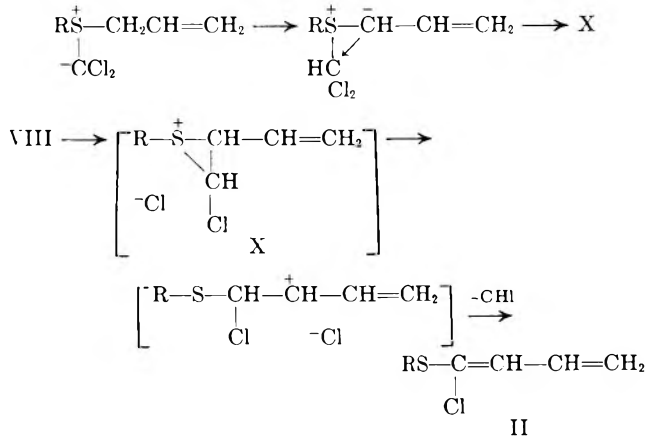
The higher boiling product obtained in some reactions with Ic was shown to be structurally related to IIIb and was assigned the structure *cis* and *trans* IIIc by analysis of the n.m.r., infrared, and ultraviolet spectra (see Experimental).

Discussion

By analogy[1,5] to reactions involving cyclic allyl sulfides and dichlorocarbene, the expected products of reaction of I with ethyl trichloroacetate and sodium methoxide are the insertion products VIII and IX.

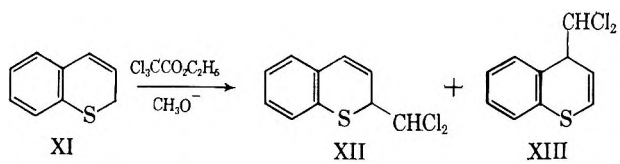


Formation of the substituted butadienes (II), instead, is consistent with this expected course of reaction if it is assumed that the preferred insertion product is VIII,[10]

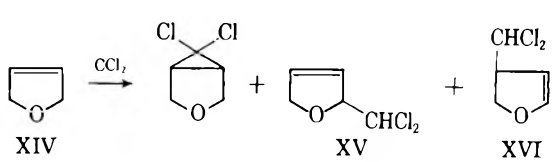


and that VIII decomposes as shown (VIII → X → II). Both of these assumptions are reasonable ones, although alternatives for the conversion of I to II (*i.e.*, I → XVII → XVIII → II) must be considered.

In the case of 2H-1-benzothiapyran (XI), the insertion products XII and XIII were formed in ratio of



approximately 2 to 1.[5] Furthermore, in the reaction of 2,5-dihydrofuran (XIV) with ethyl trichloroacetate and potassium *t*-butylate, in which both addition and insertion were noted, XV, but not XVI, was formed.[11]



With respect to rearrangement of VIII to II, as shown in VIII → X → II, there is a wealth of analogy for related rearrangements of sulfides substituted in the

(10) It is possible that X is formed directly from the proposed intermediate "ylid" (XVII). This possibility is considered later in the discussion.

(11) J. C. Anderson and C. B. Reese, *Chem. Ind.* (London), 575 (1963).

TABLE I

REACTION OF SODIUM METHOXIDE (0.13 MOLE), CYCLOHEXENE (0.10 MOLE), AND ETHYL TRICHLOROACETATE (0.13 MOLE) IN PETROLEUM ETHER CONTAINING *n*-BUTYL PHENYL SULFIDE

Sulfide added, mole	Yield of dichloronorcarane, % Impure	Pure	Recovered cyclohexene (by v.p.c.), %	Recovered sulfide, %	Recovered CCl_4, mole
0	79	73	<5		0.011
0.013	50	44	28	Small[a]	0.015
0.05	46	36	38	75[b]	0.011
0.10	30	25	48	80[b]	0.021

[a] Not determined quantitatively. [b] A small amount of higher boiling product, formulated as the sulfide corresponding to sulfone XXIV, was detected.

β-position in a manner which permits formation of three-membered ring sulfonium intermediates.[12]

A number of mechanisms can be written for the insertion of dichlorocarbene into allyl sulfides. While the course of this reaction has not been established, we have gained additional information concerning this insertion reaction which we would like to report.

Of the three gross reaction paths shown in eq. 1–3, the first can now be eliminated with some certainty.

$$\underset{\text{I}}{\text{RSCH}_2\text{CH}{=}\text{CH}_2} \underset{\text{BH}}{\overset{\text{B}^-}{\rightleftharpoons}} \text{RSCH}{-}\text{CH}{=}\text{CH}_2 \longrightarrow \text{products} \quad (1)$$

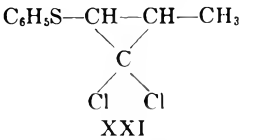
$$\text{I} + \text{CCl}_2 \longrightarrow \begin{cases} \rightarrow \text{RSCCl}_2{-}\text{CH}_2\text{CH}{=}\text{CH}_2 \xrightarrow{-\text{HCl}} \text{II} \\ \underset{\text{XVII}}{\text{RS}{-}\text{CH}_2\text{CH}{=}\text{CH}_2} \\ \quad\vdots \\ \text{CCl}_2 \rightarrow \text{VIII, IX, and/or X}^{10} \longrightarrow \text{products} \end{cases} \quad (2)$$

$$\text{I} + \text{CCl}_2 \xrightarrow{\text{direct insertion}} \text{products} \quad (3)$$

It was shown in this study that Ia is not isomerized to the vinyl sulfide XX by sodium methoxide under

$$\underset{\text{Ia}}{\text{C}_6\text{H}_5\text{S}{-}\text{CH}_2\text{CH}{=}\text{CH}_2} \underset{\text{BH}}{\overset{\text{B}^-}{\rightleftharpoons}} \underset{\text{XIXa}}{\text{C}_6\text{H}_5\text{S}{-}\text{CH}{-}\text{CH}{=}\text{CH}_2} \quad \underset{\text{XIXb}}{\text{C}_6\text{H}_5\text{SCH}{=}\text{CH}{-}\text{CH}_2^-} \longrightarrow \underset{\text{XX}}{\text{C}_6\text{H}_5\text{SCH}{=}\text{CHCH}_3}$$

conditions employed for the dichlorocarbene reaction; furthermore, the olefin recovered from the carbene reactions was Ia, uncontaminated by XX.[13] Of more significance, however, was the observation that potassium *t*-butylate in petroleum ether (b.p. 30–60°) does cause isomerization of Ia to XX, and does consequently, involve formation of the anion XIXa ↔ XIXb. When Ia was treated with potassium *t*-butylate and ethyl trichloroacetate, considerable cyclopropane XXI was formed.[14] Since no cyclopropanes were evident in reactions involving I when methoxide was used as base,



XXI

it was concluded that the carbanion XIXa ↔ XIXb was not an intermediate in these reactions.

Reaction path 2 has as its principle feature the formation of an intermediate "ylid", and was suggested originally[5] to explain the difference in behavior of vinyl and allyl sulfides with dichlorocarbene. The formation of an intermediate "ylid" is reasonable in view of the nucleophilic character of sulfur,[15] and in view of the facile formation of stable "ylids" from dichlorocarbene and triphenylphosphorus.[16]

While we have not confirmed the existence of the "ylid" intermediate we have been able to show that divalent sulfur plays a significant role in reactions involving ethyl trichloroacetate and olefins. Specifically, *sulfide sulfur inhibits formation of dichlorocarbene addition products.* For this study the reaction of ethyl trichloroacetate and sodium methoxide in olefin-free petroleum ether was carried out under controlled conditions with cyclohexene containing various quantities of *n*-butyl phenyl sulfide.

It can be seen readily from Table I that the addition of *n*-butyl phenyl sulfide does have a profound effect upon the yield of dichloronorcarane and upon the amount of recovered cyclohexene. The inhibiting effect of sulfide sulfur on dichlorocyclopropane formation was also evident from a study of the reaction of ethyl trichloroacetate and sodium methoxide with 3-butenyl phenyl sulfide (XXII). Under conditions

$$\underset{\text{XXII}}{\text{C}_6\text{H}_5\text{S}{-}\text{CH}_2\text{CH}_2\text{CH}{=}\text{CH}_2} \xrightarrow[-\text{OCH}_3]{\text{Cl}_3\text{CCO}_2\text{C}_2\text{H}_5} \underset{\text{XXIII}}{\text{C}_6\text{H}_5\text{SCH}_2\text{CH}_2\text{CH}{-}\text{CH}_2}\ \begin{matrix} & & \text{C} & & \\ & \diagup & & \diagdown & \\ & \text{Cl} & & \text{Cl} & \end{matrix}$$

identical with those employed for reactions with cyclohexene, vinyl sulfides,[1] and allyl sulfides, the sulfide XXII gave only a 17% yield of impure cyclopropane (XXIII), characterized by conversion to the corresponding sulfone. Of more significance, however, was the recovery of 50–53% of the starting olefin. That an "ylid" forms, which only slowly reacts with olefin to give adduct, is not born out by studies in which the reaction time with XXII was extended; the yields of cyclopropane XXIII were comparable.

The reaction of ethyl trichloroacetate, sodium methoxide, and saturated sulfides has not provided much useful data to date. With *n*-butyl phenyl sulfide there was obtained (1) much tar, (2) 75% recovery

(12) *Cf.* (a) C. C. Price and S. Oae, "Sulfur Bonding," The Ronald Press Co., New York, N. Y., 1962, p. 9–55; (b) W. E. Parham and M. D. Bhavsar, *J. Org. Chem.*, **28**, 2686 (1963); (c) **29**, 1575 (1964); (d) K. D. Gundermann, *Angew. Chem.*, **75**, 1194 (1963).

(13) Similar results were previously described for the olefin XI and the corresponding isomeric vinyl sulfide. See ref. 5.

(14) The reactions of vinyl sulfides with ethyl trichloroacetate and alkoxide leads to the formation of cyclopropanes; see ref. 1.

(15) For a discussion of the electrophilic character of dichlorocarbene, see (a) W. von E. Doering and W. A. Henderson, *J. Am. Chem. Soc.*, **80**, 5274 (1958); (b) R. C. Woodworth and P. S. Skell, *ibid.*, **79**, 2542 (1957).

(16) A. J. Speziale and K. W. Ratts, *ibid.*, **84**, 854 (1962).

TABLE II

REACTION OF ALLYL PHENYL SULFIDE, ALKOXIDE, AND ETHYL TRICHLOROACETATE

Sulfide Ia, mole	Alkoxide, mole	$ClCCO_2C_2H_5$, mole	Recovered olefin, %	Product yield (calcd. on Ia employed, %)ᵃ
0.18	CH_3O^- (0.28)[a]	0.26	15[b]	IIa (49)
0.20	CH_3O^- (0.20)[a]	0.20	26[b]	IIa (46)
0.10	CH_3O^- (0.20)[c]	0.10	9[b]	IIa (60)
0.22	CH_3O^- (0.30)[c]	0.27	20[b]	IIa + IIIa[d] (~45)
0.207	CH_3O^- (0.32)[c]	0.22	12[b]	IIa (52)[e]
0.10	t-$C_4H_9O^-$ (0.20)[b]	0.10	25[f]	Substituted cyclopropane[g]

[a] Dry sodium methoxide was prepared from sodium.[1] [b] No propenyl sulfide was detected in the recovered olefin. [c] Commercial sodium methoxide. [d] The structure of IIIa was not established but was assigned by analogy to IIIb. The impure diene IIa distilled first (16.0 g., b.p. 93–96° at 0.4 mm., $n^{25.5}$D 1.6154); the higher boiling IIIa (6.0 g., b.p. 90–100° at 0.04 mm., $n^{25.5}$D 1.6038) distilled with some evolution of hydrogen chloride. [e] A solution of the crude product (prior to distillation) was refluxed (1 hr.) in pyridine (30 ml.); the resulting mixture was extracted, dried, and distilled. [f] Completely isomerized (infrared and v.p.c.) to phenyl propenyl sulfide. [g] The fractionated product (7.2 g.) was shown to be principally 1,1-dichloro-2-methyl-3-phenylmercaptocyclopropane.[1] [h] Commercial potassium t-butoxide.

of sulfide, and (3) a small amount of an impure higher boiling liquid which provided a pure sulfone upon oxidation with hydrogen peroxide. The structure of

$$n\text{-}C_3H_7S\text{—}C_6H_5 \xrightarrow[(2)\ H_2O_2]{(1)\ {}^-OCH_3,CCl_3CO_2C_2H_5} C_6H_5SO_2CCl_2CHClCH_2CH_2CH_3$$

XXIV

the sulfone ($C_{11}H_{13}Cl_3O_2S$) has not been established; however, the corresponding n.m.r. spectrum suggests XXIV. The formation of the trichloro sulfide is, however, of questionable significance to the mechanism of the insertion reaction in view of the low yield, and the fact that a chlorination process is known to occur in reactions of ethyl trichloroacetate and sodium methoxide.[17,18] The reaction of saturated sulfides with dichlorocarbene precursors will, however, be the subject of further study.

Experimental

Allyl phenyl sulfide (Ia) was prepared in 87% yield by the method of Hurd and Greengard[19a] and had the following properties: b.p. 102.5–103.5° (12 mm.), n^{20}D 1.5770 (lit.[19b] n^{20}D 1.5760); $\lambda_{max}^{95\%\ alc}$ 254 mμ (ε 7130); ν^{neat} C=C (1628 cm.$^{-1}$), CH=CH_2 (908, 976, 1840 cm.$^{-1}$); n.m.r. spectrum[6] (neat): aromatic H (complex, 397–423 c.p.s., weight 4.9), =CH (complex 308–348 c.p.s., weight 1.0), =CH_2 (three split peaks of ~ equal intensity at 272, 280, and 288 c.p.s., total weight 1.9), —S—CH_2 (split doublet, 179 and 186 c.p.s., weight 1.8).

Isomerization of Allyl Phenyl Sulfide.—A mixture of Ia (11.25 g., 0.075 mole), potassium t-butoxide (17.2 g., 0.15 mole), and petroleum ether (100 ml., b.p. 30–60°) was treated exactly as in reactions containing ethyl trichloroacetate (see synthesis of II). There was obtained 9.8 g. (87% yield) of phenyl propenyl sulfide (b.p. 46–50° at 0.07 mm., n^{24}D 1.5840). Comparison of the infrared spectrum and vapor phase chromatogram (silicone grease column set at 200°, carrier He, flow ~15 p.s.i.) of the product with authentic phenyl propenyl sulfide indicated that isomerization was complete. When sodium methoxide was used in place of potassium t-butoxide no isomerization was detected.

1-Chloro-1-phenylmercaptobutadiene (IIa).—The procedure employed was essentially identical with that previously described for the preparation of 1,1-dichlorocyclopropanes from vinyl sulfides.[1] The effect of changes of mole ratio of reactants is summarized in Table II. Spectra are described in the text.

Vapor phase chromatogram showed one peak (8.9% Reoplex on Chromosorb 60–80 M at 200°, flow 30 ml. He/min. and on Carbowax 20 M on Fluoropak, 245°, carrier He at ~40 p.s.i.).

Anal. Calcd. for $C_{10}H_9ClS$: C, 61.06; H, 4.61; Cl, 18.03; S, 16.30. Found: C, 60.93; H, 4.72; Cl, 18.09; S, 16.13.

Reaction of IIa with Tetracyanoethylene (TCE).—The violet solution prepared from IIa (6.2 g., 0.032 mole), tetracyanoethylene (3.45 g., 0.027 mole), and ethyl acetate (30 ml.) was allowed to stand for 3 days, then was concentrated, and petroleum ether (b.p. 30–60°, 20 ml.) was added. The solid obtained was partially sublimed (80° at 0.05 mm.) to remove TCE, and the residue (6.2 g., m.p. 125–131°, 70% yield) was recrystallized several times from benzene and benzene–petroleum ether (b.p. 30–60°). The white solid thus obtained weighed 3.8 g. (43% yield) and melted at 143–144°. Structure IV was assigned to this product on the basis of the spectra described in the text.

Anal. Calcd. for $C_{16}H_9ClN_4S$: C, 59.16; H, 2.79; N, 17.25. Found: C, 59.37; H, 2.89; N, 17.55.

Compound IV decomposed in hot methanol (16 hr.) to a dark red solid, m.p. 186–187° dec. (from CCl_4), which was not identified.

Anal. Found: C, 67.41; H, 3.55; N, 11.34.

Reduction of 1-Chloro-1-phenylmercaptobutadiene (IIa) to 1-Chloro-1-phenylmercaptobutene-1 (V).—1-Chloro-1-phenylmercaptobutadiene (IIa, 7.0 g., 0.036 mole) was reduced with hydrogen (50 p.s.i.) in absolute ethanol (100 ml.) using 5% palladium on barium sulfate (black, 28 g.) as catalyst. After 2 hr. at room temperature 0.053 mole of hydrogen was consumed. The catalyst was removed (Filter-cel) and the residue was distilled to give (1) n-butyl phenyl sulfide, 0.4 g., b.p. 35–48° (0.03 mm.), n^{20}D 1.5500, and (2) 1-chloro-1-phenylmercaptobutene-1, 4.8 g., 68% yield, b.p. 48–51.5° (0.03 mm.), n^{26}D 1.5704.

n-Butyl phenyl sulfide, fraction 1, was identified by infrared (comparison with authentic), and by conversion to the palladium chloride complex (m.p. and m.m.p. 104–106°).[20]

Fraction 2 was redistilled (b.p. 44–46.5° at 0.02 mm., $n^{25.5}$D 1.5740) and was assigned the structure **1-chloro-1-phenylmercaptobutene-1** (V) on the basis of the spectral data described in the text. The vapor phase chromatogram showed one peak (column, Carbowax 20 M on Fluoropak, 245°, carrier He at ~40 p.s.i.).

Anal. Calcd. for $C_{10}H_{11}ClS$: C, 60.44; H, 5.58. Found: C, 60.20; H, 5.77.

The olefin V was further characterized by conversion to 1-chloro-1-phenylsulfonylbutene-1.

1-Chloro-1-phenylsulfonylbutene-1.—A mixture of V (6.6 g., 0.033 mole), acetic acid (15 ml.), and hydrogen peroxide (5 ml., 30%) was heated at 100° for 1 hr., and water (50 ml.) then was added. The resulting mixture was extracted with ether and the ether solution was washed with five portions of saturated sodium carbonate and one portion of water. The ether was dried ($MgSO_4$) and the residue (6.0 g., 79% yield) was distilled to give 4.1 g. (54% yield) of 1-chloro-1-phenylsulfonylbutene-1 (b.p. 96–99° at 0.04 mm., $n^{25.5}$D 1.5513, m.p. 31–32.5° from absolute alcohol–petroleum ether at Dry Ice temperature).

1-Chloro-1-phenylsulfonylbutene-1 showed ν^{neat} C=C (1600–1610 cm.$^{-1}$), —SO_2— (near 1310 and 1135 cm.$^{-1}$); n.m.r. spec-

(17) That a chlorination process can be involved in reactions involving ethyl trichloroacetate and sodium methoxide is evidenced by formation of carbon tetrachloride in reactions summarized in Table I.

(18) A chlorination process has also been observed in reactions involving sodium trichloroacetate. Cf. W. M. Wagner, H. Kloosterziel, and H. F. Bickel, *Rec. trav. chim.*, **81**, 925 (1962).

(19) (a) C. D. Hurd and H. Greengard, *J. Am. Chem. Soc.*, **52**, 3356 (1930); (b) D. S. Tarbell and M. A. McCall, *ibid.*, **74**, 48 (1952).

(20) V. N. Ipatieff, H. Pines, and B. S. Friedman, *ibid.*, **60**, 2731 (1938).

trum[9] (20% in CCl_4): aromatic H (complex near 441 and 428 c.p.s., weight ~5.0), =CH— (triplet, 396, 403, 410 c.p.s., J = 7.3 c.p.s., weight ~1.0), CH_3 (triplet, 53, 60, and 67 c.p.s., J = 7.3 c.p.s., weight ~3), CH_2 (complex, 115–146 c.p.s., weight ~1.8).

Anal. Calcd. for $C_{10}H_{11}ClO_2S$: C, 52.05; H, 4.81. Found: C, 51.76; H, 4.93.

Allyl *n*-butyl sulfide (Ib) was prepared in 69% yield as previously described[21] and had b.p. 66–67° (29 mm.), $n^{25.5}D$ 1.4652, lit.[21] $n^{20}D$ 1.4677; ν^{neat} C=C (1630 cm.$^{-1}$), CH=CH_2 (905, 980, and 1830 cm.$^{-1}$); $\lambda_{max}^{95\% alc}$ 207 mμ (ε 1400), 218 mμ (ε 1280); n.m.r. spectrum[9] (20% in CCl_4): CH_3 (complex 43–58 c.p.s., weight ~2.9), CH_3–CH_2–CH_2 (complex 64–94 c.p.s., weight ~3.8), –SCH_2 (complex, 127–143 c.p.s., weight ~1.8), —S–CH_2–CH= (doublet, 168 and 175 c.p.s., J = 7.0 c.p.s., weight ~2.0), —CH= (complex 304–346 c.p.s., weight ~1.0), =CH_2 (complex, 270–292 c.p.s., weight ~2.1).

1-*n*-Butylmercapto-1-chlorobutadiene (IIb).—The reaction of Ib (20.0 g., 0.154 mole), ethyl trichloroacetate (38.3 g., 0.20 mole), and commercial sodium methoxide (11.6 g., 0.21 mole, weighed in a drybox) in olefin-free petroleum ether (150 ml., b.p. 30–60°) was carried out as described for Ia. Distillation of the crude product gave 18.5 g. (68%) yield) of 1-*n*-butylmercapto-1-chlorobutadiene (b.p. 44–48° at 0.8 mm., $n^{26}D$ 1.5301).

The diene IIb showed $\lambda_{max}^{95\% alc}$ 234 mμ (ε 14,450), 280 mμ (ε 11,500); ν^{neat} C=C (1610 cm.$^{-1}$), CH=CH_2 (900, 980, and 1825 cm.$^{-1}$): n.m.r. spectrum[9] (20% in CCl_4): CH_3 (complex 43–61 c.p.s., weight ~2.9), CH_2 (complex 68–102 c.p.s., weight ~3.8), CH_2S (complex 150–168 c.p.s., weight ~2.0), =CH_2 (complex 280–303 c.p.s., weight ~2.2), =CH (complex 362–396 c.p.s., weight ~2.1); v.p.c.: one peak with shoulder (column, Dow-Corning silicone grease, carrier He ~ 40 p.s.i., 195°), two unresolved peaks (Carbowax 20 M on Fluoropak, carrier He ~40 p.s.i., 191°) of approximate peak ratio 7:8.

Anal. Calcd. for $C_8H_{13}ClS$: C, 54.37; H, 7.42. Found: C, 54.43; H, 7.59.

***cis,trans*-1-*n*-Butylmercapto-1,3-dichlorobutene-1 (IIIb). A.**—In another reaction involving Ib (27.6 g., 0.21 mole), commercial sodium methoxide (15.0 g., 0.28 mole), and ethyl trichloroacetate (48.1 g., 0.25 mole) some hydrogen chloride was evolved during distillation. There was obtained, in addition to IIb (b.p. 59–62° at 1.3 mm., $n^{26}D$ 1.5272, 15.0 g., yield 40%), a higher boiling liquid (1.3 g., b.p. 48–50° at 0.01 mm., $n^{26}D$ 1.5060) which was shown to be principally IIIb. This product evolved some hydrogen chloride upon repeated distillation and was not obtained pure.

Impure IIIb showed $\lambda_{max}^{95\% alc}$ 208 mμ (ε 6210), λ (shoulder) 225 mμ (ε 3010), λ_{max} 254 mμ (ε 2400); ν^{neat} C=C (1600 cm.$^{-1}$), and weak absorption in the region 905, 980, 1835 cm.$^{-1}$ (weak CH=CH_2, probably butadiene impurity); n.m.r. spectrum[9] (20% in CCl_4): CH_3–$(CH_2)_3$– (complex, 47–60 c.p.s., weight ~2.7), $CH_3CH_2CH_2CH_2$ and CH–CH_3 (complex, 70–96 c.p.s., weight

~6.7), S–CH_2 (complex, 150–167 c.p.s., weight ~1.8), –CH

(complex, 258–291 c.p.s., weight ~1.0), =CH (two doublets, 334, 343, and 338, 348 c.p.s., J_1 = J_2 = 9.4 c.p.s., weight ~1.0).

Anal. Calcd. for $C_8H_{14}Cl_2S$: C, 45.07; H, 6.62; Cl, 33.25; S, 15.04. Found: C, 45.90; H, 6.05; Cl, 31.91; S, 14.94.

B.—A cold (ice bath), stirred solution of 1-*n*-butylmercapto-1-chlorobutadiene (IIb, 6.0 g., 0.034 mole) in petroleum ether (30 ml., b.p. 30–60°) was treated with gaseous hydrogen chloride for 2.5 hr. The solvent was removed (rotatory evaporator), and the residue was distilled. Some hydrogen chloride was evolved during distillation; there was obtained 3.1 g. of recovered IIb and 1.9 g. of impure IIIb. Redistillation of IIIb afforded a product (0.5 g., $n^{24}D$ 1.5090, b.p. 51–52° at 0.05 mm.), which had essentially identical n.m.r. and infrared spectra as the product described in A above.

Reduction of 1-*n*-Butylmercapto-1-chlorobutadiene (IIb) to 1-*n*-Butylmercapto-1-chlorobutene-1. (VI).—The reduction of IIb (5.5 g., 0.031 mole) with hydrogen (50 p.s.i.) in absolute ethanol (50 ml.) was carried out as described for the reduction of IIa using 5% palladium on barium sulfate (black, 25 g.) as catalyst. Distillation of the crude product gave 2.5 g. of combined product which was shown by vapor phase chromatography (Carbowax 20 M on Fluoropak column, 215°, carrier He ~40 p.s.i.) to contain di-*n*-butyl sulfide (25%), IIb (small amount), and a principal product subsequently identified as VI. Fractionation of the total distillate gave pure di-*n*-butyl sulfide (b.p. 30–34° at 1.2 mm., $n^{25.5}D$ 1.4510), identified by comparison (v.p.c. and infrared spectrum) with an authentic sample, and VI (b.p. 93–94° at 19 mm., $n^{23}D$ 1.4885).

The olefin VI showed $\lambda_{max}^{95\% alc}$ 209 mμ (ε 7430), λ (shoulder) 225 mμ (ε 3130), λ_{max} 254 mμ (ε 2610); ν^{neat} C=C (1590–1600 cm.$^{-1}$), absence of absorption at 980 and 1830 cm.$^{-1}$ (no —CH=CH_2), trisubstituted olefin (835 cm.$^{-1}$); n.m.r. spectrum[9] (20% in CCl_4): CH_3 (two triplets, 45–68 c.p.s., weight ~5.4), CH_3CH_2–CH_2 (complex, 68–99 c.p.s., weight ~3.7), —SCH_2—(complex, 144–167 c.p.s., weight ~2.0), =CH— (triplet, 331, 339, 347 c.p.s., J = 7.6, weight ~1.0), =CH–CH_2 (complex, 108–144 c.p.s., weight ~2.0).

Anal. Calcd. for $C_8H_{15}ClS$: C, 53.76; H, 8.46. Found: C, 53.87; H, 8.69.

Allyl *t*-butyl sulfide (Ic) was prepared (67% yield) as previously described[22] and showed b.p. 142.5–144°, $n^{20}D$ 1.4651 (lit.[22] b.p. 139–141.5°, $n^{20}D$ 1.4638); $\lambda_{max}^{95\% alc}$ 208 mμ (ε 1410), λ (shoulder) 216 mμ (ε 850); ν^{neat} C=C (1636 cm.$^{-1}$), CH=CH_2 (908, 985, and 1830 cm.$^{-1}$); n.m.r. spectrum[9] (20% in CCl_4): $(CH_3)_3C$ (singlet, 73 c.p.s.), CH_2 (doublet, 173 and 179 c.p.s., J = 6.3 c.p.s., weight ~1.9), =CH (multiplet, 309–350 c.p.s., weight ~1.0), =CH_2 (triplet of nearly equal intensity, 278, 287, 296 c.p.s., weight ~1.9).

1-*t*-Butylmercapto-1-chlorobutadiene (IIc).—The reaction of Ic (12.0 g., 0.09 mole), ethyl trichloroacetate (24.0 g., 0.13 mole), and sodium methoxide (from 3.2 g., 0.14 g.-atom of sodium) was carried out as described for IIa. 1-*t*-Butylmercapto-1-chlorobutadiene (10.4 g., 66% yield) was collected at 83–85° (12 mm.) and showed $n^{20}D$ 1.5272; ν^{neat} C=C (1610 cm.$^{-1}$), CH=CH_2 (905, 985, and 1830 cm.$^{-1}$); $\lambda_{max}^{95\% alc}$ 246 mμ (ε 18,820), λ_{max} 285 mμ (ε 4490); n.m.r. spectrum (pure liquid)[6]: $(CH_3)_3C$ (split peak, 74 c.p.s., weight 9.4), =CH_2 (complex, 300–338 c.p.s., weight 2.0), =CH (complex 380–416 c.p.s., weight 2.0); v.p.c.: two nearly superimposed peaks (8.9% Reoplex on Chromosorb 60–80 M., He flow 30 ml./min., 150°) of relative heights 1:10, one peak (Dow-Corning silicone grease column, carrier flow He ~40 p.s.i., 195°), one peak (diisodecylphthalate column, carrier flow He ~15 p.s.i., 173°).

Anal. Calcd. for $C_8H_{13}ClS$: C, 54.37; H, 7.42; Cl, 20.06; S, 18.15. Found: C, 54.38; H, 7.64; Cl, 20.37; S, 17.87.

***cis,trans*-1-*t*-Butylmercapto-1,3-dichlorobutene-1 (IIIc).**—In another reaction of Ic (32.5 g., 0.25 mole) with ethyl trichloroacetate (68.3 g., 0.36 mole) and commercial sodium methoxide (20.4 g., 0.38 mole), distillation of the product was accompanied by elimination of some hydrogen chloride. The yield of IIc was 54% (24.0 g.). There was also obtained 2.1 g. of higher boiling material (b.p. 58–61° at 1.8 mm., $n^{25}D$ 1.5050) which was not obtained pure since it lost some hydrogen chloride upon repeated distillation. This higher boiling material was assigned structure IIIc by comparison of the following properties with those of IIIb: $\lambda_{max}^{95\% alc}$ 211 mμ (ε 10,590), λ_{max} 255 mμ (ε 3000); ν^{neat} C=C (1590 cm.$^{-1}$), weak or no absorption near 905, 915, and 1830 cm.$^{-1}$ indicating absence of —CH=CH_2; n.m.r. spectrum[9] (20% in CCl_4): *cis–trans* $(CH_3)_3C$– (split peak at 82 c.p.s.), *cis–trans* CH_3– (two split doublets 91, 98 c.p.s.), =CH— (two doublets, 347, 356 and 351, 360 c.p.s.), —CHCl (complex 257–302 c.p.s.).

Reduction of IIc to *t*-Butyl *n*-Butyl Sulfide and *cis,trans*-1-*t*-Butylmercapto-1-chlorobutene-1 (VII).—The diene IIc (10.0 g., 0.057 mole) was reduced in absolute alcohol (140 ml.) with hydrogen (50 p.s.i.) and 5% palladium on barium sulfate[23] (26 g.) as described for the reduction of IIa and IIb. Distillation of the reaction residue gave two products (A and B).

Product A (0.6 g., 6% yield, b.p. 60–65° at 24 mm., $n^{25}D$ 1.4498) was shown to be identical (v.p.c., infrared) with authentic *t*-butyl *n*-butyl sulfide (prepared, 54% yield, b.p. 62–63° at 20 mm., $n^{25}D$ 1.4453, from *t*-butylmercaptane and *n*-butyl bromide).

Product B (2.45 g., 24% yield, b.p. 35–43° at 1 mm., $n^{25}D$ 1.4860) showed by v.p.c. two peaks (ratio ~9:1, neither due to *t*-butyl *n*-butyl sulfide, on silicon oil DC-200 column set at 180°); $\lambda_{max}^{95\% alc}$ 212 mμ (ε 10,360), 258 mμ (ε 1440); ν^{neat} C=C (1590–1600 cm.$^{-1}$), absence of absorption near 905, 980, 1830 cm.$^{-1}$ (no CH=CH_2); n.m.r. spectrum[9] (20% CCl_4): —CH_3 (triplets, 50,

(21) L. Bateman and J. G. Cunneen, *J. Chem. Soc.*, 1596 (1955).

(22) D. S. Tarbell and W. E. Lovett, *J. Am. Chem. Soc.*, **78**, 2259 (1956).

(23) The Pd–$BaSO_4$ was brown (Engelhard Co.) and was more active than that employed for reduction of IIa and IIb.

57, 64 c.p.s., and 52, 59, 66 c.p.s., $J_1 = J_2 = 7.0$ c.p.s., weight ~3.3), *t*-butyl (two peaks, 78 and 80 c.p.s.), =CH— (four peaks, 339, 346, 353, 360 c.p.s., due to two nearly superimposed triplets, $J = 7.0$ c.p.s., weight ~1.0), CH_2 (split quintet 113–147, $J = 7.0$ c.p.s., weight ~2.2).

Anal. Calcd. for $C_8H_{15}ClS$: C, 53.76; H, 8.46. Found: C, 53.39; H, 8.43.

These data are consistent with the assigned structure *cis-trans* 1-*t*-butylmercapto-1-chlorobutene (VII). The butene VII (0.8 g.) was oxidized to the sulfone (0.3 g., oil), *cis,trans*-1-*t*-butylsulfonyl-1-chlorobutene-1, which showed ν^{neat} C=C (1590–1605 cm.$^{-1}$), no CH=CH_2 (absence of absorption near 985 and 1830 cm.$^{-1}$); n.m.r. spectrum[9] (20% in CCl_4): CH_3 (two triplets, 53, 61, 68 c.p.s. and 56, 67, 71 c.p.s.), *t*-butyl (split singlet, 79 c.p.s.), =CH— (five peaks, probably two triplets at 367, 375, 383 c.p.s. and 383, 391, and 399 c.p.s., weight ~1.0), CH_2 (multiplet 117–165 c.p.s., weight ~1.8).

Anal. Calcd. for $C_8H_{15}ClO_2S$: C, 45.49; H, 7.18. Found: C, 45.60; H, 7.04.

4-Phenylmercaptobutene-1 (XXII).—This sulfide (b.p. 72–74° at 1.4 mm., $n^{25}D$ 1.5621) was prepared (86% yield) from 1-bromobutene-3[24] and thiophenol as described[22] for the preparation of allyl *t*-butyl sulfide. This sulfide (XXII) showed ν^{neat} C=C (1635 cm.$^{-1}$), —CH=CH_2 (905, 983, and 1840 cm.$^{-1}$).

Anal. Calcd. for $C_{10}H_{12}S$: C, 73.11; H, 7.37. Found: C, 73.30; H, 7.61.

1,1-Dichloro-2-(2-phenylmercaptoethyl)cyclopropane (XXIII).—The reaction of XXII (16.4 g., 0.10 mole) with ethyl trichloroacetate (28.7 g., 0.15 mole) and commercial sodium methoxide (8.7 g., 0.16 mole), as described for olefins Ia–c, gave recovered sulfide XXII (8.3 g., 50%), the cyclopropane XXIII (impure, b.p. 110–130° at 0.1–0.6 mm., $n^{26}D$ 1.5771, 4.2 g., 17% yield), and residual tar (5.6 g.).

The cyclopropane XIII, after redistillation (b.p. 85–87° at 0.01 mm., $n^{26}D$ 1.5754) showed weak absorption at ν^{neat} 1635, 910, and 985 cm.$^{-1}$ assigned to olefin impurity. The cyclopropane XXIII (1.7 g., 0.006 mole) was characterized by conversion to 1,1-dichloro-2-(2-phenylsulfonylethyl)cyclopropane by oxidation with hydrogen peroxide in acetic acid. The crude oily sulfone was crystallized by cooling its solution in ethanol to Dry Ice temperature. The solid sulfone was then recrystallized from ethanol–petroleum ether (30–60°) and melted at 64.5–65.5° (0.7 g., 36% yield from XXIII).

1,1-Dichloro-2-(2-phenylsulfonylethyl)cyclopropane showed absence of olefin in its infrared and n.m.r. spectra. The n.m.r. spectrum[9] (20% in $DCCl_3$) showed aromatic H (complex, 438–453 c.p.s., weight ~4.9), SCH_2 (complex, 177–197 c.p.s., weight ~2.0), other H (complex, 57–126 c.p.s., weight ~5.2).

(24) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 1995 (1934).

Anal. Calcd. for $C_{11}H_{12}Cl_2O_2S$: C, 47.32; H, 4.33. Found: C, 47.40; H, 4.48.

The reaction XXII with dichlorocarbene precursors was carried out as described above; however, the reaction time was increased to 66 hr. Essentially identical results were obtained.

Reaction of *n*-Butyl Phenyl Sulfide with Dichlorocarbene.—The reaction of ethyl trichloroacetate (38.0 g., 0.20 mole), commercial sodium methoxide (10.8 g., 0.20 mole), and *n*-butyl phenyl sulfide (20.0 g., 0.12 mole) in olefin-free petroleum ether (90 ml., b.p. 30–60°) was carried out as described for Ia. Distillation of the residue gave recovered *n*-butyl phenyl sulfide (15.0 g., 75%). A small amount of higher boiling material (2.1 g., $n^{28}D$ 1.5596) was obtained which was not obtained pure by fractionation (b.p. 75–80° at 0.05 mm., $n^{22}D$ 1.5656). This product (2.1 g.) was oxidized with hydrogen peroxide in acetic acid and the crude sulfone was dissolved in ethanol and cooled in Dry Ice–acetone. The crude solid sulfone (0.6 g., m.p. 85–91°) was recrystallized from alcohol–petroleum ether (b.p. 30–60°); the product melted at 100–102°.

The sulfone showed $\nu^{CCl_4-CS_2}$ $-SO_2-$ (1335–1345 and 1155 cm.$^{-1}$); n.m.r. spectrum[9] (20% in $DCCl_3$): CH_3 (triplet, 47, 53, and 60 c.p.s., $J = 6.7$ c.p.s., weight ~3.2), aromatic H (two split peaks, 419–429 and 429–457 c.p.s., weight ~5.1), —CH(Cl)— (four peaks of equal intensity, probably two doublets, 218, 220, 224, and 227 c.p.s., weight ~1.0), CH_2 (multiplet, 75–111 c.p.s., weight ~2.1), CH_2 (multiplet, 111–147 c.p.s., weight ~2.0).

Anal. Calcd. for $C_{11}H_{13}Cl_3O_2S$: C, 41.85; H, 4.15; Cl, 33.70; S, 10.16. Found: C, 41.80; H, 4.12; Cl, 33.63; S, 10.07.

This product has not been identified but is tentatively assigned the structure 1-phenylsulfonyl-1,1,2 trichloropentane (XXIV).

The reaction of cyclohexene (8.2 g., 0.10 mole), ethyl trichloroacetate (24.8 g., 0.13 mole), commercial sodium methoxide (7.2 g., 0.13 mole), and *n*-butyl phenyl sulfide (0–0.10 mole) was carried out as described for Ia. The results are described in Table I. Impure **7,7-dichloronorcarane** was collected, ~b.p. 85–88° at 20 mm., $n^{24}D$ 1.4992, and showed ester carbonyl in the infrared spectrum. The material was purified by washing with two portions of concentrated sulfuric acid and with two portions of water.

The **carbon tetrachloride** and recovered **cyclohexene** were collected with solvent petroleum ether by stripping the volatile components (rotatory evaporator) from the dried reaction mixture. Known amounts of tetrachloroethylene (absent in the mixture) were added, and the carbon tetrachloride and cyclohexene were analyzed by vapor phase chromatography (column, silicone grease set at 67°, carrier He, flow ~15 p.s.i.).

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The Radiation-Induced Addition Reaction of Ethers to Chlorofluoroolefins

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The radiation-induced addition reactions of tetrahydrofuran, dioxane, and diethyl ether to chlorofluoroolefins such as 1,2,2-trichloro-2-fluoroethylene, 1,2-dichloro-1,2-difluoroethylene, and 1,1-dichloro-2,2-difluoroethylene were carried out. While the addition of tetrahydrofuran and dioxane gave mainly 1:1 adducts in appreciable yields, diethyl ether added to the olefins to give a 1:1 adduct and a 1:2 adduct in a molar ratio of about 1:1. The structures of the adducts were determined by proton n.m.r. spectroscopy.

Among the various methods[1] of preparing fluorine-containing ethers, the addition of alcohols to fluoroolefins by an ionic mechanism using sodium alkoxides was most extensively studied. On the other hand, little attention has been paid to the free-radical addition of ethers to fluoroolefins, and the only report[2] available was on the peroxide-induced addition of certain cyclic ethers to CF_2=CF_2 to give 1:1 adducts and telomers.

This study is concerned with the addition of tetrahydrofuran, 1,4-dioxane, and diethyl ether to CFCl=CCl_2, CFCl=CFCl, and CF_2=CCl_2 by γ-ray irradia-

(1) For a review of the syntheses of fluorine-containing ethers, see A. M. Lovelace, D. A. Rausch, and W. Postelnek, "Aliphatic Fluorine Compounds," Reinhold Publishing Corp., New York, N. Y., 1958, p. 155.

(2) W. E. Hanford, U. S. Patent 2,433,844 (1948).

TABLE 1

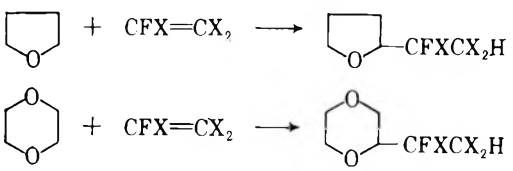
IRRADIATION CONDITIONS

Ethers	Molar ratio of ether to olefin	Irradiation time, hr.	Total dosage, r. × 10^6	—Yield,[a] %— 1:1 adduct	1:2 adduct
		$CFCl{=}CCl_2$			
Tetrahydrofuran	2.33	312	23	89	
Dioxane	2.31	313	23	23	
Diethyl ether	2.37	312	23	16	26
		$CFCl{=}CFCl$			
Tetrahydrofuran	2.28	309	23	84	
Dioxane	2.28	309	23	27	
Diethyl ether	1.96	309	23	28	30
		$CF_2{=}CCl_2$			
Tetrahydrofuran	2.31	389	24	65	4
Dioxane	2.30	389	24	5	3
Diethyl ether	2.14	359	22	15	14

[a] Based on the amount of olefin added.

tion. The reactants were irradiated in a glass tube at a rate of 0.6–0.7 × 10^5 r./hr. for a period of 2 weeks at room temperature. The irradiation conditions of each run are listed in Table I with yields based on the amount of olefin added.

While the γ-irradiation-induced addition of the cyclic ethers, tetrahydrofuran and dioxane, to chlorofluoroolefins gave mainly 1:1 adducts in appreciable yields, the addition of diethyl ether produced 1:1 adducts and 1:2 adducts in a molar ratio of about 1:1. The over-all reactions are represented by the equations



$$CH_3CH_2OCH_2CH_3 + CFX{=}CX_2 \longrightarrow CH_3CH_2OCH(CFXCX_2H)CH_3 + CH_3CH(CFXCX_2H)OCH(CFXCX_2H)CH_3$$

where X is F or Cl. Further, in the addition of these ethers to 1,1-dichloro-2,2-difluoroethylene, telomers were formed with 1:1 adducts as in the additions of aldehydes[3] and alcohols.[4]

The directions of attack of acyl and α-hydroxyalkyl radicals to the asymmetric chlorofluoroolefins in the addition of aldehydes and alcohols were determined earlier by the reactions

$$CF_2{=}CCl_2 + CH_3CHO \longrightarrow CHCl_2CF_2COCH_3 \xrightarrow[2.\ aq.\ NaOH]{1.\ K_2Cr_2O_7}$$
$$CF_2{=}CCl_2 + CH_2OH \longrightarrow CHCl_2CF_2CH_2OH \xrightarrow[2.\ aq.\ NaOH]{1.\ K_2Cr_2O_7}$$

$$CHCl_2CF_2COONa \xrightarrow{\Delta} CHCl{=}CF_2 + NaCl + CO_2$$

and were found to be the $=CF_2$ side by the identification of the olefin formed.[3,4] The ether adducts obtained in the present work, however, were so stable that such chemical methods were not practical for the determination of their structure.

The structures of 1:1 adducts and 1:2 adducts were determined by their proton n.m.r. spectra. Some examples of spectra at 60 Mc. of the 1:2 adducts of diethyl ether and 1:1 adducts of tetrahydrofuran are shown in Fig. 1 and 2, respectively. Since only a

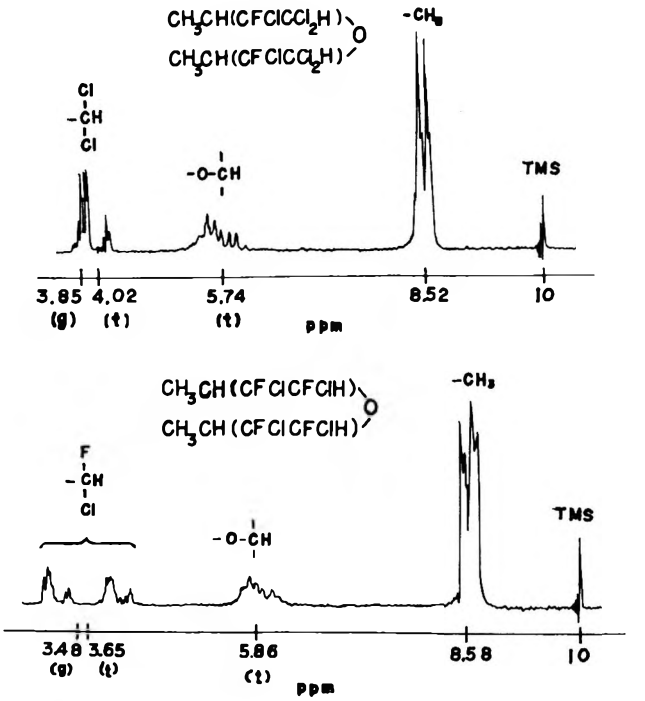


Fig. 1.—N.m.r. spectra (60 Mc.) of bis(1-methyl-2,3,3-trichloro-2-fluoropropyl) ether and bis(1-methyl-2,3-dichloro-2,3-difluoropropyl) ether in carbon tetrachloride (25%) using tetramethylsilane as internal standard at 10 (τ-scale).

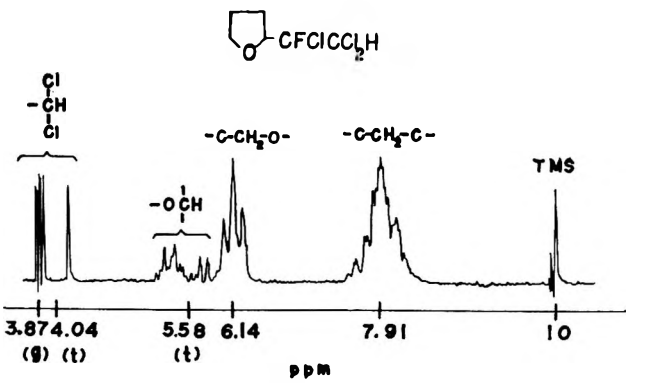


Fig. 2.—N.m.r. spectrum (60 Mc.) of 2-(1,2,2-trichloro-1-fluoroethyl)tetrahydrofuran in carbon tetrachloride (25%) using tetramethylsilane as internal standard at 10 (τ-scale).

single multiplet appears in the methyl region of the spectrum of the 1:2 adduct in Fig. 1, the chlorofluoroethyl groups must attach themselves in such a way as to preserve the symmetry of the molecule, and thus each α-hydrogen must have one of these groups attached. The large doubling of the methyl pattern is due to coupling with the remaining α-hydrogen, and the smaller doubling is probably the result of coupling with the fluorine two carbons removed.

The pattern of absorptions of protons on chlorofluoroethyl groups of $CH_3CH(CFClCHCl_2)OCH(CFClCHCl_2)CH_3$ is consistent with the presence of four partially overlapping doublets. They may be assigned to the *gauche* and *trans* form of vicinal H and F. Gutowsky and co-workers[5] reported the coupling constants of 1.00 ± 0.02 c.p.s. for J_g^{HF} and 18.2 ± 0.08 c.p.s. for J_t^{HF} of $CFCl_2CHCl_2$, and Abraham and Bernstein[6] ob-

(3) H. Muramatsu and K. Inukai, *J. Org. Chem.*, **27**, 1572 (1962); *Kogyo Kagaku Zashi*, **65**, 1992 (1962).

(4) H. Muramatsu, *J. Org. Chem.*, **27**, 2325 (1962).

(5) H. S. Gutowsky, G. G. Belford, and P. E. McMahon, *J. Chem. Phys.*, **36**, 3353 (1962).

(6) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 39 (1961).

TABLE II

CHLOROFLUORO ETHERS (1:1 ADDUCTS)

R	B.p., °C.	mm.	$n^{20}D$	d^{20}_4	MR Calcd.	MR Found	Fluorine, % Calcd.	Fluorine, % Found	Chlorine, % Calcd.	Chlorine, % Found
				$CHCl_2CFClR$						
	102–104	21	1.4739	1.412	44.03	44.06	8.58	8.49	48.04	46.85
	130–132	30	1.4762	1.467	45.68	45.67	8.00	8.05	44.80	43.91
$CH_3CH_2OCHCH_3$ |	78–79	17	1.4482	1.318	46.23	45.40	8.50	8.39	47.60	47.49
				$CHFClCFClR$						
	117–118	80	1.4416	1.393	39.25	38.91	18.54	17.94	34.60	33.54
	124–125	60	1.4439	1.451	40.89	40.45	17.20	17.20	32.09	32.29
$CH_3CH_2OCHCH_3$ |	91–93	79	1.4132	1.279	41.45	40.38	18.36	18.42	34.26	33.86
				$CHCl_2CF_2R$						
	117–118	80	1.4412	1.372	39.25	39.47	18.54	18.08	34.60	34.06
	123–124	56	1.4434	1.476	40.89	39.73	17.20	17.69	32.09	32.61
$CH_3CH_2OCHCH_3$ |	97–99	80	1.4110	1.262	41.45	40.72	18.36	18.38	34.26	34.22

TABLE III

CHLOROFLUORO ETHERS (1:2 ADDUCTS)

Compound	B.p., °C.	mm.	$n^{20}D$	d^{20}_4	MR Calcd.	MR Found	Fluorine, % Calcd.	Fluorine, % Found	Chlorine, % Calcd.	Chlorine, % Found
$CH_3CH(CFClCCl_2H)OCH(CFClCCl_2H)CH_3$	135–138	6	1.4842	1.539	70.15	69.36	10.19	10.02	57.05	56.30
$CH_3CH(CFClCFClH)OCH(CFClCFClH)CH_3$	133–134	20	1.4390	1.490	60.58	60.04	22.35	22.31	41.71	41.46
$CH_3CH(CF_2CCl_2H)OCH(CF_2CCl_2H)CH_3$	135–136	21	1.4393	1.502	60.58	59.59	22.35	22.27	41.71	41.75

tained 1.03 c.p.s. for J_g^{HF} and 18.08 c.p.s. for J_t^{HF} of the same chlorofluoroethane. Based on these values, we may assign each doublet to the *gauche* and *trans* form and get 2 c.p.s. for J_g^{HF} and 16 c.p.s. for J_t^{HF}. Although the presence of the *gauche* and *trans* form was exhibited in the resonance absorption of the proton on the α-carbons of the ether, the *trans* form is predominant and 18 c.p.s. was obtained for J_t^{HF}.

It is known[7] that J_{gem}^{HF} is severalfold larger than J_{vic}^{HF}. For example, Gutowsky, *et al.*,[5] obtained 49.1 ± 0.2 c.p.s. for J_{gem}^{HF} of $CHFClCHCl_2$. Since only the adduct from CFCl=CFCl, $CH_3CH(CFClCHF-Cl)OCH(CFClCHFCl)CH_3$, shows a large value of J^{HF}, 48 c.p.s., in our spectrum of a proton on chlorofluoroethyl group, this coupling may be due to the interaction between geminal H and F. This fact indicates accordingly that, in the adducts from CFCl=CCl_2 and CF_2=CCl_2, H and F in haloethyl groups are vicinal to each other; *i.e.*, in the addition to asymmetrical olefins, the α-ethereal radicals formed attack the =CFX side where X is F or Cl.

From the positions and areas of the absorptions in the spectra of adducts of tetrahydrofuran, we assigned the various absorptions as written in Fig. 2. The analysis of the positions and J^{HF} of peaks indicates that the chlorofluoroethyl group is on the α-carbon, and the direction of the attack of the α-ethereal radical of tetrahydrofuran is the same as in the addition of diethyl ether, and almost equal amounts of the *gauche* and *trans* form exist between the vicinal H and F on the chlorofluoroethyl group at room temperature.

Wallace and Gritter[8] found that, in the peroxide-induced free-radical addition of four-, five-, and six-membered cyclic ethers to 1-octene, ketones in addition to ethers were produced as the major products. They suggested that the intermediate α-ethereal radicals undergo decyclization. Matsuda, *et al.*,[9] however, reported that ketones were not formed in the radiation-induced addition reaction of cyclic ethers to tetrachloroethylene and they obtained α-trichlorovinyl cyclic ethers with α-tetrachloroethyl cyclic ethers. In our experiments, both the corresponding ketones, $CH_3(CH_2)_2COCFXCX_2H$ and α-chlorofluorovinyl tetrahydrofuran, were not isolated in the addition reaction of tetrahydrofuran.

In the additions of diethyl ether, however, several grams of the corresponding ketones, $CH_3COCFXCX_2H$, were obtained. These ketones were identified by comparing their retention times in the vapor phase chromatograms with those of the authentic samples which were prepared in the addition of the acetaldehyde to CFX=CX_2.[3] The structures of ketones were also confirmed by the use of mixture melting points of 2,4-dinitrophenylhydrazones of the ketones and those of authentic samples.

(7) H. S. Gutowsky, C. H. Holm, A. Saika, and G. A. Williams, *J. Am. Chem. Soc.*, **79**, 4596 (1957).

(8) T. J. Wallace and R. J. Gritter, *J. Org. Chem.*, **26**, 5256 (1961); **27**, 3067 (1962).

(9) T. Matsuda, K. Yumoto, and K. Iseda, Abstract, Symposium on Isotopes of the 4th Meeting, Tokyo, Japan, 1963.

The mechanism of the formation of these ketones may be as shown.

$$CH_3CH_2OCH_2CH_3 \xrightarrow{\gamma\text{-ray}} CH_3\dot{C}HOCH_2CH_3$$

$$CH_3\dot{C}(H)OCH_2CH_3 \longrightarrow CH_3\dot{C}{=}O + CH_3CH_3$$

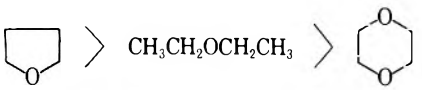
$$CH_3\dot{C}{=}O + CFX{=}CX_2 \longrightarrow CH_3COCFXCX_2\cdot$$

$$CH_3COCFXCX_2\cdot + CH_3CH_2OCH_2CH_3 \longrightarrow CH_3COCFXCX_2H + CH_3\dot{C}HOCH_2CH_3$$

Since crotonaldehyde was not isolated, another possible mechanism which proceeds through the formation of acetaldehyde would not occur appreciably.[10]

In the additions of dioxane, infrared examination of foreruns collected during product isolation revealed the presence of trace amounts of carbonyl-containing compounds, which were isolated as their 2,4-dinitrophenylhydrazones. Qualitative analyses showed the presence of fluorine and chlorine in them. Therefore, it seemed that similar radical cleavage occurred in these addition reactions. Further attempt to elucidate the structures of the compounds was not undertaken.

The physical properties and analyses of 1:1 adducts, the new fluorine-containing ethers, are shown in Table II. Table III shows those of the 1:2 adducts of diethyl ether to chlorofluoroolefins. The trends in apparent reactivity of ethers and chlorofluoroolefins observed in the addition reaction are the following.



$$CFCl{=}CCl_2 \fallingdotseq CFCl{=}CFCl > CF_2{=}CCl_2$$

Experimental[11]

Materials.—The chlorofluoroolefins used were prepared by the dechlorination of the corresponding chlorofluoroethanes with zinc dust in ethanol or 1-butanol according to the method of Henne, *et al.*[12] All of the ethers used were purified by conventional methods.

Irradiation by γ-Ray.—A mixture of chlorofluoroolefin and ether in a molar ratio of about 1:2 was added to a Pyrex tube, 20 × 5 cm. (*ca.* 300 ml.). The reaction tube was then sealed and irradiated by γ-ray from Co^{60} for a period of 2 weeks at a dose rate of 0.6–0.7 × 10^5 r./hr.

Addition Reactions of Ethers to 1,1,2-Trichloro-2-fluoroethylene.—A mixture of 95.5 g. (0.64 mole) of 1,1,2-trichloro-2-fluoroethylene and 112.5 g. (1.52 moles) of diethyl ether was sealed in a glass tube and irradiated at room temperature to a total dosage of 2.3 × 10^7 r. for a period of 312 hr. Distillation of the unchanged olefin and ether gave 22.4 g. (0.10 mole, 16% yield) of 1-methyl-2-fluoro-2,3,3-trichloropropyl ethyl ether, b.p. 75–79° (17 mm.), 30.5 g. (0.082 mole, 26% yield) of bis(1-methyl-2-fluoro-2,3,3-trichloropropyl) ether, b.p. 135–138° (6 mm.), and *ca.* 6 g. of residue.

During product isolation by distillation, 7 g. of the forefraction, b.p. 60–72° (28 mm.), was obtained. The infrared spectrum and vapor phase chromatogram showed that it was a mixture of 1,1,2-trichloro-2-fluorobutanone-3 and 1-methyl-2-fluoro-2,3,3-trichloropropyl ethyl ether. To *ca.* 3 g. of the fraction in ethanol (3 ml.), *ca.* 5 ml. of 2,4-dinitrophenylhydrazine reagent[13] was added. Yellow-orange crystals (0.4 g.) precipitated and they did not show the depression of melting point when mixed with the hydrazone of the authentic sample which was prepared by the free radical-induced addition of acetaldehyde to 1,1,2-trichloro-2-fluoroethylene.[3]

The addition reactions of tetrahydrofuran and dioxane to 1,1,2-trichloro-2-fluoroethylene were carried out under similar conditions.

Addition Reactions of Ethers to 1,2-Dichloro-1,2-difluoroethylene.—In a glass tube were sealed 113 g. (0.85 mole) of 1,2-dichloro-1,2-difluoroethylene and 171 g. (1.94 moles) of dioxane. The content of the tube were irradiated to a total dosage of 2.3 × 10^7 r. for 309 hr. Distillation of the reaction mixture under reduced pressure yielded 50 g. (0.23 mole, 27% yield) of 2-(1,2-dichloro-1,2-difluoroethyl)dioxane, b.p. 123–126° (60 mm.), and 14 g. of residue.

Using the same procedure, other ethers were added to 1,2-dichloro-1,2-difluoroethylene.

Addition Reactions of Ethers to 1,1-Dichloro-2,2-difluoroethylene.—A mixture of 131 g. (0.99 mole) of 1,1-dichloro-2,2-difluoroethylene and 164 g. (2.27 moles) of tetrahydrofuran was irradiated to a total dosage of 2.4 × 10^7 r. for 389 hr. Distillation of the irradiation products under reduced pressure gave 131 g. (0.64 mole, 65% yield) of 2-(1,1-difluoro-2,2-dichloroethyl)-tetrahydrofuran, b.p. 115–119° (80 mm.), 14 g. (0.40 mole, 4% yield) of crude 1:2 adduct, b.p. 110–113° (8 mm.), and 29 g. of a residue which seemed to be higher telomers.

Table II and III summarize the physical properties and analyses of the 1:1 adducts and 1:2 adducts prepared by the addition of ethers to chlorofluoroolefins.

Proton N.m.r. Spectra.—Spectra were obtained for 25% solution in carbon tetrachloride, using a Nihondenshi JNM-3 Type high resolution spectrometer operating at a frequency of 60 Mc. Tetramethylsilane was used as an internal reference.

Acknowledgment.—The authors wish to thank Dr. Toshio Goto of the University of Nagoya for proton n.m.r. spectrometric analyses.

(10) In the irradiation- and peroxide-induced addition reactions of acetaldehyde to chlorofluoroolefins, an appreciable amount of crotonaldehyde was produced with the 1:1 adducts; see ref. 3.

(11) All temperature readings are uncorrected.

(12) E. G. Locke, W. R. Brode, and A. L. Henne, *J. Am. Chem. Soc.*, **56**, 1726 (1934); A. L. Henne and E. C. Ladd, *ibid.*, **58**, 402 (1936).

(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 111.

The Radiation-Induced Addition Reaction of Dialkyl Phosphonates to Chlorofluoroolefins

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The radiation-induced addition reactions of dialkyl phosphonates (methyl, ethyl, and *n*-propyl) to chlorofluoroolefins such as 1,2,2-trichloro-1-fluoroethylene, 1,2-dichloro-1,2-difluoroethylene, and 1,1-dichloro-2,2-difluoroethylene were made to give the corresponding dialkyl chlorofluoroethylphosphonates. These phosphonates were hydrolyzed to the chlorofluoroethylphosphonic acids and converted to the chlorofluoroethylphosphonic dichlorides. The chlorofluoroethylphosphonic acids have an acidity similar to the ω-hydroperfluoroalkylphosphonic acids and perfluoroalkylphosphonic acids.

As part of a research program in this laboratory dealing with the radiation-induced addition reaction of organic molecules to chlorofluoroolefins,[1-3] a study has been made of the reactions of dialkyl phosphonates to chlorofluoroolefins under γ-ray irradiation.

The free-radical addition reactions of dialkyl phosphonates to ethylene and other polymerizable olefins were first reported by Hanford and Joyce[4] in a patent literature using peroxide as an initiator. Stiles and Rust[5] added dialkyl phosphonates to octene, tetradecene, and other olefins in organic solvents and Ladd and Harvey[6] added them to dodecyl allyl ether. The addition reactions to tetrafluoroethylene were carried out by Brittle and Joyce[7] to give $H(CF_2CF_2)_nPO(OR)_2$ where n = 1–6. The addition products of tetrafluoroethylene and their derivatives have been further intensively studied by Brace.[8]

The present paper is concerned with the γ-radiation-induced addition of $HPO(OR)_2$, where R is methyl, ethyl, or *n*-propyl, to 1,1,2-trichloro-2-fluoroethylene, 1,2-dichloro-1,2-difluoroethylene, and 1,1-dichloro-2,2-difluoroethylene, and the isolation of chlorofluoroethylphosphonic esters, acids, and dichlorides. The apparent reactivity of olefins and dialkyl phosphonates for the addition reaction and some properties of the 1:1 adducts and their derivatives as a function of chlorofluoroethyl group were also studied.

The reactants were irradiated in a glass tube at a rate of 0.6-0.7 × 10^5 r./hr. for a period of 2 weeks at room temperature. The irradiation conditions of each run are listed in Table I with yields based on the amounts of olefins added. Although the radiation-induced addition of 1,1,2-trichloro-2-fluoroethylene and 1,2-dichloro-1,2-difluoroethylene gave mainly 1:1 adducts in appreciable yields, 1,1-dichloro-2,2-difluoroethylene reacted with dialkyl phosphonates to give 1:1 adducts and telomers in rather poor yields. The general reaction is

$$HPO(OR)_2 + CFX{=}CX_2 \xrightarrow{\gamma\text{-ray}} CHX_2CFXPO(OR)_2$$

where X = F or Cl; R = CH_3, C_2H_5, or n-C_3H_7. The physical properties of the 1:1 adducts, the new fluorine-containing phosphonates, are shown in Table II. The trends[9] in apparent reactivity of chlorofluoroolefins and dialkyl phosphonates observed in the addition reaction were as shown.

Table I

γ-Radiation-Induced Addition of $HPO(OR)_2$ to Chlorofluoroolefins

R	Molar ratio of $HPO(OR)_2$ to olefin	Irradiation time, hr.	Total dosage, r. × 10^6	Yield[a] of 1:1 adduct, %
		$CFCl{=}CCl_2$		
CH_3	2.00	341	20	12
C_2H_5	2.00	341	20	20
n-C_3H_7	2.00	341	20	25
		$CFCl{=}CFCl$		
CH_3	3.00	230	16	48
C_2H_5	3.00	230	16	53
n-C_3H_7	3.01	230	16	68
		$CF_2{=}CCl_2$		
CH_3	2.10	390	22	3
C_2H_5	2.10	390	22	3
n-C_3H_7	2.10	390	22	2

[a] Based on the amounts of olefin added.

$$CFCl{=}CFCl > CFCl{=}CCl_2 > CF_2{=}CCl_2$$

$$R \text{ in } HPO(OR)_2: n\text{-}C_3H_7 > C_2H_5 > CH_3$$

This order of reactivity of dialkyl phosphonates is consistent with the order of electron-donating effect of alkyl groups and the similar trends in the effect of alkyl groups on the reactivity of the substrates were observed in the radiation-induced addition of alcohols[1] and aldehydes.[2]

The direction of the additions of the $\cdot PO(OR)_2$ radical formed to the asymmetrical olefins was determined by the basic hydrolysis, β-chlorine elimination reaction,[10] of the acids of 1:1 adducts, chlorofluoroethylphosphonic acids, to give chlorofluoroolefins. The structures of the olefins formed were identified by comparing their infrared spectra and gas chromatograms with those of authentic samples.

$$CHCl_2CFClPO(OR)_2 \xrightarrow{H^+} CHCl_2CFClPO(OH)_2 \xrightarrow[H_2O]{OH^-} CHCl{=}CFCl + H_3PO_4 + Cl^-$$

The formation of 1,2-dichloro-1-fluoroethylene in the hydrolysis of trichlorofluoroethylphosphonic acid showed that the $\cdot PO(OR)_2$ radical added to the $=CFCl$ side in $CFCl{=}CCl_2$. In the same way, the $\cdot PO(OR)_2$ radical was found to attack on the $=CF_2$ side of $CF_2{=}CCl_2$.

(1) H. Muramatsu, *J. Org. Chem.*, **27**, 2325 (1962).
(2) H. Muramatsu and K. Inukai, *ibid.*, **27**, 1572 (1962).
(3) H. Muramatsu, K. Inukai, and T. Ueda, *ibid.*, **29**, 2220 (1964).
(4) W. E. Hanford and R. M. Joyce, U. S. Patent 2,478,390 (1949).
(5) A. R. Stiles and F. F. Rust, U. S. Patent 2,724,718 (1955).
(6) E. C. Ladd and M. P. Harvey, U. S. Patent 2,664,438 (1953).
(7) J. A. Brittle and R. M. Joyce, U. S. Patent 2,559,754 (1951).
(8) N. O. Brace, *J. Org. Chem.*, **26**, 3197 (1961).
(9) Based on the yields of 1:1 adducts obtained.
(10) J. A. Maynard and J. M. Swan, *Proc. Chem. Soc.*, 61 (1963).

TABLE II

DIALKYL CHLOROFLUOROETHYLPHOSPHONATES

R	B.p., °C.	mm.	$n^{20}D$	d^{20}_4	MR Calcd.	MR Found	Chlorine, % Calcd.	Chlorine, % Found	Mol. wt. Calcd.	Mol. wt. Found
				$CHCl_2CFClPO(OR)_2$						
CH_3	93–94	4	1.4630	1.536	46.23	46.54	41.0	40.7	260	253
C_2H_5	100–102	4	1.4560	1.399	55.46	55.86	37.0	36.8	288	286
n-C_3H_7	105–108	4	1.4535	1.310	64.69	65.16	33.8	33.5	316	317
				$CHFClCFClPO(OR)_2$						
CH_3	91–92	6	1.4347	1.508	41.43	42.02	29.2	28.7	243	244
C_2H_5	100–102	6	1.4289	1.361	50.67	51.31	26.2	25.8	271	271
n-C_3H_7	110–112	6	1.4310	1.280	59.91	60.46	23.7	23.1	299	300
				$CHCl_2CF_2PO(OR)_2$						
CH_3	73–75	3	1.4270	1.495	41.43	41.72	29.2	28.5	243	246
C_2H_5	87–90	3	1.4265	1.350	50.67	51.50	26.2	25.3	271	275
n-C_3H_7	98–100	3	1.4257	1.263	59.91	60.64	23.7	23.0	299	295

TABLE III

CHLOROFLUOROALKYLPHOSPHONIC DICHLORIDES

Compounds	B.p., °C.	mm.	$n^{20}D$	d^{20}_4	MR Calcd.	MR Found	Chlorine, % Calcd.	Chlorine, % Found
$CHCl_2CFClPOCl_2$	87–88	8	1.5025	1.786	43.43	44.41	66.1	65.4
$CHFClCFClPOCl_2$	67–68	8	1.4695	1.761	38.65	39.88	56.4	55.9
$CHCl_2CF_2POCl_2$	67–68	8	1.4690	1.751	38.65	40.08	56.4	55.9
$H(CCl_2CF_2)_2POCl_2$[a]	120–125	8	1.4812	1.778	57.78	61.66	55.3	53.9

[a] Calcd. for $C_4HCl_6F_4OP$ (crude sample): mol. wt., 385. Found: mol. wt., 398.

After distillation of addition products, appreciable amounts of viscous liquid residues remained. These residues were treated with phosphorus pentachloride to give the products which were identified to be the chlorofluoroethylphosphonic dichlorides from their infrared spectra. The authentic dichlorides were prepared by hydrolysis of the 1:1 adducts in the presence of hydrochloric acid, followed by the treatment with phosphorus pentachloride. Thus, the residues were found to be chlorofluoroethylphosphonic acids, which seem to be formed by the hydrolysis of the 1:1 adducts with the atmospheric moisture. In order to get better yields of 1:1 adducts, therefore, the exclusion of atmospheric moisture seemed to be important in the addition reaction of dialkyl phosphonates to chlorofluoroolefins. The orders[11] of effects of chlorofluoroethyl groups and alkyl groups in dialkyl chlorofluoroethylphosphonates on apparent ease of hydrolysis with moisture follow.

$$CHCl_2CF_2 > CHFClCFCl > CHCl_2CFCl;\ CH_3 > C_2H_5 > n\text{-}C_3H_7$$

Table III shows the physical properties of chlorofluoroethylphosphonic dichlorides.

The chlorofluoroethylphosphonic acids are hygroscopic crystalline solids and their pH titration exhibited the enhanced acidity of the dibasic phosphonic acid groups as compared with unfluorinated alkylphosphonic acid.[12] The enhancement of acidity due to the inductive effect of substituted fluorine atoms in the polyfluoroalkylphosphonic acids have been reported for the perfluoroalkyl analogs[13,14] and ω-hydroperfluoroalkyl analogs.[8] The chlorofluoroethylphosphonic acids have the pK_a values close to those of ω-hydroperfluoroalkyl analogs. The calculated pK_a values taken from the titration data are listed in Table IV together with the reported data.

TABLE IV

APPARENT DISSOCIATION CONSTANTS FOR CHLOROFLUOROETHYLPHOSPHONIC ACIDS[a]

Phosphonic acids	pK_a (1st break)	pK_a (2nd break)
$CHCl_2CFClPO(OH)_2$	2.4	5.2
$CHFClCFClPO(OH)_2$	2.2	4.9
$CHCl_2CF_2PO(OH)_2$	2.2	4.9
$CH_3CH_2PO(OH)_2$[b]	2.43	8.05
$CHF_2CF_2PO(OH)_2$[c]	2.2	4.7
$CF_3PO(OH)_2$[d]	1.16	3.93

[a] The pK_a values were taken directly from the titration curves obtained with a pH meter at 0.01 M concentration. [b] Ref. 12. [c] Ref. 8. [d] Ref. 13.

Experimental[15]

Materials.—The chlorofluoroolefins used in the experiments were prepared by the dechlorination of the corresponding chlorofluoroethanes with zinc dust in ethanol or n-butanol according to the method of Henne, *et al.*[16] The dialkyl phosphonates were synthesized from phosphorus trichloride and the corresponding alcohols using ether as a solvent by the method of Combie, *et al.*[17]

Irradiation by γ-Ray.—A mixture of the chlorofluoroolefins and dialkyl phosphonate in a molar ratio of about 1:2–3 was sealed into a Pyrex tube of *ca.* 300-ml. capacity. The reaction tube was then irradiated by γ-ray from Co^{60} for a period of 2 weeks at a dose rate of $0.6–0.7 \times 10^5$ r./hr. at room temperature.

Addition Reactions of Dialkyl Phosphonates to Chlorofluoroolefins.—A mixture of 190 g. (1.14 moles) of di-n-propyl phosphonate and 50 g. (0.38 mole) of 1,2-dichloro-1,2-difluoroethylene was sealed in a glass tube and irradiated to a total dosage of 1.6×10^7 r. for a period of 230 hr. Distillation of the irradiation products under reduced pressure, after the removal of the unchanged olefin and dialkyl phosphonate, gave 76 g. (0.24 mole, 68% yield) of di-n-propyl 1,2-dichloro-1,2-difluoroethylphos-

(11) These orders were determined from the amounts of chlorofluoroethylphosphonic acids formed, when the dialkyl chlorofluoroethylphosphonates were exposed to the atmosphere.

(12) P. C. Crofts and G. M. Kosolapoff, *J. Am. Chem. Soc.*, **75**, 3379 (1953).

(13) F. W. Bennett, H. J. Emeléus, and R. N. Haszeldine, *J. Chem. Soc.*, 3598 (1954).

(14) H. J. Emeléus and J. D. Smith, *ibid.*, 375 (1959).

(15) All temperature readings are uncorrected.

(16) A. L. Henne and E. C. Ladd, *J. Am. Chem. Soc.*, **58**, 402 (1936).

(17) H. M. Combie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 380 (1945).

phonate, b.p. 110–112° (6 mm.), and 16 g. of a residue. The residue was treated with 30 g. (0.14 mole) of phosphorus pentachloride to yield 8 g. of the dichlorodifluoroethylphosphonic dichloride, which was confirmed with the authentic sample prepared as mentioned below.

Using the same procedure, other dialkyl phosphonates were added to 1,2-dichloro-1,2-difluoroethylene. The addition reactions to other chlorofluoroolefins were carried out under similar conditions. In the case of 1,1-difluoro-2,2-dichloroethylene, the telomers were obtained with the 1:1 adduct. The dichloride of 1:2 adduct was isolated by distillation after the treatment of dialkyl ω-hydroperhaloalkylphosphonates with phosphorus pentachloride.

The irradiation conditions and yields based on the amounts of olefins added for each run are shown in Table I.

Chlorofluoroethylphosphonic Acids.—The hydrolysis of chlorofluoroethylphosphonates was carried out by the procedure of Brace.[8] In a flask fitted with a reflux condenser were added 25 g. (0.09 mole) of diethyl 1,2,2-trichloro-1-fluoroethylphosphonate and 60 ml. of concentrated hydrochloric acid. The mixture was refluxed at 80–110° for 5 hr. In 1 hr., a homogeneous solution was obtained. After ether extraction of the unchanged phosphonate, the aqueous solution was distilled under reduced pressure to remove hydrogen chloride and water. A trace of water remained and was removed by the azeotropic distillation with benzene. The liquid residue, 1,2,2-trichloro-1-fluoroethylphosphonic acid, 18.5 g. (0.08 mole, 92% yield), crystallized on standing. It was hygroscopic and liquefied on absorbing moisture in the air at room temperature. 1,2-Dichloro-1,2-difluoroethylphosphonic acid and 1,1-difluoro-2,2-dichloroethylphosphonic acid were prepared in an analogous fashion.

Chlorofluoroethylphosphonic Dichlorides. To 16 g. (0.07 mole) of 1,1,2-trichloro-2-fluoroethylphosphonic acid, in a flask with a reflux condenser was added 15 g. (0.07 mole) of phosphorus pentachloride in portions. A mixture was heated mildly and, in 0.5 hr., phosphorus oxychloride began to reflux. After heating for 1 hr., phosphorus oxychloride was distilled. To the residue, 15 g. (0.07 mole) of an additional phosphorus pentachloride was added and heated for 1 hr. Distillation of the products, after the removal of phosphorus oxychloride, gave 13 g. (0.05 mole) of 1,2,2-trichloro-1-fluoroethylphosphonic dichloride, b.p. 85–88° (8 mm.), and 3 g. of a solid residue.

Using the same procedure, 1,2-dichloro-1,2-difluoroethyl- and 1,1-difluoro-2,2-dichloroethylphosphonic dichlorides were prepared. Table III summarizes the physical properties of chlorofluoroethylphosphonic dichlorides.

Basic Hydrolysis of Chlorofluoroethylphosphonic Acids. 1,2,2-Trichloro-1-fluoroethylphosphonic acid, 10 g. (0.04 mole), and 30 ml. of 10% aqueous sodium hydroxide solution were added to a flask fitted with a reflux condenser, which was in turn connected to a trap cooled in Dry Ice–acetone. The mixture was heated at 50–100° for 30 min. to yield 1 g. (0.009 mole) of an olefin. The infrared spectrum and gas chromatogram of the olefin were compared with those of 1,2-dichloro-1-fluoroethylene which was prepared by the dechlorination of 1,1,2,2-tetrachlorofluoroethane.[16]

The Reaction of Ethyl Azodicarboxylate with Monoolefins

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The reaction of monoolefins with ethyl azodicarboxylate has been investigated. Acyclic monoolefins react by a nonradical process to give additive-substitution products with a shift of the double bond. Cyclic olefins, on the other hand, react predominantly by a free-radical process. The relative reactivity of C_4 and C_5 olefins (with ethyl azodicarboxylate) and the structure of the resultant products are all consistent with a concerted "addition-abstraction" mechanism involving a six-membered transition state. The data have been interpreted in terms of charge stabilization and steric interactions in the transition state.

The additive-substitution reaction of azodiformic acid esters with olefins was first observed in 1927 but received little attention[1,2] until recently.

Huisgen and Pohl were the first to present evidence for the mechanism of azo ester–olefin reactions. They demonstrated that aromatically conjugated olefins, such as 1,2- and 1,4-dihydronaphthalene and unsymmetrically substituted 1,3-diarylpropenes, underwent substitution in the allylic position with a shift of the double bond. Free-radical initiators and inhibitors had no effect on the rate or course of the reaction with these conjugated olefins; however, the reactions of azoformate ester with cyclopentene and cyclohexene were initiated by peroxide and retarded by radical inhibitors. The authors concluded that aromatically conjugated olefins react by a multicenter process involving a cyclic electron shift while nonconjugated olefins react by a free-radical chain process.

Levina, *et al.*,[4] reported that 1,1-disubstituted 1,3-dienes, whose steric hindrance precluded the usual Diels–Alder reaction, also underwent allylic substitution. However, they did not locate the positions of the double bond in the products and assumed that it occupied the same position as in the parent diene.

Cinnamon and Weiss[5] found that the reaction of cycloheptatriene with ethyl azodicarboxylate gave the diethyl ester of cycloheptatrienylbicarbamic acid instead of the customary Diels–Alder adduct which is produced by reaction with other dienophiles such as maleic anhydride. They suggested that the driving force for this reaction was the stability of the tropylium radical or tropylium ion which could be formed through hydrogen abstraction or hydride ion abstraction, respectively, followed by collapse to the allylic-substituted cycloheptatriene.

Franzus and Surridge[6a] demonstrated that 1,3- and 1,4-cyclohexadiene, which were neither sterically hindered nor capable of producing an unusually stable species, underwent substitution at the allylic position with a corresponding shift of double bond instead of the anticipated Diels–Alder reaction which is observed with cyclopentadiene. They also demonstrated the insensitivity of this reaction to radical initiators and inhibitors. Gillis and Beck[6b] found that the reaction of sterically hindered dienes such as 2,5-dimethyl-2,4-hexadiene, which was studied previously by Russian

(1) O. Diels and K. Alder, *Ann.*, **460**, 237 (1927).
(2) K. Alder, F. Pascher, and A. Schmitz, *Ber.*, **76**, 27 (1943).
(3) R. Huisgen and H. Pohl, *ibid.*, **93**, 527 (1960).
(4) R. Y. Levina, V. S. Shabarov, and M. G. Kuzmin, *Dokl. Akad. Nauk SSSR*, **131**, 1080 (1960).
(5) J. M. Cinnamon and K. Weiss, *J. Org. Chem.*, **26**, 2644 (1961).
(6) (a) B. Franzus and J. H. Surridge, *ibid.*, **27**, 1951 (1962); (b) B. T. Gillis and P. E. Beck, *ibid.*, **27**, 1947 (1962).

TABLE I

ADDUCTS FROM THE REACTION OF ETHYL AZODICARBOXYLATE AND BUTENES (80°)[a]

	Monoadduct[c]							Diadduct[c]						
			Analysis,[e] %							Analysis,[f] %				
Olefin	Product	Yield, %[d]	C	H	N	B.p. °C., (mm.)	$n^{20}D$	Product	Yield (%)[d]	C	H	N	Mol. wt.	Total yield[d] of mono- and diadduct (%)
1-Butene	1	63.5	51.93	7.75	12.58	120 (0.025)	1.4590	2	25.0	47.43	7.10	13.92	398	88.5
cis-2-Butene	3	77.8	51.92	7.93	12.38	110–115 (0.025)	1.4565	4	15.6	47.35	6.88	13.97	403	93.4
trans-2-Butene	3	95.0	52.26	8.18	12.54	110–115 (0.025)	1.4562	...	...	...	...	...	...	95.0
Isobutylene	5	77.8	52.08	7.86	12.52	110–115 (0.025)	1.4581	6 and 7	11.2	47.66	6.78	13.28	376	89.0

[a] 100 mole % excess of olefin, reacted until azo ester was consumed. [b] 1:1 azo ester–olefin adduct. [c] 2:1 azo ester–olefin adduct. [d] Based on azo ester. [e] Calcd. for $C_{10}H_{18}O_4N_2$: C, 52.16; H, 7.88; N, 12.17. [f] Calcd. for $C_{16}H_{26}O_8N_4$: C, 47.52; H, 6.98; N, 13.86; mol. wt., 404.

TABLE II

MONOADDUCTS FROM THE REACTION OF ETHYL AZODICARBOXYLATE WITH PENTENES (80°)[a]

	Monoadduct						Hydrogenated monoadduct				
			Analysis[f]					Analysis,[g] %			
Olefin	Products	Yield, %[b]	C	H	N	B.p. °C., (mm.)	$n^{20}D$	Products	C	H	N	$n^{20}D$
1-Pentene	8	78.0	53.53	8.18	11.43	118 (0.025)	1.4590	...	...	...	...	...
2-Pentene[c]	9 and 10	92.2	53.78	8.10	11.47	122 (0.05)	1.4590	11 and 12	53.66	8.97	11.71	1.4477
trans-2-Pentene	9 and 10	90.2	53.99	8.11	11.48	110 (0.025)	1.4587	...	...	...	...	...
cis-2-Pentene	9 and 10	76.5	53.98	7.98	11.63	107 (0.025)	1.4620	11 and 12	52.96	9.02	11.16	1.4498
2-Methyl-2-butene	13	85.8	54.43	8.02	11.81	107 (0.025)	1.4608	15	53.58	8.89	11.56	1.4490
2-Methyl-1-butene	16 and 17	84.3	54.35	8.23	11.46	120–130 (0.05)	1.4604	18	53.42	8.91	11.50	1.4465
3-Methyl-1-butene	20[c]	*d*	...	...	...	...	...	...	...	...	...	...

[a] 100 mole % excess of olefin, reacted until azo ester was consumed. [b] Based on azo ester. [c] 90% yield of diadduct (2 moles of azo ester to 1 mole of olefin) isolated from the reaction of a 2:1 mole ratio of olefin to azo ester. *Anal.* Calcd. for $C_{17}H_{30}N_4O_4$: C, 48.79; H, 7.23; N, 13.37; mol. wt., 418. Found: C, 48.83; H, 7.14; N, 13.29; mol. wt., 430. [d] Monoadduct (19) isolated from 20:1 olefin–azo ester reaction mixture. *Anal.* Found: C, 54.07; H, 8.19; N, 11.69. [e] Mixture, 58% *cis*- and 42% *trans*-2-pentene (99% pure). [f] Calcd. for $C_{11}H_{20}N_2O_4$: C, 54.08; H, 8.25; N, 11.47. [g] Calcd. for $C_{11}H_{22}N_2O_4$: C, 53.64; H, 9.00; N, 11.37.

workers,[4] gave 83% of the 3-substituted product with a shifted double bond. They attributed this product to a cyclic process similar to that proposed by Huisgen.[3] The simultaneous formation of the 1-substituted diene without any shift of the double bond (15%) was attributed to a competing free-radical process.

They also demonstrated that 1,3-cyclohexadiene gave allylicly substituted 1,4-cyclohexadiene as the principal product of the reaction with ethyl azodicarboxylate, and pointed out that retention of conjugation was not a requisite for adduct formation.

Results

Effect of Structure on Products —It was considered that the reaction of azoformate ester with monoolefins warranted further investigation, and might provide an interesting system for expanding our knowledge of the properties of allylic free radicals whose reactions have been an object of interest for one of the authors.[7]

In the course of this investigation it soon became apparent that the reaction of ethyl azodicarboxylate with simple olefins (contrary to Huisgen's conclusions based on studies with cyclopentene and cyclohexene[3]) did not involve a free-radical path as the principal mode of reaction.

(7) (a) C. Walling and W. Thaler, *J. Am. Chem. Soc.*, **83**, 3877 (1961); (b) A. A. Oswald, K. Griesbaum, W. Thaler, and B. E. Hudson, *ibid.*, **84**, 3897 (1962); (c) W. Thaler, A. A. Oswald, and B. E. Hudson, Abstracts of Papers, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962, p. 65.

Reactions of ethyl azodicarboxylate with excess C_4 and C_5 monoolefins (2 moles/mole of azo ester) were carried out at 80° in sealed tubes in the presence of air. The 1:1 adducts isolated in excellent yields by distillation were water white, moderately viscous liquids. The nonvolatile distillation residues (viscous yellow oils) which proved to be diadducts containing 2 moles of ethyl azodicarboxylate per mole of olefin required no further purification. The yields, physical properties, and elemental analyses for these reactions are presented in Table I (C_4 olefins) and Table II (C_5 olefins).

The monoadducts were resolved analytically by capillary v.p.c. for the purpose of identification and quantitative analysis. These products were readily amenable to n.m.r. analysis which was used for the assignment of molecular structure and the semiquantitative analysis of mixtures, permitting direct comparison with v.p.c. determinations. N.m.r. analyses and parameters for monoadducts of ethyl azodicarboxylate with these monoolefins are presented in Tables III and IV, respectively.

The reaction of ethyl azodicarboxylate (**A**) with the four isomeric butenes (eq. 1–3) gave a total of four isomeric allylic substituted ethyl bicarbamates (monoadducts) which were resolved by capillary v.p.c.

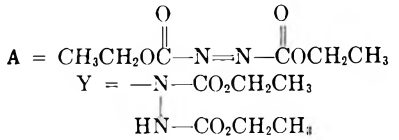


TABLE III

N.M.R. ANALYSIS OF MONOADDUCTS[a]

Olefin	Product(s)	—Methyl + methylene— Theory	Found	—Allyl[b]— Theory	Found	—OCH_2- + $-NCH_2$-[c] Theory	Found	Vinyl + -NCH<[c] Theory	Found	—>NH— Theory	Found
1-Butene	1	33.3	33.7	16.7	15.6	33.3	34.6	11.1	10.6	5.6	5.5
cis-2-Butene	3	50.0	49.3	...	...	22.2	22.8	22.2	22.6	5.6	5.3
trans-2-Butene	3	50.0	49.1	...	...	22.2	23.4	22.2	22.6	5.6	4.9
Isobutylene	5	33.3	32.4	16.7	16.7	33.3	33.7	11.1	11.6	5.6	5.6
1-Pentene	8	45.0	46.4	10.0	10.0	30.0	30.0	10.0	9.0	5.0	4.6
2-Pentene	9 and 10[d]	45.0	46.0	15.0	13.0	20.0	20.7	15.0	15.4	5.0	4.9
2-Methyl-2-butene	13	45.0	45.4	15.0	14.6	20.0	21.2	15.0	14.1	5.0	4.7
2-Methyl-1-butene	16 and 17[e]	37.5	37.1	20.0	21.7	30.0	29.2	7.5	7.4	5.0	4.6
3-Methyl-1-butene	19	30.0	32.8	30.0	29.4	30.0	29.0	5.0	4.2	5.0	4.6

[a] Comparison of area per cent with calculated values. [b] Allyl hydrogens except on carbons bearing a nitrogen. [c] Allyl hydrogens on carbons bearing a nitrogen. [d] Theory calculated for the major product (9). [e] Theory calculated for 1:1 mixture of products 16 and 17.

TABLE IV

N.M.R. PARAMETERS OF OLEFIN–ETHYL AZODICARBOXYLATE MONOADDUCTS

Olefin	Product(s)	Methyl[d]	—Methyl[e]—	Allyl-CH_3	Allyl-CH_2[f]	-OCH_2-	-N-CH_2-[g]	>C=CH_2	>C=C<H or -CH=CH-[h]	>NH[i]
1-Butene	1	...	1.2[a](7)[b] t[c]	1.7(5.5) d	...	4.1(7) q	4.0 ± 0.2	...	5.5 ± 0.2	7.7–7.9 s
2-Butene	3	1.2(7) d	1.2(7) t	...	...	4.1(7) q	...	...	...	7.4–7.7 s
Isobutylene	5	...	1.2(7) t	1.6 s	...	3.9(7) q	3.8 ± 0.2	4.5 s	...	7.2–7.5 s
1-Pentene	8	0.9(7) t	1.2(7) t	...	1.9[m]	4.0(7) q	3.9 ± 0.2	...	5.5 ± 0.2	7.8 s
2-Pentene	9 and 10	1.1(7) d	1.2(7) t	1.6(4) d	...	4.1(7) q	...	...	5.5 ± 0.2	7.5 s
2-Methyl-2-butene	13	1.3(7) d	1.2(7) t	1.7 s	...	4.1(7) q[j]	...	4.9 s	...	7.6 s
						4.2(7) q				7.4 s
2-Methyl-1-butene	16 and 17	1.1(7) t	1.2(7) t	1.6 s[k]	2.1(7) q[l]	4.1(7) q[m]	4.0 ± 0.2	4.9 s	5.4 ± 0.2	7.7 s
				1.6(7) d		4.2(7) q				7.8 s
3-Methyl-1-butene	19	...	1.2(7) t	1.5 s[n]	...	3.9(7) q	3.8 ± 0.2	...	...	6.9 s
				1.6 s						

[a] Chemical shift in p.p.m. to nearest 0.1 p.p.m.; TMS = 0 (all spectra were run in CCl_4 solution). [b] Parenthesis indicate spin–spin splitting in c.p.s. [c] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. [d] Methyl hydrogens from hydrocarbon moiety. [e] Methyl hydrogens from ethyl azodicarboxylate moiety. [f] Does not include allyl next to nitrogen. [g] Under part of OCH_2 quartet. [h] Complicated multiplet. [i] Chemical shift dependent on concentration probably due to hydrogen bonding. [j] Resolution between two -OCH_2- of azo ester have been observed infrequently (see ref. 8). [k] Two allyl methyls of 16. [l] Allylmethylene from 17. [m] 1.5-c.p.s. resolution between OCH_2 of 16 and 17. [n] 3.5-c.p.s. resolution between two different allyl methyls of 19.

$$CH_3CH_2CH{=}CH_2 + A \longrightarrow CH_3CH{=}CHCH_2Y \xrightarrow{A} \text{diadduct} \quad (1)$$
(1 → 2)

$$\textit{cis}\text{- or }\textit{trans}\text{-}CH_3CH{=}CHCH_3 + A \longrightarrow CH_3CHCH{=}CH_2 \xrightarrow{A} \text{diadduct} \quad (2)$$
(Y: 3 → 4)

$$CH_3CH{=}CH_2 + A \longrightarrow CH_2{=}CCH_2Y \quad (3)$$
(5)

$$5 + A \longrightarrow YCH_2CCH_2Y + YCH_2C{=}CHY \quad (4)$$
(6 + 7)

1-Butene gave a monoadduct which could be partially resolved by capillary v.p.c. into two peaks (83 and 17 area %). Infrared absorption at 10.3 μ indicated that the principal product was a substituted *trans*-2-olefin. N.m.r. (Tables III and IV) substantiated the presence of an internal double bond and confirmed structure **1**. It was concluded that 1-butene gave 1-(ethyl bicarbamyl)-2-butene (1) (about 83% *trans* and 17% *cis*).

cis- and *trans*-2-butene both formed the same product which gave a single new v.p.c. peak. The infrared showed typical absorption at 10.1 and 10.9 μ attributable to a monosubstituted ethylene (α-olefin). The n.m.r. spectrum of the 2-butene monoadduct was qualitatively and quantitatively consistent with 3-(ethyl bicarbamyl)-1-butene (**3**).

The n.m.r. spectra of the monoadducts from 1- and 2-butenes are presented in Fig. 1 and 2, respectively. They illustrate many of the typical proton resonance absorptions which were encountered in this study, and demonstrate the utility of this method for assigning structures to the allylic bicarbamic acid diethyl esters. Compound **1** clearly shows allylic methyl (1.7 p.p.m.) which is absent in **3**, while the remaining allylic hydrogens which are on a carbon bonded to nitrogen absorb further downfield (4 p.p.m.) and do not interfere in this region. In addition to the triplet methyl (1.2 p.p.m.) and quartet OCH_2 (4.1 p.p.m.) which are always present from the ethyl alcohol moiety of the ester, compound **3** shows a doublet methyl (1.2 p.p.m.) consistent with a 3-substituted butene-1 structure.

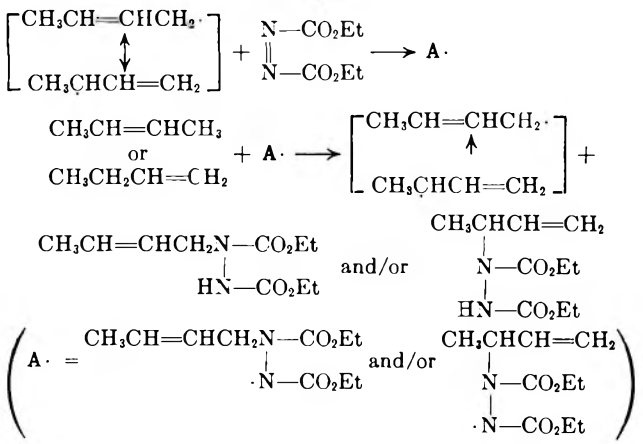
Substitution in isobutylene (eq. 4) also occurred at the allylic position to give product **5**; however, owing to the symmetry of the isobutylene molecule it was not possible to determine whether its reaction with **A** involved a shift of the double bond in a fashion analogous to the reactions with the linear C_4 olefins.

Yields of diadducts ranging from 0–25%, depending on the structure of C_4 olefin reacted, were isolated when a twofold excess of olefin was used (Table I). Larger quantities of excess olefin increased the yield of mono-

adduct at the expense of diadduct. Discussion of the effect of olefin structure on diadduct yield is best deferred to the section dealing with the relationship between olefin structure and reactivity.

The demonstration that 1- and 2-butenes gave completely different products, which contained double bonds adjacent to their original position in the parent olefin, is significant because it precludes the formation of these products by means of a free-radical chain mechanism.

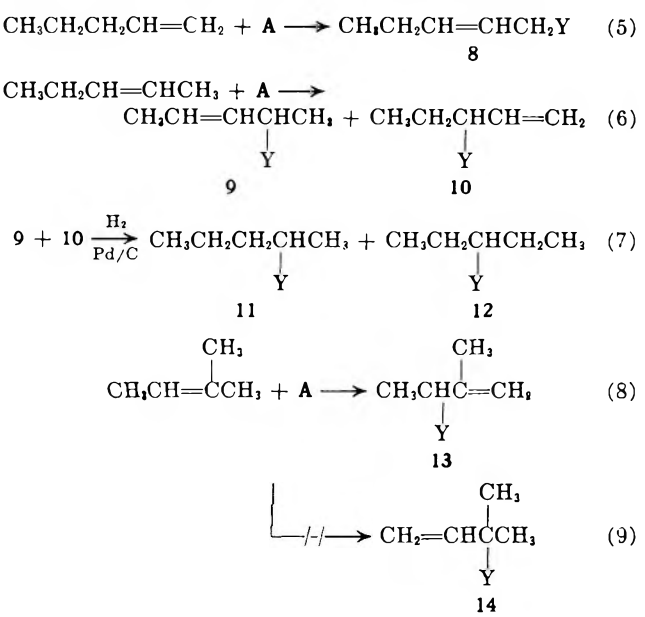
A radical chain mechanism would involve the formation of an intermediate allylic radical followed by addition of this radical across the azo double bond. The



resulting product(s) from the reactions of either 1- or 2-butene would of necessity be the same, since the same allylic radical intermediate(s) would be formed from both.

A situation in which stereochemically different intermediate allylic radicals are produced from *trans*- and *cis*-2-butene is somewhat more complicated. However, at least one intermediate allylic radical from 1-butene must still be the same as an intermediate radical derived from *cis*- or *trans*-2-butene.[7a] Therefore, the conclusion, that if a free-radical process were involved 1-butene would give the same product(s) as derived from *trans*- or *cis*-2-butene, remains unaltered.

The reaction of ethyl azodicarboxylate with a twofold excess of acyclic C_5 olefins similarly gave allylic bicaramates with a shifted double bond exclusively.



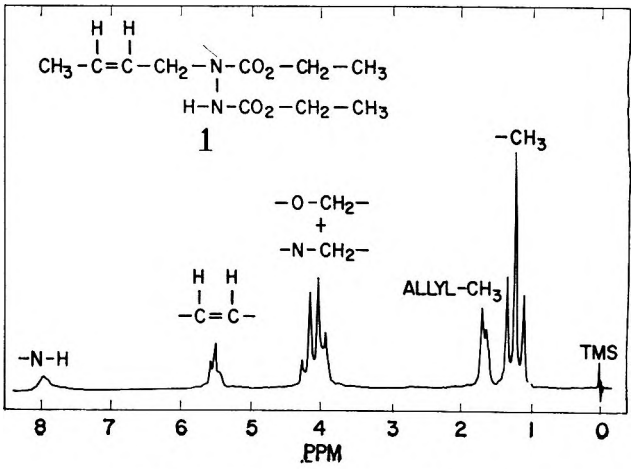


Fig. 1.—N.m.r. of adduct from 1-butene.

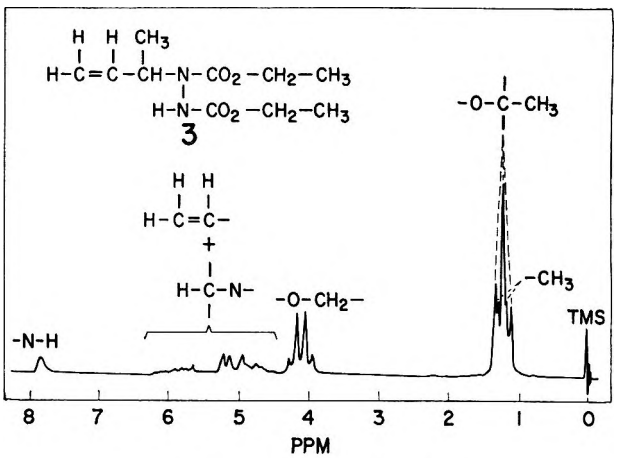
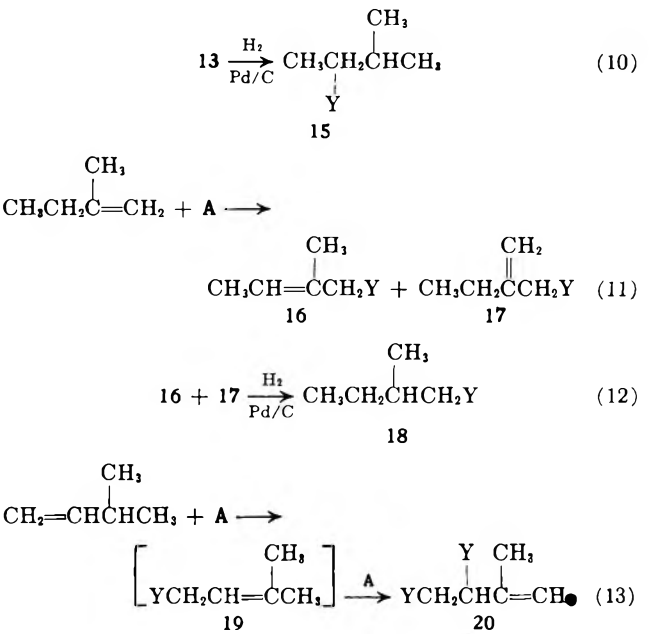


Fig. 2.—N.m.r. of adduct from 2-butene.

Pentene-1 (eq. 5) gave a single peak in the capillary v.p.c. and was shown by n.m.r. to be a 1-substituted 2-pentene. *cis*- and *trans*-pentene-2 (eq. 6) each gave the same three capillary v.p.c. peaks. Some difference in composition was observed for the product peaks from *trans*- and *cis*-olefin: *trans*-2-pentene showed P_1 30%, P_2 8%, P_3 62%; *cis*-2-pentene showed P_1 19%, P_2 16%, P_3 65%. N.m.r. indicated that these mixtures were



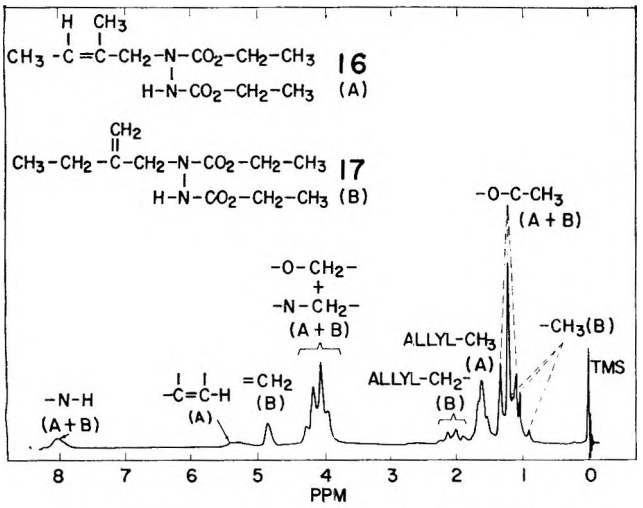


Fig. 3. N.m.r. of adducts from 2-methyl-1-butene.

mostly 4-substituted 2-olefin with lesser quantities of 3-substituted 1-olefin. Hydrogenation (eq. 7) of a distilled fraction containing 30% P_1, 4% P_2, and 66% P_3 gave two new products, P_1' 30% and P_1' 70%. The results suggest that P_1 is 3-(ethyl bicarbamyl)-1-pentene (**10**) while P_2 and P_3 are *cis*- and *trans*-4-(ethyl bicarbamyl)-2-pentene (**9**). Their infrared spectra support these assignments.

2-Methyl-2-butene upon reaction (eq. 8) gave a single product (capillary v.p.c.). N.m.r. evidence also supported the formation of a single product of structure **13** indicating that the reaction of this branched chain olefin similarly involved a shift of the double bond. No evidence could be found for the presence of any **14** which would require shifting the double bond in the opposite direction (eq. 9) to give the less stable of the two possible olefinic products. Hydrogenation of the product from reaction 8 gave only one product (**15**).

2-Methyl-1-butene was examined to discern any trend toward the formation of the thermodynamically more stable product (olefin with greatest number of alkyl substituents). To the contrary, n.m.r. showed that equal quantities of **16** and **17** were produced (Fig. 3) without regard for the stability of the double bond in the product. Capillary v.p.c. showed three peaks, P_1 48%, P_2 17%, and P_3 35%, which were consistent with a mixture of 48% **17** and 52% *cis* and *trans* **16**. Proof that **16** and **17** differed only by the position of the double bond was obtained when it was shown that all three products could be hydrogenated to a single product (**18**), whose v.p.c. retention time was quite different from isomeric **15**.

The reaction of 3-methyl-1-butene with ethyl azodicarboxylate (eq. 13) under the same conditions (twofold excess of olefin) gave only a diadduct consisting of 2 moles of ethyl azodicarboxylate to 1 of olefin. N.m.r. was consistent with structure **20**. It was possible to isolate the monoadduct **19** when a large excess (twentyfold) of olefin was used.

The observation that the 3-methyl-1-butene reacted more slowly than the olefinic monoadduct (**19**) gave qualitative evidence that 3-methyl-1-butene is a comparatively unreactive olefin, despite the fact that of all the systems investigated this product contained the most stable double bond relative to reactant. The thermodynamic stability of the products does not, therefore, appear to be an important factor directing the course of this reaction.

V.p.c. examination of the recovered excess olefin after each reaction demonstrated that no isomerization of olefin occurred under the conditions of these reactions.

In order to obtain information regarding the effect of free-radical initiators and inhibitors on the structure and distribution of products from the reaction of ethyl azodicarboxylate with C_4 and C_5 olefins, the reactions were run in the presence of benzoyl peroxide, *t*-butylcatechol, and 2,2-diphenyl-1-picrylhydrazyl. The reactions were run in degassed sealed tubes with a tenfold excess of olefin over azo ester (to avoid diadduct formation) together with each of the above modifiers at 4% of the azo ester concentration.

The free-radical inhibitors (*t*-butylcatechol and 2,2-diphenyl-1-picrylhydrazyl) were found to have no effect on the products of these reactions. The same allylic ethyl bicarbamates with their double bond shifted to the adjacent position were produced as in the previous experiments. In the presence of free radicals, generated from the decomposition of benzoyl peroxide, the principal products (>85%) remained the same as in the noncatalyzed and inhibited reactions. In addition to the customary (thermal) products, small quantities (0–15%) of products attributable to a free-radical chain process were identified. This can be exemplified by the reaction of *trans*-2-butene which customarily gave 3-(ethyl bicarbamyl)-1-butene (**3**) as the sole product. In the presence of free-radical initiator, 13% 1-(ethyl bicarbamyl)-2-butene (**1**, usual product from 1-butene) was produced along with 87% of **3**. Production of **1** from *trans*-2-butene is ascribed to an allylic radical precursor ($CH_3CH{=}CHCH_2 \cdot \leftrightarrow CH_3\dot{C}HCH{=}CH_2$) which adds across the nitrogen–nitrogen double bond to give a bicarbamyl radical. The bicarbamyl radical then abstracts a hydrogen atom from the olefin giving allylic bicarbamate products and regenerating the allylic radical intermediate.

It is significant that the relative amounts of the usual products formed under nonradical conditions, in those reactions that customarily gave more than one product, remained essentially unchanged when the reaction was run under free-radical conditions. This suggests that only a very small amount of the products which can be produced thermally are also produced by a simultaneous free-radical process. Table V gives the yield of additional products formed under radical conditions which were not produced under the usual thermal conditions. The "new" products were readily identified since all were obtainable from the nonradical (thermal) reaction with a different isomeric olefin.

TABLE V
ADDITIONAL PRODUCTS FOUND ONLY IN THE PRESENCE OF BENZOYL PEROXIDE INITIATION

Reactant	Additional Product	Yield, %
2-Butene	1	12–15
Isobutylene	...	...
Pentene-1	10	13
Pentene-2	...	...
2-Methyl-1-butene	13	6
2-Methyl-2-butene	...	...

Since it could be demonstrated that free-radical initiator caused no isomerization of olefin, it would appear safe to conclude that in the presence of free-radical initiator, these small quantities of new products were formed by means of a competing free-radical process.

The failure of free-radical inhibitors to alter the usual thermal reaction, coupled with the observation that this thermal process always proceeds with a shifting of double bond and is relatively unaffected by radical initiators, provides compelling evidence for the nonradical nature of the reaction of azodiformic acid ester with *acyclic monolefins*.[8]

Structure and Reactivity in Azoformate Ester Reactions.—The effect of olefin structure on reactivity toward ethyl azodicarboxylate was examined using competitive kinetic techniques. Relative reactivities were determined by following both the rates of disappearance of olefinic reactants and the rates of appearance of products, in different experiments, using vapor phase chromatographic analysis. The relative reactivity for two different olefins, determined from the disappearance of olefinic reactants, was calculated using the expression

$$k_A/k_B = \log \frac{(A_I)}{(A_F)} \Big/ \log \frac{(B_I)}{(B_F)}$$

where k_A/k_B is the relative rate constant for reaction with olefin A and olefin B, while $(A_I)/(A_F)$ and $(B_I)/(B_F)$ are the ratios of the initial to final olefin concentrations for olefins A and B, respectively. The initial/final olefin concentrations were calculated from the ratios of each of the olefins to an inert internal standard (such as *n*-pentane) before and after reaction. Relative reactivities for pairs of olefins, determined by following product formation, were calculated using the expression

$$k_A/k_B = \frac{(A')}{(B')} \Big/ \frac{(B)}{(A)}$$

where (A')/(B') is the molar ratio of the products after reaction and (B)/(A) is the ratio of olefinic reactants (which is essentially constant at low conversions) before reaction. Relative reactivity experiments requiring calculations based on the consumption of olefin were carried to about 50% conversion of olefinic reactants, whereas experiments using the formation of products were carried to about 5% conversion.

Results from both techniques were in fairly good agreement and gave the same order of olefin reactivities as shown in Table VI. The relative reactivities determined by following product formation gave very reproducible self-consistent results while the determination using olefin disappearance, which required cumbersome mechanical techniques, were less precise. Therefore, the data presented in Table VI were calculated from the relative rates of product formation from pairs of reacting olefins.

The absolute rate constant[9] of 1.64×10^{-4} (8 °) for the reaction of ethyl azodicarboxylate with 1,4-cyclohexadiene can, therefore, be utilized to calculate absolute rate constants from these relative reactivity data.

The greater tendency of some olefins towards diadduct formation (Table I) is in agreement with this relative reactivity data. Thus *trans*-2-butene, which forms a less reactive α-type olefinic product, gave essentially no diadduct, while isobutylene which gives the same type of double bond in the product as in the parent olefin exhibits a tendency towards diadduct formation. *cis*-2-Butene and 1-butene, whose adducts possess more reactive double bond types than the parent olefin, like isobutylene, show an increased tendency towards diadduct formation. In the sluggish 3-methyl-1-butene system, the reactivity of the initial product is so large, relative to the parent olefin, that under these same conditions (2:1 olefin-azo ester) it is almost entirely converted to diadduct.

The amount of diadduct formation is, therefore, not only dependent on the ratio of hydrocarbon (olefin) to azoformate ester but also upon the relative reactivity of the olefinic bond types of the hydrocarbon and the monoadduct.

The reaction of ethyl azodicarboxylate with cyclopentene gave the expected 2-(ethyl bicarbamyl)-1-cyclopentene as reported by Huisgen and Pohl.[3] When cyclopentene was reacted competitively with some of the aforementioned acyclic olefins, the relative reactivities showed poor reproducibility. Since all of the competitions between acyclic olefins afforded results with excellent precision, a comparison of the effects of free-radical initiator on competitions between two acyclic olefins with the effects of initiator on competitions between cyclic and acyclic olefins was made.

The data in Table VII reveal that the rates of reaction of the acyclic monoolefins were, as expected, not affected by free-radical initiator. On the other hand, the rate of reaction of cyclopentene was markedly increased by conditions favoring free-radical reaction. The poor precision observed between unmodified competitions of pentene-1 with cyclopentene can be ascribed to varying quantities of peroxidic impurity which could have been present.

The rather surprising conclusion which can be drawn from these results is that cyclopentene, unlike the acyclic olefins examined, reacts with azoformate ester preferentially by a free-radical path. This conclusion is in agreement with the observation of Huisgen and Pohl that cyclopentene and cyclohexene reacted with ethyl azodicarboxylate in a reaction that was enhanced by initiators and retarded by inhibitors of free-radical

TABLE VI

RELATIVE REACTIVITIES OF OLEFINS WITH ETHYL AZODICARBOXYLATE (80°)

C_4 Olefins (Relative to *cis*-2-Butene)	
Isobutylene	17.2
trans-2-Butene	3.73
1-Butene	2.57
cis-2-Butene	1.00
C_5 Olefins (Relative to 1-Pentene)[a,b]	
2-Methyl-2-butene	4.33
2-Methyl-1-butene	3.64
trans-2-Pentene	2.13
1-Pentene	1.00
3-Methyl-1-butene	Slow

[a] *cis*-2-Pentene reacted more slowly than 1-pentene but the very reactive 2-methyl-2-butene impurity in the 95% pure *cis*-2-pentene interfered with an accurate determination. [b] 1,4-Cyclohexadiene had an over-all reactivity of 14.7 ± 1.17 relative to pentene-1.

(8) After the present work had been concluded, Polish workers reported the results of ozonolysis experiments which confirm the shifting of the double bond position: O. Achmatowicz and O. Achmatowicz, Jr., *Roczniki Chem.* **37**, 317 (1963).

(9) B. Franzus, *J. Org. Chem.*, **28**, 2954 (1963).

TABLE VII

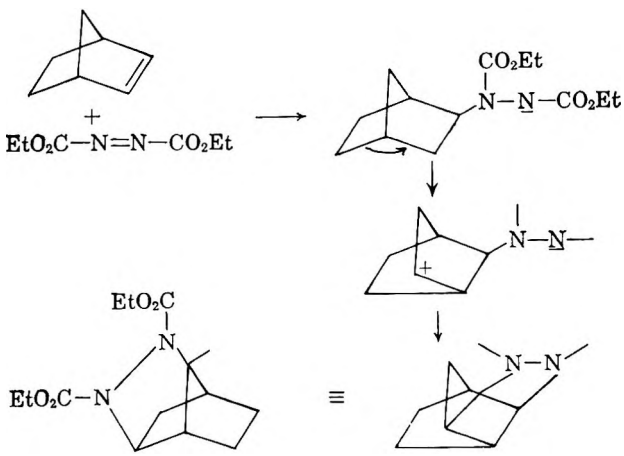
A COMPARISON OF THE EFFECTS OF FREE-RADICAL INITIATORS ON THE RELATIVE REACTIVITIES OF CYCLIC AND ACYCLIC OLEFINS TOWARD ETHYL AZODICARBOXYLATE (80°)

Olefin A / Olefin B	k_A/k_B Free-radical[a] inhibitor	Nothing added	Free-radical[b] initiator
Pentene-1 / Cyclopentene	3.70 ± 0.05	1.70 (1.18)[c]	0.300 ± 0.006
Pentene-2 / Pentene-1		2.13 ± 0.02	2.11 ± 0.01

[a] 2,2-Diphenyl-1-picrylhydrazyl and *t*-butylcatechol were each used in duplicate runs. [b] Benzoyl peroxide. [c] Poor reproducibility presumably due to varying traces of hydrocarbon peroxide.

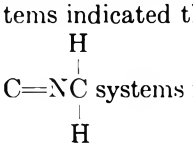
reactions.[3] It is now apparent, however, that their conclusion that nonconjugated monoolefins react by a free-radical mechanism resulted from generalization of the findings of what appears, in light of the present investigation, to be a rather special case.

The reaction of ethyl azodicarboxylate with norbornylene (95°), which cannot proceed with a shift of the double bond (Bredt's rule), gave a monoadduct whose n.m.r. is consistent with a tricyclic compound produced by the following sequence.

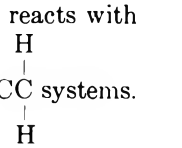


It would appear that in the absence of easily abstractable allylic hydrogens as in the case of norbornylene and norbornadiene a "free" carbonium ion is formed thereby permitting rearrangements of carbon skeletons.[10]

Some exploratory experiments with azomethine systems indicated that ethyl azodicarboxylate reacts with

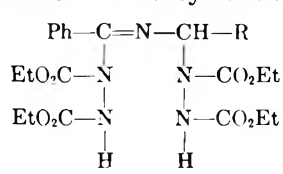


C=NC systems in the same fashion as



C=CC systems.

When ethyl azodicarboxylate reacted with the condensation product from benzaldehyde and an aliphatic amine, a diadduct of the structure (21) was formed. This structure was confirmed by n.m.r. and ultraviolet



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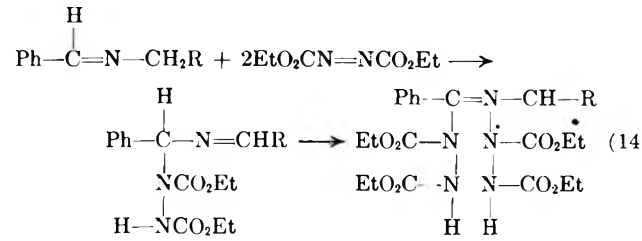
(10) S. J. Cristol, E. L. Allred, and D. L. Wetzel, *J. Org. Chem.*, **27**, 4058 (1962).



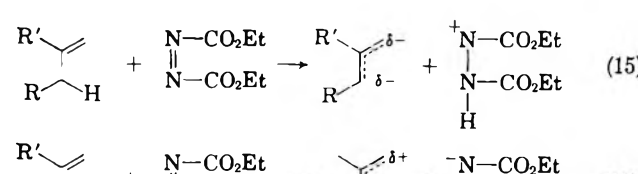
analysis. The ultraviolet showed the same absorption wave length and an almost identical molar extinction coefficient for both starting imine and diadduct. The nonconjugated monoadduct first formed is in all probability more reactive toward azo ester adduct than the conjugated starting compound accounting for the sole formation of diadduct.

Some experiments with methyl and ethyl phenylazoformate (Ph—N=NCO$_2$R, R = Me or Et) indicated that these compounds gave 1:1 adducts with simple monoolefins, with somewhat greater difficulty then the azoformate diesters. Higher reaction temperatures were required and the reactions were not so selective and had poorer yields. These condensation products were also more difficult to purify.

Discussion

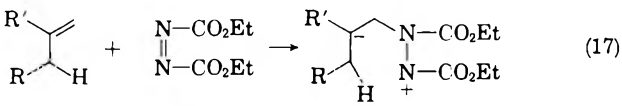
The evidence regarding product structure and the effects of initiators and inhibitors on the course and rates of the reaction of ethyl azodicarboxylate with acyclic monoolefins appears to preclude a free-radical chain mechanism. While it is not possible to describe accurately the transition state for this reaction without thoroughly investigating its kinetics, examination of the effect of olefin structure on reactivity (relative) and product structure has enabled us to make several generalizations: the relative thermodynamic stability of the olefinic product (number of alkyl substituents about the double bond) and the type of abstracted hydrogen (primary, secondary, tertiary) influences neither the reaction rate nor the structure of the product; the rate of reaction is increased by the presence of alkyl substituents on the vinyl carbon adjacent to the one which becomes bound to nitrogen; *trans* olefins are more reactive than *cis* olefins; the presence of several alkyl substituents on the allylic carbon greatly reduces the reactivity of the olefin; when more than one potential point of attack is available, attack occurs at the least hindered vinyl carbon.

Several heterolytic processes involving a sequence of two reactions can be written. The two steps involve hydrogen transfer and attack on vinyl carbon (double bond). The former may take the form of either proton transfer (eq. 15) or hydride transfer (eq. 16), while the latter may involve either nucleophilic (eq. 17) or electrophilic (eq. 18) attack upon the double bond as the rate-determining step.

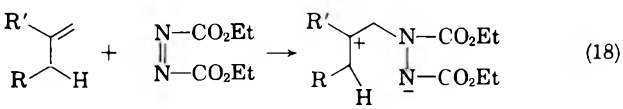


Each of these hydrogen-transfer reactions would be expected to give two different allylic bicarbamate products, since the intermediate allylic carbonium ions or carbanions have a delocalized charge and, therefore, two reactive sites. Furthermore, neither of these two reactions explains the observed increase in rate when an alkyl group (R′) is introduced onto a vinyl carbon.

Nucleophilic attack by ethyl azodicarboxylate upon the olefinic bond (eq. 17) would be expected to give the opposite of the observed increase in rate when alkyl substituents (R′) are placed on the vinyl carbon. Furthermore, nucleophilic attack by azoformate ester is out of character for such an excellent dienophile with its electron-withdrawing substituents.



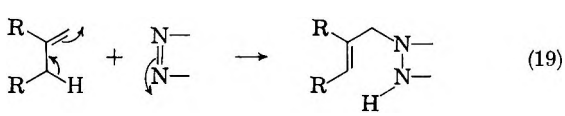
(17)



(18)

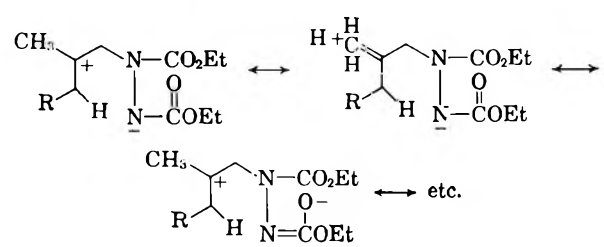
An electrophilic attack upon an olefin (eq. 18) is consistent with the observations which have been made, for example, rate enhancement by electron-donating alkyl substituents. However, electrophilic substitution like the other stepwise processes, which involve a large degree of charge formation is not consistent with the failure to incorporate deuterium in the product when the reaction is run in deuterio alcohol, as well as the comparatively small increase in rate (twentyfold) when the reaction is run in solvents of widely different polarity (cyclohexane and ethanol).[9]

It, therefore, appears that the process is a concerted one, involving a cyclic transition state similar to that first described by Arnold[11] to account for the condensation reactions of maleic anhydride with olefins, and by Huisgen[3] to explain the reaction of azoformates with aromatic olefins.

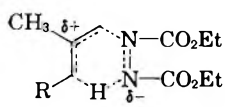


(19)

The large negative entropy of activation (about −40 e.u.) observed by Franzus[9] with azo ester–cyclic diene reactions is strongly indicative of such a concerted process (eq. 19) involving a rather rigid transition state. This process should not be interpreted as being completely synchronous; indeed, some charge development in the transition state would be anticipated. Contributing resonance structures of the type that follows



can be drawn for the transition state (22), which explain among other things the enhancement of reactivity by alkyl group substituents on the vinyl carbon *via* inductive and hyperconjugative stabilization of the incipient positive charge.[12]



22

The involvement of the depicted cyclic transition state (22) with its stringent steric requirements can account for such phenomena as the exclusive attack at the least hindered vinyl carbon of 2-methyl-2-butene, the greater reactivity of *trans* olefins compared with *cis* olefins, as well as the low reactivity of the 3-methyl-1-butene system.

In Fig. 4 it can be seen that the steric interaction of the carbethoxyl group of ethyl azodicarboxylate (which is assumed to have the lower energy *trans* configuration) with an alkyl substituent, is a rate-diminishing feature in the reaction of *cis* olefins which does not come into play with *trans* olefins.

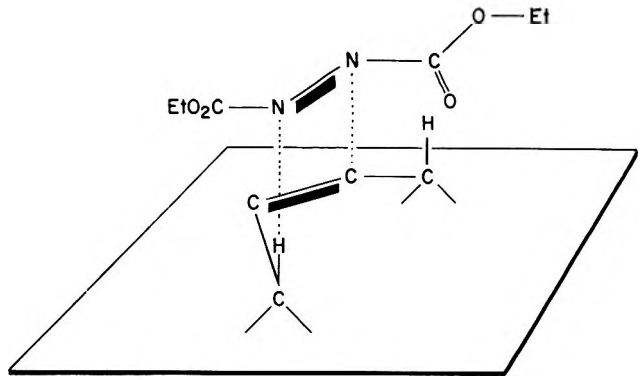


Fig. 4.—Steric interaction of carbethoxyl group with methyl group of *cis* olefin.

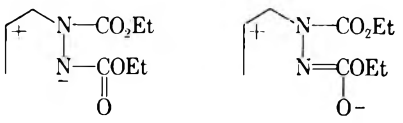
Similarly, examination of models suggests that the low reactivity of 3-methyl-1-butene can be attributed to the strained conformation, having a tertiary hydrogen coplaner with the p-orbitals of the olefinic bond, required for reaction. The assumption of such a conformation would involve considerable steric interaction between the methyl group and terminal vinyl hydrogens of 3-methyl-1-butene; it is not very favorable.

One might predict from the mechanistic picture proposed here, that the ability of such an electrophilic reagent to stabilize the negative charge developed in the transition state would be an important factor in determining its ability to participate in additive substitutions involving the addition–abstraction (cyclic) mechanism depicted (eq. 19). The greater stability of a negative charge on nitrogen compared with carbon may be one of the important features which makes azo ester–olefin reactions considerably more facile than the analogous reactions with unsaturated carbon compounds such as fumarates and maleates (as well as maleic anhydride).

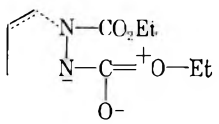
(11) R. T. Arnold and J. F. Dowdall, *J. Am. Chem. Soc.*, **70**, 2590 (1948).

(12) Similar transition state structures involving unpaired electrons instead of charge separation can also be drawn. Some uncertainty is involved in distinguishing between these two transition states; however, the twentyfold increase in rate with increased solvent polarity would appear to make the diradical type of transition state less likely.

The correctness of our emphasis on the importance of change delocalization in lowering the energy of the transition state and therefore the importance of the contribution of resonance structures, such as is shown,



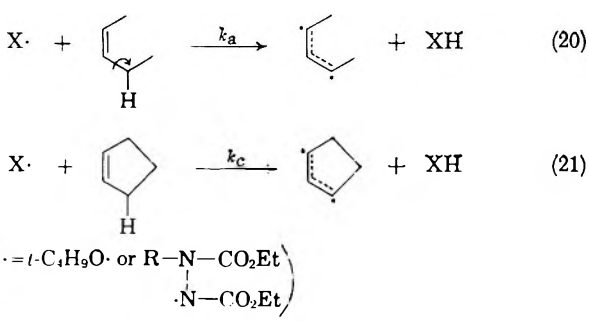
should be capable of verification. The presence of an oxygen adjacent to the carbonyl group enhances cross-conjugation structures, such as the one that follows,



which decrease the ability of the carbonyl group to delocalize the negative charge on nitrogen in the transition state relative to the ground state, thereby increasing the energy between the ground and the transition state. If this mechanistic picture is correct, replacement of the oxygen with elements less capable of interaction with the carbonyl group should enhance delocalization of the negative charge on nitrogen and should result in analogous azo compounds with enhanced reactivity. A comparison of the kinetics of the reaction of olefins with such modified azoformate esters is currently under investigation.

One is tempted to predict that a variety of unsaturated electrophilic reagents which possess the ability to delocalize effectively this incipient negative charge will prove effective in participating in additive-substitution reactions by means of such an addition–abstraction mechanism.

The preference for reaction of ethyl azodicarboxylate with cyclic olefins *via* a free-radical chain mechanism can be rationalized by comparison with data on the relative rates of allylic hydrogen atom abstraction from cyclic and acyclic olefins by *t*-butoxy radical. The preferential abstraction by *t*-butoxy radicals of allylic hydrogens from cyclohexene and cyclopentene compared with secondary and even tertiary allylic hydrogens from acyclic olefins has been attributed to the loss of a rotational degree of freedom from the acyclic system only.[7a]



Proceeding from the ground state to the transition state for the formation of an acyclic allylic radical such as 2-pentenyl free radical, which is capable of maintaining its geometry, involves the loss of a rotation about the C-3–C-4 bond. The cyclic olefin does not encounter this unfavorable entropy change between ground and transition state. Thus, the cyclic olefin has a lower free energy of activation for the abstraction of a hydrogen atom.

Similar considerations are applicable for the abstraction of allylic hydrogen atoms by RN(COOEt)NCOOEt radical. Evidently, the decreased reactivity of the *cis*-olefinic systems toward a concerted addition–abstraction type process, coupled with a more favorable entropy of activation for the formation of an allylic radical, is sufficient to make cyclic olefins such as cyclopentene react with azoformate ester preferentially by a free-radical path.

Experimental

All the hydrocarbons used in this study, with the exception of pentene-2, were Phillips Pure Grade (99% minimum purity). *trans*-2-Pentene of high purity was obtained from Farchan Research Laboratories. Phillips *cis*-2-pentene practical grade (95%) and pure grade pentene-2 (58% *cis*, 42% *trans*) were also used. Ethyl azodicarboxylate (diethyl azodicarboxylate) was purchased from Aldrich Chemical Co. and distilled before use. N.m.r. spectra were obtained using a Varian A-60 spectrometer. V.p.c. analyses were performed on a Perkin-Elmer 226 vapor fractometer using a 200-ft. capillary column coated with Surfonic TD 300 (a tridecyl alcohol–ethylene oxide adduct) operated at 160°. Several of the olefin competitions could be followed using packed column v.p.c. (1.5-m. ethylene glycol succinate on Chromsorb W, 170°); however, capillary v.p.c. was used for all purity evaluations and for a large majority of the relative rate measurements.

Noncatalyzed Reactions.—Ethyl azodicarboxylate, 34.8 g. (0.2 mole), together with 0.4 mole of olefin was placed in a glass-lined bomb (C_4 olefin) or sealed ample (C_5 olefin) and heated at 80° until the color of azo ester was essentially absent. The reaction mixtures were analyzed by v.p.c. both prior and subsequent to distillation. The monoadducts were isolated by distillation, whereas the distillation residues proved to be diadducts of high purity (Tables I and II).

Reactions in the Presence of "Modifiers".—Each of the C_4 and C_5 olefins mentioned in this study were reacted with ethyl azodicarboxylate at 80° in the presence of each of the three modifiers: benzoyl peroxide (free-radical initiator), *t*-butylcatechol, and 2,2-diphenyl-1-picrylhydrazyl (free-radical inhibitors).

Olefin (50 mmoles), 5 mmole of ethyl azodicarboxylate, and 0.2 mmole of modifier (about 4% based on azo ester) were placed in a Pyrex ampoule and degassed by alternately evacuating and pressuring with nitrogen. The tubes were then sealed and placed in a thermostated bath at 80° until azo ester had been consumed. The time necessary for complete reaction in the presence of 2,2-diphenyl-1-picrylhydrazyl was estimated from other runs (in the presence and absence of modifiers) in which color changes could be observed.

Competitions.—Approximately 50 mmoles of each of two olefins was accurately measured into a Pyrex ampoule, several microliters of the mixture were removed (for v.p.c. analysis to confirm relative concentration of the two olefins), and then approximately 5.0 mmoles of ethyl azodicarboxylate was added (20:1 olefin–azo ester). The tubes were degassed and sealed using liquid nitrogen coolant. After thawing, the contents were thoroughly mixed and placed in a constant temperature bath at 80° until azo ester was consumed. The tubes were cooled, cut open, and the ratio of the products formed determined by v.p.c. analysis. V.p.c. analyses were performed at least in triplicate for each run. Competitions with the same pair of olefins were run at least in duplicate.

Competitions which were run in the presence of initiator or inhibitor were carried out in the same manner except 5 mole % of modifier based on azo ester was added.

Reaction with Bicyclo[2.2.1]heptene-2 (Norbornylene).—Norbornylene, 12.06 g. (0.128 mole), together with 5.3 g. (0.03 mole) of ethyl azodicarboxylate was refluxed (92–95°) with 50 ml. of cyclohexane for 482 hr. after which time v.p.c. analysis indicated no further reaction was taking place. The solvent and some unreacted olefin were removed by distillation. Vapor phase chromatographic analysis (1 m. × 0.25 in. ethylene glycol succinate column at 170°, 200 cc./min. He flow) of this

TABLE VIII

N.M.R. ANALYSIS OF NORBORNYLENE ADDUCT

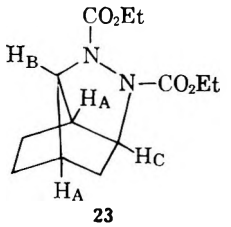
	Analysis, % Calcd.	Found	δ, p.p.m. from TMS
CH_3 + ring hydrogens	12	12	1.28 (center line)
H_A	2	2.3	2.45
H_B or H_C	1	0.9	3.66 or 4.35
OCH_2 + H_B or H_C	5	4.8	4.09, 4.13

crude product indicated four components. The major component was eluted first on an acid-washed alumina column with methylene chloride as eluent. This compound (90% pure) was rechromatographed in the same manner to 95% purity (v.p.c.) and showed no N–H absorption according to infrared analysis. Of the other three minor components, one corresponded to ethyl hydrazodicarboxylate and the other two were not identified.

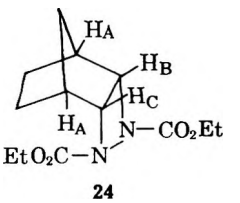
Anal. Calcd. for $C_{13}H_{20}N_2O_4$: C, 58.15; H, 7.51. Found: C, 58.32; H, 7.68.

N.m.r. was consistent with the structure **23** (see Table VIII). A cycloaddition product such as **24** would also be compatible with the observed n.m.r. if inversion of the carbethoxyl group were restricted. It is, however, likely that the inversion of these groups would be sufficiently free such that the bridgehead hydrogens would be equivalent and give a different n.m.r. spectrum from that observed.

Reaction with N-Benzylidenebutylamine.—N-Benzylidenebutylamine ($C_6H_5CH{=}NCH_2CH_2CH_2CH_3$) was prepared by azeotropic distillation of a benzene solution of *n*-butylamine and benzaldehyde (83.5% yield), b.p. 52–54° (0.2 mm.).



23



24

A sample of 16.1 g. of this imine (0.1 mole) and 4.33 g. (0.025 mole) of ethyl azodicarboxylate was placed in a 50-ml. bomb tube and heated for 45 hr. at 80°. The reaction mixture was then distilled at reduced pressure and 13.2 g. of unreacted imine recovered. The nonvolatile residue (6.2 g.) was a rather immobile liquid which was glassy when cold.

Anal. Calcd. for $C_{23}H_{35}O_8N_5$: C, 54.21; H, 6.92; N, 13.75; mol. wt., 509.6. Found: C, 53.90; H, 6.94; N, 13.86; mol. wt., 465. The analysis indicated the formation of a 2:1 azo ester–imine adduct in 97.7% yield. The n.m.r. of this product was consistent with structure **21**.

The ultraviolet spectrum of an acetonitrile solution showed a maximum at 244 mμ (ε 9410) as did the N-benzylidenebutylamine (ε 9075).

Acknowledgment—The authors wish to thank Messrs. J. J. Werner and J. H. Surridge for their very competent technical assistance.

The Reactions of Nitric Oxide with Tri- and Tetramethylethylene. The β-Nitroolefin and Nitrosite Rearrangements

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When the branched olefins trimethylethylene and tetramethylethylene were treated with nitric oxide at room temperature, reaction occurred smoothly to produce mixtures of nitroolefins (mainly) along with lesser quantities of nitrosites, dinitroalkanes, nitro alcohols, and cleavage products. The structures of most of the nitrated products were found to be analogous to those of the corresponding products derived from isobutylene or the unbranched olefins; *i.e.*, the nitro groups appeared at the less heavily substituted of the original olefinic carbons, and the other substituents or double bond termini appeared at the more heavily substituted position. In addition to these "normal" nitration products, "abnormal" allylic isomers of the β-nitroolefins appeared in considerable quantity, *e.g.*, 2-methyl-1-nitro-2-butene from trimethylethylene and 2,3-dimethyl-1-nitro-2-butene from tetramethylethylene. It was found that these arose from a remarkably facile, NO_2-catalyzed allylic rearrangement of the normal products, 2-methyl-3-nitro-1-butene and 2,3-dimethyl-3-nitro-1-butene, respectively. This rearrangement is believed to result from the addition of NO_2 to the β-nitroolefin to give a β,β′-dinitroalkyl radical which can then lose either β-nitro group to form either β-nitroolefin. It is suggested that similar eliminations of nitro groups from β-nitroalkyl radicals are also responsible for the thermal regeneration of olefins from certain nitrosites, the low kinetic chain lengths of nitroalkane chlorinations, and the very well-known NO_2-catalyzed *cis–trans* isomerization of olefins. It was long assumed that trimethylethylene nitrosite had an "abnormal" structure (secondary nitroso group, tertiary nitro) because upon treatment with alkalis or amines it yielded ketoximes, often with additional displacement of the nitro group by –OH, –NHR, etc. The present study confirmed the ketoxime formation, but showed that the original nitrosite actually had the "normal" structure (secondary nitro, tertiary nitroso) as required by the nitration mechanism. An intramolecular oxygen shift ("nitrosite rearrangement") is proposed in order to account for the ketoxime formation.

Most olefins react readily with nitric oxide containing catalytic traces of NO_2, thereby producing α- and β-nitroolefins, nitrosites, and a variety of other nitrated products. In the case of isobutylene, these products have been studied in detail and a mechanism proposed to account for the observed reaction behavior.[1] In this paper, we shall describe the products obtained from tri- and tetramethylethylene, and shall discuss two new rearrangements which were encountered during the course of these studies.

(1) J. F. Brown, Jr., *J. Am. Chem. Soc.*, **79**, 2480 (1957).

Experimental

Nitration of Trimethylethylene.—The olefin (385.5 g., 5.50 moles) was charged into a 1-l. Parr reactor fitted with a stirrer, cooling coils, and collection tank for the product gases, and flushed with dry nitrogen. Nitric oxide (205.5 g., 6.85 moles) under 50-p.s.i.g. pressure was added at a rate of 4.5 moles/hr. at 21°. The deep green liquid reaction product was subjected to a flash distillation in a falling film evaporator at 100° at 1 mm., and then further fractionated and analyzed by the general procedures[1] used for the isobutylene–nitric oxide reaction products. The indicated product composition is shown in Table I.

During the distillations, there was a considerable conversion of the nitrosite (VI) and presumably also of any N-(2-methyl-3-nitro-2-butyl)hydroxylamine present to regenerated trimethyl-

TABLE I

COMPOUNDS IDENTIFIED IN THE REACTION PRODUCT OF TRIMETHYLETHYLENE AND NITRIC OXIDE

Product	Yield, mole(s)	Estimated net yield, %
2-Methyl-3-nitro-1-butene (I)	0.50	24.6
2-Methyl-1-nitro-2-butene (II)	0.46	22.7
2-Methyl-3-nitro-2-butene (III)	0.44	21.7
2-Methyl-3-nitro-2-butanol (IV)	0.13	5.9
2-Methyl-2-nitro-2-butyl nitrate (V)	0.02	1.0
2-Methyl-3-nitro-2-nitrosobutane[a] (VI)	0.006	0.3
2,3-Dinitro-2-methylbutane (VII)	0.03	1.5
Acetaldehyde	0.01	0.0
Acetone	0.001	0.05
Methyl isopropyl ketone	0.01	0.5
Acetic acid	0.02	1.0
Nitromethane	0.02	1.0
Unidentified carbonyl compounds	0.02	1.0
Unidentified nitrile	Trace	0.0
Distillation residues[b] (VIII)	0.35	17.3
Recovered trimethylethylene	2.02	
Unrecovered and regenerated trimethylethylene (estimated)[c]	1.45	
N_2 generated during reaction	1.56	
Water	0.78	
Nitric oxide unreacted	0.06	
Nitric oxide regenerated (estimated)[c]	1.66	
Handling loss of stable products[b] (estimated)[c]	0.03	

[a] Isolated as crystalline dimer. [b] For purposes of calculation, assumed to have the composition $(C_5H_9NO_2)_x$. [c] These estimates lead to material balances in C, H, N, and O between the reactants and products.

ethylene and nitric oxide. The recovered yield of nitrosite was nil from a large-scale distillation and 4.6% from a small-scale distillation; the initial yield of nitrosite in the deep green crude product was undoubtedly greater still. Because of this tendency for certain products to revert to the starting materials,[1] and because our work-up procedure did not clearly distinguish unreacted from regenerated trimethylethylene, it was not possible to determine precisely how much trimethylethylene actually entered into the reaction. Hence, true yields of the various products obtained, based upon trimethylethylene undergoing reaction, could not be calculated. Accordingly, in Table I are reported the true molar conversions observed and the estimated net yields, *i.e.*, yields based upon the trimethylethylene which underwent reaction but was not subsequently regenerated.

2-Methyl-2-nitro-1-butene (I).—Redistillation of a crude fraction boiling at 53.5–56° (19 mm.) in a Piros-Glover spinning band column gave 2-methyl-3-nitro-1-butene, b.p. 56.5° (23 mm.), d^{20}_4 1.4352, d^{20}_4 0.982, MD 30.60. The infrared spectrum showed the characteristic bands[2] of the unconjugated nitro group at 6.47 and 7.32 μ, and the C=CH$_2$ group at 3.25, 6.04, and 10.93 μ.

Anal. Calcd. for $C_5H_9NO_2$: C, 52.2; H, 7.9; N, 12.2. Found: C, 52.6; H, 7.8; N, 12.2.

2-Methyl-1-nitro-2-butene (II).—This compound was also isolated from the crude fraction boiling at 53.5–56.5° (19 mm.) by redistillation in the Piros-Glover spinning band column; b.p. 72.5° (23 mm.), $n^{20}D$ 1.4475, d^{20}_4 0.995, MD 30.94. Upon ozonolysis acetaldehyde was obtained. The infrared spectrum showed unconjugated nitro group bands at 6.42 and 7.26 μ and a trisubstituted ethylene C–H wagging band at 11.88 μ.

Anal. Calcd. for $C_5H_9NO_2$: C, 52.2; H, 7.9; N, 12.2. Found: C, 52.6; H, 8.2; N, 12.6.

The compound was also obtained by the procedure which was originally reported to yield 2-methyl-1-nitro-1-butene.[3] A mixture of 50 ml. of butanone, 50 ml. of nitromethane, and 5 ml. of piperidine was allowed to stand 6 days at 25–30°, and then acidified and distilled to give 3.0 g. of the nitroolefin, a colorless liquid having a mild odor, b.p. 56.5–57.5° (9.5 mm.); 2 g. of 2-methyl-1-nitro-2-butanol, b.p. 86–87° (10 mm.); and 13 g. of 2-methyl-1-nitro-2-(nitromethyl)butane, b.p. 126–127° (4 mm.). The infrared spectrum of the nitroolefin agreed with that of the trimethylethylene nitration product, and was very different from that[2] of the conjugated isomer, 2-methyl-1-nitro-1-butene, which is a yellow lachrymatory oil. Presumably, the conjugated nitroolefin was formed first, and then reacted, in part with nitromethane to yield the dinitrohexane, and in part with the piperidine to yield the salt of the nitroolefin anion. The acidification of this allylic anion was observed in a separate experiment to effect protonation almost exclusively on the carbon α to the nitro group.

$$CH_3CH_2C(Me)=CHNO_2 + C_5H_{11}N \longrightarrow CH_3CH=C(Me)CHNO_2^- + C_5H_{12}N^+$$

$$CH_3CH=C(Me)CHNO_2^- + H^+ \longrightarrow CH_3CH=C(Me)CH_2NO_2$$

2-Methyl-3-nitro-2-butene (III).—It was not possible to isolate this compound in a pure state by a fractional distillation, since its boiling point was almost identical with that of 2-methyl-1-nitro-2-butene. However, by washing the crude fraction, b.p. 66° (19 mm.), with aqueous caustic it was possible to achieve separation. The alkali-insoluble product was dried and distilled, giving pure 2-methyl-3-nitro-2-butene, b.p. 69.2° (20 mm.), $n^{20}D$ 1.4618, d^{20}_4 1.006, MD 31.45. The infrared spectrum indicated the presence of a conjugated nitro group (6.62 and 7.46 μ), and an olefinic double bond (6.01 μ), but no olefinic C–H bond.

Anal. Calcd. for $C_5H_9NO_2$: C, 52.2; H, 7.9; N, 12.2. Found C, 51.9; H, 7.4; N, 12.4.

2-Methyl-3-nitro-2-nitrosobutane Dimer (VI).—This compound separated as a white crystalline solid from the deep blue distillates that boiled over the range of 66–67.1° at 10 mm. or 46.0–46.5° at 1 mm. Its melting point was extremely dependent upon the rate of heating, *i.e.*, 69–71.5° at 3°/min., 80–82° at 9°/min. The melt was deep blue liquid, indicating the presence of a tertiary nitroso group in the monomer. The infrared spectrum showed the 6.44-μ band of a secondary nitro, but not the highly characteristic bands[2] of $-C(CH_3)_2NO_2$ or secondary bis-nitroso groups.

Anal. Calcd. for $C_{10}H_{20}N_4O_6$: N, 19.2. Found: N, 18.8.

In order to replace the nitroso group by acetoxy, the dimeric nitrosite (0.19 g.) was added to 1 ml. of acetic anhydride containing a few milligrams of sulfuric acid at room temperature. The nitrosite reacted immediately with effervescence, but a faint blue color persisted for several minutes. The excess anhydride was pumped off; the residue washed was with alkali and dried to give 0.09 g. 2-methyl-3-nitro-2-butyl acetate, which had an infrared spectrum identical to that of an authentic specimen (colorless liquid, $n^{20}D$ 1.4356, or solid, m.p. 32°) prepared by the acetylation of 2-methyl-3-nitro-2-butanol.[3]

Nitration of Tetramethylethylene.—Nitric oxide (262 g., 8.75 moles) was added under 50-p.s.i.g. pressure at a rate of 4.8 moles/hr. to 421 g. (5.0 moles) of tetramethylethylene at 24° in the apparatus described above. The reaction product was chilled in an acetone–Dry Ice bath and filtered to remove the major part of the 2,3-dimethyl-2,3-dinitrobutane; the filtrate was subjected to flash distillation at 1 mm. and 100°. Further fractionation and analysis indicated the product composition shown in Table II.

As with the nitric oxide–isobutylene reaction product,[1] there were indications that very considerable changes in composition occurred during the product fractionation. First, the vacuum distillations and redistillations of the crude products were accompanied by very marked weight losses, indicating the formation of substances not condensible at −78° during the distillations. Second, there was a gradual loss in blue color and deposition of XI throughout the fractionation procedure, indicating the autoxidation and disproportionation of XII to XI. Third, infrared spectra of the first distillates indicated that they contained a considerable quantity (possibly 20% of the total crude product) of a nitrate ester, probably 2,3-dimethyl-2-nitro-3-butyl nitrate (XVII). This substances was virtually absent from the fractionated product; presumably it underwent disproportionation during the distillation. Therefore, Table II must also be regarded as indicative only of the distribution of readily isolatable or thermally stable products obtained from the tetramethylethylene–nitric oxide reaction, rather than a listing of the substances originally formed in the reaction.

2,3-Dimethyl-3-nitro-1-butene (IX).—This compound was isolated from a crude fraction boiling at 36–56° (10 mm.) by redistillation in the spinning band column; b.p. 55.1° (10 mm.), $n^{20}D$ 1.4420, d^{20}_4 0.973, MD 35.12. The infrared spectrum showed

(2) J. F. Brown, Jr., *J. Am. Chem. Soc.*, **77**, 6341 (1955).
(3) A. Lambert and A. Lowe, *J. Chem. Soc.*, 1517 (1947).

TABLE II

COMPOUNDS IDENTIFIED IN THE REACTION PRODUCT OF TETRAMETHYLETHYLENE AND NITRIC OXIDE

Product	Yield, mole(s)	Estimated net yield, %
2,3-Dimethyl-3-nitro-1-butene (IX)	0.42	14.8
2,3-Dimethyl-1-nitro-2-butene (X)	0.53	18.7
2,3-Dimethyl-2,3-dinitrobutane (XI)	0.79	27.9
2,3-Dimethyl-2-nitro-3-nitrosobutane[a] (XII)	0.48	17.0
2,3-Dimethyl-1-buten-3-ol (XIII)	0.23	8.1
2-Nitropropane	Trace	0.
Acetone (XIV)	0.27	9.5
Pinacol[b] (XV)	Trace	0[b]
Pinacolone (XVI)	0.005	
Distillation residues[c, d] (XVIII)	0.18	6.4
Recovered tetramethylethylene	0.70	
Unrecovered and regenerated tetramethylethylene (estimated)[e]	1.47	
Nitrogen generated during reaction	2.47	
Water	1.31	
Nitric oxide, unreacted	0.05	
Nitrogen generated in work-up (estimated)[e]	0.04	
Handling loss of stable products[e] (estimated)[e]	0.03	

[a] Isolated as crystalline 1:1 adduct with XI. [b] In a preliminary study of the reaction between tetramethylethylene and nitric oxide in carbon tetrachloride solution, the yield of pinacol (m.p. 41–42°; identified by infrared spectrum) rose to 5%. [c] For purposes of calculation, arbitrarily assumed to have the composition $(C_6H_{11}NO_2)_x$. [d] These residues contained traces of an unidentified nitrile and a nitrate ester XVII, believed to be 2,3-dimethyl-2-nitro-3-butyl nitrate. [e] These estimates lead to material balances between the reactants and products in C, H, N, and O.

the bands of a $C{=}CH_2$ group (3.25 and 6.00 μ) and a tertiary nitro group (6.49, 7.21, 7.24, 7.33, and 11.81 μ).

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.8; H, 8.6; N, 10.9. Found: C, 56.7, 56.2; H, 8.6, 8.5; N, 11.0.

2,3-Dimethyl-1-nitro-2-butene (X.)—This compound was obtained by redistillation of the crude fraction boiling at 57.8–59° (5 mm.); b.p. 70.8° (10 mm.), 58.5–59.8° (5 mm.), $n^{20}D$ 1.4564, d^{20}_4 0.987, MD 35.57. The infrared spectrum showed the bands of a primary nitro group (6.44, and 7.30 μ) and a tetrasubstituted ethylene (6.00 μ). Ozonolysis followed by decomposition of the ozonide over zinc dust gave acetone 2,4-dinitrophenylhydrazone, m.p. 126°.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.8; H, 8.6; N, 10.9. Found: C, 55.6; H, 8.2; N, 11.0:

2,3-Dimethyl-2-nitro-3-nitrosobutane (XII).—This substance, although a major reaction product, could not be obtained free of 2,3-dimethyl-2,3-dinitrobutane, since it was not stable enough for distillation and apparently cocrystallized with the dinitro compound to form a deep blue 1:1 adduct. Upon oxidation of this adduct with air or oxygen 2,3-dimethyl-2,3-dinitrobutane was obtained quantitatively. The infrared spectrum showed the characteristic bands of tertiary nitro groups at 6.47 and 7.44 μ, but no band indicative of olefinic, oximino, or nitrate ester groups.

Anal. Calcd. for $C_6H_{12}N_2O_2 \cdot C_6H_{12}N_2O_4$: C, 42.8; H, 7.2; N, 16.7. Found: C, 42.8; H, 6.9; N, 17.2.

Isomerization of 2,3-Dimethyl-3-nitro-1-butene.—A solution of 0.2 g. of nitrogen dioxide in 2 ml. carbon tetrachloride was added to 1.9 g. of 2,3-dimethyl-3-nitro-1-butene in 20 ml. of carbon tetrachloride over a period of 0.7 hr. at 50°. The nitrogen dioxide decolorized only slowly, either by reaction or evaporation, indicating that it was present throughout this period. The solution was then extracted with water and distilled to give a small forerun followed by 0.95 ml. of dimethylnitrobutenes, b.p. 69.5° (10 mm.), $n^{20}D$ 1.4560. The infrared spectrum of this fraction and that of the forerun indicated an over-all composition of 91% 2,3-dimethyl-1-nitro-2-butene and 9% 2,3-dimethyl-3-nitro-1-butene. The kinetics of the isomerization were examined by adding a trace of nitrogen dioxide to the nitroolefin and observing the change in refractive index. It was found that the same final index was observed regardless of whether 2,3-dimethyl-1-nitro-2-butene ($n^{20}D$ 1.4564) or 2,3-dimethyl-3-nitro-1-butene ($n^{20}D$ 1.4420) was isomerized with the nitrogen dioxide. From the initial rates of change of refractive index in runs where the initial dinitrogen tetroxide concentrations were 0.45 and 1.0 *M* it was estimated that the isomerization was 0.6 order in dinitrogen tetroxide or approximately first order in nitrogen dioxide. Simple pseudo-first-order kinetics were not followed by the isomerization, however, since the dinitrogen tetroxide catalyst was slowly consumed by addition reactions, and an unidentified high boiling adduct or substitution product ($n^{20}D$ 1.4905) was formed.

The Reaction of 2-Methyl-3-nitro-2-nitrosobutene with Alkali.—One gram (0.007 mole) of trimethylethylene nitrosite dimer was warmed to 110° to convert it to the blue monomer and then cooled and stirred with 10 ml. of 1 *N* sodium hydroxide solution (0.010 mole) for several minutes at room temperature. It failed to remain monomeric, however, and soon set up to a semisolid mass. To promote reaction, 2 ml. of methanol was added and the mixture stirred at 50–60° until the blue color disappeared. The reaction product, a very pale yellow, turbid solution, was cooled and extracted with ether to remove 0.3 g. (0.003 mole) of crude oxime ether polymer. The alkaline aqueous solution was acidified with 1 *N* sulfuric acid, and extracted with ether to give 0.040 g. of crude methoxy oxime, m.p. 79–87°.

The methoxy oxime, 3-methyl-3-methoxy-2-butanone oxime, was recrystallized from $CHCl_3$–CCl_4; m.p. and m.m.p. 89–90°, lit.[4] 92–93°. Its infrared spectrum (Nujol mull) showed characteristic ketoxime bands at 2.98, 6.07, and 10.69 μ.

Anal. Calcd. for $C_6H_{13}NO_2$: N, 10.7. Found: N, 10.8.

The oxime ether polymer was a rather viscous, almost colorless, nonvolatile, thermally stable oil, $n^{20}D$ 1.4723. Its infrared spectrum indicated the absence of more than traces of nitro groups, but the bands of oxime (3.01, 6.1, and 1.06 μ) and ether (8.63 μ) groups were prominent and a general structural similarity to the methoxy oxime was evident. Accordingly, the substance was regarded as an oxime ether polymer, $H[ON{=}C(CH_3)C(CH_3)_2]_xOH$: the analysis was in best agreement with theory for $x = 3$.

Anal. Calcd. for $C_{15}H_{29}N_3O_4$: C, 57.2; H, 9.3; N, 13.3. Found: C, 56.7; H, 8.8; N, 13.9.

Nitrations in Polar Media.—In order to examine the effect of solvent polarity upon the nitration product distributions, the reactions of nitric oxide with trimethylethylene and tetramethylethylene vapors at 24° were studied briefly. It was established that the locus of reaction in such systems was the liquid layer of highly polar nitration products on the walls of the glass bulbs used; the reactions showed induction periods unless the walls were wet with the products of a previous run or with an inert solvent. A run in which 3 mmoles of trimethylethylene was consumed gave 0.1 mmole of ketones, 0.3 mmole of 2-methyl-3-nitro-2-butyl nitrate, 0.4 mmole of other nitrates, 1.9 mmoles of unconjugated nitro compounds, presumably mainly I and II, and 0.1 mmole of the conjugated nitro compound III. Similarly, a run in which 1.0 mmole of tetramethylethylene was consumed gave about 0.1 mmole of ketones, 0.2 mmole of the nitrate XVII, 0.5–0.6 mmole of the distillable nitroolefins IX and X, and about 0.1 of the dinitro compound XI. All of these products were identified by their infrared spectra.

Discussion

The Reactions of Nitric Oxide with Tri- and Tetramethylethylene.—The results show that the nitrations of tri- and tetramethylethylene with nitric oxide are fundamentally similar to those of isobutylene.[1] In the case of tetramethylethylene, of course, no α-nitroolefin can be formed; however, as would be expected from the previously proposed mechanism, this does not interfere with the formation of a β-nitroolefin. As was also the case with isobutylene, conducting the reaction in the absence of excess liquid olefin led to an increase in the yields of those products formed *via* polar reactions. Thus, the runs with olefin vapors gave greater yields of the β-nitroolefins (ionic decomposition of the

(4) J. Schmidt, *Ber.*, **35**, 3722 (1903).

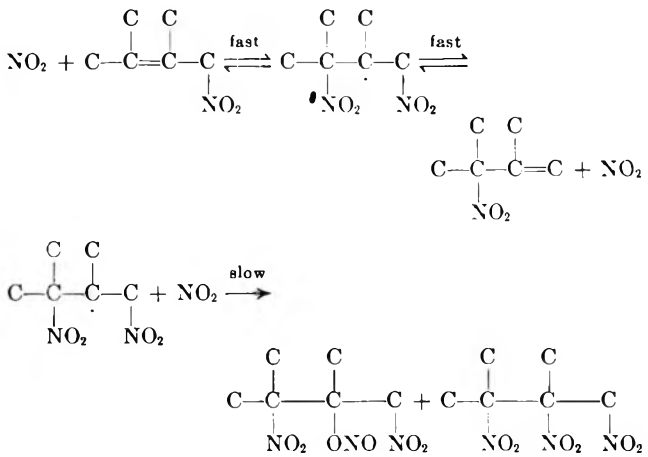
intermediate diazo nitrate) and greater yields of such substances as nitrate esters, ketones, and glycol derivatives, which are believed to be formed *via* nitrosonium ion addition processes in the primary reaction step.[2]

One respect in which the reactions of these highly branched olefins with nitric oxide differ from those of the simpler olefins is that the intermediate nitrosites appeared to be less reactive. Considerable quantities of unreacted monomeric nitrosites were present in our reaction products, dimerization of the nitrosites occurred slowly or not at all, and there seemed to be relatively little reaction between the nitrosites and the intermediate nitro alkyl radicals. The latter reaction, which would presumably give tris(nitroalkyl)hydroxylamines or tetrakis(nitroalkyl)dihydroxydrazines,[1] would lead to the formation of an α-nitroolefin (III) from trimethylethylene and nonvolatile residues from tetramethylenethylene.

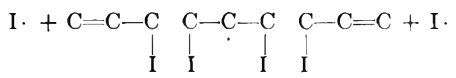
The older literature on the nitration of trimethylethylene with nitric acid[5] or "nitrous fumes,"[6] and that of *t*-amyl alcohol with nitric acid,[7] contains several reference to the formation of a "nitroisoamylene." The structure of this product has been reported as 2-methyl-3-nitro-2-butene, although its homogeneity does not seem to have been clearly established. The present finding that the "nitroisoamylene" from the nitric oxide nitration is a mixture of three closely boiling isomers suggests that the products previously obtained were also mixtures. In support of this conclusion, we may note that the "3-nitro-2-methyl-2-butene" fraction obtained by Michael and Carlson[6] gave a thiophenol adduct in only 15% yield[6] and had a refractive index between those of I and II, while pure 2-methyl-3-nitro-2-butene (III) is now known to have a much higher index. We have also observed that the nitration of trimethylethylene with absolute nitric acid likewise gives the three isomers, I, III, and III.

The Allylic Rearrangement of β-Nitroolefins.—The results showed that two isomeric β-nitroolefins were obtained from purified trimethylethylene or tetramethylethylene rather than just the one predicted by the nitration mechanism.[2] Three explanations for this finding were considered: (a) direct substitution of allylic hydrogens; (b) isomerization of the olefins, followed by normal nitric oxide–olefin reactions; and (c) isomerization of the expected β-nitroolefins I and IX. The first two explanations were readily eliminated. First, it has been observed that the allylic substitution process (*e.g.*, as in the reactions of nitric oxide, nitrogen dioxide, or dilute nitric acid with toluene or other aralkyl hydrocarbons) requires temperatures above about 120°, and gives large quantities of allylic alcohols, aldehydes, nitrates, acids, etc., in addition to nitro compounds. These were not observed in the olefin nitration products. Second, if the tetramethylethylene had first isomerized to 2,3-dimethyl-1-butene, considerable quantities of 2,3-dimethyl-1-nitro-1-butene and 3-methyl-2-(nitromethyl)-1-butene would have been expected. These could not be detected spectroscopically in our product fractions. The third explanation, namely, that the β-nitroolefins formed in the reaction are capable of undergoing allylic rearrangement, appears to be consistent with all of our observations. In particular, it is supported by the finding that nitrogen dioxide, which is known to be present in nitric oxide–olefin nitration systems, can indeed effect the interconversion of the isomeric β-nitroolefins.

We propose the following mechanism for this NO_2-catalyzed allylic rearrangement of β-nitroolefins such as the dimethylnitrobutenes.



The mechanism is thus suggested to be analogous to the allyl iodide–iodine exchange process[8] in depending upon the reversibility of the addition of a free radical to an olefin.



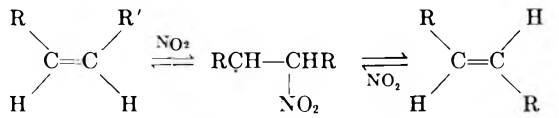
There are three other observations which also suggest that the addition of nitrogen dioxide to an olefin to give a β-nitroalkyl radical is reversible. First, we have noted that the nitrosite of isobutylene can be particularly decomposed into its components on heating.[1] The dissociation of an aliphatic nitroso compound into nitric oxide and a radical is known to occur easily,[9] and in the case of the nitrosite this would give a β-nitroalkyl radical which could then regenerate the olefin by loss of nitrogen dioxide. Second, it has been observed that the photochemical chlorination of anhydrous nitro paraffins, presumably *via* the usual free-radical chain process, is abnormally slow.[10] Evidently the kinetic chains are interrupted somehow; an attractive explanation is that this occurs through the loss of nitrogen dioxide from β-nitroalkyl radicals. Third, the reversibility of the NO_2-olefin reaction makes possible a rational interpretation of the NO_2-catalyzed *cis–trans* isomerization of olefins.

The NO_2-Catalyzed *cis–trans* Isomerization of Olefins.—The NO_2-catalyzed *cis–trans* isomerization of olefins is probably the oldest known isomerization reaction. The conversion of the liquid fat, olein, to the solid fat, elaidin, by "nitrous acid" has been known for

(5) H. Wieland and F. Rahn, *Ber.*, **54**, 1775 (1921).
(6) A. Michael and G. H. Carlson, *J. Org. Chem.*, **4**, 169 (1939).
(7) L. Haitinger, *Monatsh.*, **2**, 286 (1881).
(8) D. J. Sibbett and R. M. Noyes, *J. Am. Chem. Soc.*, **76**, 763 (1953).
(9) W. Schlenk, L. Mair, and C. Bornhardt, *Ber.*, **44**, 1169 (1911).
(10) G. D. Jones, J. Zomlefer, and K. Hawkins, *J. Org. Chem.*, **9**, 500 (1944); D. C. Sayles and E. F. Degering, *J. Am. Chem. Soc.*, **71**, 3161 (1949).

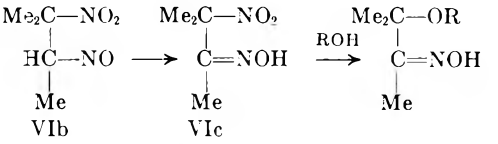
about three hundred years,[11] although the elaidin was not obtained in a pure state until 1832.[12] The reaction has also been applied to the interconversion of oleic and elaidic acids,[13,14] maleic and fumaric acids,[15] *cis*- and *trans*-stilbene,[16] erucic and brassidic acids,[14] *cis*- and *trans*-petroselenic acids,[14] and β- and γ-caryophyllene.[17]

Four facts are known about this isomerization. (a) A variety of agents capable of supplying nitrogen dioxide may be used as the catalysts, including nitric acid in which mercury[11-14] or starch[13] has been dissolved, nitrous fumes,[13] nitrogen dioxide,[13] or nitric oxide.[18] (b) The reaction is an equilibrium process and the final product is the same whether the *cis* or *trans* isomer is isomerized.[14] (c) The usual N_2O_4–olefin adducts (nitro alcohol, nitrosite) are always formed during the isomerization; in order to get predominately isomerization rather than adduct formation, it is necessary to use only small quantities of the catalyst.[14,15] (d) The N_2O_4–olefin adducts obtained are stable under the conditions of the reaction,[19] and only in special cases can they be converted back to the olefins on heating. These data, coupled with the present finding that the addition of nitrogen dioxide to an olefin to give a β-nitro alkyl radical is reversible, establish the following mechanism for the isomerization.

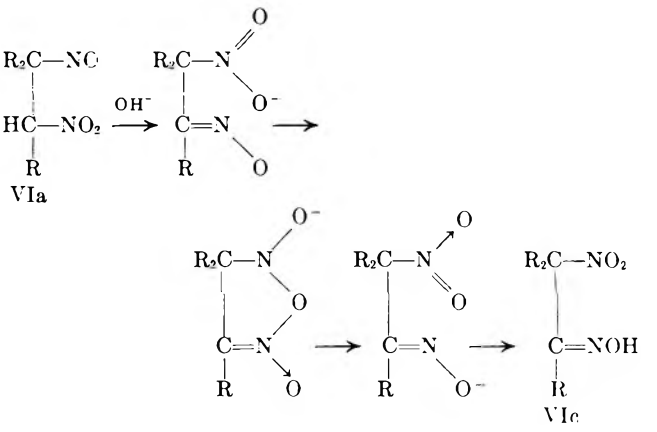


The Nitrosite Rearrangement.—In 1903 Schmidt found that trimethylethylene nitrosite (VI) dissolved slowly in cold alkali and, upon acidification, gave a colorless solid isomer.[20] This isomer (VIc) was found to be an oxime which gave sodium nitrite when warmed with sodium hydroxide. Later, Deussen found that the blue β-caryophyllene nitrosite could similarly be converted to a colorless, solid isomer.[21] In addition, he found that this oxime, the original nitrosite, β-caryophyllene nitrosochloride, and both isomers of γ-carylophyllene nitrosochloride all reacted with alkaline reagents with loss of nitrate or chloride to give identical derivatives (α-benzylamino oxime, α-ethoxy oxime, etc.). Similarly, we have now found that trimethylethylene nitrosite reacts with methanolic KOH to give an α-methoxyoxime identical with that obtained *via* the similar treatment[22] of trimethylethylene nitrosochloride, nitrobromide, or nitrosate. In addition, there are formed the oxime ether polymers resulting from the displacement of a nitro group on one nitrosite residue by the oxime hydroxyl of another.

These transformations under alkaline conditions at first attracted little attention since the older workers believed that the nitrosites of the trialkylethylenes contained secondary nitroso and tertiary nitro (or nitrite) groups. Thus, the oxime formation and displacement reactions could be very simply formulated.



However, the observation that the trimethylethylene nitrosite actually contains secondary nitro and tertiary nitroso groups (*i.e.*, has structure IVa) indicates that a rearrangement is required in order to form VIc and the α-substituted oximes. We propose to denote this shift as the *nitrosite rearrangement*, and suggest the following mechanism for it.



The nitro oxime thus formed can, of course, react further under the alkaline conditions of the reaction to give other α-substituted oximes.

Acknowledgment.—The authors wish to express their thanks to Dr. R. L. Myers, Mr. C. S. Herrick, and Dr. J. Krieble for their aid in constructing and operating the nitration apparatus used. In addition, thanks are given to Miss J. Sorensen and Mrs. M. J. Martin for the microanalyses and spectra, and Mr. E. M. Hadsell for the distillations.

(11) The discovery of this phenomenon has been attributed to Boyle in 1661; see A. W. Ralston, "Fatty Acids and Their Derivatives," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 110. Its nature appears to have been clearly defined by the end of the eighteenth century; the "American Edition of the Encyclopedia," Vol. 8, Philadelphia, Pa., 1790, p. 475, states, "Expressed oils, as well as all other fatty or unctuous substances, are considerably thickened and hardened by their union with the nitrous acid. There is only one preparation where this combination is applied to use. It is the *ungentum citrinum* of the shops. This is made by adding some quantity of melted hog's lard to a solution of quicksilver in the nitrous acid. The acid, though in a diluted state, and combined with the mercury, nevertheless acts with such force on the lard as to render the ointment almost of the consistency of tallow."

(12) F. Boudet, *Ann.*, **4**, 1 (1832).

(13) H. Meyer, *ibid.*, **35**, 174 (1840); J. Gottlieb, *ibid.*, **57**, 52 (1846).

(14) H. N. Griffith and T. P. Hilditch, *J. Chem. Soc.*, 2135 (1932).

(15) J. Schmidt, *Ber.*, **33**, 3241 (1900).

(16) C. Keller and A. Schwartz, *ibid.*, **45**, 1946 (1912).

(17) G. E. Deussen and A. Lewisohn, *Ann.*, **356**, 30 (1902); A. Aebi, D. H. R. Barton, and A. S. Lindsey, *J. Chem. Soc.*, 3124 (1953).

(18) K. Fuse and B. Tamamuski, *J. Chem. Soc. Japan*, **64**, 338 (1943).

(19) I. Egorov, *J. Russ. Phys. Chem. Soc.*, **35**, 973 (1903); *J. prakt. Chem.* **86**, 539 (1912).

(20) J. Schmidt, *Ber.*, **35**, 2323 (1903).

(21) E. Deussen and A. Lewinsohn, *Ann.* **356**, 17 (1907).

(22) J. Schmidt, *Ber.*, **35**, 3722, 3736 (1903).

Amozonolysis of Cycloolefins

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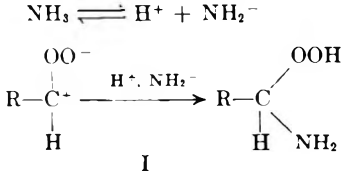
Ozonization of five-membered cycloolefins emulsified in aqueous ammonia gave six-membered aromatic heterocyclic compounds. Larger ring olefins led to polymeric imines, which could be cleaved by hydrolysis to form dialdehydes. The ozonization of cyclohexene and cyclooctene in *t*-butylamine yielded cycloolefinic *t*-butylimines. These new reactions have been named "amozonolysis."

Ozonolysis of olefins in protonic solvents usually gives hydroperoxides and aldehydes or condensation products of the two; in aprotic solvents, monomeric or polymeric ozonides and peroxides result.[1]

In our laboratories, ammonia has been used as the protonic solvent. A series of seven cyclic olefins has been ozonized in aqueous ammonia, with results that are summarized in Table I. Two cycloolefins were also ozonized in *t*-butylamine. These reactions have been named "amozonolysis."

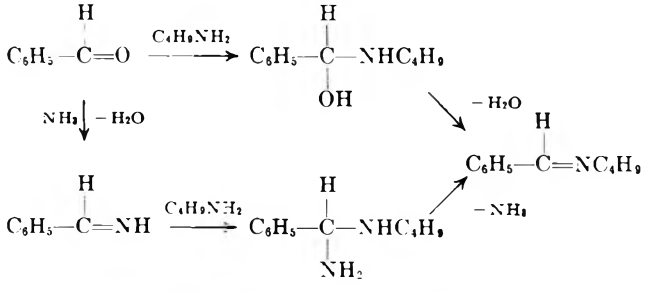
Discussion

Ammonia proved to be relatively stable towards ozone[2] in presence of the more reactive olefins. At −30° the degree of dissociation of anhydrous liquid ammonia was high enough to yield sufficient H^+ and NH_2^- to add to the zwitterion (I) in the same manner as do the more common protonic solvents.

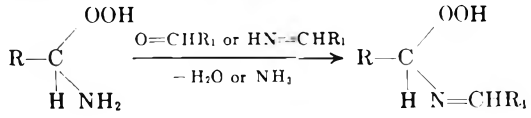


I

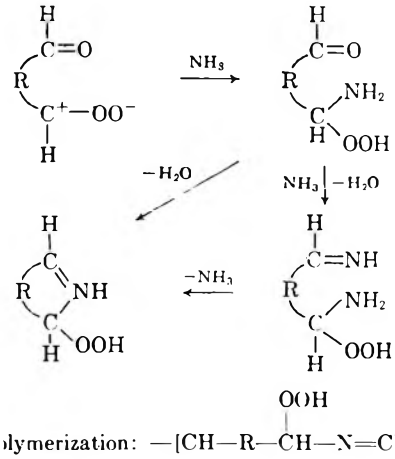
Besides this direct addition of ammonia, the carbonyl product of the ozonolysis condensed rapidly with ammonia and gave an imine. When present in the ammonia phase, alkyl amines reacted to give predominantly alkyl-substituted imino groups, in spite of excess ammonia. For example, benzaldehyde condensed with 1 mole equiv. of *n*-butylamine in an 80% aqueous ammonia emulsion to give N-butylbenzylidenimine in 91% yield. Whether the condensation proceeded directly with the carbonyl group or with the corresponding imino group formed by prior condensation of benzaldehyde with ammonia was not determined, because both paths lead to the same end product.



The higher affinity of the alkyl-substituted ammonia nitrogen towards the carbonyl group may be attributed to the increase of nucleophilic character of the amino nitrogen atom over that of unsubstituted ammonia. A similar property of the α-aminoalkylhydroperoxide led to the following condensation.



By amozonolysis of cycloolefins an analogous condensation gave cyclic or polymeric structures.

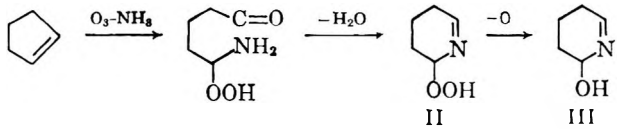


or polymerization: —[CH—R—CH—N=CH]$_n$—

The intra- or intermolecular condensation depended on the steric conditions of the olefinic starting material, which, for unbranched cycloolefins, was determined predominantly by the ring size. Thus, C_5 cycloolefins would be expected to favor intramolecular addition, yielding six-membered N-heterocyclic compounds, whereas higher cycloolefin homologs would mainly undergo polymerization.

The relatively insolubility of the cycloolefins in ammonia required the use of emulsions to obtain a sufficient interfacial contact between the olefin and ammonia. The suspended olefin droplet had to be mixed sufficiently well to allow the intermediate (I) to react instantly with the ammonia; otherwise inter- or intramolecular reactions within the aprotic environment of the droplet would lead to undesirable polyozonides and polyperoxides. Thus, selecting an emulsifier stable towards ozone and ammonia was of importance: polyoxyalkylene ethers of fatty alcohols such as Pronon and Brij were effective.

Cyclopentene should give the hydroperoxide (*II*). The stability of the hydroperoxidic group in ammonia proved to be low as might have been expected; the



II III

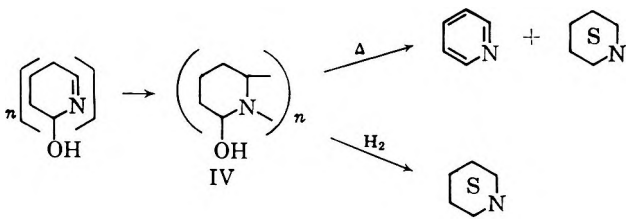
(1) P. S. Bailey, *Chem. Rev.*, **58**, 1000 (1958).
(2) I. J. Solomon, *J. Am. Chem. Soc.*, **84**, 34 (1962).

TABLE I

AMOZONOLYSIS OF CYCLOOLEFINS

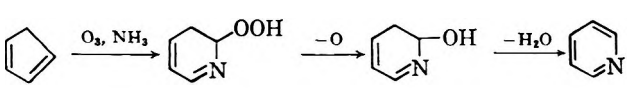
Cycloolefin	Mole	Ozone, mole	Product	Yield, mole %	Recovered starting material, mole	Product identification
Cyclopentene	0.73	0.65	Poly(2-hydroxypiperidine)	90	0.15	$[C_5H_9ON]_x$ Calcd.: C, 60.5; H, 9.2; N, 14.1. Found: C, 60.1; H, 9.0; N, 14.8.
Cyclopentadiene	0.91	0.45	Pyridine	18		Gas chromatography; mass spectroscopy
Indene	0.26	0.24	Isoquinoline	62	0.075	Mixture melting point of picrates; infrared
3-Methylindene	0.23	0.215	4-Methylisoquinoline	48	0.02	Mass spectroscopy; infrared
Indole	0.26	0.24	Quinazoline	9	0.045	Mixture melting point with authentic compound and picrates
Cyclohexene	0.37	0.33	Poly(hydroxytetramethylenimine)	80	0.049	$[C_6H_{11}ON]_x$ Calcd.: C, 63.7; H, 9.7; N, 12.4. Found: C, 64.2; H, 9.7; N, 12.9.
Cyclooctene	0.27	0.25	Poly(hydroxyhexamethylenimine)	80	0.02	$[C_8H_{13}ON]_x$ Calcd.: C, 69.0; H, 9.4; N, 10.1. Found: C, 68.5; H, 9.9; N, 11.0.

primary amozonolysis product had only 10 to 15% of the theoretical hydroperoxide content, indicating reduction by ammonia. The hydroperoxide was completely reduced by adding sulfite after amozonolysis. The 2-hydroxy-2,3,4,5-tetrahydropyridine (III) could not be isolated because of polymerization, probably by way of the —C=N double bond; it gave a resinous polymer of composition $[C_5H_9NO]_n$ (IV).

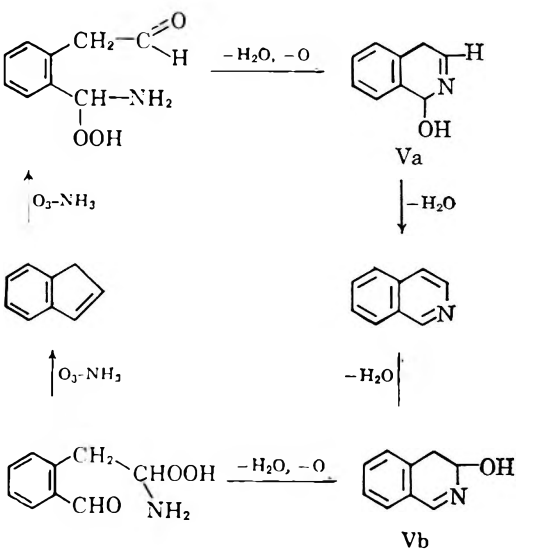


Pyrolysis of the polymer (IV) in an inert liquid gave a mixture of pyridine and piperidine in 12% yield, and minor amounts of methyl- and amino-substituted heterocyclic compounds. Attempts to hydrolyze and depolymerize IV in 5% hydrochloric acid were unsuccessful. Hydrogenation of IV in an aqueous solution at 120–130° and 600 p.s.i. of hydrogen gave 8% piperidine, as well as water-insoluble polymers.

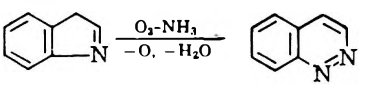
Those C_5 cycloolefins that could form stable cycloimines after dehydration of the reduced amozonolysis product gave considerably better yields of heterocyclic compounds. Thus, cyclopentadiene gave pyridine.



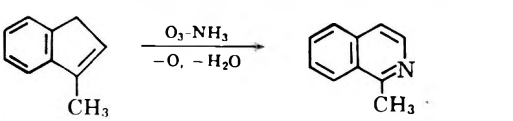
To minimize ozonolysis of the second double bond, an excesss of 1 mole equiv. of cyclopentadiene was used for the reaction. The yield of pyridine was 18%. This was due to the side reaction, polymerization of cyclopentadiene. Such polymerization almost disappeared when the double bond was conjugated with a benzene ring, as in indene. Ozonolysis of indene in ammonia gave isoquinoline in 62% yield. The collapse of the indene molozonide and subsequent amozonolysis probably gave a mixture of Va or Vb which, upon dehydration, formed isoquinoline.



Amozonolysis of 3-methylindene gave 4-methylisoquinoline in 48% yield.

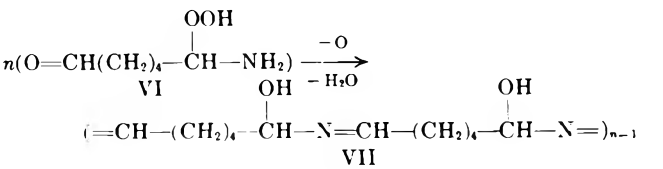


The amozonolysis of indole gave quinazoline by similar ring expansion. The low yield of 9% was



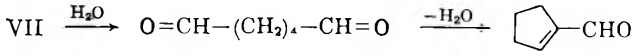
probably due to a considerable amount of ozone-catalyzed oxidation of the indole nitrogen which led partially to indigo and partially to resinous oxidation products.[3]

Cyclohexene gave the aldehyde (VI), which polymerized to form polymers. As the ammonia phase was



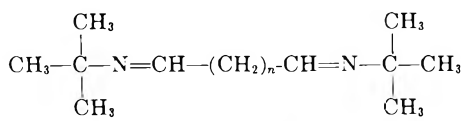
(3) C. Egler and R. Janecke, *Chem. Ber.*, **9**, 1415 (1876).

gradually displaced by water as solvent, the product precipitated as an insoluble polymer, suggesting cross linking through polyaddition of the imino groups of the linear polyimine (VII). The polymer corresponding to the formula $[-CH-(CH_2)_4-CH(OH)-N]_n$ was obtained in 80% yield. It was insoluble in common solvents and decomposed without melting at 320°. Dilute mineral acids dissolve the polymer readily, probably by salt formation, as it was reprecipitated unchanged by base. Attempted hydrogenation at high pressure and temperature failed; however, steam distillation with superheated steam gave cyclopentene-1-carboxaldehyde (VIII) in 18% yield. This indicated hydrolysis of the polymer chains to form adipic dialdehyde, which then condensed to cyclopentene-1-carboxaldehyde.



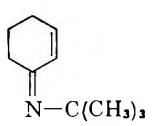
VIII

To avoid polyimine formation and possible cross linking, we used a primary amine that contained a bulky alkyl group instead of ammonia. Ozonolysis of cyclohexene in *t*-butylamine was expected to give tetramethylenedi(*t*-butylimine) (IX). However, this

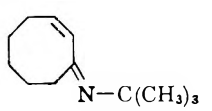


IX, $n = 4$
X, $n = 6$

amozonolysis gave a mono-*t*-butylimine (41%) to which the structure XI was assigned by mass, ultraviolet, and infrared spectroscopy; it hydrogenated to N-cyclohexyl-*t*-butylamine. No polymer was formed. XI probably formed by way of 2-cyclohexen-



XI



XII

1-one from 2-cyclohexene-1-hydroperoxide, which resulted from oxidation of cyclohexene with the O_3–O_2 gas mixture.

Amozonolysis of cyclooctene gave results similar to those for cyclohexene. Thus the reaction in ammonia led to cross-linked polyimines which were hydrolyzed by steam distillation to give suberic aldehyde in 26% yield. Ozonization in *t*-butylamine gave cyclooctene-3-*t*-butylimine (XII) in a 49% yield; it was hydrogenated to the corresponding N-cyclooctyl-*t*-butylamine. Additionally, 5% of hexamethylene-1,6-di(*t*-butylimine) (X) was formed and identified by mass spectroscopy. It indicated, in contrast to the behavior of cyclohexene, the occurrence of the "normal" amozonolysis with cyclooctene.

Amozonolysis of five-membered cycloolefins provides a novel synthetic method whereby ozone effects ring enlargement by a nitrogen atom to yield an aromatic, heterocyclic system. The method is not limited to five-membered cycloolefins, but can be extended to many other cyclic and linear olefins. With these, however, intramolecular condensation to give heterocyclic derivatives is less favorable than intermolecular addition, and polymerization by intermolecular addition is favored. Thus, six- and eight-membered cycloolefins, as well as linear terminal olefins, such as octene-1, undergo predominantly polymerization.

Experimental

The general procedure for the amozonolysis comprised emulsification of about 5% cycloolefins in the liquid ammonia phase. The cycloolefin contained 0.5% Pronon 523 (polyoxyethylene tridecyl alcohol from Process Chemicals Co.) as emulsifier. Ozonization was run at −35 to −60° in a vessel provided with a thermometer, gas vent, and a vibromixer blade (Chem. Ap. Zürich) which was attached to a hollow shaft through which the ozone–oxygen gas mixture was introduced at the bottom of the reactor. The vertical high-frequency vibration caused excellent contact among ozone, olefin, and ammonia. The reaction vessel was partially immersed in a Dry Ice–acetone bath. After introduction of the calculated amount of ozone, most of the ammonia was evaporated by being gradually warmed to room temperature; water or an organic solvent was added to keep the reaction product in solution. In some cases the incomplete reduction of the hydroperoxides by ammonia necessitated the addition of potassium sulfite. The reaction product was isolated either by extraction or by water evaporation *in vacuo*, and purified.

The same reaction products and results were obtained when liquid anhydrous ammonia was substituted by 100 wt. % aqueous ammonia. The aqueous ammonia was easier to handle and was generally used except for cyclopentene and cyclopentadiene. These cycloolefins have a low boiling point, requiring an amozonolysis temperature of −50°, at which aqueous systems freeze. The 100 wt. % aqueous ammonia solution was prepared by cooling an emulsion of 30% aqueous ammonium hydroxide and the cycloolefin to −35° in the reactor, followed by condensation of the calculated amount of ammonia. Pronon 523 worked well as emulsifier for the cycloolefins in liquid as well as aqueous ammonia. It proved inert towards ozone and oxygen and gave stable emulsions at temperatures as low as −35°. Other commercial nonionic detergents that were condensation products of ethylene oxide with fatty alcohols were also effective.

Ozone was generated by a Welsbach T 23 ozonator. Its concentration in oxygen, which served also as a carrier gas, averaged 2.8–3.0 wt. %. The ozone output of the generator was determined by passing the O_3–O_2 mixture through a 2% potassium iodide solution within a timed period, the amount of liberated I_2 being titrated with thiosulfate. The generator was calibrated for a fixed gas-flow rate, pressure, and discharge voltage on *n* g. of O_3/hr.

Cyclopentene, cyclopentadiene, indene, 3-methylindene,[3] indole, cyclohexene, and cyclooctene (all except 3-methylindene were purchased from Eastman) were treated under the described conditions. Both cyclopentene and cyclopentadiene were amozonolyzed at −50° in anhydrous ammonia to minimize the loss by evaporation by the oxygen stream. The reaction with cyclopentene gave a clear ammonia solution from which the polyimine was obtained after evaporation of ammonia. Hydrogenation of 10 g. of polyimine in 100 ml. of water with 1 g. of 5% palladium on charcoal and 0.5 g. of platinum oxide at 600 p.s.i. of hydrogen and 120–130° gave 0.8 g. of crude piperidine (10%) and 8 g. of water-insoluble polymer after 10 hr. For the pyrolysis, a solution of 10 g. of polyimine in 50 ml. of methanol was slowly added to dinonyl phthalate at 250° with stirring for 80 min. Methanol distilled with the pyrolysis products. The major component was pyridine, *ca.* 95% pure, obtained in 10% yield. With the same technique, when glycerol was used as pyrolysis medium, the polyimine unexpectedly gave piperidine as the major product along with pyridine; the total yield was 12%.

In the amozonolysis of cyclopentadiene, a 50% excess of the diolefin was used. To minimize polymerization, it was added during the reaction at such a rate that a continuous excess over the ozonized diolefin was maintained.

Indole, m.p. 52°, was dissolved in 30 g. of dimethoxyethane and this solution was emulsified. After ozonization, reduction, and refluxing, the aqueous reaction solution contained unchanged indole and other water-insoluble products which were removed

by filtration. The filtrate was evaporated to dryness in a Rinco at 30° and 10 mm. The crystalline residue was leached with anhydrous ethanol to extract the reaction product from the inorganic salts; the product was distilled *in vacuo* to isolate quinazoline.

The polymers from the cyclohexene and cyclooctene amozonolysis were insoluble in all solvents except organic and mineral acids from which they could be precipitated by base. These polymers were hydrolyzed by adding a 50% aqueous acetic acid solution to vigorously stirred water at 100° through which superheated steam (120°) was passed. The aldehydes were collected in the steam distillates and either precipitated with semicarbazide or extracted with ether. Cyclopentene-1-carboxaldehyde (15–20%) was identified as its semicarbazone, m.p. 209°, lit.[4] m.p. 208°. Suberic aldehyde (26%) gave the disemicarbazone, m.p. 183°, lit.[5,6] m.p. 183–185°.

The ozonizations of cyclohexene and cyclooctene in *t*-butylamine (500 ml.) were carried out as described with ammonia. The hydrocarbons were soluble in the butylamine and needed no emulsifier. After amozonolysis, about three-fourths of the solvent was distilled off, 200 ml. of water was added, and the reaction products were isolated by extraction with ether. Vacuum distillation gave, in the case of cyclohexene, cyclohexene-3-*t*-butylimine, 30 g. (41%), b.p. 150°. It was identified by infrared and mass spectra (parent peak at 151). As the imine was relatively unstable, it was immediately hydrogenated: 10 g. of distillate were dissolved in 100 ml. of methanol and hydrogenated at atmospheric pressure with platinum oxide catalyst, giving 7 g. of N-cyclohexyl-*t*-butylamine, b.p. 87° (37 mm.), picrate m.p. 187°.

Anal. of picrate. Calcd. for $C_{16}H_{24}N_4O_7$: C, 50.0; H, 6.3; N, 14.6. Found: C, 50.3; H, 6.5; N, 14.7.

Mass and infrared spectra were consistent with the proposed structure.

Cyclooctene gave cyclooctene-3-*t*-butylimine, 3 g. (49%), b.p. 75° (18 mm.), which was identified by the mass spectrum (parent peak at 179) and infrared. Hydrogenation of the flash distillate from the crude reaction product at 15 mm. gave N-cyclooctyl-*t*-butylamine, b.p. 59° (4 mm.), picrate m.p. 198°.

Anal. of picrate. Calcd. for $C_{18}H_{28}N_4O_7$: C, 52.4; H, 6.9; N, 13.6. Found: C, 52.2; H, 7.0; N, 13.7.

A higher boiling fraction (b.p. 102°) solidified and was identified as octamethylene-1,8-di(*t*-butylamine), m.p. 55°, by its mass spectrum (parent peak at 256) and infrared; yield 6%.

Pure *t*-butylamine reacted readily with ozone to yield 2-methyl-2-nitrosopropane. In the presence of olefins, however, oxidation of the amine was a minor reaction, owing to faster ozonolysis of the more reactive carbon–carbon double bonds.

In a competitive reaction of butylamine and ammonia with benzaldehyde, N-butylbenzylidenimine was formed by dropwise addition of 10 g. of distilled benzaldehyde together with 0.1 g. of Pronon 523 as emulsifier to a solution of 7 g. of *n*-butylamine in 100 ml. of 80% aqueous ammonia at −20° with vigorous stirring. After 4 hr. the ammonia was evaporated and the reaction product was isolated by ether extraction and distillation. N-butylbenzylidenimine, b.p. 123°, was obtained in 91–92% yield (14.2 g.). It was identified by mass and infrared spectroscopy.

To determine if hydroperoxide was reduced by ammonia, 10 g. of 2-hydroperoxyoctane[7] was emulsified in 120 ml. of 100% aqueous ammonia at −35° and stirred for 6 hr. After evaporation of ammonia, the reaction product was isolated by ether extraction and dried with anhydrous magnesium sulfate. The content of hydroperoxide in 5 g. of the reaction mixture was iodometrically titrated, showing 2.3 g. of unchanged starting material. The infrared spectrum was identical with a 1:1 mixture of authentic 2-hydroperoxyoctane and octanol-2. No carbonyl band was observed.

(4) L. Ruzicka and E. Peyer, *Helv. Chim. Acta*, **18**, 676 (1935).
(5) O. Wallach, *Ann.*, **347**, 327 (1906).
(6) K. W. Rosemund and F. Zetzsche, *Chem. Ber.*, **54**, 2889 (1921).
(7) C. Walling and S. A. Buckler, *J. Am. Chem. Soc.*, **77**, 6032 (1955).

A New Synthesis of Diaryl- and Alkylaryl-Substituted Acetylenes from α-Diketones and Triethyl Phosphite

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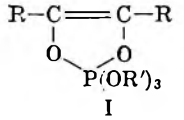
A novel method for the preparation of diaryl- and alkylaryl-substituted acetylenes from α-diketones and triethyl phosphite has been studied. When 1 mole of α-diketones was heated with 2 moles of triethyl phosphite at 215°, corresponding diaryl- and alkylaryl-substituted acetylenes were obtained in the yields ranging from 24 to 60%. Diaryl- and alkylaryl-substituted acetylenes were obtained in good yields by treating 1:1 adducts of triethyl phosphite and α-diketones in the presence of excess triethyl phosphite at 215°.

It has been recently found[1] that diphenylketene reacts with triethyl phosphite to form a 2:1 addition compound which, when pyrolyzed, is converted into diphenylacetylene, a deoxygenated product, and triethyl phosphate in fairly good yields.

$$2(C_6H_5)_2C{=}C{=}O + (C_2H_5O)_3P \longrightarrow [\text{adduct}] \xrightarrow{\Delta} C_6H_5C{\equiv}CC_6H_5 + (C_2H_5O)_3PO + \text{diphenylketene dimer}$$

Further, it has been shown that when the 2:1 adduct was heated in the presence of 1 mole of triethyl phosphite, diphenylacetylene and triethyl phosphate were obtained in good yields along with a small amount of diphenylketene dimer.

On the other hand, Ramirez[2] and Kukhtin[3] reported that tertiary phosphite esters react with α-diketones to form cyclic 1:1 adducts (I).



I

R=R′= CH_3 or C_6H_5
R=C_6H_5, R′=CH_3

In the present experiment, the decomposition of the 1:1 adduct of benzil and triethyl phosphite in the presence of 1 mole of triethyl phosphite was tried first under the assumption that it would yield diphenylacetylene, a deoxygenated product, and 2 moles of triethyl phosphate.

Indeed, when a mixture of 2 moles of triethyl phosphite and 1 mole of benzil was heated at 215° for 2.5 hr. under nitrogen, diphenylacetylene and triethyl phosphate were obtained in 60 and 88% yields, respectively, along with the diphenylketene dimer (24%).

(1) T. Mukaiyama, H. Nambu, and M. Okamoto, *J. Org. Chem.*, **27**, 3651 (1962).
(2) (a) F. Ramirez, R. B. Mitra, and N. B. Desai, *J. Am. Chem. Soc.*, **82**, 2651 (1960); (b) F. Ramirez and N. B. Desai, *ibid.*, **82**, 2652 (1960).
(3) (a) V. A. Kukhtin, *Dokl. Akad. Nauk SSSR*, **121**, 466 (1958); *Chem. Abstr.*, **53**, 11055*b* (1959); (b) V. A. Kukhtin, K. M. Kirillova, and R. R. Shagidullin, *J. Gen. Chem. USSR*, **32**, 640 (1962).

Similarly, diaryl- and alkylarylacetylenes were obtained in yields ranging from 24 to 48% by the treatment of 4,4′-disubstituted benzils or acetylbenzoyl with triethyl phosphite (see Table I).

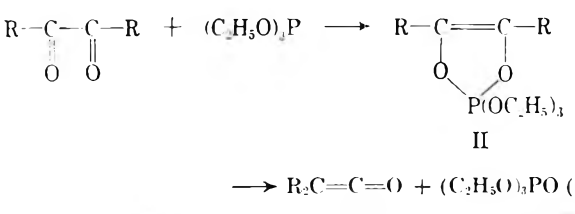
TABLE I

THE REACTION OF BENZIL (1 MOLE) WITH TRIETHYL PHOSPHITE (2 MOLES)

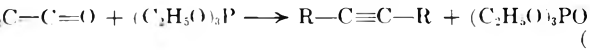
α-Diketone	Time, hr.	Disubstituted acetylene Yield, %	B.p. (mm.), °C.	M.p., °C.	Yield of $(C_2H_5O)_3PO$, %
Benzil	2.5	60	118–121 (3)		88
4,4′-Dimethylbenzil	3	28		134	61
4,4′-Dichlorobenzil	6.5	43		176	64
4,4′-Dimethoxybenzil	6	24		146	72
Acetylbenzoyl	6	41	74–75 (15)		67

However, dialkylacetylenes could not be obtained by this reaction; for example, when biacetyl and triethyl phosphite reacted at 215° for 5.5 hr., butyne-2 could not be obtained, although triethyl phosphate and various unidentified products were obtained.

These reactions could be interpreted as follows.



II



(A)

(B)

Intramolecular deoxygenation of the adduct II by the trivalent phosphorus occurs concomitant with the migration of the phenyl group on the adjacent carbon atom to yield disubstituted ketene and triethyl phosphate (step A). Disubstituted ketene thus formed is further deoxygenated by triethyl phosphite to form disubstituted acetylene and triethyl phosphate as mentioned in the previous report[1] (step B).

The initial formation of disubstituted ketene (step A) is established by the following experiment. When a mixture of benzil (1 mole) and triethyl phosphite (1 mole) was heated at 215° for 15 min. under nitrogen, diphenylketene (11% yield) and triethyl phosphate (81% yield) were obtained along with the diphenylketene dimer.

There is an alternative pathway for the deoxygenation which involves an attack of triethyl phosphite on the adduct II to yield the products directly without accompanying rearrangement. The use of isotopic carbon should be able to confirm which pathway is correct.

High yields of diphenylacetylene and triethyl phosphate resulted when the 1:1 adduct of benzil and triethyl phosphite initially prepared was heated in the presence of 5 moles of triethyl phosphite in a sealed tube at 215° for 4 hr. under nitrogen.

In similar fashion, the other diaryl- and alkylarylacetylenes were obtained in good yields (see Table II).

TABLE II

THE REACTION OF THE 1:1 ADDUCTS (1 MOLE) WITH TRIETHYL PHOSPHITE (5 MOLES)

α-Diketone	Time, hr.	Disubstituted acetylene Yield, %	B.p. (mm.), °C.	M.p., °C.	Yield of $(C_2H_5O)_3PO$, %
Benzil	4	81	113–115 (2)		78
5,5′-Dimethylbenzil	5	72		134	99
4,4′-Dichlorobenzil	7	59		176	90
4,4′-Dimethoxybenzil	7	58		146	99
Acetylbenzoyl	7	54	74–75 (15)		63

Experimental

Materials.—Triethyl phosphite (b.p. 53–54° at 14 mm.) and acetylbenzoyl (b.p. 114–116° at 20 mm.) were prepared by methods of Ford-Moore[4] and Hartman,[5] respectively. Benzil and substituted benzils were prepared by the usual methods from corresponding aldehydes.

Reaction of Benzil (1 mole) with Triethyl Phosphite (2 moles).—A mixture of benzil (4.20 g., 0.02 mole) and triethyl phosphite (6.64 g., 0.04 mole) was heated at 215° for 2.5 hr. under nitrogen until no more triethyl phosphite distilled. The fractional distillation *in vacuo* gave diphenylacetylene, 2.12 g. (60%), b.p. 118–121° (3 mm.), and triethyl phosphate, 6.36 g. (88%), b.p. 101–102° (18 mm.). A crystalline solid precipitated by the addition of a small amount of ethyl alcohol to the residue. Recrystallization from ethyl alcohol gave diphenylketene dimer, 0.92 g. (24%), m.p. 168–169°.

By a similar procedure, various diaryl- and alkylarylacetylenes were obtained from 2 moles of triethyl phosphite and 1 mole of the corresponding 4,4′-disubstituted benzil. The results are listed in Table I.

Reaction of Benzil (1 mole) with Triethyl Phosphite (1 mole).—When 4.20 g. (0.02 mole) of benzil and 3.32 g. (0.02 mole) of triethyl phosphite were heated directly in a Claisen flask at 215° under nitrogen, the reaction mixture gradually became dark brown. After heating for 15 min., it was distilled immediately giving triethyl phosphate, 2.93 g. (81%), b.p. 58–60° (3 mm.), and diphenylketene, 0.42 g. (11%), b.p. 111–114° (3 mm.). Diphenylketene dimer was obtained from the tarry residue by the method mentioned above, 0.63 g. (16%), m.p. 168–169°.

Reaction of the 1:1 Adduct (1 mole) of Benzil and Triethyl Phosphite with Triethyl Phosphite (5 moles).—The 1:1 adduct was prepared by the addition of triethyl phosphite (1.66 g., 0.01 mole) to benzil (2.10 g., 0.01 mole) with stirring under nitrogen. Benzil dissolved with liberation of heat. Triethyl phosphite (8.30 g., 0.05 mole) was added further to the resulting adduct and the mixture was heated in a sealed tube at 215° for 4 hr. under nitrogen. The reaction mixture was distilled under reduced pressure and gave diphenylacetylene, 1.43 g. (81%), b.p. 113–115° (2 mm.), and triethyl phosphate, 2.58 g. (78%), b.p. 108–110° (24 mm.); triethyl phosphite, 6.34 g., b.p. 56–58° (20 mm.), was recovered.

By a similar procedure, various diaryl- and alkylaryl-substituted acetylenes were obtained in good yields by treating the adducts in the presence of excess triethyl phosphite. The diaryl- and alkylaryl-substituted acetylenes listed in Table II were obtained as crystalline solids from ethanol.

Reaction of the 1:1 Adduct (1 mole) of Triethyl Phosphite and 4,4′-Dimethoxybenzil with Triethyl Phosphite (5 moles).—The benzils, with the exception of 4,4′-dimethoxybenzil, reacted exothermically with triethyl phosphite to form the 1:1 adducts. 4,4′-Dimethoxybenzil (2.70 g., 0.01 mole) was heated at about 60° under nitrogen with triethyl phosphite (1.66 g., 0.01 mole) until the yellowish color had disappeared. After the addition of triethyl phosphite (8.30 g., 0.05 mole) to the adduct, the mixture was heated in a sealed tube at 215° for 7 hr. under nitrogen. The precipitate of 4,4′-dimethoxydiphenylacetylene was filtered from the reaction mixture and recrystallized from ethanol, 1.38 g. (58%), m.p. 146°. The residue was distilled *in vacuo* giving triethyl phosphate, 3.30 g. (99%), b.p. 108–111° (25 mm.); triethyl phosphite, 4.49 g., b.p. 58–60° (27 mm.), was recovered.

(4) A. H. Ford-Moore and B. J. Perry, *Org. Syn.*, **31**, 111 (1951).

(5) W. W. Hartman and L. J. Roll, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 20.

Terpenoids. II. A Study of the Prins Reaction on the Isopropylidene-Type Double Bonds

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The addition of formaldehyde to isopropylidene-type trisubstituted olefinic linkages (Prins reaction) present in α- and β-santalenes and some simpler compounds has been studied, and the structures of the resulting primary alcohols have been elucidated. The tricyclene system undergoes rearrangement to the camphene system during the Prins reaction.

The Prins reaction has been applied to the preparation of useful oxygenated products from several monoterpenes and acyclic olefins.[1-3] With the ultimate object of applying the Prins reaction to the synthesis of oxygenated derivatives of possible perfumery value from α- and β-santalenes (XIV and XVIII), obtained as by-products during the distillation of Indian sandalwood oil, the Prins reaction was initially applied to model compounds, tricyclene (I) and camphene (II) representing the skeletal part of santalenes, and 2,6-dimethyloctene-2 (V) and 2-methylheptene-2 (X) representing the isopropylidene side chain. The reaction was studied under two different conditions: (i) by stirring the mixture of olefin and paraformaldehyde in equimolecular proportions in dry chloroform in the presence of anhydrous stannic chloride at room temperature, and (ii) by refluxing the olefin with equimolecular proportions of paraformaldehyde in acetic acid followed by saponification of the resulting acetate to the corresponding alcohol.

Both tricyclene (I) and camphene (II) when condensed with paraformaldehyde in refluxing acetic acid yielded an identical unsaturated acetate which on saponification gave the corresponding monoethynoid alcohol, 8-camphenylcarbinol ($C_{11}H_{18}O$) of known structure[4] (III), the product from tricyclene being formed by an initial rearrangement of the tricyclene to the camphene system. The identity of the alcohols obtained was proved by elemental analysis, hydrogenation, superimposable infrared spectra, and formation of camphenilone (IV) on oxidation. However, as expected, the alcohol obtained from camphene was optically active and that from tricyclene inactive. The cleavage of the cyclopropane ring in tricyclene during the Prins reaction is interesting. Δ^3-Carene[5] under identical conditions gives a product in which the cyclopropane ring remains intact.

2,6-Dimethyloctene-2 (V) was obtained as a single product by the Huang-Minlon reduction of citronellal.[6] Infrared spectrum and ozonolysis showed that the isopropenyl-type isomer was absent. On condensation with formaldehyde at room temperature or under thermal conditions, this hydrocarbon gives mainly an unsaturated alcohol ($C_{11}H_{22}O$) represented by the structure VI. Consistent with its structure it shows characteristic infrared bands at 3366 and 1038 ($-CH_2OH$) and 3086, 1639, and 891 ($>C=CH_2$) cm.$^{-1}$, and absorbs 1 mole of hydrogen on hydrogenation. On ozonolysis it yielded formaldehyde and the keto alcohol (VII) which gave the hydroxy acid (VIII) on hypobromite oxidation. The keto alcohol (VII) on oxidation with sodium dichromate and sulfuric acid in aqueous medium gave acetic acid and 4-methylcaproic acid (IX), the latter being obtained also by oxidation of the keto alcohol (VII) by chromic anhydride in acetic acid. The odor of the alcohol (VI) is reminiscent of that of lavandulol (XIIIa) to which it is closely related structurally.

In the same way 2-methylheptene-2 (X), obtained by the Huang-Minlon reduction of methylheptenone, on condensation with formaldehyde yielded 2-isopropenylhexanol (XI) with infrared bands at 1631 and 889 ($>C=CH_2$), and 3311 and 1042 ($-CH_2OH$). Ozonolysis yielded formaldehyde and the keto alcohol (XII) which on oxidation with sodium dichromate–sulfuric acid in aqueous medium yielded *n*-valeric acid (XIII) and acetic acid.

In conformity with the model compounds, α-santalene (XIV) on condensation with formaldehyde at room temperature in the presence of stannic chloride catalyst yielded mainly a dextrorotatory unsaturated alcohol ($C_{16}H_{26}O$), along with small amounts of oxides. The structure of the alcohol was established as 2-isopropenyl-3-(π)-tricyclylpropanol (XV) from infrared spectra and degradative studies. It showed infrared bands at 3000, 1639, and 888 ($>C=CH_2$ in an aliphatic chain); 877, 852, and 822 (π-substituted tricyclene system)[7]; and 3350 and 1044 ($-CH_2OH$) cm.$^{-1}$. Perbenzoic acid titration as well as catalytic hydrogenation under mild conditions indicated the presence of one double bond. The dihydro product showed infrared absorption at 3067, 877, 854, and 820 (π-substituted tricyclene system), and a doublet at 1383 and 1366 [$-CH(CH_3)_2$] cm.$^{-1}$. On ozonolysis it yielded formaldehyde and the keto alcohol (XVI) in which the keto group is present as methyl ketone as indicated by the bands at 1727 and 1361 cm.$^{-1}$ and a positive iodoform reaction. On oxidation by sodium dichromate–sulfuric acid in aqueous medium, the keto alcohol, consistent with its structure, yielded acetic acid and some products of skeletal rearrangement. It gave tricycloekasantalic acid (XVII) and acetic acid on oxidation by aqueous permanganate. The oxidation appears to proceed *via* a β-keto aldehyde acid which enolizes and then is cleaved and further degraded to tricycloekasantalic acid and acetic acid. The alcohol (XV) on direct oxidation by permanganate also yields the acid (XVII). Owing to the presence of

(1) E. Arundale and L. A. Mikeska, *Chem. Rev.*, **51**, 505 (1952).

(2) H. Grutter and H. Schinz, *Helv. Chim. Acta*, **35**, 505 (1952).

(3) N. C. Yang, D. D. H. Yang, and C. B. Ross, *J. Am. Chem. Soc.*, **81**, 133 (1959).

(4) G. Langlois, *Ann. chim.* (Paris), **12**, 256 (1919).

(5) G. Ohloff, H. Farnow, and W. Philip, *Ann. Chem.*, **61B**, 43 (1958).

(6) H. E. Eschinazi, *J. Org. Chem.*, **26**, 3072 (1961); Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(7) S. Ramaswami, S. K. Ramaswami, and S. C. Bhattacharyya, unpublished results.

the cyclopropane ring system, compounds of the α-santalene series, though stable towards alkali, undergo molecular rearrangements in the presence of acids.

On condensation with formaldehyde in refluxing acetic acid, α-santalene (XIV) yields mainly an unsaturated acetate, which on saponification affords the corresponding alcohol (XIX). This was separated from small amounts of oxides and diols by fractionation followed by chromatography. The hydrocarbon recovered from the reaction was found to be similar to β-santalene except in its rotation. The alcohol ($C_{16}H_{26}O$) showed infrared bands at 3390 and 1053 ($-CH_2OH$); 3096, 1656, 889, and 879 ($>C=CH_2$); and no characteristic absorption for π-substituted tricyclene system. The levorotation of the alcohol also suggested the absence of the tricyclene skeleton. Catalytic hydrogenation revealed the presence of two double bonds. Ozonolysis gave formaldehyde, thus confirming the presence of the methylenic double bond. This showed that a rearrangement of the tricyclene skeleton to the camphene system has occurred under the conditions of the reaction.

β-Santalene (XVIII) under similar conditions yielded the same alcohol (XIX) as the major product. Catalytic hydrogenation of the alcohol showed two double bonds. Ozonolysis yielded formaldehyde and the keto alcohol (XX) which showed infrared bands at 1724 (>C=O), 1364 (CH_3CO-), and 3521 and 1045 ($-CH_2OH$) cm.$^{-1}$. The keto alcohol (XX) gave a positive iodoform test. On oxidation with sodium dichromate and sulfuric acid in aqueous medium, acetic acid and camphenilonylacetic acid (XXI),[8] together with traces of dimethylnorcampholidylacetic acid (XXII), were obtained and identified by paper chromatography. Oxidation by chromic acid in acetic acid also afforded camphenilonylacetic acid.

Thus, on thermal condensation, both α- and β-santalenes yield mainly the same alcohol (XIX). Under the conditions of the reaction, the tricyclic α-santalene rearranges to the bicyclic β-santalene system. One molecule of formaldehyde may add either to the trisubstituted double bond in the side chain to give the alcohol XIX or to the exocyclic double bond in the β-santalene ring to give alcohol XXIV. The product contained two methylenic double bonds as indicated by the infrared bands at 899 ($>C=CH_2$ in the side chain) and 879 cm.$^{-1}$ ($>C=CH_2$ in the five-membered ring). Structure XXIV does not contain any methylenic double bond, whereas XIX accommodates two such bonds, one originally present in β-santalene, and the other formed by migration of the trisubstituted double bond in the side chain to the adjacent position. Results of ozonolysis also confirm this. This evidence is consistent with structure XIX for the alcohol.

Experimental

Melting points and boiling points are uncorrected. Rotations were determined in chloroform solution. Petroleum ether refers to the fraction boiling at 60–80°. Infrared spectra were measured on a Perkin-Elmer Model 137B Infrared spectrophotometer, liquid compounds as liquid film, and solid compounds as Nujol mulls. V.p.c. analyses were carried out on a Perkin-Elmer vapor fractometer 154D, using a 'P' column (succinic acid polyester of diethylene glycol) and hydrogen as carrier gas at 15 lb./sq. in. The solvent system butanol–ethanol–water (40:10:50) upper phase and ammonia (1 ml.) was used for paper chromatography.

Tricyclene (I) was prepared from *d*-camphor[9] and purified by chromatography on neutral alumina (grade I) and sublimation as a white solid, m.p. 68°; infrared bands at 3069, doublet at 1377 and 1359, 873, 856, and 818 cm.$^{-1}$.

8-Camphenylcarbinol (III) **from Tricyclene.**—Tricyclene (15 g., 0.11 mole) was refluxed with paraformaldehyde (3.6 g., 0.12 mole) and acetic acid (200 ml.) for 24 hr. in a flask fitted with a fractionating column. Removal of the solvent under vacuum and work-up according to the conventional procedure gave the acetate ester (7.9 g.) which was saponified by alcoholic potash (140 ml., 0.5 *N*) to yield 8-camphenylcarbinol (5.62 g.) as a colorless liquid, b.p. 80–85° (0.15 mm.), $n^{27}D$ 1.4977; infrared bands at 3333, 1669, doublet at 1375 and 1355, 1031, 843, and 812 cm.$^{-1}$. It absorbed 1 mole of hydrogen in acetic acid solution in the presence of Adams catalyst.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.27; H, 10.54.

Camphenilone (IV).—The alcohol (III, 2.06 g.) was oxidized by potassium permanganate (10.18 g.) in aqueous medium. Work-up yielded, in the neutral portion, camphenilone (0.61 g.) as a liquid, b.p. 104–108° (bath) at 20 mm.; infrared bands at 1726, doublet at 1382, and 1366 cm.$^{-1}$; semicarbazone, white needles (ethanol), m.p. and m.m.p. (with an authentic sample) 208°.

8-Camphenylcarbinol (III) **from camphene** (II) was prepared according to the procedure described in the literature,[4] b.p. 97–100° (7 mm.), $[\alpha]^{25}D$ +22.8°, $n^{26}D$ 1.5016. The infrared spectrum was superimposable with that of the alcohol obtained from tricyclene. Analysis, hydrogenation, and oxidation gave similar results.

2,6-Dimethyloctene-2 (V).—Citronellal was purified by the bisulfite method (100% by oximation), b.p. 73–75° (7 mm.), $[\alpha]^{28}D$ +14.81° (*c* 8.17), $n^{24}D$ 1.4474; infrared bands at 2717, 1724, 1400, and 828 cm.$^{-1}$. V was made by reducing citronellal (46.47 g.) according to the Huang-Minlon method by treating with hydrazine hydrate (30 ml., 85%), diethylene glycol (300 ml.), and potassium hydroxide (52 g.). The hydrocarbon (34.90 g.) was purified by fractionation and chromatography followed by distillation over sodium, b.p. 163° (710 mm.), $n^{24}D$ 1.4310, $[\alpha]^{24}D$ +9.2° (*c* 11.2). V.p.c. analysis showed essentially one peak; infrared bands at 1661 and 833 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{20}$: C, 85.63; H, 14.37. Found: C, 85.70; H, 14.77.

The Prins Reaction on 2,6-Dimethyloctene-2 (V).—A mixture of the hydrocarbon (V, 14.06 g., 0.10 mole), paraformaldehyde (3.56 g., 0.12 mole), and glacial acetic acid (230 ml.) was refluxed for 24 hr. in a flask fitted with a column. Work-up yielded the acetate ester (25 g.) which was saponified by alcoholic potash (100 ml., 2 *N*) to yield 2-isopropenyl-5-methylheptanol (VI, 19 g.). Chromatography on neutral alumina (500 g., grade II) yielded small quantities of oxides in the fractions eluted with petroleum ether. Pure alcohol (7.6 g.) was eluted in the benzene fractions as a colorless liquid with a pleasant odor, b.p. 123–136° (19 mm.), $[\alpha]^{24}D$ +6.82° (*c* 7.04), $n^{24}D$ 1.4540. V.p.c. analysis showed essentially a single peak; infrared bands at 3366, 3086, 1639, 1038, and 891 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.36; H, 13.00.

Catalytic Hydrogenation of the Alcohol (VI).—The alcohol (0.22 g.) was hydrogenated in acetic acid (15 ml.) in the presence of Adams catalyst (38 mg.). The volume of hydrogen absorbed (129 ml. at 17° and 712 mm.) corresponded to 0.91 mole or one double bond.

Ozonolysis of the Alcohol (VI).—The alcohol (4.89 g.) was ozonized in chloroform (100 ml.) at 0° to completion (9 hr.). The ozonide, after removal of solvent *in vacuo* was decomposed with water (60 ml.). The volatile portion gave the dimedone derivative of formaldehyde, m.p. and m.m.p. 189°. The nonvolatile portion was extracted with ether, washed with sodium bicarbonate solution, and dried (Na_2SO_4). Removal of solvent yielded the keto alcohol (VII, 4.66 g.), b.p. 135–140° (bath) at 11 mm., $n^{30}D$ 1.4433, $[\alpha]^{30}D$ +5.7° (*c* 4.04); infrared bands at 3570, 1718, 1355, and 1036 cm.$^{-1}$.

(8) L. Ruzicka and A. Roethlisberger, *Helv. Chim. Acta*, **18**, 439 (1935).

(9) H. Meerwein and K. van Emster, *Ber.*, **53**, 1815 (1920).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.98; H, 11.87.

It gave iodoform (m.p. and m.m.p. 120°) when treated with iodine and sodium hydroxide in dioxane solution.

Oxidation of the Keto Alcohol (VII) by Hypobromite.—The keto alcohol (1 g.) in dioxane (50 ml.) was treated with sodium hypobromite prepared from bromine (1.80 ml.) and sodium hydroxide (4.25 g.) in water (50 ml.) under cooling. The excess hypobromite was decomposed with sodium bisulfite. Work-up yielded the hydroxy acid (VIII, 0.74 g.), b.p. 175–190° (bath) at 3 mm.; infrared bands at 3448, 2632, 1709, 1031, and 938, cm.$^{-1}$.

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.25; H, 9.28.

A better analysis was not obtained.

Oxidation of the Keto Alcohol (VII) by Dichromate–Sulfuric Acid.—The keto alcohol (1 g.) was stirred with water (25 ml.) and powdered sodium dichromate (2.12 g.) under cooling, and sulfuric acid (2 ml.) was added dropwise. The mixture was stirred at room temperature for 8 hr. and at 80° for 2 hr. In one experiment, the reaction mixture was subjected to steam distillation at this stage, and the distillate was found to contain acetic acid by paper chromatography. In another experiment, the reaction mixture was diluted and extracted with ether. The acid portion (0.20 g.), obtained by bicarbonate extraction, was identified as 4-methylcaproic acid (IX), b.p. 180–190° (bath) at 23 mm., $n^{30}D$ 1.4230, $[\alpha]^{30}D$ +7.91° (*c* 3.16), equivalent weight 129 (theoretical, 130), R_f 0.75 (compared against an authentic sample prepared by ozonization of 2,6-dimethyloctene-2 in chloroform); infrared bands at 2632, 1695, 1403, and 934 cm.$^{-1}$. The infrared spectrum was superimposable with that of an authentic sample.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.39; H, 10.72.

The amide, white plates (ethanol), had m.p. and m.m.p. (with an authentic sample) 92°.

Anal. Calcd. for $C_7H_{15}NO$: N, 10.84. Found: N, 10.84.

The oxidation of the keto alcohol (VII, 1.09 g.) by chromic anhydride (1.11 g.) in acetic acid medium (10 ml.) also led to 4-methylcaproic acid (0.30 g.).

The Prins Reaction on 2,6-Dimethyloctene-2 (V) at Room Temperature.—A mixture of 2,6-dimethyloctene-2 (14.20 g., 0.10 mole), paraformaldehyde (3.02 g., 0.10 mole), dry chloroform (30 ml.), and anhydrous stannic chloride (0.50 ml.) was stirred at room temperature for 40 hr. Work-up, as described subsequently in the case of santalenes, yielded the crude product (13.45 g.) which was chromatographed on neutral alumina (280 g., grade II). The fractions eluted with petroleum ether consisted of oxides (5.42 g.); the alcohol (VI, 3.96 g.) was eluted in the benzene fractions.

2-Methylheptene-2 (X).—Methylheptenone (75 g., b.p. 99–100° at 65 mm., $n^{27}D$ 1.4440) was reduced according to the Huang-Minlon procedure by treatment with hydrazine hydrate (65 ml., 85%), diethylene glycol (600 ml.), and potassium hydroxide (110 g.). 2-Methylheptene-2 (50 g.) was purified by chromatography on neutral alumina (1000 g., grade I) as a colorless liquid, b.p. 100–120° (710 mm.), $n^{29}D$ 1.4153; infrared bands at 1667, 843, and 830 (>C=CH–) cm.$^{-1}$.

Anal. Calcd. for C_8H_{16}: C, 85.63; H, 14.37. Found: C, 86.20; H, 14.50.

2-Isopropenylhexanol (XI).—A mixture of 2-methylheptene-2 (X, 33.4 g., 0.30 mole), paraformaldehyde (1.50 g., 0.35 mole), and acetic acid (500 ml.) was refluxed for 26 hr. to yield the acetate ester (50 g.) which on saponification with alcoholic potassium hydroxide (300 ml., 2 *N*) followed by chromatography on neutral alumina (510 g., grade II) yielded the pure alcohol (XI, 15.10 g.) in the benzene fractions, b.p. 133–143° (bath) at 102 mm., $n^{26}D$ 1.4500; infrared bands at 3311, 3030, 1631, 1042, and 889 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{18}O$: C, 75.99; H, 12.76. Found: C, 75.97; H, 12.80.

Ozonolysis of the Alcohol (XI).—The alcohol (3.03 g.) was ozonized in chloroform (75 ml.) at 0° to completion (8 hr.). Decomposition with water (60 ml.) yielded formaldehyde (dimedone derivative, m.p. and m.m.p. 189°) and the keto alcohol (XII, 2.88 g.), b.p. 169–175° (bath) at 25 mm.; infrared bands at 3500, 1724, 1364, and 1042 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.48; H, 11.46.

It gave iodoform with iodine and alkali in dioxane solution.

Oxidation of the Keto Alcohol (XII).—The keto alcohol (1.13 g.) was oxidized with sodium dichromate (2.61 g.) and sulfuric acid (2.50 ml.) in aqueous medium. The reaction mixture was steam distilled and the distillate contained *n*-valeric acid (XIII, R_f 0.58) and acetic acid (R_f 0.23) by paper chromatography.

α- and β-Santalenes (XIV and XVIII).—α- and β-santalenes were obtained by repeated batch-strip fractionation[10] using a packed column followed by elaborate column chromatography on alumina (500-fold, grade I) of "sandalwood oil terpenes" supplied by the Government Sandalwood Oil Factory, Mysore. The purest hydrocarbons[11] showed the following properties: α-santalene, b.p. 112° (7 mm.), $[\alpha]^{29}D$ +10.84° (*c* 10.72), $n^{29}D$ 1.4833; β-santalene, b.p. 109° (3 mm.), $[\alpha]^{26}D$ −73.94° (*c* 11.67), $n^{26}D$ 1.4940.

2-Isopropenyl-3-(π)-tricyclylpropanol (XV).—A mixture of α-santalene (XIV, 100 g., 0.48 mole), paraformaldehyde (18 g., 0.60 mole), freshly distilled anhydrous stannic chloride (2.4 ml.), and dry chloroform (200 ml.) was stirred at room temperature for 40 hr. Chloroform was removed under reduced pressure, and the residue was diluted with water and warmed with ammonia. The product was repeatedly extracted with ether, washed with water, and dried (Na_2SO_4). Removal of solvent yielded the crude product (109 g.) which was fractionated to remove the low-boiling fractions consisting of α-santalene (19.3 g., b.p. 75–80° at 0.8 mm.). The residue in petroleum ether yielded a mixture of oxides (13.5 g.). The fractions eluted with ether gave after fractionation, 2-isopropenyl-3-(π)-tricyclylpropanol (XV, 18.8 g.) as a colorless, viscous liquid having a sandalwood odor, b.p. 122–125° (0.7 mm.), $[\alpha]^{23}D$ +2.66° (*c* 21.31), $n^{22}D$ 1.5018; infrared bands at 3484, 3096, 1655, 1047, 895, 882, 858, and 824 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.65; H, 11.00.

Catalytic Hydrogenation of the Alcohol (XV).—The alcohol (0.11 g.) was hydrogenated in ethanol (25 ml.) in the presence of Adams catalyst (56 mg.). The amount of hydrogen absorbed (14.90 ml. at 20° and 709 mm.) corresponded to 0.90 mole or one double bond. The dihydro product showed infrared bands at 3356, 3067, doublet at 1383, 1366, 1049, 877, 854, and 820 cm.$^{-1}$.

2-Homo-π-tricyclyl-3-ketobutanol (XVI).—The alcohol (XV, 5.02 g.) was ozonized in chloroform (100 ml.) to completion (8 hr.) at 0°. After removal of solvent under reduced pressure, the ozonide was heated with water (60 ml.) on a water bath for 4 hr. The volatile portion trapped in ice-cold water gave a copious amount of dimedone derivative of formaldehyde, m.p. and m.m.p 189°. The nonvolatile portion, after being treated with sodium bicarbonate, yielded the keto alcohol (XVI, 4.32 g.), b.p. 160–170° (bath) at 1.5 mm., $n^{26}D$ 1.4920. It gave iodoform (m.p. and m.m.p. with an authentic sample 120°) with iodine and alkali in dioxane solution; infrared bands at 3521, 3096, 1727, 1351, 1043, 878, 856, and 823 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.61; H, 10.23.

Oxidation of the Keto Alcohol (XVI). A. By Sodium Dichromate–Sulfuric Acid.—The keto alcohol (1 g.) was stirred with water (20 ml.) and finely powdered sodium dichromate (1.49 g.) under cooling. Concentrated sulfuric acid (2 ml.) was added to this dropwise, and the mixture was stirred at room temperature for 6 hr. and at 80° for 2 hr. The mixture was distilled and the earlier portions of the distillate were trapped in ice-cold liquid ammonia (3 ml.), the solution was extracted with ether, and the aqueous layer was concentrated. It was shown to contain acetic acid (R_f 0.19) by paper chromatography.

B. By Permanganate.—The keto alcohol (XVI, 1.02 g.) was stirred with water (30 ml.), and powdered potassium permanganate (2.05 g.) was added to this in five portions during 1 hr., and the stirring was continued at room temperature for 16 hr. The manganese dioxide sludge was filtered and washed with hot water. The filtrate was extracted with ether; the aqueous layer was concentrated and acidified with hydrochloric acid (1:1). The organic acid was extracted with ether, washed free of mineral acid, and dried (Na_2SO_4). Removal of solvent yielded a mixture of acids which contained mainly tricycloekasantalic acid (R_f 0.76) and small amounts of acetic acid (R_f 0.20) and another acid

(10) B. B. Ghatge and S. C. Bhattacharyya, *Perfumery Essent. Oil Record*, **47**, 353 (1956).

(11) V. Herout and collaborators [*Collection Czech. Chem. Commun.*, **22**, 773 (1957)] have recorded higher rotations for α- and β-santalenes isolated in milligram quantities. Such high rotations, however, could not be achieved in our case.

(R_f 0.51, probably a keto acid). The ketonic impurities were removed by treatment with Girard's reagent and the product was crystallized from petroleum ether to yield tricycloekasantalic acid, m.p. and m.m.p. 76°; infrared bands at 3058, 2667, 1704, 1408, 946, 878, 855, and 821 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.00; H, 9.50.

The alcohol (XV) also yielded tricycloekasantalic acid (XVII), when oxidized with permanganate as described.

The Prins Reaction on α-Santalene (XIV) under Thermal Conditions.—α-Santalene (22.4 g., 0.11 mole) was refluxed with paraformaldehyde (3.49 g., 0.11 mole) and glacial acetic acid (350 ml.) for 26 hr. Acetic acid was distilled, the residue was diluted and repeatedly extracted with ether, washed with sodium carbonate and water, and dried (Na_2SO_4). Removal of solvent yielded the unsaturated acetate (22.81 g.), which was saponified by refluxing with alcoholic potassium hydroxide (300 ml., 0.5 *N*) for 2 hr. to yield the crude product (20.56 g.). On fractionation using a spinning band column, the earlier fractions (4.17 g.) were found to consist of a β-santalene-type hydrocarbon from physical properties, elemental analysis, and infrared spectrum. The intermediate fractions (10.54 g.) consisted of the alcohol XIX. The last fractions contained mostly diols.

The alcohol XIX is a colorless liquid having a sandalwood odor, b.p. 150–155° (bath) at 1 mm., $[\alpha]^{27}D$ −11.92° (*c* 11.11), $n^{28}D$ 1.5036; infrared bands at 3333, 3050, 1631, 1037, 885, and 877 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.56; H, 11.10.

A sample of the alcohol purified by phthalization had identical properties.

It absorbed 1.93 moles of hydrogen on catalytic hydrogenation in presence of Adams catalyst in glacial acetic acid.

The Prins Reaction on β-Santalene (XVIII) under Thermal Conditions.—β-Santalene (10.7 g., 0.05 mole) was refluxed with paraformaldehyde (1.84 g., 0.06 mole) and glacial acetic acid (100 ml.) for 24 hr., and the product was worked up as in the case of α-santalene to yield the acetate ester (11 g.). This was saponified by alcoholic potassium hydroxide (140 ml., 0.5 *N*), and the product was fractionated using a spinning band column to remove unchanged β-santalene (2.74 g.) and higher boiling diols (1.52 g., b.p. 140–156° at 3 mm.). The alcohol (XIX, 4.07 g.) was further purified by chromatography on neutral alumina (100 g., grade II) when a colorless, viscous liquid having a sandalwood odor was obtained, b.p. 140–150° (bath) at 2 mm., $[\alpha]^{28}D$ −17.58° (*c* 9.98), $n^{30}D$ 1.5045. Its infrared spectrum was identical with that of the alcohol obtained from α-santalene by thermal reaction.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.62; H, 11.14.

Quantitative hydrogenation showed the presence of two double bonds.

Ozonolysis of Alcohol XIX.—The alcohol (2.70 g.) was ozonized in chloroform (25 ml.) at 0° to completion (6 hr.). After removal of solvent, the ozonide was decomposed with water (35 ml.). The volatile portion gave the dimedone derivative of formaldehyde, m.p. and m.m.p. 189°. The nonvolatile portion (XX, 1.56 g.), after being extracted with sodium bicarbonate, distilled at 170–190° (bath) at 0.4 mm.; infrared bands at 3521, 1724, and 1045 (NaCl prism), and 1732 and 1709 cm.$^{-1}$ (CaF_2 prism).

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 72.60; H, 10.34.

A better analysis could not be obtained.

Oxidation of the Keto Alcohol (XX) by Sodium Dichromate–Sulfuric Acid.—The keto alcohol (1 g.) was oxidized with sodium dichromate (1.53 g.) and sulfuric acid (1.11 ml.) in aqueous medium as described before. The reaction mixture was steam distilled; the distillate contained acetic acid (R_f 0.19), identified by paper chromatography. Work-up of the residue yielded an acid mixture which contained mainly camphenilonylacetic acid (R_f 0.51), small proportions of norcampholidylacetic acid (XXII, R_f 0.41), and acetic acid (R_f 0.19). Genuine samples of acids XXI and XXII for comparison were obtained by ozonizing bicycloekasantalic acid in acetic acid.[6]

Oxidation of the Keto Alcohol (XX) by Chromic Acid.—The keto alcohol (1 g.), when oxidized with acetic acid (10 ml.), chromic anhydride (0.98 g.) in water (1 ml.), and glacial acetic acid (10 ml.) according to the procedure described earlier, yielded the acid XXI (0.25 g.) identified by paper chromatography; methyl ester (diazomethane), b.p. 130–140° (bath) at 0.6 mm., infrared bands at 1748 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.62; H, 9.13.

Acknowledgment.—The authors are grateful to Mr. H. Gopinath for the infrared spectra, Mr. V. S. Pansare and colleagues for the microanalyses, Dr. S. Kanthamani and Dr. G. Lakshmi Kumari for paper chromatography, and Dr. V. G. Naik for the v.p.c. analysis. One of the authors (S. R.) gratefully acknowledges a Junior Research Fellowship awarded to her by the Council of Scientific and Industrial Research, Government of India, during the period of this work.

Azabicyclic Alcohols. I. Stereochemistry of the Hydroxyquinolizidines[1]

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Each of the 1-, 2-, and 3-hydroxyquinolizidine racemates has been synthesized and characterized. Configurational and conformational assignments have been made on the basis of infrared and n.m.r. spectra, gas–liquid chromatographic retention data, and chemical evidence. In all cases a *trans*-quinolizidine ring fusion is shown to exist. In the case of the 1- and 3-hydroxyquinolizidines, intramolecular hydrogen bonding occurs between the bridgehead nitrogen and an axial β-hydroxyl group.

Although the quinolizidine ring system (I) occurs in many natural products,[2] the simple hydroxyquinolizidines are not known to exist in nature. In the 1-, 2-, and 3-hydroxyquinolizidines, two epimeric racemates are possible, depending upon the configuration of the hydroxyl group relative to that of the bridgehead (C-10) hydrogen. For each epimer both a *cis* and a *trans* ring fusion are possible, and interconversion between the two forms can occur by inversion of the electron pair on the bridgehead nitrogen. Previous studies of these compounds have been reviewed.[3,4] Only recently, however, have the two epimers of the 1- and 2-hydroxyquinolizidines been characterized and configurational assignments given.[5,6] Complete

(1) Presented in part at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2) N. J. Leonard, "The Alkaloids," Vol. III, R. H. F. Manske and H. L. Holmes, Ed., Academic Press, New York, N. Y., 1953, p. 120.

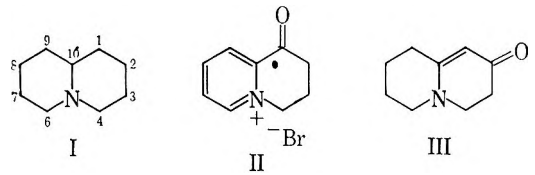
(3) W. L. Mosby, "Heterocyclic Systems With Bridgehead Nitrogen Atoms," Part Two, Interscience Publishers, Inc., New York, N. Y., 1961, p. 1001.

(4) R. E. Counsell and T. O. Soine, *J. Am. Pharm. Assoc.*, **49**, 289 (1960).

(5) G. A. Swan, *J. Chem. Soc.*, 2051 (1958).

(6) F. Bohlmann, E. Winterfeldt, O. Schmidt, and W. Reusche, *Chem. Ber.*, **94**, 1767 (1961).

conformational assignments have been made only in the 2-hydroxy series.[6] In this paper, we discuss configurational and conformational assignments and the correlations which have been made as a result of our studies of the 1-, 2-, and 3-hydroxyquinolizidines. A following paper[7] will discuss reduction studies of the corresponding ketones. Succeeding papers will deal with systematic studies of other azabicyclic alcohol systems.



I II III

Results and Discussion

Reductions of 1-, 2-, and 3-ketoquinolizidine give mixtures of the corresponding amino alcohol racemates.[7] In each system the epimers were readily separated by gas–liquid chromatography (g.l.c.) and designated A and B according to the order in which they were eluted from a Carbowax column. Retention times of these epimers and the corresponding ketones are given in Table I. In the case of the 1- and 3-hydroxyquinolizidines, the A-racemates show retention times which are significantly shorter than that of the corresponding *ketones*. Since the relative retention times of the alcohols presumably are dependent upon hydrogen bonding with the Carbowax substrate, this result suggests that intramolecular hydrogen bonding[8] between the nitrogen atom and hydroxyl group exists in epimer A of the 1- and 3-hydroxyquinolizidines.[9] Stereomodels reveal that this bonding is possible only when the β-hydroxy group is in an axial conformation.

TABLE I

G.L.C. AND pK_a DATA FOR KETO- AND HYDROXYQUINOLIZIDINES

Quinolizidine derivative	M.p., °C.	Retention time,[a] min.	pK_a[b]
1-Keto		5.7	8.06
1-Hydroxy, epimer A (VII)	80–81	4.9	10.20
1-Hydroxy, epimer B (VIII)	71–72	8.5	8.73
2-Keto		6.4	8.08
2-Hydroxy, epimer A (XI)	103–104	8.6	9.53
2-Hydroxy, epimer B (XII)	88–89	9.6	9.20
3-Keto		6.9	8.3[c]
3-Hydroxy, epimer A (IX)	23–25	4.7	9.87
3-Hydroxy, epimer B (X)	65–66	10.2	8.60

[a] Measured from air peak on a 10 ft. × 0.25 in. column of Carbowax 20 M (15%) on Gas-Chrom P support at 210° and 120 ml./min. (He). [b] 0.0050 ionic strength (μ) unless otherwise indicated. [c] 0.04 ionic strength. Estimated to be pK_a = 8.2 at 0.005 μ.

Intramolecular hydrogen bonding is not possible for either of the 2-hydroxyquinolizidine epimers with the piperidinol ring in a chair conformation, and accordingly, no anomaly is observed in the g.l.c. retention times in this system.

Infrared spectral analysis clearly corroborates the conclusions suggested by the g.l.c. results. The pertinent spectral data are summarized in Table II.

TABLE II

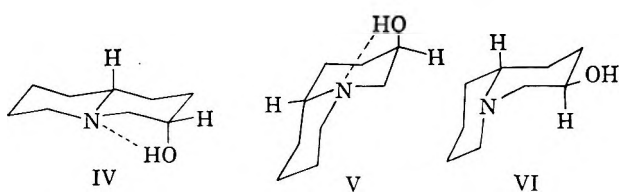
INFRARED SPECTRAL DATA[a] FOR HYDROXYQUINOLIZIDINES

Hydroxyquinolizidine, epimer	Free OH	Bonded OH— Intra	Bonded OH— Inter	Bohlmann bands
1-OH, A		3526		2800, 2777
1-OH, B	3618		3100–3400	2795, 2750
2-OH, A	3625		3100–3400	2802, 2764
2-OH, B	3620		3100–3500	2801, 2762
3-OH, A		3527		2797, 2757
3-OH, B	3609		3100–3500	2800, 2762

[a] Absorption maxima are given in cm.$^{-1}$ for the 1- and 3-hydroxy epimers in dilute carbon disulfide solution, for the 2-hydroxy epimers in dilute carbon tetrachloride solution.

In dilute carbon disulfide solution, the A-epimers of 1- and 3-hydroxyquinolizidine show no detectable absorption in the free OH stretching region ($\tilde{\nu}$ >3600 cm.$^{-1}$). In the bonded OH stretching region, however, each shows a single band whose intensity and position are unaffected by further dilution. This result is typical of intramolecularly N···HO bonded systems.[10] The B-epimers of 1- and 3-hydroxyquinolizidine and both of the 2-hydroxy epimers show the characteristically sharp free OH band above 3600 cm.$^{-1}$ and a broad hydrogen-bonded OH band in the 3100–3500 cm.$^{-1}$ region. Further dilution results in a decrease in the relative intensity of the bonded band, accompanied by a corresponding increase in that of the free OH band. In every case, the broad band was completely eliminated at high dilution. These results are typical of intermolecularly N···HO bonded systems.[10]

1- and 3-Hydroxyquinolizidines.—If one assumes only all-chair ring conformations to be important,[11] one *trans* (*e.g.*, IV) and two *cis* ring conformers (*e.g.*, V and VI) need to be considered for these systems. However, *cis* ring conformation VI may be excluded on



IV V VI

the grounds that intramolecular hydrogen bonding would not be possible for either epimer in this conformation. Intramolecularly bonded conformations IV and V, however, are of opposite configuration (*cis*-3,10-H and *trans*-3,10-H, respectively). Therefore, the fact that only one of the two epimers in both the 1-

(7) C. P. Rader, G. E. Wicks, Jr., R. L. Young, Jr., and H. S. Aaron, *J. Org. Chem.*, **29**, 2252 (1964).

(8) G.l.c. has been shown [C. H. DePuy and P. R. Story, *Tetrahedron Letters*, **No. 6**, 20 (1959)] to be useful in the detection of intramolecular hydrogen bonding between a hydroxyl group and a carbon–carbon double bond. The effect of intramolecular hydrogen bonding on relative retention times of the epimeric normuscarines has been noted (C. H. Eugster in "Advances in Organic Chemistry," Vol. II, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 450), though not in comparison to that of their carbonyl analogs.

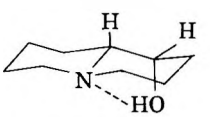
(9) Intramolecular hydrogen bonding has been shown to occur in the structurally related 3-hydroxypiperidine; *cf.* (a) G. Hite, E. E. Smissman, and R. West, *J. Am. Chem. Soc.*, **82**, 1207 (1960); (b) J. Sicher and M. Tichý, *Tetrahedron Letters*, **No. 12**, 6 (1959), and references cited therein.

(10) A. R. H. Cole in "Technique of Organic Chemistry," Vol. XI (Part 1), A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 3.

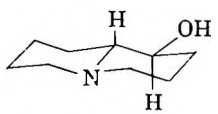
(11) Boat conformations may be excluded on the basis of unfavorable steric interactions; see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 204, *et seq.*

and 3-hydroxy systems shows intramolecular hydrogen bonding, and correspondingly, no free CH absorption, establishes that the stereochemistry of the ring fusion must be the same within the respective epimeric pairs, and that the possible equilibrium between the *cis* and *trans* ring fusions in these systems must lie so far to one side as to be undetectable by infrared methods.

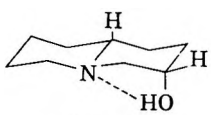
In order to make a configurational assignment for the 1- and 3-hydroxyquinolizidines, therefore, the stereochemistry of the ring fusion must be determined. Here, the empirical correlation of Bohlmann[12] may be applied. Thus, it has been shown that for quinolizidines, one or more prominent infrared bands in the 2700–2800 cm.$^{-1}$ region is indicative of a *trans* ring fusion. As summarized in Table II, all six of the hydroxyquinolizidines show these characteristic absorptions. This correlation was previously used[6] to assign the *trans* ring fusion to the 2-hydroxyquinolizidine epimers. On this basis, therefore, the configurations and prevailing conformations of the epimeric 1- and 3-hydroxyquinolizidines may be assigned as VII, VIII and IX, X, respectively.



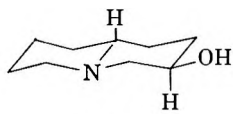
epimer A
VII



epimer B
VIII



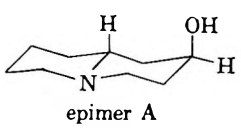
epimer A
IX



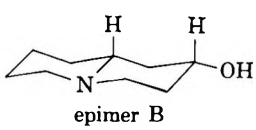
epimer B
X

The configurations of the 1-hydroxyquinolizidines previously have been assigned[5] on the basis that the catalytic reduction of 1-keto-1,2,3,4-tetrahydroquinolizinium bromide (II) gives a single 1-hydroxyquinolizidine, m.p. 80–81°, logically assigned the *cis*-1,10-hydrogen configuration. The epimeric amino alcohol, therefore, was assigned[5] the *trans*-1,10-hydrogen configuration. The fact that we have shown intramolecular hydrogen bonding for the *cis*-1,10-hydrogen epimer and the absence of such bonding for the *trans*-1,10-hydrogen epimer constitutes an independent verification of the Bohlmann correlation for both epimers. Similar chemical verification does not exist for the 3-hydroxy system.

2-Hydroxyquinolizidines.—The conformations of the 2-hydroxy epimers as previously assigned[6] are given by XI and XII. That these epimers possess an axial



epimer A
XI



epimer B
XII

and equatorial hydroxyl group, respectively, has also been established[13] by analysis of the shape of their free O–H stretching bands. This result independently establishes the *trans* ring fusion for this system, therefore, since a *cis* ring fusion should permit each epimer to assume a predominant equatorial conformation for the respective hydroxyl groups. The fact that we find the equatorial alcohol (XII) to have a slightly longer g.l.c. retention time than its epimer on the Carbowax column (Table I) is in accord with this assignment and with the g.l.c. retention times reported for axial *vs.* equatorial hydroxy decalols[14] and steroids.[15] This assignment is also in accord with a correlation by which the position of the free O–H stretching absorption (Table II) of an axial hydroxyl group has been shown[10,16] to occur at a slightly higher frequency (5–10 cm.$^{-1}$) than that of its equatorial epimer. The possibility that a significant population (>2%) of the boat conformation exists in the 2-hydroxy epimers may be dismissed on the grounds that both 2-hydroxyquinolizidines show no infrared spectral evidence of intramolecular hydrogen bonding (Table II).

Independent evidence that epimer B has a *cis*-2,10-hydrogen configuration may be obtained from the catalytic reduction of $\Delta^{1,10}$-2-ketoquinolizidine (III). Reduction of 2-ketoquinolizidine on 5% ruthenium on carbon in ethanol gives a 60:40 B–A ratio, while reduction of III under the same conditions produces an 87:13 B–A ratio.[7] Assuming that the preponderance of hydrogen adds from the same side of the molecule[17] in the $\Delta^{1,10}$-system, one concludes that the increase in the percentage of B represents an increase in that epimer which has the *cis*-2,10-hydrogen configuration.

The conformational assignments of the 1-, 2-, and 3-hydroxyquinolizidines as given above are in agreement with the theory that alkali metal–alcohol reductions of six-membered ring ketones give a preponderance (>80% in these systems[7]) of the more stable equatorial hydroxyl epimer (B) in each case.[18] The effect of intramolecular hydrogen bonding upon this equilibrium as reported[19] in the 2-tropinol system was not studied here. Our results correspond to those reported[20] for the lupinine–epilupinine system.

N.m.r. Correlations.—N.m.r. spectra of the hydroxyquinolizidine racemates were examined, and the pertinent data are summarized in Table III. The sharp hydroxyl and broader carbinol proton peaks may be readily identified, since their chemical shifts place them clearly apart from the other protons. In each system, the carbinol proton of the B-epimer absorbs at a higher field and has a greater band width (W_H) than its corresponding A-epimer. Both theory[21] and accumulated n.m.r. evidence[22] have shown that an axial carbinol proton should have a greater degree of spin–spin coupling with vicinal protons and thus give a broader peak than its equatorial counterpart. The band-width data summarized in Table III, there-

(12) (a) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); (b) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).

(13) H. S. Aaron and C. P. Rader, *ibid.*, **85**, 3046 (1963).

(14) W. Hückel, D. Maucher, O. Fechtig, J. Kurz, M. Heinzel, and A. Hubele, *Ann.*, **645**, 115 (1961).

(15) W. J. A. Vandenheuvel and E. C. Horning, *Biochim. Biophys. Acta*, **64**, 416 (1962).

(16) A. R. H. Cole, P. R. Jefferies, and G. T. A. Müller, *J. Chem. Soc.*, 1222 (1959), and preceding papers in this series.

(17) R. L. Burwell, *Chem. Rev.*, **57**, 895 (1957).

(18) In strained or hindered carbonyl ring systems, the less stable epimer may be obtained; *cf.*, ref. 28. The hydroxyquinolizidines, however, clearly do not fall in this category.

(19) M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 4642 (1960).

(20) N. J. Leonard, "The Alkaloids," Vol. VII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, p. 264.

(21) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(22) E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 4249 (1962), and references cited therein.

TABLE III

N.M.R. SPECTRAL DATA[a] FOR HYDROXYQUINOLIZIDINES

Quinolizidine	—Carbinol proton— τ	W_H[b] (c.p.s.)	—CH_2— protons not adjacent to N— τ[c]	W_H[b] (c.p.s.)
Unsubstituted			8.49	30
1-OH, epimer A	6.62	7.5	8.38	34
1-OH, epimer B	6.87	16	8.40	28
2-OH, epimer A	6.02	7	8.50	23
2-OH, epimer B[d]	6.53	23	8.35	30
3-OH, epimer A	6.26	6.5	8.49	20
3-OH, epimer B	6.38	19	8.41	24
Piperidine			8.53	7.0

[a] Obtained for 10% carbon tetrachloride solutions using tetramethylsilane as internal standard. [b] W_H = band width at one-half of the peak height. [c] Center of broad band due to these protons. [d] 20% solution.

fore, indicate that racemates A and B possess equatorial and axial carbinol hydrogens, respectively, in agreement with the conformational assignments made on the basis of the infrared and g.l.c. data. Moreover, the relative positions of the carbinol hydrogen bands of the two epimers, when compared with correlations[23] of chemical shifts of carbinol protons, also agree with these conformational assignments.

Unfortunately, we are unable to make a ring fusion assignment based upon the analysis of these n.m.r. spectra. The fact that a broad band is observed for the methylene hydrogens not adjacent to nitrogen cannot be used to assign a *trans* ring fusion (by analogy to the results reported[24] for the *cis* and *trans* decalin systems), because infrared data have shown that these *substituted* quinolizidine systems are conformationally stable regardless of the type of ring fusion. Thus, the fact that *unsubstituted* quinolizidine shows a broad band for the hydrogens not adjacent to nitrogen (Table III) is indicative of a conformationally stable *trans* ring junction (previously assigned[12a] from infrared data), since conformationally mobile piperidine shows a narrow band for these hydrogens (Table III). That the band-width criterion was not applicable to the methylquinolizidines[25] is undoubtedly due to the fact that these compounds are conformationally stable, and not to the differences in the chemical shifts of the ring protons not adjacent to nitrogen as has been suggested.[25b]

pK_a Correlations.—Relative pK_a values of the hydroxyquinolizidines are given in Table I. It should be noted that the intramolecularly bonded 1- and 3-hydroxy racemates (A) are markedly more basic than their corresponding (B) epimers (ΔpK_a of 1.5 and 1.3 units, respectively). A similar relationship has been noted in other systems[26] in which only one epimer shows intramolecular hydrogen bonding. The ΔpK_a value (0.3 units) for the nonintramolecularly bonded 2-hydroxy epimers corresponds to that (0.5 units) reported[27] for the conformationally related, nonintramolecularly bonded[28,29] tropine–pseudotropine system. It is our intention to discuss more fully at a later date the relative basicity of these and related epimeric amino alcohols.

Experimental

All melting points are corrected. Picrate and hydrobromide derivatives were customarily prepared in ether (occasionally in ethanol) and recrystallized from the indicated solvent. The pK_a data were obtained from the half-neutralization point of the titration curve using 0.050 *N* acid and a Beckman Model H-2 pH meter which had been standardized near the pK_a point with commercial buffer solutions. The amine sample was dissolved in sufficient water such that the ionic strength (μ) at the pK_a point would be 0.0050.

The solutions for the n.m.r. spectra were prepared from spectral grade carbon tetrachloride taken directly from the bottle. For 1-hydroxyquinolizidine epimer A, however, freshly distilled solvent was used, and here the hydroxyl and carbinol protons were found to split each other (J = 10.5 c.p.s.). Addition of deuterium oxide resulted in a merging of the carbinol proton multiplets and a disappearance of the hydroxyl proton peak. All proton magnetic resonance spectra were obtained with a Varian Model A-60 spectrometer using Varian precision 5-mm. sample tubes.

A Perkin-Elmer Model 421 dual-grating spectrophotometer was used in all infrared studies. A slit program of 1000 × 1 was used with a scan rate of 110 cm.$^{-1}$/min. The positions of all spectral band maxima should be accurate within ±2 cm.$^{-1}$. Reagent grade solvents were used without further purification.

Ketoquinolizidines.—1-Ketoquinolizidine was synthesized[30] by slight modifications of known[4] procedures. Diethyl piperidyl-1-γ-butyrate-2-carboxylate,[31] b.p. 117–119° (0.65 mm.), single peak (10 min.) on 15% Carbowax 20 M g.l.c. column (5 ft.) at 228° (60 ml./min., He), obtained in 72% yield from undistilled ethyl pipecolate, was cyclized using potassium *t*-butoxide in a Dieckmann condensation to give a 76% yield of 1-ketoquinolizidine, b.p. 106° (13 mm.), n^{20}D 1.4935; lit.[31] b.p. 104° (12 mm.), n^{20}D 1.4935.

The 2- and 3-ketoquinolizidines were synthesized by Regis Chemical Co. under a U. S. Army Chemical Research and Development Contract. 2-Ketoquinolizidine had b.p. 64–69° (1 mm.), n^{26}D 1.4920, picrate m.p. 209–210° (aqueous ethanol); lit.[32] b.p. 70° (1 mm.), picrate m.p. 211°, 209–210°.[33] 3-Ketoquinolizidine had b.p. 65° (0.6 mm.), n^{22}D 1.4930, picrate m.p. 179° (acetone); lit.[34] b.p. 62–63° (0.65 mm.), n^{20}D 1.4926, picrate m.p. 180–182°, 181°.[4] The ketoquinolizidines described above all gave single peaks by g.l.c. analysis (Table I).

Hydroxyquinolizidines.—These were obtained by reduction[7] of the corresponding ketoquinolizidines. Small samples of the pure epimers were isolated by g.l.c. (*cf.* Table I). Larger samples of the 2-hydroxy racemates were chromatographed on Woelm alumina (neutral, activity grade IV) as previously described[6] to give epimer A, m.p. 103–104° (petroleum ether, b.p. 30–55°), lit.[6] m.p. 103–104°, picrate m.p. 189–190° (acetone); and epimer B, m.p. 88–89° (petroleum ether), lit.[6] m.p. 88–89°, picrate m.p. 168–169° (acetone).[35]

The 1-hydroxyquinolizidines (*ca.* 2.5 g.) were chromatographed in ether on grade IV Woelm alumina (300 g.). Each was then recrystallized from petroleum ether to give epimer A, 0.25 g., m.p. 80–80.5°, lit.[5] m.p. 80°, picrate m.p. 156–157° (95% ethanol), lit.[5] m.p. 152–153°, hydrobromide m.p. 231–232° (ace

(23) It has been established that an axial carbinol proton will absorb at a higher field than its equatorial counterpart. See (a) E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, **No. 17**, 741 (1962); (b) J. I. Musher, *J. Chem. Phys.*, **35**, 1159 (1961).

(24) (a) J. Musher and R. E. Richards, *Proc. Chem. Soc.*, 230 (1958); (b) W. B. Moniz and J. A. Dixon, *J. Am. Chem. Soc.*, **83**, 1671 (1961).

(25) (a) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962); (b) 2653 (1962).

(26) H. Rapoport and S. Masamune, *J. Am. Chem. Soc.*, **77**, 4330 (1955); D. E. Ayer, G. Büchi, P. Reynolds-Warnhoff, and D. M. White, *ibid.*, **80**, 6146 (1958).

(27) T. A. Geissman, B. D. Wilson, and R. B. Medz, *ibid.*, **76**, 4182 (1954).

(28) H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963).

(29) H. S. Aaron and C. P. Rader, Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 42Q.

(30) An additional sample was obtained from Olin Mathieson Chemical Corp. under a U. S. Army Chemical Research and Development Contract.

(31) W. A. Reckhow and D. S. Tarbell, *J. Am. Chem. Soc.*, **74**, 4960 (1952).

(32) G. R. Clemo, T. P. Metcalfe, and R. Raper, *J. Chem. Soc.*, 1429 (1936).

(33) H. J. Rhodes and T. O. Soine, *J. Am. Pharm. Assoc.*, **45**, 746 (1956).

(34) N. J. Leonard and S. H. Pines, *J. Am. Chem. Soc.*, **72**, 4931 (1950).

(35) K. Winterfeld, W. Zengerling, and M. Rink [*Ann.*, **597**, 110 (1955)] obtained a picrate, m.p. 166–167°, from 2-hydroxyquinolizidine of unspecified epimeric content.

tone ethanol), lit.[5] m.p. 232–233°; and epimer B, 1.0 g., m.p. 71–72°, lit.[5] m.p. 72°, picrate[36] m.p. 174–176° (95% ethanol), hydrobromide m.p. 242–244° (acetone), lit.[5] m.p. 243–244°. Unexpectedly, epimer B was the first eluted from the alumina column in this series. A mixed middle fraction was also obtained.

The 3-hydroxyquinolizidines were isolated by distillation. Thus, 8.0 g. of 3-ketoquinolizidine in 25 ml. of absolute ethanol was completely reduced in 1.5 hr. over 2.0 g. of 5% ruthenium on carbon (Engelhard Industries, Inc.) at 70 p.s.i.g. and 28° in a Parr hydrogenation apparatus. The catalyst was filtered off and the solvent was removed under reduced pressure to give a 76:24 A–B ratio (g.l.c. analysis). Distillation gave fraction 1, 4.0 g. (>98% A), b.p. 51° (0.25 mm.), $n^{28}D$ 1.4930; and fraction 2, 2.8 g. (65% A), b.p. 51–72° (0.25 mm.). Fraction 1 solidified in the freezer to give epimer A, m.p. 23–25°.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; O, 10.31; equiv. wt., 155.2. Found: C, 69.8; H, 11.0; O, 10.6; equiv. wt., 156.

The picrate of A was prepared in ether and gave m.p. 115–117°. Attempts to recrystallize this picrate led to material which melted lower and over a wider range. The hydrobromide gave m.p. 206–208° (acetone).

Anal. Calcd. for $C_9H_{18}BrNO$: C, 45.77; H, 7.68. Found: C, 45.7; H, 7.7.

3-Hydroxyquinolizidine, epimer B, was obtained by reduction of 5.0 g. of 3-ketoquinolizidine in 25 ml. of absolute ethanol over 1.0 g. of 10% palladium-on-carbon catalyst (A. D. Mackay and Co.) at 70 p.s.i.g. of hydrogen and 25°. Reduction was completed in 1 hr. The catalyst was filtered off, and the solvent was removed under reduced pressure to give a 3:97 A–B product ratio (g.l.c. analysis). Distillation (78–81°, 0.25 mm.) gave fraction 1, 0.4 g. (94% B); fraction 2, 1.2 g. (97% B); and fraction 3, 2.6 g. (99% B). On standing in the freezer, fraction 3 crystallized to give epimer B, m.p. 59–62°, which upon recrystallization from petroleum ether melted at 65–66°.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; equiv. wt., 155.2. Found: C, 69.6; H, 11.0; N, 9.1; equiv. wt., 153.

The hydrobromide of B gave m.p. 239–240.5° (acetone–methanol, 2:1).

Anal. Calcd. for $C_9H_{18}BrNO$: C, 45.77; H, 7.68. Found: C, 45.5; H, 7.8.

The picrate of B gave m.p. 161.5–162° upon precipitation from ether.[38]

Acknowledgment.—Some of the infrared spectral data were obtained by Mr. R. Piffath; the elemental analyses were carried out by the Microanalytical Laboratory of the Chemical Research Division of these laboratories.

(36) Picrate m.p. 174–175°[37] and 175.5–176.5°[4] have been obtained from products now known[7] to have been about 84:16 B–A.

(37) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 443 (1955).

(38) A picrate, m.p. 161.5–162.5°, has been obtained[4,37] by recrystallization of the product from a mixture now known[7] to have been about 85:15 B–A.

Azabicyclic Alcohols. II. Chemical and Catalytic Reduction of the Ketoquinolizidines[1]

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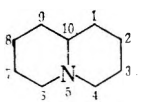
Catalytic hydrogenations of 1-, 2-, and 3-ketoquinolizidine have been studied on platinum oxide, rhodium, ruthenium, and palladium. Epimeric racemates of the corresponding hydroxyquinolizidines have been obtained in proportions which vary with the nature of the catalyst and acidity of the reducing medium. On platinum oxide and rhodium some hydrogenolysis of the carbon–oxygen bond occurs. The unprotonated bridgehead nitrogen atom appears to influence the stereochemistry of the hydrogenations by virtue of its ability to bond with the surface and thus produce an "anchor effect." Alkal. metal–ethanol and metal hydride reductions of these ketones give a predominance of the equatorial hydroxyl epimer in all cases.

The addition of hydrogen to a cyclic ketone is capable of providing a convenient method of stereoselective synthesis. It also provides a direct insight into the stereochemistry and mechanism governing the attack of the carbonyl group by various reducing agents. The structural elucidation of the 1-, 2-, and 3-hydroxyquinolizidine racemates (I)[2] has permitted a systematic stereochemical study of the chemical and catalytic reduction of the corresponding ketones.

The general theory of the stereochemistry of catalytic hydrogenation has been summarized by Burwell.[3] In an extended series of investigations,[4] each of the four possible decalone racemates has been reduced catalytically on platinum and by chemical methods. The stereochemical data for the chemical reduction



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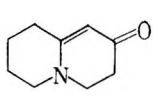


II

of various substituted cyclohexanones has recently been reviewed.[5]

The basic purpose of this research was to determine the extent by which the stereoselectivity of the addition of hydrogen to an azabicyclic ketone would vary as a function of substrate, reducing agent, catalyst, conditions, *etc.* In several previous investigations of this general type, appreciable confusion has arisen in the determination of the relative amounts of stereoisomers resulting from the reduction *per se*. The recent development of gas–liquid chromatography (g.l.c.) has provided a most convenient and reliable method for the analysis of reduction mixtures.[6]

(1) Presented in part at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964).

(3) R. L. Burwell, *Chem. Rev.*, **57**, 895 (1957).

(4) (a) W. Hückel, *Nachr. Ges. Wiss. Göttingen Jahresber. Geschaftsjahr Math. physik. Kl. Fachgruppe: I*, 43 (1923); (b) W. Hückel, *Ann.*, **441**, 1 (1925); (c) W. Hückel, *ibid.*, **451**, 109 (1927); (d) W. Hückel, *ibid.*, **533**, 1 (1938); (e) W. Hückel and G. Stelzer, *Chem. Ber.*, **88**, 984 (1955); (f) W. Hückel, D. Maucher, O. Fechtig, J. Kurz, M. Heinzel, and A. Hubele, *Ann.*, **645**, 115 (1961).

(5) A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron*, **18**, 705 (1962).

(6) S. Siegel and B. Dmuchovsky, *J. Am. Chem. Soc.*, **84**, 3132 (1962); W. C. Dauben and R. E. Bozak, *J. Org. Chem.*, **24**, 1596 (1959); H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *ibid.*, **28**, 2407 (1963).

TABLE I

COMPOSITION OF MIXTURES RESULTING FROM CATALYTIC HYDROGENATIONS OF KETOQUINOLIZIDINES

Quinolizidine hydrogenated	Catalyst	Medium	Products, %[a]			Hydrogenation, %
			Racemate A	Racemate B	Quinolizidine	
1-Keto	PtO_2	EtOH	33	67	0	100
1-Keto	PtO_2	Aqueous HCl	55	40	5	100
1-Keto	5% Rh–C	EtOH	26	74	0	100
1-Keto	5% Rh–C	Aqueous HCl	43	57	0	100
1-Keto	5% Ru–C	EtOH	71	29	0	100
1-Keto	5% Ru–C	Aqueous HCl	81	19	0	20–75
1-Keto	10% Pd–C	EtOH	7	93	0	100
1-Keto	10% Pd–C	Aqueous HCl	68	32	0	47
2-Keto	PtO_2	EtOH	26	74	0	98
2-Keto	PtO_2	Aqueous HCl	3	78	19	100
2-Keto	5% Rh–C	EtOH	15	85	0	100
2-Keto	5% Rh–C	Aqueous HCl	36	62	2	100
2-Keto	5% Ru–C	EtOH	40	60	0	100
2-Keto	5% Ru–C	Aqueous HCl	33	67	0	100
2-Keto	10% Pd–C	EtOH	5	95	0	20
2-Keto	10% Pd–C	Aqueous HCl	26	74	0	10–65
3-Keto	PtO_2	EtOH	29	71	0	100
3-Keto	PtO_2	Aqueous HCl	33	33	34	100
3-Keto	5% Rh–C	EtOH	19	81	0	100
3-Keto	5% Rh–C	Aqueous HCl	73	6	21	100
3-Keto	5% Ru–C	EtOH	72	28	0	100
3-Keto	5% Ru–C	Aqueous HCl	86	14	0	83–100
3-Keto	10% Pd–C	EtOH	3	97	0	100
3-Keto	10% Pd–C	Aqueous HCl	82	18	0	32–90
$\Delta^{1,10}$-2-Keto	PtO_2	EtOH	29	67	4	100
$\Delta^{1,10}$-2-Keto	PtO_2	Aqueous HCl	2	98	0	100
$\Delta^{1,10}$-2-Keto	5% Ru–C	EtOH	13	87	0	100

[a] See ref. 2 for structural assignments of the hydroxyquinolizidines.

Results

Table I summarizes the products obtained from the catalytic hydrogenations of 1-, 2-, and 3-ketoquinolizidine in both ethanol and aqueous HCl. In the 1- and 3-hydroxyquinolizidines, racemate A has the *cis*-1,10- and *cis*-3,10-hydrogen configurations, respectively; racemate B of the 2-hydroxyquinolizidines has the *cis*-2,10-hydrogen configuration. In each case, the A and B racemates are axial and equatorial alcohols, respectively. Preparative scale reductions using smaller catalyst–substrate ratios gave A–B ratios in reasonable accord with the results listed in Table I. For example, the hydrogenation of 3-ketoquinolizidine on 5% ruthenium on carbon in ethanol gave an A–B ratio of 76:24 and on 10% palladium on carbon in ethanol a ratio of 3:97. The hydrogenation of $\Delta^{1,10}$-2-ketoquinolizidine (II) gave only the 2-hydroxyquinolizidine racemates and quinolizidine as products.

For the acidic hydrogenations, no distinct correlation of racemate ratios appears to exist as one proceeds from catalyst to catalyst with each of the three ketones. The ethanolic hydrogenations, however, clearly reveal that on the four catalysts the percentage of the axial hydroxyl epimer always decreases in the order Ru > PtO_2 > Rh > Pd. On each of the four catalysts in ethanol, the hydrogenations of 1- and 3-ketoquinolizidine give results which are quite similar quantitatively.

Since it is known that cyclic alcohols may undergo epimerization on a metal catalyst,[7] attempts were made to isomerize a mixture of the 2-hydroxyquinolizidines (A–B = 47:53) over each of the metal catalysts used in this study. Isomerizations were tried in both ethanol and aqueous HCl (pH 1–2) using the same procedures and methods of work-up as were used in the ketone hydrogenations. In all cases, the composition of the 2-hydroxyquinolizidine mixture remained the same within experimental error. It may thus be concluded that once the amino alcohol has been desorbed from the active surface, it cannot undergo subsequent isomerization. Hence, the relative amounts of amino alcohols obtained from the ketoquinolizidine hydrogenations are the result of the original reduction process on the catalyst.

The relative amounts of hydroxyquinolizidine racemates resulting from chemical reductions of the corresponding ketones are given in Table II. With each ketone, the relative proportions of amino alcohol

TABLE II

COMPOSITION OF MIXTURES RESULTING FROM CHEMICAL REDUCTIONS OF KETOQUINOLIZIDINES

Quinolizidine reduced	Reducing agent	% racemate, A–B[a]
1-Keto	Na, EtOH	18:72
1-Keto	K, EtOH	17:83
1-Keto	$LiAlH_4$	16:84
1-Keto	$NaBH_4$	17:83
2-Keto	Na, EtOH	10:87
2-Keto	K, EtOH	4:90
2-Keto	$LiAlH_4$	11:89
2-Keto	$NaBH_4$	10:90
3-Keto	Na, EtOH	16:81
3-Keto	K, EtOH	19:69
3-Keto	$LiAlH_4$	16:84
3-Keto	$NaBH_4$	12:88

[a] See ref. 2 for structural assignments of racemates. In those reductions in which the sum of A and B does not equal 100, the remainder of the products consisted of minor g.l.c. peaks which were not identified.

(7) R. J. Wicker, *J. Chem. Soc.*, 2165 (1956).

racemates resulting from all of the chemical reducing agents are very similar, with the equatorial epimer always predominating.

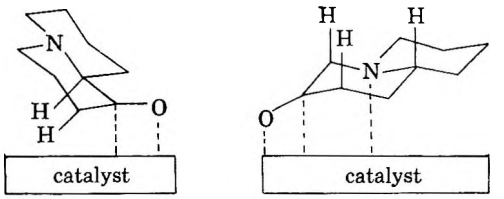
Discussion

Catalytic Hydrogenations.—The great variation of racemate ratios resulting from the ketoquinolizidine hydrogenations clearly reveals the extent to which the stereochemistry of a given catalytic hydrogenation can vary as a function of catalyst and medium. Any explanation of these stereochemical results should be based upon the influence which solvent and catalyst can exert upon the different modes of adsorption of the carbonyl group on the active spots of the catalyst. With the practical catalysts used in this work, the nature and structure of these active spots is presently so poorly understood[8] that any valid interpretation of the experimental data must be related to the structure of the substrate rather than that of the active catalyst. It is logical to assume[9] that the carbonyl group will preferentially be adsorbed so as to minimize the steric interaction between the surface and the remainder of the molecule. The hydrogen will then be added from the catalyst side of the functional group.[10] The relative amounts of amino alcohol racemates thus obtained from the catalytic hydrogenations should be determined by the relative ease of the two modes of adsorption of the carbonyl group on the active surface. Since all of these hydrogenations were carried out at room temperature, it is reasonable to conclude that the hydrogenations are proceeding through the keto rather than the enol form.[11]

The preceding paper in this series[2] has discussed the stereochemistry of the quinolizidine ring system. Due to the possibility of an equilibrium between *cis* and *trans* ring fusions, any attempt to correlate the stereochemistry of the ketoquinolizidine hydrogenations with the various possible conformations of the respective ketones is, at best, difficult. If it may be assumed that each of the three ketones is preferentially adsorbed as a *trans* ring-fusion conformer,[12] one is led to some interesting conclusions. The increased amount of the axial hydroxyl epimer as one proceeds from Pd to Rh to PtO_2 to Ru in each set of ethanolic hydrogenations indicates that the ease of equatorial addition of hydrogen increases in the same order. This, in turn, should reflect the ease, relative to other possible conformers, with which the *all-chair trans* ring-fusion conformer is adsorbed on the catalyst surfaces within this series. III depicts the preferred mode of adsorption of the all-chair *trans* ring-fusion conformer of 1-ketoquinolizidine. Thus for each ketone the ease of adsorption of this conformer in ethanol appears to decrease in the order, Ru > PtO_2 > Rh > Pd.

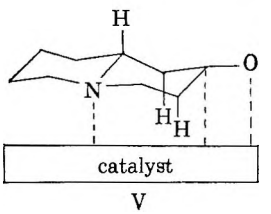
The hydrogenations of 1- and 3-ketoquinolizidine reveal that on each catalyst the proportion of the equatorial hydroxyl epimer is increased when the solvent is changed from aqueous HCl to ethanol. Assuming again a *trans* ring fusion, it is seen that the presence of the unshared pair of electrons on the bridgehead nitrogen appears to induce more addition of hydrogen from their side of the ring system. This leads to the postulation that the nitrogen may be forming a dative bond with the surface, thus producing an "anchor effect" which will favor the addition of hydrogen from the side opposite the C-10 bridgehead hydrogen. The operation of the anchor effect in 3-ketoquinolizidine is depicted by IV. The extent to which the anchor effect will influence the stereochemistry of the hydrogenation should be determined by the availability of a catalyst site at an appropriate distance (approximately 2.4 Å.) from the site activating the carbonyl carbon. It is well known that, in general, compounds with an unshared pair of electrons on nitrogen are more readily hydrogenated in acid than in basic solution. This may be ascribed to the ability of the unshared nitrogen electrons to bond with the active surface and thus poison it.[13] The amino nitrogen has been shown[14] to be capable of catalyst poisoning only when it has an unshared pair of electrons and is thus "unshielded."

For 2-ketoquinolizidine, the anchor effect (V) predicts an increasing amount of the axial hydroxyl epimer as one proceeds from the protonated to the free amino ketone. This prediction is followed on platinum oxide



III

IV



V

and ruthenium but not on palladium and rhodium. The explanation for the apparently anomalous behavior on the last two catalysts could lie in the fact that in 2-ketoquinolizidine the carbonyl group is farthest from the nitrogen, and the operation of the anchor effect which requires the simultaneous adsorption of both functional moieties must overcome the steric hindrance imposed by the axial hydrogens at C-1 and C-3 (V).

(8) G. C. Bond, "Catalysis by Metals," Academic Press, New York N. Y., 1962, Chapter 3.

(9) S. Siegel, *J. Am. Chem. Soc.*, **75**, 1317 (1953).

(10) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *ibid.*, **64**, 1985 (1942). An alternative mechanism for the hydrogenation of ketones [J. H. Brewster, *ibid.*, **76**, 6361 (1954)], which proposes the addition of a hydride ion from the catalyst and a proton from the solvent, is less compatible with the wealth of existing catalytic and physicochemical knowledge concerning hydrogenation than is that of a mechanism involving chemisorption of the carbonyl group and addition of both hydrogens from the catalyst.

(11) Ref. 8, p. 335; L. C. Anderson and N. W. MacNaughton, *J. Am. Chem. Soc.*, **64**, 1456 (1942).

(12) The *trans* ring fusion has been shown to be greatly preferred by the 1-, 2-, and 3-methyl- and 1-, 2-, and 3-hydroxyquinolizidines (*cf.* preceding paper in this series and references contained therein). Analogy with the well-known decalin ring system also predicts a prevalence of the *trans* ring fusion in the ketoquinolizidines. The recent report of S. F. Mason, K. Schofield, and R. J. Wells, [*Proc. Chem. Soc.*, 337 (1963)] tends to confirm this assumption.

(13) In the case of platinum oxide, the decreased activity in nonacidic media has been ascribed to the presence of small amounts of alkali in the catalyst see, C. W. Keenan, B. W. Giesemann, and H. A. Smith, *J. Am. Chem. Soc.*, **76**, 229 (1954). This, however, should not impair the ability of the free amino nitrogen to bond with the active catalyst surface.

(14) E. B. Maxted, "Advances in Catalysis," Vol. III, Academic Press, New York, N. Y., 1951, p. 136.

This type of hindrance does not occur in the adsorption of 1- and 3-ketoquinolizidine since there will be no axial hydrogens between the carbonyl group and the bridgehead nitrogen on the catalyst side of the ring system. As indicated above, the all-chair *trans* ring-fusion conformer appears to be less readily adsorbed on palladium and rhodium than on platinum oxide and ruthenium. The relative ease of adsorption of this conformer, therefore, should reflect the susceptibility of the catalyst surface toward steric hindrance offered by axial hydrogens.

The small but appreciable quantity of quinolizidine resulting from the hydrogenations on PtO_2 in acid agrees with evaporated film studies[15] which have shown platinum to be the most active transition metal in ketone hydrogenolysis. It is interesting that no hydrogenolysis was observed for the reductions of the saturated ketones on PtO_2 in ethanol.

The hydrogenations of $\Delta^{1,10}$-2-ketoquinolizidine (II) on platinum suggest that the α,β-unsaturated ketone is first reduced at the carbon–carbon double bond, desorbed from the catalyst, readsorbed, and then reduced at the carbonyl group. Corroboration for this comes from recent work[16] which has revealed the analogous $\Delta^{1,9}$-octalone-2 to be hydrogenated on platinum oxide to a mixture of the 2-decalones. On ruthenium, however, it appears that most of the hydrogen is added to II during one period of adsorption on the catalyst, since all-*cis* addition will give the equatorial hydroxyl epimer. These results demonstrate that the assumption of all-*cis* catalytic addition of hydrogen to polyunsaturated compounds should be used with care.

Chemical Reductions.—The alkali metal–alcohol reductions all follow Barton's rule[17] in that the more stable equatorial epimer is the principal product. Such reductions of cyclic ketones are generally conceded to give an equilibrium mixture of epimeric alcohols provided the reduction conditions, especially temperature,[18] are properly maintained. Thus the alkali metal–ethanol reductions of the ketoquinolizidines are subject to thermodynamic control.

The results of this study parallel those of sodium–ethanol and sodium–2-butanol reductions of tropinone[19] which were found to give epimeric ratios of tropine and pseudotropine closely approximating that of the equilibrium composition. It should be pointed out that the epimeric mixtures obtained from the ketoquinolizidine reductions do not reflect the relative stability of the amino alcohols themselves but rather that of their alkoxide ions in equilibrium with a large excess of ethoxide ion in benzene–ethanol solution. Equilibrations of the *cis*-2-decalols in decalin have shown[20] the equilibrium ratio of the alcohols to be significantly different from that of the corresponding alkoxides. The same may well be true for the hydroxyquinolizidines.

(15) C. T. H. Stoddard and C. Kemball, *J. Colloid Sci.*, **11**, 532 (1956); C. Kemball and C. T. H. Stoddard, *Proc. Roy. Soc.* (London), **A246**, 521 (1958).

(16) R. L. Augustine, *J. Org. Chem.*, **28**, 152 (1963). In our work, no attempt was made to stop the hydrogenation at the dihydro stage and identify a reduction intermediate.

(17) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(18) K. D. Hardy and R. H. Wicker, *J. Am. Chem. Soc.*, **80**, 640 (1958).

(19) A. H. Beckett, H. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).

(20) O. R. Rodig and L. C. Ellis, *J. Org. Chem.*, **26** 2197 (1961).

The exact nature of the species by which hydrogen is added to the carbonyl carbon in alkali metal–alcohol reductions is unknown. Hückel[21] has suggested that the electrons are first added to the carbonyl group followed by the addition of hydrogen as protons. Whatever the nature of the species, it must be reasonably small in size since, as the ketoquinolizidines and other cyclic ketones have shown, these reductions have very little susceptibility to steric crowding around the trigonal carbon.

The rather close correspondence between the stereochemical results of the alkali metal–ethanol and the metal hydride reductions suggests that the latter may also be directed by thermodynamic control. Such, however, is not the case. It has been shown that epimeric mixtures of tropine–pseudotropine[19] and the 2-methylcyclopentanols[22] are not isomerized under actual reduction conditions. The metal hydride reductions of the ketoquinolizidines thus are apparently not directed by true thermodynamic control. These reductions are subject to product development control[23] since the relative stability of the epimeric alcohols appears to dictate the ratio in which they are obtained. This control is due to the relative stability of the transition states leading to the two epimers paralleling that of the epimers themselves. This indicates that the energy maximum lies at a position on the reaction coordinate such that the transition state partakes of much of the character of the product.

Since product development control will govern the stereochemistry of metal hydride reductions only in the absence of appreciable crowding around the carbonyl carbon, it may be concluded that the approach of the incipient hydride ion to this carbon of the ketoquinolizidines is relatively unhindered. A further conclusion is that the size of the species attacking the carbonyl group is of no consequence in determining the stereochemistry of the ketoquinolizidine reductions.

Experimental

Ketoquinolizidines.—The syntheses of 1-, 2-, and 3-ketoquinolizidine were the same as previously reported.[2] The amino ketones were isolated by vacuum distillation in purity greater than 99.5% as shown by gas–liquid chromatographic analysis. Since these compounds deteriorate and darken upon exposure to air, they were stored in 5-ml. serum bottles under nitrogen at −10°. The serum bottles were fitted with rubber caps through which samples could be drawn with a syringe. $\Delta^{1,10}$-2-Ketoquinolizidine was prepared according to the published procedure.[24] The amino ketone (m.p. 80–81°) was recrystallized from ether and gave an ultraviolet spectrum which coincided with that of the previous report.

Hydrogenation Catalysts.—Commercial catalysts were used in all catalytic hydrogenations. Platinum oxide catalyst was obtained from J. Bishop and Co. Platinum Works, Malvern, Pa. The 10% palladium-on-carbon catalyst was procured from A. D. Mackay, Inc., New York, N. Y., whereas, the 5% ruthenium-on-carbon and the 5% rhodium-on-carbon catalysts were supplied by Englehard Industries, Newark, N. J. All catalysts were stored in tightly closed bottles and used as received.

Catalytic Hydrogenations in Ethanol.—In 5.0 ml. of absolute ethanol was dissolved 0.12–0.15 ml. of the desired ketone.

(21) W. Hückel, M. Maier, E. Jordan, and W. Seeger, *Ann.*, **616**, 58 (1958).

(22) J. B. Umland and M. I. Jefriam, *J. Am. Chem. Soc.*, **78**, 2788 (1956).

(23) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *ibid.*, **78**, 2579 (1956).

(24) F. Bohlmann, E. Winterfeldt, O. Schmidt, and W. Reusche, *Chem. Ber.*, **94** 1774 (1961).

The catalyst (50–100 mg.) was added and the reduction was carried out in a Parr low-pressure hydrogenation apparatus, the total volume of which had been reduced to 545 ml. All hydrogenations were carried out for 30–120 min. at room temperature and 50–60 p.s.i.g. hydrogen pressure. Samples of the filtered reduction mixture were evaporated under a stream of nitrogen to approximately one-tenth their original volume and analyzed by gas–liquid chromatography.

Catalytic Hydrogenations in Aqueous HCl.—The catalyst (50–100 mg.) was added to a solution of the ketone (0.12–0.15 ml.) in 5 ml. of 0.2 *N* hydrochloric acid giving a pH of 1–2. The hydrogenation was carried out using the apparatus and conditions described for the ethanolic hydrogenations. Dilute sodium hydroxide (10%) was added to the filtered reduction mixture until the pH rose to 13. The alkaline solution was extracted with four 10-ml. aliquots of chloroform. From the combined chloroform aliquots approximately 90% of the solvent was removed by distillation through a small Vigreux column. The remaining solution was then concentrated with a stream of nitrogen and analyzed by gas–liquid chromatography.

Alkali Metal–Ethanol Reductions.—In 3 ml. of anhydrous reagent grade benzene was placed the metal (0.6 g. of sodium or 0.9 g. of potassium). To this was added dropwise a solution of 0.12–0.15 ml. of the ketone in 2.0 ml. absolute ethanol. After 2 hr. of reflux, distilled water (5 ml.) was added to the mixture. The aqueous phase was extracted with two 5-ml. aliquots of benzene to quantitatively remove the amino alcohols. The benzene aliquots were combined, concentrated, and analyzed by gas–liquid chromatography.

Sodium Borohydride Reductions.—The ketone (0.12–0.15 ml.) was added dropwise to a solution of sodium borohydride (0.10 g.) in distilled water (5.0 ml.). The mixture was permitted to stand overnight. Concentrated ammonium hydroxide (1.0 ml.) was added and the mixture was allowed to stand for an additional 1–2 hr. The solution was saturated with sodium chloride and extracted with five 10-ml. aliquots of benzene to remove quantitatively the mixture of amino alcohols. The benzene aliquots were combined, concentrated, and then analyzed by g.l.c.

Lithium Aluminum Hydride Reductions.—To 0.10 g. of lithium aluminum hydride in 5.0 ml. of anhydrous ether in an ice bath was added dropwise 0.12–0.15 ml. of ketone; the mixture was warmed to room temperature. Thirty minutes later 0.25 ml. of distilled water was added followed by 0.20 ml. of sodium hydroxide (10%). After standing overnight, the ethereal solution was decanted, filtered, and then analyzed by g.l.c.

Gas–Liquid Chromatographic Analysis.—All g.l.c. analyses were carried out with a 10 ft. × 0.25 in. column of Carbowax 20 M (15%) on Gas-Chrom P support.[2] Column temperatures of 208–212° and helium flow rates of 120–150 ml./min. were used. Symmetrical peaks were obtained with a minimum of tailing. Peaks corresponding to the epimeric racemates, parent ketone, and quinolizidine were identified by infrared and g.l.c. comparison with known samples of each. In the catalytic and metal hydride reductions, no other products resulted. Preparative scale catalytic reductions gave yields which were essentially quantitative. Some of the alkali metal–alcohol reductions gave small but appreciable proportions (3–12%) of foreign products which were not identified.

Quantitative determinations of the relative amounts of amino alcohols were made by measuring their relative peak areas on the gas–liquid chromatograms. These measurements were normally made with a disk integrator. Check measurements made by cutting out the peaks and weighing them on an analytical balance or by taking the product of the peak height (h) times the peak width at $h/2$ gave results which were identical with those of the disk integrator within 2%. The detector response of the Aerograph A-90-P apparatus used for all analyses was shown to be the same for racemates A and B of each set of amino alcohols. This was accomplished by analyzing mixtures containing known amounts of pure A and pure B.

In order to demonstrate that the work-up procedures used for the various reductions did not alter the relative amounts of racemates resulting from the reductions themselves, mixtures containing known amounts of quinolizidine and each of the 3-hydroxyquinolizidines were subjected to each of the work-up procedures and then analyzed by g.l.c. In all cases the relative amounts of the constituents were not altered by the work-up to an extent greater than 2%. Since the ratio of 3-hydroxyquinolizidines is more susceptible to alteration during work-up than either of the other sets of amino alcohol racemates,[25] it may be concluded that the methods of work-up of the other reduction mixtures have not altered the epimeric ratios by any significant amount.

The A–B racemate ratios from the various chemical and catalytic reductions were found to be reproducible within ±3%, which is the approximate limit of the error resulting from the work-up procedures and the g.l.c. analyses. This is the same limit of experimental error as has resulted[19] from infrared analyses of tropine–pseudotropine reduction mixtures.

(25) Preliminary experiments using a different work-up procedure revealed the difference in volatility to be the greatest potential source of A–B alteration during the work-ups. This difference is greatest for the 3-hydroxyquinolizidines.

Michael Additions of Nitroform. III. The C_9 Precursor, Potassium Methyl 4,4-Dinitro-2-hydroxybutyrate

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From the examination of the changes in the ultraviolet spectra with time of the nitroform–methyl acrylate system and methyl 4,4,4-trinitrobutyrate decomposition in aqueous dioxane (pH ≈5), it was shown that potassium methyl 4,4-dinitro-2-hydroxybutyrate is the precursor of dimethyl 4,4-dinitro-2-hydroxypimelate (C_9). The only path for the formation of potassium methyl 4,4-dinitro-2-butenoate was found to be the elimination of the elements of nitrous acid from methyl 4,4,4-trinitrobutyrate. The isolation and characterization of potassium methyl 4,4-dinitro-2-hydroxybutyrate and the potassium salt of 5,5-dinitro-3-hydroxypentan-2-one, the methyl vinyl ketone analog, are described. With acrylonitrile as the augend, spectral evidence for the presence in solution of the potassium salt of 3,3-dinitropropionaldehyde was obtained.

The addition of nitroform (pK ≈0)[1] to methyl acrylate in moderately to strongly acidic aqueous solutions was found to give excellent yields of methyl 4,4,4-trinitrobutyrate (MeTNB). The first evidence of competing side reactions was found in a study of the effect of pH upon the yield of MeTNB.[2] In a methanol–water system at pH 1 to ≈3.5, the yield of MeTNB varied between 80 and 90%. On increasing the pH to ≈4.2, the yield of MeTNB fell sharply to 65%. Another sharp decrease in yield occurred on increasing the pH to ≈5, where the yield of MeTNB obtained was only 21%. Under the low yield conditions, it was not possible to recover substantial quantities of unreacted nitroform. This indicated that the low yields were not caused by a pH-dependent equilibrium reaction.

(1) S. S. Novikov, V. I. Slovetski, S. A. Shevelev, and A. A. Fainzil'berg, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 598 (1956).

(2) Private communication, M. E. Hill of these laboratories.

This observation remained untouched until a kinetic investigation of the addition of nitroform to methyl acrylate was undertaken. Lack of constancy of the specific rate constants throughout a given run, determined by the rate of formation of MeTNB in an acetate buffer, once again suggested the presence of competing reactions. The kinetic experiments were abandoned in favor of synthetic studies.

When the reaction of equimolar quantities of nitroform and sodium acetate with a 200% molar excess of methyl acrylate was carried out in 33% aqueous methanol, the expected adduct MeTNB was isolated in 56.5% yield. In addition, there was obtained a 24.7% yield of a denitrosation product, dimethyl 4,4-dinitro-2-hydroxypimelate (C_9).[3]

$$HC(NO_2)_3 + CH_2{=}CHCO_2CH_3 \xrightarrow[MeOH\text{-}H_2O]{OAc^-} C(NO_2)_3CH_2CH_2CO_2CH_3 + C(NO_2)_2(CH_2CH_2CO_2CH_3)(CH_2CHOHCO_2CH_3)$$

MeTNB; C_9

Under somewhat more alkaline conditions, potassium trinitromethide and methyl acrylate in 50% methanol yielded a third product, potassium methyl 4,4-dinitro-2-butenoate (DNU). The results are summarized by the following equation.

$$K^+{}^-C(NO_2)_3 + CH_2{=}CHCO_2CH_3 \xrightarrow[H_2O]{MeOH} MeTNB\ (10.9\%) + C_9\ (31.1\%) + K^+{}^-C(NO_2)_2CH{=}CHCO_2CH_3$$

DNU (34.5%)

The isolation of the unsaturated ester, DNU, at first suggested that it could be the precursor of C_9 by undergoing hydration to the α-hydroxydinitro ester[4] which would add to another mole of methyl acrylate to yield C_9. However, the ester DNU was found to be unreactive under the reaction conditions. In addition, the ester DNU did not add to methyl acrylate under Michael conditions to yield dimethyl 4,4-dinitro-2-heptenedioate. This ruled out the possibility that this diester could be the precursor of C_9 by adding the elements of water to its double bond.

The first evidence for a logical precursor for C_9 came from the reaction of acrylamide with potassium trinitromethide in "absolute" methanol. Under these conditions, the potassium salt of 4,4-dinitro-2-hydroxybutyramide was obtained.[5] Unlike the ester DNU, this saturated amide readily added to methyl acrylate under Michael conditions to yield the C_9 analog, 6-carbomethoxy-4,4-dinitro-2-hydroxyhexanamide.

Attempts to prepare the potassium salt of methyl 4,4-dinitro-2-hydroxybutyrate (DNS) by this procedure gave a 50% yield of the unsaturated ester DNU together with a 23% yield of MeTNB and only a 4.4% yield of C_9. Therefore, it appeared that the α-hydroxydinitro ester DNS was the precursor of C_9, but under a variety of reaction conditions it successfully evaded capture and seemed to be a rather reactive intermediate.

Spectrophotometric Studies.—From the above results, it seemed that the best approach to follow for the detection of the C_9 precursor DNS was to study the changes in the total ultraviolet spectrum of the reaction of nitroform with methyl acrylate. Based upon previous synthetic results,[3,5] a 1:1 acetic acid–acetate buffer system in 50 vol. % dioxane was selected as the reaction medium.

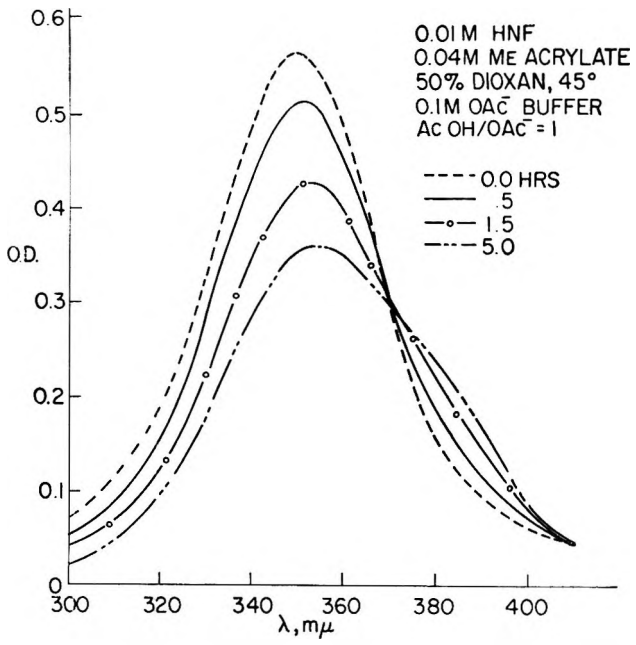


Fig. 1.—Spectral changes *vs.* time for 0.01 *M* HNF, 0.04 *M* methyl acrylate, 0.1 *M* OAc^-, AcOH–OAc^- (1:1), 50% dioxane at 45°: ----, 0.0 hr.; ———, 0.5 hr.; —O—, 1.5 hr.; —·—·—, 5.0 hr.

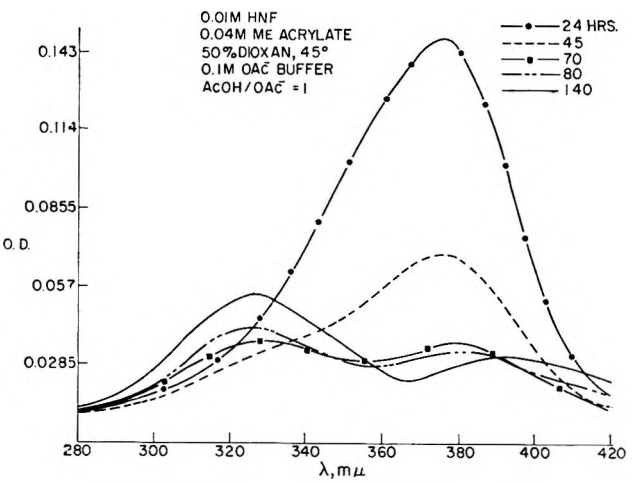


Fig. 2.—Spectra changes *vs.* time, reactants as in Fig. 1.: —●—, 24 hr.; ----, 45 hr.; —■—, 70 hr.; —·—·—, 80 hr.; ———, 140 hr.

Figures 1 and 2 give the total spectrum of the nitroform–methyl acrylate system at various times. Inspection of the spectra in Fig. 1 shows that as the reaction progresses the absorption maximum at 350 mμ for nitroform[6] decreases. Although this was expected, the increased absorption on the long wave-length side of the maximum, coupled with the shift of this absorption maximum to longer wave lengths with time, indicated that a new polynitro anion was being formed. The regular decrease in the absorption with time on the short wave-length side of the absorption maximum was taken as evidence for the fact that this new polynitro

(3) L. A. Kaplan and M. J. Kamlet, *J. Org. Chem.*, **27**, 780 (1962).

(4) This possibility was thought to be extremely remote since the unsaturated ester DNU would be expected to yield the β-hydroxy derivative.

(5) M. J. Kamlet and L. A. Kaplan, *J. Org. Chem.*, **28**, 2128 (1963).

(6) J. Hine and L. A. Kaplan, *J. Am. Chem. Soc.*, **82**, 2915 (1960).

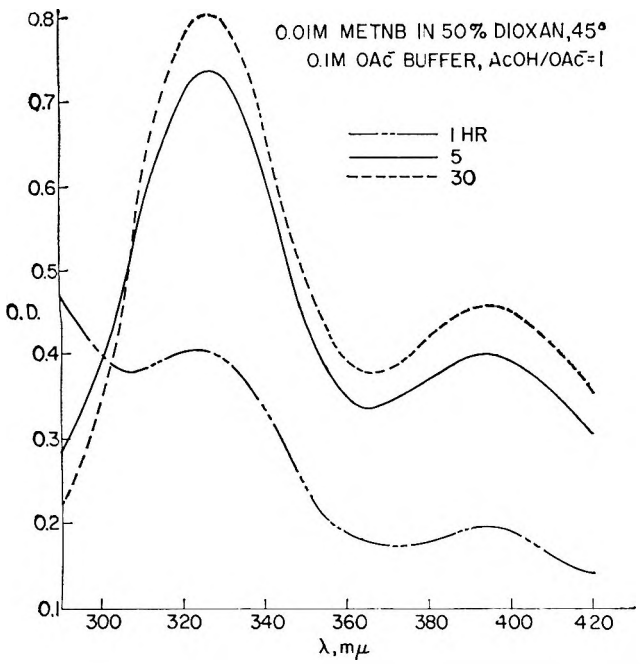


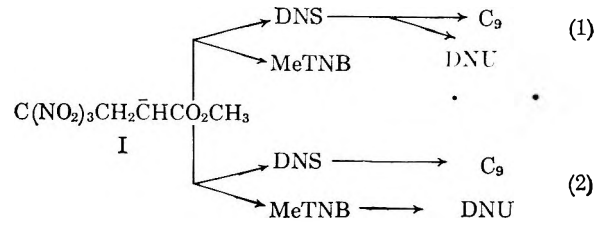
Fig. 3.—Spectral changes *vs.* time for 0.01 *M* MeTNB, 0.1 *M* OAc^-, AcOH–OAc^- (1:1), 50% dioxane at 45°: ——, 1 hr.; ——, 5 hr.; – – – –, 30 hr.

anion was *not* the unsaturated ester DNU, as this anion has twin maxima: $\lambda_{max}^{dil\ KOH}$ 326 mμ (log ε 4.24), 396–402 (3.98).[5] The observed spectrum shift is best correlated with the presence of the heretofore undetected precursor of C_9, potassium methyl 4,4-dinitro-2-hydroxybutyrate (DNS). This polynitro anion would be expected to have an absorption maximum at about 380 mμ.[7]

Allowing the reaction to proceed further (Fig. 2) shows that at the end of 24 hr. the original nitroform maximum at 350 mμ has not only shifted out to 380 mμ, but it has also undergone a considerable decrease in intensity.[8] This is consistent with the DNS reacting further with methyl acrylate to yield C_9. The appearance of a slight inflection at ≈330 mμ in this spectrum is indicative of the formation of the unsaturated ester DNU (*vide supra*). After 45 hr., both the decrease in the absorption of the 380-mμ maximum and the increased absorption of the inflection at ≈330 mμ are more pronounced.

The remaining spectra in Fig. 2 show that, with increasing time, the inflection at ≈330 mμ increases in intensity and becomes a true absorption maximum at ≈325 mμ and, as the 380-mμ absorption maximum disappears, a new long wave-length band at ≈400 mμ takes its place. This observation is consistent with the slow formation of the unsaturated ester DNU.

By analogy with the nitroform–β-nitrostyrene system,[5] the anion I would be formed by the addition of trinitromethide ion to methyl acrylate. On the basis of the above spectral data, two schematic paths seemed reasonable (eq. 1 and 2).



Inspection of the two paths shows that, in path 1, DNS is the common precursor for C_9 and DNU and, under the reaction conditions, the normal Michael adduct MeTNB is stable. Path 2 predicts that the adduct MeTNB is not stable under the reaction conditions, and that its decomposition is responsible for the formation of DNU. It should be noted that there was no evidence of reversal of the adduct MeTNB to trinitromethide ion found in the spectra of the forward reaction[9] compared with the nitroform–β-nitrostyrene system where the adduct is quantitatively converted to trinitromethide ion and β-nitrostyrene in a pyridine–pyridinium ion buffer system.[6]

It appeared that it would be relatively simple to differentiate between the two possible paths by measuring the spectral changes with time of a MeTNB solution under the identical reaction conditions. Fig. 3 shows that, after 1 hr., this spectrum is vastly different from that of the forward reaction (Fig. 1) in that it exhibits absorption maxima at ≈323 and 400 mμ,[10] but no inflections at 350 and/or 380 mμ.[9]

After 5 hr., the spectrum (Fig. 3) exhibits the typical twin maxima of DNU at ≈323 and ≈395–400 mμ. The ratio, $O.D._{325}/O.D._{390}$ was found to be 1.79. For an authentic sample of DNU, this ratio equals 1.85. A comparison of the spectrum after 30 hr. with that of the forward reaction after 24 hr., Fig. 2, showed the complete absence of the 380-mμ absorption maximum due to DNS in the reverse reaction. Allowing this reaction to proceed for a period of better than 100 hr. produced no change in the shape of the spectral envelope. The decomposition of MeTNB under these conditions, therefore, gives essentially quantitative yields of the unsaturated ester DNU.

The almost complete absence of DNU in the forward reaction until 24 to 45 hr. and the absence of DNS in the reverse reaction suggest that DNS is not the precursor of DNU. It will be shown that the reaction of DNS with methyl acrylate under these conditions yields C_9 as the sole product. The spectrum of this reaction at various times showed no evidence of DNU formation (*vide infra*). This observation, together with the one that MeTNB is essentially quantitatively decomposed to DNU under these conditions, made path 2 the best representation of the over-all reaction.

Synthetic Studies.—The above spectral data (Fig. 1 and 2) also suggest that the α-hydroxydinitro ester

(7) For the corresponding amide, $\lambda_{max}^{dil\ KOH}$ 380 mμ (log ε 4.22).[5] See too, M. J. Kamlet and D. J. Glover, *J. Org. Chem.*, **27**, 537 (1962).

(8) All spectra in Fig. 1 and 2 are converted to equivalent dilutions so that the relative concentrations of the intermediates and products at various time intervals may be compared.

(9) Work now in progress on the effect of substituents on the course of the reverse reaction indicates that there is some reversal of MeTNB to nitroform[6] and possibly DNS under these conditions. These reaction paths represent about 5% of the total reaction under these conditions. The significance of this result will be reported in a future communication.

(10) The spectra in Fig. 3 have *not* been normalized to account for dilutions of the reaction mixture, and the relative concentrations at the various times can *not* be compared. The spectrum measured after 1 hr. is that of the undiluted reaction mixture, 0.01 *M* MeTNB. Calculations based on $O.D._{325}$ show that less than 0.2% of the MeTNB has reacted during this time interval. After 1.5 hr., 35% of the nitroform has reacted to form MeTNB and DNS (Fig. 1). The decomposition of the product MeTNB under these conditions is too slow to interfere with the spectrophotometric study of the addition of nitroform to methyl acrylate. The presence of end absorption in the 1-hr. spectrum (Fig. 3) is due to carbonyl and nitro group absorption as this solution is essentially 0.01 *M* in MeTNB.

DNS was present as a stable intermediate in moderate concentrations during the earlier stages of the forward reaction and should be able to be isolated from the reaction mixture. This hypothesis was tested by treating methyl acrylate with an excess of potassium trinitromethide in an aqueous dioxane solution containing 1 equiv. of potassium acetate. Under these conditions, the competing reactions, Michael addition of DNS to methyl acrylate to form C_9 and the protonation of the anion I to form MeTNB, would be minimized. The reaction was followed spectrophotometrically and when the ratio $O.D._{380}/O.D._{350}$ reached a maximum, the reaction was stopped. This point corresponded to a maximum yield of DNS.

After extraction with ether and removal of the unchanged potassium trinitromethide, a lemon yellow salt was obtained in 36% yield. The salt analyzed well for potassium methyl 4,4-dinitro-2-hydroxybutyrate (DNS) and had $\lambda_{max}^{dil\ KOH}$ 378 mμ (log ε 4.23).[7] In the infrared, the spectrum exhibited the expected absorption bands for the functionality present: 1730 for ester carbonyl,[11] 3250–3470 and 3540 for hydroxyl,[12] and 1167 and 1242 cm.$^{-1}$ for nitro groups in $-C(NO_2)_2-$.[13]

Spectrophotometric analysis of the mother liquors from the isolation of DNS did not indicate that any other polynitro anions [DNU or $C(NO_2)_3^-$] were present. Work-up of the ether extracts of the reaction mixture gave the expected by-products, MeTNB and C_9. The absence of DNU in the reaction products of this short-stopped reaction confirmed the conclusions reached in the preliminary spectral comparison experiments as to its mode of formation.

$$C(NO_2)_3^- + CH_2{=}CHCO_2CH_3 \xrightarrow[\text{aq. dioxane}]{OAc^-}$$
$$\text{MeTNB (12.6\%)} + C_9\text{ (23.2\%)} + \text{DNS (36\%)}$$

The preliminary spectroscopic and analytical evidence points to the fact that DNS was indeed the α-hydroxydinitro ester. This structural assignment was readily confirmed by treating DNS with methyl acrylate in an aqueous dioxane acetic acid–acetate buffer. The previously characterized C_9[3] was obtained in 78% yield. The lack of side reactions in this Michael addition was shown initially by the total ultraviolet spectrum of the reaction mixture determined at various times throughout the course of the reaction. These spectra, Fig. 4, show a regular decrease in the optical density at the absorption maximum which corresponds to the formation of C_9. Additionally, there is a regular decrease in the optical density on both sides of the absorption maximum, thus precluding the formation of such by-products as DNU or other polynitro anions in this reaction.

Other evidence for the singular path that this reaction takes came from kinetic measurements.[14] The specific rate constants calculated for several runs, followed to about 99% completion, exhibited no downward drift. This would not be the expected result if other polynitro anions were being produced in concurrent side reactions.

(11) R. N. Jones in "Chemical Applications of Spectroscopy in Techniques of Organic Chemistry," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956.

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 203, *et. seq.*

(13) L. A. Kaplan, *J. Org. Chem.*, **29**, 1638 (1964).

(14) The complete results will be reported in a future communication.

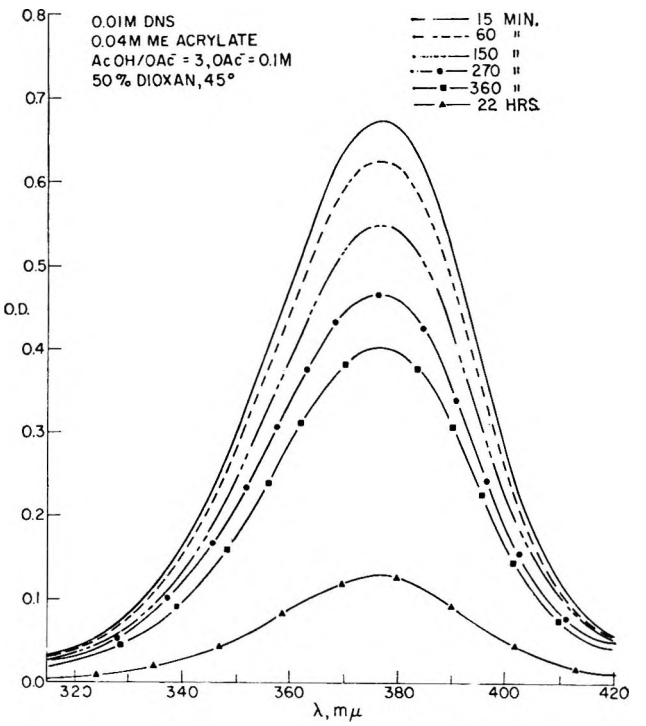


Fig. 4.—Spectral changes *vs.* time for 0.01 *M* DNS, 0.04 *M* methyl acrylate, 0.1 *M* OAc^-, AcOH–OAc^- (1:1), 50% dioxane at 45°: ———, 15 min.; – – – –, 60 min.; —·—·—, 150 min. —●—, 270 min.; —■—, 360 min.; —▲—, 22 hr.

The synthetic procedure for the preparation of DNS was extended to other acrylic systems to see if analogous α-hydroxydinitro derivatives could be isolated. Under similar conditions, the reaction of potassium trinitromethide with methyl vinyl ketone gave the expected product, 5,5-dinitro-3-hydroxypentan-2-one, as the potassium salt (II). This salt had the characteristic ultraviolet absorption spectrum, $\lambda_{max}^{dil\ KOH}$ 378 mμ (log ε 4.22), and in the infrared had absorption bands at 1700, 3375, and 1160 and 1243 cm.$^{-1}$ for the carbonyl, hydroxyl, and nitro groups in the $-C(NO_2)_2-$ function, respectively.

$$C(NO_2)_3^- + CH_2{=}CHCOCH_3 \longrightarrow$$
$$^-C(NO_2)_2CH_2CHOHCOCH_3$$
$$\text{II (33.9\%)}$$

With acrylonitrile as the acrylic augend, it was predicted that the potassium salt of 3,3-dinitropropionaldehyde (IV) would be obtained by the following sequence.

$$C(NO_2)_3^- + CH_2{=}CHCN \longrightarrow \underset{\text{III}}{^-C(NO_2)_2CH_2CHOHCN} \longrightarrow$$
$$^-C(NO_2)_2CH_2CHO + HCN$$
$$\text{IV}$$

The α-hydroxydinitro derivative III produced in this reaction would be the cyanohydrin of 3,3-dinitropropionaldehyde. Under the reaction conditions the cyanohydrin equilibrium should be shifted in the direction of the aldehyde IV. When this reaction was followed spectrophotometrically, the 350-mμ absorption maximum for nitroform shifted to ≈357 mμ compared with the methyl acrylate or methyl vinyl ketone systems where the shift was generally to 370 to 375 mμ. After removing the unchanged potassium trinitromethide, the residual solution exhibited an absorption maximum at ≈360 mμ as compared with the methyl acrylate or

methyl vinyl ketone products which had absorption maxima at ≈380 mμ.

Utilizing similar isolation procedures, it was not possible to obtain a solid potassium salt from the acrylonitrile reaction. However, the presence of an absorption maximum at ≈365 mμ is characteristic of the chromophore system $-C(NO_2)_2-CH_2-Y$, where Y is an electron-attracting substituent.[7] Thus, for 3,3-dinitropropionitrile, 2,2-dinitroethanol, and 2,2-dinitroethylamine, $\lambda_{max}^{dil\ KOH}$ is 362.5, 365, and 362 mμ, respectively.[7] Based upon the ultraviolet spectrum of the reaction mixture after removal of unchanged potassium trinitromethide, it appeared that the product remaining in solution was 3,3-dinitropropionaldehyde.

Experimental[15,16]

Spectrophotometric Studies.—The nitroform–methyl acrylate system was studied by thermostating 10 ml. of 0.400 *M* methyl acrylate in dioxane, 10 ml. of 1.00 *M* acetic acid in dioxane, 10 ml. of 1.00 *M* sodium acetate in water, and about 50 to 55 ml. of 50 v./v. % dioxane at 45° in a 100-ml., low actinic volumetric flask for at least 20 min. At the end of this time, 10 ml. of 0.100 *M* nitroform in water was added; the resulting solution was made up to volume with 50 v./v. % dioxane at 45°, thoroughly mixed by shaking, and returned to the thermostat. At appropriate times, 5-ml. aliquots of this solution were taken and diluted to 50 ml. with water to quench the reaction. A 4-ml. aliquot of the resulting solution was then diluted to 100 ml. with water after first adding 5 ml. of 20% sodium acetate solution. The spectrum of this dilution was then determined on the Cary Model 14 recording spectrophotometer, scanning at a rate of 15 mμ/min. For the spectra determined after 5 hr., dilutions were chosen to give optical density readings between 0.3 and 1.0 at the absorption maxima. These values were then normalized to the 5- to 50-ml., 4- to 100-ml. dilution to obtain the data plotted in Fig. 2.

For the decomposition of methyl 4,4,4-trinitrobutyrate, Fig. 3, a similar procedure was followed using 0.100 *M* methyl 4,4,4-trinitrobutyrate in dioxane in place of nitroform and methyl acrylate. The spectra in Fig. 3 have *not* been normalized for different dilution factors.

For the reaction of DNS with methyl acrylate, the procedure was identical with that used in studying the nitroform–methyl acrylate system, using 10 ml. of 0.100 *M* DNS in water in place of the aliquot of nitroform stock solution. For all of the spectra in Fig. 4 except the 22-hr. spectrum, the dilution procedure was the same as that described for the early part of the nitroform–methyl acrylate runs. For the spectrum after 22 hr., the dilution was 5 to 50 ml., then 10 to 100 ml. The data for this spectrum have been divided by 2.5 before plotting in Fig. 4.

Synthetic Studies. Potassium methyl 4,4-dinitro-2-hydroxybutyrate (DNS) was prepared by dissolving 0.12 mole (22.7 g.) of potassium trinitromethide and 0.1 mole (9.8 g.) of potassium acetate in 200 ml. of 50% dioxane. To the resulting solution, heated to 45 to 50°, was added 0.1 mole (8.6 g.) of methyl acrylate. The spectrum of this reaction mixture was followed with a Cary Model 14 spectrophotometer by making appropriate dilutions of small samples of the reaction mixture at various times. These spectra were not unlike those in Fig. 1. After 180 min., calculations based upon optical density measurements at 350 and 380 mμ showed that there was 0.025 mole of trinitromethide ion and 0.034 mole of the α-hydroxydinitro ester, DNS, present in the reaction mixture. As the $O.D._{380}/O.D._{350}$ ratio had reached a maximum at this time, the reaction was stopped by cooling to ambient temperature.

The dark red solution was extracted with three 100-ml. portions of ether and the combined extracts were washed with water until the washings were essentially colorless. The organic phase was then dried over Drierite and saved for C_9 and MeTNB isolation (*vide infra*).

The dark red aqueous phase was warmed on the steam bath to expel the residual ether and then cooled in ice. A yellow crystalline solid separated which was collected on a Büchner funnel, washed with methanol then ether, and air-dried. This procedure yielded 4.58 g. (20.8%) of a dark yellow product, $\lambda_{max}^{H_2O}$ 350 mμ. The ultraviolet spectrum of this material was identical with that of potassium trinitromethide. This salt was unchanged starting material.

The filtrate, but not the washings, from the above procedure was diluted with twice its volume of absolute methanol and cooled to about −10° in a Dry Ice–acetone bath. A microcrystalline yellow solid separated. This was collected on a Büchner funnel, washed with cold methanol and ether, and air-dried to yield 3.89 g. of material having $\lambda_{max}^{dil\ KOH}$ 378 mμ, $O.D._{380}/O.D._{350}$ = 2.24.

The mother liquors from the preceding crop were diluted with an additional 100 ml. of absolute methanol and cooled in Dry Ice–acetone as previously. An additional 1.85 g. of lemon yellow crystals were obtained, $\lambda_{max}^{dil\ KOH}$ 378 mμ, $O.D._{380}/O.D._{350}$ = 2.16.

The addition of 400 ml. of absolute methanol to the mother liquors followed by cooling to −20 to −30° in Dry Ice–acetone gave a final crop of 1.80 g. of the yellow salt, $\lambda_{max}^{dil\ KOH}$ 378 mμ, $O.D._{380}/O.D._{350}$ = 2.09. An analytical sample of the salt was prepared by recrystallization from a large volume of methanol.

Anal. Calcd. for $C_5H_7KN_2O_7$: C, 24.4; H, 2.9; K, 15.9; N, 11.4. Found: C, 24.1, 23.2, 23.7; H, 3.3, 3.0, 2.8; K, 15.3, 15.4; N, 11.7, 11.1, 11.1.

Principal infrared absorption bands were carbonyl, 1730; hydroxyl, 3250–3470 and 3540; $-C(NO_2)_2-$, 1167 and 1242 cm.$^{-1}$. The ultraviolet absorption maximum was $\lambda_{max}^{dil\ KOH}$ 378 mμ (log ε 4.23).

The mother liquors from the final crop were subjected to analysis by ultraviolet absorption spectroscopy. The filtrates were made up to 1000 ml. and then diluted by a factor of 2500, with a small amount of dilute potassium hydroxide added to the final dilution. The optical density of this final dilution was determined at 380 mμ: $O.D._{380}$ = 0.306, 0.304; 10^5[DNS] = 1.81 *M*, 10^3[DNS] = 4.5 *M*. The total yield of the α-hydroxydinitro ester DNS was 36% based upon methyl acrylate.

The combined dried ether extracts were treated with Darco decolorizing charcoal and evaporated to dryness. The residual oil was slurried with a mixture of 20 ml. of *n*-hexane and 5 ml. of ether. By this procedure there was obtained 3.40 g. of a white crystalline solid melting at 71.5–4.5° (authentic C_9, m.p. 73–74°). This corresponded to 0.0116 mole of C_9 or a 23.2% yield based upon methyl acrylate.

The solvent phase from this work-up was evaporated to yield 2.98 g. of a colorless, viscous oil melting at 15–20° (authentic MeTNB, m.p. 27–28°). This represents a 12.6% yield based upon methyl acrylate. The total materials balance based upon methyl acrylate is therefore 71.8%.

5,5-Dinitro-3-hydroxypentan-2-one (potassium salt) was prepared by treating 0.12 mole (22.7 g.) of potassium trinitromethide, 0.1 mole (9.8 g.) of potassium acetate, and 0.1 mole (7.0 g.) of methyl vinyl ketone in 200 ml. of 50% dioxane at 50° as described previously. The reaction in this case was quite exothermic and the solution turned very dark almost immediately upon the addition of the methyl vinyl ketone. After 30 min., a constant ultraviolet spectrum was obtained ($\lambda_{max}^{H_2O}$ 370 mμ), and the solution was cooled to room temperature. The solution was extracted with three 100-ml. portions of ether.

The aqueous phase, after the residual ether had been removed on the steam bath, was cooled to 0 to −5°, whereupon a yellow solid separated. This product was collected by filtration, washed with absolute methanol (washings discarded) and ether, and dried. There was obtained 3.73 g. of a yellow salt, $\lambda_{max}^{H_2O}$ 350 mμ. This was unchanged potassium trinitromethide.

The mother liquors ($\lambda_{max}^{H_2O}$ 375 mμ) were diluted with 50 ml. of absolute methanol and cooled to about −10°. A yellow-orange solid separated. It was collected by filtration, washed with absolute methanol and ether, and dried. This procedure gave 3.70 g. of a crystalline solid, $\lambda_{max}^{dil\ KOH}$ 378 mμ.

The mother liquors were cooled to −20° and a second crop of 4.10 g. of a yellow-orange salt was obtained, $\lambda_{max}^{dil\ KOH}$ 377 mμ. On cooling the mother liquors to as low as −40°, only small amounts of material separated which could not be collected on a Büchner funnel.

(15) Many of the compounds described are explosive in nature and quite sensitive to impact or grinding. Appropriate precautions should be taken in their handling.

(16) Microanalyses were performed by Dr. Mary Aldridge, Department of Chemistry, American University, Washington, D. C. Infrared spectra were determined in Nujol mulls with a Beckman IR-4 spectrophotometer.

An analytical sample was obtained by recrystallization of the combined crops from a large volume of methanol as small yellow-orange plates.

Anal. Calcd. for $C_5H_7KN_2O_6$: C, 26.1; H, 3.1; K, 17.0; N, 12.2. Found: C, 26.2, 25.9; H, 3.1, 3.4; K, 16.9, 16.7; N, 12.5, 12.2.

Principal infrared absorption bands were carbonyl, 1690; hydroxyl, 3375; $-C(NO_2)_2^-$, 1160 and 1243 cm.$^{-1}$. The ultraviolet absorption maximum was $\lambda_{max}^{pH\ KOH}$ 378 mμ (log ε 4.22).

3,3-Dinitropropionaldehyde (potassium salt) was prepared by treating 0.1 mole (22.7 g.) of potassium trinitromethide, 0.1 mole (9.8 g.) of potassium acetate, and 0.1 mole (5.3 g.) of acrylonitrile in 200 ml. of 50% dioxane at about 60°. Samples of the reaction mixture were analyzed spectrophotometrically throughout the 150-min. reaction period. During this time there was a gradual shift of λ_{max} from 350 to about 357 mμ.

At the end of 150 min., the mixture was cooled to ambient temperature and extracted with three 100-ml. portions of ether. The aqueous phase was cooled to about −5°, whereupon a yellow crystalline solid separated. This product after washing with methanol and ether weighed 5.28 g. and proved to be unchanged potassium trinitromethide, λ_{max} 350 mμ.

Diluting the mother liquors with an equal volume of methanol and cooling to about −30 to −40° in Dry Ice–acetone gave only small amounts of a gummy solid. This material had λ_{max} 368 mμ while the mother liquors after removal of the unchanged potassium trinitromethide had λ_{max} 360 mμ.

Reaction of Potassium Methyl 4,4-Dinitro-2-hydroxybutyrate (DNS) with Methyl Acrylate.—Fifteen thousandths of a mole (3.69 g.) of DNS, 0.03 mole (2.58 g.) of methyl acrylate, 25 ml. of 1 *M* acetic acid in dioxane, and 50 ml. of water were heated on the steam bath for 3 hr. The resulting mixture was diluted with 200 ml. of water and extracted with five 100-ml. portions of ether, after first adjusting the pH of the solution to between 7 and 8 with sodium carbonate. The combined ether extracts were dried over calcium sulfate and the ether was removed on the steam bath to leave a viscous oil. This oil solidified on cooling to yield 3.42 g. of a white solid melting at 72–75°.

After recrystallization from ether, this product melted at 74–75° and did not depress the melting point of an authentic sample of dimethyl 4,4-dinitro-2-hydroxypimelate (C_9). Spectrophotometric analysis of the residual aqueous phase showed that less than 10^{-4} moles of DNS remained in solution.

Acknowledgment.—This work was supported by the Foundational Research Fund of the U. S. Naval Ordnance Laboratory, Task F.R.-44. The assistance of Messrs. F. Taylor, Jr., and B. Wilkerson in preparing some of the intermediates used in this work and discussions with Drs. D. V. Sickman and M. J. Kamlet are appreciated.

Cyclization of Isothiocyanates as a Route to Phthalic and Homophthalic Acid Derivatives[1,2]

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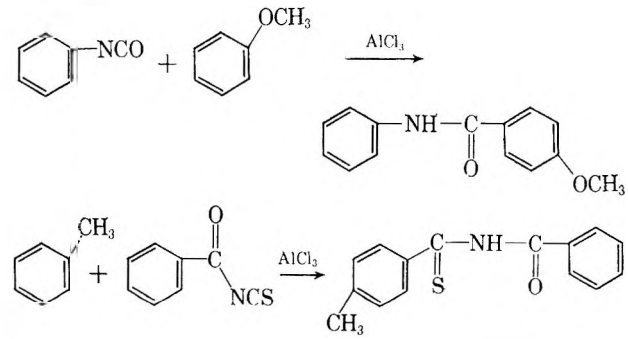
Under Friedel–Crafts conditions, benzoyl isothiocyanates undergo cyclization to monothiophthalimides, and phenylacetyl isothiocyanates give monothiohomophthalimides. The thioimides may be converted to their oxygen analogs, reduced to isoquinoline derivatives, or hydrolyzed to the dicarboxylic acids. The cyclization shows great selectivity when two different *ortho* positions are open for ring closure.

Although there exist numerous methods for the introduction of a carboxyl group into an aromatic ring, they are almost exclusively limited to bimolecular electrophilic substitution reactions, with concomitant uncertainty about the site of introduction, the *para* position usually being favored over the *ortho* position. Prominent examples of such methods include the Gattermann and the Gattermann–Koch reactions,[3,4] the Hoesch reaction,[5] the Vilsmeier–Haack reaction,[6] the Reimer–Tiemann reaction,[7] the Kolbe reaction,[8] bromination followed by the Grignard reaction with carbon dioxide, and the Friedel–Crafts acylation reaction. The use of isocyanates as acylating agents has been studied intermittently since 1885, when Leuckart first produced *p*-methoxybenzanilide by treatment of anisole with phenyl isocyanate and aluminum chloride,[9] but the yields in these and other studies were often low owing in part to the rapid decomposition of the reagents. The use of acyl isothiocyanates was first reported by Wheeler[10] in the reaction of toluene with benzoyl isothiocyanate.



It occurred to us that aromatic acyl and alkyl isothiocyanates would possess sufficient reactivity to serve as intramolecular acylating agents in order to provide a synthetic route to phthalic acids from benzoic acids and to homophthalic acids from phenylacetic acids. This paper reports the results of these studies.[11]

(1) Taken in part from the doctoral thesis of R. O. Kan, University of Michigan, 1961.

(2) For a preliminary communication describing some of the results reported here, see P. A. S. Smith and R. O. Kan, *J. Am. Chem. Soc.*, **82**, 4753 (1960).

(3) (a) L. Gattermann, *Ber.*, **31**, 1149 (1898); (b) N. O. Calloway, *Chem. Rev.*, **17**, 327 (1935).

(4) (a) L. Gattermann and J. A. Koch, *Ber.*, **30**, 1622 (1897); (b) N. N. Crounse, *Org. Reactions*, **5**, 290 (1949).

(5) (a) J. Houben and W. Fischer, *Ber.*, **66**, 339 (1933); (b) P. E. Spoerri and A. S. DuBois, *Org. Reactions*, **5**, 387, 1949.

(6) L. F. Fieser, J. L. Hartwell, J. E. Jones, J. H. Wood, and R. W. Frost, *Org. Syn.*, **20**, 11 (1940).

(7) K. Reimer and F. Tiemann, *Ber.*, **9**, 824 (1876).

(8) (a) H. Kolbe, *J. prakt. Chem.*, [2]**10**, 89 (1874); (b) R. Schmitt, *ibid.*, [2]**31**, 397 (1885).

(9) R. Leuckart and M. Schmidt, *Ber.*, **18**, 2338 (1885).

(10) H. L. Wheeler, *Am. Chem. J.*, **26**, 345 (1901).

(11) One such example had been previously reported in the conversion of α-naphthyl isothiocyanate to thionaphthacarbostyril [N. S. Dokunikhin and L. A. Gaeva, *Zh. Obshch. Khim.*, **24**, 1871 (1954)], but, in view of our results, the structure of the product should be reinvestigated.

TABLE I

ISOTHIOCYANATES, R—NCS, AND CORRESPONDING N-PHENYLTHIOUREAS, RNHCSNHC$_6$H$_5$

Isothiocyanate	B.p. (mm.) or m.p., °C.	Yield, %	N-Phenyl-thiourea, m.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Benzoyl[a]	143 (20)	77.5							
m-Toluyl	95 (0.7)	82.5	113	66.64	5.23	10.37	66.64	5.24	10.27
p-Toluyl	92 (0.4)	72	132–133	66.64	5.23	10.37	66.61	5.23	10.32
3,5-Dimethylbenzoyl	99 (1.5)[b]	62.5							
m-Methoxybenzoyl	104 (0.3)	77	104–105	62.91	4.93	9.78	62.78	5.03	10.00
3,5-Dimethoxybenzoyl	158 (1.3)	22	125.5	60.64	5.10	8.86	60.64	5.03	8.68
3,4,5-Trimethoxybenzoyl[c]	98	76.3							
Benzyl[d]	141 (21)	60–82							
β-Phenylethyl[e]	95 (0.8)	75[f]							
Phenylacetyl	103 (1.7)	50–79	107–108	66.64	5.22	10.36	66.77	5.33	10.44
m-Tolylacetyl	98 (0.2)	65.3	132	67.57	5.68	9.85	67.69	5.76	9.77
p-Tolylacetyl	*g*		150–151	67.57	5.68	9.85	67.60	5.64	9.66
m-Methoxyphenylacetyl	128 (0.3)	24.7	104	63.97	5.38	9.33	63.96	5.41	9.30
p-Methoxyphenylacetyl	123 (0.4)	66.5	123	63.97	5.38	9.33	64.12	5.42	9.48
p-Chlorophenylacetyl	116 (0.5)	63	136–137	59.11	4.30	9.20	59.22	4.35	9.36
Diphenylacetyl	*g*		173	72.80	5.24	8.09	72.59	5.29	8.11
Cinnamoyl	119 (0.2)	75	163–164	68.05	5.00	9.92	68.20	5.00	10.04
3-Thenoyl	76 (0.3)	72	152	54.94	3.84	10.68	55.01	4.00	10.74
3-Phenanthreneacetyl	*g*		198–198.5	74.48	4.90	7.56	74.35	4.80	7.24
3-Phenanthroyl	*g*		183–184	74.13	4.53	7.86	74.39	4.64	7.80
α-Naphthoyl	152 (0.7), 35	52.7	154	70.56	4.60	9.14	70.58	4.72	9.22
β-Naphthoyl	74	43.8	148.5	70.56	4.60	9.14	70.49	4.59	9.23
α-Naphthylacetyl	*g*	72	125	71.22	5.03	8.75	71.04	6.26	8.82
Cyclohexene-1-acetyl	77 (0.5)	31–44	110	65.70	6.57	10.22	65.68	6.47	10.29
Cyclohexene-1-carbonyl	90 (0.5)	54–82	121–122	64.60	6.15	10.77	64.68	6.14	10.82
Benzhydryl[h]	58	41.7[f]							

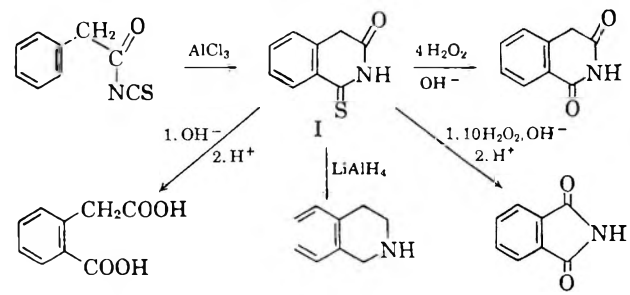
[a] J. C. Amberlang and T. S. Johnson, *J. Am. Chem. Soc.*, **61**, 632 (1939). [b] *Anal.* Calcd. for $C_9H_5NO_2S$: C, 62.80; H, 4.75; N, 7.32. Found: C, 62.74; H, 4.91; N, 7.26. [c] W. H. Perkins and C. Weizmann, *J. Chem. Soc.*, **89**, 1649 (1906). [d] W. Schneider, D. Glibbens, G. Hüllweck, and W. Steibelt, *Ber.*, **47**, 1248 (1914). [e] J. v. Braun and H. Deutsch, *ibid.*, **45**, 2188 (1912). [f] Prepared following the procedure of M. L. Moore and F. S. Crossley, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 599. [g] Not distilled, but used as such. [h] O. H. Wheeler and I. Lerner, *Am. Chem. J.*, **26**, 345 (1901).

Results

Acyl isothiocyanates used in these studies are conveniently prepared from lead thiocyanate and the corresponding acyl halide[12]; alkyl isothiocyanates were prepared from the amine, carbon disulfide, and ethyl chloroformate by the modified Kaluza reaction.[13] The isothiocyanates were converted to the N-substituted N′-phenylthioureas by treating with aniline for characterization purposes. A list of those prepared is given in Table I.

When phenylacetyl isothiocyanate was refluxed with 2.2 molar equiv. of aluminum chloride in carbon disulfide for a few hours, or stirred in *sym*-tetrachloroethane on a steam bath for 30 min., and the reaction mixture decomposed with ice and water, a bright orange solid (I) remained, which melted at 221–222° after recrystallization from glacial acetic acid. Prolonged hydrolysis with concentrated potassium hydroxide converted I to homophthalic acid; lithium aluminum hydride reduction resulted in the formation of 1,2,3,4-tetrahydroisoquinoline, while treatment with hydrogen peroxide produced the sulfur-free homophthalimide, or, when used in excess, the phthalimide. These conversions (Chart I) unequivocally identified the compound as 2a-thiohomophthalimide [or 1-thio-1,2,3,4-tetrahydro-1,3(2H,4H)-isoquinolinedione by *Chemical Abstracts* nomenclature].

CHART I



Similarly, a variety of ring- and also methylene-substituted phenylacetyl isothiocyanates underwent such intramolecular ring closure in yields varying from 40 to 74% (Table II). The products were degraded in a manner similar to that depicted in Chart I, in order to establish their identities. Where the corresponding homophthalimides or homophthalic acids were not previously reported, the imides were also oxidized to the corresponding phthalimides[14] for identification.

Not unexpectedly, benzoyl isothiocyanates underwent such ring closure with much greater reluctance; the attachment of the carbonyl group directly to the aromatic ring greatly deactivates the ring towards electrophilic substitution, necessitating the presence of other electron-donating groups in order to overcome

(12) A. E. Dixon and J. Taylor, *J. Chem. Soc.*, **93**, 684 (1908).

(13) W. R. Vaughan, M. V. Anderson, H. S. Blanchard, and D. I. McCane *J. Org. Chem.*, **20**, 819 (1955).

(14) The mechanism of this oxidation, which involves ring contraction by benzilic acid rearrangement, is to be discussed in another paper; a preliminary report has been given [P. A. S. Smith and R. O. Kan, *J. Am. Chem. Soc.*, **83**, 2580 (1961)].

TABLE II

CYCLIZATION OF ISOTHIOCYANATES

A. Arylacetyl Isothiocyanates, $R_2CHCONCS$

R	Thioimide [substituted 1-thio-1,3(2H,4H)-isoquinolinedione]	M.p., °C.	Reaction time, hr.	Yield, %
Phenyl, H	Unsubstituted[a]	221–222	3	74
m-Tolyl, H	6-Methyl[b]	198–199	4	42
p-Tolyl, H	7-Methyl[c]	230	4	48
m-Methoxyphenyl, H	6-Methoxy[d]	224–225	4	42
p-Chlorophenyl, H	7-Chloro[e]	238–239	4	40
Diphenyl	4-Phenyl[f]	166–167	0.5	40
α-Naphthyl, H	5,6-Benzo[g]	254–255	16	41
3-Phenanthryl, H	(?)[h]	240–280		
1-Cyclohexenyl, H	5,6,7,8-Tetrahydro, hydrate (?)[i]	197	0.5–4	48

B. Aroyl Isothiocyanates, ArCONCS

Ar	Thioimide (substituted 1-thio-1,3-isoindolinedione)	M.p., °C.	Reaction time, hr.	Yield, %
Phenyl	None			
m-Tolyl	7-Methyl[j]	192	96	45
p-Tolyl	None			
3,5-Xylyl	5,7-Dimethyl[k]	209–210	24	65
m-Methoxyphenyl	None			
3,5-Dimethoxyphenyl	None			
3,4,5-Trimethoxyphenyl	None			
α-Naphthyl	None			
β-Naphthyl	6,7-Benzo[l]	248–249	48	25
3-Thienyl	4-Thio-4,6(5H)-thieno[2,3-*c*]-pyrroledione[m]	183	24	12

C. Other Isothiocyanates, RNCS

R	Product	M.p., °C.	Reaction time, hr.	Yield, %
Benzyl	None			
β-Phenylethyl	1-Thiodihydroisocarbostyryl[n]	98–99	30	40

[a] *Anal.* Calcd. for C_9H_7NOS: C, 61.00; H, 3.98; N, 7.91. Found: C, 61.03; H, 4.16; N, 7.88. [b] *Anal.* Calcd. for $C_{10}H_9NOS$: C, 62.82; H, 4.75; N, 7.32. Found: C, 62.80; H, 4.88; N, 7.42. [c] *Anal.* Calcd. for $C_{10}H_9NOS$: C, 62.82; H, 4.75; N, 7.32 Found: C, 63.13; H, 4.40; N, 7.39. [d] *Anal.* Calcd. for $C_{10}H_9NO_2S$: C, 57.96; H, 4.36; N, 6.76. Found: C, 57.74; H, 4.58; N, 6.54. [e] *Anal.* Calcd. for C_9H_6ClNOS: C, 51.07; H, 2.86; N, 6.62. Found: C, 51.19; H, 2.99; N, 6.57. [f] *Anal.* Calcd. for $C_{15}H_{11}NOS$: C, 71.12; H, 4.38; N, 5.55. Found: C, 70.96; H, 4.41; N, 5.39. [g] *Anal.* Calcd. for $C_{13}H_9NOS$: C, 68.89; H, 3.99; N, 6.16. Found: C, 68.73; H, 4.17; N, 6.32. [h] Orange powder. *Anal.* Found: C, 62.74; H, 3.69; N, 4.32; ash, 2.99. All attempts at purification by recrystallization from a variety of solvents were unsuccessful. [i] White powder after crystallization from benzene–petroleum ether mixture. *Anal.* Calcd. for $C_9H_{11}NOS$: C, 59.67; H, 6.08; N, 8.85. Calcd. for $C_9H_{13}NO_2S$: C, 54.25; H, 6.54; N, 7.03. Found: C, 54.89; H, 6.56; N, 7.02. [j] *Anal.* Calcd. for C_9H_7NOS: C, 61.00; H, 3.98; N, 7.91. Found: C, 61.20; H, 4.25; N, 7.89. [k] *Anal.* Calcd. for $C_{10}H_9NOS$: C, 62.82; H, 4.75; N, 7.32. Found: C, 63.04; H, 4.76; N, 7.41. [l] *Anal.* Calcd. for $C_{12}H_7NOS$: C, 67.61; H, 3.30; N, 6.58. Found: C, 67.40; H, 3.45; N, 6.68. [m] *Anal.* Calcd. for $C_9H_3NOS_2$: C, 42.58; H, 1.79; N, 8.28. Found: C, 42.70; H, 2.02; N, 8.06. [n] *Anal.* Calcd. for C_9H_9NOS: C, 66.25; H, 5.52; N, 8.59. Found: C, 66.64; H, 5.50; N, 8.57.

this effect. Thus, benzoyl isothiocyanate failed to cyclize at all under a wide variety of conditions, while the substituted benzoyl isothiocyanates, which are listed in Table II, did so only after considerably longer reaction times.

1-Cyclohexeneacetyl isothiocyanate gave an unexpectedly colorless product, whose analysis indicated the presence of the elements of one molecule of water more than required by the thioimide structure. Although the infrared spectrum (amide doublet at 1700 and 1780 plus strong bands at 1040–1060 and 1200–1200, cm.$^{-1}$, part of which may be due to thionamide) and tests for unsaturation with bromine and with permanganate were consistent with the thioimide structure, the indentification should be regarded as uncertain.

It is of interest to note that *m*-toluyl isothiocyanate formed exclusively the product resulting from carboxylation in the position *ortho* to the methyl group, II, thus providing a facile route to 3-methylphthalic acid and its derivatives. *m*-Tolylacetyl isothiocyanate, on the other hand, cyclized to the opposite side, *para* to the methyl group, to give III, the structure of which was established by oxidation to trimellitic acid (Chart II) and degradation to 4-methylphthalimide.

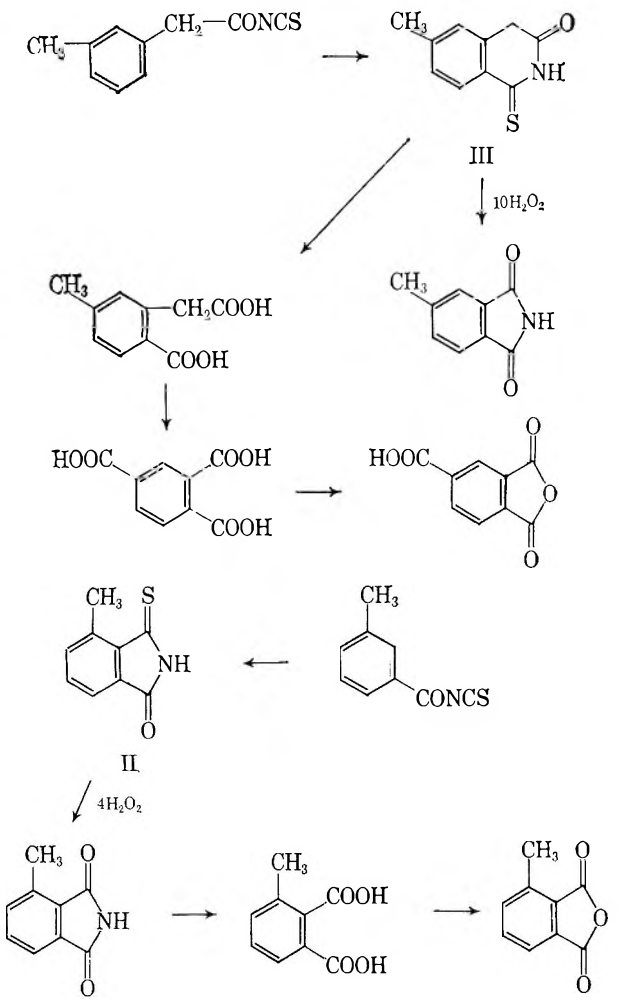
An attempt to extend this synthetic method to other systems met with only partial success. Thus α-naphthylacetyl isothiocyanate produced the thioimide resulting from attack on the β-position, whereas α-naphthoyl isothiocyanate could not be made to react. β-Naphthoyl isothiocyanate reacted by closure to the α-position, however. In addition, 3-thenoyl isothiocyanate cyclized to the 2-position, but in poor yield.

Finally, aralkyl isothiocyanates were briefly examined; only phenethyl isothiocyanate was cyclized successfully, to form 1-thiodihydroisocarbostyril in 40% yield.

The thioimides as a class, of which previously only one example has been reported,[15] were rose red when five-membered (except for brown thionaphthalimide), and brown-orange to yellow-orange when six-membered.

(15) M. E. Baguley and J. A. Elvidge, *J. Chem. Soc.*, 709 (1957).

CHART II



The electronic absorption spectra in ethanol solution showed four or more bands, of which that of lowest frequency, presumably resulting from an n–π^* transition in the thiocarbonyl group,[16] fell in the region of 3250 to 4500 Å. (log ϵ 3–3.9). The infrared spectra showed amide doublets, at 1700–1740 cm.$^{-1}$ for the five-membered rings, and at 1680–1690 cm.$^{-1}$ for the six-membered rings.

Hydrolysis of the products to the dicarboxylic acids was difficult; reflux periods up to several days with 25% potassium hydroxide solution were sometimes required, although the result was always eventually successful.

The processes of cyclization of aroyl isothiocyanates, or of arylacetyl isothiocyanates followed by ring contraction, open a general route to aromatic *ortho* dicarboxylic acids hitherto available only with difficulty or not at all.

Experimental[17]

Preparation of Isothiocyanates.—A mixture of 1 mole of the acid chloride, 140 g. (1 mole) of lead thiocyanate, and 250 ml. of benzene was refluxed for 5 hr., after which a small amount of Norit was added, and refluxing continued for an additional 5 min.

(16) M. J. Janssen, *Rec. trav. chim.*, **79**, 454, 464, 1066 (1960).

(17) Melting points are corrected and boiling points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer, from films or Nujol mulls. Ultraviolet-visible spectra were recorded with a Cary recording spectrophotometer, Model 11.

TABLE III

CARBOXYLIC ACIDS OBTAINED FROM CYCLIZED ISOTHIOCYANATES

Acid	Yield, %	M.p., °C.
Homophthalic	61	181[a]
5-Methylhomophthalic[b]	87	202[b]
4-Methylhomophthalic[c]	91	201
5-Methoxyhomophthalic	Good	225[d]
4-Chlorohomophthalic	>50	197[e]
α-Phenylhomophthalic	94	173[f]
1-Homo-1,2-naphthalic[g]	10, >50[h]	214–215
2-Carboxycyclohexene-1-acetic	Good	166[i]
3-Methylphthalic	80	157–158[j]
3,5-Dimethylphthalic	Good	176[k]
1,2-Naphthalic	40	175[l]
Thiophene-2,3-dicarboxylic	75	270[m]
o-(2-Aminoethyl)benzoic, hydrochloride	Good[n]	194–198[o]

[a] Lit. m.p. 181° [W. Davies and H. G. Poole, *J. Chem. Soc.*, 1616 (1928)]. [b] *Anal.* Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.20; equiv. wt., 97. Found: C, 61.90; H, 5.28; equiv. wt., 94, 97. [c] *Anal.* Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.20; equiv. wt., 97. Found: C, 61.66; H, 5.31; equiv. wt., 95.5, 99.5. [d] Lit. m.p. 222° [S. N. Chakravarti and N. Swaminathan, *J. Indian. Chem. Soc.*, 11, 101 (1934)]. [e] Lit. m.p. 191–192° [D. E. Adams and T. F. Grey, *J. Chem. Soc.*, 3518 (1955)]. [f] G. F. Koelsch, *J. Am. Chem. Soc.*, **58**, 1321 (1936). [g] *Anal.* Calcd. for $C_{13}H_{10}O_4$: C, 67.83; H, 4.38; equiv. wt., 115. Found: C, 67.68; H, 4.47; equiv. wt., 116. [h] From hydrolysis in 90% orthophosphoric acid for 5 hr. at 140°. [i] Lit. m.p. 166° [G. A. R. Kon and H. R. Nanji, *J. Chem. Soc.*, 2426 (1932)]. [j] Lit.[26] m.p. 154°. [k] Lit. m.p. 183° [L. Ruzicka, *Helv. Chim. Acta*, **19**, 419 (1936)]. [l] Lit.[24] m.p. 175°. [m] Lit. m.p. 268–270° [B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.*, **18**, 138 (1953)]. [n] From hydrolysis in refluxing concentrated hydrochloric acid. [o] Lit.[18] m.p. 199–200°. Neutralizing a small sample with sodium bicarbonate solution, evaporation of the water, and heating of the residue for 2 hr. at 170° gave 3,4-dihydroisocarbostyryl, m.p. 68° (lit.[18] m.p. 70–71°).

Subsequently the mixture was filtered twice through the same Büchner funnel, where the solid collected in the first pass removed the last traces of finely divided solid from initial filtrate. The solvent was removed under aspirator vacuum, and the residual isothiocyanate was distilled *in vacuo* just prior to use since, after a few hours standing in air, the light yellow liquids rapidly decomposed and turned dark. For this reason, most of the products were not analyzed but, for characterization, were converted to the corresponding phenylthioureas by warming for 5 min. with aniline in methanol solution.

The acyl isothiocyanates showed the characteristic infrared absorption in the form of a broad band or a doublet in the range 1930–2000 cm.$^{-1}$, and carbonyl stretching at or near 1700 cm.$^{-1}$. The acyl isothiocyanate absorption thus falls at distinctly lower frequencies than that of alkyl isothiocyanates (*e.g.*, benzyl, 2025 and 2040 cm.$^{-1}$; β-phenylethyl, 2020 and 2040 cm.$^{-1}$).

Cyclization of Isothiocyanates.—One equivalent of the isothiocyanate was added slowly with stirring over 5–15 min., during which time the vessel was cooled in ice–water, to 250 ml. of carbon disulfide and 2.2 molar equiv. (86 g.) of anhydrous powdered aluminum chloride. After the addition, the cooling bath was removed, and the mixture was refluxed (infrared lamp) for periods varying from 4 hr. to 4 days. It was cooled again in an ice bath, and a mixture of 100 ml. of water and 20 ml. of concentrated hydrochloric acid was added dropwise over 0.5 hr. Stirring was continued until most of the solid that had deposited had been decomposed, after which it was collected by suction filtration. Evaporation of the filtrate yielded only 3 to 4% additional product. The solid thus obtained was dried in an oven at 40° or in a vacuum desiccator to remove all traces of carbon disulfide and was recrystallized from glacial acetic acid after treatment with a little Norit. The thioimides obtained in this manner are listed in Table III.

sym-Tetrachloroethane was used as solvent also in some cases. It was removed at the end of the reaction by steam distillation. The reaction times needed were generally lower. Phenylacetyl isothiocyanate required 12 min. of warming on a steam bath in *sym*-tetrachloroethane, against 3 hr. of refluxing in carbon disul-

fide to obtain a similar yield. The product required more extensive purification, however, and the yields never exceeded those obtained by the use of carbon disulfide. Other catalysts, such as stannic chloride and ferric chloride, proved to be ineffective.

Conversion of Thioimides to Dicarboxylic Acids.—In a 100-ml., round-bottom, one-necked copper flask were placed 3 g. of a thioimide and 40 ml. of 25% aqueous potassium hydroxide. The mixture was refluxed until no evolution of ammonia was observed (24–72 hr.), followed by acidification, extraction with ether, and evaporation of the extracts under a stream of air. In this manner the acids listed in Table III were obtained. The melting points recorded were those observed with rapid heating or in a preheated bath; slow heating gave lower, less sharp, melting points. Melting was in all cases accompanied by gas evolution, presumably resulting from anhydride formation.

Reduction of 2-Thiohomophthalimides.—To 100 ml. of anhydrous ether containing 1.071 g. of lithium aluminum hydride (5 molar equiv.) was added 1 g. of 2a-thiohomophthalimide [1-thio-1,3(2H,4H)-isoquinolinedione] in two portions, over 2 min. The mixture was stirred under reflux for 15 hr., after which it was cooled. A mixture of 2 ml. of water and 2 ml. of 10% sodium hydroxide solution was added carefully and stirring was continued for another hour. After filtration and washing of the precipitate with anhydrous ether, the solvent was removed under the aspirator, and a saturated solution of picric acid in ethanol was added to the residue. The picrate of 1,2,3,4-tetrahydroisoquinoline formed in 47% yield on standing, m.p. 195°, lit.[18] m.p. 195–196°. Similarly, a 50% yield of 1,2,3,4-tetrahydroisoquinoline, isolated as its picrate, was obtained from the reduction of thio-3,4-dihydroisocarbostyril. A yield of 40% of 6-methyl-1,2,3,4-tetrahydroisoquinoline (as its picrate, m.p. 214°, lit.[19] m.p. 205°) was obtained by the reduction of 5-methyl-2a-thiohomophthalimide [1-thio-6-methyl-1,3(2H,4H)-isoquinolinedione].

Oxidation of Homophthalic Acids.—An aqueous solution of 0.5 g. of 5-methylhomophthalic acid and an excess of potassium permanganate was refluxed for 8 hr., filtered, and acidified. Evaporation to dryness in an air stream, extraction of the residue with boiling, glacial acetic acid, and cooling of the extract gave 0.3 g. (55%) of trimellitic acid, m.p. 225° dec. (lit. m.p. 226–227°,[20] 238°[21]). Refluxing this product with acetic anhydride for 2 hr., removal of reagent and acetic acid *in vacuo*, and sublimation of the residue at 200–220° (12 mm.) gave trimellitic anhydride, m.p. 160°, lit.[22] m.p. 162.5–163.5°.

Similar treatment of 5-methoxyhomophthalic acid gave 4-methoxyphthalic acid, m.p. 170°, lit.[23] m.p. 171–172°. Sublimation at 220° gave 4-methoxyphthalic anhydride, m.p. 95°, lit.[23] m.p. 94–95°.

Oxidation of Thiohomophthalimides to Phthalimides.—To a solution of 0.5 g. of 1-thio-1,3(2H,4H)-benzo[*d*]isoquinolinedione (the thiohomophthalimide from α-naphthylacetyl isothiocyanate) in 5 ml. of water containing 0.5 g. of potassium hydroxide was slowly added 2.8 ml. (10 molar equiv.) of 30% hydrogen peroxide. After 4 hr. at room temperature, the solution was acidified with concentrated hydrochloric acid and heated on the steam bath for 20 min. Upon chilling, there was obtained 0.35 g. (81%) of 1,2-naphthalimide as yellow needles, m.p. 223° after recrystallization from acetic acid, lit.[24] m.p. 224°.

Anal. Calcd. for $C_{12}H_7NO_2$: C, 72.42; H, 3.55; N, 7.04. Found: C, 72.25; H, 3.65; N, 7.00.

In a similar manner, 6-methyl-1-thio-1,3(2H,4H)-isoquinolinedione (the thiohomophthalimide from *m*-tolylacetyl isothiocyanate) was converted in 61% yield to 4-methylphthalimide, m.p. 196° (lit.[25] m.p. 196°, depressed by admixture with the known 3-methyl isomer).

Anal. Calcd. for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.70. Found: C, 67.39; H, 4.49; N, 8.91.

3-Methylphthalimide.—Sublimation at 110° (20 mm.) of the 3-methylphthalic acid obtained from *m*-tolulyl isothiocyanate by cyclization and hydrolysis gave 3-methylphthalic anhydride, m.p. 117–118°, lit.[26] m.p. 117–118°. Equal weights of 28% ammonium hydroxide and the 3-methylphthalic anhydride were heated for 2 hr. at 150–180°. Recrystallization of the crude product from hot water gave 3-methylphthalimide, m.p. 188–189° (lit.[27] m.p. 189–190°) in good yield.

(18) E. Bamberger and W. Dieckmann, *Ber.*, **26**, 1205 (1893).
(19) J. von Braun, G. Blessing, and R. S. Cahn, *ibid.*, **57**, 908 (1924).
(20) W. H. Perkin and J. F. S. Stone, *J. Chem. Soc.*, **127**, 2275 (1925).
(21) G. T. Morgan and E. A. Coulson, *ibid.*, 2551 (1929).
(22) W. Schultze, *Ann.*, **359**, 129 (1908).
(23) W. W. Prichard, *J. Am. Chem. Soc.*, **78**, 6137 (1956).
(24) E. F. Bradbrook and R. P. Linstead, *J. Chem. Soc.*, 1739 (1936).
(25) S. von Niementowski, *Monatsh.*, **12**, 620 (1891).
(26) F. Mayer and O. Stark, *Ber.*, **64**, 2003 (1931).
(27) S. Gabriel and A. Thieme, *ibid.*, **52**, 1079 (1919).

Optically Active Amines. II. The Optical Rotatory Dispersion Curves of the N-Benzylidene and Substituted N-Benzylidene Derivatives of Some Open-Chain Primary Amines[1,2]

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Most of the optically active N-benzylidene, N-*o*-methoxybenzylidene, N-salicylidene, N-5-nitrosalicylidene, N-5-chlorosalicylidene, and N-5-bromosalicylidene derivatives of α-phenyl- and α-benzylethylamine and of *sec*-butylamine were prepared and their electronic absorption spectra and optical rotatory dispersion curves were measured. Cotton effects could be observed only in the rotatory dispersion curves of the N-salicylidenes and the N-5-chloro- and N-5-bromosalicylidenes of α-phenyl- and α-benzylethylamine. A comparison of these curves with that displayed by N-salicylidene-*sec*-butylamine suggests that, for the aralkylamine derivatives, there may be present rotationally significant interactions of the π-electron systems of the phenyl and benzyl groups with the N-salicylidene moiety which, for the derivatives with the (*S*)-configuration, result in strong positive Cotton effects near 410 and 315 mμ.

Many Schiff bases derived from aldehydes and ketones and optically active open-chain amines exhibit notably high rotatory powers at the sodium D-line. Betti[5] has recorded values for numerous derivatives of benzaldehyde and substituted benzaldehydes and (+)-1-(α-aminobenzyl)-2-naphthol ($[\phi]_D$ +147°) and observed marked differences, apparently related to the strengths of the acids corresponding to the aldehydes. For example, the derivative prepared from *p*-N,N-dimethylaminobenzaldehyde has an extremely high posi-

(1) Paper I: H. E. Smith, M. E. Warren, Jr., and A. W. Ingersoll, *J. Am. Chem. Soc.*, **84**, 1513 (1962).
(2) A preliminary report of some of this work was presented before the Combined Southeast and Southwest Regional Meeting of the American Chemical Society, New Orleans, La., 1961, Abstract 162.
(3) Part of this work is from the M.A. Thesis of S. L. Cook, Vanderbilt University, June, 1962, and part from the Ph.D. Thesis of M. E. Warren, Jr., Vanderbilt University, June, 1963.
(4) National Defense Education Act Fellow, 1959–1962.
(5) M. Betti, *Trans. Faraday Soc.*, **26**, 337 (1930).

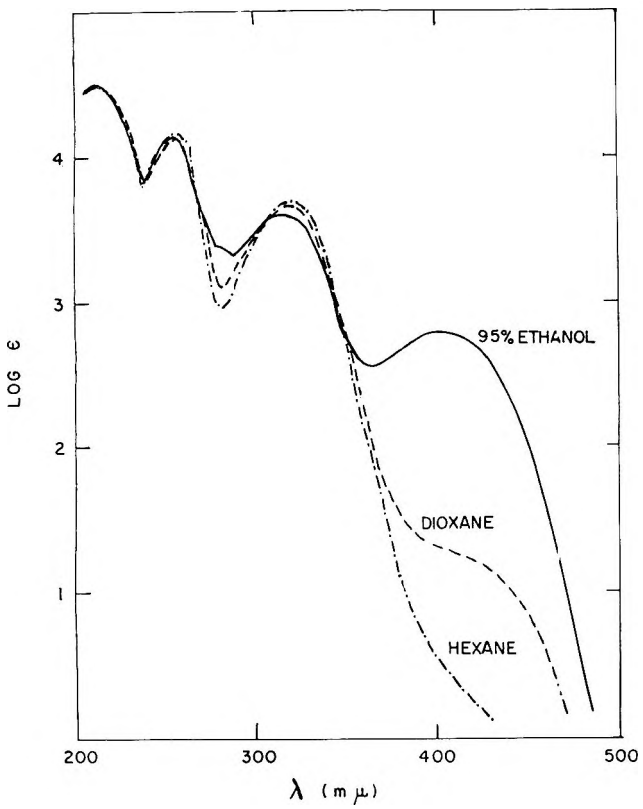


Fig. 1.—Electronic absorption spectra of (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa) in 95% ethanol, dioxane, and hexane.

tive rotation ([φ]D −2676°), while that of *o*-nitrobenzaldehyde is negative ([φ]D −991°). Nerdel, Becker, and Kresze[6] have measured the optical rotatory dispersion curves[7] in a limited wave-length region, 656 to 486 mμ, of a number of Schiff bases prepared from (*S*)-(−)-α-phenylethylamine ([φ]D −48°) and various aromatic aldehydes including benzaldehyde and the three isomeric pyridylaldehydes. All of these derivatives in benzene, ethanol, chloroform, and dioxane display plain positive curves[7] in the spectral region studied and, with few exceptions, show molecular rotations at the sodium D-line of over 100°, with some over 300°. As an extension of these studies Terent'ev, Potapov, and co-workers[8] have examined the Schiff bases formed from a considerable number of aromatic aldehydes and a series of optically active aralkylamines, including α-phenylethylamine[8a] and α-benzylethylamine,[8b] and of *sec*-butylamine.[8c] All of these derivatives display much higher rotatory powers than the corresponding amines. Similarly, Taguchi and Ishida[9] have prepared the N-benzylidene, N-*p*-nitrobenzylidene, and N-isobutylidene derivatives of ethyl D-methioninate ([φ]D +16°), with sodium D-line molecular rotations of +332, +213, and +142°, respectively. Bergel and co-workers[10] have also reported high molecular rotations, some over 200°, for the Schiff bases of α- and β-amino acid esters and amides and of (*S*)-(+)-α-benzylethylamine.

Considering the phenomenon of optical activity,[11] one may assume that the presence in these Schiff bases of optically active azomethine chromophores[12] is associated with these high rotatory powers. This suggests that measurements of the optical rotatory dispersion curves for these compounds would be of some interest and perhaps of some utility in the establishment of the absolute configuration of optically active primary amines. In this connection, Klyne[13] has measured the rotatory dispersion curve for ethyl N-cyclopentylidene-L-tyrosinate. This compound, with an isolated azomethine group not expected to show absorption due to this chromophore above 200 mμ,[12a] is strongly levorotatory at 589 mμ and does display a strong negative plain rotatory dispersion curve from 600 to 300 mμ. Of more interest, however, would be similar measurements with Schiff bases derived from aromatic aldehydes, these bases displaying strong electronic absorption bands above 240 mμ,[12b,14-17] and some time ago we initiated[2] an extensive study of the optical rotatory dispersion curves of such compounds.[18]

We now wish to report such measurements using some Schiff bases prepared by the condensation of benzaldehyde and substituted benzaldehydes with (*S*)-(−)- and (*R*)-(+)-α-phenylethylamine,[19] (*S*)-(+)-α-benzylethylamine,[20] and (*S*)-(+)-*sec*-butylamine.[21]

Results

The N-benzylidene and substituted N-benzylidene derivatives prepared for this study and their respective rotatory powers and electronic absorption maxima occurring above 225 mμ are collected in Table I.[22] Eight of the compounds listed (Ia–IIIc) have been prepared previously.[8] Since similar Schiff bases of aralkyl- and alkylamines are reported[23] to be optically stable during distillation at moderate temperatures or during crystallization, it can be assumed on the basis of the rotatory powers of the respective amines used that the Schiff bases reported here are essentially optically pure.

It is to be noted in Table I that the spectra of the several derivatives prepared from a particular aldehyde

(6) F. Nerdel, K. Becker, and G. Kresze, *Ber.*, **89**, 2862 (1956).

(7) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(8) (a) A. P. Terent'ev and V. M. Potapov, *Zh. Obshch. Khim.*, **28**, 1161 (1958); (b) **28**, 3323 (1958); (c) V. M. Potapov, A. P. Terent'ev, and R. I. Sarybaeva, *ibid.*, **29**, 3139 (1959); (d) V. M. Potapov and A. P. Terent'ev, *ibid.*, **30**, 666 (1960); (e) V. M. Potapov, A. P. Terent'ev, and S. P. Spivak, *ibid.*, **31**, 2415 (1961).

(9) T. Taguchi and T. Ishida, *Pharm. Bull.* (Tokyo), **5**, 181 (1957).

(10) (a) F. Bergel and G. E. Lewis, *Chem. Ind.* (London), 774 (1955); (b) F. Bergel, G. E. Lewis, S. F. D. Orr, and J. Butler, *J. Chem. Soc.*, 1431 (1959); (c) F. Bergel and J. Butler, *ibid.*, 4047 (1961).

(11) A. Moscowitz; *cf.* ref. 7, Chapter 12.

(12) (a) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold, Ltd., London, 1954, p. 56; (b) P. Brocklehurst, *Tetrahedron*, **18**, 299 (1962).

(13) W. Klyne; *cf.* ref. 10c.

(14) J. Hires and L. Hackl, *Acta Univ. Szeged. Acta Phys. Chem.*, **5**, 19 (1959).

(15) V. M. Potapov, V. M. Dem'yanovich, L. I. Lazutina, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **32**, 1187 (1962).

(16) D. Heinert and A. E. Martell, *J. Am. Chem. Soc.*, **85**, 183 (1963).

(17) D. Bertin and M. Legrand, *Compt. rend.*, **256**, 960 (1963).

(18) During the course of this investigation, Potapov, Dem'yanovich, Lazutina, and Terent'ev[15] have reported the optical rotatory dispersion curves of (*R*)-(−)-N-benzylidene-α-*p*-tolylethylamine in methanol and in benzene, measurements being reported to only 334 mμ. More recently Bertin and Legrand[17] have established the absolute configurations of a number of 20-amino steroids by observation of the circular dichroism of the corresponding N-salicylidene derivatives.

(19) W. Leithe, *Ber.*, **64**, 2827 (1931).

(20) P. Karrer and K. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951).

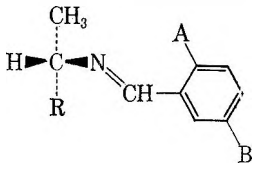
(21) J. A. Mills and W. Klyne, "Progress in Stereochemistry," Vol. 1, Academic Press, Inc., New York, N. Y., 1954, p. 195.

(22) For the sake of clarity, the rotatory powers of all of the Schiff bases in Table I and elsewhere in this section and in the Discussion are given for the (*S*)-isomer, although for some it was the (*R*)-isomer which was prepared and to which the Roman numerals refer in the Experimental.

(23) S. K. Hsü, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.*, 1778 (1935).

TABLE I

ROTATORY POWERS AND ELECTRONIC ABSORPTION SPECTRA OF SOME OPTICALLY ACTIVE SCHIFF BASES IN ABSOLUTE ETHANOL



Compound	Substituents R	A	B	$[\phi]_D$,[a] degrees	Electronic absorption spectrum, max.[b]			
Ia	C_6H_5	H	H	+159				249 (4.31)
Ib	$C_6H_5CH_2$	H	H	+569				248 (3.84)
IIa	C_6H_5	CH_3O	H	−48		304 (3.80)		251 (4.21)
IIb	$C_6H_5CH_2$	CH_3O	H	+433		305 (3.75)		252 (4.20)
IIc	C_2H_5	CH_3O	H	+113		304 (4.00)		250 (4.40)
IIIa	C_6H_5	OH	H	+424[c]	404 (2.78)[d]	315 (3.61)	283 (3.35)[e]	256 (4.14)
IIIb	$C_6H_5CH_2$	OH	H	+828	402 (3.01)[d]	315 (3.58)	280 (3.44)[e]	253 (4.09)
IIIc	C_2H_5	OH	H	+104	401 (2.93)	312 (3.59)	278 (3.40)[e]	253 (4.09)
IVa	C_6H_5	OH	NO_2	+222	392 (3.99)[d]	348 (4.02)	253 (4.17)	233 (4.11)[e]
IVb	$C_6H_5CH_2$	OH	NO_2	+608	391 (4.01)[d]	354 (4.12)	248 (4.13)	228 (4.08)
IVc	C_2H_5	OH	NO_2	+151	390 (4.08)[d]	348 (4.11)	257 (4.27)	230 (4.07)[e]
Va	C_6H_5	OH	Cl	+239	415 (2.80)[d]	328 (3.55)	280 (3.21)[e]	254 (3.96)
Vb	$C_6H_5CH_2$	OH	Cl	+737	414 (3.01)[d]	327 (3.53)	278 (3.28)[e]	254 (3.98)
VIa	C_6H_5	OH	Br	+164	415 (2.68)	328 (3.60)	282 (3.12)[e]	253 (4.04)
VIb	$C_6H_5CH_2$	OH	Br	+592	413 (3.06)[d]	327 (3.55)	278 (3.36)[e]	254 (4.01)

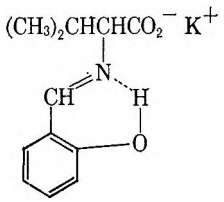
[a] Molecular rotation calculated as $[\alpha]_D \times$ mol. wt./100; c 0.4–1.3; temperature, 20–27°. [b] Wave lengths are given in mμ, numbers in parentheses are log ε. [c] Methanol as solvent. [d] 95% ethanol as solvent. [e] Shoulder.

are essentially identical. The presence of a phenyl group in the amine moiety apparently does not produce a significant effect in the spectrum.

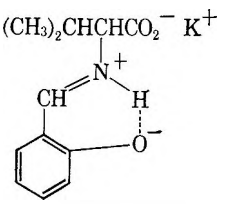
In complete agreement with the spectra reported for N-benzylidenemethylamine[12b] and N-benzylidene-α-p-tolylethylamine,[15] for each N-benzylidene derivative (Ia and Ib) in ethanol, only a band near 249 mμ was observed. A long wave-length band comparable with that for benzaldehyde at 280 mμ[24] was not observed.[25] On the other hand, for the derivatives of *o*-methoxybenzaldehyde (IIa–IIc), there appear, in addition to a strong band (log ε 4.5) near 211 mμ, two bands at nearly the same wave lengths as the two absorption bands displayed by *o*-methoxybenzaldehyde.[26] In contrast, the N-salicylidene derivatives (IIIa–IIIc, Fig. 1) and the substituted N-salicylidene derivatives (IVa–VIb) display in ethanol, in addition to bands at shorter wave lengths, multiple bands above 225 mμ, the presence of which has been interpreted in two ways.

Hires and Hackl[14] have found that the band near 410 mμ in the electronic absorption spectra of the N-salicylidene derivatives of benzylamine, *p*-toluidine, and isopropylamine and of N,N′-bis(salicylidene)ethylenediamine in ethanol changes in dioxane to a distinct shoulder and in hexane is absent. Based on this and other spectral data, Hires and Hackl suggest that the band is due to an intermolecular hydrogen bond complex of the salicylidene derivatives and solvents with an unshared pair of electrons.

An alternative explanation has been advanced by Heinert and Martell[16,27] who have observed a similar multiplicity of bands in the electronic absorption spectra of the α-amino acid potassium salt Schiff bases of 3-hydroxypyridine-4-aldehyde, 3-hydroxypyridine-2-aldehyde, and salicylaldehyde in dioxane and in methanol. From a careful study of both the infrared and electronic absorption spectra of these derivatives they have concluded that the multiplicity of bands in dioxane and in methanol is due to an equilibrium between tautomeric forms, for the potassium N-salicylidenevalinate represented as VIIa and VIIb, with an equilibrium constant in dioxane equal to unity and with band assignments as shown with VIIa and VIIb.



318 and 257 mμ
VIIa



411 and 278 mμ
VIIb

The electronic absorption spectra of the three N-salicylidene derivatives (IIIa–IIIc) in dioxane and in hexane reveal essentially the same solvent effects as reported by Hires and Hackl.[14] As seen in Fig. 1, for (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa) the band in ethanol at 404 mμ is a broad shoulder in dioxane and is almost absent in hexane. The other band near near 315 mμ in both solvents is essentially identical in wave length but slightly higher in intensity. All three derivatives display almost identical spectra in a given solvent.

With respect to the optical rotatory dispersion measurements, the two N-benzylidene derivatives (Ia and Ib) in ethanol display positive plain curves to about 290 mμ (Fig. 2). Precise measurements of their rotatory powers were not possible at the dilutions necessary to penetrate further into the strong absorption band at 249 mμ.

(24) Ref. 12a, p. 126.

(25) For the classifications and recent discussions concerning the origin of the various bands in the electronic absorption spectra of aromatic compounds, see A. Burawoy, *Tetrahedron*, **2**, 122 (1958); S. F. Mason, *Quart. Rev.* (London), **15**, 287 (1961); and also footnote 8 in ref. 16.

(26) A. Burawoy and J. T. Chamberlain, *J. Chem. Soc.*, 2310 (1952).

(27) D. Heinert and A. E. Martell, *J. Am. Chem. Soc.*, **84**, 3257 (1962); **85**, 188 (1963).

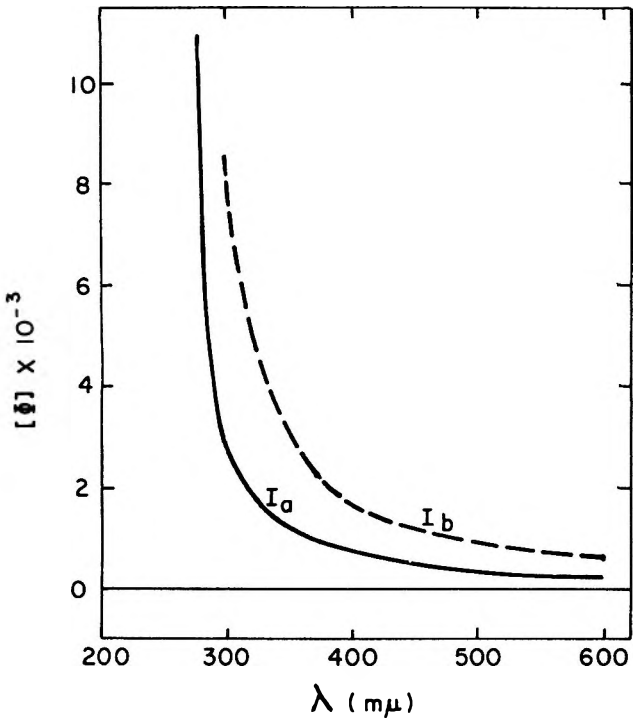


Fig. 2.—Optical rotatory dispersion curves of (*S*)-(+)-N-benzylidene-α-phenylethylamine (Ia) and (S)-(+)-N-benzylidene-α-benzylethylamine (Ib) in absolute ethanol.

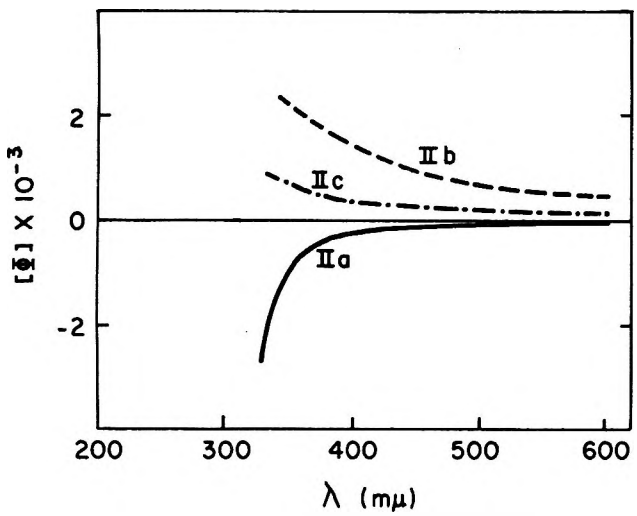


Fig. 3.—Optical rotatory dispersion curves of (*S*)-(−)-N-*o*-methoxybenzylidene-α-phenylethylamine (IIa), (*S*)-(+)-N-*o*-methoxybenzylidene-α-benzylethylamine (IIb), and (*S*)-(+)-*o*-methoxybenzylidene-*sec*-butylamine (IIc) in absolute ethanol.

For the N-*o*-methoxybenzylidene derivatives (IIa–IIc) in ethanol, plain rotatory dispersion curves were observed to about 330 mμ (Fig. 3), beyond which precise measurements were not possible. The curve for (*S*)-(−)-N-*o*-methoxybenzylidene-α-phenylethylamine (IIa) is negative while those for the other two derivatives, both with the same absolute configuration as IIa, are positive.

In contrast to these measurements, (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa) and (*S*)-(+)-N-salicylidene-α-benzylethylamine (IIIb) in ethanol display anomalous optical rotatory dispersion curves (Fig. 4) with two positive Cotton effects centered near 410 and 315 mμ and associated with the absorption bands

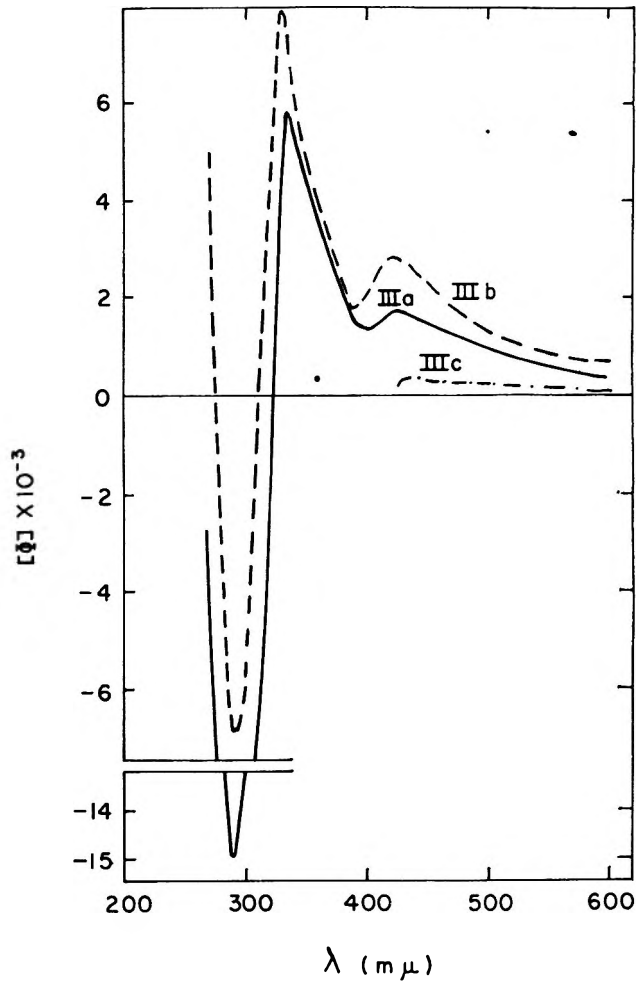


Fig. 4.—Optical rotatory dispersion curves of (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa), (S)-(+)-N-salicylidene-α-benzylethylamine (IIIb), and (*S*)-(+)-N-salicylidene-*sec*-butylamine (IIIc) in 95% ethanol.

near 403 and 315 mμ. In each curve, the amplitude of the Cotton effect at the longer wave length is much smaller than that at the shorter. In comparison, (*S*)-(+)-N-salicylidene-*sec*-butylamine (IIIc) is much weaker in rotatory power above 437 mμ than the derivatives of the aralkylamines. With IIIc in ethanol only one rather weak extremum at 437 mμ was observed, and measurements of rotatory powers below 425 mμ were not possible.

The intense absorption of the (*S*)-N-5-nitrosalicylidene derivatives (IVa–IVc) in ethanol prevented reliable measurements of rotatory powers beyond about 440 mμ. Over this short spectral region, however, the three derivatives displayed plain positive curves.

The N-5-chlorosalicylidene and N-5-bromosalicylidene derivatives of (*S*)-(−)-α-phenylethylamine (Va and VIa) and of (*S*)-(+)-α-benzylethylamine (Vb and VIb) had essentially the same electronic absorption spectra and optical rotatory dispersion curves in ethanol as the corresponding N-salicylidene derivatives.

Some optical rotatory dispersion curves of the N-salicylidene derivatives were observed in dioxane and in hexane as well as in ethanol. In dioxane, each aralkylamine derivative (IIIa and IIIb) displayed only one Cotton effect (Fig. 5), centered near 315 mμ and associated with the absorption band near 318 mμ. No anomaly in the dispersion curve was observed to be as-

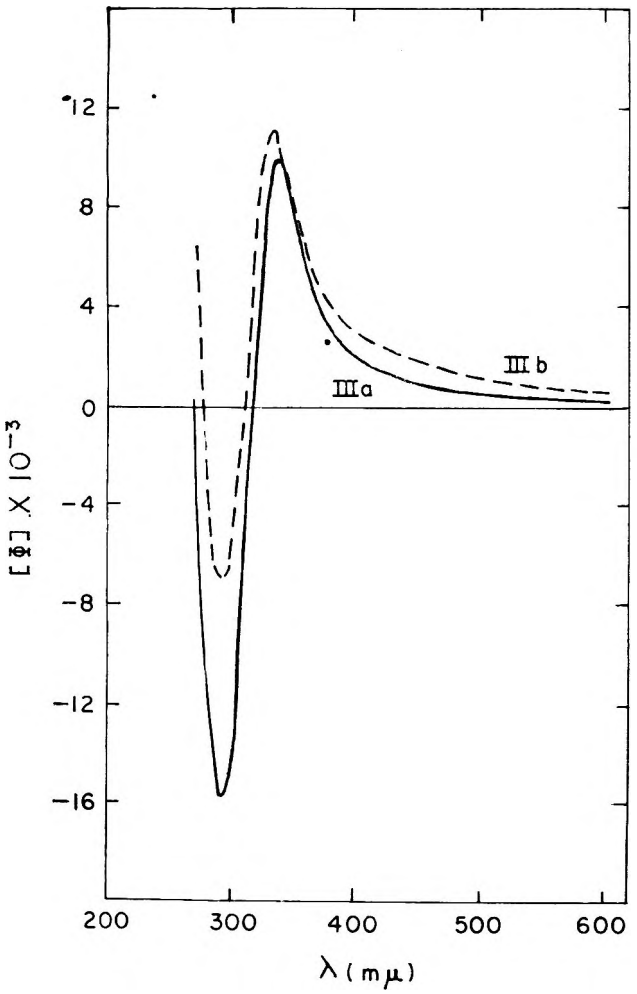


Fig. 5.—Optical rotatory dispersion curves of (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa) and (*S*)-(+)-N-salicylidene-α-benzylethylamine (IIIb) in dioxane.

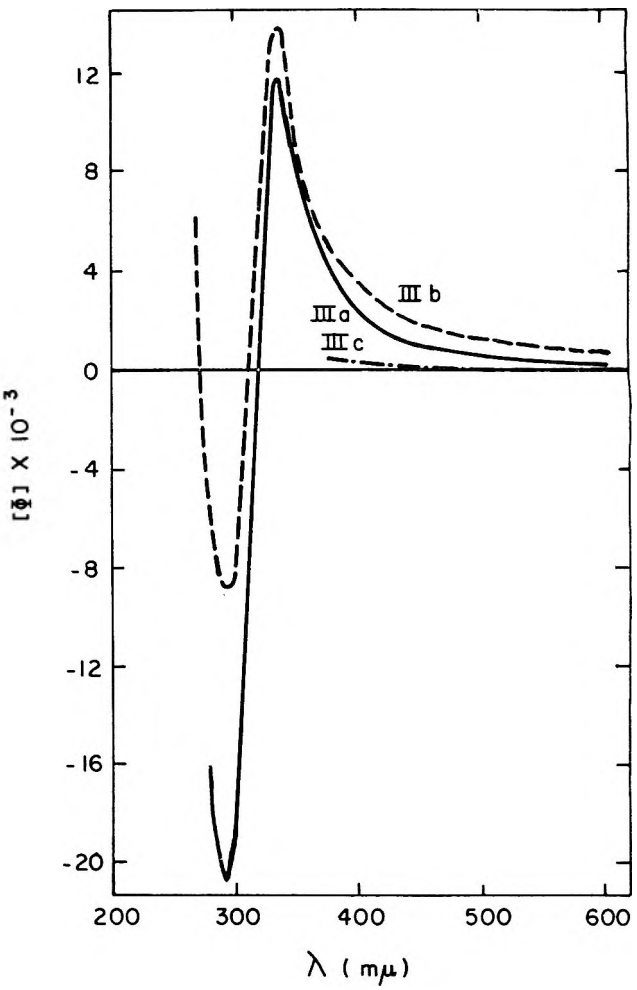


Fig. 6.—Optical rotatory dispersion curves of (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa), (*S*)-(+)-N-salicylidene-α-benzylethylamine (IIIb), and (*S*)-(+)-N-salicylidene-*sec*-butylamine (IIIc) in hexane.

sociated with the shoulder in the absorption spectrum centered at 410 mμ, even when the concentration of each derivative during these measurements was increased enough to compensate for the decrease in the molecular extinction coefficient in this spectral region. These observations are in agreement with those recently reported by Bertin and Legrand[17] who have prepared the N-salicylidene derivatives of some 20-amino steroids. The derivatives with the 20α-configuration display in dioxane positive circular dichroism curves with a single positive maximum[28] at 315 mμ. For those with the 20β-configuration the curves are negative with one negative maximum[28] also at 315 mμ.

In hexane, the optical rotatory dispersion curves of the aralkylamine N-salicylidene derivatives (IIIa and IIIb) were found to be anomalous, both displaying one Cotton effect centered at about 315 mμ (Fig. 6), very similar to the effect seen in dioxane. With (*S*)-(+)-N-salicylidene-*sec*-butylamine (IIIc), however, the extremely low rotatory power prevented observation of the dispersion curve below 375 mμ, and above this wave length only a plain positive dispersion curve was observed.

Comparison of the amplitudes of the Cotton effects displayed by the N-salicylidene, N-5-chlorosalicylidene, and N-5-bromosalicylidene derivatives of the aralkylamines reveals that in ethanol the longer wave-length Cotton effects for the α-benzylethylamines are always greater than those for the corresponding α-phenylethylamines; the converse is true for those at the shorter wave lengths. In addition, for the two aralkylamine derivatives for which solvent effects were studied (IIIa and IIIb), the disappearance of the longer wavelength Cotton effects in changing the solvent from ethanol to dioxane, and then to hexane, is accompanied by successive increases in the amplitudes of the Cotton effects centered at about 315 mμ. In both dioxane and hexane, the larger amplitude for the effect is displayed by the α-phenylethylamine derivative.

Discussion

It is evident from the results outlined above that the optical rotatory dispersion curves of the N-salicylidene derivatives are of the most interest. Although the dispersion curves displayed by the N-benzylidene and N-*o*-methoxybenzylidene derivatives indicate that optically active absorption bands associated with the aldehyde moiety may be primarily responsible for the direction and magnitude of their rotatory powers at the sodium D-line, the present experimental difficulties in observing the relevant Cotton effects make these measurements of limited value.

(28) C. Djerassi and E. Bunnenberg, *Proc. Chem. Soc.*, 299 (1963).

With the N-salicylidene derivatives, however, some comment should be made concerning the interpretation of the changes which occur in their electronic spectra with changes in solvent. The conclusion drawn by Heinert and Martell[16,27] to explain similar changes in the spectra of α-amino acid potassium salt Schiff bases may also explain the changes observed in the absorption spectra of the N-salicylidene derivatives of α-phenyl- and α-benzylethylamine and *sec*-butylamine in going from ethanol to hexane as solvent (Fig. 1). Thus, for each derivative in ethanol there may exist an equilibrium between tautomers analogous to VIIa and VIIb, and for each aralkylamine derivative in ethanol two Cotton effects are observed in the rotatory dispersion curve. In hexane, the equilibrium is shifted so that only the tautomer analogous to VIIa is present in a significant enough concentration to be observed in the absorption spectrum and in the rotatory dispersion curve. In dioxane, however, the shoulder centered at about 410 mμ was found for the aralkylamines and 20-amino steroid[17] derivatives to be optically inactive. Thus, the presence of this shoulder in the electronic spectrum of each of these derivatives is not adequately explained by assuming that it merely represents a decreased but significant concentration of the tautomer analogous to VIIb.

As far as can be measured, the optical rotatory dispersion curves of the N-salicylidene derivatives, all with the (*S*)-configuration, are, at a particular wave length, of the same sign and all of the observed Cotton effects are positive. As seen in Fig. 4 and 6, however, the striking difference in the rotatory powers of the derivatives of the aralkylamines and that of *sec*-butylamine suggest that with the former the large amplitudes of the Cotton effects near 410 and 315 mμ may be due to rotationally significant interactions of the π-electron systems of the phenyl and benzyl groups and the salicylidene moiety, and not solely to the larger steric requirements of these groups. Thus the sign of the Cotton effects may be primarily dependent on the relative rotatory contributions of all conformers having the phenyl and N-salicylidene groups properly oriented for high optical activity.[29]

In some respects, the interactions may be analogous to that between the π-electrons and the carbonyl group in optically active β,γ-unsaturated and α-phenyl ketones,[30] which sometimes results in Cotton effects near 300 mμ of much greater amplitude than those displayed at the same wave length by optically active saturated ketones. It is to be noted, however, that, while the electric dipole transition moment responsible for the marked increase in the rotational strength of an unsaturated ketone also gives rise to an intensity enhancement of the associated absorption band near 300 mμ,[30] no such enhancements are observed in the electronic absorption spectra of the N-salicylidene aralkylamine derivatives.

For the other N-benzylidene and substituted N-benzylidene derivatives of the aralkylamines, similar rotationally significant interactions of the π-electron systems of the phenyl groups and the aldehyde moieties may be present, resulting in extremely high rotatory powers at the sodium D-line (Table I).

Further optical rotatory dispersion measurements with the Schiff base derivatives of other optically active amines are now in progress.

Experimental[31]

Preparation of Schiff Bases.—The amine was added to 0.01 to 0.03 mole of aldehyde in 10 ml. of solvent, warmed if necessary to effect solution of the aldehyde. The mixture was warmed on the steam plate for 15 min. and then allowed to stand at room temperature overnight, during which time the derivative separated as a crystalline solid or as an oil.

Solids were collected by filtration and recrystallized from appropriate solvents to constant melting points. The reported yields were calculated on the basis of materials with constant melting points. Samples for microanalysis were dried overnight at moderate temperatures and 0.1 mm.

For the oils, the reaction solvents were removed at reduced pressure and the derivatives were purified by distillation. All of the purified oils were shown by infrared absorption measurements to be free of the starting aldehydes.

Rotatory Dispersion (R.D.) Measurements.—All rotatory dispersion measurements were obtained using a Rudolph automatic recording spectropolarimeter, Model 260/658/850/810-614, equipped with a double monochromator. The voltage applied to the photomultiplier tube (RCA 7200) was monitored and, for all measurements, cut-off was indicated when this voltage reached 900 v. The slit width was 0.40 mm. with a scan speed of 20 mμ/min., a symmetrical angle of 7°, and a sample tube length of 10.00 mm. All solvents were purified.

Rotatory dispersion curves are reported by indicating for each concentration used the molecular rotation, [φ], at 600 mμ or at the wave length at which cut-off occurred at the next higher concentration, at 589 mμ if included, at the shortest wave length before cut-off, and at each extremum.

In one series of measurements, the optical rotatory dispersion curve of racemic N-5-bromosalicylidene-α-phenylethylamine was observed from 600 to 250 mμ at the same concentrations as used for the optically active form. Over this entire region the observed rotation of this compound was not greater than ±0.005°.

(*R*)-(+)-α-Phenylethylamine.—Racemic α-phenylethylamine was resolved as previously described[32] using N-acetyl-L-leucine. The optically active free base had b.p. 86° (22 mm.), $n^{25}D$ 1.5241, d^{20}_4 0.948, and $[\alpha]^{23}D$ +39.9° (neat); lit.[33] d^{15}_4 0.956, $[\alpha]^{15}D$ +40.7° (neat). Except for the preparation of (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa), this sample of amine was used in the preparation of all optically active α-phenylethylamine Schiff base derivatives.

(S)-(+)-α-Benzylethylamine.—The amine was prepared by decomposition of the commercially available optically active hydrochloride salt. The free base had b.p. 96° (22 mm.), $n^{25}D$ 1.5159. d^{20}_4 0.930 and $[\alpha]^{25}D$ +34.1° (neat); lit.[34] d^{15}_4 0.940,

(29) In this connection it is interesting to note that application of the atomic and conformational asymmetry rules to the prediction of the rotatory powers of α-phenylalkylamines and alcohols [J. H. Brewster, *Tetrahedron Letters*, **No. 20**, 23 (1959)] requires that the amino and hydroxyl groups, usually with rotational ranks lower than that of the carbon sequence [J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959)], be assigned ranks higher than this sequence when they are α to a phenyl ring, suggesting the occurrence of rotationally significant interactions of these two substituents with phenyl groups.

(30) K. Mislow, M. A. W. Glass, A. Moscowitz, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 2771 (1961); A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *ibid.*, **84**, 1945 (1962); K. Mislow and J. G. Berger, *ibid.*, **84**, 1956 (1962); K. Mislow, *Ann. N. Y. Acad. Sci.*, **93**, 457 (1962); S. F. Mason, *J. Chem. Soc.*, 3285 (1962); *Mol. Phys.*, **5**, 343 (1962).

(31) All melting points were taken in capillary tubes and are corrected. Boiling points are not corrected. Microanalyses were done in part by Galbraith Laboratories, Inc., Knoxville, Tenn., and in part by Midwest Microlab, Inc., Indianapolis, Ind. Electronic absorption spectra were obtained using an Applied Physics Corp., Model 14, spectrophotometer employing 1-cm. quartz cells and purified solvents, and measurements were made from 700 mμ at initial concentrations of greater than 0.001 *M*. Optical rotatory power measurements at the sodium D-line were obtained with a visual polarimeter using 1-dm. tubes. Molecular rotations, [φ], were calculated as [α] × mol. wt./100.

(32) H. D. DeWitt and A. W. Ingersoll, *J. Am. Chem. Soc.*, **73**, 5782 (1951).

(33) W. Leithe, *Monatsh.*, **51**, 381 (1929).

(34) W. Leithe, *Ber.*, **65**, 660 (1932).

$[\alpha]^{15}D$ +35.6° (neat). This sample of amine was used in the preparation of all α-benzylethylamine Schiff base derivatives.

(S)-(+)-*sec*-**Butylamine.**—Racemic *sec*-butylamine was resolved as previously described[35] using (+)-tartaric acid. The optically active free base had b.p. 62.5–63.5°, $n^{25}D$ 1.3930, d^{20}_4 0.719, and $[\alpha]^{25}D$ +8.1° (neat); lit.[36] b.p. 63°, d^{20}_4 0.731, $[\alpha]^{20}D$ +7.8° (neat). Except for the preparation of *(S)*-(+)-*o*-methoxybenzylidene-*sec*-butylamine (IIc), this sample of amine was used to prepare all *sec*-butylamine Schiff base derivatives. For the preparation of IIc, another sample of (+)-*sec*-butylamine, resolved as above but partially racemic, was used. This latter material had b.p. 62.5–63.5°, $n^{25}D$ 1.3928, d^{20}_4 0.718, and $[\alpha]^{25}D$ +6.3° (neat).

(R)-(−)-**N-Benzylidene-α-phenylethylamine** (Ia).—Addition of *(R)*-(+)-α-phenylethylamine to a 10% excess of benzaldehyde in methanol gave Ia (88% yield), a light yellow oil, b.p. 119–120° (0.8 mm.), $n^{25}D$ 1.5857, $[\alpha]^{22}D$ −76°, $[\phi]^{22}D$ −159° (*c* 1.3, absolute ethanol); lit.[8a] $n^{20}D$ 1.5888, $[\phi]^{18}D$ −160° (*c* 5.0, methanol); R.D. (Fig. 2) in absolute ethanol, 26°: (*c* 1.1) $[\phi]_{600}$ −160°, $[\phi]_{589}$ −160°, $[\phi]_{338}$ −1350°; (*c* 0.011) $[\phi]_{338}$ −1300°, $[\phi]_{280}$ −11,000°.

(S)-(+)-**N-Benzylidene-α-benzylethylamine** (Ib).—Addition of *(S)*-(+)-α-benzylethylamine to a 9% excess of benzaldehyde in benzene gave Ib (86% yield), a light yellow oil, b.p. 118–120° (0.8 mm.), $n^{25}D$ 1.5715, $[\alpha]^{20}D$ +255°, $[\phi]^{20}D$ +569° (*c* 1.2, absolute ethanol); lit.[8b] for the *(R)*-isomer, $n^{20}D$ 1.5736, $[\phi]^{19}D$ −544° (*c* 4.0, methanol); R.D. (Fig. 2) in absolute ethanol, 26°: (*c* 1.2) $[\phi]_{600}$ +570°, $[\phi]_{589}$ +580°, $[\phi]_{460}$ +1120°; (*c* 0.12) $[\phi]_{460}$ +890°, $[\phi]_{320}$ +5220°; (*c* 0.012) $[\phi]_{320}$ +4900°, $[\phi]_{300}$ +8500°.

(R)-(+)-**N-*o*-Methoxybenzylidene-α-phenylethylamine** (IIa).—Addition of *(R)*-(+)-α-phenylethylamine to a 3% excess of *o*-methoxybenzaldehyde in benzene gave IIa (61% yield), a light yellow oil, b.p. 140–141° (0.5 mm.), $n^{25}D$ 1.5890, $[\alpha]^{26}D$ +20° $[\phi]^{26}D$ +48° (*c* 1.0, absolute ethanol); lit.[8a] $n^{20}D$ 1.5894, $[\phi]^{20}D$ +74°[37] (*c* 3.6, methanol); R.D. (Fig. 3) in absolute ethanol, 24–26°: (*c* 1.0) $[\phi]_{600}$ +47°, $[\phi]_{589}$ +47°, $[\phi]_{350}$ +1000°; (*c* 0.23) $[\phi]_{350}$ +1000°, $[\phi]_{340}$ +1300°; (*c* 0.023) $[\phi]_{340}$ +1400°, $[\phi]_{327}$ +2800°.

(S)-(+)-**N-*o*-Methoxybenzylidene-α-benzylethylamine** (IIb).—Addition of *(S)*-(+)-α-benzylethylamine to a 5% excess of *o*-methoxybenzaldehyde in benzene gave IIb (69% yield), a light yellow oil, b.p. 133° (0.3 mm.), $n^{25}D$ 1.5768, $[\alpha]^{24}D$ +171°, $[\phi]^{24}D$ +433° (*c* 1.2, absolute ethanol); lit.[8b] for the *(R)*-isomer $n^{20}D$ 1.5782, $[\phi]^{20}D$ −440° (*c* 2.3, methanol); R.D. (Fig. 3) in absolute ethanol, 26°: (*c* 1.1) $[\phi]_{600}$ +447°, $[\phi]_{589}$ +458°, $[\phi]_{345}$ +2334°; (*c* 0.11) $[\phi]_{345}$ +2000°, $[\phi]_{333}$ +2300°; (*c* 0.011) $[\phi]_{333}$ +2500°, $[\phi]_{315}$ +3600°.

(S)-(+)-**N-*o*-Methoxybenzylidene-*sec*-butylamine** (IIc).—Addition of a 25% excess of *(S)*-(+)-*sec*-butylamine[38] to *o*-methoxybenzaldehyde in methanol gave IIc (97% yield), a light yellow oil, b.p. 75–79° (0.5 mm.), $n^{25}D$ 1.5304, $[\alpha]^{21}D$ +59°, $[\phi]^{25}D$ +113° (*c* 1.3, absolute ethanol); lit.[8e] $n^{20}D$ 1.5350, $[\phi]D$ +98.7° (methanol); R.D. (Fig. 3) in absolute ethanol, 26°: (*c* 5.2) $[\phi]_{600}$ +108°, $[\phi]_{589}$ +112°, $[\phi]_{348}$ +660°; (*c* 0.52) $[\phi]_{348}$ +700°, $[\theta]_{334}$ +840°; (*c* 0.10) $[\phi]_{334}$ +780°, $[\phi]_{332}$ +840°; (*c* 0.010) no observable rotation to cut-off at 320 mμ.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96. Found: C, 75.34, 75.50; H, 9.07, 9.19.

(S)-(+)-**N-Salicylidene-α-phenylethylamine** (IIIa).—A sample of IIIa provided by Dr. A. W. Ingersoll, Vanderbilt University, was after recrystallization yellow, flattened prismatic masses, m.p. 75–76° (methanol), $[\alpha]^{25}D$ +188°, $[\phi]^{25}D$ +424° (*c* 1.2, methanol); lit.[8a] m.p. 76°, $[\phi]^{20}D$ +433° (*c* 2.1, methanol); electronic spectrum (Fig. 1) in dioxane: log $\epsilon^{shoulder}_{410\ m\mu}$ 1.27, log $\epsilon^{max}_{318\ m\mu}$ 3.68, log $\epsilon^{max}_{257\ m\mu}$ 4.16; electronic spectrum (Fig. 1) in hexane: log $\epsilon^{max}_{320\ m\mu}$ 3.70, log $\epsilon^{shoulder}_{265\ m\mu}$ 4.13, log $\epsilon^{max}_{255\ m\mu}$ 4.18; R.D. (Fig. 4) in 95% ethanol, 22°: (*c* 0.10) $[\phi]_{600}$ +380°, $[\phi]_{589}$ +380°, $[\phi]_{428}$ +1800°, $[\phi]_{397}$ +1400°, $[\phi]_{350}$ +2600°; (*c* 0.010) $[\phi]_{350}$ +2700°, $[\phi]_{337}$ +5900°, $[\phi]_{291}$ −15,000°, $[\phi]_{270}$ −2700°; R.D. (Fig. 5) in dioxane, 22–23°: (*c* 1.65) $[\phi]_{600}$ +356°, $[\phi]_{589}$ +368°, $[\phi]_{385}$ +2550°; (*c* 0.010) $[\phi]_{385}$ +2700°, $[\phi]_{336}$ +10,000°, $[\phi]_{294}$ −16,000°, $[\phi]_{270}$ +200°; R.D. (Fig. 6) in hexane, 22°: (*c* 0.37) $[\phi]_{600}$ +270°, $[\phi]_{589}$ +280°, $[\phi]_{390}$ +2580°; (*c* 0.0073) $[\phi]_{390}$ +2200°, $[\phi]_{336}$ +12,000°, $[\phi]_{290}$ −21,000°, $[\phi]_{280}$ −16,000°.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71. Found: C, 79.79; H, 6.84.

(S)-(+)-**N-Salicylidene-α-benzylethylamine** (IIIb).—Addition of *(S)*-(+)-α-benzylethylamine to a 13% excess of salicylaldehyde in methanol gave IIIb (64% yield), flat yellow prisms, m.p. 58–60° (95% ethanol), $[\alpha]^{24}D$ +346°, $[\phi]^{24}D$ +828° (*c* 1.0, absolute ethanol); lit.[8b] m.p. 47–54°, $[\phi]^{20}D$ +1135°. (*c* 2.4, methanol); electronic spectrum in dioxane: log $\epsilon^{shoulder}_{410\ m\mu}$ 1.35, log $\epsilon^{max}_{317\ m\mu}$ 3.65, log $\epsilon^{shoulder}_{261\ m\mu}$ 4.08, log $\epsilon^{max}_{255\ m\mu}$ 4.13; electronic spectrum in hexane: log $\epsilon^{max}_{318\ m\mu}$ 3.67, log $\epsilon^{shoulder}_{262\ m\mu}$ 4.10, log $\epsilon^{max}_{255\ m\mu}$ 4.15; R.D. (Fig. 4) in 95% ethanol, 22°: (*c* 0.050) $[\phi]_{600}$ +810°, $[\phi]_{589}$ +810°, $[\phi]_{424}$ +2900°, $[\phi]_{387}$ +1900°, $[\phi]_{340}$ +6800°; (*c* 0.010) $[\phi]_{340}$ +6700°, $[\phi]_{333}$ +7900°, $[\phi]_{294}$ −6900°, $[\phi]_{270}$ +5000°; R.D. (Fig. 5) in dioxane, 22°: (*c* 1.00) $[\phi]_{600}$ +728°, $[\phi]_{589}$ +762°, $[\phi]_{375}$ +4470°; (*c* 0.010) $[\phi]_{375}$ +4600°, $[\phi]_{334}$ +11,000°, $[\phi]_{293}$ −7000°, $[\phi]_{270}$ +6500°; R.D. (Fig. 6) in hexane, 22°: (*c* 0.25) $[\phi]_{600}$ +840°, $[\phi]_{589}$ +870°, $[\phi]_{360}$ +6770°; (*c* 0.010) $[\phi]_{360}$ +6700°, $[\phi]_{336}$ +14,000°, $[\phi]_{295}$ −9000°, $[\phi]_{270}$ +6200°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16. Found: C, 80.26; H, 7.10.

(S)-(+)-**N-Salicylidene-*sec*-butylamine** (IIIc).—Addition of *(S)*-(+)-*sec*-butylamine to an 11% excess of salicylaldehyde in methanol gave IIIc (84% yield), a yellow oil, b.p. 70–71° (0.3 mm.), $n^{25}D$ 1.5395, $[\alpha]^{27}D$ +59°, $[\phi]^{27}D$ +104° (*c* 1.1, absolute ethanol); lit.[8e] $n^{20}D$ 1.5435, $[\phi]D$ +145.2° (methanol); electronic spectrum in dioxane: log $\epsilon^{shoulder}_{392\ m\mu}$ 1.51, log $\epsilon^{max}_{316\ m\mu}$ 3.65, og $\epsilon^{shoulder}_{258\ m\mu}$ 4.06, log $\epsilon^{max}_{254\ m\mu}$ 4.09; electronic spectrum in hexane: log $\epsilon^{max}_{317\ m\mu}$ 3.67, log $\epsilon^{shoulder}_{260\ m\mu}$ 3.99, log $\epsilon^{max}_{254\ m\mu}$ 4.02; R.D. (Fig. 4) in 95% ethanol, 22°: (*c* 0.31) $[\phi]_{600}$ +130°, $[\phi]_{589}$ +130°, $[\phi]_{437}$ +370°, $[\phi]_{432}$ +320°; (*c* 0.077) $[\phi]_{432}$ +370°, $[\phi]_{425}$ +200°; (*c* 0.012) no observable rotation to cut-off at 265 mμ; R.D. (Fig. 6) in hexane, 22°: (*c* 2.0) $[\phi]_{600}$ +93°, $[\phi]_{589}$ +98°, $[\phi]_{375}$ +474°; (*c* 0.010) no observable rotation to cut-off at 325 mμ.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.86; H, 8.67.

(R)-(−)-**N-5-Nitrosalicylidene-α-phenylethylamine** (IVa).—Addition of *(R)*-(+)-α-phenylethylamine to a 41% excess of 5-nitrosalicylaldehyde in methanol gave IVa (74% yield), yellow needles, m.p. 102–103° (methanol), $[\alpha]^{25}D$ −82°, $[\phi]^{25}D$ −222° (*c* 0.4, absolute ethanol); R.D. in 95% ethanol, 23°: (*c* 0.23) $[\phi]_{600}$ −310°, $[\phi]_{589}$ −320°, $[\phi]_{450}$ −1550°; (*c* 0.058) $[\phi]_{450}$ −1500°, $[\phi]_{445}$ −1700°; (*c* 0.012) no observable rotation to cut-off at 430 mμ.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22 Found: C, 66.62, 66.78; H, 5.34, 5.14.

(S)-(+)-**N-5-Nitrosalicylidene-α-benzylethylamine** (IVb).—Addition of *(S)*-(+)-α-benzylethylamine to a 21% excess of 5-nitrosalicylaldehyde in methanol gave IVb (83% yield), yellow needles, m.p. 95–97° (heptane), $[\alpha]^{26}D$ +214°, $[\phi]^{25}D$ +608° (*c* 1.2, absolute ethanol); R.D. in 95% ethanol, 26°: (*c* 0.23) $[\phi]_{600}$ +756°, $[\phi]_{589}$ +820°, $[\phi]_{450}$ +2700°; (*c* 0.023) $[\phi]_{450}$ +2500°, $[\phi]_{432}$ +5500°; (*c* 0.0023) no observable rotation to cut-off at 280 mμ.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67. Found: C, 67.56; H, 5.85.

(S)-(+)-**N-5-Nitrosalicylidene-*sec*-butylamine** (IVc).—Addition of a 3% excess of *(S)*-(+)-*sec*-butylamine to 5-nitrosalicylaldehyde in absolute ethanol gave IVc, collected in three crops of fine yellow prisms. A serial recrystallization of these crops from heptane indicated that the original amine contained a slight amount of the racemic form: head fraction (2%), m.p. 60–62°, $[\alpha]^{21}D$ +54° (*c* 1.0, absolute ethanol); middle fraction (27%), m.p. 60–62°; foot fraction (17%), m.p. 59–60°, $[\alpha]^{22}D$ +64° (*c* 1.0, absolute ethanol). After sublimation at 59° (1.5 mm.), the foot fraction, m.p. 59–60°, $[\alpha]^{22}D$ +68°, $[\phi]^{22}D$ +151° (*c* 1.0, absolute ethanol), was used for spectroscopic and rotatory dispersion measurements; R.D. in 95% ethanol, 26°: (*c* 0.74) $[\phi]_{600}$ +160°, $[\phi]_{589}$ +170°, $[\phi]_{458}$ +513°; (*c* 0.030) $[\phi]_{458}$ +200°, $[\phi]_{442}$ +750°; no measurements were made at greater dilutions.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35. Found: 59.43; H, 5.85.

(R)-(−)-**N-5-Chlorosalicylidene-α-phenylethylamine** (Va).—Addition of a 9% excess of *(R)*-(+)-α-phenylethylamine to 5-chlorosalicylaldehyde in heptane gave Va (55% yield), fine yellow prisms, m.p. 111–113° (heptane), $[\alpha]^{22}D$ −92°, $[\phi]^{22}D$ −239° (*c* 1.0, absolute ethanol); R.D. in 95% ethanol, 26°: (*c* 0.55) $[\phi]_{600}$ −317°, $[\phi]_{589}$ −331°, $[\phi]_{460}$ −1050°; (*c* 0.11) $[\phi]_{460}$

(35) A. Fleury-Larsonneau, *Bull. soc. chim. France*, **6**, 1576 (1939).

(36) W. Leithe, *Ber.*, **63**, 800 (1930).

(37) In ref. 8a, $[\alpha]^{20}D$ (*c* 3.6, methanol) is reported as +70°.

(38) This amine had $[\alpha]^{25}D$ +6.3° and was partially racemic. The rotatory powers for IIc have been corrected by multiplying all rotational values by the factor 8.1/6.3.

$-970°$, $[\phi]_{445}$ $-1110°$, $[\phi]_{408}$ $-470°$, $[\phi]_{354}$ $-3120°$; (*c* 0.011) $[\phi]_{354}$ $-3100°$, $[\phi]_{350}$ $-5400°$, $[\phi]_{305}$ $+11,000°$, $[\phi]_{270}$ $-3500°$.

Anal. Calcd. for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43. Found: C, 69.41; H, 5.69.

(*S*)-(+)-N-5-Chlorosalicylidene-α-benzylethylamine (Vb).—Addition of (*S*)-(+)-α-benzylethylamine to a 1% excess of 5-chlorosalicylaldehyde in methanol gave Vb (63% yield), microscopic light yellow needles, m.p. 75–76° (heptane), $[\alpha]^{22}D$ $+264°$, $[\phi]^{22}D$ $+737°$ (*c* 1.0, absolute ethanol); R.D. in 95% ethanol, 26°: (*c* 1.0) $[\phi]_{600}$ $+829°$, $[\phi]_{589}$ $+869°$, $[\phi]_{470}$ $+1960°$; (*c* 0.051) $[\phi]_{470}$ $+2000°$, $[\phi]_{447}$ $+2300°$, $[\phi]_{403}$ $+850°$, $[\phi]_{360}$ $+4300°$; (*c* 0.021) $[\phi]_{360}$ $+4000°$, $[\phi]_{350}$ $+5000°$, $[\phi]_{308}$ $-6600°$, $[\phi]_{280}$ $+400°$.

Anal. Calcd. for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89. Found: C, 70.27; H, 6.13.

(*R*)-(−)-N-5-Bromosalicylidene-α-phenylethylamine (VIa).—Addition of (R)-(+)-α-phenylethylamine to a 13% excess of 5-bromosalicylaldehyde in methanol gave VIa (90% yield), yellow needles, m.p. 130–132° (95% ethanol), $[\alpha]^{25}D$ $-54°$, $[\phi]^{25}D$ $-164°$ (*c* 0.4, absolute ethanol); R.D. in 95% ethanol, 26°: (*c* 0.60) $[\phi]_{600}$ $-190°$, $[\phi]_{589}$ $-220°$, $[\phi]_{470}$ $-850°$; (*c* 0.096) $[\phi]_{470}$ $-1100°$, $[\phi]_{448}$ $-1400°$, $[\phi]_{409}$ $-760°$, $[\phi]_{370}$ $-2500°$; (*c* 0.0096) $[\phi]_{370}$ $-3200°$, $[\phi]_{351}$ $-6300°$, $[\phi]_{298}$ $+9500°$, $[\phi]_{275}$ $+1900°$.

Anal. Calcd. for $C_{15}H_{14}BrNO$: C, 59.22; H, 4.64. Found: C, 59.03; H, 4.93.

(±)-N-5-Bromosalicylidene-α-phenylethylamine.—Addition of a 56% excess of (±)-α-phenylethylamine to 5-bromosalicylaldehyde in 95% ethanol gave the Schiff base (91% yield), yellow needles, m.p. 105–106° (95% ethanol).

Anal. Calcd. for $C_{15}H_{14}BrNO$: C, 59.22; H, 4.64. Found: C, 58.97; H, 4.63.

(*S*)-(+)-N-5-Bromosalicylidene-α-benzylethylamine (VIb).—Addition of (*S*)-(+)-α-benzylethylamine to an 18% excess of 5-bromosalicylaldehyde in methanol gave VIb (86% yield), microscopic light yellow needles, m.p. 87–88° (95% ethanol), $[\alpha]^{25}D$ $+186°$, $[\phi]^{25}D$ $+592°$ (*c* 0.9, absolute ethanol); R.D. in 95% ethanol, 26°: (*c* 0.30) $[\phi]_{600}$ $+640°$, $[\phi]_{589}$ $+680°$, $[\phi]_{470}$ $+1900°$; (*c* 0.061) $[\phi]_{470}$ $+2200°$, $[\phi]_{444}$ $+2900°$, $[\phi]_{403}$ $+900°$, $[\phi]_{360}$ $+4400°$; (*c* 0.012) $[\phi]_{360}$ $+3700°$, $[\phi]_{349}$ $+5300°$, $[\phi]_{306}$ $-5000°$, $[\phi]_{280}$ $+2600°$.

Anal. Calcd. for $C_{16}H_{16}BrNO$: C, 60.39; H, 5.07. Found: C, 60.31; H, 5.24.

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Peptide Synthesis. II. Convenient Synthesis of *p*-Nitrobenzyl Esters of Amino Acids and Peptides

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p-Nitrobenzyl tosylate undergoes ready nucleophilic attack with displacement of the $(-OSO_2C_6H_4CH_3)^-$ ion when it is treated with the sodium or trialkylammonium salt of carbobenzoxyamino acids and peptides. The yields of *p*-nitrobenzyl esters thus prepared are consistently better than 70%. Included are the *p*-nitrobenzyl esters of carbobenzoxyglycine, carbobenzoxy-L-phenylalanine, and carbobenzoxy-L-threonine, and the dipeptide esters of carbobenzoxyglycyl-L-leucine and carbobenzoxy-L-prolyl-L-phenylalanine. By use of this procedure, N-tritylglycine and N-trityl-L-tryptophan were converted into the corresponding *p*-nitrobenzyl esters. Detritylation of the latter by mild acid solvolysis afforded the respective *p*-nitrobenzyl esters of glycine and L-tryptophan, both isolated as the *p*-toluenesulfonates. Similarly, the tripeptide derivative, N(im)-benzyl-L-histidyl-L-prolyl-L-phenylalanine *p*-nitrobenzyl ester di-*p*-toluenesulfonate, was prepared. Esterification of the C-terminal carboxyl end proceeded, in all cases tested, with no detectable amount of racemization.

During the course of synthetic studies with angiotensin analogs[2] carried out in this laboratory, it was found preferable to cover the C-terminal carboxyl group of amino acids and peptides by the *p*-nitrobenzyl group. In contrast to benzyl esters which are labile to anhydrous hydrogen bromide, the *p*-nitrobenzyl esters exhibit a marked stability to acid cleavage.[3] This permits a selective splitting of the N-carbobenzoxy group of an intermediate peptide, while retaining the C-terminal carboxyl end protected by the *p*-nitrobenzyl group. The latter is readily removed by catalytic hydrogenation.

Reports on the syntheses of *p*-nitrobenzyl esters involve the carbon tetrachloride azeotropic method[3] and the alkylation of N-acylamino acids with *p*-nitrobenzyl bromide or chloride in the presence of a tertiary base.[4]

The azeotropic method affords high yields, but when applied in the case of peptides, with prolonged heating for 2–3 days in acidic medium, it is not free of complications. Furthermore, this method is not suitable in the case of complex peptides having polyfunctional groups protected by various labile groups, like trityl or other acid sensitive groups. On the other hand, the direct alkylation with *p*-nitrobenzyl bromide or chloride would involve undesirable side reactions in the case of N-acylpeptides.

In view of the importance of preparing *p*-nitrobenzyl esters of peptides at any stage during synthetic work on polypeptides, the potentialities of *p*-nitrobenzyl tosylate as the alkylating agent have been investigated.

p-Nitrobenzyl tosylate was prepared some years ago by Tipson,[5] and more recently by Kochi and Hammond,[6] during kinetic studies of the solvolysis rates of tosylates. The method consisted of the tosylation of *p*-nitrobenzyl alcohol in dry pyridine. We did not pursue this method, however, since we have found that reaction of the silver *p*-toluenesulfonate with *p*-nitrobenzyl bromide affords the desired ester in high and reproducible yield. By Tipson's method the partial solvation of the so-formed *p*-nitrobenzyl tosylate by

(1) This investigation was supported in part by the Royal Hellenic Research Foundation, to which we are indebted.

(2) D. Theodoropoulos and J. Gazopoulos, *J. Chem. Soc.*, 3861 (1960); D. Theodoropoulos, *Nature*, **194**, 283 (1962).

(3) J. E. Shields, W. H. McGregor, and F. H. Carpenter, *J. Org. Chem.*, **26**, 1491 (1961).

(4) (a) R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **42**, 972 (1959); (b) H. Schwarz and K. Arakawa, *J. Am. Chem. Soc.*, **81**, 5691 (1959).

(5) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(6) J. K. Kochi and G. S. Hammond, *J. Am. Chem. Soc.*, **75**, 3443 (1953).

pyridine is a possibility; hence the crude ester thus obtained requires several recrystallizations before analysis.[6]

The use of *p*-nitrobenzyl tosylate as the alkylating agent has given remarkable results. When the sodium or trialkylammonium salt of carbobenzoxy amino acids and peptides was heated for a short time with the equivalent amount of *p*-nitrobenzyl tosylate in acetone or acetone–dimethylformamide solution, the corresponding *p*-nitrobenzyl ester was obtained in high yield. As examples of N-acylamino acids, carbobenzoxyglycine, carbobenzoxy-L-phenylalanine, and carbobenzoxy-L-threonine were used; when these were treated by the procedure described in this paper, the corresponding *p*-nitrobenzyl esters were obtained in yields consistently better than 70%.

$$Z\text{—HNCH(R)COO}^{-}X^{+} + CH_3C_6H_4SO_2O\overset{+}{C}H_2C_6H_4NO_2 \longrightarrow Z\text{—HNCH(R)COOCH}_2C_6H_4NO_2 + CH_3C_6H_4SO_2ONa$$

Z = carbobenzoxy; X = Na or $(C_2H_5)_3N$

In the case of carbobenzoxy-L-threonine, no side reaction with its secondary function was detected. The preparation of carbobenzoxy-L-threonine calls for some comment, since difficulty was experienced in obtaining pure crystalline material when carbobenzoxylation of L-threonine was conducted in sodium hydroxide or magnesium oxide solution.[7] However, when the reaction was carried out in dilute bicarbonate solution, the desired product, carbobenzoxy-L-threonine, was readily obtained in crystalline form.

In order to ascertain that no racemization takes place during the preparation of *p*-nitrobenzyl esters of N-acylamino acids, the crude esters of carbobenzoxy-L-phenylalanine and carbobenzoxy-L-threonine were hydrogenated over palladium black. The amino acids, which were recovered in 95% yield, exhibited the specific rotation of L-phenylalanine and L-threonine.

In addition to carbobenzoxy amino acids, N-trityl-amino acids have been esterified by the procedure reported in this paper. The sensitive N-trityl group survives during this esterification process and the corresponding N-tritylamino acid *p*-nitrobenzyl esters were readily obtained. With N-tritylglycine the yield of *p*-nitrobenzyl ester was 95%, while the yield from direct alkylation with *p*-nitrobenzyl bromide, after prolonged reaction time, was only 67%. Similarly, N-trityl-L-tryptophan was converted into its corresponding *p*-nitrobenzyl ester; subsequent facile removal of the N-trityl group by mild acid solvolysis afforded L-tryptophan *p*-nitrobenzyl ester *p*-toluenesulfonate in 50% over-all yield. Its absorption spectrum and chromatographic behavior on paper indicated neither oxindole nor any ninhydrin- nor Ehrlich-positive impurity.

Synthesis of L-tryptophan *p*-nitrobenzyl ester *p*-toluenesulfonate either by the azeotropic method[3] or by decarbobenzoxylation of the corresponding ester by hydrogen bromide should be met with reserve; the sensitivity of tryptophan derivatives to the action of hydrogen bromide is well known.[8]

(7) E. Baer and F. Eckstein, *J. Biol. Chem.*, **237**, 1449 (1962).

(8) D. Theodoropoulos and J. S. Fruton, *Biochemistry*, **1**, 933 (1962).

An important advantage in our procedure for the synthesis of *p*-nitrobenzyl esters lies in the fact that it is not restricted to the N-acylamino acid stage. This can be accomplished most satisfactorily with N-acylpeptides. Carbobenzoxyglycyl-L-leucine was readily converted into its corresponding *p*-nitrobenzyl ester in 87% yield. The product was an oil and exhibited an optical value of $[\alpha]^{27}D$ −8.9° ± 1° as 5.48% solution in ethyl acetate. Catalytic hydrogenation of it afforded glycyl-L-leucine, homogeneous according to paper chromatography and with specific rotation in agreement to that reported.[9]

Emphasis has been placed upon the synthesis of carbobenzoxy-L-prolyl-L-phenylalanine *p*-nitrobenzyl ester, since this peptide derivative contains the C-terminal amino acid sequence 7–8 of angiotensin.[10] Carbobenzoxy-L-prolyl-L-phenylalanine, reported[11] as an oil, was obtained in solid form by saponification of the corresponding methyl ester. The N-acyldipeptide, either *via* its sodium or trialkylammonium salt, reacted with *p*-nitrobenzyl tosylate to produce crystalline *p*-nitrobenzyl ester in 86% yield. The optical integrity of the ester was established by hydrogenating it to the free dipeptide, prolylphenylalanine. The latter was proved to be all L–L- in comparison with the optical value reported for this peptide.[11]

Extension of this esterification procedure to the synthesis of a tripeptide ester gave a quite remarkable yield considering the small amounts of reactants used (see Experimental). Thus, N-trityl-N(im)-benzyl-L-histidyl-L-prolyl-L-phenylalanine was converted to its corresponding *p*-nitrobenzyl ester, and the latter, by mild solvolysis in ethanol containing 2 equiv. of *p*-toluenesulfonic acid, afforded N(im)-benzyl-L-histidyl-L-prolyl-L-phenylalanine *p*-nitrobenzyl ester di-*p*-toluenesulfonate in 81% over-all yield. The above sequence is contained as amino acids 6–8 in isoleucine angiotensin[10] and this intermediate would serve in further studies with this hormone.

The above tripeptide acid, N-trityl-N(im)-benzyl-L-histidyl-L-prolyl-L-phenylalanine, was built up by condensation of L-prolyl-L-phenylalanine methyl ester hydrochloride[1] with N-trityl-N(im)-benzyl-L-histidine diethylammonium salt using dicyclohexylcarbodiimide[12] as condensing agent. The resulting ester, N-trityl-N(im)-benzyl-L-histidyl-L-prolyl-L-phenylalanine methyl ester, was then saponified with no difficulty to give the desired tripeptide acid.

In relation to the synthesis of histidyl peptides it should be emphasized that N-trityl-N(im)-benzyl-L-histidine diethylammonium salt may serve, in this connection, as an additional intermediate; other intermediates, like carbobenzoxy-N(im)-benzyl-L-histidine and N(im)-benzyl-L-histidine methyl and benzyl esters[13] have found considerable use in recent synthetic work.[14]

(9) H. Carpenter and T. Gish, *J. Am. Chem. Soc.*, **74**, 3818 (1952); D. Theodoropoulos and J. Gazopoulos, *J. Org. Chem.*, **27**, 2091 (1962).

(10) L. T. Skeggs, W. H. Marsch, J. R. Kahn, and N. P. Shumway, *J. Exptl. Med.*, **102**, 435 (1955).

(11) H. Schwarz, F. M. Bumpus, and I. H. Page, *J. Am. Chem. Soc.*, **79**, 5697 (1957).

(12) J. Sheehan and G. Hess, *ibid.*, **77**, 1067 (1955).

(13) D. Theodoropoulos, *J. Org. Chem.*, **21**, 1550 (1956); D. Theodoropoulos and G. Fölsch, *Acta Chem. Scand.*, **12**, 1955 (1958).

(14) E. Wünsch, *Angew. Chem.*, **71**, 743 (1959); W. Stoffel and L. C. Craig, *J. Am. Chem. Soc.*, **83**, 145 (1961); G. Losse and G. Müller, *Ber.*, **94**, 2768 (1961); K. D. Kopple, R. R. Jarabak, and P. L. Bhatia, *Biochemistry*, **2**, 958 (1963).

Experimental

p-Nitrobenzyl Tosylate.—A solution of silver nitrate (16.9 g., 0.1 mole) in 20 ml. of distilled water was mixed with sodium *p*-toluenesulfonate dihydrate (23 g., 0.1 mole) and dissolved in an equal amount of water with stirring. The precipitate thus formed was filtered by suction, washed with 5 ml. of cold water, and dried *in vacuo* over P_2O_5 in the absence of light yielding 21 g. (75%), m.p. 225° dec. The silver salt (15.3 g.) was suspended in 100 ml. of dry chloroform containing 11 g. of *p*-nitrobenzyl bromide and the mixture was boiled under reflux for 24 hr. in the dark. The reaction mixture was then filtered, the filtrate was evaporated *in vacuo*, and the remaining residue was filtered by addition of cold petroleum ether (b.p. 50–70°); 13.6-g. (88%) yield, m.p. 86–88°. One recrystallization from isopropyl alcohol–petroleum ether yielded 12.1 g. (80%), m.p. 103° (lit.[6] m.p. 103–105°.) The crude ester, m.p. 86–88°, was pure enough and used for further processing.[15]

Carbobenzoxy-L-threonine. In a 1-l. round flask equipped with a mechanical stirrer and immersed in an ice–water bath, were placed 13 g. (0.1 mole) of L-threonine, $[\alpha]^{27}D$ −26.9 ± 0.5° (*c* 3, water), and 400 ml. of 0.4 *M* sodium bicarbonate solution. To the well-stirred mixture was added 20 ml. (20% excess) of carbobenzoxy chloride over a period of 2 hr. (1 ml. every 6 min.). After this time the stirring was continued for an additional hour. The reaction mixture was then extracted twice with ether and the water layer was acidified to congo red with hydrochloric acid. The oily precipitate was cooled in the refrigerator overnight, and the next day upon scratching with a glass rod began to crystallize. The crude product weighed 12 g. and had m.p. 102–105° (lit.[7] m.p. 103–104°). Extraction of the water layer with ethyl acetate, drying of the solvent, and evaporation to dryness afforded an additional amount of 7 g. of product, m.p. 99–101°.

Carbobenzoxy-L-threonine *p*-Nitrobenzyl Ester.—To a solution of 2.7 g. (0.01 mole) of carbobenzoxy-L-threonine in 5 ml. of absolute methanol was added 0.55 g. (0.01 mole) of sodium methylate and the mixture evaporated to dryness. The residue was almost dissolved in 15 ml. of acetone–dimethylformamide (2:1), 3.07 g. (0.01 mole) of *p*-nitrobenzyl tosylate (crude ester) was added, and the mixture was boiled under reflux. After 5 min. a fluffy insoluble material (sodium *p*-toluenesulfonate) began to appear. Boiling was continued for 30 min. and then insoluble material was filtered off and the filtrate was evaporated *in vacuo* at temperature never above 40°. When acetone was removed, the remaining dimethylformamide solution was diluted with 500 ml. of water, The product crystallized immediately; for complete precipitation, however, it was cooled for several hours in the refrigerator. It was filtered, washed well with bicarbonate solution and water, and dried, yielding 3 g. (77%), m.p. 95–97°. On recrystallization from ethanol–ether–petroleum ether (1:1:2) it yielded 2.4 g. (61%), m.p. 111–112°, $[\alpha]^{25}D$ −12.4 ±0.5° (*c* 2.5, chloroform). Its absorption spectrum in ethanol indicated a minimum at 230 mμ and a maximum at 270 mμ (ϵ_{mol} 9250).

Anal. Calcd. for $C_{19}H_{20}N_2O_7$: C, 58.7; H, 5.1; N, 7.2. Found: C, 58.8; H, 5.3; N, 7.1.

A solution of 1 g. of carbobenzoxy-L-threonine *p*-nitrobenzyl ester (crude product) in acetic acid–water was hydrogenated over palladium black. The catalyst was removed by filtration and washed several times with acetic acid–water, and the combined filtrate was evaporated to dryness. The peptide, which was isolated by addition of acetone, weighed 0.287 g. (95%) and without recrystallization possessed specific rotation $[\alpha]^{25}D$ −26.2 ± 0.5° (*c* 3, water).

Carbobenzoxy-L-phenylalanine *p*-Nitrobenzyl Ester.—Carbobenzoxy-L-phenylalanine (2.96 g., 0.01 mole) and *p*-nitrobenzyl tosylate (3.07 g., 0.01 mole) were treated according to the procedure described above, yielding 3.5 g. (81%), m.p. 97–99°. The product was recrystallized from benzene–petroleum ether, yielding 3.2 g. (75%), m.p. 105–106°, $[\alpha]^{27}D$ +7.1 ±0.5° (*c* 3, chloroform).

Anal. Calcd. for $C_{24}H_{22}N_2O_6$: C, 65.3; H, 5.1; N, 6.4. Found: C, 66.4; H, 5.1; N, 6.6.

Hydrogenolysis of 1 g. of carbobenzoxy-L-phenylalanine *p*-nitrobenzyl ester (crude product), in the usual manner, afforded 0.341 g. (93%) of L-phenylalanine with specific rotation of $[\alpha]^{26}D$ −35.3 ± 0.5° (*c* 1.6, water). Authentic L-phenylalanine, used as the starting material, exhibited $[\alpha]^{26}D$ −35.5 ± 0.5° (*c* 1.6, in water).

Carbobenzoxyglycine *p*-Nitrobenzyl Ester. A.—This compound was prepared in a manner similar to that outlined above, yielding 2.7 g. (80%), m.p. 107–109° (lit.[4b] m.p. 107–109.5°).

B.—Carbobenzoxyglycine (2 g., 0.01 mole) was dissolved in dry acetone by addition of 1.01 g. (0.01 mole) of triethylamine. To this solution 3.07 g. (0.01 mole) of *p*-nitrobenzyl tosylate was added and the mixture was boiled under reflux for 1 hr. During that time triethylammonium *p*-toluenesulfonate precipitated. The reaction mixture was filtered, the filtrate was evaporated to dryness, and the residue, upon addition of water and cooling, crystallized. It was washed with dilute bicarbonate solution and water, and dried, yielding 3.1 g. (90%). It was recrystallized from isopropyl alcohol, yielding 2.6 g. (78%), m.p. 107–109°.

Anal. Calcd. for $C_{17}H_{16}N_2O_6$: C, 59.2; H, 4.6; N, 8.1. Found: C, 59.3; H, 4.6; N, 8.3.

N-Tritylglycine *p*-Nitrobenzyl Ester. A.—Treatment of the sodium or triethylammonium salt of N-tritylglycine in similar fashion afforded the corresponding *p*-nitrobenzyl ester in 95% yield. The crude product was dissolved in ethyl acetate and this solution was washed with 5% aqueous diethylamine solution and water, and dried. Removal of the solvent *in vacuo* gave 4.2 g. (93%) of product, m.p. 106–107°. It was recrystallized from chloroform–ether–petroleum ether (1:2:3), in 80% yield, m.p. 125–126°.

B.—A solution of N-tritylglycine (3.17 g., 0.01 mole), triethylamine (1.01 g., 0.01 mole) and *p*-nitrobenzyl bromide (2.1 g., 0.01 mole) in 10 ml. of dry chloroform was boiled under reflux for 6 hr. and then kept at room temperature for an additional 24 hr. The solution was diluted with 100 ml. of chloroform and this solution was washed with 5% aqueous diethylamine and water, and dried. The solvent was evaporated *in vacuo* and upon addition of petroleum ether the residue crystallized, yielding 2.9 g. (64%), m.p. 126°.

Anal. Calcd. for $C_{28}H_{24}N_2O_4$: C, 74.3; H, 5.4; N, 6.1. Found: C, 74.2; H, 5.2; N, 6.2.

Glycine *p*-Nitrobenzyl Ester *p*-Toluenesulfonate.—A solution of N-tritylglycine *p*-nitrobenzyl ester (2.2 g., 0.005 mole) and 0.95 g. (5% excess) of *p*-toluenesulfonic acid monohydrate in 10 ml. of acetone was boiled under reflux for 10 min. During this time a white precipitate was formed which was filtered and washed with dry ether, yielding 1.95 g. (96%), m.p. 200–201°. A sample recrystallized from isopropyl alcohol–ether had m.p. 200–202.

Anal. Calcd. for $C_{16}H_{18}N_2O_7S$: C, 51.6; H, 4.8; N, 7.5. Found: C, 51.6; H, 4.8; N, 7.1.

L-Tryptophan *p*-Nitrobenzyl Ester *p*-Toluenesulfonate.—Using 2.2 g. (0.005 mole) of N-trityl-L-tryptophan diethylammonium salt,[16] N-trityl-L-tryptophan *p*-nitrobenzyl ester (2.5 g.) was obtained in the same manner described for the threonine derivative. The crude ester (2.5 g.) was dissolved in 5 ml. of acetone, a few drops of diethylamine and 5 ml. of dry ether were added, and the solution was cooled in the refrigerator overnight. The resulting slight precipitate was removed by filtration, the filtrate was evaporated to dryness, and the residue was solidified by addition of water, yielding 2.4 g. (dried over P_2O_5 *in vacuo*). Detritylation was effected by dissolving it in 10 ml. of ethanol, adding 0.9 g. of *p*-toluenesulfonic acid monohydrate, and boiling for 5 min. Ethanol was removed *in vacuo* and replaced by dry ether. The resulting oil was triturated with a glass rod and the solvent was decanted. Addition of isopropyl alcohol caused the oily product to crystallize, yielding 1.2 g. (50%), m.p. 200–202°. On recrystallization from ethanol–ether it had m.p. 206–207°, $[\alpha]^{25}D$ +12.8 ± 0.5° (*c* 2, dimethylformamide). An 80% ethanolic solution of the product gave an absorption spectrum with a maximum at 280 mμ (ϵ_{mol} 13,800) and a minimum at 235 mμ (ϵ_{mol} 1950). Paper chromatography in 1-butanol–pyridine–acetic acid–water (15:10:3:12) revealed only one ninhydrin- and Ehrlich-positive spot, R_f 0.94. In the latter chromatographic system L-tryptophan had R_f 0.51.

Anal. Calcd for $C_{25}H_{28}N_3O_7S$: C, 58.6; H, 4.9; N, 8.2. Found: C, 58.4; H, 5.2; N, 8.5.

(15) Attempted synthesis of benzyl tosylate from silver *p*-toluenesulfonate and benzyl chloride or bromide, under exactly the same conditions, resulted in the formation of a pitch-black product. It seems that prolonged heating of the reaction mixture favors self-alkylation of the so-formed benzyl tosylate *via* formation of benzyl carbonium ions $ArCH_2^+$; this is in line with the varying stability of tosylates.[6]

(16) G. Stelakatos, D. Theodoropoulos and L. Zervas, *J. Am. Chem. Soc.*, **81**, 2884 (1959).

Carbobenzoxyglycyl-L-leucine *p*-Nitrobenzyl Ester.—Starting with 1.8 g. (0.005 mole) of carbobenzoxyglycyl-L-leucine, m.p. 101–102°, $[\alpha]^{25}D$ −18.5 ± 0.5° (*c* 1.39, *N* NaOH), the *p*-nitrobenzyl ester was obtained as a waxy product, yield 2.2 g. (96%), $[\alpha]^{27}D$ −8.9 ± 1° (*c* 5.48, ethyl acetate).

Hydrogenolysis of the above ester (2.2 g.) in the usual manner afforded 1.2 g. (70%) of glycyl-L-leucine (crude product), $[\alpha]^{25}D$ −36° (*c* 2, water).

Carbobenzoxy-L-prolyl-L-phenylalanine.—Carbobenzoxy-L-prolyl-L-phenylalanine methyl ester (2.05 g., 0.005 mole), obtained by condensation of carbobenzoxy-L-proline with L-phenylalanine methyl ester by the dicyclohexylcarbodiimide method,[12] was dissolved in 10 ml. of ethanol and 5 ml. of *N* sodium hydroxide was added. After 1 hr. the solution was diluted with 50 ml. of water and unhydrolyzed material was extracted with ether. The water layer was acidified to congo red with hydrochloric acid and the resulting oil was taken up in ether. The ethereal solution was extracted with dilute bicarbonate solution; the latter was acidified with hydrochloric acid. The oily product was taken up in ether and this solution was washed with water until it was free from acid and then was dried with anhydrous sodium sulfate. The solvent was evaporated to dryness and the residue was kept *in vacuo* over P_2O_5 for 24 hr. The substance then solidified and had m.p. 123–124°, yield 1.4 g. (73%), $[\alpha]^{20}D$ −36.6 ± 0.5° (*c* 2, chloroform).

Anal. Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.6; H, 6.1; N, 7.0. Found: C, 66.3; H, 6.2; N, 6.8.

Carbobenzoxy-L-prolyl-L-phenylalanine *p*-Nitrobenzyl Ester.—A solution of 1.98 g. (0.005 mole) of carbobenzoxy-L-prolyl-L-phenylalanine, 0.5 g. (0.005 mole) of triethylamine and 1.5 g. (0.005 mole) of *p*-nitrobenzyl tosylate in 10 ml. of dry acetone was boiled under reflux for 1 hr. The solvent was evaporated to dryness and replaced with ethyl acetate. This solution was washed well with dilute bicarbonate solution and water, and dried. The solvent was removed *in vacuo* and the remaining residue, upon addition of a few milliliters of isopropyl alcohol and cooling, was crystallized, yielding 2.3 g. (86%), m.p. 86–87°. On recrystallization from isopropyl alcohol–petroleum ether it had m.p. 87–89°.

Anal. Calcd. for $C_{29}H_{29}N_3O_7$: C, 65.5; H, 5.4; N, 7.9. Found: C, 65.7; H, 5.5; N, 8.0.

A portion of the above ester (1 g.) was hydrogenated over palladium black in ethanol–acetic acid solution. The dipeptide (0.3 g.), L-prolyl-L-phenylalanine, thus obtained had $[\alpha]^{20}D$ −39.6 ± 1° (*c* 1.7, 6 *N* HCl). This optical value was in good agreement to that reported for the recrystallized product.[11]

N-Trityl-N(im)benzyl-L-histidine Diethylammonium Salt.—To a solution of N(im)benzyl-L-histidine[17] (2.54 g., 0.01 mole), diethylamine (3 ml., 0.03 mole), water (4 ml.), and isopropyl alcohol (8 ml.) was added trityl chloride (3.6 g., 0.013 mole) with shaking over a period of 1 hr. at room temperature. Water (10 ml.) was then added and the reaction mixture was extracted with two 50-ml. portions of chloroform. The chloroform extract was dried over sodium sulfate and the solvent was evaporated to dryness. The remaining residue, upon addition of dry ether and cooling overnight, was crystallized, yielding 1.4 g. (25%), m.p. 135–137°. On recrystallization from isopropyl alcohol–ether it had m.p. 146–148° (dried under high vacuum over P_2O_5), yield 1.3 g., $[\alpha]^{20}D$ +14.7 ± 0.5° (*c* 1.5, chloroform).

Anal. Calcd. for $C_{36}H_{40}N_4O_2$: C, 77.1; H, 7.1; N, 9.9. Found: C, 77.4; H, 7.2; N, 10.1.

N-Trityl-N(im)-benzyl-L-histidyl-L-prolyl-L-phenylalanine.—N-Trityl-N(im)-benzyl-L-histidine diethylammonium salt (2.8 g., 0.005 mole) and L-prolyl-L-phenylalanine methyl ester hydrochloride[2] (1.56 g., 0.005 mole) were coupled by means of dicyclohexylcarbodiimide (1 g.) in methylene chloride. After 24 hr. the filtrate was washed with two 25-ml. portions of 5% aqueous diethylamine solution and water, dried, and then concentrated *in vacuo* at 35°. The remaining sirupy ester (2.9 g.) was saponified with 4.2 ml. (10% excess) of 1 *N* NaOH in 5 ml. of ethanol. After 1 hr. the reaction mixture was diluted with 30 ml. of water and acidified with acetic acid. The resulting precipitate was filtered, washed well with water, and dried, yielding 2.4 g. For purification it was dissolved in ethyl acetate (5 ml.), diethylamine (0.5 ml.) was added, and the solution was kept in the refrigerator overnight. The diethylammonium salt of N-trityl-N(im)-benzyl-L-histidyl-L-prolyl-L-phenylalanine, which was precipitated completely by addition of 10 ml. of ether, was isolated by filtration; it was then suspended in water and acidified with acetic acid. The product thus obtained weighed 2.3 g. (82%), $[\alpha]^{22}D$ −5.5° (*c* 4, chloroform), and melted completely at 145°, with previous softening at 130°.

Anal. Calcd. for $C_{46}H_{45}N_5O_4$: C, 75.4; H, 6.1; N, 9.5. Found: C, 75.1; H, 7.0; N, 9.7.

N(im)-Benzyl-L-histidyl-L-prolyl-L-phenylalanine *p*-Nitrobenzyl Ester Di-*p*-Toluenesulfonate.—To a solution of 0.9 g. of N-trityl-N(im)-benzyl-L-histidyl-L-prolyl-L-phenylalanine and 0.17 ml. of triethylamine in 5 ml. of dry acetone was added 0.38 g. of *p*-nitrobenzyl tosylate. The mixture was boiled under reflux over a period of 1 hr. and then the solvent was evaporated *in vacuo*. The remaining residue was taken up in ethyl acetate and this solution was washed with 5% aqueous diethylamine and water, and dried. After evaporation of the solvent the residue was dissolved in 5 ml. of ethanol and detritylated by addition of 0.48 g. of *p*-toluenesulfonic acid monohydrate and boiling of the reaction mixture for 5 min. under reflux. Ethanol was then removed *in vacuo* and a few milliliters of isopropyl alcohol were added. Upon scratching with a glass rod the product began to crystallize. Complete crystallization, however, was effected by addition of dry ether and cooling; the over-all yield was 81% (0.97 g.), m.p. 170–171° (softens at 110°). On recrystallization from isopropyl alcohol–ether the product (0.87 g.) had identical m.p. 170–171°, $[\alpha]^{20}D$ −8.7 ± 1° (*c* 1, dimethylformamide), −20.1 ± 0.5° (*c* 3, 50% acetic acid). Paper chromatography (Whatman No. 1) in 1-butanol–pyridine–acetic acid–water (15:10:3:12) revealed only one ninhydrin-positive spot, R_f 0.97. The data from elementary analysis accorded best with that calculated for the monohydrate.

Anal. Calcd. for $C_{48}H_{52}N_6O_{12}S_2 \cdot H_2O$: C, 58.4; H, 5.5; N, 8.5. Found: C, 58.2; H, 5.2; N, 8.2.

(17) V. du Vigneaud and O. Behrens, *J. Biol. Chem.*, **117**, 27 (1937).

Studies on the Mechanism of the Direct Acylation of Amino Acids and Related Compounds in Nonaqueous Solvents[1]

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The mechanism of direct acylation was investigated using L-leucine and dichloroacetyl chloride in anhydrous ethyl acetate as the model system. The kinetic data fit quite closely to the differential equation developed from theoretical considerations. Because of its bearing on the interpretation of the kinetic data, the solubility of L-leucine in anhydrous ethyl acetate was determined and was found to increase as the water content of the solvent decreased. The results permit a reasonable suggestion for the chemical structure of the intermediate formed in the course of the acylation process. The system is of interest as a heterogeneous reaction in which the rate of dissolution of the suspended, crystalline reactant is rate controlling.

The direct method of acylation[3-5] provides an easy method for the acylation of amino acids, peptides, and hydroxy acid esters. In contrast to the Schotten–Baumann reaction, direct acylation proceeds in anhydrous ethyl acetate without a base to accept the liberated hydrogen chloride. For preparative acylations, one suspends the amino acid in ethyl acetate, adds the acid chloride, and refluxes the mixture. The acylated amino acid, which is soluble in ethyl acetate, is separated from the unchanged amino acid by filtration. A crystalline product is usually obtained when the solvent is drawn off by a stream of air. Although the synthetic value of this reaction has been cataloged,[3-5] the reaction mechanism has not been investigated. Since amide bonds are formed (as well as ester), involving amino acids, interest is generated in what mechanistic analogies could be drawn to *in vivo* biochemical acylations. As a first step, a kinetic scheme for this reaction has been developed, using L-leucine and dichloroacetyl chloride for the initial model system. For kinetic purposes, it was profitable to determine the solubility of L-leucine in the reaction solvent. Qualitative observations were made on the effect of size and form of the suspended amino acid crystals on reaction rate. Additionally, other anhydrous solvents were tested as reaction media. The results allow the postulation of a reasonable structure for the responsible acylating intermediate.

Most important, the investigation is of interest as one of the rare instances allowing a quantitative kinetic study of a heterogeneous reaction between a crystalline and a dissolved organic reagent.

Experimental

Materials.—L-Leucine, General Biochemicals, Inc., was recrystallized from water and dried in a vacuum desiccator over phosphorus pentoxide. The amino acid flakes were pulverized to a fine powder using a Waring Blendor. The powder was forced through a 48-mesh (297 μ) sieve and caught on a 60-mesh (250 μ) sieve. The purity of the amino acid was confirmed by decomposition point range, optical rotation, and paper chromatography.

Dichloroacetyl chloride, Eastman reagent grade, was distilled under nitrogen before use (30 mm., 40–41°).

Ethyl acetate, J. T. Baker Chemical Co., anhydrous grade, was distilled at atmospheric pressure. The purity of the ethyl acetate was confirmed by boiling point range and refractive index. The initial product contained 0.02% water, as determined by the Karl Fischer method. By drying the above product over Molecular Sieves, the water content was reduced to 0.005%.

Kinetic Reaction Procedure.—Kinetic runs were carried out in the modified 250-ml. round-bottom Pyrex flask shown in Fig. 1. Capillary tube, A, was used to obtain reaction samples that were free of suspended amino acid particles. This capillary was also used to introduce a dry nitrogen gas atmosphere over the reaction mixture. The acid chloride was introduced by means of the outlet, B. Stirring was accomplished by a magnetic stirrer, C and D, encased in a polyethylene bag, E, which contained the indicating form of Drierite, F, to detect water leaks. Sampling was done with the aid of the Thomas–Seligson-type pipet shown in Fig. 2. Outlet A was connected to a source of vacuum, and outlet B to a 1:1 propanol–water diluent reservoir contained in a buret. The pipet stem, C, was fashioned from a 5-μl. pipet, though the total volume of the stem ranged from 0.081 ml. at 30° to 0.074 ml. at 65° (calibrated with mercury for the different temperatures of the runs). Tygon tubing, D, was used to connect the 10/30 $\overline{\$}$ male joint, E, to the pipet stem; the pipet stem was able to move through the joint.

L-Leucine (0.656 g., the quantity that would make a 0.1 *M* solution in 50 ml. of ethyl acetate if the amino acid were entirely dissolved) was suspended in 47 ml. of anhydrous ethyl acetate and allowed to reach saturation solubility. During this period the magnetic stirrer was allowed to reach a uniform rate and air was excluded from the reaction flask by forcing dry nitrogen through the capillary inlet, A, Fig. 1. A solution of dichloroacetyl chloride in 3 ml. of ethyl acetate was heated to reaction temperature and introduced into the stirred mixture through outlet B, Fig. 1. The clock was started at this point and the stopcock of outlet B was allowed to remain open as an escape vent for the nitrogen. A cold finger was placed in the portion of outlet B above the stopcock to reduce possible loss of solvent and acid chloride due to evaporation. At exactly 50 sec., the first sample was taken by withdrawing the nitrogen inlet tube in capillary A and attaching the sampling pipet to the capillary tube through the standard taper joint system. Under the demand of the vacuum, a sample of the reaction mixture was filtered through the glass wool filter of the capillary tube into the pipet filling the whole pipet cavity to the stopcock plug. The sampling-pipet assembly was now withdrawn from the capillary tube and the sample remaining in the capillary tube was forced back into the reaction mixture by reapplying the positive pressure of nitrogen. Meanwhile the contents of the sampling pipet stem were simultaneously discharged into test tubes and diluted by turning the stopcock so that the diluent would flow through the pipet. The reaction samples were diluted to a total volume of 1 ml. with propanol–water diluent from a buret connected to A, Fig. 2. This not only destroyed any acid chloride in the reaction sample, but diluted it tenfold. The test tubes were stoppered and set aside for the analytical procedure. The entire sampling process took approximately 10 sec. Samples were withdrawn every minute for the first 10 min. of the reaction.

Two aliquots, varying in size from 20 to 100 μl., of each reaction sample were placed into test tubes containing 2 ml. of 1 *N* KOH in 50% ethanol. The test tubes were capped and placed in boiling water. After 45 min., the test tubes were removed and

(1) Presented in part before the Division of Biological Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) Excerpted in part from the thesis submitted by C. B. Warren in partial fulfillment of the requirements for the degree of Master of Science.

(3) E. Ronwin, *J. Org. Chem.*, **18**, 127 (1953).

(4) E. Ronwin, *ibid.*, **18**, 1546 (1953).

(5) E. Ronwin, *ibid.*, **22**, 1180 (1957).

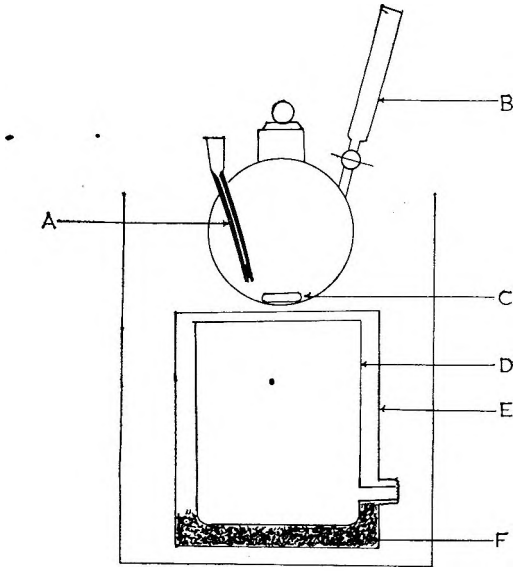


Fig. 1.—Reaction flask: A, capillary tube with glass-wool filter in tip and 10/30 ☨ female joint on outer end; B, outlet with stopcock to permit entry of acid chloride solution and exit of nitrogen gas; C and D, magnetic stirrer; E, polyethylene bag; and F, Drierite.

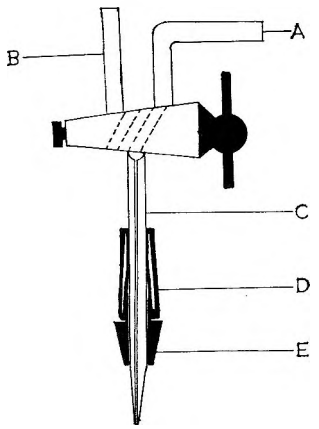


Fig. 2.—Sampling pipet: A, outlet connecting to vacuum source; B, outlet to buret containing 50% propanol–water diluent; C, pipet stem; D, tygon tubing; and E, 10/30 ☨ male joint.

the solution was neutralized with 1 *N* HCl.[6] The concentration of free amino acid in the hydrolyzed samples was determined by the ninhydrin reaction.[7]

Solubility Determinations.—L-Leucine (0.656 g.) was suspended in anhydrous ethyl acetate at various temperatures and stirred 1 hr. which assured saturation. The mixture was then poured through a sintered-glass filter which was preheated to the desired temperature by pouring through warm solvent. The clear solution was than taken to less than 1-ml. volume with the aid of a stream of air and 3 ml. of 1 *N* HCl was added to the residue (this increased the aqueous solubility of the L-leucine without affecting its quantitative determination). Then 3 ml. of 1 *N* KOH solution was added and aliquots of the resulting solution were analyzed for the quantity of L-leucine present by the ninhydrin procedure.

Results and Discussion

Solubility of L-Leucine in Ethyl Acetate.—As a result of its bearing on the interpretation of the kinetic data, as will be indicated below, the determination of the solubility of the amino acid in ethyl acetate was of value. The results are presented in Fig. 3, for the temperature range between 35 and 65° and for solution in ethyl acetate containing 0.02%, as well as 0.005% water. It is obvious that the lower the water content of the solvent, the greater the solubility of the amino acid. This is interesting in view of the fact that L-leucine is soluble in water to the extent of 2.3 g./100 g. of water at 0° to 3.8 g./100 g. of water at 75°, which is some 10,000 times greater than its solubility in the most anhydrous ethyl acetate available to us.[8]

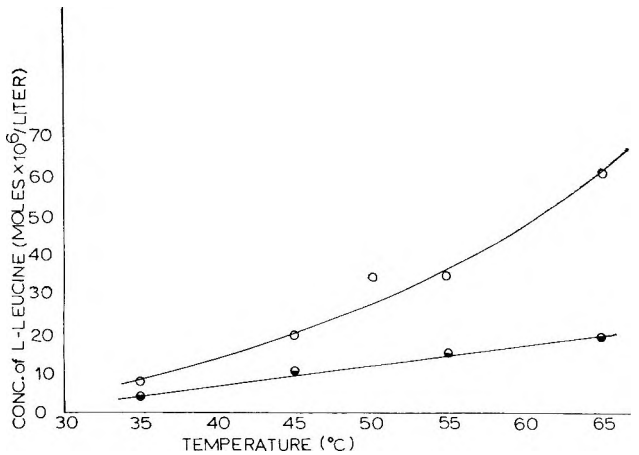


Fig. 3.—Solubility of L-leucine in ethyl acetate as a function of temperature: ◒, ethyl acetate containing 0.02% water; and O, ethyl acetate containing 0.005% water.

While the time to attain saturation varied with temperature, saturation occurred within 30 min. at all temperatures in the range from 35 to 65°. As it is important from the kinetic viewpoint, as well as from the question of reproducibility, the amino acid was always brought to saturation by allowing a 45- to 60-min. equilibration period with the solvent at the reaction temperature prior to the addition of the acid chloride.

Kinetic Studies.—Consider the system where S = suspended L-leucine (a surface area); $[L_s]$ = dissolved L-leucine; $[A]$ = acid chloride; $[p]$ = products. These relations and rate expressions can be derived.

$$S \underset{k_5}{\overset{k_4}{\rightleftharpoons}} [L_s] + [A] \xrightarrow{k_1} [p]$$

The reaction is commenced with the amino acid at its saturation solubility from which one of two cases holds: either the amino acid remains at saturation in the solvent (case I; that is the rate is governed by a homogeneous reaction), or the rate of solution of the amino acid becomes rate controlling (case II; that is the rate of dissolution of the solid reagent is insufficient to maintain the equilibrium concentration of the amino acid in solution).

For case I, it is self-evident that

$$dp/dt = v = k_1[L_s][A] \quad (1)$$

(6) It was found empirically that hydrolysis was complete within 30 min., the extra 15 min. being employed as a precautionary measure. L-Leucine was not destroyed by the hydrolytic step.

(7) S. Moore and W. H. Stein, *J. Biol. Chem.*, **176**, 376 (1948).

(8) The seeming incredibility of this result stimulated a reinvestigation by Ronwin and Horn. The unpublished results of experiments in which the water content of the ethyl acetate ranged from 0.005 to 0.1% show an unmistakably gradual, *decreasing* solubility of the amino acid in these mixtures as the water content increases. At 65°, the drop in solubility of L-leucine in going from ethyl acetate containing 0.005% water to ethyl acetate containing 0.05% water is approximately one-half.

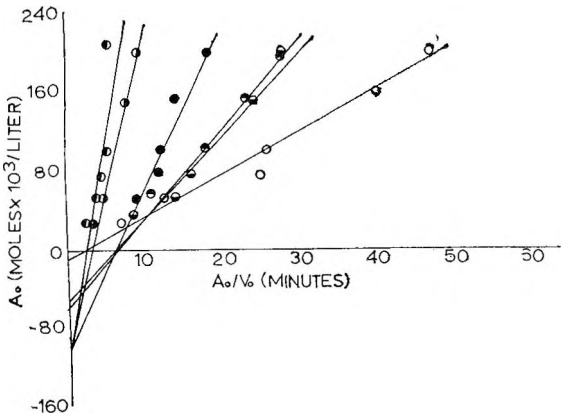


Fig. 4.—Plot of the initial concentration of dichloroacetyl chloride *vs.* the initial concentration of dichloroacetyl chloride/initial rate of the reaction run in ethyl acetate containing 0.02% water and saturated with L-leucine: ○, 35°; ◒, 40°; ◓, 45°; ●, 50°; ◑, 55°; and ◐, 65°.

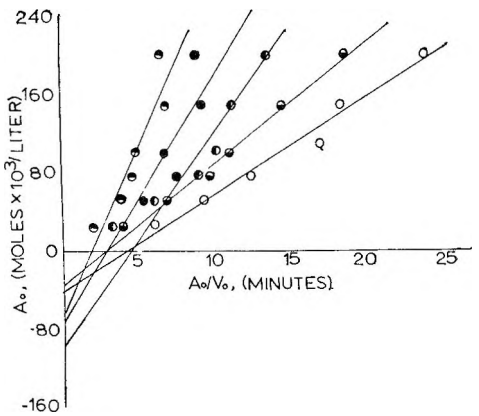


Fig. 5.—Plot of the initial concentration of dichloroacetyl chloride *vs.* the initial concentration of dichloroacetyl chloride/initial rate of the reaction run in ethyl acetate containing 0.005% water and saturated with L-leucine: ○, 40°; ◒, 45°; ◐, 50°; ●, 55°; and ◓, 65°.

For case II, assuming a steady state for $[L_s]$

$$d[L_s]/dt = 0 = k_4S - (k_5S + k_1[A])[L_s] \qquad (2)$$

Solving for $[L_s]$ and substituting in eq. 1 yields[9a]

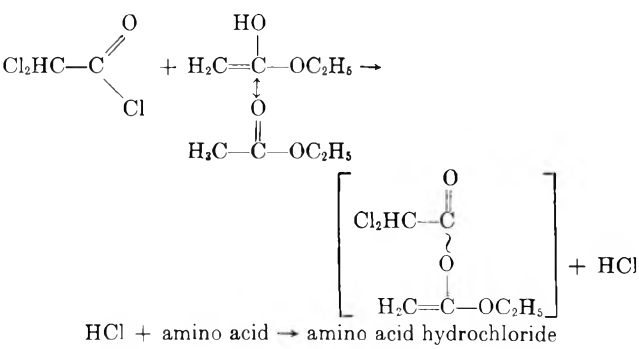
$$[A] = k_4S[A]/v - \frac{k_5S}{k_1} \qquad (3)$$

If eq. 3 holds, then the plot of the initial acid chloride concentration, $[A]$ *vs.* the initial acid chloride concentration divided by the initial velocity of the reaction, $[A]/v$, will be a straight line with a negative intercept equal to k_5S/k_1 and a positive slope equal to k_4S. Figures 4 and 5 are plots of $[A]$ *vs.* $[A]/v$ at temperatures ranging from 35 to 65° and water concentrations of 0.02 and 0.005%. The fit of the empirical results to the theoretical equation is satisfactory. All the points fall within the interval allowed by experimental error. The correlation coefficient ranges from 0.90 to 0.95.

The stoichiometry of the reaction is of obvious interest to an understanding of the acylation mechanism. In the acylation of *m*-nitroaniline in benzene by benzoyl chloride, Hinshelwood[9b] noted that one-half of the amine served as acceptor of the liberated hydrogen chloride. On the other hand, Ronwin[3-5] noted preparative yields, based on the amino acid, of over 50% (occasionally quantitative) in several cases, although the greater number of reactions resulted in less than 50% yields. For the specific case at hand, Ronwin reported a yield of 28% dichloroacetyl-L-leucine.[4] Using 0.1-mole quantities of each of the reactants in 50 ml. of anhydrous ethyl acetate at 50°, under an atmosphere of dry nitrogen gas, a quantitative yield of dichloroacetyl-L-leucine was obtained. The difference in yield is simply explained in that Ronwin's original reaction conditions, adopted empirically for preparative purposes only and without study of the effect of conditions, are at some variance with the more ideal reaction conditions used in this study. The result establishes the reaction stoichiometry as 1:1 amino acid–acid chloride, which supports the rate equation developed for the reaction and dictates that any proposed mechanism for the reaction must not require any of the amino acid to serve *solely* as acid acceptor. The result is of additional interest since the suspended amino acid is almost immediately, upon inclusion of the acid chloride into the reaction medium, converted to the hydrochloride salt; nevertheless, it goes on to react so that virtually none of it is limited to the function of acid acceptor. It is also obvious that by choosing proper reaction conditions, preparative yields can be pushed to quantitative levels.

Proposed Reaction Intermediate.—When the amino acid, suspended in ethyl acetate, is quickly treated with acid chloride and immediately filtered off, the filtered material is no longer free amino acid but identical with the hydrochloride salt. Since the water content of the ethyl acetate, even at 0.02%, is insufficient to create total hydrolysis of the acid chloride quantities used, the origin of the hydrogen chloride demands explanation. Additionally, when reaction is attempted between the hydrogen chloride salt of the amino acid and the free acid corresponding to the acid chloride, no product is obtained. Further, the determination of the molecular weight of the acid chloride in ethyl acetate by the boiling-point elevation procedure resulted, both in the case of dichloroacetyl chloride as well as for benzoyl chloride, in values which are almost one-half their actual molecular weights (Table I); yet, free benzoic acid in ethyl acetate yields the correct molecular weight by the same procedure.[10] Thus, the acid chlorides act in ethyl acetate as though they yield two particles.

The above experimental results indicate that (1) the acid chloride must be the initial and sole source of the hydrogen chloride produced, and (2) the acid chloride reaction to yield the hydrogen chloride must leave a



HCl + amino acid → amino acid hydrochloride

(9) (a) For the reader who may wonder, the symbols k_2 and k_3 were deliberately not used. (b) C. N. Hinshelwood, *J. Chem. Soc.*, 1353 (1936).

(10) International Critical Tables, Vol. III, McGraw-Hill Book Co. Inc., New York, N. Y., 1928, p. 340.

TABLE I

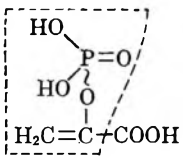
THE APPARENT MOLECULAR WEIGHT OF DICHLOROACETYL CHLORIDE AND BENZOYL CHLORIDE IN ETHYL ACETATE DETERMINED BY BOILING POINT ELEVATION

Acid chloride	Molality[a]	B.p. elevation, °C.[b] Calcd.	B.p. elevation, °C.[b] Obsd	Mol. wt. Obsd.	Mol. wt. Actual	Mol. wt. ratio, obsd./actual
Dichloroacetyl chloride	0.436	0.59	1.02	89.4	147.4	0.59
Benzoyl chloride	0.617	0.85	1.64	72.4	140.5	0.52

[a] Solvent, ethyl acetate containing 0.005% water. For molecular weight of dichloroacetyl chloride: weight of ethyl acetate was 67.759 g.; weight of dichloroacetyl chloride was 4.360 g. For molecular weight of benzoyl chloride: weight of ethyl acetate was 71.134 g.; weight of benzoyl chloride was 6.170 g. [b] Cottrell boiling point apparatus employing a Beckman thermometer. All boiling points were determined in a nitrogen atmosphere.

form which retains acylating activity and which is not the free acid. These considerations lead to the suggestion that the hydrogen chloride is generated in the preceding manner which also gives rise to a reasonable structure that can be expected to be actively acylating and, additionally, accounts for the molecular weight observations.

The intermediate in brackets would essentially be a "high energy" anhydride type. Although there is no scientific reason why a precedent for the above compound type is necessary in order to validate the suggestion, some degree of precedence is found in the consideration of the structure of phosphoenol pyruvate,



wherein the difference with the proposed intermediate shown above is simply that one-half of the "anhydride" is phosphate in phosphoenol pyruvate and carboxylate in the proposed intermediate.

Upon reaction with amino acid (or amino acid hydrochloride), the intermediate would yield the acylated amino acid and free the hydrogen chloride as well as a molecule of solvent.

Other Experiments.—It was observed that the acylation of L-leucine by dichloroacetyl chloride did not proceed in the following solvents: triethyl orthoformate, methyl formate, N,N-dimethylformamide. The reaction does proceed in *n*-butyl acetate, *n*-propyl acetate, and methyl acetate. In each case, the product (dichloroacetyl-L-leucine) was identified by its m.p. 119–122°.[4] These results tend to support the acylating intermediate structure proposed above. It is of interest that the product from the methyl acetate reaction is difficult to crystallize, though success is eventually achieved; whereas, the product from the other acetates crystallizes fairly readily.

Although a quantitative study has yet to be undertaken, definite evidence was obtained that both particle size and form (flake or powder) of the amino acid affect the rate of reaction. This led to the use of a uniformly purified and treated batch of L-leucine throughout this study.

Acknowledgment.—The authors are indebted to Dr. Kenneth F. O'Driscoll of this department for his development of the rate equation and for his helpful discussions throughout this study.

The Preparation and Some Reactions of N′-Fluorodiimide N-Oxides,[1] R—N(O)=NF

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A variety of N-substituted N′-fluorodiimide N-oxides, R–N(O)=NF, have been prepared by the reaction of nitroso compounds with either tetrafluorohydrazine or pyridine–difluoramine mixtures. Some reactions of those novel azoxy compounds with nucleophilic reagents were investigated and a new synthesis of unsymmetrical azoxy compounds was discovered. Reduction yielded anilines or hydrazines.

The preparation and thorough characterization of N-trifluoromethyl-N′-fluorodiimide N-oxide (I, R = CF_3) was reported recently.[2] This N-fluoroazoxy compound was obtained from the ultraviolet or thermally activated reaction of trifluoronitrosomethane and tetrafluorohydrazine. Two convenient methods for the preparation of alkyl- and aryl-N′-fluorodiimide N-oxides from nitroso compounds in solution are reported here.

In inert solvents such as chlorobenzene, carbon tetrachloride, or methylene chloride, C-nitroso monomers absorb tetrafluorohydrazine (N_2F_4) at subatmospheric pressure and are converted to the corresponding N′-fluorodiimide N-oxide (Table I). The reaction proceeded readily at 0–20° if the blue-green color of the nitroso monomer were visible in the solution. Only with the last three nitroso dimers listed in Table I was heating necessary; at 60–80° in chlorobenzene solution sufficient monomer was present to cause these reactions to proceed at a reasonable rate. N′-Fluorodiimide N-oxides also were produced when di-

(1) This research was supported by the Advanced Research Projects Agency under Army Ordnance Contract No. DA-01-021 ORD-11909.

(2) J. W. Frazer, B. E. Holder, and E. F. Worden, *J. Inorg. Nucl. Chem.*, **24**, 45 (1962).

TABLE I

N-SUBSTITUTED N′-FLUORODIIMIDE N-OXIDES, R—N(→O)=NF

R	B.p. (mm.) and m.p., °C.	Yield, %	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	F^{19} n.m.r.,[a] c.p.s.
Phenyl[b]	78 (4)	53[c]	51.43	3.60	20.00	51.36	3.69	20.57	−4742
o-Tolyl	84 (2)	27[d]	54.54	4.58	18.18	54.74	4.68	18.39	−5167
m-Tolyl	54 (0.1)	49[d]	54.54	4.58	18.18	54.27	4.73	17.40	−4695
p-Tolyl	60 (0.2)	43[c]	54.54	4.58	18.18	54.57	4.72	17.74	−4642
o-Chlorophenyl	*e*	23[d]			16.05			16.22	−5264
p-Chlorophenyl	54	50[d]	41.28	2.31	16.05	41.56	2.37	15.70	−4807
p-Bromophenyl	83	60[c]	32.90	1.84	12.79	33.19	2.04	12.35	−4871
p-Nitrophenyl	108	*f*	38.93	2.18	22.70	39.20	2.27	21.67	−4951
t-Butyl	56 (64)	33[d]	39.99	7.55	23.32	41.02[i]	7.61	23.79	−4759
2-Nitro-2-propyl	62 (4.5)	38[d]	23.86	4.00	27.81	24.94[i]	3.70	27.95	−5063
2-Chloro-2-propyl	68 (59)	41[d]	25.63	4.30	19.93	27.17[i]	4.51	20.09	−4943
Trifluoromethyl	*g*	29[d]							−4748
Benzyl	70 (0.1)	60[c]	54.54	4.58	18.18	55.16	4.74	17.71	−5020
β-Phenylethyl[h]	80 (0.1)	85[c]	57.13	5.39	16.66	57.04	5.58	17.83	−5036
Cyclohexyl	70 (0.1)	90[c]	49.30	7.59	19.17	49.43	7.22	18.98	−4830

[a] At 40 Mc., relative to external trifluoroacetic acid. [b] Calcd. for F: 13.56. Found: 13.16. [c] Yield from tetrafluorohydrazine. [d] Yield from difluoramine method. [e] Sample chromatographed, not distilled. [f] Yield not determined. [g] Infrared and mass spectra of the product were identical with those published.[2] Sample isolated by fractionation *in vacuo*. [h] Calcd. for F: 11.3. Found: 11.4. [i] Efforts to effect purification and repeated combustion analyses failed to yield satisfactory C and H data.

$$R{-}NO \xrightarrow[HNF_2\text{–pyridine}]{N_2F_4\text{ or}} R{-}\underset{\displaystyle O}{\overset{\displaystyle \uparrow}{N}}{=}NF \quad (I)$$

fluoramine,[3] diluted with nitrogen as a carrier gas, was swept into a pyridine–methylene chloride solution of the nitroso compound. Table I summarizes these preparations.

The radical mechanism suggested to account for the formation[2] of I, R = CF_3, affords a logical explanation for these tetrafluorohydrazine reactions. Apparently the glass surface, the solvent, and the nitroso compound act as the fluorine acceptors in this reaction, since silicon tetrafluoride and fluorosilicates are by-products, and the F^{19} n.m.r. spectra of chlorobenzene solutions from the reactions show C–F absorption. Highly colored organic products also are formed.

$$R{-}NO + NF_2\cdot \longrightarrow \left[R\underset{\displaystyle O^-}{\overset{\displaystyle |}{N}}{-}NF_2 \right]^{+} \longrightarrow R{-}\underset{\displaystyle O}{\overset{\displaystyle \uparrow}{N}}{=}NF + [F\cdot]$$

Since tetrafluorohydrazine conceivably could arise from an oxidation–reduction reaction of difluoramine, pyridine, and a nitroso compound, the radical pathway may account for N′-fluorodiimide N-oxide formation in the difluoramine reactions. However, ionic (NF_2^-) and nitrene (:NF) mechanisms cannot be ruled out at this time.[4]

The infrared spectra of N′-fluorodiimide N-oxides (see Table II) are characterized by strong bands at 10.7–11.2 μ, which are probably due to the N–F stretching vibrations,[5] and at 6.7–6.8 μ which are characteristic of azoxy compounds.

Conclusive evidence for the structure assigned to these fluoroazoxy compounds was obtained from their reaction with Grignard reagents. In the aromatic series displacement of fluoride ion by the organometallic reagent gave azoxy compounds in respectable yields[6] (Table III[7]).

$$Ar{-}N(\rightarrow O){=}NF + RMgX \longrightarrow Ar{-}\underset{\displaystyle O}{\overset{\displaystyle \uparrow}{N}}{=}N{-}R$$

Because unsymmetrical azoxy compounds may be obtained by a similar and simpler route,[7] no efforts were made to optimize the yield data of Table III. The experimental method of choice appeared to be the addition of a slight excess of the Grignard reagent to a solution of the N-fluoroazoxy compound at 0°. Aliphatic N′-fluorodiimide N-oxides could not be used successfully in this azoxy synthesis, probably because

TABLE II

SPECTRAL CHARACTERISTICS OF Ar—N(→O)=NF

Aryl group	Infrared absorption λN–F, μ	Ultraviolet spectra (cyclohexane) λ_{max}, mμ	ϵ_{max}
Phenyl	11.15	243	8,400
p-Tolyl	11.15	216	7,100
		253	7,400
o-Tolyl	11.2	No maximum	
m-Tolyl	10.7	247	8,600
p-Bromophenyl	11.15	258	12,100
o-Chlorophenyl	11.15	267	1,490
		273	1,480
p-Chlorophenyl	11.15	252	11,000

(3) J. P. Freeman, A. Kennedy, and C. B. Colburn, *J. Am. Chem. Soc.*, **82**, 5304 (1960).

(4) These species have been proposed as intermediates in the reactions of difluoramine with amines [C. L. Bumgardner, K. J. Martin, and J. P. Freeman, *ibid.*, **85**, 97 (1963)].

(5) The N–F stretching vibrations of difluorodiazine occur at 10–11 μ [R. H. Sanborn, *J. Chem. Phys.*, **33**, 1855 (1960)].

(6) A small amount of displacement on fluorine with the formation of fluorocarbon and N_2O apparently took place also. Methyl fluoride (*ca.* 11%) and N_2O (10%) were trapped from the nitrogen sweep of the reaction of the methyl Grignard reagent and N-*p*-chlorophenyl-N′-fluorodiimide N-oxide, and were identified by their mass spectra. Signals due to aromatic C–F groups could also be observed in the n.m.r. spectra of residues from reactions with aryl Grignard reagents.

(7) Characterization of the azoxy compounds reported in Table III was carried out in conjunction with the study of the reaction of Grignard reagents and organonitrosohydroxylamine tosylates, R—N(→O)=N—OTs, and was reported there [T. E. Stevens, *J. Org. Chem.*, **24**, 311 (1964)].

TABLE III

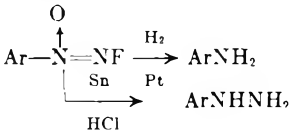
AZOXY COMPOUNDS FROM N′-FLUORODIIMIDE N-OXIDES

Diimide, Ar—N(→O)=NF, Ar	Grignard reagent R	Azoxy compounds,[a] Ar—N(→O)=N—R % yield
Phenyl	Phenyl	44
Phenyl	*p*-Chlorophenyl	74
p-Chlorophenyl	Phenyl	57
p-Bromophenyl	Phenyl	51
p-Chlorophenyl	*p*-Tolyl	62
Phenyl	*n*-Butyl	34
p-Bromophenyl	Ethyl	79[b]
p-Chlorophenyl	Methyl	46[c]
Phenyl	Ethyl	25

[a] See ref. 7. [b] Based on recovered starting material. [c] See ref. 6.

of the active hydrogen available to the organometallic reagent.

Reduction of the aromatic N′-fluorodiimide N-oxides was studied briefly. Catalytic hydrogenation with Adams catalyst in ethanol solution of the phenyl, *m*-tolyl, and *p*-tolyl isomers gave the corresponding aniline. Reduction with tin and hydrochloric acid converted I (R = phenyl), *p*-chlorophenyl, or *p*-bromophenyl, to the aromatic hydrazine.



Qualitatively, the aromatic diimides were much more stable than the aliphatic compounds. For example, the 2-chloro-2-propyl compound in refluxing chlorobenzene was converted to nitrous oxide and 2-chloropropene, but the aromatic diimides were not affected by similar treatment.[8] This thermal elimination reaction will be studied with other aliphatic azoxy compounds.

Experimental[9]

Reaction of Nitrosobenzene and Difluoramine.—A solution of 3.1 g. (29 mmoles) of nitrosobenzene in pyridine–methylene chloride (15:75 ml.) was stirred at about 20° while 30 mmoles of difluoroamine, generated by heating an acidified aqueous solution of difluorourea, was carried into the solution by a slow stream of nitrogen. When the difluoramine addition was complete, the methylene chloride–pyridine solution was poured into ice–water. The organic layer was separated and washed with water and dilute aqueous hydrochloric acid. The residue remaining after the methylene chloride had been removed at reduced pressure was combined with the residue from another nitrosobenzene–HNF_2 run of the same size. Distillation of the combined residues gave, after the removal of a small amount of nitrosobenzene that had sublimed into the condenser, N-phenyl-N′-fluorodiimide N-oxide, 3.4 g. (42%), b.p. 78° (4 mm.), $n^{20}D$ 1.5334.

Reaction of 2-Nitro-2-nitrosopropane and Difluoroamine.—A solution of 3.54 g. (30 mmoles) of 2-nitro-2-nitrosopropane in 30 ml. of pyridine and 90 ml. of methylene chloride was stirred at 20° while 40 mmoles of difluoramine was passed into the solution as described above. When the difluoramine addition was completed, the reaction mixture was poured into water and processed as described above. Distillation of the residue obtained on evaporation of the methylene chloride solvent gave N-(2-nitro-2-propyl)-N′-fluorodiimide N-oxide, 1.72 g. (38%), b.p. 62° (4.5 mm.), $n^{20}D$ 1.4349.

Reaction of Nitrosobenzene and Tetrafluorohydrazine.—A solution of 5.0 g. (46.6 mmoles) of nitrosobenzene in 50 ml. of chlorobenzene was stirred at 6° under 235-mm. pressure of tetrafluorohydrazine; the total volume of the system was about 2 l. The pressure began to drop immediately, and the solution was allowed to warm to 30° over 2 hr. No additional tetrafluorohydrazine was consumed (total pressure then was 128 mm.). A total of 23 mmoles of tetrafluorohydrazine was consumed and 0.73 mmole of silicon tetrafluoride and 1.9 mmoles of nitrous oxide were produced. The chlorobenzene solution was passed through a silica gel column packed in pentane. The material eluted by pentane–methylene chloride (2:1 and 1:1) was distilled to give N-phenyl-N′-fluorodiimide N-oxide, 3.45 g. (53%), b.p. 78° (4 mm.).

Reaction of Tetrafluorohydrazine and *p*-Bromonitrosobenzene.—A suspension of 1.0 g. of *p*-bromonitrosobenzene in 7 ml. of chlorobenzene was degassed on a vacuum line. The mixture was cooled to −196°, and tetrafluorohydrazine, 126 ml. (STP), was condensed into the U-tube. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. As the chlorobenzene melted, the solution darkened rapidly. After stirring at ambient temperature for 2 hr., the reaction mixture was chilled in ice while the gases were distilled through −80 and −196° traps. The −196° trap contained 94 ml. (STP); the mass spectrum of this fraction indicated a composition of 90% N_2F_4, 3% N_2O, 6% NO, and 1% of C–F material (the last product is a contaminant in the N_2F_4 used). A total of 1.85 mmoles (73%) of tetrafluorohydrazine was consumed. The chlorobenzene solution was removed from the U-tube and chromatographed on a pentane-packed silica gel column. Elution of the column with pentane–methylene chloride gave a solid fraction weighing 1.03 g. One recrystallization from hexane gave N-*p*-bromophenyl-N′-fluorodiimide N-oxide, 0.70 g. (60%), m.p. 82–84°.

Reaction of β-Phenylnitrosoethane Dimer and Tetrafluorohydrazine.—A solution of 3.55 g. (13.1 mmoles) of β-phenylnitrosoethane dimer[10] in 55 ml. of chlorobenzene was stirred at 55–70° under an atmosphere of tetrafluorohydrazine (a 3.85-g. sample of N_2F_4 gave a pressure of 347 mm. in volume of about 2 l.). After 3 hr. the pressure had decreased to 175 mm., and the gases were removed *in vacuo*. A total of 0.93 g. of tetrafluorohydrazine, 1.0 mmole of silicon tetrafluoride, 1.7 mmoles of nitric oxide, and 0.2 mmole of nitrous oxide were recovered (by mass spectrum). The chlorobenzene solution was chromatographed on a silica gel column. Elution of the column with pentane–methylene chloride gave N-β-phenylethyl-N′-fluorodiimide N-oxide, 3.76 g. (85%), as a pale yellow oil. A sample prepared earlier was isolated by distillation, b.p. 80° (0.1 mm.).

Reduction of N-*p*-Bromophenyl-N′-fluorodiimide N-Oxide.—To a mixture of 0.500 g. of the N-oxide and 2.1 g. of tin was added 3.7 ml. of concentrated aqueous hydrochloric acid over a 5-min. period. The mixture was warmed on the steam bath for 30 min., then allowed to stand overnight at room temperature. Water and enough 40% sodium hydroxide solution to make the solution basic were added, and the organic product was extracted with methylene chloride. Evaporation of the methylene chloride and recrystallization of the residue from hexane gave *p*-bromophenylhydrazine, 0.303 g. (71%), m.p. 104–106°, lit.[11] m.p. 105°.

Catalytic Hydrogenation of N-*p*-Tolyl-N′-fluorodiimide N-Oxide.—A 233-mg. sample of the N-oxide in 11 ml. of ethanol containing 25 mg. of platinum oxide was hydrogenated at atmospheric pressure and 26°. Hydrogen uptake began immediately; a total of 134 ml. (STP) of hydrogen was taken up in 70 min. (theory for 4 equiv. of hydrogen is 135.2 ml.). The catalyst was removed from the solution by filtration; the filtrate was stripped to dryness at reduced pressure. The solid residue was extracted with hot hexane. Evaporation of the hexane left 72 mg. (44%) of white crystals, the infrared spectrum of which was identical with that of *p*-toluidine. A 67-mg. portion of this solid was benzoylated in the Schotten–Baumann manner. The benzoyl derivative, after one recrystallization from hexane–methylene

(8) Aromatic N′-fluorodiimide N-oxides were recovered unchanged after being heated to reflux in acetic acid, diethylamine, concentrated aqueous hydrochloric acid, or methanolic sodium methoxide. They also were recovered after solution in concentrated sulfuric acid or boron trifluoride–ether at 25°. In concentrated sulfuric acid at 70° N_2, N_2O, NO, and SiF_4 were formed, but no organic product could be characterized.

(9) Melting points and boiling points are uncorrected.

(10) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 6522 (1959).

(11) J. E. Humphries, E. Bloom, and R. Evans, *J. Chem. Soc.*, **123**, 1766 (1923).

chloride, weighed 108 mg. (81%) and melted at 156–157°. A mixture melting point determination with the benzoyl derivative of *p*-toluidine (m.p. 157–158°) was 157–158°. The infrared spectra of the samples were identical.

Pyrolysis of N-(2-Chloro-2-propyl)-N′-fluorodiimide N-Oxide in Chlorobenzene.— A solution of 0.55 g. (3.9 mmoles) of the N′-fluorodiimide in 15 ml. of chlorobenzene was refluxed for 2 hr. while a nitrogen stream swept the off-gases through a −20° condenser and through traps cooled to −78 and −196°. The chlorobenzene solution was cooled while the nitrogen sweep was maintained. The −196° trap collected only N_2O (by mass spectrum), 85.5 ml. (STP), 3.8 mmoles. No SiF_4 was detected. The −78° trap collected 64.3 ml. (STP), 2.9 mmoles, of 2-chloropropene. The infrared and mass spectra were identical with those of an authentic specimen.

Reaction of N-Phenyl-N′-fluorodiimide N-Oxide and the *n*-Butyl Grignard Reagent.—A solution of 0.71 g. of the above diimide in 25 ml. of tetrahydrofuran was stirred at ice-bath temperature while 9.5 ml. of 0.8 *M* *n*-butyl Grignard reagent in tetrahydrofuran was added over 10 min. The reaction mixture was allowed to warm to 25° (90 min.), and then was poured over an ice–dilute hydrochloric acid mixture. The organic product was isolated by extraction with methylene chloride and was chromatographed on silica gel. Elution of the column with pentane–methylene chloride (1:1) gave N-phenyl-N′-*n*-butyldiimide N-oxide, 0.306 g. (34%), as a yellow oil; ultraviolet (cyclohexane), λ_{max} 246 mμ (ϵ_{max} 10,300).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.46; H, 7.97; N, 16.08.

Reaction of the Phenyl Grignard Reagent and N-*p*-Chlorophenyl-N′-fluorodiimide N-Oxide.—A solution of 0.350 g. of the above diimide in 20 ml. of ether was stirred at ice-bath temperature while about 3 mmoles of the phenyl Grignard reagent in 2 ml. of ether was added dropwise. The reaction temperature was allowed to increase to 22° over 1 hr., then the mixture was quenched in ice–water and hydrochloric acid. The organic product was isolated by ether extraction. Chromatography of the organic residue over silica gel gave N-*p*-chlorophenyl-N′-phenyldiimide N-oxide, 0.264 g. (57%), m.p. 81–82°.[7]

Anal. Calcd. for $C_{12}H_9ClN_2O$: N, 12.04. Found: N, 12.23.

Reaction of the *p*-Chlorophenyl Grignard Reagent and N-Phenyl-N′-fluorodiimide N-Oxide.—A solution of 1.02 g. (7.3 mmoles) of the above diimide in 25 ml. of tetrahydrofuran was stirred at ice-bath temperature under an atmosphere of nitrogen while 7.7 ml. of 1.1 *M* *p*-chlorophenylmagnesium bromide in tetrahydrofuran was added dropwise. The mixture was allowed to warm to 20° over 1 hr., and then quenched in iced aqueous hydrochloric acid. The organic product was isolated by extraction with methylene chloride. The methylene chloride was removed at reduced pressure. The last traces of solvent were removed by pumping *in vacuo* through a −80° trap. An F^{19} n.m.r. scan of the material trapped at −80° showed peaks at −4800 c.p.s. (40 Mc., CF_3COOH standard), due to the starting N′-fluorodiimide, and at +1531 c.p.s., due to 4-chlorofluorobenzene. Chromatography of the residue over silica gel as usual gave an azoxybenzene fraction of 1.27 g. (74.6%). One recrystallization of this material from hexane gave N-phenyl-N′-*p*-chlorophenyldiimide N-oxide, 1.07 g., m.p. 68–69°, lit.[7] m.p. 68°.

Structure and Configuration of Isojervine[1]

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Isojervine, an isomer obtained on acid treatment of jervine, is shown to possess structure II from chemical and physical evidence.

The elucidated structure[2] of jervine (I) has been shown to explain all but one of the diverse reactions[3] of the alkaloid. Isojervine,[4] an unexpected product obtained on acid treatment of pseudojervine has received no generally accepted structural assignment.[5] In a preliminary communication[6] we reported that structure II was consonant with all chemical and spectral data obtained from isojervine[7] and the present paper describes the full details.

Isojervine (II), $C_{27}H_{39}O_3N$, m.p. 116–118°, was obtained in crystalline form by treatment of jervine according to Jacobs' procedure,[4] together with a new isomer, m.p. 262–263°. Isojervine is moderately stable toward acid and very sensitive to alkali, in contrast to jervine. It possesses a characteristic ultraviolet absorption spectrum[8] (Fig. 1), showing strong end absorption (ϵ 9200 at 220 mμ) with inflection at 252 mμ (ϵ 2900) and a maximum at 330 mμ, the intensity (ϵ 250) of which is considerably higher than that of usual ketones. The infrared spectrum[9] exhibits an α,β-unsaturated carbonyl peak at 1684 and 1630 cm.$^{-1}$ and the chemical data[4,8] show the presence of two hydroxyl groups and a secondary amino group; that is, the ether linkage of jervine is cleaved in isojervine. Isolation of 2-ethyl-3-hydroxy-5-methylpyridine on selenium dehydrogenation[10] proves that isojervine contains the same nitrogen ring skeleton as that of jervine.

Reduction of II with lithium in liquid ammonia at −70° in presence of methanol has now afforded "α-dihydrojervinol"[8] (III), showing that the carbocyclic ring system of jervine is still retained, and three double bonds are, therefore, present in isojervine. The result also established that not only the ketonic function of isojervine exists at C-11, but also that two hydroxyl groups are located at C-3 and C-23 in "α-dihydrojervinol" and isojervine.

The abnormal ultraviolet absorption spectrum of II and the higher pK_a value (7.12 in 50% ethanol) of N-methylisojervine (IV) than that (6.08) of N-methyljervine[11] (V) led us to assume, at first, that one of the three double bonds might be conjugated with nitrogen.

(1) Part I of "C-Nor-D-homosteroids and Related Alkaloids."

(2) J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin, and A. Klingsberg, *J. Am. Chem. Soc.*, **73**, 2970 (1951).

(3) K. J. Morgan and J. A. Barltrop, *Quart. Rev.* (London), **12**, 34 (1958).

(4) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **155**, 565 (1944).

(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, p. 851.

(6) T. Masamune, M. Takasugi, H. Suzuki, S. Kawahara, M. Gohda, and T. Irie, *Bull. Chem. Soc. Japan*, **35**, 1749 (1962).

(7) After we had completed this work, Dr. O. Wintersteiner of the Squibb Institute and Professor W. G. Dauben of California University informed us that they also have arrived at the same structure as ours. Their results have now been published in (a) *Tetrahedron Letters*, 795 (1962), and (b) *J. Org. Chem.*, **28**, 293 (1963), respectively.

(8) W. A. Jacobs and C. F. Huebner, *J. Biol. Chem.*, **170**, 635 (1947).

(9) B. M. Iselin and O. Wintersteiner, *J. Am. Chem. Soc.*, **77**, 5318 (1955).

(10) W. A. Jacobs and Y. Sato, *J. Biol. Chem.*, **181**, 55 (1949).

(11) K. Saito, H. Suginome, and M. Takaoka, *Bull. Chem. Soc. Japan*, **11**, 172 (1936).

This compound (IV), m.p. 221–222°, was obtained by acid treatment of V or by methylation of II with methyl iodide. However, the ultraviolet spectra of isojervine (II), the triacetate (IIa), and the N-methyl derivative (IV) in ethanol were completely identical with that of isojervine in ethanol containing hydrochloric acid (0.1 *N*). Furthermore, isojervinol (VI), m.p. 210–211°, which was formed by reduction of II with lithium aluminum hydride or sodium borohydride and was very unstable to acid, exhibited only weak end absorption (ϵ 2990 at 220 mμ). These facts[12,13] indicated that no double bond was conjugated with another or with the nitrogen.

Of three double bonds, one was shown to be located at C-5–C-6 by the Oppenauer oxidation; oxidation of isojervine with cyclohexanone and aluminum isopropoxide in toluene yielded isojervone[14] (VII), m.p. 112–114°, which was very unstable in air in contrast to the stable diacetate (VIIa), m.p. 202–204°. Hydrogenation of II led to saturation of this 5,6-double bond; that is, treatment of II with hydrogen and platinum in acetic acid gave stereoisomeric dihydroisojervines[15] (VIII, m.p. 154–155°, and IX, m.p. 114–115°). The absorption maxima of VIII and IX were not only shifted to the shorter wave length (239 and 236 mμ) but also intensified from 2900 to 10,000 (Fig. 1). The higher melting isomer (VIII) was presumed to be fused by A–B *trans* linkage, because VIII was a main product of the hydrogenation. The Oppenauer oxidation of VIII produced dihydroisojervone (X), m.p. 108–110°, only in a low yield, which exhibited ultraviolet absorption similar to VIII, and a considerable amount of the starting material was recovered unchanged. Compound X was also obtained by oxidation of VIII with chromic anhydride in better yield. Similarly, IX was oxidized to yield the corresponding dihydroisojervone (XI) which showed one spot on the paper chromatogram, though it was not isolated in crystalline form. Reduction of X with sodium borohydride gave the original alcohol (VIII) as a major product. In such a reduction of an unhindered ketone, the equatorial isomer is the major product.[16a] Since VIII has a 3β-hydroxyl group,[16b] VIII must possess an A–B *trans* configuration. The difference[17a,b] between the optical rotatory dispersion curves of X and VIII, considered to represent the absorption characteristics of the 3-ketone, showed a positive Cotton effect (Fig. 2). Application of the octant rule[17c]

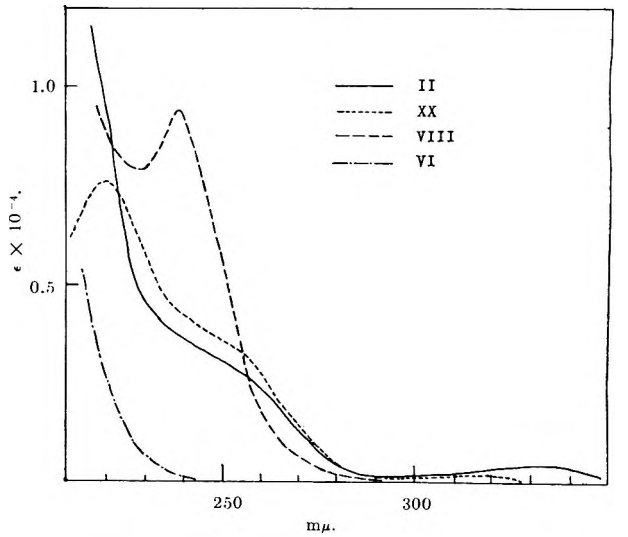


Fig. 1.—Ultraviolet absorption spectra of various isojervine derivatives; solvent, ethanol.

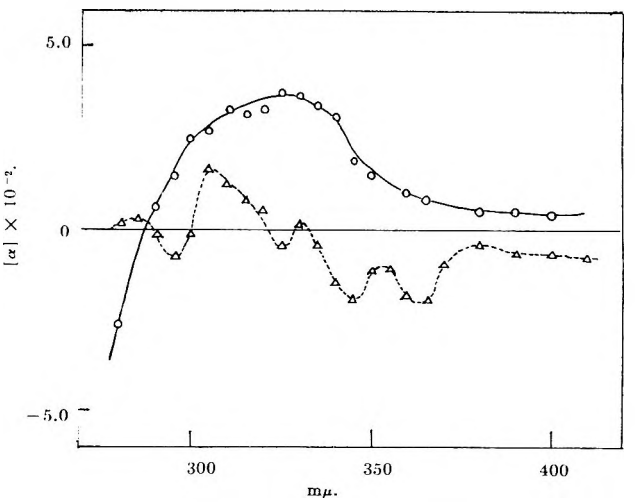


Fig. 2.—The differences in the optical rotatory dispersion curves of dihydroisojervones and dihydroisojervines: O, *trans* (X–VIII); Δ, *cis* (XI–IX); solvent, ethanol.

supported the conclusion on the stereochemistry of the A–B ring junction mentioned above.

A double bond conjugated with the carbonyl group is shown to exist at C-8–C-9. As mentioned above, the absorption maximum at 252 mμ in I was shifted to 239 mμ in VIII and also the carbonyl peak (1700 cm.$^{-1}$) of I was displaced to a longer wave length (1684 cm.$^{-1}$) in II, suggesting[18,19] that the double bond would occupy an endocyclic position; that is, it would be located at C-8–C-9 or C-12–C-14. Furthermore, the atypical spectrum of II with its relatively weak absorption near 250 mμ was changed to one typical for an α,β-unsaturated ketone (in VIII and IX) by saturation of the 5,6-double bond. On the other hand, the reduction of the keto group of II leading to VI caused the loss of absorption above 220 mμ. This spectroscopic behavior of II, VIII, and VI completely paralleled that of 1-acetyl-1,4-cyclohexadiene[20] and, thus, the double bond must be

(12) R. Adams and L. E. Mahon, *J. Am. Chem. Soc.*, **64**, 2588 (1942); N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *ibid.*, **77**, 439 (1955); N. J. Leonard, P. D. Thomas, and V. W. Gash, *ibid.*, **77**, 1552 (1955).

(13) N. J. Leonard and D. M. Locke, *ibid.*, **77**, 437 (1955).

(14) *Cf.* ref. 5, p. 177. The molecular rotation differences (ΔM_D) for the transformation II to VII, I to Δ^4-jervone, and III to "α-dihydrojervinolone" prepared by the Oppenauer oxidation of III were 748, 669, and 731°, respectively. To the contrary, the values were only 136 and 131° for the changes of VIII to X and IX to XI.

(15) The dihydroisojervine of m.p. 155° (as hydrate) described in the preliminary communication (ref. 6) was a mixture of the compounds VIII and IX. These gave almost the same R_f value on the paper chromatogram.

(16) (a) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956); O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962). (b) See ref. 37.

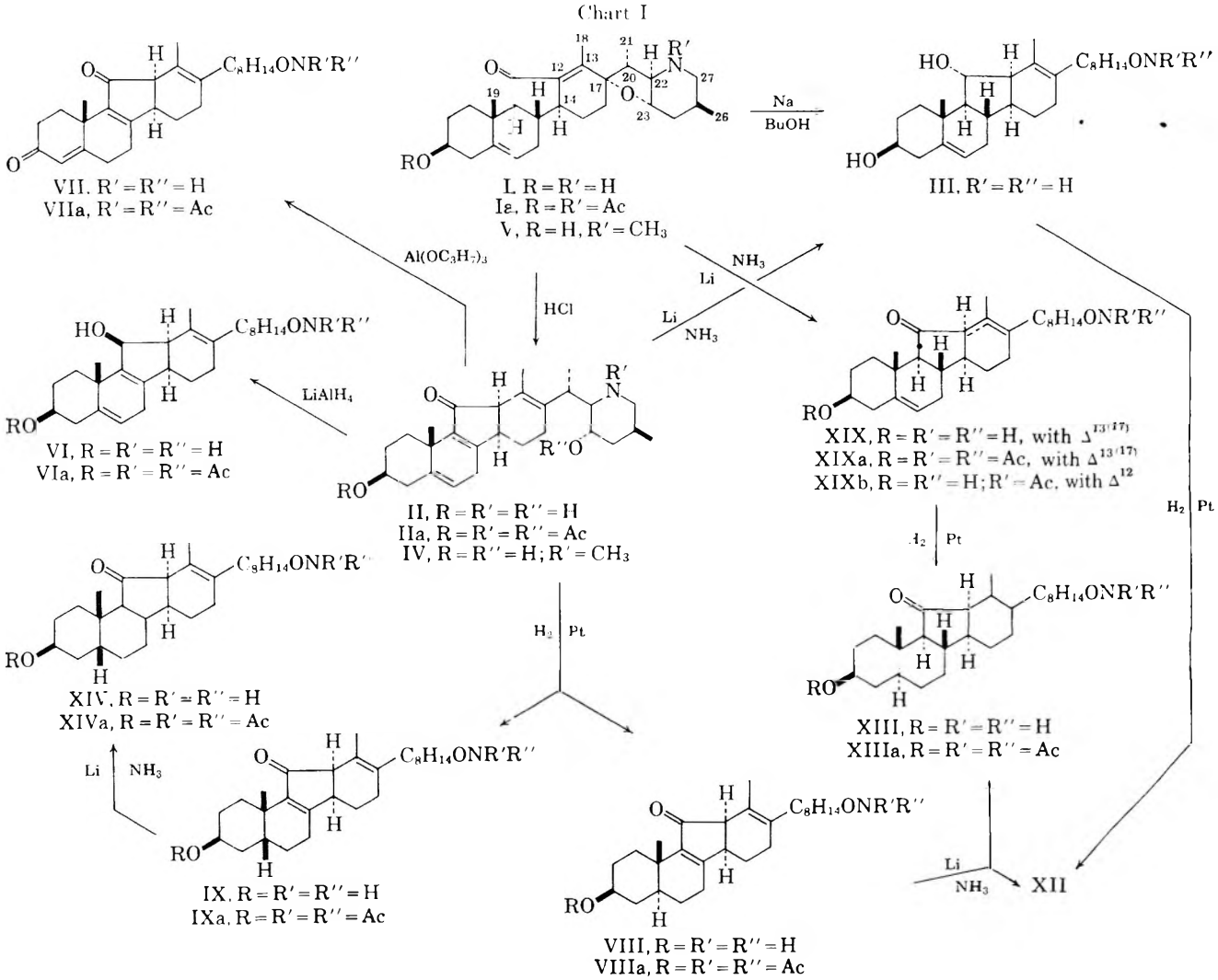
(17) (a) For additivity of the molecular rotatory dispersion curve, see W. Klyne, *Tetrahedron*, **13**, 29 (1961); C. Djerassi, E. Lunde, and A. A. Akhrem, *J. Am. Chem. Soc.*, **84**, 1249 (1962). (b) The corresponding difference between XI and IX indicated an unexplainable curve (Fig. 2). This suggests that IX would exist in a nonsteroid form. (c) C. Djerassi, *ibid.*, **78**, 6362 (1956); W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *ibid.*, **83**, 4013 (1961).

(18) K. Hirayama, "Zikken Kagaku Koza," Vol. I, the Chemical Society of Japan, Ed., Maruzen Co., Tokyo, 1961, p. 71.

(19) D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *J. Am. Chem. Soc.*, **82**, 4012 (1960).

(20) E. A. Braude, E. R. H. Jones, F. Sondheimer, and J. B. Toogood, *J. Chem. Soc.*, 607 (1947); E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *ibid.*, 4073 (1956).

Chart I



located at C-8–C-9. The n.m.r. spectral data, which will be discussed later, support this view.

Hydrogenation of VIII was found not to proceed under usual conditions, suggesting that a remaining double bond was sterically hindered, probably tetrasubstituted. The n.m.r. spectrum of IIa gave a sharp singlet at τ 8.09 due to a methyl group attached to an olefinic carbon comparable to that at τ 7.81 due to the 18-methyl of diacetyljervine (Ia). Thus the double bond must exist either at C-13–C-17 or C-17–C-20. The Birch reduction of VIII resulted in formation of a mixture of compounds. Chromatographic separation on paper led to the isolation of two crystalline substances, m.p. 142–143° and m.p. 167–168°, besides some unchanged starting material. The higher melting compound (XII) showed no carbonyl band in the infrared spectrum and was proved to be a dihydro derivative of the alcohol (III) by hydrogenation. This base (XII) was also formed in good yield by the Birch reduction of VIII in the presence of methanol. The compound XIII[21] of m.p. 143° showed an absorption band due to a saturated five-membered ring ketone at 1732 cm.$^{-1}$, which indicated the reduction of the 8,9-double bond. The Birch reduction of IX yielded a new compound (XIV),[21] m.p. 147–148°, which had a carbonyl peak at 1731 cm.$^{-1}$ and was isomeric with XIII. These tetrahydroisojervines (XIII and XIV) were acetylated for direct comparison with "22,27-imino-$\Delta^{17(20)}$-jervene-3,23-diol-11-one 3,23,N-triacetate" (XV) already prepared by Wintersteiner *et al.*[22] However, neither the triacetate (XIIIa), m.p. 167–169°, of XIII nor the corresponding isomer (XIVa), m.p. 190–191°, of XIV was found to be identical with the known compound (XV).[23] (See Chart I.)

5α-Dihydroisojervine (VIII) was treated with potassium *t*-butoxide in refluxing *t*-butyl alcohol; if the isolated double bond is located at C-13–C-17, one ought to expect the migration of the double bond to the α,β-position relative to the keto group.[24] Careful chromatographic fractionation of the product yielded a crystalline compound (XVI), $C_{27}H_{41}NO_3$, m.p. 143–145°. It had a maximum at 239 mμ (ϵ 8600) in the ultraviolet spectrum, indicating the presence of a simple α,β-unsaturated keto group. Acetylation of XVI with acetic anhydride and pyridine on a steam bath afforded a base which gave one spot on the paper. While it was obtained only in amorphous form, the elementary

(21) In the preliminary communication (ref. 6), the compounds XIII and XIV were called β- and α-tetrahydroisojervines, respectively.

(22) O. Wintersteiner, M. Moore, and B. M. Iselin, *J. Am. Chem. Soc.*, **76**, 5609 (1954).

(23) The n.m.r. spectrum of Wintersteiner's compound (XV) showed a weak peak at τ 4.11 due to an olefinic proton. In view of the easy hydrogenation of this compound, the location of a double bond at C-17–C-20 seems to be improbable.

(24) R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey, and N. L. Wendler, *J. Am. Chem. Soc.*, **76**, 4013 (1954).

analysis fitted the molecular formula $C_{31}H_{45}NO_5$, corresponding to the diacetate (XVIa) of XVI. The infrared spectrum showed only three maxima at 1726, 1685, and 1629 cm.$^{-1}$ in the 6-μ region, showing the absence of an N-acetyl group. The n.m.r. spectrum of XVI or XVIa exhibited a new sharp singlet at τ 8.73 corresponding to three protons instead of the 18-methyl signal (τ 8.08) seen in the spectrum of the triacetate (VIIIa) of VIII. Thus, nitrogen is bonded with the carbon to which the 18-methyl is attached. Furthermore, XVI and XVIa were found to be weak bases, the pK_a values being 6.12 and 4.47, respectively. These results established that the compound of m.p. 145° possesses structure XVI, and that the formation of XVI took place through a reaction analogous to the formation of jervisine as elaborated by Wintersteiner, *et al.*[25] Apparently the reaction of VIII leading to XVI involves migration of the 13,17-double bond[26] to the 12,13-position followed by cyclization. Thus, II is the most probable structure for isojervine.

Consideration of the n.m.r. spectra (Fig. 3) confirms the disposition of a double bond at C-8–C-9 and the configuration of the 12-carbon. Triacetylisojervine (IIa) showed a doublet centered at τ 8.91 (J = 7 c.p.s.) involving six protons and a sharp singlet at τ 8.71 corresponding to three protons along with a singlet at τ 8.09 due to 18-methyl. While the doublet is associated with the C-26 and C-21 methyl groups and the signals due to those groups coincided fortuitously, the signal at τ 8.71 must be attributed to 19-methyl and is shifted abnormally to the lower field as compared with that of diacetyljervine (τ 8.99) or "diacetyl-Δ^{13}-jervine"[9] (τ 8.87). The resonance fields of the angular methyl at C-10 vary depending on the nature and position of other substituents nearby and the shifts of 19-methyl caused by the fields due to the magnetic anisotropy of those substituents have been found to be additive with normal steroids.[27,28] This principle of additivity was observed for a number of C-nor-D-homosteroids and related alkaloids,[29] though the magnitude of the shifts due to substituents in the C-ring do not correspond to those observed with normal steroids. The 19-methyl signals of XIIIa and "22,27-imino-Δ^{16}-jervene-3,23-diol-11-one triacetate"[22] (XVII) appeared at τ 9.17 and 9.16, respectively, and the corresponding peak of the 16,17-dihydro derivative[22] (XVIII) of XVII also appeared at the same region (τ 9.17). This indicated that there was no contribution from the 13,17- or 16,17-double bond. Contribution from 5,6- and 8,9-double bonds was estimated as follows; the Birch reduction of jervine afforded 8,9-dihydroisojervine (XIX), m.p. 162–163°. The structure of XIX was confirmed by transformation of XIX into XIII by hydrogenation.

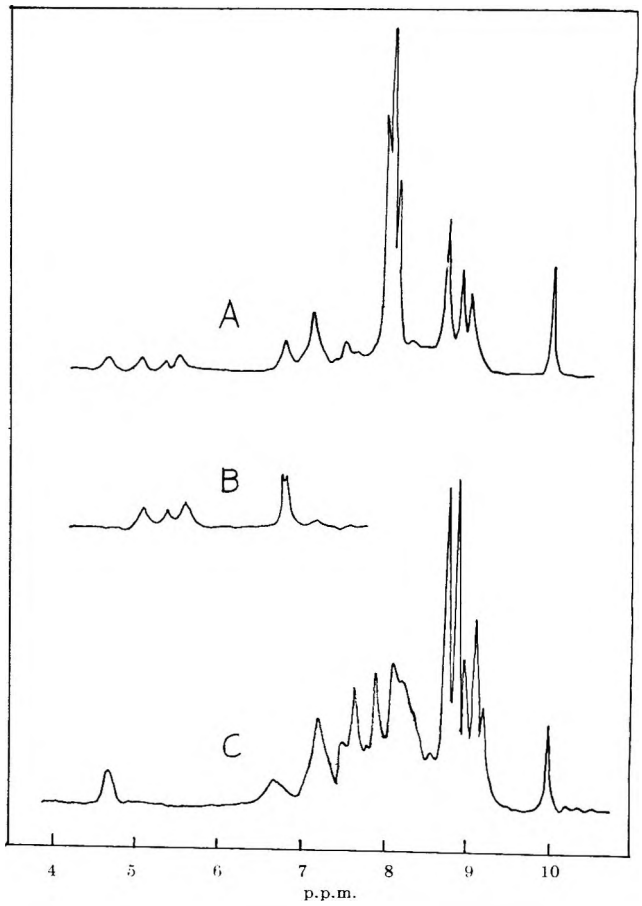
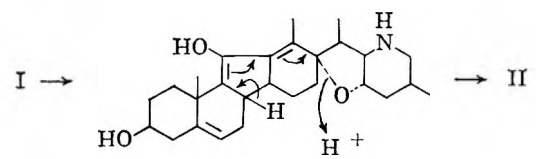


Fig. 3.—The n.m.r. spectra of isojervine derivatives: A, triacetylisojervine (IIa); B, triacetyltetrahydroisojervine (XIIIa); C, a new isomer (XX); solvent, deuteriochloroform; 60 Mc.; internal reference, tetramethylsilane.

As the angular methyl groups of VIIIa and the triacetate (XIXa), m.p. 163–164°, of XIX appeared at τ 8.99 and 8.98, the 5,6- and 8,9-double bonds[30] were shown to shift the 19-methyl signal to the lower field by 0.18 and 0.19 p.p.m., respectively. If the principle of additivity was applicable to triacetylisojervine (IIa), the angular methyl signal should appear at τ 8.80. In order to explain the abnormal ultraviolet absorption of 1-acetyl-1,4-cyclohexadiene, Braude[20] postulated that there would be interaction between the π-electrons of the two double bonds. If so, a similar interaction would be obtained between the 5,6- and 8,9-double bonds of IIa, and the discrepancy (0.09 p.p.m.) of the observed value from the calculated would be explicable by assuming the extra magnetic field associated with such interaction as mentioned above.[31]

The formation of isojervine from jervine is considered to involve the following sequence,[32] and thus there is a



(25) O. Wintersteiner and M. Moore, *J. Am. Chem Soc.*, **75**, 4938 (1953); **78**, 6193 (1956).

(26) Migration of the 13,17-double bond to the 12,13-position followed by *no* cyclization was observed with triacetyl-8,9-dihydroisojervine (XIXa); treatment of XIXa with potassium hydroxide in refluxing methanol afforded an N-acetate (XIXb), $C_{29}H_{43}NO_4$, m.p. 213–215°. The spectra indicated the presence of an α,β-unsaturated keto group [ultraviolet, λ_{max} 254 mμ (ϵ 19,000); infrared, ν_{max} 1704 and 1610 cm.$^{-1}$; n.m.r., a singlet at τ 7.82 (3H, 18-methyl protons)] and an N-acetyl group [infrared, ν_{max} 1610 cm.$^{-1}$; n.m.r., a singlet at τ 7.90 (3H)].

(27) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961); J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958); E. R. Malinowski, M. S. Manhas, G. E. Müller, and A. K. Bose, *Tetrahedron Letters*, 1161 (1963).

(28) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).

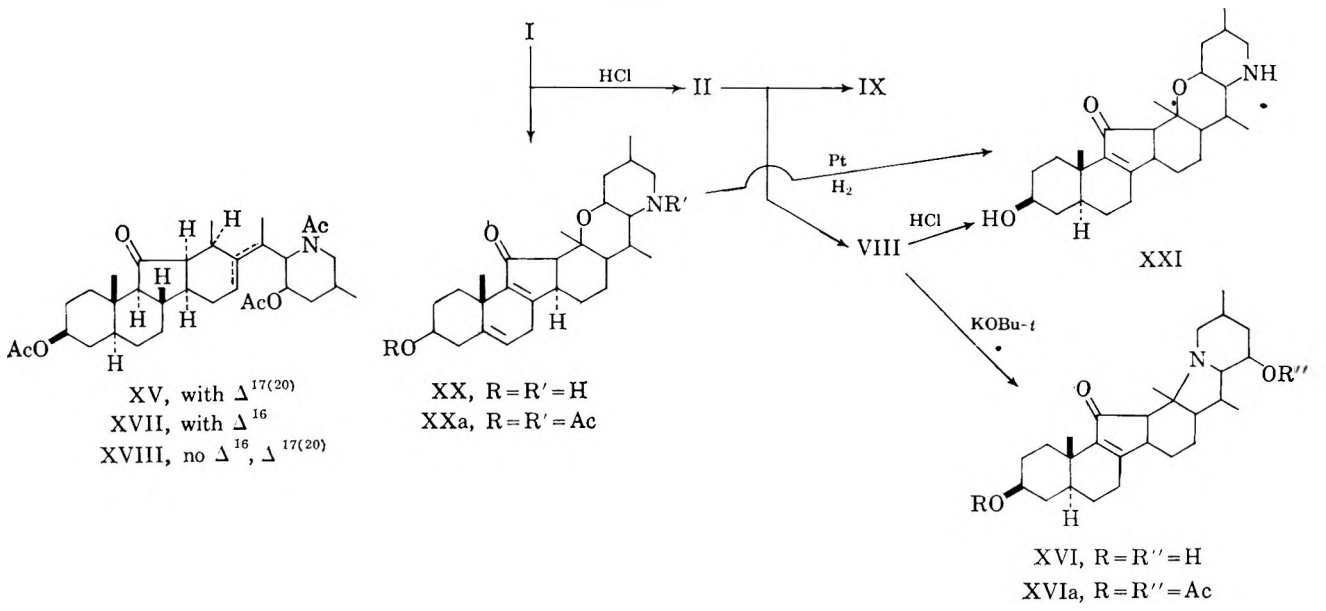
(29) T. Masamune, *et al.*, unpublished observations.

(30) The contribution of the 8,9-double bond in normal steroids was shown to be about 0.10 p.p.m.: ref. 27 and J. S. G. Cox, E. O. Bishop, and R. E. Richards, *J. Chem. Soc.*, 5118 (1960).

(31) The angular methyl signals of IXa and XIVa appeared at τ 8.77 and τ 8.67, respectively, and these extraordinary shifts to the lower field will be discussed in the subsequent papers; *cf.* D. M. Bailey, D. P. G. Hamon and W. S. Johnson, *Tetrahedron Letters*, 555 (1963).

(32) W. G. Dauben, personal communication.

CHART II



new asymmetric center in isojervine at C-12. The n.m.r. spectrum of XIIIa showed in low field absorptions for three protons on C-3, C-22, and C-23 as broad peaks[33a] in the region near τ 5 and for about two protons as a relatively sharp peak centered at τ 6.71. The latter signal was shown to be a doublet (J = 1.7 c.p.s. and half-width = 4.9 c.p.s.) and the doublet peak was attributed to the 12-hydrogen by comparison of the spectra of various isojervine derivatives (IIa, VIIIa, XIIIa, and XVIII).[33b] The coupling constant between the protons at C-12 and C-14 gives dihedral angles of about 60 or 105°, using Conroy's graph,[34] and these values are consistent with C–D *cis*-fused linkage. Models of isojervine with such C–D *cis* configuration indicate that there will be nonbonded interaction between the 11-keto group and the 13,17-double bond. The ultraviolet absorption of the carbonyl group at 330 mμ with high intensity[35,36] supports this view as mentioned above. Since the configuration[37] of jervine is known, the hydrogen on C-12 of isojervine must have the α-configuration.

The isomer XX of m.p. 263° obtained in the preparation of isojervine had the molecular formula $C_{27}H_{39}NO_3$. Acetylation of XX gave the O,N-diacetate (XXa), m.p. 201–202°, indicating that the hydroxyl group on C-23 of isojervine had recombined with the carbocyclic ring. The infrared spectrum of XX showed the presence of an α,β-unsaturated keto group (bands at 1683 and 1630 cm.$^{-1}$) and a double bond at C-5–C-6 (band at 1063 cm.$^{-1}$). The ultraviolet spectrum had maxima at 220 mμ (ϵ 7600) and at 316 mμ (ϵ 180) and also an inflection at 252 mμ (ϵ 3500), and the whole curve was similar to that of isojervine. Hydrogenation of XX led to the formation of the dihydro derivative (XXI), m.p. 230–232°, which was also obtained when 5α-dihydroisojervine (VIII) was treated with methanol saturated with hydrogen chloride at room temperature. The transformation of XX to XXI caused the same hypsochromic and hyperchromic effects on the ultraviolet absorption as observed on hydrogenation of isojervine. The n.m.r. spectrum (Fig. 3) of XX showed two sharp singlets at τ 8.72 and 8.84 and two doublets centered at τ 9.02 (J = 7 c.p.s.) and 9.13 (J = 6 c.p.s.), respectively. Apparently, the latter two signals are due to 21- and 26-methyl groups or *vice versa*[38a,b] and the τ 8.72 peak can be attributed to the 19-methyl. The second

(33) (a) Contrary to the broad peak centered near τ 5.3 due to 3-hydrogen, absorption for 22- and 23-hydrogens is separated into three main signals centered near τ 4.9, 5.1, and 5.4. This absorption curve was characteristic for all acetylated jervine derivatives formed by cleavage of the ether linkage. (b) The absorption for the remaining one proton would be due to β-hydrogen at C-1; *cf.* D. H. Williams, N. S. Bhacca, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2810 (1963).

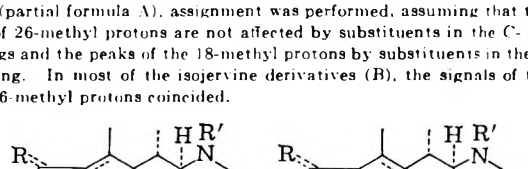
(34) H. Conroy, "Advances in Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, p. 311.

(35) H. Birnbaum, R. C. Cookson, and N. Lewin, *J. Chem. Soc.*, 1224 (1962).

(36) The end absorption in the ultraviolet spectrum of IIa would be associated not only with this interaction but also with the isolated tetrasubstituted 13,17-double bond itself. *Cf.* R. A. Micheli and T. H. Applewhite, *J. Org. Chem.*, **27**, 345 (1962); P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(37) As for the stereochemistry of jervine, see the following papers: ref. 25; J. Sicher and M. Tichý, *Tetrahedron Letters*, 6 (1959); S. Okuda, K. Tsuda, and H. Kataoka, *Chem. Ind.* (London), 512 (1961); R. L. Augustine, *ibid.*, 1448 (1961); H. Mitsuhashi and Y. Shimizu, *Tetrahedron*, **19**, 1027 (1963).

(38) (a) Alkali treatment (1 *N* potassium hydroxide in refluxing ethanol under nitrogen stream for 1 hr.) of XXI gave a resinous product which showed at least five spots on the paper but not a spot corresponding to XXI. As 12,13-dihydrojervine is stable under the conditions, this result suggests that in XXI the oxygen on the 23-carbon would be attached to the β-carbon (13-carbon) relative to the 11-keto group. A compound corresponding to the main spot was isolated and had m.p. *ca.* 130° (from isopropyl ether); λ_{max} 237 mμ (ϵ 11,000); ν_{max} 1678, 1630, and 1037 cm.$^{-1}$. These physical constants and the R_f value suggested it was a crude dihydroisojervine but a small amount of the product did not permit further examination. (b) The structure in which the 23-oxygen is attached to the 17-carbon as in jervine can be excluded on the basis of the sharp *singlet* at τ 8.84, as far as the carbocyclic and nitrogen ring systems are retained. For reference, the chemical shifts of 18-, 21-, and 26-methyl protons of jervine and isojervine derivatives are shown in Table I. Those values depend on the substituents in the C- and/or D-rings and also in the nitrogen ring. In jervine derivatives (partial formula A), assignment was performed, assuming that the signals of 26-methyl protons are not affected by substituents in the C- and/or D-rings and the peaks of the 18-methyl protons by substituents in the nitrogen ring. In most of the isojervine derivatives (B), the signals of the 21- and 26-methyl protons coincided.



A B

TABLE I

CHEMICAL SHIFTS OF THE 18-, 21-, AND 26-METHYL PROTONS OF JERVINE AND ISOJERVINE DERIVATIVES

Substituents			Number of compounds	Chemical shifts (τ) of methyl protons		
Double bond	R	R′	examined	18-	21-	26-
			Jervine Derivatives (A)			
12, 13	O	Ac	2	7.77, 7.79	9.12, 9.14	8.96, 8.98
None	O	Ac	2	9.08, 9.09	9.18, 9.19	8.98, 8.99
12, 13	H_2	Ac	1	8.29	9.16	8.99
12, 13	β-OH	Ac	1	8.10	9.15	8.98
None	β-OH	Ac	1	9.07?	9.17	8.98
None	α-OH	Ac	1	9.07	9.18	8.96
12, 13	O	H	3	7.79–7.85	9.04–9.06	9.04–9.06
None	O	H	2[a]	9.07, 9.09	9.07, 9.09	9.07, 9.09
12, 13	O	CH_3	1	7.78	8.94	8.94
12, 13	H_2	CH_3	2	8.34, 8.37	8.93, 8.96	8.93, 8.96
None	O	CH_3	1	9.07	8.98	8.98
			Isojervine Derivatives (B)			
8, 9; 13, 17	O	Ac	4	8.05–8.09	8.89–8.92	8.89–8.92
13, 17	O	Ac	4	8.10–8.12	8.86–8.90	8.86–8.90
13, 17	H_2	Ac	1	8.35	8.92	8.92
11, 12; 13, 17	H	Ac	1	8.17	8.86	8.86
8, 9; 13, 17	β-OH	Ac	1	8.18	8.87	8.87
13, 17	β-OH	Ac	1	8.30	8.87	8.87
13, 17	O	H	1	8.12	(8.89 and 9.18)[b]	
8, 9; 13, 17	O	H	2	7.99, 8.01	(8.88, 8.89 and 9.16, 9.18)[b]	

[a] 12,13-Dihydrojervine and tetrahydrojervine. [b] Assignment was not possible.

signal with a τ-value of 8.84 p.p.m. must be, therefore, absorption of the C-18 methyl. On the basis of these facts, one might conclude that the isomer of m.p. 263° possesses structure XX. (See Chart II.)

Experimental

The melting points are uncorrected. The optical rotations and the ultraviolet spectra were measured in ethanol and the infrared spectra in Nujol unless otherwise stated. The n.m.r. spectra were taken in deuteriochloroform at 60 Mc. using tetramethylsilane as an internal standard. The basicity measurements were carried out according to Thomson's procedure[39] in 50% ethanol at 20°.

Preparation of Isojervine[4,9] (II) and a New Isomer (XX).—To a methanol solution (210 ml.) saturated with hydrogen chloride was added jervine (7.0 g.) in 3 min. under stirring and cooling with ice, and the whole solution was continuously stirred for 1 hr. at room temperature. After removal of the solvent under reduced pressure below 45°, water (500 ml.) was added to the residue, which was made alkaline to pH 8.8 with 10% aqueous sodium carbonate. On treatment of the aqueous solution with chloroform, the chloroform compound of isojervine separated and was collected by filtration. Recrystallization from acetone yielded pure isojervine (6.0 g.), m.p. 116–118°. The chloroform solution obtained on filtration of the chloroform compound was evaporated to dryness and acetone was then added to the residue, yielding a crystalline substance (XX, 106 mg.) of m.p. 251–255°, which gave one spot on the paper chromatogram.[40] Two recrystallizations from methanol raised the melting point to 262–263°; $[\alpha]^{23}D$ +33° (*c* 0.126); λ_{max} 220 mμ (ϵ 7600) and 316 (180) and an inflection at 252 (3500); ν_{max} 1683, 1630, and 1063 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}NO_3$: C, 76.19; H, 9.24; N, 3.29. Found: C, 76.17, 75.91; H, 9.20, 9.42; N, 3.40.

Compound XX (100 mg.) was dissolved in a mixture of acetic anhydride (1 ml.) and pyridine (1 ml.), and the solution was allowed to stand at room temperature overnight and then heated on a steam bath for 30 min. The product crystallized on removal of acetic anhydride and pyridine and was recrystallized from aqueous ethanol. The diacetate (XXa, 95 mg.), m.p. 201–202°, was obtained; λ_{max} 220 mμ (ϵ 10,000) and an inflection at 252 mμ (ϵ 4500); ν_{max} 1727, 1701, 1636, 1594, 1252, and 1031 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{43}NO_5$: C, 73.05; H, 8.50; N, 2.75. Found: C, 73.08, 73.25; H, 8.78, 8.68; N, 3.13, 3.19.

The Birch Reduction of Isojervine.—To liquid ammonia (80 ml.) containing methanol (3 ml.) was added isojervine (0.5 g.) dissolved in tetrahydrofuran (5 ml.) and to the solution was added lithium metal (0.16 g.) at −70° during 15 min. under stirring. The mixture was stirred for another 10 min. After addition of ammonium chloride (1.7 g.) and removal of the solvent, the residue was treated with water and chloroform. The chloroform solution gave a resinous substance after drying and evaporation, which crystallized on addition of acetone. Recrystallization from a mixture of acetone and methanol afforded white crystals (III, 0.19 g.), m.p. 200–222°.

Anal. Calcd. for $C_{27}H_{43}NO_3$: C, 75.48; H, 10.09. Found: C, 75.26; H, 10.14.

No depression of melting point was observed on admixture of the product (III) with "α-dihydrojervinol" obtained by reduction of jervine with sodium and butanol.[8] The infrared spectra of the two compounds were also identical in Nujol and chloroform.

Isojervone (VII).—Isojervine (502 mg.) was dissolved in toluene (100 ml.) and 35 ml. of the solvent was distilled to remove moisture by azeotropization. To the solution was added freshly distilled cyclohexanone (8 ml.), and 8 ml. of the solvent was again removed. A dry toluene solution (5 ml.) of aluminum isopropoxide (1.50 g.) was added, and the mixture was refluxed for 7 hr. After removal of the solvent by steam distillation, the residue was repeatedly extracted with chloroform. The chloroform solutions were combined, washed with water, dried over sodium sulfate, and evaporated *in vacuo* to yield an unstable resin which was crystallized from acetone. Recrystallization from acetone gave isojervone (VII, 62 mg.), m.p. 112–114° dec. Paper chromatography showed that the product was homogeneous, but no satisfactory analysis was obtained because it was unstable in the air; $[\alpha]^{19}D$ +140°; λ_{max} 234 mμ (ϵ 22,000) and 320 mμ (ϵ 310); ν_{max} 1682, 1642, and 1620 cm.$^{-1}$.

The crude Oppenauer oxidation product, obtained from 500 mg. of isojervine, was directly acetylated with acetic anhydride (5 ml.) and pyridine (5 ml.). The crude acetate was chromatographed on Merck acid-washed alumina (10 g.). Fractions eluted with petroleum ether–benzene (1:1) and benzene were collected and triturated with acetone to afford crude diacetylisojervone (VIIa, 68 mg.), m.p. 188–195°. It had m.p. 202–204° after two recrystallizations from aqueous ethanol: $[\alpha]^{23}D$ +211°; λ_{max} 234 mμ (ϵ 27,000) and 320 mμ (ϵ 240); ν_{max} 1736, 1675, and 1641 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{41}NO_5$: C, 73.34; H, 8.14; N, 2.76. Found: C, 73.60; H, 8.17; N, 2.70.

(39) G. Thomson, *J. Chem. Soc.*, 1113 (1946).

(40) The paper chromatographic system used was that of J. Levine and H. Fischbach, *J. Am. Pharm. Assoc. Sci. Ed.*, **46**, 191 (1957); ethylene chloride–Cellosolve Acetate–pyridine (15:10:1 v.v.).

Dihydroisojervines (VIII and IX).—Isojervine (6.00 g.) recrystallized from ethanol was hydrogenated in acetic acid (80 ml.) in the presence of prereduced Adams catalyst (1.07 g.), and 354 cc. of hydrogen (1.18 moles) was taken up after 7 hr. After removal of the catalyst and the solvent, the residue was diluted with water, made alkaline with aqueous sodium carbonate, and treated with chloroform. A large amount of material, consisting of chloroform addition compounds of dihydroisojervines (6.52 g., m.p. 129–140°), remained suspended between the aqueous and chloroform layers and was collected by filtration. The aqueous filtrate was further extracted with chloroform repeatedly and the extract was combined with the chloroform filtrate. The chloroform solution was washed with water, dried, and concentrated to give additional solid substances (0.13 g., m.p. 134–143°). These chloroform compounds were combined and recrystallized from aqueous acetone to yield a mixture of dihydroisojervines (VIII and IX, 3.35 g.), m.p. 147–149°. After three further recrystallizations from aqueous acetone, the pure 5α-dihydroisojervine (VIII, 1.74 g.) was obtained and had m.p. 154–155° (as hydrate) and 171.5–172.5° (after drying), $[\alpha]^{23}D$ −21.1°; λ_{max} 239 mμ (ε 9400) and 326 mμ (ε 210); ν_{max} 1680, 1626, and 1040 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3$: C, 75.83; H, 9.66; N, 3.28. Found: C, 75.65; H, 9.55; N, 3.46.

After concentration of the first mother liquor and removal of a mixture of VIII and IX (1.13 g.), m.p. 135–140°, by filtration, the filtrate was further concentrated to give a single compound (0.46 g.), m.p. 128–133° dec., which was shown to be 5β-dihydroisojervine (IX) isomeric with VIII after purification by prolonged paper chromatography. The final product (IX), on recrystallization from acetone, had m.p. 114–115° dec., $[\alpha]^{23}D$ −49.0°; λ_{max} 236 mμ (ε 11,000) and 337 mμ (ε 250); ν_{max} 1716 (acetone), 1687, 1631, and 1030 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3 \cdot CH_3COCH_3 \cdot H_2O$: C, 71.53; H, 9.81. Found: C, 71.44; H, 9.46.

5α-Dihydroisojervine (VIII, 203 mg.) was treated with acetic anhydride (1 ml.) and pyridine (2 ml.) at room temperature for 19.5 hr. and then heated at 100° for 10 min. The mixture was poured into cold water to give a crystalline product which was collected by filtration and recrystallized twice from aqueous ethanol, yielding 193 mg. of the triacetate (VIIIa), m.p. 208–210°, $[\alpha]^{23}D$ +68.8°; λ_{max} 234 mμ (ε 14,000) and 332 mμ (ε 180); ν_{max} 1737, 1685, 1634, 1244, and 1024 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{47}NO_6$: C, 71.58; H, 8.56; N, 2.53. Found: C, 71.68; H, 8.51; N, 2.43.

5β-Dihydroisojervine (IX, 99 mg.) was acetylated under the same conditions as mentioned above and the crude triacetate (IXa, 93 mg.) thus obtained was recrystallized from aqueous ethanol to yield the pure compound (72 mg.), m.p. 174–176°, $[\alpha]^{23}D$ +56°; λ_{max} 236 mμ (ε 11,000) and 328 mμ (ε 180); ν_{max} 1740, 1683, 1633, 1242, and 1023 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{47}NO_6$: C, 71.58; H, 8.56; N, 2.53. Found: C, 71.59; H, 8.64; N, 2.83.

Dihydroisojervones (X and XI). A.—A mixture of 5α-dihydroisojervine (VIII, 472 mg.) and cyclohexanone (8 ml.) was dissolved in toluene (100 ml.) and 40 ml. of the solvent was distilled. To the solution was added aluminum isopropoxide (1.50 g.) in dry toluene (5 ml.), and the whole solution was refluxed for 10 hr. After removal of the solvent by steam distillation, the residue was repeatedly extracted with chloroform. The chloroform solution was evaporated to yield a resin. The paper chromatogram indicated that it was a mixture of the starting material and an oxidation product, dihydroisojervone. The resin was chromatographed on ten sheets of paper (Toyō Roshi No. 50, 20 × 40 cm.) and bands corresponding to dihydroisojervone were cut out and treated with aqueous ammonia and chloroform. On concentration of the chloroform solution, 5α-dihydroisojervone (X, 20 mg.) crystallized and was collected by filtration. The filtrate was evaporated to dryness and chromatographed on silicic acid (1.5 g.) using chloroform as solvent to give additional crystals (40 mg.). Recrystallization from acetone yielded plates, m.p. 108–110° dec.; $[\alpha]^{23}D$ 0°, $[\alpha]^{23}_{350}$ +179° (dioxane); λ_{max} 238 mμ (ε 9900) and 325 mμ (ε 320); ν_{max} 1714, 1679, and 1626 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}NO_3 \cdot 2CH_3COCH_3$: C, 73.15; H, 9.49. Found: C, 73.52; H, 9.27.

B.[41]—To 5α-dihydroisojervine (VIII, 405 mg.) dissolved in dimethylformamide (12 ml.) were added chromic anhydride (405 mg.) and concentrated sulfuric acid (8 drops) under ice cooling, and the whole solution was allowed to stand at room temperature for 10 hr. After decomposition of the excess chromic anhydride with 10% aqueous sodium bisulfite (≈ ml.), the solution was made alkaline to pH 8.2 with 10% aqueous sodium carbonate and extracted with four 10-ml. portions of chloroform. The chloroform solution was evaporated to dryness after being washed with water (30 ml.) and the residue was dissolved in ether. The mixture of bases in the ether solution was extracted with 2 *N* hydrochloric acid (2 × 12 ml.) and the acidic solution was made alkaline with 6 *N* ammonia and then treated with chloroform. The chloroform solution gave a brown oil (382 mg.), which crystallized on trituration with acetone and a small quantity of water. Recrystallization from aqueous acetone yielded 5α-dihydroisojervone (X, 147 mg.), m.p. 108–110° dec. Paper chromatography showed that more than 50% of the filtrate was the ketone X.

C.—5β-Dihydroisojervine (IX, 106 mg.) was oxidized and worked up in a manner similar to B, and gave an oily base (103 mg.). The oil was dissolved in chloroform and chromatographed on silicic acid (1 g.) using chloroform as solvent to yield oily 5β-dihydroisojervone (XI, 36 mg.), which showed one spot on the paper; $[\alpha]^{23}D$ −23°; λ_{max} 236 mμ (ε 10,000) and 326 mμ (ε 300); ν_{max} 1714, 1684, and 1616 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}NO_3$: C, 76.19, H, 9.24. Found: C, 75.98; H, 9.30.

Hydride Reduction[42] of 5α-Dihydroisojervone (X).—5α-Dihydroisojervone (XII, 50 mg.) was treated with sodium borohydride (20 mg.) in absolute ethanol at 20° for 1 hr. under stirring. After decomposition of the excess sodium borohydride with acetone (1 ml.) the solution was evaporated to dryness and the residue was shaken with chloroform and water. The chloroform solution gave a crystalline substance on removal of the solvent, which was recrystallized from aqueous acetone to yield 5α-dihydroisojervine (VIII, 28.1 mg.), m.p. 154–156°. The infrared spectrum and paper chromatography showed that more than 50% of the filtrate was the alcohol (VIII).

N-Methylisojervine (IV).—N-Methyljervine[11] (V, 4.50 g.) was added to methanol (135 ml.), saturated at 0° with hydrogen chloride, with stirring in the course of 6 min. and stirred at 0° for 1.5 hr. The red solution was evaporated *in vacuo* and diluted with water (500 ml.). It was made alkaline to pH 8.0 with 10% aqueous sodium carbonate and shaken with chloroform. Solid chloroform addition compounds were formed and collected by filtration. The aqueous layer of the filtrate was repeatedly extracted with chloroform and all chloroform solutions were combined, washed with water, and concentrated to 20 ml. to give solid materials (0.95 g.). The solid materials were combined and recrystallized from methanol–acetone to yield of N-methylisojervine (IV, 1.34 g.), m.p. 221–222°. It was also obtained by methylation of isojervine with methyl iodide and sodium carbonate in low yield; $[\alpha]^{23}D$ −9°; λ_{max} 327 mμ (ε 350), inflection at 245 (4400), and end absorption at 215 (11,000); ν_{max} 1673, 1631, and 1066 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{41}NO_3$: C, 76.49; H, 9.40; N, 3.19. Found: C, 76.53; H, 9.68; N, 2.97.

Isojervinol (VI). A.—To a solution of isojervine (499 mg.) in dry tetrahydrofuran (25 ml.) was added lithium aluminum hydride (250 mg.) in the same solvent (7 ml.) and the whole mixture was stirred under nitrogen. After 18.6 hr., the reaction mixture was treated cautiously with water (1.4 ml.) and filtered. The filtrate was evaporated under reduced pressure, diluted with water, and extracted with chloroform repeatedly. The combined chloroform solution was washed with water, dried, and evaporated. The residue yielded a crystalline substance (VI, 134 mg.), m.p. 198–203°, on trituration with acetone. After two recrystallizations from methanol–acetone, it had m.p. 210–211°, $[\alpha]^{23}D$ −33.2°; ultraviolet spectrum, only end absorption (ε 6400 at 212 mμ), $\lambda_{max}^{0.1\ N\ HCl\ EtOH}$ 311 mμ (ε 12,000); infrared spectrum, no band near 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3$: C, 75.83; H, 9.66; N, 3.28. Found: C, 75.54; H, 9.76; N, 3.27.

B.—Sodium borohydride (150 mg.) was added to a solution of isojervine (300 mg.) in tetrahydrofuran (20 ml.) and the reaction mixture was refluxed for 10 hr. under nitrogen and then kept at room temperature for 14 hr. The excess reducing agent was decomposed with acetone (3 ml.) and the mixture was evaporated under reduced pressure. Water was added to the residue, and the mixture was repeatedly extracted with chloroform. The

(41) Cf. G. Snatzke, *Ber.*, **94**, 729 (1961).

(42) Cf. O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1286 (1953).

combined chloroform solutions were washed with water, dried, and evaporated. Trituration of the residue with acetone yielded isojervinol (VI, 142 mg.), m.p. 204–208°, which after recrystallization from methanol–acetone had m.p. 206.5–207.5°.

Isojervinol (30 mg.) was treated with acetic anhydride (0.5 ml.) and pyridine (0.5 ml.) at room temperature for 12 hr. The excess of acetic anhydride was decomposed with methanol and the solution was evaporated to give an oily residue. On addition of water the residue crystallized gradually and recrystallization from aqueous ethanol yielded triacetylisojervinol (VIa, 26 mg.) which melted at 123°, solidified, and again melted at 181–183° dec.; ν_{max} 3400, 1728, 1617, 1237, and 1026 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{47}NO_6$: C, 71.58; H, 8.56. Found: C, 71.40; H, 8.68.

The Birch Reduction of Dihydroisojervines (VIII and IX).—To a refluxing solution of liquid ammonia (100 ml.) containing lithium (41 mg.) was added 5α-dihydroisojervine (VIII, 498 mg.) in tetrahydrofuran (6 ml.) during 2 min. under stirring. The mixture was continuously stirred for 5 min., when the blue color of the reaction mixture almost disappeared. Ammonium chloride (1 g.) was added and the resulting colorless solution was kept at room temperature to remove ammonia. When the residue was diluted with water and shaken with chloroform, a solid material (487 mg.) insoluble in the two layers appeared and was collected by filtration. The chloroform extract of the aqueous filtrate and the chloroform layer were combined, washed with water, dried over sodium sulfate, and evaporated to dryness. The residue and the solid material mentioned above were mixed and chromatographed on twelve sheets of paper. There appeared three bands when developed with bromophenol blue indicator. Each of the bands was cut out, collected, made alkaline with aqueous ammonia, and extracted with chloroform repeatedly.

The residue from the chloroform extract of the most mobile band yielded on trituration with chloroform crude 5α-tetrahydroisojervine needles (XIII, 152 mg.), m.p. 138–142°, m.p. 142–143° on recrystallization from aqueous acetone, $[\alpha]^{23}D$ +12°; λ_{max} 310 mμ (ε 240) and end absorption (ε 4300 at 215 mμ); ν_{max} 1732, 1039, and 1029 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{43}NO_3$: C, 75.48; H, 10.09; N, 3.26. Found: C, 75.29; H, 10.05; N, 3.21.

The middle band gave a crystalline product which was shown to be the unchanged 5α-dihydroisojervine by comparison of its chromatographic behavior and infrared spectrum with that of the starting material (VIII). The least mobile band afforded a crystalline product which upon recrystallization from chloroform gave hexahydroisojervine leaflets (XII, 13 mg.), m.p. 167–168°, $[\alpha]^{23}D$ −51°; ultraviolet spectrum, only end absorption (ε 3100 at 215 mμ); infrared spectrum, no carbonyl band near 1700 cm.$^{-1}$

Anal. Calcd. for $C_{27}H_{45}NO_3$: C, 75.13; H, 10.51; N, 3.25. Found: C, 74.85; H, 10.30; N, 3.28.

Hexahydroisojervine (XII) was also obtained by catalytic hydrogenation of "α-dihydrojervinol"; "α-dihydrojervinol" (III, 514 mg.) was dissolved in acetic acid (25 ml.) and hydrogenated over Adams platinum oxide (108 mg.) at room temperature. During 2.5 hr., 34 ml. of hydrogen (1.2 moles) was absorbed. After removal of the catalyst and the solvent, the residue was made alkaline with aqueous sodium carbonate and extracted with chloroform. The extract was dried over sodium sulfate and concentrated to yield a crystalline product (XII, 296 mg.), m.p. 163–165°. The infrared spectrum was identical with that of hexahydroisojervine. For analysis it was recrystallized twice from acetone, m.p. 122° dec.

Anal. Calcd. for $C_{27}H_{45}NO_3 \cdot CH_3COCH_3$: C, 73.57; H, 10.50; N, 2.86. Found: C, 73.53; H, 10.37; N, 3.01.

In another experiment where a mixture of dihydroisojervines (VIII and IX) was used as a starting material, the product showed a new spot on the paper beside those corresponding to the three compounds XII, VIII, and XIII, which appeared between the spots of XIII and VIII. A compound corresponding to the new spot was isolated by a treatment similar to that described above, and it crystallized on trituration with chloroform. Recrystallization from aqueous acetone gave isomeric 5β-tetrahydroisojervine leaflets (XIV), m.p. 147–148°. The yield was comparable with that of XIII. XIV had $[\alpha]^{23}D$ +83.0°; λ_{max} 302 mμ (ε 200) and end absorption (ε 5700 at 215 mμ); ν_{max} 1731, 1066, and 1029 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{43}NO_3$: C, 75.48; H, 10.09; N, 3.26. Found: C, 75.37; H, 10.08; N, 3.43.

5α-Tetrahydroisojervine (XIII, 95 mg.) was dissolved in acetic anhydride (1 ml.) and pyridine (1 ml.). The mixture was kept at room temperature for 11 hr. and then heated at 100° for 10 min. It was poured into cold water and the solid material thus obtained was recrystallized twice from aqueous ethanol to yield the triacetyl derivative as needles (XIIIa, 84 mg.), m.p. 167–169°, $[\alpha]^{23}D$ +83°; λ_{max} 307 mμ (ε 7,400) and end absorption (ε 250) at 215 mμ); ν_{max} 1738, 1632, 1238, and 1026 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{49}NO_6$: C, 71.32; H, 8.89; N, 2.52. Found: C, 71.49; H, 8.83; N, 2.71.

5β-Tetrahydroisojervine (XIV, 28 mg.) was similarly acetylated with acetic anhydride (0.4 ml.) and pyridine (0.4 ml.). The reaction mixture was worked up as usual and gave the corresponding triacetyl derivative as needles (XIVa, 25 mg.), m.p. 190–191° on recrystallization from aqueous ethanol, $[\alpha]^{23}D$ +110°; λ_{max} 308 mμ (ε 250) and end absorption (ε 8100 at 215 mμ); ν_{max} 1732, 1639, 1237, and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{49}NO_6$: C, 71.32; H, 8.89; N, 2.52. Found: C, 71.54; H, 9.07; N, 2.55.

Alkali Treatment of 5α-Dihydroisojervine (VIII).—A solution of 5α-dihydroisojervine (VIII, 1.02 g.) in *t*-butyl alcohol (20 ml.) containing 1 *N* potassium *t*-butoxide was refluxed for 1 hr. under a stream of nitrogen. The solution was evaporated *in vacuo*, diluted with water (40 ml.), and treated with chloroform. The chloroform solution gave a resin (1.03 g.) after being washed with water and dried. A paper chromatogram indicated that no starting material had survived. The resin was chromatographed on silicic acid (22 g.) using chloroform as eluent to yield crystalline material (283 mg.). Two recrystallizations from aqueous methanol yielded XVI as rods, m.p. 143–145°; $[\alpha]^{23}D$ +19°, $[\alpha]^{23}_{350}$ −382°; λ_{max} 239 mμ (ε 8600); ν_{max} 1670 and 1621 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1684 and 1629 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3$: C, 75.83; H, 9.66; N, 3.28. Found: C, 75.69; H, 9.66; N, 3.51.

The rearranged product (XVI, 193 mg.) was treated with acetic anhydride (3 ml.) and pyridine (3 ml.) and heated on a steam bath for 1 hr. The solution was worked up as usual to yield a resin (227 mg.), which was chromatographed on silicic acid using chloroform as eluent to afford an amorphous base, $[\alpha]^{23}D$ −11°, $[\alpha]^{23}_{350}$ −383°; λ_{max} 237 mμ (ε 8900); ν_{max} 1738, 1696, and 1640 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1726, 1685, and 1629 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{45}NO_5$: C, 72.76; H, 8.86; N, 2.74. Found: C, 72.65; H, 8.68; N, 2.72.

8,9-Dihydroisojervine (XIX).—To a refluxing solution of liquid ammonia (90 ml.) containing lithium (163 mg.) was added jervine (999 mg.) in dioxane (about 30 ml.) during 2 min. under stirring, and the whole mixture was stirred for another 5 min. The blue color of the reaction mixture disappeared on addition of ammonium chloride (3 g.) and then the ammonia was removed. The residue was treated with chloroform (100 ml.), and the chloroform solution was washed with water to remove dioxane and dried. The chloroform solution gave crude XIX, which crystallized as the chloroform compound (1.0 g.), m.p. 130°, on scratching. Recrystallization from acetone gave 8,9-dihydroisojervine (770 mg.), m.p. 159–160°. Two recrystallizations from acetone yielded an analytical sample (330 mg.), m.p. 162–163°; λ_{max} 312 mμ (ε 300) and end absorption (ε 5000 at 220 mμ); ν_{max} 1735 and 1060 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3$: C, 75.83; H, 9.66; N, 3.28. Found: C, 76.04; H, 9.66; N, 3.06.

8,9-Dihydroisojervine (102 mg.) was acetylated with acetic anhydride (1 ml.) and pyridine (1 ml.) at room temperature. The product (86 mg.) crystallized on trituration with ethyl acetate and had m.p. 160–162°. Recrystallization from aqueous ethanol yielded pure triacetate (XIXa, 45 mg.), m.p. 163–164°, ν_{max} 1732 and 1638 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{47}NO_6$: C, 71.58; H, 8.56. Found: C, 71.88, 71.40; H, 8.47, 8.59.

Hydrogenation of 8,9-Dihydroisojervine (XIX).—8,9-Dihydroisojervine (100 mg.) was hydrogenated over Adams platinum (50 mg.) in acetic acid (2 ml.) at room temperature for 3 hr. After removal of the catalyst and the solvent, the residue was treated with chloroform and 6 *N* ammonia (1 ml.) when a solid material (86 mg.), insoluble in the two layers, appeared and was collected by filtration. The solid and an amorphous base (38 mg.) obtained from the chloroform solution were mixed and chromatographed on seven sheets of paper. There appeared three bands when developed with bromophenol blue indicator. Each of the bands was cut out, collected, and treated with aqueous ammonia and chloroform. The residue (34 mg.) obtained from the most mobile band crystallized on trituration with chloroform. Two recrystallizations from aqueous acetone gave 5α-tetrahydroisojervine (XIII, 13.5 mg.), m.p. 143–144°. The infrared

spectrum was identical with that of the 5α-tetrahydrosojervine obtained by the Birch reduction of VIII. The middle band yielded a crystalline product (16.8 mg.), which had m.p. 135–137° on recrystallization from aqueous ethanol. The infrared spectrum showed no absorption of a carbonyl group and was different from that of III or XII.

Alkali Treatment of Triacetyl-8,9-dihydroisojervine (XIXa).—A solution of triacetyl-8,9-dihydroisojervine (XIXa, 30 mg.) in methanol (2 ml.) containing 10% potassium hydroxide was refluxed for 2 hr. under a stream of nitrogen. The solution was evaporated *in vacuo*, diluted with water, and treated with chloroform. The chloroform solution afforded a crystalline material (XIXb, 20 mg.), which had m.p. 213–215° on recrystallization from aqueous methanol; λ_{max} 254 mμ (ε 19,000); ν_{max} 3370, 1704, 1610, and 1055 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{43}NO_4$: C, 74.16; H, 9.23. Found: C, 74.01; H, 9.15.

The Dihydro Derivative of The Isomer (XX). A.—The compound (XX, 0.23 g.) was hydrogenated over prereduced Adams platinum (0.1 g.) in acetic acid (10 ml.) at room temperature, and after 6 hr. 13.4 ml. of hydrogen was absorbed (calculated for 1 mole, 12.7 ml.). The crystalline substance obtained after the usual work-up was recrystallized from acetone and the dihydro derivative (XXI, 0.12 g.), m.p. 230–232°, was obtained; λ_{max} 239 mμ (ε 12,800); ν_{max} 1691, 1630, and 1035 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3$: C, 75.83; H, 9.66; N, 3.28. Found: C, 75.52; H, 9.76; N, 3.31.

B.—The dihydro derivative (XXI) was also obtained from 5α-dihydroisojervine (VIII); a solution of VIII (60 mg.) in methanol (8 ml.) was saturated with hydrogen chloride and allowed to stand at room temperature for 2 days. Water was added to the residue obtained on removal of the solvent under reduced pressure. The aqueous solution was made alkaline to pH 8 with 5% aqueous sodium carbonate, when a solid material (the starting material, 35 mg.) separated. After filtration, the aqueous solution was repeatedly extracted with chloroform. The chloroform solution gave a resin on removal of the solvent, which was chromatographed on paper. Five bands appeared on the chromatogram. The middle band was cut out and treated with aqueous ammonia and chloroform. The chloroform solution gave an amorphous substance which crystallized on trituration with acetone. On recrystallization from acetone, a crude sample of XXI (3.5 mg.), m.p. 220–227°, was obtained, which showed the practically same infrared spectrum and R_f value as the pure dihydro derivative mentioned above.

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Syntheses of Jasmone and the Related Compounds. II.[1] Preparation of *trans*-Jasmone and Allethrone

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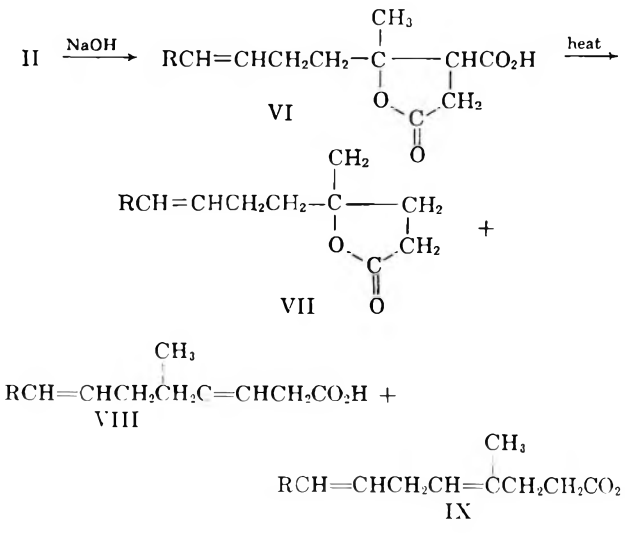
trans-Jasmone (Vb) and allethrone (Va) were synthesized from γ-methyl-γ-(3,4-dibromoalkyl)paraconic acids (III) by cyclodehydration with polyphosphoric acid followed by debromination with zinc. The acids III were obtained by bromination of γ-methyl-γ-alkenyl-α,β-dicarbethoxybutyrolactones (II) followed by heating with hydrochloric acid. Care was required in order to avoid the migration of and addition to the side-chain double bond.

In the previous paper,[2] a synthesis of 2,3-dialkyl-2-cyclopenten-1-ones including dihydrojasmone from γ,γ-dialkylparaconic acids was described. A synthesis of cyclopentenones (V) with an unsaturated side chain such as *trans*-jasmone[3–5] (Vb) and allethron[6] (Va) was undertaken. In order to avoid the migration of and addition to the double bond, a reaction sequence as illustrated in Scheme I was followed.

Reaction of ethyl β-methyl-β-alkenylglycidates (I) with sodium malonate afforded γ-methyl-γ-alkenyl-α,β-dicarbethoxybutyrolactones (II). Bromination of II followed by heating with hydrochloric acid gave γ-methyl-γ-(3,4-dibromoalkyl)paraconic acids (III). Treatment of III with polyphosphoric acid as described previously[2] resulted in the formation of methyldibromoalkylcyclopentenones (IV) which were subsequently debrominated with activated zinc[7] to give the expected cyclopentenones (V), including *trans*-jasmone (Vb) and allethrone (Va). The structures of these cyclopentenones were established by infrared spectra as well as conversion into the well-defined crystalline derivatives.

Saponification of II with aqueous sodium hydroxide followed by decarboxylation in glacial acetic acid[2] gave paraconic acids (VI). These were identical with the paraconic acids obtained by debromination of III, indicating that during the treatment of the lactone diesters (II) with alkali no shift of the double bond in the alkenyl group took place. Further evidence supporting the



(1) Part I[2] concerned the preparation of dihydrojasmone and the homologs from γ,γ-dialkyl paraconic acid.

(2) K. Sisido, S. Torii, and M. Kawanisi, *J. Org. Chem.*, **29**, 904 (1964).

(3) W. Treff and H. Werner, *Chem. Ber.*, **68**, 640 (1935).

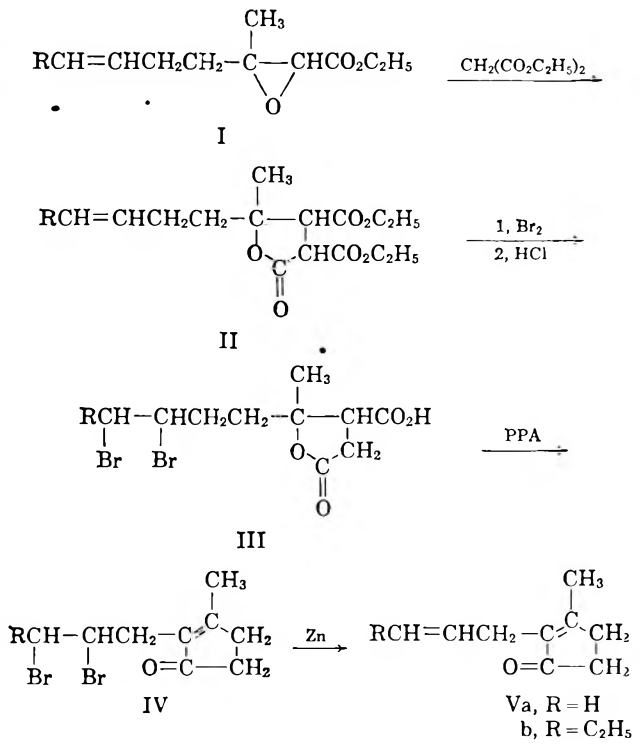
(4) H. Hunsdiecker, *ibid.*, **75**, 460 (1942).

(5) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 869 (1952).

(6) L. Crombie, A. J. B. Edger, S. H. Harper, M. W. Lowe, and D. Thompson, *ibid.*, 3552 (1950).

(7) F. Bohlmann and K. Kieslich, *Chem. Ber.*, **87**, 1363 (1954).

SCHEME I



absence of the migration was obtained by ozonolysis of VI and by gas chromatography of the methyl ester of VI.

Thermal decarboxylation[8] of the paraconic acids (VI) afforded the butyrolactones (VII) and the two isomeric diunsaturated carboxylic acids (VIII and IX).

The unsaturated paraconic acids (VI) could not be prepared by the ordinary method through lactonization[2] of Stobbe half-esters[9] prepared by the reaction of methyl alkenyl ketones with diethyl succinate because of an inevitable addition of the lactonization reagent, *i.e.*, hydrogen halide, to the double bond.

For the synthesis of cyclopentenones (V) the direct cyclodehydration of γ-methyl-γ-alkenylparaconic acids (VI) or -butyrolactones (VII) would appear to be more straightforward. Due to the double bond migration, however, VI and VII did not give single products when heated with polyphosphoric acid.

This treatment of γ-methyl-γ-(3-hexenyl)paraconic acid (VIb) afforded a mixture of cyclopentenones accompanied by the corresponding acid anhydride (XI) and the butyrolactone (VII). The infrared spectra of the cyclopentenone mixture showed an absorption of an isolated double bond (1660 cm.$^{-1}$) and a conjugated double bond (1640 cm.$^{-1}$), indicating the shift of the original double bond toward the direction of the cyclopentenone ring.[10] When the mixed cyclopentenones were heated at 200° for 2 hr., the spectrum of the conjugated double bond became stronger at the expense of the band at 1660 cm.$^{-1}$. Elliott[11] described similar double bond migration by heat in the case of pyrethrone. γ-Methyl-γ-(3-butenyl)paraconic acid (VIa) gave a resinous material upon the same treatment.

Experimental[12]

Ethyl β-Methyl-β-(3-butenyl)glycidate (Ia).—To a mixture of 19.8 g. (0.2 mole) of allylacetone[13] (b.p. 131–132°, lit.[13] b.p. 127–132°) and 24.5 g. (0.2 mole) of ethyl chloroacetate, 22.4 g. of potassium *t*-butoxide in 160 ml. of dry *t*-butyl alcohol was added. The mixture was stirred at 10–15° for 1 hr. and, after addition of ice–water, the reaction mixture was extracted with ether. The product obtained on evaporation of the ethereal solution was distilled under reduced pressure to give 36.3 g. (80% based on allylacetone) of ethyl β-methyl-β-(3-butenyl) glycidate (Ia), b.p. 128.5° (30 mm.), n^{23}D 1.4436; ν_{max} (neat) 3070, 1640, 992, and 910 cm.$^{-1}$ (terminal vinyl group). Gas chromatography showed a single peak.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.40; H, 8.76.

In a similar way, from 25.2 g. (0.2 mole) of *trans*-oct-5-en-2-one[5] [ν_{max} (neat) 1710 (carbonyl) and 965 cm.$^{-1}$ (*trans* double bond); 2,4-dinitrophenylhydrazone, m.p. 55–56°, lit.[5] m.p. 56°], 33 g. (78%) of **ethyl β-methyl-β-(3-hexenyl)glycidate (Ib)** was obtained, b.p. 138° (14 mm.), n^{20}D 1.4517, ν_{max} (neat) 965 cm.$^{-1}$ (*trans* double bond).

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.08; H, 9.52.

Reaction of Ethyl β-Methyl-β-(3-butenyl)glycidate (Ia) with Diethyl Malonate.—To a mixture of 13.6 g. (0.2 mole) of sodium ethoxide and 37.5 g. (0.25 mole) of diethyl malonate in 120 ml. of anhydrous ethanol, 15.4 g. (0.1 mole) of ethyl β-methyl-β-(3-butenyl)glycidate (Ia) was added and refluxed for 20 hr. The mixture was acidified and taken up in ether. The ether layer was washed with sodium bicarbonate solution and, after drying over sodium sulfate, evaporated *in vacuo*. Distillation of the residue yielded 13.5 g. (45.4% based on glycidate) of γ-methyl-γ-(3-butenyl)-α,β-dicarbethoxybutyrolactone (IIa), b.p. 172° (2 mm.), n^{23}D 1.4615; ν_{max} (neat) 3080, 1640, 992, and 905 (terminal vinyl), 1790 (lactone carbonyl), and 1750 and 1740 cm.$^{-1}$ (ester carbonyls).

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.63; H, 7.60.

Similarly, from 15.4 g. (0.1 mole) of ethyl β-methyl-β-(3-hexenyl)glycidate (Ib), 18 g. (58%) of **γ-methyl-γ-(3-hexenyl)-α,β-dicarbethoxybutyrolactone (IIb)**, b.p. 162° (0.9 mm.), n^{20}D 1.4661, was obtained; ν_{max} (neat) 968 (*trans* double bond), 1785 (lactone carbonyl), 1750 and 1740 cm.$^{-1}$ (ester carbonyls).

Anal. Calcd. for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.72; H, 8.11.

γ-Methyl-γ-(3,4-dibromobutyl)paraconic Acid (IIIa) *via* Dibromolactone Diesters.—Bromination of 29.8 g. (0.1 mole) of γ-methyl-γ-(3-butenyl)-α,β-dicarbethoxybutyrolactone (IIa) was carried out in 50 ml. of carbon tetrachloride at −5° with 16 g. of bromine. The dibromide was heated vigorously with 100 ml. of concentrated hydrochloric acid for 6 hr. until the evolution of hydrogen chloride ceased and then cooled to room temperature. Precipitated solid was collected and a further amount of dibromolactone acid was extracted from the residual black material with hot water. Thus, 54.4 g. (76%) of γ-methyl-γ-(3,4-dibromobutyl)paraconic acid (IIIa) was obtained, m.p. 126°, ν_{max} (neat) 1745 cm.$^{-1}$ (paraconic acid carbonyl).[2]

Anal. Calcd. for $C_{10}H_{14}Br_2O_4$: C, 33.54; H, 3.94. Found: C, 33.63; H, 3.94.

In a similar way, from 32.6 g. (0.1 mole) of γ-methyl-γ-(3-hexenyl)-α,β-dicarbethoxybutyrolactone (IIb), 38.1 g. (78%) of **γ-methyl-γ-(3,4-dibromohexyl)paraconic acid (IIIb)**, m.p. 122°, was obtained, ν_{max} (neat) 1745 cm.$^{-1}$ (paraconic acid carbonyl).

(8) W. S. Johnson and R. H. Hunt, *J. Am. Chem. Soc.*, **72**, 935 (1950).

(9) W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 26 (1951).

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., London, 1958, p. 35.

(11) M. Elliott, *Chem. Ind.* (London), 1142 (1960).

(12) Microanalyses were performed by Miss Kenko Ogawa of this laboratory.

(13) M. S. Schechter, N. Green, and F. B. Laforge, *J. Am. Chem. Soc.*, **71**, 3165 (1949).

Anal. Calcd. for $C_{12}H_{18}Br_2O_4$: C, 37.33; H, 4.70. Found: C, 37.66; H, 4.93.

***trans*-Jasmone (Vb) by Dehydration of γ-Methyl-γ-(3,4-dibromohexyl)paraconic Acid (IIIb).**—A mixture of 5 ml. of polyphosphoric acid (82–83% P_2O_5) and 7.7 g. (0.021 mole) of γ-methyl-γ-(3,4-dibromohexyl)paraconic acid (IIIb) was heated at 140–145° for 30 min. to complete the decarboxylation; 30 ml. of water, 20 ml. of benzene, and 10 ml. of ether were added to this mixture. The organic layer was separated from resinous by-products and washed with sodium bicarbonate solution and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated. The infrared absorption of this residue showed four bands in the carbonyl region at 1698, 1765, 1780, and 1840 cm.$^{-1}$, indicating that the residue comprised three components such as cyclopentenones (IV), lactone, and acid anhydride. The cyclopentenone and the lactone could be isolated by column chromatography on alumina using chloroform as an eluent. Repeated chromatography on alumina carried out with a mixture of carbon tetrachloride, petroleum ether (b.p. 40–60°) and chloroform (3:3:1 by volume) gave two fractions. From the first principal fraction 2.7 g. (40% based on IIIb) of 3-methyl-2-(2,3-dibromopentyl)-2-cyclopentenone-1 (IVb) was isolated, ν_{max} (neat) 1698 (carbonyl) and 1640 cm.$^{-1}$ (ethylene). The second minor fraction afforded 1.2 g. (19% based on IIIb) of γ-methyl-γ-(3,4-dibromohexyl)butyrolactone whose infrared spectrum was identical in every fine detail with that of the compound described in the subsequent paragraph.

The dibromocyclopentenone (IVb) was treated with 3 g. of activated zinc powder[7] in 3 ml. of 95% ethanol under reflux for 10–15 hr. Upon cooling to the room temperature, 5 ml. of water was added and the reaction product was extracted with ether. The ether layer was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated. Distillation of the residue under diminished pressure afforded 0.42 g. (31% based on IVb) of 3-methyl-2-(*trans*-2-pentenyl)-2-cyclopentenone-1, *i.e.*, *trans*-jasmone (Vb): b.p. 118° (13 mm.), $n^{20}D$ 1.4992; lit.[4] 142° (23 mm.), $n^{20}D$ 1.4974; semicarbazone m.p. 230°, lit.[4] m.p. 200–202°; 2,4-dinitrophenylhydrazone m.p. 127°, lit.[4] m.p. 128.5°; λ_{max} 258 mμ (ε 19,000) in ethanol. The ketone, semicarbazone, and 2,4-dinitrophenylhydrazone gave correct analyses. Infrared spectra were identical with those of the reported charts.[4]

Similarly from 3.6 g. (0.01 mole) of γ-methyl-γ-(3,4-dibromobutyl)paraconic acid (IIIa) there was obtained 0.24 g. (18.5%) of allethrone (Va): b.p. 120° (3 mm.), lit.[6] b.p. 63–70° (0.3 mm.); $n^{20}D$ 1.4501; ν_{max} (neat) 3080, 1640, 995, and 906 (terminal vinyl group), and 1698 and 1640 cm.$^{-1}$ (cyclopentenone); 2,4-dinitrophenylhydrazone m.p. 171–172°, lit.[6] m.p. 172°; λ_{max} 258 mμ (ε 19,250) in ethanol. These gave correct analyses for carbon and hydrogen.

Saponification of Lactone Diesters (IIa) with Sodium Hydroxide to Give Paraconic Acid (VIa).—A mixture of 15 g. (0.01 mole) of γ-methyl-γ-(3-butenyl)-α,β-dicarbethoxybutyrolactone (IIa) in 100 ml. of 1 *N* sodium hydroxide was refluxed for 4–5 hr. and neutralized to pH 6.5–7 with dilute sulfuric acid. When water was evaporated *in vacuo*, there were obtained in semisolid state lactonedicarboxylic acids, which were boiled for 30 min. of glacial acetic acid until the evolution of carbon dioxide ceased. Acetic acid was removed and 150 ml. of water was added. The precipitated light brown solid was recrystallized from a mixture of water and ethanol (10:1) to give 5.6 g. (60% based on lactone diesters) of γ-methyl-γ-(3-butenyl)paraconic acid (VIa), m.p. 135°; ν_{max} (neat) 1745 (paraconic acid), 3080, 1635, 985, and 910 cm.$^{-1}$ (terminal vinyl). The same acid was obtained from IIIa by the treatment with zinc powder.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.69; H, 7.13.

Bromination of 9.9 g. (0.05 mole) of VIa was carried out with 8 g. of bromine in 30 ml. of of anhydrous chloroform at −5°. Recrystallization of the dibromide from water–ethanol (10:1) gave 17.2 g. (96%) of IIIa, m.p. and m.m.p. 126°.

Methyl γ-Methyl-γ-(3-butenyl)paraconate.—This compound (b.p. 134° at 3 mm., $n^{20}D$ 1.4688) was obtained by esterification of VIa with diazomethane. This showed a single gas chromatographic peak [6-ft. "Shimadzu Thermol-3" (silicone) column; retention time, 5.0 min. at 237°; 55 ml. of nitrogen/min.]. Infrared spectra of terminal vinyl group were the same as those of the acid VIa.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 62.25; H, 7.60. Found: C, 62.59; H, 7.78.

γ-Methyl-γ-(*trans*-3-hexenyl)paraconic Acid (VIb).—From 16.3 g. (0.05 mole) of γ-methyl-γ-(3-hexenyl)-α,β-dicarbethoxybutyrolactone (IIb), 7.3 g. (65%) of γ-methyl-γ-(*trans*-3-hexenyl)paraconic acid (VIb) was obtained, m.p. 138°, ν_{max} (neat) 965 (*trans* double bond) and 1745 cm.$^{-1}$ (carbonyl).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.79; H, 7.91.

In order to confirm the position of the double bond, with 0.45 g. (2 mmoles) of γ-methyl-γ-(*trans*-3-hexenyl)paraconic acid (VIb) ozonolysis was carried out in chloroform at 0°. The ozonide was decomposed in 50 ml. of boiling water. Distilled volatile material was converted into the corresponding 2,4-dinitrophenylhydrazone, which was proved to be propionaldehyde derivative by the correct analysis for carbon and hydrogen, comparison of R_f values of the paper chromatography, and mixture melting point with an authentic compound.

Debromination of γ-Methyl-γ-(3,4-dibromohexyl)paraconic Acid (IIIb).—The treatment of 7.7 g. (0.02 mole) of IIIb with 4.5 g. of zinc powder as above gave 4.1 g. (90%) of γ-methyl-γ-(*trans*-3-hexenyl)paraconic acid (VIb), m.p. 138°. The mixture melting point with the paraconic acid obtained by hydrolysis of lactone diester (IIb) showed no depression, ν_{max} (neat) 964 cm.$^{-1}$ (*trans* double bond).

Decarboxylation of γ-Methyl-γ-(3-hexenyl)paraconic Acid (VIb).—A mixture of 4.5 g. (0.02 mole) of γ-methyl-γ-(*trans*-3-hexenyl)paraconic acid (VIb) and 0.05 g. of potassium hydrogen sulfate was treated at 230–250° for 4 hr. and there was obtained, as a neutral substance, 2.2 g. (61% based on VIb) of γ-methyl-γ-(*trans*-3-hexenyl)butyrolactone (VIIb), b.p. 136° (13 mm.), $n^{20}D$ 1.4700, ν_{max} (neat) 1760 cm.$^{-1}$ (lactone carbonyl).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.40; H, 9.80.

Ozonolysis of VIIb gave, as a volatile fragment, only propionaldehyde, which was identified as the corresponding 2,4-dinitrophenylhydrazone.

As acidic products of pyrolysis, there was obtained 1.3 g. (37%) of a mixture of **4-methyldeca-3,7- and 4,7-dienoic acids (VIIIa and IXb)**, b.p. 132° (2.5 mm.), $n^{20}D$ 1.4698, ν_{max} (neat) 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.29; H, 9.80.

In the n.m.r. spectra of VIIIb and IXb, the methylene signal adjacent to the carboxylic acid group in structure VIIIb appeared at τ 6.9 and 7.1 as a doublet due to spin–spin coupling to the adjacent proton. Integration of the doublet signals gave area equivalent to one proton, suggesting the presence of equal amounts of each isomer.

The mixed acids VIIIb and IXb, after esterification with diazomethane followed by reaction with excess phenyl magnesium bromide[14] to produce **1,1-diphenyl-4-methyldeca-1,3,7- and 1,4,7-triene**, b.p. 145° (1.5 mm.), $n^{20}D$ 1.5928, showed an ultraviolet absorption at λ_{max} 251 mμ (ε 9000) in ethanol. The proportion of VIIIb and IXb was calculated[9] to exist in an equal ratio.

Anal. Calcd. for $C_{23}H_{26}$: C, 91.33; H, 8.67. Found: C, 90.48; H, 8.79.

Decarboxylation of γ-Methyl-γ-(3-butenyl)paraconic Acid (VIa).—A mixture of 9.9 g. (0.05 mole) of γ-methyl-γ-(3-butenyl)paraconic acid (VIa) and 0.03 g. of potassium hydrogen sulfate was treated at 230–250° for 4 hr. and there was obtained 5 g. (65%) of γ-methyl-γ-(3-butenyl)butyrolactone (VIIa), b.p. 119° (10 mm.), $n^{20}D$ 1.4672; ν_{max} (neat) 3080, 1640, 992, and 905 (terminal vinyl), and 1765 cm.$^{-1}$ (lactone carbonyl).

Anal. Calcd. for $C_8H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.23; H, 9.10.

The lactone VIIa gave a single gas chromatographic peak.

As an acidic component, there was obtained 2.1 g. (28%) of a mixture of **4-methylocta-3,7- and 4,7-dienoic acids (VIIIa and IXa)**, b.p. 105° (2 mm.), $n^{20}D$ 1.4681.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.15; H, 9.10.

N.m.r. spectra of the mixed acids, VIIIa and IXa, exhibited a signal for the methylene adjacent to the carboxylic acid group in VIIIa similar to that of VIIIb.

Cyclodehydration of γ-Methyl-γ-(3-hexenyl)paraconic Acid (VIb).—To 2 ml. of polyphosphoric acid (82–83% P_2O_5) warmed at 100–120° was added 2.02 g. (0.01 mole) of γ-methyl-γ-(*trans*-3-hexenyl)paraconic acid (VI). The mixture was heated under 10 mm. gradually in the course of 30 min. to a final temperature

(14) *Cf.* L. Crombie and A. G. Jacklin, *J. Chem. Soc.*, 1622 (1957).

of 135°. During this period, vigorous evolution of carbon dioxide occurred. After the decomposition reaction subsided, the temperature was raised gradually during 3 hr. to 160°, when crude cyclopentenone together with lactone, dicarboxylic acids, and the acid anhydride[2] were distilled. From the ethereal solution of this crude cyclopentenone acidic material was removed with 5% potassium carbonate solution. The ether layer was washed with water, dried, and evaporated.

In order to separate the cyclopentenone from the mixture, Girard P reagent[15] was employed. To a boiling mixture of 1.4 g. of Girard P reagent, 16 ml. of ethanol, 2.7 ml. of methanol, and 2 g. of acetic acid, 1.2 g. of the crude cyclopentenone was added. After boiling for 1 hr., the mixture was poured into a solution of 3 g. of sodium carbonate in 100 ml. of ice–water. The neutral solution was extracted twice with ether and 12 ml. of 12 *N* sulfuric acid was added. The ether layer was washed with sodium bicarbonate solution as well as saturated sodium chloride solution, dried, and evaporated. On redistillation of the residue there was obtained 0.6 g. (32% based on VIb) of the isomer of *trans*-jasmone, b.p. 85° (1.5 mm.), $n^{20}D$ 1.5069; ν_{max} (neat) 980 (cross-conjugated *trans* double bond), 970 (*trans* double bond), 1698 (carbonyl), and 1640 and 1660 cm.$^{-1}$ (ethylenic bond).

On heating this material at 200° for 2 hr., double bond migration was noticed on an examination of the infrared spectrum.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 79.77; H, 9.79.

2,4-Dinitrophenylhydrazone of the cyclopentenone melted at 213–215°.

Anal. Calcd. for $C_{17}H_{20}O_4N_4$: C, 59.29; H, 5.85. Found: C, 59.37; H, 6.15.

Similar treatment of 1.82 g. (0.01 mole) of γ-methyl-γ-(3-hexenyl)butyrolactone (VIIb) with polyphosphoric acid afforded 0.65 g. (41%) of the cyclopentenone, b.p. 90° (2 mm.). The infrared spectra were identical with those of the material prepared from VIb.

(15) A. Girard and G. Sandalesco, *Helv. Chim. Acta*, **19**, 1095 (1936).

Dehydration of γ-Methyl-γ-(3-butenyl)paraconic Acid (VIa).—Reaction of γ-methyl-γ-(3-butenyl)paraconic acid (VIa) with polyphosphoric acid was examined under 10 mm. at 135–145°, but the mixture became too sticky, and no volatile material was obtained.

γ-Methyl-γ-(3,4-dibromohexyl)butyrolactone.—Bromination of 18.2 g. (0.1 mole) of γ-methyl-γ-(3-hexenyl)butyrolactone (VIIb) was carried out in 30 ml. of carbon tetrachloride at −5° with 16 g. of bromine. On removal of the solvent *in vacuo*, there was obtained 34 g. of γ-methyl-γ-(3,4-dibromohexyl)butyrolactone, $n^{20}D$ 1.5332, ν_{max} (neat) 1770 cm.$^{-1}$ (lactone carbonyl). Attempted purification failed because the substance decomposed on heating. This material, however, gave satisfactory analyses without further purification.

Anal. Calcd. for $C_{11}H_{18}Br_2O_2$: C, 38.62; H, 5.30. Found: C, 38.98; H, 4.99.

Dehydration of γ-Methyl-γ-(3,4-dibromohexyl)butyrolactone.—A mixture of 1.5 ml. of polyphosphoric acid and 3.4 g. (0.01 mole) of γ-methyl-γ-(3,4-dibromohexyl)butyrolactone was stirred at 145° for 30 min. After treating the reaction mixture in the same way as described above on the paraconic acid (IIIb), there was obtained 2.1 g. of the reaction products which contained the desired cyclopentenone IVb together with unchanged lactone. In order to separate the cyclopentenone, Girard P reagent was employed. From 2.1 g. of the mixture, 1.3 g. (40%) of IVb was obtained. The infrared spectra of the dibromocyclopentenone were superimposable in every fine detail with those of the compound obtained from the corresponding paraconic acid IIIb.

Allethrone (Va) by Dehydration of γ-Methyl-γ-(3,4-dibromobutyl)butyrolactone.—A mixture of 5 ml. of polyphosphoric acid and 6.8 g. (0.022 mole) of γ-methyl-γ-(3,4-dibromobutyl)butyrolactone (prepared from VIIa by bromination as described above) was heated at 130–145° for 30 min., and to this mixture 30 ml. of water and 10 ml. of benzene were added. On debromination of the reaction mixture in the same way as described above, there was obtained 0.6 g. (21% based on dibromobutyrolactone) of allethrone (Va), b.p. 120° (30 mm.). The infrared spectra were identical with those of the compound described in a preceding paragraph.

The Structure of Carnosol

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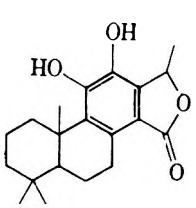
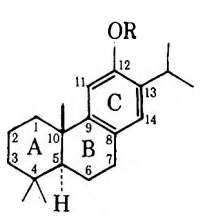
Carnosol is shown to be a phenolic diterpenic lactone of the ferruginol type. Its biosynthesis as well as that of the related tanshinones is discussed. A proton magnetic resonance study of the derivatives of carnosol, ferruginol, and totarol is presented.

Over 20 years ago a bitter principle was isolated from sage, *Salvia carnosa* Dougl.[4] The natural substance was named carnosol and noted to be a diphenolic, ester-containing $C_{19}H_{26}O_4$ hydrophenanthrene. While nothing further has been reported on this compound, another bitter principle, picrosalvin, was isolated recently from two other species of sage, *Salvia officinalis* L. and *Salvia triloba* L.,[5] as well as from rosemary, *Rosmarinus officinalis* L. (see Experimental), and recorded to be a $C_{20}H_{26}O_4$ *o*-diphenolic hydrophenanthrene lactone of structure I. The similarity of the physical and chemical properties of the two principles suggested that they may be the same natural product. As a consequence, a direct comparison of the two substances and their derivatives was made (see Experimental)[6] and their identity established. In view of the priority of the work of



I



IIa, R=H
b, R=Bz
c, R=Ac
d, R=Me

(1) Universität Würzburg.

(2) Indiana University.

(3) National Science Foundation Cooperative Predoctoral Fellow, 1962–.

(4) A. I. White and G. L. Jenkins, *J. Am. Pharm. Assoc., Sci. Ed.*, **31**, 33, 37 (1942).

(5) (a) C. H. Brieskorn and A. Fuchs, *Chem. Ber.*, **95**, 3034 (1962). (b) Undoubtedly this substance is identical with the $C_{20}H_{26}O_4$ compound isolated from *Salvia officinalis* L. by M. M. Janot, H. Pourrat, and J. LeMen [*Ann. pharm. franç.*, **10**, 433 (1952)].

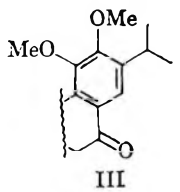
(6) The authors are most grateful to Professor A. I. White for his gift of carnosol and its derivatives.

White and Jenkins,[4] the name carnosol will be used for the bitter principle henceforth.

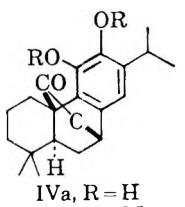
Various results from the last structure analysis militated against formula I for carnosol. The chemical shifts of the hydrogen signals of the methyl groups (0.88, 0.93, 1.15, and 1.26 p.p.m.) in the proton magnetic resonance spectrum of carnosol diacetate could not account for the placement of a methyl group on a phthalide nucleus. The carbonyl absorption, 5.73 μ, in the infrared spectra of carnosol, its diacetate, and its dimethyl ether lay between the regions characteristic of the carbonyl bands of γ- and δ-lactones and, hence, was doubtful support for the phthalide moiety in I. Finally, the possible identity of one of the selenium dehydrogenation products of carnosol with retene[7] was incompatible with formula I and more in line with a carnosol structure based on the ferruginol (IIa) nucleus.

Further strengthening of this view came from the observation of the alkaline hydrogen peroxide oxidation of carnosol yielding isobutyric acid as well as from closer inspection of the p.m.r. spectra of the carnosol derivatives. The spectra of both the diacetate and dimethyl ether revealed signals characteristic of an aromatic hydrogen and isopropyl hydrogens (*vide infra*).[8] These facts in conjunction with the previous data[5] indicated carnosol to be an 11-hydroxyferruginol derivative.

This formulation limited the lactone carbonyl carbon of carnosol to a nuclear position in the ferruginol skeleton, replacing one of the three remaining methyl groups. The oxygen terminus of the lactone group could be located safely at C-7 on the basis of the downfield 5.4 p.p.m. methine signal present in the p.m.r. spectra of the natural product and its two derivatives. Furthermore, the presence of oxygen at C-7, a benzylic position, was confirmed by the hydrogenolysis of carnosol dimethyl ether to a carboxylic acid and by the preparation of a sugiol derivative (III) from carnosol dimethyl ether on alkaline hydrolysis, esterification with diazomethane, and manganese dioxide oxidation. The reported ease of decarboxylation of carnosol and its quinone[5] indicated both endings of the lactone moiety to be benzylic. On the assumption of carnosol being a diterpene biosynthetically related to ferruginol and hence of A–B *trans* configuration, the further structure analysis was predicted on IVa as a reasonable, working formula.

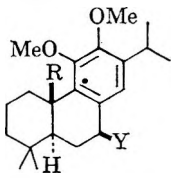


III



IVa, R = H
b, R = Me
c, R = Ac

In order to check the implied carnosol–ferruginol relationship, the following experiments were performed. Carnosol dimethyl ether was converted to a diol (Va) on lithium aluminum hydride reduction and the diacetate (Vb) of the diol was hydrogenolyzed catalytically to a monoacetate (Vc). Hydrolysis of the latter and Sarett oxidation of the resultant alcohol (Vd) gave an aldehyde (Ve) whose Wolff–Kishner reduction led to a degradation product whose structure had to be that of 11-methoxyferruginol methyl ether (Vf) on the basis of the above carnosol formula (IVa). As a consequence, authentic Vf was synthesized.



Va, R = CH_2OH; Y = OH
b, R = CH_2OAc; Y = OAc
c, R = CH_2OAc; Y = H
d, R = CH_2OH; Y = H
e, R = CHO; Y = H
f, R = Me; Y = H
g, R = CO_2H; Y = H
h, R = CO_2Me; Y = H, 7-keto

Treatment of ferruginol benzoate (IIb) with sodium methoxide and thereafter with *p*-nitrobenzenediazonium chloride yielded 11-*p*-nitrophenylazoferruginol. Sodium dithionite reduction of the methyl ether of the azophenol followed by diazotization of the resultant, air-sensitive 11-aminoferruginol methyl ether in methanolic sulfuric acid led to 11-methoxyferruginol methyl ether (Vf), identical in all respects with the carnosol degradation product. Thus, the absolute configuration of carnosol is that shown in IVa.[9]

Biosynthetic Considerations.—As the structure IVa indicates, carnosol represents an interesting high state of oxidation of the ferruginol (II) skeleton. Its oxidized C-7 is reminiscent of similar groupings in the naturally occurring oxidation products of ferruginol: dehydroferruginol (VIa),[10] sugiol (VIb),[11] and cryptojaponol (VIc).[12,13] Since C-7 is benzylic, it would be expected to be a readily oxidizable site in the ferruginol skeleton. An equally easy site of oxidation, in view of its *ortho* relationship to a phenolic hydroxyl group, is C-11. As a consequence, the catechol moiety of cryptojaponol (VIc) and carnosol (IVa) is illustrative of an early intermediate in the oxidative metabolism of the sensitive phenolic ring of ferruginol. Further oxidation of the catechol system would be expected to lead to the hydroxyhydroquinone unit VII and, thereafter, the hydroxyquinone system represented by royleanone (VIIIa),[14] acetoxyroyleanone (VIIIb),[14] dehydroroylea-

(7) The hydrocarbon fraction (B³) of the dehydrogenation mixture now has been shown by gas phase chromatography to be composed of retene, pimanthrene, and two minor constituents (see Experimental).

(8) An exhaustive study of the p.m.r. spectra of ring-C aromatic, tricarbocyclic, diterpenic substances (R. W. J. Carney, Ph. D. Dissertation, Iowa State University, 1962) has yielded the needed models for the present work.

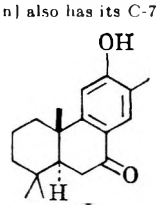
(9) The strain in the six-membered lactone ring accounts for the unusual infrared carbonyl absorption of the natural product.[5]

(10) J. Bæson Bredenberg, *Acta Chem. Scand.*, **11**, 932 (1957).

(11) C. W. Brandt and B. R. Thomas, *J. Chem. Soc.*, 2442 (1952).

(12) T. Kondo, M. Suda, and M. Teshima, *J. Pharm. Soc. Japan*, **82**, 1252 (1962).

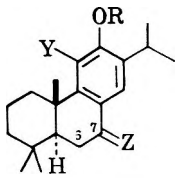
(13) Nimbiol (i), another diterpenic, ring-C phenolic, natural product [E. Wenkert, V. I. Stenberg, and P. Beak, *J. Am. Chem. Soc.*, **83**, 2320 (1961), and references therein] also has its C-7 in a high state of oxidation.



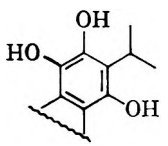
I

(14) O. E. Edwards, G. Feniak, and M. Los, *Can. J. Chem.*, **40**, 1540 (1962).

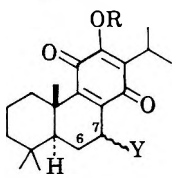
none (VIIIc),[14] and horminone (VIIId).[15] Predictably, *Salvia officinalis* L., the plant whose leaves had yielded carnosol, now was shown to contain royleanone (VIIIa) and the two derivatives VIIIb and VIIIc in its roots.



VIa, R = Y = H; Z = H_2, 6,7-dehydro
b, R = Y = H; Z = O
c, R = Me; Y = OH; Z = O
d, R = Me; Y = NH_2; Z = H_2
e, R = H; Y = *p*-$O_2NC_6H_4N_2$; Z = H_2
f, R = Me; Y = *p*-$O_2NC_6H_4N_2$; Z = H_2
g, R = Ac; Y = H; Z = O
h, R = Me; Y = H; Z = O

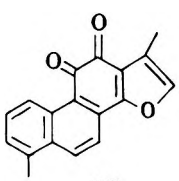


VII

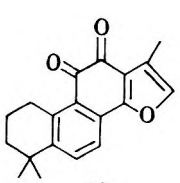


VIIIa, Y = R = H
b, Y = OAc; R = H
c, Y = R = H, 6,7-dehydro
d, Y = OH; R = H
e, Y = H; R = Me

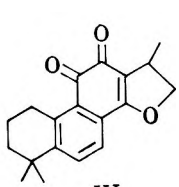
The unusually high state of oxidation of the angular C-10 substituent of carnosol is a clue to the biosynthesis of the natural quinones of *Salvia miltiorrhiza* Bge., tanshinone-I (IX), tanshinone-II (X), and cryptotanshinone (XI).[16] Oxidative decarboxylation of the carnosol system would lead to the aromatic ring B common to the tanshinones, while oxidation of its isopropyl side chain (by benzylic oxidation followed by dehydration or by prototropic rearrangements of the quinone) and subsequent oxidation of the isopropenylcatechol yield an isopropenyl product (XII). Hydration of the latter affords a metastable alcohol (XIII) expected to undergo intramolecular addition to the quinone unit thereby producing the leuco cryptotanshinone functionality (XIV). Further oxidation of the latter would lead to the tanshinones. Thus it appears that carnosol may be an important intermediate in the metabolic paths of oxidative transformations of the ferruginol ring system.



IX



X



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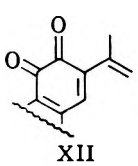

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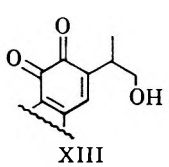
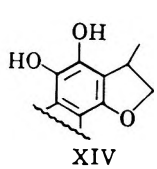
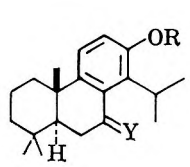


XIII

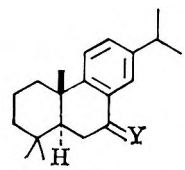


XIV

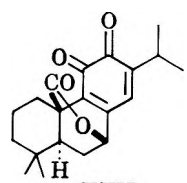
Proton Magnetic Resonance Spectra.—The present study necessitated an inspection of the p.m.r. spectra of carnosol (IVa) and its derivatives. For comparison the spectra of ferruginol (IIa) and totarol (XVa)[17] and their derivatives were studied also. The spectral investigation of 32 compounds—dehydroabietane (XVIa)[18] and its 7-keto derivative (XVIb),[18] ferruginol derivatives IIa–d and VId–f, sugiol derivatives VIb,g,h,[11] totarol derivatives XVa–d,[17,19,20] royleanone derivatives VIIIa,b,d,e,[14,15] and carnosol derivatives IVa–c, Va–h, and XVII—yielded interesting data of diagnostic value in structure determination.



XVa, R = H; Y = H_2
b, R = Ac; Y = H_2
c, R = H; Y = HOH
d, R = Ac; Y = O



XVIa, Y = H_2
b, Y = O



XVII

Ring-A substituents at C-4 and C-10 gave characteristic p.m.r. signals. In the absence of neighboring polar functions the C-4 methyl groups showed a chemical shift of 0.91–0.98 p.p.m. often in form of a six-proton singlet. The methyl signals of the 7-keto compounds appear as two three-proton singlets, one at the normal position (0.92–0.94 p.p.m.) and the other downfield at 0.99–1.01 p.p.m. A similar separation of the methyl signals can be observed in the spectra of the substances containing 10-carbonyl functions. In the cases of the nonrigid 10-carbonyl examples, the equatorial 4-methyl signals appear at normal positions (0.97–0.99 p.p.m.), while the axial 4-methyl groups are shifted diamagnetically to 0.81–0.83 p.p.m. The shielding effect of *ca.* 0.1 p.p.m. by the 10-carbonyl groups on the hydrogens of the axial 4-methyl group is similar to the diamagnetic shielding of the 10-methyl function by the axial C-4 carbonyl-containing groups in podocarpic acid derivatives (XVIII).[8] The 4-methyl signals of the rigid lactones are less well separated (0.86–0.87, 0.90–0.91 p.p.m.). The involvement of the 10-carbonyl

XVIII

(15) This diterpenic quinone was isolated originally by A. Goris from *Horminum pyrenaicum* L. and was shown to be 7-hydroxyroyleanone by J. LeMen and P. Potier. (The authors are most grateful to Professor LeMen for this information.)

(16) (a) R. H. Thomson, "Naturally Occurring Quinones," Academic Press, New York, N. Y., 1957; p. 260; (b) Y. Okumura, H. Kakisawa, M. Kato, and Y. Hirata, *Bull. Chem. Soc. Japan*, **34**, 895 (1961).

(17) The authors are most grateful to Dr. J. C. Dacre (University of Otago, Dunedin, New Zealand) for a sample of totarol acetate.

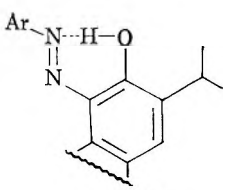
(18) E. Wenkert, P. Beak, R. W. J. Carney, J. W. Chamberlin, D. B. R. Johnston, C. D. Roth, and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1963).

(19) The two 7-oxygenated totarol derivatives XVc and d were kindly furnished to us by Dr. B. R. Thomas.

(20) Y. Chow and H. Erdtman, *Acta Chem. Scand.*, **16**, 1305 (1962), and references therein.

groups in these cases in a new ring distorts them from their original axial conformation and thus alters their nonbonded interaction with the C-4 substituents.

The normal chemical shift of 10-methyl groups is 1.14–1.20 p.p.m., while the 10-methyl signals in 7-keto compounds and in substances containing 11-methoxy and amino groups appear at 1.22–1.24 p.p.m. and 1.31–1.34 p.p.m., respectively. 7-Ketototarol acetate (XVd), a compound whose ketonic function is buttressed seriously by the ring-C substituents and whose ring B, as a consequence, would be expected to be distorted when compared with sugiol acetate (VIg), has its 10-methyl group more shielded, 1.12 p.p.m. While the 10-methyl group in the azo derivative VIf is shielded in a manner similar to that of the 11-amino compound VId, the C-10 substituent in the azophenol VIe is greatly deshielded, 1.63 p.p.m. Presumably, the bulky arylazo group is nonplanar with ring C in the case of the methyl ether VIf (probably protruding perpendicularly on the α-side of the diterpenic framework), while being held in the ring-C plane by hydrogen bonding (*cf.* XIX) in the azophenol (VIe). The 10-methyl signal of royleanone methyl ether (VIIIe), 1.31 p.p.m., is reminiscent of that of the 11-methoxy and amino cases. Hydrogen bonding in the other royleanones appears to be responsible for the diamagnetic shift (1.22–1.25 p.p.m.) of their 10-methyl signals.[21]



XIX

As the above data on methyl groups indicate, the chemical shift of the hydrogens of the C-10 substituents in the presence of 11-methoxy groups is *ca.* 0.3–0.4 p.p.m. downfield of the corresponding hydrogens in a saturated environment. A similar paramagnetic shift was observed for the hydrogens of a 10-aldehydo group, from δ = 9.9 to 10.23 p.p.m. (*cf.* Ve)[8]; of 10-hydroxymethyl groups, from δ = 3.7 to 4.01–4.02 p.p.m. (two-proton, broad singlet)[22]; and of 10-acetoxymethyl groups, from $\delta_A + \delta_B$ 2 = 4.1 to 4.55, 4.65 p.p.m. (AB pattern, J = 11.6 c.p.s.).

The two-proton signal characteristic of the 7-methylene group is a broad triplet at 2.7–3.1 p.p.m., while that of the 6-methylene group in 7-keto cases is the AB part of an ABX pattern at 2.6–3.0 p.p.m.[23] The aromatic hydrogen at C-14 of C-7-saturated cases suffers a paramagnetic shift of 1.0–1.3 p.p.m. upon introduction of a 7-keto function. The normal position of the doublet (J = 7 c.p.s.) of the 13-isopropyl methyl groups is 1.16–1.26 p.p.m. The introduction of 7-keto groups causes a paramagnetic shift within this range, while O-methylation or -acetylation of 11- or 12-phenolic groups results in a diamagnetic shift. While the isopropyl methyl signals of the quinones of the royleanone type (VIII) fall within the above range, the doublet of the isopropyl methyl groups of carnosol quinone (XVII) appears at 1.11 p.p.m. Substitution of the 12-hydroxy groups leads to twinning of the isopropyl methyl signals with a separation of the doublet of up to 0.04 p.p.m. Presumably, an increase of the steric requirement of the neighboring function causes a preferred conformation of the isopropyl group wherein its methyl constituents reside in different shielding zones of the aromatic nucleus. This conformation is probably one in which a methyl group and the methine hydrogen scissor the C-12 oxygen-containing function. Even this conformation is destabilized in a fair number of cases of further crowding by C-11 substituents. Thus, in contrast to ferruginol methyl ether (IId) which shows two doublets, its 11-arylazo derivative (VIf) reveals only one.

The isopropyl hydrogen signals of totarol and its derivatives (XV) are anomalous. The downfield shift from within the range of 1.16–1.26 to 1.33 p.p.m. of the methyl doublet in the p.m.r. spectrum of the natural product (XVa) and its similarity with that of 7-hydroxytotarol (XVc), 1.33 and 1.45 p.p.m. (one methyl being further deshielded by the C-7 hydroxyl oxygen), suggest that in these cases of nonbonded interaction with the *peri*-methylene substituents at C-7 the preferred conformation of the isopropyl group is one wherein its methyl groups scissor the phenolic hydroxyl function while the C-7 substituents scissor the isopropyl methine hydrogen. As a consequence, it is not surprising that the septet signal of the central hydrogen of the isopropyl group of totarol (XVa) appears at the extreme downfield end of the 2.9–3.3-p.p.m. range common to all ferruginol-type compounds and that this signal occurs at a more striking downfield position, 3.54 p.p.m., in the spectrum of 7-hydroxytotarol (XVc). As expected, the isopropyl methine hydrogen signal of 7-ketototarol acetate (XVd) is shifted even more paramagnetically, 3.75 p.p.m. The identity of position of the methine hydrogen signal of the isopropyl groups of totarol (XVa) and totarol acetate (XVb) shows the conformation of the alkyl groups of these two substances to be the same. However, the slight twinning of the methyl doublets, 1.24 and 1.26 p.p.m., in the spectrum of the latter indicates a preferred conformation of the acetyl group out of the plane of the aromatic ring. Probably this still applies to the case of 7-ketototarol acetate (XVd, δ_{Me} = 1.23 and 1.33 p.p.m.), although the wider separation of the two doublets suggests that the orientation of the isopropyl group is slightly off its aforementioned conformation.

Experimental[24]

Isolation of Carnosol and the Royleanones.—A survey of the *Labiatae* genera closely related to *Salvia* revealed the presence of carnosol only in *Rosmarinus officinalis* L. Extraction of the leaves[6] and the roots (*vide infra*) gave results parallel with those ob-

(21) Y. Kondo, I. Ikenoue, and T. Takemoto [*Chem. Pharm. Bull.* (Tokyo), **11**, 678 (1963)] reported the chemical shifts of the methyl groups of ferruginol acetate (IIe) and sugiol acetate (VIg), but assigned them incorrectly.

(22) A. Gaudemer, J. Polonsky, and E. Wenkert, *Bull. soc. chim. France*, 407 (1964).

(23) *Cf.* J. B-son Bredenberg and J. N. Shoolery, *Acta Chem. Scand.*, **14**, 556 (1960).

(24) All melting points are uncorrected. Infrared spectra were obtained on Perkin-Elmer spectrophotometers, Model 21 or Model 137 B, with sodium chloride optics. The p.m.r. spectra were taken in dilute deuteriochloroform solution, with tetramethylsilane as internal standard, on a Varian Associates Model A-60 spectrometer. Ultraviolet spectra were obtained with either a Perkin-Elmer spectrophotometer, Model 202, or Zeiss spectrophotometer, PMQ II. Optical rotations are of 95% ethanol solutions recorded on a Rudolph and Sons polarimeter, Model 70. Thin-layer chromatography (t.l.c.) was run on 5 × 20 cm. glass plates coated with silica gel G and developed with 10% ether in hexane or 5% ethyl acetate in chloroform. The spots were detected by the use of iodine vapor.

tained for *Salvia officinalis* L.[5]: 1.2% (by dry weight) carnosol in the leaves and the royleanones in the roots. (Unfortunately insufficient root material was available for isolation and characterization, but t.l.c. of the extract gave a pattern similar to that of *Salvia officinalis* L.)

Dried root material 500 g., of *Salvia officinalis* L. was extracted with hexane yielding 10.5 g. of a dark brown resin. This was dissolved in 95% ethanol and allowed to stand. Yellow crystals separated from the solution and were filtered off, yielding 1.5 g. of crystalline material. Its recrystallization from ethanol gave yellow crystals of 7-acetoxyroyleanone, m.p. 211–213°; spectra: infrared (KBr), OH 3.05 (m), C=O and C=C 5.83 (s), 6.05 (s), 6.12 (s), 6.22 (w) μ; ultraviolet, λ_{max}^{MeOH} 272 mμ (log ϵ 4.07) and 406 (2.88); Rast mol. wt. 370. (calcd., 374.5) Direct melting point and spectral comparison with authentic acetoxyroyleanone proved them to be identical.[25]

Evaporation of the filtrate and chromatography of the residue on silica showed the presence of three more hydroxyquinones. The first, eluted by 19:1 hexane–ether, was identified as royleanone by direct comparison with material prepared by hydrogenolysis of acetoxyroyleanone.[14] The second minor hydroxyquinone could not be obtained in pure form by chromatography or crystallization. However, it was identified as 6,7-dehydroroyleanone by comparison of its spectral (infrared and ultraviolet) properties and its t.l.c. behavior with those of authentic 6,7-dehydroroyleanone, prepared by elimination of the acetoxy group of acetoxyroyleanone.[14] The third minor hydroxyquinone has not been obtained in sufficient quantity to allow identification.

Identification of Carnosol.—The p.m.r. and infrared spectra of carnosol and picrosalvin were superimposable and their mixture melting point gave no depression.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.69; H, 7.93. Found: C, 72.91; H, 7.94.

The p.m.r. and infrared spectra of carnosol diacetate and picrosalvin diacetate were superimposable and their mixture melting point gave no depression.

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.29. Found: C, 69.47; H, 7.17.

The p.m.r. and infrared spectra of carnosol dimethyl ether and picrosalvin dimethyl ether were superimposable.

TABLE I

G.P.C. ANALYSIS OF DEHYDROGENATION PRODUCT B[b]

Compound	Reported R_L[a]	Product B R_L[b]
Phenanthrene	1.00	1.00
1-Methylphenanthrene	1.52	1.60
Pimanthrene	2.13	2.14[c]
1-Methyl-7-ethylphenanthrene	2.83	2.74
Retene	3.33	3.30[d]

[a] A. J. Solo and S. W. Pelletier, *Anal. Chem.* **35**, 1584 (1963). [b] Column: 20% silicone gum rubber SE-30 on Chromosorb P 60–80, 6-ft. × 0.25-in. o.d.; temperature of 250° isothermal; He flow rate of 70 ml./min. (on an Aerograph A-90-P). [c] Shown to be identical with pimanthrene by addition of authentic pimanthrene. [d] Shown as identical with retene by addition of authentic retene.

Oxidation of Carnosol.—A solution of 100 mg. of carnosol in 50 ml. of 0.1 *N* aqueous sodium hydroxide was treated with 0.5 ml. of 30% hydrogen peroxide at 75°. The temperature was maintained for 3 hr., during which time four additional 0.5-ml. portions of peroxide were added. The brown-red color of carnosol in alkaline solution disappeared after about 1 hr. The solution was made acid to congo red with phosphoric acid and distilled, the volume being maintained at 20–50 ml. by periodic addition of water. Approximately 100 ml. of distillate was collected. This distillate was made basic with 0.1 *N* sodium hydroxide and concentrated to about 2 ml. Reacidification of the concentrate with phosphoric acid was followed by extraction with five 3-ml. portions of ether. The combined extracts were dried, concentrated, and analyzed by g.p.c. (Perkin-Elmer fractometer 116E, 2 m. × 6.35 mm., silicone oil D.C. 200 at 130°, and 90 ml. min. flow rate of He). The major peak was shown to be identical with isobutyric acid by relative retention time and by admixture of authentic acid.

(25) The authors are indebted to Dr. O. E. Edwards (National Research Council, Ottawa, Canada) who graciously supplied authentic acetoxyroyleanone for comparison.

Reductions of Carnosol Dimethyl Ether.—A mixture of 50 mg. of 10% palladium–charcoal, 80 mg. of carnosol dimethyl ether, and 1 drop of concentrated sulfuric acid in 10 ml. of glacial acetic acid was hydrogenated at 20° for 36 hr. The catalyst was filtered and the solution was diluted with 50 ml. of water and extracted with ether. The extract was washed with water, dried, and evaporated to dryness. Crystallization of the residue from 95% ethanol yielded 45 mg. of colorless crystals of acid Vg, m.p. 210–211°; $[\alpha]^{25}D$ +114° (*c* 0.1); infrared spectrum (Nujol), C=O 5.92 (s) μ.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.19; H, 8.87.

To a solution of 1.5 g. of carnosol dimethyl ether in 100 ml. of dry ether was added 0.9 g. of lithium aluminum hydride, and the mixture was refluxed for 3 hr. The excess hydride was destroyed by addition of ethyl acetate followed by 50 ml. of water and 10 ml. of 1 *M* sulfuric acid. The organic layer was separated, washed with water, and dried. Evaporation of the extract and crystallization of the residual gum from methanol–water gave 1.35 g. of colorless crystals of diol Va, m.p. 197–198°, $[\alpha]^{25}D$ +94° (*c* 0.22).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.63; H, 9.49.

Acetylation of 1.2 g. of the diol with excess acetic anhydride and pyridine (overnight at room temperature) gave 1.22 g. of a colorless, oily diacetate (Vb) which could not be crystallized; p.m.r. spectrum, 3-proton singlets at 1.90 and 2.14 p.p.m. (acetyl methyls), 2-proton AB pattern $\delta_A + \delta_B/2 = 4.65$ p.p.m. (J = 11.6 c.p.s., acetoxymethyl methylene), 1-proton triplet at 6.08 p.p.m. (J = 8.4 c.p.s., C-7 methine).

A mixture of 0.2 g. of 10% palladium–charcoal and 1.2 g. of the diacetate in 50 ml. of glacial acetic acid was hydrogenated for 12 hr. at room temperature and atmospheric pressure. The catalyst was filtered and the solvent was removed *in vacuo*. The remaining colorless oil of acetate Vc, 1.02 g., showed one spot by t.l.c. but could not be induced to crystallize; spectra: infrared (film), C=O 5.77 (s) μ; p.m.r., 3-proton singlet at 1.86 p.p.m. (acetyl methyl), 2-proton AB pattern $\delta_A + \delta_B/2 = 4.55$ p.p.m. (J = 11.6 c.p.s., acetoxymethyl methylene), 2-proton multiplet at 2.88 p.p.m. (C-7 methylene).

A solution of 0.98 g. of the acetate (Vc) in 10 ml. of methanol and 50 ml. of 5% methanolic potassium hydroxide was refluxed for 0.5 hr. The solution was cooled, diluted with 50 ml. of water, and extracted with ether. The residue, 0.88 g., was crystallized from 95% ethanol yielding colorless needles of alcohol Vd, m.p. 85–86°; $[\alpha]^{25}D$ +98° (*c* 0.18); infrared spectrum (KBr), OH 2.82 (w) C=C 6.26 (w) μ.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.35; H, 10.01.

Oxidation of Carnosol Derivatives.—A solution of crude alkaline hydrolysis product of carnosol dimethyl ether,[5] 300 mg., in 25 ml. of ether was treated with excess diazomethane in ether for 2 hr. The solvent was removed *in vacuo* and the residue was chromatographed on silica. Elution with chloroform yielded a colorless oil, 0.270 mg., which could not be crystallized. Treatment of a solution of 250 mg. of the crude hydroxyester in 30 ml. of dry ether with 2.5 g. of activated manganese dioxide for 12 hr. at room temperature, removal of the suspended material by filtration, and evaporation of the solvent gave 245 mg. of colorless, oily keto ester III (showing one spot by t.l.c.), which could not be crystallized; spectra: infrared (film), C=O 5.79 (s), 5.94 (s), C=C 6.29 (s) μ; ultraviolet (methanol), λ_{max} 220 mμ (log ϵ 4.45), 273 (4.12). Its 2,4-dinitrophenylhydrazone melted at 152–155°.

Anal. Calcd. for $C_{29}H_{36}N_4O_5$: N, 9.85. Found: N, 9.66.

A solution of 850 mg. of alcohol Vd was treated with 0.5 g. of chromium trioxide in 20 ml. of pyridine. The mixture was stirred overnight at room temperature, then diluted with 100 ml. of water and extracted with ether. The extract was washed with 1 *N* hydrochloric acid solution and dried; the ether was evaporated. Crystallization of the residue, 750 mg., from methanol gave colorless needles of the aldehyde Ve, m.p. 116–117°; $[\alpha]^{25}D$ +59° (*c* 0.19); spectra: infrared (Nujol), aldehyde CH 3.64 (w), C=O 5.74 (s), C=C 6.35 (w) μ; p.m.r., 1-proton singlet at 10.23 p.p.m. (aldehyde methine).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.67; H, 9.32.

11-*p*-Nitrophenylazoferruginol (VIe).—A solution of 1.00 g. of ferruginol benzoate and 5.0 g. of sodium methoxide in 100 ml. of methanol was warmed on a steam bath for 0.5 hr. and then cooled in an ice bath at 0–5°. A solution of *p*-nitrophenyldiazonium

chloride, prepared by the addition of a solution of 210 mg. of sodium nitrite in 10 ml. of water to a cold solution of 400 mg. of *p*-nitroaniline in 20 ml. of 1 *N* hydrochloric acid, was added slowly with stirring. The dye was precipitated by the addition of excess water and filtered. Crystallization from 95% ethanol afforded 640 mg. of 11-*p*-nitrophenylazoferruginol, m.p. 163–165°; spectra: infrared (Nujol), C=C 6.22 (m) μ; ultraviolet (methanol), λ_{max} 283 mμ (log ϵ 2.31), 379 (3.07), 479 (2.54); p.m.r., 1-proton singlet at 6.98 p.p.m. (C-14 H), 4-proton multiplet at 8.05 p.p.m. (aromatic hydrogens).

Anal. Calcd. for $C_{26}H_{33}N_3O_3$: C, 71.69; H, 7.64. Found: C, 71.22; H, 7.72.

11-*p*-Nitrophenylazoferruginol Methyl Ether (VIf).—A solution of 435 mg. of VIe and 1.0 ml. of dimethyl sulfate in 100 ml. of dry acetone was refluxed for 18 hr. over 20 g. of anhydrous potassium carbonate. The carbonate was filtered and the solution was evaporated *in vacuo*. Crystallization of the residue from absolute alcohol gave 385 mg. of the azo compound VIf, m.p. 165–167°; spectra: infrared (Nujol), C=C 6.21 (m) μ; ultraviolet (methanol), λ_{max} 281 mμ (log ϵ 3.87), 335 (2.62), 490 (2.09); p.m.r., 3-proton singlet at 3.43 p.p.m. (O-methyl).

Anal. Calcd. for $C_{27}H_{35}N_3O_3$: C, 72.13; H, 7.85. Found: C, 71.97; H, 7.94.

11-Aminoferruginol Methyl Ether (VId).—A mixture of 350 mg. of VIf and 5.0 g. of sodium hydrosulfite in 100 ml. of 95% ethanol was refluxed on a steam bath. Enough water was added to form a homogeneous solution. After 3 hr. the color of the solution changed from blood red to pale yellow. The cooled solution was then poured into an equal volume of water and extracted with three 50-ml. portions of chloroform. The extract was dried and the solvent was removed *in vacuo*. Chromatography of the residual light brown oil, 319 mg., on neutral alumina (activity I) gave 119 mg. of a yellow oil on elution with 1:1 hexane–benzene, whose p.m.r. spectrum was compatible with 11-aminoferruginol methyl ether: 6-proton singlet at 0.98 p.p.m. (C-4 methyls), 3-proton singlet at 1.34 p.p.m. (C-10 methyl), 3-proton doublet at 1.19 p.p.m. (J = 7.0 c.p.s., i-Pro methyls), 1-proton septet at 3.18 p.p.m. (J = 7.0 c.p.s., i-Pro methine), 2-proton multiplet at 2.78 p.p.m. (C-7 methylene), 3-proton singlet at 3.70 p.p.m. (O-methyl), 2-proton multiplet at 3.85 p.p.m. (amino hydrogens), 1-proton singlet 6.35 at p.p.m. (C-14 H).

11-Methoxyferruginol Methyl Ether (Vf).—A solution of 550 mg. of the aldehyde Ve in 8 ml. of diethylene glycol with 0.5 g. of sodium hydroxide and 1 ml. of 90% hydrazine hydrate was heated to 120°. Methanol, 1 ml., was added and the solution refluxed for 10 hr. Water, methanol, and the excess hydrazine hydrate were removed by distillation, and the residue was refluxed for another 8 hr. at 195–205°. The reaction mixture was cooled, diluted with water, and extracted with ether. The extract was dried and the solvent was evaporated. The dark, viscous residue was chromatographed on 15 g. of neutral alumina (activity I). Elution with 20% ether in hexane gave 60 mg. of a white solid. Crystallization from methanol yielded colorless needles of VIf, m.p. 89–90.5°; $[\alpha]^{25}D$ +104° (c 0.13); spectra: infrared (Nujol), C=C 6.24 (w) μ; p.m.r., 3-proton singlet at 1.31 p.p.m. (C-10-methyl).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.78; H, 10.29.

A solution of 119 mg. of VId in 25 ml. of methanol was acidified with 25 drops of concentrated sulfuric acid, cooled to 0–5° in an ice bath and mixed with a solution of 35 mg. of sodium nitrite in methanol. The mixture was allowed to warm slowly to 25° and then was refluxed on the steam bath for 0.5 hr. The cooled solution was neutralized with saturated sodium bicarbonate and extracted with methylene chloride. The extract was dried and the solvent was removed *in vacuo*. A chloroform solution of the residual dark oil was filtered through a short alumina column and the eluted pale yellow oil was distilled. The distillate solidified and was crystallized from methanol yielding 43 mg. of Vf, m.p. 89.5–90.5°; $[\alpha]^{25}D$ +100° (c 0.42); spectra identical with those of Vf above.

Acknowledgment.—The authors are indebted to the Fond der chemischen Industrie and the deutsche Forschungsgemeinschaft for support of the work at the Universität, Würzburg, and to the U. S. National Science Foundation for aid of the investigation at Indiana University.

Synthesis of Isoquinolines. I.[1] Copyrine and Isoquinoline Systems Derived from 3-Cyano-4-methylpyridine[2,3]

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3-Cyano-4-methylpyridine was converted to 3-phenyleopyrine and 8-oxo-6-phenyl-5,6,7,8-tetrahydroisoquinoline. In the course of the work, an apparently anomalous intramolecular Ritter reaction was observed.

The synthesis of isoquinoline systems from a preformed pyridine nucleus offers numerous possibilities for placing substituent groups in either ring. As part of a continuing effort along these lines, some further reactions of 3-cyano-4-methylpyridine[5] (**1**) have been explored. The ready availability of this compound[5] as well as its two reactive functions make it an attractive starting material for construction of a second ring. Since some fruitless effort had already been expended upon the preparation of an isoquinoline system,[5] it seemed more reasonable to direct this work toward copyrine (2,7-diazanaphthalene). Thus, a copyrine system was realized and even, finally, an isoquinoline system.

The nitrile function was chosen as the first point of attack (Scheme I). Accordingly, **1** was reduced catalytically to 3-(aminomethyl)-4-methylpyridine (**2**) in 84% yield. The formation of secondary amines[6] was suppressed by saturating the solvent with gaseous ammonia. The amine **2** was characterized by two derivatives, a benzamide and an acetamide (**3**). Attempts to convert **3** to the dicyclic product **4** by boiling in acetic anhydride or by treatment with sodium hydride were not successful.

Treatment of the amine **2** with *m*-nitrobenzaldehyde converted it to the imine **5** in 95% yield. An attempt to convert **5** to the dicyclic product **6** by refluxing it with acetic anhydride and sodium acetate was not successful. However, a product was isolated which

(1) This paper represents the beginning of a new series. For our preceding work on isoquinoline alkaloids, see J. M. Bobbitt, R. Ebermann, and M. Schubert, *Tetrahedron Letters*, 575 (1963).

(2) This paper was presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

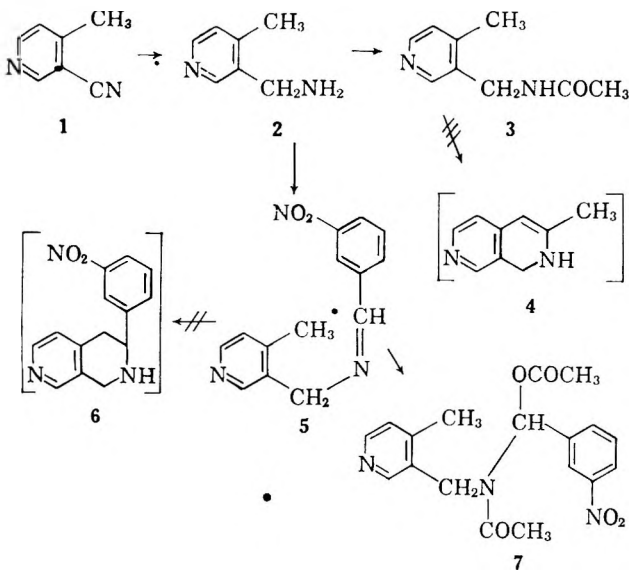
(3) This investigation was supported in part by Research Grant No. CY-3905 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(4) Abstracted in part from the Ph.D. Dissertation of R. E. Doolittle, The University of Connecticut, Storrs, Connecticut, 1965.

(5) J. M. Bobbitt and D. A. Scola, *J. Org. Chem.*, **25**, 560 (1960).

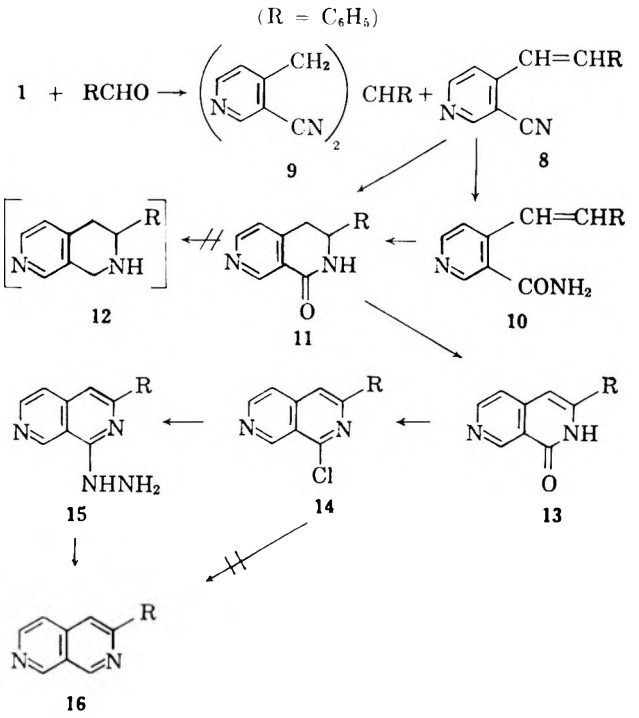
(6) H. Adkins and H. I. Cramer, *J. Am. Chem. Soc.*, **52**, 4349 (1930).

SCHEME I



SCHEME II

(R = C_6H_5)



displayed an infrared spectrum of both an acetate and an acetamide. Structure **7** was assigned to this product on the basis of a previously observed[7] reaction of this type.

The methyl group of **1** was chosen next for possible extension to another ring (see in Scheme II). This method, which was finally successful, followed a route similar to, but not identical with, that used by Ikekawa[8] for the synthesis of copyrine and 3-methylcopyrine. Treatment of **1** with benzaldehyde in the presence of acetic anhydride[9] or hydrochloric acid[10] converted it to 3-cyano-4-stilbazole (**8**) in 29 to 40% yield. The low yield was partially due to the formation of a second product, which was formulated as **9** as a result of its analysis and infrared spectrum. Compound **9** clearly arises from further condensation of the stilbazole with starting material. Although the hydrochloric acid reaction gave slightly lower yields of product, it was preferred since less **9** was formed.

The nitrile group of **8** was hydrolyzed with Amberlite IRA-401-OH[5] to produce 3-carbamyl-4-stilbazole (**10**) in 83% yield. Treatment of either the nitrile **8** or the amide **10** with polyphosphoric acid[11] led to the formation of the dicyclic structure, 1-oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine (**11**), in yields of 90 to 95%.

The conversion of **8** to **11** in an intramolecular Ritter reaction is in apparent contradiction to several reports[12-15] that unsaturated nitriles do not undergo cyclization to lactams when the ring to be formed is of seven members or less. The usual result is either predominant[15] or total formation of an unsaturated ketone. In the present case, the lactam formation may be attributed to an electron-withdrawing effect that the pyridinium nucleus has on the double bond. This electron deficiency would cause inhibition of the acylation reaction leading to ketone formation and allow the slower lactam formation to occur.

Reduction of the lactam **11** with a large excess of lithium aluminum hydride failed to yield the desired 3-phenyl-1,2,3,4-tetrahydrocopyrine (**12**).

Since the reduction to a tetrahydro system appeared to be difficult, the paths leading to the completely aromatic system were explored. Thus, the aromatization of **11** proceeded smoothly in *p*-cymene with a 10% palladium-on-charcoal catalyst to yield 1-oxo-3-phenyl-1,2-dihydrocopyrine (**13**) in 96% yield. This compound had been prepared previously[16] and formulated as 1-oxo-1,4-dihydrocopyrine. However, structure **13** seems to be more in line with the infrared spectrum. The physical constants of **13** agreed with those recorded.[16]

The amide **13** was converted to 1-chloro-3-phenylcopyrine (**14**) in 75% yield by treatment with phosphorus oxychloride according to the method of Ikekawa.[8] Attempted hydrogenolysis of **14** with palladium chloride or palladium on calcium carbonate led to complex mixtures of partially hydrogenated materials, thus paralleling previous work.[17]

An alternate method[8] involving hydrazinolysis of the chloride and oxidation of the hydrazino derivative was then attempted. The halide **14** reacted readily with hydrazine hydrate in ethanol to yield the relatively unstable 1-hydrazino-3-phenylcopyrine (**15**) in 90% yield. Subsequently, **15** was oxidized to 3-phenylcopyrine (**16**) in 55% yield with cupric sulfate.[8,18] The amine was characterized as a monopicrate and a monostyphnate. The structure of **16** was assigned on the basis of its mode of formation, its analysis, and the similarity of

(7) M. Passerini and M. Pia Macentelli, *Gazz. chim. ital.*, **58**, 641 (1928); *Chem. Abstr.*, **23**, 2951 (1929); J. B. Ekeley, M. C. Swisher, and C. C. Johnson, *Gazz. chim. ital.*, **62**, 81 (1932); *Chem. Abstr.*, **26**, 3239 (1932); A. W. Burgstahler, *J. Am. Chem. Soc.*, **73**, 3021 (1951).

(8) N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **6**, 268 (1958); *Chem. Abstr.*, **53**, 372 (1959).

(9) B. D. Shaw and E. A. Wagstaff, *J. Chem. Soc.*, 77 (1933).

(10) M.-C. Chiang and W. H. Hartung, *J. Org. Chem.*, **10**, 21 (1945).

(11) R. K. Hill, *ibid.*, **22**, 830 (1957).

(12) R. K. Hill and R. T. Conley, *J. Am. Chem. Soc.*, **82**, 645 (1960).

(13) R. T. Conley and M. C. Annis, *J. Org. Chem.*, **27**, 1961 (1962).

(14) R. T. Conley and B. E. Nowak, *ibid.*, **27**, 1965 (1962).

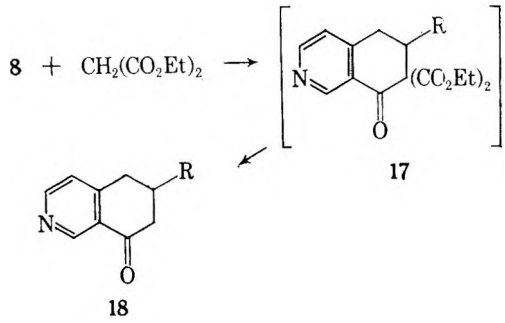
(15) R. T. Conley and R. J. Lange, *ibid.*, **28**, 210 (1963).

(16) F. Krohnke, K. Ellegast and E. Bertram, *Ann.*, **600**, 198 (1956).

(17) B. M. Ferrier and N. Campbell, *J. Chem. Soc.*, 3513 (1960).

(18) H. E. Baumgarten and H. C. Su, *J. Am. Chem. Soc.*, **74**, 3828 (1952).

SCHEME III
(R = C_6H_5)



its ultraviolet spectrum with that of 2-phenylnaphthalene.[19]

Finally, an isoquinoline system was realized (see Scheme III). Treatment of the stilbazole **8** with ethylmalonate and sodium ethoxide, followed by acid hydrolysis led to the formation of 8-oxo-6-phenyl-5,6,7,8-tetrahydroisoquinoline (**18**) in 64% yield. The structure was assigned on the basis of the analysis of **18**, an oxime, a picrate, and a styphnate, and the infrared spectrum (1680 cm.$^{-1}$). The reaction can be envisioned as a base-catalyzed addition of ethyl malonate to the double bond of the stilbazole followed by a Dieckmann-type condensation, hydrolysis, and decarboxylation.

Experimental[20]

Thin layer chromatography[21] was used extensively during this investigation. All analytical samples were examined by this method before analysis. It was used to follow the course and rate of several of the reactions. The areas of the layers containing the products were visualized by either spraying the layer with modified Dragendorff reagent[22] or by examining the layer under ultraviolet light.

3-(Aminomethyl)-4-methylpyridine (2).—3-Cyano-4-methylpyridine (**1**, 25 g.) was dissolved in 225 ml. of absolute ethanol which had been previously saturated with gaseous ammonia. Approximately 3 g. (one teaspoon) of W-5[23] Raney nickel catalyst was added and the mixture was shaken in a Parr low-pressure hydrogenator under 50 lb. of hydrogen, until the theoretical quantity of hydrogen had been absorbed (6 hr.). The catalyst was removed by filtration; the filtrate was distilled at atmospheric pressure through a 10 × 1 cm. column equipped with a tantalum wire spiral to remove the ethanol, and the residue was distilled at reduced pressure. The product **2**, 21.5 g. (84%), distilled as a clear liquid, b.p. 63° (0.12 mm.), $n^{22}D$ 1.5492.

Anal. Calcd. for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.80; H, 8.49; N, 22.81.

The **benzamide** of **2** was prepared by a standard method[24] and had m.p. 111–112.5° (cap.) after four recrystallizations from absolute ethanol.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.48; H, 6.12; N, 12.08.

3-Acetamidomethyl-4-methylpyridine (3).—The acetamide **3** of 3-(aminomethyl)-4-methylpyridine was prepared according to a standard procedure.[24] After four recrystallizations from absolute ethanol, it had m.p. 81–82°.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 66.12; H, 7.45; N, 16.94.

Attempted Preparation of 3-Methyl-1,2-dihydrocopyrine (4). Acetic Anhydride Method.—3-Acetamidomethyl-4-methylpyridine (**3**, 0.5 g.) was dissolved in 25 ml. of distilled acetic anhydride and refluxed for 24 hr. The solution was cooled and poured into water. The aqueous solution was made alkaline with sodium carbonate and extracted with chloroform. The chloroform extract was examined by thin layer chromatography using chloroform–ethanol (95:5) as developer and showed only the presence of the starting amide **3**.

Attempted Preparation of 3-Methyl-1,2-dihydrocopyrine (4). Sodium Hydride Method.—3-Acetamidomethyl-4-methylpyridine (**3**) (0.5 g., 0.00305 mole) and sodium hydride (0.0745 g., 0.0031 mole), as a 25% suspension in mineral oil, were heated under reflux for 8 hr. in 15 ml. of dry *m*-xylene. The mixture was cooled and 15 ml. of water was cautiously added. The layers were separated and the aqueous layer was extracted with 25 ml. of ether. The ether and xylene solutions were combined and examined by thin layer chromatography using chloroform–ethanol (95:5) as developer. Only starting material **3** could be detected.

3-(N-*m*-Nitrobenzylideneaminomethyl)-4-methylpyridine (5).—3-(Aminomethyl)-4-methylpyridine (**2**, 24.4 g., 0.2 mole) and *m*-nitrobenzaldehyde (30.0 g., 0.22 mole) were dissolved in 300 ml. of dry benzene. The mixture was heated under reflux, and the water was azeotropically removed with a Dean–Stark water separator. The theoretical amount of water (0.2 mole) was collected in 6 hr. The yellow solution was concentrated under vacuum to give 48.5 g. (95%) of **5**. The imine had m.p. 96.5–97.5° after one recrystallization from 1 l. of heptane–benzene (20:1).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.57; H, 5.08; N, 16.64.

Attempted Preparation of 3-(*m*-Nitrophenyl)-1,2,3,4-tetrahydrocopyrine (6).—This is a modification of the method of Shaw and Wagstaff.[9] 3-(N-*m*-Nitrobenzylideneaminomethyl)-4-methylpyridine (**5**, 2.55 g., 0.01 mole), freshly fused sodium acetate (1.64 g., 0.02 mole), and 20 ml. of acetic anhydride were heated under reflux for 1 hr. The mixture was cooled and poured into ice and water. It was made alkaline with sodium carbonate and extracted with chloroform. The chloroform extract was evaporated to give 3.5 g. of a dark yellow oil which was dissolved in benzene and chromatographed over 100 g. of silica gel using benzene–ethanol (20:1) as eluent. Fractions of 10 ml. were collected. Fractions 5 through 8 were shown by thin layer chromatography, using chloroform–ethanol (95:5) as developer, to contain one compound and they were combined. A yellow oil (**7**), 1.3 g., was obtained which showed infrared absorption (thin film) at 1680 (CONHR) and 1760 cm.$^{-1}$ ($OCOCH_3$) (see discussion).

3-Cyano-4-stilbazole (8). Acetic Anhydride Method.[9]—3-Cyano-4-methylpyridine (**1**, 5.9 g., 0.05 mole), benzaldehyde (5.5 g., 0.052 mole), and 20 ml. of distilled acetic anhydride were sealed in a glass ampoule. The ampoule was heated in an oil bath at 120° for 24 hr., then cooled to −80°, and opened. The contents were poured into 100 ml. of water and ice, and the solution was made alkaline with sodium carbonate and steam distilled to remove unchanged benzaldehyde. The contents of the flask were extracted with chloroform and the chloroform extract was evaporated to a solid residue. This was sublimed at 125° (0.04 mm.) to give 4.1 g. (40%) of **8**. This product was shown by thin layer chromatography, using ether as developer, to contain a slight impurity. An analytical sample of **8** was obtained by using preparative thin layer chromatography with ether as developer. This was followed by five recrystallizations from hexane–benzene (1:1) to give the pure material, m.p.

(19) It has been stated that the replacement of as many as two carbons by nitrogens in an aromatic system does not appreciably change its ultraviolet spectrum; see A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold, Ltd., London, 1957, p. 154.

(20) All melting points were taken on a Kofler micro hot-stage apparatus or in an open capillary tube and are corrected. The infrared spectra, ultraviolet spectra, and refractive indices were taken on a Perkin-Elmer Infracord, Cary-14 recording spectrophotometer and an Abbé refractometer respectively. The microanalyses were performed by H. Frohofer of the Organic Chemistry Institute of the University of Zürich, Switzerland; Geller Laboratories of Bardonia, N. Y.; Drs. Weiler and Strauss, Microanalytical Laboratory, Oxford, England; Microanalytical Laboratory, Brugg, Switzerland. Thin layer chromatography was done on silica gel G (Brinkmann, Westbury, N. Y.) layers, 250 μ thick. Preparative thin layer chromatography was done on silica gel G layers, 1 mm. thick, prepared with a Stahl-Desaga apparatus (Brinkmann).

(21) J. M. Bobbitt, "Thin-Layer Chromatography," Reinhold Publishing Co., New York, N. Y., 1963.

(22) R. Munier and M. Macheboeuf, *Bull. Soc. Chim. Biol.*, **33**, 846 (1951); *Chem. Abstr.*, **46**, 4171 (1952).

(23) H. Adkins and H. R. Billica, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 176.

(24) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 226.

118–120°; infrared absorption in potassium bromide: 1610 (C=C) and 2205 cm.$^{-1}$ (C≡N).

Anal. Calcd. for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.61; H, 4.93; N, 13.45.

The solid **9**, which remained in the sublimation pot, was washed out with ether and gave 3.0 g. of a solid with m.p. 180–181°. This was shown by thin layer chromatography, using ether as developer, to be the same as the impurity in the sublimate of **8**. The analytical sample, after recrystallization from absolute ethanol and sublimation at 150° (0.04 mm.), had m.p. 180–181°; infrared absorption in potassium bromide: 2210 cm.$^{-1}$ (C≡N).

Anal. Calcd. for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27. Found: C, 77.65; H, 4.96; N, 17.39.

3-Cyano-4-stilbazole (8). Hydrochloric Acid Method.[10]—3-Cyano-4-methylpyridine (**1**, 5.9 g., 0.05 mole), benzaldehyde (5.88 g., 0.055 mole), and 7 ml. of concentrated hydrochloric acid were heated under reflux for 2 days. The cooled reaction mixture was treated in exactly the same manner as in the acetic anhydride method. 3-Cyano-4-stilbazole was isolated in 29% yield; however, it was shown by thin layer chromatography, using ether as developer, to contain only a trace of the impurity **9**.

3-Carbamyl-4-stilbazole (10).—Crude 3-cyano-4-stilbazole (**8**, 2.0 g.), 2.0 g. of wet Amberlite IRA-401-OH anion-exchange resin,[5] and 75 ml. of distilled water were stirred and refluxed for 10 hr. The mixture was cooled and filtered. The precipitate, consisting of product and resin, was extracted with boiling ethanol. The ethanol was evaporated under vacuum to yield 1.8 g. (83%) of **10**. The analytical sample, after recrystallization from absolute ethanol, had m.p. 196.5–197.5°; infrared absorption in potassium bromide: 1630 (C=C), shoulder at 1650 cm.$^{-1}$ (CONR$_2$).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.08; H, 5.35; N, 12.29.

1-Oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine (11). From 3-Carbamyl-4-stilbazole.—This is essentially the method of Hill.[11] Crude 3-carbamyl-4-stilbazole (**10**, 0.250 g.) and polyphosphoric acid (15.0 g.) were mixed in a 40-ml. test tube. The tube was heated in an oil bath at 135° and stirred vigorously until all the solid had dissolved. The mixture was poured while still hot into 100 ml. of ice and water, and the acid solution was extracted with 25 ml. of chloroform. The acid solution was neutralized with sodium carbonate and the mixture was extracted with chloroform. The chloroform was evaporated to give an oil which solidified upon trituration with dry ether. The solid was sublimed at 150° (0.04 mm.), to give 0.225 g. (90%) of **11**. The analytical sample upon recrystallization from hexane–benzene (1:1) had m.p. 160–162°; infrared absorption in potassium bromide: 1650 cm.$^{-1}$ (CONHR).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.97; H, 5.35; N, 12.16.

1-Oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine (9). From 3-Cyano-4-stilbazole.—3-Cyano-4-stilbazole (**8**, 0.5 g.) was heated and stirred with 9.0 g. of polyphosphoric acid in a test tube at 130° until all the solid material had dissolved. The reaction was then treated in the same manner as in the preparation from **10**. This method gave 0.464 g. (90%) of lactam **11**.

Attempted Reduction of 1-Oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine (11). With Lithium Aluminum Hydride.—This is essentially the technique used to reduce N-phenylsuccinimide.[25] 1-Oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine (**11**, 0.255 g., 0.0011 mole) was placed in the thimble of a micro Soxhlet extractor. A solution of lithium aluminum hydride (0.350 g., 0.0092 mole) in 70 ml. of anhydrous ether was placed in the flask of the extractor. The material was extracted until the thimble was empty (3 days). The suspension was cooled in an ice bath and was hydrolyzed by the method of Amundsen,[26] which involved the addition of 0.4 ml. of water, 0.3 ml. of 20% sodium hydroxide, and 1.4 ml. of water in that order. The suspension was filtered and the precipitated hydroxides were pulverized and extracted several times with ether. The ether extracts and original filtrate were evaporated to give an oil. Thin layer chromatography, using ether as developer, indicated the presence of three products in addition to starting material. Upon repeating the experiment using tetrahydrofuran as solvent, essentially identical results were obtained.

(25) W. G. Brown, *Org. Reactions*, **6**, 492 (1951).

(26) L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

1-Oxo-3-phenyl-1,2-dihydrocopyrine (13).—This is a modification of two other procedures.[27,28] 1-Oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine (**11**, 2.0 g.) and 10% palladium-on-charcoal catalyst[29] (0.5 g.) were heated under reflux, with vigorous stirring, in 75 ml. of dry *p*-cymene. The mixture was cooled and filtered. The solid which consisted of charcoal and product was extracted in a Soxhlet extractor with methanol for 3 days. The methanol was evaporated under vacuum to give 1.9 g. (96%) of **13**. The analytical sample after recrystallization from absolute ethanol had m.p. 239–239.5° (cap.), lit.[16] m.p. 237–238°; infrared absorption in potassium bromide: 1620 (C=C), 1650 (CONHR) and 3170 cm.$^{-1}$ (N–H).

1-Chloro-3-phenylcopyrine (14).—This is the method used by Ikekawa.[8] 1-Oxo-3-phenyl-1,2-dihydrocopyrine (**13**, 3.0 g.) and 25 ml. of phosphorus oxychloride were heated to 180° in a sealed ampoule for 24 hr. The ampoule was cooled and opened, and the contents were poured into ice and water. The acid solution was neutralized with sodium carbonate and extracted with chloroform. The chloroform extract was evaporated under vacuum to give a dark oily residue. This was sublimed at 110° (0.04 mm.), yielding 2.44 g. (75%) of white crystalline **14**. The melting point was 128–130° and the sublimed material was used directly for the analytical sample.

Anal. Calcd. for $C_{14}H_9ClN_2$: C, 69.86; H, 3.77; Cl, 14.73; N, 11.64. Found: C, 70.20; H, 3.50; Cl, 14.76; N, 11.76.

Attempted Preparation of 3-Phenylcopyrine (16). Using Palladium Chloride.—This is the method used by Bobbitt and Scola[5] for the preparation of **1**. 1-Chloro-3-phenylcopyrine (**14**, 0.048 g., 0.002 mole) was dissolved in 25 ml. of methanol containing 0.2 g. (0.0021 mole) of potassium acetate. Freshly prepared palladium chloride[30] (5.0 mg.) was added and the mixture was hydrogenated at atmospheric pressure until the theoretical amount of hydrogen had been absorbed (2 hr.). The highly fluorescent yellow mixture was filtered, and the filtrate was examined by thin layer chromatography with ether as developer. This indicated the presence of about five products. This mixture was not further investigated.

Attempted Preparation of 3-Phenylcopyrine (16). Using Palladium on Calcium Carbonate.—This is the procedure used by Ikekawa.[8] 1-Chloro-3-phenylcopyrine (**14**, 0.048 g., 0.002 mole) was dissolved in 25 ml. of absolute ethanol and 10 mg. of palladium-on-calcium carbonate catalyst[31] was added and the mixture was subjected to hydrogenation at atmopheric pressure. After 6 hr. the catalyst was removed by filtration and the filtrate was examined by thin layer chromatography using ether as developer. This showed the presence of three products, two of which were a yellow fluorescent color. Consequently, the hydrogenolysis route was abandoned.

1-Hydrazino-3-phenylcopyrine (15).— This is the procedure described by Ikekawa[8] for 1-hydrazinocopyrine. 1-Chloro-3-phenylcopyrine (**14**, 0.200 g., 0.00831 mole) and 85% hydrazine hydrate (5 ml., 5 g., 0.1 mole) were dissolved in 25 ml. of absolute ethanol. The mixture was refluxed for 4 hr., cooled, and diluted with 50 ml. of water. The solution was filtered and the precipitate was washed with water. The hydrazine (**15**, 0.177 g.) was obtained in 90% yield. It had m.p. 214–216° dec. (cap.). A satisfactory analytical sample could not be obtained as the material underwent extensive decomposition upon recrystallization.

Anal. Calcd. for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.90; H, 5.14; N, 24.96.

3-Phenylcopyrine (16). From 15.—This is essentially the method of Baumgarten and Su.[18] Crude 1-hydrazino-3-phenylcopyrine (**15**, 0.177 g.) was suspended in 100 ml. of distilled water, stirred, and heated to boiling. Cupric sulfate (0.598 g.) dissolved in 50 ml. of water was added dropwise. Vigorous gas evolution took place. The cupric sulfate solution was added over a period of 2 hr. and the mixture was stirred and refluxed for 2 hr. longer, cooled, and made strongly alkaline with 20% sodium hydroxide. The gelatinous mixture was continuously extracted with ether for 24 hr. The ether was evaporated under vacuum and the crystalline residue was purified by preparative

(27) R. P. Linstead and K. O. A. Michaelis, *J. Chem. Soc.*, 1134 (1940).

(28) E. C. Horning, M. G. Horning, and G. N. Walker, *J. Am. Chem. Soc.*, **71**, 169 (1949).

(29) Matheson Coleman and Bell, East Rutherford, N. J.

(30) F. P. Treadwell and W. T. Hall, "Analytical Chemistry," 9th Ed., John Wiley and Sons, Inc., New York, 1955, p. 525.

(31) A. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1959, p. 167.

thin layer chromatography using ether as the developer. The band containing the product could be seen readily under ultraviolet light. This was scraped off, and the product was extracted from the silica gel with chloroform in a Soxhlet extractor. The chloroform was evaporated and the residue was sublimed at 100° (0.04 mm.) to give 0.086 g. (55%) of pure material with m.p. 126–128°; infrared absorption in potassium bromide: 1610 cm.$^{-1}$ (aromatic); ultraviolet absorption in 95% ethanol (max.): 295 mμ (log ε 3.96), 254 (4.34), and 230 (4.05); ultraviolet absorption spectrum of 2-phenylnaphthalene in 95% ethanol (max.)[32]: 288 mμ (log ε 4.1), 259 (4.1), and 251 (4.8).

Anal. Calcd. for $C_4H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.76; H, 4.81; N, 13.59.

A **monopicrate**, m.p. 210–211°, was prepared in ethanol and recrystallized from the same solvent.

Anal. Calcd. for $C_{22}H_{13}N_5O_7$: C, 55.18; H, 3.01; N, 16.09. Found: C, 55.19; H, 3.18; N, 16.06.

A **monopicrolonate**, m.p. 255–256° dec. (cap.), was prepared in ethanol and recrystallized from the same solvent.

Anal. Calcd. for $C_{24}H_{18}N_6O_5$: C, 61.27; H, 3.86; N, 17.87. Found: C, 61.13; H, 3.95; N, 18.19.

8-Oxo-6-phenyl-5,6,7,8-tetrahydroisoquinoline (18).—Sodium (287.5 mg., 0.0125 g.-atom) was dissolved in 35 ml. of anhydrous ethanol. Ethyl malonate (2.0 g., 0.0125 mole) was added, followed by 2.060 g. (0.01 mole) of 3-cyano-4-stilbazole (**8**). The red solution was stirred for 8 hr. at room temperature. Subsequent examination by thin layer chromatography, using ether as developer, showed the absence of any starting material. The ethanol was evaporated under vacuum and the oily red residue was heated under reflux for 6 hr. with 60 ml. of 3 *N* hydrochloric acid. The cooled acid solution was extracted once with 25 ml. of ether, made slightly alkaline with solid sodium bicarbonate, and extracted six times with 35-ml. portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate. The chloroform was evaporated to give 2.5 g. of oil. The oil was dissolved in ether, evaporated on 5 g. of deactivated neutral alumina, and chromatographed on 100 g. of neutral alumina, activity grade IV (Brockmann). The column was developed using gradient elution. The first solvent was 1 l. of *n*-pentane followed by 1 l. of ether–*n*-pentane (25:75), followed by 1 l. of ether–*n*-pentane (40:60). Fractions of 15 ml. were collected and examined by thin layer chromatography using ether–*n*-pentane (75:25) as the developer. Fractions 1–72 contained nothing. Fractions **73–80** contained an impurity. Fractions **81–100** contained impurity and a trace of the product. Fractions **101–150** contained pure product. The latter were combined and evaporated to yield 1.433 g. (64% yield) of 8-oxo-6-phenyl-5,6,7,8-tetrahydroisoquinoline (**15**). After sublimation (110° at 0.04 mm.) and three recrystallizations from benzene–hexane (1:1), the ketone had m.p. 83–84°; infrared absorption in potassium bromide: 1680 cm.$^{-1}$ (ArCO—).

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.93; H, 5.91; N, 6.37.

An oxime, m.p. 228–229° (cap.), was prepared in aqueous ethanol and recrystallized from the same solvent.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.34; H, 6.06; N, 11.71.

A picrate, m.p. 154–157° (cap.), was prepared in ethanol and recrystallized from the same solvent.

Anal. Calcd. for $C_{21}H_{16}N_4O_8$: C, 55.76; H, 3.57; N, 12.38. Found: C, 55.84; H, 3.70; N, 12.39.

A **styphnate**, m.p. 190–191° (cap.), was prepared in ethanol and recrystallized from the same solvent.

Anal. Calcd. for $C_{21}H_{16}N_4O_9$: C, 53.85; H, 3.44; N, 11.96. Found: C, 53.80; H, 3.60; N, 12.03.

(32) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **60**, 940 (1938).

Thio Sugars. III. Synthesis and Rearrangement of 2-(3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranosyl)-2-thiopseudourea Dihydrobromide and Analogs[1]

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Condensation of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-galactopyranosyl bromide hydrobromide (I) with thiourea in acetone solution gave 2-(3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranosyl)-2-thiopseudourea dihydrobromide (II) crystallizing with 1 mole of acetone and further characterized as the diflavianate; condensation in a 2-propanol medium gave predominantly isopropyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranoside hydrobromide (IV). Improved preparative directions are cited for the D-*gluco* analog (V) of II and it is shown that some isopropyl tetra-*O*-acetylglycoside is likewise formed when V is prepared in 2-propanol solution. Substance V was further characterized as its diflavianate. Substance II, an analog of the radiation protective agent 2-(2-aminoethyl)-2-thiopseudourea (AET), undergoes rearrangement in neutral solution to 3,4,6-tri-*O*-acetyl-2-deoxy-2-guanidino-1-thio-β-D-galactose hydrobromide (III). Determination of III and its D-glucose analog (VI) by thiol assay is described.

In the first paper[2] in this series we reported the preparation of 2-(3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea dihydrobromide (V), and a subsequent paper[3] described the rearrangement undergone by V at pH 7 in aqueous solution to give 3,4,6-tri-*O*-acetyl-2-deoxy-2-guanidino-1-thio-β-D-glucose (VI). Systems of this type are of interest as potential radiation protective agents, since they incorporate into a carbohydrate matrix the functional groups of 2-(2-aminoethyl)-2-thiopseudourea (AET). The latter[4] is one of the most effective agents known for the protection of biological systems against ionizing radiation,[5] but its high toxicity is a disadvantage. It was hoped that carbohydrate derivatives would function as protective compounds with low toxicity. The present work describes the synthesis of the D-galactose analog (II) of V, together with further studies on V. A study of the rearrangement of II and V to the corresponding guanidino thiols (III and VI) is also described. It was considered that the D-galactose derivative (II) would be less readily metabolizable than the D-glucose analog

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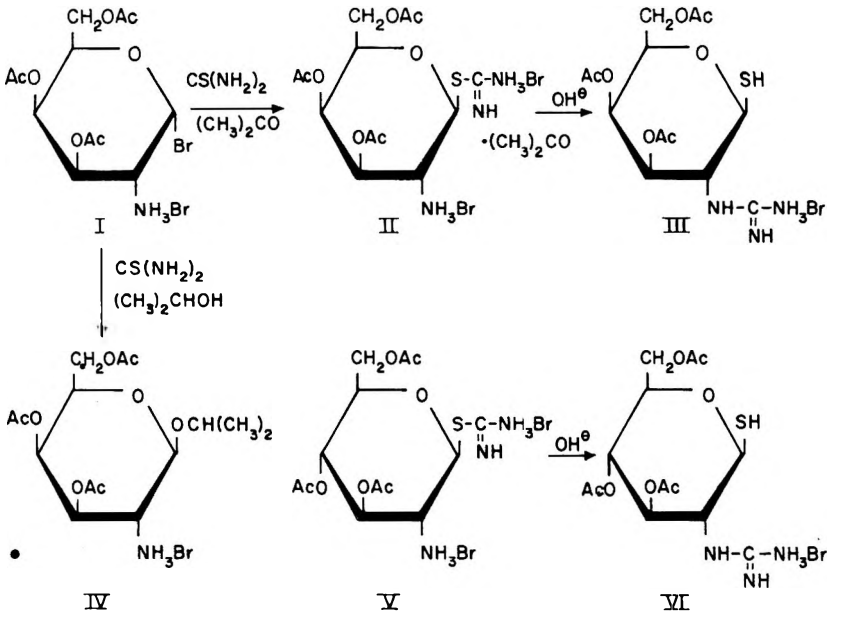
(2) D. Horton and M. L. Wolfrom, *J. Org. Chem.*, **27**, 1794 (1962).

(3) M. L. Wolfrom, D. Horton, and D. H. Hutson, *ibid.*, **28**, 845 (1963).

(4) J. X. Khym, R. Shapira, and D. G. Doherty, *J. Am. Chem. Soc.*, **79**, 5663 (1957); D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *ibid.*, **79**, 5667 (1957).

(5) D. G. Doherty, in "Radiation Protection and Recovery," A. Hollaender, Ed., Pergamon Press, London, 1960, p. 45.



(V), and might thus be more effectively transported *in vivo* to the site of action.

3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-α-D-galactopyranosyl bromide hydrobromide[6] (I), prepared from 2-amino-2-deoxy-D-galactose hydrochloride[7] in one step, underwent condensation with thiourea smoothly in boiling acetone solution, to give 2-(3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranosyl)-2-thiopseudourea dihydrobromide (II) as a well-crystallized product in high yield; its infrared spectrum was closely similar to that of the D-glucose analog[2] (V) in the region 2.5–9.0 μ, and its specific rotation (−8°) was indicative of the β-D configuration. The crystalline product was a solvate, having 1 mole of acetone of crystallization, as determined by elemental analysis and by quantitative determination of acetone as the crystalline 2,4-dinitrophenylhydrazone. The acetone was tenaciously retained, even on recrystallization from different solvents. Treatment of an aqueous solution of II with flavianic acid (2,4-dinitro-1-naphthol-7-sulfonic acid) gave a crystalline diflavianate salt analog of II in high yield as a monohydrate. Attempted preparation of II from I and thiourea, in a 2-propanol medium, a procedure effective[2] for preparation of the D-glucose analog (V), was found to give, as major product, a nonreducing substance having the analysis, specific rotation, and infrared spectrum required for isopropyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranoside hydrobromide (IV). Only a small proportion of the thiourea condensation product (II) was formed under these reaction conditions.

A re-examination of the reaction conditions[2] leading to 2-(3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea dihydrobromide (V) indicated that improvements could be made by substitution of acetone in place of 2-propanol as the condensation medium, with precipitation of the product in microcrystalline form instead of isolation by slow crystallization. The X-ray powder diffraction pattern attested to the crystallinity of the precipitated product. Aqueous flavianic acid converted V into the crystalline diflavianate salt, isolated in high yield as a monohydrate. Numerous preparations of V were made, by the original procedure[2] with 2-propanol as the reaction medium, and also with acetone as solvent; better yields were obtainable in the latter solvent. On some occasions, a small proportion (about 10%) of a side product separated directly from the reaction mixture when 2-propanol was used as solvent. Analytical data indicated this product to be isopropyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside hydrobromide. Its structure was proved by acetylation to isopropyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside, synthesized independently by the condensation of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[2,8] with 2-propanol in benzene solution in the presence of mercuric cyanide.[9] No crystalline products were obtained on attempts to deacetylate V or to prepare the disulfide of its rearranged product (VI).

When an aqueous solution of 2-(3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranosyl)-2-thiopseudourea dihydrobromide (II) was treated with base to bring the pH to 7, or if II was dissolved in a phosphate buffer (pH 7.0), a very rapid rearrangement to the guanidino thiol (III) took place, as shown by the fact that the product gave positive reactions for thiol and for the guanidino function. The behavior of II in undergoing the rearrangement is thus closely similar to that of the D-glucose analog[3] (V).

The release of free thiol on rearrangement of II and V was determined by the thiol assay procedure of Basford and Hunnekens,[10] as used by Doherty and associates.[4] Reference thiol derivatives, also determined by this procedure, were 2-guanidinoethanethiol (prepared by rearrangement of 2-(2-aminoethyl)-2-thiopseudourea hydrobromide in a neutral buffer solution), and 1-thio-D-glucose (prepared in solution by saponification of 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucose[2]).

(6) M. L. Wolfrom, W. A. Cramp, and D. Horton, *J. Org. Chem.*, **28**, 3231 (1963).

(7) A product of Pfanstiehl Laboratories, Waukegan, Ill. The authors thank Dr. D. G. Doherty for a gift of some of the material used in this work.

(8) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

(9) B. Helferich and K. F. Wedemeyer, *Ann.*, **563**, 139 (1949).

(10) R. E. Basford and F. M. Hunnekens, *J. Am. Chem. Soc.*, **77**, 3873 (1955).

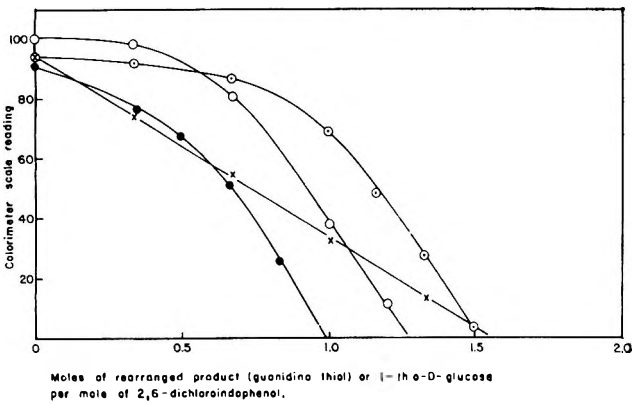


Fig. 1.—Thiol assay on products as rearranged to ×, 2-guanidinoethanethiol; O, III; ⊙, VI, and ●, 1-thio-β-D-glucopyranose. See Experimental section for details.

The determination[10] utilizes the decoloration of the blue dye 2,6-dichloroindophenol by free thiol, and the amount of decoloration, determined photocolorimetrically against a standard, gives the desired titre. It can be seen (Fig. 1) that, for 2-guanidinoethanethiol, the decoloration of the dye is linearly related to the amount of thiol added, and complete decoloration occurred when 1.6 moles of thiol per mole of dye had been added. In the case of the sugar thiol derivatives the relation was not linear (Fig. 1); the extrapolated values for complete decoloration gave, per mole of dye, thiol consumptions of 1.3, 1.5, and 1.0 moles of III, VI, and 1-thio-D-glucose, respectively. Basford and Hunnekens[10] postulate two alternative mechanisms for the reduction of 2,6-dichloroindophenol by thiols, one requires 1 molar equiv., the second requires 2 molar equiv. of thiol per mole of dye. The observed values for III, VI, and 2-guanidinoethanethiol would suggest the involvement of both reaction pathways.

Experimental[11]

2-(3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranosyl)-2-thiopseudourea Dihydrobromide Monoacetonate (II).—To a solution of thiourea (0.18 g.) in warm anhydrous acetone (30 ml.) was added 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-galactopyranosyl bromide hydrobromide[6] (I, 1.00 g.), and the mixture was refluxed 30 min. Refrigeration overnight gave crystalline II, yield 0.95 g. (82%), m.p. 159–161° dec. Recrystallization was readily effected from methanol–ethyl acetate or from acetone to give analytically pure material which contained 1 molar equiv. of acetone of crystallization. It had m.p. 161–163° dec., $[\alpha]^{23}D$ −8 ± 2° (*c* 0.89, methanol); λ_{max}^{KBr} 5.70 (OAc), 6.1 (C=N) μ; X-ray powder diffraction data[12]: 15.19 s, 11.63 vs (1), 7.56 s, 6.56 w, 6.19 m, 5.64 s, 4.87 s, 4.67 w, 4.48 vs (2,2), 4.29 vs (2,2), 4.00 s, 3.65 vs (3) Å.

Anal. Calcd. for $C_{19}H_{24}Br_2N_3O_{12}S\cdot(CH_3)_2CO$: C, 32.94; H, 5.01; Br, 27.39; N, 7.25; S, 5.51; $(CH_3)_2CO$, 9.95. Found: C, 32.97; H, 5.05; Br, 27.04; N, 7.24; S, 5.43; $(CH_3)_2CO$, 9.82.

The acetone of crystallization in II was determined quantitatively by precipitation of the 2,4-dinitrophenylhydrazone. The precipitating reagent was prepared by dissolving 2,4-dinitrophenylhydrazine (2 g.) in methanol (30 ml.), adding water (10 ml.) and concentrated sulfuric acid (4 ml.), then filtering. To a solution of crystalline II (200 mg.) in water (3 ml.) was added an excess of the 2,4-dinitrophenylhydrazine reagent. The orange precipitate was filtered after 12 hr. and dried to constant weight at room temperature. Analysis of the precipitate gave acceptable values for acetone 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_9H_{10}N_4O_4$: C, 45.37; H, 4.23. Found: C, 45.32; H, 4.48.

Product II tenaciously retained 1 mole of acetone of crystallization, even after repeated recrystallization from methanol–ethyl acetate; the product showed no change in melting point or X-ray powder diffraction pattern. Removal of the acetone by heating or by repeated codistillation with another solvent gave noncrystallizable sirups.

2-(3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranosyl)-2-thiopseudourea Diflavianate Monohydrate.—A 0.5 *M* aqueous solution of flavianic acid (2,4-dinitro-1-naphthol-7-sulfonic acid) was added dropwise to a solution of 2-(3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranosyl)-2-thiopseudourea dihydrobromide (II, 100 mg.) in water (5 ml.) until no further precipitation was observed. The oil which separated solidified on refrigeration, and the solid was washed by decantation with water at 0°. Recrystallization from absolute ethanol gave pure material, as a lemon yellow monohydrate, yield 145 mg. (85%), m.p. 182–184° dec.

Anal. Calcd. for $C_{33}H_{33}N_7O_{23}S_3\cdot H_2O$: C, 39.29; H, 3.56; N, 9.74; S, 9.16. Found: C, 39.11; H, 3.78; N, 9.85; S, 9.14.

Thin layer chromatography[11] of the product, with 3:1 ethanol–water eluent, revealed the product as a single discrete zone, R_f 0.8.

Isopropyl 3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranoside Hydrobromide (IV).—This compound was the major product when condensation of I with thiourea was attempted, with 2-propanol as solvent. To a solution of thiourea (0.18 g.) in warm 2-propanol (30 ml.) was added 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-galactopyranosyl bromide hydrobromide[6] (I, 1.00 g.), and the mixture was refluxed 30 min. The isopropyl tri-*O*-acetylglycoside crystallized on cooling, yield 0.57 g. (60%), m.p. 248–252°, $[\alpha]^{24}D$ −27.5 ± 2° (*c* 2.1, methanol); X-ray powder diffraction data[12]: 15.19 s, 12.52 vs (1), 8.19 w, 5.34 s, 5.16 m, 4.84 w, 4.69 s, 4.53 s, 4.33 m, 4.21 w, 3.90 vs (2,2), 3.71 vs (2,2), 3.58 w, 3.47 m, 3.40 vs (3), 3.20 m Å.

Anal. Calcd. for $C_{15}H_{26}BrNO_8$: C, 42.07; H, 6.12, Br, 18.67; N, 3.27. Found: C, 42.41; H, 6.43; Br, 19.37; N, 3.44.

The product was nonreducing to Benedict solution. Thin layer chromatography of the residual mother liquors indicated that little of the condensation product II had been formed in the reaction.

Preparation of 2-(3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea Dihydrobromide (V).—This compound is formed readily under the reaction conditions described by Horton and Wolfrom[2] but crystallization is often slow, even on nucleation. It was found that substitution of dry acetone as the reaction medium, instead of 2-propanol, gave the most consistent results in the reaction. Evaporation of the reaction solution, dissolution of the sirup in 2-propanol, followed by cautious addition of ethyl acetate, then petroleum ether (b.p. 30–60°), caused the separation of V as microcrystalline material in yields of 55–80%. This product had X-ray powder diffraction pattern, specific rotation, and infrared spectrum identical with those of the product prepared by the original procedure[2]; the melting point (167–174° dec.) was about 9° lower than that of the slowly crystallized material. Attempts to deacetylate V by acid-catalyzed methanolysis or to obtain the disulfide of VI by iodine oxidation following rearrangement did not lead to definitive products of predictable analysis.

On some occasions, when V was prepared by the procedure of Horton and Wolfrom,[2] a small proportion (10%) of product separated directly from the cooled 2-propanol reaction medium. Recrystallization of this side product from 2-propanol gave fine needles, m.p. 238–240° dec., $[\alpha]^{24}D$ −22 ± 2° (*c* 3.03, methanol); λ_{max}^{KBr} 5.72 (OAc) μ, NHAc absent; X-ray powder diffraction data[12]: 11.52 vs (1), 8.12 w, 5.31 s, 4.98 w, 4.62 vs (3), 4.17 w, 3.92 vs (2), 3.36 s, 2.89 m Å. This product was identified, by con-

(11) Melting points were taken on a Fisher-Johns apparatus. The $[\alpha]D$ values were measured with a 2-dm. polarimeter tube. Microanalyses were performed by W. N. Rond. Infrared spectra were measured on a Perkin-Elmer Infracord Model 137 infrared spectrophotometer. The potassium bromide pellets were pressed from a finely ground mixture of the substance with dried A.R. grade potassium bromide. Thin layer chromatography was carried out with silica gel G (E. Merck, Darmstadt, Germany) activated at 100°, and zones were revealed by spraying with concentrated sulfuric acid, with subsequent heating at 100°.

(12) Interplanar spacing Å., Cu Kα radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very. First few strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities.

versions shown below, as **isopropyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside hydrobromide**.

Anal. Calcd. for $C_{15}H_{26}BrNO_8$: C, 42.07; H, 6.12; Br, 18.67; N, 3.27. Found: C, 42.06; H, 6.28; Br, 19.9; N, 3.27.

2-(3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea Diflavianate Monohydrate.—This derivative was prepared from the dihydrobromide salt V (100 mg.) by a procedure essentially similar to that used in preparation of the D-*galacto* analog. The yellow product crystallized from absolute ethanol, yield 0.150 g. (88%), m.p. 179–180° dec. The melting point was not changed by further recrystallization.

Anal. Calcd. for $C_{33}H_{33}N_7O_{23}S_3 \cdot H_2O$: C, 39.29; H, 3.56; N, 9.74; S, 9.16. Found: C, 39.68; H, 3.85; N, 9.63; S, 8.96.

The product showed a single zone, R_f 0.8, on thin layer chromatography with 3:1 ethanol–water developer.

Isopropyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside. **A. From 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl Chloride**.—To a solution of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[2,8] (4.0 g.) in dry benzene (75 ml.) was added 2-propanol (3.0 ml.) and mercuric cyanide (3.6 g.). The mixture was stirred overnight, chloroform (150 ml.) was added, and the solution was extracted with three 20-ml. portions of water, dried over anhydrous magnesium sulfate, and evaporated to a sirup, which crystallized from methylene chloride–ether as fine needles, yield 2.68 g. (63%), m.p. 169–170°, $[\alpha]^{22}D$ +22 ± 2° (c 0.65, chloroform); λ_{max}^{KBr} 5.75 (OAc), 6.07, 6.45 (NHAc) μ; X-ray powder diffraction data[12]: 11.63 vs (1), 8.50 s, 7.97 w, 7.25 s, 6.70 m, 6.24 m, 5.83 w, 5.25 m, 4.72 vs (2), 4.51 s, 4.37 vs (3), 4.23 m Å.

Anal. Calcd. for $C_{17}H_{27}NO_9$: C, 52.43; H, 6.99; N, 3.60. Found: C, 52.40; H, 7.13; N, 3.72.

B. From Isopropyl 2,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside Hydrobromide.—A solution of isopropyl 2,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside hydrobromide (0.3 g.) in pyridine (5 ml.) and acetic anhydride (2.5 ml.) was maintained at room temperature for 15 hr., poured on ice, and the product extracted with chloroform. The washed and dried extract was evaporated and the residue was crystallized from methanol–ether to give needles, yield 0.21 g. (63%), m.p. 169–170°, $[\alpha]^{22}D$ +24 ± 2° (c 0.77, chloroform), identical by mixture melting point, elemental analysis, X-ray powder diffraction pattern, and infrared spectra with the product isolated under **A** above. Both samples migrated as a single zone, R_f 0.45, on thin layer chromatography with 4:1 benzene–methanol as developer.

Rearrangement of 2-(3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranosyl)-2-thiopseudourea Dihydrobromide (II).—Aqueous solutions of II gave a negative thiol reaction, but, after adjusting to pH 7 by the addition of sodium hydroxide solution or phosphate buffer, the solution gave strong thiol reactions with sodium nitroprusside or 2,6-dichloroindophenol, and also gave a strong Sakaguchi reaction.[13] These data indicate that II had undergone rearrangement to the guanidino thiol III.

(13) R. A. B. Bannard, A. A. Casselman, W. F. Cockburn, and G. M. Brown, *Can. J. Chem.*, **36**, 1541 (1958).

Thiol Assay Procedure.—Free thiol was determined[10] by adding a solution of the thiol to a solution of the dye 2,6-dichloroindophenol, and determining photocolorimetrically the extent to which the dye was decolorized. A Klett-Summerson photoelectric colorimeter, with a Wratten No. 70 (dark red) filter transmitting at 650–700 mμ, was used. A 0.4 *M* phosphate buffer solution, pH 7.0, was prepared from potassium dihydrogen phosphate (9.1 g.) and disodium hydrogen phosphate (18.9 g.) made up to 1 l. with distilled water. A stock solution of the dye was prepared by dissolving sodium 2,6-dichloroindophenol dihydrate (4 mg.) in buffer (200 ml.). For each determination, a blank was prepared from the stock dye solution (5.00 ml.) and 0.2 *N* hydrochloric acid (1.00 ml.). The resultant 5×10^{-5} *M* solution showed no significant change in pH, and it gave a colorimeter scale reading of 100 ± 4 units; the zero reading was made with distilled water. Solutions for thiol assay were prepared in 0.2 *N* hydrochloric acid at a concentration of 1×10^{-3} *M*, and the determination was performed by adding to an aliquot of this solution sufficient 0.2 *N* hydrochloric acid to bring the volume to 1.00 ml., and subsequently adding 5.00 ml. of the stock dye solution. The colorimeter reading was taken, in stoppered tubes, 2–3 min. after mixing, when decoloration of the dye was at a maximum. Colorimeter readings were plotted against thiol concentration, and the curves were extrapolated to zero reading, the point which corresponded to complete bleaching of the dye.

Rearrangement of Amino 2-Thiopseudourea Derivatives to Guanidino Thiols and Determination of Thiol. A. 2-(2-Aminoethyl)-2-thiopseudourea (AET).—A 10^{-3} *M* solution of 2-(2-aminoethyl)-2-thiopseudourea in 0.2 *N* hydrochloric acid was used, the rearrangement taking place on addition to the neutral buffer system. A linear plot of sample added against dye bleached, was obtained (Fig. 1), and extrapolation to total bleaching of dye showed that approximately 1.6 moles of substance per mole of dye was required.

B. 2-(3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea Dihydrobromide (V).—A 10^{-3} *M* solution of V in 0.2 *N* hydrochloric acid was used in the determination. A nonlinear plot of sample added against dye bleached was observed (Fig. 1), and extrapolation to total bleaching of dye indicated consumption of approximately 1.5 moles of rearranged V (VI) per mole of dye.

C. 2-(3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranosyl)-2-thiopseudourea Dihydrobromide (II).—Under the conditions of the above determination (B) the rearranged D-galactose derivative (III) gave a nonlinear plot (Fig. 1), with an extrapolated value for total bleaching of approximately 1.3 moles of III per mole of dye.

Thiol Assay on 1-Thio-D-glucose.—A solution of 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose[2] (20.0 mg.) in dry methanol (5.0 ml.) was treated, under nitrogen, with 1 *N* methanolic sodium methoxide (0.5 ml.), and after a short time the solution was made up to 100 ml. with 0.2 *N* hydrochloric acid. The resultant solution was used in the thiol assay, and a nonlinear plot was observed (Fig. 1). The extrapolated value for total bleaching of the dye was 1 mole of 1-thio-D-glucose per mole of dye.

Studies of Terpene Chemistry. I. The Acid-Catalyzed Dimerization of Citronellal[1]

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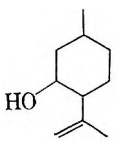
The bromination of citronellal gives a mixture of bromo ethers and bromo alcohols. The bromo alcohol mixture contains 8-bromomenthols which are dehydrobrominated to yield isopulegol. Debromination of the bromo ether mixture affords a dimeric unsaturated ether, $C_{20}H_{34}O$. The same unsaturated ether is obtained from the acid-catalyzed condensation of citronellal and isopulegol and from citronellal alone. We conclude that the products from the bromination of citronellal are formed by bromination of the acid-catalyzed cyclization and dimerization products. The dimeric unsaturated ether is shown to have structure **3** by degradative and spectroscopic studies.

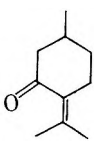
In the course of studies of the synthesis of carbocyclic systems, the products from the bromination of citronellal have been examined. The bromination of citronellal was first reported by Wright[2] in 1874, and the first detailed description for the bromination was given by Kremers[3] in 1892. These authors described the bromination products of citronellal as unstable oils which could not be characterized. In our hands, the bromination products result from bromination of the acid-catalyzed cyclization and dimerization products of citronellal.

The bromination of citronellal in ether solution at 0° gives a mixture of bromo ethers and bromo alcohols in a ratio of 3:1. The bromination products showed signs of decomposition during storage at room temperature and we were not able to obtain satisfactory analytical data. All attempts at purification by crystallization or distillation met with failure.

Dehydrobromination of the bromo alcohols with hot collidine gave a mixture of isopulegols (**1**) which was identical with a commercial preparation. Oxidation of the isopulegol afforded isopulegone, characterized as the 2,4-dinitrophenylhydrazone, which could be isomerized to pulegone (**2**). Chromic acid oxidation of the bromo alcohol mixture afforded the corresponding bromo ketones which were converted to pulegone upon treatment with calcium carbonate in *N*,*N*-dimethylacetamide. These results indicate that the bromo alcohol fraction is a mixture of stereoisomers of 8-bromomenthol which may also contain some 8,9-dibromomenthols.



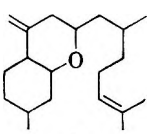
1



2

Treatment of the bromo ethers with lithium in liquid ammonia gave a mixture which showed three peaks on vapor phase chromatography. The major component, comprising about 76% of the mixture, was shown to be an olefinic ether, $C_{20}H_{34}O$, from combustion analyses, molecular weight determination, and spectroscopic data. The minor products had spectral characteristics similar to those of the main product, but they were not examined further. Treatment of the crude bromination product with zinc in ethanol afforded isopulegol and the same mixture of unsaturated ethers. Hence, some of the bromines are vicinal. Analyses of the bromo ether fraction gave high values for bromine calculated on the basis of a tetrabromo ether and bromination of a sample of the total unsaturated ethers yielded a mixture of bromo ethers whose infrared spectrum was identical with the original mixture of bromo ethers. The same olefinic ether is obtained from the condensation of citronellal and isopulegol or citronellal alone in ether solution at room temperature in the presence of *p*-toluenesulfonic acid. Hence, it appears that the products from the bromination of citronellal, under the conditions used in the present investigation, arise from bromination of the acid-catalyzed cyclization and dimerization products of citronellal.

Microhydrogenation of the dimeric unsaturated ether indicated two double bonds and the infrared spectrum of this material shows no hydroxyl or carbonyl absorption, but peaks at 1650, 1100, and 900 cm.$^{-1}$ consistent with the presence of carbon–carbon double bonds and an ether. Structure **3** is proposed for the olefinic ether on the basis of degradative and spectroscopic evidence presented below.



3

The proton magnetic resonance spectrum of the olefinic ether shows a one-proton triplet at δ 4.94 with J = 5.0 c.p.s. and broad singlet at δ 4.54 corresponding to two protons. The triplet at δ 4.94 is identical with the signal of the vinyl proton of citronellal. The signal at δ 4.54 is consistent with the presence of an *exo* methylene group as suggested by the 900-cm.$^{-1}$ band in the infrared spectrum.

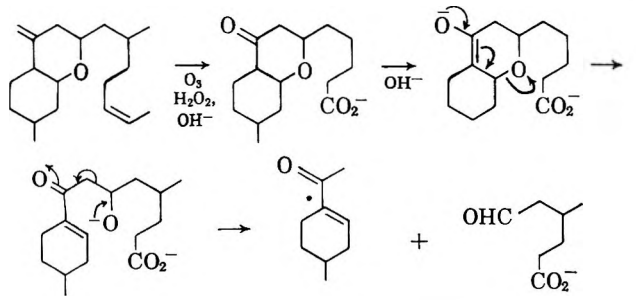
Three fragments were identified from the ozonolysis of the unsaturated ether. Ozonolysis in methylene chloride afforded acetone in 70% yield isolated as the 2,4-dinitrophenylhydrazone. While it was not possible to isolate formaldehyde from ozonolysis in methylene chloride, ozonolysis in acetic acid followed by reductive work-up yielded formaldehyde in 25% yield as the dimedon derivative. Ozonolysis in methylene chloride followed by oxidative work-up furnished 1-acetyl-4-methylcyclohexene in 15% yield, characterized as the 2,4-dinitrophenylhydrazone. An authentic sample of 1-acetyl-4-methylcyclohexene was prepared by the ozonolysis of isopulegol followed by dehydration of the intermediate ketol. The 1-acetyl-4-methylcyclohexene is

(1) Supported by a Frederick Gardner Cottrell grant from the Research Corporation and the National Science Foundation, Grant GP-252.

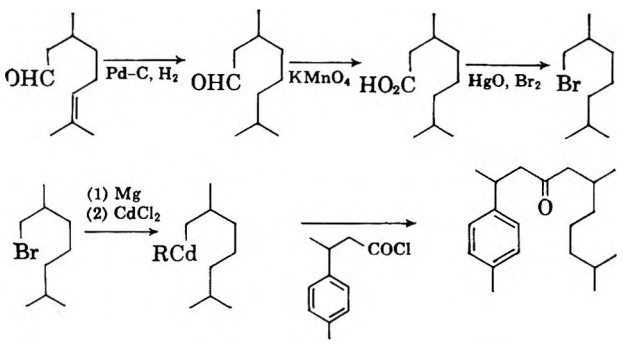
(2) C. R. A. Wright, *Pharm. J.*, **5**, 233 (1874).

(3) E. Kremers, *Am. Chem. J.*, **14**, 203 (1892).

thought to be formed by alkaline cleavage of the ozonolysis product. The cleavage is viewed as a β-elimination followed by a reverse aldol. This degradation provides evidence regarding the position of the ether bridge.



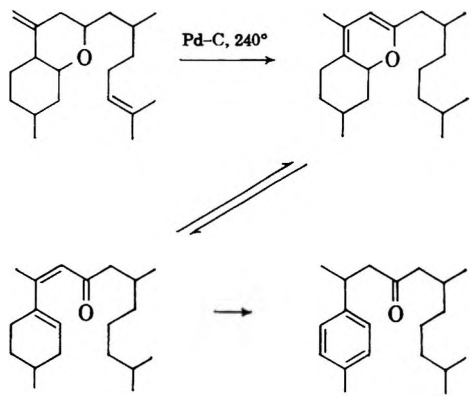
Dehydrogenation of the unsaturated ether gave a high yield of (6*R*)-2-(*p*-tolyl)-6,10-dimethyl-4-undecanone, obtained as an equimolar mixture of epimers at C-2. The structure of the ketone was suggested from its spectroscopic properties (see Experimental) and oxidation with potassium permanganate to yield dihydrocitronellic acid. The structure of the dehydrogenation ketone was confirmed by the synthesis outlined below.



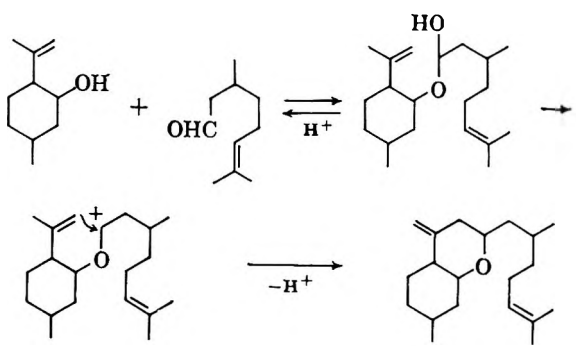
The synthesis proceeded smoothly and the final step, the reaction of the cadmium reagent from (2*R*)-2,6-dimethylheptyl bromide with racemic 3-(*p*-tolyl)butyryl chloride, afforded the desired ketone which was identical in all respects including rotation, with the dehydrogenation ketone. Since the synthetic ketone is almost certainly an equimolar mixture of epimers at C-2, we conclude that the dehydrogenation ketone is also a mixture of epimers.

Since cleavage of the ether occurs without loss of any carbons, the ether linkage must be part of a ring. The protons adjacent to oxygen in the olefinic ether appear in the proton magnetic resonance spectrum as a multiplet at δ 3.33, but no reliable conclusions can be drawn about the size of the oxygen-containing ring. However, neither the vinyl protons nor the protons adjacent to oxygen are abnormally deshielded indicating that the ether bridge is not allylic. This conclusion is supported by the stability of the unsaturated ether to solutions of alkali metals in liquid ammonia.

Assuming no molecular rearrangement during dehydrogenation, the dehydrogenation indicates one site of attachment of the oxygen. The mechanism of formation of the dehydrogenation ketone requires further comment. It seems likely that the oxygen-containing ring is dehydrogenated first to yield the pyran. In the presence of a hydrogenation catalyst at elevated temperatures, the pyran would be expected to be in equilibrium with the dienone, which would suffer aromatization to the observed product. There is ample analogy for the postulated isomerization of the pyran derivative to the dienone. The thermochromism of spiropyrans is ascribed to thermal interconversion of the pyran to the dienone.[4] It has also been found that enol ether of *cis*-β-ionone is isomerized to *trans*-β-ionone by iodine at room temperature or ultraviolet light.[5] In the present case, the dienone would be expected to aromatize with concomitant reduction of the isolated double bond in the presence of a hydrogenation catalyst. It is interesting to note that the tetrahydro ether, prepared by hydrogenation of the unsaturated ether, yields the same ketone upon dehydrogenation.



It seems quite certain that the dimeric bromo ethers obtained from the bromination of citronellal arise from the acid-catalyzed condensation of isopulegol and citronellal. The formation of 8-bromomenthol in the reaction undoubtedly proceeds by the same carbonium ion which leads to isopulegol and there is little doubt that isopulegol is present in the reaction mixture. There are many analogies for the formation of pyran derivatives from the acid-catalyzed condensation of aldehydes and homoallylic alcohols.[6] It seems likely that there is ample hydrogen bromide present in the bromination mixture to catalyze the observed cyclizations since the bromine was not purified before use and a variety of side reactions would lead to additional hydrogen bromide.



(4) C. F. Koelsch, *J. Org. Chem.*, **16**, 1362 (1951).

(5) G. Büchi and N. C. Yang, *J. Am. Chem. Soc.*, **79**, 2318 (1957).

(6) A. T. Blomquist and J. Wolinsky, *ibid.*, **79**, 6025 (1957); L. J. Dolby and M. J. Schwarz, *J. Org. Chem.*, **28**, 1456 (1963); N. LeBel, R. N. Liesmer, and E. Melamedbasich, *ibid.*, **28**, 615 (1963); J. Cologne and P. Boisde, "Les Heterocycles Oxygenes," National Center of Scientific Research, Paris, 1962, p. 171.

Experimental[7]

Bromination of Citronellal.—A solution of (+)-citronellal (10 g., 0.07 mole) in 100 ml. of anhydrous ether was brominated by the dropwise addition of bromine (3.7 ml., 0.07 mole) over a period of 1 hr. at 0°. The ether solution was washed successively with water, 10% sodium bicarbonate solution, and the aqueous sodium thiosulfate. After drying over anhydrous magnesium sulfate, the solution was concentrated to a heavy yellow oil. This oil was chromatographed on grade III Woelm alumina (400 g.) to yield two fractions: fraction I, 15 g., eluted with 300 ml. of petroleum ether (30–60°); and fraction II, 5.0 g., eluted with 300 ml. of ethyl ether.

Fraction I was a heavy colorless oil, $[\alpha]^{25}D$ −13.5° (*c* 1.356, chloroform), $n^{25}D$ 1.5307, which was unstable to storage at room temperature; infrared: 1480, 1375, 1100, 815, and 770 cm.$^{-1}$. There was negligible absorption in the ultraviolet. The n.m.r. spectrum showed a complex multiplet at δ 4.00 and additional complex absorption in which there were evident two prominent singlets at δ 2.00 and 1.73 and a doublet at 0.97.

Fraction II was a colorless oil, $[\alpha]^{25}D$ +3.33° (*c* 2.116, chloroform), $n^{25}D$ 1.4961, which also decomposed on standing at room temperature; infrared: 3400, 2900, 1450, 1370, and 1100 cm.$^{-1}$.

Conversion of 8-Bromomenthol to Isopulegol.—A solution of 0.236 g. of 8-bromomenthols (from fraction II) in collidine (10 ml.) was refluxed for 15 min. The brown mixture was cooled and quenched in dilute sulfuric acid and ice and extracted with ether. The ether layer was washed with water and with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The crude product was chromatographed on grade I Woelm alumina. The material (50 mg.), 30% yield, eluted from the column with 30% ethyl acetate–ethyl ether, was shown to be isopulegol by the gas chromatographic and infrared comparison with authentic isopulegol. Both the isopulegol obtained from dehydrobromination of fraction II and commercial isopulegol showed two peaks (3:1) upon gas chromatography using a TCEP column at 140°.

Isopulegone 2,4-Dinitrophenylhydrazone.—A sample of isopulegol (0.300 g., 0.0019 mole), obtained from fraction II, was oxidized by the method of Brown and Garg.[8] The crude ketone (0.200 g., 68%) gave an orange 2,4-dinitrophenylhydrazone, m.p. 136–137°, which did not depress the melting point of authentic isopulegone 2,4-dinitrophenylhydrazone, m.p. 140–141°. The ultraviolet spectrum (λ_{max}^{EtOH} 230 and 357 mμ) and the infrared spectrum (1755, 1650, 1460, 1360, 1100, and 900 cm^{-1}) of this material were also identical with those of isopulegone 2,4-dinitrophenylhydrazone (m.p. 140–141°), prepared similarly from commercial isopulegol. The analytical sample melted at 140–141° after several crystallizations from 95% ethanol.[9]

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.71; H, 6.05; N, 17.08.

Isomerization of Isopulegone to Pulegone.—Isopulegone (0.500 g.) in 50 ml. of 0.1 *N* ethanolic sodium hydroxide was refluxed for 142 min. The reaction mixture was acidified and extracted with ether. The ether extracts were washed with sodium bicarbonate then water. The dried ether solution was concentrated and the residual oil gave a red 2,4-dinitrophenylhydrazone, m.p. 136–137° after crystallization from petroleum ether (30–60°). This material did not depress the melting point of authentic pulegone 2,4-dinitrophenylhydrazone, m.p. 139–140° (lit.[10] m.p. 142° from petroleum ether, m.p. 149–150° from methanol), and the infrared spectra (KBr disk) were superimposable.

Chromic Acid Oxidation of 8-Bromomenthol.—The Brown and Garg[8] procedure was employed on 0.6 g. (0.0025 mole) of 8-bromomenthol. This gave a bromo ketone ($\nu_{max}^{CHCl_3}$ 1715 cm.$^{-1}$) which was used immediately in the following elimination reaction.

Conversion of 8-Bromomenthone to Pulegone.—A solution of 8-bromomenthone (0.062 g.) in *N*,*N*-dimethylacetamide (25 ml.) over 0.4 g. of calcium carbonate was refluxed for 30 min. Upon work-up, a ketonic product was obtained which gave a red 2,4-dinitrophenylhydrazone, m.p. 130–140°, which was identical with authentic pulegone 2,4-dinitrophenylhydrazone.

Lithium–Liquid Ammonia Debromination of the Bromo Ethers.—A solution of 2.14 g. (0.0034 mole) of I in anhydrous ether was added dropwise to a stirred solution of lithium metal (1.5 g., 0.21 g.-atom) in 100 ml. of anhydrous liquid ammonia. After 2 hr., the excess lithium was destroyed with ammonium chloride and the ammonia was allowed to evaporate. The usual work-up yielded 0.85 g. (85%) of a light yellow oil, b.p. 140–145° (4.5 mm.). Vapor phase chromatography on a 5-ft. column of Carbowax 20 M on firebrick showed three peaks. The first peak eluted comprised about 80% of the mixture. Material purified by preparative vapor phase chromatography[7] at 200° showed b.p. 142–144° (4.5 mm.), $[\alpha]^{25}D$ −17.6° (*c* 0.393, ethyl acetate), $n^{25}D$ 1.4905; infrared: 2980, 1650, 1383, 1225, 1102, 1090, 950, 890, 675, and 636 cm.$^{-1}$. Only end absorption was observed in the ultraviolet. The n.m.r. spectrum showed the following bands: δ 4.95 (t), 4.54 (s), 3.38 (m), 1.92 (m), 1.58 (d), 1.22 (m), and 0.85 (d).

Anal. Calcd. for $C_{20}H_{34}O$: C, 82.54; H, 11.80. Found: C, 82.30; H, 12.05.

Anal. Calcd. H_2 uptake for two double bonds in $C_{20}H_{34}O$: 146 mg./mmole of H_2. Found: 161 mg. of sample/mmole of H_2.

Zinc Reduction of the Bromination Products of Citronellal.—A solution of the crude bromination product from citronellal (200 g., 0.33 mole) in 2.0 l. of absolute ethanol was treated with 100 g. of zinc powder. This mixture was refluxed with stirring for 5 days. Portions of fresh zinc were added periodically. Addition of EDTA[11] to complex the zinc salts formed did not seem to influence the nature of the product, but it was added to the larger runs. The reaction mixture was filtered through a sintered-glass funnel, diluted with water, and extracted with ether. The ether extracts were dried over magnesium sulfate and the solvent was removed by flash distillation at atmospheric pressure. The residual oil was fractionally distilled to give 15 g. (15%) of isopulegol, and 50 g. (55%) of a mixture of olefinic ethers which was identical with the product obtained from the lithium–liquid ammonia debromination of fraction I.

Bromination of the Olefinic Ether Mixture.—A 1.8-g. (0.003 mole) sample of the bromo ethers was treated with zinc in refluxing ethanol with stirring for 3 days. The usual work-up gave 0.6 g. of the debromo ether (75% yield). The gas chromatogram of this material as well as the infrared spectrum were identical with those of the ether mixture from previous runs. This material was rebrominated in ether to yield 1.2 g. of bromo ethers. The infrared spectrum of this material and that of the original bromo ethers were found to be completely superimposable.

Attempted Cleavage of the Desbromo Ether with Sodium–Liquid Ammonia.—A solution of the olefinic ether (6.0 g., 0.020 mole) and sodium metal (3.0 g., 0.13 g.-atom) in 500 ml. of liquid ammonia was stirred for 5 hr. Only starting material could be isolated upon work-up.

Hydrogenation of the Olefinic Ether.—A solution of the olefinic ether (1.90 g.) in ethanol containing sufficient petroleum ether (30–60°) to make a homogeneous solution and one drop of 70% perchloric acid was hydrogenated over 100 mg. of 10% palladium-on-carbon catalyst in a low pressure hydrogenator. The product was a colorless oil, 1.80 g. (94%), b.p. 151–153° (4.0 mm.), $n^{25}D$ 1.4679, $[\alpha]^{25}D$ −7.88° (*c* 1.840, chloroform). The n.m.r. spectrum of the tetrahydro ether showed a two-proton multiplet at δ 3.38 and a doublet at 0.90.

Anal. Calcd. for $C_{20}H_{38}O$: C, 81.56; H, 13.01; mol. wt., 294.50. Found: C, 81.59; H, 12.77; mol. wt., 300.

Ozonolysis of the Olefinic Ether.—A solution of the unsaturated ether (1.0 g.) in methylene chloride (75 ml.) was ozonized at −80°

(7) All melting points and boiling points are uncorrected; distillations were carried out using a 65-cm. modified Podbielniak tantalum spiral column. A Wilkens Model A-90-P gas chromatograph and a Nester and Faust Prepko gas chromatograph with a commercial Carbowax 6000 column were used for vapor phase chromatography. Infrared spectra were determined with a Beckman IR-7 infrared spectrophotometer and ultraviolet spectra were measured with a Cary Model 11 spectrophotometer. Proton magnetic resonance spectra were determined in carbon tetrachloride solution using tetramethylsilane as internal standard with a Varian A-60 spectrometer. Microanalyses are by Micro-Tech Laboratories, Skokie, Ill.; Pascher and Pascher Laboratories, Bonn, Germany; and Berkeley Analytical Laboratories, Berkeley, Calif.

(8) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

(9) The melting point of (+)-isoisopulegone 2,4-dinitrophenylhydrazone is recorded as 144–145°; the stereochemistry and purity of our preparation of isopulegone 2,4-dinitrophenylhydrazone are not certain [G. Ohloff, J. Osiecki, and C. Djerassi, *Ber.*, **95**, 1400 (1962)].

(10) (a) O. L. Brady, *J. Chem. Soc.*, 758 (1931); (b) W. Kuhn and H. Schinz, *Helv. Chim. Acta*, **36**, 161 (1953).

(11) Ethylenediaminetetraacetic acid tetrasodium salt.

until a blue color persisted. The solvent was carefully removed under vacuum at room temperature to give an oily ozonide. The ozonide was treated with 20 ml. of water and enough zinc powder to complete the decomposition. This mixture was allowed to stand for 2 hr. after which it was heated on a steam bath under nitrogen and the effluent gases were bubbled through a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. This procedure gave acetone 2,4-dinitrophenylhydrazone (70%), m.p. 123–124°.

The ozonolysis of the olefinic ether (0.200 g.) in 20 ml. of glacial acetic acid was carried out at room temperature. The resulting solution was stirred with 10 ml. of water and zinc powder (0.5 g.) for 2 hr. and steam distilled. The steam distillate was treated with a solution of dimedon in water and the pH was adjusted to 3 with sodium acetate. A white precipitate (54 mg., 25%) was obtained which gave white needles, m.p. 190–192° after one recrystallization from ethanol. This material did not depress the melting point of an authentic sample of the dimedon derivative of formaldehyde. The infrared spectra of these two derivatives were superimposable.

Ozonolysis of the Olefinic Ether–Oxidative Procedure.—A solution of the desbromo ether (1.0 g., 0.003 mole) in 50 ml. of methylene chloride was ozonized at −70° until a blue color persisted. The solvent was removed under vacuum at room temperature. The oily residue was treated with 30 ml. of 20% sodium hydroxide and 20 ml. of 30% hydrogen peroxide solution. The reaction mixture was allowed to stand overnight at room temperature, after which it was heated on a water bath until oxygen evolution subsided. The reaction mixture was steam distilled and the steam distillate was extracted with ether. Evaporation of the ether gave 78 mg. (15%) of an oil which showed strong ultraviolet absorption at 238 mμ; infrared: 1660 and 1640 cm.$^{-1}$. A sample of this oil gave a crimson 2,4-dinitrophenylhydrazone, m.p. 205–207°. The ultraviolet spectrum of this derivative showed strong absorption at λ_{max}^{EtOH} 255 and 376 mμ.

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.47; H, 5.69; N, 17.56. Found: C, 56.2; H, 6.0; N, 17.8.

This material was identified as 1-acetyl-4-methylcyclohexene 2,4-dinitrophenylhydrazone by infrared and melting point comparison with an authentic sample.

2,4-Dinitrophenylhydrazone of 1-Acetyl-4-methylcyclohexene.—A solution of 0.200 g. (0.0012 mole) of isopulegol was ozonized in glacial acetic acid (50 ml.). The reaction mixture was stirred with zinc powder (2.0 g.) and 50 ml. of water for 2 hr. The usual work-up gave an oil, 0.194 g. (95%), which showed infrared absorption at 3400 and 1710 cm.$^{-1}$. This β-keto alcohol was treated with excess 2,4-dinitrophenylhydrazine reagent and heated to reflux for 15 min. The 2,4-dinitrophenylhydrazone of 1-acetyl-4-methylcyclohexene was isolated as a red crystalline solid, m.p. 205–207°, λ_{max}^{EtOH} 255 and 376 mμ.

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.47; H, 5.69; N, 17.56. Found: C, 56.66; H, 5.76; N, 18.00.

When the β-keto alcohol was refluxed with a 2% solution of *p*-toluenesulfonic acid, 1-acetyl-4-methylcyclohexene was obtained. The infrared spectrum of the crude ketone showed absorption at 1660 and 1640 cm.$^{-1}$. This material gave the same 2,4-dinitrophenylhydrazone as obtained in the direct treatment of the keto alcohol with refluxing 2,4-dinitrophenylhydrazine reagent.

The Acid-Catalyzed Condensation of Citronellal and Isopulegol.—An ether solution of citronellal (2.0 g., 0.013 mole) and isopulegol (2.0 g., 0.013 mole) was stirred overnight at room temperature. The infrared spectrum was measured immediately on mixing and again at the end of the stirring period. The second sample showed a new absorption at 1240 cm.$^{-1}$, a region characteristic of hemiacetals, and carbonyl absorption at 1710 cm.$^{-1}$. *p*-Toluenesulfonic acid (40 mg.) was added to this mixture and stirring was continued for 12 hr. The ether solution was washed with 10% sodium carbonate solution, sodium bisulfite solution, and water. Evaporation of the dried ether solution *in vacuo* gave 4.0 g. of an oil which was chromatographed on grade III Woelm alumina. Elution with petroleum ether (30–60°) afforded 2.0 g. (57%) of an oil. Vapor phase chromatography yielded the same olefinic ether obtained by debromination of the bromination products of citronellal. The same product could be obtained by treatment of citronellal alone with catalytic amounts of *p*-toluenesulfonic acid, whereas isopulegol alone did not give this product.

Dehydrogenation of the Olefinic Ether.—A mixture of 3.8 g. (0.013 mole) of the unsaturated ether and 30% palladium on charcoal (100 mg.) was heated under nitrogen at 240° for 36 hr. Subsequent runs were monitored by gas chromatography and it was shown that the reaction was essentially complete in 5–10 hr. Gas chromatographic assay of this product showed three major peaks. The retention times of these components were 16, 20.2, and 75 min. (Carbowax 20 M, 150°) in the ratio of 1:1:12. This mixture was fractionated carefully three times to yield an oil, b.p. 139–140° (0.75 mm.), $n^{25}D$ 1.4834, $[\alpha]^{25}D$ +3.86° (*c* 1.550, chloroform), which was identical with an authentic sample of (6*R*)-2-(*p*-tolyl)-6,10-dimethyl-4-undecanone. This material showed infrared absorption at 1712 (ketonic carbonyl), aromatic overtone bands at 1900, strong absorption at 1500 and 817 cm.$^{-1}$ for 1,4-disubstituted benzene. The ultraviolet spectrum of this material showed λ_{max}^{EtOH} 277 (ε 425) and 285 mμ (425). The n.m.r. spectrum exhibited a singlet at δ 6.9 (aromatic C-H), a singlet at 2.20 (3 protons) ascribed to the toluene-type methyl, and a complex quartet at 3.17 ascribed to the proton at C-2. The C-3 protons were seen as a doublet at δ 2.50, J = 7 c.p.s., and the protons at C-5 appeared as a doublet at δ 2.05, J = 7 c.p.s. The same ketone was obtained from dehydrogenation of the tetrahydro ether under the same conditions.

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.40; H, 11.16. Found: C, 83.72; H, 11.16.

Permanganate Oxidation of the Dehydrogenation Ketone.—A solution of the dehydrogenation ketone (1.2 g.) in acetone was treated with potassium permanganate (1.8 g.) and the mixture was heated at 40–50° with stirring for 4 hr. The carboxylic acids were isolated in the usual manner and esterified with methanol, 2,2-dimethoxypropane, and a trace of sulfuric acid. Vapor phase chromatography of the esters using a 5-ft. column of Carbowax 20-M on firebrick at 180° showed a peak at 3.8 min. identified as methyl dihydrocitronellate by comparing the retention time and infrared spectrum of the collected peak with those of an authentic sample.

(+)-Dihydrocitronellal.—A solution of 30.0 g. of citronellal (0.19 mole) in anhydrous ethyl acetate (300 ml.) and 0.5 g. of 10% palladium-on-carbon catalyst was hydrogenated with a Parr low-pressure hydrogenation apparatus. After 3 hr., the absorption of hydrogen ceased and the mixture was filtered. Evaporation of the solvent and fractional distillation yielded 23 g. (77%) of dihydrocitronellal, b.p. 83–88° (12 mm.), $n^{25}D$ 1.4301, $[\alpha]^{25}D$ +7.49° (*c* 1.868, chloroform); lit.[12] b.p. 81.5–82° (13 mm.), $n^{25}D$ 1.4273, $[\alpha]^{12}D$ +10.80°.

(+)-Dihydrocitronellic Acid.—The procedure of Ruhoff[13] was used to convert 37.0 g. (0.23 mole) of dihydrocitronellal to 29.0 g. (75%) of dihydrocitronellic acid, b.p. 139–145° (10 mm.), $n^{25}D$ 1.4314, d^{25} 0.875, $[\alpha]^{25}D$ +4.25°; lit.[14] b.p. 139–141° (1.5 mm.), n^{17} 0.880, $[\alpha]^{25}D$ +4.2°.

(2*R*)-2,6-Dimethylheptyl Bromide.—The method of Cristol and Firth[15] was used to convert dihydrocitronellic acid to 2,6-dimethylheptyl bromide. From 49.4 g. (0.288 mole) of dihydrocitronellic acid, there was obtained 16.3 g. (29%) of (2*R*)-2,6-dimethylheptyl bromide, b.p. 87–90° (11 mm.), $[\alpha]^{25}D$ −1.25° (*c* 2.38, chloroform); lit.[14] b.p. 82.5° (12 mm.), $[\alpha]^{25}D$ −0.4°.

3-(*p*-Tolyl)butyryl chloride was prepared by refluxing 5.0 g. (0.028 mole) of 3-(*p*-tolyl)butyric acid, prepared by the method of Wotiz, Matthews, and Greenfield,[16] with excess thionyl chloride for 3 hr. This method afforded 5.1 g. (95%) of 3-(*p*-tolyl)-butyryl chloride, b.p. 133–137 (16 mm.), lit.[17] b.p. 125° (9mm.)

(6*R*)-2-(*p*-Tolyl)-6,10-dimethyl-4-undecanone.—The Grignard reagent from (2*R*)-2,6-dimethylheptyl bromide (5.0 g., 0.024 mole) was prepared in anhydrous ether using 0.80 g. (0.025 g.-atom) of magnesium turnings and a small amount of 1,2-dibromoethane as an entraining agent. This reagent was converted to the corresponding cadmium reagent by the addition of anhydrous cadmium chloride (2.25 g., 0.012 mole) according to the method

(12) S. Sabetay and J. Bleger, *Bull. soc. chim.*, **43**, 839 (1928).

(13) J. R. Ruhoff, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 315.

(14) P. C. Jocelyn and N. Polgar, *J. Chem. Soc.*, 132 (1953).

(15) S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).

(16) J. H. Wotiz, J. S. Matthews, and H. Greenfield, *J. Am. Chem. Soc.*, **75**, 6342 (1953).

(17) H. Rupe and F. Wiederkehr, *Helv. Chim. Acta*, **7**, 654 (1924).

outlined by Cason and Prout.[18] A solution of 3-(*p*-tolyl)butyryl chloride (3.1 g., 0.015 mole) in benzene (30 ml.) was added dropwise to the cadmium reagent and resulting mixture was refluxed for 5 hr. The usual work-up followed by fractional distillation gave 1.4 g. (28%) of ketone, b.p. 151–155° (1.1 mm.), $n^{25}D$ 1.4843, $[\alpha]^{25}D$ +4.38° (*c* 1.5860, chloroform).

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.40; H, 11.16. Found: C, 83.45; H, 10.95.

The infrared spectrum, gas chromatogram, and n.m.r. spectrum of this ketone were found to be identical with those of the ketone obtained from dehydrogenation of the unsaturated ether.

(18) J. Cason and F. S. Prout, *J. Am. Chem. Soc.*, **66**, 46 (1944).

Friedel–Crafts Isomerization. VII.[1a] Aluminum Chloride Catalyzed Isomerization of the *t*-Butyltoluenes

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The isomerization of *o*-, *m*-, and *p*-*t*-butyltoluene with water-promoted aluminum chloride in excess of the *t*-butyltoluenes (heterogeneous system) and in nitromethane solution (homogenous system) was investigated. The isomer distributions were established using gas–liquid chromatography. The equilibrium isomer mixture starting from any of the isomers contains about 64% of the *m*- and 36% of the *p*-*t*-butyltoluene isomer.

Acid-catalyzed isomerization of the isomeric xylenes,[2] ethyltoluenes,[3] and cymenes[4] was investigated in considerable detail. Particularly the work of Allen established rate and equilibrium data of these three compound equilibrations.

The problem of aluminum chloride catalyzed isomerization of *t*-butyltoluenes was considered by Allen in the case of *p*-*t*-butyltoluene.[5]

This work was mainly concerned with the demonstration that intermolecular isomerization of neat *p*-*t*-butyltoluene is not possible and that the isomerization in aromatic hydrocarbon solvent (*o*-xylene), consequently, is entirely a dealkylation–alkylation process. It was concluded by Allen that the process is entirely intermolecular and involves only *t*-butylation of formed toluene, as *p*-*t*-butyltoluene can not be butylated.

Previous investigations have not considered the isomerization of *m*- and *o*-*t*-butyltoluene; neither was the equilibrium composition of the *t*-butyltoluenes established.

Results and Discussion

The isomerization of *o*-, *m*-, and *p*-*t*-butyltoluene with water-promoted aluminum chloride (heterogeneous system) and with aluminum chloride in nitromethane (homogeneous system) was investigated at room-temperature (~25°). The isomer distributions were established using gas–liquid chromatography.

Results of the rearrangement of *p*- and *m*-*t*-butyltoluene are presented in Tables I to IV. The equilibrium mixture contains about 63–64% *m*- and 36–37% *p*-*t*-butyltoluene with no *ortho* isomer present. Rearrangements in nitromethane solution are much slower than those of the neat compounds. Neat *p*-*t*-butyltoluene, for example, when isomerized with water-promoted aluminum chloride, reached equilibrium in about 60 min. (Table I), but over 20 hr. was needed in nitromethane solution (Table III). In the isomerization of the undiluted, neat isomers as well as in nitromethane solution, the main disproportionation products are toluene and di-*t*-butyltoluenes which are found in very roughly the same molecular amounts. The total of disproportionation products increased with time and at equilibrium amounted to about 30–50 mole % of total aromatic.

TABLE I

ISOMERIZATION OF *p*-*t*-BUTYLTOLUENE WITH WATER-PROMOTED ALUMINUM CHLORIDE (HETEROGENEOUS)

Time, min.	% *meta*	% *para*	% toluene	% 3,5-di-*t*-butyltoluene
1	14	86	6	5
2	21	79	8	7
4	37	63	12	8
6	44	56	13	9
10	54	46	13	10
15	61	39	15	11
25	60	40	17	12
40	59	41	17	11
60	63	37	18	12
90	62	38	22	15
150	64	36	20	15

TABLE II

ISOMERIZATION OF *m*-*t*-BUTYLTOLUENE WITH WATER-PROMOTED ALUMINUM CHLORIDE (HETEROGENEOUS)

Time, min.	% *meta*	% *para*	% *toluene*	% 3,5-di-*t*-butyltoluene
1	88	12	6	7
2	80	20	10	15
4	74	26	11	16
6	70	30	14	20
10	66	34	15	21
15	64	36	16	21
25	64	36	18	18
40	64	36	22	20
60	64	36	25	23
120	64	36	29	22
180	64	36	35	28

(1) (a) Part VI: *J. Org. Chem.*, **28**, 1912 (1963). (b) To whom correspondence should be addressed at The Dow Chemical Co., Eastern Research Laboratory, Framingham, Mass.

(2) R. H. Allen and L. D. Yats, *J. Am. Chem. Soc.*, **81**, 5289 (1959).

(3) R. H. Allen, L. D. Yats, and D. S. Erley, *ibid.*, **82**, 4853 (1960).

(4) R. H. Allen, T. Alfrey, Jr., and L. D. Yats, *ibid.*, **81**, 42 (1959).

(5) R. H. Allen, *ibid.*, **82**, 4856 (1960).

TABLE III

ISOMERIZATION OF *p*-*t*-BUTYLTOLUENE WITH ALUMINUM CHLORIDE IN NITROMETHANE SOLUTION

Time, hr.	% *meta*[a]	% *para*[a]	% toluene	% 3,5-di-*t*-butyltoluene
1	3	97	4	6
2	5	95	7	7
3	13	87	11	16
4	24	76	15	20
5	33	67	15	17
6	41	59	17	18
7	48	52	18	22
8	53	47	14	20
23	63	37	15	23
27	64	36	14	22
73	65	35	17	24
79	64	36	18	22
96	64	36	19	20

[a] Normalized.

TABLE IV

ISOMERIZATION OF *m*-*t*-BUTYLTOLUENE WITH ALUMINUM CHLORIDE IN NITROMETHANE SOLUTION

Time, hr.	% *meta*[a]	% *para*[a]	% toluene	% 3,5-di-*t*-butyltoluene
3	94	6	3	5
6	85	15	6	8
30	64	36	7	12
49	64	36	13	20
71	63	37	12	21
95	64	36	13	18
118	64	36	19	20

[a] Normalized.

There were always present varying amounts of further products of disproportionation (transalkylation), among which benzene, *t*-butylbenzene, and *p*-di-*t*-butylbenzene were identified. Benzene and *p*-di-*t*-butylbenzene obviously originate from the acid-catalyzed disproportionation of *t*-butylbenzene. The presence of *t*-butylbenzene indicates that under the present conditions the methyl group also displays some migratory ability. However, the relative amount of *t*-butylbenzene found at any time before equilibrium was reached was always below 5% of total aromatic present, with less than 1% benzene and 2% *p*-di-*t*-butylbenzene also present.

Allen found[5] that, in *o*-xylene solution at 0° employing *o*-xylene and *p*-*t*-butyltoluene in a ratio of 9:1 and total aromatic and aluminum chloride in a ratio of 100:1, the *t*-butyl group could be transferred to *o*-xylene without isomerizing *p*-*t*-butyltoluene. Transalkylation was orders of magnitude faster than isomerization.

Furthermore, treatment of *p*-*t*-butyltoluene with anhydrous HCl and 1 mole of aluminum chloride at 0° showed that it alkylates chloride ion more readily than it undergoes isomerization intramolecularly. The toluene formed then permits intermolecular isomerization. This led to the conclusion that *p*-*t*-butyltoluene isomerizes exclusively through the intermolecular mechanism.

It might be expected that in replacing *o*-xylene (or toluene) by benzene, as the added aromatic, a slowing down of transalkylation will be observed since benzene is a weaker nucleophile than either *o*-xylene or toluene. The primary products would be toluene and *t*-butylbenzene. Toluene could react in a further transalkylation reaction with both the σ-complexes of the starting isomer and the σ-complex of *t*-butylbenzene to form the products.

Taking *p*-*t*-butyltoluene and benzene in a molar ratio of 1:2 using 0.01 mole of aluminum chloride per mole of *t*-butyltoluene, equilibrium was reached in about 30 min. The products of transalkylation, toluene, and *t*-butylbenzene, were found to be present in a molar ratio of about 1:1 and at equilibrium accounted for 75–80 mole % of the original amount of *p*-*t*-butyltoluene used (Table V). Some *p*-di-*t*-butylbenzene and 1,3,5-di-*t*-butylbenzene was also detected. In the absence of benzene, using the same alkylbenzene–catalyst ratio, equilibrium was reached in about 60 min., with toluene at equilibrium accounting for about 10% of total aromatic. It appears, therefore, that, at room temperature in the presence of a small amount of catalyst under heterogeneous conditions, the rates of isomerization of *p*-*t*-butyltoluene with and without added benzene are, while still different, of comparable magnitude, in contrast to the reaction as carried out by Allen.

TABLE V

ISOMERIZATION OF *p*-*t*-BUTYLTOLUENE WITH WATER-PROMOTED ALUMINUM CHLORIDE IN THE PRESENCE OF BENZENE[a]

Time, min.	% *meta*[b]	% *para*[b]	% toluene	% *t*-butylbenzene	% *p*-di-*t*-butylbenzene
1	5	95	5	3	
2	6	94	8	6	
4	11	89	16	12	1
6	22	78	21	15	1
10	29	71	31	23	3
15	59	41	34	38	3
25	61	39	41	39	3
40	63	37	41	39	2
60	63	37	37	39	3

[a] 0.01 mole of aluminum chloride/mole of *p*-*t*-butyltoluene. [b] Normalized.

The absence of *o*-*t*-butyltoluene from the equilibrium mixture can be understood for steric reasons, and the results of the isomerization of the *meta* and *para* isomers show that the isomerization of the *ortho* isomer is an irreversible process.

As the isomerization of *o*-*t*-butyltoluene proved too fast for measurement under conditions where the isomerization of the *meta* and *para* isomers could easily be followed, the rearrangement was investigated in a more dilute solution containing 50 moles of nitromethane and 0.8 mole of aluminum chloride per mole of *o*-*t*-butyltoluene (Table VI). *o*-*t*-Butyltoluene disappeared in 13 min., forming a mixture of *meta* and *para* isomers. During isomerization, the ratio of the normalized per cent of *meta* and *para* isomer remained practically constant (2.5:3), leading to the kinetically controlled formation of 25% *meta* and 75% *para*. Subsequent isomerization to the final (thermodynamic) equilibrium of about 64% *meta* and 36% *para* is much slower. Equilibrium was reached in about 20 hr. Similar results were obtained at 0°.

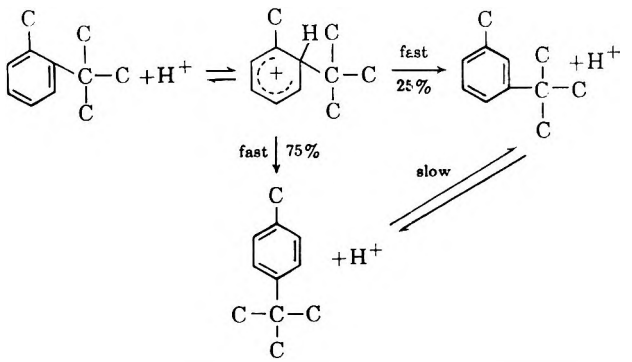
In the over-all isomerization of *o*-*t*-butyltoluene, the concentration of *para* isomer goes through a maximum. The mainly kinetically controlled part of the isomerization can be described by the following scheme.

TABLE VI

ISOMERIZATION OF *o*-*t*-BUTYLTOLUENE WITH ALUMINUM CHLORIDE IN NITROMETHANE SOLUTION

Time, min.	% *ortho*[a]	% *meta*[a]	% *para*[a]
2	96	Trace	4
3	69	8	23
4	58	11	31
5	41	16	43
6	26	20	54
7	14	23	63
8	10	24	66
9	5	25	70
10	2	25	73
11	1	28	71
12	1	24	75
13	Trace	25	75
15	0	25	75
75	0	27	73
135	0	30	70
210	0	36	64
255	0	40	60
315	0	45	55
375	0	48	52
495	0	56	44
21 hr.	0	61	39
30 hr.	0	61	39
57 hr.	0	62	38
71 hr.	0	63	37

[a] Normalized.



The situation is reminiscent of the isomerization of *o*-bromotoluene[6] where a fast *ortho–para* conversion was found indicating the possibility of complete detachment of the moving entity from the aromatic ring. A π-type intermediate might however also be postulated as it was demonstrated to play a role in the Friedel–Crafts *t*-butylation of toluene.[7] As the isomerization is fast, it is reasonable to suggest that the *t*-butyl group is not completely detached from the aromatic ring, but stays in interaction through a π-type of intermediate. Complete detachment with a real dealkylation–alkylation mechanism would be expected to be a much slower process, owing to the low concentration of the alkylable aromatic present in the system.

(6) G. A. Olah and M. W. Meyer, *J. Org. Chem.*, **27**, 3464 (1962).

(7) G. A. Olah, S. H. Flood, and M. E. Moffatt, *J. Am. Chem. Soc.*, **86**, 1060 (1964).

In the absence of rate data, no decision can be reached as to the contribution of the 1,2-shift mechanism to the isomerization of the undiluted isomers at low catalyst concentration. However, the formation of substantial amounts of *meta* isomer in the fast first stage of the isomerization seems to indicate that a concurrent 1,2-shift mechanism contributes to the reaction. Friedel–Crafts *t*-butylation of toluene under kinetic conditions generally yields only 6% of the *meta* isomer.[7]

Experimental

Starting Materials.—*p*-*t*-Butyltoluene used was Eastman White Label, containing 97% *para* and 3% *meta* isomer. *m*-*t*-Butyltoluene was American Petroleum Institute standard sample. *o*-*t*-Butyltoluene was obtained from Dr. B. S. Friedman, Sinclair Research Inc., Harvey, Ill., containing 95% *ortho* and 3% *para* isomer, and 2% unknown material.

General Process of Isomerization.—Reactions were carried out in stoppered flasks, in the case of heterogeneous reaction, with magnetic stirring. Unless indicated otherwise, 0.2 mole of aluminum chloride was used per mole of *t*-butyltoluene, and 1 ml. of water was added as a promoter. Isomerizations of *m*- and *p*-*t*-butyltoluene in nitromethane solution were carried out using equal weights of aromatic and solvent. Samples were drawn periodically, the reaction was stopped with water, and the organic material was extracted with ether. Dried ether extracts were analyzed by gas–liquid chromatography. Only a small quantity of *o*-*t*-butyltoluene was available. It was used in quantities of 50 mg. in any one run, and the reactions were carried out in capped vials. All isomerizations were carried out at ~52°.

In the tables the amounts of *o*-, *m*- and *p*-*t*-butyltoluene are given as normalized %. Per cent given for other materials represent mole % of total aromatic present.

Gas–Liquid Chromatographic Analysis.—The analyses were carried out on Perkin-Elmer Model 154-D and Model 226 vapor fractometers equipped with Golay-type capillary columns and hydrogen flame ionization detectors. Peak areas were directly obtained by the use of a high speed Infotronics Model CRS-1 integrator. Columns used were 150 ft. and were coated with polypropylene glycol (PPG) and *m*-bis(*m*-phenoxyphenoxy)-benzene (MBMA) modified with 20% Apiezon L grease, respectively. The polypropyleneglycol column was operated at 105° with a carrier He gas pressure of 10 p.s.i., whereas the MBMA column was operated at 100° with a carrier He gas pressure of 20 p.s.i. Characteristic retention times of *t*-butyltoluenes, toluene and di-*t*-butyltoluene observed are summarized in Table VII following.

TABLE VII

RETENTION TIMES OF TOLUENE, *t*-BUTYLTOLUENES, AND 3,5-DI-*t*-BUTYLTOLUENE[a]

Compound	PPG column	MBMA column
Toluene	9.1	4.3
o-*t*-Butyltoluene	33.2	24.1
m-*t*-Butyltoluene	25.4	18.6
p-*t*-Butyltoluene	26.7	17.7
3,5-di-*t*-Butyltoluene	76.1	43.6

[a] Values are given in minutes.

Acknowledgment.—We are grateful to Dr. B. S. Friedman, Sinclair Research, Inc., for a sample of *o*-*t*-butyltoluene.

Friedel–Crafts Isomerization. VIII.[1a] Aluminum Chloride Catalyzed Isomerization of the Diethylbenzenes

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The isomerization of *o*-, *m*-, and *p*-diethylbenzene with water-promoted aluminum chloride was investigated. The isomer distributions were established using gas–liquid chromatography. The equilibrium isomer mixture starting from any of the isomers contains about 3% *o*-, 69% *m*-, and 28% *p*-diethylbenzene. The isomerizations proceed by a predominant 1,2-shift mechanism, although they are accompanied by substantial disproportionation to ethylbenzene and triethylbenzene.

Despite the importance of diethylbenzenes as by-products in the ethylation of benzene and starting materials for the production of divinylbenzenes, no data have been published on the isomerization of diethylbenzenes or the equilibrium mixture of the isomers.

Results and Discussion

The isomerization of neat *o*-, *m*-, and *p*-diethylbenzene with water-promoted aluminum chloride was investigated and the isomer distribution at equilibrium was established using gas–liquid chromatography. In nitromethane solution the isomerization was too slow to be conveniently followed.

Results are presented in Table I to V. Starting with any one of the isomers, an equilibrium mixture containing about 3% *ortho*, 69% *meta*, and 28% *para* isomer was obtained. There are always formed products of disproportionation (transalkylation) among which chiefly are ethylbenzene and 1,3,5-triethylbenzene. The sum of ethylbenzene and 1,3,5-triethylbenzene at equilibrium amounts to about 40 mole % of total aromatic. Later peaks in the gas chromatogram indicated the presence of higher boiling materials. They never amounted, however, to more than about 5 mole % and no attempts at identification were made.

TABLE I

ISOMERIZATION OF *o*-DIETHYLBENZENE WITH WATER-PROMOTED ALUMINUM CHLORIDE

Time	% *ortho*[a]	% *meta*[a]	% *para*[a]	% ethylbenzene	% triethylbenzene
1 min.	92	7	1	2	
2	88	11	1	3	
4	86	13	1	5	
6	83	15	2	9	
10	82	16	2	6	
15	73	23	4	10	<1
25	35	57	8	19	3
40	16	63	21	21	6
1 hr.	8	65	27	21	11
2	4	65	31	20	22
3	3	67	30	19	20
5	3	68	29	16	21
6	3	69	28	15	21
48	3	69	28	19	16
100	3	71	26	17	22
140	2	69	29	15	19

[a] Normalized.

TABLE II

ISOMERIZATION OF *m*-DIETHYLBENZENE WITH WATER-PROMOTED ALUMINUM CHLORIDE

Time	% *ortho*[a]	% *meta*[a]	% *para*[a]	% ethylbenzene	% triethylbenzene
1 min.	0	100	0	0	0
6	Trace	>99	<1	4	1
15	<1	99	<1	9	6
25	<1	99	1	13	9
40	1	92	7	16	11
1 hr.	1	90	9	18	17
1.5	2	83	15	21	18
2	3	78	19	20	17
3	2	76	22	21	19
5	3	70	27	18	18
6	2	71	27	20	21
8	3	70	27	21	20
32	2	69	29	23	20
52	2	70	28	20	22
72	3	69	28	21	19

[a] Normalized.

TABLE III

ISOMERIZATION OF *p*-DIETHYLBENZENE WITH WATER-PROMOTED ALUMINUM CHLORIDE

Time	% *ortho*[a]	% *meta*[a]	% *para*[a]	% ethylbenzene	% triethylbenzene
1 min.	0	<1	99	1	
10	0	1	99	4	
15	<1	1	98	4	
25	<1	3	97	6	
40	<1	4	96	10	1
1 hr.	1	7	93	12	2
1.5	1	10	89	17	3
2	2	13	85	17	5
2.5	2	18	80	18	6
3.5	2	24	74	19	9
4.5	2	29	69	20	12
5.5	3	32	65	14	16
6.5	2	35	63	17	18
9	3	43	54	14	21
22	3	47	50	16	18
55	3	58	39	19	19
75	3	68	29	18	23
96	3	68	29	20	22

[a] Normalized.

Table I indicates that, in the isomerization of *o*-diethylbenzene at room temperature, the *para* isomer appears only after a significant amount of *meta* isomer has formed, indicating the 1,2-shift mechanism predominated. Starting with the *para* isomer (Table III), the data do not suggest a fast *para–ortho* conversion, and a 1,2-shift mechanism can again be assumed despite

(1) (a) Part VII: *J. Org. Chem.*, **29**, 2310 (1964). (b) To whom correspondence should be addressed at The Dow Chemical Co., Eastern Research Laboratory, Framingham, Mass.

TABLE IV

ISOMERIZATION OF *o*-DIETHYLBENZENE WITH WATER-PROMOTED ALUMINUM CHLORIDE IN THE PRESENCE OF BENZENE

Time	% *ortho*[a]	% *meta*[a]	% *para*[a]	% ethylbenzene	% triethylbenzene
1 min.	93	6	1	1	0
10	88	11	1	9	0
15	85	14	1	13	<1
25	74	24	2	23	<1
40	66	31	3	24	1
1 hr.	56	40	4	39	2
1.5	47	47	6	41	3
2	41	52	7	46	6
2.5	34	52	9	47	5
3	35	55	9	44	5
4	32	58	10	48	5
5	24	64	12	53	5
6	19	67	14	56	5
7	16	68	16	58	5
8	9	71	20	63	3
9	5	72	23	71	2
22	3	70	27	79	<1
25	3	70	27		<1
28	3	70	27	78	<1
46	3	69	28		

[a] Normalized.

TABLE V

ISOMERIZATION OF *o*-DIETHYLBENZENE WITH WATER-PROMOTED ALUMINUM CHLORIDE IN THE PRESENCE OF BENZENE AT 0°

Time min.	% *ortho*[a]	% *meta*[a]	% *para*[a]	% ethylbenzene
0	98.3	0.9	0.8	*b*
6	98	1.3	0.7	1
10	97.2	2.1	0.7	2
12	96.5	2.9	0.6	3
14	95.6	4.0	0.4	4
16	94.1	5.2	0.7	6
18	93.1	6.3	0.6	6
20	91.2	8.0	0.8	8
22	89.6	9.8	0.6	9
24	87.6	11.8	0.6	10.9
26	85.3	13.7	1.0	19
28	80.3	18.8	0.9	35
30	76.7	22.1	1.2	15

[a] Normalized. [b] Starting materials, see Experimental section.

the fact that the evidence is less convincing owing to the small amount of *ortho* isomer present at equilibrium.

Certain similarities can be expected to exist between the isomerization of the xylenes and the diethylbenzenes with aluminum chloride. The isomerization of xylenes with aluminum chloride was studied kinetically by Allen and Yats[2] as a three-compound equilibration involving six rate constants.

It was found that in toluene solution the rate constants of the *ortho–para* as well as those of the *para–ortho* conversion are equal to zero, indicating that the isomerization of xylenes takes place through a 1,2-shift mechanism exclusively. Similar conclusions were reached by Brown and Jungk.[3]

In the absence of rate constants for the isomerization of diethylbenzenes, a qualitative picture as to the extent to which the intra- and intermolecular mechanisms operate may be gained by carrying out the isomerization in added aromatic. In the presence of added aromatic, transalkylation products will be present in higher concentrations and, if the transalkylation mechanism contributes to the isomerization, an increase in rate should result.

Conversely, if the isomerization takes place predominantly by a 1,2-shift mechanism, the added aromatic would act as a diluent only and a decrease in rate might result.

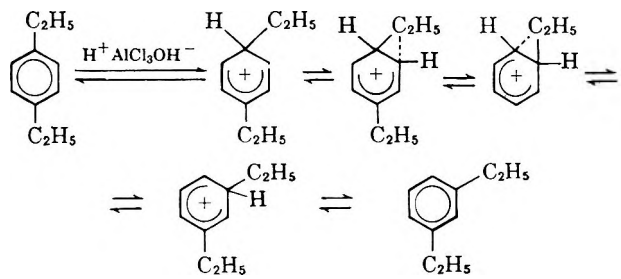
To test this possibility, the isomerization of *o*-diethylbenzene was carried out in the presence of an equal weight of benzene.

Equilibrium was reached in about 20 hr. (Table IV) compared with 3 hr. in the absence of benzene (Table I). The latter, therefore, acts largely as a diluent. Further evidence for the intramolecular rearrangement is presented in Table V, where *o*-diethylbenzene was isomerized in the presence of benzene at 0°. In 30 min., the normalized % *o*-diethylbenzene decreased to 77%, 22% *meta* isomer appeared, while the *para* isomer did not increase in that time.

The mechanism of the isomerization of the diethylbenzenes in accordance with the experimental data of time–composition studies can be best explained by a sequence of 1,2-shifts, as shown in Scheme I in the case of *p*-diethylbenzene.

SCHEME I

1,2-SHIFT MECHANISM OF THE ISOMERIZATION OF DIETHYLBENZENE



Disproportionation results *via* transalkylation of diethylbenzene by the intermediate σ-complex. Thus, a substantially bulky alkylating agent is involved which contributes, besides the possibility of consecutive isomerization, to the formation of 1,3,5-triethylbenzene.

Experimental

Materials.—Diethylbenzenes were obtained from the Aldrich Chemical Co., Milwaukee, Wis. *o*-Diethylbenzene contained 93% *ortho*, 6% *meta*, and 1% *para* isomer; *m*-diethylbenzene contained 99.9% *meta* isomer; and *p*-diethylbenzene contained 99.9% *para* isomer.

General Process of Isomerization.—Reactions were carried out in stoppered flasks with magnetic stirring. The amounts used were 0.2 mole of aluminum chloride/mole of diethylbenzene, and 1 ml. of water was added as a promoter. Samples were drawn periodically, the reaction was stopped with water, and the organic material was extracted with ether. The dried ether extracts were analyzed by gas–liquid chromatography. All the isomerizations were carried out, if not otherwise indicated, at ~25°.

Results are given in normalized % of *ortho*, *meta*, and *para* isomer. Numbers given for other materials represent mole % of total aromatic present.

o-Diethylbenzene used for the run described in Table V was purified using a preparative gas–liquid chromatograph (Wilkins

(2) H. Allen and L. D. Yats, *J. Am. Chem. Soc.*, **81**, 5289 (1959).
(3) H. C. Brown and J. Jungk, *ibid.*, **77**, 5579 (1955).

Aerograph) with a 20-ft. Versamid column at 165°. The purified product contained 98.3% *o*-, 0.9% *m*-, and 0.8% *p*-diethylbenzene.

Gas–Liquid Chromatographic Analysis.—Gas–liquid chromatographic analyses were carried out on a Perkin-Elmer Model 226 vapor fractometer equipped with a 150-ft. *m*-bis(*m*-phenoxyphenoxy)benzene-coated (modified by 20% Apiezon L grease) capillary column and hydrogen flame ionization detector. Column temperature was at 80° with He carrier gas pressure of 20 p.s.i. Peak areas were directly determined by the use of a high speed electronic Infotronics Model CRS-1 integrator. Characteristic retention times are shown in Table VI.

TABLE VI

RETENTION TIMES OF ETHYLBENZENE, DIETHYLBENZENES, AND 1,3,5-TRIETHYLBENZENE

Compound	Retention time, min.
Ethylbenzene	7.3
o-Diethylbenzene	23.9
m-Diethylbenzene	20.6
p-Diethylbenzene	21.8
1,3,5-Triethylbenzene	38.6[a]

[a] At 110°; He, 30 p.s.i.

Friedel–Crafts Isomerization. IX.[1a] Aluminum Chloride Catalyzed Isomerization of the Diisopropylbenzenes

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Contribution No. 113 from the Exploratory Research Laboratory, Dow Chemical of Canada, Limited, Sarnia, Ontario, Canada

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The isomerization of *o*-, *m*-, and *p*-diisopropylbenzene with water-promoted aluminum chloride was investigated. The isomer distributions were established by gas–liquid chromatography. The equilibrium isomer mixture starting from any of the isomers contains about 68% *m*- and 32% *p*-diisopropylbenzene, with no *ortho* isomer present. The isomerizations proceed by a predominant 1,2-shift mechanism, although they are accompanied by substantial disproportionation to cumene and 1,3,5-triisopropylbenzene.

The aluminum chloride catalyzed isomerization of cymenes was investigated by Allen, Alfrey, and Yats.[2] No investigation of the acid-catalyzed isomerization of diisopropylbenzenes was reported.

Results and Discussion

The isomerization of *o*-, *m*-, and *p*-diisopropylbenzene with water-promoted aluminum chloride was investigated and the isomer distribution at equilibrium was established using gas–liquid chromatography.

Results are presented in Tables I–III. The equilibrium mixture contains about 68% *m*- and 32% *p*-diisopropylbenzene, with no *ortho* isomer present. There were always formed products of disproportionation (transalkylation), among which cumene and 1,3,5-triisopropylbenzene are the main ones. Cumene and 1,3,5-triisopropylbenzene at equilibrium amounted to about 40 mole % of total aromatic present. Later peaks in the gas chromatograms indicated the presence of higher boiling materials. These materials were present in small amounts only, and no attempts were made at

TABLE I

ISOMERIZATION OF *p*-DIISOPROPYLBENZENE WITH WATER-PROMOTED ALUMINUM CHLORIDE

Time	% *ortho*	% *meta*	% *para*	% cumene	% 1,3,5-triisopropylbenzene
1 min.	0	1	99	<0.5	
15	0	4	96	2	
1 hr.	0	17	83	8	
1.5	0	42	58	15	14
4.5	0	59	41	18	18
5.5	0	64	36	18	19
6	0	66	34	18	21
65	0	65	35	26	25
71	0	66	34	22	26
88	0	64	36	20	27
95	0	67	33	22	23

TABLE II

ISOMERIZATION OF *m*-DIISOPROPYLBENZENE WITH WATER-PROMOTED ALUMINUM CHLORIDE

Time	% *ortho*	% *meta*	% *para*	% cumene	% triisopropylbenzene
1 min.	0	>99	<1	<1	
10	0	99	1	2	
15	0	97	3	5	2
25	0	89	11	9	4
40	0	79	21	13	9
1 hr.	0	74	26	19	13
2	0	69	31	25	19
3	0	67	33	24	22
60	0	66	34	25	27
65	0	65	35	23	21
71	0	66	34	19	25
88	0	67	33	21	24
95	0	66	34	22	20

TABLE III

ISOMERIZATION OF *o*-DIISOPROPYLBENZENE WITH WATER-PROMOTED ALUMINUM CHLORIDE IN THE PRESENCE OF BENZENE

Time, min.	% *ortho*[a]	% *meta*[a]	% *para*[a]	% cumene	% 1,3,5-triisopropylbenzene
1	92	8	Trace	7	~0.5
2	79	18	3	15	~0.5
4	57	37	6	24	~0.5
6	11	74	15	39	3.5
10	Trace	82	18	47	2.0
75	0	78	22	51	1.5
25	0	74	26	56	1.5
40	0	72	28	61	1.5
60	0	71	29	69	2.0
90	0	69	31	73	<1.0
120	0	69	31	78	<1.0
150	0	68	32	80	<1.0
180	0	68	32	81	<1.0

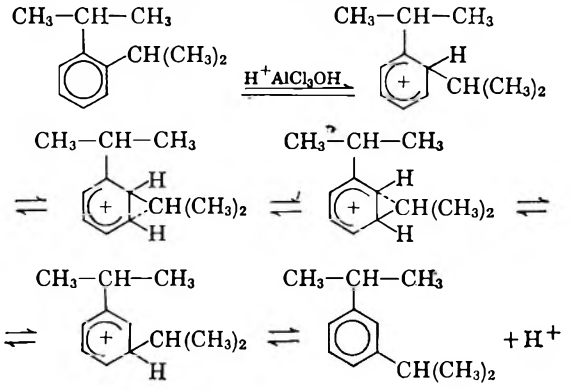
[a] Normalized.

(1) (a) Part VIII: *J. Org. Chem.*, **29**, 2313 (1964). (b) To whom correspondence should be addressed at The Dow Chemical Co., Eastern Research Laboratory, Framingham, Mass.

(2) R. H. Allen, T. Alfrey, Jr., and L. D. Yats, *J. Am. Chem. Soc.*, **81**, 42 (1959).

SCHEME I

1,2-SHIFT MECHANISM OF THE ISOMERIZATION OF DIISOPROPYLBENZENES



identification. The absence of *o*-diisopropylbenzene from the equilibrium mixture can be understood for steric reasons, as in the case of the previously investigated terphenyls[3] and *t*-butylbenzenes.[4] The isomerization of neat *o*-diisopropylbenzene was too fast to follow conveniently; therefore, the isomerization of *o*-diisopropylbenzene was investigated in the presence of an equal weight of benzene at 0° (see Table IV).

TABLE IV

ISOMERIZATION OF *o*-DIISOPROPYLBENZENE IN THE PRESENCE OF BENZENE AT 0° WITH WATER-PROMOTED ALUMINUM CHLORIDE

Time, min.	% *ortho*[a]	% *meta*[a]	% *para*[a]	% cumene
0.5	98	2	0	1
2.5	97	3	0	2
3	96	4	0	1
4	96	4	0	2
4.5	94	6	0	2
5	92	8	Trace	4
5.5	91	9	Trace	4
6	88	11	<1	6
6.5	85	14	<1	4
7	83	16	<1	7
7.5	79	20	<1	10
8	73	26	1	12
8.5	68	30	2	11
9	59	39	2	14
9.5	41	55	4	17

[a] Normalized.

Following the isomer distribution with time shows that a considerable amount of *meta* isomer forms before the *para* isomer shows any increase. It seems, therefore, that the diisopropylbenzenes isomerize with aluminum chloride under heterogeneous conditions predominantly by a 1,2-shift mechanism, as do the xylenes, diethylbenzenes,[1] terphenyls,[3] and fluorobiphenyls.[6] At the same time, the intramolecular isomerization is accompanied by substantial disproportionation to cumene and 1,3,5-triisopropylbenzene. Disproportion in all probability results through transalkylation of diisopropylbenzene by the intermediate σ-complex, a substantially bulky alkylating agent not capable of alkylation *ortho* to an isopropyl group and thus helping, besides consecutive isomerization, the preferential formation of 1,3,5-triisopropylbenzene.

Experimental

Starting Materials.—The isomeric diisopropylbenzenes were obtained from The Dow Chemical Company, Midland, Mich. *o*-Diisopropylbenzene contained 93% *ortho* isomer, 98% after purification by gas chromatography; *m*-diisopropylbenzene contained 98% *meta*, 1.5% *ortho*, and 0.5% *para* isomer; and *p*-diisopropylbenzene contained 99% *para* and 1% *meta* isomer.

General Process of Isomerizations.—Reactions were carried out in stoppered vessels with magnetic stirring. The amounts used were 0.2 mole of aluminum chloride/mole of diisopropylbenzenes; 1 ml. of water was added as a promoter. Samples were drawn periodically, the reaction was stopped with water, and the organic material was extracted with ether. The dried ether extracts were analyzed by gas–liquid chromatography. All isomerization were carried out, if not otherwise indicated, at ~25°.

Results are given in normalized % of *ortho*, *meta*, and *para* isomer. Numbers given for other materials represent mole % of total aromatic present.

Gas–Liquid Chromatographic Analysis.—Gas–liquid chromatographic analyses were carried out on Perkin-Elmer Model 154-D and Model 226 vapor fractometers equipped with Golay-type capillary columns and hydrogen flame ionization detectors. Peak areas were directly obtained by the use of a high speed electronic Infotronics Model CRS-1 integrator. Columns used were 150 ft. and coated with polypropylene glycol (PPG) and *m*-bis(*m*-phenoxyphenoxy)benzene (MBMA) modified with 20% Apiezeon L grease, respectively. The PPG column was operated at 105° with a He carrier gas pressure of 15 p.s.i. whereas the MBMA column was operated at 100° with a He carrier gas pressure of 20 p.s.i. Characteristic retention times are given in Table V.

TABLE V

RETENTION TIMES OF CUMENE, DIISOPROPYLBENZENES, AND 1,3,5-TRIISOPROPYLBENZENE[a]

Compound	PPG column	MBMA column
Cumene	9	6.7
o-Diisopropylbenzene	24.2	20.7
m-Diisopropylbenzene	21.5	18.1
p-Diisopropylbenzene	25.8	22.5
1,3,5-Triisopropylbenzene	49.7	45.5

[a] In minutes.

(3) G. A. Olah and M. W. Meyer, *J. Org. Chem.*, **27**, 3682 (1962).
(4) G. A. Olah, M. W. Meyer, and N. A. Overchuk, *ibid.*, **29**, 2310 (1964).
(5) R. H. Allen and L. D. Yats, *J. Am. Chem. Soc.*, **81**, 2589 (1959).
(6) G. A. Olah and M. W. Meyer, *J. Org. Chem.*, **28**, 1912 (1963).

Selective Friedel–Crafts Reactions. I. Boron Halide Catalyzed Haloalkylation of Benzene and Alkylbenzenes with Fluorohaloalkanes

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Contribution No. 102 from the Exploratory Research Laboratory, Dow Chemical of Canada, Limited, Sarnia, Ontario, Canada

Received August 9, 1963

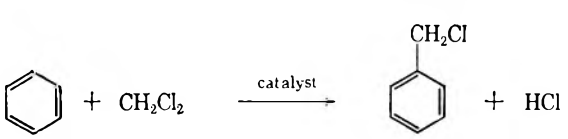
A general new haloalkylation method has been found in the boron halide catalyzed alkylation of benzene (and other aromatics) with fluorohaloalkanes. The C–F bond reacts preferentially over the C–Cl, C–Br, or C–I bonds, allowing the chloro-, bromo-, and iodoalkylations to proceed in high yield with a minimum of dialkylation. The order of reactivity of the boron trihalide catalysts is $BI_3 > BBr_3 > BCl_3 > BF_3$, whereas the reactivity of the carbon–halogen bonds in the investigated dihalides is C–F > C–Cl > C–Br > C–I.

Although the Friedel–Crafts reactions are some of the most versatile tools of organic chemistry, there are often serious limitations in their use. One of these is encountered in reactions where more than one reactive, functional group or atom is present. Such a group can interact with catalyst and lead to unwanted reactions. This lack of "selectivity" is well demonstrated in attempted alkylations with vinyl chloride or ethylene dichloride in the presence of aluminum chloride or related catalysts. No compound containing a chloroethyl or a vinyl group is obtained. Owing to the presence of two reactive functional groups (olefinic double bond and chlorine atom in one case and two chlorine atoms in the other), the reactions proceed rapidly past the point of initial haloalkylation and lead to mixtures derived from secondary alkylation.

Di- and polyhaloalkanes are well known and easily available alkylating agents. However, apart from a few exceptions, Friedel–Crafts alkylation involving these compounds does not stop at the primary haloalkylated product. Instead, polycondensation products are obtained, mainly because the haloalkylated substances formed in the first reaction step are more reactive than the starting polyhaloalkanes.

Many investigators have studied the reaction of chloroform with benzene in the presence of aluminum chloride, but it was Boeseken[2a] who first obtained a haloalkylated product from the reaction mixture. Boeseken found that diphenylmethane, triphenylmethane, and triphenylchloromethane are formed in the reaction. Benzene also reacts with carbon tetrachloride and $AlCl_3$.[2] The main product under ordinary conditions is dichlorodiphenylmethane (90%).

The Friedel–Crafts reaction of aromatics with methylene chloride proceeds with substitution of both chlorine atoms. No simple chloromethylation of aromatics with dichloromethane according to the reaction shown



has been achieved. Under the reaction conditions that have been used, the intermediately formed benzyl chloride reacts at once with a second molecule of benzene to form diphenylmethane. Weak Friedel–Crafts catalysts like $ZnCl_2$, $SnCl_4$, and BCl_3, which generally are useful in chloromethylations, do not effect alkylations with dihalomethanes.

In the aluminum chloride catalyzed reaction of benzene with 1,2-dichloroethane a small amount of ethylbenzene and triphenylethane is obtained.[3] Diphenylethane is, however, the main product.[4] With 1,2-dibromoethane and toluene in the presence of aluminum chloride, ditolylethane can be isolated. Similarly, mesitylene and 1,2-dibromoethane afford mesitylethane.[5]

No simple chloroethylation with 1,2-dichloroethane according to the equation

$$C_6H_6 + ClCH_2CH_2Cl \xrightarrow{AlCl_3} C_6H_5CH_2CH_2Cl + HCl$$

is possible under used conditions, as the initially formed (2-chloroethyl)benzene immediately reacts with a second molecule of benzene to form 1,2-diphenylethane.

1,2-Dichloropropane and benzene in the presence of aluminum chloride give 1,3-diphenylpropane.[4,6]

1,4-Dihaloalkanes preferentially afford cycloalkylation products through the intermediate formation of a (4-haloalkyl)arene. The latter by an intramolecular alkylation step yields the cyclocondensation product.[7]

Very few examples of haloalkylations with dihaloalkanes have been reported. When 1-chloro-3-bromopropane is reacted with benzene at 6–12° in the presence of $AlCl_3$, (3-bromopropyl)benzene[8] forms (60% yield), but at a higher temperature diphenylpropane is the product. Schmerling, *et al.*,[9a] have found that certain dihaloalkanes, in which one halogen atom is attached to a tertiary and the other halogen to a primary carbon atom, react with aromatic hydrocarbons in the presence of an aluminum chloride–nitroalkane catalyst to form (haloalkyl)arenes. Schmerling, *et al.*, have also found that 1,2-dichlorobutane reacts with benzene in the presence of aluminum chloride at 0–25° to form 1-chloro-2-phenylbutane.[9b]

Results and Discussion

In previous work we have reported the Friedel–Crafts alkylation of aromatics with alkyl fluorides in

(1) To whom correspondence should be addressed at The Dow Chemical Co., Eastern Research Laboratory, Framingham, Mass.

(2) (a) J. Boeseken, *Rec. trav. chim.*, **22**, 301 (1903); (b) H. Gomberg and J. R. Jickling, *J. Am. Chem. Soc.*, **37**, 2575 (1915).

(3) R. D. Silva, *Bull. soc. chim. France*, **36**, 24 (1881).

(4) R. D. Silva, *Compt. rend.*, **89**, 606 (1879).

(5) F. Wenzel and R. Kugel, *Monatsh.*, **35**, 953 (1914).

(6) R. D. Silva, *Jahresber. Fortschr. Chem.*, 379 (1879).

(7) H. A. Bruson and G. W. Kroeger, *J. Am. Chem. Soc.*, **62**, 36 (1940).

(8) I. Tsukervanik and K. Yatsimirskii, *J. Gen. Chem. USSR*, **10**, 1075 (1940).

(9) (a) L. Schmerling, R. W. Welch, and J. P. West, *J. Am. Chem. Soc.*, **78**, 5403 (1956); (b) L. Schmerling, R. W. Welch, and J. P. Lewis, *ibid.*, **79**, 2636 (1957).

TABLE I

BORON HALIDE CATALYZED ALKYLATION OF AROMATICS WITH ALKYL FLUORIDES

Alkyl fluoride	Catalyst	% yield of alkylate: C_6H_6	$C_6H_5CH_3$	1,2-$(CH_3)_2C_6H_4$	1,2,3-$(CH_3)_3C_6H_3$
CH_3F	BF_3	58	62		
C_2H_5F		77	81	83	79
n-C_3H_7F		80	77		
i-C_3H_7F		82	84	72	70
t-C_4H_9F		74	70	76	69
$C_6H_{11}F$		80	83		
CH_3F	BCl_3		60		
C_2H_5F		69	78	80	76
i-C_3H_7F		63	72	77	
t-C_4H_9F		60	73	75	
sec-C_4H_9F			68		
$C_6H_{11}F$			81		
CH_3F	BBr_3		54		
C_2H_5F			63		
i-C_3H_7F		72	79	66	70
t-C_4H_9F		65	76		
sec-C_4H_9F			71		
C_6H_{11}			89		
i-C_3H_7F	BI_3	60	64	69	
t-C_4H_9F		64	69	70	
$C_6H_{11}F$			90		

the presence of a BF_3 catalyst.[10] Extension of this investigation has now shown that alkyl fluorides, such as methyl, ethyl, isopropyl, *sec*-butyl, *t*-butyl, and cyclohexyl fluoride, are also able to alkylate aromatics in the presence of BCl_3, BBr_3, or BI_3 as the catalyst. Yields from 54–90% of alkylated product can be obtained The alkylation results are summarized in Table I.

As a rule, if alkyl chlorides,[11] bromides,[12] or iodides are used in boron trifluoride catalyzed reactions, no alkylation takes place. This is definitely true for primary alkyl halides. With secondary and tertiary halides, some alkylation was observed in the present work using BI_3 or BBr_3 as the catalyst. The yields, however, were negligible compared with alkylations using alkyl fluorides.

The observed difference between the reactivity of alkyl fluorides and the other alkyl halides towards boron halides has enabled us to carry out Friedel–Crafts haloalkylations with dihaloalkanes in which one of the halogen atoms is fluorine.

Fluorochloro-, fluorobromo- and fluoroiodoalkanes were found to be effective chloro-, bromo- and iodoalkylating agents in the Friedel–Crafts alkylations of benzene and alkylbenzenes in the presence of a boron halide catalyst.

$$ArH + F(CH_2)_nX \longrightarrow Ar(CH_2)_nX$$
$$n > 1;\ X = Cl, Br, I$$

Fluorohaloalkanes used in the boron halide catalyzed haloalkylations included 1-chloro-2-fluoroethane, 1-bromo-2-fluoroethane, 1-iodo-2-fluoroethane, 1-bromo-3-fluoropropane, 1-bromo-2-fluoropropane, 1-chloro-4-fluorobutane, 1-bromo-4-fluorobutane, and 1-bromo-3-fluorobutane. Data obtained are summarized in Table II.

Boron halides, other than the fluoride, also effect halogen exchange of the fluorohaloalkanes as shown.

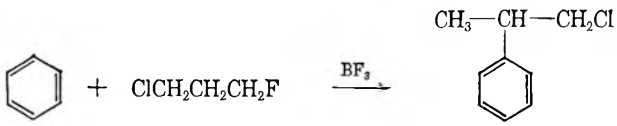
$$3F(CH_2)_nCl + BCl_3 \rightarrow 3Cl(CH_2)_nCl + BF_3$$

Thus, a decreased amount of fluorohaloalkane is available for haloalkylation. Consequently, yields obtained using boron fluoride as the catalyst are generally higher than those obtained with BCl_3, BBr_3, or BI_3, although longer reaction times are needed than in reactions involving other boron halide catalysts. 1-Chloro-2-fluoroethane chloroalkylates aromatics with good yields in the presence of BI_3 or BBr_3 as the catalyst (the strongest of the boron halides), but no alkylation was achieved when weaker BCl_3 or BF_3 were employed as catalysts.

The relative order of catalyst activity thus found is $BI_3 > BBr_3 > BCl_3 > BF_3$. This sequence is in agreement with the relative Lewis acid strengths of the boron halides determined by the measurement of the heats of formation of their complexes.[13–15]

The substantially higher reactivity of the C–F bond over that of the C–Cl, C–Br, and C–I bonds in Lewis acid catalyzed reactions of fluorohaloalkanes is at first sight unexpected in view of the carbon–halogen bond energies, which show increasing strength from iodine to fluorine. However, the base strength of halide reagents in Friedel–Crafts systems is a consequence of a number of contributing factors involving both the donor base and acceptor acid. Mentioned are only the more important: (a) electronegativity of the halogen ligands (which is in the order F > Cl > Br > I), (b) bond lengths and strengths in interaction with catalyst, and (c) steric effects. The high polarity of the C–F bond to be cleaved as well as the high bond energy of the B–F bond to be formed by the interaction with the Lewis halide catalyst, together with an obviously small steric hindrance, must contribute substantially to the high reactivity of the C–F bond.

It is interesting to note that, if BF_3 is used as the catalyst in reactions of straight-chain fluorohaloalkanes, almost complete isomerization of the alkyl chain occurs,



whereas, in the case of the other boron halide catalysts, the isomerized product amounts to only 5–15%. The isomerization observed with boron trifluoride is probably due to the cocatalytic effect of HF formed in the reaction, providing the strong conjugate acid $HF + BF_3$. No similar conjugate acid is known with hydrogen halides and the other boron trihalides. No attempt was made, however, in the present investigation to determine the isomer distribution of the fluoroalkylmethylbenzenes obtained.

No halomethylation was obtained when halofluoromethanes were used. The deactivating effect of more than one halogen atom attached to the same carbon, renders the C–F bond unreactive.

The reactions described above for the haloalkylation (except halomethylation) of arenes seem to have gen-

(10) G. A. Olah, S. J. Kuhn, and J. A. Olah, *J. Chem. Soc.*, 2174 (1957).
(11) W. Wohl and E. Wertyporoch, *Ber.*, **64**, 1357 (1931).
(12) R. L. Burwell, Jr. and S. Archer, *J. Am. Chem. Soc.*, **64**, 1032 (1942).
(13) A. W. Laubengeyer and D. S. Sears, *ibid.*, **67**, 164 (1945).
(14) H. C. Brown and R. R. Holmes, *ibid.*, **78**, 2173 (1956).
(15) N. N. Greenwood and B. G. Perkins, *J. Chem. Soc.*, 1141 (1960).

TABLE II

HALOALKYLATION OF BENZENE AND ALKYLBENZENES WITH FLUOROHALOALKANES

Aromatic hydrocarbon	Haloalkane	Catalyst	—Reaction conditions— Temp., °C.	Time, min.	Product	% yield
Benzene	1-Chloro-2-fluoroethane	BBr_3	−10	30	(2-Chloroethyl)benzene	50
Benzene	1-Chloro-2-fluoroethane	BI_3	−10	30	(2-Chloroethyl)benzene	55
Toluene	1-Chloro-2-fluoroethane	BBr_3	−20	30	(2-Chloroethyl)toluenes	60
Toluene	1-Chloro-2-fluoroethane	BI_3	−20	30	(2-Chloroethyl)toluenes	63
m-Xylene	1-Chloro-2-fluoroethane	BBr_3	−20	30	(2-Chloroethyl)-*m*-xylene	62
m-Xylene	1-Chloro-2-fluoroethane	BI_3	−20	30	(2-Chloroethyl)-*m*-xylene	65
Mesitylene	1-Chloro-2-fluoroethane	BBr_3	−20	30	(2-Chloroethyl)mesitylene	70
Benzene	1-Bromo-2-fluoroethane	BF_3	20	240	(2-Bromoethyl)benzene	94
Benzene	1-Bromo-2-fluoroethane	BCl_3	−10	30	(2-Bromoethyl)benzene	61
Benzene	1-Bromo-2-fluoroethane	BBr_3	−10	30	(2-Bromoethyl)benzene	60
Benzene	1-Bromo-2-fluoroethane	BI_3	−10	30	(2-Bromoethyl)benzene	57
Toluene	1-Bromo-2-fluoroethane	BF_3	20	240	(2-Bromoethyl)toluenes	92
m-Xylene	1-Bromo-2-fluoroethane	BF_3	20	240	(2-Bromoethyl)-*m*-xylene	90
Mesitylene	1-Bromo-2-fluoroethane	BF_3	20	240	(2-Bromoethyl)mesitylene	93
Benzene	1-Iodo-2-fluoroethane	BF_3	0	15	(2-Iodoethyl)benzene	63
Benzene	1-Chloro-3-fluoropropane	BF_3	0–10	60	(1-Methyl-2-chloroethyl)benzene	90
Benzene	1-Chloro-3-fluoropropane	BCl_3 or BBr_3	0–10	30	(3-Chloropropyl)benzene (90%) and (1-methyl-2-chloroethyl)benzene (10%)	63
Benzene	1-Chloro-2-fluoropropane	BF_3	−10–+10	60	(1-Methyl-2-chloroethyl)benzene	92
Benzene	1-Bromo-3-fluoropropane	BF_3	0–20	120	(1-Methyl-2-bromoethyl)benzene	89
Benzene	1-Bromo-3-fluoropropane	BCl_3 or BBr_3	−10	30	(3-Bromopropyl)benzene	60
Benzene	1-Bromo-2-fluoropropane	BF_3	−10–+10	60	(1-Methyl-3-bromoethyl)benzene	91
Benzene	1-Chloro-4-fluorobutane	BF_3	−10	30	(1-Methyl-3-chloropropyl)benzene	84
Benzene	1-Chloro-4-fluorobutane	BCl_3 or BBr_3	−10	30	(1-Methyl-3-chloropropyl)benzene (15–30%) and (4-chlorobutyl)-benzene (70–85%)	57
Benzene	1-Bromo-4-fluorobutane	BF_3	−10–+10	30	(1-Methyl-3-bromopropyl)benzene	80
Benzene	1-Bromo-4-fluorobutane	BCl_3 or BBr_3	0–10	60	(1-Methyl-3-bromopropyl)benzene (30%) and (4-bromobutyl)benzene (70%)	61
Benzene	1-Bromo-3-fluorobutane	BF_3	−10–+10	60	(1-Methyl-3-bromopropyl)benzene	81

eral and wider application and further uses for this method can be expected by employing different fluorohaloalkanes.

Catalysts other than boron halides, which are useful in effecting haloalkylations with fluorohaloalkanes, include titanium and stannic tetrafluorides and, to a certain degree, their tetrachlorides and tetrabromides.

An essential property of the catalyst is that it should effect haloalkylations, without causing either excessive secondary alkylation, which would lead to diarylalkanes or to halogen exchange taking place. The more reactive aluminum and ferric halides are less suited, because of their lack of selectivity with regard to secondary alkylations. They are useful in haloalkylations with longer chain α,ω-fluoroalkanes, where the reactivity of the (haloalkyl)arenes produced is not too high. It is also advantageous to use the catalysts in the form of less active complexes, such as those with nitromethane. The $AlCl_3 \cdot CH_3NO_2$ or $FeCl_3 \cdot CH_3NO_2$ complexes in nitromethane solution are considerably less active catalysts than the noncomplexed halides in hydrocarbon media. Side reactions, such as the subsequent formation of diarylalkanes, can thus be very much reduced.

Experimental

The fluorohaloalkanes used have been prepared by the halogen-exchange reaction of the corresponding dichloro- or dibromoalkanes with HgF_2.[16] 1-Fluoro-2-iodoethane was prepared by the interaction of 1-fluoro-2-bromoethane and NaI in acetone.[17] The boron halides were commercial products of the highest available purity. The reactions were carried out with care to exclude moisture.

A. Boron Halide Catalyzed Alkylation of Aromatics with Alkyl Fluoride.—Alkyl fluoride, 0.25 mole, was dissolved in 1.0 mole of aromatic hydrocarbon cooled to −20 to −30°. Then a solution of 0.08 mole of boron halide in 0.25 mole of aromatic hydrocarbon was added dropwise to the well-stirred reaction mixture. After the addition of the boron halide, the reaction mixture was stirred for 10 min. (having been allowed to warm to room temperature). The organic layer was washed three times with water, separated, dried over $CaCl_2$. The products were separated by fractional distillation and analyzed by gas–liquid chromatography and by their n.m.r. spectra. Yields of alkylated products obtained are summarized in Table I, based on alkyl fluorides used.

B. Haloalkylations in the Presence of BF_3 as Catalyst.—The corresponding fluorohaloalkane, 0.5 mole, was dissolved in 2.0 moles of aromatic hydrocarbon and BF_3 gas was introduced into the mixture in a slow stream for 15 min. Depending on the reactivity of the fluorohaloalkane, the temperature of the mixtures was kept between −20 and 30°. The mixture was then worked up as in A. (For details of experimental conditions and yields of haloalkylated products see Table II.)

C. Haloalkylations in the Presence of BCl_3, BBr_3, and BI_3 as Catalysts.—Fluorohaloalkane, 0.5 mole, was dissolved in 2.0 moles of aromatic hydrocarbon, and 0.166 mole of boron halide dissolved in 0.5 mole of aromatic was added dropwise to the well-

(16) A. L. Henne and T. Midgely, *J. Am. Chem. Soc.*, **58**, 884 (1936).
(17) J. Hine and R. G. Ghir, *J. Org. Chem.*, **23**, 1550 (1958).

stirred reaction mixture. The reaction started immediately. The temperature of the reaction mixture was kept between −20 and 30°. After the addition of the boron halide, the reaction mixture was processed as in A.

All the haloalkylated products were known from the literature and were identified by their physical data, infrared and n.m.r. spectra, halogen analyses, and gas–liquid chromatography, using a Perkin-Elmer Model 154-C vapor fractometer.

The Hydroboration of Trialkylated Ethylenes. The Configurations of Carvomenthol and Its Geometric Isomers

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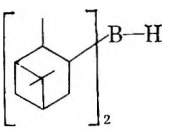
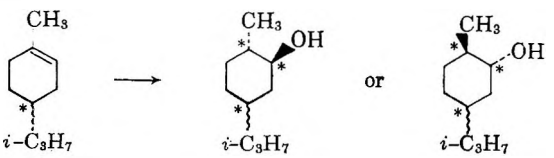
While *cis* dialkylated ethylenes undergo asymmetric, stereoselective hydroboration with optically active diisopinocampheylborane, trialkylated ethylenes undergo hydroboration stereoselectively but not asymmetrically. The results of the hydroboration of 1-*p*-menthene provide a direct chemical basis on which to make configurational assignments for the 2-*p*-menthanol geometric isomers.

A few years ago Brown and Zweifel[1] reported the conversion of *cis* dialkylated ethylenes to the corresponding optically active secondary alcohols *via* hydroboration, oxidation, and hydrolysis. The key step in the sequence involved the use of optically active diisopinocampheylborane (I) to achieve asymmetric, stereoselective hydroboration.



I

This paper reports the results of our attempts to prepare optically pure secondary alcohols from trialkylated ethylenes *via* the same reaction sequence. The objective was to prepare any one of the 2-*p*-menthanol optical isomers free of its enantiomer and diastereoisomers. Hydroboration of the readily available (+)-1-*p*-menthene[2] with I seemed to offer an efficient, direct route free of troublesome isomer separation problems. The over-all reaction (hydroboration, oxidation, and hydrolysis) was visualized as taking place as shown.



II III IV

Thus, (+)-1-*p*-menthene would provide the optical purity required in position 4 of the product, and efficient, asymmetric, stereoselective hydroboration would provide the optical purity required at positions 1 and 2 of the product.

Before experimenting with diisopinocampheylborane (I) of high optical purity, a more readily obtainable material, containing about 75% of one optical isomer and about 25% of the other, was used. The anticipated end product would be a mixture of diastereoisomers III and IV in the same ratio as that of the enantiomers in the hydroborating agent, *i.e.*, 3 to 1, or 1 to 3. Such a result would justify the hydroboration of II with less plentiful diisopinocampheylborane (I) of high optical purity to obtain a single 2-*p*-menthanol optical isomer. After the steps of hydroboration, oxidation, and hydrolysis, (−)-carvomenthol, $[\alpha]^{25}D$ −25.40°, and (+)-isocarvomenthol, $[\alpha]^{25}D$ +16.30°, were isolated in a *1.3 to 1.0 ratio*. Based on these specific rotations, both compounds are at least 90% optically pure.[3]

Hydroboration of the same olefin with diborane also gave carvomenthol and isocarvomenthol in the same ratio. Thus, the optical activity of the diisopinocampheylborane (I) played no special role in controlling the optical purity of positions 1 and 2 of the product, and asymmetric hydroboration did not take place.

In order to determine the structural features of 1-*p*-menthene which preclude asymmetric, stereoselective hydroboration, the hydroboration of two simple olefins, *cis*-2-butene and 3-methyl-2-butene, with the hydroborating agent I of high optical purity was studied. *cis*-2-Butene, the simplest *cis* dialkylated ethylene, has been converted with this hydroborating agent by Brown and Zweifel[1] to 2-butanol of 87% optical purity. In our hands, *cis*-2-butene yielded 2-butanol, $[\alpha]^{25}D$ −12.0°. Leroux and Lucas[4] report $[\alpha]^{25}D$ −13.51° for L(−)-2-butanol. Hence our product is about 89% optically pure and the experiment confirms the work of Brown and Zweifel.[1] On the other hand, 3-methyl-2-butene, the simplest trialkylated ethylene, yielded 3-methyl-2-butanol, $[\alpha]^{25}D$ +0.4°. Pickard and Kenyon[5] report $[\alpha]^{20}D$ +4.85° for (+)-3-methyl-2-butanol. Hence our product is only about 8% optically pure.

These experiments show that, while *cis* dialkylated ethylenes undergo asymmetric, stereoselective hydroboration with I, trialkylated ethylenes do not. Thus, branching on one carbon atom of an olefinic bond precludes asymmetric addition of optically active diisopinocampheylborane. It should be remembered that α-pinene (a trialkylated ethylene) reacts asymmetrically with diborane but does not react with diisopinocampheylborane.[1]

Zweifel, *et al.*,[6] have pointed out the importance of the asymmetric bulk of optically active diisopinocampheylborane in the asymmetric, stereoselective hydro-

(1) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 486 (1961).

(2) W. Newhall, *J. Org. Chem.*, **23**, 1274 (1958).

(3) J. L. Simonsen ["The Terpenes," Vol. 1, Cambridge University Press, Cambridge, 1947, p. 252] lists the following specific rotations at 16° for 2-*p*-menthanol isomers: *d*-carvomenthol, +26°; *l*-isocarvomenthol, −18°; *l*-neocarvomenthol, −42°; *l*-neoisocarvomenthol, −35°.

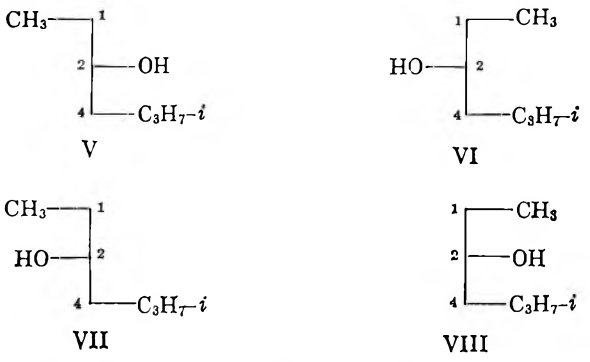
(4) P. J. Leroux and H. J. Lucas, *J. Am. Chem. Soc.*, **73**, 41 (1951).

(5) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **101**, 620 (1912).

(6) G. Zweifel, N. R. Ayyangar, and H. C. Brown, *J. Am. Chem. Soc.*, **84**, 4342 (1962).

boration of *cis* dialkylated ethylenes. Brown and Zweifel[1] have shown that trialkylboranes are produced in these reactions. Our experiments indicate that trialkylated ethylenes do not form trialkylboranes efficiently by reaction with I. A partial detachment from boron of the optically active alkyl groups originally attached to boron in the hydroborating agent has been observed instead. In hydroboration reactions in which the molar ratio of 1-*p*-menthene to diisopinocampheylborane was varied from 0.5 to 1.0, α-pinene was observed as a product. Moreover, the amount of α-pinene formed was directly proportional to the menthene–diisopinocampheylborane molar ratio. This increase in α-pinene concentration with increasing 1-*p*-menthene concentration suggests a displacement reaction in which 1-*p*-menthene effects a displacement of isopinocampheyl groups from boron. Zweifel, *et al.*,[7] attribute the formation of α-pinene in the reaction of the *trans* dialkylated ethylene, •*trans*-4-methyl-2-pentene, with diisopinocampheylborane to a disproportionation of the hydroborating agent prior to the hydroboration of the slowly reacting *trans* olefin. Whatever the actual reaction path of trialkylated ethylenes with bulky hydroborating agents may prove to be, it is different from that of *cis* dialkylated ethylenes.[6]

This work has made possible the assignments of geometric configuration for the 2-*p*-menthanol isomers. The four geometric configurations are shown schematically.



Read, *et al.*,[8] have shown that carvomenthol and neocarvomenthol are epimeric at position 2. They have offered strong indirect evidence that the methyl and isopropyl groups in these two isomers are in the *trans* configuration, and have assigned structure V to carvomenthol and structure VII to neocarvomenthol. Bose,[9] on the basis of conformational analysis, agrees with these assignments. Bose[9] seems to have made the only structural assignments to the remaining two isomers, having suggested that isocarvomenthol is VIII, and that neoisocarvomenthol is VI. These latter two assignments are the reverse of the assignments which shall be made in this paper on the basis of direct chemical evidence.

The work presented proves that both carvomenthol and isocarvomenthol contain methyl and hydroxyl groups in the *trans* configuration because in the preparation of these isomers *via* the hydroboration of 1-*p*-menthene, the hydrogen atoms at positions 1 and the hydroxyl groups at positions 2 are affixed in the *cis* configuration.[10] If, as argued by Read and others,[8] carvomenthol has methyl and isopropyl groups in the *trans* configuration, carvomenthol is indeed V and isocarvomenthol must be VI; and since carvomenthol and neocarvomenthol are epimeric at position 2, neocarvomenthol must be VII and neoisocarvomenthol, VIII.

Experimental

Materials.—A sample of (+)-α-pinene, $[\alpha]^{25}D$ +47.8°, was kindly furnished by Dr. Frances Greer of the Research Department, Naval Stores Division, Hercules Powder Co.

Hydroboration Reaction.—In the preparation of hydroborating agents and in the hydroboration reactions, established procedures were followed.[1,11]

Gas Chromatographic Analysis of Products.—Reaction mixtures were analyzed on a Perkin-Elmer Model 154C instrument with a thermistor-type detector and a 12 ft. × 0.25 in. o.d. stainless steel column packed with 25% poly-1,2-butanediol succinate on acid-washed Chromosorb W. Column temperature was 150° and helium flow rate was 65 ml./min.

Isolation of Reaction Products.—The butanols and the menthanols were isolated by gas chromatography using a Wilkens Autoprep Model A-700 instrument operated isothermally. For the butanols, a 20 ft. × 0.375 in. o.d. aluminum column packed with 25% Carbowax 20M on acid-washed silanized Chromosorb W was used. Repetitive automatic 50-μl. samples were chromatographed at 150° column temperature and 200 ml./min. helium flow rate. For the menthanols, a 55 ft. × 0.375 in. o.d. aluminum column packed with 25% poly(diethylene glycol) succinate on acid-washed, silanized Chromosorb W was used. Automatic repetitive on-column 200-μl. injections were made at 160° column temperature, 310° detector temperature, and 200 ml./min. helium flow rate.

Menthanol Derivatives.—3,5-Dinitrobenzoates were prepared in the usual manner and recrystallized from absolute ethanol. The derivative of (−)-carvomenthol had m.p. 104–104.5°; that of (+)-isocarvomenthol, m.p. 108.5–109°. Melting points were determined in capillary tubes and are uncorrected. Simonsen[3] lists m.p. 107, 111, 129, and 71–72°, respectively, for the 3,5-dinitrobenzoates of *d*-carvomenthol, *l*-isocarvomenthol, *l*-neocarvomenthol, and *l*-neoisocarvomenthol.

(7) G. Zweifel, N. R. Ayyangar, and H. C. Brown, *J. Am. Chem. Soc.*, **85**, 2072 (1963).

(8) (a) J. Read and R. G. Johnston, *J. Chem. Soc.*, 226 (1934); (b) R. G. Johnston and J. Read, *ibid.*, 1138 (1935); (c) N. L. McNiven and J. Read, *ibid.*, 159 (1952).

(9) A. K. Bose, *Experientia*, **8**, 458 (1952).

(10) H. C. Brown and G. Zweifel [*J. Am. Chem. Soc.*, **81**, 247 (1959)] have shown conclusively that hydroboration of 1-methylcycloalkenes with diborane leads to *trans*-2-methylcycloalkanols.

(11) H. C. Brown and B. C. Subba Rao, *ibid.*, **81**, 6428 (1959).

Solvents of Low Nucleophilicity. IV. Addition of Acetic, Formic, and Trifluoroacetic Acid to Branched Alkenes[1]

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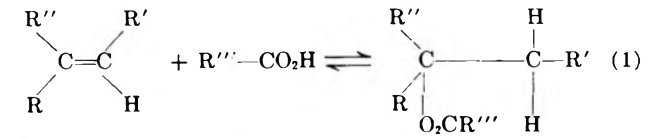
Received July 12, 1963

Approximate equilibrium constants for the addition of acetic, formic, and trifluoroacetic acid to 1-methylcycloalkenes and 2-methyl-2-butene were determined for 0.1 *M* solutions of alkene at 35°. The previously noted failure of formic and acetic acid to add to branched alkenes was due to the presence of alkene at equilibrium and, in the case of formic acid, to the low solubility of alkenes of higher molecular weight in the acid. The addition of trifluoroacetic acid to branched alkenes, followed by hydrolysis of the resulting tertiary trifluoroacetates, was found, in agreement with a previous report, to be an advantageous method for preparing tertiary alcohols. A basic fore column useful for gas chromatographic analysis of acidic solutions is described.

In previous work[3] trifluoroacetic acid was found to add to unbranched alkenes in Markovnikov fashion at moderate temperatures. The resulting secondary trifluoroacetates were stable under the reaction conditions. In the work reported here, the addition of trifluoroacetic, formic, and acetic acid to branched olefins to give the less stable tertiary esters was studied (eq. 1).



(1)

$K_1 = \frac{[\text{ester}]}{[\text{alkene}]}$ $K_{-1} = \frac{[\text{alkene}]}{[\text{ester}]}$ (excess acid assumed to be present)

Most of our work involved studies of the equilibrium constants for addition of the various acids to the branched olefins. Because of the rapidity with which some of the equilibria were established, the quantitative analysis of some of the equilibrium mixtures was difficult, but we obtained gas chromatographic results (*cf.* Table I) in which there is essentially the same variation of equilibrium constant with alkene structure in the three different solvents. Furthermore, the gas chromatographic equilibrium constants are supported in several instances by independent titrimetric and preparative experiments. Accordingly, we believe that our work provides a sound basis for the planning of further experiments involving the addition of carboxylic acids to branched alkenes.

Acetic Acid.—Equilibrations in acetic acid were carried out, starting from the olefins and also from the corresponding tertiary acetates, in the presence of *p*-toluenesulfonic acid monohydrate. After several days (which was required for complete equilibration in some cases at least) the amount of alkene present in 1-μl. aliquots was determined by gas chromatography.

Formic Acid.—In the case of the formic acid reactions at 35°, equilibrium was approached only from the olefin side, except for equilibrations involving the 2-methyl-2-butyl system. Equilibrium was complete after a few minutes as indicated by the constancy of olefin concentrations obtained by gas chromatography and by titrimetric analysis using iodine monobromide (Hanus solution).[4] Titrimetric analysis was of limited but still useful accuracy because of reaction of some of the tertiary esters with iodine monobromide. The gas chromatographic values are subject to a different possible error: the equilibria were established so rapidly that changes in the olefin concentration due to changes in temperature may have occurred in the syringe or injection port. This error was minimized by keeping the injection port near 35° as described in the Experimental section. The approximate agreement between the equilibrium constants determined by the two methods indicates that our results, although inexact, are free of gross errors.

Trifluoroacetic Acid.—Equilibrium in trifluoroacetic acid was established at a rate too fast to measure. Accordingly, the gas chromatographically measured olefin concentrations are perhaps subject to a greater error than in the case of the formic acid reactions. However, the important feature of the results, shown in Table I, is the relatively small concentration of alkene present at equilibrium in the case of all alkenes except 1-methylcyclooctene, for which addition is unfavorable because of steric interactions in the product. The favorable equilibrium constants suggested the possibility of preparing tertiary trifluoroacetates and (by hydrolysis) alcohols *via* addition of trifluoroacetic acid to branched alkenes. Further study showed that relatively unstable trifluoroacetate esters were readily obtained, provided distillations were carried out at room temperature. However, the preparation of tertiary alcohols by basic hydrolysis of the undistilled trifluoroacetate esters was found to be the preferable procedure when the alcohols were desired. Similar findings are reported in a patent[5] whose abstract appeared during the last phases of our work. Yields of alcohols obtained *via* addition of trifluoroacetic acid to the alkene are shown in Table II. As far as we know, the trifluoroacetic acid method for accomplishing the indirect hydration of branched alkenes is the only one which is reasonably free of difficulties due to unfavorable equilibrium constants or solubility problems.

(1) (a) Gas chromatographic equipment used in this study was purchased in part with funds from a National Science Foundation Grant (NSF G20904) and in part with a grant-in-aid from the Allied Chemical Corp. (b) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962; Organic Abstracts, p. 70 Q.

(2) This paper is based on the M.S. research of E. V. P. Tao.

(3) (a) P. E. Peterson, *J. Am. Chem. Soc.*, **82**, 5834 (1960); (b) P. E. Peterson and G. Allen, *J. Org. Chem.*, **27**, 1505 (1962); (c) P. E. Peterson and G. Allen, *J. Am. Chem. Soc.*, **85**, 3608 (1963).

(4) Titrimetric experiments indicated that 2-methyl-2-butene and 2-methyl-2-butyl formate approached equilibrium with half-lives of 1 to 2 min., but other compounds may have reacted even more rapidly.

(5) Esso Research and Engineering Co., German Patent 1,112,057 (Appl. 1954); *Chem. Abstr.*, **56**, 5834 (1962).

TABLE I

EQUILIBRIUM CONSTANTS FOR ADDITION OF ACIDS TO BRANCHED ALKENES AT 35°

	Acetic acid[a]		Formic acid			Trifluoroacetic acid	
Alkene	K	$\frac{1}{K_{-1}}$	K, gas chromatographic	K, titrimetric	Recovery, %[b]	K, gas chromatographic	Recovery, %[b]
2-Methyl-2-butene	0.78	0.78	>10	>10	97	88	96
1-Methylcyclopentene	0.12	0.14	1.7	1.3	86	9.7	87
1-Methylcyclohexene	0.32	0.19	6.0	6.9	88	61	92
1-Methylcycloheptene	0.06	0.02	1.5	0.3	83	1.7	92
1-Methylcyclooctene	0.0	0.0	0.05	0.03		0.2	

[a] K and K_{-1} are the gas chromatographically determined equilibrium constants for the reactions starting from alkene and from tertiary acetate, respectively. In the absence of experimental error, the values for K and $1/K_{-1}$ would be equal. See eq. 1 for the definition of K and the Experimental section for the method of measurement. [b] The "recovery" figures are calculated from the total quantity of volatile products eluted from the gas chromatograph, determined by comparison with standard samples. As indicated in the Experimental section, these figures serve as a check on the equilibration method and on the gas chromatographic procedure.

TABLE II

YIELDS OF ALCOHOLS

Alcohol	Yield, %
2-Methyl-2-butanol	42
1-Methylcyclopentanol	50
1-Methylcycloheptanol	43
1-Methylcyclooctanol[a]	

[a] The distillate was alkene, but the pot residue was 1-methylcyclooctanol as shown by the infrared spectrum, which was identical with that of an authentic sample prepared from cyclooctanone and methylmagnesium iodide.

Discussion

The tendency of the acids in our study to add to alkenes may be seen from Table I to parallel the order of acid strength, although the correlation may be accidental. Previously, Altschul[6] noted a similar correlation for equilibrations in acidified dioxane as shown by the equilibrium constants for the reaction of isobutene with benzoic acid (1.47) and *p*-nitrobenzoic acid (3.57). It may be noted (*cf.* eq. 1) that during the addition reaction an O–H bond is broken and an O–C bond is formed. If there is any generality to the correlation of acid strength with equilibrium constants, the correlation may be expressed by stating that the O–H bond strength is somewhat more strongly affected by electron availability in the acid moiety than is the O–C bond strength in the corresponding ester. The failure of acetic acid to add to various branched olefins at equilibrium might have been inferred from the previous success achieved in equilibrating exocyclic and endocyclic olefins in acetic acid–toluenesulfonic acid.[7] Our study differs from the previous one in that 0.1 *M* alkenes solutions were used (approximately 1%), instead of the 10% solutions used previously, and in the assurance that ester–alkene equilibration occurred, achieved by allowing the reaction to proceed to equilibrium starting both from the ester and the alkene.[8] It appears that esters cannot be prepared in good yield from branched olefins and acetic acid simply because of an unfavorable equilibrium constant.[9]

In the case of formic acid and trifluoroacetic acid the equilibrium tends to lie on the side of the ester for most of the branched alkenes. The solubility of 1-methylcycloheptene and 1-methylcyclooctene was so low in formic acid, however, that 0.1 *M* solutions could not be employed. Accordingly, the low yield of formates achieved by shaking branched alkenes with formic acid[10] is due to the fact that only a small portion of the alkene dissolves; the amount of ester in equilibrium with the dissolved alkene may represent only a small yield based on the total alkene present.

Inspection of Table I reveals that the equilibrium constants in the three acid solvents exhibit similar variations as a function of alkene structure. Furthermore, the variation is essentially that expected based on the assumption that eclipsed hydrogens and other steric interactions in the esters are the most important factors affecting the relative tendency of the various alkenes to react with acids (*cf.* ref. 7). Interestingly, such steric interactions should be approximately independent of acid structure since the $-CO_2-$ group, which perhaps accounts for most of the effect, is common to all carboxylic acids.

Interest in the stereochemistry of the addition of electrophilic reagents to alkenes has been revived by the finding of predominant *cis* addition in certain instances.[11] It is clear from the reversible character of the addition of acids to branched alkenes that stereochemical studies in these systems could be carried out only with exacting care to distinguish between rate and equilibrium controlled products. The latter type of product is clearly the one which will result from ordinary preparative procedures.

The results of our study likewise emphasize the need to consider possible reversible addition of acids to akenes in studies of the stereochemistry of cyclization reactions (*cf.* 12). If concerted stereospecific polyene ring closures occur, such reactions must proceed faster

(6) (a) R. Altschul, *J. Am. Chem. Soc.*, **68**, 2605 (1946); (b) *cf.* also "Methoden der Organischen Chemie," (Houben-Weyl), Vol. VIII, 4th Ed., E. Müller, Ed., George Thieme Publishers, Stuttgart, Germany, 1952, p. 535.

(7) A. C. Cope, D. Ambros, E. Ciganek, C. F. Howell, and Z. Jacura, *J. Am. Chem. Soc.*, **82**, 1750 (1960).

(8) Based on the gas chromatographically determined quantities of ester reported in ref. 7, equilibrium was probably achieved; the amounts of ester present indicate that the equilibrium constants for the addition were somewhat greater in the 10% solutions equilibrated at 25° than in our study.

(9) (a) Under strictly anhydrous conditions even more alkene might be present than we observed, since traces of water in our solvent probably caused the formation of some alcohol along with the acetates (*cf.* ref. 7). (b) The yields of 1-methylcyclohexene and 1-methylcyclohexyl acetate in the cleavage of bicyclo[4.1.0]heptane with acetic acid–toluenesulfonic acid probably represent the equilibrium mixture [R. T. LaLonde, *J. Org. Chem.*, **27**, 2276 (1962)]. (c) For an instance of possible equilibrium control in the addition of acetic acid to dienes see Glidden Co., British Patent 859,657 (Jan. 25, 1951); *Chem. Abstr.*, **55**, 17,507 (1961).

(10) C. Barkenbus, M. B. Naff, and K. E. Rapp, *J. Org. Chem.*, **19**, 1316 (1954).

(11) M. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.*, **85**, 2245, 2248, 3645 (1963).

(12) (a) G. Stork and A. W. Burgstahler, *ibid.*, **77**, 5068 (1955); (b) P. A. Stadtler, H. Eschenmoser, H. Schinz, and G. Stork, *Helv. Chim. Acta*, **40**, 2091 (1957).

than the competing addition–elimination reactions, since the intermediates in addition–elimination reactions could cyclize in a nonstereospecific manner. Concerted acid-catalyzed cyclizations, if they can be realized experimentally, will accordingly occur under milder conditions than addition–elimination reactions.

Experimental

Chemicals.—The 1-methylcycloalkenes were obtained from the Aldrich Chemical Co. with the exception of 1-methylcyclooctene which was prepared by dehydration of 1-methylcyclooctanol,[13] obtained from cyclooctanone and methylmagnesium iodide.[14] 2-Methyl-2-butene (99%) was obtained from Matheson Coleman and Bell. The preparation of the other 1-methylcycloalkanols *via* the corresponding trifluoroacetates is described in another portion of the Experimental section. Reagent grade acetic acid and toluenesulfonic acid monohydrate were used without further purification. Formic acid (98%) was dried according to the published method[15] by distilling through a 3-ft. jacketed column packed with glass helices. The center cut was stored in a closed three-neck flask with fittings for dispensing acid by pumping in air through a drying tube. Trifluoroacetic acid (Allied Chemical Co.) was distilled through a Vigreux column, and sodium trifluoroacetate (Columbia Organic Chemicals Co.) was added to give a 0.125 *M* solution. The various tertiary alcohols were acetylated by the published method[16] to give the tertiary acetates containing some unreacted tertiary alcohol, as shown by gas chromatography on a Dow-Corning 550 silicone oil column.

Equilibrations.—The amount of alkene or ester required to give a 0.1 *M* solution was weighed in a 10-ml. volumetric flask and diluted to the volume of the flask with one of the following solvents: acetic acid, 0.0145 *M* in toluenesulfonic acid monohydrate; formic acid; or trifluoroacetic acid, 0.125 *M* in sodium trifluoroacetate. In the case of 1-methylcycloheptene and 1-methylcyclooctene, 0.05 *M* solutions of alkene in formic acid were used because the solubility of these alkenes appeared to be insufficient to allow the preparation of 0.1 *M* solutions. The solutions were allowed to come to equilibrium in a constant temperature bath maintained at 35.0 ± 0.05° according to a Bureau of Standards calibrated thermometer. Equilibrium was established in a few days in the acetic acid solutions, in 15 min. or less in the formic acid solutions, and at a rate too fast to measure in the trifluoroacetic acid solution. Samples (2-ml. for titration or 1-μl. for gas chromatography) were withdrawn for analysis as described in one of the following sections.

Gas Chromatography.—An F. and M. Model 609 flame ionization gas chromatograph fitted with a disk integrator and a 6-ft. column of Haloport F coated with 5% dimer acid–silicone oil 550 was employed in the gas chromatographic analyses in the case of the acetic acid equilibrations. Originally it was hoped that this packing would allow each of the carboxylic acid solvents to be eluted as a relatively sharp peak which might not interfere with analysis of most of the esters and alkenes. In practice, acetic acid did give a well-shaped peak, but, at the high sensitivity setting used for the analysis of the dilute solutions employed in this study, the tail of the acetic acid peak prevented a rapid return to a level baseline. Accordingly, only the 2-methyl-2-butyl system could be analyzed for all components (alkene, ester, and alcohol), since the components in this case were eluted before the acetic acid peak. In the other analyses of acetic acid solutions, one of the earlier versions of a short basic fore column (described in detail in later portions of the Experimental) was used to absorb acetic acid. Only relatively low temperatures could be employed with this fore column. Accordingly, only the alkene peak was obtained. Equilibrium constants were based on the alkene concentrations determined by comparing the area of the alkene peak with that of a standard solution of the alkene in acetic acid.

Analyses of the formic and trifluoroacetic acid solutions were carried out with the aid of an improved basic fore column. The fore column was "S-shaped" and contained firebrick coated with potassium carbonate and Carbowax 20 M. (The preparation of the packing is described in the next section.) The 6–12-in. fore column was attached by tubing connectors to a 6-ft. Dow-Corning 550 silicone oil column. In a preliminary investigation 1-μl. samples of the appropriate compounds in the *t*-amyl series were injected, and the resulting peak areas (1000-16 sensitivity) were divided by the densities to give area counts per milligram. The basic fore column converted the formate partially to the corresponding alcohol, as shown by the presence of a well-shaped peak having the retention time of *t*-amyl alcohol, and converted the trifluoroacetate entirely to alcohol. It is possible that adsorbed water or water of hydration present in the fore column hydrolyzed the esters. Results of the calibration study (compound and counts per milligram) were as follows: *t*-amyl alcohol, 1300; *t*-amyl acetate, 1620; *t*-amyl trifluoroacetate, 779 (eluted as alcohol); *t*-amyl formate, 1250 (formate peak) plus 203 (alcohol peak). Based on these results, formates and alcohols give similar area counts per milligram. In subsequent determinations this relationship was assumed for the other (unavailable) alcohol–formate pairs.

In gas chromatographic analyses of equilibrations in formic and trifluoroacetic acid, 1-μl. samples of a freshly mixed solution of alkene in the acid at 35° were injected into the chromatograph. The injection port was maintained at approximately 35 ± 10° by means of Dry Ice cooling of the injection port when necessary. (Separate experiments indicated that equilibration occurred to some extent in the injection port; a high injection port temperature resulted in larger alkene peaks and a low injection port temperature gave smaller alkene peaks than those obtained at 35°. Presumably, no further reaction occurred after the samples evaporated in the injection port, as judged by the agreement of the gas chromatographic results with results determined by titration of formic acid equilibrations.) The improved fore column used in the formic and trifluoroacetic acid equilibrations permitted the observation of both alkene and alcohol peaks in the case of trifluoroacetic acid and of alkene, alcohol, and formate peaks in the case of formic acid, except for the reactions of 1-methylcyclooctene. Column bleeding and the resultant baseline instability made analysis for cycloheptanol at the equilibrium concentration (approximately 0.03 *M*) moderately difficult at 150°. Accordingly, measurements in the cyclooctyl system were limited to the alkene peak.

Gas chromatographic equilibrium constants reported in Table II were calculated from the observed values by these equations.

$$K_{F_3CCO_2H} = \frac{[\text{alcohol}]}{[\text{alkene}]}$$

$$K_{HCO_2H} = \frac{[\text{alcohol}] + [\text{formate}]}{[\text{alkene}]}$$

The quantities in brackets represent molar concentrations, determined by comparison of the peak area with that of a standard sample of similar concentration in acetic acid. As has been mentioned, it was assumed that alcohols and formates gave the same area response on a weight basis. The "recoveries" of products were calculated by dividing the sum of the molar concentrations of all products observed during the gas chromatographic analysis of an equilibrium mixture by the initially employed alkene concentration. These values, reported in Table I, show that polymerization was not appreciable during the time (less than 30 min.) required to chromatograph several duplicate samples. After several hours polymerization did occur in some experiments involving trifluoroacetic acid as shown by the clouding of the solutions due to separation of insoluble polymer. The yields reported are probably not significantly different from 100%, the discrepancies between 100% and the observed values indicating the accuracy limitations of the gas chromatographic method.

Basic Packing for Fore Column.—Anhydrous potassium carbonate (36 g.) was dissolved in 180 ml. of water, and the solution was added to 90 g. of 60–80-mesh firebrick. The water was removed by means of a rotary evaporator. A solution of Carbowax 20 M (12.6 g.) in 250 ml. of absolute ethanol was added, and the packing was again dried on a rotary evaporator. Gas chromatography using a dimer acid–silicone oil column showed that the packing in a 6- to 12-in. fore column effectively removed acetic acid. Packing emptied from a fore column after use showed a sharp division between the acidic and basic portions as shown by tests with wet pH paper. Omission of the Carbowax 20 M led to a basic packing which gave skewed peaks.

Preparation of Tertiary Alcohols.—In a representative example, 1-methylcyclohexene (19.2 g.) was dissolved in a cooled mixture of 40 ml. of trifluoroacetic acid and 2 ml. of 0.125 *M* sodium

(13) F. K. Signaigo and P. L. Cramer, *J. Am. Chem. Soc.*, **55**, 3526 (1933).
(14) H. C. Brown and M. Borkowski, *ibid.*, **74**, 1894 (1952).
(15) P. D. Bartlett, C. E. Dills, and H. G. Richey, Jr., *ibid.*, **82**, 5414 (1960).
(16) J. G. Traynham and O. S. Pascual, *J. Org. Chem.*, **21**, 1362 (1956).

trifluoroacetate in trifluoroacetic acid. (The sodium trifluoroacetate is not essential and was added only to ensure the absence of adventitious traces of strong acid which could cause polymerization.) Ether (50 ml.) and 40% potassium hydroxide (150 ml.) were added with continued cooling of the mixture. The erlenmeyer flask containing the two-phase mixture was stoppered, and the mixture was magnetically stirred at room temperature for 24 hr. The ether layer was separated, and the water layer was extracted with three additional small portions of ether. (Gas chromatography showed that only one extraction was necessary.) Drying the ether layers (magnesium sulfate) and distilling gave 14.2 g. (62%) of 1-methylcyclohexanol, b.p. 78–79° (41 mm.). The low yields may be associated with the difficulty of thoroughly drying ether solutions of alcohols.

Solvents of Low Nucleophilicity. V. Platinum-Catalyzed Hydrogenation of Ketones, Tertiary Alcohols and Esters, and Tosylates in Acidic Solvents Including Trifluoroacetic Acid[1a]

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The platinum-catalyzed hydrogenation of acyclic and cyclic ketones in trifluoroacetic acid at atmospheric pressure occurs at approximately three times the rate for comparable hydrogenations in acetic acid at relatively high ketone concentrations where rates in some instances are approximately zero order in ketone concentration. At lower ketone concentrations, the rates become strongly dependent upon the ketone concentration and structure. Under these conditions, hydrogenations in acetic acid are subject to acid catalysis, especially in the case of ketones for which adsorption on the catalyst surface may be attended by unfavorable steric interactions. Tertiary alcohols and esters are hydrogenated in trifluoroacetic acid, probably *via* a reversibly formed alkene intermediate. The rates of solvolysis of secondary tosylates in trifluoroacetic acid can be followed by hydrogenation of the alkene formed during the solvolysis.

Ketone Hydrogenations. Introduction.—The platinum-catalyzed hydrogenation of ketones has not been studied very extensively, although one attempt to systematize the existing information may be mentioned. Brewster advanced the hypothesis that the reduction of carbonyl groups in acidic media proceeds *via* transfer of a hydride ion from the catalyst surface to the carbonyl carbon of the protonated ketone, while reduction in neutral solvents proceeds *via* transfer of a hydride ion to the carbonyl oxygen.[2] The former process presumably leads to axial alcohols starting from 2-substituted cyclohexanones, while the latter gives predominantly equatorial alcohols. Since the experimental evidence upon which the proposal is based is quite limited, the Brewster hypothesis must be regarded primarily as a stimulus for further studies, particularly in regard to the effect of the solvent acidity upon ketone hydrogenations. Recently the hydrogenation of ketones and alkenes in a variety of solvents in the presence of a supported platinum catalyst was studied.[3] Ketones were found to be reduced slowly in certain neutral solvents (methanol, ethyl acetate), whereas alkenes were reduced readily in all solvents. These results, which will be discussed in a later section, also serve to emphasize the role of the solvent in ketone hydrogenations.

Ketone Hydrogenations. Results.—The present work involved hydrogenation of ketones in acetic and trifluoroacetic acid at atmospheric pressure in the presence of prereduced Adams catalyst (platinum oxide).[4] Our initial efforts were prompted by the observation that trifluoroacetic acid appeared to be a particularly effective solvent for ketone hydrogenations. In the course of optimizing the procedure used for hydrogenations in trifluoroacetic acid we recognized that hydrogenation rates were in some but not all instances dependent upon the ketone concentration.

Specifically in the case of cyclohexanones we found that at high ketone concentrations the rates of hydrogen uptake were approximately independent of the ketone concentration (zero order in ketone). The acyclic ketones appeared to approach zero-order behavior, although not so closely. Cyclic ketones other than cyclohexanones exhibited some decrease of the rate with time, indicative of a concentration dependence, but the fact that at higher ketone concentrations all ketones underwent hydrogenation at similar rates (*cf.* Table I) may indicate that initially a zero-order behavior was approached. A convenient (though not necessarily correct) interpretation of these observations is that at higher ketone concentrations all active sites of the catalyst are occupied by ketone molecules

TABLE I

RATES OF HYDROGENATION OF KETONES IN ACETIC AND TRIFLUOROACETIC ACID

Ketone	Hydrogen uptake, ml./min.[a] CF_3CO_2H	CH_3CO_2H
Cyclopentanone	6	2.4
Cyclohexanone	10.5	3.5
Cycloheptanone	4.7	2.5
Cyclooctanone	5.7	1.8
Acetone	10	1.5
4-Heptanone	10	1.8
2-Methylcyclohexanone	9.4	3.1

[a] Initial rates are given. Conditions: 25.0°, atmospheric pressure, 0.25 ml. of ketone, 5 ml. of solvent, 25 mg. of prereduced platinum oxide, 50-ml. erlenmeyer flask, magnetic stirrer.

(1) (a) Support from the General Chemical Division, Allied Chemical Corp. is gratefully acknowledged. (b) National Science Foundation undergraduate research participant.

(2) J. Brewster, *J. Am. Chem. Soc.*, **76**, 6361 (1954).

(3) E. Breitner, E. Roginski, and P. N. Rylander, *J. Org. Chem.*, **24**, 1855 (1959).

(4) The usual laboratory apparatus was refined by the use of a jacketed hydrogen buret and a jacketed hydrogenation flask maintained at 25.0° by circulating water and also by the inclusion of a sensitive butyl tartrate manometer which permitted precise adjustment of the mercury leveling bulb, following a coarse leveling of the mercury manometer. Another useful feature of the apparatus was a serum cap through which samples could be injected by means of a hypodermic syringe without interrupting the hydrogenation.

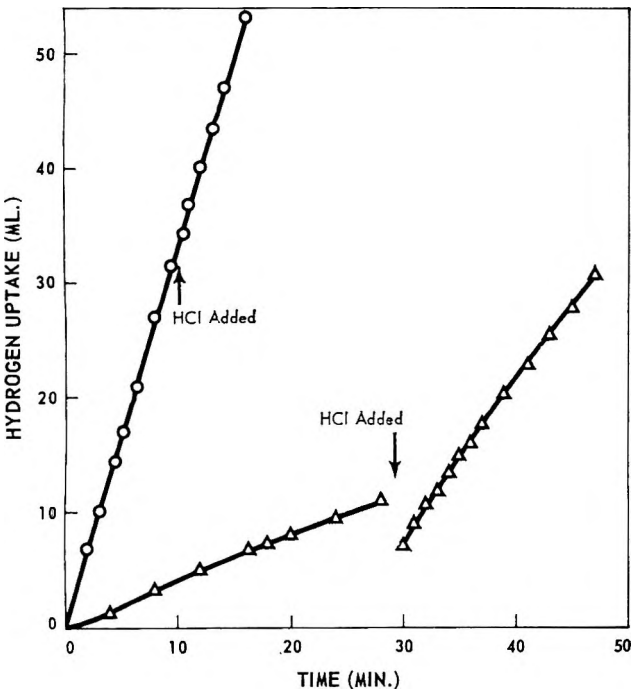


Fig. 1.—Effect of added hydrochloric acid upon hydrogenation of a relatively high concentration of cyclohexanone in acetic acid (O-O-O) and a relatively low concentration of cyclopentanone in acetic acid (Δ-Δ-Δ).

and that the rate of hydrogenation of adsorbed ketone is similar for all ketones.

At low ketone concentrations, rates of hydrogenation increased with increasing ketone concentration, especially for those ketones where unfavorable steric interactions would attend the conversion of the trigonal ketonic carbon atom to a tetrahedral carbon atom (cyclopentanone and cycloheptanone, compared to cyclohexanone). Furthermore, the rates of hydrogenation were found to be highly dependent upon the ketone structure at low ketone concentrations, as shown by the slow rate of hydrogenation of cyclopentanone and cycloheptanone, compared to cyclohexanone (*cf.* Table II). These results suggest that under these conditions the active sites of the catalyst are only partially occupied by ketone molecules, the least hindered ketone being adsorbed to the greatest extent.

TABLE II

RATES OF HYDROGENATION AT LOW KETONE CONCENTRATION BEFORE AND AFTER ADDITION OF CYCLOHEXANONE

Ketone	Solvent	Hydrogen uptake, ml./min.
Cyclopentanone	CF_3CO_2H	2.3 (6)
Cyclopentanone	CH_3CO_2H	0.4[a] (5)
Cycloheptanone	CH_3CO_2H	0.8[a] (3.0)

[a] Initial rates are given for hydrogenation of 0.25 ml. of ketone in 100 ml. of solvent in the presence of 50 mg. of prereduced platinum oxide. After approximately 30 min., 0.25 ml. of cyclohexanone was injected. The resulting increased rates are shown in parentheses. The conditions for the experiment involving trifluoroacetic acid were similar except that 0.5 ml. of cyclopentanone was used.

The concentration effects described in the preceding two paragraphs were inferred in part from the shape of plots of the rates of hydrogen uptake *vs.* time. Confirmatory evidence was obtained from experiments in which successive portions of ketone were injected during a hydrogenation, in order to increase the ketone concentration while holding other variables constant. In each case, the series of injections and rate measurements was completed before a large proportion of the ketone had been reduced. Accordingly, the total ketone concentration could be approximated as the sum of the concentrations due to the individual injections. The results, shown in Table III, indicate that at moderate concentrations of cyclohexanone in acetic acid the rate of hydrogenation is, in fact, unchanged upon injection of additional ketone. (It may be seen that this rate was reasonably reproducible in successive experiments. Accordingly, the difficulties sometimes involved in the comparison of successive experiments involving heterogeneous catalysis are not of major significance in our experiments.) Table III also illustrates the previously mentioned dependence of the rate of reduction of cyclopentanone upon the ketone concentration when the total ketone concentration is low. The observed rates are seen to be somewhat less than first order in ketone concentration.

TABLE III

EFFECT OF KETONE CONCENTRATION ON THE RATE OF HYDROGENATION[a]

Ketone	Total ketone added, ml.	Hydrogen uptake, ml./min.
Cyclohexanone[b]	0.25	1.66[c]
	0.50	1.75
	1.0	1.65 (3.21)[d]
Cyclopentanone[e]	0.25	0.10
	0.50	0.16
	1.0	0.24

[a] We are indebted to Mr. Robert Belloli, undergraduate research assistant, for performing these experiments. [b] Conditions: 25.0°, 5 ml. of acetic acid, 25 mg. of platinum oxide, 50-ml. erlenmeyer flask, constant-speed magnetic stirrer. [c] In separate experiments involving the same conditions, the rates were 1.53, 1.55, and 1.50 ml./min. [d] The higher rate (3.21 ml./min.) was obtained by replacement of the constant-speed stirrer with the variable-speed stirrer used to obtain the rates in Tables I and II. Increasing the stirring speed to approximately the maximum usable rate increased the rate of hydrogen uptake to the value shown, which is similar to that reported in Table I. [e] Conditions: 25.0°, 100 ml. of acetic acid, 50 mg. of platinum oxide, 500-ml. erlenmeyer flask, constant-speed magnetic stirrer.

Additional experiments were carried out to determine the effect of other variable factors in the hydrogenations. Rates of hydrogenation of 0.25 ml. of 2-methylcyclohexanone in trifluoroacetic acid in the presence of 25 mg. of prereduced platinum oxide were determined using 10-, 25-, and 50-ml. erlenmeyer flasks. The observed rates were 2.2, 6.7, and 7.6 ml./min., respectively. In view of these results, a 50-ml. flask was used for the experiments reported in Table I. It seems likely that the rate of hydrogen diffusion into the liquid layer was the limiting factor when the smallest flasks were used, although poor stirring and a resulting poor catalyst dispersal may have been a factor.

The effect of stirring speed is shown in Table III. The data in this table were obtained with a constant-speed magnetic stirrer, whereas all other experiments were performed with a variable-speed stirrer operating at a higher stirring rate (essentially the maximum usable rate). Slower hydrogen uptake was observed with the slower stirrer, although again it is not known

whether the rate of hydrogen diffusion or the efficiency of catalyst dispersal was the factor involved. It should be noted that the data in Table II, Table III, and Fig. 1 were obtained by successive injections of small amounts of ketone (or hydrochloric acid) without interruption of the hydrogenation. Effects due to variations in stirring speed, catalyst activity, and other possible variables were "cancelled out" by this procedure; accordingly, these experiments are considered to be particularly definitive.

In an experiment designed to evaluate the effect of solvent upon the catalyst prereduction step, samples of platinum oxide were prereduced in 5 ml. of acetic acid and 5 ml. of trifluoroacetic acid, respectively. Then 5-ml. of the other acid was added *via* a hypodermic syringe to give in both cases a solvent containing 50% by volume of each acid. Finally 0.25 ml. of 2-methylcyclohexanone was hydrogenated. In both instances the rate was 3.2 ml./min., compared with rates of 1.9 and 6.1 ml./min., for reactions in acetic and trifluoroacetic acid under the same conditions (25-ml. flask). From these results it appears that the activity of the catalyst is not dependent upon the solvent in which it is prereduced. Accordingly, the influence of solvent upon ketone hydrogenation rates, observed in our study, occurs during the ketone reduction step.

Rates of reduction were shown in one instance to be roughly proportional to the amount of catalyst used. Finally, the effect of added hydrochloric acid upon the rate of hydrogenation in acetic acid was evaluated in several instances in order to test predictions based on Brewster's mechanism. The results are described in the next section.

Ketone Hydrogenations. Discussion.—Based on the results reported in Table I, trifluoroacetic acid appears to be the best solvent yet found for the platinum-catalyzed hydrogenation of ketones. For preparative hydrogenations in trifluoroacetic acid, a relatively high concentration of ketone should be used in order to avoid the slow rates observed in dilute solutions where the rate becomes dependent upon the ketone concentration. It is interesting that an organic chemist desiring to hydrogenate a few milligrams of ketone would perhaps choose the least effective conditions—hydrogenation on a relatively large volume of acetic acid.

The alcohol product from the hydrogenation of 2-methylcyclohexanone in trifluoroacetic acid was largely esterified. However, the trifluoroacetate esters obtained from reduction in trifluoroacetic acid are more readily hydrolyzed to the alcohol[5] than the corresponding acetates which may be formed during hydrogenations in acetic acid.

Our observations concerning the dependence of ketone hydrogenation rates upon the ketone concentration have some interesting implications, provided the protonated ketone is assumed to be the species reduced, as postulated by Brewster.[2] Consider first the zero-order hydrogenation of moderate concentrations of cyclohexanone in acetic acid. If it is further postulated that all of the ketone-adsorbing catalyst sites are occupied by ketone molecules under these conditions, two alternatives are possible. Either the adsorbed ketone molecules are all protonated or else the unprotonated adsorbed ketone molecules are not reduced at an appreciable rate. In the latter case addition of a strong acid should increase the proportion of protonated ketone molecules and lead to an increase in the hydrogenation rate. The results of such an experiment are shown in Fig. 1. Injection of 0.05 ml. of 37% hydrochloric acid into 0.7 ml. of hydrogenating ketone in 10 ml. of acetic acid did not change the rate of hydrogenation measureably, although a qualitative test using *p*-nitroaniline as an indicator showed that the acidity of the solution was markedly increased. In view of the low concentration of protonated ketone in acetic acid, this experimental result is perhaps surprising since it seems to imply that the catalyst sites are in fact occupied exclusively by protonated ketone molecules. At this point one might be led to question the original hypotheses involving hydrogenation *via* the protonated ketone and complete occupancy of the catalyst sites. Fortunately an additional critical experiment was possible. Under conditions of approximate first-order hydrogenation at low ketone concentrations, the catalyst hydrogenation sites must, according to the interpretation under consideration, be only partially occupied by protonated ketone molecules in order to account for the concentration dependence. Increasing the solvent acidity should increase the hydrogenation rate, since the proportion of occupied sites would be increased. The results of an experiment designed to test this point are also shown in Fig. 1. In striking contrast to the result observed in the previously described zero-order hydrogenation, injection of 0.4 ml. of 37% hydrochloric acid into a hydrogenating solution of 0.3 ml. of cyclopentanone in 100 ml. of acetic acid resulted in a 4- to 5-fold rate increase. (The break in the plot of hydrogen uptake is attributed to evolution of hydrogen chloride.) Under these conditions (dilute solution of ketone), the rate of hydrogenation of cyclohexanone was also increased by added hydrochloric acid, but not very markedly. Accordingly, the effect of added strong acid is not upon the rate of dissolution of hydrogen (as suggested by a referee), since the previously observed large increase in rate would then have been expected also in the case of cyclohexanone.

It may be concluded that our results support the previously postulated hydrogenation mechanism[2] involving a protonated ketone as the intermediate, although alternative interpretations are possible. The effectiveness of added strong acids as a hydrogenation promoter (*cf.* papers cited in ref. 2) is seen to be intimately connected with the type of rate dependence observed, which in turn is a function of both the ketone concentration and the presumed steric requirements of the adsorbed ketone molecule. The picture which has emerged is a satisfying one, in that previous results are well accommodated, and a number of new hydrogenation studies involving stereochemical effects, competitive hydrogenations, added ionic materials, and quantitative acidity correlations are suggested.

It is noteworthy that in the previous study[3] of ketone hydrogenation in acetic acid, a slow rate of hydrogenation of cyclopentanone compared to cyclohexanone and a decrease of the cyclopentanone hydrogenation rate with time were observed, in analogy with our results. However, the decreasing rate observed in a number of instances in the earlier study was at-

(5) See ref. 8 for a simple hydrolysis procedure.

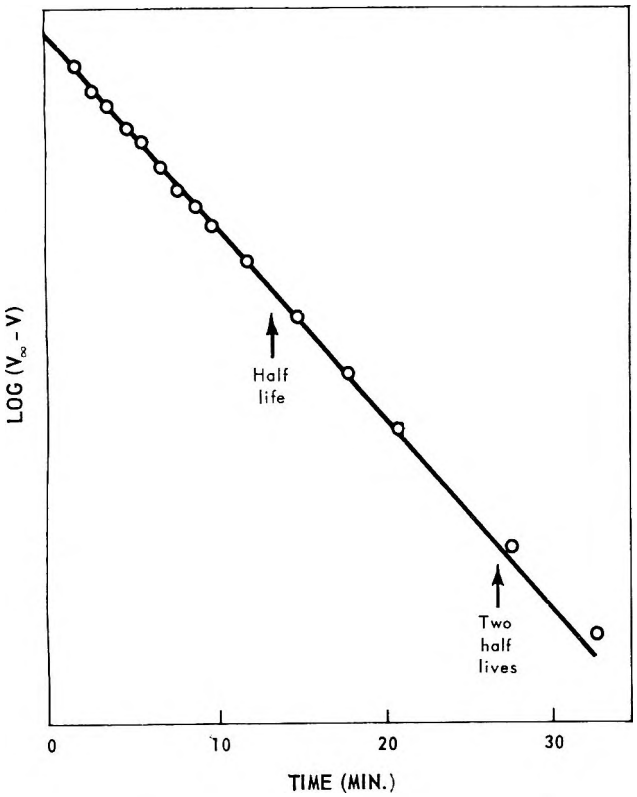


Fig. 2.—First-order rate plot for hydrogenation of 3-hexyl tosylate.

tributed to slow catalyst poisoning. In the present study catalyst poisoning was ruled out by the observation that the rate of hydrogen uptake during the hydrogenation of cyclopentanone and cycloheptanone at low concentration was increased greatly by the introduction of cyclohexanone (*cf.* Table II). Furthermore, injection of an additional quantity of the same ketone increased the hydrogenation rate, as expected if the rate is a function of the ketone concentrations. Interestingly, the previous study involved low ketone concentrations. Accordingly, the previous results can probably be reinterpreted as reflecting the limited tendency of some of the ketones to undergo adsorption on the catalyst, as postulated in our own study.

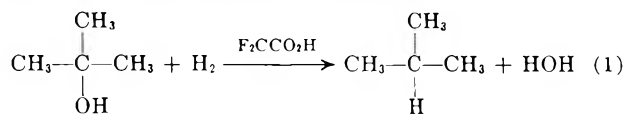
In solvents such as ethyl acetate and methanol, ketones were reduced quite slowly; furthermore, the rates seemed to be relatively independent of ketone structure.[3] It seems possible that these nucleophilic solvents compete effectively with ketone molecules for the catalyst sites. Since alkenes are reduced effectively in these solvents, indicating that carbon–carbon double bonds are effectively adsorbed in competition with solvent molecules, it is tempting to speculate that the enol form of the ketone is the species reduced in these solvents, at least in the case of the less readily adsorbed ketones.[6]

(6) Stereochemical implications need not be construed from such a mechanism since alkene hydrogenations are not always highly stereospecific; *cf.* (a) S. Siegel and G. V. Smith, *J. Am. Chem. Soc.*, **82**, 6082 (1960); (b) S. Siegel and B. Dmuchovsky, *ibid.*, **84**, 3132 (1962). Furthermore if a hydride ion (instead of a hydrogen atom) is transferred from the catalyst surface, the following intermediate postulated by Brewster could be obtained from the enol.

Finally it may be pointed out that the type of substrate concentration dependence observed in our studies appears to be paralleled in alkene reductions. Thus, various alkenes hydrogenate at similar zero-order rates in the presence of platinum, although competition studies show that the catalyst exhibits high selectivity toward less hindered alkenes.[6b] Our study suggests that the selectivity would lead to a dependence of the rate of hydrogenation upon the alkene structure at sufficiently low alkene concentrations. Indeed, a recent study[7] appears to provide an example of such behavior involving both the characteristic dependence of rate upon alkene structure and the concomitant dependence of rate upon alkene concentration, judged from the curved plots of hydrogen uptake *vs.* time. If our interpretation is correct, Brown and Brown's P-2 nickel boride catalyst adsorbs alkenes less strongly than platinum, facilitating the study of selectivity by the observation of hydrogenation rates rather than by the observation of products formed in competition experiments.

Hydrogenation of Tertiary Alcohols and Esters.—Studies in our laboratory had previously indicated that tertiary esters are in equilibrium with the corresponding alkenes in trifluoroacetic acid.[8] Although the concentration of olefin at equilibrium was small, it was thought that complete reaction of the ester might be obtained if the olefins were trapped by catalytic hydrogenation to the alkane. This was found to be the case; hydrogen uptake occurred according to a first-order rate law, as shown by the fact that a plot of log ($V_\infty - V$) *vs.* time was a straight line, where V_∞ is the volume of hydrogen taken up at seven or more half-lives and V is the volume at earlier times. First-order hydrogen uptake indicates either that all alkene molecules formed underwent hydrogenation or that a constant fraction of the alkene molecules formed were hydrogenated before they underwent addition of trifluoroacetic acid to reform the tertiary ester.

It was also shown that *t*-butyl alcohol was hydrogenated (eq. 1) with a half-life of 50 min. at 23°. In this experiment 4 ml. of trifluoroacetic acid, 25 mg. of platinum oxide, and 0.2 g. of alcohol were employed. Actually it is likely that the *t*-butyl alcohol was converted to the trifluoroacetate by a rapid carbonium ion reaction prior to hydrogenation (*cf.* ref. 8).



(1)

The reaction just described might have some value in accomplishing the selective removal of a tertiary oxygen from a polyfunctional molecule and in studying the rates of carbonium-ion reactions as a function of the structure of the substrate.

Hydrogenation of Solvolyzing Tosylates.—It was previously shown that the solvolysis of hexyl tosylates in trifluoroacetic acid gave predominantly hexenes which then underwent addition of trifluoroacetic acid at a moderate rate.[9] In the present study hexenes were found to undergo rapid platinum-catalyzed hydrogenation in trifluoroacetic acid. The rate of reaction was

(7) H. C. Brown and C. A. Brown, *ibid.*, **85**, 1003, 1005 (1963).
(8) P. E. Peterson and E. V. P. Tao, *J. Org. Chem.*, **29**, 2322 (1964).
(9) P. E. Peterson, *J. Am. Chem. Soc.*, **82**, 5834 (1960).

TABLE IV

RATES OF SOLVOLYSIS AND PER CENT ELIMINATION AT 25° FOR HEXYL TOSYLATES IN TRIFLUOROACETIC ACID[a]

Reactant	$k \times 10^4$ sec.$^{-1}$	Elimination, %
2-Hexyl tosylate	1.92 (2.2)	87.5 (83.5)
3-Hexyl tosylate	8.54 (7.5)	80.9 (84)

[a] Values were determined by hydrogenation; the values in parentheses were previously determined (gas chromatographic) from ref. 9.

constant (zero order in alkene concentration) until hydrogenation was almost complete, suggesting that, if the solvolysis of a tosylate in trifluoroacetic acid were carried out under hydrogenation conditions, the alkene product might be reduced essentially as fast as it was formed. Hydrogenation did, in fact, occur as expected provided freshly prepared tosylates were used. A first-order plot of the hydrogen uptake is shown in Fig. 2 for the hydrogenation of 3-hexyl tosylate. A single experiment yields both the rate constant for tosylate solvolysis and the per cent elimination. Results for the hexyl tosylates are given in Table IV. These reasonably precise results are in agreement with approximate values previously determined by a gas chromatographic method.

It is noteworthy that the sulfur-containing tosylates do not poison the catalyst. A slightly discolored tosylate which had stood at room temperature for several days did poison the catalyst, however, probably because traces of polymer were present as a result of an elimination reaction followed by acid-catalyzed polymerization. Traces of pyridine in the tosylate samples were also suspected of causing anomalous hydrogenation behavior.[10]

(10) P. E. Peterson and R. E. Kelly, Jr., unpublished work.

Terminal Benzoylation of Certain β-Keto Sulfones to Form Diketo Sulfones by Means of Sodium Hydride. Dibenzoylation of Dimethyl Sulfone[1]

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Benzoylations at the methyl groups of benzenesulfonylacetone and methyl phenacyl sulfone were effected with methyl benzoate by means of sodium hydride to form the corresponding terminal derivatives. The twofold terminal benzoylation of dimethyl sulfone to form the corresponding diketo sulfone was accomplished similarly. Sodium hydride appears not to produce initially the dicarbanion of the β-keto sulfone, which is the reactive intermediate in the analogous reaction employing potassium amide.

Benzoylation at the methyl group of benzenesulfonylacetone (I) has previously been accomplished through dicarbanion II, which was prepared by means of two molecular equivalents of potassium amide in liquid ammonia. Thus II condensed with methyl benzoate to form the terminal derivative III.[2]

$C_6H_5SO_2CH_2COCH_3$ (I) $\quad C_6H_5SO_2\bar{C}HCO\bar{C}H_2$ (II)

$C_6H_5SO_2CH_2COCH_2COC_6H_5$ (III)

Benzoylations at the methyl groups of keto sulfones I and IV have now been realized by means of sodium hydride in refluxing 1,2-dimethoxyethane (monoglyme) even though this reagent may not produce dicarbanions as intermediates.

$C_6H_5COCH_2SO_2CH_3$ (IV) $\quad C_6H_5COCH_2SO_2CH_2COC_6H_5$ (V)

The product from I was identified as methyl derivative III by comparison with an authentic sample prepared through II.[2] By analogy, the product from the benzoylation of IV was expected to be its methyl derivative V, not the possible methylene derivative VI or VII. In agreement with this, the product failed to give a positive enol test with ethanolic ferric chloride indicating that it was not VI, and its infrared spectrum was consistent with V, not VII. Its spectrum showed a band at 1690 cm.$^{-1}$ for the carbonyl group[3] and bands at 1330 and 1145 cm.$^{-1}$ for the sulfonyl group.[4] Had the product been the possible methylene derivatives VI, it should have given a positive enol test since VI is a β-diketone having an α-hydrogen; had the product been enol benzoate VII, it should have shown an infrared spectrum somewhat different from that observed.

$C_6H_5C(=O)CH(C_6H_5CO)SO_2CH_3$ (VI) $\quad C_6H_5C(OCOC_6H_5)=CHSO_2CH_3$ (VII)

Structure V was confirmed by its n.m.r. spectrum, which showed besides the aromatic proton resonance (intensity = 10) only a single peak located at τ 5.02 (intensity = 4), indicative of two identical methylene groups. No peak was observed in the region that may be ascribed to a terminal methyl group as in structure VI or VII. The n.m.r. spectrum of the parent compound IV showed peaks at τ 5.37 and 6.89, which were assigned to the methylene and methyl groups, respectively.[5]

The yields of diketo sulfones III and V from keto sulfones I and IV were 55 and 78%, respectively. The yield of III by the earlier potassium amide method was 60% based on the ester but the per cent conversion of I to III was only 30%.[2]

Since sodium hydride was found to effect the benzoylation of not only keto sulfone IV to form V but also of

(1) Supported by the National Institutes of Health.

(2) W. I. O'Sullivan, D. F. Tavares, and C. R. Hauser, *J. Am. Chem. Soc.*, **83**, 3453 (1961).

(3) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 134.

(4) See ref. 3, p. 360.

(5) H.-D. Becker and G. B. Russell, *J. Org. Chem.*, **28**, 1896 (1963).

TABLE I

BENZOYLATIONS OF KETO SULFONES AND DIMETHYL SULFONE WITH METHYL BENZOATE BY MEANS OF SODIUM HYDRIDE IN MONOGLYME

Starting sulfone	Mole	Ester, mole	NaH, mole	Monoglyme, ml.	Time, hr.	Product, number	M.p., °C.	Yield, %
Benzenesulfonylacetone	0.05	0.075	0.25	200	5	III	144–146[a]	low
	0.05	0.075	0.25	200	17	III	144–146[a]	55
Methyl phenacyl sulfone	0.02	0.03	0.08	100	5	V	124–125	78
Dimethyl sulfone	0.1	0.1	0.2	300	4	IV	107–108.5[b]	67
	0.2	0.2	0.4	300	9	IV	107–108.5[b]	83
Dimethyl sulfone	0.05	0.15	0.3	200	5	V	124–125	66
	0.1	0.25	0.5	200	19	V	124–125	87

[a] Lit.[2] m.p. 145–146.5°. [b] Lit. m.p. 106–107°[5] and 107.5–108°.[6]

TABLE II

HYDROGEN EVOLVED ON ADDITION OF KETO SULFONES TO SODIUM HYDRIDE IN MONOGLYME AND ON SUBSEQUENT ADDITION OF METHYL BENZOATE

	—H_2 from addition of keto sulfone—			—H_2 on subsequent addition of ester—			—Reaction period—	
Keto sulfone	Calcd. for 1 mol. equiv., ml.	Found, ml.	% of theory	Calcd. for 2 molecular equiv., ml.	Found, ml.	% of theory	Time,[a] hr.	Half-time,[b] min.
Benzenesulfonylacetone	1121	979	87	2242	2160	97	44	420
Methyl phenacyl sulfone	1121	1080	96	2242	2116	94	17	45

[a] This is the period of hydrogen evolution after ester had been added. [b] This period has been approximated from the periodic readings.

dimethyl sulfone to give IV, this reagent was expected to bring about twofold benzoylation of dimethyl sulfone to afford V in a single experiment. Dibenzoylation was realized to produce V in 87% yield (eq. 1); this method is recommended for the synthesis of V (see Table I).

$$CH_3SO_2CH_3 + 2C_6H_5COOCH_3 \xrightarrow[2\ \text{acid}]{1.\ \text{NaH (excess)}} V \qquad (1)$$

Dimethyl sulfone has previously been benzoylated with methyl benzoate by sodium in benzene[6] and by potassium *t*-butoxide in dimethyl sulfoxide[5] to form IV in yields of 44 and 90%, respectively. Our yield of IV with sodium hydride was 83%.

The terminal benzoylations of keto sulfones I and IV by sodium hydride are rather remarkable since excess of this reagent appears to effect ionization of only a methylene hydrogen of I or IV, not both a methylene and methyl hydrogen as observed with excess potassium amide.[2] Thus, only one molecular equivalent of hydrogen was evolved from I or IV in the presence of four molecular equivalents of sodium hydride in refluxing monoglyme. However, two more equivalents of hydrogen were evolved when methyl benzoate was subsequently added (see Table II). These results indicate that I or IV is converted initially only to its monocarbanion, for example, IV′, and that a methyl hydrogen of IV′ is gradually removed as a proton[7] as the condensation proceeds with the ester; a methylene hydrogen of the resulting monocarbanion of the condensation product is evidently ionized to form the dicarbanion of the product (Scheme A).

SCHEME A

$$IV \xrightarrow[\text{excess}]{NaH} C_6H_5\bar{C}HSO_2CH_3 + H_2$$

IV′

$$\downarrow C_6H_5COOCH_3$$

$$V \xleftarrow{\text{acid}} C_6H_5\bar{C}HSO_2\bar{C}HCOC_6H_5 + 2H_2$$

The fact that monocarbanion IV′ undergoes benzoylation more readily than monocarbanion I′a–b (see Tables I and II) is not surprising since, whereas the methyl hydrogens of IV′ are activated by the sulfone group, the methyl hydrogens of I′a–b should be deactivated somewhat by resonance form I′b.

$$\underset{\text{I′a}}{C_6H_5SO_2\bar{C}HCOCH_3} \longleftrightarrow \underset{\text{I′b}}{C_6H_5SO_2CH{=}\overset{O^-}{\overset{|}{C}}CH_3}$$

Experimental[8]

Benzoylations of Keto Sulfones and Dimethyl Sulfone.—To a stirred slurry of sodium hydride[9] in monoglyme at reflux, under dry nitrogen, was added a solution of the appropriate sulfone and methyl benzoate in 1,2-dimethoxyethane (monoglyme) over a period of *ca.* 20 min. Refluxing was continued for an appropriate period, and most of the solvent was then removed under reduced pressure. The resulting paste was cooled in an ice–water bath, and 150 ml. of ether was added. After stirring the mixture, 150 ml. of cold water was added; initially, the water was added dropwise until the excess sodium hydride was destroyed. The layers were separated. The ethereal layer was extracted with three 100-ml. portions of cold water, and these extracts were combined with the original aqueous layer. To the resulting aqueous solution was added 100 g. of crushed ice followed by 50 ml. of 12 *N* hydrochloric acid. The resulting precipitate was removed by filtration, washed with water, and recrystallized from 95% ethanol. The results are summarized in Table I.

Diketo sulfone III was identified by the mixture melting point method and by comparison of its infrared spectrum with that of an authentic sample of III prepared as described previously.[2]

(6) W. E. Truce and R. H. Knospe, *J. Am. Chem. Soc.*, **77**, 5063 (1955).

(7) The dicarbanion is not necessarily formed since removal of the proton might be accompanied by simultaneous condensation with the ester in a termolecular mechanism.

(8) Melting points were taken on a Thomas-Hoover "Uni-Melt" which had been calibrated with melting point standards. Infrared spectra were determined with a Perkin-Elmer Infracord, Model 137, by the potassium bromide pellet method. N.m.r. were determined with a Varian A-60 high resolution spectrometer. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(9) Sodium hydride was obtained from Metal Hydrides, Inc., as an approximately 50% dispersion in mineral oil and was used as received.

A sample of diketo sulfone V (m.p. 124–125°) was analyzed.

Anal. Calcd. for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67; S, 10.61. Found: C, 63.52; H, 4.76; S, 10.54.

Although diketo sulfone IV was known,[4,5] a sample of it (m.p. 107–108.5°) was analyzed.

Anal. Calcd. for $C_9H_{10}O_3S$: C, 54.52; H, 5.08; S, 16.18. Found: C, 54.32; H, 5.04; S, 15.97.

Measurement of Hydrogen Evolution.—In a 500-ml. two-necked flask equipped with a tightly fitting addition funnel (with a pressure equalizing side arm) and an efficient reflux condenser was placed 50 ml. of purified monoglyme and 0.25 mole of sodium hydride.[9] The upper end of the condenser was fitted with a gas take-off which was connected to an American Meter Company wet test meter filled with water. The system was flushed with dry nitrogen, and a solution of 0.05 mole of a β-keto sulfone in 100 ml. of monoglyme was placed in the addition funnel. The system was closed, and the flask was placed on the steam bath. When thermal equilibrium was established, an initial reading was taken on the test meter. The solution in the funnel was then added during 10–12 min. After the solution had been added, readings were taken periodically until the hydrogen evolution ceased. This required 30–40 min. The system was opened, and a solution of 0.075 mole of methyl benzoate in 50 ml. of monoglyme was placed in the addition funnel. The apparatus was closed, equilibrium was established, an initial reading was taken, and the ester solution was added during a period of 5–7 min. Readings were then taken periodically until gas evolution was no longer detectable. The values were corrected for temperature, pressure, and water vapor pressure. The results were summarized in Table II.

Diphenylcyclobutadienoquinone. III.[1] Attempted Synthesis of 1,2-Diphenylcyclobutadiene[2]

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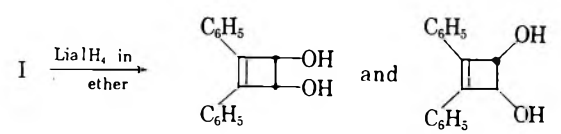
With the object of realizing a synthesis of 1,2-diphenylcyclobutadiene, further study has been made of diphenylcyclobutadienoquinone as a suitable precursor. Lithium aluminum hydride reduction of this diketone in ether gives mainly *cis*-1,2-diphenylcyclobutene-3,4-diol (23%) as well as some (3%) of the corresponding *trans*-diol. Reaction of the *cis*-diol with phosphorus tribromide affords smoothly (73%) *cis*-3,4-dibromo-1,2-diphenylcyclobutene. All efforts to prepare and isolate (or trap) the desired cyclobutadiene *via* debromination of the *cis*-dibromide with lithium amalgam, zinc dust, or nickel carbonyl have given only intractable polymeric organic products. Infrared studies of the *cis* and *trans* isomers of 1,2-diphenylcyclobutene-3,4-diol suggest that in the *cis*-1,2-diol there is intramolecular OH · · · π-electron hydrogen bonding with the cyclobutene double bond. Evidence that similar hydrogen bonding obtains for the *trans*-diol as well is not conclusive.

A considerable effort has been made in recent years by many investigators to prepare and isolate, or trap, *bona fide* cyclobutadienes. With diphenylcyclobutadienoquinone (I) readily available in the Cornell Laboratories,[1b] studies of this diketone as a precursor for the possible synthesis of 1,2-diphenylcyclobutadiene (II) were encouraged. The present report presents results of these investigations that supplement those presented earlier.[1b] In particular, this article describes efforts to realize the diene II *via* debromination of 3,4-dibromo-1,2-diphenylcyclobutene. Since this approach to a cyclobutadiene, *i.e.*, dehalogenation of 3,4-dihalo-1-cyclobutenes, has been widely and successfully used by many investigators to prepare cyclobutadienes *transiently*,[4] the method merited consideration for specific application to the 1,2-diphenyl-1-cyclobutene system.

Lithium aluminum hydride reduction of the dione I in solvent ether gave *cis*-1,2-diphenylcyclobutene-3,4-diol (III), m.p. 135.5–136.5°, in 23% yield, and the corresponding *trans*-diol IV (3%), as well as products from expected ring-opening side reactions.[5] Only the *trans*-diol IV (5.5%), m.p. 183–184.5°, was formed upon $LiAlH_4$ reduction in tetrahydrofuran.[7] The two diols showed the following ultraviolet absorption maxima: the *cis*-diol III at 227 (ε 16,500) and 292 mμ (12,000); the *trans*-diol IV at 228 (ε 15,800) and 292 mμ (12,500). Unlike *cis*-tetramethylcyclobutenediol,[8]



III (23%)
m.p. 135.5–136.5°

IV (3%)
m.p. 183–184.5°

(1) (a) For the preceding paper in this series, see A. T. Blomquist and P. R. Maitlis, *J. Am. Chem. Soc.*, **84**, 2329 (1962). (b) For papers closely related to this study, *i.e.*, "Diphenylcyclobutadienoquinone I and II," see A. T. Blomquist and E. A. LaLancette, *ibid.*, **83**, 1387 (1961), and **84**, 220 (1962).

(2) For preliminary portions of this study, see (a) Abstracts of Papers, the 135th National Meeting of the American Chemical Society, Boston, Mass., April, 1959, p. 54-O; (b) Abstracts of Papers, presented at the 16th National Organic Chemical Symposium of the American Chemical Society, Seattle, Wash., June 15–17, 1959, p. 11.

(3) Supported by funds from the Sage Fellowship, summer, 1957; Procter and Gamble Fellow, summer, 1958; American Cyanamid Fellow, summer, 1959; Allied Chemical and Dye Fellow, 1959–1960.

(4) R. Criegee and G. Schröder, *Ann.*, **623**, 1 (1959); M. Avram, E. Marica, and C. D. Nenitzescu, *Chem. Ber.*, **92**, 1088 (1959); M. Avram, E. Marica, J. Pogany, and C. D. Nenitzescu, *Angew. Chem.*, **71**, 626 (1959); C. D. Nenitzescu and M. Avram, *ibid.*, **72**, 39 (1960); M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **79**, 1701 (1957); C. D. Nenitzescu, M. Avram, and D. Dinu, *Chem. Ber.*, **90**, 2541 (1957); M. Avram, D. Dinu, and C. D. Nenitzescu, *Chem. Ind.* (London), 257 (1959); M. Avram, D. Dinu, G. Mateescu, and C. D. Nenitzescu, *Chem. Ber.*, **93**, 1789 (1960).

(5) Reaction of the compound I with aqueous methanolic sodium hydroxide results in cleavage of the cyclobutene ring to give, as isolable products, benzaldehyde and α-keto-βγ-diphenyl-γ-butyrolactone. Similarly, ring cleavage occurs in the reaction of the diketone I with *o*-phenylenediamine to produce 3-phenylacetyl-2-phenylquinoxaline.[1b] The reduction of the related phenylcyclobutadienoquinone with either sodium borohydride or lithium aluminum hydride is reported[6] to yield intractable products. See also M. P. Cava, D. R. Napier, and R. J. Pohl, *J. Am. Chem. Soc.*, **85**, 2076 (1963).

(6) J. D. Roberts, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **17**, 104 (1956).

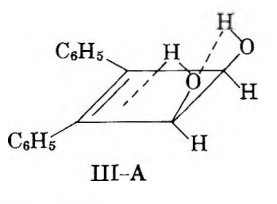
(7) Oily products obtained in the reductions were not characterized. However, both reductions afforded a solid crystalline accessory product of m.p. 196–197°, having λ_{max}^{KBr} 5.95 μ and indicative of the occurrence of ring opening.

(8) R. Criegee and G. Louis, *Chem. Ber.*, **90**, 417 (1957).

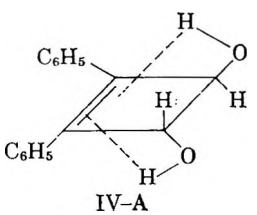
the *cis*-diol III failed to isomerize when treated with acid.

The above assignments of configuration to the two diols, III and IV, were made on the basis of infrared analysis[9] and reaction with potassium triacetyl osmate. The diol obtained as the major product in the $LiAlH_4$ reduction of the diketone I in ether showed infrared absorption maxima, in carbon tetrachloride solution, at 3602 and 3557 cm.$^{-1}$; correspondingly, the diol isolated from reduction in tetrahydrofuran (insoluble in carbon tetrachloride) has only a single absorption maximum (OH region) at 3603 cm.$^{-1}$ in chloroform solution. Since *cis*-1,2-diols inevitably show two infrared maxima in the OH region and *trans*-1,2-diols but one,[10] the diol of m.p. 135.5–136.5° is assigned the *cis* configuration III and the one of m.p. 183–184.5°, the *trans* configuration.

Information pertinent to the nature of OH hydrogen bonds in the *cis*- and *trans*-diols III and IV was also provided by infrared analysis after an appropriate correction had been made to adjust the observed OH band for the *trans*-diol IV, measured in chloroform, to a value which would have been observed had it been possible to examine the *trans*-diol in carbon tetrachloride solution. Since it has generally been found that alcohols show OH absorption bands some 10 to 21 cm.$^{-1}$ higher in carbon tetrachloride solution than in chloroform,[11] an approximate average of this increase, 15 cm.$^{-1}$, was added to the observed value for the *trans* isomer to give an "adjusted" value of 3618 cm.$^{-1}$ for the OH infrared band for the *trans*-diol IV. Further, saturated alcohols generally do not absorb[12] much below 3520 cm.$^{-1}$. Accordingly, the more intense, higher frequency band at 3602 cm.$^{-1}$ observed for the *cis*-diol III is considered not to arise from the presence of a "free OH" but is assigned to an OH· · ·π-electron hydrogen bond[13] that probably involves the cyclobutene double bond; and the band at 3557 cm.$^{-1}$ is assigned to the normal —O—H· · ·O— hydrogen bond present in *cis*-1,2-diols.[14] The need for applying a correction factor to the observed band of the *trans*-diol (chloroform solution) makes for some ambiguity with this isomer. It is probable that much weaker OH· · ·π-electron bonding obtains here owing to availability of two OH groups for such bonding. Based on the above, the *cis*- and *trans*-diols are represented by the formulations III-A and IV-A, respectively.



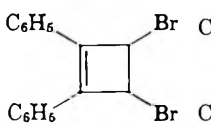
III-A



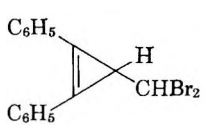
IV-A

In accord with the above infrared studies, the lower melting glycol III obtained from reduction of the diketone I in ether gave a positive test with potassium triacetyl osmate, indicative of a *cis*-1,2-diol, whereas the higher melting isomer formed by reduction in tetrahydrofuran gave a negative test with the reagent, indicative of a *trans*-1,2-diol.[8,15]

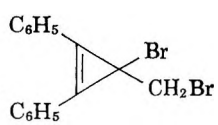
Reaction of the *cis*-diol III with phosphorus tribromide gave a white, crystalline dibromide (V, 73%), m.p. 115–116°, which had the molecular formula $C_{16}H_{12}Br_2$. Although this dibromide V gave an immediate precipitate with alcoholic silver nitrate, it failed to undergo solvolysis under conditions used successfully by Criegee and Louis[16] to effect solvolysis of 1,2,3,4-tetramethyl-1,2-dichlorocyclobutene; the starting dibromide V was recovered together with a small amount of an oil that presumably resulted from ring opening. Although this dibromide V was thought to be the desired 3,4-dibromo-1,2-diphenylcyclobutene (V), the cyclopropene derivatives VI and VII were also considered as other possible structures for the dibromide; the latter could arise *via* pinacol-type rearrangements. Since the n.m.r. spectrum[17] of the dibromide shows a singlet at 5.28 p.p.m. and a multiplet centered at 7.43 p.p.m. in a 1:5 ratio (relative to an internal tetramethylsilane standard at 60 Mc./sec.) the cyclopropene structure VI can be eliminated. Choice between the two remaining structures V and VII could be made on the basis of the ultraviolet spectrum observed in ethanolic solution for the dibromide at hand. This spectrum showed two principal maxima at 238 mμ (ϵ 26,000) and 303 (19,500) with a shoulder at 230 (23,300). This spectrum compares favorably with those observed for other closely related diphenylcyclobutene systems prepared at Cornell.[1b,18]



V



VI



VII

Although the ultraviolet spectrum of the dibromide in question shows a 10-mμ bathochromic shift relative to the cyclobutene diols III and IV, it is in even greater variance with that expected for a compound of structure VII. Breslow and co-workers[19] have found that 1,2-diphenylcyclopropenes absorb at about 306 and 320 mμ (ϵ *ca.* 28,000) and at 225 and 230 (*ca.* 20,000); *i.e.*, the strongest absorption is at higher wave lengths. In contrast, the reverse is true for 1,2-diphenylcyclobutene systems. In addition, the spectra of diphenylcyclopropenes show more fine structure than diphenylcyclobutenes. All of the foregoing suggests that the dibromide in question is in fact V and not VII. Finally, if the structure VII were the correct structure of the "di-

(9) Through the agency of Dr. E. J. Moriconi we are indebted to Dr. Paul von R. Schleyer for the infrared studies which were made with a Perkin-Elmer Model 21 spectrometer equipped with a lithium fluoride prism.

(10) F. A. Smith and E. C. Creity, *J. Res. Natl. Bur. Std.*, **46**, 145 (1951); L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952); **76**, 4323 (1954); **80**, 5950 (1958).

(11) J. J. Fox and A. E. Martin, *Proc. Roy. Soc.* (London), **A162**, 419 (1937); A. V. Stuart, *J. Chem. Phys.*, **21**, 1115 (1953); A. R. H. Cole and A. J. Michell, *J. Chem. Soc.*, 2005 (1959).

(12) P. von R. Schleyer, private communication; see P. von R. Schleyer, D. S. Trifan, and R. Bacskai, *J. Am. Chem. Soc.*, **80**, 6691 (1958).

(13) For other examples, see A. W. Baker and A. T. Shulgin, *ibid.*, **80**, 5358 (1958); **81**, 4524 (1959).

(14) For the interpretation of results obtained from similar systems, see E. J. Moriconi, W. T. O'Connor, L. P. Kuhn, E. A. Keneally, and F. T. Wallenberger, *ibid.*, **81**, 6475 (1959).

(15) R. Criegee, B. Marchand, and H. Wannowius, *Ann.*, **550**, 99 (1942).

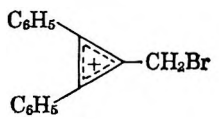
(16) The conditions used were those described by Criegee and Louis to effect readily the solvolysis of *cis*-3,4-dichloro-1,2,3,4-tetramethylcyclobutene to the corresponding *cis*-diol (ref. 8).

(17) The spectrum was determined by Varian Associates, Palo Alto, Calif., using a deuteriochloroform solution.

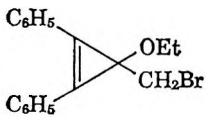
(18) A. T. Blomquist and Y. C. Meinwald, *J. Am. Chem. Soc.*, **79**, 5317 (1957); **81**, 667 (1959).

(19) R. Breslow and C. Yuan, *ibid.*, **80**, 5991 (1958); R. Breslow, R. Winter, and M. Battiste, *J. Org. Chem.*, **24**, 415 (1959).

bromide," it should form the corresponding diphenylcyclopropenyl cation VIII quite readily. However, the ultraviolet spectrum of the dibromide in acetonitrile–10% ethanol (conditions favorable for the presence of the ether IX) showed maxima at 238 mμ (ε 26,400) and 303 (20,400) with a shoulder at 230 (23,800). Also, the ultraviolet spectrum of the dibromide in acetonitrile–10% ethanol–0.1 *N* hydrochloric acid (conditions favorable for the cyclopropenium ion) revealed no shift with respect to the position or intensity of the



VIII

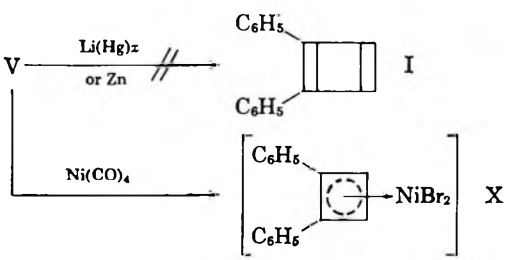


IX

absorption maxima. These results are in marked contrast to the reported behavior of diphenylcyclopropene systems, where appreciable changes occur under similar conditions.[20,21] Thus, structure VII for the dibromide can be eliminated and, accordingly, the dibromide must be 3,4-dibromo-1,2-diphenylcyclobutene (V).

The stereochemistry of the dibromide V is not known with complete certainty but it is probably *cis*. A chloroform solution of 3,4-dibromo-3,4-bis(bromomethyl)-1,2-diphenyl-1-cyclobutene,[18] which probably has a *trans* configuration, shows an ultraviolet maximum at 288 mμ (ε 19,500), but the long wave-length maximum of the dibromide V (in chloroform solution) remains at 303 mμ. It is probable, therefore, that the bathochromic shift observed for the compound V is a consequence of interactions of cisoid bromine atoms.[22]

Dehalogenation of the dibromide V with 0.5% lithium amalgam[16,24] failed to give 1,2-diphenylcyclobutadiene (II) or to generate such an intermediate which could be trapped by the diene cyclopentadiene. Instead, only an intractable polymeric crimson oil could be isolated which resisted all attempts at characterization. The infrared spectrum of this oil closely resembled the spectrum of a polystyrene film. Similar results were obtained in the zinc dust debromination of compound V.



Finally, the dibromide V reacted very slowly with nickel carbonyl. The amount of unchanged dibromide recovered and nickel bromide formed (up to 100%) varied with reaction conditions. The polymeric organic product formed could not be characterized. The nickel complex X, if formed, apparently decomposed readily to release nickel bromide and afforded a polymeric organic product. These results contrast markedly with those reported by Freedman for the stable tetraphenylcyclobutadiene–nickel bromide complex.[25]

Experimental[26]

***cis*-1,2-Diphenylcyclobutene-3,4-diol (III).**—A solution of 4.96 g. (21.1 mmoles) of unrecrystallized diketone[1b] in 13 ml. of dry benzene was added over a 10-min. period to a stirred slurry of 0.46 g. of lithium aluminum hydride in 90 ml. of dry ether. The mixture was stirred at 25° for 1 day, cooled to −6°, and then treated by the dropwise addition of 25 ml. of water followed by the addition of 50 ml. of 10% sulfuric acid. The aqueous acid layer was extracted with three 25-ml. portions of ether, and the combined organic solutions were washed successively with 25 ml. of saturated sodium bicarbonate solution, 50 ml. of water, and 25 ml. of saturated aqueous sodium chloride solution. Concentration of the dried organic solution gave, in two crops, an impure sample of the *cis*-1,2-diol III which, after recrystallization from carbon tetrachloride, afforded 1.14 g. (23%) of the pure diol III, m.p. 135.5–136.5°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.75; H, 5.68.

Further concentration of the carbon tetrachloride mother liquor gave 80 mg. of a white crystalline solid, m.p. 193–196°, λ_{max}^{KBr} 5.95 μ (indicative of a ring-opened product). A very slow evaporation of the original ether–benzene solution at room temperature deposited 0.16 g. (3%) of impure *trans*-diol IV.

Variations in the above procedure, *i.e.*, inverse addition of reactants or neutral conditions in the hydrolysis step, failed to increase the yield of the diol III.

***trans*-1,2-Diphenylcyclobutene-3,4-diol (IV).**—During a 10-min. period, 4.2 g. of the diketone I in 50 ml. of freshly purified tetrahydrofuran (THF)[27] was added to a cold (0°), stirred solution of 0.374 g. of $LiAlH_4$ in 50 ml. of dry THF. The mixture was stirred at room temperature for 21 hr. and then treated, by slow addition, with ethyl acetate to consume unchanged $LiAlH_4$. After the subsequent addition of water, the mixture was filtered from the insoluble granular salts, and the aqueous filtrate was extracted with ether. A solution of the inorganic salts, in a minimum amount of 10% hydrochloric acid, was also extracted with ether. The combined ether extract was washed with a saturated sodium bicarbonate solution, dried, and taken to dryness. The oil thus obtained crystallized from carbon tetrachloride to give 0.46 g. of a white solid (very impure diol IV) as well as a trace of a solid which had m.p. 273–275°. Fractional crystallization of the above impure diol IV from 1:1 ethanol–ethyl acetate effected a partial separation into approximately equal amounts of the *trans*-diol IV, m.p. 183–184.5°, and an unknown compound, m.p. 196–197°, λ_{max}^{KBr} 5.95 μ. This sample of the diol IV was analyzed.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.87; H, 5.84.

Infrared Studies of the Diols III and IV.—In a 1-cm. cell a carbon tetrachloride solution of the *cis*-diol III at a concentration of 6.5 mg./ml. showed two infrared bands at 3604 and 3559 cm.$^{-1}$. In a 5-cm. cell the bands were observed to be 3601 and 3555 cm.$^{-1}$. The assignments, that were based on average values, were made as follows: the more intense, higher frequency band at *ca.* 3602 cm.$^{-1}$ was attributed to an OH···π-electron bond with the cyclobutene double bond and the band at *ca.* 3557 cm.$^{-1}$ to the normal OH···O bond present in *cis*-1,2-diols.

The *trans*-diol IV, insoluble in carbon tetrachloride, is only slightly soluble in chloroform. Its infrared spectrum, in a saturated solution of chloroform, showed a weak band at 3603 cm.$^{-1}$. Since alcohols absorb at higher frequencies in carbon tetrachloride *vs.* chloroform, a correction of absorption was made in order to compare the observations made of the *cis*- and *trans*-diols. Suggested correction values[11] for this are 10, 15, and 21 cm.$^{-1}$. Accordingly, after application of the average correction

(20) D. G. Farnum and M. Burr, *J. Am. Chem. Soc.*, **82**, 2651 (1960).

(21) R. Breslow, J. Lockhart, and H. W. Chang, *ibid.*, **83**, 2375 (1961).

(22) Since the preparation of V, Criegee and Noll have noted[23] that only *cis*-3,4-dibromo-1,2,3,4-tetramethylcyclobutene was obtained when either the *cis* or *trans* isomer of 1,2,3,4-tetramethylcyclobutene-3,4-diol was treated with hydrogen bromide. Similarly, from either the *cis* or *trans* forms of Criegee's diol, reaction with either hydrogen chloride or thionyl chloride affords only *cis*-3,4-dichloro-1,2,3,4-tetramethylcyclobutene.

(23) R. Criegee and K. Noll, *Ann.*, **627**, 1 (1959).

(24) G. Wittig and L. Pohmer, *Chem. Ber.*, **89**, 1334 (1956).

(25) H. H. Freedman, *J. Am. Chem. Soc.*, **83**, 2194 (1961); *J. Org. Chem.*, **27**, 2298 (1962).

(26) All melting points, taken with a Mel-Temp apparatus, are uncorrected. Ultraviolet spectra were determined with Beckman DK and Cary 14 instruments.

(27) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p. 292.

value of 15 cm.$^{-1}$, the *trans*-1,2-diol IV is predicted to show infrared absorption at 3618 cm.$^{-1}$ in carbon tetrachloride solution. This is indicative of an OH$\cdots\pi$-electron interaction that is much weaker than observed for the *cis*-diol III.

Reaction of the Diols III and IV with Potassium Triacetyl Osmate.[15]—The diol III reacted rapidly with triacetyl osmate, indicative of *cis*-1,2-diol configuration. The diol IV, however, was unreactive in this reaction in support of a *trans* arrangement of hydroxyl groups.

3,4-Dibromo-1,2-diphenylcyclobutene (V).—To a solution of the diol III (0.955 g., 4 mmoles) in a cooled (−50°) solution of chloroform, 1.11 g. (4.1 mmoles) of phosphorus tribromide was added. This mixture was allowed to stand at −50° for 5 hr., at 25° for 48 hr., and finally refluxed for 14 hr. After the addition of more chloroform, the mixture was poured carefully into an ice–water mixture. (The yellow solid deposited on the sides of the flask during the period of reflux was also dissolved in water and added to the chloroform solution.) After the chloroform solution had been separated, the remaining aqueous phase was extracted with additional chloroform. The combined chloroform solutions, after successive washings with saturated sodium bicarbonate and saturated aqueous sodium chloride, were dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a crystalline residue which was recrystallized from 30–60° petroleum ether to give, in several crops, a total of 1.06 g. (73%) of the dibromide V. A sample of the compound V, m.p. 115–116° from petroleum ether, was analyzed.

Anal. Calcd. for $C_{16}H_{12}Br_2$: C, 52.78; H, 3.32; Br, 43.89. Found: C, 52.69; H, 3.34; Br, 43.91.

A crystalline modification of V, m.p. 103–104°, was isolated during the recrystallizations of the desired dibromide. The infrared spectrum of this dibromide was identical with the compound of m.p. 115–116°.

Attempted Solvolysis of the Dibromide V.—A solution of 64 mg. of V in 4 ml. of acetone was treated with 0.35 ml. of water and a "spatula tip" of sodium bicarbonate. The mixture was allowed to stand for 10 days at room temperature, the bicarbonate was filtered, and the acetone filtrate was taken to dryness. Extraction of the residue with petroleum ether gave a residual yellow oil (3 mg.) that was washed with water. The infrared spectrum of this oil showed λ_{max} 5.70 (C=O) and 2.72 μ (OH) which indicated that some ring opening had occurred even under these relatively mild conditions. The petroleum ether extract consisted of unchanged dibromide V.

Preparation of 0.5% Lithium Amalgam.[8,24]—The procedure described by Criegee and Louis[8] gave a nonhomogeneous mixture of solid and liquid amalgams. A more uniform product was obtained by shaking 2 g. of lithium with 400 g. of mercury for 4 hr. at 200–218° in an evacuated steel bomb. The solid amalgam thus obtained was separated from the liquid amalgam, which was discarded, and stored in a screw cap bottle.

Debromination of the 1,2-Dibromo Compound (V) with Lithium Amalgam.—A mixture of 0.50 g. (1.37 mmoles) of the dibromide V and 7.8 g. of 0.5% lithium amalgam (100% excess) in 80 ml. of anhydrous ether was shaken at room temperature for 20 hr. and then filtered; the mercury residue was also shaken with ether. The combined ether solutions, orange-red in color, were washed thoroughly with water, dried, and brought to dryness *in vacuo* at 25°. The residual, nonbromine-containing oil, 0.280 g. (100%), resisted all attempts to effect its purification. The infrared spectrum of this crude oil was very similar to that of a polystyrene film. Although the two spectra were identical in the 2.5–7-μ region, the product oil showed a few additional bands: 7.46 (m), 8.90 (s), 11.18 (w), and 11.49 μ (w). The ultraviolet spectrum of the oil showed maxima at 269 and 310 mμ.

The same oil was isolated when debromination was carried out in the presence of cyclopentadiene which was used as a reagent to trap any transiently formed 1,2-diphenylcyclobutadiene. Finally, similar results were again observed when debromination was carried out under the conditions used by Cava and Napier[28] to dehalogenate 1,2-dibromobenzocyclobutene.

Debromination of the Dibromide V with Nickel Carbonyl.—This experiment was carried out under a slow stream of dry nitrogen to remove carbon monoxide as liberated. Nickel carbonyl (0.7 ml.) was distilled into a cooled flask (−70°) that contained 0.7 g. (1.92 mmoles) of the dibromide V in 25 ml. of anhydrous ether. The reaction mixture was refluxed and became purple in color after 10 min. The red-brown mixture, formed after a reaction period of 101.5 hr., was filtered to separate a brown solid which was washed with ether. This solid (0.692 g.) failed to melt below 400°. The residual crimson oil obtained from the original filtrate was identical (infrared analysis) with the crimson oil (175 mg.) isolated by chloroform extraction of the original brown solid product. The purple solid (517 mg.) which remained after the chloroform extraction was partially soluble in water to give a green solution. Insoluble in water was 47 mg. of a black solid, m.p. 310–320° dec.

The green aqueous solution was shown to contain nickel bromide by positive tests with silver nitrate and dimethylglyoxime. Quantitative analysis of the aqueous solution (dimethylglyoxime reagent) showed that it contained 1.92 mmoles (100%) of nickel bromide.

Extraction of the combined fractions of crimson oil (described above) with petroleum ether gave a yellow solution and an insoluble red-brown solid. Attempted crystallization of the latter afforded only an oil. The yellow petroleum ether extract produced an intractable orange powder that showed strange behavior when a melting point determination was carried out; *i.e.*, it darkened and sintered at 100–120°, then melted at 165–180° and 250–260°.

Reaction of the dibromide V with nickel carbonyl for 65.5 hr. produced 74% of an equivalent of nickel bromide.

In contrast to the foregoing, reaction in a sealed tube of 1.24 g. of the dibromide V with 1 ml. of nickel carbonyl in 50 ml. of ether for 21 hr. at 25° and 42 hr. at 38–40° resulted in 89% recovery of unchanged dibromide and the formation of an intractable orange solid.

(28) M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **79**, 1705 (1957).

The Wittig Reaction with Five- and Six-Membered Cyclic Ketones and Their Benzylidene Derivatives[1]

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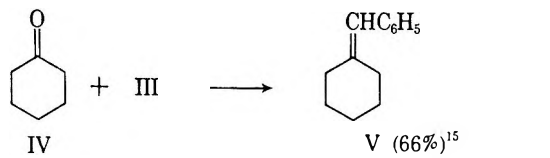
A number of benzylidenecycloalkanes have been prepared utilizing the reaction of benzylidenetriphenylphosphorane and the corresponding cycloalkanone or benzylidenecycloalkanone. Mono-, 1,2-di-, and 1,2,3-tribenzylidenecyclohexane, mono- and 1,2-dibenzylidenecyclopentane, and 1-benzylideneindane were prepared successfully; attempted reactions with 2,5-dibenzylidenecyclopentanone, 1-tetralone, 2-benzylideneindanone-1, and 2-benzylidenetetralone-1 were unsuccessful. In reactions of cyclopentanones, anion formation and base-catalyzed condensations constitute major competitive reactions. In the attempted reaction with 2-benzylideneindanone, a dimer was formed by a base-catalyzed aldol process.

The formation of the synthetically important mono- (I) and polyalkylidenecycloalkanes (II) has been achieved by a number of conventional procedures, primarily alcohol dehydration[2] and amine N-oxide[3] and carboxylate[4] pyrolyses. However, each of these procedures is limited in application and utility. Double bond migration has been commonly observed in both alcohol dehydrations[2] and amine N-oxide pyrolyses[3]; thus, dehydration of 1-benzylcyclopentanol leads to the predominant formation of 1-benzylcyclopentene rather than the *exo* isomer.[2a] The formation of II from alkylidenecycloalkanones by Grignard procedures is complicated by the occurrence of 1,4-additions. Although the pyrolysis of carboxylates is reported to proceed without double bond migration,[4a] aromatization often occurs at the high temperatures necessary for gas-phase pyrolyses.[4b] In an effort to develop a more generally applicable route for the formation of I and II, a study of the Wittig reaction[5] with cycloalkanones and benzylidenecycloalkanones has been carried out. The potential advantages of the Wittig reaction for these syntheses are the specific double bond placement observed with this reaction[5] and the ready availability of the starting ketones.

While no extensive study of the formation of I and II by means of the Wittig reaction has been carried out previously, a number of simple compounds of type I have been prepared by this procedure. Benzylidenecyclohexane,[6,7] methylenecyclopentane,[8] -heptane,[9] and -octane,[9] ethylidenecycloheptane,[10] and ethyl cyclohexylidene acetate[11] are representative examples. Although Wittig reactions have been carried out with a wide variety of α,β-unsaturated ketones,[5,12] only three isolated examples of 1,4-additions have been reported.[12-14] In the only reported example of a Wittig reaction with an alkylidenecycloalkanone, Inhoffen has shown that 2-methylenecyclohexanone undergoes 1,4-addition.[13] In the present study, benzylidenecycloalkanes were chosen as model compounds, since it was felt that the occurrence of 1,4-addition would be less likely than with simpler alkylidenecycloalkanones.

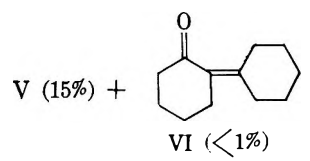
Results

Benzylidenecyclohexanes.—The results of the reactions of a number of cyclohexanones and benzylidenetriphenylphosphorane (III) are summarized in the following equations; unless otherwise noted, the phosphorane was generated by the action of ethanolic sodium ethoxide on benzyltriphenylphosphonium chloride in absolute ethanol

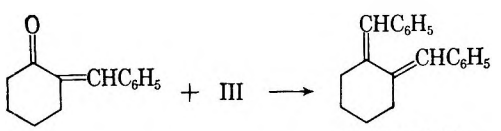


IV V (66%)[15]

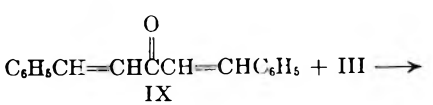
IV + III (n—C_4H_9Li generation) ⟶



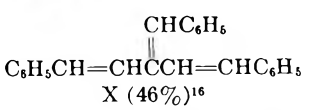
VI (<1%)



VII VIII (37.5%)



IX



X (46%)[16]

In the reaction of XIII, triphenylphosphine oxide (70.4%) was isolated, indicating that a Wittig reaction had probably occurred; however, none of the anticipated product (XV) could be isolated by column chro-

(1) This study was supported in part by a grant (G-11280) from the National Science Foundation.

(2) (a) E. L. Eliel, J. W. McCoy, and C. C. Price, *J. Org. Chem.*, **22**, 1533 (1957); (b) H. J. Schaeffer and C. J. Collins, *J. Am. Chem. Soc.*, **78**, 124 (1956).

(3) A. C. Cope, C. L. Bumgardner and E. E. Schweizer, *ibid.*, **79**, 4729 (1957).

(4) (a) W. J. Bailey and R. A. Baylouny, *J. Org. Chem.*, **27**, 3476 (1962); (b) W. J. Bailey and J. Rosenberg, *J. Am. Chem. Soc.*, **77**, 73 (1955).

(5) U. Schollkopf, *Angew. Chem.*, **71**, 260 (1959).

(6) G. Wittig and W. Haag, *Chem. Ber.*, **88**, 1654 (1955).

(7) U. Schollkopf, Dissertation Thesis, Tubingen, 1955; cited in ref. 5.

(8) C. H. Collins and G. S. Hammond, *J. Org. Chem.*, **25**, 1434 (1960).

(9) A. Schriesheim, R. J. Muller, and C. A. Rowe, Jr., *J. Am. Chem. Soc.*, **84**, 3164 (1962).

(10) A. C. Cope and J. K. Hecht, *ibid.*, **85**, 1780 (1963).

(11) G. Fodor and I. T. Tomoskozi, *Tetrahedron Letters*, **16**, 579 (1961).

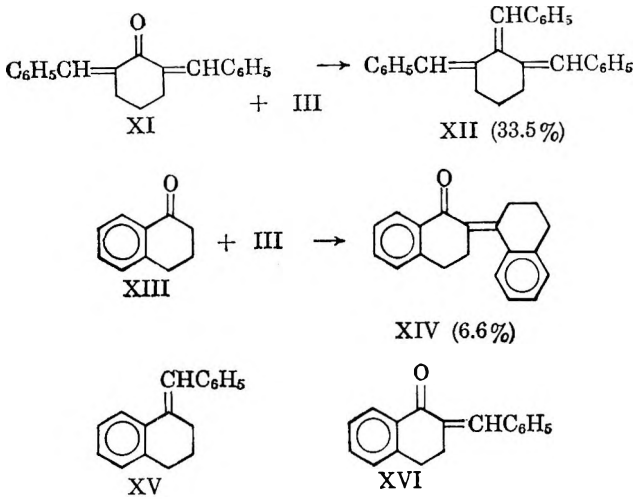
(12) F. Bohlmann, *Chem. Ber.*, **89**, 2191 (1956).

(13) H. H. Inhoffen, K. Bruckner, G. F. Domagk, and H. Erdmann, *ibid.*, **88**, 1415 (1955).

(14) J. P. Freeman, *Chem. Ind.* (London), 1254 (1959).

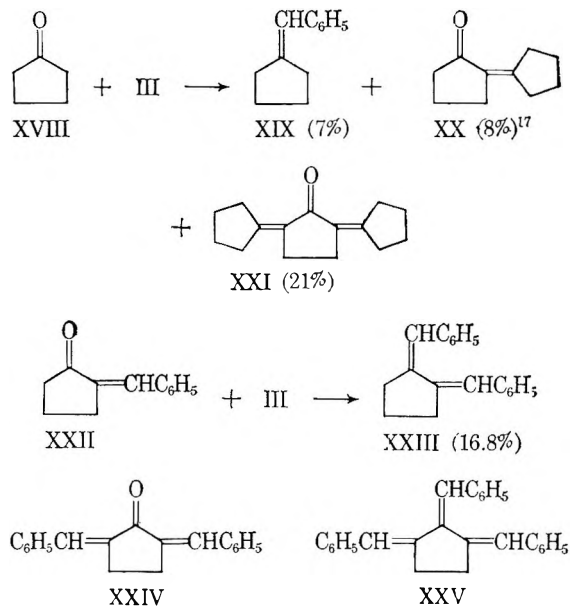
(15) Previously prepared by Wittig and Haag[6] in 60% yield by an identical procedure.

(16) Previously prepared by Bohlmann in unspecified yield by a Wittig procedure.[12]



matography and no evidence for its formation was obtained. In addition to the phosphine oxide and recovered XIII, the condensation product (XIV) of XIII was the only material isolated. Attempted reaction of XVI and III led to the recovery of XVI; no evidence for the formation of the expected product, 1,2-dibenzylidenetetralin (XVII), was obtained.

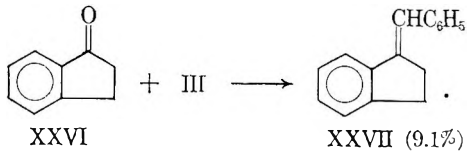
Benzylidenecyclopentanes.—In an attempt to prepare XXV, four separate reactions of III and XXIV



were carried out using both sodium ethoxide and phenyllithium as bases for the generation of the phosphorane. In no case was any evidence obtained indicating the formation of XXV or triphenylphosphine oxide; only the starting phosphonium salt (37–47%) and XXIV (43–80%) were isolated. In each reaction, addition of III to XXIV led to the formation of a deep red solution indicating carbanion formation; an attempted trap of the carbanion by alkylation was unsuccessful.

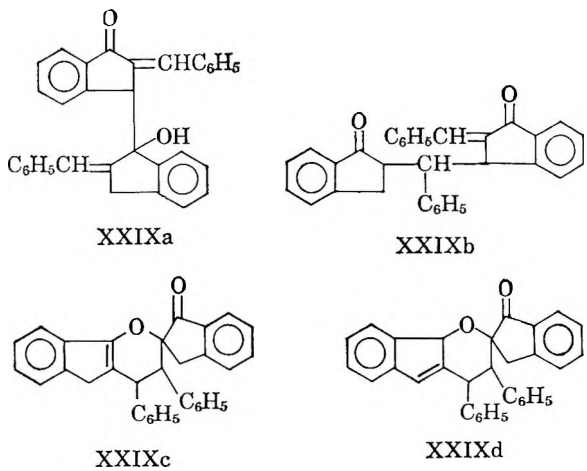
By analogy with the 1-tetralone (XIII) reaction, base-catalyzed condensation of XXVI was anticipated, but no 2-(1-indanylidene)indanone-1 was detected in the reaction products. XXVII had been previously reported as the product from the reaction of indene and

(17) The mixture of XIX and XX could not be separated by distillation, but the components were identified and estimated by quantitative g.l.c.



sodium benzylate in the presence of nickel in benzyl alcohol.[18]

In the attempted formation of 1,2-dibenzylideneindane by reaction of III and 2-benzylideneindanone (XXVIII), the only product isolated (74–87%) was a dimer (XXIX) formed as a result of base-catalyzed self-addition of XXVIII. Elemental analyses and molecular weight determinations indicated the compound to be a simple dimer rather than any dehydrated product. Four dimeric structures were considered: the simple aldol (XXIXa), the Michael adduct (XXIXb), and two isomeric Diels–Alder or cyclized



Michael adducts (XXIXc and d).[19] Evidence for the mode of formation of the dimer was obtained from its preparation in near quantitative yield by treatment of XXVIII with sodium hydride in refluxing glyme. Attempted dehydration of the dimer with iodine in refluxing xylene was unsuccessful; however, the failure of this reaction is not unexpected since there would be a marked steric barrier to the dehydration of XXIXa to the corresponding fulvalene.

Initial evidence favoring structures XXIXa, c, and d was obtained from the infrared spectrum of the dimer which showed a single unsplit carbonyl absorption at 1701 cm.$^{-1}$ (five-membered cyclic ketone[20]). Structure XXIXb would be expected to possess either a doublet or two carbonyl absorptions. The dimer was converted to its oxime which analyzed satisfactorily for a monooxime rather than the bisoxime to be expected from XXIXb; the infrared spectrum of the oxime lacked carbonyl absorption providing further support for the elimination of structure XXIXb. Weak absorption at 3580 cm.$^{-1}$ was also observed, but the band was not sufficiently strong to make more than a tentative hydroxyl (XXIXa) assignment. The carbonyl stretching frequency (1701 cm.$^{-1}$) observed for XXIX is significantly lower than that observed for 1-indanone (1722

(18) S. S. Hirsch, D. H. Lorenz, and E. I. Becker, *J. Org. Chem.*, **23**, 1829 (1958).

(19) We are indebted to the referee for suggesting structures XXIXc and d for the dimer.

(20) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 148–149.

TABLE I

P.M.R. SPECTRA[a]

Compound	Chemical shifts (τ)			
	α-CH_2	β,γ-CH_2	Vinyl	Aromatic
V	7.75 m (3.9)	8.45 m (1.9)	3.80 s (1.0)	2.90 s (5.0)
	7.75 m (4.0)	8.50 m (2.0)	3.78 s (1.0)	2.86 s (4.9)[b]
VIII	7.42 m (4.0)	8.37 m (4.0)	3.43 s (2.0)	2.80 s (10.0)
XII	7.30 t (4.0)[c]	8.25 m (2.1)	3.72 s (0.9)	2.78 m (15.0)
			3.32 d (1.9)	
XIX	7.68 m (3.9)	8.47 m (3.9)	3.72 q (1.0)[d]	2.97 m (5.0)[b]
XXVII	6.97 m[e]	6.97 m (3.9)[e]	3.12 t (1.0)	2.75 m (9.2)
XI	7.13 t (4.0)	8.20 q (1.9)	2.33 t (2.0)	2.67 m (9.9)
XVI	7.05 m[e]	7.05 m (4.0)[e]	2.27 t (1.0)	2.69 m (8.9)
XXVIII	5.95 d (2.0)[f]	...	[g]	2.38 m (10.0)[h]
	6.05 d (2.0)[f]	...	[g]	2.60 m (10.0)

[a] All spectra were recorded in CCl_4 solution (saturated) unless otherwise noted. Relative integrated intensities are noted in parentheses. Peak structures are assigned as multiplets (m), singlets (s), doublets (d), triplets (t), and quintuplets (q); chemical shift values cited represent centers of absorption. [b] As neat liquid. [c] J_{HH} = 7.0 c.p.s. [d] J_{HH} = 2.4 c.p.s. [e] Methylenes (α- and β-) coincident. [f] Geminal J_{HH} = 3.0 c.p.s. [g] Vinyl hydrogens obscured by aromatic protons. [h] In acetone-d_6 solution.

cm.$^{-1}$),[21] but is similar to that observed for 2-benzylideneindanone (1697 cm.$^{-1}$),[21] supporting a tentative assignment of structure XXIXa and providing evidence against structures XXIXc and d.

The ultraviolet spectrum of XXIX showed maxima at 248 and 295 mμ (ϵ 25,200 and 4970). 1-Indanone absorbs at 243 mμ (ϵ 12,300),[21] while 2-benzylideneindanone absorbs at 227 and 318 mμ (ϵ 9850 and 22,500).[21] The observed spectrum is consistent with structures XXIXc and d, since it may be considered as a composite of the two isolated chromophores, 1-indanone and styrene (λ_{max} 244 mμ, ϵ 12,000). However, a molecular model of XXIXa indicates attainment of coplanarity of the benzylideneindanone system to be difficult because of bond oppositions with the hydroxyl function and the indanyl system. As a consequence of this disruption of coplanarity in the α,β-unsaturated ketone chromophore, XXIXa might be expected to show the observed absorption. Additionally, the longer wave length band (295 mμ) is consistent with structure XXIXa, but not with either XXIXc or d.

Unequivocal assignment of structure XXIXa to the dimer was provided by its proton magnetic resonance spectrum. In addition to a complex multiplet in the aromatic region (τ 2.0–2.7, relative intensity 19.9), signals at 7.91 (singlet, exchangeable), 5.93 (doublet, J_{HH} = 3.0 c.p.s.), and τ 4.68 (singlet) with relative intensities of 1.0:1.9:1.0 were observed. The intensities and chemical shift values for the three signals are consistent with their assignment as the hydroxyl, methylene, and methine protons, respectively, of XXIXa. A similar coupling constant was observed for the methylene protons in 2-benzylideneindanone (XXVIII). In XXIXa, the vinylic protons are obscured by the aromatic proton absorptions; in model structures such as XXVIII a similar shift of the vinyl proton into the aromatic region is observed. Markedly different and more complex proton spectra would be anticipated for both XXIXc and d. Structure XXIXc should show aromatic, methylene (two doublets), and methine (AB pattern) signals in the intensity ratio 18:4:2, while XXIXd should show aromatic plus vinyl, methylene (one doublet), and methine (AB plus singlet) signals with intensities 19:2:3. The observed spectrum is compatible with neither of these expectations and the dimer is consequently assigned structure XXIXa.

The physical properties of XXIXa agree with those reported for a compound obtained by the reaction of 1-indanone and benzaldehyde in the presence of alcoholic potassium hydroxide; no structure was given by the original workers, but the compound was considered to be a bisbenzylidene-1-indanone.[22]

The structures assigned to the olefins prepared in this study were substantiated by elemental analyses and infrared and ultraviolet spectra. In all cases, their proton magnetic resonance spectra were consistent with assigned structures. Integrated intensities for ring methylene protons and the absence of benzylic methylene absorptions showed the corresponding *endo* isomers to be absent, establishing specific double bond placement by these Wittig processes and lack of isomerization under the conditions of the reaction. The spectra of a number of representative compounds are summarized in Table I.[23]

Discussion

The results of this study indicate that the Wittig reaction can be applied with moderate success to the formation of I and II from cyclopentanones and cyclohexanones; the occurrence of base-catalyzed condensations of the starting ketones, particularly in the cyclopentanone series, constitutes a major limitation.

The study shows further that there is a marked difference in the behavior of five- and six-membered cyclic ketones towards III. Consistently higher yields of olefins are obtained in the cyclohexanone reactions and extensive condensation is observed only in the cyclopentanone reactions. This difference in behavior has not been reported previously in simple Wittig reactions with cycloalkanones but is readily explicable in terms of the known differences in the chemistry of these ketones and the accepted mechanism of the Wittig reaction; in particular, these results support the mechanistic conclusions of Speziale and Bissing.[24] The

(21) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80**, 893 (1958).

(22) J. N. Chatterjea and K. Prasad, *J. Indian Chem. Soc.*, **34**, 375 (1957).

(23) A more detailed consideration of the proton spectra of these and related benzylidenecycloalkanones and -cycloalkanes with particular emphasis on couplings and J-values will be presented in a separate communication.

(24) A. J. Speziale and D. E. Bissing, *J. Am. Chem. Soc.*, **85**, 1888 (1963).

Wittig reaction is generally considered to proceed by the nucleophilic attack of the phosphorane carbon on the carbonyl group to produce an intermediate betaine which undergoes elimination of phosphine oxide to produce the olefinic product.[25] In this process, the carbonyl carbon atom undergoes two configurational changes: sp^2 (carbonyl) → sp^3 (betaine) → sp^2 (olefin). Speziale and Bissing[24] have shown recently that in the reactions of a stable phosphorane, carbomethoxymethylenetriphenylphosphorane, the formation of the betaine is rate determining and reversible and the second step, betaine decomposition, is rapid. Numerous previous studies have established the large differences in rates of addition to cyclopentanones and cyclohexanones[26] and have led to the generalizations of Brown[26a]; *i.e.*, an sp^2–sp^3 configurational change for a ring carbon is favored in cyclohexanones and opposed in cyclopentanones with the sp^3–sp^2 change favored in the latter ketones. The observed preference for reaction of III with cyclohexanones rather than cyclopentanones indicates that in this series, as in the reactions studied by Speziale, betaine formation is rate determining since the sp^2–sp^3 configurational change is involved in this step and is favored in cyclohexanones. If betaine decomposition (sp^3–sp^2 change) were rate determining, cyclopentanones would be expected to show a higher order of reactivity than cyclohexanones toward III. Thus, this study indicates that betaine formation may be rate determining in the reactions of unstable as well as stable[24] phosphoranes. No experiments designed to test the reversibility of betaine formation were carried out in this study.

As a partial test of this interpretation, the reaction of benzaldehyde and cyclopentylidenetriphenylphosphorane (XXX) was carried out; the expected olefin (XIX) was obtained in 34% yield as contrasted to the 7% yield obtained by the reaction of cyclopentanone and III. Since the cyclopentylidene carbon of XXX has a configuration intermediate between sp^3 and sp^2, betaine formation would be expected to be kinetically more favorable than in the cyclopentanone reaction.

The fact that the rate-determining step is kinetically slow in the reactions of cyclopentanones with III, in comparison with cyclohexanone reactions, provides an explanation for the base-catalyzed condensations observed in the former reactions. In the absence of any rapid consumption of ketone by betaine formation, either the basic phosphorane (III) or the strong base (sodium ethoxide, phenyllithium) used to generate III from the phosphonium salt could attack the α-hydrogen leading to anion formation and subsequent condensation. The reactions of cyclopentanone (XVIII) and cyclohexanone (IV) provide an excellent example of this competition. In the reaction of III with IV, betaine formation is rapid and only a small amount of condensation product is formed; in the reaction of III with XVIII, the slower rate of betaine formation leads to significant amounts of anion formation leading to condensation as the major process (80% of total products). The lack of reactivity of 2,5-dibenzylidenecyclopentanone (XXIV) can similarly be attributed to anion formation; the marked red color associated with anions was observed when this compound was treated with III or other bases. Schriesheim and co-workers have postulated that the facile formation of anions from cyclopentanes is due to the planarity of the ring system which allows a maximum p–π overlap in the transition state.[26c] In XXIV three trigonal ring carbons lead to a completely planar molecule and formation of the carbanion is facilitated. The lack of self-condensation of XXIV reflects the stability of the anion and the hindered nature of the carbonyl group. In the case of 2-benzylideneindanone (XXVIII), anion formation is facile since the methylene group is activated by both styryl and phenyl groups and the self-condensation proceeds readily since the carbonyl is less hindered than that of XXIV. No attempt to detect condensation products in the reaction of III with 2-benzylidenecyclopentanone was carried out, but in analogy with XXIV and XXVIII, it is probable that some anion formation occurs.

The lack of olefin formation and the extensive base-catalyzed condensation encountered with 1-tetralone (XIII) are anomalous; 1-indanone (XXVI), which would be expected to follow the general behavior of the cyclopentanones, gives 1-benzylideneindane and no condensation products. Other anomalous reactions of these ketones have been observed. Cook and Lawrence have shown that XIII undergoes self-condensation to produce XIV as the major product on treatment with cyclohexylmagnesium chloride,[27] and Coles and co-workers have shown that XIII polymerizes in the presence of trace amounts of nitrogen tetraoxide while XXVI forms the isonitroso ketone (50%) upon treatment with this reagent.[28]

The only other reported citation of base-catalyzed carbonyl reactions competing with normal Wittig reactions is contained in the recent work of Butler and co-workers.[29] The failure to obtain olefin formation in the reactions of *n*-butyraldehyde and 5-hexenal with simple ylides was attributed to competing aldol condensation of the aldehydes. Acrolein similarly failed to give a Wittig product, presumably because of its ability to undergo facile base-initiated polymerization.

Steric hindrance about the carbonyl group of the cyclic ketones apparently exerts little influence on the course of the Wittig reactions. Thus, both the mono- and dibenzylidene derivatives of cyclohexanone lead to the formation of the corresponding olefin in approximately equal yields, and benzylidenecyclopentanone forms the olefin in higher yield than does cyclopentanone. However, steric hindrance about the carbonyl group cannot be eliminated as a factor in promoting the competitive base-catalyzed condensations in the cyclopentanones.

The ultraviolet absorption spectra of mono- (V), 1,2-di- (VIII), and 1,2,3-tribenzylidenecyclohexane (XII) showed the usual influence of steric disruption of coplanarity in conjugated systems, *i.e.*, shifts of absorption maxima to shorter wave lengths than observed in

(25) For a summary of primary references regarding the mechanism of the Wittig reaction, see ref. 5 and 24.

(26) (a) H. C. Brown and G. Ham, *J. Am. Chem. Soc.*, **78**, 2735 (1956), and preceding papers; (b) A. C. Cope, C. L. Bumgardner, and E. E. Schweizer, *ibid.*, **79**, 4729 (1957); (c) A. Schriesheim, R. J. Muller, and C. A. Rowe, Jr., *ibid.*, **84**, 3164 (1962).

(27) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 1431 (1936).

(28) H. W. Coles, R. H. F. Manske, and T. B. Johnson, *J. Am. Chem. Soc.*, **51**, 2269 (1929).

(29) C. F. Hauser, T. W. Brooks, M. L. Miles, M. A. Raymond, and G. B. Butler, *J. Org. Chem.*, **28**, 372 (1963).

coplanar model systems.[30,31] As anticipated, the spectrum of V (λ_{max} 244 mμ, ε 12,700) is nearly identical with that of styrene (λ_{max} 244 mμ, ε 11,700–12,000) indicating no deviation from coplanarity in the styryl system. As anticipated for the conjugated system, VIII absorbs at longer wave length (285 mμ, ε 19,000) than does V, but its absorption maximum has undergone a 47–51-mμ hypsochromic shift relative to coplanar model compounds (*trans*-1,4-diphenylbutadiene, λ_{max} 332 mμ[32]; 1,2-dibenzylidenecyclopentane, λ_{max} 336 mμ[33]). The positions of maximum absorption of VIII and 1-phenylbutadiene[30] are approximately the same, indicating that in VIII only one phenyl group is effectively conjugated with the diene system. Tribenzylidenecyclohexane (XII) absorbs at even lower wave lengths (275 mμ) than does VIII, indicating even greater deviations from coplanarity; the acyclic analog, β,β-distyrylstyrene, which presumably possesses a nearly planar structure has major maxima at 295 and 330 mμ.[12] Molecular models (Dreiding) of XII and VIII do not indicate any reasonable conformations in which phenyl–phenyl oppositions are absent and in which coplanarity is possible.

Experimental[34]

Benzylidenecyclohexane (V).—A solution of 20.0 g. (0.052 mole) of benzyltriphenylphosphonium chloride in 100 ml. of absolute ethanol was treated with 100 ml. of a 0.5 *M* solution of sodium ethoxide in ethanol with continuous stirring under an atmosphere of nitrogen; the orange color of the phosphorane (III) appeared immediately. After the solution was stirred for 10 min., 4.9 g. (0.05 mole) of cyclohexanone was added. The mixture was refluxed for 4 hr., cooled, and filtered; the filtrate was concentrated on a steam bath to precipitate unreacted phosphonium salt and sodium chloride. After removal of the precipitated salts, the filtrate was distilled to yield 2.06 g. (66%) of V, b.p. 117–121° (6 mm.), lit.[6] b.p. 124.5–126.5° (12 mm.). Extraction of the distillation residues with a chloroform–benzene mixture gave 3.4 g. (67%) of triphenylphosphine oxide. The ultraviolet spectrum of V had a maximum at 244 mμ (ε 12,700), lit.[6] λ_{max} 243 mμ (ε 12,900).

The preparation of V was repeated using the same molar quantities of phosphonium salt and cyclohexanone in benzene with *n*-butyllithium employed for the generation of III. After a 26-hr. reaction period, a yield of 16% of V was obtained by distillation, b.p. 88–95° (0.7 mm.). A sample of the distilled material was examined by g.l.c.[34]; two peaks (retention times of 60 and 69 min.) were observed and identified as V and cyclohexylidenecyclohexanone (XX),[35] respectively, by comparison with authentic samples. Quantitative g.l.c. showed 97% of V and 3% of XX. A small sample of XX was trapped from the g.l.c. effluent; the proton spectrum of this material showed methylene absorptions in the τ 7.0–8.5 region as the only observable signals. The absence of signals in the region normally associated with vinyl protons (τ 4.0–5.0 for trisubstituted olefins[36]) confirmed the structure as XX, eliminating the isomeric 2-(1-hexenyl)cyclohexanone and 2-cyclohexyl-2-cyclohexenone[35b] as structural possibilities.

1,2-Dibenzylidenecyclohexane (VIII).—A solution of 19.9 g. (0.05 mole) of phosphonium salt and 9.3 g. (0.05 mole) of 2-benzylidenecyclohexanone[37] in 100 ml. of 0.5 *M* ethanolic sodium ethoxide was refluxed for 22 hr.; the reaction mixture was quenched with 150 ml. of water and extracted with two 100 ml. portions of ether. The combined ether extracts were dried over magnesium sulfate and concentrated on a steam bath; trituration of the residues with 50 ml. of 95% ethanol led to crystallization of the product. VIII, 3.5 g. (37.5%), was purified by washing with 200 ml. of boiling ethanol and melted at 137.5°. Concentration of the filtrates and trituration with petroleum ether (b.p. 90°) yielded 7.2 g. (51%) of triphenylphosphine oxide.

Anal. Calcd. for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 91.99, H, 8.03.

The ultraviolet spectrum of VIII showed a band at 285 mμ (ε 19,000) and VIII absorbed in the infrared ($CHCl_3$) at 1626 w, 1600 s, 1575 w, 1493 s, 1445 s, 1260 w, 1136 w, 1070 m, 1028 m, 971 w, 917 m–s, 838 m, and 820 w cm.$^{-1}$.

β,β-Distyrylstyrene (X).—This preparation was carried out in the same manner as that of VIII using 0.05 *M* quantities of phosphonium salt, dibenzylideneacetone, and sodium ethoxide in 100 ml. of ethanol and a reflux period of 12 hr. Isolation of the product in the same manner as for VIII gave 7.1 g. (46%) of crude X melting at 104–107°. X was recrystallized from 95% ethanol and dried under vacuum over sulfuric acid, m.p. 106–108°, lit.[12] m.p. 110°.

Anal. Calcd. for $C_{24}H_{20}$: C, 93.46; H, 6.54. Found: C, 93.22; H, 6.57.

The ultraviolet spectrum of X showed maxima at 237, 299, and 331 mμ (ε 16,400, 29,800, and 29,900). Bohlmann[12] reports maxima at 234, 295, and 330 mμ (ε 20,900, 33,900, and 29,500).

1,2,3-Tribenzylidenecyclohexane (XII).—The reaction of 13.7 g. (0.05 mole) of 2,6-dibenzylidenecyclohexanone,[37] 0.05 mole of phosphonium salt, and 0.05 mole of sodium ethoxide in 100 ml. of ethanol was carried out at reflux for 18 hr. The product was isolated in the same manner as VII. XII was obtained in a crude yield of 33.5% (5.3 g.), m.p. 110–111°; recrystallization from 95% ethanol gave a constant melting point of 113.5–114.5°. The ethanolic mother liquors from the isolation and purification of XII gave 5.45 g. (42.3%) of triphenylphosphine oxide and 1.25 g. of the starting ketone.

Anal. Calcd. for $C_{27}H_{24}$: C, 93.06; H, 6.94. Found: C, 93.18; H, 7.05.

XII showed a maximum in the ultraviolet at 275 mμ (ε 27,800) and in the infrared had bands at 1629 w, 1600 m, 1574 w, 1495 s, 1445 m–s, 1145 w–m, 1124 w–m, 1073 m, 1029 m, 917 m–s, 873 m–s, 841 w, 769 w–m, 754 w–m, 725 w, and 698 s cm.$^{-1}$.

Attempted Synthesis of 1-Benzylidenetetralin (XV).—A mixture of 7.3 g. (0.05 mole) of 1-tetralone (XIII), 0.05 mole of phosphonium salt, and 0.05 mole of *n*-butyllithium in 70 ml. of anhydrous benzene was refluxed for 21 hr., cooled, and quenched with 150 ml. of water. The aqueous layer was extracted with 150 ml. of ether and the combined organic layers were dried over sodium sulfate, and concentrated on a steam bath. Trituration of the residues with ether and petroleum ether (b.p. 30–60°) gave 7.8 g. (70%) of triphenylphosphine oxide. The filtrate was treated with 95% ethanol which led to the precipitation of 0.45 g. (6.6%) of 2-(1-tetrylidene)tetralone-1 (XIV). The product was recrystallized from 95% ethanol to give a constant melting point of 133.0–133.5°, lit.[27] m.p. 130.0–130.5°. The ultraviolet spectrum was essentially identical with that reported[38] and XIV showed a strong band at 1669 cm.$^{-1}$ (α,β-unsaturated aryl ketone).

The reaction was repeated using a 5-hr. reaction period at room temperature and a 1-hr. reflux period. The only materials isolated were triphenylphosphine oxide (31%), XIV (4.4%), and unreacted XIII (17%). XIII was isolated by Florisil chromatography (elution with benzene) of the petroleum ether fractions.

(30) H. H. Jaffe and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 196–233.

(31) Thorough studies of the spectra of the analogous benzylidenecycloalkanes have been reported: ref. 21; H. S. French and L. Wiley, *J. Am. Chem. Soc.*, **71**, 3702 (1949).

(32) A. Sandoval and L. Zeichmeister, *ibid.*, **69**, 553 (1947).

(33) C. G. Overberger and J. R. Hall, *J. Org. Chem.*, **26**, 4359 (1961).

(34) All melting points are uncorrected; microanalyses were performed by Galbraith Laboratories. Infrared spectra were recorded on Perkin-Elmer Model 21 and Beckman IR-8 spectrophotometers; ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer using dilute solutions in 95% ethanol. G.l.c. analyses were carried out on an F and M Model 500 gas chromatograph using a 21-ft. Apiezon L (16.9% on Chromosorb W, 110–120 mesh) column at a column temperature of 200° and a helium flow rate of 24 ml./min. Proton magnetic resonance spectra were determined with a Varian Associates A-60 spectrometer; we are indebted to Dr. B. L. Shapiro and Miss M. Gordon for assistance in the determination of proton spectra.

(35) (a) K. Kunze, *Ber.*, **59**, 2086 (1926); (b) J. Reese, *ibid.*, **76**, 384 (1942).

(36) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 61; N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962.

(37) D. Vorlander and K. Kunze, *Ber.*, **59**, 2078 (1926).

(38) M. Orchin, L. Reggel, and A. Friedel, *J. Am. Chem. Soc.*, **71**, 2243 (1949).

2-Benzylidenetetralone-1 (XVI).—A mixture of 5.30 g. (0.05 mole) of benzaldehyde and 7.20 g. (0.05 mole) of 1-tetralone was poured into 20 ml. of 80% sulfuric acid; after the reaction mixture was stirred for 1 hr., it solidified to a red mass which was triturated with ice water and filtered to give 10.1 g. (87%) of XVI, m.p. 103.0–103.5°. Cromwell and co-workers[39] report a melting point of 107°; the ultraviolet and infrared spectra of X agreed with reported values.[39] Attempted preparation of X by the reported method[39] was unsuccessful.

Attempted Synthesis of 1,2-Dibenzylidenetetralin (XVII).—A mixture of 0.02 mole of 2-benzylidenetetralone (XVI), 0.02 mole of phosphonium salt, and 0.02 mole of ethanolic sodium ethoxide was refluxed for 3 hr. XVI (49% recovery) and triphenylphosphine oxide (19.5%) were the only materials isolated; no evidence for the formation of XIII was observed.

Benzylidenecyclopentane (XIX). A. Reaction of Cyclopentylidenetriphenylphosphorane (XXX) and Benzaldehyde.—A mixture of 20.5 g. (0.05 mole) of cyclopentyltriphenylphosphonium bromide,[40] 5.3 g. (0.05 mole) of benzaldehyde, and 0.05 mole of *n*-butyllithium in 110 ml. of anhydrous benzene was refluxed for 3 hr., cooled, and concentrated on a steam bath. Distillation of the residues gave 2.66 g. (33.8%) of XIX, b.p. 82–84° (1 mm.), lit.[41] b.p. 85–86° (1.9 mm.). XIX had a maximum at 256 mμ (ε 18,700) and bands in the infrared at 3058 w, 3030 w–m, 2950 s, 2865 m, 2833 w, 1616 w, 1592 w, 1481 w–m, 1439 m, 1422 w–m, 1070 w, 1025 w, 1010 w, 950 vw, 905 w–m, 732 m, and 690 s cm.$^{-1}$.

B. Reaction of Benzylidenetriphenylphosphorane (III) and Cyclopentanone (XVIII).—A mixture of 0.05 mole of phosphonium salt, 0.05 mole of XVIII, and 0.05 mole of *n*-butyllithium in benzene was refluxed for 19 hr., cooled, and quenched with water. The aqueous layer was extracted with ether and the combined organic layers were dried over sodium sulfate and distilled at 0.7 mm. to yield two fractions: A, b.p. 75–80°, 0.60 g.; B, b.p. 140–155°, 0.75 g. Fraction A was subjected to g.l.c. analysis which showed two peaks (retention times 41 and 51 min.) which were identified as cyclopentylidenecyclopentanone[42] (XX) and XIX, respectively, by comparison of their g.l.c. behavior with authentic samples. Quantitative g.l.c. analysis indicated fraction A to consist of 53% XX and 47% XIX, total yields 8 and 7%, respectively. Fraction B was identified as dicyclopentylidenecyclopentanone (XXI) by a comparison of its infrared spectrum with that of an authentic sample. The structures of XX and XXI were confirmed by their proton spectra which showed only methylene absorptions (τ 7.0–8.5); the absence of olefinic proton signals[36] eliminated the possibility of *endo* isomeric structures for these compounds.

1,2-Dibenzylidenecyclopentane (XXIII).—A mixture of 5.0 g. (0.031 mole) of 2-benzylidenecyclopentanone,[43] 0.031 mole of phosphonium salt, and 100 ml. of 0.31 *M* ethanolic sodium ethoxide was refluxed for 5 hr., cooled, and filtered to give 0.90 g. of XXIII. An additional 0.30 g. of XXIII was obtaind by concentration of the filtrate for a total yield of 1.20 g. (16.8%). XXIII was recrystallized from a mixture of benzene and hexane and melted at 157–159°, lit.[33] m.p. 153.4–156.1°. Concentration of the ethanolic filtrate and trituration with petroleum ether (b.p. 30–60°) yielded 3.8 g. (47.3%) of triphenylphosphine oxide. XXIII has maxima at 236 and 332 mμ (ε 9090 and 30,500), lit.[33] λ_{max} 336 mμ (ε 30,600).

Attempted Synthesis of 1,2,3-Tribenzylidenecyclopentane (XXV).—The reaction of 2,5-dibenzylidenecyclopentanone[44] and the phosphonium salt was attempted four times using both sodium ethoxide and phenyllithium as bases for the generation of III. The only material which was isolated was unreacted ketone (78–80%).

1-Benzylideneindane (XXVII).—A mixture of 6.6 g. (0.05 mole) of 1-indanone (XXVI), 0.05 mole of phosphonium salt, and 0.05 mole of *n*-butyllithium in 70 ml. of benzene was refluxed for 23 hr., cooled, and quenched with water. The aqueous layer was extracted with 100 ml. of ether and the combined organic layers were dried over sodium sulfate and concentrated on a steam bath. Trituration of the residue with petroleum ether (b.p. 30–60°) gave 6.25 g. (45%) of triphenylphosphine oxide. The filtrate was concentrated and triturated with hot 95% ethanol to give XXVII, 0.94 g. (9.1%); XXVII was recrystallized from 95% ethanol, m.p. 73.0–74.5°, lit.[18] m.p. 73.4–74.4°.

Anal. Calcd. for $C_{16}H_{14}$: C, 93.17; H, 6.84. Found: C, 93.29, 93.07; H, 6.80, 6.74.

The reaction was repeated with a reflux time of 1 hr. After removal of triphenylphosphine oxide, the petroleum ether soluble material was chromatographed carefully on a Florisil column. The only materials isolated were XXVII (3%) and the phosphine oxide (13.6%) by elution with benzene and acetone, respectively.

2-Benzylideneindanone (XXVIII).—A mixture of 1.06 g. (0.01 mole) of benzaldehyde and 1.49 g. (0.011 mole) of 1-indanone was treated with 14 ml. of 80% sulfuric acid. The reaction mixture solidified to a brown mass after stirring for 30 min.; trituration with ice–water and filtration gave 1.65 g. (75%) of XXVIII, m.p. 106–109°, lit.[21] m.p. 109–111°. The ultraviolet spectrum of XXIII is identical with that reported.[21] The compound has previously been prepared by basic catalysis,[21] but consistently better results were obtained in the present study with the sulfuric acid catalyst.

Attempted Synthesis of 1,2-Dibenzylideneindane. Formation of 3-(1-Hydroxy-2-benzylidene-1-indanyl)-2-benzylideneindanone-1 (XXIXa).—A mixture of 5.50 g. (0.025 mole) of XXVIII, 0.025 mole of phosphonium salt, and 100 ml. of 0.25 *M* ethanolic sodium ethoxide solution was stirred at room temperature for 2 hr.; during this period the characteristic orange color of IV faded to yellow. The reaction mixture was quenched with 48% hydrobromic acid and was extracted with 100 ml. of chloroform. Concentration of the chloroform extract gave 4.60 g. (84%) of XXIXa, m.p. 214–221°. XXIXa was recrystallized from absolute ethanol to a constant melting point of 228–233°.

Anal. Calcd. for $C_{32}H_{24}O_2$: C, 87.24; H, 5.49; mol. wt., 440. Found: C, 86.55, 86.65; H, 5.48, 5.57; mol. wt., 458, 468, 453.[45]

The dimer had maxima at 248 and 295 mμ (ε 25,200 and 4970), a shoulder at 290 mμ (ε 4810), and a minimum at 276 mμ (ε 3070). XXIX showed bands in the infrared at 3058 w, 3030 w, 3003 w–m, 2933 w–m, 1701 s, 1600 m, 1582 sh, 1490 w, 1460 w–m, 1449 w–m, 1422 w, 1323 w–m, 1280 m, 1149 w, 1116 w, 1107 w, 1010 w, 952 w, 908 w, 875 w, 762 m, 725 m, and 702 m cm.$^{-1}$ ($CHCl_3$); 3580 cm.$^{-1}$ (KBr).

XXIXa was converted to its oxime by refluxing a mixture of 1 g. of XXIXa, 4 g. of potassium hydroxide pellets, and 1 g. of hydroxylamine hydrochloride in 80 ml. of 95% ethanol for 2 hr.; the mixture was filtered while hot and acidified with 10% hydrochloric acid to precipitate the oxime. After recrystallization from glacial acetic acid, the oxime of XXIX melted at 266–268°. Its infrared absorption spectrum showed the absence of any carbonyl absorption.

Anal. Calcd. for $C_{32}H_{25}NO_2$ (oxime of XXIXa): C, 84.37; H, 5.53; N, 3.08. Calcd. for $C_{32}H_{26}N_2O_2$ (bisoxime of XXIXb): C, 81.67; H, 5.57; N, 5.95. Found: C, 84.02, 84.15; H, 5.69, 5.74; N, 2.69, 2.77.

XXIXa was also prepared by refluxing a 1:1 molar mixture of XXVIII and sodium hydride in glyme for 24 hr. The product separated when the reaction mixture was quenched with water; XXIXa was collected and recrystallized from 95% ethanol, m.p. 226–228° (99.5%). The material was identical in all respects with that prepared previously.

(39) A. Hassner, N. H. Cromwell, and S. J. Davis, *J. Am. Chem. Soc.*, **79**, 230 (1957).

(40) F. Ramirez and S. Levy, *ibid.*, **79**, 67 (1957).

(41) L. S. McNamara and C. C. Price, *J. Org. Chem.*, **27**, 1230 (1962).

(42) R. Mayer, *Ber.*, **89**, 1443 (1956).

(43) A. P. Phillips and J. Mentha, *J. Am. Chem. Soc.*, **78**, 140 (1956).

(44) D. Vorlander and K. Hobohm, *Ber.*, **29**, 1836 (1896).

(45) Molecular weight determinations were carried out with a Mechrolab vapor pressure osmometer, Model 301A, using dilute solutions of the dimer in benzene at 37°. We are indebted to Mr. M. Bollinger for carrying out these determinations.

The Chemistry of Methyl Vinyl Ketone. I. The Acetoethylation of Ketones

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The anions of a number of ketones react in the Michael condensation with methyl vinyl ketone to give either acetoethylated products, the normal open-chain Michael adducts (A), or mixtures of A and cyclohexanone derivatives (B), which appear to arise from A by intramolecular aldol condensations.

The scope and limitations of the cyanoethylation[2] and pyridylethylation[3-5] of a large variety of ketones have been studied. However, a comparable study of the reactions of ketones with methyl vinyl ketone has apparently not been reported. Although many ketones have been condensed with methyl vinyl ketone, these reactions have been usually effected as part of a synthetic scheme aimed at preparing other compounds, *e.g.*, steroid intermediates. The purpose of the present paper is to study the scope and limitations of the Michael condensation of a series of representative ketones with methyl vinyl ketone.[6]

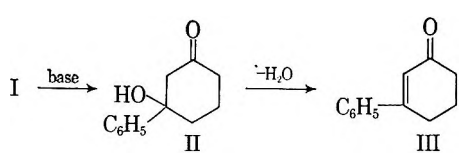
Since these reactions, in a strictly formal sense, involve the initial introduction of an acetoethyl group, $CH_3COCH_2CH_2$, into the ketone in place of an α-hydrogen atom, it is suggested that these reactions be called acetoethylations.

$$RCOCH_2R' + CH_2{=}CHCOCH_3 \xrightarrow{\text{base}} RCOCHR'(CH_2CH_2COCH_3)$$

Orienting experiments were performed with acetophenone since it has only one α-carbon atom with active hydrogen atoms. Depending on reaction conditions (Table I), the expected open-chain product (I), 1-phenylhexane-1,5-dione, 3-phenyl-3-hydroxycyclohexanone (II), 3-phenylcyclohex-2-enone (III), or a mixture of I and II was obtained. It appears that II arises from I by an intramolecular aldol condensation and III arises from the dehydration of II. It is interesting to note that, although the stoichiometry of the reaction requires only 1 mole of acetophenone per

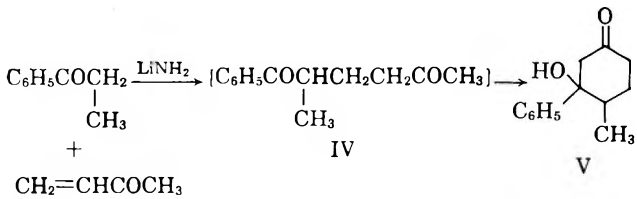
$$C_6H_5COCH_3 + CH_2{=}CHCOCH_3 \xrightarrow{\text{base}} C_6H_5COCH_2CH_2CH_2COCH_3$$

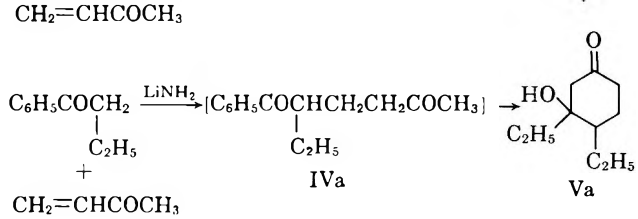
I



mole of methyl vinyl ketone, considerably higher yields of products were obtained using a 2:2:1 molar ratio of acetophenone–base–methyl vinyl ketone (compare runs 4, 5, and 6).

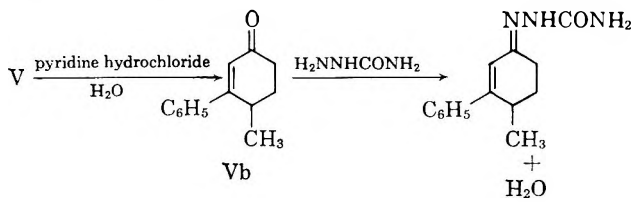
From the reactions of methyl vinyl ketone with propiophenone and *n*-butyrophenone, none of the open-chain acetoethylated products, IV and IVa, were isolated. Instead, the cyclized products, 3-phenyl-3-hydroxy-4-methylcyclohexanone (V, 52.4%) and 3-phenyl-3-hydroxy-4-ethylcyclohexanone (Va, 53%), were obtained.





The structure of V was elucidated from its infrared spectrum which showed the presence of both carbonyl and hydroxyl groups and the absence of vinyl group absorption thus ruling out the possibility that the anion of propiophenone had added across the carbonyl group of methyl vinyl ketone.

The formation of the semicarbazones of V and Va was accompanied by dehydration when these derivatives were prepared by McElvain's[7] semicarbazide hydrochloride pyridine method. In a separate experiment, it was shown that, although V is not dehydrated by pyridine alone, this dehydration was effected in 97% yield by pyridine hydrochloride.



Acetone, like acetophenone, was acetoethylated to give heptane-2,6-dione in low yield (7.4%). This 1,4-diketone had been prepared previously in 16% yield.[8] by the reaction of acetone with 4-diethylamino-2-butanone methiodide.

Methyl *n*-propyl ketone behaved like *n*-butyrophenone and gave the cyclic ketone VII in low yield (15.5%), probably *via* VI. That the initial condensation product is VI, *i.e.*, that methyl *n*-propyl ketone has been

(1) Monsanto Chemical Co. Research Fellow, 1957-1959. This paper is based on a portion of the thesis presented by N. C. Ross to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

(2) "The Chemistry of Acrylonitrile," American Cyanamid Co., 1959, pp. 18-19 and 92-120.

(3) R. Levine and M. H. Wilt, *J. Am. Chem. Soc.*, **74**, 342 (1952).

(4) M. H. Wilt and R. Levine, *ibid.*, **75**, 1368 (1953).

(5) G. Magnus and R. Levine, *J. Org. Chem.*, **22**, 270 (1957).

(6) An excellent review of much of what has been published has been summarized by E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

(7) S. M. McElvain, "The Characterization of Organic Compounds," Rev. Ed., The Macmillan Co., New York, N. Y., 1953, p. 193.

(8) N. S. Gill, K. B. James, F. Lions, and K. T. Potts, *J. Am. Chem. Soc.*, **74**, 4923 (1952).

TABLE I

REACTIONS OF ACETOPHENONE WITH METHYL VINYL KETONE (MVK)

Moles of reactants				Reaction		
Acetophenone	MVK[a]	Base	Base	time, hr.[b]	Products	% yield
0.6	0.2	0.03	Triton B[c]	2	I[d,e]	14
0.4	0.2	0.03	Triton B[c]	48	III[d,f]	8
0.4	0.2	0.08	$KOC(CH_3)_3$	2	none	
0.3	0.3	0.3	$NaNH_2$[g]	0	I	19
0.5	0.25	0.5	$NaNH_2$[g]	0	I	34
0.5	0.25	0.5	$LiNH_2$[g]	0	I	37
					II[h]	3.2

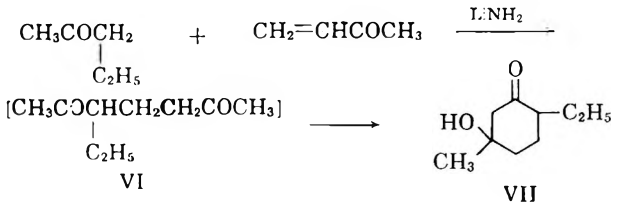
[a] MVK in 100–150 ml. of ether was added slowly to the base and acetophenone. [b] Reaction time after the addition of the MVK which required 60–80 min. [c] This is a 38% aqueous solution of benzyltrimethylammonium hydroxide. [d] Considerable amounts of polymerized MVK were also formed. [e] I is 1-phenylhexane-1,5-dione, m.p. 67.2–67.6° from petroleum ether (60–70°). *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.77; H, 7.42. Found: C, 75.80; H, 7.50. Dioxime, m.p. 122.4–123.4° from ethanol–water. *Anal.* Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.44; H, 7.31. Found: C, 65.00; H, 6.91. [f] III is 3-phenylcyclohex-2-enone, m.p. 63.8–64.2°; F. C. Novello, E. M. Christy, and J. M. Sprague [*J. Am. Chem. Soc.*, **75**, 1330 (1953)] report 63.8–64.6°. Semicarbazone, m.p. 212–213° from 95% ethanol. [g] The alkali amides were prepared in and the reactions were run in liquid ammonia. [h] II is 3-phenyl-3-hydroxycyclohexanone, m.p. 152–153° from petroleum ether (90–100°). *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.77; H, 7.42. Found: C, 75.73; H, 7.25. When II was treated with semicarbazide hydrochloride and pyridine, it was dehydrated and gave the semicarbazone of III, m.p. 212–213°. *Anal.* Calcd. for $C_{13}H_{15}N_3O$: C, 68.09. H, 6.59. Found: C, 67.92; H, 6.49.

TABLE II

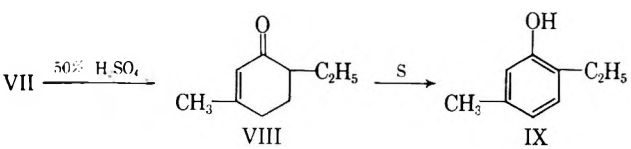
REACTIONS OF CYCLOHEXANONE AND 2-METHYLCYCLOHEXANONE WITH METHYL VINYL KETONE

Reactants			Products, % yield	
Ketone, moles	Base, moles	MVK, moles	Hydroxydecalone	Ketooctalin
Cyclohexanone, 0.5	$LiNH_2$,[a] 0.5	0.25	XI,[b] 14.4	XII,[c] 35.0
0.4	Triton B,[d] 0.03	0.2	11.2	30.6
0.4	KOH, 0.08	0.2	2.4	38.5
2-Methylcyclohexanone, 0.5	$LiNH_2$,[a] 0.5	0.25	XIV,[e] 9.5	XV,[f] 24.7
0.4	Triton B,[d] 0.09	0.2	0	45.8
0.4	KOH, 0.03	0.2	0	55.5

[a] This was prepared in and the reaction was run in liquid ammonia. [b] This is 9-hydroxy-2-decalone, b.p. 132–136°, m.p. 146.0–146.9°. *Anal.* Calcd. for $C_{10}H_{16}O_2$: C, 71.48; H, 9.60. Found: C, 71.60; H, 9.77. [c] This is 2-keto-$\Delta^{1,9}$-octalin, b.p. 103–104° at 2 mm. (see ref. 10). Both XI and XII gave the same semicarbazone, m.p. 206–207° (see ref. 10). [d] This is a 38% aqueous solution of benzyltrimethylammonium hydroxide. [e] This is 2-keto-9-hydroxy-10-methyldecalin, m.p. 120.8–121.4°. *Anal.* Calcd. for $C_{11}H_{18}O_2$: C, 72.50; H, 9.96. Found: C, 72.61; H, 9.77. [f] This is 2-keto-10-methyl-$\Delta^{1,9}$-octalin, b.p. 111–112° at 2.5 mm. (see ref. 10). Both XIV and XV gave the same semicarbazone, m.p. 204–205° (see ref. 10).



acetoethylated at its α-methylene carbon atom, has precedent in the work of Wilt and Levine[4] who showed that Michael condensations between 2-vinylpyridine and unsymmetrical dialkyl ketones occur at the more highly substituted α-carbon atoms of the ketones. The structure of VII was established with certainty by dehydrating it to 3-methyl-6-ethylcyclohex-2-enone (VIII), which was then aromatized to IX by heating it with sulfur.



Methyl isopropyl ketone did not undergo the Michael condensation with methyl vinyl ketone under the reactions used in the present study.

While the acyclic ketones showed little or no (0–15.5%) tendency to add to methyl vinyl ketone, the cyclic ketones, cyclopentanone, cyclohexanone, and 2-methylcyclohexane, reacted readily to give fair to good yields of condensation products. Cyclopentanone, when converted to its anion, was acetoethylated to give 2-(3-ketobutyl)cyclopentanone in 40% yield. This same compound had been prepared earlier in 28% yield by Gill, *et al.*,[5] by the high temperature reaction of cyclopentanone with the methiodide of 4-diethylamino-2-butanone in the presence of catalytic amounts of base. Also, Bergmann and Corett[9] found that cyclopentanone reacts with methyl vinyl ketone in the presence of a basic ion-exchange resin gave a 30% yield of $\Delta^{4,5}$-perhydroindanone-3 and none of the normal acetoethylated product.

Both cyclohexanone and 2-methylcyclohexanone reacted (Table II) with methyl vinyl ketone to give the decalone derivatives, XI, XII, XIV, and XV, probably *via* the intermediates X and XIII, respectively (see Scheme I).

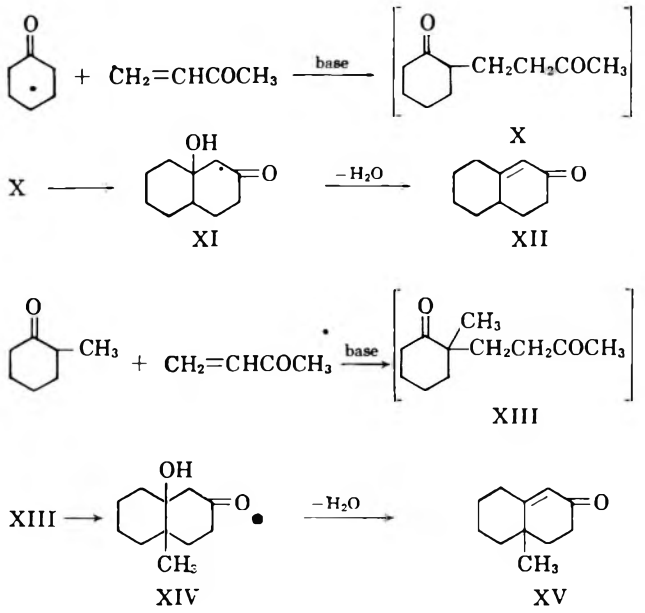
The 2-keto-$\Delta^{1,9}$-octalin (XII) had been obtained as the only product[10] in 17.3% yield by condensing the methiodide of 4-diethylamino-2-butanone with 2-carbethoxycyclohexanone followed by hydrolysis and decarboxylation. Similarly, the reaction of this methiodide with 2-methylcyclohexanone gave 2-keto-10-methyl-$\Delta^{1,9}$-octalin (XV) in 35–40% yield. More recently, Stork and Landesman[11] have prepared XII in 66% yield from the reaction of the pyrrolidine enamine

(9) E. E. Bergmann and R. Corett, *J. Org. Chem.*, **23**, 1507 (1958).

(10) E. C. DuFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

(11) G. Stork and H. K. Landesman, *J. Am. Chem. Soc.*, **78**, 5129 (1956).

SCHEME I



of cyclohexanone with methyl vinyl ketone. In addition, Johnson, *et al.*,[12] treated cyclohexanone with methyl vinyl ketone in the presence of Triton B and get a 25% yield of XI which was dehydrated to XII in high yield by reaction with sodium methoxide.

Apparently, when methyl benzyl ketone was treated with methyl vinyl ketone using lithium amide, sodium amide, Triton B (38% aqueous benzyl trimethylammonium hydroxide), or ethanolic potassium hydroxide as the condensing agent, 3-phenylheptane-2,6-dione (XVI) was formed initially. However, XVI was not isolated from the reactions. In every case (Table III), intramolecular aldol condensation occurred to give substituted cyclohexanone derivatives. Thus, XVI may

TABLE III

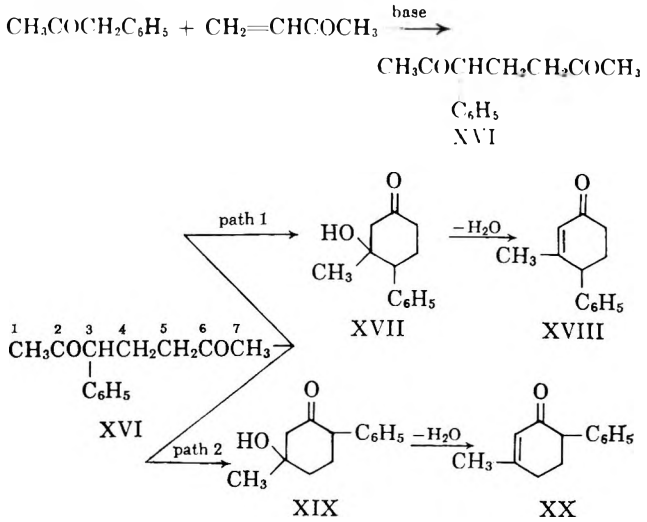
REACTIONS OF METHYL BENZYL KETONE (MBK) WITH METHYL VINYL KETONE (MVK)[a]

Reactants		
Base	Base–MBK, moles	Products, % yield
$LiNH_2$[b]	1:1	XVII,[c] 28.2
		XVIII,[d] 27.7
$NaNH_2$[b]	0.14:1	XVIII,[d] 45.3
		XX,[e] 10.3
Triton B[f]	0.14:1	XVIII,[d] 32.7
		XX,[e] 46.5
KOH[g]	0.16:1	XX,[e] 58.2

[a] Two moles of MBK per mole of MVK were used. [b] This was prepared in and the reaction was run in liquid ammonia. [c] This is 3-methyl-3-hydroxy-4-phenylcyclohexanone, m.p. 142.4–143.0° from petroleum ether (60–70°). *Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.42; H, 7.89. Found: C, 76.83; H, 7.74. [d] This is 3-methyl-4-phenylcyclohex-2-enone, b.p. 129° at 2 mm., m.p. 39.2–40.2° from petroleum ether (30–60°). *Anal.* Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.48. Found: C, 83.99; H, 4.80. Both XVII and XVIII gave the same semicarbazone, m.p. 203–204° from 95% ethanol. *Anal.* Calcd. for $C_{14}H_{17}N_3O$: C, 69.12; H, 7.04. Found: C, 68.82; H, 7.24. [e] This is 3-methyl-6-phenylcyclohex-2-enone, m.p. 62–63° from petroleum ether (b.p. 30–60°). *Anal.* Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.93; H, 7.93. [f] This is a 38% aqueous solution of benzyltrimethylammonium hydroxide. [g] This is a 30% ethanolic solution of potassium hydroxide.

(12) W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *J. Am. Chem. Soc.*, **82**, 614 (1960).

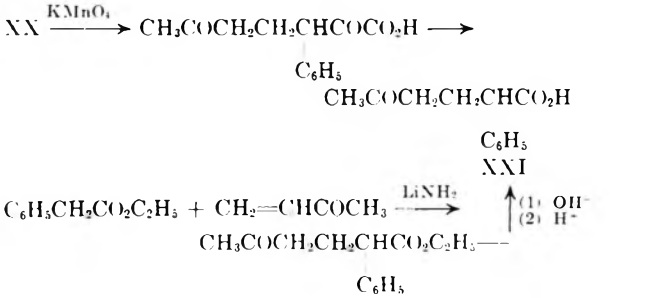
SCHEME II



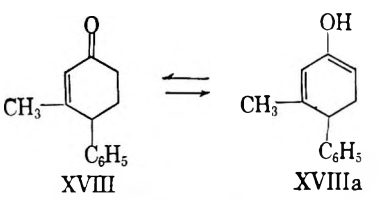
undergo intramolecular condensation in two ways as shown in Scheme II.

In path 1, the "number 2" carbonyl group of XVI is attacked by the "number 7" methyl group to give 3-methyl-3-hydroxy-4-phenylcyclohexanone (XVII). Path 2 results from the attack of the "number 1" methyl group on the "number 6" carbonyl group to give 3-methyl-3-hydroxy-6-phenylcyclohexanone (XIX). Dehydration of XVII and XIX then gives 3-methyl-4-phenylcyclohex-2-enone (XVIII) and 3-methyl-6-phenylcyclohex-2-enone (XX), respectively. Three of the possible products, XVII, XVIII, and XX, have been isolated and identified. It is interesting to note that earlier, Cologne, *et al.*,[13] isolated only XX in 63% yield from the interaction of methyl benzyl ketone (4 equiv.) with methyl vinyl ketone (1 equiv.) using potassium methoxide as the condensing agent.

The structure of XX was established by permanganate oxidation to 2-phenyl-5-ketohexanoic acid (XXI), which was shown to be identical with the acid which was obtained by hydrolysis of the condensation product of ethyl phenylacetate with methyl vinyl ketone.

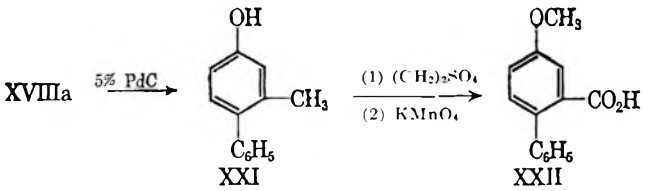


A similar oxidation was attempted without success on XVIII, the isomer of XX. However, XVIII was aromatized to XXI *via* its enol form, XVIIIa, by reaction



(13) J. Cologne, J. Dreux, and R. Chapurlat, *Compt. rend.*, **251**, 252 (1960).

with 5% palladium on charcoal. Then, XXI was methylated and the resulting ether was oxidized to 2-carboxy-4-methoxybiphenyl (XXII), a known compound.



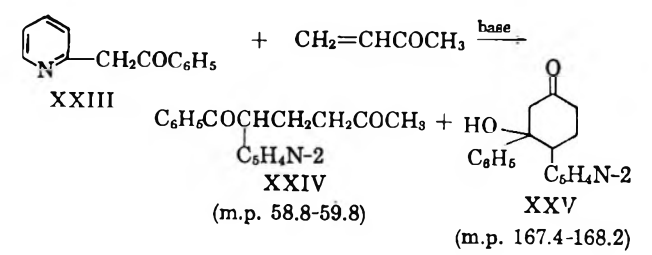
Since the 3-hydroxycyclohexanone derivatives are dehydrated during the formation of their semicarbazones, it was possible to identify XVII by showing that its semicarbazone was identical with that which was obtained from XVIII.

Finally, the reactions of the three highly reactive ketones, desoxybenzoin, 2-phenacylpyridine, and phenacylpyrazine, with methyl vinyl ketone were studied. From these reactions high yields (Table IV) of only the acetoethylated compound (in the case of phenacylpyrazine) or a mixture of the acetoethylated and the intramolecular aldol cyclohexanone derivative (in the cases of desoxybenzoin and 2-phenacylpyridine) were obtained.

That intramolecular aldol condensation did not occur in the reaction of phenacylpyrazine with methyl vinyl ketone may be due to the insolubility of the initially formed 1-phenyl-3-pyrazyl-1,5-dione in the reaction medium.

Experiments seven and eight in Table IV indicate that reaction time has a pronounced effect on the ratio of products obtained in the reaction of desoxybenzoin with methyl vinyl ketone. If the reaction is permitted to run for only 0.5 hr. after the complete addition of the reactants, nearly equivalent amounts of the open-chain compound, 1,2-diphenylhexane-1,5-dione (25.7%), and the cyclic ketone, 3,4-diphenyl-3-hydroxycyclohexanone (35%), are obtained. However, if the reaction time is increased to 1 hr., the yield of combined products is increased greatly and an 89.5% yield of the former and a 10.5% yield of the latter compound are obtained

In the acetoethylation of 2-phenacylpyridine (XXIII) two compounds, XXIV and XXV, were obtained. In this connection, it should be pointed out that earlier 2-phenacylpyridine hydrochloride had been treated with methyl vinyl ketone and alcoholic potassium hydroxide



by Beyer, *et al.*,[14] who obtained a compound, m.p. 166°. Although they did not elucidate its structure these workers claim that they obtained XXIV. From our work there is little doubt that they prepared XXV.

(14) H. Beyer, W. Lassig, and G. Schudy, *Ber.*, **90**, 592 (1957).

Experimental[15]

The Reaction of Acetophenone with Methyl Vinyl Ketone Using Lithium Amide as the Condensing Agent.—Lithium amide (0.5 mole) was prepared from lithium[16] (3.5 g., 0.5 mole) dissolved in 400 ml. of anhydrous liquid ammonia using a reactor which consisted of a 1-l., three-neck, round-bottom flask equipped with ground glass joints and fitted with a slip-seal stirrer, an addition funnel, and a Dry Ice condenser (fitted with a drying tube filled with Drierite). The procedure which was used followed that which was employed earlier.[17]

Acetophenone (0.5 mole, 60.0 g.), in 25 ml. of anhydrous ether, was added to the rapidly stirred, gray suspension of lithium amide over a 15-min. period and then the reaction mixture was stirred for an additional 15 min. Methyl vinyl ketone (0.25 mole, 17.2 g.), in 150 ml. of anhydrous ether, was added over a 1-hr. period, and the reaction was then immediately quenched by the addition of solid ammonium chloride (0.51 mole, 27.1 g.).

After the ammonia had been displaced by ether, the reaction mixture was poured onto ice, acidified with concentrated hydrochloric acid, and extracted with several portions of ether. The combined extracts were dried over anhydrous sodium sulfate, and the solvent and unreacted acetophenone were removed. Vacuum distillation of the residue gave 18.9 g. of mixed products, b.p. 125–150° at 1 mm. This mixture solidified and was fractionally recrystallized from petroleum ether (60–70°) to give 17.4 g. (37%) of 1-phenylhexane-1,5-dione, m.p. 67.2–67.6°, and 1.5 g. (3.2%) of 3-phenyl-3-hydroxycyclohexanone, m.p. 152.0–153.0°.

The Reaction of 2-Phenacylpyridine with Methyl Vinyl Ketone Using Triton B as the Condensing Agent.—Methyl vinyl ketone (0.15 mole, 10.5 g.) in 100 ml. of ether was added over a 1-hr. period to a mixture of 2-phenacylpyridine[18] (0.8 mole, 59.1 g.) and 12 ml. of 38% aqueous solution of benzyltrimethylammonium hydroxide (Triton B) in 150 ml. of ether and 30 ml. of dioxane at 0–5°. The reaction mixture was stirred for 1 hr. at room temperature during which time a solid formed and was filtered to give 16.2 g. (40.6%) of 3-phenyl-3-hydroxy-4-(2-pyridyl)cyclohexanone, m.p. 167.4–168.2° from petroleum ether (90–100°). The filtrate was poured over ice and neutralized with concentrated hydrochloric acid to give a second solid. Filtration gave 15.2 g. (37.9%) of 1-phenyl-2-(2-pyridyl)hexane-1,5-dione, m.p. 58.8–59.8° from petroleum ether (30–60°).

The Reaction of Cyclohexanone with Methyl Vinyl Ketone Using Ethanolic Potassium Hydroxide as the Condensing Agent.—Methyl vinyl ketone (0.20 mole, 14.0 g.) in 100 ml. of ether was added over a 1-hr. period to a mixture of cyclohexanone (0.40 mole, 39.2 g.) and ethanolic potassium hydroxide (0.08 mole, 4.5 g. in 15 ml. of ethanol) in 150 ml. of ether at 0°. The reaction mixture was stirred for 1 hr. at room temperature and was then processed in the usual manner to give 18.0 g. of recovered cyclohexanone, b.p. 57–61° at 27 mm.; 11.5 g. (38.5%) of 2-keto-$\Delta^{1,9}$-octalin, b.p. 106–108° at 3.5 mm.; and 0.8 g. (2.4%) of 9-hydroxy-2-decalone, m.p. 146.0–146.6°.

Proof of Structure of 2-Ethyl-5-methyl-5-hydroxycyclohexanone. A. Dehydration of 2-Ethyl-5-methyl-5-hydroxycyclohexanone.—A mixture of 2-ethyl-5-methyl-5-hydroxycyclohexanone (0.029 mole, 4.5 g.) and 75 ml. of a 50% aqueous solution of sulfuric acid was refluxed 1 hr. The reaction mixture was cooled, poured over ice, and was then extracted with ether. After the ether extracts were dried over anhydrous sodium sulfate, the solvent was removed by distillation at atmospheric pressure. The residue consisted of 3.9 g. of what was believed to be crude 3-methyl-6-ethylcyclohex-2-enone and was used directly in the next reaction.

B. **Aromatization of 3-Methyl-6-ethylcyclohex-2-enone.**—A mixture of 3-methyl-6-ethylcyclohex-2-enone (0.29 mole, 3.9 g.) and sulfur (0.29 mole, 0.962 g.) was refluxed for 1 hr. The reaction mixture was extracted with ether and the ether was evaporated leaving a tarry residue. The tarry residue was taken up in petroleum ether (60–70°) from which an oil separated.

(15) The methyl vinyl ketone which was used in this study was supplied through the courtesy of Charles Pfizer and Co., New York, N. Y.

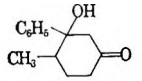
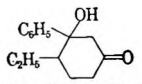
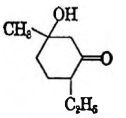
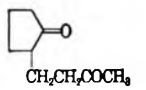
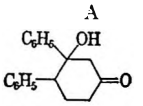
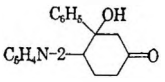
(16) The lithium which was used in this study was supplied through the courtesy of Lithium Corporation of America.

(17) M. Hamell and R. Levine, *J. Org. Chem.*, **15**, 162 (1950).

(18) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

TABLE IV

REACTIONS OF OTHER KETONES WITH METHYL VINYL KETONE[a]

Ketone, (moles)	Base (moles)	Reaction time, hr.	Product	% yield	B.p. (mm.) or m.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Propiophenone (0.5)	$LiNH_2$[b] (0.5)	0[c]		52.4	133–134[d,e]	$C_{13}H_{7}O_2$	76.42	76.36	7.89	7.67
n-Butyrophenone (0.5)	$LiNH_2$[b] (0.5)	0[c]		53.0	133–134[d,f]	$C_{14}H_{19}O_2$	77.07	76.75	7.31	7.57
Acetone (0.5)	$LiNH_2$[b] (0.5)	0[c]	$CH_3CO(CH_2)_3COCH_3$	7.4	97–103 (12)[g]					
Methyl *n*-propyl (0.5)	$LiNH_2$[b] (0.5)	0[c]		15.5	120.2–120.8[h]	$C_9H_{16}O_2$	69.20	68.86	10.33	10.05
Cyclopentanone (0.5)	$LiNH_2$[b] (0.5)	0[c]		40	98–99 (2)[i–k]					
Phenacylpyrazine (0.15)	Triton B[l] (6 ml.)	1.0	$C_6H_5COCHCH_2CH_2COCH_3$ | $C_4H_3N_2$	95.0	107.6–108.0[m]	$C_{16}H_{16}N_2O_2$	71.68	71.59	6.01	5.96
Desoxybenzoin (0.275)	Triton B[l] (6 ml.)	0.5	$C_6H_5COCH(C_6H_5)CH_2CH_2COCH_3$	25.7	71.6–72.2[n]	$C_{18}H_{18}O_2$	81.19	81.43	6.81	7.28
			A  B	35.0	208.5–209.5[o]	$C_{18}H_{18}O_2$	81.19	81.06	6.81	7.04
(0.3)	(7 ml.)	1.0	A	89.0	71.6–72.2					
			B	10.5	208.5–209.5					
2-Phenacylpyridine (0.3)	Triton B[l] (12 ml.)	1.0	$C_6H_5COCHCH_2CH_2COCH_3$ | C_5H_4N—2 XXIII	40.6	58.8–59.8[p]	$C_{17}H_{17}NO_2$	76.38	75.88	6.43	6.20
			 XXIV	37.9	167.4–168.2[q]	$C_{17}H_{17}NO_2$	76.38	76.46	6.43	6.74

[a] In all experiments 1 equiv. of methyl vinyl ketone was used for 2 equiv. of the ketone which was being acetoethylated. [b] The reaction was run in a mixture of 400 ml. of liquid ammonia and 250 ml. of anhydrous ether as the solvent. [c] The reaction was quenched with solid ammonium chloride immediately after the MVK was added. [d] Recrystallized from petroleum ether (90–100°). [e] By using the semicarbazide hydrochloride–pyridine method, the product gave the semicarbazone of 3-phenyl-4-methylcyclohex-2-enone, m.p. 204–205° from 95% ethanol. *Anal.* Calcd. for $C_{14}H_{17}N_3O$: C, 69.12; H, 7.04. Found: C, 69.27; H, 6.87. [f] The product gave (see footnote *e*) the semicarbazone of 3-phenyl-4-ethylcyclohex-2-enone, m.p. 194–195° from 95% ethanol. *Anal.* Calcd. for $C_{15}H_{19}N_3O$: C, 70.02; H, 7.44. Found: C, 69.98; H, 7.49. [g] Disemicarbazone, m.p. 212–213° from 95% ethanol [R. G. Fargher and W. H. Perkin, *J. Chem. Soc.*, **105**, 1361 (1914)]. [h] The product gave (see footnote *e*) the semicarbazone of 3-methyl-6-ethylcyclohex-2-enone, m.p. 200–201° from 95% ethanol. *Anal.* Calcd. for $C_{10}H_{17}N_3O$: C, 61.50; H, 8.78. Found: C, 61.23; H, 8.94. [i] This compound gave a disemicarbazone, m.p. 220–221°. *Anal.* Calcd. for $C_{11}H_{20}N_6O_2$: C, 49.23; H, 7.55. Found: C, 49.41; H, 7.53. [j] Ref. 10 reports the melting point of this desemicarbazone to be 229°. [k] This reaction failed with Triton B as the catalyst. [l] Triton B is a 38% aqueous solution of benzyltrimethylammonium hydroxide. [m] This compound gave a disemicarbazone, m.p. 205–206° from 95% ethanol. *Anal.* Calcd. for $C_{18}H_{22}N_8O_2$: C, 56.52; H, 5.80. Found: C, 56.30; H, 5.45. [n] This compound gave a dioxime, m.p. 118.8–119.8° from 95% ethanol. *Anal.* Calcd. for $C_{18}H_{20}N_2O_2$: C, 73.16; H, 6.82. Found: C, 73.43; H, 6.89. [o] This compound (see footnote *c*) gave the semicarbazone of 3,4-diphenylcyclohe -2-enone, m.p. 218–219° from 95% ethanol. *Anal.* Calcd. for $C_{18}H_{19}N_3O$: C, 74.97; H, 5.96. Found: C, 75.12; H, 6.39. [p] This compound gave a disemicarbazone, m.p. 212.0–212.5° from 95% ethanol. *Anal.* Calcd. for $C_{19}H_{23}N_7O_2$: C, 59.83; H, 6.08. Found: C, 59.51; H, 5.75. [q] This compound (see footnote *e*) gave the semicarbazone of 3-phenyl-4-(2-pyridyl)cyclohex-2-enone, m.p. 215.5–216.0° from 95% ethanol. *Anal.* Calcd. for $C_{18}H_{19}N_4O$: C, 70.33; H, 6.23. Found: C, 69.99; H, 5.99.

The oil consisted of 1.0 g. (25.9%) of crude 2-ethyl-5-methylphenol.

A sample of the 2-ethyl-5-methylphenol was converted to its *p*-nitrobenzoate, m.p. 87.8–88.2° (from 95% ethanol),[19] alone and when mixed with an authentic sample.

Proof of Structure of 3-Methyl-6-phenylcyclohex-2-enone.—The reactor was charged with 3-methyl-6-phenylcyclohex-2-enone (0.025 mole, 4.7 g.) dissolved in 50 ml. of acetone. Potassium permanganate (0.072 mole, 12.0 g.) was added over a 2-hr. period holding the reaction temperature at 0° by means of an ice bath. After complete addition of the potassium permanganate, the reaction mixture was stirred for 18 hr. at room temperature. The solid which was present was removed by filtration and washed with 30 ml. of acetone. The solid was then suspended in 250 ml. of water and a solution of 30 ml. of concentrated sulfuric acid in 75 ml. of water was added slowly. Then solid sodium bisulfite was added in small portions until the reaction mixture became homogenous. The aqueous solu-

(19) G. Baddeley, *J. Chem. Soc.*, 330 (1944).

tion was then extracted with several portions of ethyl acetate. The extracts were combined and dried over anhydrous sodium sulfate, and then the ethyl acetate was removed by atmospheric distillation. Vacuum distillation of the product residue gave 2.0 g. (59.1%) of 2-phenyl-5-ketohexanoic acid, b.p. 155–184° at 2.5 mm., m.p. 69.8–70.2° from petroleum ether alone and when mixed with an authentic sample.

Synthesis of an Authentic Sample of 2-Phenyl-5-ketohexanoic Acid.—Ethyl 2-phenyl-5-ketohexanoate was prepared from the reaction of ethyl phenylacetate and methyl vinyl ketone. The ester (0.019 mole, 4.0 g.) was added to a solution of potassium hydroxide (0.23 mole, 13.0 g.) in 50 ml. of water. The mixture was refluxed for 2 hr., poured into 100 ml. of cold water, acidified with dilute hydrochloric acid, and extracted with several portions of ether. The combined extracts were dried over anhydrous sodium sulfate and the solvent was distilled. The residue solidified and gave 4.0 g. (75.5%) of 2-phenyl-5-ketohexanoic acid, m.p. 69.2–70.5° from petroleum ether (30–60°). A mixture melting point between this acid and that which was obtained in the last experiment showed no depression.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.56; H, 6.76.

This keto acid gave a 2,4-dinitrophenylhydrazone, m.p. 167.6–168.6° from 95% ethanol.

Anal. Calcd. for $C_{18}H_{18}N_4O_6$: C, 55.95; H, 4.70. Found: C, 55.72; H, 4.42.

Attempted Oxidation of 3-Methyl-4-phenylcyclohex-2-enone.—3-Methyl-4-phenylcyclohex-2-enone (0.025 mole, 4.7 g.) was dissolved in 50 ml. of acetone at 0°. Potassium permanganate (0.095 mole, 15.0 g.) was added over a 2-hr. period maintaining the reaction temperature at 0°, and the mixture was then stirred at room temperature for 48 hr. The reaction was processed using the method described above in the oxidation of the isomeric ketone, 3-methyl-6-phenylcyclohex-2-enone, to give 3.9 g. (83%) of recovered 3-methyl-4-phenylcyclohex-2-enone, b.p. 100–103° at 0.3 mm., m.p. 39–40°.

Proof of Structure of 3-Methyl-4-phenylcyclohex-2-enone. A. Reduction of 3-Methyl-4-phenylcyclohex-2-enone.—3-Methyl-4-phenylcyclohex-2-enone (0.015 mole, 3.0 g.) and 0.6 g. of 5% palladium on charcoal were dispersed in 3.0 ml. of *p*-cymene in a 5-ml. flask connected to a reflux condenser. Using a metal bath as a heating source, the reaction mixture was refluxed at 180° for 30 hr. Nitrogen gas was used intermittently to flush out the hydrogen gas produced in the reaction. At the end of the reaction period, the mixture was cooled and the palladium catalyst was filtered. The solution was poured over ice and made basic with 50% sodium hydroxide. An organic layer separated. This consisted of *p*-cymene and unreacted 3-methyl-4-phenylcyclohex-2-enone and was discarded. The aqueous phase was made acid with hydrochloric acid and extracted with several portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and then the ether was removed by distillation at atmospheric pressure. Vacuum distillation of the residue gave 1.6 g. (53.4%) of 4-hydroxy-2-methylbiphenyl, b.p. 112–122° at 0.6 mm.[20]

B. Reaction of 2-Methyl-4-hydroxybiphenyl with Dimethyl Sulfate.—2-Methyl-4-hydroxybiphenyl (0.0054 mole, 1.0 g.), sodium hydroxide (0.0054 mole, 0.20 g.), and dimethyl sulfate (0.0054 mole, 0.7 g.) in 8 ml. of water were heated in a boiling water bath for 0.5 hr. The reaction mixture was cooled and extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and then the ether was removed by distillation. Approximately 1.0 g. of a residue remained. This was assumed to be 2-methyl-4-methoxybiphenyl and was used directly in the next reaction.

C. Oxidation of 2-Methyl-4-methoxybiphenyl.—2-Methyl-4-methoxybiphenyl (0.005 mole, 1.0 g.) and sodium hydroxide (0.10 mole, 4.0 g.) were placed in 60 ml. of water. Potassium permanganate (0.015 mole, 2.4 g.) was added, and then the reaction mixture was stirred between 90–100° for 30 min. at which time the red color of the mixture was discharged. The reaction mixture was filtered, and the aqueous layer was acidified and extracted with ether. The ether was evaporated and a solid residue (0.5 g., 43.8%) remained of crude 4-methoxybiphenyl-2-carboxylic acid. After recrystallization from water the 2-carboxy-4-methoxybiphenyl melted at 139–141°[20] alone and when mixed with an authentic sample.

(20) N. Chatterjee, *J. Indian Chem. Soc.*, **12**, 410 (1935).

The Chemistry of Methyl Vinyl Ketone. II. Reactions with Esters, β-Keto Esters, Malonic Ester, Amines, Tar Bases, and Inorganic Salts

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Several esters, β-keto esters, malonic ester, amines, and inorganic salts have been acetoethylated in good yields with methyl vinyl ketone. Although γ-picoline gives the expected acetoethylated product, 5-(4-pyridyl)-2-pentanone, the reaction of α-picoline with methyl vinyl ketone gives the alcohol, 3-(2-picolyl)-3-hydroxy-1-butene. A possible explanation for these anomalous results is presented.

In the first paper of this series,[2] we described the Michael condensations of a series of ketones, as the addenda, with methyl vinyl ketone as the acceptor molecule. The present report is concerned with the use of esters, β-keto esters, malonic ester, amines, tar bases, and inorganic salts as addenda.

Reactions of Methyl Vinyl Ketone (II) with Simple Esters.—The attempted acetoethylation of ethyl acetate with II using both potassium *t*-butoxide and lithium amide as the condensing agents gave none of the expected product, ethyl 5-ketohexanoate. The former reaction gave polymer and starting materials, while, in the latter reaction, ethyl acetate was self-condensed to give a 40% yield of ethyl acetoacetate.

Although the reaction of II with ethyl phenylacetate (I) using potassium *t*-butoxide as the condensing agent gave a 28.5% yield (see Table I) of the desired product, ethyl 2-phenyl-5-ketohexanoate (III), repeating this reaction with lithium amide as the condensing agent gave a mixture of III (29.5%) and 1,3-diphenyl-3-carbethoxyheptane-2,6-dione (VI, 13.8%). Apparently I self-condensed to ethyl α,γ-diphenylacetoacetate (IV), which is then acetoethylated to give VI (p. 2348).

Reactions of II with Malonic Ester and β-Keto Esters.—Malonic ester was acetoethylated to give good yields, 40.8% and 82.7%, respectively, of the expected product, ethyl 2-carbethoxy-5-ketohexanoate (VII) using Triton B and ethanolic potassium hydroxide as the condensing agents. The structure of the product

(1) Monsanto Chemical Co. Research Fellow, 1957–1959. This paper is based on a portion of the thesis submitted by N. C. Ross to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

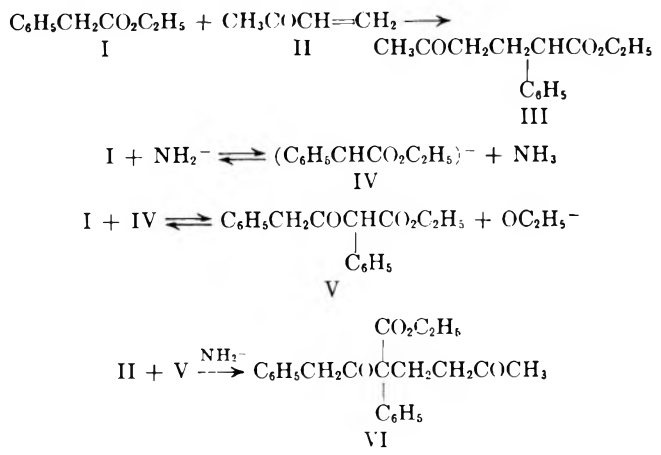
(2) N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2341 (1964).

TABLE I

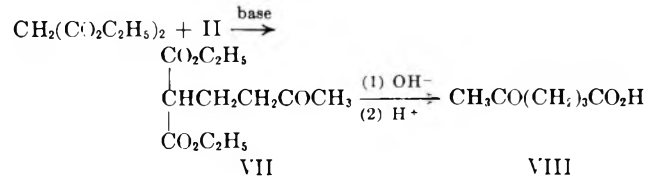
REACTIONS OF VARIOUS SUBSTRATES WITH METHYL VINYL KETONE[a]

Substrate (moles)	Base (moles)	Product	% yield	B.p. (mm.) or m.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$C_6H_5CH_2CO_2C_2H_5$ (0.2)	KOC_4H_9-t (0.054)	$CH_3COCH_2CH_2CHCO_2C_2H_5$ (III, C_6H_5)	28.5	113 (0.38)	$C_{14}H_{18}O_3$[b]	71.65	71.62	7.73	7.78
(0.5)	$LiNH_2$ (0.5)	III	29.5	157–163 (1.7)					
		$C_6H_5CH_2COCCH_2CH_2COCH_3$ (VI, $CO_2C_2H_5$, C_6H_5)	13.8	125.2–126.0	$C_{22}H_{24}O_4$	74.97	74.69	6.87	7.08
$CH_2(CO_2C_2H_5)_2$ (0.4)	Triton B[c] (5 ml.)	$CH(CO_2C_2H_5)_2(CH_2CH_2COCH_3)$ (VII)	40.8	119–120 (1.8)					
(0.4)	KOH[d] (0.1)	VII	82.7		$C_{11}H_{18}O_5$	57.30	56.99	7.88	7.65
$CH_3COCH_2CO_2C_2H_5$ (0.4)	Triton B[c] (5 ml.)	$CH_3COCHCO_2C_2H_5$ ($CH_2CH_2COCH_3$)	48.2	126–128 (4)[e]					
(0.5)	KOH[d] (0.13)	IX	90.7						
$C_6H_5COCH_2CO_2C_2H_5$ (0.4)	Triton B[c] (5 ml.)	$C_6H_5COCHCO_2C_2H_5$ ($CH_2CH_2COCH_3$) (XI)	86.3	181–183 (3)	$C_{15}H_{18}O_4$	68.70	68.54	6.92	6.71
n-$C_3H_7NH_2$ (0.4)	f	$(n\text{-}C_3H_7NH_2CH_2CH_2COCH_3)^+ HC_2O_4^-$ (XIV)	94.2	149.4–149.8 dec.[g]	$C_9H_{17}NO_5$	49.30	48.90	7.83	8.03
$C_6H_{11}NH_2$[h] (0.4)	f	$(C_6H_{11}NH_2CH_2CH_2COCH_3)^+ Cl^-$ (XV)	94.5	131.0–132.0[i]	$C_{10}H_{19}ClNO$	58.37	58.07	9.80	9.49
t-$C_4H_9NH_2$ (0.4)	f	$(t\text{-}C_4H_9NH_2CH_2CH_2COCH_3)^+Cl^-$ (XVI)	62.3	123.8–124.8[j]	$C_8H_{18}ClNO$	53.40	53.05	9.60	9.74
$C_6H_5NH_2$ (0.6)	f	$C_6H_5NHCH_2CH_2COCH_3$ (XIII)	69.0	113–116 35.2–35.8 (1.5)[k]					
$(C_2H_5)_2NH$ (0.8)	f	$(C_2H_5)_2NCH_2CH_2COCH_3$ (XVII)	92.5	69–71 (12)[l]					
C_4H_9NO[m] (0.4)	f	$C_4H_8ONCH_2CH_2COCH_3$ (XVIII)	89.3	85–87 (2)[n]					
$C_5H_4NCH_3$-2[o] (0.5)	$NaNH_2$ (0.5)	$(C_6H_4NCH_2\text{-}2)C(OH)(CH_3)(CH{=}CH_2)$ (XXIII)	22.2	79.5 (1.8)[p]	$C_{10}H_{13}NO$	73.59	73.24	7.84	7.94
	C_6H_5Li (0.5)	XXIII	61.5						
$C_5H_4NCH_3$-4[q] (0.5)	$NaNH_2$ (0.5)	$(C_6H_4NCH_2\text{-}4)CH_2CH_2COCH_3$ (XIX)	24.7	112–114 (2)[r]					
Na_2S (0.4)		$CH_3COCH_2CH_2SH$ (XXVII)	28.8	77 (30)[s]	C_4H_8OS	45.20	45.31	7.75	7.65
		$(CH_3COCH_2CH_2)_2S$ (XXVIII)	29.9	102–107 (1)[t]					
KCN (0.2)	CH_3CO_2H (0.2)	$CH_3COCH_2CH_2CN$ (XXIX)	39.6	112–113 (15)[u]					

[a] In all experiments 1 equiv. of methyl vinyl ketone was used for 2 equiv. of the substrate. [b] 2,4-Dinitrophenylhydrazone, m.p. 88–89° from 95% ethanol. *Anal.* Calcd. for $C_{22}H_{22}N_4O_8$: C, 57.96; H, 5.48. Found: C, 57.79; H, 5.55. [c] This is a 38% aqueous solution of benzyltrimethylammonium hydroxide. [d] Dissolved in 20 ml. of 95% ethanol. [e] See ref. 5. [f] No added catalyst. [g] Picrate of 4-*n*-propylamino-2-butanone, m.p. 158.4–159.4°, from 95% ethanol. *Anal.* Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.57; H, 5.06. Found: C, 43.38; H, 5.37. [h] This is cyclohexylamine. [i] Benzenesulfonamide of 4-cyclohexylamino-2-butanone, m.p. 106.6–107.4°. *Anal.* Calcd. for $C_{16}H_{23}NO_4S$: C, 62.10; H, 7.51. Found: C, 61.80; H, 7.32. Hydrogen oxalate of 4-*t*-butylamino-2-butanone, m.p. 125.6–125.8°. *Anal.* Calcd. for $C_{10}H_{19}NO_5$: C, 51.48; H, 8.21. Found: C, 51.15; H, 8.01. [k] Semicarbazone, m.p. 163–164° [A. T. Babazan and N. P. Gambaryan, *Izv. Akad. Nauk. Arm., SSR*, **3**, 563 (1950); *Chem. Abstr.*, **47**, 3266 (1953)]. Also see ref. 7. [l] See ref. 9. [m] This is morpholine. [n] Picrate, m.p. 112.6–113.6° (see ref. 10). [o] This is 2-picoline. [p] Picrate, m.p. 143.8–144.8° from 95% ethanol. *Anal.* Calcd. for $C_{16}H_{16}N_4O_8$: C, 48.99; H, 4.11. Found: C, 48.69; H, 4.30. Picrate of 5-(2-pyridyl) 2-pentanone, m.p. 106° (see ref. 13). [q] This is 4-picoline. [r] See ref. 11. [s] 2,4-Dinitrophenylhydrazone, m.p. 129.2–129.8° from 95% ethanol. *Anal.* Calcd. for $C_{10}H_{12}N_4O_4S$: C, 42.24; H, 4.26. Found: C, 41.94; H, 4.09. [t] Disemicarbazone, m.p. 226–227° from 95% ethanol (see ref. 19). [u] 2,4-Dinitrophenylhydrazone, m.p. 146.0–146.8° from 95% ethanol (see ref. 14).

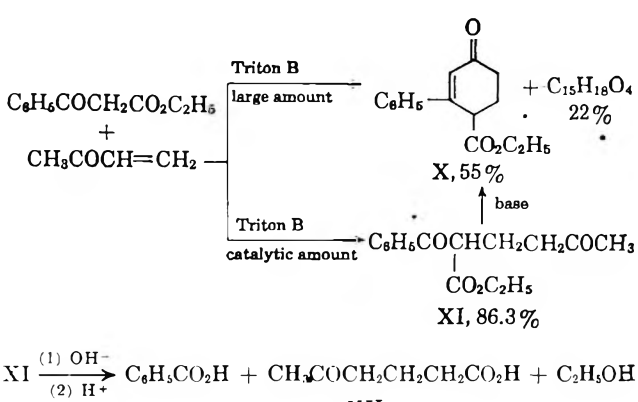


was established by hydrolysis and subsequent decarboxylation to the known 5-ketohexanoic acid (VIII) in 41.6% yield. Prior to our work, Tsuruta[3] effected the acetoethylation of dimethylmalonate in unreported yield using a catalytic amount of sodium methoxide as the condensing agent. Also, Kress[4] diacetoethylated malonic ester in 85% yield by the interaction of the ester (1 equiv.) with II (2 equiv.) in the presence of Triton B.



Ethyl acetoacetate also condenses with II to give good to high yields of 3-carbethoxyheptane-2,6-dione (IX) when either Triton B (48.2%) or ethanolic potassium hydroxide (90.7%) is used as the condensing base. This compound has also been prepared similarly by Henecka[5] in 85–88% yield except that sodium methoxide was used as the condensing agent.

Walker[6] has reported that the reaction of essentially equivalents of ethyl benzoylacetate and II in the presence of a large amount of Triton B gave a 55% yield of 3-phenyl-4-carbethoxycyclohex-2-enone (X) and 22% yield of a compound, $C_{15}H_{18}O_4$, whose structure was not elucidated. In the present study, it was found that none of X was obtained when ethyl benzoylacetate (2 equiv.) was allowed to react with II (1 equiv.) in the presence of a catalytic amount of Triton B. Instead, the normal acetoethylated product, 1-phenyl-2-carbethoxyhexane-1,5-dione (XI), was obtained in 86.3% yield. It is quite likely that, in Walker's reaction, XI was formed initially and that in the presence of the large amount of Triton B it underwent intramolecular aldol condensation followed by dehydration to give X. The structure of XI was established by cleaving it with alkali to give the expected products, benzoic acid and 5-ketohexanoic acid (XII) (see col. 2. top).



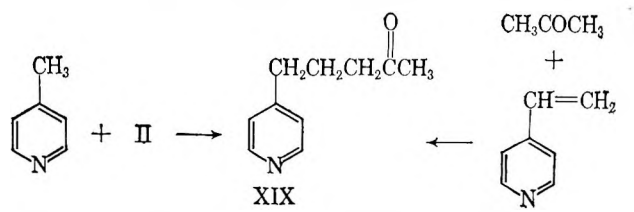
Reactions of II with Amines.—With the exception of a few aromatic amines,[7,8] the addition of primary amines to II appears not to have been reported. The amines are apparently sufficiently basic so that they add to II without any added catalyst.

Although Murata and Arai[7] reported that a 2-week reaction period is necessary to acetoethylate aniline in 78% yield, in the present study a 69% yield of 4-anilino-2-butanone (XIII) was isolated after a reaction time of only 20 hr. This ketoamine decomposes upon distillation but it was purified and stored as a white, crystalline solid.

Three primary alkylamines added readily to II: Since the products are unstable as the free bases, they were isolated and purified as their hydrogenoxalates or hydrochlorides. Thus, 4-*n*-propylamino-2-butanone hydrogen oxalate (XIV, 94.2%), 4-cyclohexylamino-2-butanone hydrochloride (XV, 94.5%), and 4-*t*-butylamino-2-butanone hydrochloride (XVI, 62.3%) were prepared.

Diethylamine and II gave 4-diethylamino-2-butanone (XVII) in 92.5% yield as compared with a 66% yield by the Mannich reaction.[9] Similarly, the acetoethylation of morpholine gave N-(3-ketobutyl)morpholine (XVIII) in 89.3% yield as compared with a 73% yield by the Mannich reaction.[10]

Reactions of II with Tar Bases—2-Picoline and 4-picoline, both of which have acidic hydrogen atoms in their methyl groups, have been condensed with II. The sodium derivative of 4-picoline was acetoethylated to give 5-(4-pyridyl)-2-pentanone (XIX, 24.7%) which had been prepared previously[11] in 5% yield by the condensation of acetone with 4-vinylpyridine. By contrast, the sodium derivative of 2-picoline does not undergo Michael addition to II but reacts with this



ketone by what, in an over-all sense, amounts to 1,2-addition to give the tertiary alcohol, 3-(2-picolyl)-3-hydroxy-1-butene (XX), in 22.2% yield. The yield of XX is increased to 61.5% when 2-picolyllithium (prepared from 2-picoline and phenyllithium) is used in place of 2-picolylsodium.

(3) T. Tsuruta, *Bull. Inst. Chem. Res. Kyoto Univ.*, **31**, 190 (1953); *Chem. Abstr.*, **49**, 6183 (1955).

(4) B. H. Kress, U. S. Pat. 2,540,267; *Chem. Abstr.*, **45**, 5720 (1951).

(5) H. Henecka, *Ber.*, **81**, 179 (1948).

(6) G. N. Walker, *J. Am. Chem. Soc.*, **77**, 3664 (1955).

(7) N. Murata and H. Arai, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **56**, 809 (1953).

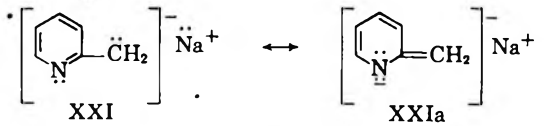
(8) H. Hopff and H. Spong, German Patent, 840,546 (June 3, 1952); *Chem. Abstr.*, **47**, 1739 (1953).

(9) E. C. du Feu, F. J. McQuillan, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

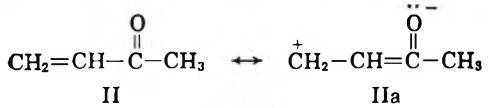
(10) R. H. Harradence and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1938); *Chem. Abstr.*, **37**, 5855 (1943).

(11) G. Magnus and R. Levine, *J. Org. Chem.*, **22**, 270 (1957).

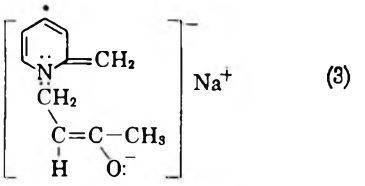
A possible scheme to explain the difference in the nature of the products which are obtained from the reactions of 2- and 4-picoline with II is shown in eq. 1–4.



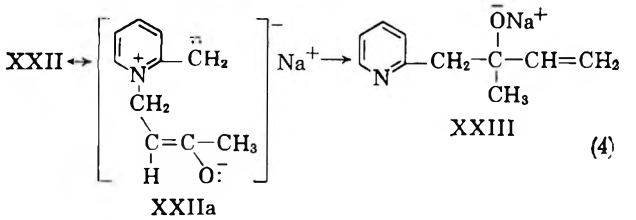
(1)



(2)



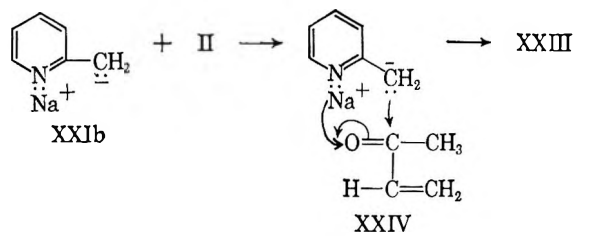
(3)



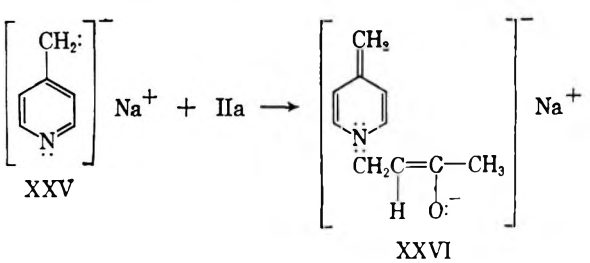
(4)

It is envisioned that the contributing resonance structure XXIa reacts with IIa by forming a carbon to nitrogen bond to give XXII (eq. 3). Then, XXIIa (one of the resonance forms of XXII) undergoes intramolecular reaction with the formation of a carbon to carbon bond and rupture of a carbon to nitrogen bond. The over-all result is the formation of XXIII, the sodium salt of 3-(2-picolyl)-3-hydroxy-1-butene.

An alternate route can be imagined for the formation of XXIII. If XXI is envisioned as having the extreme structure XXIb with the sodium ion electrostatically bonded to nitrogen, then XXIb may react with II by forming a carbon to carbon bond to give XXIII *via* the six-membered transition state (XXIV).



While 4-picolylsodium (XXV) can also react with IIa by forming a carbon to nitrogen bond to give XXVI, which is analogous to XXII, subsequent rearrangement of XXVI cannot occur to give the 4-pyridyl isomer of XXIII. Compound XXVI can only revert to IIa and XXV, which then undergo a normal Michael condensation to give XIX.



That the tertiary alcohol was obtained in the 2-picoline reaction rather the isomeric acetoethylated product, 5-(2-pyridyl)-2-pentanone, was shown by a comparison of the physical properties of the alcohol with those of an authentic sample of the ketone.[12,13]

Reactions of II with Inorganic Salts.—Finally, two salts containing highly nucleophilic groups, *viz.*, sodium sulfide and potassium cyanide, were added to II. The reaction of sodium sulfide, with II in aqueous solution gave two products, 4-mercapto-2-butanone (XXVII, 28.8%) and bis(3-ketobutyl) sulfide (XXVIII, 29.9%). These results, which were obtained by using 2 equiv. of sodium sulfide per equivalent of II in an attempt to make XXVII the only or major product, appear to indicate that the initially formed ketomercaptan reacts more rapidly with more II to give the thio ether than the sodium sulfide reacts with II to give the mercaptan.

$$Na_2S + II \longrightarrow \underset{\text{XXVII}}{CH_3COCH_2CH_2SH} + \underset{\text{XXVIII}}{(CH_3COCH_2CH_2)_2S}$$

In order to have potassium cyanide react with II it was found necessary to produce hydrogen cyanide. This was done by liberating the hydrogen cyanide *in situ* by adding the potassium cyanide slowly to an ethanolic solution of II and glacial acetic acid. In this way a 39.6% yield of γ-ketovaleronitrile (XXIX) was obtained. The present one-step route to this

$$KCN + II \xrightarrow{CH_3CO_2H} \underset{\text{XXIX}}{CH_3COCH_2CH_2CN}$$

ketonitrile is superior to that in the literature[14] which involves the cyanoethylation of nitroethane to 4-nitrobutylcyanide in 29% yield followed by hydrolysis to the desired product in unreported yield.

Experimental[15]

Reaction of Ethyl Phenylacetate with II Using Lithium Amide as the Condensing Agent.—Lithium amide (0.5 mole), ethyl phenylacetate (0.5 mole), and II (0.25 mole) were allowed to react as described earlier[2] for the acetoethylation of acetophenone. The reaction mixture was poured onto ice and was extracted (basic extract) with several portions of ether. The aqueous phase was then acidified with dilute hydrochloric acid and was extracted (acidic extract) with several portions of ether. Both extracts were dried over anhydrous sodium sulfate and the solvent was distilled. Vacuum distillation of the residue from the basic extract gave 42.3 g. (51.6%) of recovered ethyl phenylacetate, b.p. 70–75° at 1.7 mm.; 17. g. (29.5%) of ethyl 2-phenyl-5-ketohexanoate (III), b.p. 113° at 0.38 mm.; 8.0 g. (13.8%) of 1,3-diphenyl-3-carbethoxyheptane-2,6-dione (VI), b.p. 157–163° at 1.7 mm. (m.p. 125.2–126.0° from 95% ethanol); and 13.0 g. of a tarry, nondistillable residue. The diketo ester gave a bis-2,4-dinitrophenylhydrazone, m.p. 192–193° (from 95% ethanol).

Anal. Calcd. for $C_{34}H_{32}N_8O_{10}$: C, 57.29; H, 4.53. Found: C, 57.41; H, 4.57.

Distillation of the residue from the acidic extract gave 4.0 g. (5.9%) of phenylacetic acid, m.p. 76–77° alone and when mixed with an authentic sample.

(12) W. E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, **69**, 2461 (1947).

(13) R. Levine and M. H. Wilt, *ibid.*, **74**, 342 (1952).

(14) G. D. Buckley, T. J. Elliott, F. G. Hunt, and A. Lowe, *J. Chem. Soc.*, 1505 (1947).

(15) The methyl vinyl ketone which was used in this study was supplied through the courtesy of Charles Pfizer and Co., New York, N. Y.

Reaction of Diethyl Malonate with II Using Ethanolic Potassium Hydroxide as the Condensing Agent.—II (0.2 mole, 14.0 g.), in 100 ml. of ether, was added over 90 min. to a mixture of diethyl malonate (0.4 mole, 64.0 g.) and potassium hydroxide (0.10 mole, 5.2 g. in 20 ml. of 95% ethanol) in 150 ml. of ether at 15°. The reaction mixture was stirred for an additional 2 hr. at room temperature, poured onto ice, acidified with dilute hydrochloric acid, and processed to give 33.3 g. of recovered diethyl malonate, b.p. 108–113° at 20 mm., and 38.1 g. (82.7%) of ethyl 2-carbethoxy-5-ketohexanoate (VII), b.p. 119–120° at 1.8 mm. A sample of VII (0.05 mole, 11.5 g.) was added slowly to a refluxing solution of potassium hydroxide (0.19 mole, 10.6 g.) in 15 ml. of water and the mixture was refluxed for 2 hr. Then an additional 15 ml. of water was added and 11 ml. of liquid was distilled to remove the ethanol. The mixture was cooled and concentrated sulfuric acid (0.18 mole, 17.6 g. in 24 ml. of water) was added slowly. The mixture was refluxed for an additional 3 hr. It was then cooled and extracted with ether. The ether extracts were dried and the solvent was removed by distillation at atmospheric pressure. Vacuum distillation of the residue gave 2.7 g. (41.6%) of 5-ketohexanoic acid (VIII), b.p. 132–133° at 4 mm.[16]; semicarbazone, m.p. 172.6–173.4°.[16]

Reaction of Ethyl Benzoylacetate with II Using Triton B as the Condensing Agent.—II (0.2 mole, 14.0 g. in 100 ml. of dioxane) was added over 90 min. to a mixture of ethyl benzoylacetate (0.4 mole, 76.4 g.) and 5 ml. of Triton B (38% aqueous solution) in 150 ml. of dioxane at 30°. The reaction mixture was stirred for an additional hour at room temperature and was then processed in the regular manner to give 33.4 g. of recovered ethyl benzoylacetate, b.p. 126–131° at 3 mm., and 45.1 g. (86.3%) of 1-phenyl-2-carbethoxyhexane-1,5-dione (XI), b.p. 181–183° at 3 mm. A sample of XI (0.05 mole, 13.1 g.) was added slowly to a solution of potassium hydroxide (0.25 mole, 14.0 g. in 15.0 ml. of water), and the mixture was refluxed for 2 hr. The mixture was poured over ice and acidified with dilute hydrochloric acid. Benzoic acid (3.0 g., 49.2%, m.p. 121–122° alone and when mixed with an authentic sample) was filtered and the filtrate was then extracted with ether. After drying the ether extracts and removing the solvent, the residue was distilled to give an additional 0.8 g. (18.1%) of benzoic acid (b.p. 128–138° at 5 mm., m.p. 121–122°) and 0.9 g. (13.2%) of 5-ketohexanoic acid (XII), b.p. 138–140° at 5 mm.[16]; semicarbazone,[16] m.p. 173–174°.

Reaction of *n*-Propylamine with II.—II (0.2 mole, 14.0 g. in 50 ml. of anhydrous ether) was added over a 40-min. period to *n*-propylamine (0.4 mole, 23.6 g. in 100 ml. of anhydrous ether) at 0–5°. The reaction mixture was stirred for an additional 2 hr. at room temperature and then the ether and unchanged *n*-propylamine were removed at 100 mm. The residue was diluted with 250 ml. of anhydrous ether and then oxalic acid dihydrate (0.2 mole, 18.0 g.) was added, and the hydrogenoxalate salt which precipitated was filtered to give 40.7 g. (94.2%) of 4-*n*-propylamino-2-butanone hydrogenoxalate (XIV), m.p. 149.4–149.8° dec.

The picrate of 4-*n*-propylamino-2-butanone was prepared as follows. The hydrogenoxalate was decomposed with 50% aqueous sodium hydroxide solution. The free 4-*n*-propylamino-2-butanone was extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and the ether was removed. The residual 4-*n*-propylamino-2-butanone was treated with a saturated ethanolic solution of picric acid to give its picrate, m.p. 158.4–159.4° from 95% ethanol.

Reaction of Cyclohexylamine with II.—II (0.2 mole, 14.0 g. in 50 ml. of anhydrous ether) was added over a 30-min. period to a solution of cyclohexylamine (0.4 mole, 29.7 g. in 100 ml. of anhydrous ether) at 0°. The reaction was stirred for an additional 90 min. at room temperature, and the ether and most of the unchanged cyclohexylamine were removed by distillation at 100 mm. The residue was diluted with 150 ml. of anhydrous ether and was saturated with dry hydrogen chloride to give 49.2 g. of a mixture of amine hydrochlorides. A benzene–petroleum ether (30–60°) mixture dissolved the hydrochloride of 4-cyclohexylamino-2-butanone (XV), while the hydrochloride of cyclohexylamine was not soluble. Filtration gave 10.1 g. (18.7%) of cyclohexylamine hydrochloride, m.p. 203–204°.[17] Evaporation of the benzene–petroleum ether solution gave 39.1 g. (94.5%) of XV, m.p. 131.0–132.0°.

The benzenesulfonamide of XV, m.p. 106.6–107.4°, was prepared as follows. An ether solution of the amine was obtained by decomposing its hydrochloride with 50% aqueous sodium hydroxide solution and extracting the mixture with ether. The ether was evaporated and the benzenesulfonamide was made according to the method of Shriner and Fuson.[18]

Reaction of Morpholine with II.—II (0.2 mole, 14.0 g. in 50 ml. of ether) was added over 60 min. to morpholine (0.4 mole, 34.8 g. in 100 ml. of ether) at 0–5°. The reaction was stirred for an additional 2 hr. at room temperature and the ether was distilled at atmospheric pressure. Vacuum distillation of the residue gave 28.0 g. (89.3%) of N-3-ketobutylmorpholine (XVIII), b.p. 85–87° at 2 mm.[10]; picrate, m.p. 112.6–113.6° from 95% ethanol.[10]

Reaction of 2-Picoline with II Using Phenyllithium as the Condensing Agent.—Phenyllithium (0.5 mole) was prepared in 400 ml. of anhydrous ether. 2-Picoline (0.5 mole, 46.6 g. in 25 ml. of anhydrous ether) was added over a 20-min. period after which the mixture was refluxed an additional 0.5 hr. The mixture was cooled to 0–2° with an an external ice–salt bath, and methyl vinyl ketone (0.25 mole, 17.2 g. in 100 ml. of anhydrous ether) was added over a 50-min. period. The reaction mixture was permitted to warm to room temperature (15 min.) and then the reaction was quenched by pouring it over ice. The reaction was processed to give 27.2 g. of recovered 2-picoline, b.p. 35–55° at 50 mm.; 24.9 g. (61.5%) of 3-(2-picolyl)-3-hydroxybutene (XXIII), b.p. 83–86° at 2.2 mm.; and 9.2 g. of a tarry, nondistillable residue. The infrared spectrum of XXIII showed the presence of a hydroxyl group and an olefinic bond and the absence of carbonyl absorption which would be present if the compound were 5-(2-pyridyl)-2-pentanone.

Reaction of 4-Picoline with II Using Sodium Amide as the Condensing Agent.—4-Picoline (0.5 mole, 46.6 g. in 25 ml. of anhydrous ether) was added to a rapidly stirred sodium amide suspension (0.5 mole in 600 ml. of anhydrous liquid ammonia) over a 20-min. period. The mixture was stirred for an additional 15 min. and then II (0.25 mole, 17.2 g. in 150 ml. of anhydrous ether) was added over a 1-hr. period, immediately after which the reaction was quenched with excess ammonium chloride (0.51 mole, 27.1 g.). The ammonia was replaced by ether and the mixture was poured over ice. Then the mixture was acidified with 100 ml. of hydrochloric acid and extracted with ether. Both the acid and basic extracts were dried over anhydrous sodium sulfate and the ether was removed at atmospheric pressure. Less than 1 g. of residue was obtained from the acid extract. Vacuum distillation of the basic product residue gave 22.4 g. of recovered 4-picoline, b.p. 50–66° at 50 mm., and 10.0 g. (24.7%) of 5-(4-pyridyl)-2-pentanone (XIX), b.p. 112–114° at 2 mm.[11]; picrate, m.p. 113–115° from 95% ethanol, alone and when mixed with an authentic sample.[11]

Reaction of Sodium Sulfide with II.—II (0.2 mole, 14.0 g.) was added over a 40-min. period to a solution of sodium sulfide ($Na_2S \cdot 9H_2O$) (0.4 mole, 96.1 g. in 100 ml. of water) with the temperature controlled between 10° and 20°. The reaction mixture was stirred for an additional 3 hr. at room temperature. It was poured over ice, neutralized with hydrochloric acid, and extracted with ether. The dried (anhydrous sodium sulfate) ether extracts were distilled at atmospheric pressure to remove the solvent. Vacuum distillation of the residue gave 6.0 g. (28.8%) of 4-mercapto-2-butanone (XXVII), b.p. 35–36° at 2 mm. and 77° at 30 mm.; and 5.2 g. (29.9%) of bis(3-ketobutyl) sulfide (XXVIII), b.p. 102–107° at 1 mm.[19]; disemicarbazone, m.p. 226–227° from 95% ethanol.[19]

Reaction of Potassium Cyanide with II.—Potassium cyanide (0.2 mole, 13.0 g. in 75 ml. of water) was added over 30 min. to a solution of II (0.2 mole, 14.0 g.) and glacial acetic acid (0.2 mole, 12.0 g.) in 200 ml. of ethanol with the temperature held at 35°. The reaction mixture was stirred at room temperature for 3 hr., and then 150 ml. of a mixture of water and ethanol was distilled. The reaction mixture was then processed in the normal manner to give 7.6 g. (39.6%) of γ-ketovaleronitrile (XXIX), b.p. 112–113° at 15 mm.[14]; 2,4-dinitrophenylhydrazone, m.p. 146.0–146.8° from 95% ethanol.[14]

(16) C. W. Yoho and R. Levine, *J. Am. Chem. Soc.*, **74**, 5597 (1952).

(17) F. B. Guyot and R. Fournier, *Bull. soc. chim.*, **47**, 205 (1930).

(18) R. C. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 48.

(19) N. McGinnis and R. Robinson, *J. Chem. Soc.*, 404 (1941).

Microbiological 16-Oxidation of Estr-4-en-3-one

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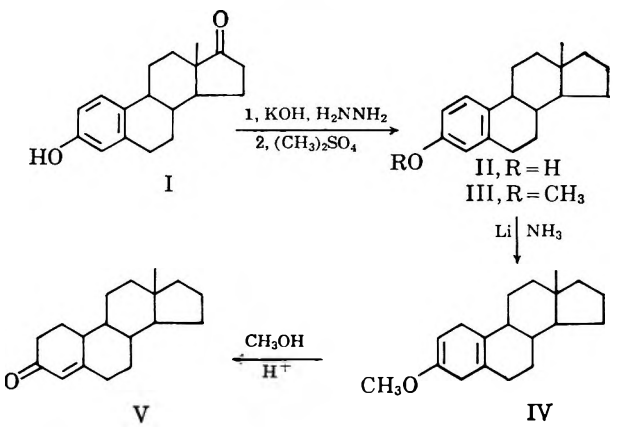
The preparation of estr-4-en-3-one and its use as a substrate in fermentations to yield 16-substituted products are described. Microbiological dehydrogenation of the products produced the known 3-hydroxyestra-1,3,5(10)-trien-16-one.

Microbiological transformation of the previously unreported steroid, estr-4-en-3-one (V), was attempted in order to provide intermediates for the preparation of various hydroxylated derivatives of 3-hydroxyestra-1,3,5(10)-triene (II). Direct fermentations of II with many microorganisms failed to provide such products in significant quantity.

The fermentation substrate, estr-4-en-3-one (V), was prepared by the route outlined in Scheme I. A Huang-

SCHEME I



Minlon reduction[1] of estrone (I) and methylation of the intermediate 3-hydroxyestra-1,3,5(10)-triene (II) produced 3-methoxyestra-1,3,5(10)-triene[2] (III) in good yield. A modified Birch reduction[3] of III yielded the previously unreported 3-methoxyestra-2,5(10)-diene (IV), which was readily hydrolyzed to V.

Three crystalline products (two monohydroxylated, VI and VIII, and a dione, VII) were isolated from a fermentation of estr-4-en-3-one (V) with *Bacillus megaterium* (NRRL-B938). The relative proportions of these products varied from run to run since the fermentation conditions and nutrient media also differed. Compounds VI and VII were also isolated from a fermentation of V with *Cephalosporium acremonium* (NRRL 3092). Since oxidation of both VI and VIII with chromic acid in acetone provided the dione VII, it was apparent that the substrate V had been oxidized at the same carbon atom to yield the three products, and also that the newly introduced hydroxyl groups in VI and VIII were epimeric. Moreover, D-ring substitution was inferred, since the infrared spectrum of VII showed the presence of a five-membered ring ketone. Since the products, VI, VII, and VIII were demonstrably different from the C-17 oxygenated compounds 19-nortestosterone and 19-norandrostenedione, oxidation could only have occurred at C-15 or C-16. Fermentations of VI, VII, and VIII with *Nocardia coralina* (ATCC 999) aromatized the A ring with concurrent oxidation of the hydroxyl groups of VI and VIII to provide in good yield the known[4] 3-hydroxyestra-1,3,5(10)-trien-16-one (IX), whose identity was confirmed by preparation of the benzoate (X). These results confirmed the position of substitution in compounds VI, VII, and VIII, but left unresolved the configuration of the hydroxyl groups in VI and VIII.

Our assignment of configuration is based on three considerations. Fermentation of V with *Streptomyces roseochromogenes* (ATCC 3347), a culture noted for 16α-hydroxylation of a wide range of steroids,[5] yielded primarily VIII. Secondly, the changes in molecular rotation on acetylation [$-54°$ for VIII and $+6°$ for VI (Table I)] agree with the $-37°$ for α and $+17°$ for β found for the analogous estrone derivatives.[6] Finally, reduction of the dione VII with aluminum *t*-butoxide[7] yielded mostly VI. From these data it appears that VI is 16β-hydroxyestr-4-en-3-one and VIII is 16α-hydroxyestr-4-en-3-one.

TABLE I

MOLECULAR ROTATION DIFFERENCES OF 16-SUBSTITUTED STEROIDS

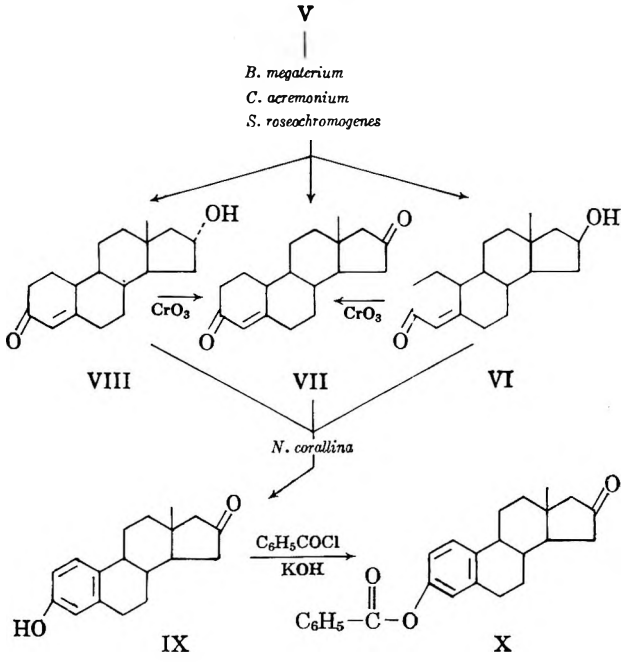
Steroid	MD, deg.	ΔMD, deg. (type)
Estr-4-en-3-one	+62	...
Estr-4-ene-3,16-dione	−400	−462 (C=O)
16α-Hydroxyestr-4-en-3-one	+54	−8 (α-OH)
16α-Acetoxyestr-4-en-3-one	±0	−54 (α-OH → α-OAc)
16β-Hydroxyestr-4-en-3-one	+62	±0 (β-OH)
16β-Acetoxyestr-4-en-3-one	+68	+6 (β-OH → β-OAc)
3-Hydroxyestra-1,3,5(10)-triene[a]	+236	...
3-Hydroxyestra-1,3,5(10)-trien-16-one[b]	−235	−471 (C=O)
3,16α-Dihydroxyestra-1,3,5(10)-triene[c]	+231	−5 (α-OH)
16α-Acetoxy-3-hydroxyestra-1,3,5(10)-triene[c,d]	+194	−37 (α-OH → α-OAc)
3,16β-Dihydroxyestra-1,3,5(10)-triene[c]	+202	−34 (β-OH)
16β-Acetoxy-3-hydroxyestra-1,3,5(10)-triene[c,d]	+219	+17 (β-OH → β-OAc)

[a] V. Prelog, L. Ruzicka, and P. Wieland, *Helv. Chim. Acta*, **28**, 250 (1945). [b] See ref. 1. [c] See ref. 6. [d] Calculated by subtracting the Δ^{OAc} value for estrone from the lit.[6] MD values for the 3,16-diacetates.

Microbiological 16β-hydroxylation of steroids has been only rarely reported. Herzog, *et al.*,[8] isolated

(1) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949).
(2) A. Butenandt and U. Westphal, *Z. physiol. Chem.*, **223**, 147 (1934).
(3) A. L. Wilds and A. J. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).
(4) M. N. Huffman and M. H. Lott, *ibid.*, **73**, 878 (1951).
(5) C. E. Holmlund, L. I. Feldman, R. H. Blank, N. Barbacci, and B. Nielsen, *Sci. Rept. Inst. Super. Sanita*, **1**, 289 (1961).
(6) M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, **215**, 627 (1955).
(7) J. W. Ralls, U. S. Patent 2,778,841 (1957).
(8) H. L. Herzog, M. J. Gentles, A. Baseh, W. Coscarelli, M. E. A. Zeitz, and W. W. Charney, *J. Org. Chem.*, **25**, 2177 (1960).

SCHEME II



nine crystalline products from a fermentation of testosterone with *Wojnowicia graminis*. The major product was 16α-hydroxytestosterone; 16β-hydroxytestosterone and 16-ketotestosterone were isolated in much smaller amounts. J. de Flines, *et al.*,[9] found that 16β-hydroxy-19-nortestosterone and, to a considerably lesser extent, 16-keto-19-nortestosterone were produced in fermentations of 19-nortestosterone with *Mycosphaerella latebrosa*. Dodson and Mizuba,[10] who obtained 16β-hydroxytestosterone and 16-ketotestosterone from the fermentation of androstenedione with *Corticium centrifugum*, have suggested that the 16β-hydroxylated product might have resulted from 16α-hydroxylation of androstenedione, followed by isomerization of this 16,17-ketol, and reduction of the resulting 16-keto group.

Laboratory-scale fermentations of V, VI, VII, and VIII with the three organisms, *C. acremonium*, *B. megaterium*, and *S. roseochromogenes*, all resulted in mixtures of VI, VII, and VIII. These results show that a mechanism exists for the interconversion of 16α- and 16β-isomers, probably *via* the 16-ketone, and suggest the presence of 16α-hydroxy steroid and 16β-hydroxy steroid dehydrogenases in these fermentations. In fermentations of V with *C. acremonium* and *B. megaterium*, 16β-hydroxyestr-4-en-3-one (VI) appeared to be formed first, probably by 16β-hydroxylation of V, and subsequently to be converted to VII and VIII. With *S. roseochromogenes*, however, the first abundant product was 16α-hydroxyestr-4-en-3-one (VIII); VI and VII were formed later.

C. acremonium has been reported to form testololactone and testolic acid from androstenedione and progesterone.[11] No analogous product was found in the fermentation of VII with this culture. Apparently the enzyme(s) that oxidize(s) the 17- or 20-keto steroids is unable to catalyze a similar reaction with the 16-keto steroid.

(9) J. de Flines, W. F. van der Waard, W. J. Mijs, and S. A. Szpilfogel, *Rec. trav. chim.*, **82**, 121 (1963).

(10) E. M. Dodson and S. Mizuba, *J. Org. Chem.*, **27**, 698 (1962).

(11) C. E. Holmlund, R. H. Blank, K. J. Sax, and R. H. Evans, Jr., *Arch. Biochem. Biophys.*, **103**, 105 (1963).

Experimental

Melting points are corrected. Partition chromatography was performed on columns of diatomaceous earth moistened with 50% (w./v.) of the lower phase of a solvent system composed of water, methanol, dioxane, and cyclohexane. The particular solvent system employed is identified by the respective volume ratios of these individual components, *e.g.*, 2:4:1:10. The columns were eluted with the upper phase of the same solvent system or with the upper phase of systems with different volume ratios. Adsorption chromatography was done on columns of silica gel (Davison, Grade 62, 60-200 mesh). Fractions from both partition and adsorption columns are identified by reference to the volume of eluate collected. Thin-layer chromatography was done on silica gel G[12] activated for 30 min. at 100°. The plates were developed with benzene–acetone (7:3 by volume), and the steroids were detected by spraying the plates with sulfuric acid and heating until the steroid was charred.

3-Methoxyestra-1,3,5(10)-triene (III).—Crude damp 3-hydroxyestra-1,3,5(10)-triene (II), prepared from 99.5 g. of estrone by Huang-Minlon reduction,[1] was dissolved in a mixture of 1.6 l. of dioxane and 1 l. of water, and the solution was treated with 33 g. of 86% potassium hydroxide in 150 ml. of water. Dimethyl sulfate (45 ml.) was added, and the mixture was heated on the steam bath for 2 hr. During this time additional dioxane and water were added to prevent the separation of a second phase. An additional 33 g. of potassium hydroxide and 20 ml. of dimethyl sulfate were added and heating was continued for 2 hr. The reaction mixture was poured onto 2 kg. of ice, and the crude 3-methoxyestra-1,3,5(10)-triene (III) was collected and washed with water. On fractional crystallization from methanol a total of 86.5 g. (86.5% based on estrone) of III, m.p. 78–79°, was obtained. Butenandt and Westphal[2] reported m.p. 76.5°.

3-Methoxyestra-2,5(10)-diene (IV).—A mixture of 7.5 g. of 3-methoxyestra-1,3,5(10)-triene in 20 ml. of ethanol, 100 ml. of anhydrous ethyl ether, and 500 ml. of liquid ammonia was treated with 7 g. of lithium metal, which was added in small pieces during stirring over a 2-hr. period. The reaction was continued until an aliquot diluted with ethanol no longer showed appreciable absorption at 280 mμ. After evaporation of the ammonia, the excess lithium was destroyed by careful addition of ethanol and water. The mixture was diluted with water and the product was extracted with ether. After washing and drying, the ether extract was concentrated and the product was crystallized. Fractional crystallization from ether gave a first crop of 4.8 g. of IV, m.p. 91–93°, $[\alpha]^{25}D$ +69° ($CHCl_3$).

Estr-4-en-3-one (V).—A suspension of 5.7 g. of 3-methoxyestra-2,5(10)-diene in 48 ml. of methanol and 2 ml. of concentrated hydrochloric acid was warmed gently on a steam bath until solution was complete. After about 15 min. the solution was treated with 5 ml. of 5 *N* sodium hydroxide solution and a little water. The mixture was cooled in a Dry Ice–methanol bath, and 4.2 g. of crystalline estr-4-en-3-one, m.p. 63.4–65°, was collected. Recrystallization of this material from aqueous methanol yielded pure V, m.p. 65.5–66.75°, $\lambda_{max}^{CH_3OH}$ 240 mμ (ϵ 16,000), $[\alpha]^{25}D$ +44° ($CHCl_3$), $[\alpha]^{25}D$ +24 (CH_3OH).

Anal. Calcd. for $C_{18}H_{26}O$ (mol. wt. 258.39): C, 83.66; H, 10.14. Found: C, 83.97; H, 10.32.

Isolation of 16β-Hydroxyestr-4-en-3-one (VI) from the Fermentation of Estr-4-en-3-one (V) with *B. megaterium*.—Thirty liters of a medium consisting of 1500 g. of glucose, 600 g. of lactalbumin hydrolysate,[13] and 150 g. of corn steep liquor was adjusted to pH 6.5 with dilute sodium hydroxide solution, and was inoculated with 3.3% by volume of a 24-hr. inoculum of *B. megaterium*. The fermentation mash was stirred and aerated at 28° during 48 hr., at which time a solution of 3.0 g. of estr-4-en-3-one in 100 ml. of methanol was added. After an additional 6.5 hr. the fermentation mash was adjusted to pH 6.5 with dilute hydrochloric acid, and was extracted with an equal volume of chloroform. The chloroform extract was separated, and the aqueous layer was twice extracted with half its volume of fresh chloroform. The combined chloroform extract was concentrated under vacuum to 4 l., dried over magnesium sulfate, stirred with 5 g. of decolorizing carbon, and filtered. Concentration of the filtrate yielded an oily residue that was dissolved in 200 ml. of a 3:1 (v./v.) methylene chloride–hexane mixture. Adsorption chromatography on a 300-g. column on silica gel was carried out by elution,

(12) Obtained from E. Merck AG, Darmstadt; *cf.* E. Stahl, *Pharm. Rundschau*, **1**, 1 (1959).

(13) Sheffield Chemical, Norwich, N. Y.

with 1800 ml. of the above solvent mixture, followed by 8 l. of 2% acetone in methylene chloride, and 3 l. of 10% acetone in methylene chloride. The steroid obtained by evaporation of solvent from the 3.8–6.8-l. portion of the eluate was crystallized from acetone–hexane to yield 50 mg. of 16β-hydroxyestr-4-en-3-one (VI), m.p. 149–150.5°, $[\alpha]^{25}D$ +22.8 (c 1.05, CH_3OH), $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 17,350).

Anal. Calcd. for $C_{18}H_{26}O_2$ (mol. wt. 274.39): C, 78.78; H, 9.55. Found: C, 79.21; H, 9.81.

16α-Hydroxyestr-4-en-3-one (VIII), 16β-Hydroxyestr-4-en-3-one (VI), and Estr-4-ene-3,16-dione (VII).—The fermentation of a second portion of estr-4-en-3-one (V, 2.0 g.) with *B. megaterium* was done in a medium composed of 400 g. of lactalbumin hydrolysate,[13] 400 g. of glucose, and 144 g. of corn steep liquor in water to make 20 l. Five per cent by volume of a 24-hr. inoculum was added and the culture was grown for 24 hr. prior to the addition of the steroid in methanol solution. After 23 hr. the fermentation was stopped, and the steroid was extracted with chloroform as described above. Evaporation of the chloroform extract afforded 133 g. of viscous oil. Chromatography on a 600-g. column of silica gel was accomplished by elution with 50% methylene chloride in hexane (12 l.), 60% methylene chloride in hexane (2 l.), 80% methylene chloride in hexane (2 l.), methylene chloride (7 l.), 5% ether in methylene chloride (1 l.), 10% ether in methylene chloride (1 l.), 50% ether in methylene chloride (4 l.), and 5 l. of ether.

Partition chromatography of the residue obtained on evaporation of solvent from the 8.0–11.7-l. portion of the eluate was carried out on a 400-g. column of diatomaceous earth moistened with 200 ml. of the lower phase of a 2:4:1:10 solvent system. Elution of the column with 1 l. of the upper phase of the above system and 2 l. of the upper phase of a 2:6:1:10 system provided a fraction (1.0–1.9 l. of eluate) which yielded, on concentration and crystallization of the residue from aqueous methanol, 700 mg. of estr-4-ene-3,16-dione (VII), m.p. 139.5–140.5°. Additional product was recovered from the mother liquors.

The 11.7–15.9-l. fraction collected from the adsorption column was concentrated to a residue, which was chromatographed on a partition column of 75 g. of diatomaceous earth moistened with 37.5 ml. of the lower phase of a 2:2:2:10 solvent system. Elution of the column with the upper phase of this system produced two steroid-containing fractions, 90–165 ml. and 215–330 ml. Concentration of the first fraction and crystallization of the residue from aqueous methanol yielded 70 mg. of estr-4-ene-3,16-dione, m.p. 135–136.5°. Similar work-up of the second fraction gave 13 mg. of 16β-hydroxyestr-4-en-3-one (VI), m.p. 146.8–148.3°.

The 17.5–18.7-l. fraction collected from the adsorption column was concentrated to a residue which was further purified by partition chromatography on a column of 300 g. of diatomaceous earth moistened with 150 ml. of the lower phase of a 2:2:4:10 solvent system. Elution with the upper phase of this solvent system and concentration of the 825–1265-ml. fraction yielded a residue containing 16α-hydroxyestr-4-en-3-one (VIII), which was crystallized from ethyl acetate–hexane. Recrystallization of the product from the same solvents yielded 157 mg. of VIII, m.p. 163–164°, $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 16,600), $[\alpha]^{25}D$ +21° (CH_3OH).

Estr-4-ene-3,16-dione (VII). A.—A solution of 50 mg. of 16β-hydroxyestr-4-en-3-one (VI) in 25 ml. of chromic acid–acetone reagent[14] was allowed to stand at room temperature for 10 min. Methanol was added to consume excess oxidant, and the solution was diluted with water and extracted with methylene chloride. The extract was dried over magnesium sulfate, filtered, and the solvent was evaporated. Crystallization of the residue from aqueous methanol and aqueous acetone afforded 22 mg. of estr-4-ene-3,16-dione (VII), m.p. 138.5–139.5°, $[\alpha]^{25}D$ −147° (CH_3OH), $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 17,400); λ_{max}^{KBr} 5.73 (5-membered ring ketone), 5.99, and 6.17 μ.

B.—A solution of 60 mg. of 16α-hydroxyestr-4-en-3-one (VIII) in 30 ml. of chromic acid–acetone reagent[14] was treated as above. The crude product was purified by partition chromatography on a 20-g. diatomaceous earth column using a 2:4:1:10 solvent system. The 41–90-ml. fraction was concentrated to a residue, which was crystallized from aqueous methanol; 32 mg. of estr-4-ene-3,16-dione (VII), m.p. 140.5–141.5°, $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 16,300), $[\alpha]^{25}D$ −147° (CH_3OH), was collected.

(14) One milliliter of a stock solution of 20 g. of chromic anhydride and 32 g. of concentrated sulfuric acid in water to make 100 ml. is diluted to 100 ml. with acetone; *cf.* S. C. Pan, *Anal. Chem.*, **34**, 766 (1962).

Anal. Calcd. for $C_{18}H_{24}O_2$ (mol. wt. 272.37): C, 79.37; H, 8.88. Found: C, 79.51; H, 9.05.

Isolation of Estr-4-ene-3,16-dione (VII) and 16β-Hydroxyestr-4-en-3-one (VI) from the Fermentation of Estr-4-en-3-one (V) with *Cephalosporium acremonium*.—An inoculum prepared by growing a culture of *Cephalosporium acremonium* (NRRL 3092) as described under Laboratory Fermentation Studies was used to inoculate three 750-ml. portions of the same medium in 4-l. erlenmeyer flasks. Each flask was shaken for 24 hr. at 28°, and a concentrated solution of 500 mg. of V in methanol was divided equally among the three vessels. After shaking at 28° for 51 hr. the fermentations were combined, and the pH adjusted to 2.5 with 5 *N* hydrochloric acid. The mixture was extracted twice with an equal volume of methylene chloride. After filtration of the aqueous phase, the filtrate was again extracted with methylene chloride and the combined extract was concentrated to an oily residue (8.5 g.). Partition chromatography of the residue on a 150-g. column of diatomaceous earth moistened with 75 ml. of the lower phase of a 2:4:1:10 solvent system was accomplished by elution with 500 ml. of the upper phase of the above system, 700 ml. of a 2:2:1:10 system, and 1 l. of a 2:2:2:10 system. Crystallization from acetone–water of the residue obtained on evaporation of the 420–630-ml. fraction gave 10 mg. of estr-4-ene-3,16-dione (VII), m.p. 133–137°, which was identified by its infrared absorption spectrum and by mixture melting point with an authentic sample. Crystallization from acetone–hexane of the residue obtained on evaporation of the eluate between 1.2 and 1.6 l. gave 13 mg. of 16β-hydroxyestr-4-en-3-one (VI), m.p. 146.5–148.5°, which was similarly identified.

Isolation of 16α-Hydroxyestr-4-en-3-one (VIII) from the Fermentation of Estr-4-en-3-one (V) with *S. roseochromogenes* (ATCC 3347).—Five per cent of a 48-hr. inoculum of *S. roseochromogenes* was used to inoculate 20 l. of a growth medium composed of 4% corn starch, 2.5% corn steep liquor, 0.5% calcium carbonate, 0.5% dibasic potassium phosphate, and 0.2% lard oil in water. After the culture was grown for 24 hr. at 28° a solution of 2 g. of V in 100 ml. of methanol was added to the fermentor, and the fermentation was continued for 30 hr. The mash was extracted once with an equal volume of chloroform and re-extracted twice with half-volumes of chloroform. The combined extract was concentrated to an oil, which was subjected to partition chromatography on a column composed of 700 g. of diatomaceous earth moistened with 350 ml. of the lower phase of a 2:4:1:10 solvent system. The column was eluted with 12 l. of the upper phase of this system and with the upper phase of 2:4:2:10 (2.5 l.), 2:2:2:10 (2.5 l.), 2:2:4:10 (3.4 l.), and 2:2:10:10 systems. The steroid obtained on concentration of the 6.0–10.0-l. fraction was fractionally crystallized from ethyl acetate–hexane to yield 280 mg. of VIII, m.p. 163–163.5°, $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 16,200), $[\alpha]^{25}D$ +20° (CH_3OH).

Anal. Calcd. for $C_{18}H_{26}O_2$ (mol. wt. 274.39): C, 78.78; H, 9.55. Found: C, 78.93, 78.41; H, 9.78, 9.71.

Isolation of 3-Hydroxyestra-1,3,5(10)-trien-16-one (IX) from the Fermentation of Estr-4-ene-3,16-dione with *Nocardia corallina* (ATCC 999).—Three 4-l. erlenmeyer flasks each containing 750 ml. of a growth medium composed of 10 g. of glucose, 1 g. of yeast extract (Difco), 2.5 g. of sodium chloride, 4 g. of beef extract (Armour), and 4 g. of peptone (Difco) per liter of water were inoculated with 100 ml. of a culture of *Nocardia corallina* grown at 37° in the same medium for 6 hr. and the flasks were incubated at 24° on a reciprocating shaker for 16 hr. Under aseptic conditions 165 mg. of estr-4-ene-3,16-dione was added to each flask in 35 ml. of methanol, and the fermentation was continued for 24 hr. The combined fermentation mixture was stirred with an equal volume of methylene chloride. After separation of the phases, the aqueous phase was re-extracted with two half-volumes of methylene chloride. Evaporation of the solvent from the combined extract left an oily residue which was chromatographed on a 200-g. column of diatomaceous earth moistened with 100 ml. of a 2:4:1:10 solvent system. The column was eluted with 900 ml. of upper phase from the above system, 900 ml. of a 2:2:1:10 system, and 1 l. of a 2:2:2:10 system. The solvent was evaporated from the 686–3411-ml. fraction, and the residue was dissolved in ethyl acetate. The solution was treated with decolorizing carbon, filtered, and concentrated with hexane to yield 333 mg. (67%) of 3-hydroxyestra-1,3,5(10)-trien-16-one, m.p. 244.5–246°. Huffman and Lott[4] report m.p. 243.5–245.5 for this product.

3-Benzoyloxyestra-1,3,5(10)-trien-16-one (X).—One drop of benzoyl chloride was added to a solution of 10 mg. of 3-hydroxy-

estra-1,3,5(10)-trien-16-one in 0.4 ml. of 20% sodium hydroxide, and the solution was mixed. When the product crystallized, the solution was diluted with water and filtered, and the product was recrystallized three times from methanol. The 5 mg. of X thus obtained melted at 225.5–229°. Huffman and Lott[4] report m.p. 223.5–224.5°.

16β-Acetoxyestr-4-en-3-one.—Acetylation of 16β-hydroxyestr-4-en-3-one (75 mg.) in 2 ml. of pyridine with 0.5 ml. of acetic anhydride yielded 75 mg. of crude product, m.p. 87.5–89.5°. Two recrystallizations from aqueous acetone yielded 35 mg. of 16β-acetoxyestr-4-en-3-one, m.p. 90–90.5°, $[\alpha]^{25}D$ +21.5° (CH_3OH), $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 15,000).

Anal. Calcd. for $C_{20}H_{28}O_3$ (mol. wt. 316.42): C, 75.91; H, 8.92. Found: C, 75.67; H, 9.01.

16α-Acetoxyestr-4-en-3-one.—Acetylation of 16α-hydroxyestr-4-en-3-one (100 mg.) in 5 ml. of pyridine with 1 ml. of acetic anhydride yielded an oil, which showed no optical rotation, $\lambda_{max}^{CH_3OH}$ 239.5 mμ (ε 15,000). The infrared absorption spectrum showed the presence of an ester group but no hydroxyl group; λ_{max}^{KBr} 5.72, 5.93, 6.12, and 7.99 μ.

Aluminum *t*-Butoxide Reduction of Estr-4-ene-3,16-dione (VII).—A solution of 100 mg. of VII in 10 ml. of benzene and 1 ml. of 2-butanol was slowly distilled until 2.5 ml. of distillate was collected. Then 74 mg. of aluminum *t*-butoxide was added, and the mixture was refluxed for 5 hr. After cooling and dilution with 10 ml. of benzene the mixture was washed once with 30 ml. of 5% sodium hydroxide solution and thrice with 10-ml. portions of water. The organic layer was dried over magnesium sulfate, and the residue obtained on evaporation of solvent was chromatographed on a 25-g. silica gel column by development with 425 ml. of methylene chloride–hexane (1:1), 500 ml. of methylene chloride–hexane (3:1), 1 l. of methylene chloride, and 500 ml. of ether–methylene chloride (1:9).

Examination of the eluate by paper chromatography showed starting material in the 490–970-ml. fraction. The 1480–1820-ml. fraction contained 16β-hydroxyestr-4-en-3-one, and the 2170–2330-ml. fraction contained a smaller amount of the 16α-isomer.

Laboratory Fermentation Studies.—Laboratory-scale fermentations were conducted in the following manner. Inoculum was prepared by transferring an aqueous suspension of the culture to a 500-ml. erlenmeyer flask containing 100 ml. of a medium consisting of lactalbumin hydrolysate[13] (20 g.), glucose (20 g.), corn steep liquor (5 g.), and water to make 1000 ml. The pH was adjusted to 7.0. The culture was incubated on a reciprocating shaker; *B. megaterium* was incubated at 37° for 7 hr.; *C. acremonium* and *S. roseochromogenes* were incubated at 28° for 64 hr. In each instance 5 ml. of the microbial suspension was used to inoculate 100 ml. of fresh medium in 500-ml. erlenmeyer flasks. All cultures were than shaken at 28° for 24 hr. prior to addition of the steroid substrate. Each steroid was added in methanolic solution to provide a concentration of 100 μg./ml. in the flask. Aliquots were removed at intervals and extracted with a three-volume portion of ethyl acetate, and the extract was analyzed by thin layer chromatography.

A mixture of compounds, VI, VII, and VIII, was observed in one or more of the samples removed from the fermentations of V, VI, VII, and VIII with each organism. The mobilities of these compounds on silica gel G developed with benzene–acetone (7:3 v./v.) were as follows: V, R_f 0.68–0.74; VI, R_f 0.42–0.46; VII, R_f 0.55–0.62; and VIII, R_f 0.34–0.38. After spraying with sulfuric acid and heating, the 3,16-dione (VII) shows a distinctive olive green color prior to charring.

Acknowledgment.—We thank Mr. L. Brancone and associates for analytical data, Mr. W. Fulmor and associates for infrared and ultraviolet absorption spectra and rotation data, Dr. J. Schultz and staff for conducting pilot plant fermentations, and Mr. M. Dann and staff for extraction of pilot plant fermentations and concentration of the extracts.

Application of Spin Decoupling and 100-Megacycle Spectra to Characterization of Carbohydrates. Novel Synthesis of a Cyclohexanetetrol[1,2]

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Reaction of 5,6-anhydro-*allo*-inositol diketal with hydrogen bromide–acetic acid unexpectedly gave a dibromocyclohexanetetrol tetraacetate, from which was obtained a new cyclohexanetetrol, m.p. 193°. By use of spin decoupling and 100-Mc. spectra, this tetrol was shown to have the structure 1,2,3,5 and the configuration *meso* (123/5). Another diastereomer, m.p. 180°, prepared in 1954 from *myo*-inositol, was shown by 60- and 100-Mc. spectra to have the configuration *meso* (13/25). Configurational assignments have also been made to two optically active diastereomers, prepared by Dangschat and Fischer in 1939. By means of rotation predictions, it is now shown that their isomers of reported molecular rotations −90 and −12° have the absolute configurations L (12/35) and L (125/3), respectively.

For n.m.r. configurational studies, spin coupling is a generally useful and often indispensable phenomenon, but there are times when it produces such spectral complexity that interpretation becomes impossibly difficult. This has been especially true for carbohydrate spectra,[5] because of the numerous similar functional groups.

It now appears that such difficulties can largely be overcome, owing to two lately reported n.m.r. developments. The first development, spin decoupling,[6,7] permits the simple uncoupled signal of almost any chosen proton, or set of protons, in a molecule to be observed. Although anticipated by Bloch[6] as early as 1954, spin decoupling has only recently become fully practical and convenient for general use. The

(1) Presented by G. E. M. to the Division of Organic Chemistry at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2) Paper 18 on Cyclitol Stereochemistry by G. E. McCasland and coworkers; for recent papers in this series, see *J. Org. Chem.*, **28**, 2093 (1963); **29**, 724 (1964); *J. Am. Chem. Soc.*, **85**, 2866 (1963).

(3) To whom any requests for reprints should be sent (University of San Francisco).

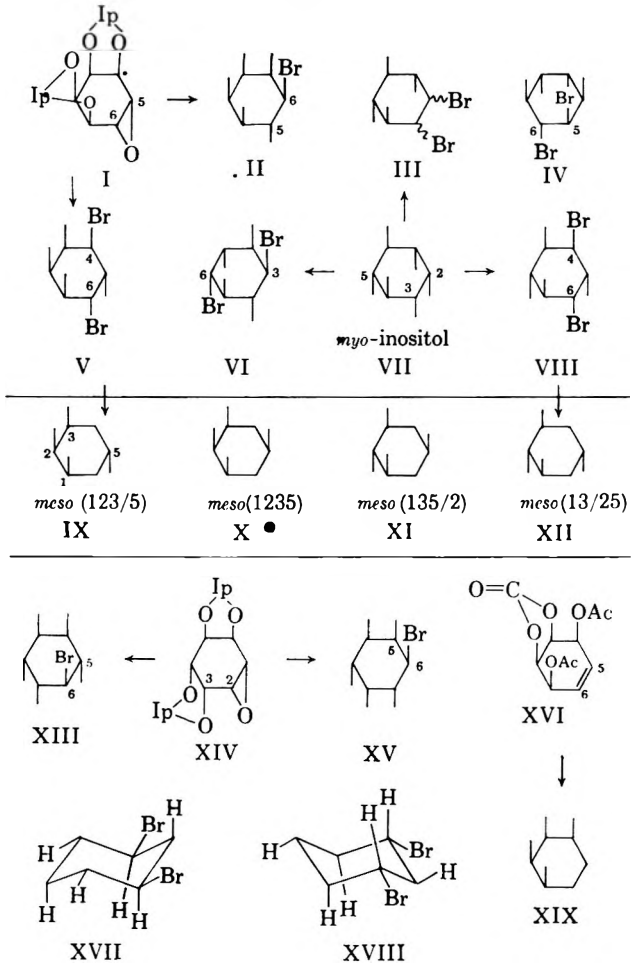
(4) Varian Associates.

(5) For our own previous n.m.r. studies on carbohydrates (cyclitols), see G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery: (a) *J. Org. Chem.*, **28**, 894 (1963); (b) *J. Am. Chem. Soc.*, **83**, 4243 (1961); (c) **83**, 2335 (1961); (d) (with A. Furst), *J. Org. Chem.*, **28**, 456 (1963); (e) G. E. McCasland, S. Furuta, and A. Furst, *ibid.*, **29**, 724 (1964).

(6) Double irradiation was originated by F. Bloch [*Phys. Rev.*, **93**, 944 (1954); **94**, 496 (1954)]. The theory was developed by A. Bloom and J. N. Shoolery [*ibid.*, **97**, 1261 (1955)]. The first application to proton–proton spin decoupling was by W. Anderson [*ibid.*, **102**, 151 (1956)], who studied 2,3-dibromopropene and 2,2-dichloroacetaldehyde. For a recent review, see J. Baldeschwieler and E. Randall, *Chem. Rev.*, **63**, 81 (1963).

(7) The spin-decoupling method used here is that described by R. Freeman and D. Whiffen [*Mol. Phys.*, **4**, 321 (1961)]. The instrumentation is described by L. F. Johnson, Varian Associates Technical Information Bulletin, Vol. 3, No. 3, Palo Alto, Calif., 1963, pp. 5–7, 11–13.

CHART I



second development is the recent use in numerous laboratories of higher frequency apparatus for proton spectra, *i.e.*, 100 Mc. (23.5 kilogauss) in place of 60 Mc. (14.1 kilogauss). With the resultant spreading out of signals, the interpretation of very difficult spectra is often greatly facilitated. It is especially helpful to make successive proton spectral observations on the same sample at 60 Mc. and then at 100 Mc. By well-known principles, spin couplings (field invariant) can then be unequivocally distinguished from chemical shifts. This approach has occasionally been employed in the past with other frequency combinations.

Since few applications of spin decoupling or 100-Mc. spectra to carbohydrates have yet been reported, we now describe the use of these techniques for certain cyclohexanetetrol[8] configurational studies, in order to help demonstrate the power[9] of these new methods.

The occasion for our present research was the preparation of a cyclohexanetetrol, m.p. 193°, by a novel and unexpected synthesis (Chart I). The first step was reaction of 5,6-anhydro-*allo*-inositol diketal[10d,11] (I)

(8) Regarding the possible biological significance of these dideoxy inositols, see (a) H. Eagle and G. E. McCasland, *Biochemistry*, **2**, 1125 (1963); (b) *Chem. Eng. News*, **40**, 51 (1962).

(9) L. Jackman has suggested that spin decoupling and improvements in magnet materials may increase the value of n.m.r. to organic chemists "by an order of magnitude" ("Applications of Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p. 5).

(10) S. J. Angyal, personal communications: (a) April, 1960; (b) June, 1956; (c) S. J. Angyal and P. Gilham, *J. Chem. Soc.*, 3698 (1957); (d) S. J. Angyal and P. Gilham, *ibid.*, 375 (1958).

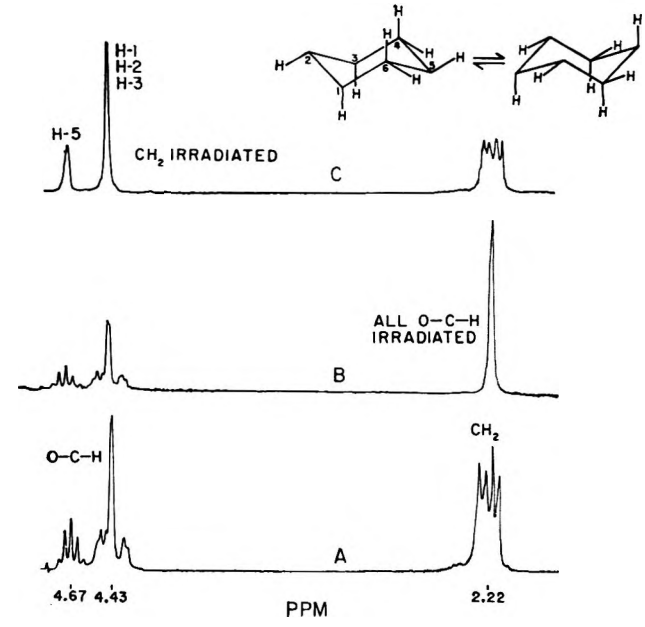
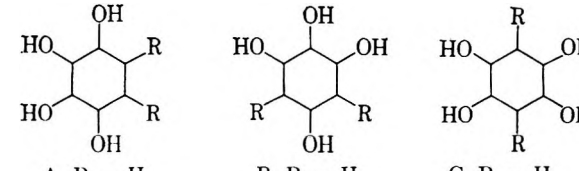


Fig. 1.—(A) 100-Mc. n.m.r. spectrum of 1,2,3,5-cyclohexanetetrol, m.p. 193°, in deuterium oxide; (B) O–C–H protons irradiated; (C) methylene protons irradiated.

with hydrogen bromide in acetic acid at room temperature. In previous work,[5c] the diastereomer XIV with this reagent gave a high yield of monobromo pentaacetate products, XIII and XV. Our new reaction was thus expected to produce the diastereomeric monobromo pentaacetate (II), especially since the monobromopentol (II) is in fact the product with hydrogen bromide *in water*.[5b]

To our surprise, the actual HBr–AcOH product, which crystallized in high yield directly from the reaction mixture, contained two atoms of bromine, and turned out to be a dibromocyclohexanetetrol tetraacetate, m.p. 173°. This was hydrolyzed to the dibromotetrol, m.p. 182°, which on hydrogenolysis gave a new cyclohexanetetrol, m.p. 193° dec. For such a tetrasubstituted cyclohexane, three structures (A, B, C), which we call *ortho*, *meta*, and *para*, are possible. To ascertain the actual structure, 100-Mc. spectra and spin decoupling were employed. (In the present instance, decoupling at 60 Mc. would also have been satisfactory.)



N.m.r. Structural Proof for the Cyclohexanetetrol, M.p. 193°.—The spectrum of the new tetrol in deuterium oxide was recorded at 100 Mc. (Fig. 1-A). Values of the chemical shift are taken as positive when downfield from the zero reference signal of a capillary of tetramethylsilane. These values, stated in p.p.m., may differ somewhat from the true δ-values based on a tetramethylsilane internal reference. Spin-coupling con-

(11) Each "ketal" or "diketal" mentioned here is a normal acetonation product.

stants are given in c.p.s. In the figures, H, the applied field, increases from left to right.

The four methylene protons produce the quartet at 2.22 p.p.m., and the four O–C–H protons the complex pattern at 4.43 and 4.67. Since the methylene quartet was almost unchanged at 60 Mc. (not shown), the splitting is attributed to spin coupling only.

When integrals of spectra are obtained using the Varian V-3521 integrator in the HR-60 or HR-100 systems, they are the result of 2-Kc. field modulation and audio-phase detection.[7] By using a low modulation index, high radiofrequency power, and proper phasing, one can obtain spectra 2 Kc. below or above the actual radiofrequency. In this mode of operation spin–spin decoupling is easily achieved by field modulating with a larger index using an additional audio frequency which will create a large side-band component of the radiofrequency power elsewhere within the spectrum.[7] This irradiating field is large enough to effectively "stir up" the spin states of the nuclei precessing at the frequency of the irradiating field, thus allowing any nuclei which are normally spin coupled to the irradiated group to see only an average (zero) spin state.

When operating on the lower 2-Kc. side band, the additional audio-frequency modulator must be tuned to a value less than 2 Kc. by an amount approximately equal to the chemical shift of two spin-coupled groups in order to record a spectrum showing a decoupled high field group. Figure 1-B was obtained by using an irradiating modulation frequency, ω_2, which was approximately 233 c.p.s. less than the nominally 2-Kc. detecting side-band frequency, ω_1. By using a sufficiently large modulation index at ω_2 it was possible to produce a component of the radiofrequency power near 4.5 p.p.m. large enough to perturb all of the various O–C–H resonances while observing the CH_2 signals. The methylene quartet is thus collapsed to a singlet, confirming that there is little or no chemical shift between the four methylene protons. These protons are spectroscopically equivalent, although geometrically not strictly equivalent.

An *ortho–meta–para* structural decision can now be achieved by reviewing the methylene proton environments possible in the various configurations and conformations. For an *ortho* structure, none of the six configurations would permit a conformation with all methylene protons equivalent.[12] For a *para* structure, two of the five configurations[5a] permit conformations with equivalent methylene protons; however, these conformations would also require equivalence of the O–C–H protons,[5a] which is not found (Fig. 1-C). The one remaining possibility for the cyclohexanetetrol, m.p. 193°, then is the *meta* structure. This structure in certain configurations can have conformations with the methylene protons equivalent, as explained below.

The *meta* structural assignment is supported by certain other evidence. The reported properties of the six diastereomeric *ortho* tetrols and derivatives were compared with those of the new tetrol and its tetraacetate (m.p. 118°) and tetrabenzoate (m.p. 189°). Four of the six isomers were promptly excluded. It appeared for a time that Criegee's isomer,[13] m.p. 222°, might be identical with our new tetrol,[14] since it has an all-*cis* configuration (XIX) resembling that of the anhydro diketal I. Criegee's isomer was finally excluded on the basis of the tetrabenzoate melting point, and also by synthesis of the previously unreported tetraacetate, m.p. 65°, which was nonidentical with our new tetraacetate, and not a dimorph. The new tetraacetate of m.p. 65° was prepared from the unsaturated carbonate diacetate XVI.[13] The (12/34) tetrol and its tetraacetate have suitable melting points, but this isomer is excluded by the n.m.r. data.

To exclude the *para* structure, we synthesized all five of the possible diastereomers,[5a] none of which were identical with the new cyclohexanetetrol, m.p. 193°.

These results help to confirm the *meta* assignment based on n.m.r. For the *meta* structure, four *meso* and two racemic configurations are predicted (Table I). To ascertain the actual configuration, 100-Mc. spectra and spin decoupling were again employed. Although the tetraacetate spectrum, Fig. 2, is more easily interpreted (see below), evidence from Fig. 1 will first be considered.

Table I

The 1,2,3,5 or *meta* Cyclohexanetetrols

Configuration and favored conformation	M.p., °C. (molecular rotation) Tetrol	Tetraacetate	Tetrabenzoate	Ref.
meso Diastereomers				
(1235), X, EAEE				
(123/5), IX, EAEA ⇌ AEAE	193 dec.	118	189	*a*
(135/2), XI, EEEE				
(13/25), XII, EEEA	180	86	206	*a, b*
Active or Racemic Diastereomers				
(12/35), XX, AEEE	151 (−90°)			*c, d*
(125/3), XXII, EAAE ⇌ AEEA	208 (−12°) or 200			*c, d*

[a] This article. [b] Ref. 23. [c] Ref. 18. [d] Ref. 29.

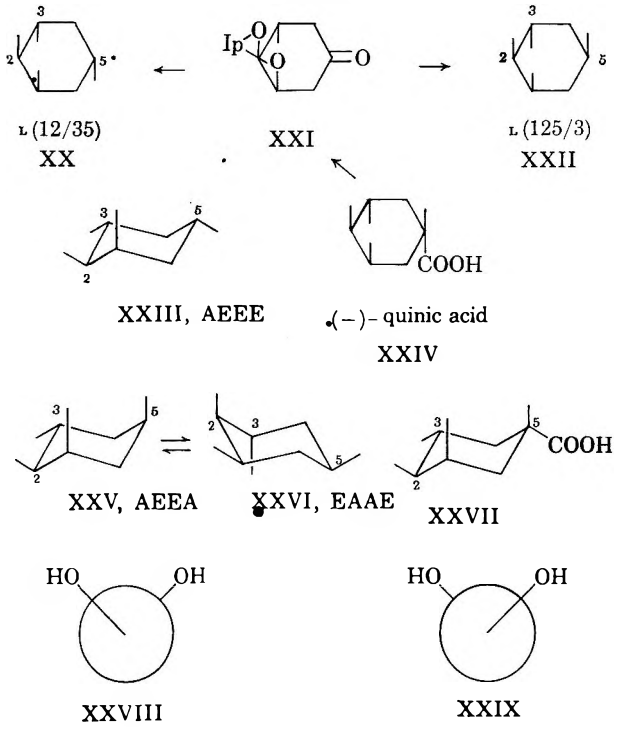
N.m.r. Configurational Proof for the Cyclohexanetetrol, M.p. 193°.—As noted, spectroscopic (but not necessarily geometric) equivalence of the methylene protons was demonstrated by irradiation of the O–C–H protons (Fig. 1-B). The next experiment was to irradiate the methylene protons at their resonant frequency while observing the O–C–H signals. When this was done the O–C–H pattern collapsed into two sharp singlets (Fig. 1-C). The smaller singlet (4.67 p.p.m.) must be produced by H-5, which no longer is coupled with any neighboring proton. The larger (4.43 p.p.m.) must be produced by H-1, H-2, and H-3, revealing that there is little if any chemical shift between these three protons. Although H-1 and H-3 might be geometrically equivalent in any of the *meso* configurations (IX–XII), the spectroscopic equivalence of H-2 must be attributed to an accidental degeneracy in the spectrum.

(12) In any of the six *ortho* diastereomers, the two protons *within* a methylene group cannot be equivalent, because one proton has a *cis* neighboring hydroxyl group, the other a *trans*. (The neighbor on the other side in each case is the remaining methylene group.) The two methylene protons "above" the ring plane, or "below" it, are also nonequivalent, except in the two *meso* diastereomers, because of the nonsymmetrical disposition of the hydroxyl groups at positions 1 and 4, or 2 and 3.

(13) R. Criegee and P. Becher, *Chem. Ber.*, **90**, 2516 (1957). We would like to thank Professor Criegee for a generous sample of the carbonate diacetate of conduritol-D.

(14) The new cyclohexanetetrol melts with decomposition at 193° in a sealed capillary, but in an open capillary slowly darkens and decomposes over a wide range near 220°.

CHART II



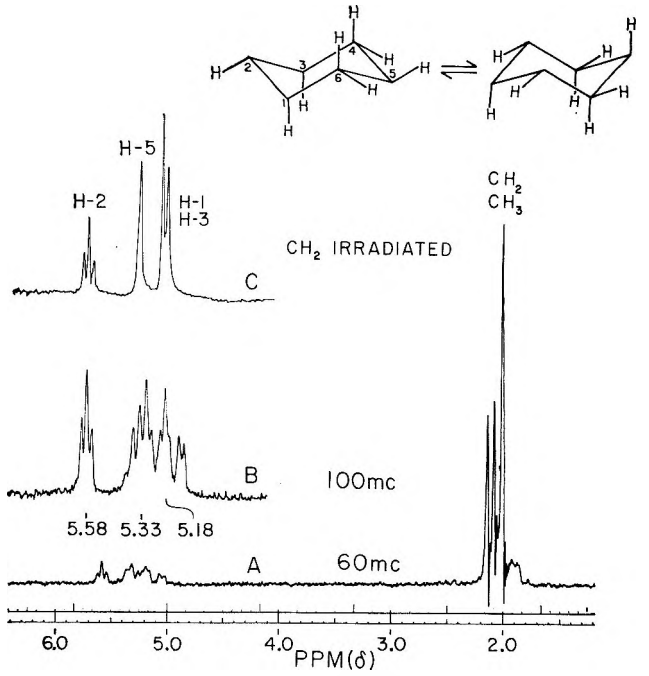


Fig. 2.—N.m.r. spectrum in chloroform-*d* of the tetraacetate, m.p. 118°, from 1,2,3,5-cyclohexanetetrol, m.p. 193°: (A) at 60 Mc., (B) at 100 Mc., (C) at 100 Mc.; methylene protons irradiated.

Since H-1 and H-3 are equivalent, and since the two methylene protons "above" (and also the two "below") the ring are equivalent, the molecule must have a plane of symmetry. This plane, which passes through positions 2 and 5 (see formulas in Fig. 1) is perpendicular to the ring plane. Thus one may exclude the two active (or racemic) configurations[15] (12/35) XX, and (125/3) XXII (Chart II).

In the remaining four (*meso*) configurations, geometric equivalence for two protons *within* the same methylene group is not possible. Nevertheless, the situation of equivalence can be approximated[16,17] if two conditions are met by the methylene protons, *e.g.*, at position 4: (1) the neighboring protons (H-3, H-5) must have a *trans*, not *cis*, configuration; and (2) each methylene proton must be partly axial, partly equatorial in its time-average n.m.r. response.

Condition 2 implies mobile equilibrium between two chair conformations of nearly equal energy, which in the case of a cyclohexanetetrol must be diaxial–diequatorial. Similar requirements apply to the methylene protons at positions 6, and their neighbors (H-1, H-5).

The configurations *meso* (1235) or "all-*cis*", and *meso* (135/2) (formulas X and XI) can be excluded because they violate both conditions 1 and 2. The configuration *meso* (13/25) XII, satisfies condition 1 but violates condition 2.

The one remaining possibility for the new cyclohexanetetrol, m.p. 193°, is the configuration *meso* (123/5) IX, which does meet both of the conditions.

Two additional facts support this assignment.

(1) The stereoisomer *meso* (13/25), m.p. 180°, which is the only other *meso* isomer meeting condition 1, has been shown to be nonidentical with the tetrol, m.p. 193°, by comparison of the n.m.r. spectra. which are very different.

(2) The levorotatory stereoisomer[18] (125/3) XXII, which is the only other isomer meeting condition 2, has also been shown to be nonidentical with our new tetrol, by comparison of n.m.r. spectra. Although the (125/3) isomer was optically active (molecular rotation −12°, m.p. 208°), and our isomer inactive, the nonidentity of the spectra *in solution* shows a difference in diastereomeric configurations.

The remaining features of the spectra (Fig. 1) may now be examined. At 4.67 p.p.m. (Fig. 1-A) the signal for H-5 appears as a quintet, due to spin coupling with the four equivalent methylene protons. The methylene signal (2.22 p.p.m.) appears as a pair of doublets, because of coupling of the methylene protons with H-3 and H-5, or H-1 and H-5.

The observed H-5 splittings (Fig. 1-A) show an average coupling constant of 3.8 c.p.s. between H-5 and the methylene protons. The individual coupling constants in such a system cannot be directly calculated from the observed splittings.[19,20] However, time averaging for both conformations of constants EE, EA, AE, and AA (normal values: 3, 3, 3, and 8 c.p.s.) would give an average coupling constant for H-5 of 4.2 c.p.s., not far from the observed 3.8.

(15) Following *Chemical Abstracts* practice, we number the *meta* cyclohexanetetrols "1,2,3,5," *not* "1,3,4,5." For specifying configuration by the fractional system, the longest series of smallest numbers is placed in the numerator, *e.g.*, "(125/3)," *not* "(1/235)." For further explanation, see our previous articles.

(16) When a methylene group in a cyclohexane ring has two like neighboring *trans* substituents, the axial methylene proton in one chair conformation will have an immediate environment which is identical with that of the axial methylene proton in the other conformation; likewise for the equatorial methylene protons. If the methylene group has two neighboring *cis* substituents, this will not be true. The "immediate environment" here includes the system -CHY-CH_2-CHY- and the three remaining ring carbon atoms, but not necessarily the substituents on the three remaining ring carbon atoms.

(17) Compare 1,3-cyclohexanediol studies by H. Finegold and H. Kwart, *J. Org. Chem.*, **27**, 2361 (1962); also the 2,4-pentanediol studies by J. Pritchard and R. Vollmer, *ibid.*, **28**, 1545 (1963).

(18) G. Dangschat and H. O. L. Fischer, *Naturwiss.*, **27**, 756 (1939).

(19) R. Abraham and H. Bernstein, *Can. J. Chem.*, **39**, 216 (1961).

(20) D. Grant and H. Gutowsky, *J. Chem. Phys.*, **34**, 699 (1961).

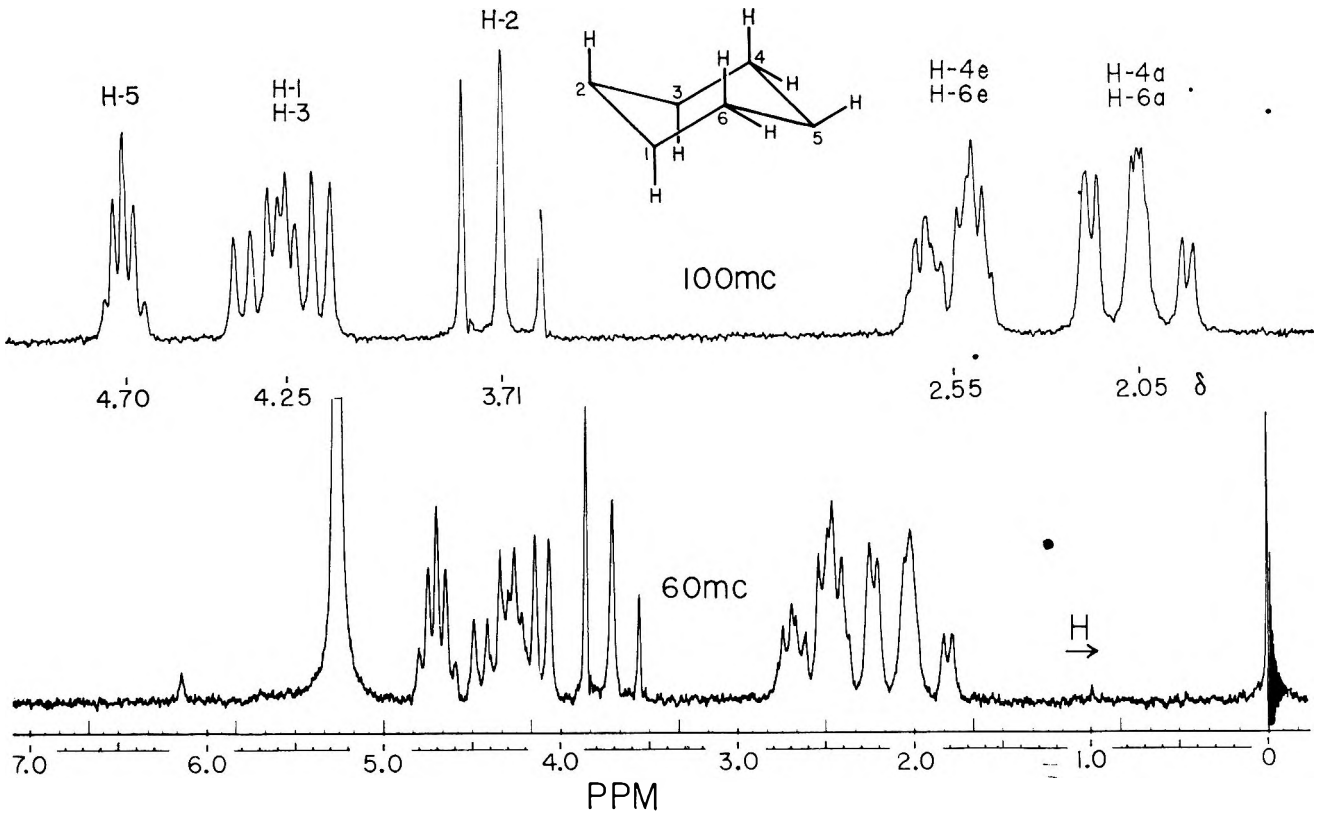


Fig. 3.—N.m.r. spectra of 1,2,3,5-cyclohexanetetrol, m.p. 180°, in deuterium oxide at 60 and 100 Mc.

The pattern at 4.43 p.p.m. in the nondecoupled spectrum (Fig. 1-A) for H-1, H-2, and H-3 is not easily interpreted, owing in part to the fact that H-1 and H-3 are coupled with methylene protons, but H-2 is not.

Spectrum of the Tetraacetate, M.p. 118°.—A sample of the tetraacetate from the new m.p. 193° cyclohexanetetrol was first examined in chloroform-*d* at 60 Mc. (Fig. 2-A). In the region δ 2.00–2.15 (p.p.m. downfield from dissolved tetramethylsilane) there are signals due to four acetate methyl groups, of which only two are equivalent (no doubt at positions 1 and 3). The methylene signals are partly obscured by the methyl signals. The four O–C–H protons produced a poorly resolved pattern in the region δ 5.0–5.7, which was considerably improved at 100 Mc. (Fig. 2-B), but still difficult to interpret. To remove the difficulty, spin decoupling was again employed.

Irradiation of the four methylene protons (which in the tetraacetate are not necessarily equivalent) at their resonant frequency caused the O–C–H pattern to collapse into a singlet, a doublet, and a triplet (Fig. 2-C).

The singlet (δ 5.33) must be due to H-5, which no longer is coupled with any neighboring proton. The doublet (δ 5.18) must be due to the equivalent pair (H-1 and H-3), now coupled only to H-2. The triplet (δ 5.58) must be due to H-2, coupled only to H-1 and H-3, and thus unaffected by the methylene decoupling (Fig. 2-B, 2-C).

The small constant (2.3 c.p.s.) between H-2 and its neighbors is consistent with time averaging of EA and AE couplings. These n.m.r. results support assignment of the configuration *meso* (123 5) IX to the cyclohexanetetrol, m.p. 193°, and its tetraacetate.

Acetylation caused a downfield shift of 0.66 p.p.m. for H-5, and 0.75 p.p.m. for H-1 and H-3. Since the downfield shift for H-2 was 1.15 p.p.m., its degeneracy with H-1 and H-3 was destroyed, and separate signals were obtained (compare Fig. 1-C and 2-C).[21]

N.m.r. Configurational Proof for the Cyclohexanetetrol, M.p. 180°, of Horswill and McCasland.—When *myo*-inositol (VII) is heated with acetyl bromide, one of the products is a dibromocyclohexanetetrol tetraacetate, m.p. 130°.[22–24] This can be hydrolyzed to the dibromotetrol, m.p. 216°, for which a *meta* structure, E, was proposed[25] and is now confirmed.

In 1954 Horswill[23b] converted this dibromotetrol to a cyclohexanetetrol, m.p. 180°, which also appeared to have the *meta* structure; B. McCasland and Horswill[23b] assigned this tetrol the tentative configuration *meso* (13/25) XII, based on assumptions regarding the acetyl bromide reaction mechanism. This structural and configurational assignment has

(21) The relatively great downfield shift of H-2, compared with H-1 and H-3, on acetylation can possibly be attributed to the fact that H-2 is more equatorial in the tetraacetate than in the tetrol, and H-1 and H-3 more axial. This in turn would result from a relatively large population of that conformation in which the acetate groups at 1 and 3 are equatorial.

(22) (a) H. Müller, *J. Chem. Soc.*, **91**, 1790 (1907); (b) **101**, 2383 (1912); (c) E. Griffin and J. Nelson, *J. Am. Chem. Soc.*, **37**, 1552 (1915); (d) A. Menzel, M. Moore, and O. Wintersteiner, *ibid.*, **71**, 1268 (1949); (e) E. Flynn, Ph.D. Thesis, University of Illinois (with Professor H. E. Carter), 1949; (f) M. L. Wolfrom, J. Radell, R. Husband, and G. E. McCasland, *J. Am. Chem. Soc.*, **79**, 160 (1957).

(23) G. E. McCasland and E. C. Horswill, *ibid.*, (a) **75**, 4020 (1953); (b) **76**, 2373 (1954). In the latter article Kubler's m.p. 176° dibromocyclohexanetetrol was inadvertently omitted from the list of known isomers (see formula IV).

(24) *myo*-Inositol reacts with hot acetyl bromide to give not only the *meta*- and *para*-dibromocyclohexanetetrol tetraacetates reported by previous investigators, but also an *ortho* isomer (B. Franck, personal communication, Aug., 1962); see formula III, Chart I.

(25) The structural proof for the dibromocyclohexanetetrol, m.p. 216°, was based on periodate studies, which seem highly reliable because (after further oxidation) a dibromohydroxyglutaric acid was actually *isolated*, confirming the *meta* structure.[22c] The corresponding tetrol, m.p. 180°, gave an unequivocal 2 moles/mole uptake of periodate, also indicating a *meta* structure (McCasland and Horswill, 1954).

now been fully confirmed. Although the 60-Mc. spectrum might have provided this confirmation, interpretation was greatly facilitated by recording both the 100- and 60-Mc. spectra. (Fig. 3).

At 100 Mc., the spectrum spread out into five well-separated patterns, shown by integration to contain 1, 2, 1, 2, and 2 protons, from left to right. The pattern separations must represent chemical shifts, since they are dependent on the magnetic field strength.

The triplet at 3.71 p.p.m. must result from spin coupling, since the splittings are essentially constant at 14.1 and 23.5 kilogauss. The triplet must correspond to H-2, which is coupled with the equivalent pair (H-1 and H-3). The coupling constant of about 9 c.p.s. demonstrates that H-2, and also H-1 and H-3, must be axial.[26]

The quintet at 4.70 p.p.m. (Fig. 3) must be produced by H-5, which is coupled with about equal constants of 3.0 c.p.s. to the four methylene protons. The coupling must be EE or EA, and establishes H-5 as equatorial. The H-5 pattern appears at lower field than the axial proton signals, as would be expected.

From the demonstrated conformational sequence (AAAE) at positions (1,2,3,5), the configuration *meso* (13/25) is fully established, confirming the 1954 assignment.

The (H-1 and H-3) diaxial assignment is supported by analysis of the octet at 4.25 p.p.m. which shows splittings[27,28] of 11.8, 9.0, and 4.7 c.p.s., due to AA, AA, and AE coupling of H-1 with the three protons at positions 2 and 6, and of H-3 with protons at 2 and 4.

Since this tetrol exists in a single, favored conformation (Table I) axial–equatorial time averaging is not encountered, and the equatorial methylene pattern is located about 0.50 p.p.m. downfield from axial, as might be expected. As in all the *meso* isomers (IX–XII) the two methylene protons "above" the ring are equivalent and likewise the two "below."

The methylene patterns (each presumably of 8 lines) may be attributed to spin couplings (large, small, small) of the equatorial protons (2.55 p.p.m.) with geminal and neighboring protons, and to couplings (large, large, small) of the axial protons (2.05 p.p.m.).

The **tetraacetate,** m.p. 86°, from the tetrol, m.p. 180°, was also examined, in chloroform-*d* at 60 Mc. (not shown). A wide methylene pattern (55 c.p.s.) confirmed nonequivalence of axial and equatorial methylene protons, but detailed interpretation was not accomplished.

Optical Rotatory Configurational Proof for the Two Active Diastereomers of 1,2,3,5-Cyclohexanetetrol.—In 1939, Dangschat and Fischer[18] degraded natural levorotatory quinic acid (XXIV) into a ketal (XXI) of 3,4,5-trihydroxycyclohexanone. From this intermediate by reduction and deacetonation were obtained two epimeric *meta* cyclohexanetetrols, XX and XXII, m.p. 151° (molecular rotation −90°), and m.p. 208°[18] or 200°[29] (molecular rotation −12°). The epimer m.p. 151° was reportedly obtained with aluminum isopropoxide; the epimer 208°, with hydrogen–nickel (reactions probably not stereospecific).[29] There was no basis at the time for deciding which epimer was which, but now methods for optical rotation prediction now permit a decision.[30,31]

According to Whiffen[30] or Brewster,[30] each diol grouping in the "front-left" conformation XXVIII contributes +45° to the molecular rotation; in the "front-right" XXIX, −45°; and in a diaxial conformation, 0°.

The L (12/35) epimer XX, with a single favored (AEEE) conformation XXIII, would then have a predicted rotation: −45° + −45° = −90°. The epimer of reported[18] molecular rotation −90° (m.p. 151°) can be assigned this absolute configuration.

Since the rotational contribution of an isolated dissymmetric center is assumed negligible, it might appear that epimerization at position 5 (formula XX) could not change the molecular rotation. However, such an epimerization can *indirectly* affect the rotation if it causes a shift in ratio of the molecule's two chair conformations.

Since the epimer L (125/3) is diaxial–diequatorial, it would consist of two conformations, XXV and XXVI, of roughly equal energy, in mobile equilibrium. The predicted molecular rotation for conformation XXV is −90°, as before; but for conformation XXVI it is +45° + 0° = + 45°. The epimerized tetrol should then be more dextrorotatory, or less levorotatory, so that the m.p. 208° epimer (molecular rotation −12°) can reasonably be assigned the absolute configuration L (125/3).

From the observed rotation, −12°, the estimated conformational ratio, XXV–XXVI, is about 2:3. The nearly equal molecular populations are perhaps due to competing effects of steric repulsion and hydrogen bonding between 1,3-diaxial hydroxyl groups.

In a similar manner one can predict the rotation of quinic acid itself from its known absolute configuration and assumed favored conformation XXVII. Assuming negligible contribution by the C(OH)(COOH) dissymmetric center, the predicted molecular rotation is −45° + −45° = −90° (found,[32] −84°).

Structure and Formation of the Dibromotetrol Tetraacetate, M.p. 173°.—The crystalline product obtained by reaction of the anhydro diketal (I) with HBr–AcOH was shown by microanalysis and infrared and nuclear magnetic resonance spectra to be a dibromocyclohexanetetrol tetraacetate. The *ortho* structure was excluded by nonreaction with sodium iodide[33,34] (see Experimental).

(26) Note that the axial O–C–H protons in the n.m.r. discussion correspond to equatorial functional groups, and vice versa.

(27) R. Lemieux, R. Kullnig, H. Bernstein, and W. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(28) S. Brownstein and R. Miller, *J. Org. Chem.*, **24**, 1886 (1959).

(29) The two Dangschat–Fischer tetrols were recently prepared again by S. J. Angyal and P. A. J. Gorin (personal communication, Aug., 1962). Hydrogenation of the triolone ketal, using platinic oxide (not nickel) followed by deacetonation, reportedly gave a 77:23 ratio of the (125/3) and (12/35) epimers, from which was isolated the pure (125/3) epimer, m.p. 200°. We would like to thank Drs. Angyal and Gorin for a sample of their product, m.p. 200°.

(30) J. Brewster, *J. Am. Chem. Soc.*, **81**, 5483 (1959); D. Whiffen, *Chem. Ind.* (London), 964 (1956).

(31) We would like to thank Professor S. J. Angyal for suggesting the use of rotation predictions in cyclitol studies (personal communication, Feb., 1960). We applied such predictions in 1961 to certain quercitols [*J. Am. Chem. Soc.*, **83**, 2335 (1961)]. According to recent word from Professor Angyal and P. Gorin they have independently assigned absolute configurations to the Dangschat–Fischer tetrols in agreement with those proposed by us, presumably on the basis of rotation calculations.

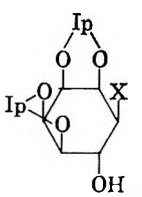
(32) (a) T. Posternak, "Les Cyclitols," Hermann, Paris, 1962 [for review see *J. Am. Chem. Soc.*, **85**, 2189 (1963)]; (b) p. 269.

The *meta* structure was established by successive conversion to the dibromotetrol V and the tetrol IX.

The dibromo tetraacetate, m.p. 173°, has now been shown by n.m.r. spectra to have the *trans*-dibromo configuration V (not XVII or XVIII); details will be given in a subsequent publication.

In early experiments, periodate titrations on the new dibromotetrol V and tetrol IX seemed to favor an *ortho* or *para* structure (see Experimental). Since other anomalous periodate results on cyclitols have been reported,[35] and since the *ortho* and *para* tetrol structures have now been firmly excluded by synthesis and n.m.r. data, the matter has not been pursued further.

No mechanism has yet been established for the remarkable reaction by which the HBr–AcOH reagent [36d] at room temperature converts the epoxide diketal (I) into a dibromo product (V, tetraacetate). An acceptable mechanism would need to explain these facts: (1) the same reagent with other diastereomers (*e.g.*, XIV) gave only monobromo products; (2) the same reagent with *epi*-inositol diketal[37] (XXX) failed to give any bromine-containing product,[38] despite similarity in the configurations; (3) the same reagent with the bromopentol diketal XXXI failed to give any of the dibromo tetraacetate V.



XXX, X = OH
XXXI, X = Br

From this last experiment, it appears that rearward, ring-opening attack by bromide ion on an epoxide ring carbon (position 6, formula I) must take place *after* similar attack on a ketal ring carbon (position 4). (Protonation of oxygen would facilitate each attack.)

Experimental[36]

All melting points have been corrected and, unless noted otherwise, were measured on a Nalge–Axelrod micro hot stage. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. n.m.r. spectra (100-Mc.) were obtained with Varian HR-100 and 60-Mc. spectra with Varian A-60 high resolution spectrometers. Spin-decoupling experiments were accomplished through the use of a modified Varian V-3521 integrator.[7] Deuterium oxide[36b] with tetramethylsilane[36c] external reference was used as solvent for cyclohexanetetrols and dibromotetrols; chloroform-*d*[36a] with tetramethylsilane internal reference, for tetraacetates and tetrabenzoates.

Infrared spectra were measured on a Perkin-Elmer Model 137 Infracord recording spectrometer.

Darco G-60 decolorizing charcoal[36c] was used. Each solid filtration residue was washed with an appropriate wash solvent, and the wash liquid was combined with an appropriate filtrate. Each crop of crystals was dried to constant weight *in vacuo*, in some cases with the use of heat. Each nonaqueous solution to be evaporated was dried with an appropriate desiccant. All evaporations were performed under reduced pressure.

DL (1234/56) Diastereomer of 4,6-Dibromo-1,2,3,5-cylcohexanetetrol Tetraacetate (V), M.p. 173°.—To 240 mg. of 1,2:3,4-di-*O*-isopropylidene-5,6-anhydro-*allo*-inositol[10c] (m.p. 102°) was added 3.0 ml. of commercial[36d] 30% hydrogen bromide in glacial acetic acid, and the solution was stirred 12 hr. at room temperature (anhydrous conditions). Acetic anhydride (2.0 ml.) was added and stirring was continued for 12 hr. more. The powdery crystals were collected and dried over sodium hydroxide.

The crude product was taken up in 3.0 ml. of hot absolute ethanol and the solution was treated with charcoal, and then kept at 0° for 12 hr. or longer. The crystals were collected, giving 350 mg. (74%) of product, m.p. 172–173°. A sample was recrystallized again for analysis, melting point unchanged.

Anal. Calcd. for $C_{16}H_{21}BrO_{10}$: C, 42.40; H, 4.67; Br, 17.63. Calcd. for $C_{14}H_{18}Br_2O_8$: C, 35.46; H, 3.83; Br, 33.71. Found: C, 35.56; H, 3.74; Br, 33.46.

The infrared spectrum showed strong carbonyl absorption at 1750 cm.$^{-1}$, and no hydroxyl absorption. It resembled that of other dibromocyclohexanetetrol tetraacetate isomers, and not that of a bromocyclohexanepentol pentaacetate. The n.m.r. spectrum was recorded.

Sodium Iodide Test for Vicinal Dibromides.[33,34]—To 30 mg. of the dibromo tetraacetate (m.p. 173°) in a 200 × 4 mm. Pyrex tube was added a solution of 75 mg. of sodium iodide in 0.5 ml. of acetone. The tube was flushed with nitrogen, cooled with Dry Ice, and sealed off in a flame. The tube was heated at 100° for 15 hr. The tube contents were then slightly yellow (not red-brown), and no (sodium bromide) crystals were visible. A control tube from which the dibromo tetraacetate had been omitted showed no visible difference.

DL (1234/56) Diastereomer of 4,6-Dibromo-1,2,3,5-cyclohexanetetrol (V), M.p. 182°.—A solution of 350 mg. of the tetraacetate (m.p. 173°) in 6.0 ml. of a molar solution of hydrogen chloride in 50% (v./v.) ethanol was boiled under reflux for 5 hr., then evaporated. Absolute 2-methyl-1-propanol (3.0 ml.) was added and evaporation was repeated; the addition and evaporation were then again repeated. The residue was taken up in 2.0 ml. of hot 2-propanol (treated with charcoal). After 12 hr. at 0° (small yield of crystals separated), the solution was warmed to room temperature, and petroleum ether (b.p. 65–110°) was added. After an additional 12-hr. period at 0°, the crystals were collected and washed with 2-propanol, giving 200 mg. (88%) of the desired product, m.p. 180–182°.

Anal. Calcd. for $C_6H_{10}Br_2O_4$: C, 23.55; H, 3.29; Br, 52.24. Found: C, 23.57; H, 3.39; Br, 51.96.

The n.m.r. spectrum in deuterium oxide contained signals for two Br–C–H protons and four O–C–H protons crowded together into two narrow patterns centered at 4.8 and 4.9 p.p.m. The area of the latter pattern corresponded to one proton.

***meso* (123/5) Diastereomer of 1,2,3,5-Cyclohexanetetrol (IX), M.p. 193°.**—To a solution of 200 mg. of the dibromotetrol (m.p. 182°) in 5.0 ml. of water was added 0.5 g. of moist Raney nickel catalyst and 0.2 g. of moist Amberlite IR-45 ion-exchange resin.[36f] The mixture was hydrogenated at 3 atm. and room temperature for 6 hr., then filtered. The filtrate was freed of nickel ions by treatment with Amberlite IR-120 (H^+) resin,[36f] then adjusted to pH 5 by stirring with Amberlite IR-45 resin. The filtrate from the resin treatment was evaporated, giving an oil which was taken up in 3.0 ml. of absolute ethanol (treated with charcoal). After 12 hr. the crystals which had separated were collected, giving 60 mg. (62%) of product, m.p. (in a sealed capillary) 192–193° dec. A sample was recrystallized again from abso-

(33) R. Shriner, R. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc. New York, N. Y., 1956, p. 159.

(34) The reaction of 1,2-dibromocyclohexane with sodium iodide to give cyclohexene, iodine, and sodium bromide proceeds rapidly only with the *trans* diastereomer. However, the *cis* diastereomer may react slowly, probably because it reacts slowly with iodide to give the *trans* iodobromide, which can then undergo the usual rapid elimination reaction (D. Cram and G. Hammond, "Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 401). Little, if any, information is available on the behavior of dibromodideoxy carbohydrates in this reaction. However, the comparable reaction of cyclitol ditosylates with sodium iodide to give cyclohexenetetrols (conduritols) has been carried out (Angyal and Gilham, 1958).

(35) S. J. Angyal and L. Anderson, *Advan. Carbohydrate Chem.*, **14**, 150 (1959); see ref. 22d; J. Green, "The Carbohydrates," W. Pigman, Ed., Academic Press, New York, N. Y., 1957, pp. 350, 351.

(36) Products that were used in experiments were obtained from the following companies: (a) Merck Sharp and Dohme of Canada, Ltd., Montreal; (b) Nichem, Inc., Bethesda, Md.; (c) Anderson Chemical Co., Weston, Mich.; (d) Distillation Products Industries, Rochester, N. Y.; (e) Darco Division, Atlas Powder Co., Wilmington, Del.; (f) Resinous Products Division, Rohm and Haas Co., Philadelphia, Pa.

(37) The 1,2:3,4 and 1,2:4,5 di-*O*-isopropylidene derivatives of *epi*-inositol have very nearly the same melting point, but can be distinguished by a qualitative periodate test.

(38) The expected bromopentol pentaacetate, m.p. 153°, had previously been prepared by reaction of *epi*-inositol itself with hot acetyl bromide; see G. E. McCasland and J. Reeves, *J. Am. Chem. Soc.*, **77**, 1812 (1955).

lute ethanol for analysis, melting point unchanged. The infrared spectrum was very similar to that of the m.p. 180° diastereomer.

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.44; H, 8.20.

In some earlier runs the product was recrystallized from aqueous ethanol and then appeared to melt with decomposition (slow darkening) at about 220° in an open capillary. Its nonidentity with a 1,2,3,4-cyclohexanetetrol of reported[13] m.p. 222° was shown by comparison of the tetraacetates (see below).

The n.m.r. spectrum in deuterium oxide at 60 and 100 Mc. was examined with the aid of spin decoupling.

Periodate Titrations of the Cyclohexanetetrol, M.p. 193°, and Dibromocyclohexanetetrol, M.p. 182°.—(Figures in parentheses refer to the dibromotetrol.) To a 14.8-mg. (13.0 mg.) sample of the tetrol (dibromotetrol), was added 50 ml. (25 ml.) of 0.200 *M* (0.0196 *M*) sodium metaperiodate and water *q.s.* 100 ml. (50 ml.). Ten-milliliter aliquots of the clear solution were withdrawn at intervals for titration. Each aliquot was immediately mixed with 25 ml. (15 ml.) of 0.0100 *N* sodium arsenite, 10 ml. (5 ml.) of saturated sodium bicarbonate, and 1 ml. (0.5 ml.) of 1.2 *M* potassium iodide. After 15 min., the excess arsenite was determined by iodometric titration. The titration results were as follows.

Time, hr.	0	0.5	1.0	3.0	3.5	5.0	17.5	24.0
Periodate consumed, moles/mole								
Tetrol	0	3.1	3.1	3.2		3.3	3.5	4.0
Dibromotetrol	0	2.4	2.6		3.2	3.4		4.7

A control analysis on a sample of DL-*trans*-1,2-cyclohexanediol showed the expected 1 mole/mole of periodate uptake.

meso (**123/5**) **Diastereomer of 1,2,3,5-Cyclohexanetetrol Tetraacetate (IX), M.p. 118°.**—A mixture of 40 mg. of the tetrol (m.p. 193°) with 30 mg. of fused sodium acetate and 3.0 ml. of redistilled acetic anhydride was boiled under reflux for 4 hr. The crude product, isolated in the usual manner, was a sirup. A solution of this sirup in 3.0 ml. of hot 2-propanol was treated with charcoal, and the filtrate was concentrated to 2.0 ml. Petroleum ether (3.0 ml.) was added, and the mixture was kept at 0° for 12 hr. The crystals were collected, giving 60 mg. of colorless needles, m.p. 117–118°. A sample was recrystallized again for analysis, melting point unchanged.

Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 52.98; H, 6.12.

The infrared spectrum was very similar to that of the m.p. 86° diastereomer except in the region 8.5–12 μ. A 15-mg. second crop, m.p. 116–118°, was obtained, total yield 88%.

The n.m.r. spectrum in chloroform-*d* at 60 and 100 Mc. was examined, with the aid of spin decoupling. The 60-Mc. integral showed 16 protons, with steps of 1, 3, and 12 protons. Only the latter step was sharply defined.

meso (**123/5**) **Diastereomer of 1,2,3,5-Cyclohexanetetrol Tetrabenzoate (IX), M.p. 189°.**—To 50 mg. of the tetrol (m.p. 193°) was added 0.31 g. of redistilled benzoyl chloride and 2.0 ml. of anhydrous pyridine. The mixture was stirred at room temperature for 24 hr. The crude product, isolated in the usual manner, was a viscous clear oil. This was taken up in 3.0 ml. of hot absolute ethanol (treated with charcoal), and the solution was kept at 0° for 24 hr. The colorless needles were collected, giving 60 mg. (31%) of product, m.p. 188–189°. A sample was recrystallized again for analysis, melting point unchanged.

Anal. Calcd. for $C_{34}H_{28}O_8$: C, 72.33; H, 5.00. Found: C, 72.32; H, 5.19.

The infrared spectrum was similar to that of the m.p. 206° diastereomer in the region 2.5–7.5 μ.

N.m.r. Spectrum of the M.p. 180° Diastereomer of 1,2,3,5-Cyclohexanetetrol (XII).—A sample of the crude tetrol (2.6 g.), prepared by Horswill[23b] in 1954, was recrystallized from 90% ethanol (treated with charcoal), giving 1.4 g. of colorless crystals, m.p. 179–180° (lit. m.p. 181.5–182.5°). The n.m.r. spectrum in deuterium oxide was recorded at 60 and 100 Mc. The 60-Mc. integral showed 8 protons with steps at 1, 2, 1, and 4 protons. Only the first step was sharply defined.

N.m.r. Spectrum of the M.p. 86° Diastereomer of 1,2,3,5-Cyclohexanetetrol Tetraacetate (XII).—A 450-mg. sample of the tetrol (m.p. 180°) was acetylated in the usual manner, giving 610 mg. of twice-recrystallized (from absolute ethanol)[39] product, m.p. 84–86° (lit.[23b] m.p. 91–92°). The spectrum in chloroform-*d* was recorded at 60 Mc. The acetate methyl signals in the spectrum consisted of sharp 9-proton and 3-proton peaks (δ 2.08 and 2.15). The equivalence of three (instead of two) methyl groups may be due to accidental degeneracy. The O–C–H chemical shifts were compressed into a 19-c.p.s. pattern, compared with 74 c.p.s. in the tetrol, so that interpretation was not possible. The wide methylene pattern was partly obscured by the methyl signals.

N.m.r. Spectrum of (−)-(125/3) Stereoisomer of 1,2,3,5-Cyclohexanetetrol (XXII).—A small sample of the tetrol,[18] which had been prepared by Angyal and Gorin[29] (m.p. 200°) was examined in deuterium oxide at 60 Mc. using a microcell.[40] The spectrum showed a complex methylene pattern centered at 2.3 p.p.m., and complex O–C–H patterns centered at 4.17 and 4.5 p.p.m. The spectrum was decidedly different from that of the (optically inactive) 193° diastereomer.

Nonreaction of DL-1,2:3,4-Di-*O*-isopropylidene-*epi*-inositol (XXX) with Hydrogen Bromide.—To 130 mg. of the *epi*-inositol 1,2:3,4-diketal,[10d,37] m.p. 181°, was added 2.0 ml. of commercial 30% hydrogen bromide in glacial acetic acid. The solution was stirred for 1 day at room temperature. The orange solution was evaporated. To the residual brown oil was added 2.0 ml. of 50% aqueous acetic acid, and the mixture was heated at 90–100° for 1 hr. The solution was evaporated, and the evaporation was repeated after addition of 2.0 ml. of toluene.

Redistilled acetic anhydride (2.0 ml.) and 20 mg. of fused sodium acetate were added, and the mixture was boiled for 4 hr. On evaporation there was obtained an oil, which was taken up in 2.0 ml. of 2-propanol (treated with charcoal), and the solution was kept at 0° for 12 hr. A 160-mg. yield of *epi*-inositol hexaacetate, m.p. 186–188° (lit.[32] m.p. 188°), was obtained. A sodium fusion test for halogen was negative.

DL (12346/5) Stereoisomer of 1,2:3,4-Di-O-isopropylidene-6-bromoquercitol (Bromocyclohexanepentol Diketal) (XXXI).—To 170 mg. of the bromopentol[5b] (m.p. 209°) was added a solution of 290 mg. of fused zinc chloride in 10 ml. of acetone. The mixture was stirred at 25° for 5 days. Since a solid residue was still present, the mixture was boiled for 3 hr., giving a clear solution. To the cooled solution was added 1.38 g. of anhydrous potassium carbonate in 1.9 ml. of water, and the mixture was stirred 0.5 hr., and then filtered. The solid residue was washed with three 5-ml. portions of acetone, and the combined acetone filtrate was dried and evaporated, giving 100 mg. of colorless residue.

This was recrystallized from absolute ethanol (treated with charcoal), giving 70 mg. of colorless crystals, m.p. 206–207° with sublimation (capillary). A second crop of 15 mg. (total yield 38%), m.p. 205–206° (cap.) with sublimation, was obtained.

Anal. Calcd. for $C_{12}H_{19}BrO_5$: C, 44.59; H, 5.93; Br, 24.73. Found: C, 44.75; H, 5.83; Br, 24.75.

When this product was dissolved in a solution of hydrogen bromide in acetic acid and the solution was kept at room temperature for many hours, no crystals separated, and none of the expected dibromocyclohexanetetrol tetraacetate could be isolated from the reaction mixture.

meso (**1234**) **or All-*cis* Diastereomer of 1,2,3,4-Cyclohexanetetrol Tetraacetate (XIX), M.p. 65°.**—From 0.84 g. of conduritol-D 2,3-carbonate 1,4-diacetate,[13] there was obtained in the manner previously reported about 300 mg. of dihydroconduritol-D as a sirup (lit.[13] m.p. 222°).

A mixture of the sirup with 0.1 g. of fused sodium acetate and 4.0 ml. of redistilled acetic anhydride was boiled under reflux for 4 hr. The crude product, isolated in the usual manner, was a sirup, which turned crystalline when vacuum-dried over phosphorus pentoxide for 24 hr. The product was recrystallized from a 1:3 mixture of 2-propanol and petroleum ether (b.p. 65–110°), giving 130 mg. (13% based on carbonate diacetate) of the desired tetraacetate, m.p. 65.0–65.5°. A sample was recrystallized for analysis, melting point unchanged.

Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 52.85; H, 6.55.

(39) The spectrum contained a very small triplet at 1.28 p.p.m. probably due to a trace of ethanol impurity. This may have lowered the melting point but did not appreciably affect the remaining n.m.r. signals.

(40) The microcell technique has been described by J. N. Shoolery, in Varian Associates Technical Information Bulletin, Vol. 3, No. 3, Palo Alto, Calif., 1963, pp. 8,9.

The product was not identical with the m.p. 118° diastereomer, and not a dimorph.

Infrared Spectra.—The research spectrum was recorded, using the potassium bromide pellet method, for each new compound. The spectra showed the principal expected peaks, but have not been interpreted in detail.

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Photochemical Reactions of Diketones. II.[1a,b] The 1,2-Addition of Substituted Toluenes to 9,10-Phenanthrenequinone

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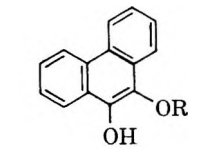
Reversible photochemical addition of substituted toluenes to phenanthrenequinone (PQ) proceeds *via* 1,2-addition to give 9,10-dihydro-9-hydroxy-9-X-benzyl-10-ketophenanthrenes (**6**) contrary to earlier reports that 1,4-addition occurs in these reactions. In addition to physical evidence, this was established by conversion of both phenanthrenequinone and the *p*-xylene–phenanthrenequinone adduct (**6d**) to *trans*-9,10-dihydro-9,10-dihydroxy-9,10-bis(*p*-methylbenzyl)phenanthrene (**7d**). Attempted synthesis of the *cis* isomer of **7d** was not successful. These results contrast with the 1,4-additions of ethers and aldehydes to phenanthrenequinone; the relative rates of addition of benzaldehyde, dioxane, and *p*-xylene to phenanthrenequinone were 48:2.7:1. The mono(*p*-methylbenzyl) ether (**2**) of 9,10-dihydroxyphenanthrene was synthesized by a new and apparently general method; photoirradiation of **2** afforded the 1,2-adduct **6d**.

In connection with the study[1b] of the photochemical addition of ethers to 9,10-phenanthrenequinone (PQ) to give products typified by the dioxane adduct (**1**), we have reinvestigated the photoaddition of *p*-xylene and related compounds to 9,10-phenanthrenequinone. This reaction was first reported in 1914 by Benrath and Von Meyer[2] and was re-examined almost 40 years later by Moore and Waters.[3] The earlier workers proposed that the 1:1 adducts obtained by sunlight irradiation of solutions of phenanthrenequinone in *o*- or *p*-xylene, mesitylene, pesudocumene, or quinaldine were substituted monobenzyl ethers (**2**) of 9,10-dihydroxyphenanthrene (**3**). This assignment was based on analogy with the photoaddition of aldehydes to phenanthrenequinone reported earlier by Klinger[4] to give monoesters (**4**) of **3** and, on degradations to **3**, phenanthrenequinone and phenanthrene quinhydrone. The surprising observation that the infrared spectrum of the *p*-xylene–phenanthrenequinone adduct exhibited both hydroxyl (2.98 μ) and carbonyl (5.96 μ) absorption was rationalized by the later workers on the assumption that appreciable tautomerization of the phenol **2** to the corresponding keto form occurred.[5]

If structure **2** were correct, the *p*-xylene–phenanthrenequinone adduct would be expected to exhibit an ultraviolet spectrum very similar to the spectra of the ether (**1**) and aldehyde (**4**) adducts. Further, the spectrum should be changed markedly in alkaline solution owing to conversion to the corresponding phenoxide ion as was observed with **1** and **4**. In fact, the ultraviolet spectrum of the *p*-xylene–phenanthrenequinone adduct (two maxima) was significantly different from the spectra of compounds of types **1** and **4** (six maxima) and remained unchanged on prolonged standing in alkaline solution. These results as well as the infrared data would be satisfactorily accommodated by the assumption that 1,2-addition of *p*-xylene to phenanthrenequinone had occurred to give 9,10-dihydro-9-hydroxy-9-(*p*-methylbenzyl)-10-ketophenanthrene (**6d**).[7a,b] The n.m.r. spectrum of the adduct exhibited singlets at τ 6.0 (hydroxyl proton, broad), 7.01 (CH_2), and 7.72 (CH_3) (relative intensities 1:2:3), and complex absorption at τ 2–3 (aromatic protons) in agreement with the revised structure.



1, R = 

2, R = *p*-$CH_3C_6H_4CH_2$–

3, R = H

4, R = $C_6H_5\overset{\|}{C}=O$

Chemical evidence confirmed the correctness of this conclusion. Reaction of phenanthrenequinone with an equimolar quantity of *p*-methylbenzyl magnesium bromide led to formation, in low yield, of a substance identical with the photoadduct; the other products isolated were recovered phenanthrenequinone and 1,2-bis-*p*-tolylethane, the product of Grignard coupling.

(1) (a) Presented in part at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962; (b) for the previous paper in this series, see M. B. Rubin, *J. Org. Chem.*, **28**, 1949 (1963).

(2) A. Benrath and A. Von Meyer, *J. prakt. Chem.*, **89**, 258 (1914).

(3) R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 3405 (1953).

(4) H. Klinger, *Ann.*, **249**, 137 (1888).

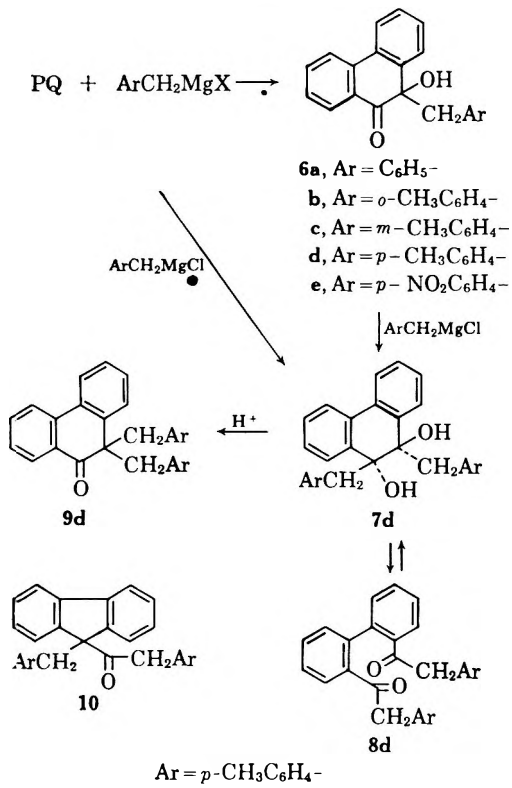
(5) 9,10-Dihydro-9-ketophenanthrene has been prepared[6] and reported to be unstable in air and to undergo rapid change in solution.

(6) E. J. Moriconi, F. T. Wallenberger, L. P. Kuhn, and W. F. O'Connor, *J. Org. Chem.*, **22**, 1651 (1957).

(7) (a) W. I. Awad and A. R. A. Raouf, *ibid.*, **22**, 881 (1957), have described the related substance, 9,10-dihydro-9-hydroxy-9-phenyl-10-ketophenanthrene [λ_{max} 245, 270 (sh), and 330 mμ in reasonably close agreement with the spectrum of the photoadduct of phenanthrenequinone and *p*-xylene]; (b) Ramart-Lucas, M. J. Matti, and T. Guilmart, *Bull. soc. chim. France*, 1215 (1948), report λ_{max} 278 and 330 mμ for 9,10-dihydro-9,9-dimethyl-10-ketophenanthrene.

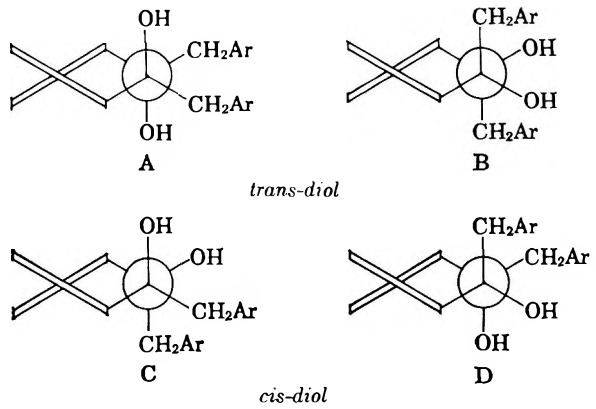
Reaction of either the photoadduct or phenanthrenequinone with excess *p*-methylbenzyl magnesium chloride furnished, in good yield in both cases, the identical product, *trans*-9,10-dihydro-9,10-dihydroxy-9,10-bis-(*p*-methylbenzyl)phenanthrene (**7d**). These results are consistent only with formulation of the adduct as **6d**.[8] (See Scheme I.)

SCHEME I



The assignment of *trans* stereochemistry to the diol **7d** was based on analogy with the addition of a variety of other Grignard reagents to phenanthrenequinone.[6] In addition, the presence of a sharp hydroxyl band in the infrared suggested the absence of hydrogen bonding as had been observed[6] for *trans*-9,10-dihydro-9,10-dihydroxy-9,10-diarylphenanthrenes in contrast to the two bands (bonded and nonbonded OH) observed in the spectra of *cis* isomers. The n.m.r. spectrum of **7d** exhibited the expected complex aromatic absorption at τ 2–3.5, a pair of AB doublets due to the methylene protons at 6.79 and 7.24 (J_{AB} = 14 c.p.s.), and singlets at 7.44 (OH) and 7.70 (CH_3). The assignments were consistent with relative intensity measurements and were confirmed by the spectrum of the deuteroxy compound which was unchanged from that of **7d** except for disappearance of the singlet at τ 7.44. The observation of identical chemical shifts for the two hydroxyl protons is to be expected in the *trans* isomer since the two hydroxyl groups are equivalent in either conformation (A and B, Scheme II) of this isomer. This is not true for the *cis* isomer where the hydroxyl groups are not equivalent (*cf.* C and D), although it should be noted that

SCHEME II



exchange processes or rapid interconversion of C and D by inversion of the biphenyl could result in observation of a single hydroxyl resonance.

In order to obtain further evidence on the stereochemistry of **7d**, the synthesis of its *cis* isomer was attempted. Cyclizations of a number of 2,2′-diaroylbiphenyls to *cis*-9,10-dihydro-9,10-dihydroxy-9,10-diarylphenanthrenes (or mixtures in which the *cis* isomer predominated) have been reported[6,9] using a variety of pinacol-forming reagents such as magnesium–magnesium iodide couple, sodium amalgam, or zinc in acid or alkaline medium. The diketone, 2,2′-bis(*p*-methylphenylacetyl)biphenyl (**8d**), required for such cyclization attempts could be readily obtained by oxidation of **7d** with chromic anhydride in acetic acid. The methylene protons in this compound did not appear as an AB quartet in the n.m.r. spectrum, instead a broad line at τ 6.09 (half width, 5 c.p.s.) was observed. Cyclizations of **8d** with zinc in acetic acid or magnesium–magnesium iodide afforded **7d**; no isomeric pinacol could be isolated.[10] In the latter case, 1,2-bis-*p*-tolylethane (17%) and phenanthrenequinone (52%) were also isolated. These must have resulted from cleavage of **8d**[11] since the pinacol, **7d**, was recovered unchanged after treatment under the same reaction conditions. Photochemical pinacol formation[12] was also investigated; irradiation of **8d** in isopropyl alcohol solution for 24 hr. afforded quantitative recovery of starting material. This result might have been attributed to an unfavorable equilibrium[12]; however, irradiation of **7d** in acetone solution also resulted in recovery of starting material. The photochemical cleavage of **7d** could be effected by irradiation in benzene solution containing *p*-benzoquinone.[13]

(8) After preparation of this paper was completed, the Doctoral Dissertation of G. Pfundt (Göttingen, 1962) came to our attention. Pfundt concluded that the adduct **6b** of phenanthrenequinone and *o*-xylene possessed the structure illustrated on the basis of spectroscopic evidence and conversion to an acetate exhibiting ester and conjugated carbonyl absorption in the infrared.

(9) W. E. Bachmann, *J. Am. Chem. Soc.*, **54**, 1969 (1932).

(10) A similar result has been reported by Th. Zincke and W. Tropp [*Ann.*, **363**, 302 (1908)], who observed that cyclization of 2,2′-bisphenylacetylbiphenyl with zinc and hydrochloric acid or zinc and potassium hydroxide led to a product identical with the product obtained from addition of excess benzyl magnesium chloride to phenanthrenequinone. Examination of models suggests that the conformation of the biphenyl required for cyclization to *cis* glycol is considerably more hindered when the 2,2′-substituents are benzyl ketones than when they are phenyl ketones.

(11) Cleavage of a diketone by magnesium–magnesium iodide couple has been reported by G. W. Griffin and R. B. Hager [*J. Org. Chem.*, **28**, 599 (1963)], who observed acetophenone as a by-product in cyclizations of 1,2-dibenzoylethane.

(12) A. Schönberg, "Präparative Organische Photochemie," Springer-Verlag, Berlin, 1958, pp. 111, 112. To our knowledge, no examples of intramolecular reactions of this type to give cyclic pinacols have been recorded and the stereochemical result of such a cyclization, if effected, remains an open question.

(13) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 67 (1944); ref. 12, p. 113.

Acid-catalyzed rearrangement of **7d** led to 9,10-dihydro-9,9-bis(*p*-methylbenzyl)-10-ketophenanthrene (**9d**). The alternate possible structure of 9-(*p*-methylbenzyl)-9-(*p*-methylphenylacetyl)fluorene (**10**) was ruled out on the basis of the presence of a conjugated carbonyl group (6.0 μ), the similarity of the ultraviolet spectrum to that of **6d**, and the appearance of the methylene protons as a single pair of AB doublets at τ 6.32 and 6.81. Although the *trans*-diaxial relationship between a hydroxyl group and the migrating *p*-methylbenzyl group obtains in both conformations (C and D) of the *cis* isomer of **7d** and in neither conformation (A and B) of the *trans* isomer, the result of acid-catalyzed rearrangement cannot be taken as evidence in support of the *cis* configuration since previous work[6,9] has established that both *cis*- and *trans*-9,10-dihydro-9,10-dihydroxy-9,10-diarylphenanthrenes rearrange in the presence of acid to the same 9,10-dihydro-9,9-diaryl-10-ketophenanthrenes.[14]

Returning to the photochemical reaction, adducts **6a**, 90% yield, and **6c**, 95%, could be obtained from irradiation of phenanthrenequinone in toluene or *m*-xylene contrary to the earlier report.[2] Isolation of these products as well as the known[2] *o*-xylene adduct (**6b**) was conveniently effected by chromatography on Florisil. The ultraviolet spectra of **6a–d** were essentially identical; all exhibited hydroxyl and conjugated carbonyl absorption in the infrared. A broad singlet at about τ 6.0 due to the hydroxyl proton was observed (at identical concentrations) in the n.m.r. spectra of the four adducts. The adduct **6b** from *o*-xylene, in which considerable interaction between the methyl group and the adjacent aromatic ring of the dihydrophenanthrene can occur, showed a shift of the methyl singlet from the usual value of τ 7.7 to 8.08 and the methylene absorption appeared as a pair of lines (6.90, 6.97) in contrast to the singlet observed with the unsubstituted and *m*- and *p*-substituted compounds. An adduct (**6e**) was obtained by irradiation of a mixture of phenanthrenequinone and *p*-nitrotoluene in benzene solution; based on its spectral properties, this also resulted from 1,2-addition to phenanthrenequinone.

The 1,2-additions of these substituted toluenes to phenanthrenequinone provide a marked contrast to the additions of ethers and aldehydes which proceed in high yield to give products of 1,4-addition. The differences in behavior cannot be ascribed to experimental variables, since the products formed in irradiations of phenanthrenequinone with dioxane–*p*-xylene or benzaldehyde–*p*-xylene mixtures were the same adducts **1**, **4**, and **6d**, as established by chromatographic separation and spectral analysis. The relative rates of benzaldehyde, dioxane and *p*-xylene additions to phenanthrenequinone were 48:2.7:1. These values were observed at approximately 60% reaction; as would be expected of reversible processes (*vide infra*), the relative rates varied with extent of reaction. While the present lack of detailed information makes it inappropriate to speculate on the mechanism(s) of these additions, it might be noted that the currently accepted picture[1b,3,15a,b,c] of phenanthrenequinone photoadditions is not inconsistent with either 1,2- or 1,4-addition processes. Thus, the semiquinone radical resulting from abstraction of hydrogen by photoexcited phenanthrenequinone is a resonance hybrid of (among others) structures (E and F) in which the unpaired electron is localized on oxygen or carbon. Addition of an acyl, benzyl, or ether radical could then take place at either of these positions to give the two types of adducts observed.

It had previously been observed[1b] that the dioxane–phenanthrenequinone addition was photochemically reversible and the approximate composition of the photostationary state determined. Reversibility of the *p*-xylene–phenanthrenequinone addition was also established by isolation of phenanthrenequinone and *p*-xylene (detected by gas chromatography) upon irradiation of a dilute benzene solution of **6d**. Attempts to determine the composition of the photostationary state were not successful in this instance because of the accumulation of phenanthrene quinhydrone and other, unidentified by-products upon prolonged irradiation of benzene solutions containing either **6d** or an equimolar mixture of phenanthrenequinone and *p*-xylene. For example, after 24-hr. irradiation of 0.0198 *M* **6d** there was obtained 42% of recovered **6d** and 16% of phenanthrenequinone; under similar conditions 0.0198 *M* phenanthrenequinone and 0.0198 *M* *p*-xylene afforded 31% of **6d** and 20% of recovered phenanthrenequinone. The photochemical reversibility of the benzaldehyde–phenanthrenequinone addition was also demonstrated by irradiation of 0.0067 *M* **4** in benzene solution which afforded 30% of recovered **4** and 34% of phenanthrenequinone after 9 hr.

The demonstration that all of these additions are photochemically reversible suggested that equilibrium factors might be responsible for the differing modes of addition. In order to investigate this possibility, the mono(*p*-methylbenzyl) ether (**2**) of **3**, possessing the structure originally proposed[2] for the photoadduct of phenanthrenequinone and *p*-xylene, was synthesized (*vide infra*) and its photochemical behavior examined. Irradiation of 0.02 *M* **2** in benzene solution for 10 hr. afforded 28% of recovered **2** and 33% of **6d**, the 1,2-adduct. After more prolonged irradiation, the only adduct which could be isolated was **6d**. Comparison with the results obtained in the attempted determination of the photostationary state of the phenanthrenequinone–*p*-xylene addition suggests that the conversion of **2** to **6d** proceeds directly rather than *via* reversal to a mixture of phenanthrenequinone and *p*-xylene followed by 1,2-addition. This question, as well as the equilibrium between 1,2 and 1,4 adducts of benzaldehyde and dioxane, is being investigated further.

Previously reported methods[15b,16–18] for the synthesis of monoethers of **3** have afforded low (or unreported) yields and do not appear to be of general applicability. The availability of derivatives of **3**, namely the ether and aldehyde adducts with phenanthrenequinone, in which one of the hydroxyl groups is protected as an acetal or ester derivative, suggested a desirable alternative for the synthesis of **2**. Alkylation of the dioxane adduct (**1**) with *p*-methylbenzyl chloride produced a

(14) These reactions presumably involve, for the *trans* isomer at least, the intervention of an "open" carbonium ion: *cf.* C. J. Collins, W. T. Rainey, W. B. Smith, and I. A. Kaye, *J. Am. Chem. Soc.*, **81**, 460 (1959); C. J. Collins and B. M. Benjamin, *ibid.*, **85**, 25 (1963).

(15) (a) H. J. L. Bäckström, *Z. Physik. Chem.*, **25**, 99 (1934); *Naturwissenschaften*, **22**, 170 (1934); (b) R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 238 (1953); (c) G. O. Schenck, *Z. Elektrochemie*, **64**, 997 (1960).

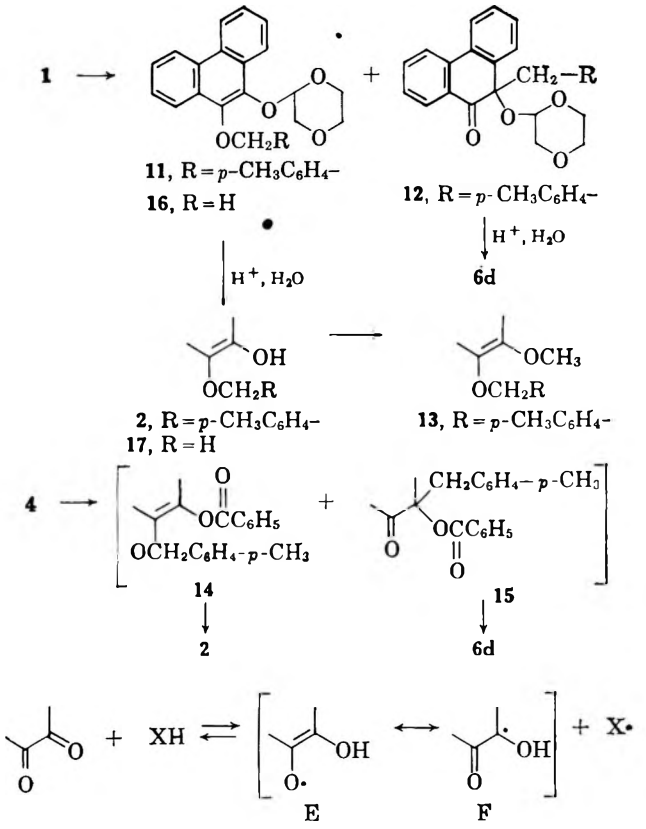
(16) F. R. Japp, *Ber.*, **12**, 1306 (1897).

(17) S. Goldschmidt and W. Schmidt, *ibid.*, **55**, 3197 (1922).

(18) E. Fourneau and J. Matti, *Bull. soc. chim. France*, **9**, 633 (1942).

mixture from which the desired O-alkylated product, 9-dioxanyloxy-10-(*p*-methylbenzyloxy)phenanthrene (**11**), could be isolated in 70% yield (Scheme III). The ultraviolet spectrum of **11** exhibited the characteristic features of a 9,10-dioxyphenanthrene[7b] and its properties in the infrared and n.m.r. were consistent with the assigned structure. A second product, 9-dioxanyloxy-9-(*p*-methylbenzyl)-10-ketophenanthrene (**12**), resulting from C-alkylation of **1**, was obtained in 13%

SCHEME III



yield. While **12** could not be obtained crystalline, the spectral properties were in agreement with the structure assigned and further confirmation was provided by acid-catalyzed hydrolysis to **6d**.

Similarly, acid-catalyzed hydrolysis of **11** led to isolation of **2** (54%), obtained as a low-melting solid which underwent fairly rapid decomposition in air (possibly accounting for the moderate yield) but could be stored for several months in an inert atmosphere at low temperature. **2** exhibited the expected ultraviolet spectrum, hydroxyl absorption in the infrared, and lines with the appropriate relative intensities at τ 6.0 (CH_2) and 8.18 (CH_3) as well as complex absorption at τ 2–3 due to the aromatic and phenolic protons. It was further characterized by methylation to stable 9-methoxy-10-(*p*-methylbenzyloxy)phenanthrene (**13**) which also exhibited the appropriate spectral properties. When the same reaction sequence was applied to the benzaldehyde adduct (**4**), hydrolysis of the intermediate O- and C-alkylated products (**14** and **15**) occurred in the alkylation step to give a mixture from which **2** (10%) and **6d** (19%) were isolated.

The method of synthesis described above would appear to be generally applicable for the preparation of monoethers and unsymmetrically substituted diethers of dihydric phenols provided that the appropriate quinone undergoes photoaddition reactions with ethers or aldehydes.[9] It has been utilized for the synthesis of the monomethyl ether (**17**) of **3** in 63% yield from **1**; an earlier method,[17] reaction of **3** with dimethyl sulfate in alkaline solution, afforded 7–12% of desired product.

Experimental[20]

9,10-Dihydro-9-hydroxy-9-(*p*-methylbenzyl)-10-ketophenanthrene (6d). A. By Photoirradiation.—A suspension of 2.00 g. of phenanthrenequinone in 20 ml. of *p*-xylene was irradiated for 67 hr. Unreacted quinone (0.32 g.) was removed by filtration and the filtrate adsorbed on 50 g. of Florisil. Elution with 250 ml. of 10% benzene in petroleum ether (b.p. 66–75°) afforded 60 mg. of white solid, m.p. 82–83°, identical with authentic 1,2-bis-*p*-tolylethane. Elution with 500 ml. each of 90% benzene–petroleum ether and pure benzene gave 2.00 g. (67%, 91% based on recovered quinone) of light yellow solid, m.p. 125–127°. Elution with ethyl acetate gave an additional 0.28 g. of quinone. A portion of the product crystallized from methylene chloride–petroleum ether had m.p. 129–129.5° (lit.[2,3] m.p. 129–130°); λ_{max} 242 mμ (ϵ 25,000), 248 infl. (23,400), 275 infl. (7600), and 327 (2800); 2.88 and 5.96 μ (KBr). The ultraviolet spectrum was unchanged after 6 hr. in 0.1 *N* sodium hydroxide solution (70% dioxane) at room temperature. N.m.r. showed bands at τ 6.00, 7.01, and 7.72 (relative intensities 1:2:3); complex absorption at 2–3 and 3.03 (doublet, J_{AB} = 8 c.p.s.), 3.29 (J = 8 c.p.s.).

A 64% yield (88% based on recovered phenanthrenequinone) of **6d** was obtained when a Corning C.S.-0-52 filter (<0.5% transmission at 334; <5% at 340, and 65% at 360 mμ) was used.

B. From Phenanthrenequinone and *p*-Methylbenzyl Magnesium Bromide.—The Grignard reagent prepared from 1.403 g. of freshly distilled *p*-methylbenzyl bromide and 0.179 g. of magnesium in 15 ml. of dry ether was diluted with 10 ml. of anisole and then added dropwise during 1 hr. to a stirred, refluxing solution of 1.53 g. of phenanthrenequinone in a mixture of 65 ml. of benzene and 10 ml. of anisole. After the addition was complete, the dark solution was cooled and poured onto iced 1 *M* sulfuric acid; benzene was added. The yellow phenanthrenequinone, 0.760 g., m.p. 209–210°, which separated was removed by filtration. The layers were then separated; the benzene layer was washed with water, dried over anhydrous sodium sulfate, concentrated to about 15 ml., and filtered to give 0.39 g. of additional phenanthrenequinone, m.p. 209–210°.

The filtrate was absorbed on 50 g. of Florisil. Elution with 500 ml. of benzene gave 0.62 g. of 1,2-bis-*p*-tolylethane as a white solid, m.p. 74–78°. A second benzene fraction gave 112 mg. (5%, 68% based on recovered phenanthrenequinone) of light yellow solid, m.p. 124–128°. Recrystallization from benzene–petroleum ether raised the melting point to 127.5–128.5°, which was undepressed on mixture with the product obtained by photoirradiation; infrared spectra were identical. An additional 0.27 g. of quinone was obtained by elution of the column with ethyl acetate (total recovered quinone, 1.42 g.).

***trans*-9,10-Dihydro-9,10-dihydroxy-9,10-bis-(*p*-methylbenzyl)-phenanthrene (7d). A. From 6d.**—Anisole (8 ml.) was added to 10 ml. of the Grignard solution prepared from 10.0 g. of freshly distilled *p*-methylbenzyl chloride and 1.72 g. of magnesium in 100 ml. of ether under nitrogen. **6d** (200 mg.) and 8 ml. of anisole were added and the solution then was refluxed with stirring. After 2 hr., 5 ml. of toluene were added and refluxing was continued. After a total reaction time of 7 hr., the green solution was cooled. 5% hydrochloric acid and ethyl acetate were added, and the layers were separated. The organic layer was

(19) For a summary of quinone photoadditions see "Präparative Organische Photochemie," A. Schönberg, Springer-Verlag, Berlin, 1958; also P. de Mayo in "Advances in Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960.

(20) Melting points are corrected. Ultraviolet spectra were determined in methanol solution unless noted otherwise. N.m.r. spectra were determined at 60 Mc. in 0.3 *M* deuteriochloroform solution using tetramethylsilane as internal standard. Photoirradiations were performed at 30° C. in Pyrex vessels in an atmosphere of nitrogen; the light source was a 1000-w. General Electric water-cooled, high pressure mercury vapor lamp (AH-6) with Pyrex jacket.

washed with water and brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*; the oily residue was chromatographed on 25 g. of Florisil. Elution with 250 ml. of petroleum ether gave 211 mg. of 1,2-bis-*p*-tolylethane, m.p. 80–83°. Elution with 50% benzene–petroleum ether gave 250 mg. (93%) of **7d** as white needles, m.p. 146–150°. The analytical sample m.p. 149.5–150.5°, was obtained by crystallization from petroleum ether and had λ_{max} 273 mμ (ε 15,200), 210 (36,000); and 2.88 μ (CH_2Cl_2). N.m.r. showed bands at τ 6.79 (doublet, J_{AB} = 14 c.p.s.), 7.24 (*d*, *J* = 14 c.p.s.), 7.44, and 7.70; aromatic protons, complex absorption at 2–2.8, 2.98 (*d*, *J* = 8 c.p.s.), and 3.34 (*d*, *J* = 8 c.p.s.).

Anal. Calcd. for $C_{30}H_{28}O_2$: C, 85.68; H, 6.71. Found: C, 86.22; H, 6.58.

Crystallization of 173 mg. of **7d** from a mixture of 1 ml. of acetone and 0.5 ml. of deuterium oxide afforded white needles of deuterated **7d**. One crystallization from petroleum ether gave 107 mg., m.p. 148.5–151°, λ_{max} 3.88 μ (KBr). The n.m.r. spectrum was identical with that described above except for the almost complete disappearance of the line at τ 7.44.

B. From Phenanthraquinone.—To the remainder of the Grignard solution described above was added 2.00 g. of phenanthraquinone, 50 ml. of anisole, and 45 ml. of toluene. After 5-hr. stirring at reflux, the dark, blue-green solution was worked up as described above to give 2.43 g. of 1,2-bis-*p*-tolylethane and 3.60 g. (86%) of faintly yellow crystals of **7d**. Recrystallization from methylene chloride–petroleum ether gave white needles, m.p. 149–150.5°, which showed no depression on mixture with the product from procedure A; the infrared spectra were identical.

2,2′-Bis(*p*-methylphenylacetyl)biphenyl (8d). A. By Chromic Acid Oxidation of 7d.—A solution of 2.72 g. of chromium trioxide in 27 ml. of water was added during 6 min. to a stirred solution of 8.0 g. of **7d** in 80 ml. of acetic acid at 70°. After stirring for an additional 8 min., 10 ml. of water was added, and the solution was seeded and allowed to cool. Filtration afforded 7.95 g. of light yellow solid which gave 5.78 g. (82%) of **8d**, m.p. 83°, in two crops upon crystallization from isopropyl ether. The analytical sample, m.p. 83–84°, was obtained by crystallization from this solvent and had λ_{max} 290 mμ (ε 3100), 210 (43,000); 6.02 μ (KBr). N.m.r. showed bands at τ 6.09 (singlet, half width 5 c.p.s.) and 7.68; aromatic protons, complex absorption at 2–3 and 2.93 (doublet spacing, 3 c.p.s.).

Anal. Calcd. for $C_{30}H_{26}O_2$: C, 86.09; H, 6.26. Found: C, 85.89; H, 5.78.

B. By Photochemical Cleavage of 7d.—A solution of 330 mg. of **7d** and 259 mg. of sublimed *p*-benzoquinone in 14 ml. of benzene was irradiated for 3.5 hr. After removal by filtration of the black needles of quinhydrone (178 mg.) which had separated during the course of the irradiation, the filtrate was concentrated on the steam bath under aspirator pressure until no further sublimation of quinone was observed. The residue was chromatographed on 15 g. of alkaline alumina. Elution with 50 and 90% benzene–petroleum ether yielded 84 mg. of colorless oil which was crystallized from isopropyl ether to give 54 mg. of **8d**, m.p. 83–84°.

Elution with benzene afforded 174 mg. of crystalline material, identical with **7d** by comparison of infrared spectra. Irradiation of **7d** in acetone solution for 17 hr. resulted in quantitative recovery of starting material.

Cyclizations of 8d. A. With Zinc and Acetic Acid.—A mixture of 341 mg. of diketone **8d**, 2 g. of zinc dust, 2 ml. of methylene chloride, and 2 ml. of acetic acid was stirred at room temperature for a total of 23 hr. with additional zinc (1 g.) and acetic acid (1 ml.) being added after 17 hr. Unreacted zinc was removed by filtration and washed with methylene chloride. The filtrate and washings were concentrated under reduced pressure on the steam bath to give 336 mg. of partly crystalline product which was chromatographed on 15 g. of Florisil. Elution with 50 and 90% benzene in petroleum ether afforded 262 mg. (77%) of white crystals, m.p. 146–149°. One crystallization from petroleum ether gave 199 mg. of **7d**, m.p. 150–151°, identical by infrared analysis with the product of Grignard addition to phenanthrenequinone. Elution of the column with ethyl acetate yielded 10 mg. of phenanthrenequinone.

B. With Magnesium–Magnesium Iodide.—A mixture of 1.0 g. of iodine and 0.5 g. of magnesium powder in 10 ml. of anhydrous ether and 20 ml. of anhydrous benzene under nitrogen was stirred at room temperature for 15 min. when the iodine color had faded to a pale yellow. One gram of dike one **8d** was then added and the mixture was refluxed with stirring under nitrogen for 4 hr. and let stand at room temperature overnight. The solution was then filtered and the filtrate was shaken with cold dilute hydrochloric acid, the color changing from green to orange. After washing with water and saturated salt solution, the organic layer was dried over anhydrous sodium sulfate and taken to dryness under reduced pressure on the steam bath. The red, amorphous residue (1.03 g.) was chromatographed on 50 g. of Florisil with 500-ml. fractions being collected.

Elution with petroleum ether furnished 43 mg. (17%) of 1,2-bis-*p*-tolylethane, identified by its infrared spectrum. Elution with two fractions of 50% and one of 60% benzene in petroleum ether furnished 385 mg. of crystalline product, which afforded 154 mg. (15%) of white crystals on crystallization from isopropyl ether with m.p. 150–151°, m.m.p. (with **7d**) 149.5–150.5°; infrared spectra were identical. No additional crystalline material could be obtained from the mother liquors nor did rechromatography on Florisil afford crystalline material.

After elution of 154 mg. of amorphous material with benzene, the column was eluted with ethyl acetate to give 258 mg. (52%) of crystalline phenanthrenequinone.

C. With Light.—A solution of 197 mg. of **8d** in 15 ml. of isopropyl alcohol was irradiated for 17 hr. Removal of solvent under reduced pressure gave a light yellow solid which exhibited an infrared spectrum unchanged from that of starting material.

9,10-Dihydro-9,9-bis(*p*-methylbenzyl)-10-ketophenanthrene (9b).—A solution of 217 mg. of **7d** in the minimum volume of hot acetic acid (*ca.* 1 ml.) containing two drops of concentrated sulfuric acid was heated on the steam bath for 15 min. The solution was cooled and a few drops of water were added. The supernatant liquid was decanted from the resulting oil which solidified on standing. The solid was washed with water and crystallized from absolute alcohol to give 106 mg. (43%) of light yellow prisms, m.p. 148–153°. The analytical sample was obtained by crystallization from methylene chloride–methanol and had m.p. 156–156.5°; m.m.p. (with starting material) 120–137°; λ_{max} 245 mμ (ε 30,000), 253 infl. (25,000), 301 infl. (2500), 339 (3300); 6.0 μ (KBr). N.m.r. showed bands at τ 6.32 (doublet, J_{AB} = 14 c.p.s.), 6.81 (*d*, *J* = 14 c.p.s.), and 7.97; aromatic protons at 2–3 and 3.40 (singlet).

Anal. Calcd. for $C_{30}H_{26}O$: C, 89.51; H, 6.51. Found: C, 89.10; H, 6.65.

9,10-Dihydro-9-hydroxy-9-benzyl-10-ketophenanthrene (6a).—After irradiation of 1.00 g. of phenanthrenequinone in 50 ml. of toluene for 17 hr., the solvent was removed on the steam bath under reduced pressure and the dark residue (1.68 g.) was chromatographed on 60 g. of Florisil. Elution with 750 ml. of 50% and 500 ml. of 80% benzene–petroleum ether yielded 1.30 g. (90%) of light yellow crystals of **6a**, m.p. 70–75°. The analytical sample was obtained by crystallization from petroleum ether and had m.p. 81–82°; λ_{max} 242 mμ (ε 27,500), 248 infl. (25,000), 275 infl. (7,700), and 327 2800; 2.84, 5.94, and 6.28 μ (CH_2Cl_2). N.m.r. showed bands at τ 6.0, 6.99 and aromatic protons.

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 83.63; H, 5.40.

9,10-Dihydro-9-hydroxy-9-(*o*-methylbenzyl)-10-ketophenanthrene (6b).—After irradiation of 1.94 g. of phenanthrenequinone in 50 ml. of *o*-xylene at reflux under nitrogen with a General Electric S-4 lamp for 13 hr., the reaction mixture was filtered to remove a small amount (107 mg.) of phenanthrene quinhydrone; and the filtrate adsorbed on 100 g. of Florisil. Elution with 90% benzene–petroleum ether and pure benzene afforded 1.72 g. (66%, 90% based on recovered phenanthrenequinone) of **6b**, m.p. 152–154° (lit.[2] m.p. 149°). The melting point was unchanged after crystallization from benzene–petroleum ether. **6b** had λ_{max} 242 mμ (ε 27,000), 248 infl. (24,000), 275 infl. 8900, and 327 (2900); 2.86 and 5.93 μ (KBr). N.m.r. showed bands at τ 6.0, 6.94 (doublet, spacing 5 c.p.s.), 8.06, and aromatic protons.

Elution with ethyl acetate yielded 0.66 g. of phenanthrenequinone.

9,10-Dihydro-9-hydroxy-9(*m*-methylbenzyl)-10-ketophenanthrene (6c).[21]—Irradiation of 1.82 g. of phenanthrenequinone in 50 ml. of *m*-xylene for 12 hr. and chromatography as described for the *ortho* isomer afforded 1.72 g. (65%, 95% based on recovered phenanthrenequinone) of **6c** as nearly white crystals, m.p. 90–92°. The analytical sample was obtained by crystallization from benzene–petroleum ether and had m.p. 96–97°; λ_{max} 242 mμ (ε 25,500), 248 infl. (23,000), 275 infl. (7900), and 327

(21) Experiment was performed by Mr. R. M. Kopchik.

(2800); 2.82 and 5.94 μ (KBr). N.m.r. showed bands at τ 6.0, 7.02, 7.80, and aromatic protons.

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.89; H, 5.87.

Elution with ethyl acetate yielded 0.64 g. of phenanthrenequinone.

9,10-Dihydro-9-hydroxy-9-(*p*-nitrobenzyl)-10-ketophenanthrene (6e).—A mixture of 1.0 g. of phenanthrenequinone and 6.0 g. of *p*-nitrotoluene in 50 ml. of benzene was irradiated for 47 hr. when all the quinone had dissolved. After removal of benzene, the brown product was chromatographed on 200 g. of Florisil. Elution with 3 l. of 2% ethyl acetate in benzene afforded 440 mg. (38%, 85% based on recovered phenanthrenequinone) of yellow crystals, m.p. 166–172°. The analytical sample was obtained by crystallization from 1:1 benzene–petroleum ether as nearly white crystals, m.p. 176°; λ_{max} 244 mμ (ϵ 29,600), 250 (29,000), 279 (18,000), and 325 infl. (4000); 2.82, 6.00, 6.28, 6.66, 7.50 μ (KBr). N.m.r. showed bands at τ 1.9–3.1, 5.9 and 6.90.

Anal. Calcd. for $C_{21}H_{15}NO_4$: C, 73.03; H, 4.38; N, 4.06. Found: C, 72.73; H, 4.12; N, 4.17.

Elution of the column with ethyl acetate afforded 695 mg. of unreacted phenanthrenequinone.

Competition Reactions. A. Dioxane–*p*-Xylene.—A solution of 0.500 g. (2.5 m*M*) of phenanthrenequinone, 325 mg. (3.7 m*M*) of dioxane, and 382 mg. (3.7 m*M*) of *p*-xylene made up to 50 ml. with benzene was irradiated under the usual conditions for 5 hr. After removal of solvent under reduced pressure, the residue was chromatographed on 40 g. of Florisil. The column was eluted with three 250-ml. fractions of 90% benzene–petroleum ether [234 (pure 1), 76, and 30 mg.]: one fraction of benzene (23 mg.), one fraction of 1% ethyl acetate–benzene (84 mg., pure **6d**), and pure ethyl acetate (141 mg., phenanthrenequinone). Individual fractions were analyzed from their ultraviolet spectra using ϵ_{310} 10,400 and ϵ_{325} 900 for **1** and ϵ_{310} 2620 and ϵ_{325} 3600 for **6d**. The total amount of **1** obtained was 322 mg. (43.5%) and of **6d** was 125 mg. (16%), corresponding to a molar ratio of 2.73:1.

B. Benzaldehyde–*p*-Xylene.—A solution of 0.350 g. (1.75 m*M*) of phenanthrenequinone, 0.322 g. (3 m*M*) of freshly distilled benzaldehyde, and 5.168 g. (48.8 m*M*) of *p*-xylene made up to 50 ml. with benzene was irradiated for 2 hr. After concentration under reduced pressure on the steam bath, the residue was chromatographed on 30 g. of Florisil. Elution with 500 ml. of 30% benzene in petroleum ether gave 20 mg. of amorphous material; 500 ml. of 50% benzene in petroleum ether and 500 ml. of pure benzene gave 298 mg. of white crystals; additional benzene eluted only traces of material; and ethyl acetate afforded 117 mg. of recovered phenanthrenequinone. The ultraviolet spectrum of the crystalline material was determined in dioxane solution (0.0199 mg./ml.); optical densities were 4.61 at 306 mμ and 1.28 at 325 mμ. The yields, calculated using ϵ_{306} 9000 and ϵ_{325} 2500 for **4** and ϵ_{306} 1500 and ϵ_{325} 3600 for **6d**, were 220 mg. (42%) of **4** and 75 mg. (14%) of **6d**. Corrected for the sixteenfold excess of *p*-xylene used, the relative rates were 48:1 (benzaldehyde–*p*-xylene). Infrared spectra of mixtures exhibited the characteristic features of **4** and **6d**.

In a comparable experiment, the ratio was 36:1 after 3-hr. irradiation.

Attempted Determination of the Composition of the Photostationary State in the *p*-Xylene–Phenanthrenequinone Reaction. A. Forward Reaction.—A solution of 413 mg. (1.98 m*M*) of phenanthrenequinone and 209 mg. (1.98 m*M*) of *p*-xylene in 100 ml. of benzene was irradiated in the usual manner and 20-ml. aliquots were withdrawn after 21 and 41 hr. After removal of solvent under reduced pressure, the residues (104 and 106 mg.) were chromatographed on 6 g. of Florisil and four fractions were collected. Fraction 1, eluted with petroleum ether and 30% benzene in petroleum ether consisted of unidentified oils having no selective ultraviolet absorption. Fraction 2, eluted with 30 and 90% benzene in petroleum ether and pure benzene, consisted of the adduct **6d** (the amount was checked by ultraviolet analysis). Fraction 3, eluted with ethyl acetate, consisted of phenanthrenequinone, and fraction 4, eluted with methanol, consisted of phenanthrene quinhydrone. The mixture after 21 hr. contained 22 mg. of fraction 1, 48 mg. of fraction 2, 21 mg. of fraction 3, and 8 mg. of fraction 4. After 41 hr. the corresponding quantities were 30, 28, 19, and 19 mg.

B. Reverse Reaction.—Irradiation of a solution of 622 mg. (1.98 m*M*) of **6d** followed by analysis as described above gave the following results: after 24 hr. (117-mg. total wt.), 33, 44, 11, and 13 mg.; after 48 hr. (118 mg.), 29, 34, 15, and 17 mg.; and, after 72 hr. (110 mg.), 21, 29, 18, and 22 mg. A sample of the solution after 48-hr. irradiation was chromatographed on a silicone oil column (DC-200) at 100°. The only peak observed (except for solvent benzene) had a retention time of 5.2 min. identical with the retention time observed under the same conditions with an 0.5% solution of *p*-xylene in benzene.

Photoirradiation of 9,10-Dihydroxyphenanthrene Monobenzoate (4).—A solution of 100 mg. of **4**[1b] in 50 ml. of benzene was irradiated for 9 hr. After removal of solvent the residue was chromatographed on 5 g. of Florisil. Elution with 80 and 90% benzene in petroleum ether and pure benzene afforded 30 mg. of recovered **4a**. Elution with ethyl acetate gave 23 mg. (34%) of phenanthrenequinone, m.p. 205–208°.

9-Dioxanyloxy-10-(*p*-Methylbenzyloxy)phenanthrene (11) and 9-Dioxanyloxy-9-(*p*-methylbenzyl)-10-keto-9,10-dihydrophenanthrene (12).—A mixture of 500 mg. of dioxane–phenanthrenequinone adduct (**1**), 260 mg. of *p*-methylbenzyl chloride, and 234 mg. of anhydrous potassium carbonate in 10 ml. of dry acetone was refluxed with stirring for 29 hr. After removal of the acetone under reduced pressure, the residue was treated with dilute hydrochloric acid and benzene. The organic layer was separated, washed with water and saturated salt solution, dried over anhydrous magnesium sulfate, and concentrated to dryness under reduced pressure on the steam bath. Crystallization of the residue from 5 ml. of petroleum ether gave 480 mg. (71%) of **11**, m.p. 109–112°. The analytical sample of **11** was obtained by crystallization from benzene–petroleum ether and had m.p. 114–115°; λ_{max} (dioxane) 280 mμ infl. (ϵ 10,500), 293 (10,500), 305 (10,900), 324 infl. (520), 340 (810), and 357 (840); 6.18, 6.25, and no absorption at 2.5–3.05 μ (CH_2Cl_2). N.m.r. showed bands at τ 5.65 (multiplet), 6.00, 6.92–7.10 (complex absorption), 8.16, and complex absorption at 2–3.

Anal. Calcd. for $C_{26}H_{24}O_4$: C, 77.98; H, 6.04; mol. wt., 400. Found: C, 77.34; H, 6.07; mol. wt., 386.

The crude product (2.8 g.) from reaction of 2.2 g. of **1** as above was chromatographed on 150 g. of Florisil. Elution with 2 l. of 1:1 benzene–petroleum ether afforded 2.0 g. (67%) of **11**. Elution with ethyl acetate gave 0.383 g. (13%) of **12** as an orange oil which could not be obtained crystalline and which had λ_{max} (dioxane) 330 mμ (ϵ 2900); 5.95 and 6.28 μ (CH_2Cl_2). N.m.r. showed bands at τ 5.5 (multiplet), 6.0–6.5 (complex absorption), 7.02, and 7.85.

Hydrolysis of 9,10-Dihydro-9-dioxanyloxy-9-(*p*-methylbenzyl)-10-ketoanthrene (12).—A solution of 570 mg. of crude **12** in 50 ml. of methanol was treated with 20 drops of concentrated hydrochloric acid. After 15 min. at 50°, the acid was neutralized by addition of solid sodium bicarbonate, the solution was diluted with 50 ml. of water, and methanol was removed under reduced pressure on the steam bath. The aqueous residue was worked up in the usual manner affording a crude product which was crystallized once from petroleum ether to give 402 mg. (90%) of light yellow solid, m.p. 100–110°, identical by infrared spectral comparison with **6d**.

9,10-Dihydroxyphenanthrene Mono(*p*-methylbenzyl) Ether (2). A. From 11.—A solution of 2.0 g. of **11** in 200 ml. of methanol containing 3 ml. of concentrated hydrochloric acid was heated at 50° for 0.5 hr. Excess solid sodium bicarbonate was added followed by 10 ml. of water and the solution was concentrated under reduced pressure. The oily residue was extracted with ethyl acetate which was then washed with water and saturated salt solution, dried over anhydrous sodium sulfate, and concentrated to dryness under reduced pressure on the steam bath. The residue was chromatographed on 80 g. of Florisil. Elution with 2 l. of 1:9 benzene–petroleum ether gave 0.85 g. (54%) of **2**, m.p. 63–64°; λ_{max} (dioxane) 272 mμ infl. (ϵ 12,700) 299 (7200), 309 (7200), 330 infl. (700), 347 (1000), and 363 (1100); 2.80, 6.15, and 6.25 μ (CH_2Cl_2). N.m.r. showed bands at τ 6.0 and 8.18. A portion was crystallized from petroleum ether to give the analytical sample as white crystals, m.p. 72–73°. This material was stable in an inert atmosphere at 0–5° C. but darkened rapidly in air and became gummy after less than 1 day.

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.45; H, 5.81.

Elution of the column with ethyl acetate furnished 0.15 g. of phenanthrenequinone.

B. From 4.—A mixture of 630 mg. of benzaldehyde–phenanthrenequinone adduct (**4**), 310 mg. of *p*-methylbenzyl chloride,

and 280 mg. of anhydrous potassium carbonate in 10 ml. of dry acetone was refluxed with stirring for 23 hr. After removal of acetone under reduced pressure, the residue was dissolved in benzene and washed with dilute hydrochloric acid; the aqueous layer was washed with three portions of benzene. The combined benzene solutions were washed with water and saturated salt solution, dried over anhydrous sodium sulfate solution, and concentrated under reduced pressure on the steam bath. The residue (524 mg., 2.8, 5.95, 6.18 and 6.28 μ) was chromatographed on 25 g. of Florisil. Elution with 150 ml. of 20% and 200 ml. of 30% benzene–petroleum ether afforded 66 mg. (10%) of **2**, identical by infrared analysis with material described above.

Elution with 200 ml. of 50% and 150 ml. of 80% benzene–petroleum ether gave 121 mg. (19%) of **6d**, m.p. 115–125°, identical by infrared analysis with authentic sample.

Finally, elution with ethyl acetate gave 146 mg. of phenanthrenequinone.

9-Methoxy-10-(*p*-methylbenzyloxy)phenanthrene (13).—A mixture of 500 mg. of **2** from Florisil chromatography, 250 mg. of methyl iodide, and 220 mg. of anhydrous potassium carbonate in 7 ml. of acetone was refluxed with stirring for 46 hr. After removal of acetone under reduced pressure, the residue was treated with dilute hydrochloric acid which was then extracted with benzene. The benzene layer was washed with water and saturated salt solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure on the steam bath. One crystallization of the crude product from methanol gave 460 mg. (88%) of **13**, m.p. 85–89°. Further crystallization from methanol furnished the analytical sample, m.p. 87–89°; λ_{max} (dioxane) 292 mμ (ϵ 10,000), 305 (12,000), 324 (900), 341 (1200), and 358 (1200); 6.15, 6.25, and no absorption at 2.5–3.1 μ (CH_2Cl_2). N.m.r. showed bands at τ 5.97, 6.82, 8.18, and complex absorption at 2–3.

Anal. Calcd. for $C_{23}H_{20}O_2$: C, 84.12; H, 6.14. Found: C, 83.75; H, 6.66.

Photoirradiation of 9,10-Dihydroxyphenanthrene Mono(*p*-methylbenzyl) Ether (2).—A solution of 132 mg. of **2** in 21 ml. of benzene was irradiated for 10 hr. at 30° in a nitrogen atmosphere. The yellow solution was then taken to dryness under reduced pressure on the steam bath and the residue chromatographed on 6 g. of Florisil. Eluion with increasing proportions of benzene in petroleum ether to pure benzene afforded a series of amorphous fractions (88-mg. total), which were analyzed from their ultraviolet spectra. The early fractions consisted predominantly of starting material **13** and the later fractions were mainly **6d**; the yields were 36 mg. (28%) of **2** and 43 mg. (33%) of **6d**.

A comparable experiment in which **13** was irradiated for 19 hr. afforded 27% of crystalline **6d**, m.p. 118–126°, identical by infrared analysis with an authentic sample. Only a trace of unreacted **13** could be detected in this experiment.

9-Dioxanyloxy-10-methoxyphenanthrene (16).—A mixture of 2.0 g. of the adduct **1**, 1.0 g. of methyl iodide, and 0.9 g. of anhydrous potassium carbonate in 20 ml. of acetone was refluxed for 26 hr. with stirring. The crude product obtained by work-up similar to that described for the preparation of **11** was chromatographed on 100 g. of Florisil. Elution with 2.5 l. of 50%, 500 ml. of 70%, and 500 ml. of 90% benzene in petroleum ether afforded 1.59 g. (76%) of crystalline **16**, m.p. 78–79°. The analytical sample of **16** was obtained by crystallization from petroleum ether and had m.p. 80–81°; λ_{max} (dioxane) 272 mμ infl. (ϵ 19,000), 281 infl. (12,000), 293 (11,000), 304 (12,000), 326 infl. (500), 341 (850), and 357 (850); 6.15, 6.25, and no absorption at 2.5–3.1 μ (CH_2Cl_2). N.m.r. showed bands at τ 4.42 (broad), 5.86–6.28 (complex), 6.00, and complex absorption 2–3.

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.64; H, 5.92.

Further elution with pure benzene and ethyl acetate afforded 255 mg. of yellow oil (λ_{max} 2.84, 5.8, and 6.25 μ), which could not be induced to crystallize.

9,10-Dihydroxyphenanthrene Monomethyl Ether (17).—A solution of 794 mg. of **16** in 70 ml. of methanol was treated with 1 ml. of concentrated hydrochloric acid at 50° for 15 min. Work-up as described for the preparation of **13** gave 480 mg. (83%) of crystalline **17**, m.p. 106–107° (lit.[17] m.p. 103°); λ_{max} 255 mμ (ϵ 44,000), 272 infl. (13,000), 298 (7400), 308 (7200), 330 infl. (1100), 346 (1200), and 362 (1100); 2.83, 6.18, 6.28 μ (CH_2Cl_2). N.m.r. showed bands at τ 6.04 and complex absorption 2–3. This compound was considerably more stable than **2** but darkened in color after several months.

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The Separation of Ketimine Isomers[1,2]

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The separation of the geometric isomers of ketimines derived from 2-amino-5-chlorobenzophenone has been achieved by fractional crystallization. Configuration has been assigned by relating ultraviolet absorption spectra of the ketimine isomers with those of the corresponding oximes. The validity of this approach is discussed.

The separation of the geometric isomers of ketimines[3] has been claimed a number of times in the past. A review of these claims appeared in the recent paper of Curtin and Hausser[4] wherein the evidence for the presence of both *syn* and *anti* forms of some benzophenone methylimines was given. However, these authors were able to separate only one form of each imine as a stable solid. We have accomplished the preparation and separation of both forms of a number of substituted benzophenone imines. The orientation of the isomers has been established by comparison of their ultraviolet absorption spectra with those of related oximes of known configuration.[5]

The reaction between a number of *o*-aminobenzophenones and a group of primary amines led in several cases to mixtures of two products. The preparations were carried out by heating the reactants together in the presence of zinc chloride. A solvent such as xylene was used to permit azeotropic removal of the water formed as a by-product. Fractional crystallization of

(1) Presented at the 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April, 1964.

(2) A preliminary communication has appeared: S. C. Bell, G. L. Conklin, and S. J. Childress, *J. Am. Chem. Soc.*, **85**, 2868 (1963).

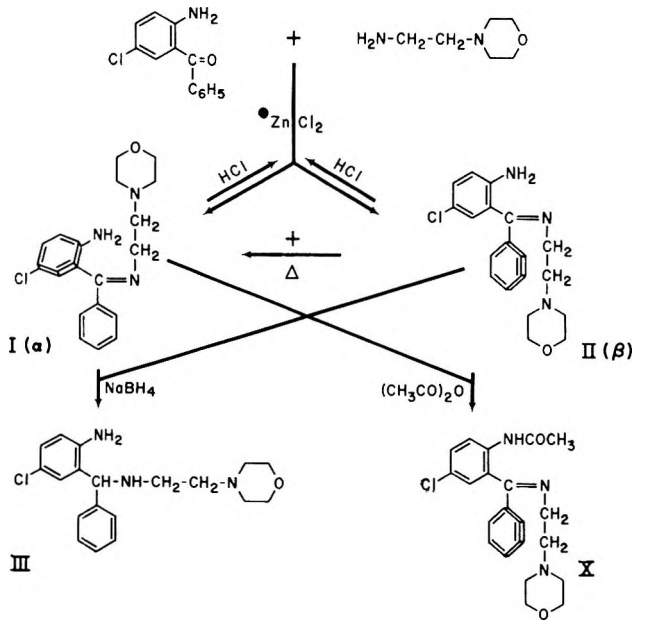
(3) A review on imines has recently been published: R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

(4) D. Y. Curtin and J. W. Hausser, *J. Am. Chem. Soc.*, **83**, 3474 (1961).

(5) After this work had been completed, a publication appeared by G. Saucy and L. H. Sternbach [*Helv. Chim. Acta*, **45**, 2226 (1962)] that described both forms of 2-methylamino-5-trifluoromethylbenzophenone methylimine. These authors attributed the longer wave-length ultraviolet absorption band of their lower melting isomer to the expanded conjugation system arising from hydrogen bonding between $NHCH_3$ and $C{=}NCH_3$. We prefer the twisted ring explanation given in the present paper since *o*-dimethylaminobenzophenone, without hydrogen bonding, has λ_{max} 385 mμ and *o*-methylaminobenzophenone is only slightly shifted to λ_{max} 392 mμ [P. Grammaticakis, *Bull. soc. chim. France*, 93 (1953)].

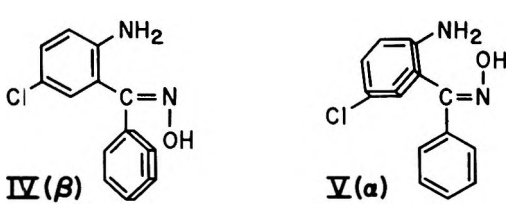
the products resulted in higher melting α-isomers and lower melting β-isomers.

2-Amino-5-chlorobenzophenone and 4-(2-aminoethyl)morpholine, for example, were treated as described. Fractional crystallization from hexane and from alcohol of the residue after evaporation of the solvent gave a less soluble, higher melting α-isomer (I) and a more soluble, lower melting β-isomer (II). Both I and II, upon treatment with aqueous acid, returned the starting materials. Both I and II, upon reduction with sodium borohydride, gave 2-amino-5-chlorobenzhydrylaminoethylmorpholine (III). Heating II without a solvent at 140–150° for 10 min. resulted in the production of I.



I (α) II (β) III V

The infrared absorption spectra of I and II were consistent with the ketimine structures. Because of the presence of the aromatic rings, no assignment of the C=N absorption could be made. The n.m.r. spectra of I and II were also consistent with the ketimine formulations but did not reveal the geometric orientation of the isomers.



IV(β) V(α)

The ultraviolet absorption spectra of I and II were quite different (Fig. 1). That of II was very similar to the absorption spectrum exhibited by the β-oxime of 2-amino-5-chlorobenzophenone (IV) in which the –OH has been shown to be *syn* to the unsubstituted phenyl.[6,7] The absorption spectrum of I was closely aligned with that of the corresponding α-oxime (V). The type of curve obtained with the two sets of isomers may be explained by assuming that, because of intramolecular crowding, the imino substituent causes the aromatic

(6) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).

(7) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **27**, 4424 (1962).

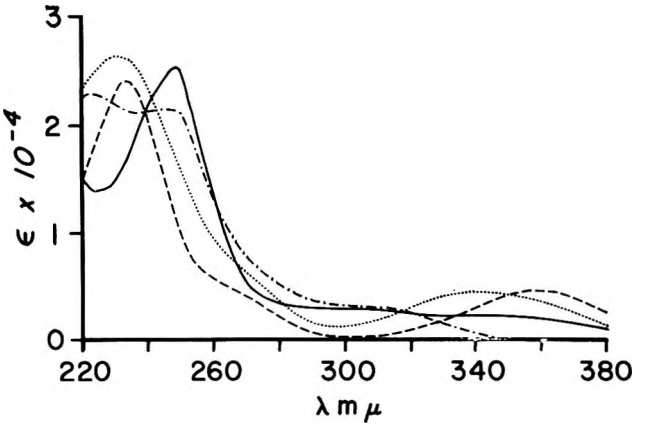
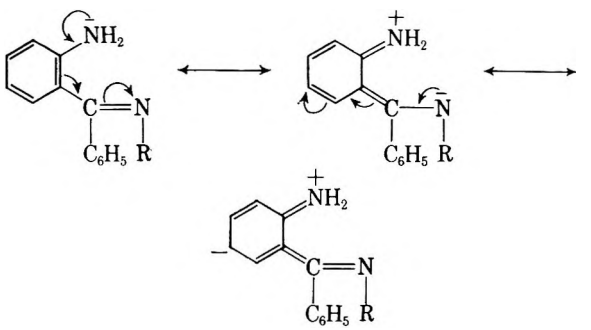
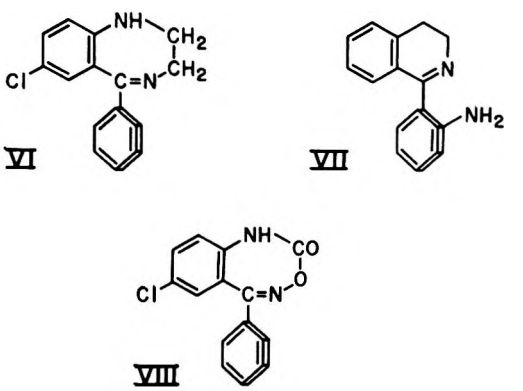


Fig. 1.—Ultraviolet absorption spectra in 95% ethanol: I, ——; II, – – –; IV, ·····; V, –·–·–.

ring of the same side to be twisted out of plane.[8] The remaining chromophores are thus $C_6H_5—\underset{|}{C}=N$ for the two α-isomers (I and V) and $o\text{-}NH_2C_6H_4—\underset{|}{C}=N$ for the two β-isomers (II and IV). An extended conjugation system is possible with the latter chromophore that may account for the absorption band above 350 mμ. In agreement with this reasoning, benzophenone oxime and benzophenone morpholinoethylimine, whose chromophore must be $C_6H_5—\underset{|}{C}=N$, have ultraviolet absorption spectra closely resembling those of the α-isomers.



It is of interest to note that 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine (VI),[9] which can be considered as a cyclic imine having its imino substituent *syn* to an amino-substituted phenyl group, had an



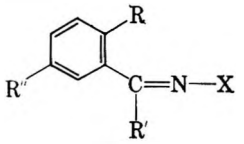
VI VII VIII

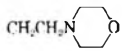
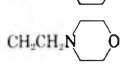
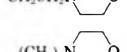
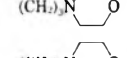
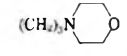
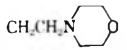
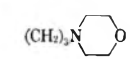
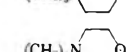
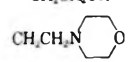
(8) An extensive discussion of this point in regard to benzophenone oximes is given by P. A. S. Smith and E. P. Antoniades, *Tetrahedron*, **9**, 210 (1960).

(9) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **28**, 2150 (1963).

TABLE I

GEOMETRICAL KETIMINE ISOMERS



Compound	Geometrical configuration[a]	R	X	R'	R''	Method[b]	Recrystn. solvent	M.p., °C.	λ_{max}^{EtOH}, mμ (ε)	Empirical formula	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	*syn*	NH_2		C_6H_5	Cl	C	C_2H_5OH	140–142	248 (25,300)	$C_{19}H_{22}ClN_3O$	66.36	6.45	12.22	66.13	6.29	12.09
II	*anti*	NH_2		C_6H_5	Cl	C	C_6H_{12}	112–114	233 (24,000) 362 (4,840)	$C_{19}H_{22}ClN_3O$	66.36	6.45	12.22	66.17	6.50	12.43
XI	*syn*	NH_2		C_6H_5	Cl	C	C_6H_{12}–C_2H_5OH	118–119	248 (25,400)	$C_{20}H_{24}ClN_3O$	67.12	6.76	11.74	67.36	6.79	11.85
XII	*anti*	NH_2		C_6H_5	Cl	C	C_2H_5OH	91–92	230 (29,700) 359 (5,000)	$C_{20}H_{24}ClN_3O$	67.12	6.76	11.74	67.23	6.76	11.94
XIII	*syn*	$NHCH_3$		C_6H_5	Cl	C	C_6H_{14}	123–125	253 (28,400)	$C_{20}H_{24}ClN_3O$	67.12	6.76	11.74	66.84	6.61	11.66
XIV	*anti*	$NHCH_3$		C_6H_5	Cl	C	C_6H_{14}	100–102	230 (30,500) 378 (6,000)	$C_{20}H_{24}ClN_3O$	67.12	6.76	11.74	66.96	6.65	11.53
XV	*anti*	NH_2	CH_2CH_2OH	C_6H_5	Cl	A, B	C_6H_6–C_6H_{12}	122–124	233 (24,100) 360 (4,650)	$C_{15}H_{15}ClN_2O$	65.56	5.50	10.20	65.80	5.55	10.40
XVI	*anti*	NH_2	$(CH_2)_3OH$	C_6H_5	Cl	A, B	C_6H_{12}	106–108	234 (25,100) 358 (5,150)	$C_{16}H_{17}ClN_2O$	66.54	5.94	9.70	66.26	5.96	9.66
XVII	*anti*	NH_2	CH_2CH_2OH	*o*-ClC_6H_4	Cl	A	C_6H_{12}	123–125	231 (29,300) 363 (5,140)	$C_{15}H_{14}Cl_2N_2O$	58.27	4.56	9.06	58.54	4.62	9.25
XVIII	*anti*	$NHCOCH_3$	$(CH_2)_3OCOCH_3$	C_6H_5	Cl	D	*i*-C_3H_7OH	118–120	237 (30,500) 330 (3,040)	$C_{20}H_{21}ClN_2O_3$	64.42	5.81	7.52	64.77	5.73	7.79
XIX	*anti*	$NHCOCH_3$	$(CH_2)_2OCOCH_3$	C_6H_5	Cl	D	C_7H_{16}	99–101	237 (30,100) 329 (3,400)	$C_{19}H_{19}ClN_2O_3$	63.59	5.34	7.81	63.73	5.38	7.60
XX	*anti*	$NHCOCH_2Cl$		C_6H_5	Cl	D	Aq. C_2H_5OH	107–109	237 (30,100) 323 (3,900)	$C_{22}H_{25}Cl_2N_3O_2$	60.83	5.80	9.67	60.92	5.88	9.44
X	*anti*	$NHCOCH_3$		C_6H_5	Cl	D, E	CH_3CN	147–149	236 (29,000) 327 (3,180)	$C_{21}H_{24}ClN_3O_2$	65.36	6.27	10.89	65.34	6.13	10.73
XXI	*anti*	$NHCOCH_3$	CH_2CH_2OH	C_6H_5	Cl	F	CCl_4–C_6H_{12}	143–145	237 (28,000) 326 (2,900)	$C_{17}H_{17}ClN_2O_2$	64.45	5.41	8.84	64.60	5.39	8.92
XXII		H		C_6H_5	H	C		180–183 (0.3)[c]	247 (14,200)	$C_{19}H_{22}N_2O$	77.51	7.53	9.52	77.74	7.54	9.23

[a] With respect to the substituted phenyl group. [b] See Experimental section. [c] Boiling point (mm.).

absorption spectrum related to that of II (Fig. 2). This indicated that the imine bond was in resonance with the fused ring and raised the question as to whether the configuration of the noncyclic imines ought to be assigned by relation to the oximes or by relation to cyclic derivatives such as VI. It was established that the usual pattern of curves was being obtained with cyclic compounds by observing the absorption spectrum of 1-*o*-aminophenyl-3,4-dihydroisoquinoline (VII) in which the imino substituent is *syn* to a benzene ring unsubstituted by an amino group. Compound VII had a spectrum corresponding to those of I and V. The more likely choice seemed to be the relation to the oximes, explaining the contrary data from the cyclic imines by assuming that the fusion of the imino substituent to a benzene ring had brought about coplanarity where none would have existed without the ring fusion. Unfortunately, the noncyclic imines we had prepared were not susceptible of direct ring closure. However, 7-chloro-5-phenyl-3,1,4-benzoxadiazepin-2(1*H*)-one (VIII) has been prepared by direct phosgenation of V.[7] The spectrum of VIII has been found to be similar to that of 2-chloroacetamido-5-chlorobenzophenone, β-oxime (IX).[10] Despite having an imine configuration opposite to that of IX, VIII has a similar ultraviolet absorption curve, hence a similar resonating pattern. The formation of the ring in VIII has caused a switch of the aromatic ring in conjugation with the imine bond from the unsubstituted phenyl to the amide-substituted fused ring.

These results tend to confirm the use of the spectra of the oximes as a basis for assigning the configuration of the noncyclic imines.

The acetylation of II produced X and this compound had the expected type of ultraviolet curve. Mild acetylating conditions did not affect I, but more vigorous conditions afforded X. The NH_2 group is more hindered in I than in II, and the more vigorous treatment evidently causes isomerization. It is of interest that the isomerization here is from α to β, whereas heating of II caused the reverse change.

The additional imines that were prepared are listed in Table I. The configurations are assigned by analogy to I and II.

Experimental

2-(2-Amino-5-chloro-α-phenylbenzylideneamino)ethanol (XV). Method A.—A solution of 3.0 g. of 2-amino-5-chlorobenzophenone and 30 ml. of ethanolamine was heated under reflux for 4 hr. After cooling, the reaction mixture was diluted with 60 ml. of water and the solid that separated was recrystallized from aqueous alcohol giving 1.0 g. of pale yellow solid, m.p. 122–124°.

Method B.—A solution of 23.0 g. of 2-amino-5-chlorobenzophenone and 40 ml. of ethanolamine was heated under reflux in 200 ml. of hexanol for 3 hr. in the presence of a small amount of zinc chloride using a Dean–Stark water separator. After the separation of water had stopped, the solvent was removed *in vacuo* and the product was washed with cyclohexane and recrystallized from isopropyl alcohol to afford 9.9 g., m.p. 122–124°.

N-[2-(2-Amino-5-chloro-α-phenylbenzylideneamino)ethyl]morpholine (I and II). Method C.—A solution of 23.1 g. of 2-amino-5-chlorobenzophenone and 45 g. of 4-[2-aminoethyl]morpholine in 100 ml. of xylene and a catalytic amount of zinc chloride was heated for 3 hr. until the theoretical amount of water had been removed azeotropically. The solvent was removed *in vacuo* and the residue was recrystallized from hexane.

(10) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

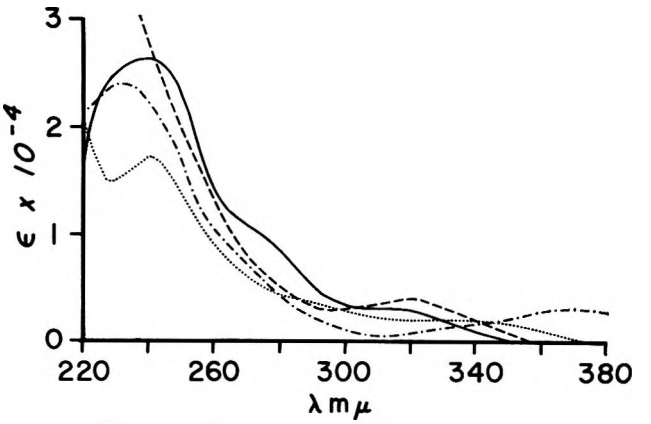


Fig. 2.—Ultraviolet absorption spectra in 95% ethanol: VI, – – –; VII, · · · · · ·; VIII, – · – · –; IX, ———.

There was obtained 7.8 g. of I, which was recrystallized again from ethanol, to give white plates, m.p. 140–142°.

The filtrate from the first recrystallization was concentrated to a small volume and, upon cooling, there was obtained II, m.p. 105–109°. Compound II was recrystallized from cyclohexane and then from aqueous alcohol to give 2.4 g. of pale yellow crystals, m.p. 112–114°.

Either I or II readily hydrolyzed to the starting products in an acid solution.

In the infrared (KBr), I had peaks at 3.06 and 3.15 μ (NH_2) as well as peaks at 6.08, 6.18, 6.29, and 6.40 μ (possible C=N). Compound II had peaks at 3.03 and 3.17 μ, as well as peaks at 6.23 (vs), 6.28 (sh), 6.34 (sh), and 6.49 μ.

N.m.r. spectra were determined in deuteriochloroform (tetramethylsilane standard) using a Varian A-60 spectrometer.

TABLE II

N.M.R. SPECTRA[a]

Proton	I	II
$-CH_2OCH_2-$	3.67 (m)	3.67 (t, J = 5)
$-CH_2N-CH_2-$ (ring)	2.48 (m)	2.40 (m)
$-CH_2N<$	2.75 (t, J = 7)	2.65 (t, J = 7)
$=NCH_2-$	3.56 (t, J = 7)	3.44 (t, J = 7)
Aromatic and NH_2	6.59–7.80 (m)	6.51–7.59 (m)

[a] Given in δ-values as p.p.m.; J values are in c.p.s.

4-[2-(2-Acetamido-5-chloro-α-phenylbenzylideneamino)ethyl]morpholine (X). Method D.—To a solution of 3.0 g. of II in 30 ml. of pyridine was added 3.0 ml. of acetic anhydride. The solution was allowed to stand for 40 min. After chilling and diluting the reaction mixture with water, the product was extracted with ether and the extracts were washed with water, dried, and evaporated. The residue was induced to crystallize by treating with hexane. Recrystallization from acetonitrile gave 1.5 g. of white crystals of X, m.p. 147–149°.

Method E.—A solution of 13.7 g. of 2-acetamido-5-chlorobenzophenone, 30 ml. of 2-aminoethylmorpholine, 100 ml. of xylene, and a catalytic amount of zinc chloride was heated for 5 hr. until the theoretical amount of water had been removed. The solvent was removed *in vacuo*, and the product was precipitated out with heptane. Recrystallization from acetonitrile afforded 5.9 g. of X, m.p. 147–149°. This was the same as the compound prepared by method D.

4-[2-(2-Amino-5-chlorobenzhydrylamino)ethyl]morpholine (III).—To a suspension of 3.0 g. of I in 75 ml. of alcohol was added with stirring 1.0 g. of sodium borohydride in 25 ml. of water. The reaction mixture was heated at 50–60° for 20 min. After cooling, the reaction mixture was carefully acidified with acetic acid, diluted with 100 ml. of water, made alkaline with sodium hydroxide, and extracted with ether. The product was removed from the ether extract with a dilute acetic acid solution. This solution was made basic with sodium hydroxide and extracted with ether. Evaporation of the ether left 1.7 g. of residue which was taken up in acetonitrile and precipitated out as the trihydrochloride salt, m.p. 178–180°. The compound was insoluble in organic solvents and was purified by triturating with warm alco-

hol. There remained 1.3 g. of white solid (III·3HCl), m.p. 185–187°.

Anal. Calcd. for $C_{19}H_{24}ClN_3O \cdot 3HCl$: C, 50.12; H, 5.98; N, 9.73. Found: C, 49.92; H, 5.86; N, 9.37.

Compound III was also prepared as a dihydrochloride salt, m.p. 199–201°.

Anal. Calcd. for $C_{19}H_{24}ClN_3O \cdot 2HCl$: C, 54.49; H, 6.26; Cl, 25.40; N, 10.03. Found: C, 54.21; H, 6.30; Cl, 25.80; N, 9.84.

Conversion of β-Form into α-Form.—Compound II (β-form) was heated to 140–150° for a few minutes. The melt was cooled and recrystallized from alcohol giving I (α-form), m.p. 140–142°.

2-(2-Acetamido-5-chloro-α-phenylbenzylideneamino)ethanol (XXI). Method F.—Compound XIX, 3.5 g., was dissolved in a solution of 5 ml. of 4 *N* sodium hydroxide and 50 ml. of ethanol. After 5 min. the solution was diluted with water to yield 1.5 g. of XXI.

Acknowledgment.—We are indebted to Dr. Gordon Ellis and his associates for the microanalyses and to Dr. Charles Hetzel and Mr. Bruce Hofmann for the spectra.

Sulfur Heterocycles from the Ring Closure of Bisarylalkyl Disulfides[1,2]

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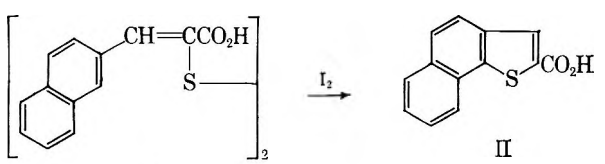
Bis(β-2-naphthylethyl) disulfide (III), bis-β-(3,4-dimethoxyphenyl)ethyl disulfide (VI), and bis(γ-2-naphthylpropyl) disulfide (X) have been synthesized. In the presence of iodine, III undergoes ring closure, giving 2,3-dihydronaphtho[1,2-*b*]thiophene (IV). An excess of iodine converts III or IV into naphtho[1,2-*b*]thiophene (V). On replacing iodine by aluminum bromide, only IV is obtained from III. Both 5,6-dimethoxybenzothiophene (VIII) and 2,3-dihydro-5,6-dimethoxybenzothiophene (VII) are obtained by the action of iodine on VI. Use of the same catalyst leads to the formation of dihydronaphtho[1,2-*b*]thiapyran (XII) from X. The identity of XII has been established by an independent synthesis. Ultraviolet spectral maxima of the products of ring closure are reported.

Disulfides have the ability to function as electrophilic reagents under the influence of acid catalysts. Several instances of their acid-catalyzed addition to olefinic double bonds have been reported[3,4] and a limited number of cases are known in which benzene derivatives undergo substitution reactions with disulfides to give thio ethers.[5,6] Analogous intramolecular interaction between a disulfide sulfur atom and an aromatic moiety in the same molecule leads to the formation of condensed thiophenes.[7,8] To answer the question as to whether or not formation of a thiophene ring, with its accompanying gain in stabilization energy, was a necessary conditions for cyclization, disulfides of the structure $(ArCH_2CH_2S)_2$ were sought in which Ar was the 2-naphthyl or the 3,4-dimethoxyphenyl radical. Results of studies on the cyclization of α,α′-dithiobis-β-arylacrylic acids support earlier evidence[5] of the electrophilic nature of the ring-closure reaction, and these groups are known to be active toward electrophilic attack.



I II

The ring closure of disulfide I proceeded smoothly, giving II in excellent yield using iodine as the catalyst in dioxane at 50° (see Table I).[7] When the same conditions were employed for the cyclization of bis(β-2-naphthylethyl) disulfide (III), the starting material was recovered. Clearly then, unsaturation in the side chain facilitates the cyclization. Boron trifluoride in benzene also failed to bring about the ring closure of III. However, when the reaction was conducted in refluxing ethylene glycol using an equimolar quantity of iodine, although more than half of the disulfide remained unchanged, an oil was obtained in 32% yield which was identified as 2,3-dihydronaphthol[1,2-*b*]thiophene (IV).[9] No IV was detected after refluxing III for 12 hr. in ethylene glycol alone.

The same product (IV) was formed when III was treated with aluminum bromide in benzene. Oxidation of IV with hydrogen peroxide gave 2,3-dihydronaphtho[1,2-*b*]thiophene 1,1-dioxide.[10] The ultraviolet spectral maxima of IV are recorded in Table II. A by-product of the reaction employing aluminum bromide was found to be β-2-naphthylethanethiol which, if it were formed also during the cyclization reaction with iodine as the catalyst, would immediately be oxidized to disulfide, thereby increasing the yield of IV.

With excess iodine, III was converted to naphtho[1,2-*b*]thiophene (V) in 60% yield and no disulfide was recovered. V was identified by oxidation to the corresponding sulfone[9] and comparison of the compound and its derivatives with authentic samples. Evidently, initially formed IV was dehydrogenated by iodine to give V, since a sample of IV, treated under similar conditions with an excess of iodine, was converted wholly to V.

Employing iodine in dioxane at 60°, a large proportion of bis-β-(3,4-dimethoxyphenyl)ethyl disulfide (VI) was recovered and less than 5% of an impure product, m.p. 65–75°, was isolated. Here again, the effect of

(1) This research was supported by the U. S. Army Research Office (Durham) under Contract No. DA-33-008-ORD-1916.

(2) A preliminary communication of a portion of this work: E. Campaigne and B. G. Heaton, *Chem. Ind.* (London), 96 (1962).

(3) B. Holmberg, *Arkiv Kemi Mineral. Geol.*, **13B**, 6 (1939); *Chem. Abstr.*, **34**, 2341 (1940).

(4) D. McCaulay and A. P. Lien, U. S. Patent 2,519,586 (Aug. 22, 1950); *Chem. Abstr.*, **44**, 10,728 (1950).

(5) S. Archer and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 4296 (1952).

(6) H. Behringer and K. Kuchinka, *Angew. Chem.*, **72**, 348 (1960).

(7) E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 39 (1956).

(8) E. Campaigne and W. E. Kreighbaum, *ibid.*, **26**, 1326 (1961).

(9) J. E. Banfield, *et al.*, *J. Chem. Soc.*, 2603 (1956).

(10) W. Davies and Q. N. Porter, *ibid.*, 2609 (1956).

TABLE I

CONDITIONS FOR RING CLOSURE OF DISULFIDES

Disulfide	Ratio,[a] moles	Conditions: Solvent	Temp., °C.	Time, hr.	% yield	Product
I	6.0	Dioxane	50	36	90	II[b]
III	6.0	Dioxane	50	32	*c*	
III	1.0	Ethylene glycol	Reflux	0.75	32	IV
III	4.0	Ethylene glycol	Reflux	12	60	V
III	*d*	Benzene	70	2.5	20	IV
III	*e*	Benzene	Reflux	10	*c*	
VI	1.0	Dioxane	60	11	5	VII
VI	2.0	Dioxane	Reflux	12	20	VII[f]
VI	1.0	Ethylene glycol	160–180	0.5	23	VII
X	4.0	Ethylene glycol	Reflux	8	25	XII
X	1.0	Glyme[g]	90	8.5	50	XII[f]

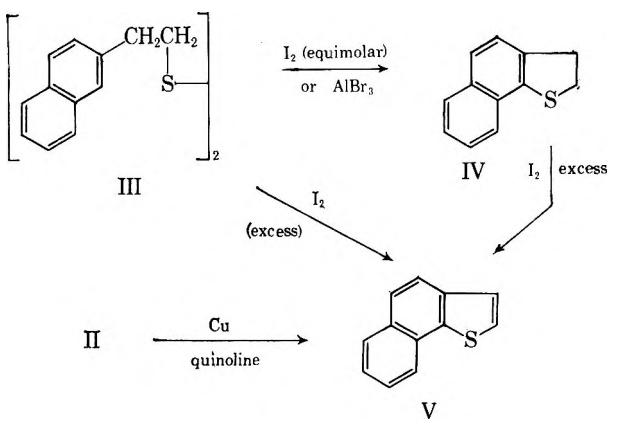
[a] Ratio of iodine–disulfide in reaction. [b] See ref. 7. [c] Starting material recovered. [d] One mole of $AlBr_3$/mole of III in place of I_2. [e] Excess BF_3 in place of I_2. [f] 8% of VIII was also produced. [g] Ethylene glycol dimethyl ether.

TABLE II

ULTRAVIOLET SPECTRAL MAXIMA OF THE PRODUCTS RESULTING FROM DISULFIDE RING CLOSURE

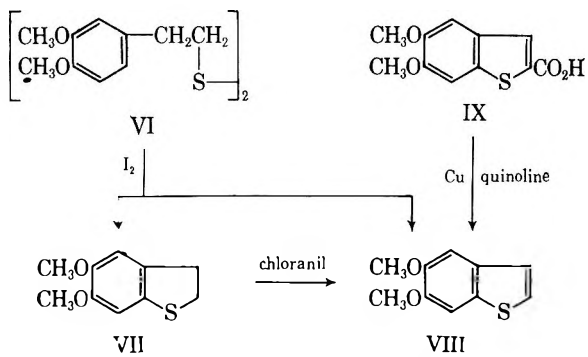
Product	λ_{max}, mμ[a]	log ϵ
IV	217	4.63
	249	4.35
	314	3.70
	323	3.70
VII	212[b]	4.41
	252	4.03
XII	219	4.66
	244	4.32
	310	3.83
V	255[c]	4.47
	260	4.61
	264	4.61
VIII	237	4.45
	264	3.97
	273	3.95
	295	3.40

[a] Solvent, 95% ethanol (except where shown). A Cary spectrophotometer, Model 14, was used in the range 200–350 mμ. [b] Wave-length range was only 200–300 mμ. [c] Cyclohexane.



the double bond in the side chain of α,α'-dithiobis-β-arylacrylic acids in facilitating ring closure is evident, since 5,6-dimethoxybenzothiophene was formed in 58% yield from α,α'-dithiobis-β-(3,4-dimethoxyphenyl)acrylic acid under similar conditions.[8] Raising the temperature to 100° and increasing the quantity of iodine gave, by column chromatography, *ca.* 20% of impure 2,3-dihydro-5,6-dimethoxybenzothiophene (VII). A major portion of the disulfide was converted into highly colored material which was strongly adsorbed on the alumina of the column.

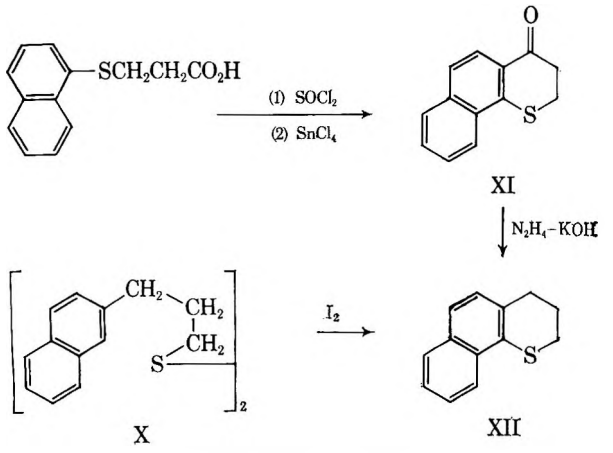
Reaction at a higher temperature in ethylene glycol for a much shorter reaction time followed by chromatography of the product mixture on alumina, afforded VII (23%), characterized by its ultraviolet spectrum, the formation of a sulfone, and dehydrogenation with chloranil to 5,6-dimethoxybenzothiophene (VIII). VIII was also isolated from the reaction along with VII, in 8% yield, and was undoubtedly obtained as a result of the dehydrogenation by iodine of initially formed VII.



The possibility of obtaining 2,3-dihydrothiapyrans by ring closure of disulfides of the type $(ArCH_2CH_2CH_2S)_2$ was examined using bis(γ-2-naphthylpropyl) disulfide (X). Excess iodine in refluxing ethylene glycol gave a liquid, $C_{13}H_{12}S$, in 25% yield. This product formed a picrate and sulfone and was shown to be dihydronaphtho[1,2-*b*]-4H-thiapyran (XII), arising as expected by cyclization of X at the 1-position, by comparison with a sample prepared from 3-(α-naphthylthio)propanoic acid *via* the thiapyrone XI.[11,12] XI exhibits an unusually low-frequency carbonyl band (1650 cm.$^{-1}$), possibly indicating electronic interaction with the sulfur atom. A much cleaner reaction, giving a 50% yield of XII, together with some unchanged X, was obtained using glycol dimethyl ether as solvent.[13] The experiments involving various conditions used in the ring closure of III, VI, and X are summarized in Table I.

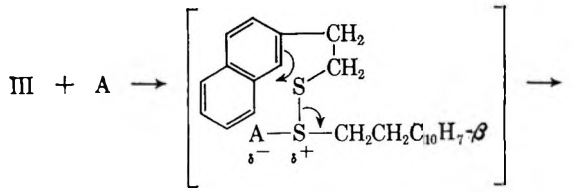
The most striking feature of the ultraviolet spectra of the ring-closed products (Table II) is the presence of an absorption peak in the region 210 to 220 mμ in the spectra of all three partially hydrogenated hetero-

(11) F. Krollpfeiffer and H. Schultze, *Ber.*, **56**, 1819 (1923).
(12) W. E. Truce and G. A. Toren, *J. Am. Chem. Soc.*, **76**, 695 (1954).
(13) E. Campaigne, L. Ergener, and B. G. Heaton, *J. Org. Chem.*, **27**, 4111 (1962).



cycles, IV, VII, and XII, and its absence in the spectra of the aromatic products V and VIII, in which absorption of comparable intensity occurs at longer wave lengths. As expected, the spectral curves obtained for IV and for XII were similar.

Spectral studies[14] indicate that charge-transfer complexes between Lewis acids and disulfides exist in solution, and it is thought that the formation of these complexes may be the initial step in the ring-closure reaction. In the acid-catalyzed formation of thiaxanthone from 2,2′-dithiosalicylic acid and benzene, Archer and Suter[5] provided evidence that protonation of the disulfide bond is the initial step, followed by electrophilic interaction of a sulfur atom with benzene, and the simultaneous cleavage of the disulfide bond, giving thiosalicylic acid as the by-product. Applied to disulfide ring closure of III with a Lewis acid A, the mechanism would be as follows.



IV + A + β-$C_{10}H_7CH_2CH_2SH$

The formation of β-(2-naphthyl)ethanethiol in the cyclization of III with aluminum bromide agrees with this scheme. Although there seems to be only one case of the isolation of a sulfenyl iodide,[15] the possible existence of such compounds as intermediates in disulfide ring closures employing iodine cannot be neglected. The presence of a sulfenyl iodide as an intermediate has been postulated in a disulfide cyclization occurring under basic conditions.[16]

Synthesis of Disulfides.—III was obtained from 2-naphthylacetic acid in 52% over-all yield,[17] as outlined in Chart I.

The preparation of VI, outlined in Chart II, proceeded *via* the azlactone XV[18] and the ester XVII.[19] Conversion of XVIII to the chloride XIXa was accomplished with thionyl chloride, as described by Barash and Osbond,[20] since treatment with phosphorus tribromide in the manner of Livshits, *et al.*,[21] caused demethylation of one methoxy group. In this connection, Gardner, Horton, and Pincock[22] have observed that in the cleavage of polyalkoxyacetophenones with hydrogen bromide it appears as though a 4-alkoxy group assists the removal of a 3-alkoxy group, but the 4-alkoxy group remains unchanged. The desired disulfide VI was obtained in 22% over-all yield from veratraldehyde.

Bis(γ-2-naphthylpropyl) disulfide (X) was synthesized as outlined in Chart III, *via* 2-bromoethylnaphthalene,[23] in 10% over-all yield.

CHART I

SYNTHESIS OF BIS(β-2-NAPHTHYLETHYL) DISULFIDE (III)

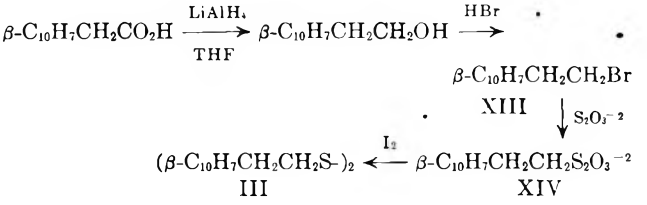
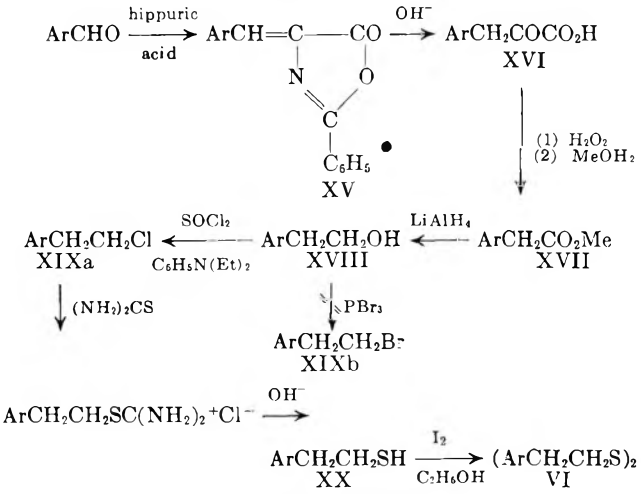


CHART II

SYNTHESIS OF BIS-β-(3,4-DIMETHOXYPHENYL)ETHYL DISULFIDE (VI)



Ar = 3,4-dimethoxyphenyl

Bis(γ-2-naphthylpropyl) disulfide (X) was synthesized as outlined in Chart III, *via* 2-bromoethylnaphthalene,[23] in 10% over-all yield.

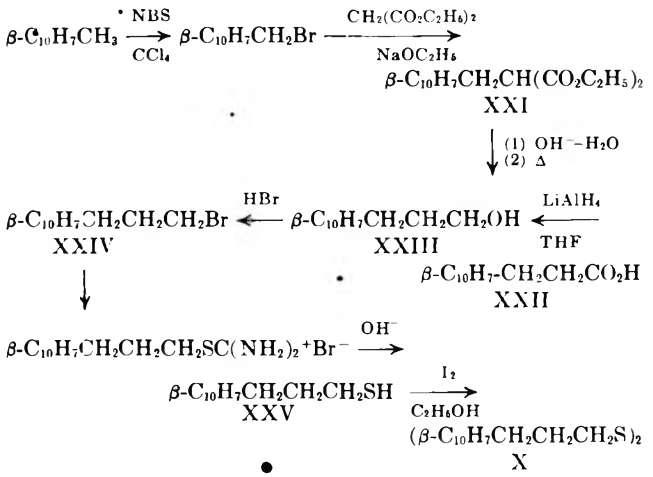
Experimental[24]

β-(2-Naphthyl)ethanol.—A solvent of 20.0 g. of β-naphthylacetic acid[25] (0.11 mole) in 100 ml. of dry tetrahydrofuran was added dropwise to a slurry of lithium aluminum hydride (6.0 g., 0.16 mole) in 140 ml. of tetrahydrofuran. After completion of the addition, the mixture was heated under reflux for 1 hr. and allowed to cool overnight. After decomposition of excess hydride with ethyl acetate followed by careful addition of 5% hydrochloric acid (100 ml.), filtration gave an ethereal filtrate which was combined with ether washings of the residue and evaporated under reduced pressure. A white solid was obtained which, after washing with water and petroleum ether, crystal-

(14) H. Tsubomura and R. P. Lang, *J. Am. Chem. Soc.*, **83**, 2085 (1961).
(15) W. E. Messer, U. S. Patent 2,370,253 (Feb. 27, 1945).
(16) L. Katz and W. Schroeder, *J. Org. Chem.*, **19**, 103 (1954).
(17) H. E. Westlake and G. Dougherty, *J. Am. Chem. Soc.*, **64**, 149 (1942).
(18) W. Kropp and H. Decker, *Ber.*, **42**, 1184 (1909).
(19) H. R. Snyder, J. S. Buck, and W. S. Ide, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 333.
(20) M. Barash and J. M. Osbond, *J. Chem. Soc.*, 2162 (1959).
(21) R. S. Livshits, *et al.*, *Zh. Obshch. Khim.*, **23**, 525 (1953).
(22) P. D. Gardner, W. J. Horton, and R. E. Pincock, *J. Am. Chem. Soc.*, **78**, 2541 (1956).
(23) N. B. Chapman and J. F. A. Williams, *J. Chem. Soc.*, 5044 (1952).
(24) All melting points are corrected. Infrared spectra were obtained using a Perkin-Elmer Infracord Model 137 G spectrophotometer. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.
(25) F. Mayer and T. Oppenheimer, *Ber.*, **49**, 2137 (1916).

CHART III

SYNTHESIS OF BIS(γ-2-NAPHTHYLPROPYL) DISULFIDE (X)



NBS = N-bromosuccinimide, THF = tetrahydrofuran

lized from petroleum ether (b.p. 30–60°) as small white needles, m.p. 69–70.5° (14.8 g., 80%). The reported[25] m.p. was 67–68°. The α-naphthylurethane was prepared in the usual way and crystallized from hexane–chloroform as feathery crystals, m.p. 153–155°.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.90; H, 5.61. Found: C, 81.17; H, 5.93.

β-(2-Naphthyl)ethyl Bromide (XIII).—β-(2-Naphthyl)ethanol (13.8 g.) was heated for 4.5 hr. under reflux with 100 ml. of 47% aqueous hydrobromic acid and then allowed to cool overnight. After the addition of 200 ml. of water, extraction with four 50-ml. portions of ether, followed by combination of the extracts and removal of solvent after washing with water gave 17.9 g. (95%) of a solid, m.p. 64.5–66.5°, which depressed the melting point of starting material to 49–53°. The product (12.5 g.) crystallized from chilled petroleum ether as needles, m.p. 64.5–66.5°.[26]

Bis[β-(2-naphthyl)ethyl] Disulfide (III).—To a solution of 11.7 g. of XIII (0.05 mole) in 125 ml. of warm ethanol was added a solution of 12.4 g. of sodium thiosulfate (0.05 mole) in 50 ml. of water. After heating the mixture under reflux for 4 hr., 6.35 g. of iodine (0.05 g.-atom) was added gradually, by drainage from a Soxhlet as described by Viscontini, *et al.*,[27] keeping the reaction mixture refluxing throughout the addition (5.5 hr.). The solid obtained on dilution of the reaction mixture with water was collected by filtration, washed well with water, and dried. Two crystallizations from *n*-hexane, employing Norit for decolorization, gave 6.4 g. (69%) of white needles, m.p. 84–85°.

Anal. Calcd. for $C_{24}H_{22}S_2$: C, 76.96; H, 5.92; S, 17.12. Found: C, 77.23; H, 5.95; S, 16.91.

With sodium nitroprusside solution, III only gave the purple color characteristic of alkyl mercaptans after treatment with warm ethanolic sodium cyanide, thus indicating the presence of the disulfide bond.

2,3-Dihydronaphtho[1,2-*b*]thiophene (IV). A. From Ring Closure of III with Iodine.—Compound III (3.74 g., 0.01 mole) in 300 ml. of ethylene glycol was heated under reflux and 2.7 g. of iodine (0.022 g.-atom) was added portionwise over a period of 30 min., after which the mixture was maintained under reflux for a further 15 min. When cool, the liquid was poured into 800 ml. of water, excess iodine was removed by addition of sodium bisulfite solution, and after cooling to 3°, filtration gave 3.15 g. of an oily brown solid. Chromatography of the product on an alumina column, using *n*-hexane and chloroform (3:1) as the eluting solvent, gave unchanged disulfide, m.p. 80–83° (2.0 g.), and a light brown oil (0.7 g.) which was shown to be essentially pure 2,3-dihydronaphtho[1,2-*b*]thiophene by the formation of a dark red picrate in the form of needles, m.p. 129–131°.

More of the oil (0.5 g.) was obtained by evaporation of ether extracts of the filtrate from above, and this material gave the same picrate, m.p. 128–129°.

B. By Interaction of Aluminum Bromide and III.—Compound III (7.7 g., 0.021 mole), dissolved in 75 ml. of sodium-dried benzene, was treated with 5.5 g. (0.021 mole) of freshly distilled aluminum bromide. The deep brown solution was heated to 70° and maintained between 60 and 70° for 2.5 hr., protected from moisture by a calcium chloride tube. On cooling, the green solution was poured slowly onto excess ice. After several hours, the benzene layer was separated, washed with three 30-ml. portions of 10% sodium hydroxide solution, then water (40 ml.), and dried over anhydrous sodium sulfate. The combined alkaline washings contained only a trace of mercaptan, as indicated by failure to bleach iodine in potassium iodide solution.

Removal of benzene by evaporation under reduced pressure gave a brown oil (7.7 g.) which was dissolved in 30 ml. of ethanol and titrated with a standard solution of iodine in ethanol. Iodine equivalent to 2.7 g. of β-(2-naphthyl)ethanethiol was consumed, and a white solid precipitated. The solid was collected by filtration, washed several times with chilled *n*-hexane, and allowed to dry. The solid (4.4 g., 57%) was purified by treatment with Norit and crystallization from *n*-hexane to give white needles (m.p. 82–83.5°) of starting material.

The filtrate was evaporated to small volume, 50 ml. of water was added, and the mixture was extracted with three 30-ml. portions of *n*-hexane. The combined extracts, after washing with dilute sodium bisulfite solution to remove iodine, were washed with water and dried over sodium sulfate. The yellow oil afforded by removal of the solvent was distilled under reduced pressure and gave 1.5 g. (20%) of IV, an almost colorless distillate, b.p. 150–158° (1.2 mm.).

Anal. Calcd. for $C_{12}H_{10}S$: C, 77.37; H, 5.41; S, 17.21. Found: C, 77.22; H, 5.37; S, 17.34.

Treatment of a small portion of the distillate with an excess of saturated ethanolic picric acid solution gave a picrate which crystallized from ethanol as dark red needles, m.p. 129.5–130°, and did not depress the melting point of the picrate of IV previously prepared. Banfield, *et al.*,[9] report dark red needles, m.p. 132°, for the picrate of IV.

Anal. Calcd. for $C_{18}H_{13}N_3O_7S$: C, 52.05; H, 3.15; N, 10.12; S, 7.72. Found: C, 52.15; H, 3.28; N, 10.11; S, 7.79.

2,3-Dihydronaphtho[1,2-*b*]thiophene 1,1-Dioxide.—A solution of 0.6 g. of IV in 8 ml. of glacial acetic acid containing 3 ml. of 30% hydrogen peroxide was heated to reflux on a steam bath for 90 min. On cooling, the mixture was poured onto ice, and the product was collected by filtration, washed with water, and dried. Recrystallization to constant melting point of the cream-colored solid (0.58 g., m.p. 171.5–176.5°) from methanol afforded 0.28 g. of white needles, m.p. 186.5–188°[10]; ν_{max}^{KBr} 2990 (aliphatic CH), 1274, 1144, and 1121 cm.$^{-1}$ ($-SO_2-$).

Anal. Calcd. for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62; S, 14.67. Found: C, 65.89; H, 4.67; S, 14.49.

Attempted Ring Closure of Bis(β-2-naphthylethyl) Disulfide. A. With Iodine in Dioxane.—A solution of 2.0 g. (0.0054 mole.) of III and 8.0 g. of iodine (0.063 g.-atom) in 80 ml. of dioxane was stirred, heated to 50°, and maintained at this temperature for 32 hr. Partial evaporation of the mixture under reduced pressure was followed by the addition of a large volume of water containing sodium bisulfite (*ca.* 10 g.). The solid reaction product was extracted with three 60-ml. portions of ether, the combined extracts were dried ($CaCl_2$) after having been washed with sodium bisulfite solution and then water, and removal of the ether under reduced pressure gave 2.0 g. of a solid residue which, on crystallization from methanol, afforded fine white needles of starting material, m.p. 81.5–83°. Concentration of the crystallization filtrate yielded only more unchanged disulfide.

B. With Boron Trifluoride Etherate in Benzene.—A solution of 7.1 g. (0.019 mole) in III in 600 ml. of dry benzene containing boron trifluoride etherate (40 ml., 47%) was heated under reflux for 10 hr. After work-up as described for the aluminum bromide reaction, removal of solvent afforded 6.6 g. of a solid, which crystallized from hexane as needles, m.p. 84–85.5°, and did not depress the melting point of the starting material.

Naphtho[1,2-*b*]thiophene (V). A. From III and an Excess of Iodine.—Iodine (10.9 g., 0.086 g.-atom) and 4.0 g. of III (0.011 mole) were heated together in 350 ml. of ethylene glycol under reflux for 12 hr. On cooling, the mixture was poured with stirring into 1 l. of water containing 6 g. of sodium bisulfite and the product was extracted with four 150-ml. portions of ether. Washing the combined extracts with water, drying (K_2CO_3), and removal of the solvent gave a dark red-brown oil. Chromatography on an alumina column, using a mixture of *n*-hexane and chloroform in the ratio 4:1, gave 2.24 g. (60%) of a light brown mobile oil, which, on treatment with an excess of saturated eth-

(26) G. T. Tatevosyan and V. O. Babayan, *Zh. Obshch. Khim.*, **22**, 1421 (1952).

(27) M. Viscontini, *et al.*, *Helv. Chim. Acta*, **37**, 375 (1954).

anolic picric acid solution, gave a picrate which crystallized from ethanol as brown needles, m.p. 142.5–144.5°.

B. From the Decarboxylation of II.—Five grams of II,[7] 1.25 g. of copper–bronze powder, and 37 ml. of quinoline were heated together slowly up to 150°, and the temperature was maintained in the range 150–170° for 1 hr., after which it was raised very slowly, over a period of 2.5 hr., to 205°. On cooling, quinoline was neutralized by the addition of 130 ml. of 10% hydrochloric acid. Steam distillation, followed by acidification of the distillate (40 ml. of concentrated HCl), extraction with three 100-ml. portions of chloroform, combination and drying (K_2CO_3) of the extracts, and removal of solvent gave 2.9 g. of an orange oil which distilled in the range 108–113° (0.2 mm.). Treatment of the distillate with picric acid in ethanol gave a picrate which after two recrystallizations from ethanol gave golden yellow needles, m.p. 146.5–147.5°.[28] A mixture melting point with the brown needles (above) was 142.5–145.5°.

C. From the Action of an Excess of Iodine on 2,3-Dihydro[1,2-*b*]thiophene.—Compound IV (1.2 g., 0.0065 mole), 3.3 g. (0.026 g.-atom) of iodine, and 100 ml. of redistilled ethylene glycol were heated together under reflux for 12.5 hr. The mixture was allowed to cool, poured into 300 ml. of water, and extracted with four 100-ml. portions of ether. The combined ether extracts were washed in turn with dilute sodium bisulfite solution, sodium bicarbonate solution, then water, dried (K_2CO_3), and the ether was removed to give a dark brown oil. Distillation of the oil under reduced pressure afforded 0.6 g. of a liquid b.p. 110–116° (0.2 mm.). The absorption maxima (255, 260, and 264 mμ) in the ultraviolet spectrum of the distillate were identical with those present in the spectrum of V derived from II by decarboxylation. This oil formed a picrate in golden yellow needles, m.p. 145.5–147°, which did not depress the melting point of the picrate derived from V (above).

Naphtho[1,2-*b*]thiophene 1,1-Dioxide.—The V (2.0 g., obtained from the decarboxylation above) was dissolved in glacial acetic acid (24 ml.), treated with 30% hydrogen peroxide (7.0 ml.), and heated 4 hr. on a steam bath. The cooled solution was poured with stirring onto ice and the product was extracted with five 50-ml. portions of chloroform. After washing the combined extracts with water, drying (K_2CO_3), and removal of the solvent, an orange-yellow solid was obtained (1.15 g.) which, after treatment with Norit and crystallization from methanol gave green-tinged platelets, m.p. 174–175°. Banfield, *et al.*,[9] report m.p. 179° for the sulfone of V, and add that the melting point is variable, depending on the rate of heating; ν_{max}^{KBr} 1131, 1155, and 1287 cm.$^{-1}$ ($-SO_2-$).

Anal. Calcd. for $C_{12}H_8O_2S$: C, 66.65; H, 3.73; S, 14.83. Found: C, 66.20; H, 4.12; S, 14.60.

The same substance, as shown by mixture melting point and congruity of infrared spectra, was obtained by similar oxidation of the oil obtained from the action of excess iodine on III.

β-(3,4-Dimethoxyphenyl)ethanol (XVIII).—Following the method of Kropp and Decker,[18] the azlactone XV, yellow prisms, m.p. 149.5–151°, was obtained in 65% yield. This was converted by the "Organic Syntheses" procedure[19] to methyl homoveratrate (XVII), b.p. 108–109° (0.22 mm.), in 55% yield. A solution of 34.5 g. (0.165 mole) of XVII in 270 ml. of dry ether was added dropwise to a stirred slurry of 10.5 g. (0.36 mole) of lithium aluminum hydride in 250 ml. of dry ether. After the addition was completed, (*ca.* 3 hr.), the mixture was heated and maintained under reflux for 75 min. with continued stirring. Excess hydride was decomposed by the addition of 25 ml. of ethyl acetate. After adding 200 ml. of chilled 2 *N* sulfuric acid to the stirred, cooled reaction mixture, the aqueous layer was separated and extracted with three 90-ml. portions of ether. The combined ethereal solutions were washed twice with dilute sodium bicarbonate solution and dried (Na_2SO_4). After removal of the solvent, the residue was distilled and 24 g. (80%) of XVIII was obtained, b.p. 124–129° (0.4 mm.). The distillate solidified after a few hours and melted at 44.5–46°.[21]

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.09; H, 7.78.

Attempted Formation of β-(3,4-Dimethoxyphenyl)ethyl Bromide.—Compound XVIII (12.2 g., 0.067 mole) was melted, then supercooled with ice–water, and stirred; before solidification could take place, phosphorus tribromide (61 g., 0.23 mole) was added dropwise over a period of 30 min. to the stirred and cooled alcohol. On completion of the addition, the mixture was allowed to warm slowly to room temperature and was then heated on a steam bath for 2 hr., protected from moisture by a calcium chloride tube.

On cooling, the reaction mixture was slowly dripped onto stirred ice and the product was extracted with four 110-ml. portions of ether. After washing the combined extracts with sodium bicarbonate solution, water, and drying (Na_2SO_4), removal of the solvent by evaporation under reduced pressure gave a light brown oil which distilled in the range 116–120° (0.4 mm.), 9.41 g.

Anal. Calcd. for $C_9H_{11}BrO_2$: C, 46.77; H, 4.80; Br, 34.58. Found: C, 46.56; H, 4.89; Br, 33.52.

A narrow and intense absorption band was present in the infrared spectrum (liquid film) at 3620 cm.$^{-1}$ (OH), and a deep green color was obtained on addition of ferric chloride solution to the distillate.

β-(3,4-Dimethoxyphenyl)ethyl Chloride (XIXa).—This compound was obtained from the corresponding alcohol by treatment with thionyl chloride, as described by Barash and Osbond,[20] b.p. 108–115° (0.3 mm.), in 90% yield.

Anal. Calcd. for $C_{10}H_{13}ClO_2$: Cl, 17.67. Found: Cl, 17.82.

β-(3,4-Dimethoxyphenyl)ethylisothiouronium Chloride.—Compound XIXa (8.7 g., 0.042 mole), dissolved in 15 ml. of 95% ethanol was treated with 3.4 g. (0.045 mole) of thiourea. The mixture was heated under reflux for 3 hr., and then the solvent was removed by evaporation under reduced pressure. The viscous residue solidified and was crystallized from a mixture of 0.5 *N* hydrochloric acid and acetone. Material with m.p. 169.5–171.5° (10.4 g.) was obtained in *ca.* 86% yield. Recrystallization gave needles, m.p. 170.5–171.5°.

Anal. Calcd. for $C_{11}H_{17}ClN_2O_2S$: C, 47.73; H, 6.19; S, 11.58. Found: C, 47.59; H, 6.25; S, 11.49.

Bis(β-3,4-dimethoxyphenylethyl) Disulfide (VI).—β-(3,4-Dimethoxyphenyl)ethylisothiouronium chloride (10.4 g.) was heated under reflux for 2 hr. with 10% sodium hydroxide solution (19 ml.). On cooling, the mixture was acidified by the addition of 10% hydrochloric acid (20 ml.) and extracted with three 20-ml. portions of chloroform. After washing the combined extracts with water, the solvent was removed under reduced pressure, leaving a residue of the mercaptan which was dissolved in 20 ml. of 95% ethanol and treated dropwise, under vigorous stirring, with a solution of 4.79 g. of iodine in 100 ml. of ethanol. After 87 ml. of solution had been added, a slight excess of iodine was present and the titration was discontinued. After cooling, the solid product was collected by filtration, washed with dilute sodium bisulfite solution, a large amount of water, and dried under reduced pressure. Crystallization gave 6.36 g. (86%) of white needles from methanol, m.p. 76.5–78°. The over-all yield from veratraldehyde was 2%; ν_{max}^{KBr} 808, 1029, 1138, 1157, 1239, 1263, and 1515 cm.$^{-1}$ (all strong).

Anal. Calcd. for $C_{20}H_{26}O_4S_2$: C, 60.88; H, 6.64; S, 16.25. Found: C, 60.78; H, 6.68; S, 16.01.

Following the technique previously described for the preparation of these derivatives,[29] the *N,N*-diphenylthiocarbamate of β-(3,4-dimethoxyphenyl)ethanethiol was obtained as white needles, m.p. 107.5–108.5°, from methanol.

Anal. Calcd. for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; S, 8.15. Found: C, 69.99; H, 6.00; S, 8.18.

2,3-Dihydro-5,6-dimethoxybenzothiophene (VII).—Preliminary attempts to cyclize VI in dioxane were unsuccessful. An equimolar solution of VI and iodine in dioxane was maintained at 60° for 11 hr., but separation of the residues on an alumina column led only to starting material in about 60% recovery. Using a 1 molar excess of iodine with VI in refluxing dioxane for 12 hr. produced about 15% of crystalline product melting at 71–73° after several recrystallizations, and having a molecular weight of 192. It was identified by comparison to the products obtained in ethylene glycol. Compound VI (5.2 g., 0.013 mole), iodine (3.35 g., 0.026 g.-atom), and ethylene glycol (200 ml., redistilled) were heated together and maintained between 160 and 180° for 35 min., after which the dark solution was allowed to cool slowly to room temperature. The reaction mixture was poured slowly into 1.2 l. of water and cooled overnight. The product was extracted with chloroform; the combined extracts were washed with bisulfite solution, then water, and dried (K_2CO_3). Removal of solvent gave a red-brown oil which was subjected to chromatography on a column of alumina (230 g.) using a 2:1 mixture of *n*-hexane and chloroform as the eluting solvent.

(28) O. Kruber and A. Raeithel, *Ber.*, **86**, 366 (1953).

(29) R. G. Hiskey, *et al.*, *J. Org. Chem.*, **26**, 4756 (1961).

The progress of elution was followed using thin-layer chromatography on silica. The first material to be eluted was 5,6-dimethoxybenzothiophene (VIII), m.p. 101–102°, lit.[7] m.p. 99–100°. The ultraviolet absorption maxima (see Table II) are in good agreement with the recorded maxima for VIII. Furthermore, the infrared spectrum (KBr mull) was identical with that of VIII, obtained by decarboxylation of IX, and no depression in melting point occurred on admixture of the material, m.p. 101°, with authentic VIII.

Further elution yielded solid (0.41 g.), m.p. 72–73.5° after recrystallization from *n*-hexane, closely followed by VII (0.78 g.) which gave flaky needles, m.p. 76–77.5°, on crystallization from *n*-hexane.

Anal. Calcd. for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16; S, 16.34. Found: C, 61.32; H, 6.05; S, 16.17.

Both the solid, m.p. 72°, and VII greatly depressed the melting point of starting material. Comparison of the infrared spectra of the solid (m.p. 72°), VII, and VIII revealed that the solid (m.p. 72°) was VII containing VIII as an impurity. Hence the total crude yield of VII is *ca.* 23% (15% after recrystallization). Neither the solid, m.p. 71–73° (above), nor that with m.p. 72–73.5° showed a melting point depression on admixture with 2,3-dihydro-5,6-dimethoxybenzothiophene.

Continued elution gave a brown oil (0.47 g.) and elution with chloroform alone gave more of the resinous oil; 0.25 g. was obtained from the evaporation of about 1 l. of eluate. Brown and green material was still strongly absorbed on the column after the passage of more than a liter of chloroform.

2,3-Dihydro-5,6-dimethoxybenzothiophene 1,1-Dioxide.—Compound VII (0.33 g.) was oxidized with 1.5 ml. of 30% hydrogen peroxide in 4 ml. of glacial acetic acid in the manner described above, and 0.23 g. of a white solid was obtained, which crystallized from methanol as prisms, m.p. 183.5–184.5°.

Anal. Calcd. for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30; S, 14.05. Found: C, 52.94; H, 5.50; S, 13.91.

5,6-Dimethoxybenzothiophene (VIII).—A solution of 0.3 g. (0.0015 mole) of VII in 10 ml. of dry xylene was treated with 0.40 g. (0.0016 mole) of chloranil. The addition of chloranil imparted a deep blue-green color to the mixture. The reactants were heated under reflux for 6 hr., and then allowed to cool to room temperature, during which time a solid separated. The solid material was separated by filtration, washed with benzene, and the combined filtrate and washings were evaporated in a stream of nitrogen on the steam bath. The residue was subjected to chromatography on an alumina (40 g.) column using a 2:1 mixture of hexane and chloroform. In this way 0.22 g. (73%) of solid, m.p. 99–101°, was obtained which crystallized from *n*-hexane as clumps of needles, m.p. and m.m.p. 101–102° with authentic VIII, m.p. 100.5–101.5°.[7]

Anal. Calcd. for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19; S, 16.51. Found C, 62.07; H, 5.04; S, 16.22.

The infrared spectra of the samples (m.p. 101–102°) derived from the cyclization, from the dehydrogenation and from decarboxylation of 5,6-dimethoxybenzothiophene-2-carboxylic acid[7] were virtually identical.

Diethyl 2-Naphthylmethylmalonate (XXI).—To a stirred solution of 40 g. (0.25 mole) of diethyl malonate in 150 ml. of dry ethanol containing dissolved sodium (5.2 g., 0.23 g.-atom) was added dropwise with stirring a solution of 49.3 g. (0.22 mole) of 2-bromomethylnaphthalene (prepared by the method of Chapman and Williams)[23] in 30 ml. of dry benzene over a period of 40 min. The mixture was stirred another 40 min. and then heated under reflux for 90 min. Removal of most of the ethanol followed by the addition of 200 ml. of water, extraction of the product with two 40-ml. portions of chloroform, combination of the water-washed extracts, drying (Na_2SO_4), and removal of the solvent gave a yellow oil which on distillation gave 34.5 g. (52%) of the desired ester, b.p. 160–169° (0.25 mm.), lit.[30] b.p. 170–174° (2 mm.).

3-(β-Naphthyl)propanoic Acid (XXII).—Hydrolysis of XXI with methanolic potassium hydroxide and decarboxylation of the resulting diacid at 180° as described by Mayer and Seiglitz,[31] gave XXII in the form of plates, m.p. 133–136° (16.5 g., 72%). Recrystallization from benzene gave colorless plates, m.p. 134–135°.[31]

γ-(2-Naphthyl)propanol (XXIII).—A solution of 15.8 g. (0.079 mole) of XXII in 80 ml. of dry tetrahydrofuran was added dropwise to a stirred suspension of 4.7 g. (0.12 mole) of lithium aluminum hydride in 120 ml. of tetrahydrofuran. After completion of the addition (*ca.* 1 hr.), the mixture was stirred under reflux for 1 hr., and left overnight at room temperature. Decomposition of excess hydride with 15 ml. of ethyl acetate was followed by the addition of 100 ml. of chilled 5% sulfuric acid. Insoluble inorganic material was separated by filtration, washed with tetrahydrofuran, and the combined filtrate and washings were evaporated under reduced pressure. Water (50 ml.) was added and the product was extracted with two 50-ml. portions of ether. The combined extracts were washed with sodium bicarbonate solution, dried (K_2CO_3), and on removal of the solvent, the residue was distilled under reduced pressure giving 13.3 g. (91%) of a viscous oil, b.p. 128–134° (0.2 mm.), which solidified, melting in the range of 36.5–38.5°. This material formed a phenylurethane melting at 95–96°. Searles[32] reported this alcohol to melt at 33° and its phenylurethane to melt at 94°.

γ-(2-Naphthyl)propyl Bromide (XXIV).—A mixture of 13.0 g. of XXIII and 100 ml. of 48% hydrobromic acid was heated under reflux for 5 hr., cooled, poured into 200 ml. of water, and the product was extracted with two 100-ml. portions of ether. After the combined extracts were washed with dilute sodium bicarbonate solution, followed by water, and dried ($MgSO_4$), removal of the solvent gave 16.9 g. (97%) of a solid which, after crystallizing from *n*-hexane, melted at 43.5–44.5°.

Anal. Calcd. for $C_{13}H_{13}Br$: C, 62.67; H, 5.26; Br, 32.07. Found: C, 62.81; H, 5.34; Br, 32.27.

γ-(2-Naphthyl)propylisothiouronium Chloride.—A solution of 16.4 g. (0.066 mole) of XXIV, and 5.0 g. (0.066 mole) of thiourea in 20 ml. of ethanol was heated under reflux for 2.5 hr. The ethanol was removed by evaporation under reduced pressure and 21.4 g. of γ-(2-naphthyl)propylisothiouronium bromide was obtained as a solid, m.p. 164.5–165.5°. Two crystallizations from 0.5 *M* hydrochloric acid gave fine needles, m.p. 173–174°, of the corresponding chloride.

Anal. Calcd. for $C_{14}H_{17}ClN_2S$: C, 59.88; H, 6.10; S, 11.42. Found: C, 59.97; H, 6.15; S, 11.37.

γ-(2-Naphthyl)propanethiol (XXV).—γ-(2-Naphthyl)propylisothiouronium bromide (21.0 g.) was heated for 2 hr. under reflux with an aqueous 5% sodium hydroxide solution. On cooling, the product was extracted with two 40-ml. portions of ether; the combined extracts were washed with water (40 ml.) and dried ($MgSO_4$). Removal of the solvent gave XXV as a red oil (12.8 g.) which was characterized by treatment of a small portion with N,N-diphenylcarbamoyl chloride according to the method of Hiskey, *et al.*[29] γ-(2-Naphthyl)propyl N,N-diphenylthiocarbamate was obtained as fine white needles from methanol, m.p. 102–103°.

Anal. Calcd. for $C_{26}H_{23}NOS$: C, 78.55; H, 5.83; S, 8.07. Found: C, 78.44; H, 5.82; S, 7.92.

Bis(γ-2-naphthylpropyl) Disulfide (X).—A solution of 8.2 g. (0.065 g.-atom) of iodine in 75 ml. of ethanol was added dropwise to a stirred suspension of 12.5 g. (0.062 mole) of XXV in 30 ml. of ethanol. After reduction of the excess of iodine with dilute sodium bisulfite solution, the mixture was cooled; the product was collected by filtration, washed with water, and dried. After treatment with Norit, 8.8 g. (70%) of white needles crystallized from *n*-hexane, m.p. 61.5–63.5°.

Anal. Calcd. for $C_{26}H_{26}S_2$: C, 77.56; H, 6.51; S, 15.93. Found: C, 77.87; H, 6.44; S, 15.72.

3-(α-Naphthylthio)propanoic Acid.—To a solution of 24 g. (0.15 mole) of α-naphthalenethiol (Eastman) and 16.2 g. (0.21 mole) of β-chloropropionic acid in 90 ml. of ethanol was added a solution of sodium (6.9 g., 0.33 g.-atom) in ethanol with stirring. The mixture was heated to reflux, under a constant stream of nitrogen for 16 hr. During this period almost all of the solvent evaporated, and the solution obtained after the addition of sodium bicarbonate solution to the residue was filtered and, on acidification, the crude acid precipitated. After washing several times with water and drying, 23.6 g. (68%) of solid which crystallized from *n*-hexane–benzene as needles, m.p. 88–90°,[11] was obtained.

Anal. Calcd. for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21; S, 13.80. Found: C, 67.19; H, 5.12; S, 14.00.

Dihydronaphtho[1,2-*b*]-4H-thiapyran-4-one (XI).—3-(α-Naphthylthio)propanoic acid (26.2 g.) dissolved in 50 ml. of anhydrous ether containing 4 drops of pyridine was treated with thionyl chloride (15.7 ml., freshly distilled) and, after 0.5 hr. at room

(30) R. Huisgen and V. Rietz, *Ber.*, **90**, 2768 (1957).

(31) F. Mayer and A. Sieglitz, *ibid.*, **55**, 1835 (1922).

(32) S. Searles, *J. Am. Chem. Soc.*, **73**, 124 (1951).

temperature, the reactants were heated for 10 min. on a steam bath. The excess of thionyl chloride and ether was removed by evaporation under reduced pressure; final traces of thionyl chloride were removed by adding benzene and evaporating again.

To a solution of the residue in 90 ml. of sodium-dried benzene cooled to 2°, was added a solution of 30 ml. of stannic chloride in 30 ml. of benzene (sodium-dried) in two equal portions, the second portion being added after the reaction mixture had cooled down to 20°. Cooling was maintained during the whole period, and *ca.* 20 min. after the initial addition the reaction mixture was poured over a mixture of ice and concentrated hydrochloric acid. After 12 hr., the benzene layer was separated, combined with a benzene extract (100 ml.) of the aqueous layer, washed with sodium bicarbonate solution, then water, and dried (K_2CO_3). The yellow solid obtained on removal of the benzene crystallized from ethanol as yellow-green prisms, m.p. 108.5–110° [11] (18.9 g., 78%), ν_{max}^{KBr} 1650 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{13}H_{10}OS$: C, 72.86; H, 4.70; S, 14.96. Found: C, 73.32; H, 4.76; S, 14.96.

The compound formed a semicarbazone which crystallized from chloroform–ethanol as fine needles, m.p. 228.5–230°.

Anal. Calcd. for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; S, 11.82. Found: C, 61.40; H, 5.22; S, 11.87.

Dihydronaphtho[1,2-*b*]-4H-thiapyran (XII). A. From Ring Closure of X.—A solution of 5.0 g. (0.012 mole) of X and 12.6 g. (0.10 g.-atom) of iodine in 450 ml. of ethylene glycol was heated under reflux for 8 hr. On cooling, the mixture was poured into 1.3 l. of water and the product was extracted with three 250-ml. portions of ether. The combined extracts were washed with dilute sodium bisulfite solution, followed by water, and dried (K_2CO_3). The dark red oil obtained on removal of the solvent was absorbed onto an alumina column (160 g.) and, on elution with a *n*-hexane–chloroform mixture (4:1), a yellow oil was obtained (1.58 g.) which distilled under reduced pressure giving 1.26 g. (25%) of an almost colorless distillate of XII, b.p. 138–142° (0.2 mm.). Vapor phase chromatography[33] indicated that the distillate was a single compound.

Anal. Calcd. for $C_{13}H_{12}S$: C, 77.95; H, 6.04; S, 16.01. Found: C, 78.25; H, 6.14; S, 15.99.

Compound X (4.44 g., 0.011 mole) and iodine (2.82 g., 0.022 g.-atom) in ethylene glycol dimethyl ether (400 ml.) were heated under reflux (90°) for 8.5 hr. After removing the bulk of the solvent by evaporation under reduced pressure, 250 ml. of water was added and the product was extracted with three 80-ml. portions of ether. After washing the combined extracts with dilute sodium bisulfite solution, then sodium bicarbonate solution, followed by water and drying, removal of the solvent and distillation of the residue under reduced pressure afforded 2.2 g. (50%) of XII as a liquid, b.p. 159–163° (0.4 mm.). The infrared spectrum of the distillate was identical with that of XII above.

The residue (1.45 g.) from the distillation, after chromatography on alumina, gave a white solid, m.p. 60.5–62.5° (0.62 g.) and m.m.p. 60.5–63.5° with starting material, m.p. 61.5–63.5°.

B. By Reduction of XI.—A modification of the Wolff–Kishner reduction used in the naphthiapyrone series was applied with success in the present case.[12] Compound XI (10.0 g.) and hydrazine hydrate (6.4 ml. of 85% aqueous solution) were heated together in diethylene glycol (65 ml., redistilled) under reflux for 1 hr. Water and excess hydrazine were then distilled until the temperature reached 195°, whereupon the solution was cooled to 110° and 8.9 g. of potassium hydroxide was added. The mixture began to boil of its own accord, and heating was resumed. When the temperature again reached 190°, refluxing was continued for 4 hr. On cooling, the liquid was poured into 250 ml. of water and extraction with four 70-ml. portions of ether followed by combination of the extracts, washing with water, drying (K_2CO_3), and removal of the ether gave 7.64 g. (82%) of a yellow oil which distilled under reduced pressure in the range of 132–138° (0.15 mm.).

The infrared spectrum (liquid film) was identical with the spectrum of XII (above). The product formed a picrate and, on oxidation, a sulfone identical with those described below prepared from the product of ring closure of the disulfide X.

Dihydronaphtho[1,2-*b*]-4H-thiapyran Picrate.—Treatment of XII with an excess of a saturated ethanolic solution of picric acid gave a picrate which crystallized from ethanol as dark red needles, m.p. 128.5–130°.

Anal. Calcd. for $C_{19}H_{15}N_3O_7S$: C, 53.14; H, 3.52. Found: C, 53.52; H, 3.29.

Dihydronaphtho[1,2-*b*]-4H-thiapyran 1,1-Dioxide.—A solution of 0.3 g. of XII in 4 ml. of glacial acetic acid was treated with 1.5 ml. of 30% hydrogen peroxide and heated for 2 hr. on a steam bath. The cooled solution was poured onto ice (30 g.) and the product was collected by filtration, washed with water, and crystallized from methanol. Recrystallization yielded 0.15 g. of light yellow plates, m.p. 164.5–166.5°; ν_{max}^{KBr} 1112 (s) and 1277 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21; S, 13.80. Found: C, 67.59; H, 4.89; S, 13.74.

(33) Using an F and M Scientific Corp. Model 500 gas chromatograph.

Organic Disulfides and Related Substances. XI. Bisalkylidene, -alkylene, and -arylene Disulfides Containing 2-Aminoethyl Moieties[1]

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Syntheses and thermal stabilities in solution are reported for a number of bisdisulfides of the general formula RSSR′SSR, where R is a 2-aminoethyl moiety. Syntheses involved reaction of appropriate thiolsulfonates with alicyclic 1,1-dithiols, aromatic and aliphatic 1,2-dithiols, and aliphatic 1,4-dithiols. 1,1-Bisdisulfides are the least stable thermally of the series of bisdisulfides studied; *the cyclohexylidene bisdisulfide is remarkably less stable than its cyclopentylidene counterpart.* Aromatic 1,2-bisdisulfides are less stable than 1,2- and 1,4-aliphatic bisdisulfides; the latter gave 1,2-dithiacyclohexane in good yield upon decomposition. Typical free bases are much less stable than hydrochloride salts and typical amides are more stable.

An earlier paper[2] described syntheses of some unsymmetrical disulfides by reaction of thiosulfonates with thiols according to the previously reported but little used reaction,[3] $RSO_2SR + R'SH \rightarrow RSSR' + RSO_2H$. This paper reports extension of this method to the synthesis of bisdisulfides by reaction of 2-aminoethyl 2-aminoethanethiolsulfonate dihydrochloride (1) or 2-acetamidoethyl 2-acetamidoethanethiolsulfonate (2) with alicyclic 1,1-dithiols, aliphatic 1,4- and 1,2-di-

(1) (a) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030. We are indebted to Drs. T. R. Sweeney and D. P. Jacobus of the Walter Reed Army Institute of Research, Washington, D. C., for certain materials and for evaluation of protection by products against lethal effects of radiation, which is now in progress. (b) Paper X: L. Field, T. F. Parsons, and R. R. Crenshaw, *J. Org. Chem.*, **29**, 918 (1964).

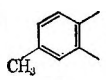
(2) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961).

(3) *Cf.* A. Schöberl and A. Wagner, "Methoden der Organischen Chemie" (Houben-Weyl), Vol. 9, E. Müller, Ed., 4th Ed., Georg Thieme Verlag, Stuttgart, 1955, p. 72.

thiols, and aromatic 1,2-dithiols, as outlined in the following equation.

$$2RSO_2R + R'(SH)_2 \longrightarrow 2RSO_2H + RSSR'SSR$$

1 and 2 — 3–10

1, R = $Cl^-H_3N^+(CH_2)_2$
2, R = $AcNH(CH_2)_2$
3, R′ =  ; R = $AcNH(CH_2)_2$
4, R′ =  ; R = $AcNH(CH_2)_2$
5, R′ = $-(CH_2)_4-$; R = $Cl^-H_3N^+(CH_2)_2$
6, R′ = $-(CH_2)_4-$; R = $AcNH(CH_2)_2$
7, R′ = $-(CH_2)_2-$; R = $Cl^-H_3N^+(CH_2)_2$
8, R′ = $-(CH_2)_2-$; R = $AcNH(CH_2)_2$
9, R′ =  ; R = $Cl^-H_3N^+(CH_2)_2$
10, R′ =  ; R = $Cl^-H_3N^+(CH_2)_2$

Bisdisulfides represent, to the best of our knowledge, a class of compounds to which virtually no attention has been given, and the method of synthesis used appears to be a most convenient one. A further basis for interest in bisdisulfides is that 2-aminoethyl disulfide (cystamine) dihydrochloride is an effective antiradiation drug,[4] and it seemed that bisdisulfides containing 2-aminoethyl moieties also might show useful activity.

Reaction procedures were similar to those previously described,[2] as were isolation methods except for the aromatic bisdisulfide dihydrochlorides **9** and **10**. With **9** and **10**, the corresponding free bases apparently were too unstable to permit isolation in the usual way by rendering the reaction mixtures basic, extracting into solvents, and reconverting to salts; so the hydrochlorides were isolated by somewhat tedious crystallization procedures directly from the acidic reaction mixtures. The 1,1-bisdisulfide salts corresponding to the alicyclic 1,1-dithiols apparently were even less stable and could not be isolated at all, although the corresponding amides could be. Consistent with these observations, disproportionation experiments discussed later showed the N-acetyl 1,1-bisdisulfides **3** and **4** to be the least stable disulfides encountered in this series, followed closely by the aromatic *o*-bisdisulfide salts **9** and **10**.

Yields of the alicyclic 1,1 compounds **3** and **4** were 99 and 59%. Yields of the aliphatic 1,2- and 1,4-bisdisulfides **5**–**8** ranged from 76 to 93%, and of the aromatic salts **9** and **10** from 38 to 49%, because of the solubility properties, tedious isolation procedures, and low stability of **9** and **10**.

Disproportionation of unsymmetrical disulfides follows the equation, $2RSSR' \rightarrow RSSR + R'SSR'$. The study of thermal disproportionation in ordinary light was desirable to permit correlating structure and stability under usual laboratory conditions, as a matter of practical interest. Furthermore, if correlation of stability with protective activity were possible it should permit design of more effective antiradiation drugs. For our bisdisulfides, one product would be expected to be polymeric, cyclic, or unstable. Examples of all three types were found.

Disproportionations were effected by heating the disulfides in water, ethanol, or mixtures of the two (depending on solubility) for 25 min. to 72 hr. (depending on stability). The extent of disproportionation was difficult to estimate but could be obtained reasonably well by separating starting material and products in various ways. Thus disproportionation of the *gem*-bisdisulfide amides **3** and **4** produces acetylcystamine (water soluble), volatile products (hydrogen sulfide and a ketone), and elemental sulfur. The tetramethylene bis compounds, **5** and **6**, gave 1,2-dithiacyclohexane, readily separable by volatilization in steam or extraction. The aliphatic and aromatic 1,2-compounds **7**–**10** gave polymers, usually separable by filtration. Although the results are not highly accurate, they do suggest the relative ease of disproportionation. Details are summarized in Table I.

The *gem*-bisdisulfides **3** and **4** are the least stable aminoethyl mixed disulfides we have encountered. Both were completely destroyed in alcohol–water at 100° in 25 min. They gave acetylcystamine almost quantitatively and hydrogen sulfide, sulfur, and the corresponding ketone in yields indicating formation of 1 mole each per mole of starting material. The solution of the cyclohexyl compound **3** became turbid almost immediately at 100°, as did the cyclopentyl compound **4** after 4–5 min.; the cyclohexyl compound thus is the less stable. In alcohol, **3** disproportionated completely in 3 hr. at 100°, while **4** was recovered quantitatively (Table I). These results present two notable features. First, the effect of water is marked in the 1,1-bis compounds, and is not paralleled by at least one other bisdisulfide (**5**), which seems to be equally stable in alcohol and water. The change may result from a change in solvent properties, such as dielectric constant, or from change in the mode of disproportionation in alcohol to hydrolytic attack of water at the *gem*-disubstituted carbon atom. The products seem to be the same in either solvent; no evidence for separate existence of a dithiacyclopropane derivative was noted. Second, and more notable, is the marked difference in stability between **3** and **4** in alcohol. *This is a remarkable difference between identical side chains on a cyclohexane as opposed to a cyclopentane ring system.* It may well have valuable diagnostic applications and be worth considerable further study.

The tetramethylene bisdisulfides **5** and **6** both gave 1,2-dithiacyclohexane. Difficulty anticipated in obtaining this compound, in view of its reported properties,[5] did not materialize. The lack of polymerization encountered suggests that thermal disproportionation may be a good general method for preparation of 1,2-dithiacycloalkanes of suitable ring size.

Table I shows that the 1,4-alkylene bisdisulfides **5** and **6** are roughly comparable in stability with their 1,2-alkylene counterparts (**7** and **8**). The hydrochlorides **5** and **7** are rather less stable than the corresponding amides **6** and **8**, however, although these differences may result partly from necessary differences in the solvents used to effect homogeneous solutions. The bisaliphatic disulfides **5**–**8** were much more stable than the 1,2-phenylene or the 1,1-cycloalkylidene compounds but apparently less stable than the previously reported simple disulfide, 2-(*t*-butyldithio)ethylamine hydrochloride.[2]

(4) J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962, pp. 33, 34, 55, and 65.

(5) A. Schöberl and H. Gräfje, *Ann.*, **614**, 79 (1958).

TABLE I

DISPROPORTIONATION OF BISDISULFIDES

Disulfide	Solvent	Temp., °C	Time	% of 1 mole per mole of original disulfide: Starting material recovered	Acetylcystamine (A) or cystamine hydrochloride (B)	Dithiacyclohexane (C), polymer (D),[a] or H_2S (E)	Disproportionation, %[b]
3	95% EtOH	100	25 min.	~100	0 (A)	<1 (E)	0
3	95% EtOH	100	45 min.	37	50 (A)	22 (E)	50–63
3	95% EtOH	100	90 min.	10	78 (A)	46 (E)	78–90
3	95% EtOH	100	3 hr.	0	~100 (A)		~100
3	35% EtOH	100	25 min.	0	~100 (A)	73 (E)[c]	~100
4	95% EtOH	100	3 hr.	~100	0 (A)	0 (E)	0
4	35% EtOH	100	25 min.	0	~100 (A)	60 (E)[c]	~100
4	35% EtOH	100	100 min.	0	~100 (A)	75 (E)	~100
5 (free base)	35% EtOH	30	13 days	0		92 (C)	>92
5	35% EtOH	30	13 days	100	0 (B)	0 (C)	0
5	1 *M* HCl	30	13 days	100	0 (B)	0 (C)	0
5 (free base)	Water	100	25 min.	<10	60 (B)	>50 (C)	60–90
5	Water	100	25 min.			0 (C)	0
5	Water	100	3 hr.	57		17 (C)	17–43
5	95% EtOH	100	3 hr.	65		19 (C)	19–35
5	1 *M* HCl	100	3 hr.	<10		75 (C)	75–90
5	Water	100	22 hr.	30		57 (C)	57–70
5	Water	100	72 hr.			80 (C)	>80
6	Abs. EtOH	100	3 hr.	77			<23
6	Abs. EtOH	100	22 hr.	62			<38
6	Abs. EtOH	100	72 hr.			20 (C)	>20
7	Water	100	3 hr.	50		21 (D)	21–50
7	Water	100	22 hr.	28		43 (D)	43–72
8	Abs. EtOH	100	3 hr.	81		0 (D)	<19
8	Abs. EtOH	100	22 hr.	66		0 (D)	<34
9	Water	100	3 hr.	0		58 (91)[d] (D)	58–91
9	Water	100	22 hr.	0	96 (B)	95 (D)	95–96
10	Water	100	3 hr.	0		100[c] (D)	~100
10	Water	100	22 hr.	0	100 (B)	100 (D)	~100

[a] Values express the percent of 1 *M* proportion of monomeric repeating unit ($CH_3C_6H_3S_2$, $C_6H_4S_2$, or $C_2H_4S_2$) isolated as polymer from 1 *M* proportion of original disulfide. [b] Based on amounts of starting material recovered and products obtained, as recorded in columns 5–7. [c] In these experiments, cyclohexanone (40%) and cyclopentanone (35%) from **3** and **4**, respectively, were isolated as 2,4-dinitrophenylhydrazones by treatment of the cold-trap contents, after evaporation, with 2,4-dinitrophenylhydrazine. A gummy yellow solid residue of impure sulfur adhered to the sides of the ampoules; crude yield ~100% of 1 mole per mole starting material in each case; vacuum sublimation gave pure sulfur, m.p. 118–119°. [d] Figure in parentheses includes semipolymeric colloidal material which probably contained aminoethyl groups. [e] No polymer precipitated; 100 represents colloidal material separated by filtration through Celite.

Disproportionation of the salt **5** was the same in water as in alcohol, but was much greater when the salt was converted to the free base by reaction with 2 moles of alkali or when the salt **5** was heated in 1 *M* hydrochloric acid instead of water. Ultraviolet irradiation of an aqueous solution of **5** caused extensive disproportionation but gave no dithiacyclohexane.

The 1,2-bisalkylene and -arylene mixed disulfides **7**–**10** all gave polymers when heated in solution. The polymers seem to age on prolonged heating, and in most cases can then be separated from the mother liquor by filtration (through Celite) and so estimated. Cystamine hydrochloride was obtained as the second product after the complete disproportionation of the salts **9** and **10**. The arylene compounds **9** and **10** disproportionate rather readily, and are comparable with the analogous compound 2-(*p*-tolyldithio)ethylamine hydrochloride.[2] However, the free bases seem to be less stable, since **9** and **10** could not be isolated after rendering reaction mixtures containing them basic although this procedure was moderately satisfactory with the 2-(*p*-tolyldithio) compound.

Unavoidable experimental differences make comparison of stabilities of aminodisulfides difficult and uncertain. The results of Table I, taken in conjunction with previous work[2] and preparative experience, nevertheless suggest that when hot solutions are used in ambient light the trends of increasing stability will be about as follows: (a) free bases << hydrochlorides < amides; (b) 1,1-bisdisulfides (**3** and **4**, even though amides) < aromatic 1,2-bisdisulfide hydrochlorides (**9** and **10**) ≳ 2-(*p*-tolyldithio)ethylamine hydrochloride[2] < 1,4- or 1,2-aliphatic bisdisulfide hydrochlorides (**5** and **7**) < 1,4- or 1,2-aliphatic bisdisulfide amides (**6** and **8**) ≳ 2-(*t*-butyldithio)ethylamine hydrochloride.[2] Efforts to develop theories which will link structure with stability toward disproportionation should be deferred until other correlations are available from work now in progress.

Experimental[6]

1,1-Bis(2-acetamidoethyldithio)cyclohexane (3).—1,1-Cyclohexanedithiol[7] (14.8 g., 0.1 mole) in methanol (100 ml.) was added to a stirred solution of 2-acetamidoethyl 2-acetamidoethanethiolsulfonate (**2**, 53.6 g., 0.2 mole)[2] in water (100 ml.)–methanol (200 ml.). After 2 hr., the solution was evaporated (25°) to a solid which was broken up with cold water (500 ml.) and isolated by filtration. Crystallization (aqueous acetone)

(6) Melting points are corrected unless otherwise specified. Analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Evaporation of solvents for isolation of products was effected under reduced pressure, usually with a rotary evaporator.

(7) J. Jentzsch, J. Fabian, and R. Mayer, *Chem. Ber.*, **95**, 1764 (1962).

gave 28.2 g. (74%) of **3** and evaporation of the mother liquor followed by crystallization from aqueous 2-propanol gave a further 9.8 g. (25%) of equally pure material, m.p. 108.5–109°, unaffected by further recrystallization. Aqueous 2-propanol is the preferred solvent.

Anal. Calcd. for $C_{14}H_{26}N_2O_2S_4$: C, 43.94; H, 6.85; N, 7.32; S, 33.52. Found: C, 43.96; H, 6.78; N, 7.23; S, 33.32.

1,1-Bis-2-(acetamidoethyldithio)cyclopentane (4).—The disulfide **4** preparation was exactly as for the cyclohexyl compound from cyclopentanedithiol[7] (4.08 g., 0.03 mole) and the thiolsulfonate **2** (16.08 g., 0.06 mole). The crude product (9.6 g., 87%, m.p. 102–103°) recrystallized from acetone gave pure **4** (6.5 g., 59%), m.p. 108–108.5°.

Anal. Calcd. for $C_{13}H_{24}N_2O_2S_4$: C, 42.36; H, 6.58; N, 7.60; S, 34.80. Found: C, 42.50; H, 6.35; N, 7.40; S, 34.96.

1,4-Bis(2-aminoethyldithio)butane Dihydrochloride (5).—1,4-Butanedithiol (15.25 g., 0.125 mole) in 35 ml. of alcohol was added to the thiolsulfonate **1** (64.25 g., 0.250 mole)[2] in 72 ml. of water with stirring. Stirring was continued for 2 hr., 50 ml. of alcohol being added to improve stirring. The solution was chilled, and the crude product collected, washed twice with absolute alcohol, and dried under vacuum, giving, 36.5 g. (fraction I), m.p. 187° dec. (Kofler). After filtration, 1.1 g. of taurine precipitated from the mother liquor. The mother liquor was evaporated to dryness, the residue taken up with water, and unchanged thiol removed by extraction with ether. The solution then was made alkaline with potassium hydroxide (16 g.) in ice–water in the presence of cold chloroform. Three chloroform extractions were made as quickly as possible. The combined chloroform extracts, after one washing with water, were immediately extracted with 10–12 ml. of 12 *N* hydrochloric acid diluted with water. Evaporation of the acid solution gave 3.5 g. (fraction II) of crystalline product, m.p. 192° dec. Fractions I and II were united and recrystallized from 2.6 l. of 85% acetone–15% water; undissolved taurine (melting point and infrared spectrum) was separated, amounting to 3.1 g. After 24 hr. at 5°, 25.9 g. of disulfide **5** with m.p. 198° dec. was collected. The mother liquor after concentration to 300 ml. and treatment as above (addition of base, extraction, etc.) yielded another crop (6.9 g.) of pure disulfide **5**, m.p. 198° dec. The total yield of recrystallized **5** was 32.8 g. (76%), and **5** was slightly hygroscopic; further recrystallization from aqueous acetone (as above) gave **5** with constant m.p. 197.5–198° dec.

Anal. Calcd. for $C_8H_{22}Cl_2N_2S_4$: C, 27.82; H, 6.42; N, 8.11; S, 37.12. Found: C, 28.00; H, 6.33; N, 7.99; S, 36.92.

1,4-Bis(2-acetamidoethyldithio)butane (6).—1,4-Dimercaptobutane (1.22 g., 0.01 mole) in 3 ml. of alcohol was poured into a solution of thiolsulfonate **2** (5.36 g., 0.02 mole) in 6 ml. of water with vigorous stirring. Two milliliters of alcohol was added to clarify the reaction mixture. Several minutes after the addition of thiol, a precipitate of disulfide **6** separated which was collected by filtration after 2 hr. of continued stirring (2.6 g.). Cooling and standing overnight resulted in a second crop of 0.9 g. The mother liquor on evaporation to thick sirup and addition of 10–15 ml. of water afforded a third crop of 100 mg. The three crops, containing acetyltaurine, were combined and recrystallized from ethyl acetate to constant melting point. There was obtained 2.70 g. (76%) of pure disulfide **6**, m.p. 83–84°.

Anal. Calcd. for $C_{12}H_{24}N_2O_2S_4$: C, 40.42; H, 6.78; N, 7.86. Found: C, 40.67; H, 6.81; N, 7.74.

1,2-Bis(2-aminoethyldithio)ethane Dihydrochloride (7).—1,2-Ethanedithiol (2.35 g., 0.025 mole) in 7 ml. of alcohol was added to the thiolsulfonate **1** (12.85 g., 0.05 mole) in 15 ml. of water with stirring. A precipitate soon separated; stirring, which was continued for 4 hr., was improved by addition of 5 ml. of alcohol. The precipitate (7.3 g.) was collected and washed with alcohol. Treatment of the mother liquor in the manner used for **5** gave only 0.1 g. more of crude disulfide **7**; the total yield of **7** was 7.4 g. (93%), m.p. 188–190°. After recrystallization to constant melting point from acetone–water (7:3), then from 95% alcohol, the melting point was 203–204° dec. During the recrystallization from alcohol, about one-tenth of the material each time was left behind (taurine).

Anal. Calcd. for $C_6H_{18}Cl_2N_2S_4$: C, 22.70; H, 5.72; N, 8.83; S, 40.41. Found: C, 22.34; H, 5.62; N, 9.16; S, 40.12.

3,4-Bis(2-aminoethyldithio)toluene Dihydrochloride (9).—The attempted synthesis of disulfide **9** by the procedure used for preparing 2-(*p*-tolyldithio)ethylamine hydrochloride[2] was unsuccessful because the free base disproportionated completely during chloroform extraction to give gummy polymer, even when the extraction was completed in seconds. The only pure product isolated was cystamine dihydrochloride. The purification procedure therefore was modified.

Toluene-3,4-dithiol (5 g., 0.032 mole) in 65 ml. of alcohol was added to the thiosulfonate **1** (16.5 g., 0.064 mole) in 38 ml. of water with stirring. The reaction flask was screened from light and stirring was continued for 4 hr. Taurine which precipitated (5 g.) was removed by filtration, and the turbid solution was clarified by filtration through Celite and Darco. The resulting clear solution on standing in normal laboratory light became turbid again in about half an hour. Water was completely evaporated and the waxy residue was rubbed several times with absolute alcohol to remove hypotaurine. Insoluble solid was dissolved in about 20 ml. of water. The resulting solution was filtered through Celite–Darco and after evaporation to 5 ml. and storage at 5° for 15 hr. yielded 65 mg. of taurine. Addition of absolute ethanol (50 ml.) caused crystallization of more taurine (580 mg.) which was separated after chilling for a few hours. The filtered solution on further addition of alcohol and chilling did not yield further precipitate. Upon complete evaporation of the solvent, there was obtained crystalline **9** having m.p. 170–172° dec., yield 1.6 g. (13%). The material was not recrystallized because of the likelihood of disproportionation.

Anal. Calcd. for $C_{11}H_{20}Cl_2N_2S_4$: C, 34.82; H, 5.31; N, 7.38; S, 33.80. Found: C, 34.80; H, 5.42; N, 7.26; S, 33.57.

Preparation on a larger scale (from 10 g. of dithiol) by essentially the same procedure afforded disulfide **9** in 38% yield, m.p. 174–174.5° dec.

1,2-Bis(2-aminoethyldithio)benzene Dihydrochloride (10).—A solution of 3.55 g. (25.0 mmoles) of 1,2-dimercaptobenzene[8] in 45 ml. of alcohol was added with stirring to a solution of 12.8 g. (50 mmoles) of thiolsulfonate **1** in 27 ml. of water. A few chips of Dry Ice were added in order to remove air from the reaction vessel. After addition was complete, cooling with ice–water for 5 min. resulted in a bulky precipitate. Stirring was continued after addition of 10 ml. of alcohol and removal of the ice bath. After 3 hr., the reaction mixture was chilled again and 4.80 g. of crystalline material was collected by filtration, m.p. 173–175° (Kofler) (fraction I). This proved to be disulfide **10** contaminated with about 15% of taurine (amount estimated from elemental analysis). After two recrystallizations from 95% ethanol, with removal of the nearly insoluble taurine, 3.70 g. (41%) of crystalline disulfide **10** was obtained having m.p. 189–190° dec.

Anal. Calcd. for $C_{10}H_{18}Cl_2N_2S_4$: C, 32.87; H, 4.96; N, 7.67. Found: C, 32.79; H, 4.85; N, 7.74.

The mother liquor of fraction I after filtration was quickly evaporated to dryness, and the waxy residue thoroughly dried over phosphorus pentoxide. The resulting hard solid was triturated with five 40-ml. portions of absolute ethanol. Insoluble material was dissolved in 10 ml. of water; the solution was clarified by filtration through Celite, then concentrated to 5 ml., and chilled. After 3 hr., there was collected 661 mg. of a mixture of disulfide and unchanged thiosulfonate **1** (fraction II). By addition of 30 ml. of absolute ethanol to the mother liquor and chilling, 613 mg. of a mixture was obtained of disulfide, taurine, and thiolsulfonate **1** (fraction III). The mother liquor after addition of 30 ml. more of absolute ethanol and standing overnight at 5° yielded 159 mg. of disulfide **10** plus thiolsulfonate **1** (fraction IV). A similar mixture (899 mg., fraction V, was obtained by complete evaporation of solvent. Fractions II and V were combined and recrystallized from 100 ml. of hot ethanol. Taurine (190 mg.) was left undissolved. Thiolsulfonate **1** (448 mg.) precipitated overnight at 5°. Upon concentration of the solution to 20 ml., 405 mg. of pure **10** was obtained, m.p. 189–190° dec., and 368 mg. more, m.p. 178–180° dec., on cooling at 5°. These two crops showed identical infrared spectra; the total yield of disulfide was 4.47 g. (49%).

1,2-Dithiacyclohexane by Disproportionation of 5 and 6.—Disulfide **5** (3.45 g., 0.010 mole) was suspended in 15 ml. of water and heated in a round-bottomed flask at reflux temperature; the disulfide dissolved completely in the hot solution. After 4 hr. of heating, crystalline 1,2-dithiacyclohexane commenced to collect at the bottom of the ice–water cooled condenser. Heating

(8) A. Ferretti, *Org. Syn.*, **42**, 54 (1962).

was prolonged for 72 hr. but was discontinued for a few minutes every 4–8 hr. to permit removal of the cyclic disulfide. After 72-hr. heating, the amount of steam-distilled product that could still be collected was of the order of a few milligrams after several hours. The total amount of cyclic disulfide obtained was 963 mg. (80%) after drying. The product after sublimation (bath temperature 40° at 16–20 mm.) had m.p. 31–31.5°, lit.[5] m.p. 30.8–31.5°.

Anal. Calcd. for $C_4H_8S_2$: C, 39.96; H, 6.70; S, 53.34. Found: C, 39.84; H, 6.53; S, 53.24.

1,2-Dithiacyclohexane from disulfide 6 was obtained by the same procedure except that the system was heterogeneous throughout.

Disproportionation Procedures.—Solutions of 1 mmole of disulfide in 10 ml. of solvent were sealed in ampoules, dropped into a boiling water bath for the selected time, and then cooled as rapidly as possible in ice. Experiments in which 1,2-dithiacyclohexane was isolated by steam volatilization were carried out in flasks connected to condensers cooled with ice. Compounds formed or left unchanged routinely were characterized by melting point and mixture melting point and/or by the infrared spectrum.

Special modifications were the following.

A. 1,1-Biscycloalkylidene Disulfides 3 and 4.—After the heating period, ampoules were throughly cooled in Dry Ice, opened, quickly connected to an apparatus such that hydrogen sulfide could be flushed out with a slow stream of nitrogen into buffered (acetate) lead nitrate solution, and then allowed to warm to room temperature. Lead sulfide was collected and weighed. Ampoule contents were washed out and evaporated, solvent and volatiles being collected in a Dry Ice trap. Ketones were isolated from the trap contents as 2,4-dinitrophenylhydrazones. Acetylcystamine was extracted from the evaporation residues with ice cold water and was recrystallized from chloroform–ether. Unchanged starting materials were extracted with 2:3 alcohol–water mixture and crystallized by chilling. Sulfur was detected in the residues by insolubility in solvents other than carbon disulfide and was separated by vacuum sublimation.

B. Tetramethylene Bisdisulfides 5 and 6.—1,2-Dithiacyclohexane crystallized readily on ice cooling of the ampoules. It was isolated by filtration using a chilled funnel or better, with the salt 5, by extraction into methylene chloride; despite the volatility of the dithiacyclohexane, it could be recovered and weighed reasonably satisfactorily by careful rapid evaporation of the dried extract. Evaporation of the aqueous layer or filtrate and consistency of the weight loss were used in several instances to substantiate the weight of dithiacyclohexane and thus provide assurance that only negligible amounts had escaped isolation. Water-soluble acetylcystamine was readily separated from insoluble 6. Cystamine hydrochloride is readily soluble in ice-cold 2 *M* hydrochloric acid, but unchanged 5 is very slightly soluble, though soluble in water, thus permitting easy separation of these residues.

C. 1,2-Bisalkylene and -arylene Disulfides 7, 8, 9, and 10.—Disulfide 8 was reported previously.[2] Polymers which separated were removed by filtration using preweighed Celite and were estimated by drying to constant weight. Soluble products and unchanged starting materials were separated by solubility relationships obviously similar to those previously described and were recrystallized to purity.

Disproportionation of Disulfide 9 at Room Temperature.—The following experiment provides information on the speed at which disproportionation of this disulfide proceeds at room temperature in ordinary laboratory light. The disulfide 9 (379 mg.) was dissolved in 8 ml. of water and the solution was left to stand. Colloidal material separated slowly, and was removed repeatedly by filtration using preweighed Celite, which then was weighed after drying to constant weight. The total cumulative amount of colloidal polymer removed (in milligrams), and its per cent of total polymer theoretically possible were the following (after the number of days shown in parentheses): 59, 38 (7); 89, 58 (14); 119, 77 (21); 139, 90 (28), 152, 99 (37); 160, 104 (45).

Disproportionation of the Free Base of Disulfide 5 at Room Temperature.—Three portions, each 0.1725 g. (0.5 mmole), of 5 were dissolved in (a) 4 ml. of water plus 1.0 ml. of 1 *M* aqueous sodium hydroxide, (b) 5 ml. of water, and (c) 5 ml. of 1 *M* hydrochloric acid. An oil rapidly separated from (a). After 13 days (a) was acidified with 2 ml. of 1 *M* hydrochloric acid; (b) and (c) were clear but (a) contained an oil which crystallized on ice cooling. All three were extracted with methylene chloride; the extracts were dried ($MgSO_4$) and evaporated. (b) and (c) gave no residue but (a) gave 55 mg. (theoretical 60 mg.). Residues on evaporation of the aqueous layers were (b) 0.173 g., (c) 0.171 g., and (a) 0.168 g.; the former two corresponded to no disproportionation and the last (allowing for 58.5 mg. of sodium chloride) to complete disproportionation.

The Preparation of Heterocyclic Organophosphorus Compounds by Cyclodehydrohalogenation[1]

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5-Chlorodibenzophosphole and 10-chlorophenoxaphosphine have been prepared in 6 and 24% yields, respectively, by dehydrohalogenation of 2-biphenylyl- and 2-phenoxyphenylphosphonous dichlorides. The phosphonous dichlorides were not isolated but underwent cyclization during the manipulations incident to their attempted isolation. 2-Benzylphenylphosphonous dichloride, however, could be isolated. It underwent cyclodehydrohalogenation to yield 5-chloro-5,10-dihydrodibenz[*b,e*]phosphorin when heated with anhydrous zinc chloride. The hydrolysis and oxidation of all three cyclic chlorophosphines yielded the corresponding cyclic phosphinic acids.

One method for preparing heterocyclic arsenic and antimony compounds is by cyclodehydration of appropriately substituted arylarsonic or arylstibonic acids. Thus phenazarsinic acid (I)[2] is readily prepared by heating *o*-arsonodiphenylamine with hydrochloric acid.[3] Freedman and Doak, however, have found that both 2-biphenylylphosphonic acid and 2-phenoxyphenylphosphonic acid fail to undergo cyclodehydration under a variety of experimental conditions.[4,5] Similarly, Campbell and Way have reported the failure of 2-biphenylylphenylphosphinic acid to cyclize when heated with polyphosphoric or sulfuric acids.[6] They were successful, however, in cyclizing the acid by heating with phosphorus pentachloride and nitrobenzene. In

(1) Supported by Research Grant GM-09479 from the National Institutes of Health, U. S. Public Health Service.

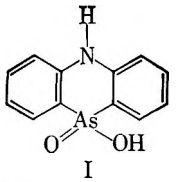
(2) In our previous papers on heterocyclic phosphorus compounds, we have employed the nomenclature of F. G. Mann, "The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, Bismuth, and Silicon," Interscience Publishers, Inc., New York, N. Y., 1950. At the suggestion of a referee and of the editor we have used Ring Index nomenclature in the present paper.

(3) C. S. Gibson and J. D. A. Johnson, *J. Chem. Soc.*, 2499 (1927).

(4) This compound has previously been named phosphafluorinic acid; *cf.* L. D. Freedman and G. O. Doak, *J. Org. Chem.*, **21**, 238 (1956).

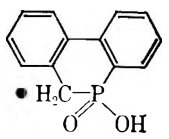
(5) L. D. Freedman, G. O. Doak, and J. R. Edmisten, *ibid.*, **26**, 284 (1961).

(6) I. G. M. Campbell and J. K. Way, *J. Chem. Soc.*, 2133 (1961).



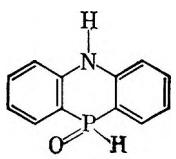
I

our laboratory this latter method has proved to be unsuccessful for the cyclization of several phosphonic acids. Lynch has recently obtained 5-hydroxy-5,6-dihydrodibenz[*b*,*d*]phosphorin 5-oxide (II) by the cyclodehydration of 2-phenylbenzylphosphonic acid.[7] In this case, however, the phosphono group was attached to a side chain rather than directly to the benzene ring.



II

There is considerable evidence that cyclodehydrohalogenation might prove to be a better means of effecting cyclization of phosphorus compounds. This method has been used successfully for obtaining heterocyclic arsenic compounds where cyclodehydration failed. Thus 10-chlorophenothiarsine was readily obtained by cyclization of 2-dichloroarsinophenyl phenyl sulfide although 2-arsonophenyl phenyl sulfide could not be cyclized.[8] Phosphorus trichloride has been condensed with diphenylamine to yield, after hydrolysis, 5,10-dihydrophenophosphazine 5-oxide (III).[9-11] The initial attack probably occurs by electrophilic attack

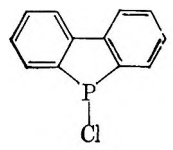


III

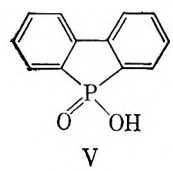
of phosphorus on a 2-position of a phenyl ring to form 2-dichlorophosphinodiphenylamine, which then loses hydrogen chloride to form the phosphazine. A similar mechanism very likely applies to the preparation of 2,8-dimethylphenoxaphosphinic acid through the condensation of phosphorus trichloride with *p*-tolyl ether.[5]

In the light of these considerations we have attempted the preparation of heterocyclic phosphorus compounds by cyclodehydrohalogenation of dichlorophosphines. In order to prepare the latter compounds we have used the excellent method recently introduced by Quin and Humphrey whereby the unisolated intermediate from the reaction of phosphorus trichloride and a diazonium salt is reduced with a metal.[12] Although Quin and Humphrey originally employed magnesium as the reducing agent, Quin[13] has informed us that aluminum is preferable for this purpose; in fact, Quin and Montgomery later employed aluminum for preparing diarylchlorophosphines.[14] For the preparation of the heterocyclic compounds described in the present paper we found that powdered aluminum was successful as a reducing agent, whereas in several attempts magnesium did not yield the desired compounds.

In the first reaction studied phosphorus trichloride was allowed to react with *o*-biphenyldiazonium fluoroborate, then the unisolated intermediate was reduced with powdered aluminum. Vacuum distillation of the reaction product, after removal of the solvent and lower boiling by-products, gave 5-chlorodibenzophosphole (IV) in 6% yield. This low yield was not unanticipated



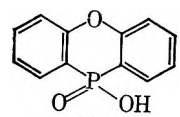
IV



V

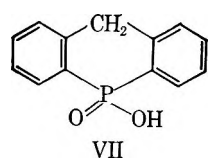
since it had previously been found that *o*-biphenylylphosphonic acid was obtained in only 9% yield from *o*-biphenyldiazonium fluoroborate and phosphorus trichloride.[15] This particular reaction was chosen, however, since the resulting 5-chlorodibenzophosphole, should be (and was) readily converted by hydrolysis and oxidation to the known 5-hydroxy-5H-dibenzophosphole 5-oxide[4] (V).

We have also prepared 10-chlorophenoxaphosphine in 24% yield starting with *o*-phenoxybenzenediazonium fluoroborate. Hydrolysis and oxidation yielded the previously unknown phenoxaphosphinic acid (VI).



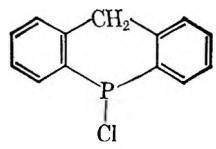
VI

In neither of the cases described above were we able to isolate the intermediate dichlorophosphines. These must have been formed but the high-temperature distillation, particularly in the presence of boron trifluoride and aluminum chloride, probably induced cyclodehydrohalogenation. Quite different results were obtained with *o*-benzylbenzenediazonium fluoroborate. Here we always obtained 2-dichlorophosphinodiphenylmethane as the principal phosphorus-containing product; in one case, however, a trace amount of 5-hydroxy-5,10-dihydrodibenz[*b*,*e*]phosphorin 5-oxide (VII) was isolated from the crude reaction mixture following hydrolysis and oxidation. The 2-dichlorophosphinodiphenylmethane was readily cyclized to the desired 5-chloro-5,10-dihydrodibenz[*b*,*e*]phosphorin (VIII) by heating with anhydrous zinc chloride. One attempt to bring about cyclization by heating the dichlorophos-



VII

(7) E. R. Lynch, *J. Chem. Soc.*, 3729 (1962).
(8) E. Roberts and E. E. Turner, *ibid.*, 1207 (1926).
(9) A. Michaelis and A. Schenk, *Ann.*, **260**, 1 (1890).
(10) P. G. Sergeev and D. C. Kudryashov, *Zh. Obshch. Khim.*, **8**, 266 (1938).
(11) M. Häring, *Helv. Chim. Acta*, **43**, 1826 (1960).
(12) L. D. Quin and J. S. Humphrey, Jr., *J. Am. Chem. Soc.*, **83**, 4124 (1961).
(13) Personal communication from Dr. Quin.
(14) L. D. Quin and R. E. Montgomery, *J. Org. Chem.*, **27**, 4120 (1962).
(15) H. H. Jaffé, L. D. Freedman, and G. O. Doak, *J. Am. Chem. Soc.*, **76**, 1548 (1954).



VIII

phine with anhydrous aluminum chloride was not successful. Hydrolysis and oxidation of VIII yielded the phosphinic acid, VII.

The failure of 2-dichlorophosphinodiphenylmethane to undergo cyclodehydrohalogenation as readily as did the two 2-dichlorophosphino compounds derived from phenyl ether and biphenyl is not unexpected. The cyclization (at least under Friedel–Crafts conditions) must involve an electrophilic attack of phosphorus on the 2-position of the neighboring ring.[16] This position will be activated more by a phenoxy group or by a phenyl group than by a benzyl group.

The ultraviolet absorption spectra of heterocyclic phosphinic acids has proved to be of value in establishing the structure for such compounds.[4,5,17] Table I lists the spectra of the three heterocyclic phosphinic acids described in the present paper together with the spectra of several closely related compounds. As indicated in the table, the spectra of phenoxaphosphinic acid and phenoxarsinic acid are virtually identical. The close resemblance of the spectra of the corresponding arsenic and phosphorus compounds has often been noted.[4,5,17–19] The spectrum of *o*-benzylphenylphosphonic acid is very similar to that of *o*-tolylphosphonic acid; the intensity of absorption of the benzyl compound is somewhat greater since it contains a second benzene ring. It is also seen that the spectrum of 5-hydroxy-5,10-dihydrodibenz[*b*,*e*]phosphorin 5-oxide is quite like the spectra of its nonheterocyclic analogs, *o*-benzylphenylphosphonic acid and diphenylphosphinic acid. This similarity is undoubtedly associated with the absence of appreciable resonance interaction between two benzene rings joined by either a methylene or a phosphinico (PO_2H) group.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA[a]

Compound	$\lambda_{max.}$, mμ	ϵ_{max}
Phenoxaphosphinic acid	215	33,900
	241	13,000
	275[b]	2,300
	287[b]	4,120
	294	5,180
Phenoxarsinic acid[c]	214	32,200
	241	12,100
	274	3,450
	288[b]	4,600
	293	5,050
5-Hydroxy-5,10-dihydrodibenz[*b*,*e*]phosphorin 5-oxide	205	36,600
	227[b]	9,180
	264[b]	1,260
	268.5	1,630
	275.5	1,610
o-Benzylphenylphosphonic acid	218[b]	15,200
	263[b]	1,020
	269	1,370
	275.5	1,260
Diphenylphosphinic acid[c]	224	14,700
	255[b]	693
	259	958
	264	1,180
	272	933
o-Tolylphosphonic acid	215	7,330
	262	443
	267.5	573
	275	464

[a] The spectra of all compounds were determined in 95% ethanol with a Perkin-Elmer Model 350 spectrophotometer. [b] Shoulder. [c] The spectrum of this compound has been determined previously with a Beckman DU spectrophotometer; *cf.* ref. 4 and 5.

(16) Similar conclusions were reached by E. Roberts and E. E. Turner [*J. Chem. Soc.*, **127**, 2004 (1925)] and by J. D. C. Mole and E. E. Turner [*ibid.*, 1720 (1939)].

(17) L. D. Freedman and G. O. Doak, *J. Org. Chem.*, **24**, 638 (1959).

Experimental[20,21]

5-Chlorodibenzophosphole.—A 3-l. three-necked flask was equipped with a reflux condenser and sealed stirrer. On top of the reflux condenser was placed a drying tube connected to a large rubber balloon which could be filled with dry nitrogen. The flask was dried by flaming and sweeping with dry nitrogen. *o*-Biphenyldiazonium fluoroborate (80.4 g., 0.3 mole), 41.2 g. of phosphorus trichloride (0.3 mole), 6 g. of cuprous bromide, and 300 ml. of ethyl acetate, previously dried over phosphorus pentoxide and distilled, were added to the flask and stirring was started. The evolution of nitrogen started immediately and was complete in about 20 min. Stirring was continued for 1 hr. longer; then 5.4 g. (0.2 mole) of powdered aluminum (Mallinckrodt) was added and the mixture was refluxed for 2 hr. The mixture was then stirred overnight at room temperature.

The contents of the flask were then transferred in portions to a 500-ml. distilling flask without exposure to the atmosphere. This was accomplished with two bent adapters. One adapter had a 75° angle, the other a 105° angle, and both possessed standard-taper joints at both ends. This system of adapters was connected between the reaction flask and the distilling flask. By swiveling this system it was possible to pour the contents into the distilling flask without admitting air. The balloon filled with nitrogen maintained a positive nitrogen pressure during these manipulations. The solvent, excess phosphorus trichloride, and other low-boiling material were stripped by distillation at reduced pressure (water aspirator). A drying tube between the aspirator and flask prevented ingress of moisture. The high-boiling material remaining in the flask was distilled at about 5 μ. The distillate was then fractionated through a 6-in. Vigreux column. The principal fraction (17.5 g.) proved to be a mixture of *o*-chlorobiphenyl and *o*-fluorobiphenyl (identified by their infrared spectra). The higher boiling fraction (3.8 g.), b.p. 146–148 (5 μ), which crystallized in the condenser and receiver, was obtained as yellow crystals, m.p. 55–56°, yield 5.8%.

Anal. Calcd. for $C_{12}H_8ClP$: C, 65.93; H, 3.59; P, 14.17. Found: C, 65.65; H, 3.69; P, 13.97.

5-Hydroxy-5H-dibenzophosphole 5-Oxide.—The oxidation of 0.52 g. of 5-chlorodibenzophosphole suspended in alkaline solution with 20 ml. of 30% hydrogen peroxide gave a 94% yield of the crude acid after acidification of the alkaline solution. After recrystallization from aqueous alcohol the compound proved to be identical (melting point and mixture melting point) with a sample of this compound prepared by a different method.[4]

10-Chlorophenoxaphosphine.—*o*-Aminophenyl phenyl ether was readily prepared by reduction of *o*-nitrophenyl phenyl ether (Eastman Kodak No. 3425) with Raney nickel and hydrogen at 50 lb. pressure. The yield of amine after recrystallization from aqueous alcohol was 96%, m.p. 46.5°. *o*-Phenoxybenzenedi-

(18) H. H. Jaffé, *J. Chem. Phys.*, **22**, 1430 (1954).

(19) L. D. Freedman, *J. Am. Chem. Soc.*, **77**, 6223 (1955).

(20) Melting points were determined on a Fisher-Johns apparatus with a thermometer calibrated against U. S. P. reference standards as previously described; *cf.* G. O. Doak and L. D. Freedman, *ibid.*, **73** 5658 (1951).

(21) Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken on a Perkin-Elmer Model 421 spectrophotometer.

azonium fluoroborate was readily prepared in 73% yield by diazotization in fluoroboric acid solution.

The reaction of this diazonium fluoroborate with phosphorus trichloride, reduction, and isolation of the 10-chlorophenoxaphosphine was carried out in the same manner as described above for 5-chlorodibenzophosphole. The reaction was run on a 0.5-mole scale; the yield of the yellow crystalline solid, m.p. 62–64°, was 28.2 g., 24%.

Anal. Calcd. for $C_{12}H_8ClOP$: C, 61.43; H, 3.44; P, 13.20. Found: C, 60.81; H, 3.51; P, 12.59.

Phenoxaphosphinic Acid.—The oxidation of 10-chlorophenoxaphosphine suspended in alkaline solution with 30% hydrogen peroxide gave, after acidification of the alkaline solution, the acid in 99% yield. It was recrystallized from alcohol, m.p. 231–234°.

Anal. Calcd. for $C_{12}H_9O_3P$: C, 62.08; H, 3.91. Found: C, 61.81; H, 3.84.

***o*-Benzylphenylphosphonous Dichloride.**—*o*-Aminodiphenylmethane[22] was converted to the diazonium fluoroborate in 83% yield by diazotization in fluoroboric acid. The reaction of this salt (113 g., 0.4 mole) with phosphorus trichloride and reduction with powdered aluminum was carried out as described above for 5-chlorodibenzophosphole. The high-boiling material that was obtained was finally fractionated through a 21-in. spinning band column. The yield of *o*-benzylphenylphosphonous dichloride was 6.9 g. (6.4%), b.p. 132–137° (0.2 mm.).

Anal. Calcd. for $C_{13}H_{11}Cl_2P$: Cl, 26.35; P, 11.51. Found: Cl, 26.10; P, 11.55.

5-Chloro-5,10-dihydrodibenz[*b*,*e*]phosphorin.—*o*-Benzylphenylphosphonous dichloride (2.04 g.) and 1.1 g. of anhydrous zinc chloride were heated together in a nitrogen atmosphere for 24 hr. The liquid was then distilled at 10 μ. The compound was obtained as yellow crystals, 25% yield, m.p. 78–86°.

Anal. Calcd. for $C_{13}H_{10}ClP$: C, 67.11; H, 4.33; P, 13.31. Found: C, 66.86; H, 4.59; P, 13.49.

5-Hydroxy-5,10-dihydrodibenz[*b*,*e*]phosphorin 5-Oxide.—5-Chloro-5,10-dihydrodibenz[*b*,*e*]phosphorin suspended in alkaline solution was oxidized with 30% hydrogen peroxide. The free acid was obtained in 81% yield when the alkaline solution was acidified. It decomposed on heating above 225°.

Anal. Calcd. for $C_{13}H_{11}O_2P$: C, 67.83; H, 4.82. Found: C, 67.51; H, 4.69.

***o*-Benzylphenylphosphonic Acid.**—*o*-Benzylphenylphosphonous dichloride was suspended in aqueous alkali and oxidized with 30% hydrogen peroxide. The acid was obtained in 92% yield by acidification of the alkaline solution. It was recrystallized from aqueous alcohol, m.p. 186–188°.

Anal. Calcd. for $C_{13}H_{13}O_3P$: C, 62.91; H, 5.28. Found: C, 62.70; H, 5.34.

(22) J. Collette, D. McGreer, R. Crawford, F. Chubb, and R. B. Sandin, *J. Am. Chem. Soc.*, **78**, 3819 (1956).

Reactions of Organometallics with Fluoroaromatic Compounds[1]

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Received October 7, 1963

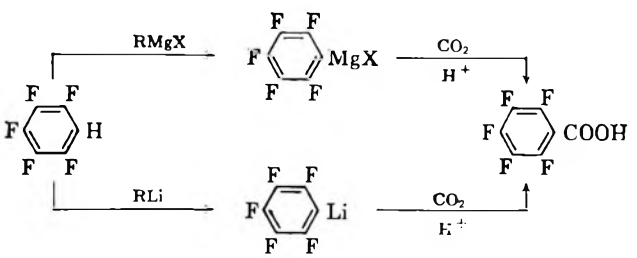
Nucleophilic displacement reactions of Grignard reagents on hexafluorobenzene in tetrahydrofuran have been studied. In general the reaction becomes more facile with the change from aryl to alkyl to allyl Grignard reagents. If the fluoroaromatic ring contains a hydrogen moiety, an acid–base reaction becomes predominant. This is true whether a Grignard or alkyllithium reagent is employed. In this manner mono- or di-Grignard and mono- or dilithio reagents of highly fluorinated benzene compounds have been prepared and converted to the corresponding acids by carbonation.

The nucleophilic substitution reactions of alkyl- and aryllithium reagents on fluoroaromatic compounds have been previously reported.[2] The reaction proceeds to give good yields of the desired alkyl fluoroaromatic compounds. Disubstitution is also possible with the second group substituting *para* to the original

$$RLi + C_6F_6 \longrightarrow RC_6F_5 + LiF$$

alkyl group. For Grignard reagents the published information is more limited. Thus, Pummer and Wall[3a] have reported that 2,3,4,5,6-pentafluorotoluene is formed in 3% yield by the reaction of methylmagnesium iodide with hexafluorobenzene. Harper and Tamborski[3b] have reported the preparation of 1,4-dibenzyl-2,3,5,6-tetrafluorobenzene in 54% yield by the reaction of benzylmagnesium chloride with hexafluorobenzene in tetrahydrofuran.

In addition to reporting further information on the substitution of Grignard reagents on hexafluorobenzene, we wish to report a new series of metalation reactions between organometallic reagents and hydrofluoroaromatic compounds. With hydrofluoroaromatics, the nucleophilic displacement of fluoride ion frequently becomes secondary to an acid–base type reaction as illustrated by the preceding equations.



Nucleophilic Displacement of Fluorine with Grignard Reagents.—The action of Grignard reagents on hexafluorobenzene in tetrahydrofuran have been studied. The reactivity of the Grignard reagents with hexafluorobenzene decreases in the following order: allyl or benzyl > alkyl > aryl. While allylmagnesium chloride reacts vigorously with hexafluorobenzene, the yield of allylpentafluorobenzene is only 26%, as a result of secondary side reactions. The reaction of benzylmagnesium chloride with hexafluorobenzene is similarly vigorous and yields 1,4-dibenzyltetrafluorobenzene in 54% yield. The reaction of 1 equiv. of ethylmagnesium bromide with hexafluorobenzene is moderate and gives ethylpentafluorobenzene in 37% yield. When the mole ratio of Grignard reagent to hexafluorobenzene is increased to 2:1, ethylpentafluorobenzene is produced in 62% yield. Based upon gas–liquid chroma-

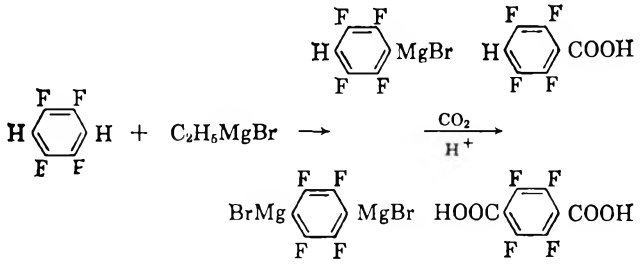
(1) This work was reported at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) (a) A. K. Barbour, M. W. Buxton, P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 808 (1961); (b) J. M. Birchall and R. N. Haszeldine, *ibid.*, 3719 (1961); (c) J. M. Birchall, T. Clarke, and R. N. Haszeldine, *ibid.*, 4977 (1962).

(3) (a) W. J. Pummer and L. A. Wall, *Science*, **127**, 643 (1958); (b) R. J. Harper and C. Tamborski, *Chem. Ind.* (London), 1824 (1962).

tography, the amount of disubstituted material produced is approximately 2%. A similar yield (2%) of dialkyl-substituted material is noted for the reaction of ethylmagnesium bromide with 2,3,4,5,6-pentafluorotoluene. These results suggest that the presence of an alkyl substituent hinders further substitution of fluorine by nucleophilic attack of the Grignard reagent. This result is consistent with the electron-donating effect of the alkyl groups. By contrast, 2,3,5,6-tetrafluoroxylene is produced in 85% yield from the reaction of methyllithium with 2,3,4,5,6-pentafluorotoluene.[2a] The reaction of phenylmagnesium bromide with hexafluorobenzene is most sluggish. There is no apparent reaction until the solution is heated to reflux. After a reflux period of 11 hr., 2,3,4,5,6-pentafluorobiphenyl in 17% yield and 1,4-diphenyl-2,3,5,6-tetrafluorobenzene in 3% yield are obtained.

Reaction of Hydrofluoroaromatic Compounds with Grignard Reagents.—Suitably activated protons in hydrofluoroaromatics may be metalated with Grignard reagents. Thus, if ethylmagnesium bromide is treated with pentafluorobenzene in tetrahydrofuran and the resultant mixture carbonated, pentafluorobenzoic acid is obtained in 85% yield. The same reaction using methylmagnesium iodide as the Grignard reagent gives pentafluorobenzoic acid in 56% yield. However, with isopropylmagnesium chloride as the Grignard reagent and with ether as the solvent, pentafluorobenzoic acid is produced in 25% yield. The reduced yield of acid in the last case probably reflects either poor metalation or incomplete carbonation of the resultant Grignard reagent in ether. Similarly, the reaction of ethylmagnesium bromide with 1,2,4,5-tetrafluorobenzene in a 3:1 mole ratio, followed by carbonation, gives 2,3,5,6-tetrafluorobenzoic acid in 29% yield and tetrafluoroterephthalic acid in 24% yield. The replacement of both hydrogens to give tetrafluoroterephthalic acid indicates that the acidity of both hydrogens in 1,2,4,5-tetrafluorobenzene are sufficiently active to react with the Grignard reagent. By contrast the treatment of 1,2,3,4-tetrafluorobenzene with ethylmagnesium bromide followed by carbonation gives none of the desired 2,3,4,5-tetrafluorobenzoic acid. This indicates that two *ortho* fluorines are required to permit metalation of tetrafluoroaromatic moieties to occur with Grignard reagents. Such is not the case when alkyllithium reagents are used for metalation as shall be shown subsequently.



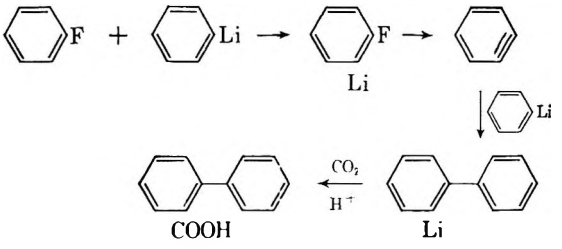
Similarly, very little metalation is observed in the reaction of ethylmagnesium bromide with 2,3,4,5,6-pentafluorotoluene. This indicates that the proton in pentafluorobenzene is more acidic than the protons in 2,3,4,5,6-pentafluorotoluene, which is the reverse of the hydrocarbon analogs. Thus, the inductive effect of the ring fluorines operates much more strongly on the ring proton than it does on the protons in the side chain of pentafluorotoluene.

The apparent change of pK_a values from benzene to pentafluorobenzene is quite significant. While benzene[4] has a pK_a value of ~50, Rochow[5] indicates that a pK_a value of 21 or less is required for substances to react with alkyl Grignard reagents. This indicates that the pK_a value of pentafluorobenzene is 21 or less and shows the marked increase in acidity from the introduction of the fluorine substituents in the ring.

Reaction of Hydrofluoroaromatic Compounds with Alkyllithiums.—Metalation is likewise observed when alkyllithium reagents are treated with hydrofluoroaromatics. The basic procedure employed in this study is that the organolithium and the fluoroaromatic are treated at −65° until Gilman color test IIA[6] indicates that the alkyllithium has been consumed. The reaction time varies from a few minutes to several hours depending upon the fluoroaromatic compound and the solvent system. At this point, the mixture is carbonated; the acid products are separated as usual.

The reaction of alkyllithium with pentafluorobenzene appears to go to completion in hexane–ether, ether, or ether–tetrahydrofuran since after carbonation crude pentafluorobenzoic acid is obtained in near quantitative yield. However, approximately 2-hr. reaction time is needed with hexane–ether as the solvent, whereas, in ether or ether–tetrahydrofuran, the reaction is complete in 5 min. The yield of pure pentafluorobenzoic acid varied between 67–83%, but the yield difference is believed due to the purification procedure employed rather than the reaction itself. No significant difference is noted whether the alkyllithium is added to the fluoroaromatic or whether inverse addition is used. It might also be noted that the perfluoroaryllithiums appear to carbonate readily in ether or tetrahydrofuran contrary to earlier published work.[7]

These results indicate that this synthesis of pentafluorophenyllithium is more facile than the earlier method reported by Coe, Stephens, and Tatlow,[7] in which metalation is accomplished by using pentafluorobromobenzene and either an alkyllithium or lithium amalgam. The metalation of a hydrogen *ortho* to a fluorine has a precedent in the classic work of Wittig, *et al.*,[8] as illustrated by the following reaction scheme.



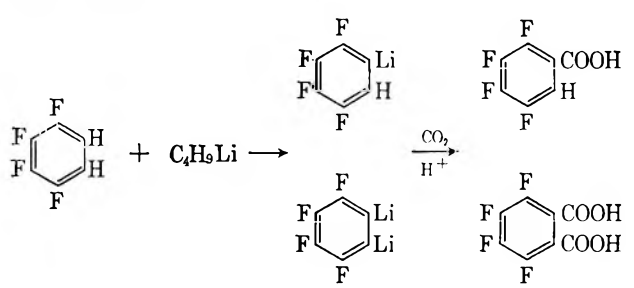
The principal difference from Wittig's work is that benzyne formation can be forestalled by maintaining the pentafluorophenyllithium at low temperatures (−50 to −65°). A similar procedure was employed by Gilman

(4) A. A. Morton, *Chem. Rev.*, **35**, 1, 1944.
(5) E. G. Rochow, D. T. Hurd, and R. N. Lewis, "The Chemistry of Organometallic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 93.
(6) H. Gilman and J. Swiss, *J. Am. Chem. Soc.*, **62**, 1847 (1940).
(7) P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 3227 (1962).
(8) G. Wittig, G. Pieper, and G. Fuhrmann, *Ber.*, **73**, 1193 (1940).

and Gorsich[9] in the preparation of 2-fluorobenzoic acid from 2-fluorophenyllithium. The work of Coe, Stephens, and Tatlow[7] does suggest, however, that the presence of a number of fluorine atoms in the ring renders the pentafluorophenyllithium more stable than the simpler 2-fluorophenyllithium. Thus, the aforementioned investigators[7] prepared pentafluorobenzaldehyde from pentafluorophenyllithium in 55% yield at 0°. Other workers[9,10] have found benzyne formation too pronounced with 2-fluorophenyllithium at this or lower temperatures (−25°) to permit the preparation of such nonbenzyne derivatives in good yields.

In the case of the reaction of an alkyllithium with 1,2,4,5-tetrafluorobenzene, the superiority of tetrahydrofuran over ether indicated previously in the literature[3b] is evident. Thus, if 2 equiv. of butyllithium are treated with 1,2,4,5-tetrafluorobenzene using tetrahydrofuran as the predominant solvent, after carbonation there is obtained tetrafluoroterephthalic acid in an 83% crude yield (68% pure) with only a 3% yield of 2,3,5,6-tetrafluorobenzoic acid. The same reaction with ether as the principal solvent gives tetrafluoroterephthalic acid in 38% yield and 2,3,5,6-tetrafluorobenzoic acid in 33% yield. By comparison, with the Grignard reagent, the yields of diacid and monoacid are 30 and 25%, respectively. That the presence of a monoorganometallic does not hinder formation of a second organometallic bond in the *para* position can be seen in the foregoing experiments. Further evidence of this effect is provided by the reaction of 1 equiv. of alkyllithium with 1,2,4,5-tetrafluorobenzene. After carbonation the monoacid, 2,3,5,6-tetrafluorobenzoic acid, is obtained in 66% yield and the disubstituted tetrafluoroterephthalic acid, is obtained in 16% yield.

The reaction of butyllithium with 1,2,3,4-tetrafluorobenzene is a case in which both the previously mentioned solvent effects and the greater metalating ability of the alkyllithium are shown. Thus, this reaction with tetrahydrofuran as the principal solvent gives 2,3,4,5-tetrafluorobenzoic acid in 36% yield and tetrafluoro-



phthalic acid in 9% yield. In addition, there are obtained neutral and acidic products containing alkyl groups, which indicate some alkylation is also occurring. By contrast in the same reaction with ether as the predominant solvent, the yield of diacid is less than 1%. Similarly, no metalation is observed with the Grignard reagent and 1,2,3,4-tetrafluorobenzene.

Experimental[11]

Ethyl-2,3,4,5,6-pentafluorobenzene.—Hexafluorobenzene (56.0 g., 0.30 mole) was added to ethylmagnesium bromide (0.62 mole) in 380 ml. of tetrahydrofuran. The reaction was mildly exothermic. At the end of 23 hr., titration indicated 0.24 mole of unchanged Grignard reagent. The reaction was hydrolyzed with 4 *N* hydrochloric acid. The organic phase was extracted with 4*N* hydrochloric acid and the aqueous phase was backextracted with pentane. The organic phases were combined, dried, and distilled through a 30-in. spinning band column. There was obtained 33.3 g. (56%) of ethyl-2,3,4,5,6-pentafluorobenzene, b.p. 130–132°. The vapor phase chromatograms of the other fractions indicated a total product yield of 36.5 g. (62%). The middle cut, b.p. 132°, $n^{23}D$ 1.4087, was submitted for analysis. Vapor phase chromatography of the other distillation cuts also indicated 8% hexafluorobenzene, 7% pentafluorobenzene, and 10% higher aromatics (2% maximum of diethyltetrafluorobenzene).

Anal. Calcd. for $C_8H_5F_5$: C, 48.98; H, 2.57; F, 48.43. Found: C, 48.95; H, 2.56; F, 48.70.

In a similar experiment, a 1.2:1 mole ratio of Grignard reagent to hexafluorobenzene gave ethyl-2,3,4,5,6-pentafluorobenzene in 37% yield.

Allyl-2,3,4,5,6-pentafluorobenzene.—Allylmagnesium chloride (0.31 mole, 210 ml. of a tetrahydrofuran solution) was added dropwise over a 2-hr. period to an ice–water cooled solution of hexafluorobenzene (55.8 g., 0.30 mole) in 85 ml. of tetrahydrofuran. The solution turned wine red immediately and the color gradually deepened. After the reaction was stirred for an additional hour, titration indicated 85% of the Grignard had been consumed. The ice-cooled reaction mixture was hydrolyzed with 300 ml. of 4 *N* hydrochloric acid. The aqueous layer was extracted with ether–pentane (80–20), the extract was combined with the organic fraction, and the dried mixture was fractionated through a 30-in. spinning band column. There was obtained 8.60 g. (14%) of allyl-2,3,4,5,6-pentafluorobenzene, b.p. 148–149°, $n^{23}D$ 1.4265. The vapor phase chromatograms of the other fractions indicated a total yield of 16.0 g. (26%) of allyl-2,3,4,5,6-pentafluorobenzene.

Anal. Calcd. for $C_9H_5F_5$: C, 51.92; H, 2.43; F, 45.63. Found: C, 51.93; H, 2.57; F, 45.38.

The F^{19} nuclear magnetic resonance of a solution in carbon tetrachloride showed a quartet centered at 66.7, a triplet centered at 80.1, and a multiplet centered at 85.6 p.p.m. from trifluoroacetic acid. These were assigned as due to *ortho*, *para*, and *meta* fluorine, respectively. The proton nuclear magnetic resonance showed three multiplets in area ratio of 1:2:2 at 5.89, 5.10, and 3.45 p.p.m. from tetramethylsilane.

2,3,4,5,6-Pentafluorotoluene.—Methyl iodide (47 g., 0.33 mole) dissolved in 20 ml. of tetrahydrofuran was added to a tetrahydrofuran solution of pentafluorophenylmagnesium bromide prepared from 47 g. (0.33 mole) of pentafluorobromobenzene and 7.29 g. (0.30 g.-atom) of magnesium. The reaction was stirred overnight and then was hydrolyzed with 6 *N* hydrochloric acid. The aqueous layer was extracted with pentane and combined with the organic layer. The organic layer was extracted with water several times and then dried. Vapor phase chromatography indicated 2,3,4,5,6-pentafluorotoluene was produced in a 56% yield and pentafluorobenzene in 21% yield. A good separation of these two materials by fractionation was not possible since only 15.1 g. (27%) of 2,3,4,5,6-pentafluorotoluene was obtained, b.p. 115–116°, $n^{22}D$ 1.4021 (lit.[2b] $n^{20}D$ 1.4023).

2,3,4,5,6-Pentafluorotoluene.—Methylmagnesium iodide (0.132 mole, 120 ml. of a tetrahydrofuran solution) was added to an ice bath-cooled solution of hexafluorobenzene (11.2 g., 0.060 mole) in 55 ml. of tetrahydrofuran. The temperature was raised in 5° increments from 5 to 50°. No noticeable reaction occurred so the reaction was stirred overnight at room temperature. Titration of an aliquot indicated little reaction had occurred. A 5-ml. aliquot was removed, hydrolyzed, extracted with pentane, and washed with dilute hydrochloric acid. Examination of the vapor phase chromatogram of this mixture indicated that 2,3,4,5,6-pentafluorotoluene was formed in approximately 2% yield.

(9) H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.*, **78**, 2217 (1956).

(10) H. Gilman and R. D. Gorsich, *ibid.*, **79**, 2625 (1957); **77**, 3919 (1955).

(11) All reactions were carried out under an atmosphere of dry, oxygen-free nitrogen. All melting points are uncorrected. Alumina column separations were carried out on Woelm neutral grade alumina. Vapor phase chromatographic analyses were carried out on an F and M Model 500 gas chromatogram. A 2-ft. silicone gum rubber (20%) on Chromasorb P (60–80 mesh) using helium carrier gas at about 60 ml./min. was used. The temperature for most analyses was programmed at 7.9°/min.

1,4-Dibenzyl-2,3,5,6-tetrafluorobenzene.—Ether was removed by distillation from 300 ml. of an ether–tetrahydrofuran (5:1) solution containing benzylmagnesium chloride (0.42 mole) until the vapor temperature reached 58°. Then 50 ml. of tetrahydrofuran was added followed by hexafluorobenzene (34.5 g., 0.185 mole) in increments of 7.0, 14.0, 5.8, and 1.9 g. The hexafluorobenzene was added over a 2.5-hr. period and vigorous refluxing was noted except with the final increment. The mixture was stirred for 30 min. and then hydrolyzed with 5 ml. of water. A mixture of ligroin and ether (1:1) was added and the inorganic salts were removed by filtration. Removal of the ether–tetrahydrofuran led to crystallization of the product. There was collected 32.94 g. (54%) of a white solid, m.p. 117–121°. A sample was recrystallized from hexane to give 1,4-dibenzyl-2,3,5,6-tetrafluorobenzene, m.p. 120–121.5°.

Anal. Calcd. for $C_{20}H_{14}F_4$: C, 72.72; H, 4.27; F, 23.00. Found: C, 72.62; H, 4.10; F, 23.30.

The F^{19} nuclear magnetic resonance of a solution in carbon tetrachloride showed a single sharp resonance with a chemical shift of 65.9 p.p.m. from trifluoroacetic acid. This is consistent with a *para* orientation of the benzyl groups. The proton nuclear magnetic resonance showed two peaks in area ratio of 5:2 at 7.42 and 4.08 p.p.m. from tetramethylsilane. The larger peak was assigned to the aromatic protons while the smaller peak was assigned to the methylene protons.

Ethyltetrafluorotoluene.—Ethylmagnesium bromide (0.079 mole, 50 ml. of a tetrahydrofuran solution) was added to 2,3,4,5,6-pentafluorotoluene (11.8 g., 0.065 mole) in 40 ml. of tetrahydrofuran. The reaction was stirred overnight. A 5-ml. aliquot was removed, hydrolyzed, extracted with pentane, and washed with dilute hydrochloric acid. Analysis of the vapor phase chromatogram indicated that alkylation to ethyltetrafluorotoluene had occurred to a maximum of 2%. The remaining mixture was carbonated and did not give any 2,3,4,5,6-pentafluorophenylacetic acid after work-up.

2,3,4,5,6-Pentafluorobiphenyl.—Hexafluorobenzene (37.6 g., 0.202 mole) in 60 ml. of tetrahydrofuran was added to phenylmagnesium bromide (0.50 mole in 300 ml. of tetrahydrofuran). No reaction was indicated either initially or after intermittent heating. The reaction was then refluxed for 11 hr. The mixture was hydrolyzed by pouring it into dilute hydrochloric acid. The aqueous layer was extracted with ether; the ether and tetrahydrofuran were removed by distillation and replaced with hexane. The hexane solution was then placed on a large alumina column. First, the column was eluted with petroleum ether (b.p. 60–90°), then with ether and acetone. From the petroleum ether extracts there was obtained a white solid product. This was recrystallized several times from hexane and once from ethanol. There was obtained 3.40 g. of 2,3,4,5,6-pentafluorobiphenyl, m.p. 109–110° (lit.[12] m.p. 110.5–112°). The other fractions were 1.45 g., m.p. 107.5–109° (94% $C_{12}H_5F_5$ and 6% $C_{12}H_{10}$); 4.80 g., m.p. 69–80° (50% $C_{12}H_5F_5$ and 40% $C_{12}H_{10}$); 4.90 g., m.p. 50° (20% $C_{12}H_5F_5$ and 77% $C_{12}H_{10}$). The product composition was determined by vapor phase chromatography. The yield of crude 2,3,4,5,6-pentafluorobiphenyl was 17% (7% pure yield).

From the ether and acetone fraction there was obtained 2.0 g. of a white solid, m.p. 230–245°. Repeated recrystallization from benzene gave a white solid, 0.86 g., m.p. 251–254°, which was shown to be 1,4-diphenyl-2,3,5,6-tetrafluorobenzene by a mixture melting point and comparison of infrared spectrum with that of a known material.[13]

Reaction of Pentafluorobenzene with Ethyl Grignard Reagent.—Ethylmagnesium bromide (0.128 mole in 80 ml. of tetrahydrofuran) was added to a stirred and water-cooled solution of pentafluorobenzene (16.8 g., 0.10 mole) in 50 ml. of tetrahydrofuran. The first 40 ml. was added initially, the remaining 40 ml. was added dropwise in 2 hr. During the 5-hr. total reaction period 86% of the theoretical amount of gas (C_2H_6) was evolved. The mixture was cooled in an ice bath and was carbonated by the addition of solid carbon dioxide. The mixture was hydrolyzed with 6 *N* hydrochloric acid. The aqueous layer was ether extracted. The organic layer was placed in 4 *N* hydrochloric acid and distilled. The fraction boiling between 40–98° contained 0.7 g. (4%) of unchanged pentafluorobenzene (based on v.p.c.). The perfluorobenzoic acid steam distilled with the hydrochloric acid above 100°. The acidic distillate was ether extracted, the ether replaced with hexane, and the acid recrystallized from hexane. There was obtained 17.93 g. (85%) of pentafluorobenzoic acid, m.p. 102.5–104° (lit.[14] m.p. 103–104°).

In a parallel reaction, methylmagnesium iodide (0.115 mole) was treated with pentafluorobenzene (0.100 mole) for 1 day. Gas evolution (CH_4) was 75%. The mixture was carbonated and pentafluorobenzoic acid was obtained in 56% yield after a similar work-up. Vapor phase chromatographic analysis of the low-boiling distillate showed 39% recovery of pentafluorobenzene.

Reaction of 1,2,4,5-Tetrafluorobenzene with Ethyl Grignard Reagent.—Ethylmagnesium bromide (0.30 mole in 170 ml. of tetrahydrofuran) was added to 1,2,4,5-tetrafluorobenzene (14.7 g., 0.098 mole) in 70 ml. of tetrahydrofuran. The reaction mixture was stirred for an additional 3.5 hr. until gas evolution (C_2H_6) seemed to stop. The mixture was cooled in an ice bath and carbonated by the addition of solid carbon dioxide.

The reaction mixture was hydrolyzed with 6 *N* hydrochloric acid. The mixture was added to a large volume of 4 *N* hydrochloric acid and distilled. The fraction boiling to 104° was collected, extracted with pentane, and washed repeatedly with dilute hydrochloric acid. The vapor phase chromatogram of this showed it contained 6.26 g. (43% recovery) of unchanged 1,2,4,5-tetrafluorobenzene. The distillate, b.p. 104–108°, was extracted with ether. The ether was replaced with hexane and all hexane extracts combined. From the hexane was obtained 5.60 g. (29%) of 2,3,5,6-tetrafluorobenzoic acid, m.p. 150.5–152° (lit.[15] m.p. 154°). The nondistilled aqueous acid layer was extracted with ether. The crude acid, obtained after removal of ether, was extracted with boiling hexane. The hexane-insoluble white solid was recrystallized from water to give 5.61 g. (24%) of tetrafluoroterephthalic acid, m.p. 281.5–282.5° (lit.[16] m.p. 283–284°).

In a similar experiment, a 2:1 mole ratio of Grignard reagent to 1,2,4,5-tetrafluorobenzene was treated overnight. Carbonation and a similar work-up gave 2,3,5,6-tetrafluorobenzoic acid in 25% yield and tetrafluoroterephthalic acid in 30% yield.

Reaction of 1,2,3,4-Tetrafluorobenzene with Ethyl Grignard Reagent.—Ethylmagnesium bromide (0.180 mole in 100 ml. of tetrahydrofuran) was added to 1,2,3,4-tetrafluorobenzene (15 g., 0.10 mole) in 70 ml. of tetrahydrofuran. The reaction mixture was heated at 40° for 7 hr. and stirred at room temperature for 3 days. A 5-ml. aliquot was removed, hydrolyzed, and extracted with pentane for (v.p.c.) analysis. The remainder of the reaction was carbonated by the addition of solid carbon dioxide, acidified, and worked up in the usual manner. No fluorinated benzoic acid could be isolated. Analysis of the aliquot by vapor phase chromatography indicated that alkylation occurred at most to a maximum of 10%.

Reaction of Pentafluorobenzene with Butyllithium. A.—Pentafluorobenzene (16.8 g., 0.10 mole) in 50 ml. of diethyl ether was added to a cooled (−70°) stirred solution of *n*-butyllithium[17] (0.1 mole in 80 ml. of hexane solution) over a period of 14 min. The temperature was not allowed to rise over −55° during the addition. Gilman color test IIA[6] was negative only after 2 hr. indicating absence of *n*-butyllithium. The reaction was then carbonated by bubbling carbon dioxide into the solution. The mixture was allowed to warm to room temperature with continued carbonation. The reaction was then hydrolyzed with 300 ml. of 6 *N* hydrochloric acid and then extracted with diethyl ether. The dried ether extracts were distilled, leaving 21.0 g. (99%) of crude pentafluorobenzoic acid, m.p. 100–105°. One recrystallization from hexane yielded 14.3 g. (68%) of pure pentafluorobenzoic acid as the first crop, m.p. 106° (lit.[14] m.p. 103–104°).

B.—The above experiment was repeated except that freshly prepared butyllithium in diethyl ether was used. Gilman color test IIA was negative within 5 min. indicating a faster reaction. The yield of pentafluorobenzoic acid, m.p. 106°, was 80.9%.

C.—Repeating the experiment as in B except that an equal volume of tetrahydrofuran was added to the prepared butyllithium ether solution gave pentafluorobenzoic acid, m.p. 106.5–107.5°, in 82% yield. Gilman color test IIA again was negative within 5 min. indicating a faster reaction in this solvent pair.

(12) J. M. Birchall, R. N. Haszeldine, and A. R. Parkinson, *J. Chem. Soc.*, 4966 (1962).

(13) D. Holland, G. Moore, and C. Tamborski, unpublished work, gave m.p. 253–256°.

(14) E. Nield, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 166 (1959).

(15) D. J. Alsop, J. Burdon, and J. C. Tatlow, *ibid.*, 1801 (1962).

(16) B. Gething, C. R. Patrick, and J. C. Tatlow, *ibid.*, 1574 (1961).

(17) Commercially prepared in hexane solution, Foote Mineral Co., Exton, Pa.

Reaction of 1,2,4,5-Tetrafluorobenzene with Butyllithium. Method A. Tetrahydrofuran Solvent.—1,2,4,5-Tetrafluorobenzene (15.0 g., 0.10 mole) in 20 ml. of tetrahydrofuran was added to a cooled (−70°), stirred solution of *n*-butyllithium[17] (0.20 mole, in 135 ml. of hexane) dissolved in 270 ml. of tetrahydrofuran. The addition took 10 min. and the temperature was not allowed to rise over −55°. After 20 min. Gilman color test IIA was negative. The mixture was then carbonated by bubbling carbon dioxide into the reaction. The mixture was allowed to warm to room temperature with continued carbonation. The reaction was then hydrolyzed with 300 ml. of 6 *N* hydrochloric acid. This two-phase mixture was then placed in a flask equipped with a short-path Vigreux column and distilled. The aqueous distillate, boiling between 100 and 108°, was extracted with diethyl ether, dried over magnesium sulfate, and aspirated on a water bath. The residue of 0.62 g. (3.2%) had m.p. 149–152° and was identified by mixture melting point and infrared analysis as 2,3,5,6-tetrafluorobenzoic acid. The solid pot residue from the above distillation, 19.9 g. (84%), m.p. 261–276°, was recrystallized from water to yield as the first crop 16.1 g. (67%), m.p. 283° (lit.[16] m.p. 283–285°), of tetrafluoroterephthalic acid. This material was characterized by infrared analysis and a mixture melting point with an authentic sample.

Method B. Diethyl Ether Solvent.—The above experiment was repeated except that diethyl ether was used in place of the tetrahydrofuran. Gilman color test IIA, however, was negative only after 2 hr. Carbonation and work-up as above yielded 6.5 g. (33%) of crude 2,3,5,6-tetrafluorobenzoic acid, m.p. 147–151°, 9.0 g. (37.7%) of crude tetrafluoroterephthalic acid, m.p. 276–278° (after one recrystallization from water), and 1.4 g. of an unidentified acidic material, m.p. 337.5–340°.

Reaction of 1,2,3,4-Tetrafluorobenzene with Butyllithium in Tetrahydrofuran.—1,2,3,4-Tetrafluorobenzene (15.0 g., 0.10 mole) in 20 ml. of tetrahydrofuran was added to a cooled (−70°), stirred solution of *n*-butyllithium[17] (0.20 mole in 135 ml. of hexane) dissolved in 270 ml. of tetrahydrofuran. The addition took 13 min. and the temperature was not allowed to rise over −55°. After 18 min. Gilman color test IIA was negative. The mixture was then carbonated by bubbling carbon dioxide into the reaction. The mixture was allowed to warm to room temperature with continued carbonation. The reaction was then hydrolyzed with 300 ml. of 6 *N* hydrochloric acid. This two-phase mixture was then placed into a flask equipped with short-path Vigreux column and distilled. The aqueous distillate boiling between 100 and 108° was extracted with diethyl ether. The diethyl ether was extracted with 5% sodium hydroxide solution. The extracted ether layer was dried and the ether was removed by distillation leaving 2.51 g. of a nonacidic liquid. Infrared analysis of this material suggested that it was an alkylated fluorobenzene. Vapor phase chromatographic analysis indicated that this material was a three- or four-component mixture.

The sodium hydroxide extract of the ether layer was acidified with 6 *N* hydrochloric acid and extracted with diethyl ether. The ether layer was dried and the solvent ether was removed by distillation to yield 6.04 g. of a semisolid material. This material was recrystallized from petroleum ether (b.p. 60–90°) and produced 4.14 g. of 2,3,4,5-tetrafluorobenzoic acid, m.p. 92–92.5°.

Anal. Calcd for $C_7H_2F_4O_2$: C, 43.32; H, 1.04; F, 39.15. Found: C, 43.44; H, 1.19; F, 39.26.

The pot residue from the original distillation through the Vigreux column was extracted with diethyl ether. The ether was extracted with 5% sodium hydroxide solution. The basic solution was acidified with 6 *N* hydrochloric acid and again extracted with diethyl ether. The ether solution was dried over magnesium sulfate and distilled to remove the solvent leaving 8.96 g. of a dark brown semisolid material. This material was recrystallized from petroleum ether (b.p. 90–120°) several times to yield 2.23 g. of tetrafluorophthalic acid, m.p. 151–152° (lit.[16] m.p. 153–154°). In addition 4.25 g. of an unidentified material was obtained whose infrared spectrum showed both alkyl substitution as well as a carboxylic acid function.

Acknowledgment.—The authors wish to thank J. V. Pustinger, Jr., of the Monsanto Research Corporation for the determination and interpretation of the n.m.r. spectra reported in this work. The F^{19} spectra were run on a Varian V-4300-2 D.P. spectrometer at 40.0 Mc./sec. Chemical shifts are reported in parts per million from trifluoroacetic acid.

Isomerization of the Ascorbic Acids

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The rare L-araboascorbic and D-xyloascorbic acids are herein shown to be formed from their well-known epimers, L-xyloascorbic and D-araboascorbic acids, respectively, when they are heated with excess base in aqueous methanol. Their formation is shown to proceed *via* racemization of the asymmetric ring carbon (C-4), resulting in an approximately equal mixture of C-4 epimers at equilibrium in each case. Methods are described for the separation and purification of isomers, thus providing a new, convenient route to these uncommon ascorbic acids.

It has been known for a long time that esters of L-*xylo*-hexulosonic (2-keto-L-gulonic) and D-*arabino*-hexulosonic (2-keto-D-gluconic) acids are converted by bases *via* internal alcoholysis to the corresponding ascorbic acids, L-xyloascorbic and D-araboascorbic acid, respectively.[1] We wish to report the previously unrecorded fact that these reactions, when conducted with excess base, lead to racemization at C-4 of the product and that the rare ascorbic acids, L-araboascorbic and D-xyloascorbic acid, are formed in each case in about equal amount with the common epimer, L-ascorbic and D-isoascorbic acid, respectively.

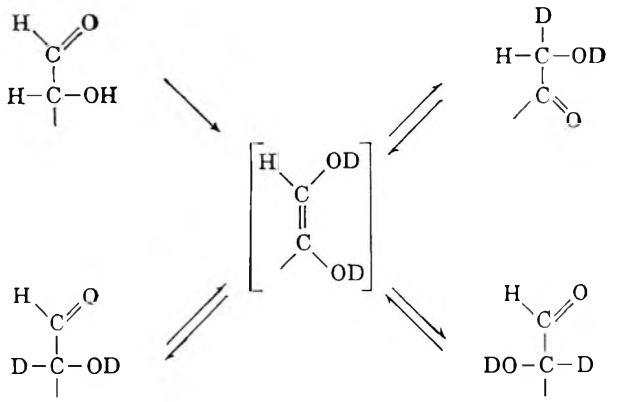
Surprisingly little degradation is involved, and our initial, chance chromatographic detection of the phenomenon has led to the development of a convenient synthetic method for the preparation of these uncommon ascorbic acids, heretofore obtainable only *via* rare sugars or cumbersome fragment condensation methods.[2] The racemizations involved present rather interesting and novel carbohydrate behavior and so will be discussed in some detail.

Reducing sugars are relatively stable in weakly acid solutions, but in alkaline solution they are subject to isomerizations, cleavages, and condensations. In fact, the classic Lobry de Bruyn–Alberda van Ekenstein transformation of aldoses by base to mixtures of C-2

(1) T. Reichstein and A. Grüssner, *Helv. Chim. Acta*, **17**, 311 (1934); U. S. Patent 2,265,121; U. S. Patent 2,301,811.

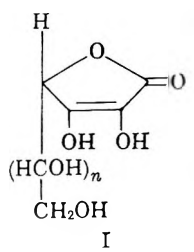
(2) B. Helferich and O. Peters, *Ber.*, **70**, 464 (1937); "The Vitamins," Vol. I, Sebrell and Harris, Ed., Academic Press, New York, N. Y., 1954, pp. 198–202.

epimers and ketoses[3] has become a significant synthetic tool in sugar chemistry. The mechanistic pathway for this isomerization involves an enediol intermediate according to Sowden and Schaffer.[4] Thus, D-glucose is isomerized by alkali in heavy water to products in which carbon-bonded deuterium is incorporated.

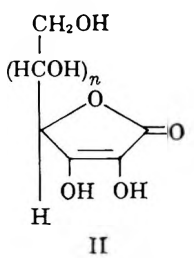


Similar configurational changes at C-2 upon treatment with alkaline reagents have been reported for aldonic lactones[5] and sugar acids.[6] However, in general, these latter substances are relatively stable and withstand prolonged heating with base before the onset of significant isomerization.

The present case concerns the ascorbic acids, a group of compounds similar in part to the sugar lactones. These acids, represented by formulas I and II, are derivable from both 2- and 3-keto sugar acids by lactonization and enolization.



I

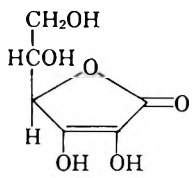


II

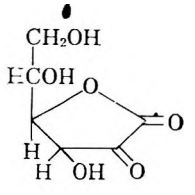
The chemistry of ascorbic acid is usually interpreted on the basis of structure III, although it could theoretically react to some extent of course in any one of its various tautomeric modifications, V, VI, and VII.

Although the ketonic structures V and VI can readily be drawn, the enediolic form III certainly predominates, as indicated by chemical evidence,[7] X-ray findings,[8] and high-intensity absorption in the ultraviolet (log ϵ 4.0 at λ_{max} 244 mμ), all indicating an α,β-unsaturated carbonyl structure.

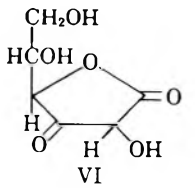
As stated initially, we found chromatographic indication that the treatment of methyl L-*xylo*-hexulosonate



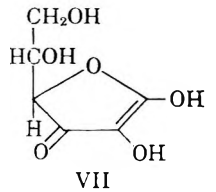
III



V



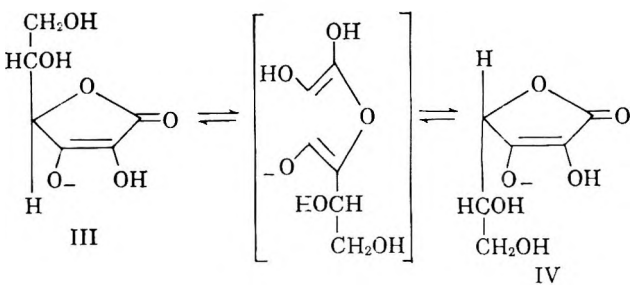
VI



VII

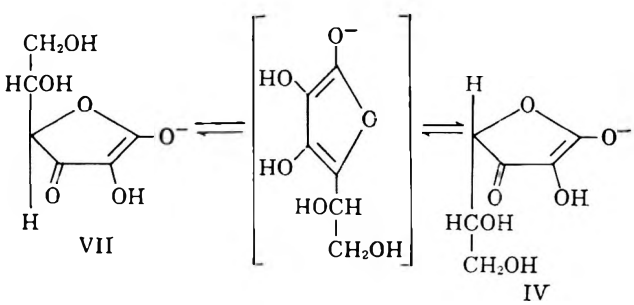
(methyl 2-keto-L-gulonate) in aqueous methanol with excess potassium hydroxide leads first to L-xyloascorbic acid and then, subsequently, to an araboascorbic acid. That the araboascorbic acid is derived from sequential isomerization rather than concomitant formation was evident from the identical behavior of pure xyloascorbic acid when subjected to the conditions of its own formation. The chromatographic evidence was then confirmed by driving the isomerization to equilibrium and separating the reaction mixture *via* fractional crystallization from acetonitrile to yield both L-xyloascorbic acid (III) and more soluble L-arabascorbic acid (IV.)

Mechanistically, formation of L-araboascorbic acid from L-xyloascorbic acid must involve racemization at C-4, probably *via* enolization of the anion of the unsaturated lactone of III with loss of configuration leading to a mixture of the epimeric anions of III and IV.



III IV

Alternatively, a similar but possibly less likely path can be drawn through the anion of the tautomeric enediol VII,[9] and of course this possibility cannot be excluded, *per se*.



VII IV

In any case, both foregoing paths depend upon the lability of the proton at C-4. Although there is no literature evidence that the C-4 bonded hydrogen would

(3) Product composition and equilibrium point in the Lobry de Bruyn transformation [C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *Rec. trav. chim.*, **14**, 195 (1895)] have been reported to be cation dependent in some but not all cases; see W. Pigman, "The Carbohydrates," Academic Press, New York, N. Y., 1957.

(4) J. C. Sowden and R. Schaffer, *J. Am. Chem. Soc.*, **74**, 505 (1952).

(5) W. N. Haworth and C. W. Long, *J. Chem. Soc.*, 345 (1929).

(6) E. Fischer, *Ber.*, **23**, 799 (1890); H. T. Bonnett and F. W. Upson, *J. Am. Chem. Soc.*, **55**, 1245 (1933).

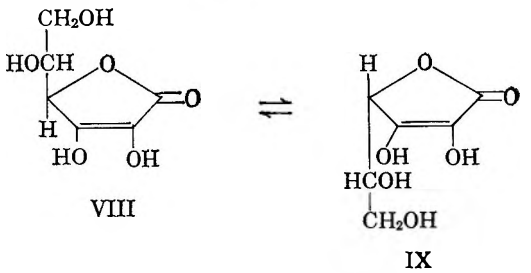
(7) R. W. Herbert, E. L. Hirst, E. G. V. Percival, R. J. N. Reynolds, and F. Smith, *J. Chem. Soc.*, 1270 (1933).

(8) E. G. Cox, *Nature*, **130**, 205 (1932); **131**, 402 (1933); E. G. Cox and T. H. Goodwin, *J. Chem. Soc.*, 769 (1936).

(9) See W. N. Haworth, E. L. Hirst, F. Smith, and W. J. Wilson, *ibid.*, 829 (1937), for evidence which supports the existence of the tautomeric 3-keto structure (VII). The reaction of ascorbic acid with one molecular proportion of diazomethane yields mainly 3-O-methylascorbic acid and in small proportion the isomeric 1-methyl derivative.

be active, attention is called to Weigl's work on the infrared spectrum of deuterated ascorbic acid,[10] which he interpreted to indicate that at least one of the hydrogens attached to carbon was exchangeable. In addition, the kinetics of the system as revealed by polarimetry and thin layer chromatography lend support to a tautomeric interpretation, the equilibration character of the reaction being clearly evident. Aliquots after various reaction times were separated on silica gel coated plates, and comparison of optical densities in the ultraviolet at peak absorption (244 mμ) permitted quantitative evaluation of the changing ratio of species. In addition, the changing optical rotation of the reaction mixture was followed to constancy which indicated similarly that equilibration was nearly complete in about 17 hr. with the ratio of L-xyloascorbic to L-araboascorbic acid being approximately 1.3:1.0.

These findings suggested that D-araboascorbic acid (VIII) would equilibrate with D-xyloascorbic acid (IX) and, indeed, this was found to be the case.



Thus, identical treatment of the common D-araboascorbic acid in refluxing aqueous methanol with excess potassium hydroxide gave a mixture of starting material and D-xyloascorbic acid. Here, too, polarimetry and thin layer chromatography indicated near equilibration in about 16 hr., with D-xyloascorbic acid predominating over the D-araboascorbic acid isomer in a ratio of about 1.2:1.0.

In summary, these reactions provide a convenient route to the C-4 epimer of any given ascorbic acid. However, no simple synthesis of L-ascorbic acid (D at C-4) *via* this route would be practical since the necessary (L at C-4) precursors (L-fructose, L-glucose, etc.) are not readily available from natural sources.

Experimental[11]

Separation of Isomers.—Resolution of the ascorbic acids by thin layer chromatography (t.l.c.) has not been reported previously.[12] Numerous paper chromatographic separations of greater or less efficacy have been reported,[13] but none lends itself to a rapid analysis or actual isolation of components. T.l.c. on silica gel coated plates gives a rapid and clean separation of xyloascorbic and araboascorbic acids, and this procedure could be used readily for the actual isolation of milligram quantities of the isomers. The plates are prepared by mixing silica gel G[14] (30 g.) with water (60 ml.) containing metaphosphoric acid (1.8 g.) and applying this slurry with an applicator to five 20 × 20 cm. glass plates to give a film 0.25 mm. thick. The plates are air-dried and then activated by drying overnight in an oven at 110°. Chromatoplates prepared in this manner are developed, after spotting with the mixture to be separated, in a system of acetonitrile–butyronitrile–water (66:33:2). The irrigation period is about 45 min., during which the solvent front rises about 17 cm. Spot or zone position is detected by spraying with 5% iodine in chloroform or 0.08% 2,6-dichlorophenolindophenol in ethanol. Under these conditions, the xyloascorbic acids have an R_f value of 0.26, and the araboascorbic acids, 0.38. Two- to 200-μg. mixtures can be separated in this manner; larger samples form diffuse spots.

Estimation of Ratio of Isomers.—The speed and sharpness of separation of the isomers by t.l.c. make this technique useful for semiquantitative analysis. Synthetic mixtures of L-xyloascorbic acid and D-araboascorbic acid were dissolved in water and chromatographed as described. Each mixture was spotted, together with an adjacent guide spot. After resolution, the plates were partially masked to permit selective spraying of the guide strips and the corresponding areas on the adjacent unsprayed strip were then scraped off into 15-ml. centrifuge tubes. The material obtained was eluted by adding 5 ml. of methanol, stirring thoroughly, and centrifuging. The clear, supernatant solution was analyzed directly for enediolic lactone content by measurement of the maximum optical density (244 mμ). Typical results are given in Table I.

TABLE I

EFFICACY OF SEPARATION AND RECOVERY OF MIXTURES OF THE ASCORBIC ACIDS *via* T.L.C. ON SILICA GEL

Mixture	Isomer	Applied, μg.	Recovered, μg.	Recovery, %
1	L-XAA[a]	41.0	41.6	101
	D-AAA[b]	63.5	61.0	96
2	L-XAA	82.0	75.0	92
	D-AAA	127.0	120.0	95

[a] L-Xyloascorbic acid. [b] D-Araboascorbic acid.

Polarimetry.—The isomerizations were also followed *via* the changing optical rotations of the reaction mixtures. Under the basic reaction conditions used, the observed rotations are those of the potassium salts of the acids. Zero-time readings are for the solutions in alkaline, aqueous methanol prior to heating. The solutions were then brought to reflux, and aliquots were removed with time, cooled to 27°, and their optical rotations measured. All values are the observed rotations in 2-dm. tubes.

Isomerization of L-Xyloascorbic Acid.—A solution of 17.6 g. (0.1 mole) of L-xyloascorbic acid in 200 ml. of 50% aqueous methanol containing 11.2 g. (0.2 mole) of potassium hydroxide was heated to refluxing. The composition of the reaction mixture was followed by t.l.c. and polarimetry. Observed rotational changes are shown in Table II.

TABLE II

ROTATIONAL CHANGES OF L-XYLOASCORBIC ACID IN BASE

Time, hr.	$[\alpha]^{27}D$, deg.	Time, hr.	$[\alpha]^{27}D$, deg.
0	24.90	12	8.01
1	22.60	14.5	6.58
2	20.28	15.5	6.14
4	16.55	17.25	5.47
6.25	13.24	24	3.56
7.5	11.51	34	2.53
9.5	9.92	40	2.31

T.l.c. after 1 hr. indicated, in addition to the L-xyloascorbic acid, a faster moving indophenol-reducing material with R_f of 0.38, consistent with an araboascorbic acid. With time the more mobile spot increased in intensity, as that of the less mobile decreased, until both became approximately equal. Quantitative analysis of another similar run, *via* t.l.c., indicated equilibration to be near completion between 16 and 24 hr., with a ratio of about 1.3:1.0 of xyloascorbic–araboascorbic species (Table III). After 15 hr. at reflux, the reaction solution was cooled and acidified

(10) J. W. Weigl, *Anal. Chem.*, **24**, 1483 (1952).

(11) Melting points were taken on a microscope hot stage and are not corrected. Infrared spectra were run on a Perkin-Elmer Infracord. Ultraviolet spectra were measured with a Cary 11 recording spectrophotometer. Optical rotations of reaction solution were determined at 27 ± 2° on a Hilger polarimeter, and of crystalline products on a Carl Zeiss photoelectric polarimeter at the same temperature by D. Williams.

(12) We are indebted to R. Singleton for the design of this system.

(13) W. I. Patterson and L. C. Mitchell, *J. Assoc. Offic. Agr. Chemists*, **36**, 1127 (1953); Y. Chen, F. A. Isherwood, and L. W. Mapson, *Biochem. J.*, **55**, 821 (1953); L. W. Mapson and S. M. Partridge, *Nature*, **164**, 479 (1949).

(14) E. Merck, A. G., Darmstadt.

TABLE III

CHANGING ISOMER RATIO WITH ISOMERIZATION OF L-XYLOASCORBIC ACID

Time, hr.	L-XAA/L-AAA	Time, hr.	L-XAA/L-AAA
0	100/0	8	70/30
1	91/9	12	63/37
4	77/23	16	60/40
6	74/26	24	57/43
		28	57/43

TABLE IV

ROTATIONAL CHANGES OF D-ARABOASCORBIC ACID IN BASE

Time, hr.	$[\alpha]^{27}D$	Time, hr.	$[\alpha]^{27}D$
0	24.72	11	6.00
1	22.16	13	4.41
2	19.59	15	3.18
5	13.95	16.75	2.43
7	11.25	24.5	−0.02
9	8.17	31	−1.09
		33	−1.42

with 95 g. (100% excess) of Amberlite IR-120 (H^+). The resin was removed and the filtrate concentrated *in vacuo* to remove the methanol. Lyophilization of the residual aqueous solution yielded an amorphous yellow solid which, on crystallization from acetonitrile, yielded three crops of recovered L-xyloascorbic acid and finally a fourth crop of crystals (3.9 g.). Infrared and ultraviolet spectra, m.p. 166–170° dec., and $[\alpha]^{27}D$ +13° identified the final material to be L-araboascorbic acid.[15]

(15) T. Reichstein, A. Grüssner, and R. Oppenauer, *Helv. Chim. Acta*, **17**, 510 (1934).

TABLE V

CHANGING ISOMER RATIO WITH ISOMERIZATION OF D-ARABOASCORBIC ACID

Time, hr.	D-AAA/D-XAA	Time, hr.	D-AAA/D-XAA
0	100/0	9	58/42
1	90/10	11	56/44
3	83/17	17	48/52
5	74/26	24	47/53

Isomerization of D-Araboascorbic Acid.—Similar treatment of D-araboascorbic acid in an identical system yielded the optical rotation measurements shown in Table IV. T.l.c. here indicated formation of a less mobile species, R_f 0.26, comparable to that of a xyloascorbic acid, with equilibration near completion between 17 and 24 hr., with a ratio of about 1.0:1.1 of araboascorbic–xyloascorbic isomers (Table V).

A similar processing of the reaction mixture after 15 hr. of refluxing produced a crude yellow solid which, on fractional crystallization from acetonitrile, yielded a first crop (5.8 g.) of colorless crystals. Recrystallization from the same solvent gave material melting at 188–190° dec. with infrared and ultraviolet spectra identical with those for L-xyloascorbic acid. A mixture of this material with an equal amount of authentic L-xyloascorbic acid depressed the melting point to 170°, the value reported for the DL pair.[16] The optical rotation of the isolated material was levoratotory ($[\alpha]^{27}D$ −16°) thus identifying it as D-xyloascorbic acid.[16,17]

(16) T. Reichstein, A. Grüssner, and R. Oppenauer, *ibid.*, **16**, 1019 (1933).

(17) R. G. Ault, D. K. Baird, H. C. Carrington, W. N. Haworth, R. W. Herbert, E. L. Hirst, E. G. V. Percival, F. Smith, and M. Stacey, *J. Chem. Soc.*, **16**, 1019 (1933).

Selective Cleavage of Ornithyl and Diaminobutyryl Peptides[1]

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Received February 7, 1964

The selective cleavage of the N-α-naphthylamides of L-ornithylglycylglycine, L-2,4-diaminobutyrylglycylglycine, and L-ornithyl-L-leucylglycine leading to the lactams and dipeptide naphthylamides was studied. Although alkaline or acidic aqueous systems did not yield satisfactory results, selective cleavage could be demonstrated in absolute ethanol in the presence of triethylamine at 65°. Since glycylglycyl units are particularly prone to alkaline hydrolysis, the presence of this moiety in a peptide affords a very severe test for the selectivity of the cleavage. The scission of the leucylglycine derivative was slow but highly specific, a result attributable to steric hindrance.

Intramolecular nucleophilic attack of an amino group on a peptide can lead to lactam formation and scission of an amide bond under exceptionally mild conditions. Thus, Holley and Holley[3] found that if an aqueous solution of N-(2-amino-4-carbomethoxyphenyl)glycylglycylglycine is held at 25° for 5 hr. or at 70° for 15 min., the dihydroquinoxalone derivative and glycylglycine are obtained in very high yields. Another example of this type of facile peptide cleavage is the removal of the chloroacetyl group from N-chloroacetyl peptides with *o*-phenylenediamine, a reaction that is completed in aqueous solution at 100° after 1 hr.[4] Since in the above cases the attacking group is an aromatic amino group, it seemed of interest to ascertain whether lactam formation could also lead to selective peptide bond cleavage with aliphatic amines. An earlier study by Barrass and Elmore[5] on the cleavage of α-N-tosyl-DL-ornithylglycine and α-N-tosyl-L-2,4-diaminobutyrylglycine to yield the lactams and glycine gave no direct information on this point. With those substances there is no way of ascertaining the degree of cleavage specificity, nor do their results lend themselves readily to quantitative interpretation.

Most of the work reported here deals with the cleavage of the N-α-naphthylamides of L-ornithylglycylglycine, L-2,4-diaminobutyrylglycylglycine, and L-ornithyl-L-leucylglycine. The presence of the glycylglycine moiety affords a particularly stringent test for the specificity of the cleavage procedure since studies by Levene, *et al.*,[6] and by Synge[7] have shown this grouping to be the most susceptible to base- or acid-catalyzed hydrolysis. Information on the effects of steric hindrance was obtained from the leucylglycine derivative. The presence of the α-naphthylamide group permits

(1) Supported in part by Grant GM 05492, National Institutes of Health.

(2) Taken in part from the Ph.D. Dissertation of M. A. Lipson, State University College of Forestry, Syracuse University, July, 1963. National Science Foundation Predoctoral Cooperative Graduate Fellow, 1961–1963.

(3) R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, **74**, 5445 (1952).

(4) R. W. Holley and A. D. Holley, *ibid.*, **74**, 3069 (1952).

(5) B. C. Barrass and D. T. Elmore, *J. Chem. Soc.*, 4830 (1957).

(6) P. A. Levene, R. C. Steiger, and A. Rothen, *J. Biol. Chem.*, **97**, 717 (1932).

(7) R. L. M. Synge, *Biochem. J.*, **39**, 351 (1945).

TABLE I

CLEAVAGE OF PEPTIDE α-NAPHTHYLAMIDES[a]

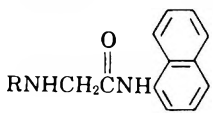
Peptide-naphthylamides	Time, hr.	Amount unchanged, %	Dipeptide naphthylamide, %	Glycine naphthylamide, %
L-Orn-Gly-Gly-	36	15	72	5
	48	8	73	11
	72	3	80	17
L-Dab-Gly-Gly-	36	49	42	5
L-Orn-L-Leu-Gly-	36	71	24	0

[a] In 0.05 *M* triethylamine in ethanol at 65°.

solutions in absolute ethanol containing 0.05 *M* triethylamine at 65°. Data on the cleavage of the naphthylamides are summarized in Table I. In addition to the listed products, the expected lactams were qualitatively detected with ninhydrin sprays. In no case could the presence of ornithine, diaminobutyric acid, or free naphthylamine be demonstrated. It is seen that although peptide bond cleavage through lactam formation with aliphatic amino groups is much slower than with *o*-phenylenediamine derivatives, it nevertheless

TABLE II

PHYSICAL CONSTANTS AND ANALYSES OF THE GLYCINE-N-α-NAPHTHYLAMIDES



R	Yield, %	M.p., °C.	$[\alpha]^{25}D$	R_f	Color with ninhydrin	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
Cbz-[a]	43	150–152				71.84	71.78	5.42	5.32	8.38	8.56		
Cbz-Gly-[b]	47	199–200				67.51	67.07	5.41	5.79	10.74	10.75		
Cbz-L-Leu-[c]	50	162–164	−5.3[d]			69.76	69.59	6.53	6.59	9.39	9.56		
DiCbz-L-Dab-Gly-[e]	49	194–196	−38.6[f]			65.27	64.59	5.64	5.79	11.19	11.31		
DiCbz-L-Orn-Gly-[g]	60	189–191	−8.4[f]			65.71	65.65	5.83	5.94	10.95	11.12		
DiCbz-L-Orn-L-Leu-[h]	65	172–175	−13.2[f]			67.32	67.28	6.52	6.88	10.07	10.13		
H·HOAc[i,j]	74	165–166 dec.		0.73	Brown	64.60	64.92	6.20	6.06	10.76	10.68		
Gly-·HCl[i,k]	88	246–248 dec.		0.62	Yellow	57.24	56.83	5.49	5.69	14.30	14.48	12.07	12.25
L-Leu-·HCl[i]	47	205–207	+39.5[l]	0.85	Blue	61.79	61.95	6.91	7.04	12.01	11.77	10.14	10.83
L-Dab-Gly-·2HCl[i,m]	76		−25.8[l]	0.33	Brown	50.24	49.49	5.86	6.25	16.28	16.11	16.48	16.98
L-Orn-Gly-·2HCl[i,m]	75		+26.1[l]	0.28	Purple	51.35	51.47	6.13	6.38	15.76	14.97	15.96	16.05[j]
L-Orn-L-Leu-·2HCl[i,m,n]	80		−8.6[l]	0.60	Blue	55.20	54.45	7.05	7.20	14.00	13.90	14.17	14.02[j]

[a] Coupling product of carbobenzoxyglycine and α-naphthylamine. [b] Coupling product of carbobenzoxyglycylglycine and α-naphthylamine. [c] Coupling product of carbobenzoxy-L-leucylglycine and α-naphthylamine. [d] *c* 0.4% in dimethylformamide. [e] Coupling product of dicarbobenzoxy-L-diaminobutyric acid [S. Wilkinson, *J. Chem. Soc.*, 104 (1951)] and α-naphthylamine. [f] *c* 1% in dimethylformamide. [g] Coupling product of dicarbobenzoxy-L-ornithylglycylglycine and α-naphthylamine. Recrystallized from 90% ethanol. [h] Coupling product of dicarbobenzoxy-L-ornithine [R. L. M. Synge, *Biochem. J.*, **42**, 99 (1948)] and L-leucylglycinenaphthylamide hydrochloride. Product forms a gel that crystallizes very slowly from aqueous ethanol at room temperature. [i] Hydrogenolysis of the carbobenzoxy derivative was carried out at room temperature and 1 atm. using 50–75 mg. of palladium black/mmole in ethanol containing an excess of acetic acid. Hydrogen was passed through the mixture with mechanical shaking until carbon dioxide evolution ceased. The filtered solution was evaporated under reduced pressure and the residue was treated with a slight excess of 0.5 *N* hydrochloric acid, evaporated, and crystallized from appropriate solvents. [j] The carbon analysis for glycine-N-α-naphthylamide hydrochloride, m.p. 220–225 dec., was low. Calcd. for $C_{12}H_{12}N_2O$·HCl: C, 60.89; H, 5.53; Cl, 14.98; N, 11.84. Found: C, 59.08; H, 5.79; Cl, 14.96; N, 12.15. [k] Neut. equiv.: calcd., 290; found, 294. [l] *c* 1% in 0.5 *N* hydrochloric acid. [m] The hydrochloride was obtained as a gel or glass that could not be crystallized owing to hygroscopic properties. Purification was achieved by precipitation from alcoholic solution with ether. The compound was dried to constant weight at 80° prior to analysis. The acetate was also noncrystalline. [n] Treatment of the dicarbobenzoxy derivative with 30% hydrogen bromide in acetic acid did not yield a crystalline dihydrobromide.

quantitative spectral determination of the cleavage products and prevents side reactions at the C-terminals.

In preliminary studies it was found that cyclization was too slow to be of value unless the pH was raised to the point at which a significant concentration of the free amino groups was present. The tendency toward lactam formation under a variety of conditions decreased from L-ornithine methyl ester to L-ornithinamide to L-ornithylglycylglycine. Storage of ornithinamide for 24 hr. at 25° in 0.5 *M* phosphate buffer of pH 8.9 gave complete conversion to the lactam, conditions under which the tripeptide was recovered unchanged. Further trials with L-ornithylglycylglycine in aqueous alkaline solutions either at higher temperatures or higher pH values gave unsatisfactory results due to nonspecific cleavage. However, nonaqueous systems provided a more favorable reaction medium. Optimum results were obtained with approximately 0.01 *M* peptide proceeds faster than the cleavage of the highly susceptible glycylglycine bond. The time study with L-ornithylglycylglycine-α-naphthylamide shows that the longer the reaction time the lower the selectivity of the cleavage. Presumably, the nonspecific cleavage is due to base-catalyzed alcoholysis. Lactam formation with L-2,4-diaminobutyrylglycylglycine-α-naphthylamide was somewhat slower than for the ornithine analog, resulting in a decrease in the specificity of the cleavage. The cleavage of L-ornithyl-L-leucylglycine-α-naphthylamide proceeded with the highest selectivity and at the slowest rate. Both of these results are attributable to steric hindrance. It is, therefore, concluded that the selectivity with which ornithine and 2,4-diaminobutyric acid containing peptides can be cleaved by the procedure outlined here depends on the amino acid sequence of the peptide chains. Completely specific scission would probably be encountered only

rarely, but, since lactam formation has been shown to be faster than glycylglycyl cleavage, a significant degree of selectivity should be obtainable in all cases.

Experimental[8]

Dicarbobenzoxy-L-ornithine Methyl Ester.—This compound was prepared from dicarbobenzoxy-L-ornithine[9] and ethereal diazomethane, m.p. 71–72° from chloroform–ligroin.

Anal. Calcd. for $C_{22}H_{26}N_2O_6$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.83; H, 6.37; N, 6.04.

Dicarbobenzoxy-L-ornithinamide.—Dicarbobenzoxy-L-ornithine methyl ester, 1 g., was stored overnight at 0° in 10 ml. of methanolic ammonia. Filtration yielded 600 mg. of amide, 62%, m.p. 168.

Anal. Calcd. for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.31; N, 10.52. Found: C, 62.93; H, 6.34; N, 9.84.

L-Ornithylglycylglycine was prepared by a modification of the method used by Goldschmidt and Rosculet.[10] Dicarbobenzoxy-L-ornithylglycylglycine was synthesized by direct coupling of dicarbobenzoxy-L-ornithine[9] and sodium glycylglycinate with ethyl chloroformate[11]; m.p. 169–171° from ethyl acetate–ligroin; Goldschmidt and Rosculet[10] reported m.p. 125–126°. Because of discrepancy in melting point, our preparation was analyzed.

Anal. Calcd. for $C_{25}H_{30}N_4O_8$: C, 58.35; H, 5.88; N, 10.89; neut. equiv., 514. Found: C, 58.18; H, 5.89; N, 11.31; neut. equiv., 513.

Hydrogenolysis at room temperature and 1 atm. in the presence of palladium black, 75 mg./mmole, in 80% aqueous acetic acid containing a slight excess of hydrochloric acid yielded noncrystalline L-ornithylglycylglycine hydrochloride, R_f 0.08, purple color with ninhydrin; $[\alpha]^{25}D$ +22.0° (*c* 1%, 0.5 *N* HCl); Goldschmidt and Rosculet[10] reported $[\alpha]^{25}D$ +25.9° (*c* 2%, 0.5 *N* HCl).

Anal. Calcd. for $C_9H_{18}N_4O_4 \cdot HCl$: C, 38.23; H, 6.77; Cl, 12.54; N, 19.82. Found: C, 38.39; H, 6.80; Cl, 12.90; N, 19.70.

The naphthylamide derivatives were prepared by the coupling procedure of Vaughan and Osato.[11] Physical constants and analytical data for these compounds are listed in Table II. In addition to the chromatographic data recorded in Table II, the R_f values and ninhydrin colors of the compounds listed below were obtained: ornithinamide prepared by hydrogenolysis of the dicarbobenzoxy derivative, 0.04, purple; L-ornithine hydrochloride, 0.08, purple; ornithine methyl ester dihydrochloride,[12] 0.10, purple; 2,4-diaminobutyric acid hydrochloride, 0.12, purple; glycylglycine, 0.12, yellow; glycine, 0.18, brown; 3-amino-2-pyrrolidone hydrochloride,[13] 0.24, yellow; 3-amino-2-piperidone hydrochloride,[12] 0.28, yellow; and α-naphthylamine, 0.91, tan.

Cleavage Procedures.—Peptides at concentrations of 2 mg./ml. were allowed to react at controlled temperatures between 25 and 85° in 2-ml. sealed glass ampoules, and the reaction was terminated by cooling or mild acidification. Aliquots (10 μl.) were spotted in triplicates on Whatman No. 1 filter paper and chromatographed at room temperature using *n*-butyl alcohol–acetic acid–water, 4:1:5 (v./v.) as the mobile phase, and the products were detected qualitatively either by ninhydrin sprays or with a Mineralite, Model SL 2537 hand lamp. The sections containing the ultraviolet-absorbing compounds were cut out, the substances were eluted with water, and the eluates were made up to 4 ml. Under the elution conditions used, variable amounts of ultraviolet-absorbing impurities were detected which we could not remove satisfactorily. However, the interference of these compounds could be minimized by using aqueous extracts from the sections of the chromatograms adjacent to the naphthylamide spots as spectrophotometric blanks and taking readings at 292 mμ. The choice of this wave length rather than the absorption maximum, 281 mμ, represents a compromise between minimum interference by the impurities and loss of sensitivity of the detection procedure. Corrections for losses during chromatography and elution of the compounds were made through the use of calibration curves. The average molar extinction coefficient, ε, of the six naphthylamide salts in aqueous solutions at 292 mμ was 5190 ± 4%, and at 281 mμ it was 6100 ± 4%. The average molar extinction coefficient for the carbobenzoxynaphthylamides in 95% ethanol at 290 mμ, their absorption maximum, was 7050 ± 1%.

(8) All melting points were determined with a Mel-Temp heating block in capillary tubes and are uncorrected. Analyses are by George Robertson, Florham Park, N. J. R_f values were obtained on Whatman No. 1 filter paper with *n*-butyl alcohol–acetic-acid–water, 4:1:5 (v./v.), descending.

(9) R. L. M. Synge, *Biochem. J.*, **42**, 99 (1948).

(10) S. Goldschmidt and G. Rosculet, *Chem. Ber.*, **93**, 2387 (1960).

(11) J. R. Vaughan and R. L. Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952).

(12) E. Fischer and G. Zemplén, *Chem. Ber.*, **42**, 4878 (1909).

(13) S. Wilkinson, *J. Chem. Soc.*, 104 (1951).

A Carbon-by-Carbon Degradation of Carbon-14-Labeled Nicotinic Acid[1]

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A carbon-by-carbon chemical degradation of carbon-14-labeled nicotinic acid is presented which is capable of giving the specific activity of each carbon atom in the molecule directly. With reasonably good counting equipment, the method can be applied to nicotinic acid containing 5 μc. of activity in 2–3 mmoles. Randomly labeled acid containing this level of activity would produce carbon dioxide in the final stages with a specific activity of about 0.1 mμc./mg. of carbon.

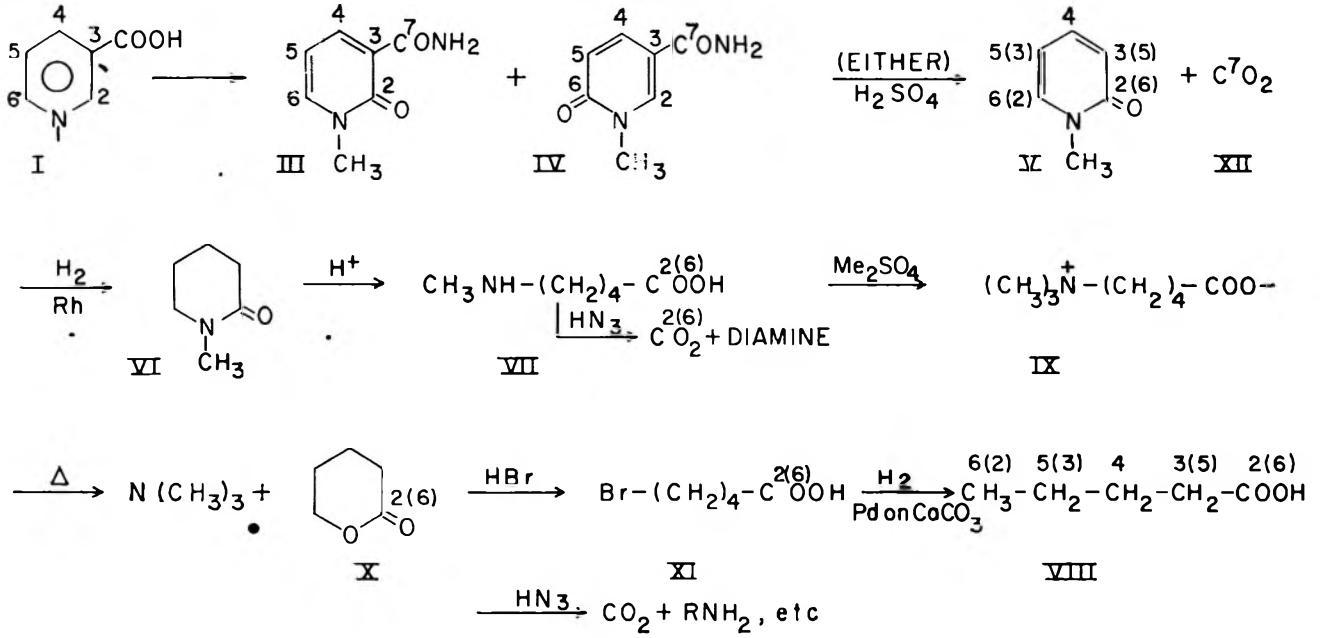
The carbon-by-carbon degradation of the pyridine ring of nicotinic acid (I) has become an increasingly necessary step in the elucidation of some biochemical pathways by C^{14} tracer methods. No complete degradation scheme applicable directly to I has been available so far, although several partial degradations of the pyridine ring of I and of ricinine have been published which have made the specific activity of each of the ring carbon atoms potentially available.[2] Starting from I, these would require total amounts of activity of the order of 0.2–0.5 mc., however.[2f] A scheme is presented here which is capable of yielding the specific activity of each of the pyridine ring carbon atoms of labeled I unambiguously, in essentially a single sequence of reactions. This method can easily be applied to an amount of I containing 5 μc. of total C^{14} activity if reasonably good counting equipment is available[3] (low level liquid scintillation, or, preferably, low level gas

(1) Research performed under the auspices of the U. S. Atomic Energy Commission at Brookhaven National Laboratory and under Grants G12855 and GB1129 from the National Science Foundation at Columbia University.

(2) (a) T. Griffith, K. P. Hellman, and F. U. Byerrum, *J. Biol. Chem.*, **235**, 800 (1960); (b) T. Griffith and R. U. Byerrum, *Biochem. Biophys. Res. Commun.* **10**, 293 (1963); (c) A. R. Friedman and E. Leete, *J. Am. Chem. Soc.*, **85**, 2141 (1963); (d) P. F. Juby and L. Marion, *Can. J. Chem.*, **41**, 117 (1963); (e) J. M. Essery, P. F. Juby, L. Marion, and E. Trumbull, *ibid.*, **41**, 1142 (1963); (f) R. K. Gholson, Oklahoma State University, private communication.

(3) D. R. Christman, *Nucleonics*, **19**, No. 5, 51 (1961).

SCHEME I



counting methods). Even using solid counting of barium carbonate, the scheme should give reasonable results starting with 50–100 μc. of total C^{14} activity in I. Each reaction is run on a desirable mass scale, dilutions with inactive material being made at various appropriate stages.

The sequence of reactions used is shown in Scheme I. I, in the form of its amide methioidide (II), is oxidized to a mixture of the corresponding 2- (III) and 6-pyridones (IV),[4,5] which are separated by means of an alumina column. Each of these pyridones is then decarboxylated in 60% sulfuric acid over a period of several days, during which time carbon dioxide (XII) is trapped and counted to give the specific activity of the original carboxyl group of the nicotinic acid. This reaction is analogous to the known decarboxylation of ricinine under similar conditions.[6]

The mother liquor from it contains N-methyl-2-pyridone (V) regardless of the pyridone carboxamide used. In one case, the carbonyl group is at the original ring position 2, and in the other at the original position 6. These pyridones are reduced to the corresponding piperidone (VI) by hydrogen, using 5% rhodium on alumina as the catalyst, and VI is hydrolyzed with dilute hydrochloric acid to δ-methylaminovaleric acid (VII). In one case the carboxyl carbon is the original C-2 of the pyridine ring, and in the other case the C-6.

Although δ-dimethylaminovaleric acid has been degraded to allylacetic acid *via* its N-oxide,[2d] in our hands a better yield of the ultimately desired valeric acid (VIII) has been more readily obtained by conversion of VII to its betaine (IX) by means of dimethyl sulfate,[7] thermal decomposition of IX (in an inert atmosphere) to δ-valerolactone (X),[8] hydrolysis of X in concentrated hydrobromic acid to give δ-bromovaleric acid (XI),[9] and the nearly quantitative hydrogenolysis of this compound, using palladium on calcium carbonate as catalyst.[10] Allylacetic acid, once obtained, can be reduced equally easily to VIII by hydrogen, using various catalysts. Attempts to deaminate IX to allylacetic acid *via* the Emde reduction were unsuccessful however.

To this point, the over-all yield of the series of reactions from *each* pyridone is about 1%, and each portion of VIII contains about 10 mμc. of activity, total, starting with 5 μc. of acid.

Each portion of VIII can be completely degraded carbon by carbon by the Schmidt reaction,[11,12] starting in one case with the original C-2 and in the other with the original C-6. However, a total of five consecutive Schmidt reactions, two starting from one of the valeric acids and three from the other, gives the activity of each of the original ring carbons directly, and any additional Schmidt reactions duplicate results already obtained. It is necessary to purify (preferably by gas chromatography) each subsequent acid, since some chain cleavage occurs during the oxidation of the amine product of the Schmidt reaction.[11b] It is possible easily to run a series of three Schmidt reactions starting from 0.5 g. of thallium valerate (XIII, the most convenient form in which to handle and purify these acids in the running of this reaction).[12]

This degradation scheme is currently being applied in this laboratory to the degradation of the pyridine ring of nicotine. The nicotine is obtained by feeding various precursors related to the Krebs cycle to excised tobacco roots growing in sterile culture medium.[13] The results of these biochemical studies will be published later, although some representative results of several

(4) M. E. Pullman and S. P. Colowick, *J. Biol. Chem.*, **206**, 121 (1954).
(5) R. F. Dawson, D. R. Christman, A. D'Adamo, M. L. Solt, and A. P. Wolf, *J. Am. Chem. Soc.*, **82**, 2628 (1960).
(6) E. Winterstein, J. Keller, and A. B. Weinhagen, *Arch. Pharm.*, **255**, 513 (1917).
(7) E. M. Gal, R. E. Spenger, and D. M. Greenberg, *J. Org. Chem.*, **15**, 1261 (1950).
(8) R. Willstatter and W. Kuhn, *Ber.*, **37**, 1853 (1904).
(9) N. Isenberg, J. B. Liebsohn, and V. E. Merola, *Can. J. Chem.*, **40**, 831 (1962).
(10) M. Busch and H. Stöve, *Ber.*, **49**, 1073 (1916).
(11) (a) E. F. Phares, *Arch. Biochem. Biophys.*, **33**, 173 (1951); (b) E. F. Phares, and S. F. Carbon, *ibid.*, **33**, 179 (1951).
(12) R. C. Anderson and A. P. Wolf, Brookhaven National Laboratory Report BNL-3222, 1957.
(13) D. R. Christman and R. F. Dawson, *Biochem.*, **2**, 182 (1963).

TABLE I

COMPARISON OF NICOTINIC ACID AND PYRIDONE DECARBOXYLATIONS[a,b]

Compound[c]	Sp. act.[d]	CO_2 sp. act.[d]	% CO_2, total act.[e]
Nicotinic acid	75.1	65.5	87.0
2-Pyridone	0.182	0.174	95.6
6-Pyridone	0.248	0.211	85.0
Nicotinic acid	27.0	5.39	20.0
2-Pyridone	35.3	7.31	20.7
6-Pyridone	32.4	6.19	19.1
Nicotinic acid	6.12	0.678	11.1
2-Pyridone	14.9	1.63	10.9
6-Pyridone	39.6	4.58	11.7

[a] Nicotinic acid decarboxylated by pyrolysis of its calcium salt.[5] [b] Each compound was diluted separately after its preparation, before decarboxylation. [c] The first group was obtained from feeding of alanine-2-C^{14}; the second from alanine-3-C^{14}; the third from glycerol-1-C^{14}.[13] [d] Specific activities are expressed in mμc./mmole. Standard deviation is 3%. [e] Standard deviation is ±5%.

TABLE II

SCHMIDT DECARBOXYLATION OF δ-METHYLAMINOVALERIC ACIDS[a]

Source of acid[b]	Sp. act.[c]	CO_2 sp. act.[c]	% of total pyridine ring[d]
2-Pyridone	0.0158	0.00390	24.6 (C^2)
6-Pyridone	0.0186	0.00152	8.2 (C^6)

[a] From feeding of alanine-2-C^{14}. [b] Each compound was diluted separately after its preparation, before decarboxylation. [c] Specific activities are expressed in mμc./mmole. Standard deviation is 3%. [d] Standard deviation is ±5%.

stages of this degradation scheme are shown in Tables I and II.

In cases where very little activity is incorporated into the pyridine ring or where a rapid result is desired for C-2 or C-6 of the ring, the Schmidt reaction can be applied directly to VII, obtained by hydrolysis of VI. About 25–50 mg. of the acid is required for this procedure when gas counting is employed. This precludes the further degradation of this portion of the available material, however, since unsatisfactory results are obtained in the oxidation of diamines to dicarboxylic acids and in their subsequent degradation by the Schmidt method.

Experimental[14]

Nicotinamide.—I (200–400 mg.) is refluxed for 3 hr. with redistilled thionyl chloride (4 ml./100 mg. of acid) in a small round-bottomed flask with a neck about 4 in. long. A drying tube is used at the top of the reflux condenser. The condenser is then connected to the flask by a 120° elbow, and a receiver with a vacuum takeoff is provided. While the receiver is cooled in dry ice, a vacuum of about 1 cm. is applied and the reaction vessel is shaken gently while being heated to 30–40° by a heating mantle. After the excess thionyl chloride has distilled off, the flask containing nicotinoyl chloride is cooled with Dry Ice while a stream of gaseous ammonia is passed into the vessel until about 15 ml. of liquid ammonia are present. The flask is then lifted above the Dry Ice level and held there while the excess ammonia slowly boils off. The residue is then dissolved in a little water and passed onto a column of AG 3-X4 resin about 6 cm. long and 2 cm. in diameter. The resin (a specially prepared equivalent of IRA-400) is base washed, then thoroughly water washed, before use. The first 20 ml. of eluate (containing much ammonium chloride) is discarded, then the nicotinamide is eluted with about 500 ml. of water (unreacted I is retained by the resin). The water is then evaporated under vacuum, and the dry residue extracted with about 5 ml. of hot methanol (some ammonium chloride is carried along, but most remains undissolved at this point).

For 200 mg. of I, the volume of methanol is reduced to about 0.5 ml.; then about 0.15 ml. of methyl iodide is added and II is prepared as previously described, in an over-all yield of about 70%.[5]

From this II, the corresponding pyridones (III and IV) are prepared by oxidation with basic potassium ferricyanide, as previously described.[5] The yield of each pyridone is 20–25% from the methiodide.

Decarboxylation of Pyridones.[6]—Either III or IV (1–2 mmoles) is placed in a 50-ml. flask fitted with both a gas inlet tube and a long neck with a cold finger reflux condenser. The outlet of the condenser leads to a spiral gas trap, fitted with stopcocks at each end, *via* a joint for later attachment to a vacuum line. About 15 ml. of 60% sulfuric acid is added to the reaction flask and helium is bubbled through the solution at a rate of about 1 bubble per second. After the air in the system has been displaced by helium, the flask temperature is raised to just under reflux temperature and held there for 2–5 days until approximately the calculated amount of XII has been evolved. A much slower evolution may be noted after this point, owing to slow decomposition of the reaction products. During the first half of the reaction, the specific activity of the evolved XII agrees closely with that obtained by the pyrolysis of the corresponding calcium nicotinate (Table I). However, after that point the specific activity changes slowly, probably owing to the above mentioned decomposition. This is especially true during the decarboxylation of IV, which proceeds more slowly than does that of III. The water content should be maintained at roughly its starting level throughout the decarboxylation process.

When it is desired to trap XII (from the original carboxyl group) for counting purposes, liquid nitrogen is applied to the trap until sufficient XII has accumulated; the stopcocks are closed and the trap is removed to a vacuum system, where XII is measured and transferred to a counter. After the helium has been pumped away, the liquid nitrogen is replaced by a Dry Ice bath in order that XII can be removed without liberating water from the trap. This XII shows no discernible impurities when subjected to gas chromatographic analysis. From III, XII evolves at a rate of about 1 mg. of carbon in 2 hr., and from IV it evolves at less than half this rate.

After evolution of XII about equals the calculated amount, the solution is cooled and diluted to about 50 ml. with water. It is taken to pH 8 with solid sodium carbonate and then is continuously extracted for 1 day with chloroform. The chloroform is evaporated under mild vacuum at room temperature. The residual oil (V) is taken up in about 20 ml. of glacial acetic acid and about an equal weight of 5% rhodium on alumina is added. This mixture takes up the maximum amount of hydrogen at atmospheric pressure within 30 min., and the yield of pyridone can be indirectly ascertained from the amount of hydrogen taken up. The solution is then filtered, most of the acetic acid is removed under vacuum at room temperature, and the residual oil is refluxed for 2 days with 10 ml. of 6 *N* hydrochloric acid. The excess acid is removed under vacuum and the solid residue is dissolved in water; then small portions of thoroughly washed, base-form AG3-X4 resin are added until the pH is raised to 6.5. After filtration, the water is removed and the residue is thoroughly dried, and VII, m.p. 134–135°, is obtained by recrystallization from about 1:3 ethanol–ether (yield ~30% from pyridone).

Betaine of VII (IX).—About 3 mmoles of VII is dissolved in 3 ml. of water containing 1 equiv. of potassium hydroxide. While the reaction mixture is shaken vigorously, 1 ml. of dimethyl sulfate and 5 ml. of water containing 10 mequiv. of potassium hydroxide are added alternately, dropwise over about 0.5 hr. The solution is refluxed for 15 min., cooled, and taken to pH 7 with sulfuric acid, then evaporated to dryness. The dry solid is triturated with hot ethanol to extract the IX from inorganic material, and it can be crystallized as the dihydrate from a little ethanol plus about five times the volume of ether (m.p. 225° dec.). If sulfate is still present in the ethanol extract, it can be removed by adding dilute barium hydroxide solution until the pH has again been raised to about 6 and no more barium sulfate precipitates, then filtering, and repeating the evaporation and trituration.

(14) All C^{14} counting was performed by proportional gas counting of carbon dioxide. *Cf.* D. R. Christman, N. E. Day, P. R. Hansell, and R. C. Anderson, *Anal. Chem.*, **27**, 1935 (1955).

Formation of δ-Valerolactone (X).[8]—About 0.5 g. of IX is placed in an L-shaped side arm on an ordinary, straight vacuum trap. The outlet of this trap goes to a second trap and thence to a vacuum line. The first trap is provided with a joint so that it can be dismantled in the subsequent operations. The first trap is cooled with Dry Ice and the second with liquid nitrogen, after a pressure of about 0.8 atm. of helium has been introduced. The side arm, containing the betaine, is heated to 225°, and after about 1 min. the helium is slowly bled out of the system *via* the vacuum line. The system is then pumped for about 15 min., during which time trimethylamine collects in the second trap and X distils into the first trap.

δ-Bromovaleric Acid (XI).—X is washed out of the first trap with about 10 ml. of 48% hydrobromic acid and the solution is refluxed overnight.[9] Ether extraction gives XI, m.p. 137–139° (recrystallized from petroleum ether, b.p. 30–60°), in about 10% yield from IX.

Thallium Valerate (VIII).—A solution of 135 mg. of XI in 10 ml. of ethanol is dehalogenated with hydrogen at 1 atm., using 0.5 g. of 5% palladium on calcium carbonate as the catalyst.[10] The calculated amount of hydrogen is taken up in about 10 min., after which the solution is filtered and the ethanol removed under vacuum. The residue is taken up in water, acidified with sulfuric acid, and continuously extracted overnight with ether. A little less than 1 equiv. of an aqueous solution of thallous hydroxide is added to the ether extract and the mixture is stirred vigorously while the base is added to a phenolphthalein end point. This is taken to dryness and the crude XIII is triturated with several milliliters of absolute ethanol (inorganic thallium salts are insoluble). Then about twice the amount of ether is added to the supernatant ethanol and the product is obtained by refrigeration. The yield is about 90%, m.p. 160–164°. This salt can be used directly in running the Schmidt reaction.[12] The subsequent acids, made by the oxidation of the next lower amine (obtained in running the Schmidt reaction), are treated similarly after having been purified by gas chromatography. Each Schmidt reaction, from material based on either pyridone, gives XII representing one specific carbon atom in the original pyridine ring of nicotinic acid. The average activity level from 5 μc. of randomly labeled I is about 0.1 mμc./mg. of carbon.

Peroxytrifluoroacetic Acid–Boron Fluoride as a Source of Positive Hydroxyl[1,2]

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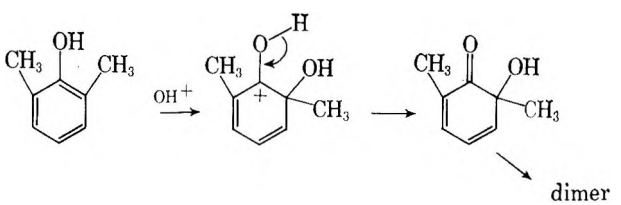
Peroxytrifluoroacetic acid–boron fluoride is shown to be an excellent reagent for effecting electrophilic aromatic hydroxylations with efficient use of the peracid. Mesitylene gave mesitol (88%), isodurene gave isodurenol (65%), but benzene gave only trace amounts of phenol. Prehnitene gave isodurenol, 2,3,5- and 2,3,6-trimethylphenol, 4,5,6,6-tetramethylcyclohexadienone, and 2,2′,3,3′,4,4′,5,5′-octamethyldiphenylmethane in addition to the expected prehnitol. These products can be rationalized by electrophilic attack of positive hydroxyl at substituted, as well as unsubstituted, aromatic carbon atoms, with 1,2-alkyl shifts in the former instance, and by hydride abstraction from methyl groups *para* to a phenolic hydroxyl.

It has long been recognized that organic peracids are sources of electrophilic (positive) hydroxyl in their reactions with the carbon–carbon double bond[4] and with certain aromatic hydrocarbons.[5] The hydroxyl cation was the assumed intermediate in the conversion of mesitylene to mesitol by hydrogen peroxide in acetic–sulfuric acid.[6] A Lewis acid (boron fluoride etherate) has been used in place of mineral acid with hydrogen peroxide to oxidize *m*-xylene, in low yield, to phenols and quinones.[7]

Peroxytrifluoroacetic acid was considered[8] to be an excellent source of positive hydroxyl, because the trifluoroacetate ion is a good leaving group. Using excess peracid, Musgrave, *et al.*, obtained 30–40% conversions of alkylbenzenes to phenols and quinones.[9] The orientation of the xylenols (2,4- and 2,6-) from *m*-xylene supported the contention that the reaction involved positive hydroxyl, rather than hydroxyl radicals.[10] The reaction has been extended to the preparation of *o*- and *p*-methoxyphenols from anisole and analogous phenoxyphenols from diphenyl ether.[11] The products from 2,6-dimethylphenol and peroxytrifluoroacetic acid depend upon reaction conditions; either 2,6-dimethylbenzoquinone or 6-hydroxy-2,6-dimethyl-2,4-cyclohexadienone dimer may predominate, slow addition of peroxide to the phenol favoring the latter (2,6-dimethyl-3-hydroxybenzoquinone is a minor reaction product).[12] Dienone dimer is presumably formed by attack of OH^+[13] at an already substituted position.[14]



It was considered likely that, if a Lewis acid facilitates the cleavage of hydrogen peroxide[7] and of certain diacyl

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support (G-488C).

(2) For a preliminary account, see C. A. Buehler and H. Hart, *J. Am. Chem. Soc.*, **85**, 2177 (1963).

(3) National Science Foundation Cooperative Fellow, 1962–1963.

(4) For a review, see D. Swern, *Org. Reactions*, **7**, 378 (1953).

(5) I. M. Roitt and W. A. Waters, *J. Chem. Soc.*, 3060 (1949).

(6) D. H. Derbyshire and W. A. Waters, *Nature*, **165**, 401 (1950); no experimental details are given.

(7) J. D. McClure and P. H. Williams, *J. Org. Chem.*, **27**, 24 (1962); this reagent converts aliphatic ketones to esters at room temperature in good yield.

(8) R. D. Chambers, P. Goggin, and W. K. R. Musgrave, *J. Chem. Soc.*, 1804 (1959).

(9) Conversions were calculated on the basis of hydrocarbon consumed; in fact, if calculated on amount of peracid used, they are much lower. The experimental technique described in the present paper (*vide infra*) affords much better conversions than previously reported,[8] even without boron fluoride.

(10) The hydroxyl radical, however, is also electrophilic; see R. O. C. Norman and G. K. Radda, *Proc. Chem. Soc.*, 138 (1962). The question of whether the hydroxyl radical or the cation is involved in certain metal-catalyzed aromatic hydroxylations of biochemical interest is still unsettled; see R. Stewart, "Oxidation Mechanisms," W. A. Benjamin, Inc., New York, N. Y., 1964, p. 159; also, G. A. Hamilton and J. P. Friedman, *J. Am. Chem. Soc.*, **85**, 1008 (1963).

(11) J. D. McClure and P. H. Williams, *J. Org. Chem.*, **27**, 627 (1962).

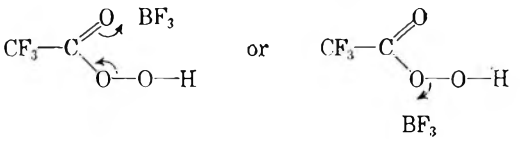
(12) J. D. McClure, *ibid.*, **28**, 69 (1963).

(13) The symbol OH^+ is used for convenience throughout this paper. It is recognized that the precise nature of the positive hydroxyl species is unknown; it may have trifluoroacetate or other ligands attached.

(14) The author[12] prefers a cyclic transition state involving initial hydrogen bonding of peracid to the phenolic hydroxyl, but this does not appear to be required.[15]

(15) A. J. Waring and H. Hart, *J. Am. Chem. Soc.*, **86**, 1454 (1964).

peroxides[16] to furnish positive oxygen fragments, it might also facilitate OH^+ formation from peroxytrifluoroacetic acid. This paper describes the use of CF_3CO_3H–BF_3 as a reagent for the oxidation of several methylbenzenes.



Results and Discussion

Addition of peroxytrifluoroacetic acid to a solution of excess mesitylene in methylene chloride, through which boron fluoride was passed, led to an exothermic reaction. The temperature was kept below 7° and an 88% yield of mesitol was obtained.[17] When the boron fluoride was omitted, the yield dropped to 45%. These yields are calculated on the amount of peracid used and represent a considerable improvement over an earlier procedure,[8] wherein the yield based on consumed mesitylene was equally high, but the conversion based on peracid was only 17%. "Aluminum trifluoroacetate," a white solid obtained from reaction of aluminum chloride with trifluoroacetic acid, was not so effective as boron fluoride but did improve the conversion (based on peracid) to 65%. It seems likely, then, that Lewis acids do function as catalysts for the oxidation, facilitating heterolytic cleavage of the O–O bond in the peracid.

Isodurene was readily converted in good yield to isodurenol by a similar one-step oxidation, but, when the reaction was applied to benzene, the yield of phenol was very small and an intractable black solid was obtained. One difficulty which must be overcome for the yield to be high is that the first oxidation product is, in general, more easily oxidized than the starting hydrocarbon. If, however, hydroxylation leads to a phenol in which positions *ortho* and *para* to the entering hydroxyl group are blocked, as in the case of mesitylene and isodurene, further oxidation is sufficiently slow that one can isolate the phenol in good yield. Use of an excess of hydrocarbon over peracid also improves the yield.[18]

The best evidence that the oxidation is the result of electrophilic substitution by OH^+, or some complexed form of it, and is not due to a reaction of hydroxyl radicals comes from a detailed study of the products from the oxidation of prehnitene (I).

Table I summarizes the oxidation products from prehnitene and peroxytrifluoroacetic acid, with and without boron fluoride. The catalytic effect of boron fluoride is again apparent. With it, peracid was used with 86% efficiency; without it, only 30% of the theoretical amount of prehnitene was oxidized. Although oxidized prehnitene was not quantitatively accounted for, the recovery is reasonably satisfactory when one includes the unidentified residues.

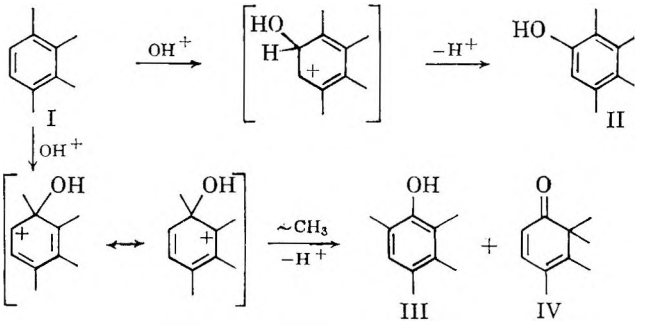
TABLE I

SUMMARY OF THE OXIDATION OF PREHNITENE WITH PEROXYTRIFLUOROACETIC ACID

	With BF_3		Without BF_3	
Prehnitene used (moles)	121.0		121.0	
Peracid used (mmoles)	38.3		38.3	
Prehnitene recovered (mmoles)	87.9		109.4	
Prehnitene oxidized (%)	86.2		30.3	
Products	mmoles	% of prehnitene oxidized	mmoles	% of prehnitene oxidized
Prehnitol (II)	3.0	9.1	2.2	19.0
Isodurenol (III)	1.2	3.6	2.0	17.2
4,5,6,6-Tetramethyl-2,4-cyclohexadienone (IV)	0.58	1.8	1.1	9.5
Unknown, mass 182	...	...	2.0	17.2
2,3,5-Trimethylphenol (X)	4.8	14.5	0.9	7.8
2,3,6-Trimethylphenol (XII)	1.8	5.4		
2,2′,3,3′,4,4′,5,5′-Octamethyldiphenylmethane (XI)	3.9	23.6	*a*	
Total	15.3	58.0	8.2	70.7
Residue (g.)	1.2		0.8	

[a] This product was present in the residue and identified by n.m.r., but was not isolated or quantitatively determined.

The three C_{10} products obtained with BF_3 can be accounted for by attack of OH^+ at an unsubstituted position, or at C-1 of prehnitene. The same products were obtained in somewhat greater yield (based on prehnitene oxidized) without BF_3; clearly BF_3 either catalyzes further reactions of II–IV, or generates a more reactive form of OH^+ which further oxidized these products.



Isolation of dienone IV constitutes excellent evidence that the hydroxylation involves cationic rather than radical intermediates, since the Wagner–Meerwein rearrangement necessary for its formation is not unusual, whereas a free-radical rearrangement of this type would be exceptional. Musgrave and co-workers[8] isolated a product, 2,3,5-trimethylbenzoquinone, from the oxidation of mesitylene with peroxytrifluoroacetic acid which also arises by a Wagner–Meerwein rearrangement. The structural assignment for IV rests on the following data. It has infrared bands at 1663 and 1630 cm.$^{-1}$ and an ultraviolet spectrum in ethanol, λ_{max} 327 mμ (log ε 3.48). These compare favorably with known similarly substituted dienones V[19] [1667, 1634 cm.$^{-1}$; λ_{max}^{EtOH} 328

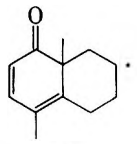
(16) See, for example, J. T. Edward, H. S. Chang, and S. A. Samad, *Can. J. Chem.*, **40**, 804 (1962); also D. Z. Denney, T. M. Valega, and D. B. Denney, *J. Am. Chem. Soc.*, **86**, 46 (1964).

(17) Subsequent experiments by A. J. Waring, have shown that the conversion is essentially quantitative at −40°, using 1 mole of boron fluoride per mole of peracid.

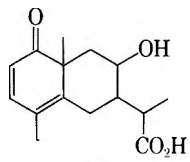
(18) It is perhaps noteworthy that recovered hydrocarbon is not appreciably isomerized.

(19) L. Mandell, D. Cane, and G. E. Kilpatrick, *J. Am. Chem. Soc.*, **83**, 4457 (1961).

mμ (log ε 3.55)] and VI[20] [1663, 1633 cm.$^{-1}$; λ_{max}^{EtOH} 320 mμ (log ε 3.69)]. The n.m.r. spectrum of IV showed singlets at τ 8.85 and 8.15 with six protons each (aliphatic and allylic methyls) and doublets at τ 4.19 and



V

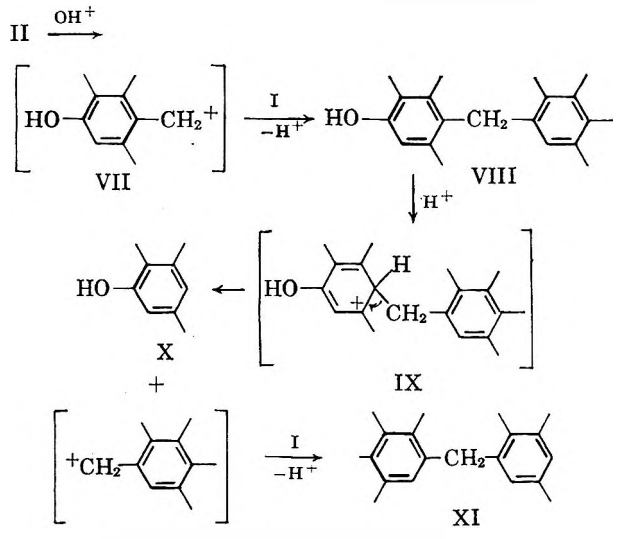


VI

3.26 (J = 9.5 c.p.s.) each corresponding to a single vinyl proton. IV gave a 2,4-dinitrophenylhydrazone with a satisfactory microanalysis.[21]

Another C_{10} product was obtained in rather substantial amounts from the oxidation without BF_3, but was not produced (or was destroyed) when BF_3 was used. Its structure is not yet certain.[22]

2,3,5- and 2,3,6-trimethylphenols are apparently derived from loss of the 4-methyl group from II and III, respectively. This methyl shows up as the extra carbon atom in the octamethyldiphenylmethane (XI). The trimethylphenols probably do not result from oxidation of demethylated prehnitene, because recovered excess prehnitene was almost free of isomers or lower homologs, and it is unreasonable that trimethylbenzenes should not be recovered if such a process were involved (*i.e.*, there is no reason why trimethylbenzenes should all be oxidized to phenols, when the prehnitene is partially recovered). Furthermore, isomers of X and XII were not detected. A more plausible mechanism



for the conversion of II to X and XI is shown in the scheme. Hydride abstraction from an already hydroxylated ring is facilitated by resonance stabilization of the resulting 4-hydroxybenzyl cation. Although postulated intermediate VIII was not isolated in the present reaction, similar products have been obtained with other substrates.[2] The hydroxyl group in VIII facilitates debenzylation, leading ultimately to X and XI. An analogous scheme starting with III accounts for the 2,3,6-trimethylphenol (XII). This mechanism requires that the yield of X plus XII equal the yield of XI. In fact (Table I), this sum exceeds the yield of XI, but the yield of XI is based on isolated, pure crystalline product and may be low (that of X and XII is based on v.p.c. curves). At any rate, they are the same order of magnitude. The ratio of yields of II:III is approximately the same as X:XII, which would be expected if X and XII arise from the demethylation of II and III, respectively, since there should be a negligible difference in the hydride abstraction rates for the two compounds.

The yield of hydride abstraction products (X–XII) is very much lower (and the yield of II and III correspondingly higher) when boron fluoride is omitted (Table I). Either BF_3 is involved (but not necessary) for the hydride transfer, or a "hotter" ozidizing agent is produced with BF_3 present. The yield of dienone IV is also higher without BF_3; this is not surprising, since the Lewis acid might polymerize IV.

Extension of this oxidation to other substrates will be the subject of future reports.

Experimental

Oxidation of Mesitylene.—A methylene chloride solution of peroxytrifluoroacetic acid was prepared by mixing 35 g. (0.167 mole) of trifluoroacetic anhydride, 50 ml. of methylene chloride, and 4.0 ml. (0.147 mole) of 90% hydrogen peroxide at 0°, then allowing the solution to warm to room temperature for several minutes. This peracid solution, cooled to 0°, was added dropwise to a solution of 56.1 g. (0.468 mole) of mesitylene in 100 ml. of methylene chloride, during which time boron fluoride was bubbled through the reaction mixture. The reaction was strongly exothermic, and the temperature was kept below 7° by a salt–ice bath. After addition was complete (2.5 hr.), the solution was allowed to warm to room temperature, 100 ml. of water was added, and the aqueous layer was separated and washed with three 25-ml. portions of methylene chloride. Combined organic layers were washed with 10% sodium bisulfite until washings gave a negative potassium iodide reaction, 10% sodium bicarbonate, then dried over anhydrous magnesium sulfate. After solvent removal, the residue was distilled through a 1-ft. helices-packed column, giving 32.0 g. of recovered mesitylene, b.p. 84–86° at 35 mm., and 17.7 g. of mesitol (88.5% based on peracid), b.p. 98° at 10 mm., m.p. and m.m.p. 69–70°. The tarry residue weighed 2 g.

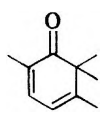
Several modifications gave the following results. When only a slight excess of mesitylene (18.7 g.) was used (all other amounts and conditions constant), 6.0 g. of mesitol (30% based on peracid used), 7.0 g. of recovered mesitylene, and 5.7 g. of tarry residue was obtained.

When boron fluoride was omitted from the experiment described in detail above, but all other conditions were maintained, there was obtained 9.67 g. (45%) of mesitol, 39.0 g. of recovered mesitylene, and 4.25 g. of residue.

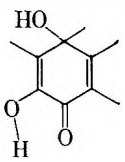
A material approximating aluminum trifluoroacetate in composition could be used in place of boron fluoride. To a stirred slurry of 22.3 g. (0.167 mole) of anhydrous aluminum chloride in 50 ml. of methylene chloride was added, dropwise, 57.0 g. (0.50 mole) of trifluoroacetic acid. The vigorously evolved hydrogen chloride was swept by nitrogen into an alkali trap (0.44 mole, 88% of theory for "aluminum trifluoroacetate"). After addition was complete, solvent was removed by warming to 60°, leaving a white-brown precipitate, to which 56.1 g.

(20) W. Cocker, *Chem. Ind.* (London), 1041 (1955).

(21) The chemical shifts and n.m.r. pattern eliminate this alternative structure for the dienone (see especially ref. 15 for model compounds).



(22) A structure which is reasonably consistent with the data (see Experimental), and which is mechanistically plausible, is shown below, but further work is needed for a positive identification of this product.



(0.468 mole) of mesitylene was added. Peroxytrifluoroacetic acid (from 19.1 g. of trifluoroacetic acid, 50 ml. of methylene chloride, and 4.0 ml. of 90% hydrogen peroxide) was added, the temperature being kept at 25–30° during addition (2.5 hr.) by ice-bath cooling. Work-up gave 37.5 g. of unchanged mesitylene, 13.0 g. (65%) of mesitol, and 2.0 g. of residue.

Oxidation of Isodurene.—The reaction procedure was the same as the first one described for mesitylene. Isodurene (54.0 g., 0.410 mole) in 100 ml. of methylene chloride was treated with peroxytrifluoroacetic acid prepared from 30.9 g. (0.147 mole) of trifluoroacetic anhydride, 50 ml. of methylene chloride, and 3.7 ml. of 90% hydrogen peroxide. After hydrolysis and removal of the solvent, the dark brown liquid residue was chromatographed on alumina. Elution with petroleum ether (b.p. 60–90°) gave 33.5 g. of recovered isodurene, b.p. 76–78° at 10 mm. Elution with ether gave 12.9 g. (62.7%) of isodurenol, m.p. 79–81°.[23]

Oxidation of Prehnitene.—The reaction procedure was the same as described in detail for mesitylene, the amounts of reactants being 16.24 g. (0.121 mole) of prehnitene in 100 ml. of methylene chloride, and peroxytrifluoroacetic acid prepared from 9.0 g. (0.0424 mole) of trifluoroacetic anhydride, 30 ml. of methylene chloride, and 1.04 ml. (0.0383 mole) of 90% hydrogen peroxide. After reaction, 100 ml. of water was added, the layers separated, and the aqueous layer was saturated with sodium chloride and extracted with methylene chloride. Combined organic layers were washed with 10 ml. of 10% sodium bisulfite, 10 ml. of 10% sodium bicarbonate, and then extracted with 40 ml. of Claisen's alkali (14 g. of potassium hydroxide dissolved in 10 ml. of water, diluted with methanol to 40 ml.).

The alkaline extract was washed with methylene chloride, acidified with hydrochloric acid, saturated with salt, and extracted with ether. After drying (magnesium sulfate) and removal of the solvent, there remained 1.58 g. of residue which was taken up in carbon tetrachloride and vapor chromatographed[24] at 152°. The five well-resolved peaks were identified in order of retention time as prehnitene (7.6%); 2,3,6-trimethylphenol (15.8%), m.p. 59–61° (lit.[25] m.p. 62°), infrared identical to published spectrum[26]; 2,3,5-trimethylphenol (40%), m.p. 91–93°, λ_{max} (cyclohexane) 282, 278, and 273 mμ, infrared identical to published spectrum[26] (lit.[23] m.p. 95–96°, λ_{max} 282, 278, and 274 mμ); isodurenol (10.2%), m.p. and m.m.p. 81°, infrared and n.m.r. spectra identical with those of an authentic sample; prehnitol (27.4%), m.p. 81–83°, λ_{max} (ethanol) 277.5, 282.5, and 286.5 mμ, infrared identical to published spectrum[26] [lit.[27] m.p. 86–87°, λ_{max}[28] (ethanol) 277.5, 282.5, and 286.5 mμ].

The neutral fraction after Claisen's alkali extraction was washed with water, then dried over magnesium sulfate. After removal of solvent, the residue was distilled through a 7-in. vacuum-jacketed Vigreux column, giving 11.1 g. of prehnitene, b.p. 85–90° at 16 mm., pure by v.p.c., and a second fraction (0.71 g.), b.p. 90–125° at 16 mm. This fraction was analyzed by v.p.c., and contained 79.4% prehnitene, 12.2% **4,5,6,6-tetramethyl-2,4-cyclohexadienone**, 3.65% 2,3,5-trimethylphenol, 2.56% isodurenol, and 2.24% prehnitol, in order of increasing retention time. The ketone had infrared bands at 1663 and 1630 $cm.^{-1}$, a λ_{max} (ethanol) at 327 mμ (log ε 3.48), and its n.m.r. spectrum in carbon tetrachloride had singlets at τ 8.85 and 8.15 (six protons each) and doublets at τ 4.19 and 3.26, J = 9.5 c.p.s., one proton each. The ketone was converted to its 2,4-dinitrophenylhydrazone by standing with the reagent in ethanol for 7 days, followed by reflux for 30 min. Water was added to the cooled solution, and the resulting precipitate was extracted with chloroform, dried with magnesium sulfate and Bentonite[29]; the solvent was removed, and the residue was recrystallized from 95% ethanol, giving deep red crystals, m.p. 153°.

Anal.[30] Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.97. Found: C, 58.28; H, 5.53; N, 16.89.

The residue (2.55 g.) from distillation of the neutral fraction was chromatographed on Fluorosil using petroleum ether as eluant. There was obtained 1.10 g. of 2,2′,3,3′,4,4′,5,5′-octamethyldiphenylmethane, m.p. 150–151° (from ethanol). Its ultraviolet spectrum had λ_{max} (cyclohexane) 271 mμ (ε 290). The n.m.r. in carbon tetrachloride had bands at τ 7.92, 7.87 and 7.83 (24 protons), at 6.27 (two protons), and at 3.61 (two protons). The mass spectrum[31] had M^+ at 280 (calcd. mol. wt., 280.4).

Anal. Calcd. for $C_{21}H_{28}$: C, 89.94; H, 10.06. Found: C, 90.04; H, 9.86.

The material was identical (mixture melting point and infrared and n.m.r. spectra) with an authentic sample prepared from prehnitene, paraformaldehyde, and sulfuric acid.[32]

The remaining neutral product (1.20 g.) was eluted from Fluorosil with ether–methanol. It was tarry, could not be crystallized, and had carbonyl bands in the infrared and n.m.r. bands from τ 7.60 to 8.70, but no bands from 2.0 to 3.8.

The reaction was repeated, except that the peroxide was intentionally omitted. From 8.12 g. of prehnitene there was recovered 7.50 g. (92.5%) of distilled, v.p.c. pure starting material; no other products were isolated.

The oxidation was repeated omitting the boron fluoride but otherwise using the same amounts of materials as described above. The residue from the Claisen's alkali extract weighed 1.05 g. and consisted of 8.1% prehnitene, 6.8% of a mixture of 2,3,6- and 2,3,5-trimethylphenol, an unidentified material (34.5%) not present when BF_3 was used, 20.9% isodurenol, and 29.8% prehnitol. The as yet unidentified[22] product had a molecular weight (mass spectrometry) of 182 (possibly $C_{10}H_{14}O_3$); the base peak was at mass 43. Its infrared spectrum showed hydroxyl (3.0 μ), broad carbonyl (5.8–5.9 μ), and carbon–carbon double bond (6.10 μ). It had a broad λ_{max} (ethanol) at 264 mμ (log ε 3.80). Its n.m.r. spectrum had singlets at τ 7.23, 7.87, 7.97, 8.35, and 8.72 with areas roughly 2:6:3:3:3, but the band at 7.87 was probably much too large because of trimethylphenol impurity (peak at mass 136).

The neutral fraction gave 14.28 g. of recovered prehnitene and 1.43 g. of a dark-brown liquid residue. This was separated into volatile (0.63 g.) and nonvolatile (0.80 g.) portions by distillation at 0.07 mm., with a pot temperature of 180°. The volatile fraction consisted of (v.p.c.) 51.2% prehnitene, 26.6% 4,5,6,6-tetramethyl-2,4-cyclohexadienone, 7.5% 2,3,5-trimethylphenol, 12.4% isodurenol, and 2.7% prehnitol. The nonvolatile product contained a trace of the octamethyldiphenylmethane, but was mainly nonaromatic with an infrared spectrum nearly identical with a similar product from the boron fluoride catalyzed oxidation.

Oxidation of Benzene.—A solution of 36.7 g. (0.468 mole) of benzene in 100 ml. of methylene chloride was oxidized, at <7°, with peroxytrifluoroacetic acid prepared from 35.1 g. (0.167 mole) of trifluoroacetic anhydride, 50 ml. of methylene chloride, and 4.3 ml. (0.157 mole) of 90% hydrogen peroxide. Boron fluoride was bubbled through the reaction mixture during the oxidation. The reaction mixture turned blue immediately and darkened during the reaction. Hydrolysis precipitated 5.5 g. of a black solid, which burned with difficulty and failed to melt below 250°. Alkaline extraction (20% sodium hydroxide) gave 1.0 g. of phenol; the neutral fraction gave 22.0 g. of recovered benzene.

Repetition, but with a sevenfold excess of benzene (85.7 g., 1.1 mole) gave similar results. Oxidation on this scale, but using "aluminum trifluoracetate" in place of boron fluoride gave only 2.5 g. of phenol. When the original oxidation was repeated without the boron fluoride, the black solid was not produced; much benzene was recovered, plus a small amount of tar.

(23) D. H. Hey, *J. Chem. Soc.*, 1581 (1931).

(24) An Aerograph Model A-90-P gas chromatograph, with 20% silicone gum rubber (SE-30) on 60/80-mesh Chromasorb W, was used for analytical and preparative separations. Products were identified by retention time, and by physical properties of collected material.

(25) G. T. Morgan and A. E. J. Pettit, *J. Chem. Soc.*, 418 (1934).

(26) "Satdler Standard Spectra," Satdler Research Laboratories, Philadelphia, Pa., 1962.

(27) A. Tohl, *Ber.*, **21**, 904 (1888).

(28) "Organic Electronic Spectral Data," Vol. I, M. J. Kamlet, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 352.

(29) H. Shine, *J. Org. Chem.*, **24**, 252 (1959).

(30) Spang Microanalytical Laboratories, Box 1111, Ann Arbor, Mich.

(31) We are indebted to S. Meyerson, American Oil Co., Whiting, Ind., for all mass spectra reported in this paper.

(32) H. A. Smith and C. M. Welch, *J. Am. Chem. Soc.*, **73**, 4391 (1951).

Syntheses and Some Reactions of Allophanoyl Chlorides[1a]

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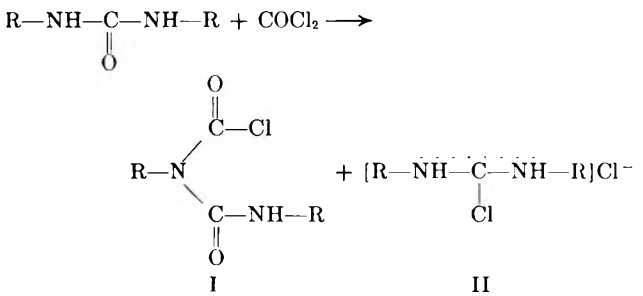
Cyclic and acyclic N,N′-Dialkylallophanoyl chlorides (I), a new class of intermediates, were synthesized from N,N′-disubstituted ureas and phosgene. The effect of substituent on the course of the reaction and some reactions of the allophanoyl chlorides are discussed.

Allophanic acid derivatives, especially the esters, the allophanates,[2] are known; however, the corresponding acid chlorides, the substituted allophanoyl chlorides, are not known. Allophanoyl chloride, although not characterized, was reported.[3]

The reaction of N,N′-dialkylureas with phosgene is reported[4] to give N,N′-dialkylchloroformamidine hydrochlorides (II). The formation of II suggests that phosgene is attacked by the oxygen rather than the nitrogen atom of the ureas. These results could have been expected in view of the facile reaction of N-alkylcarboxamides with phosgene which afforded high yields of the corresponding imide chlorides.[5]

Reinvestigation of the reaction of N,N′-dialkylureas with phosgene showed that in all cases studied, in addition to the reported N,N′-dialkylchloroformamidines (II), N,N′-dialkylallophanoyl chlorides (I) were formed. The distribution of I and II can be slightly controlled by the reaction conditions; however, structural features of the starting N,N′-dialkylureas seem to be the dominant factor (see Table I).



a, R = methyl
b, R = *n*-butyl
c, R = *n*-octadecyl
d, R = isopropyl
e, R = cyclohexyl

From Table I it appears evident that the steric factor mainly determines the course of the reaction. Thus, when the substituents are primary alkyls, the main product is allophanoyl chloride, arising from the nucleophilic attack of the urea nitrogen on phosgene, but, when the substituents are secondary alkyls, the main product is chloroformamidine hydrochloride.

The proportions of I and II could be determined by infrared spectroscopy, I showing a C=O band at 5.73–5.82 μ, II a C=N band at 5.95–6.02 μ.

The structure of the allophanoyl chlorides has been established by elemental analysis, infrared spectroscopy (NH, 2.94–3.02 μ; C=O, 5.73–5.82 μ), and conversion to the allophanates and biurets by means of sodium alkoxide and amines, respectively.

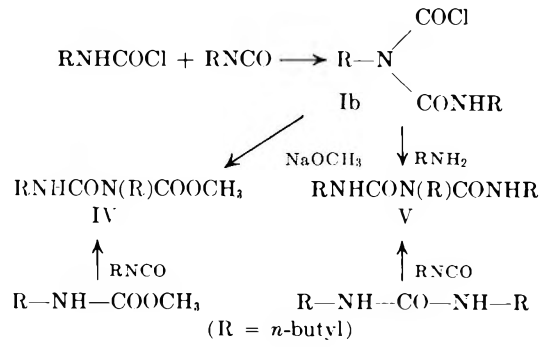
TABLE I

REACTION OF N,N′-DIALKYLUREAS WITH PHOSGENE[a]

Starting urea	N,N′-Dialkylallophanoyl chloride (I),[b] % yield	N,N′-Dialkylchloroformamidine·HCl (II), % yield
Dimethyl	71	28
Di-*n*-butyl	70.5	24
Di-*n*-octadecyl	69	28
Diisopropyl	6.7	75.6[c]
Dicyclohexyl	12.5	77.8

[a] Runs in ethylene dichloride at 2–5°. [b] The yields of I are not optimum yields. [c] Also 8.2% of N,N′-diisopropylchloroformamidine-N-carbonyl chloride was isolated. While phosgene does not react with I, with II it forms chloroformamidine-N-carbonyl chlorides.[6]

As a model compound, Ib was converted with sodium methoxide to methyl 2,4-di-*n*-butylallophanate (IV), which was found to be identical with a sample prepared from methyl N-*n*-butylcarbamate and *n*-butyl isocyanate. Similarly, Ib reacts with *n*-butylamine to give 1,3,5-tri-*n*-butylbiuret (V), which was synthesized independently from 1,3-di-*n*-butylurea and *n*-butyl isocyanate. Further evidence for the structure of Ib is its synthesis from *n*-butyl isocyanate and *n*-butylcarbamoyl chloride.



The structure of the chloroformamidine hydrochlorides (II) was confirmed by infrared spectroscopy, by conversion to guanidine hydrochlorides with primary amine, and by dehydrochlorination to carbodiimides with tertiary amine. Thus IIb was converted to di-*n*-butylcarbodiimide (III) using triethylamine, and IIb with *n*-butylamine afforded 1,2,3-tri-*n*-butylguanidine hydrochloride.

In the presence of triethylamine, N,N′-di-*n*-butylurea reacts with excess phosgene to give a mixture of Ib (31%) and N,N′-di-*n*-butylchloroformamidine-N-carbonyl chloride (VI, 69%). The latter is formed by addi-

(1) (a) Presented at the XIXth International Congress of Pure and Applied Chemistry, London, 1963; (b) To whom all inquiries should be directed.

(2) H. W. Blohm and E. I. Becker, *Chem. Rev.*, **51**, 471 (1952).

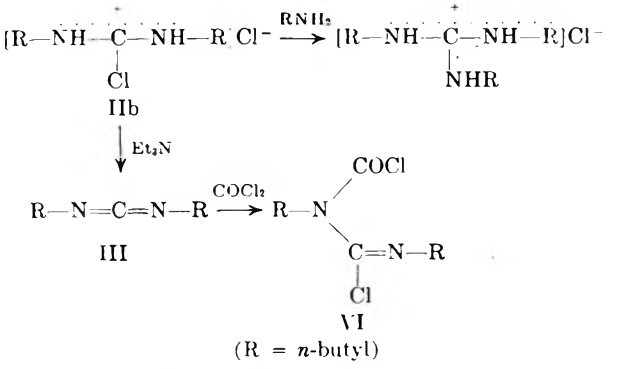
(3) C. Steigerwald, German Patent 238,961; *Chem. Zentr.*, **II**, 1285 (1911).

(4) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).

(5) I. Ugi, F. Beck, and U. Fetzer, *Ber.*, **95**, 126 (1962).

(6) H. Ulrich and A. A. R. Sayigh, *J. Org. Chem.*, **28**, 1427 (1963).

tion of phosgene to the intermediate di-*n*-butylcarbodiimide (III, R = *n*-butyl). Phosgene adds readily to carbodiimides at room temperature.[6]

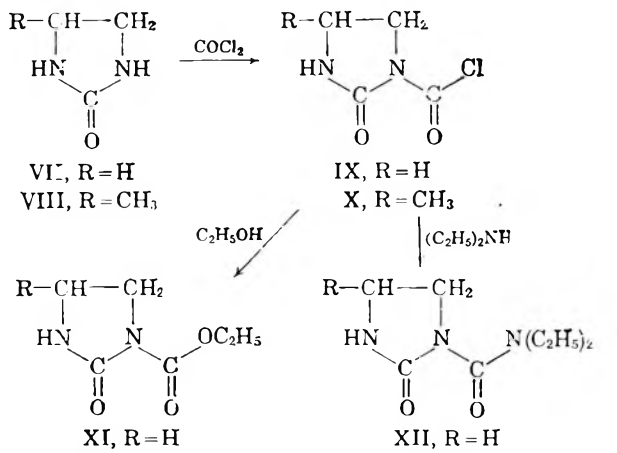


Cyclic alkylureas, such as ethyleneurea (VII) and propyleneurea (VIII), react similarly, apparently exclusively by N-attack, to form the corresponding cyclic allophanoyl chlorides (2-imidazolidinone-N-carbonyl chlorides, IX and X), since the yields of these are high and since the characteristic 6.0-μ[7] (C=N) absorption of the possible O-attack products (1-chloroimidazolines) was entirely absent. Similarly, ethyleneurea reacts with phosphorus pentachloride to give products arising only from N-attack.[8]

The assigned structure of X is based on the hypothesis that attack by the N-atom next to the primary carbon atom is more likely.

The infrared spectra of IX and X in chloroform show a characteristic triple band pattern in the carbonyl region (5.52, 5.67, and 5.77 μ) and two absorptions in the NH region, 2.93 and 3.1 μ, for the free and associated NH absorptions, respectively.

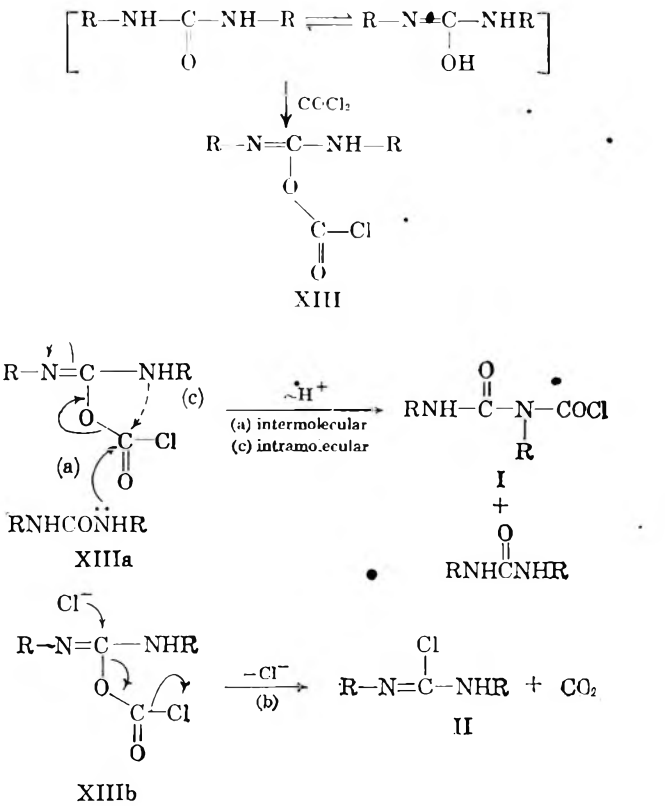
Further confirmation of the proposed structure is the reaction of IX with ethanol and with diethylamine to give XI and XII, respectively.



Perhaps one can accommodate the formation of the two major products I and II from a single intermediate XIII formed initially by a nucleophilic attack of the oxygen of the urea or pseudourea on phosgene. An intermolecular attack by the nucleophilic nitrogen of a second molecule of urea on this intermediate (process a) or even an intramolecular displacement (process c) can give I, while an attack by chloride ion (process b) would give II.

(7) P. T. Stoffel and A. T. Speciale, *J. Org. Chem.*, **27**, 3079 (1962).

(8) H. Najer, R. Giudicelli, and T. Sette, *Bull. soc. chim. France*, 2114 (1961).



This mechanism is consistent with our observation that the ratio of II:I is increased with higher chloride ion concentration. Thus, when a soluble quaternary ammonium chloride or a polar solvent is used in the reaction, the formation of II is favored over I.

Experimental

2,4-Di-*n*-butylallophanoyl Chloride (Ib). A. From 1,3-Di-*n*-butylurea and Phosgene in Ethylene Dichloride.—To 22.4 g. (0.13 mole) of 1,3-di-*n*-butylurea in 150 ml. of ethylene dichloride at 2° was added a solution of 13.8 g. (0.14 mole) of phosgene in 72 ml. of ethylene dichloride. After stirring for 1 hr. at room temperature and purging with nitrogen at 80°, the solvent was evaporated. The residue was extracted with four 200-ml. portions of dry ether, and evaporation of the ether afforded 21.5 g. (70.5%) of 2,4-di-*n*-butylallophanoyl chloride (Ib). Distillation of a 2-g. sample *in vacuo* afforded 1.8 g., b.p. 98° (0.5 mm.); $n^{23}D$ 1.4662; $\lambda_{max}^{CHCl_3}$ (infrared) 2.99, 3.42, 5.73, 6.55, 6.85, 7.25, 7.45, 8.47, 9.12, and 10.17 μ.

Anal. Calcd. for $C_{10}H_{19}ClN_2O_2$: C, 51.17; H, 8.15; N, 11.97. Found: C, 51.36; H, 8.32; N, 12.00.

The oily ether-insoluble material (7.1 g., 24%) was identified as N,N'-di-*n*-butylchloroformamidine hydrochloride (IIb) by its infrared spectrum (C=N, 6.0 μ), which was superimposable on that of N,N'-di-*n*-butylchloroformamidine hydrochloride prepared from di-*n*-butylcarbodiimide and hydrogen chloride, and by quantitative conversion to the known di-*n*-butylcarbodiimide, b.p. 33–34° (0.1 mm.), $n^{23}D$ 1.4482, upon addition of 2 equiv. of triethylamine to a benzene solution of IIb.

B. From 1,3-Di-*n*-butylurea and Phosgene in Benzene.—A solution of 51.6 g. (0.3 mole) of 1,3-di-*n*-butylurea in 216 ml. of benzene was added dropwise to a cold (8–10°), stirred solution of 73.7 g. (0.74 mole) of phosgene in 300 ml. of benzene while purging with nitrogen to remove the generated hydrogen chloride. After the addition was finished, the solution was heated to 80° to remove the excess phosgene. Evaporation of the benzene afforded 70.7 g. (calcd. 70.3 g.) of 2,4-di-*n*-butylallophanoyl chloride (Ib). The infrared spectrum of the obtained material was identical with that of distilled material obtained according to method A.

Anal. Calcd. for $C_{10}H_{19}ClN_2O_2$: Cl, 15.3. Found: Cl, 15.6.

C. From 1,3-Di-*n*-butylurea and Phosgene in Chloroform.—A solution of 13.9 g. (0.14 mole) of phosgene in 72 ml. of chloroform

was added dropwise to a stirred, cold (3–5°) solution of 22.4 g. (0.13 mole) of 1,3-di-*n*-butylurea in 150 ml. of chloroform. By the work-up procedure used in A, 14.7 g. (48.2%) of Ib and 14.1 g. (47.9%) of the ether-insoluble IIb was obtained.

D. **From 1,3-Di-*n*-butylurea and Phosgene in the Presence of Triethylamine.**—To 51.6 g. (0.3 mole) of 1,3-di-*n*-butylurea in 516 ml. of benzene, 60.6 g. (0.6 mole) of triethylamine was added. After cooling to 8–10°, about 0.5 mole of phosgene was added. The reaction mixture was purged with nitrogen at 80° for 30 min. After filtration of the triethylamine hydrochloride and evaporation of the benzene, 75.2 g. of a mixture of N,N′-di-*n*-butylchloroformamidine-N-carbonyl chloride (VI[6]) and Ib was obtained as shown by the infrared spectrum; VI is characterized by the C=N absorption at 5.98 μ, Ib by the NH band at 2.99 μ.

Since separation of VI and Ib was not possible by distillation, the yield of these substances was achieved by the following procedure. A 10-g. sample was refluxed in *o*-dichlorobenzene for 1 hr., thereby decomposing the 2,4-di-*n*-butylallophanoyl chloride to *n*-butyl isocyanate while leaving VI unchanged. According to quantitative infrared studies, the *n*-butyl isocyanate obtained corresponded to 31 ± 5% of Ib. Thus the yield of VI is 69 ± 5% (by difference and infrared analysis; *i.e.*, quantization of the C=N absorption at 5.98 μ compared with an authentic sample prepared from di-*n*-butyl carbodiimide and phosgene).

E. **From *n*-Butyl Isocyanate and *n*-Butylcarbamoyl Chloride.**—To 9.9 g. (0.1 mole) of *n*-butyl isocyanate was added 13.5 g. (0.1 mole) of *n*-butylcarbamoyl chloride. The mixture was slowly heated and finally refluxed (110–115°) for 15 min. Removal of the excess of starting materials *in vacuo* afforded 6.15 g. (51.5%) of slightly impure Ib as evidenced by its infrared spectrum. The C=O absorption at 5.73 μ was compared with that of a pure standard and a purity of 95 ± 5% was observed.

Reaction of Ib with Sodium Methoxide.—A solution of 0.6 g. of sodium methoxide in 10 ml. of methanol was added to 2.34 g. (0.01 mole) of Ib in 10 ml. of methanol. After standing for 20 hr., the methanol was evaporated and the residue was extracted with ether. Evaporation of the ether gave 1.8 g. (78%) of methyl 2,4-di-*n*-butylallophanate (IV), b.p. 95–97° (0.4 mm.). The infrared spectrum of IV was identical with that of IV synthesized from methyl N-*n*-butylcarbamate and *n*-butyl isocyanate.

Reaction of Ib with *n*-Butylamine.—Dropwise addition of a solution of 46.9 g. (0.2 mole) of Ib in 150 ml. of benzene to a stirred mixture of 32.12 g. (0.44 mole) of *n*-butylamine in 250 ml. of benzene, followed by removal of *n*-butylamine hydrochloride and evaporation of the solvent yielded 54.1 g. (99.8%) of crude 1,3,5-tri-*n*-butylbiuret (V). Distillation afforded 42.9 g. (79.3%) of pure V, b.p. 170° (0.1 mm.); $\lambda_{max}^{CHCl_3}$ (infrared) 2.9, 3.08, 3.43–3.5, 5.9, 6.08, 6.6, and 6.8 μ.

Anal. Calcd. for $C_{13}H_{29}N_3O$: N, 15.48. Found: N, 15.72.

Methyl 2,4-Di-*n*-butylallophanate (IV).—To 40 g. (0.3 mole) of methyl N-*n*-butylcarbamate in 100 ml. of xylene, 30 g. (0.3 mole) of *n*-butyl isocyanate was added. After reflux (140°) for 18 hr., the solvent was evaporated and the residue was distilled *in vacuo*. Thus 20 g. (50%) of methyl 2,4-di-*n*-butylallophanate, b.p. 95–97° (0.4 mm.), $n^{23}D$ 1.4510, was obtained; $\lambda_{max}^{CHCl_3}$ 3.03, 3.43–3.5, 5.84, 5.95 (weak), 6.5, 6.87, 7.3, 7.74, and 8.62 μ.

Anal. Calcd. for $C_{11}H_{22}N_2O_3$: N, 12.17. Found: N, 12.40.

1,3,5-Tri-*n*-butylbiuret (V).—To 17.2 g. (0.1 mole) of 1,3-di-*n*-butylurea in 100 ml. of toluene was added 9.9 g. (0.1 mole) of *n*-butyl isocyanate. After refluxing (110°) for 18 hr., the solvent was evaporated and the residue was distilled to give 26 g. (96%) of 1,3,5-tri-*n*-butylbiuret (V), b.p. 170° (0.1 mm.). The infrared spectrum of the distilled material was identical with that of V obtained from Ib and *n*-butylamine.

N,N′-Di-*n*-butylchloroformamidine Hydrochloride (IIb).—To 15.9 g. (0.1 mole) of di-*n*-butylcarbodiimide in 100 ml. of chloroform, hydrogen chloride was added until the exothermic reaction ceased. The excess of hydrogen chloride was removed with nitrogen, and evaporation of the solvent afforded 22.2 g. (97.7%) of N,N′-di-*n*-butylchloroformamidine hydrochloride (IIb); $\lambda_{max}^{CHCl_3}$ (infrared) 3.25, 3.42, 6.0, 6.42, 6.82, and 7.25 μ.

Reaction with *n*-Butylamine.—To 2.27 g. (0.01 mole) of IIb in 10 ml. of chloroform, 1.4 g. of *n*-butylamine was added dropwise with ice cooling. The chloroform was evaporated. Addition of water to the residue precipitated 1.2 g. (45.7%) of 1,2,3-tri-*n*-butylguanidine hydrochloride, m.p. 207–208°; $\lambda_{max}^{CHCl_3}$ (infrared): NH, 3.17 μ; C=N; 6.15 μ.

Anal. Calcd. for $C_{13}H_{30}ClN_3$: C, 59.25; H, 11.46; N, 15.93. Found: C, 59.25; H, 11.51; N, 16.24.

Reaction with Triethylamine.—To 2.27 g. (0.1 mole) of IIb in 20 ml. of dry benzene was added 2.02 g. (0.02 mole) of triethylamine. After stirring for 1 hr., 2.6 g. (94.5%) of triethylamine hydrochloride was filtered off. Evaporation of the benzene afforded 1.5 g. (97.2%) of di-*n*-butylcarbodiimide, b.p. 33–34° (0.1 mm.), $n^{22}D$ 1.4482; $\lambda_{max}^{CHCl_3}$ (infrared) 3.45–3.5, 4.73, 6.83, and 7.45 μ (lit.[9] b.p. 84–85° at 10 mm.).

2,4-Dimethylallophanoyl Chloride (Ia).—Procedure A afforded 28% of the ether-insoluble N,N′-dimethylchloroformamidine hydrochloride (IIa), m.p. 138–140°, lit.[4] m.p. 138–143°; $\lambda_{max}^{CHCl_3}$ (infrared) 3.15, 3.4, 5.95, 6.23, 6.8, 7.2, 8.75, and 9.62 μ. Upon evaporation of the ether, 70.9% of 2,4-dimethylallophanoyl chloride (Ia), m.p. 36°, was obtained; $\lambda_{max}^{CHCl_3}$ (infrared) 2.98, 3.4, 5.75, 6.53, 7.03, 7.68, 9.35, and 9.85 μ.

Anal. Calcd. for $C_4H_7ClN_2O_2$: N, 18.61. Found: N, 18.40.

2,4-Di-*n*-octadecylallophanoyl Chloride (Ic).—According to procedure A, 28.1% of N,N′-di-*n*-octadecylchloroformamidine hydrochloride (IId), m.p. 104° (ethyl acetate), was obtained; λ_{max}^{KBr} (infrared) 3.05, 3.45–3.52, 6.16, 6.32, 6.79, and 13.87 μ.

Anal. Calcd for $C_{37}H_{76}Cl_2N_2$: N, 4.53. Found: N, 4.62.

Evaporation of the ether gave 69% of 2,4-di-*n*-octadecylallophanoyl chloride (Ic), m.p. 68–69° (acetone); $\lambda_{max}^{CHCl_3}$ (infrared) 3.02, 3.48–3.53, 5.8, 6.6, 6.85, and 9.1 μ.

Anal. Calcd. for $C_{38}H_{75}ClN_2O_2$: N, 4.48. Found: N, 4.70.

2,4-Diisopropylallophanoyl Chloride (Id).—According to procedure A, 75.1% of the ether-insoluble N,N′-di sopropylchloroformamidine hydrochloride (IId) was obtained, m.p. 97–100°, lit.[4] m.p. 100–105°; $\lambda_{max}^{CHCl_3}$ (infrared) 3.24, 3.42, 6.02, 6.45, 6.8, 7.15, and 8.88 μ. Evaporation of the ether gave a mixture of products from which distillation afforded 8.2% of N,N′-diisopropylchloroformamidine-N-carbonyl chloride,[6] b.p. 55–58° (0.3 mm.); $\lambda_{max}^{CHCl_3}$ (infrared) 5.75 (C=O) and 6.0 μ (C=N).

Recrystallization of the distillation residue from ligroin gave 6.7% of 2,4-diisopropylallophanoyl chloride (Id), m.p. 63°; $\lambda_{max}^{CHCl_3}$ (infrared) 3.02, 3.25, 3.43, 5.82, 6.67, 6.85, 7.18, 7.3, 7.85, 8.65, and 9.6 μ.

Anal. Calcd. for $C_8H_{15}ClN_2O_2$: C, 46.49; H, 7.31; N, 13.55. Found: C, 46.42; H, 7.50; N, 13.61.

2,4-Dicyclohexylallophanoyl Chloride (Ie).—Procedure A afforded 77.8% of N,N′-dicyclohexylchloroformamidine hydrochloride (IIe), m.p. 143–144°, lit.[10] m.p. 139–141°. On evaporation of the ethereal solution, 12.5% of 2,4-dicyclohexylallophanoyl chloride (Ie), m.p. 127–128° (*n*-hexane), was obtained; $\lambda_{max}^{CHCl_3}$ (infrared) 2.95, 3.25, 3.45, 5.82, 6.67, 6.87, 7.22, 7.45, 7.8, 8.75, and 9.3 μ.

Anal. Calcd. for $C_{14}H_{13}ClN_2O_2$: N, 9.77. Found: 9.55.

2-Imidazolidinone-N-carbonyl Chloride (IX).—Into 100 ml. of ethylene dichloride at 70–75° was admitted gaseous phosgene at a rate of *ca.* 127 ml./min. for 3 min. (0.02 mole of phosgene). Thereafter, simultaneous with the continued addition of phosgene, a hot solution (75–80°) of 17.2 g. (0.20 mole, recrystallized, m.p. 133–135°) of ethyleneurea dissolved in 220 ml. of ethylene dichloride was added at a rate of about 6.5-ml. increments/min., completing the addition in about 35 min. (0.2 mole of phosgene).

After the addition, phosgenation was continued 2 min., and then the hot mixture was purged for 0.5 hr. with nitrogen. The hot solution was filtered, and upon cooling to 15 to 20° deposited 25.6 g. (86%) of crystalline 2-imidazolidinone-N-carbonyl chloride, m.p. 155–157°. A second crop, 1.6 g., m.p. 150–153°, was obtainable from the mother liquors; $\lambda_{max}^{CHCl_3}$ (infrared) 2.93, 3.12, 5.52, 5.67, 5.80, 6.75, 7.25, 7.51, 7.76, and 8.67 μ; λ_{max}^{KBr} (infrared) 3.15, 5.55, 5.84, 6.78, 7.25, 7.55, 7.8, and 8.75 μ.

Anal. Calcd. for $C_4H_5ClN_2O_2$: C, 32.32; H, 3.39; Cl, 23.87; N, 18.86. Found: C, 32.06; H, 3.35; Cl, 23.84; N, 19.0.

Reaction with Ethanol.—A solution of 4.46 g. (0.03 mole) of IX in 50 ml. of ethanol was refluxed (80°) for 1 hr. Evaporation of the excess ethanol and trituration with small portions of benzene and chloroform with intermittent evaporation gave 4.5 g. (95%) of 1-carbethoxy-2-imidazolidinone (XI), m.p. 123.5–124.5° (chloroform).

Anal. Calcd. for $C_6H_{10}NO_3$: C, 45.58; H, 6.38; N, 17.72. Found: C, 45.54; H, 6.60; N, 17.90.

(9) E. Schmidt, F. Hitzler, E. Lahde, R. Herbeck, and M. Pezzati, *Ber.* **71B**, 1933 (1938).

(10) M. Seefelder, German Patent 1,119,258 (Dec. 14, 1961).

Reaction with Diethylamine.—A solution of 1.5 g. (0.02 mole) of diethylamine in 10 ml. of benzene was added at once to a stirred suspension of 1.5 g. (0.01 mole) of IX in 20 ml. of benzene at room temperature. Filtration and evaporation afforded 1.39 g. (75%) of 1-(*N*,*N*-diethylcarbamoyl)-2-imidazolidinone (XII), b.p. 150° (0.5 mm.), m.p. 55–57°.

Anal. Calcd. for $C_8H_{15}N_3O_2$: C, 51.87; H, 8.16; N, 22.68. Found: C, 51.78; H, 8.19; N, 22.92.

Propyleneurea (3-Methyl-2-imidazolidinone, VIII).—To 39 g. (0.49 mole) of 1,2-diaminopropane (propylenediamine) and 80 g. (1.0 mole) of 50% sodium hydroxide in 100 ml. of water, 49.5 g. (0.5 mole) of phosgene was added at 10–20° while maintaining good agitation. The water was evaporated *in vacuo* and the residue was extracted with ethylene dichloride. Evaporation of the solvent gave 21.9 g. (43.7%) of methyl-2-imidazolidinone (VIII), m.p. 125–127°; $\lambda_{max}^{CHCl_3}$ (infrared) 2.93, 3.13, 3.40, 5.90, 6.7, 6.95, 7.25, and 7.95 μ.

Anal. Calcd. for $C_4H_8N_2O$: C, 48.00; H, 8.06; N, 28.00. Found: C, 47.92; H, 8.32; N, 27.91.

Methyl-2-imidazolidinone-*N*-carbonyl Chloride (X).—A solution of 10 g. (0.1 mole) of VIII in 100 ml. of ethylene dichloride was added from a heated (60°) addition funnel simultaneously with 10 g. (0.1 mole) of phosgene to 100 ml. of ethylene dichloride at 72–77°. After purging with nitrogen for 30 min., the reaction mixture was filtered while hot. On cooling, 9.5 g. (58.6%) of methyl-2-imidazolidinone-*N*-carbonyl chloride (X), m.p. 145–146°, separated.

Anal. Calcd. for $C_5H_7ClN_2O_2$: C, 36.92; H, 4.34; N, 17.23. Found: C, 36.90; H, 4.44; N, 16.42.

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Allene Chemistry. II.[1] Free-Radical Addition of Hydrogen Bromide to Allene

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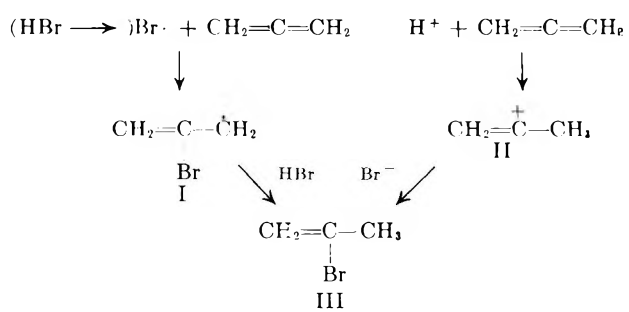
The free-radical addition of hydrogen bromide to allene was examined under different reaction conditions and the product mixtures were analyzed by capillary gas–liquid chromatography and n.m.r. spectroscopy. The ultraviolet light catalyzed gas phase reaction of equimolar amounts of the reactants at ambient temperatures yielded 2-bromopropene as the major product, along with minor amounts of 1,2-dibromopropane and 2,2-dibromopropane. No measurable terminal attack was observed. Equimolar amounts of the reactants in the liquid phase produced 2-bromopropene, 3-bromopropene, 1,2-dibromopropane, and in some cases also 1,3-dibromopropane in varying relative amounts, depending on the reaction conditions. Attack of the bromine atoms at the terminal positions of allene increased from 7% at ambient temperatures to 24% at −40° and 36% at −70°. Up to 48% of terminal attack was observed when a propane solution containing 1 mole of each of the reactants was irradiated at −70°. Reaction of excess allene with hydrogen bromide at −70° yielded mainly the monoadducts 2-bromopropene and 3-bromopropene, but none of the isomeric 1-bromopropenes, thus excluding any significant amount of isomerization of allene to methylacetylene. The amount of terminal attack decreased drastically with an increasing excess of allene. Reactions of excess hydrogen bromide with allene were complicated by competing ionic addition reactions leading to considerable amounts of 2,2-dibromopropane.

The problem of terminal *vs.* center attack in free-radical addition reactions to allene was outlined in our previous paper dealing with thiol addition reactions.[1] We proposed there that the observed preference of thiyl radicals for the terminal positions of allene may be a consequence of the particular geometry of the allene molecule. It was pointed out that, owing to perpendicular arrangement of its π-orbitals, the incipient radical derived from a center attack will not be resonance stabilized and its formation may, therefore, require a higher activation energy than does the formation of the vinylic radical derived from a terminal attack. A similar idea was advanced independently by Jacobs and Illingworth.[2] The exclusive terminal attack of CF_3 radicals, reported by Haszeldine and co-workers[3] in the photoaddition of trifluoroiodomethane to allene, seems also to agree with this concept.

Kovacic and Leitch[4] arrived at the opposite conclusion in interpreting the homolytic addition of hydrogen bromide to allene. They isolated 2-bromopropene (III) as the major reaction product and reasoned that the reaction should proceed *via* the resonance-stabilized 2-bromopropenyl radical (I). However, the homolytic conditions claimed were not supported by control experiments. Thus, an ionic reaction path *via* the carbonium ion intermediate II was not ruled out. Such a path would be analogous to the addition of hydrogen chloride[5] and hydrogen fluoride[6] to allene, both of which occur in the usual Markownikoff manner to yield the corresponding 2-halopropenes and/or 2,2-dihalopropanes. Furthermore, Kovacic and Leitch's experiments were apparently carried out in the gas phase and, therefore, cannot be directly related to the previously reported radical additions to allene which were generally carried out in the liquid phase.



In view of our continued interest in allene chemistry, we investigated the free-radical addition of hydrogen bromide to allene in detail.

(1) Part I: K. Griesbaum, A. A. Oswald, E. R. Quiram, and W. Naegele, *J. Org. Chem.*, **28**, 1952 (1963).

(2) T. L. Jacobs and G. F. Illingworth, Jr., *ibid.*, **28**, 2692 (1963).

(3) R. N. Haszeldine, K. Leedham, and R. B. Steele, *J. Chem. Soc.*, 2020 (1954).

(4) D. Kovacic and L. C. Leitch, *Can. J. Chem.*, **39**, 3636 (1961).

(5) T. L. Jacobs and R. N. Johnson, *J. Am. Chem. Soc.*, **82**, 6397 (1960).

(6) P. R. Austin, U. S. Patent 2,585,529 (1952).

Results

Hydrogen bromide and allene were allowed to react under different reaction conditions, varying reaction temperature, type of initiation, reaction medium, relative reactant ratios, and reaction phase. The crude reaction products were in each case analyzed by capillary gas–liquid chromatography (Fig. 1) and semiquantitative n.m.r. spectroscopy (Fig. 2). The predominantly free-radical character of these reactions was supported by the marked enhancement of their reaction rates over those of the corresponding "dark" reactions (Table I).

Reaction in the Gas Phase.—The ultraviolet light induced reaction of an equimolar mixture of allene and hydrogen bromide in the gas phase at ambient temperatures proceeded at a fast rate. Within 3 hr. a conversion of 88% was achieved, while the corresponding "dark" reaction reached only 8% conversion in the same time. The major reaction product was 2-bromopropene, along with some 1,2-dibromopropane and very little 2,2-dibromopropane (Table I). The latter may even have been formed during work-up of the reaction mixture. No product derived from an apparent terminal attack of bromine on allene could be detected with the analytical tools used. This is in good agreement with the findings of Kovachic and Leitch.[4]

Reactions in the Liquid Phase.—Most of the previously reported free-radical additions to allene[1-3] had been carried out either with equimolar amounts of reactants or with a slight excess of one reactant over the other. As it was the objective of this work to provide data comparable with that of the reported thiol[1,2] and trifluoroiodomethane[3] additions, the major part of our studies was carried out with equimolar mixtures of hydrogen bromide and allene and, unless mentioned otherwise, without a diluent.

Equimolar Amounts of Reactants.—The ultraviolet light catalyzed reaction at ambient temperatures produced 2-bromopropene (III) as the major reaction product, along with some 3-bromopropene (V) and little 1,2-dibromopropane (VII). The amount of formal terminal attack of bromine on allene, as represented by the occurrence of 3-bromopropene at 25°, was 7%. At −40° the same adducts were formed; however, their relative ratios were changed. More of the diadduct VII was observed and the amount of the terminal-attack product V had increased to 24%. At −70° the symmetrical diadduct 1,3-dibromopropane (VIII) was formed in addition to the three adducts III, V, and VII. The two diadducts VII and VIII now comprised 27% of the adduct mixture as compared with the formation of only 4% diadduct at ambient temperatures and 13% at −40°. The amount of terminal attack products (*viz.*, V and VIII) had increased to 36%.

Combined initiation by 2,2′-azobisisobutyronitrile (AIBN) and ultraviolet light at −70° caused an approximately threefold rate enhancement over the merely ultraviolet light catalyzed reaction. The products formed were the same and their distribution was similar to that of the ultraviolet light catalyzed addition. The amount of terminal attack products (V and VIII) had increased to 43%.

Ultraviolet light irradiation of a propane solution which was one molar for each of the reactants again produced the four adducts III, V, VII, and VIII at −70°. The amount of terminal attack products (V and VIII) was 48%.

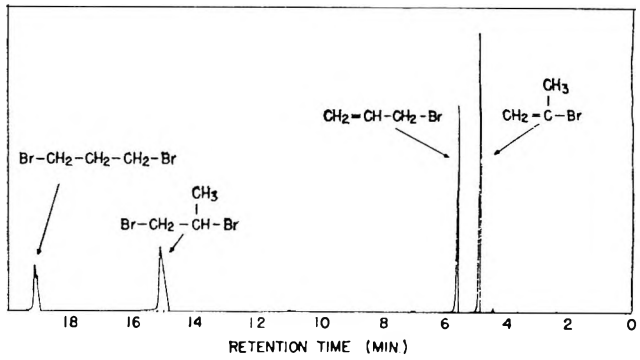


Fig. 1.—Gas chromatogram of a crude hydrogen bromide–allene adduct mixture.

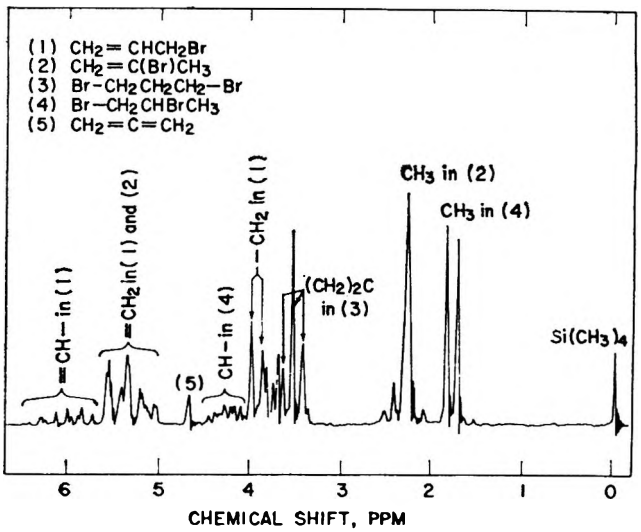


Fig. 2.—N.m.r. spectrum of hydrogen bromide–allene adduct mixture.

Excess of Allene.—The ultraviolet light induced reaction of hydrogen bromide with an excess of allene at −70° resulted in the formation of the monoadducts III and, to a much lesser extent, V, along with only minor amounts (2–3%) of the diadduct VII. The amount of the terminal attack products decreased from 36% in the reaction of equimolar amounts of the reactants to 30% with a fivefold excess of allene and 8% with a tenfold excess.

The reactions of excess allene with hydrogen bromide permit some conclusions with regard to the possible isomerization of allene to methylacetylene under the free-radical conditions employed. We have shown in independent experiments that at −70° hydrogen bromide adds approximately three times as fast to methylacetylene as it does to allene. Any methylacetylene formed should, therefore, show up in the form of its respective free-radical mono- (IV) and or diadduct (VII).[7] However, we could demonstrate by g.l.c. retention times (*cf.* Tables I and II)[8] and n.m.r. analy-

(7) The photochemical addition of hydrogen bromide to methylacetylene at −78° had been previously reported to yield mainly *cis*-1-bromopropene, along with some 1,2-dibromopropane; see P. S. Skell and R. G. Allen, *J. Am. Chem. Soc.*, 80, 5997 (1958).

(8) G.l.c. analysis of a synthetic blend, containing 2-bromopropene, 3-bromopropene, and the isomeric 1-bromopropenes gave a complete resolution. As one would anticipate on the basis of the individual retention times, the peaks for the isomeric 1-bromopropenes appeared between those of 2-bromopropene and 3-bromopropene.

TABLE I

EXPERIMENTAL AND ANALYTICAL DATA OF HYDROGEN BROMIDE–ALLENE ADDITIONS

Ratio of HBr–C_3H_4	Type of initiation	Temp., °C.	Time, hr.	Yield, %	Relative amounts of components in mixture,[a] mole %: $BrCH_2CH{=}CH_2$[g]	$Br(CH_2)_3Br$[h]	$CH_2{=}CBrCH_3$[i]	$BrCHCH_2Br$ (CH₃)	$CH_3CBr_2CH_3$[k]	Terminal attack on allene, %[l]
1[b]	ultraviolet	ambient	3	88[c]	trace		85	13	2	<1
1	ultraviolet	ambient	8.5	93	7	trace	89	4	trace	7
1	ultraviolet	−40	21	83	24	trace	63	13		24
1	ultraviolet	−70	18.5	92[d]	27	9	46	18		36
1	ultraviolet, AIBN	−70	6	88[d]	30	13	33	24		43
1[e]	ultraviolet	−70	19	82	37	11	28	24		48
10	ultraviolet	−70	21	99		43		34	23	43
0.5	ultraviolet	−70	19	81	30		68	3		30
0.1	ultraviolet	−70	69	63[f]	8		89	2		8

[a] Based on g.l.c. analysis. [b] Gas phase reaction. [c] Compared with 8% yield in the corresponding "dark" reaction. [d] A "dark" reaction gave only 13% yield in 25 hr. [e] Reaction carried out in 1 *M* propane solution. [f] The gas chromatogram in this case showed some peaks of intermediate and higher retention times, suggesting that telomerization may have occurred. [g] Retention time 5.6 min. [h] Retention time 19.1 min. [i] Retention time 4.8 min. [j] Retention time 15.1 min. [k] Retention time 9.5 min. [l] Calculated as the sum of the mole % of 3-bromopropene and 1,3-dibromopropane.

TABLE II

EXPERIMENTAL AND ANALYTICAL DATA OF HYDROGEN BROMIDE ADDITIONS TO METHYLACETYLENE, 2-BROMOPROPENE, AND 3-BROMOPROPENE

Unsaturate used, mole %	HBr, mole %	Type of initiation	Temp., °C.	Time, hr.	Yield, %	Relative amounts of products formed,[a] mole %: $BrCH{=}CHCH_3$[b] *cis*[c]	*trans*[d]	$Br(CH_2)_3Br$	$BrCHCH_2Br$ (CH₃)	$CH_3CBr_2CH_3$
$HC{\equiv}CCH_3$ 0.1	0.1	ultraviolet	−70	5	80	74	23		3	
$HC{\equiv}CCH_3$ 0.05	0.5	ultraviolet	−70	2:40	68	35	12		49	4
$CH_2{=}CHCH_2Br$ 0.1	0.1	ultraviolet	−70	29	94			100		
$CH_2{=}CHCH_2Br$ 0.1	0.1	ultraviolet AIBN	−70	19	92			100		
$CH_2{=}CBrCH_3$ 0.1	0.1	ultraviolet	−70	21	89				45	55
$CH_2{=}CBrCH_3$ 0.1	0.1	ultraviolet AIBN	−70	20	87				86	14

[a] Based on g.l.c. analysis. [b] The configuration has been assigned based on Skell's experience that under similar conditions the *cis* compound was produced in a larger ratio (see ref. 7). [c] Retention time 5.1 min. [d] Retention time 5.3 min.

sis[9] that neither of the isomeric 1-bromopropenes (IV) was present in our adduct mixtures which were derived from reactions of excess allene with hydrogen bromide. These observations place, therefore, an upper limit of 2–3% (*i.e.*, the amount of the diadduct VII formed) for for the amount of isomerization of allene to methylacetylene under the prevailing reaction conditions.

Excess of Hydrogen Bromide.—The ultraviolet light induced reaction of excess hydrogen bromide with allene produced the diadducts 1,2-dibromopropane (VII), 1,3-dibromopropane (VIII), and 2,2-dibromopropane (VI). The latter probably arose through competing ionic addition reactions, which are known to be favored in halogen acid media.[10a]

Model experiments showed that even in an equimolar mixture of hydrogen bromide and 2-bromopropene at −70° ionic reaction took place to a considerable extent.[11] Thus, the merely ultraviolet light catalyzed addition yielded a mixture consisting of 45% of 1,2-dibromopropane and 55% of 2,2-dibromopropane. The combined initiation by ultraviolet light and AIBN, on the other hand, apparently greatly favored the free-radical reaction, yielding 86% of 1,2-dibromopropane and 14% of 2,2-dibromopropane (Table II).

No complicating ionic reaction was observed in either the ultraviolet light catalyzed or the ultraviolet–AIBN catalyzed reaction of equimolar amounts of hydrogen bromide and 3-bromopropene. The reaction yielded 1,3-dibromopropane as the only detectable product, in agreement with previous findings[12] (Table II).

Discussion

On the basis of all of our results, we believe that the free-radical addition of hydrogen bromide to allene in the liquid phase generally follows the reaction paths indicated by the solid arrows and not the theoretically also possible alternate routes indicated by the dotted arrows.

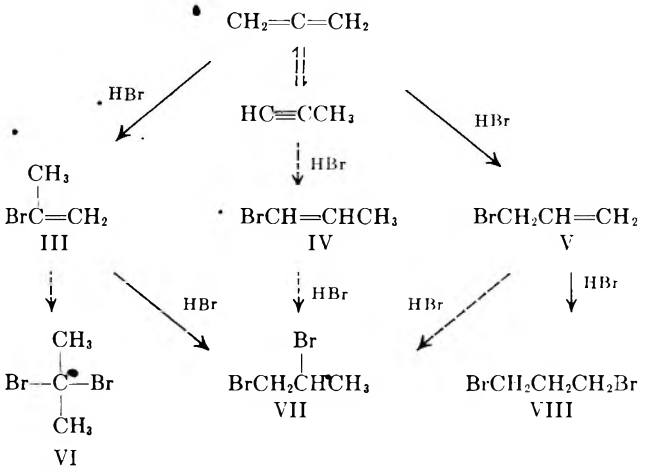
The selectivity of the addition varies characteristically with such conditions as reaction temperature or relative reactant ratios. Increasing reaction temperature and increasing excess of allene over hydrogen bromide cause a decrease in the formation of terminal attack products. It seems, therefore, that the previously reported strong preference for the formation of center attack products[4] is restricted to reactions at elevated temperatures or with an excess of allene, while reactions at lower temperatures and with equimolar

(9) The n.m.r. spectrum of a mixture of the isomeric 1-bromopropenes exhibited two methyl doublets (further split by remote coupling with the vinylic proton at C-1), centered at 1.65 and 1.73 p.p.m., respectively. These signals were absent in the spectrum of the reaction mixture derived from reaction of excess allene with hydrogen bromide.

(10) (a) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957; (a) p. 294; (b) p. 292.

(11) M. S. Kharasch, H. Engelmann, and F. R. Mayo [*J. Org. Chem.*, **2**, 288 (1937)] apparently did not obtain a complete selectivity in this reaction either.

(12) M. S. Kharasch and F. R. Mayo, *J. Am. Chem. Soc.*, **55**, 2468 (1933).



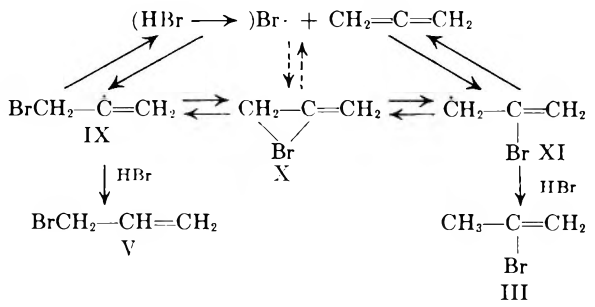
amounts of the reactants lead to almost equal amounts of terminal and center attack products.

The observed increase of terminal attack products with decreasing reaction temperature parallels our previous experience in the addition of methanethiol to allene.[1] Although this effect is more pronounced in the hydrogen bromide–allene additions (*viz.*, 29 *vs.* 6% in methanethiol reactions), it may well represent a common feature of free-radical additions to allene in general. The reported lower amounts of terminal attack products in the free-radical addition of thiols to allene at elevated temperatures[13] (approximately 80°) may also be indicative of such a correlation.

A consideration of the known free-radical additions to allene may suggest a similar correlation between the rate of the second propagation step and the course of the reaction; it seems that slower chain transfer leads to more terminal attack. Thus, under comparable conditions (ambient temperatures, ultraviolet irradiation) increasing terminal attack has been reported in this sequence: HBr (7%), C_6H_5SH[1] (83%), CH_3SH[1] (90%), H_2S[14] (98%), and CF_3I[3] ("exclusively"). Whether this observed trend is real or merely coincidental can, however, not be decided on the basis of the sparse data available.

While the present work describes the gross results of the free-radical addition of hydrogen bromide to allene, this question of the point of initial attack of bromine on allene remains unanswered. Skell and co-workers[15] reported recently that α-bromoalkyl radicals, the postulated first intermediates in free-radical additions of hydrogen bromide to olefins[10b] (*e.g.*, IX or XI in the case of allene), undergo fast rearrangements, possibly *via* bridged-radical intermediates[16] (*e.g.*, X in the case of allene).

On the basis of this argument, 2-bromopropene (III) can be envisaged to be derived from an initial terminal attack of bromine on allene to form the vinylic radical IX, which then rearranges to the more stable allylic radical XI. In other words, the preferential formation of the "center attack product" 2-bromopropene does not necessarily reflect a preferential attack of the bromine atom at the center position of allene, but may



equally well be due to the greater migratory aptitude of bromine compared with, *e.g.*, thiyl groups.

To complicate matters even more, Abell and Piette[17] reported recently that the initial attack of a bromine atom in free-radical hydrogen bromide additions leads directly to a bridged radical, *e.g.*, of type X.[18] If this is so, it would render any discussion on the point of initial attack immaterial, since the problem would then be one of a selective ring opening of this bridged radical in the second propagation step.

In view of these complications the observed product distributions in our hydrogen bromide–allene additions do not necessarily reflect the selectivities of the initial attack of bromine on allene. Additional work on this aspect of the problem is under way.

Experimental

Materials.—The allene used was pure according to g.l.c. analysis. Hydrogen bromide of 99.8% minimum purity, propane of 99.99% purity, and methylacetylene of 96% minimum purity were purchased from Matheson. The g.l.c. and n.m.r. reference samples of 3-bromopropene, 1,2-dibromopropane, and 1,3-dibromopropane were Matheson products; 2-bromopropene was purchased from Chemicals Procurement Laboratories. The samples were all redistilled before use.

Method of Analyses.—All the adduct mixtures were analyzed by capillary g.l.c. on a Perkin-Elmer Model 226 linear programmed temperature gas chromatograph under the conditions reported for the methanethiol–allene adducts in the previous paper of this series.[1]

Allene was analyzed on a F and M Model 500 gas chromatograph using a 10-ft. column packed with 20% dimethylsulfolane on Chromosorb P. The column temperature was maintained at 30°.

N.m.r. spectra were recorded and integrated on a Varian Model A-60 proton resonance spectrometer.

Addition of HBr to Allene in the Gas Phase.—The ultraviolet light catalyzed reactions were carried out in a 2-l., one-necked, round-bottomed quartz flask; the uninitiated reactions were carried out in a darkened 2-l., one-necked Pyrex flask. The flask was arranged upside down and its neck was tightly connected to the top of a 10-ml. graduated cylinder which contained an outlet on its side. After the whole system was evacuated, 2 g. (0.05 mole) of allene and 4 g. (0.05 mole) of HBr were condensed into the graduated cylinder, which was kept at the temperature of liquid nitrogen. Then the system was closed, the cooling bath was removed, and the reactants were allowed to completely evaporate into the evacuated 2-l. flask at room temperature.

On irradiation of the flask with a 100-W Hanovia utility lamp, the reaction mixture became hazy after about 3 to 5 min. and the precipitation of a thin liquid layer, probably the adduct product, began on the inside walls. Although some reaction may have occurred in this liquid phase, the abundance of monoadduct suggests that this was not a serious complication.

After the reaction was over, the graduated cylinder was cooled to −78° and the reaction flask was gently warmed up to promote

(13) H. J. Van der Ploeg, J. Knotnerus, and B. F. Bickel, *Rec. trav. chim.*, **81**, 775 (1962).

(14) Unpublished results from this laboratory.

(15) P. S. Skell, R. G. Allen, and N. D. Gilmour, *J. Am. Chem. Soc.*, **83**, 504 (1961).

(16) P. S. Skell, D. L. Tuleen, and P. D. Readio, *ibid.*, **85**, 2849 (1963).

(17) P. I. Abell and L. H. Piette, *ibid.*, **84**, 916 (1962).

(18) The particular evidence presented by Abell and Piette was subsequently refuted by M. C. R. Symons [*J. Phys. Chem.*, **67**, 1566 (1963)]. However, the general concept of bridged radicals seems to be deriving increasing support from chemical evidence.

condensation of the adduct into the graduated cylinder. The product was analyzed in the same manner as described above.

Addition of HBr to Allene or Methylacetylene in the Liquid Phase.—The ultraviolet light catalyzed reactions were carried out in 100-ml. quartz tubes, which were either sealed or closed by a Teflon-tipped needle valve (obtained from Fisher and Porter Co., Clifton, N. J.) that was sealed to the top of the tube. The non-initiated reactions were carried out in Pyrex tubes which were "darkened" with a black enamel (from Krylon, Inc., Morristown, Pa.).

Allene (or methylacetylene) and HBr were condensed into the tubes at the temperature of liquid nitrogen through a vacuum system. The evacuated closed tubes were then transferred into a temperature-controlled water or "Freon" bath. A 100-W Hanau ultraviolet immersion lamp (obtained from G. W. Gates and Co., Long Island, N. Y.) was used for the initiation. If the reaction was carried out below room temperature the lamp was surrounded by a quartz mantle to insulate it against excessive cooling.

After an arbitrary period of reaction time, the tubes were transferred to a liquid nitrogen bath and opened. The unreacted gases were allowed to evaporate through a drying tube filled with anhydrous calcium sulfate ("Drierite"). The remaining adduct mixtures in the tube were slightly yellow to dark brown mobile liquids. They were analyzed as such by g.l.c. and n.m.r.

Vacuum distillation of an adduct mixture derived from the reaction of equimolar amounts of hydrogen bromide and allene produced 1,3-dibromopropane as the highest boiling component and left no residue. This indicates that, when equimolar amounts of reactants or an excess of HBr are used, telomerization is insignificant and that the g.l.c. method, therefore, can provide a complete analysis of these adduct mixtures.

The use of stringent precautions is recommended for carrying out these reactions regardless of the reaction temperature employed. In one case a vigorous explosion occurred when an equimolar mixture of allene and HBr was irradiated at room temperature for approximately 5 min. The explosion was preceded by a yellow flash in the reaction tube. In a second case a mixture containing allene, methylacetylene, and HBr in the relative molar ratios of 1:1:2 exploded when it was irradiated at −70°. In both cases the experiments were well shielded and no one was injured. The reasons for these explosions are unknown.

Acknowledgment.—The authors thank their colleague, Dr. R. B. Long, for supplying them with samples of pure allene and Miss M. Doolan for carrying out the g.l.c. analyses. The skillful technical assistance of Mr. A. M. Palmer in carrying out experiments is particularly acknowledged.

Sodium- and Potassium-Induced Reactions of β-Methylstyrene[1,2]

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Considerable difference was observed in the reactions of β-methylstyrene (I) in nonexchanging solvents in the presence of dispersed sodium or potassium. At 100–155°, in the presence of sodium, I underwent mainly dimerization to 1,5-diphenyl-4-methyl-1-pentene (V, yield 80–87%), whereas the fastest reaction in the presence of the more electropositive potassium was hydrodimerization resulting in 1,4-diphenyl-2,3-dimethylbutane (IV, optimal yield 85–93% at 80–100°). The two reactions are mechanistically different: dimerization of I is a typical carbanion-catalyzed chain reaction, whereas hydrodimerization, which probably involves the intermediate formation of an anionic free radical, is a noncatalytic reaction requiring 2 g.-atoms of metal per mole of hydrodimer formed. Dimer V underwent a slow decomposition and recombination leading to the formation of 1,3-diphenyl-2-methylpropane (III) and to a C_{11} hydrocarbon (II) to which the structure 3-methyl-4-phenylcyclobutene was assigned. The mechanism of the reaction is discussed.

It has been reported[4,5] recently that α- and β-methylstyrene react with alkylbenzenes in the presence of dispersed potassium to form 1,3-diphenylalkanes. In the case of β-methylstyrene (I) the relative rate of aralkylation was found[5] to decrease sharply with increased size of the substituent in the alkylbenzene reactant, while, simultaneously, the dimerization and concurrent hydrodimerization of I became increasingly competitive.

As an extension of the above work the reactions of I have been separately studied in nonexchanging media. Comparative experiments were carried out employing dispersed sodium or dispersed potassium as a catalyst. The effect of temperature upon the relative rate of dimerization and upon the partial evolution of the dimer into secondary products was also studied by performing the reaction in four different alkylcyclohexane solvents at their respective boiling points: cyclohexane (80°), methylcyclohexane (100°), ethylcyclohexane (132°), and isopropylcyclohexane (155°). The course of the reaction at a given temperature was followed by plotting the product composition as a function of reaction time.

The experimental procedure was similar to that described previously.[6] The reaction products were separated and analyzed by a combination of fractional distillation, gas chromatography, hydrogenation, and ozonation, as well as by infrared, ultraviolet, and n.m.r. spectroscopy. Part of the compounds formed were identified by comparison with pure synthetic samples.

Results and Discussion

As seen from Table I there is considerable difference in the composition of products obtained in the experiments with sodium and potassium catalysts.

The main dimerization product in the presence of dispersed sodium is 1,5-diphenyl-4-methyl-1-pentene (V). The dimer is obtained in high yields (80–90%) at 100° and extended reaction time (expt. 1) or at 155° and short contact time (expt. 4); the reaction under these conditions can be conveniently employed as a preparative method.

(1) Paper XXVII of the series "Base-Catalyzed Reactions." For paper XXVI, see E. M. Lewicki, H. Pines, and N. C. Sih, *Chem. Ind.* (London), 154 (1964).

(2) This work had been supported in part by the National Science Foundation Grant G14503.

(3) On leave of absence from the Weizmann Institute of Science, Rehovoth, Israel, 1959–1961.

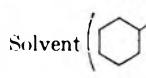
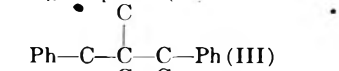
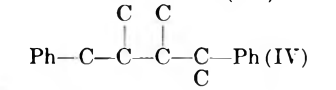
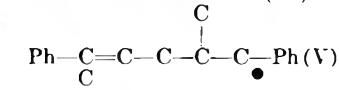
(4) J. Shabtai and H. Pines, *J. Org. Chem.*, **26**, 4225 (1961).

(5) J. Shabtai, E. M. Lewicki, and H. Pines, *ibid.*, **27**, 2613 (1962).

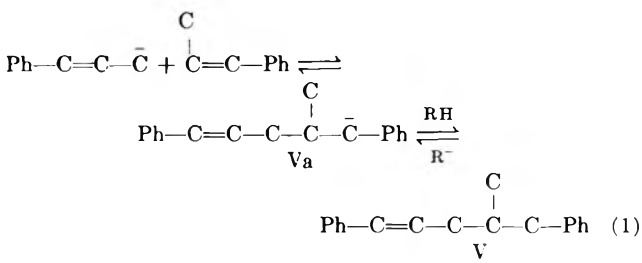
(6) H. Pines and J. Shabtai, *ibid.*, **26**, 4220 (1961).

TABLE I

COMPOSITION OF PRODUCTS OBTAINED FROM THE SODIUM- AND POTASSIUM-CATALYZED REACTIONS OF β-METHYLSTYRENE (I)

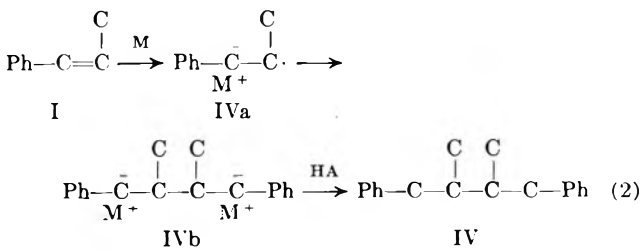
Experiment	1	2	3	4	5	6	7	8	9	10	11
Catalyst	Na	Na	Na	Na	Na	K	K	K	K	K	K
Temperature, °C.	100	132	132	155	155	80	100	100	132	155	155
Solvent (), R =	CH_3	C_2H_5	C_2H_5	i-C_3H_7	i-C_3H_7	H	CH_3	CH_3	C_2H_5	i-C_3H_7	i-C_3H_7
Reaction time,[a] hr.	5	5	8	1	5	4	1	4	4	5	9
Conversion, mole %[b]	12	63	94	77	100	4	21	43	72	100	100
Product component, wt. %											
Ph—C	1.5	1.7	2.7	0.8	1.0	...	...	...	1.0	<0.1	<0.1
Ph—C—C—C	0.3	1.2	2.6	1.2	2.7	0.5	3.0	2.6	1.7	0.2	0.2
C_{11} compound (II)[c]	3.2	5.0	6.4	0.2	1.0	...	...	...	5.8	0.1	0.1
	1.4	1.7	2.1	0.7	0.8	...	...	...	6.5	12.1	14.3
	2.7	6.0	7.9	12.6	16.4	92.8	84.1	80.7	42.0	30.2	29.8
	86.5	72.6	62.8	81.0	68.0	3.0	5.4	6.7	27.8	29.5	24.9
	1.4	6.3	7.0	2.5	4.1	1.2	1.5	2.5	6.0	16.5	17.0
Higher boiling	3.0	5.5	8.5	1.0	6.0	2.5	6.0	7.5	9.2	11.4	13.7

[a] Including the time of addition of I. [b] In each experiment were used 18 g. (0.15 mole) of I, 80 g. of solvent, and 2 g. (0.087 g.-atom) of sodium or 2.2 g. (0.056 g.-atom) of potassium. [c] Assigned structure: 3-methyl-4-phenylcyclobutene (see Experimental). [d] Includes olefins with the same skeleton: expt. 1–9, 2–10%; expt. 10 and 11, 20–21%.



(1)

Increase in temperature or reaction time results in somewhat larger amounts of other products. It was proposed[4] that the hydrodimer IV arises from the dimerization of the alkali metal ion-radical salt IVa; the product may accumulate during the reaction in the form of the dimeric salt IVb or be converted into IV by reacting with the monomer or by the decomposition of the reaction mixture with ethanol.



(2)

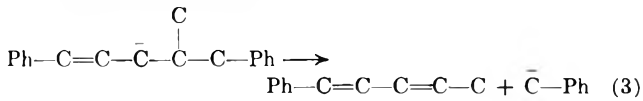
Reaction 2 occurs to a limited extent in the presence of sodium, but its rate relative to that of reaction 1 seems to increase somewhat with temperature (compare expt. 2 and 5).

Winstein and Lapporte[7] have independently obtained compound IV from I by Conant's method,[8] which involves treatment of a β-alkylstyrene with sodium–potassium alloy in ether and subsequent quenching of the reaction mixture with alcohol.

(7) S. Winstein, private communication.

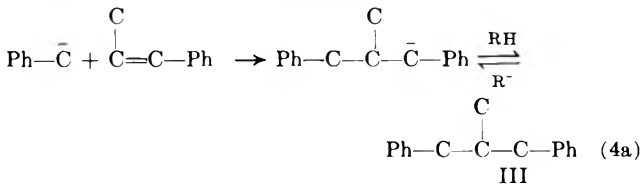
(8) J. B. Conant and A. H. Blatt, *J. Am. Chem. Soc.*, **50**, 551 (1928).

The presence of toluene and compound II in the product indicates that V undergoes to a slight extent cleavage into a C_7 and a C_{11} unit. Such reaction can be assumed to involve metalation of V at the allylic position, followed by splitting of the resulting carbanion.



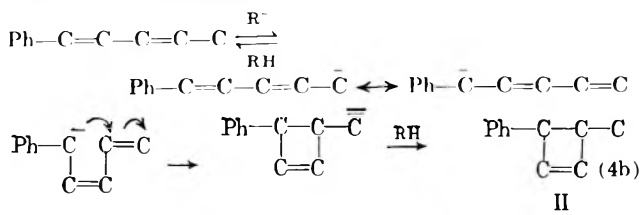
(3)

The benzyl carbanion obtained can form toluene by proton abstraction or react with β-methylstyrene to give 1,3-diphenyl-2-methylpropane (III).[5]



(4a)

On the other hand the phenylpentadiene produced can polymerize into high boiling products or it can undergo cyclization and form compound II by the following mechanism.



(4b)

Support for the proposed formation of phenylpentadiene as a precursor of II was obtained by a separate experiment. A reaction was carried out exactly under the conditions of expt. 9 and about 90 min. after completing the addition of I, 1-phenyl-1,3-pentadiene (1.44 g., 0.01 mole) was injected in the reacting mixture. The yield of II increased from 5.8%

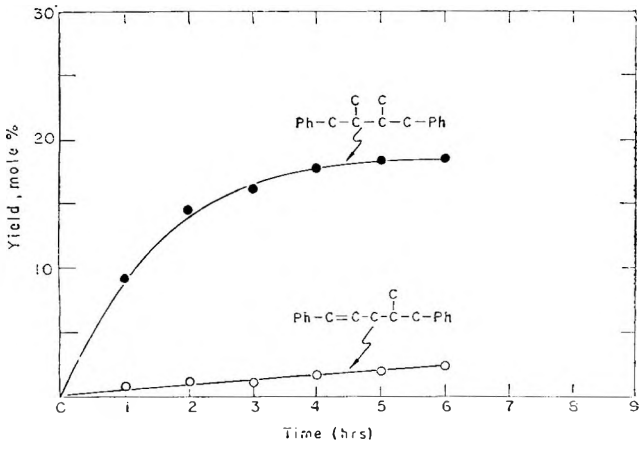


Fig. 1.—Relative rate of formation of 1,5-diphenyl-4-methyl-1-pentene and 1,4-diphenyl-2,3-dimethylbutane from β-methylstyrene at 100°, in the presence of potassium.

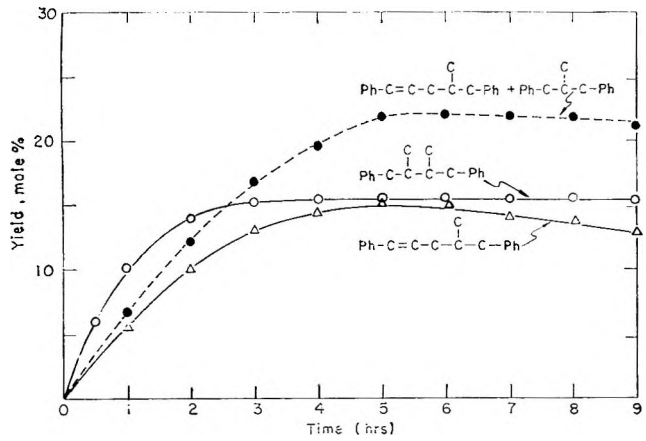


Fig. 2.—Relative rate of dimerization and hydrodimerization of β-methylstyrene at 155°, in the presence of potassium; formation of: (a) 1,5-dipenyl-4-methyl-1-pentene (V); (b) 1,4-diphenyl-2,3-dimethylbutane (IV); and (c) IV + 1,3-diphenyl-2-methylpropane (III).

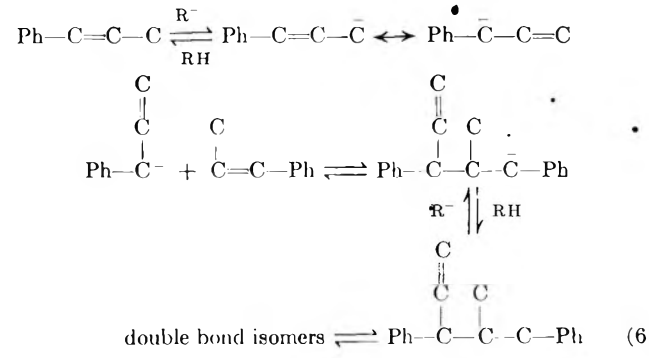
(expt. 9) to 9.1%, corresponding to a 40% transformation of the diene into compound II.

The formation of high boiling material is probably accompanied to some extent by hydride-transfer reactions[6] as indicated by the presence of small amounts of *n*-propylbenzene.

$$\mathrm{Ph{-}C{\equiv}C{-}C} \underset{-H^-}{\overset{H^-}{\rightleftharpoons}} \mathrm{Ph{-}\bar{C}{-}C{-}C} \underset{R^-}{\overset{RH}{\rightleftharpoons}} \mathrm{Ph{-}C{-}C{-}C} \quad (5)$$

On the other hand, *n*-propylbenzene has been shown[5] to react with β-methylstyrene with the formation of compound VI. Olefins possessing the skeleton of VI (footnote *d*, Table I) may result by hydride transfer reaction of the intermediate carbanion (Ph—C(C$_2$)-C(C)—$\bar{C}$—Ph). A second possibility, however, is that dimerization of I occurs to some extent by a path different from reaction 1; the carbanion derived from I in the initiation step may react as a "benzylic" rather than an "allylic" carbanion.

In the presence of dispersed potassium, between 80–100° (Table I, expt. 6–8), hydrodimerization of I (reaction 2) is strongly predominant. This probably depends on the stronger electropositive character of potassium. In the presence of potassium the rate of



formation of the anionic free radical IVa followed by dimerization (reaction 2) is much faster than the rate-determining step of reaction 1.

Figure 1 shows that at 100° the relatively much faster reaction 2, producing hydrodimer IV, reaches a standstill after about 4 hr., although the total conversion of I at this point is less than 50%. On the other hand, the slow reaction 1 continues normally beyond this point. At 155° (Fig. 2) reaction 1 becomes increasingly competitive, but otherwise the pattern is preserved. Reaction 2 is practically stopped after 2.5 hr., whereas reaction 1 continues and compound V reaches a maximum concentration after about 5 hr. The decrease in the concentration of V at longer contact time is obviously due to the splitting reaction 3. Since the benzyl carbanion, produced by this cleavage, reacts almost quantitatively with I to form compound III, the latter can serve as a measure of the amount of the dimer consumed in the secondary reaction. It is seen (Fig. 2, dotted line) that, if compound III is taken into account, the total yield of V after 5 hr. (21.9 mole %) is actually larger than that of the hydrodimer IV (15.3 mole %).

The observed change in the relative rate of the competing hydrodimerization and dimerization reactions at longer contact time can be explained by considering the mechanistically different character of reactions 1 and 2.

Reaction 2, which involves the formation and dimerization of an anionic free radical, is a non-catalytic reaction requiring 2 g.-atoms of potassium per mole of hydrodimer formed. Calculations on this basis show that in all experiments in the presence of potassium the total molar amount of hydrodimer formed approaches but does not exceed the required double gram-atomic amount of potassium. Thus, with 2.2 g. (0.056 g.-atom) of potassium employed in each experiment, the total amounts of hydrodimer, after completion of reaction 2, are as follows (mole): expt. 8, 0.026; expt. 9, 0.023; expt. 11, 0.023. (In the low conversion expt. 6 and 7, reaction 2 is not completed and the amount of hydrodimer is consequently lower than calculated.) It is, therefore, obvious that the interruption of the fastest reaction 2 corresponds to the point of nearly complete consumption of all the metallic potassium available.

Reaction 1, on the other hand, is a typical carbanion-catalyzed chain reaction, which requires only a small amount of potassium for producing the initiating species (R^-K^+). This reaction, therefore, continues to proceed uninterrupted even after the metallic potassium has been gradually consumed in the formation of compound V.

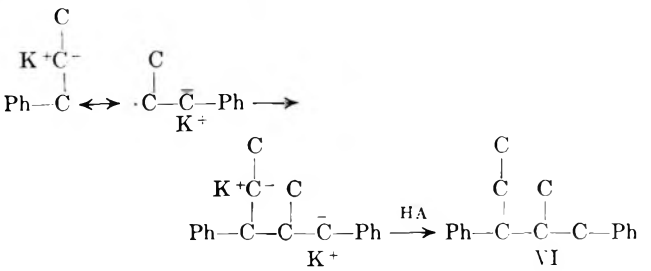
The following phenomena are also observed in the presence of potassium (Table I, expt. 6–11).

Compound I reacts at a low rate, even at 80° (expt. 6), whereas practically no reaction is observed at this temperature in the presence of sodium. At 80–100° no toluene or compounds II and III are present in the product. This is obviously due to the very low rate of formation of V at this temperature and to the absence of the secondary reactions 3 and 4, which are based on V as a precursor.

At 132° (expt. 9), owing to the increase in amount of V, reactions 3 and 4 do take place as indicated by the appearance of compounds II and III. It should be noted that this temperature is optimal for the formation of compound II, both in the presence of potassium or sodium.

At 155° (expt. 10), the toluene and compound II seem to be involved in further reaction. Toluene is almost completely consumed in reaction 4a, giving increased amounts of compound III, whereas II is obviously unstable at this temperature and is converted into high boiling products. It has been shown recently[9] that cyclobutenes substituted in the allylic position undergo easy thermal splitting. Thus, 3-methylcyclobutene is cleaved at the biallylic (3,4-) position to give 1,3-pentadiene already at 160°. In the present case compound II can probably likewise undergo thermal splitting to an open-chain diene, which may then polymerize under the experimental conditions.

The increase in the amount of compound VI at 155° may be due to an increase in the extent of the hydride transfer reaction 5 with temperature. It is not excluded, however, that a part of VI results from hydrodimerization of I by a path alternative to reaction 2.



On the other hand, the increase in the amount of olefins having the skeleton of VI (Table I, footnote *d*) indicates that reaction 6 increases somewhat in importance under these conditions. It is seen, therefore, that both the dimerization and hydrodimerization of I proceed in a somewhat less selective manner in the presence of potassium at 155°.

Experimental

Apparatus and Procedure.—The apparatus consisted essentially of a three-necked flask, provided with a high speed (7500 r.p.m.) stirrer and a sampling device, permitting the withdrawal of small liquid samples (~0.1 ml.) during the reaction.

The experiments were carried out under a slow stream of dry helium. In each case, the proper alkylcyclohexane, 20 g., was introduced in the flask and to this was added sodium, 2 g. (or potassium, 2.2 g.), freshly cut under the same solvent. The mixture was then brought to boiling and stirred for 45–60 min. Another portion of the solvent, 40 g., was added slowly (30 min.) and the mixing continued for 1 hr. To the fine, white-colored dispersion obtained was added dropwise (1 hr.) a solution of I (18 g.) in the same alkylcyclohexane (20 g.). I was >99% pure and contained 35% of the *cis* and 65% of the *trans* isomer. The color of the dispersion turned immediately brown and later deep brown or black. No promoter was employed in any of the experiments as the quick change in color indicated that compound I itself immediately provides the necessary initiating species. Samples of the reacting mixture were withdrawn every 15–30 min. and, after treatment with ethanol, examined by gas chromatography.

The final product was cooled to 0–5° and the catalyst decomposed with ethanol. The solution obtained was washed with 10% aqueous hydrochloric acid, followed by 10% aqueous sodium bicarbonate, dried, and the solvent removed at 100 mm.

Identification of Reaction Products. 1,4-Diphenyl-2,3-dimethylbutane (IV).—This compound was isolated in about 99% purity by fractional distillation of the product formed at 100° in the presence of potassium (expt. 8). It had b.p. 118–122° (0.5 mm.), $n^{20}D$ 1.5455, and was later shown by gas chromatography to consist of a nearly equimolar mixture of the *erythro* and *threo* isomers; the retention volumes of the two components, relative to *n*-hexylbenzene, were isomer I, 9.2, and isomer II, 10.0 (14-ft. column, filled with 8% silicon oil on Chromosorb; helium flow rate 40 ml./min.; temperature 200°).

Anal. Calcd. for $C_{18}H_{22}$: C, 90.67; H, 9.31. Found: C, 90.89; H, 9.15.

Compound IV did not contain any olefinic unsaturation and showed the following infrared absorption maxima (in $cm.^{-1}$; intensity: s, strong; m, medium; w, weak): 698 (s), 733 (s), 746 (s), 785 (w), 798 (w), 845 (w), 912 (w), 1037 (m), 1071 (w), 1103 (w), 1116 (w), 1162 (w), 1185 (w), 1365 (w), 1388 (m), 1462 (s), 1502 (s), 1615 (m), 1712 (w), 1750 (w), 1815 (w), 1884 (w), 1963 (w), 2900 (w), 2950 (s), 2980 (s), 3065 (s), 3100 (w).

The mass spectra[7] of IV showed that the compound has mol. wt. 238. Also, in agreement with the assigned structure, the n.m.r. spectrum of IV indicated that the sum of benzylic and tertiary hydrogen atoms (six) is equal to the sum of methyl hydrogens.

The structure of compound IV was conclusively established by comparison with a sample of *erythro*- and *threo*-1,4-diphenyl-2,3-dimethylbutane, synthesized by independent means (see below). The compared hydrocarbons showed identical retention volumes and infrared and n.m.r. spectra.

1,5-Diphenyl-4-methyl-1-pentene (V).—This compound was isolated in a pure form (>99%) by fractional distillation of the product obtained at 132° in the presence of sodium. It had b.p. 140–141° (0.55 mm.), $n^{20}D$ 1.5710, and contained a phenyl-conjugated double bond as determined by ultraviolet analysis [λ_{max} 2500 Å., (ϵ 14,300)] and semimicro hydrogenation.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.46; H, 8.54. Found: C, 91.35; H, 8.50.

The product of hydrogenation of V was identified as 1,5-diphenyl-2-methylpentane by comparison of its infrared spectrum and retention volume with those of a synthetic sample. After establishing the skeleton of V, the position of the double bond was determined by ozonation.

The dimer, 1.5 g., was dissolved in carbon tetrachloride, 30 ml., and ozonized at −20° for 2 hr. After removing most of the solvent, the ozonide was decomposed by boiling with 30 ml. of a solution consisting of equal volumes of 10% aqueous sodium bicarbonate and 30% hydrogen peroxide. The acid product obtained (1.65 g., 96% of theoretical) was purified by sublimation at 0.5 mm. and identified by gas chromatography (see Analytical) as a nearly equimolar mixture of benzoic and γ-phenylisovaleric acid.

Compound II.—The structure of 3-methyl-4-phenylcyclobutene was assigned to this hydrocarbon, which was isolated in nearly 99% purity by fractional distillation of the combined products of several experiments carried out at 132° in the presence of potassium (expt. 9). It had b.p. 143° (60 mm.), $n^{20}D$ 1.5340.

Anal. Calcd. for $C_{11}H_{12}$: C, 91.60; H, 8.40. Found: C, 91.48; H, 8.55.

Compound II contained one double bond as determined by semimicro hydrogenation. The ultraviolet spectrum [λ_{max} 2480 Å. (ϵ 1,380)] showed that the double bond is not conjugated with the benzene ring; the absorption maxima, however, appears at a shorter wave length, whereas the molecular extinction is some-

(9) E. Gil-Av and J. Shabtai, *J. Org. Chem.*, **29**, 257 (1964).

what higher compared to that of aromatic olefins with an open side chain.[10]

Evidence for the presence of a cyclobutene ring in II was provided by the infrared spectrum, which showed the following adsorption maxima (in cm.$^{-1}$; intensity: s, strong; m, medium; w, weak): 668 (w), 700 (s), 834 (w), 844 (w), 868 (m), 891 (m), 927 (w), 966 (w), 1002 (m), 1012 (m), 1037 (m), 1077 (m), 1138 (w), 1163 (w), 1188 (w), 1241 (w), 1271 (w), 1376 (e), 1461 (s), 1491 (w), 1508 (s), 1540 (w), 1575 (w), 1600 (w), 1612 (s), 1754 (w), 1813 (w), 1880 (w), 1960 (w), 2900 (m), 2970 (s), 3070 (m), 3130 (m).

As seen, the =C—H stretching absorption appears at 3130 cm.$^{-1}$, which is characteristic[11] for a cyclobutene without a substituent at the double bond (cyclobutene,[11] 3126 cm.$^{-1}$; 3-methylcyclobutene,[9] 3130 cm.$^{-1}$). Also, typically for a strained four-membered ring[11] the C=C stretching frequency is very low (1575 cm.$^{-1}$), as found in cyclobutene (1565 cm.$^{-1}$) and 3-methylcyclobutene (1566 cm.$^{-1}$). It is significant that apart from the band at 1575 cm.$^{-1}$ the spectrum of II contains a second weak band at 1600 cm.$^{-1}$, which is also observed in the spectrum of 3-methylcyclobutene.[9] The well-defined doublet exhibited by the latter compound (1566–1600 cm.$^{-1}$) seems to be characteristic for cyclobutenes with an alkyl or aryl substituent in the 3 position; a similar doublet has been observed at higher frequencies in the spectra of 3-alkylcyclopentenes[12] (1616–1650 cm.$^{-1}$) and 3-alkylcyclohexenes[13] (1650–1685 cm.$^{-1}$). The specific absorption pattern[14] in the 1700–2000-cm.$^{-1}$ range and the strong band at 700 cm.$^{-1}$ show that the benzene ring in II is monosubstituted.

Ozonation of II under the above conditions (see compound V) gave as the sole product (yield, 94%) a semisolid acid, which failed to crystallize from a number of solvents, including carbon tetrachloride. The acid contained two carboxylic groups, as determined by neutralization in alcoholic solution, and analyzed for the expected α-methyl-α'-phenylsuccinic acid.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.20; H, 5.94.

(10) R. N. Jones, *Chem. Rev.*, **32**, 35 (1943).

(11) R. C. Lord and D. G. Rea, *J. Am. Chem. Soc.*, **79**, 2401 (1957).

(12) S. Pinchas, J. Shabtai, J. Herling, and E. Gil-Av, *J. Inst. Petrol.*, **45**, 311 (1959).

(13) J. Shabtai, S. Pinchas, J. Herling, C. Greener, and E. Gil-Av, *ibid.*, **48**, 13 (1962).

(14) C. W. Young, R. B. Du Wall, and N. Wright, *Anal. Chem.*, **23**, 709 (1951).

Sources and Synthesis of Pure Hydrocarbons.—1,3-Diphenyl-2-methylpropane (III) and 1,3-diphenyl-2-methylpentane (VI) were available from previous work.[15] 1-Phenyl-1,3-pentadiene was synthesized by N. C. Sih of our laboratory.

1,5-Diphenyl-2-methylpentane.—This compound was synthesized through the Grignard reaction of 1-bromo-3-phenylpropane with phenyl-2-propanone. The intermediate carbinol, **1,5-diphenyl-2-methyl-2-pentanol**, b.p. 213–214° (18 mm.), $n^{20}D$ 1.5568, was obtained in 64% yield. It was dehydrated over Harshaw alumina[15] at 330–340° and the resulting mixture of two double-bond isomers was hydrogenated at 150° and 120-atm. hydrogen pressure over chromia–alumina. After distillation the obtained 1,5-diphenyl-2-methylpentane was 99% pure, b.p. 126–127° (0.4 mm.), $n^{20}D$ 1.5413.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.65; H, 9.31. Found: C, 90.53; H, 9.35.

1,4-Diphenyl-2,3-dimethylbutane (IV).—This compound was obtained by reacting an ethereal solution of 1-phenyl-2-chloropropane at reflux temperature with magnesium turnings. The chloride was prepared by reacting 1 mole of 1-phenyl-2-propanol dissolved in 1 mole of pyridine with 1.3 moles of thionyl chloride.

The 1,4-diphenyl-2,3-dimethylbutane obtained consisted of a 40:60% mixture of *erythro* and *threo* isomers, having retention times identical with the compound IV obtained from the dimerization of β-methylstyrene.

Analytical.—Preparative fractional distillation of reaction products was carried out at reduced pressure on a 20 cm. × 12 mm. column, filled with stainless steel wire gauze packing, or when necessary (*e.g.*, in the isolation of compound II) on a Piros-Glover spinning band column.

Quantitative analyses of product components, as well as of hydrogenation or ozonation products, were carried out by gas chromatography on a programmed temperature apparatus (F and M, Model 300). Several types of columns were used including (a) a 9-ft. column, filled with 10% silicone gum rubber on Chromosorb P; and (b) a 14-ft. column with 8% silicone (DC 550 fluid) on the same support. In the analysis of acids the liquid phase was silicone, containing 10% stearic acid.

N.m.r. spectra were measured on a Varian spectrometer.

Acknowledgment.—Thanks are due to Mr. Ed M. Lewicki for valuable laboratory assistance.

(15) H. Pines and W. O. Haag, *J. Am. Chem. Soc.*, **82**, 2471 (1960).

Synthesis of 1-Butene-2,4-sultam

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The chlorosulfonylation of 1,4-dichlorobutane has been effected in refluxing sulfur dioxide solution to give 1,4-dichlorobutane-2-sulfonyl chloride. The latter has been converted to 4-chloro-1-butene-2-sulfonamide by treatment with triethylamine and ammonia, and the chlorobutenesulfonamide has been cyclized to 1-butene-2,4-sultam by treatment with alcoholic alkali. The sultam is a colorless, uncrystallizable oil which darkens on exposure to air and polymerizes on distillation at reduced pressure. Its crystalline N-benzenesulfonyl derivative melted at 134–135°. The sultam polymerized by Michael addition in the presence of strong base, giving a water-insoluble solid, m.p. 170–190°, $[\eta]$ 0.08 dl./g. Preliminary investigation has indicated that the sultam can also polymerize by radical-initiated olefin addition and by sustained ring opening.

In a general study of the preparation and polymerization of aliphatic sultams,[2] we have examined the effect of an exocyclic double bond on the reactivity of the five-membered sultam ring. Although the literature contains no examples of simple methylene-substituted sultams, it seemed reasonable to suppose the chlorosulfonylation[3] of aliphatic dihalides would afford a synthetic route to unsaturated sultams by the transformations indicated below for the preparation of 1-butene-2,4-sultam (I).[4]

The attempted chlorosulfonylation of II by the method successfully applied to 1-chlorobutane by

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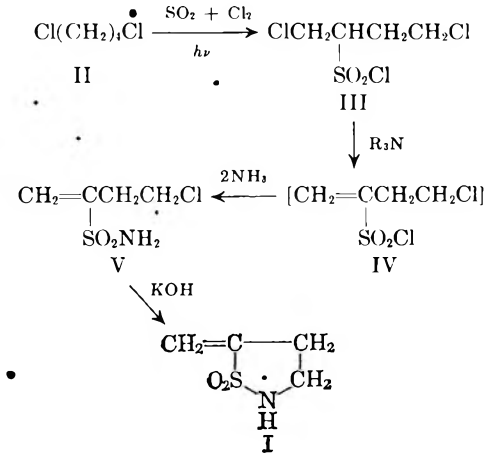
(2) (a) A. D. Bliss, W. K. Cline, C. E. Hamilton, and O. J. Sweeting, *J. Org. Chem.*, **28**, 3537 (1963); (b) A. D. Bliss, W. K. Cline, C. E. Hamilton, and O. J. Sweeting, *J. Polymer Sci.*, to be published.

(3) C. F. Reed, U. S. Patent 2,056,090 (June 30, 1936); *Chem. Abstr.*, **30**, 5593 (1936).

(4) We have followed the common practice of naming sultams as derivatives of the longest hydrocarbon chain to which both sulfur and nitrogen are attached [R. Helferich, K. Geist, and H. Plümpe, *Ann.*, **651**, 17 (1962), *q.v.*] rather than by the cumbersome and seldom-used heterocyclic nomenclature suggested in "The Naming and Indexing of Chemical Compounds from Chemical Abstracts," American Chemical Society, 1962, in which I would be named 5-methyleneisothiazolidine 1,1-dioxide.



Helberger, Manecke, and Fischer[5] led exclusively to the formation of chlorinated products, principally 1,2,4-trichlorobutane and some tetrachlorobutane. Similarly, the use of sulfuryl chloride with a pyridine catalyst in the presence of light[6] merely resulted in the chlorination of II. The preparation of III was effected by treating an illuminated solution of II in 3 moles of refluxing sulfur dioxide with a 1:1 mixture of chlorine and sulfur dioxide. The reaction could be catalyzed by benzoyl peroxide[7] or α,α'-azodiisobutyronitrile[8] in the presence of light, but the accelerating effect of these materials was short lived. The best catalyst for the reaction was an acetyl alkanesulfonyl peroxide generated *in situ* by initially adding acetic anhydride and benzoyl peroxide to the sulfur dioxide solution and passing in a small amount of oxygen with the mixture of sulfur dioxide and chlorine.[9]

Despite the high concentration of sulfur dioxide employed and the low temperature of the reaction, both factors which tend to favor chlorosulfonylation over chlorination,[6] III was formed in only 30% yield, the major product being a mixture of polychlorinated butanes. The symmetry of 1,4-dichlorobutane (II) and the effect of the two chlorine atoms in suppressing attack on the carbons to which they are attached[5] prevents the formation of monosulfonyl chlorides other than III. The yield of III could be increased by using still larger amounts of liquid sulfur dioxide, but the reaction then became very slow and excessive amounts of sulfuryl chloride were formed.

When the reaction was initiated in excess liquid sulfur dioxide, and chlorine alone was passed in, the rate of hydrogen chloride evolution increased as the reaction proceeded, as a result of the depletion of sulfur dioxide. The sulfonyl chlorides obtained under these conditions, unlike III, evolved both hydrogen chloride and sulfur dioxide and formed black tars upon attempted distillation at reduced pressure.

The reaction of III with ethereal ammonia resulted in a partial elimination of the chlorine in the 1-position and gave a 35% yield of 4-chloro-1-butene-2-sulfonamide (V) along with large amounts of what appeared to be polymeric aminoalkane sulfonamides. The infrared spectra of these products showed strong primary sulfonamide absorptions, but were distinctly different from that of poly-4-chloro-1-butene-2-sulfonamide prepared by treating a chloroform solution of V with benzoyl peroxide. The polymers were tentatively identified as condensation products of 1-amino-4-chlorobutane-2-sulfonamide (VI), which probably was formed by direct displacement of chlorine from the 1-position of 1,4-dichlorobutane-2-sulfonamide. Since V could be recovered unchanged after standing for 1 week at room temperature in an ethereal ammonia solution, VI and its condensation products cannot have arisen by the addition of ammonia to the double bond of V. This contrasts with the behavior of ethenesulfonamide, which has been shown to add ammonia readily.[10-12] It was found, however, that the stronger base, butylamine, did react slowly with V at room temperature, producing butylamine hydrochloride and probably also giving some addition to the double bond, although identification of the addition products was not certain. It appears possible to account for the by-products in the reaction of III with ammonia as condensation products of VI along with some products of addition of V and VI.

One mole of triethylamine reacted rapidly and quantitatively with III at 0° and presumably formed 4-chloro-1-butene-2-sulfonyl chloride (IV), in a manner analogous to the formation of ethenesulfonyl chloride from 2-chloroethanesulfonyl chloride and 2,6-lutidine.[12] The intermediate was not isolated, but was caused to react directly with 2 moles of ammonia to give V in a yield of 85%.

The cyclization of V occurred readily in dilute alcoholic solutions of alkali hydroxides, forming salt in 96% yield, a small amount of ether-insoluble gum, and a 90% yield of a colorless oil with the spectral characteristics of 1-butene-2,4-sultam (I). The oil resisted all attempts at crystallization and darkened rapidly upon attempted vacuum distillation. The material instantly decolorized acidic potassium permanganate solution and rapidly added bromine (neither reaction is shown by propanesultam or 1,4-butanesultam). The reaction of benzenesulfonyl chloride with a solution of the oil in aqueous sodium hydroxide gave a 91% yield of the crystalline N-benzenesulfonyl derivative, which also decolorized permanganate and added bromine. The nuclear magnetic resonance spectrum of the N-benzenesulfonyl derivative showed resonances at 5.7 and 6.0 p.p.m. (from internal tetramethylsilane standard) proving the presence of the exocyclic methylene group. The sultam ring protons on C-3 gave a resonance at 2.95 p.p.m. and those on C-4 at 3.68 p.p.m. The protons of the aromatic ring were in the normal position for a sulfone. There was also an indication that a small amount of the isomeric N-benzenesulfonyl-2-butene-2,4-sultam was present. Resolution was not sufficiently high to permit quantitative estimation of the amount, but it could not have exceeded 4%.

(5) J. H. Helberger, G. Manecke, and H. M. Fischer, *Ann.*, **562**, 23 (1949).

(6) M. S. Kharasch, T. H. Chao, and H. C. Brown, *J. Am. Chem. Soc.*, **62**, 2393 (1940).

(7) Farbwerke Hoechst A.-G., German Patent 854,046 (Oct. 30, 1952); *Chem. Abstr.*, **50**, 10,131 (1956).

(8) Soc. Anon. des Manufactures des Glaces et Produits Chimiques de Saint-Gobain, French Patent 1,023,736 (March 23, 1953); *Chem. Abstr.*, **52**, 5459 (1958).

(9) R. Graf, German Patent 841,147 (June 13, 1952); *Chem. Abstr.*, **47**, 4897 (1953).

(10) A. S. Matlack, *J. Org. Chem.*, **23**, 729 (1958).

(11) A. A. Goldberg, *J. Chem. Soc.*, 464 (1945).

(12) C. S. Rondestvedt, Jr., *J. Am. Chem. Soc.*, **76**, 1926 (1954).

When the cyclization of V was run in solutions more concentrated than about 0.5 *M*, substantial amounts of a solid, water-insoluble polymeric material formed. The same polymer could be prepared by treatment of an alcohol solution of I with catalytic amounts of alkalies or sodium alkoxides or by the bulk polymerization of I with a sodium hydride catalyst. The infrared spectra of these polymers showed strong SO_2 absorptions, but no NH or unsaturation. The spectrum, the mode of formation, and the analysis of the material strongly suggested that it was a polymer formed by the sustained Michael addition of I. Breslow, Hulse, and Matlack[13] have shown that this type of polymerization can occur with ethenesulfonamide, acrylamide, and other materials which, like I, contain an activated double bond and an acidic function.

Very cursory investigation has indicated that I can polymerize by ring opening under the same conditions as propanesultam[2,14] and by radical-initiated olefin addition as well as by sustained Michael addition.

Experimental

1,4-Dichlorobutane-2-sulfonyl Chloride (III).—A 500-ml., three-necked flask, fitted with a stirrer, Dry Ice reflux condenser, gas inlet tube, and drying tube was cooled by means of a Dry Ice–acetone bath and charged with approximately 135 ml. (3 moles) of anhydrous sulfur dioxide. To this was added 127 g. (1.0 mole) of 1,4-dichlorobutane (Eastman White Label), 5.0 ml. of acetic anhydride, and a small amount of benzoyl peroxide.[9] The mixture was stirred, allowed to reflux, illuminated with a 500-w. incandescent lamp placed approximately 3 in. from the flask, and treated with a gaseous mixture of oxygen (20 ml./min.), sulfur dioxide (190 ml./min.), and chlorine (190 ml./min.). Reaction started immediately and hydrogen chloride was evolved.

By passing the exit gas through a Dry Ice trap and then into a known amount of standard alkali, it was estimated that 1 mole of hydrogen chloride would be evolved in 2.75 hr. (1.3 moles of chlorine); the chlorine and sulfur dioxide were shut off at the end of that time, but oxygen input and illumination were continued. Hydrogen chloride continued to evolve for about 10 min. and then stopped abruptly. The oxygen flow and the illumination were interrupted and the liquid sulfur dioxide was allowed to evaporate. Dissolved gases and most of the sulfuryl chloride produced were removed at room temperature and 50-mm. pressure. The residue, which weighed 200.7 g., was distilled at a pressure of 13 mm. The distillation produced 27.6 g. of sulfuryl chloride (which passed into the Dry Ice trap), 97.0 g. of a chlorinated butane mixture boiling over the range 29–43°, 63.5 g. of a sulfonyl chloride boiling at 99–100°, and 7.9 g. of black, tarry residue. The chlorinated butane fraction was found by vapor phase chromatography and infrared spectroscopy to contain 0.15 mole of 1,4-dichlorobutane, approximately 0.5 mole of 1,2,4-trichlorobutane, and a small amount of an unidentified higher boiling component. The sulfonyl chloride fraction was redistilled at 12.5 mm., yielding 6.5 g. boiling at 95–98°, 37.6 g. boiling at 98.0–98.3°, 11.3 g. boiling at 98.3–100.0°, and 6.1 g. of brown liquid residue. The center cut was shown by vapor phase chromatography to consist of a single major component. The detection of minor constituents was not possible because of some decomposition of the material on the chromatographic column. Infrared and nuclear magnetic resonance spectroscopy identified the material as III. Principal infrared absorptions (μ) were 3.30 (w), 3.38 (w), 6.87 (m), 6.95 (m), 7.25 (vs), 7.55 (w), 7.70 (m), 7.80 (w), 8.20 (m), 8.61 (vs), 12.4 (m), 13.1 (m), 13.6 (m), 14.2 (m), and 14.8–15.0 (m).

The nuclear magnetic resonance spectrum showed resonances (from internal tetramethylsilane standard) at 4.05 (multiplet) for the protons of C-1, 4.2 (multiplet) for the methine, 2.65 for the C-3 methylene, and 3.78 p.p.m. (multiplet) for the C-4 methylene.

Anal. Calcd. for $C_4H_7Cl_3O_2S$: C, 21.30; H, 3.13; Cl, 47.16. Found: C, 21.57; H, 3.33; Cl, 48.96, 48.14.

4-Chloro-1-butene-2-sulfonamide (V).—A solution of 5.0 g. (22 mmoles) of III in 100 ml. of anhydrous ether was cooled in ice and treated with 2.2 g. (22 mmoles) of triethylamine in 20 ml. of ether. A white precipitate formed immediately. The mixture was allowed to warm to room temperature and filtered. The solid, washed with ether and dried, 3.0 g. (100%), melted at 251–253°, unchanged on admixture with authentic triethylamine hydrochloride. The filtrate, which had the characteristic odor of a sulfonyl chloride, was again cooled in an ice bath and treated with anhydrous ammonia until it became basic. A white solid was removed by filtration, washed with ether, dried, and found to weigh 1.4 g. (The calculated quantity of ammonium chloride is 1.2 g.) The extraneous material was not identified. Ether was removed from the filtrate at reduced pressure, yielding a slightly yellow oil, which did not completely redissolve in 50 ml. of anhydrous ether. The solution was decanted from 0.5 g. of viscous yellow oil, treated with decolorizing carbon, and filtered. The colorless filtrate was treated with petroleum ether (b.p. 30–60°) to faint turbidity and chilled, producing 3.2 g. (85%) of a white crystalline compound which melted at 67–68°.[15] Two recrystallizations from mixed ether and petroleum ether raised the melting point to 68–69°. The substance was identified as V by infrared spectroscopy and elemental analysis. Principal infrared absorptions (μ) were 2.90 (s), 3.09 (s), 3.18 (m), 3.33 (m), 6.45 (s), 6.85 (m), 6.98 (m), 7.60 (vs), 8.45 (m), 8.70 (vs), 8.80 (vs), 10.5 (s), 11.0 (s), 11.7 (m), 13.2 (s), and 14.3–15 (s).

Anal. Calcd. for $C_4H_8ClNO_2S$: C, 28.32; H, 4.75; N, 8.26; Cl, 20.90. Found: C, 28.46; H, 4.87; N, 8.15; Cl, 21.20.

1-Butene-2,4-sultam (I).—To a solution of 9.203 g. (54.3 mmoles) of V in 50 ml. of anhydrous methanol containing 0.2 g. of N,N-dimethylaniline, was added a solution of 2.173 g. (54.3 mmoles) of sodium hydroxide in 50 ml. of methanol. An intense yellow color developed immediately, but faded to pale yellow within 1 min. After the solution had refluxed for 2 hr., bumping caused by precipitated salt became severe and the mixture was cooled and filtered. The salt was washed with 20 ml. of methanol and the filtrate and washings were combined and again refluxed. After a total of 8 hr. at reflux, the solution had become neutral and was cooled and filtered. The filtrate was evaporated at reduced pressure, leaving a yellow oil and a substantial amount of salt. The oil was dissolved in 15 ml. of anhydrous ethanol and filtered. The combined salt residues from all of the operations were dried and found to weigh 3.026 g. (95.7%). The ethanol filtrate was treated with ether to faint turbidity and chilled, but only a small amount of dark yellow gum separated. The solution was decanted and evaporated *in vacuo* to a yellow oil, which weighed 6.61 g. (91.4%). Treatment of an ethanol solution of the oil with decolorizing carbon gave, on evaporation of the alcohol, 6.35 g. of a colorless oil which resisted all attempts at crystallization and darkened and became viscous on attempted distillation at 0.8 mm. The oil instantly decolorized permanganate and rapidly added bromine. Upon exposure to the atmosphere, it slowly developed a reddish color. It was identified as I on the basis of its infrared spectrum and elemental analysis. Principal infrared absorptions (μ) were 3.05 (vs), 3.25 (m), 3.37 (m), 3.43 (m), 6.12 (w), 6.50 (w), 6.68 (m), 6.80 (m), 7.05 (s), 7.30 (s), 7.7 (vs), 8.60 (vs), 8.9 (vs), 9.65 (s), 10.0 (s), 10.4 (s), 10.75 (s), 11.4 (m), and 13.2 (b).

Anal. Calcd. for $C_4H_7NO_2S$: C, 36.07; H, 5.30; N, 10.52. Found: C, 36.30, 36.25; H, 5.74, 5.65; N, 10.84.

N-Benzenesulfonyl-1-butene-2,4-sultam.—To a solution of 1.4 g. (0.01 mole) of 1-butene-2,4-sultam in 20 ml. of water was added 0.8 g. (0.02 mole) of sodium hydroxide and 3.5 ml. (0.02 mole) of benzenesulfonyl chloride. The mixture was stirred for 6 hr. at room temperature. A substantial amount of white solid was removed by filtration and washed three times with 20-ml. portions of water and six times with 20-ml. portions of ethanol. The odorless, neutral product was dissolved in acetone, treated with charcoal to remove a slight yellow color, and filtered. Evaporation of the filtrate gave 2.5 g. (91%) of white crystals melting at 133–134°. Three recrystallizations from ethanol raised the melting point to 134–135°. The material rapidly decolorized aqueous acidic permanganate and slowly added bromine. Its

(13) D. S. Breslow, G. E. Hulse, and A. S. Matlack, *J. Am. Chem. Soc.*, **79**, 3760 (1957).

(14) W. H. Libby, U. S. Patent 2,983,713 (May 9, 1961).

(15) In the first preparation of this compound, a different crystalline modification (needles) melting at 53.0–53.5° was obtained. This changed spontaneously to the higher melting form (without alteration of its spectrum or analysis) and was never obtained again.

infrared spectrum showed no NH absorptions. The nuclear magnetic resonance spectrum showed resonances (from internal tetramethylsilane standard) at 2.95, 3.68, 5.7, and 6.0 p.p.m. The protons of the aromatic ring were in the normal position for a sulfone.

Anal. Calcd. for $C_{10}H_{11}NO_4S_2$: C, 43.94; H, 4.06; N, 5.13. Found: C, 44.06; H, 4.02; N, 5.11, 5.13.

Ammoniation of the Products of Chlorosulfonylation of 1,4-Dichlorobutane.—The total reaction mixture from the chlorosulfonylation of 1 mole of II, after removal of dissolved gas and sulfuryl chloride, was dissolved in 1 lb. of anhydrous ether and filtered. The yellow filtrate was diluted with another pound of ether and placed in a 3-l. flask fitted with stirrer, thermometer, gas inlet tube, and calcium chloride drying tube. The solution was cooled to −10° with an ice–salt bath and treated with anhydrous ammonia at the rate of 250 ml./min. After a 1.3-mole addition of ammonia, the mixture became basic. Filtration and vacuum-drying yielded 90.4 g. of white solid, which was extracted with 500 ml. of hot ethanol, then with 500 ml. of hot acetone. The residue (66 g.) was shown by chloride analysis and vacuum sublimation of an aliquot to contain 54 g. (1.0 mole) of ammonium chloride, 12 g. of a polymeric solid (m.p. 150–170° to a viscous melt) which showed strong sulfonamide absorptions in the infrared, and a trace of an ammonium alkanesulfonate (barium nitrate precipitation). Evaporation of the alcohol–acetone extract gave 24 g. of dark oil which, except for about 1 g. of gum, dissolved readily in petroleum ether, had a strong odor of chlorinated butane, and gave a very poorly resolved infrared spectrum that showed no SO_2 absorptions. The ether filtrate of the reaction products, which after standing overnight at room temperature had deposited a small amount of yellow gum, was decanted and evaporated at reduced pressure to a yellow oil. The oil was washed three times by decantation with 250-ml. portions of petroleum ether. Evaporation of the petroleum ether extracts gave 85 g. of a mixture of chlorinated butanes, which showed no sulfonyl absorptions in the infrared. The residue from the extraction, 51.2 g., left a small gummy residue when treated with ether. The ether solution was decanted, treated with petroleum ether to faint turbidity, and chilled, which caused the separation of a dark yellow viscous oil. The solution was decanted, again treated with petroleum ether to turbidity, and cooled, whereupon a light yellow, fluid oil separated. Another repetition of this treatment gave 26 g. of yellow crystalline solid melting at 61–64°. Treatment of an ether solution of the material with decolorizing carbon and two recrystallizations from ether–petroleum ether gave 19 g. of white plates melting at 68–69°,[15] identified as V by infrared spectroscopy, elemental analysis, and mixture melting point. The spectra of the oily products were very similar to that of the crystalline sulfonamide.

Anal. Calcd. for $C_4H_8ClNO_2S$: C, 28.32; H, 4.75; N, 8.26; Cl, 20.90. Found: C, 28.40; H, 4.63; N, 8.31; Cl, 21.14.

Ammoniation of 1,4-Dichlorobutane-2-sulfonyl Chloride.—A solution of 10.05 g. (0.04 mole) of III in 100 ml. of ether was added slowly to an ice-cold mixture of 10 ml. of concentrated aqueous ammonia and 100 ml. of ether. Upon completion of the vigorous reaction, a small amount of water was added to the mixture to dissolve a white solid, and the layers were separated. A gummy white precipitate appeared during the drying of the ether layer over magnesium sulfate. The solution was filtered and evaporated at reduced pressure to 7.1 g. of colorless oil. Ether then dissolved only about half of this material. The solution was decanted, treated with petroleum ether to faint turbidity, and chilled, giving 2.8 g. of sticky white crystals. Recrystallization from mixed ether and petroleum ether gave 2.4 g. (35%) of a crystalline solid melting at 68–69°, unchanged on admixture with authentic V. Infrared examination showed the ether-insoluble oil to be a sulfonamide with a spectrum very similar to that of the crystalline material.

Treatment of V with Ammonia.—To a mixture of 1.5 ml. of concentrated aqueous ammonia and 10 ml. of ether was added 0.5 g. of V in 5 ml. of ether. The mixture was allowed to stand at room temperature for a week. The ether solution was then dried over magnesium sulfate, filtered, and evaporated, yielding 0.5 g. of white crystalline solid melting at 68–69°, unchanged on admixture with the starting material.

Treatment of V with Butylamine.—A solution of 0.5 g. of V in 10 ml. of ether was treated with 0.5 ml. of anhydrous butylamine and allowed to stand at room temperature for 4 days. The ether was decanted from a sticky white solid and evaporated to a colorless oil. The material oiled out of solutions of ether and petroleum ether upon cooling and did not crystallize when seeded with V. Its infrared spectrum showed a broad, poorly resolved absorption in the 2.95–3.10-μ region which was interpreted as a combination of amine N–H and sulfonamide N–H bonds.

Polymerization of V.—A solution of 1.0 g. of V in 5 ml. of chloroform was treated with a small amount of benzoyl peroxide and warmed on the steam bath. After about 5 min., a white precipitate began to appear. After 2 hr., the solution was cooled and filtered, giving 0.2 g. of slightly yellow solid which gave a viscous melt at 170–180°. The material was soluble in water, slightly soluble in alcohol, and insoluble in ether. Its infrared spectrum showed strong primary sulfonamide peaks, carbon–chlorine absorptions, and no definite indications of unsaturation. The spectrum was distinctly different, particularly in the 2.95–3.10-μ region, from the spectra of the polymeric sulfonamides obtained by the ammoniation of III.

Polymerization of I. A.—A solution of 5.0 g. of I in 50 ml. of chloroform was treated with a small amount of benzoyl peroxide and warmed on the steam bath. A white precipitate appeared after about 1 min., but apparently stopped coming out after approximately 5 min. The addition of more catalyst caused more solid to form, but the reaction again stopped after a few minutes. The solution was cooled and filtered, giving 0.5 g. of a light tan solid which gave a viscous melt at 190–210°. The infrared spectrum resembled that of I except for the absence of the double bond absorption at 6.10 μ and some differences in the 10.5–11.5-μ region. Its intrinsic viscosity in dimethyl sulfoxide solution was 0.04 dl./g.

B.—To a solution of 2.0 g. of I in 20 ml. of anhydrous ethanol was added 1 drop of N,N-dimethylaniline and 2 drops of a 2% solution of sodium ethoxide in ethanol. After 2 hr. at reflux, the mixture was cooled and filtered to remove a gummy white solid. The solid was washed with water and dried, yielding 0.5 g. of white powder which melted at 170–190°. Short, brittle fibers could be pulled from the viscous melt. The polymer had an intrinsic viscosity of 0.06 dl./g. in dimethyl sulfoxide. Its infrared spectrum showed strong sulfonyl absorptions, but no NH peaks and no unsaturation. The water-soluble portion of the reaction product was a viscous oil with weak sulfonamide NH absorptions in its infrared spectrum. Principal infrared absorptions (μ) were 3.31 (m), 3.45 (m), 6.91 (m), 7.28 (m), 7.75 (s), 8.02 (m), 8.50 (m), 8.84 (s), 9.70 (m), and 13.2–13.4 (s).

Anal. Calcd. for $C_4H_7NO_2S$: C, 36.07; H, 5.30; N, 10.52. Found: C, 35.71, 35.75; H, 5.39, 5.36; N, 10.11, 10.13.

C.—A small test tube was charged with 2.0 g. of I. The liquid was purged with dry nitrogen and heated to 127° for 30 min. To the hot sultam was then added 5 mg. of sodium hydride, and the mixture was allowed to react under nitrogen at 127° for 18 hr. The viscous brown liquid product was cooled and treated with 20 ml. of cold water. A yellow, granular solid was removed by centrifugation, washed five times with water and twice with acetone, and dried *in vacuo*. The material weighed 0.62 g. (30%), melted at 175–90°, and had an infrared spectrum identical with that of the polymer prepared in the preceding experiment. Its intrinsic viscosity in dimethyl sulfoxide was 0.08 dl./g. The water-soluble portion of the product was a yellow gum.

Formation of a Polymer of 1-Butene-2,4-sultam from 4-Chloro-1-butene-2-sulfonamide.—To a solution of 5.1 g. (0.03 mole) of V in 15 ml. of anhydrous ethanol containing 1 drop of N,N-dimethylaniline was added a solution of 1.2 g. (0.03 mole) of sodium hydroxide in 15 ml. of ethanol. The solution was refluxed for 3 hr.; it was then very weakly basic. A sudden precipitation of slightly gummy white solid ensued and continued for about 30 min. The mixture was cooled and filtered to give, after drying *in vacuo*, 3.75 g. of sticky white solid. This material, extracted three times with 20-ml. portions of water and twice with 20-ml. portions of ethanol, and dried *in vacuo*, weighed 1.2 g., melted at 170–90°, had an intrinsic viscosity of 0.07 dl./g. in dimethyl sulfoxide, and an infrared spectrum identical with those of the polymers prepared by the treatment of I with catalytic amounts of base. The alcoholic filtrate of the reaction products was evaporated at reduced pressure to a yellow oil. Extraction of the oil with ether left 0.7 g. of viscous dark yellow liquid. The ether extract was treated with decolorizing carbon and evaporated at reduced pressure to 1.3 g. (32%) of a colorless oil with an infrared spectrum identical with that of the 1-butene-2,4-sultam previously prepared.

Acknowledgment.—We are indebted to Dr. H. Agahigian for obtaining and interpreting the nuclear magnetic resonance spectra of 1,4-dichlorobutane-2-sulfonyl chloride and of N-benzenesulfonyl-1-butene-2,4-sultam, and to Dr. Sidney Siggia and the staff of the Olin Mathieson Central Analytical Department for microanalyses, infrared spectroscopy, vapor phase chromatography, and intrinsic viscosity determinations.

A Convenient, New Synthesis of *p*-Sexiphenyl from Biphenyl or *p*-Terphenyl in the Presence of Lewis Acid Catalyst–Oxidant[1]

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p-Sexiphenyl can be prepared in improved yield by a simple, one-step procedure involving treatment of biphenyl with aluminum chloride–cupric chloride, ferric chloride, or molybdenum pentachloride. Small amounts of *p*-quaterphenyl and higher molecular weight products were also formed. Under similar conditions, *p*-terphenyl yielded predominantly the dimer-type product, *p*-sexiphenyl. In attempted copolymerization of biphenyl and *p*-terphenyl, the main product obtained was *p*-sexiphenyl. Cuprous chloride proved to be a very effective inhibitor in the biphenyl–aluminum chloride–cupric chloride system. Studies were made of the relative rates of reaction for the monomers, benzene, biphenyl, and *p*-terphenyl, based on hydrogen chloride evolution. The theoretical aspects are discussed.

Aromatic hydrocarbons in the *p*-polyphenyl series have attracted considerable attention because of their good thermal stability, high melting points, insolubility, electronic configuration, and the interest in them as moderators in nuclear reactors. Previously, the individual, higher, isolable *p*-polyphenyls have usually been prepared by classical methods, such as the Ullmann coupling, Fittig reaction, or the Grignard synthesis. However, these routes suffer from one or more of the following limitations: very low yields, necessity of drastic conditions, tedious purifications, difficulties in reproducing results, multistep syntheses from the aromatic hydrocarbon precursor, and the formation of gross mixtures due to competing reactions.

Since our work is primarily concerned with *p*-sexiphenyl, discussion of the prior literature will be limited to this homolog. For example, in the Ullmann synthesis from 4-iodo-*p*-terphenyl and silver powder at 330°, Pummerer and Bittner[3] remarked on the difficulty of effecting condensation. Subsequently, this method was applied to a mixture of 4-iodobiphenyl, 4,4′-diiodobiphenyl, and copper powder, which provided a 25% yield based upon the iodo aromatics.[4a] In a modified version, Kuhn[4b] obtained *p*-sexiphenyl by zinc–acetic acid reduction of the product derived from 4,4′-diiodobiphenyl and copper. More recently,[5] Nozaki and co-workers[6] also investigated the Ullmann procedure with 4-iodo-*p*-terphenyl and reported a 10% yield based upon the *p*-terphenyl precursor in this multistep synthesis. In connection with their studies of *p*-polyphenyls and the corresponding methylated derivatives, Kern and Wirth[7] utilized the Ullmann and Grignard reactions for preparative purposes. In addition, the catalytic reduction of *p*-dibromobenzene in the presence of methanol afforded a gross mixture from which *p*-sexiphenyl was isolated in 0.7% yield.[8]

The objective of the present work was to effect the nuclear coupling of biphenyl and of *p*-terphenyl by treatment with a Lewis acid catalyst and oxidant, and to investigate the theoretical aspects.

Results and Discussion

We have succeeded in synthesizing *p*-sexiphenyl in good yield and high purity by a novel, one-step procedure involving biphenyl–Lewis acid catalyst–oxidant. Inexpensive, readily available starting materials are used. Under mild conditions, biphenyl was converted to the trimer-type product on treatment with aluminum chloride–cupric chloride, ferric chloride, or molybdenum pentachloride. Minor amounts of higher *p*-polyphenyls were formed, as well as small quantities of *p*-quaterphenyl. The isolated products were characterized by comparison with authentic materials (melting points and ultraviolet and infrared spectra). Apparently, the formation of *p*-sexiphenyl from biphenyl–aluminum chloride–cupric chloride proceeds as indicated below.

$$3\ \text{biphenyl} + 4CuCl_2 \xrightarrow{AlCl_3} p\text{-sexiphenyl} + 4CuCl + 4HCl$$

This transformation resembles the synthesis of bimesityl from mesitylene and ferric chloride.[9] Furthermore, analogy may be drawn to the conversion of benzene to *p*-polyphenyl,[10-12] except that the product from biphenyl is of much lower molecular weight.

The biphenyl reaction was investigated at some length with the aim, in part, of determining the optimum conditions for *p*-sexiphenyl formation (Table I). We found that the reaction, which proceeded with good rapidity, was quite sensitive to changes in the $AlCl_3$–$CuCl_2$ molar ratio. The yield of *p*-sexiphenyl attained a maximum

(1) Paper VII: "Polymerization of Aromatic Nuclei," from the Ph.D. Thesis, 1964, of R. M. Lange, Case Institute of Technology; presented at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) Department of Chemistry Fellow, Case Institute of Technology, 1962–1963.

(3) R. Pummerer and K. Bittner, *Ber.*, **57**, 84 (1924).

(4) (a) R. Pummerer and L. Seligsberger, *ibid.*, **64**, 2477 (1931); (b) R. Kuhn, *Ann.*, **475**, 131 (1929).

(5) NOTE ADDED IN PROOF.—J. A. Cade and A. Pilbean [*J. Chem. Soc.*, 114 (1964)] report a 29% yield (crude) of *p*-sexiphenyl from *p*-terphenyl *via* treatment of 4-bromo-*p*-terphenyl with butyllithium.

(6) T. Nozaki, M. Tamura, Y. Harada, and K. Saito, *Bull. Chem. Soc. Japan*, **33**, 1329 (1960).

(7) W. Kern and O. H. Wirth, *Kunststoffe-Plastics*, **6**, 12 (1958).

(8) M. Busch, W. Weber, *et al.*, *J. prakt. Chem.*, **146**, 1 (1936).

(9) P. Kovacic and C. Wu, *J. Org. Chem.*, **26**, 759 (1961).

(10) P. Kovacic and A. Kyriakis, *J. Am. Chem. Soc.*, **85**, 454 (1963).

(11) P. Kovacic and R. M. Lange, *J. Org. Chem.*, **28**, 968 (1963).

(12) P. Kovacic and F. W. Koch, *ibid.*, **28**, 1864 (1963).

TABLE I

BIPHENYL AND METAL HALIDES[a]

Metal halide	Mole	Temp., °C.	Crude product, g.	Yield, %[b] *p*-Quaterphenyl	Yield, %[b] *p*-Sexiphenyl
$CuCl_2$–$AlCl_3$	0.25:0.25	80–85	17	2	40
$CuCl_2$–$AlCl_3$	0.25:0.5	80 ± 2	21.8	<1	67[c]
$CuCl_2$–$AlCl_3$	0.25:0.25	155–160	30[d]		
$CuCl_2$–$AlCl_3$[e]	0.25:0.25	50 ± 2	11.5	2	22
$CuCl_2$–$AlCl_3$[e]	0.25:0.25	80 ± 2	12	0	22
$CuCl_2$–$AlCl_3$[e]	0.25:0.25	100 ± 2	15	0	7
$CuCl_2$–$AlCl_3$[e,f]	0.125:0.25	80 ± 2	0.4		
$FeCl_3$[e,g]	0.25	80–83	8.5	3	17
$FeCl_3$[e]	0.25	80 ± 2	3.5	0.9	6.7
$FeCl_3$	0.25	80–83	5	1.3	7
$FeCl_3$–$AlCl_3$[e,h]	0.25:0.50	80 ± 2	2.8	1.0	4.1
$FeCl_3$–$AlCl_3$[e,g,h]	0.25:0.50	80 ± 2	7.6	3.6	12
$MoCl_5$	0.25	80–83	9.3	7	5
$MoCl_5$–$AlCl_3$[e,h]	0.25:0.50	80 ± 2	30	7.1	9.8
$CuCl_2$[i]	0.25	80 ± 2	0	0	0
$AlCl_3$[i]	0.25	80 ± 2	0.066[j]	0	0

[a] Biphenyl, 0.5 mole; 0.5 hr. [b] Sublimed material, based on the oxidant. [c] Yield 52% after recrystallization from 1,2,4-trichlorobenzene. [d] Black tar. [e] In *o*-dichlorobenzene (3 moles). [f] Biphenyl, 0.25 mole; CuCl, 0.25 mole. [g] Water, 0.25 mole, as cocatalyst. [h] Time, 2 hr. [i] Time, 1.5 hr. [j] Unidentified (not a *p*-polyphenyl).

(67% good purity, 52% analytically pure) at an $AlCl_3$–$CuCl_2$ ratio of 2:1, and then fell as the ratio decreased. Evidence was obtained from studies on the benzene polymerization[13] that cuprous chloride inhibits reaction, apparently by placing the aluminum chloride catalyst in an inactive complex form, C_6H_6–CuCl–$AlCl_3$.[14] A similar situation prevailed in the case of biphenyl since only a negligible yield of product was obtained when cuprous chloride was added initially in large amount. The hypothesis concerning complex formation was supported by solubility data. Cuprous chloride was essentially insoluble in biphenyl–*o*-dichlorobenzene at 80°. When aluminum chloride was added in the ratio, $AlCl_3$:CuCl = 1, almost all of the solid dissolved indicating the presence of a soluble, ternary complex.

When the temperature was increased from 80 to 155–160°, a black, intractable tar was formed, presumably as a result of polymerization and isomerization under the more drastic conditions. With dichlorobenzene as solvent at 80°, the principal effect was a decrease in the yield of *p*-sexiphenyl. In a further examination of the temperature variable, experiments were carried out at 50, 80, and 100° in the solvent system. The yield was essentially the same at the lower temperatures, but decreased markedly at 100°. At the higher temperature, the product was highly colored and difficult to purify.

Ferric chloride and molybdenum pentachloride also produced nuclear coupling with formation of *p*-sexiphenyl. However, these metal halides generally proved to be less effective than aluminum chloride–cupric chloride. In *o*-dichlorobenzene, addition of water as cocatalyst resulted in a significant increase in the yield of *p*-sexiphenyl from the ferric chloride reaction. Several experiments were performed with aluminum chloride added as the catalyst. Surprisingly, not only was there little change in the yield of desired product, which was difficult to purify, but also the aluminum chloride acted as an inhibitor in the presence of ferric chloride or molybdenum pentachloride. In comparison with the other metal halides, aluminum chloride–cupric chloride gave higher ratios of *p*-sexiphenyl–*p*-quaterphenyl in the product mixture. This may be related to the high strength of aluminum chloride as a Lewis acid. Approximately the same amount of higher molecular weight residue, 15–20% of the crude product, was obtained from the sublimations in all cases.

Gas chromatography of chloroform extracts of the crude reaction products revealed the presence of only unchanged aromatic monomer. It is interesting that nuclear chlorination[15] of biphenyl by the metal halides does not compete effectively with the coupling reaction.

Similarly, reaction variables were investigated in the case of *p*-terphenyl with *o*-dichlorobenzene as solvent (Table II). The results paralleled those observed with biphenyl. In addition, an increase in the ratio of metal halides–*p*-terphenyl acted to enhance the *p*-sexiphenyl yield. At higher temperatures (120°), some isomerization occurred as evidenced by the presence of *m*-terphenyl.

Olah and Meyer, as well as Swisher, investigated the isomerization of terphenyls induced by aluminum chloride at about 140–220°.[16] Each of the isomers yielded an equilibrium mixture consisting of approximately 63% *m*- and 35% *p*-terphenyl.[16a]

Ferric chloride and molybdenum pentachloride were inferior to the combination of aluminum chloride–cupric chloride. In an investigation involving ferric chloride and water cocatalyst, the nature of the solvent appeared to play an important role. With 1,2,4-trichlorobenzene, the yield of *p*-sexiphenyl was substantially lower than with *o*-dichlorobenzene. This result brings to mind the recent work of Choi and Brown[17] concerning solvent effects in gallium bromide catalyzed alkylations.

Attempted copolymerization of biphenyl and *p*-terphenyl, in the presence of ferric chloride, molybdenum pentachloride, or aluminum chloride–cupric chloride with *o*-dichlorobenzene as solvent, yielded

(13) P. Kovacic and J. Oziomek, *J. Org. Chem.*, **29**, 100 (1964).

(14) R. W. Turner and E. L. Amma, *J. Am. Chem. Soc.*, **85**, 4046 (1963).

(15) P. Kovacic and N. O. Brace, *ibid.*, **76**, 5491 (1954); P. Kovacic, C. Wu, and R. W. Stewart, *ibid.*, **82**, 1917 (1960); P. Kovacic and R. M. Lange, unpublished work.

(16) (a) G. A. Olah and M. W. Meyer, *J. Org. Chem.*, **27**, 3682 (1962); (b) R. D. Swisher, U. S. Patent 2,363,209 (1944).

(17) S. U. Choi and H. C. Brown, *J. Am. Chem. Soc.*, **85**, 2596 (1963).

TABLE II

p-TERPHENYL AND METAL HALIDES[a]

Metal halide	Mole	Temp., °C	Time, hr.	Crude product, g.	*p*-Sexiphenyl yield, %[b]
$CuCl_2$–$AlCl_3$	0.125:0.125	80 ± 2	0.5	6.4	19
$CuCl_2$–$AlCl_3$	0.125:0.25	80 ± 2	0.5	12.1	34
$CuCl_2$–$AlCl_3$	0.25:0.25	80 ± 2	0.5	22.2	30
$CuCl_2$–$AlCl_3$	0.50:0.25	80 ± 2	0.5	31.6	22
$CuCl_2$–$AlCl_3$	0.25:0.25	80 ± 2	1.5	26.1	35
$CuCl_2$–$AlCl_3$	0.25:0.25	120 ± 2	0.5	10.8	6
$MoCl_5$	0.25	80 ± 2	2	20.8	16
$MoCl_5$[c]	0.2	215 ± 7	0.5	21.6	13
$FeCl_3$[d]	0.125	80 ± 2	2	6.7	17
$FeCl_3$[d,e]	0.125	80 ± 2	4	3.8	9
$CuCl_2$	0.25	80 ± 2	1.5	0	0
$AlCl_3$	0.25	80 ± 2	1.5	0.7[f]	0.6

[a] *p*-Terphenyl, 0.25 mole; *o*-dichlorobenzene, 3 moles. [b] Sublimed material, based on the oxidant. [c] No solvent. [d] Water, 0.125 mole, as cocatalyst. [e] In 1,2,4-trichlorobenzene (3 moles). [f] M.p. (crude) 450–455°; infrared spectrum identical with that of *p*-sexiphenyl.

TABLE III

BIPHENYL–*p*-TERPHENYL WITH METAL HALIDES[a]

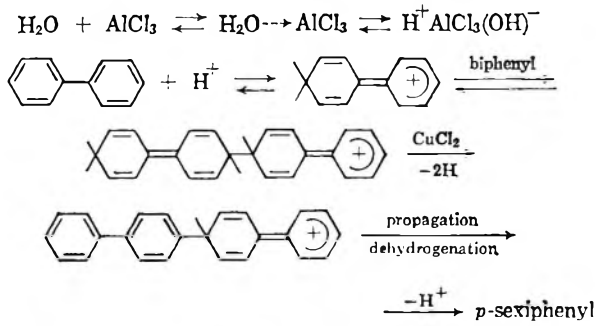
Metal halide	Mole	Time, hr.	Crude product, g.	Yield, %[b] *p*-Quarterphenyl	*p*-Quinquephenyl	*p*-Sexiphenyl
$CuCl_2$–$AlCl_3$	0.125:0.125	0.5	8.2	3	0	20
$FeCl_3$[c]	0.125	2	4.2	<1	<1	12
$MoCl_5$	0.125	2	3.4	<1	0	4

[a] Biphenyl, 0.125 mole; *p*-terphenyl, 0.125 mole; *o*-dichlorobenzene, 3 moles; 80 ± 2°. [b] Sublimed material, based on the oxidant. [c] Water, 0.125 mole, as cocatalyst.

predominantly *p*-sexiphenyl with only trace amounts of *p*-quaterphenyl and *p*-quinquephenyl (Table III).

Studies were made of the reaction rates for the aromatic monomers, benzene, biphenyl, and *p*-terphenyl, in the system, aluminum chloride–cupric chloride–*o*-dichlorobenzene. The reactions were followed by titration of the evolved hydrogen chloride, and the relative rates obtained by comparison of the rate curves for the first 3 min. of reaction. In all cases, linearity pertained in this region. At 80° the relative rates were found to be for benzene, 1.00; biphenyl, 0.83; and *p*-terphenyl, 0.57. Interestingly, at 40° the observed relative rates were, for benzene, 1.00; and biphenyl, 5.22.

Comparison of the present results with the polymerization of benzene to *p*-polyphenyl[10–12] reveals interesting similarities and differences. We propose that the reaction proceeds by an oxidative cationic mechanism similar to that advanced for the benzene polymerization.



Aluminum chloride is designated the catalyst and cupric chloride the oxidant. In control experiments, no reaction occurred with either biphenyl or *p*-terphenyl when the aluminum chloride was omitted. In the absence of cupric chloride, biphenyl–aluminum chloride gave a negligible amount of unidentified solid, and, with *p*-terphenyl, less than 1% of *p*-sexiphenyl was formed.

In previous related investigations,[18] it was found that biphenyl, when heated with aluminum chloride, yielded benzene, *p*-terphenyl, *p*-quaterphenyl, toluene, methylcyclopentane, cyclohexane, and resins. On treatment with aluminum chloride at elevated temperatures and for prolonged periods,[19] benzene was converted to biphenyl, phenylcyclohexane, phenylmethylcyclopentane, diphenylcyclohexane, and uncharacterized polymers. Apparently, in the absence of an added oxidant, the intermediates may undergo disproportionation and rearrangement under the proper conditions.

Ferric chloride[12] and molybdenum pentachloride[11] can presumably function in a dual capacity, both as catalyst and oxidant. Since the data for aluminum chloride–cupric chloride indicate the importance of a high catalyst–oxidant ratio, the generally inferior results with ferric chloride and molybdenum pentachloride might be attributed, in part, to destruction of the catalyst by reduction.

The data from the biphenyl reaction, in addition to earlier studies[20] involving benzene polymerization, suggest the operation of a cocatalytic effect with ferric chloride. Compounds of the Brønsted acid type, *e.g.*, water, functioned as cocatalysts. In the case of aluminum chloride and molybdenum pentachloride, the reasoning is by analogy to the benzene–ferric chloride reaction and the cationic polymerization of olefins.[21]

(18) C. Friedel and J. M. Crafts, *Compt. rend.*, **100**, 692 (1885); Yu. K. Yur'ev and R. Ya. Levina, *Sci. Rep. Moscow State Univ.*, **3**, 203 (1934); *Chem. Abstr.*, **30**, 8191 (1936); K. Shishido and I. Irie, *J. Soc. Chem. Ind. Japan*, **48**, 10 (1945); *Chem. Abstr.*, **42**, 6343 (1918).

(19) C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1941, p. 716; M. G. Gonikberg and A. E. Gavrilova, *J. Gen. Chem. USSR*, **22**, 1429 (1952).

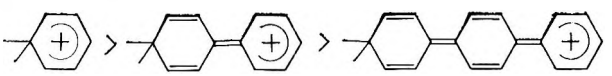
(20) P. Kovacic and C. Wu, *J. Polymer Sci.*, **47**, 45 (1960); P. Kovacic, F. W. Koch, and C. E. Stephan, *ibid.*, **2A**, 1193 (1964).

(21) D. C. Pepper, *Quart. Rev.* (London), **8**, 88 (1954); "Cationic Polymerization and Related Complexes," P. H. Plesch, Ed., Heffer, Cambridge, England, 1953.

There is evidence to support existence of the complexes, H_2O–$AlCl_3$[22] and H_2O–$AlBr_3$,[23] as well as the interaction of σ-complexes, $(ArH_2)^+(Al_2X_7)^-$, with additional molecules of aromatic substrate.[24] Proton-initiated intramolecular coupling of aromatic nuclei is apparently involved in the conversion of β,β-di(1-naphthyl)ethylene to 9-methyl-1,2,7,8-dibenzfluorene by treatment with stannic chloride.[25]

The hypothesis concerning the dehydrogenation of cyclohexadiene units to aromatic structures is supported by the facile transformation of 1,4-cyclohexadiene to benzene on treatment with ferric chloride[12] or molybdenum pentachloride.[11] Furthermore, Nonhebel[26] found that 9,10-dihydroanthracene is smoothly dehydrogenated by cupric halides under mild conditions. Admittedly, the exact stage at which dehydrogenation occurs during nuclear coupling, as well as the mechanism, is unknown.

It is significant that benzene yields *p*-polyphenyl, whereas, under similar conditions, biphenyl produces mainly a trimer-type product, and *p*-terphenyl affords a dimer-type. In searching for a rationalization, one must realize that the situation is quite complicated. Various factors should be considered, *e.g.*, the relative susceptibility of the aromatic monomers to attack, and possible catalysis or inhibition by the reduced metal halide. Furthermore, one cannot afford to overlook the possible influence of the solvent or excess aromatic monomer. Ease of termination would be enhanced by coordination of the growing carbonium ion with an aromatic molecule. This interpretation has been used previously to explain the effect of aromatic additives on molecular weight in the cationic polymerization of styrene.[27] In addition, the increasing ease of termination in the order, *p*-terphenyl > biphenyl >> benzene, suggests that the relative stabilities of the postulated σ-complex intermediates may be an important factor. Based on the degree of resonance stabilization, the order of reactivity would be



It is reasonable to correlate the increasing ease of termination with increasing degree of delocalization.

These transformations of biphenyl and *p*-terphenyl can be classified as an extension of the Scholl reaction. Our mechanistic interpretation is analogous to that proposed for the Scholl reaction by Nenitzescu and Balaban.[28]

Experimental[29]

Materials.—Anhydrous cupric chloride was dried at 130°; anhydrous molybdenum pentachloride was weighed under dry nitrogen; *o*-dichlorobenzene and 1,2,4-trichlorobenzene were distilled from calcium hydride.

Instrumental Procedure.—Ultraviolet spectra were taken in chloroform solution and infrared spectra in potassium bromide pellets; gas chromatography was done using a 9-ft. column, 20% silicone rubber on Chromosorb P, 100–350° at 11°/min., helium at 50 ml./min.

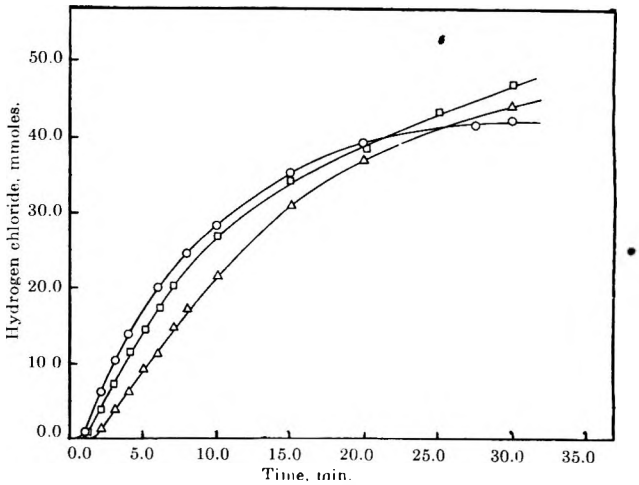


Fig. 1.—Rates of hydrogen chloride evolution in the reaction of (O) benzene, (□) biphenyl, and (△) *p*-terphenyl with cupric chloride–aluminum chloride in *o*-dichlorobenzene at 80–81°.

Biphenyl–Aluminum Chloride–Cupric Chloride. General Procedure.—Anhydrous aluminum chloride (66.6 g., 0.5 mole) was added to biphenyl (77 g., 0.5 mole) with stirring under dry nitrogen at 75°. After anhydrous cupric chloride (33.6 g., 0.25 mole) was introduced in the closed system by a suitable addition device, the reaction mixture was stirred efficiently under nitrogen at 80 ± 2° for 30 min. The evolved acid gas was titrated with standard base. Then, the molten mixture was quickly poured into 500 ml. of 18°, hydrochloric acid and steam distilled. After the residue was pulverized with water in a blender, it was treated with hydrochloric acid, triturated repeatedly with ethanol, and sucked dry. Trituration with concentrated hydrochloric acid was continued until the filtrate became colorless, followed by washing with boiling water until a negative test (silver nitrate) for chloride ion was obtained. The crude product, a light brown powder, was dried at 130°; yield 21.8 g.

A portion (0.58 g.) on fractional sublimation at 290–310° (0.015 mm.) gave *p*-quaterphenyl, 3 mg., m.p. 308–310°, lit.[30] m.p. 310°; authentic material, m.p. 306–308°, m.m.p. 306–308°. The infrared and ultraviolet spectra were identical with those of the authentic material.

Continued sublimation at 400–440° (0.015 mm.) yielded *p*-sexiphenyl, 0.506 g., m.p. 452–456°. Recrystallization from 1,2,4-trichlorobenzene produced pure product, 0.387 g., m.p. 465–467°, mixture melting point with authentic material was not depressed; ultraviolet spectrum λ_{max} 316 mμ, lit.[30] λ_{max} 317 mμ; infrared spectrum, absorption maximum, 811 cm.$^{-1}$.

Anal. Calcd. for $C_{36}H_{26}$: C, 94.28; H, 5.72. Found: C, 94.14; H, 5.70.

The infrared spectrum of the sublimation residue exhibited a major band at 807 cm.$^{-1}$.

***p*-Terphenyl–Aluminum Chloride–Cupric Chloride.**—The general procedure was followed for the most part with *o*-dichlorobenzene as solvent. In the work-up procedure, steam distillation was omitted and the residue, after ethanol treatment, was triturated repeatedly with chloroform. The dry solid was then triturated with concentrated hydrochloric acid.

Sublimation yielded *p*-sexiphenyl and residual material (infrared absorption maximum, 807 cm.$^{-1}$).

Solubility of Metal Halides in Biphenyl–*o*-Dichlorobenzene.—A mixture of cupric chloride (8.4 g., 0.063 mole), biphenyl (19.2 g., 0.125 mole), and *o*-dichlorobenzene (100 g.) was stirred for 30 min. at 80°. After filtration of the hot mixture, the residue was washed with ligroin (25 ml., b.p. 30–60°) and sucked dry for several minutes; weight of cupric chloride residue, 8.25 g. The solubility of other metal halides was determined in a

(22) C. D. Nenitzescu, M. Avram, and E. Sliam, *Bull. soc. chim. France*, 1266 (1955).
(23) F. Fairbrother and W. C. Frith, *J. Chem. Soc.*, 2975 (1953).
(24) H. C. Brown and W. J. Wallace, *J. Am. Chem. Soc.*, **75**, 6268 (1953).
(25) G. Wolf, *ibid.*, **75**, 2673 (1953).
(26) D. C. Nonhebel, *J. Chem. Soc.*, 1216 (1963).
(27) N. Tokura, M. Matsuda, and Y. Watanabe, *J. Polymer Sci.*, **62**, 135 (1962).
(28) C. D. Nenitzescu and A. Balaban, *Ber.*, **91**, 2109 (1958).
(29) Melting points (block) are uncorrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.
(30) E. H. Smith, "Polyphenyls," Literature Search, U. S. Atomic Energy Commission, ER-8098, 1956.

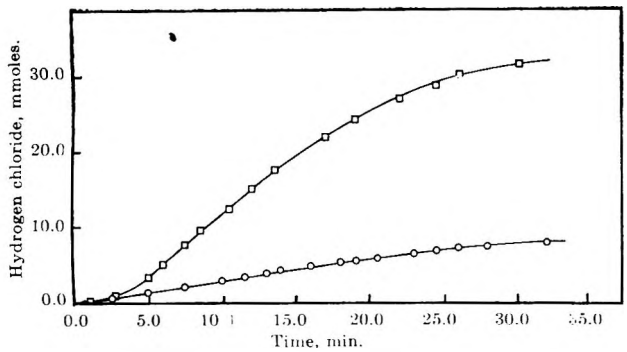


Fig. 2.—Rates of hydrogen chloride evolution in the reaction of (O) benzene and (□) biphenyl with aluminum chloride–cupric chloride in *o*-dichlorobenzene at 40°.

similar manner [metal halide, g. (mole), undissolved halide, g.]: cuprous chloride, 6.24 (0.063), 6.23; aluminum chloride, 8.40 (0.063), 0.92; aluminum chloride–cuprous chloride, 8.30:6.24 (0.063:0.063), 1.0.

Relative Rates. A. Benzene, Biphenyl, and *p*-Terphenyl at 80°.—The reactions were carried out according to the general procedure with the aromatic reactant (0.125 mole) in *o*-dichlorobenzene (1.5 moles). After the introduction of anhydrous aluminum chloride (0.063 mole), the mixture was heated to 79° with vigorous stirring under dry nitrogen (flow rate, 140 ml./min.). Anhydrous cupric chloride (0.063 mole) was added in a single portion and the reaction was followed at 80–81° by titration of the evolved acid gas with standard base. The rate data (average of two runs; deviation, ±7%) are summarized in Fig. 1.

B. Benzene and Biphenyl at 40°.—Rate data (average of two runs; deviation, ±2%) obtained at 40–41° in a similar manner are plotted in Fig. 2.

Authentic *p*-Sexiphenyl.—Synthesis of this compound was accomplished according to the procedure of Nozaki and coworkers,[6] m.p. 460–462° (sublimation and crystallization from 1,2,4-trichlorobenzene), lit.[30] m.p. 465°; infrared spectrum, absorption maximum, 811 cm.$^{-1}$; ultraviolet spectrum, λ_{max} 317 mμ.

Acknowledgment—The authors wish to express their thanks to the National Science Foundation for partial support of this work.

Silicic Acid Chromatographic Study of the Catalytic Hydrogenation Products of 9,10-Epoxystearates[1]

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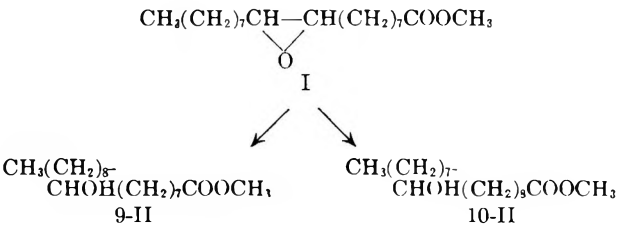
Hydrogenation of methyl *cis*-9,10-epoxystearate over palladium on charcoal in glacial acetic acid yields a mixture shown by silicic acid column chromatography to consist mainly of hydroxystearates, together with smaller amounts of stearate and ketostearates. Contrary to conclusions reached in earlier studies, degradation of the principal product (purification of the intermediate ketostearates, oximinostearates, and Beckmann-rearranged isomeric amido esters solely by adsorption chromatography assuring no discrimination between positional isomers) demonstrates that the 9- and 10-hydroxystearates are in fact formed in equal amounts.

Catalytic hydrogenolytic opening of the oxide ring of methyl 9,10-epoxystearates (I), (or of the free acids, readily obtained[2] by action of peracids on oleic and elaidic acids, would be expected *a priori* to yield equal amounts of DL-9- and -10-hydroxystearates (II), since the methyl and carboxyl termini of the oxide ring substituents are far too remote to impress any appreciable asymmetric reactivity on the site of reaction by inductive effects conducted along the long intervening polymethylene chains. Zook and Knight,[3] for example, have shown that a carboxyl group only two methylene groups away has very little influence on the randomness with which HBr adds to an olefinic center. Even more directly pertinent is the recent report[4] that catalytic hydrogenation of *cis*-6,7-epoxystearic acid yields equal amounts of DL-6- and -7-hydroxystearic acids.



It is therefore difficult to rationalize the claims of a number of investigators[5-8] who have, without exception, indicated the predominant formation of 10-II[9] by hydrogenation of I. The patent improbability of such conclusions recommends careful examination of the evidence upon which they were based. In every case, samples of the product of interest were isolated by crystallization and identified solely (with a single exception[6]) on the basis of the melting behavior of the hydroxy acids, of the keto acids obtained from them by chromic acid oxidation, or of the corresponding semicarbazones. Following careful study of the phase properties of the 9- and 10-keto- and -DL-hydroxystearic acids, Cochrane and Harwood[10] have recently called attention to the strong possibility that these findings (together with a number of others bearing on the course of related reactions) were misinterpreted.

(1) This paper is based on work performed under Contract AT(04-1)-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles.

(2) T. W. Findley, D. Swern, and J. T. Scanlan, *J. Am. Chem. Soc.*, **67**, 412 (1945).

(3) H. D. Zook and J. A. Knight, *ibid.*, **76**, 2302 (1954).

(4) S. P. Fore and W. G. Bickford, *J. Org. Chem.*, **26**, 2104 (1961).

(5) I. G. V. Pigulevskii and Z. Y. Rubashko, *J. Gen. Chem. USSR*, **9**, 829 (1939); *Chem. Abstr.*, **34**, 3782 (1940).

(6) J. Ross, A. I. Gebhart, and J. F. Gerecht, *J. Am. Chem. Soc.*, **71**, 284 (1949).

(7) C. H. Mack and W. G. Bickford, *J. Org. Chem.*, **18**, 686 (1953).

(8) F. J. Julietti, J. F. McGhie, B. L. Rao, W. A. Ross, and W. A. Cramp, *J. Chem. Soc.*, 4517 (1960).

(9) Even, in one case,[7] to the exclusion of 9-II; cursory perusal of the literature has revealed occurrence of at least two instances in which this claim has led to preparation of "authentic" samples of 10-hydroxystearic acid by this procedure.

(10) C. C. Cochrane and H. J. Harwood, *J. Org. Chem.*, **26**, 1278 (1961).

It seems important to point out that in none of these studies of the course of hydrogenation of I (or of the corresponding free acids) was it established that isolation by crystallization is indiscriminate with respect to the isomers of II or of its derivatives. Moreover, in none were the structures of the products confirmed by unequivocal degradation techniques.

Interest in the 9- and 10-hydroxystearic acids in connection with other studies[11] thus led to the present reexamination of the catalytic hydrogenation products of the 9,10-epoxystearates, using silicic acid column adsorption chromatography (instead of crystallization or recrystallization) to isolate truly representative samples of the desired product and to purify intermediates in its systematic degradation to substances, the structure and relative yields of which would establish its composition conclusively.

Hydrogenation of chromatographically purified methyl *cis*-9,10-epoxystearate (*cis*-I, see Fig. 1a) under conditions essentially identical with those employed by Mack and Bickford[7] and chromatography of the total reaction product on a column of activated silicic acid disclosed (see Fig. 1b) that, in addition to the major product (hydroxystearate, peak C), two others (peaks A and B) of lower adsorption affinity are produced.

Substance A was identified by chromatographic behavior, melting point, and mixture melting point as methyl stearate. Although elimination of epoxide oxygen from certain specially substituted ethylene oxides by catalytic hydrogenation has been reported,[12] such an eventuality does not appear to have been recognized previously in the case of simpler epoxides.[13] Since the hydroxy esters are clearly not intermediates in the formation of stearate, it might be imagined that the deoxygenation involves essentially simultaneous addition of four hydrogen atoms to one side of the oxide ring, in which case the reaction would be expected, for steric reasons, to proceed more readily with the *cis* than with the *trans* epoxide. The latter (*trans*-I) was indeed found to give a smaller yield of stearate under the same conditions.[16]

On the basis of its chromatographic behavior alone, product B (Fig. 1b) might have been thought to be residual unchanged epoxy ester. It is considerably higher melting (42°) than the starting material (m.p. 17°), however, and was shown by infrared spectrophotometry to be methyl ketostearate (presumably an equimolar mixture of the 9- and 10-isomers; the mixture of ketostearates obtained by chromic acid oxidation of the major hydrogenation product C melts at 41°).

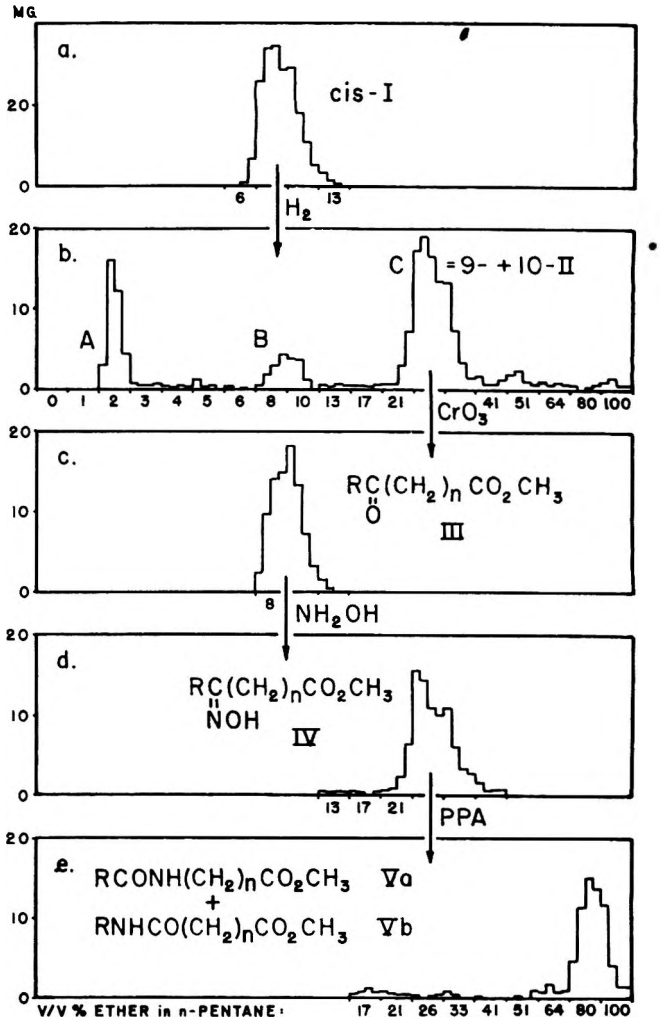


Fig. 1.—Silicic acid column chromatograms of *cis*-I, of its hydrogenation products, and of intermediates in the degradation of the major product. Weights of material eluted by half column-volumes of solvent are plotted against the compositions of the *n*-pentane–diethyl ether solvent mixtures employed in developing the chromatogram. The limited solubility of V in less polar solvent mixtures necessitated use in its chromatography (Fig. 1c) of six column-volumes of 13% ether in pentane in place of the usual (and essentially equivalent in elution efficacy) two volumes each of the 0–10% mixtures before continuing the development with the standard series, which is indicated in full on the Fig. 1b abscissa; PPA = polyphosphoric acid; R = C_8H_{17} or C_9H_{19}; n = 8 or 7, respectively.

Coleman and Swern[17] have also identified ketostearic acids among products of hydrogenation of the free acid corresponding to I under the conditions employed here. Although the mechanism of this isomerization has not been established, its occurrence suggests that to some extent the epoxide group, following attachment of the first ring-opening hydrogen atom, may, instead of adding a second to give the major product (hydroxystearate), return another to the catalyst, yielding a keto (or the tautomeric enol) group which is inert toward hydrogenation over palladium. It was established that the keto esters are neither present in the starting material nor produced by action of glacial acetic acid (solvent used during hydrogenation) on the epoxy esters.

That the major product (peak C, Fig. 1b) of the hydrogenation of *cis*-I is indeed a mixture is immediately ap-

(11) D. R. Howton, *Radiation Res.*, **20**, 161 (1963).

(12) R. E. Lutz and J. L. Wood, *J. Am. Chem. Soc.*, **60**, 224 (1938); O. Gawron, T. P. Fondy, and D. J. Parker, *J. Org. Chem.*, **28**, 700 (1963).

(13) While the present work was in progress, Fore and Bickford[4] reported that catalytic hydrogenation of *cis*-6,7-epoxystearic acid also yielded some stearic acid. That such oxides may react in this way is of considerable interest in connection with the polemic of Walsh[14] and Robinson[15] over the former's "π-complex" depiction of the ethylene oxide group. One argument cited against the concept was that "... ethylene oxide is not reduced to ethylene ..." It seems reasonable to suggest involvement of an olefinic intermediate (which may, of course, never escape the catalyst surface) in the reductions at hand.

(14) A. D. Walsh, *Nature*, **159**, 165 712 (1947).

(15) R. Robinson, *ibid.*, **159**, 400 (1947); **160**, 162 (1948).

(16) The over-all rate of hydrogenation of the *trans* isomer is one-tenth that of the *cis*. In terms of the influence of the different configurations of these substances on their adsorption properties, this observation parallels that of the appreciably lower adsorption affinity of the *trans* ester for silicic acid (see Experimental).

(17) J. E. Coleman and D. Swern, *J. Am. Oil Chemists' Soc.*, **32**, 221 (1955).

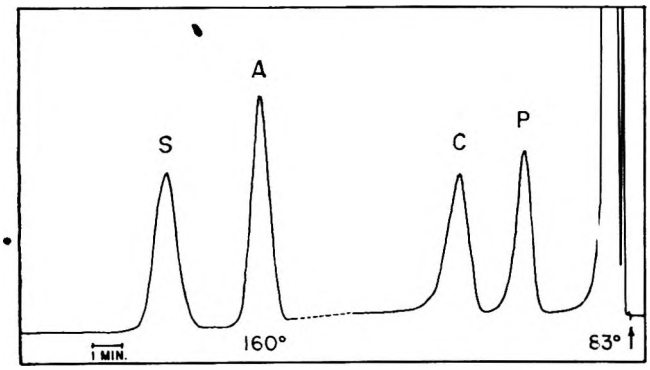


Fig. 2.—Gas chromatogram of neutral methyl esters obtained by methanolysis of amido esters (V). Reading from the right, the first peak following injection (arrow) is solvent (toluene), followed by pelargonate (P), and caprate (C). A portion of the graph (see dotted section) has been deleted, where the column temperature was increased rapidly (at 30°/min.) and the base line readjusted manually. The peaks of azelate (A) and sebacate (S) then follow.

parent from its melting point (44–45°; 9- and 10-II melt[10] at 50–51.5° and 54–55°, respectively). Its composition was established by application of the conventional degradation procedure outlined in Fig. 1 and by gas chromatographic determination of the relative amounts of both mono- and dicarboxylic esters obtained by action of boron trifluoride–methanol on the amido esters (V).

Each intermediate in the degradation was purified solely by chromatography on silicic acid, advantage being taken of the fact that differences in the adsorption affinities of close positional isomers are small, while those between the successive types of substances involved in the degradation sequence are large (Fig. 1).[18]

Oxidation of the hydroxy esters (II) by means of the chromic acid–pyridine reagent of Sarett[19] gave the keto esters (III), m.p. 41°, which were converted in the usual way to the oily oximino esters (IV). Beckmann rearrangement of the esters IV, induced by action of polyphosphoric acid,[20] gave a mixture of amido esters (V), m.p. 43–44°. In order to minimize differential loss of the relatively volatile monocarboxylic esters, a technique by which V could be methanolyzed in a sealed tube was devised, using N-*n*-heptylcaprylamide (derived from di-*n*-heptyl ketone by the same series of reactions used in converting III to V) as a model substance. As indicated in Diagram I below, methanolysis of the amido esters derived from 9-hydroxystearate yields methyl caprate (C) and dimethyl azelate (A), while those from 10-hydroxystearate give methyl pelargonate (P) and dimethyl sebacate (S).

After heating a sample of the mixed amido esters (V) with boron trifluoride–methanol in a sealed tube at 100° for 52 hr. (conditions calculated to result in 94% methanolysis), the reaction mixture was partitioned between water and toluene and samples of the dried toluene phase were analyzed by gas chromatography on a polyester column; a typical chromatogram is shown in Fig. 2.

DIAGRAM I

$$CH_3(CH_2)_8CHOH(CH_2)_7COOCH_3 \quad 9\text{-II}$$

$$\downarrow$$

$$CH_3(CH_2)_8NHCO(CH_2)_7COOCH_3 \longrightarrow CH_3(CH_2)_8NH_2 + (CH_2)_7(COOCH_3)_2$$

A

$$+$$

$$CH_3(CH_2)_8CONH(CH_2)_7COOCH_3 \longrightarrow NH_2(CH_2)_7COOCH_3 + CH_3(CH_2)_8COOCH_3$$

C

$$CH_3(CH_2)_7CHOH(CH_2)_8COOCH_3 \quad 10\text{-II}$$

$$\downarrow$$

$$CH_3(CH_2)_7NHCO(CH_2)_8COOCH_3 \longrightarrow CH_3(CH_2)_7NH_2 + (CH_2)_8(COOCH_3)_2$$

S

$$+$$

$$CH_3(CH_2)_7CONH(CH_2)_8COOCH_3 \longrightarrow NH_2(CH_2)_8COOCH_3 + CH_3(CH_2)_7COOCH_3$$

P

Data obtained from this and other chromatograms, including those given by known-composition mixtures of authentic esters, permitted evaluation of mole ratios P–C = 0.95 and S–A = 1.01, which represent the ratio of 10- to 9-hydroxystearate in the products of 9,10-epoxystearate hydrogenation and lead to the conclusion that opening of the epoxide ring in either of the two possible directions is essentially indiscriminate.[21]

Experimental

Melting points were obtained using open capillary tubes heated at 1°/min. (at the melting point) in a silicone oil bath or, for material melting below room temperature (only the temperature of disappearance of the solidus is reported for such samples), in water or acetone baths contained in an unsilvered cylindrical Dewar flask. All melting points are corrected.

Analyses were performed by the Elek Micro Analytical Laboratories, Los Angeles, Calif.

Adsorption chromatography was carried out as described in some detail elsewhere,[11] using 3.2 × 10 cm. columns of J. T. Baker Chemical Co. silicic acid powder, untreated except for activation *in situ* by prewashing with acetone, ether, and *n*-pentane (Phillips Petroleum Co. "Pure Grade"). With certain lots of this adsorbent, cutting with 5% (by weight) of Celite 545 was necessary to obtain satisfactory flow rates. Chromatograms were developed with *n*-pentane mixed with regularly increased amounts of ether, using two column-volumes of each of a standard series of mixtures (see abscissas of Fig. 1) unless otherwise indicated, and collecting one-half column-volume eluate fractions.

Oleic acid was obtained[22] from olive oil by saponification and removal of saturated fatty acids from the resulting mixture by low temperature crystallization from acetone.

Elaidic acid was prepared by selenium-catalyzed isomerization of oleic acid[23] followed by purification by repeated crystallization from acetone at −20° until the product was gas chromatographically pure. A sample of methyl elaidate obtained in the course of chromatographically purifying incompletely epoxidized elaidic acid (see below) melted at 10.2°, in agreement with an earlier report.[24]

(18) Inasmuch as the yields in none of the four degradation steps is quantitative, it has been assumed that no appreciable discrimination between positional isomers occurs during the reactions involved; the final result supports the validity of this assumption.

(19) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 427 (1953).

(20) E. C. Horning and V. L. Stromberg, *ibid.*, **74**, 2680 (1952).

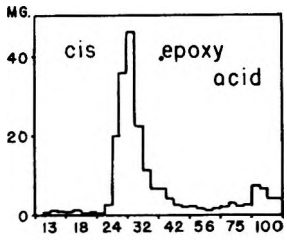
(21) Although some additional uncertainty is involved in quantitative comparison of gas chromatographic analysis of different types of substances (*e.g.*, mono- and dicarboxylic esters), the ratios S–P = 0.92 and A–C = 0.87 appear to suggest that the type Va amido ester may be formed in somewhat greater amount than type Vb; see Fig. 1e and Experimental.

(22) H. B. Knight, E. F. Jordon, Jr., E. T. Roe, and D. Swern, "Biochemical Preparations," Vol. 2, E. G. Ball, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 100.

(23) D. Swern, H. B. Knight, O. D. Shreve, and M. R. Heether, *J. Am. Oil Chemists' Soc.*, **27**, 17 (1950).

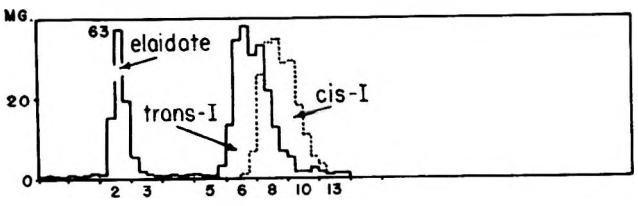
(24) H. Appel, H. Böhm, W. Keil, and G. Schiller, *Z. physiol. Chem.*, **282**, 225 (1947).

cis- and *trans*-9,10-epoxystearic acids were prepared[2] from oleic and elaidic acids, respectively, by action of peracetic acid. Repeated recrystallization of the *cis* isomer from petroleum ether (60–70°), methanol, and acetone gave material melting as high as 57.0–58.4°, lit.[25] m.p. 58.1–58.7°, but chromatography of the corresponding methyl ester (*cis*-I, see below) disclosed the presence of about 20% of more strongly adsorbed substances. Chromatography of the free acid gave similar results, the purified material (81% recovery) showing m.p. 56.8°. (Note that development of this chromatogram was initiated with 13% ether in pentane and that a series of mixtures somewhat different from that ordinarily used was employed thereafter.)

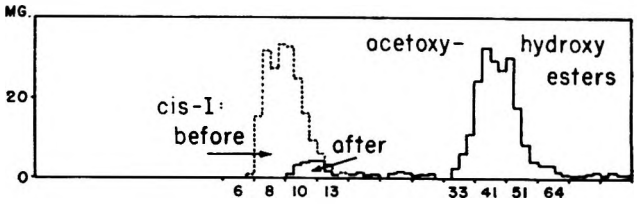


Methyl *cis*-9,10-epoxystearate (*cis*-I) was obtained by action of diazomethane (from N-nitroso-N-methylurea or from "Diazald," Aldrich Chemical Co., the corresponding *p*-toluenesulfonamide derivative) on solutions of the crude free acid in ether containing 10 vol. % methanol.[26] Chromatography gave a 75% yield of the pure ester, m.p. 17.3° (lit.[27] m.p. 18°, lit.[2] m.p. 15–16.5°), the major contaminating material being more strongly adsorbed on silicic acid. (The silicic acid adsorption chromatogram of *cis*-I is shown in Fig. 1a and, in comparison with the *trans* isomer, below.) Rechromatography results in an essentially quantitative recovery of the epoxy ester, accompanied by no additional appreciable quantity of material having altered chromatographic characteristics. Infrared examination of material from the leading edge of the epoxy ester peak (the isomeric keto esters III are slightly less strongly adsorbed than *cis*-I) showed no ketone carbonyl absorption. Chromatographic analysis of commercial "epoxy methyl stearate" (Metro Industries) revealed 33% of material, m.p. about 10°, showing chromatographic behavior of *cis*-I, 15% of less strongly adsorbed material (78.7% methyl palmitate, 15.6% stearate, 3.3% oleate by gas chromatography), and 47% of more strongly adsorbed material exhibiting strong OH absorption in the infrared.

Methyl *trans*-9,10-Epoxystearate (*trans*-I).—Treatment of a sample of the crude *trans* acid with diazomethane, followed by chromatography of the product, revealed presence of considerable residual unchanged elaidic acid, from which, however, the desired epoxy ester was readily separated; 302 mg. of acid yielded 104 mg. of methyl elaidate, m.p. 10.2°, having, as expected, essentially the same chromatographic behavior as methyl stearate (see peak A, Fig. 1b), and 187 mg. of the desired *trans*-I, m.p. 26.7° (in good agreement with the 25° figure given by Nicolet and Poulter,[27] but considerably below the 32–33.5° melting point cited by Bauer and Bähr.[28] This substance is appreciably less strongly adsorbed by silicic acid than the *cis* isomer.



Reaction of *cis*-I with acetic acid is of interest because of the possible importance of competitive opening of the oxide ring (giving stable acetoxyhydroxystearates) during hydrogenation, and in evaluation of acetic acid-induced isomerization[29] as a possible mode of formation of keto esters found in the hydrogenation mixture. A 192-mg. sample of chromatographed *cis*-I was dissolved in 4.8 ml. of glacial acetic acid and allowed to stand at room temperature (25 ± 1°) for exactly 1 week, the resulting solution was freed of solvent by lyophilization, the residual solid was treated with diazomethane in the usual way (there was no overt evidence of presence of free carboxylic acids), and the product was chromatographed on silicic acid. Unchanged starting material (8%, free of keto group absorption in the infrared) and 197 mg. of methyl 9(10)-acetoxy-10(9)-hydroxystearates, m.p. 41–42°, were obtained.



Recrystallization of the acetoxyhydroxy esters from *n*-pentane gave colorless needles, m.p. 40.7–41.0°.

Anal. Calcd. for $C_{21}H_{40}O_5$: C, 67.7; H, 10.8. Found: C, 67.5; H, 10.5.

Quantitative results of the chromatographic analysis permit evaluation of a rate constant, 8.6×10^{-4} l./mole hr., for the solvolysis of *cis*-I by acetic acid at 25°, in substantial agreement with approximate data reported by Findley, *et al.*,[2] and by King[30] with reference to reactivity of the corresponding free acid; the *trans* acid is reported[30] to be considerably less reactive. It is thus clear that little ring opening by solvent should occur in the short periods of time required to carry out these hydrogenations; this conclusion is borne out by the absence of more than traces of material more strongly adsorbed than II among the hydrogenation products obtained from either isomer of I (see Fig. 1b).

Hydrogenation of Epoxides.—Of the numerous hydrogenations of both isomers of I and of the *cis* free acid which were carried out, those described in detail here were representative with respect to results and serve best for direct comparison of behavior of the *cis* and *trans* epoxides. (The esters are preferred starting materials because they are more easily purified and yield a product mixture which may be chromatographed without further treatment; they are, however, disadvantageous from the standpoint that a fraction of the product is very strongly bound to the charcoal on which the catalyst is supported. The free-acid forms of the reduction products are more easily extracted from charcoal but are much less soluble in acetic acid and, although tending to supersaturate, occasionally crystallize from the hydrogenation mixture.)

In a quantitative hydrogenation apparatus employing mercury in the gas buret and operated at room temperature and atmospheric pressure, 400 mg. of 5% palladium on charcoal (Matheson Coleman and Bell) in 2.0 ml. of glacial acetic acid was saturated with hydrogen, and 180 mg. (0.517 mmole) of *cis*-I in 2.0 ml. of the same solvent was injected by hypodermic syringe into the vessel of the apparatus (a 15-ml. graduated centrifuge tube topped by a standard-taper joint). Hydrogen uptake was rapid and complete in about 10 min. The catalyst was centrifuged from the mixture and washed with four 1-ml. portions of acetic acid and the solvent was lyophilized from the combined supernates, leaving 132.2 mg. of solid residue; extraction of the catalyst with successive 5-ml. quantities of ether gave 15.0, 10.9, and 5.5 mg. of additional material, leaving about 17 mg. unrecovered. Chromatography (see Fig. 1b) of the product gave (in order of elution or increasing polarity) 34.6 mg. (20.1% based on starting material) of methyl stearate, m.p. 39.3–40.0°, 38.7–39.8° after mixing with the authentic substance, m.p. 38.6–39.3°; 14.7 mg. (8.1%) of III, m.p. 40.6–42.0°, identified additionally by infrared absorption and chromatographic behavior; 104.3 mg. (57.5%) of II, m.p. (of major fraction from center of peak) 43.2–43.8° (identified by degradation, see below); and 4.7 mg. (2.3%) of material tentatively identified by its chromatographic behavior as acetoxyhydroxystearate. In further confirmation of the identification of the products, the amount of hydrogen required to produce them is calculated to be 0.642 mmole (observed, 0.653).

Hydrogenation of 160 mg. (0.512 mmole) of *trans*-I under the same conditions resulted in uptake of 0.510 mmole of hydrogen, requiring about 131 min. Comparison of initial slopes of plots

(25) L. P. Witnauer and D. Swern, *J. Am. Chem. Soc.*, **72**, 3364 (1950).
(26) H. Schlenk and J. L. Gellerman, *Anal. Chem.*, **32**, 1412 (1960).
(27) B. H. Nicolet and T. C. Poulter, *J. Am. Chem. Soc.*, **52**, 1186 (1930).
(28) K. H. Bauer and O. Bähr, *J. prakt. Chem.*, [2]**122**, 203 (1929).
(29) *Cf.* D. H. R. Barton, C. J. W. Brooks, and N. J. Holness, *J. Chem. Soc.*, 278 (1951).
(30) G. King, *ibid.*, 37 (1943).

of hydrogen uptake *vs.* time show that *cis*-I is reduced 10.0 times as rapidly as the *trans* isomer. Lyophilization of the original supernate from the centrifuged reaction mixture, together with three 5-ml. acetic acid washings, gave 115 mg. of white solid; 5-ml. washings of the catalyst with ether yielded 15.3, 6.2, and 6.3 mg. of additional product, leaving about 18 mg. still unaccounted for and presumably strongly adsorbed on the charcoal-supported catalyst. Chromatography of the product mixture gave 18.0 mg. (11.8%) of methyl stearate, 18.3 mg. (11.5%) of III, and 87.1 mg. (54.1%) of II, m.p. 43.7–44.7°.

Methyl Ketostearates (III).—Chromic oxide (93.1 mg., 0.93 mmole) was cautiously stirred into 0.9 ml. of reagent pyridine and 99.8 mg. (0.318 mmole) of II (chromatographically isolated from the hydrogenation products of *cis*-I) was added in another 0.9-ml. portion of pyridine. After the mixture had been stirred overnight at room temperature, 3.6 ml. of water was added and the product was extracted with three 5-ml. portions of ether. The extract was washed with 2-ml. portions of 1.5 *N* HCl until a strongly acidic aqueous phase was obtained (five were required) and then with 5 ml. of saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and freed of solvent. The residual solid was chromatographed on silicic acid (see Fig. 1c), giving 85.8 mg. (86.5%) of III, m.p. (of major fraction of peak) 40.8–41.3°.

Methyl Oximino Esters (IV).—A mixture of the above III (85.8 mg., 0.275 mmole), 2 mole equiv. each of hydroxylamine hydrochloride and anhydrous sodium acetate, and 1 ml. of absolute methanol in a 15-ml. centrifuge tube was boiled in steam with stirring until the solvent had evaporated. The residual mixture of solid and oil was partitioned between water and ether, the ether extract was dried over magnesium sulfate and freed of solvent, and the residual oil was chromatographed on silicic acid (see Fig. 1d), giving 87.8 mg. (97.5%) of IV, which failed to solidify on standing at 0°. Interestingly, II and IV exhibit essentially identical chromatographic behavior.

Methyl Amido Esters (V).—IV (85.0 mg.) was mixed with 2.9 g. of sirupy polyphosphoric acid (Matheson Coleman and Bell) in a 15-ml. centrifuge tube and the light brown frothy mixture was heated 20 min. on a steam bath with occasional stirring. After diluting the mixture with 14.5 ml. of water, the product was extracted with ether, the extracts were washed with three 5-ml. portions of water, dried over magnesium sulfate, treated with diazomethane (providing evidence that some hydrolysis of the carbomethoxy group had occurred), and the crude product was dissolved in a small amount of 13% ether in pentane and chromatographed on silicic acid (see Fig. 1e).[31] Pooled fractions eluted by 80% ether in pentane and by ether alone gave 61.0 mg. (71.8%) of V, buff-colored solid, m.p. 43.2–44.4°. (About 5 mg. of partially crystalline material eluted with 64% ether in pentane was rejected, perhaps unwisely, since this may account for the apparent slight asymmetry of oxime rearrangement indicated by analysis of the methanolysis products.) Carbon analyses of this mixture of substances were consistently high.

Anal. Calcd. for $C_{16}H_{37}NO_3$: C, 69.7; H, 11.4; N, 4.3. Found: C, 71.1, 70.9; H, 11.2, 11.0; N, 4.7, 4.4.

Methanolysis of Amido Esters (V).—A necked-down 6-in. Pyrex test tube was charged with 30.1 mg. of V and 0.5 ml. of boron trifluoride–methanol reagent (Applied Science Laboratories, Inc., presumably[32] 125 g./1 l.), sealed, and left in the chamber of an Abderhalden drying apparatus heated by boiling water vapors for 52 hr. After cooling in ice, the tube was opened, 0.3 ml. of toluene and 3 ml. of water were added, and the toluene phase was washed with four 0.5-ml. portions of water, dried over magnesium sulfate, and submitted to gas chromatographic analysis, using a Loenco Model 70 Hi-Flex apparatus fitted with a 3.3 ft. × 0.125 in. i.d. column of 17% ethylene glycol succinate on 60–80-mesh, acid-washed Chromosorb W. Helium was employed as the carrier gas, and the effluent was analyzed by thermal conductivity. Areas of peaks (see Fig. 2) were evaluated as the product of height times width at half-height (areas of the slightly skew monocarboxylate peaks were checked by weighing tracing cutouts). Area ratios were related to mass ratios by reference to data obtained from contemporary runs of mixtures of authentic esters of known composition closely matching that of the neutral methanolysate. In this way, it was determined that the ratio of methyl pelargonate (P) to caprate (C) was 0.95, while that of sebacate (S) to azelate (A) was 1.01. The ratios S–P = 0.92 and A–C = 0.87 appear to indicate appreciable differences in prevalence of the two possible routes of Beckmann rearrangement of the oximino esters (S and P, for example, being derived from the same oximino ester but from different amides arising from that precursor), although the possibility exists (see above) that a portion of the type Vb amido ester may have been omitted from the chromatographic sample submitted to methanolysis.

(31) Because of the limited solubility of V in less polar solvent mixtures, six column-volumes of 13% ether were substituted in initial development of this chromatogram for the usual two volumes each of the 0–10% solvent mixtures. Experience with other substances has shown that this alternative development regime (which, incidentally, involves use of the same total amount of *ether*) has little effect on the emergence behavior of relatively strongly adsorbed solutes and saves time and pentane.

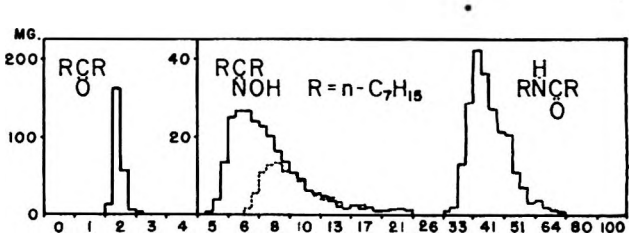
(32) L. D. Metcalfe and A. A. Schmitz, *Anal. Chem.*, **33**, 363 (1961).

Di-*n*-heptyl ketone was prepared by dry distillation of calcium caprylate (*n*-octanoate). The crude product was washed with water, dried, redistilled, permitted to crystallize from the resulting light yellow oil, centrifuged free of noncrystalline material, chromatographed on silicic acid, and yielded a colorless solid, m.p. 41.0–41.6°, lit.[33] m.p. 41°, having chromatographic behavior essentially indistinguishable from that of monocarboxylic esters (see below and methyl stearate, peak A, Fig. 1b). Gas chromatography (Wheelco Model 10, argon carrier gas, Ra ionization detector, 40 × 0.25 in. ethylene glycol succinate on Chromosorb W column, 148°) of the ketone showed it to be free of homologs, and to have a retention time of 0.83 relative to that of methyl myristate, which contains the same number of carbon atoms.

Di-*n*-heptyl ketoxime was prepared from the ketone as described above (see preparation of IV). The chromatographically purified derivative (see graph below) was obtained in 89% yield, m.p. 20.9–21.2°, lit.[33] m.p. 20°. Chromatograms of this substance at two quite different loads (see graph below: broken tracing, 84 mg.; solid tracing, 222 mg.) serve to illustrate the fact that the leading edge of such peaks tends to be load dependent (substances which are able to function as hydrogen-bond donors appear particularly prone to exhibit this behavior), while the trailing edge remains little affected by load and hence is more reliably characteristic. Chromatograms of *cis*-I before and after diminishing to 8% of the original quantity by treatment with acetic acid (see above) also illustrate this effect.

N-*n*-Heptylcaprylamide.—As described in detail for conversion of IV to V, action of 4.0 g. of polyphosphoric acid on 216 mg. of diheptyl ketoxime gave an essentially quantitative yield of the isomeric amide, m.p. 58.1–58.3° (previously unreported), after chromatography on silicic acid and recrystallization from *n*-pentane at 0°. Six column-volumes of 13% ether in pentane were used in place of the more usual 0–10% mixtures in early development of the chromatogram of this amide. The magnitude of the adsorptivity contribution of the –NHCO– group manifest in the chromatographic behavior of this substance (and of V) is worthy of note.

Anal. Calcd. for $C_{15}H_{31}NO$: C, 74.6; H, 12.9; N, 5.8. Found: C, 74.5; H, 12.8; N, 5.8.



Boron Trifluoride Methanolysis of N-Heptylcaprylamide.—In order to delineate appropriate conditions for the methanolysis of V, a mixture of 11.9 mg. of methyl pelargonate (internal standard), 22.7 mg. of the amide, and 0.5 ml. of the boron trifluoride–methanol reagent was sealed in a Pyrex tube and heated at 100° for exactly 1 hr. Contents of the cooled tube were distributed between toluene and water, and the toluene phase (after washing with water and drying over magnesium sulfate) was submitted to gas chromatographic analysis to determine the extent (5.3%) to which methyl caprylate had been formed from

(33) A. D. Petrov and E. P. Kaplan, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 539 (1949); *Chem. Abstr.*, **44**, 1887*h* (1950).

the amide. From this information it was estimated that 94% methanolysis of amides of this type (*e.g.*, V) should require 52 hr. under these conditions.

Acknowledgment.—The authors wish to record their indebtedness to Mr. Robert W. Green for assistance in preparation of certain substances used in this study, to Dr. G. A. Dhopeshwarkar for a generous sample of elaidic acid, and to Mr. George Alexander for infrared absorption determinations. A summer fellowship granted by the National Foundation supported in part the contribution of the junior author (R. W. K., Jr.) to this study.

Transformations of N-Acyl-ε-caprolactams and the Synthesis of DL-Lysine

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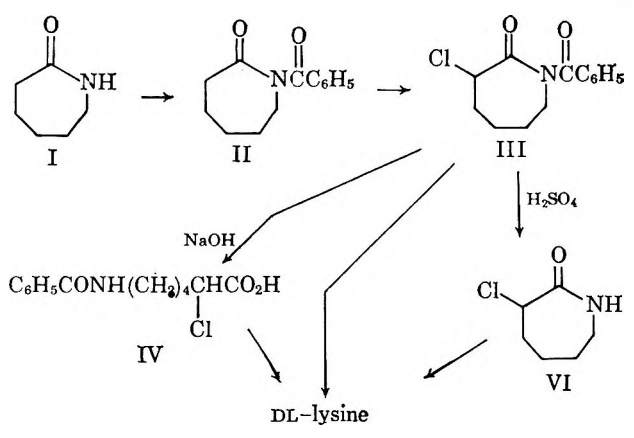
Unlike ε-caprolactam, N-benzoyl-ε-caprolactam undergoes monochlorination in the α-position to give N-benzoyl-α-chloro-ε-caprolactam. Alkaline hydrolysis of this acylated lactam furnishes ε-benzamido-α-chlorocaproic acid and cleavage of the benzoyl group with sulfuric acid provides α-chloro-ε-caprolactam. These cleavage products have been converted into DL-lysine in high over-all yield.

ε-Caprolactam has been an attractive starting material for the synthesis of lysine in recent years because of its availability and structural advantages. Introduction of the requisite amino group into ε-caprolactam by direct monochlorination in the α-position followed by ammonolysis has not been successful, the chlorination product being α,α-dichloro-ε-caprolactam.[1,2] The dichloro derivative, prepared by use of phosphorus pentachloride, has been converted into the monochloro compound and thence to lysine.[1] The monochlorocaprolactam has also been prepared from the N-chloro derivative.[3]

In contrast to the behavior of ε-caprolactam, N-benzoyl-ε-caprolactam (II) undergoes monochlorination smoothly through the agency of sulfuryl chloride to give N-benzoyl-α-chloro-ε-caprolactam (III).



The chlorination of N-benzoyl-ε-caprolactam, prepared by benzoylation in dimethylaniline, was subjected to intensive study. With chlorine only a small amount of N-benzoyl-α-chloro-ε-caprolactam could be isolated.[4] The best method consisted of chlorination with a slight excess of sulfuryl chloride in a mixture of carbon tetrachloride and cyclohexane at 40° for 24 hr. Under these conditions, N-benzoyl-α-chloro-ε-caprolactam (III) was produced in 89% yield.

Selective ring opening of N-benzoyl-α-chloro-ε-caprolactam (III) without loss of the benzoyl group or replacement of chlorine was accomplished by hydrolysis of III with sodium hydroxide in aqueous methanol. The product, ε-benzamido-α-chlorocaproic acid (IV), was found to be completely stable under the mild alkaline medium required for ring opening and was formed in 95% yield. The small amount of benzoic acid produced probably resulted from attack on the benzoyl group before ring opening. This undesired cleavage was minimized either by conducting the reaction in a solvent mixture in which III was slightly soluble or by slow addition of alkali to a hot solution of III.

The conversion of ε-benzamido-α-chlorocaproic acid into lysine was carried out by the conventional means of amination and hydrolysis.[5a,6] The over-all yield from ε-caprolactam was 73%.

Acidic hydrolysis of III provided another route to DL-lysine. In contrast to aqueous alkaline hydrolysis, concentrated sulfuric acid cleaved the benzoyl group with complete selectivity to α-chloro-ε-caprolactam (VI) in 95% yield simply by allowing a solution of III in sulfuric acid to stand at room temperature for 4 hr. The synthesis of DL-lysine was completed by ammonolysis of α-chloro-ε-caprolactam (VI) with fortified aqueous ammonia followed by hydrolysis of α-amino-ε-caprolactam (VII). These transformations have already been reported.[1a,b] Lysine was produced from VI in 72% yield or 60% from caprolactam.

Diacylamines, a class to which the N-benzoylcaprolactams belong, are known to be highly reactive toward nucleophilic and electrophilic reagents. A recent study[7] has shown in the case of N-acylbenzanilides that the stronger acid is liberated by alkaline hydrolysis and the weaker acid is liberated by cleavage in concentrated sulfuric acid. This pattern was followed upon treatment of III with these reagents.

N-Benzoyl-ε-caprolactam (II) behaved in the same manner as III toward sodium hydroxide but surprisingly underwent ring cleavage to the extent of 80% upon treatment with sulfuric acid, a reagent which effected cleavage of the benzoyl group in III.

(1) (a) R. J. Wineman, E. T. Hsu, and C. E. Anagnostopaulos, *J. Am. Chem. Soc.*, **80**, 6233 (1958); (b) W. C. Francis, J. R. Thornton, J. C. Werner, and T. R. Hopkins, *ibid.*, **80**, 6238 (1958); (c) H. R. Richenbacher and M. Brenner, *Helv. Chim. Acta*, **41**, 181 (1958).

(2) J. V. Braun and A. Heymons, *Ber.*, **63**, 502 (1930).

(3) A. O. Rogers, U. S. Patent 3,045,009 (1962).

(4) G. Steinbrunn, German Patent 855,260 (1952).

(5) (a) A. Galat, *ibid.*, **69**, 86 (1947); (b) H. Shechter and J. C. Kirk, *ibid.*, **73**, 3087 (1951).

(6) J. C. Eck and C. S. Marvel, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 374.

(7) A. H. Lamberton and A. E. Standage, *J. Chem. Soc.*, 2957 (1960).

Experimental

Melting points are not corrected. Microanalyses were carried out by Mr. R. N. Boos and his associates.

N-Benzoyl-ε-caprolactam (II).—To a mixture of 45.2 g. (0.40 mole) of ε-caprolactam and 56.7 ml. (0.44 mole) of N,N-dimethylaniline was added 61.9 g. (0.44 mole) of benzoyl chloride. The temperature rose to 80°. The mixture was heated and stirred at 90° for 3 hr., cooled to 70°, and poured into a solution of 8 ml. of 2.5 *N* hydrochloric acid in 400 ml. of water. The crystalline lumps were broken up, collected on a filter, washed with water, and dried, 84.5 g. (97.3%), m.p. 68–70.5°, lit.[8] m.p. 67–69.5°.

N-Benzoyl-α-chloro-ε-caprolactam (III).—To a suspension of 43.4 g. (0.2 mole) of N-benzoyl-ε-caprolactam (II) in 11 ml. of carbon tetrachloride and 33 ml. of cyclohexane was added 17.0 ml. (0.21 mole) of sulfuryl chloride. The mixture was heated with stirring to 40° and maintained at 40–42° for 24 hr. The mixture was evaporated to dryness *in vacuo* and the residue was stirred with 50 ml. of isopropyl alcohol at 70° for a few minutes. The suspension was cooled to 0–5° for 1 hr. and filtered, and the product was washed with cold isopropyl alcohol and dried in air, 45.0 g. (89.3%), m.p. 120–122°, lit.[1a] m.p. 122–123°. A sample was prepared for analysis by recrystallization from ethanol, m.p. 120–121.5°.

Anal. Calcd. for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; Cl, 14.08; N, 5.57. Found: C, 61.93; H, 5.31; Cl, 14.30; N, 5.47.

ε-Benzamido-α-chlorocaproic Acid (IV) from III.—To a suspension of 10.08 g. (0.04 mole) of N-benzoyl-α-chloro-ε-caprolactam (III) in 20 ml. of methanol and 5 ml. of water was added 20.4 ml. of 1.96 *N* sodium hydroxide over 40 min. with the temperature being maintained at 2–4°. The mixture was stirred for 1 hr. at 0–3°, treated with another 2 ml. of base, and stirred for an additional 3 hr. at 0–3°. The mixture was acidified by the addition of 5.1 ml. of concentrated hydrochloric acid, diluted with 30 ml. of water, and concentrated *in vacuo* to remove the methanol. The slurry was cooled to 0–5° and filtered; the product was washed free of chloride ion, yielding 10.17 g. (94.5%), m.p. 137.5–139°, lit.[5a,b] m.p. 137.8–138.8°. No depression of melting point was observed with an authentic sample.

ε-Benzoyllysine (V) from IV.—A mixture of 13.5 g. (0.05 mole) of ε-benzamido-α-chlorocaproic acid (IV), 13 ml. of methanol, and 25 ml. of water was heated in a glass-lined shaker bomb. The mixture was cooled in a Dry Ice bath and 72 g. of liquid ammonia was added. The mixture was shaken at 105° for 1 hr., cooled, transferred to a flask, and concentrated to a thick slurry. The product was filtered and washed with water and methanol, 11.4 g. (91%), m.p. 270–272° dec., lit.[9] m.p. 268° dec.

With minor changes in procedure, the lactam (II) and the chlorolactam (III) were converted into benzoyllysine without isolation of intermediates in yields of 71 and 86%, respectively.

DL-Lysine from V.—A solution of 12.5 g. (0.05 mole) of benzoyllysine (V) in a mixture of 76.5 ml. of concentrated hydrochloric acid and 50 ml. of water was boiled under reflux for 24 hr., cooled in an ice bath, filtered to remove benzoic acid, and evaporated to dryness. The residue was triturated with 30 ml. of acetone and filtered; the cake was washed with two 15-ml. portions of acetone. The colorless DL-lysine dihydrochloride weighed 10.76 g. (98.7%). The over-all yield from caprolactam was 73.5%.

Anal. Calcd.: N, 13.39. Found: N, 13.18.

The dihydrochloride was converted into DL-lysine monohydrochloride in 95.7% yield by treatment with pyridine in ethanol.[6]

α-Chloro-ε-caprolactam (VI) from III.—To 140 ml. of concentrated sulfuric acid was added in portions 100.4 g. (0.4 mole) of N-benzoyl-α-chloro-ε-caprolactam (III), the temperature being maintained below 25°. The mixture was stirred for 1 hr. without external heating (temperature rose to 38°) and then at 50° for 2 hr. The mixture was cooled to 25°, poured onto 1 kg. of ice, neutralized with concentrated ammonium hydroxide, and extracted with three 500-ml. portions of chloroform. The chloroform solution was evaporated to give 56.2 g. (95.3%), m.p. 91.5–93°, lit. m.p. 97–98°[5b] and 92.5–93.5°.[1a] A sample, recrystallized from petroleum ether (b.p. 30–60°) melted at 92–93°.

Anal. Calcd. for $C_6H_{10}ClNO$: C, 48.80; H, 6.83; Cl, 24.03. Found: C, 48.94; H, 6.83; Cl, 23.93.

The chlorolactam (VI) was reconverted to the starting benzoyllactam (III) by the procedure employed in the preparation of II, yielding 99.5%, m.p. 120–122°, no depression with II.

DL-Lysine from VI.—A mixture of 7.4 g. (0.05 mole) of α-chloro-ε-caprolactam (VI), 222 ml. of concentrated ammonium hydroxide, and 102 g. of anhydrous ammonia was heated in a bomb at 110° for 8 hr. The reaction mixture was evaporated to dryness, and the residue was triturated with a large volume of acetone. The crude α-amino-ε-caprolactam (VII) was filtered and dried, 7.9 g.

The crude aminolactam (3.0 g.) was hydrolyzed by the procedure used for V to give 3.9 g. of crude DL-lysine dihydrochloride. The dihydrochloride (1.1 g.) was converted into the monohydrochloride by treatment with pyridine in ethanol, 0.7 g., m.p. 257° dec. The yield from VI was 72%.

DL-Lysine by Ammonolysis of III.—A mixture of 8.0 g. (0.032 mole) of N-benzoyl-α-chloro-ε-caprolactam (III) and 128 ml. of concentrated ammonium hydroxide was heated in a bomb at 85–90° for 7.5 hr. The reaction mixture was evaporated to dryness. The residual oil was boiled in 200 ml. of concentrated hydrochloric acid for 13 hr. The solution was cooled to 0°, filtered to remove insoluble material, and evaporated to dryness. The solid residue was boiled with 40 ml. of alcohol for a few minutes and the mixture was cooled to 5° and filtered to remove ammonium chloride. The filtrate was treated with 3.3 ml. of pyridine, whereupon DL-lysine monohydrochloride slowly crystallized. The product was filtered and washed with alcohol, 1.2 g. (20.5%), m.p. 250° dec.

Reaction of N-Benzoyl-ε-caprolactam (II) with Sulfuric Acid.—To 35 ml. of concentrated sulfuric acid was added in portions 21.7 g. (0.1 mole) of N-benzoyl-ε-caprolactam (II), the temperature being maintained below 25°. The mixture was stirred at room temperature for 4 hr., poured onto 250 g. of ice, whereupon crystallization slowly took place. The ε-benzamidocaproic acid was filtered and triturated with water, 19.6 g. (83.5%), m.p. 79–81.5°. No depression in melting point was observed with an authentic sample.

Under similar conditions N-benzoyl-α-chloro-ε-caprolactam (III) was converted into α-chloro-ε-caprolactam (VI) in 93% yield, m.p. 91–95°.

Reaction of N-Benzoyl-ε-caprolactam (II) with Sodium Hydroxide.—To a suspension of 10.85 g. (0.05 mole) of N-benzoyl-caprolactam (II) in 25 ml. of methanol and 6.2 ml. of water was added 25.2 ml. of 2 *N* NaOH over 30 min. The solution was allowed to stir at room temperature for 3 hr. and the methanol was removed by distillation at 30–35°. The residue was diluted with 10 ml. of water, acidified with a mixture of 4.5 ml. of concentrated hydrochloric acid and 4.5 ml. of water, and stirred overnight. The ε-benzamidocaproic acid was filtered and washed with water, 9.5 g. (81%), m.p. 73–77°.

Under similar conditions N-benzoyl-α-chloro-ε-caprolactam (III) was converted into ε-benzamido-α-chlorocaproic acid (IV) in 89% yield, m.p. 139–140.5°.

Mild Ammonolysis of N-Benzoyl-α-chloro-ε-caprolactam (III).—Anhydrous ammonia was passed into a boiling solution of 25.2 g. (0.10 mole) of N-benzoyl-α-chloro-ε-caprolactam in 200 ml. of methanol for 1 hr. The solution was cooled to 25°, saturated with ammonia, and allowed to stand for 3 days. The crystals were filtered, washed with methanol, and dried, 12.3 g., m.p. 159–161°. Recrystallization from water raised the melting point to 160–161°.

Anal. Calcd. for $C_{13}H_{17}ClN_2O_2$: C, 58.2; H, 6.38; Cl, 13.18; N, 10.41. Found: C, 58.15; H, 6.27; Cl, 12.9; N, 10.20.

The infrared spectrum (Nujol mull) showed peaks at 3.05–3.1 and 3.2 (N—H), and 6.0 μ, (C=O). Other bands at 6.15–6.2, 6.35–6.40, and 6.45 μ are consistent with the structure of ε-benzamido-α-chlorocaproamide (VIII).

A second crop of 3.2 g. (m.p. 155–158.5°) was obtained from the mother liquor to bring the approximate total yield to 58%.

Reaction of N-Benzoyl-ε-caprolactam (II) and Caprolactam with Ammonium Hydroxide.—A mixture of 5 g. (0.023 mole) of N-benzoyl-ε-caprolactam (II) and 92 ml. of concentrated ammonium hydroxide was heated in a bomb at 85–90° for 7.5 hr. The mixture was evaporated to dryness and triturated with 20 ml. of water, 1.84 g. (66%). The product melted at 128–130° and did not depress the melting point of benzamide.

Caprolactam was treated in a similar manner with ammonium hydroxide. A quantitative recovery of caprolactam was obtained.

(8) H. K. Hall, Jr., M. K. Brandt, and R. M. Mason, *J. Am. Chem. Soc.*, **80**, 6420 (1958).

(9) J. von Braun, *Ber.*, **42**, 844 (1909).

Properties and Reactions of Mesomeric Phosphonium Salts[1]

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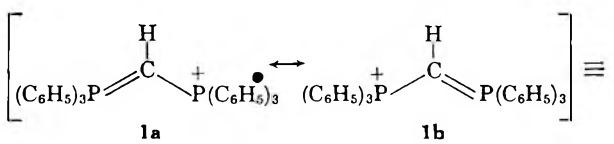
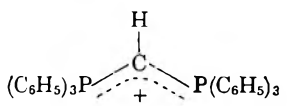
The triphenylphosphonium methylenetriphenylphosphorane cation (1) has been shown to be mesomeric. A number of salts possessing this stable cation have been synthesized, including the inner salt triphenylphosphoniumtriphenylboronyl methylenetriphenylphosphorane (11). The photochromism of triphenylphosphonium methylenetriphenylphosphorane tetraphenylboron (12) is described.

Recent investigations[2-4] of the reaction of triphenylphosphine with methylene bromide have led to the discovery of stable salts possessing the triphenylphosphonium methylenetriphenylphosphorane cation (**1a–c**).



1a **1b**



1c

A number of new salts of this type have been prepared and the previously assumed mesomeric nature of the cation has been confirmed.

The essential precursor in the synthesis work was methylenebis(triphenylphosphonium bromide) (**2**) which was prepared by the reaction of triphenylphosphine with methylene bromide or bromomethyltriphenylphosphonium bromide (**3**) in molten triphenylphosphate. The corresponding diphosphonium chloride (**4**) and iodide (**5**) could then be prepared by metathesis reactions of **2**. These acidic salts were easily dehydrohalogenated with aqueous bases or *n*-butyllithium in hexane to produce triphenylphosphonium methylenetriphenylphosphorane salts. Triphenylphosphonium methylenetriphenylphosphorane chloride (**7**) was also prepared by the reaction of hexaphenylcarbodiphosphorane[2,5] (**8**) with hydrochloric acid. Metathesis of triphenylphosphonium methylenetriphenylphosphorane bromide (**6**) gave an alternate route to the iodide (**9**). The bromide (**6**) and chloride (**7**) formed stable complexes with ferric chloride. The iodide (**9**) gave a triiodide complex (**10**) on reaction with iodine. Scheme I summarizes these reaction paths.

Both physical and chemical evidence indicate that the triphenylphosphonium methylenetriphenylphosphorane cation is better represented by the symmetrical mesomeric structure **1c** than by an ylide form. The phosphorus atoms in the cation were shown to be equivalent by the presence of a single P^{31} n.m.r. absorption (Table I). Additionally, the single, nonaromatic proton absorption appeared as a triplet, the nature of which indicated that the phosphorus environments were identical. The stability suggested by the mesomeric structure **1c** was reflected in the relative inertness of the cation towards reaction with hot aqueous carbonate, benzyl bromide, or acetone.

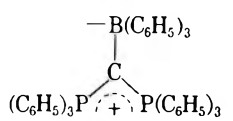
TABLE I

N.M.R. SPECTRAL DATA

Compound	Chemical shifts (p.p.m.)[a] P^{31}	H^1 Aromatic	H^1 Nonaromatic	B^{11}
2	−18.4[b]	7.3–8.2 (m)[c,d]	6.75 (t)[e]	
3	−24.0	7.8–8.8 (m)	6.22 (d)	
6	−21.2	7.7–8.2 (m)	2.00 (t)	
9	−21.1	7.8–8.2 (m)	2.00 (t)	
11	−20.9	7.5–8.1 (m) 7.0–7.4 (m)		19.0[f]
12	−20.8	7.1–8.1 (m)	1.80 (t)	25.0

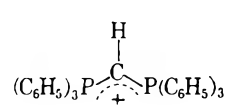
[a] Reference standards were 85% phosphoric acid, tetramethylsilane, and triethylborate. [b] P^{31} spectra of **3**, **6**, **9**, and **12** in chloroform (10–20 wt. %), **2** in 80% methanol–water (10 wt. %), and **11** in methylene chloride (11 wt. %). [c] H^1 spectra of **3**, **6**, **9**, and **12** (5–10 wt. %) and **11** (saturated solution) in deuteriochloroform, **2** in methanol (20 wt. %). [d] m = multiplet, t = triplet, and d = doublet. [e] Nonaromatic, J_{HP} = 16 c.p.s. for **2**, 6 c.p.s. for **3**, **6**, **9**, and **12**. [f] B^{11} spectrum of **11** in methylene chloride (13 wt. %), **12** in chloroform (17 wt. %).

Replacement of the single nonaromatic proton in **1c** by the triphenyl boron group resulted in the formation of the mesomeric inner salt[6] triphenylphosphoniumtriphenylboronyl methylenetriphenylphosphorane (**11**).



11

Compound **11** was synthesized by the addition of triphenylboron to hexaphenylcarbodiphosphorane (**8**). Triphenylphosphonium methylenetriphenylphosphorane tetraphenylboron (**12**), fluoborate (**13**), and borohydride[4] (**14**) were prepared from **6** by metathesis reactions for comparison with the inner salt (**11**).



12, X = $B(C_6H_5)_4$
13, X = BF_4
14, X = BH_4

(1) This work was sponsored in part by the Office of Naval Research, 1961.

(2) F. Ramirez, N. B. Desai, B. Hansen, and N. McKelvie, *J. Am. Chem. Soc.*, **83**, 3539 (1961).

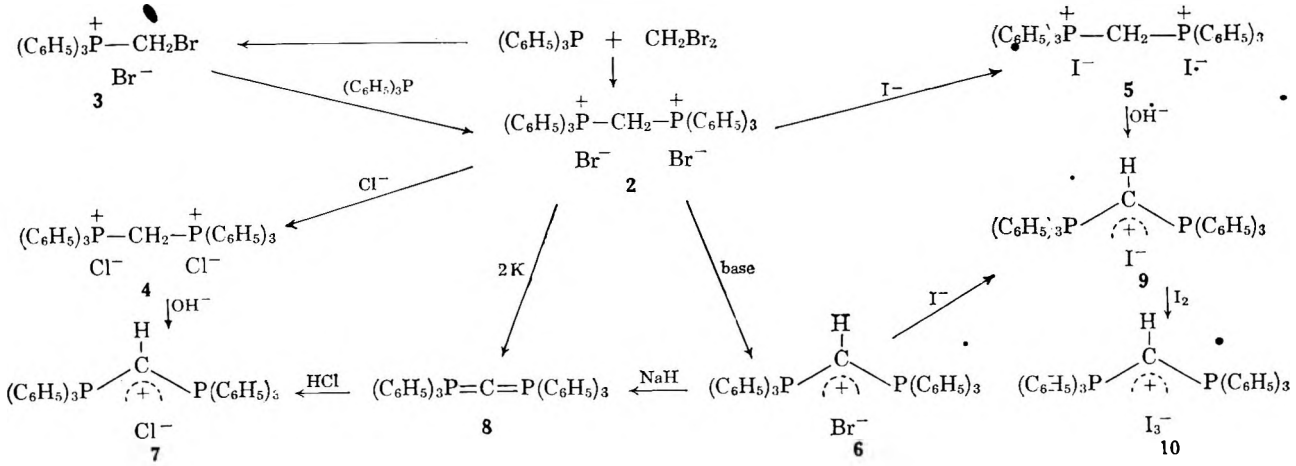
(3) C. N. Matthews, J. S. Driscoll, J. E. Harris, and R. J. Wineman, *ibid.*, **84**, 4349 (1962).

(4) J. S. Driscoll and C. N. Matthews, *Chem. Ind.* (London), 1282 (1963).

(5) Hexaphenylcarbodiphosphorane (**8**) is triboluminescent. When crystals of **8** are crushed in a dry, nitrogen atmosphere, a green-white light flash is emitted from the compound.

(6) The synthesis of the nonmesomeric inner salt $(C_6H_5)_3P^+-CH_2-B^-(C_6H_5)_3$ has been reported by D. Seyferth and S. O. Grim [*J. Am. Chem. Soc.*, **83**, 1613 (1961)].

SCHEME I



The inner salt (**11**) had a phosphorus n.m.r. spectrum characteristic of the mesomeric cation. The nonaromatic absorption, corresponding to the lone proton on the central carbon atom of **12**, was not observed in the proton spectrum of **11**. The B^{11} absorption of the inner salt indicated that an unsymmetrical tetravalent boron atom was covalently bonded to the mesomeric phosphonium system. The very broad B^{11} absorption of **11** (half-peak width 5 p.p.m.) contrasted markedly with the sharp B^{11} absorption of **12** (half-peak width 0.9 p.p.m.). The broadening is probably due to quadruple relaxation effects present in **11**, but absent in **12** with its symmetrical boron anion.[7]

During the structural studies on the boron-containing salts, it was observed that the tetraphenylboron derivative (**12**) was markedly photochromic. The white, crystalline solid became orange-red when exposed to an ultraviolet lamp, sunlight, or an incandescent bulb, the rate of change being most rapid with the first source and slowest with the last. As has been found in numerous other photochromic systems, **12** exhibited a color change only in the solid state.[8]

The appearance of color was accompanied by the formation of a radical species with an electron paramagnetic resonance (e.p.r.) g value of 2.0065. No hyperfine structure was present in the solid state e.p.r. spectrum (Fig. 1).

The white and colored forms of **12** had identical infrared spectra. The ultraviolet spectra of the two forms were quantitatively the same.

Crystal form appeared to be important in the photochromic phenomenon, since samples of **12** which were melted and resolidified were not photochromic. Although no change was observed in the infrared spectrum of a sample of **12** after melting, a 2° increase in the melting point of the resolidified sample indicated a possible polymorphic change.

Upon removal of the radiation source, the sample color faded from orange-red to yellow over a 24-hr. period. While samples faded at approximately the same rate in air or nitrogen, evacuated samples faded at a much slower rate. Relative to the rate at room temperature, the decoloration was very rapid at 190° and greatly slowed at −70°.

While **12** showed the most dramatic light-induced color change, compounds **9**, **14**, **2**, **11**, **4**, **3**, **5**, **13**, and **7** were also photochromic. They are listed in the order of decreasing rate of color formation. Compounds **6** and **10** had no apparent photochromic properties.

Experimental[9]

Materials.—*n*-Butyllithium (Foote Mineral Co.) was used as a 15% solution in hexane. Sodium hydride (Metal Hydrides) was used as a 50% dispersion in mineral oil. Triphenylboron (Aldrich) and nitrogen gas were used as obtained. Diglyme (dimethyl ether of diethylene glycol) was distilled from sodium hydride directly into reaction vessels.

Spectra.—Infrared spectra were determined in potassium bromide pellets with a Perkin-Elmer Model 21 spectrophotometer. The spectra of the methylenebis(triphenylphosphonium halides) were essentially identical. Characteristic absorption bands occurred at 2600 (m),[10] 1105 (s), and 815 (s) cm.$^{-1}$. Absorptions characteristic of triphenylphosphonium methylenetriphenylphosphorane compounds were a triplet at 1227 (s), 1182 (m), and 1157 (w), a doublet at 1100 (s) and 1073 (w), and a triplet at 1027 (w), 1008 (m), and 989 (s) cm.$^{-1}$.

Ultraviolet spectra were determined in solution with a Cary Model 14A recording spectrophotometer.

Proton n.m.r. spectra were determined with a Varian Model A-60 spectrometer at 60 Mc. P^{31} and B^{11} spectra were determined with a Varian Model V-4300-2 high resolution n.m.r. spectrometer at 16.2 and 12.8 Mc., respectively.

E.p.r. spectra were determined with a Varian 4500 spectrometer at 9.525 kMc. The magnetic field sweep covered the range 50–4000 gauss. The resonance of diphenylpicrylhydrazyl was observed at 3396 gauss.

Irradiation Experiments.—The sample prepared for the e.p.r. study was irradiated in a quartz tube with a Hanovia UVS-250 lamp at a distance of 15 cm.

The qualitative photochromism studies were carried out in a horizontal, water-cooled (21°), quartz reflux condenser with a Hanovia lamp, Model 30600, at a distance of 4 cm. in a nitrogen atmosphere. There was no apparent difference between quartz and Pyrex containers with respect to the rate of color formation or fading.

Bromomethyltriphenylphosphonium Bromide (3).—A stirred solution of triphenylphosphine (1049 g., 4.0 moles), methylene bromide (347.8 g., 2.0 moles), and toluene (2000 ml.) was heated at reflux for 24 hr. under nitrogen. The resulting suspension was filtered and the solid was dried at 80° (20 mm.) to yield 572.1 g. of tan crystals, m.p. 221–237°. The product was dissolved in methanol, reprecipitated with ethyl acetate, filtered, and washed with ether to give 335 g. (38%) of white needles, m.p. 236.5–241.5°, lit.[2] m.p. 240–241°, λ_{max}^{EtOH} 228 mμ (ε 27,200).

(7) N^{14} quadrupole broadening in unsymmetrical ammonium compounds has been demonstrated by R. A. Ogg and J. D. Ray [*J. Chem. Phys.*, **26**, 1339 (1957)].

(8) G. H. Brown and W. G. Shaw, *Rev. Pure Appl. Chem.*, **11**, 2 (1961).

(9) Melting points are corrected. Microanalyses were performed by Schwarzkopf Laboratory, Woodside, N. Y.

(10) The letters s, m, and w refer to strong, medium, and weak, respectively.

The infrared spectrum of the product was identical with that of an authentic sample of **3** prepared by the method of Ramirez.[2]

Methylenebis(triphenylphosphonium bromide) (2). Method A.—Methylene bromide (17.4 g., 0.1 mole) was added to a stirred solution of triphenylphosphine (52.4 g., 0.2 mole) in 125 g. of triphenyl phosphate at 86° in an atmosphere of nitrogen. The ensuing mixture was heated at 98–110° for 22.5 hr. and then at 145–150° for an additional 5 hr. Benzene (200 ml.) was added to the stirred slurry at 80–100°, and the mixture was filtered to yield a tan solid. After a benzene wash, the solid (62.5 g.) was twice taken up in warm methanol, reprecipitated with ethyl acetate, and dried at 80° (20 mm.) to yield white needles of **2** monohydrate (26.5 g., 36%), m.p. 311.5–314.5°.

Anal. Calcd. for $C_{37}H_{32}Br_2P_2 \cdot H_2O$: H_2O, 2.51. Found: H_2O, 2.56 (Karl Fischer).

The infrared spectrum of the hydrate was identical with that of an anhydrous reference sample prepared by the method of Ramirez[2] except that an additional band was present at 3400 cm.$^{-1}$ (H_2O). The reference sample, dried at 100° (0.1 mm.), m.p. 310–310.5°, lit.[2] m.p. 308–310°, had the correct elemental analysis. The monohydrate was dehydrated at 100° (0.1 mm.). Small amounts of impurities apparently cause large variations in the melting point of **2**.

Method B.—Triphenylphosphine (5.24 g., 20 mmoles), bromomethyltriphenylphosphonium bromide (8.72 g., 20 mmoles), and 25.0 g. of triphenyl phosphate were stirred under nitrogen at 135–140° for 5 hr. The mixture, which was cooled to room temperature, stirred with 80 ml. of benzene, and allowed to stand for 18 hr., gave 12.6 g. of a hygroscopic solid. Upon solution in methanol and reprecipitation with ethyl acetate, 6.18 g. (43%) of **2** monohydrate, m.p. 303–308°, was obtained. The product was identified by its infrared spectrum.

Methylenebis(triphenylphosphonium chloride) Monohydrate (4).—A chloride ion-exchange resin (Rohm and Haas Amberlist-XN-1002, 50 g.) was placed in a 21.6 × 2.5 cm. column. It was treated successively with 200 ml. of methanol, 21 g. of HCl in 140 ml. of methanol, and 300 ml. of methanol. A solution of 3.58 g. (50 mmoles) of methylenebis(triphenylphosphonium bromide) in 20 ml. of methanol was placed on the column and eluted with 300 ml. of methanol. Removal of the solvent gave a viscous oil which after trituration with ethyl acetate yielded a solid, 2.64 g., m.p. 232–239°. This material was dissolved in 10 ml. of methanol and reprecipitated with 70 ml. of ethyl acetate. The product was dried at 55° (0.1 mm.) to give 2.15 g. (68%) of the white monohydrate, m.p. 239.5–246° (shrinking at 224°). Drying at 100° (0.1 mm.) caused dehydrochlorination.

Anal. Calcd. for $C_{37}H_{32}Cl_2P_2 \cdot H_2O$: C, 70.82; H, 5.46; Cl, (total), 11.30; Cl (ionic), 11.30; P, 9.87; H_2O, 2.89. Found: C, 70.43; H, 6.39; Cl (total), 11.27; Cl (ionic), 11.36; P, 9.49; H_2O, 2.29.

Methylenebis(triphenylphosphonium iodide) (5).—A solution of methylenebis(triphenylphosphonium bromide) (3.49 g., 5 mmoles) in deaerated methanol (30 ml.) was added to a stirred solution of potassium iodide (8.3 g., 50 mmoles) in deaerated methanol (80 ml.). Crystals began to separate immediately. The mixture was stirred for 30 min. and filtered to yield 3.85 g. of product, m.p. 304–311° dec. The solid was recrystallized from methanol under nitrogen to yield 2.27 g. (58%) of pale yellow needles, m.p. 301–307° dec. Two further recrystallizations from methanol under nitrogen raised the melting point to 306–311° dec.

Anal. Calcd. for $C_{37}H_{32}I_2P_2$: C, 55.44; H, 4.05; I, 32.48; P, 7.82. Found: C, 55.48; H, 4.25; I, 32.43; P, 7.85.

Hexaphenylcarbodiphosphorane (8).—Upon addition of 2.0 g. (3 mmoles) of triphenylphosphonium methylenetriphenylphosphorane bromide to a mixture of sodium hydride in mineral oil (0.15 g., 3 mmoles) and diglyme (50 ml.), slow gas evolution resulted. The temperature was raised to reflux over a 20-min. period, during which time the suspension color changed from light green to yellow. The reaction was stopped after 30 min., when gas evolution had ceased. The hot solution was filtered in a dry nitrogen atmosphere. A small amount of starting material precipitated from the yellow filtrates and was filtered. The filtrates were evaporated *in vacuo* to a moist solid. Nitrogen was reintroduced into the apparatus. The yellow solid was washed with 50 ml. of anhydrous ether to yield 0.67 g. (42%) of hexaphenylcarbodiphosphorane, m.p. 196–203°. This material was similar to a reference sample (m.p. 198–201°) prepared using potassium metal as the base, lit.[2] m.p. 208–210°.

Triphenylphosphonium Methylenetriphenylphosphorane Bromide (6).—To a stirred suspension of 17.5 g. (25 mmoles) of methylenebis(triphenylphosphonium bromide) in 600 ml. of anhydrous ether under a nitrogen atmosphere was slowly added 15.0 ml. (25 mmoles) of *n*-butyllithium in hexane. A buff-colored suspension formed, becoming creamy white after 2 hr. of stirring. A white solid (17 g.) was filtered from the colorless ether filtrate and was extracted several times with a mixture of methylene chloride and water. The combined methylene chloride portions were washed with water and dried over anhydrous magnesium sulfate, to give a pale yellow solution. Evaporation yielded a white solid (13 g.) which was recrystallized twice from methylene chloride–ethyl acetate to give 10 g. (65%) of fine white crystals, m.p. 272–274°, λ_{max}^{EtOH} 268 mμ (ε 7900). The infrared spectrum of this compound was identical with that of a reference sample[2,3] prepared by the use of aqueous sodium carbonate as base.

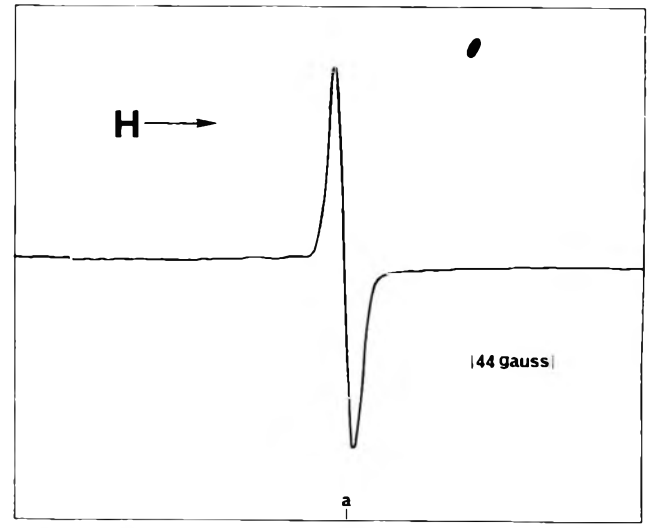


Fig. 1.—E.p.r. spectrum of triphenylphosphonium methylenetriphenylphosphorane tetraphenylboron (12) after ultraviolet irradiation; a, diphenylpicrylhydrazyl absorption position.

Triphenylphosphonium Methylenetriphenylphosphorane Bromide–Ferric Chloride Complex.—To a suspension of anhydrous ferric chloride (3.12 g., 19.3 mmoles) in 400 ml. of methylene chloride was added 11.9 g. (19.3 mmoles) of triphenylphosphonium methylenetriphenylphosphorane bromide in a dry nitrogen atmosphere. The mixture was stirred for 18 hr. and filtered to remove a small amount of orange solid. The filtrate was evaporated *in vacuo* to give a red-gold solid, m.p. 220–224°. The solid was extracted with 25 ml. of absolute ethanol, filtered, and dried (70° at 15 mm.) to yield 13.8 g. (91%) of the product, m.p. 228–229°. Recrystallization of the complex from ethanol gave red-gold needles, m.p. 230–230.5°.

Anal. Calcd. for $C_{37}H_{31}BrCl_4FeP_2$: C, 56.99; H, 4.01; Br, 10.25; Cl, 13.64; Fe, 7.16; P, 7.94. Found: C, 57.23; H, 4.34; Br, 10.19; Cl, 13.89; Fe, 6.60; P, 8.12.

Triphenylphosphonium Methylenetriphenylphosphorane Chloride (7). Method A.—Small pieces of potassium (1.75 g., 45 mmoles) were added to 100 ml. of dry diglyme and the mixture was heated to 150°. Methylenebis(triphenylphosphonium bromide) (14.0 g., 20 mmoles) was quickly added. The solution slowly turned orange during a 1-hr. reflux period. The solution was filtered while hot in a dry, nitrogen atmosphere. Hydrochloric acid (0.1 *N*, 150 ml.) was added to the orange filtrate containing hexaphenylcarbodiphosphorane. An immediate decoloration of the solution took place. The colorless solution was extracted with 100 ml. of chloroform. The chloroform layer was separated, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to yield 6.05 g. of a white solid, m.p. 224–230°. The solid was extracted with 150 ml. of hot ethyl acetate, washed with 100 ml. of ether, and extracted with 100 ml. of hot benzene to yield 3.9 g. of white solid, m.p. 224–235° (positive Beilstein test). This material was thoroughly mixed with 100 ml. of water, filtered, and dried to yield 1.03 g. (14%) of the white product, m.p. 267–272°. Recrystallization from methylene chloride–ether raised the melting point to 274–276°.

Anal. Calcd. for $C_{37}H_{31}ClP_2$: C, 77.55; H, 5.45; Cl, 6.91; P, 10.89. Found: C, 77.69; H, 5.48; Cl, 6.81; P, 10.84.

Method B.—To a stirred solution of 1.38 g. (13 mmoles) of sodium carbonate in 15 ml. of water, was added 1.38 g. (2.3 mmoles) of methylenebis (triphenylphosphonium chloride) monohydrate. The suspension was refluxed for 2.5 hr., and the oily mixture cooled to room temperature. The resulting crystals were filtered and washed with water to give 1.24 g. of crude product, m.p. 266–268°. Reprecipitation from methylene chloride–hexane gave raised m.p. 271.5–273° and yielded 0.96 g. (75%) of a white solid which had an infrared spectrum identical with that of the product of method A. A mixture melting point showed no depression.

Triphenylphosphonium Methylenetriphenylphosphorane Chloride–Ferric Chloride Complex.[11] **Method A.**—A mixture of methylene chloride (85.0 g., 1.0 mole) and triphenylphosphine (262.0 g., 1.0 mole) was heated with agitation for 6 hr. at 160° in a 316 stainless steel pressure vessel. After cooling, the viscous green material was partially extracted from the bomb with 850 ml. of hot methanol to give a suspension of red-gold needles in a green solution. The residual green tar was completely removed from the bomb by the addition of 360 ml. of hot methylene chloride to yield a green solution. Evaporation of the solution gave a mixture of red-gold crystals and a green solid. The green solid was extracted from the red-gold crystals with six 50-ml. portions of methanol. The two crops of red-gold crystals were combined yielding 51.9 g. (70 mmoles) of the complex, m.p. 238–239°. Recrystallization from methanol did not change the melting point.

Anal. Calcd. for $C_{37}H_{31}Cl_4FeP_2$: C, 60.44; H, 4.25; Cl, 19.29; Fe, 6.92; P, 8.42. Found: C, 60.77; H, 4.43; Cl, 19.10; Fe, 7.06; P, 8.27.

Method B.—Ferric chloride was stirred with triphenylphosphonium methylenetriphenylphosphorane chloride in methylene chloride. Filtration and evaporation of the solvent gave light gold-colored crystals. Recrystallization from absolute ethanol gave gold-colored crystals, m.p. 237.5–238.5°, which gave no melting point depression when mixed with the material from method A.

Triphenylphosphonium Methylenetriphenylphosphorane Iodide (9). Method A.—To a solution of 8.50 g. (51.2 mmoles) of potassium iodide in 125 ml. of absolute methanol was added 3.00 g. (4.87 mmoles) of triphenylphosphonium methylenetriphenylphosphorane bromide.

The solution was refluxed for 2 hr. and cooled to room temperature. Water (2.5 l.) was added and the resulting white precipitate was filtered in the dark. After drying at 25° (0.5 mm.), 3.1 g. (96%) of light yellow solid, m.p. 252–254°, was obtained. This compound showed a positive Beilstein test and a depressed melting point (250–259°) with starting material. Reprecipitation from methylene chloride–hexane gave light yellow crystals, m.p. 253–254°, λ_{max}^{EtOH} 268 mμ (ε 7775).

Anal. Calcd. for $C_{37}H_{31}IP_2$: C, 66.87; H, 4.70; I, 19.10; P, 9.32. Found: C, 67.19; H, 4.69; I, 18.97; P, 9.41.

Method B.—Methylenebis(triphenylphosphonium iodide) (0.93 g., 1.2 mmoles) was added to a solution of sodium carbonate (0.71 g., 6.7 mmoles) in 10 ml. of water and the suspension was stirred under reflux for 3 hr. The oily mixture was cooled to room temperature. Filtration yielded 0.72 g. of pale yellow solid, m.p. 250–254°. Recrystallization from methanol gave 0.36 g. (45%) of pale yellow crystals, m.p. 252–255°. A mixture melting point with an authentic sample was not depressed. The infrared spectrum of the sample was identical with the product of method A.

Triphenylphosphonium Methylenetriphenylphosphorane Triiodide (10).—A solution of 12.0 g. (18.1 mmoles) of triphenylphosphonium methylenetriphenylphosphorane iodide in 150 ml. of chloroform was added dropwise to a stirred solution of 4.59 g. (18.1 mmoles) of iodine in 450 ml. of chloroform during a 12-min. period. The reaction mixture gradually changed from a purple to a dark brown color. The solution was stirred for an additional 30 min., then evaporated *in vacuo* to yield 15.4 g. of brown solid. The solid was extracted with 500 ml. of hot methanol, leaving 12.9 g. (77%), of brown product, m.p. (color change at 174°) 193–196°. Recrystallization from methanol gave brown needles, m.p. 199–199.5°.

Anal. Calcd. for $C_{37}H_{31}I_3P_2$: C, 48.39; H, 3.40; I, 41.46; P, 6.75. Found: C, 48.47; H, 3.56; I, 41.38; P, 7.01.

Triphenylphosphoniumtriphenylboronyl Methylenetriphenylphosphorane (11).—Hexaphenylcarbodiphosphorane was prepared from triphenylphosphonium methylenetriphenylphosphorane bromide (17.3 g., 28 mmoles) and 1.40 g. (36 mmoles) of potassium in 150 ml. of dry diglyme.[2] The yellow-orange solution was filtered while hot in a dry nitrogen atmosphere. To the stirred filtrates at reflux (under nitrogen) was slowly added a solution of 7.5 g. (32 mmoles) of triphenylboron in 150 ml. of dry diglyme. During the 4.5-hr. reflux period, the orange turbid solution became brown. The solvent was removed at reduced pressure, 5 ml. of methanol was added to the residue, and the resulting buff-colored solid was filtered. After extracting this material with boiling ether for 30 min., 3.2 g. (17%) of the inner salt, m.p. 241–248° (negative Beilstein test), was obtained. Recrystallization in the presence of activated charcoal from methylene chloride–ethyl acetate gave off-white crystals, m.p. 254–256°, $\lambda_{max}^{CH_3CN}$ 267 mμ (ε 9440).

Anal. Calcd. for $C_{55}H_{45}BP_2$: C, 84.83; H, 5.82; B, 1.39; P, 7.96; mol. wt., 779. Found: C, 85.12; H, 5.88; B, 1.46; P, 7.42; 7.79; mol. wt., 725.

Triphenylphosphonium Methylenetriphenylphosphorane Tetraphenylboron (12).—To 175 ml. of hot distilled water was added 12.7 g. (20.6 mmoles) of triphenylphosphonium methylenetriphenylphosphorane bromide and 7.0 g. (20.5 mmoles) of sodium tetraphenylboron. The suspension was refluxed for 4 hr., cooled to room temperature, and filtered. The resulting white powder was dissolved in 150 ml. of methylene chloride and the solution was dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a white solid which was dried at 25° (0.1 mm.) to yield 18.4 g. of product, m.p. 200–205°. One recrystallization from acetone–ether in the presence of activated charcoal gave 13.6 g. (78%) of white crystals, m.p. 205–208°, $\lambda_{max}^{CH_3CN}$ 267 mμ (ε 10,800).

Anal. Calcd. for $C_{61}H_{51}BP_2$: C, 85.50; H, 6.00; B, 1.26; P, 7.23. Found: C, 85.33; H 6.09; B, 0.97; P, 7.40.

Triphenylphosphonium Methylenetriphenylphosphorane Fluoborate (13). Method A.[12]—To a stirred mixture of 8.76 g. (12.5 mmoles) of methylenebis(triphenylphosphonium bromide) in 300 ml. of dry ether under a nitrogen atmosphere at 0°, was slowly added 7.5 ml. of *n*-butyllithium in hexane (12.5 mmoles). Boron trifluoride etherate (36.0 g., 250 mmoles) was added dropwise to the suspension. An additional 12.5 mmoles of *n*-butyllithium was then added, and the white suspension was warmed to room temperature and stirred for an additional 3 hr. The mixture yielded 10.5 g. of white solid which was dissolved in 500 ml. of a 2:3 methylene chloride–water mixture. The organic layer was separated and dried over magnesium sulfate. Evaporation of the filtrates *in vacuo* gave white crystals (6.5 g. 83%). Recrystallization from absolute ethanol gave white needles, m.p. 259.5–260.5°, λ_{max}^{EtOH} 267 mμ (ε 7360).

Anal. Calcd. for $C_{37}H_{31}BF_4P_2$: C, 71.17; H, 5.00; B, 1.73; F, 12.17; P, 9.92. Found: C, 71.52 H, 5.55; B, 1.51; F, 11.98; P, 10.04.

Method B.—To a solution of 3.56 g. (32.4 mmoles) of sodium fluoroborate in 75 ml. of water was added 2.00 g. (3.24 mmoles) of triphenylphosphonium methylenetriphenylphosphorane bromide. The mixture was refluxed for 65 min. and filtered hot. The resulting solid, 1.94 g. (96%), m.p. 242.5–250°, showed a negative Beilstein test and a melting point depression with starting material. Recrystallization from absolute ethanol produced white needles, m.p. 253–257°, which showed no melting point depression on admixture with the product from method A.

Triphenylphosphonium Methylenetriphenylphosphorane Borohydride (14).—Triphenylphosphonium methylenetriphenylphosphorane bromide (10.0 g., 16 mmoles) was added to a stirred, freshly prepared solution of 6.35 g. (170 mmoles) of sodium borohydride in 500 ml. of methanol. After 5 min., the clear solution was added to 3 l. of distilled water, resulting in the precipitation of the product. The suspension was stirred for 5 min. and filtered. The white solid was washed with 250 ml. of distilled water and dried at 80° (15 mm.). The white powder,

(11) The acidic diphosphonium salt (4-anhydrous), a proposed intermediate in this reaction, apparently attacked the stainless steel reactor to produce ferric chloride and **7** which combined to form a complex.

(12) This unexpected synthesis of **13** occurred during an attempt to prepare the boron trifluoride analog of **11**.

8.46 g. (96%), m.p. 210–211° dec., was recrystallized from ethanol–ether to give white needles, m.p. 211–211.5° dec., λ_{max}^{EtOH} 267 mμ (ε 7840).

Anal. Calcd. for $C_{37}H_{35}BP_2$: C, 80.44; H, 6.39; B, 1.96; P, 11.21. Found: C, 80.87; H, 6.34; B, 1.67; P, 11.26.

Acknowledgment.—We wish to thank J. E. Strobel, R. H. Campbell, M. H. Landon, W. T. Cave, and W. S. Coakley for assistance in the spectroscopic investigations.

Reactions of 3-Bromooxindoles. The Synthesis of 3-Methyleneoxindole[1]

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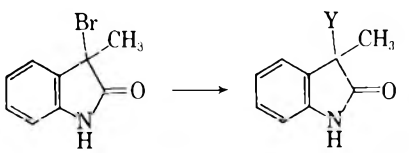
3-Alkyl-3-bromooxindoles underwent facile replacement of the halogen by nucleophiles, including alkoxide, hydroxide, and thiophenoxide ions, and piperidine. With 3-bromooxindole-3-propionic and butyric acids lactone formation took place in the presence of base, but oxindole-3-acetic acid underwent decarboxylation and dehydrobromination to 3-methyleneoxindole. The last compound readily underwent conjugate addition with thiophenol and amines. From hydrolysis of 3-bromooxindole-3-butyric acid in acidic media, the free dioxindole acid was obtained rather than the lactone. Some lactone was obtained from dioxindole-3-propionic acid, but again lactonization under acidic conditions did not take place readily. Attempts to hydrolyze 3-bromooxindole-3-acetic acid to dioxindole-3-acetic acid, under acidic conditions, were unsuccessful. The ultraviolet, infrared, and proton magnetic resonance spectra of a variety of oxindoles and dioxindoles are tabulated and discussed.

In a previous paper a convenient one-step synthesis of 3-bromooxindoles by reaction of the corresponding indoles with N-bromosuccinimide (NBS) was described.[2] The ready accessibility of the 3-bromooxindoles by this new method has led to a study of some aspects of their chemistry, with particular attention to the reactions of the 3-bromooxindole-3-alkanoic acids,[3] and some of the compounds derived therefrom.

Although the 3-bromooxindoles are stable crystalline compounds, the bromine, activated by the adjacent phenyl and carbonyl groups, is very reactive. A precipitate is formed with alcoholic silver nitrate within 3 sec. at room temperature, and replacement of the halogen by nucleophilic agents occurs with ease.[4] Sub-



I IIa, Y = OH; b, Y = OCH_3; c, Y = SC_6H_5; d, Y = NC_5H_{10} (1)

stitution has been effected by nucleophiles of the oxygen, sulfur, and nitrogen series, as shown in eq. 1. 3-Methyldioxindole was also prepared in one over-all step from skatole by addition of sodium bicarbonate to the reaction mixture after formation of I, and treatment of 3-methyloxindole with bromine followed by hydrolysis *in situ* gave 5-bromo-3-methyldioxindole. Structures of the products (II) were confirmed by n.m.r., which showed in all cases a singlet of the proper intensity for the 3-methyl group (Table II). No evidence was found for the presence of the isomeric 3-methylene derivatives, such as 3-(phenylthiomethyl)oxindole (XIII), which could conceivably have been formed by elimination, followed by addition of the nucleophile to the resulting conjugated system (X). In the one case for which both isomers were available (IIc and XIII), they were readily distinguishable by n.m.r. and by the reactivity of isomer XIII towards base (see below).

Intramolecular nucleophilic displacement by carboxylate ion in the side chain at the 3-position was also observed. In basic solution both 3-bromooxindole-3-propionic acid (IIIa) and 3-bromooxindole-3-butyric acid (IIIb) underwent ring closure to the corresponding lactones (IV). Reference has been made in the previous paper[2] to the direct conversion of indole-3-propionic acid to the lactone IVa by reaction with NBS in the presence of sodium bicarbonate and to the formation of the closely related lactone of α-acetamidodioxindole-3-propionic acid under similar conditions. Since basic conditions promote 3-bromination of an oxindole, reaction of an indole with NBS in a basic hydrolytic medium might serve as a general synthetic route to dioxindoles, similar to the reactions of hypochlorite and lysergic acid derivatives.[2,5,6]

In contrast to the facile lactonization effected by base, hydrolysis of the 3-bromooxindole-3-alkanoic acids (IIIa and IIIb) under acidic conditions, which repress ionization of the carboxyl group, led to the corresponding dioxindole-3-alkanoic acids (VI). Although some lactone was formed along with the dioxindole in the propionic acid case, dioxindole-3-butyric acid was the sole product (76% yield) from IIIb. The reluctance of the dioxindole acids to undergo ring closure was further demonstrated by the following reactions. The dioxindolebutyric acid (VIb) was recovered unchanged after (1) 1 hr. in refluxing 0.05 *M* hydrochloric acid, (2) 30 min. in refluxing glacial acetic acid, or (3) 1 hr. in acetic anhydride at 60°. Ring closure was effected by re-

(1) Presented in part before the Organic Division of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2) R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, **29**, 1206 (1964).

(3) Other methods for preparing 3-bromooxindoles are mentioned in ref. 2. It should be noted in addition that replacement of the dioxindole hydroxyl by reagents such as thionyl chloride is apparently a satisfactory route to 3-halooxindoles [J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 4789 (1957); see also P. L. Julian, E. W. Meyer, and H. C. Printy "Heterocyclic Compounds," Vol. III, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 247], which has not been used extensively.

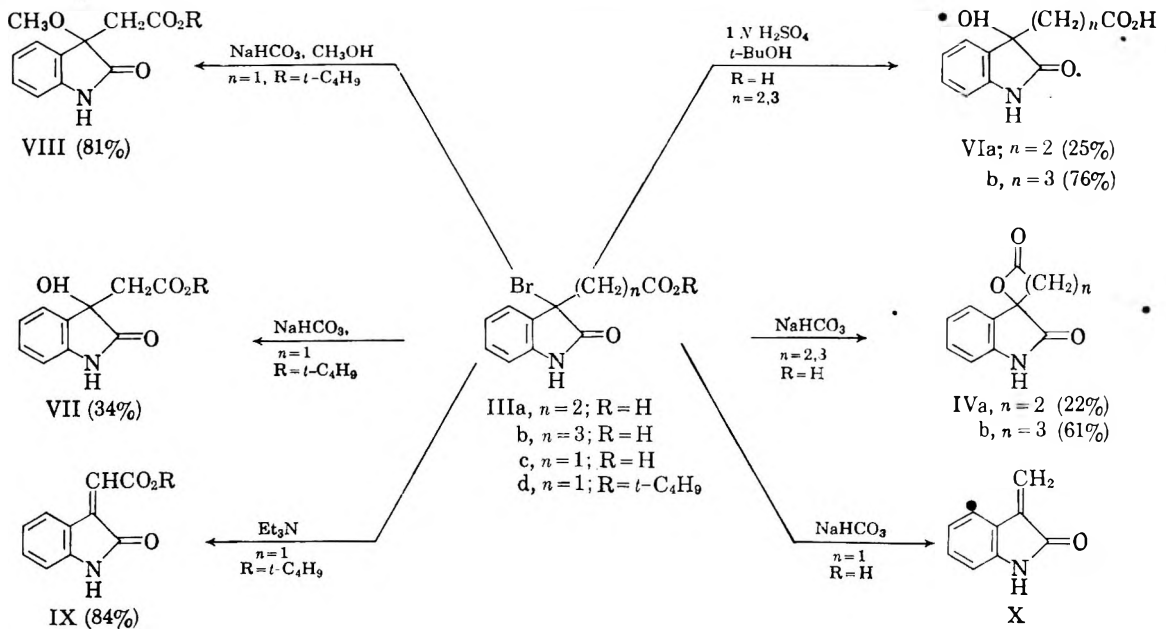
(4) A few examples of hydrolysis of 3-halooxindoles have been reported, including the conversion of 3,3-dihalooxindoles to isatin derivatives [E. Fisher and O. Hess, *Ber.*, **17**, 559 (1884); A. Michaelis, *ibid.*, **30**, 2811 (1897)] and replacement of the 3-halogen by alkoxide as reported by Bruce and Sutcliffe[3] for 3-chloro-3-phenyloxindole.

(5) F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **42**, 793 (1959).

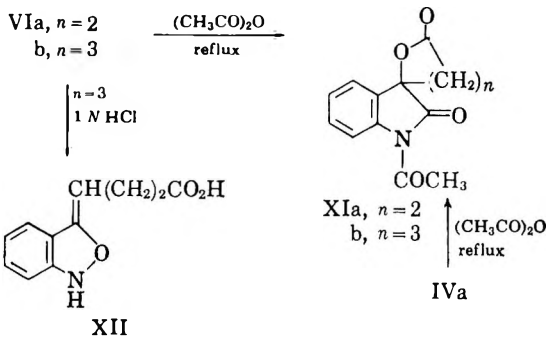
(6) The previous paper[2] should be consulted for a discussion of the effect of the medium on the mode of bromination of oxindoles.

CHART I

REACTIONS OF 3-BROMOOXINDOLES



fluxing VIb with acetic anhydride, which gave N-acetyldioxindole-3-butyric acid lactone (XIb) in 75% yield. When VIb was treated with 1 *N* hydrochloric acid for 2 days, including 1 hr. under reflux, a compound with the spectral characteristics of 3-ethylideneoxindole (Table I) was obtained. Isolation of material of this type, presumably XII, indicates that dehydration is preferred to ring closure.



The dioxindolepropionic acid (VIa) cyclized somewhat more readily, as would be expected for formation of a five-membered ring,[7] but even after 4 days at room temperature in 0.2 *M* sulfuric acid in *t*-butyl alcohol only 30% of the lactone (IVa) was isolated and an equal quantity of starting material was recovered. Refluxing acetic anhydride converted VIa to XIa, which was also prepared by acetylation of the lactone IVa.

Although at first sight the resistance of the dioxindole acids to ring closure[8] appeared unusual in view of the facile ring closure of γ- and δ-hydroxy acids of simpler structure, examination of the literature disclosed that a carboxyl adjacent to the hydroxyl inhibits lactonization. Thus, α-hydroxyadipic acid was obtained from its diester by boiling for 10 hr. with concentrated hydrochloric acid.[9] Possibly the electron density of the hydroxyl group is reduced sufficiently by the adjacent carbonyl group to make it relatively unreactive. No evidence of strain or steric hindrance was found in molecular models of the spirolactones (IV).

Attempts to prepare the unknown dioxindole-3-acetic acid by acidic hydrolysis of 3-bromooxindole-3-acetic acid were unsuccessful. A tetrahydropyranyl ester of IIIc was prepared and hydrolyzed by bicarbonate to the dioxindole, but surprisingly, the ester could not be cleaved by acid even under forcing conditions.[10]

In contrast to the behavior of its higher homologs, 3-bromooxindole-3-acetic acid (IIIc) on treatment with base underwent conversion to 3-methyleneoxindole (X)[10] by a process of decarboxylation and dehydrobromination like that which is characteristic of the structurally related β-halo-β-phenylpropionic acids.[11]

The decomposition of 3-bromooxindole-3-acetic acid was more rapid in water than in ethanol and was essentially instantaneous when base-catalyzed. By contrast, *t*-butyl 3-bromooxindole-3-acetate (IIId) reacted with water and with methanol to yield *t*-butyl dioxindole-3-acetate (VII) and *t*-butyl 3-methoxyoxindole-3-acetate (VIII), respectively. In ether in the presence of triethylamine, *t*-butyl isatylidene-3-acetate (IX) was formed.

Although it is unstable in concentrated solutions, we have succeeded in isolating 3-methyleneoxindole as a

(7) E. L. Eliel, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 116.

(8) Dioxindole-3-propionic acid has been known for some time as a stable substance with no tendency to undergo lactone formation in the presence of acid [P. L. Julian, H. C. Printy, and E. E. Dailey, *J. Am. Chem. Soc.*, **78**, 3501 (1956)], while a closely related malonic acid did readily lactonize [P. L. Julian, E. E. Dailey, H. C. Printy, H. L. Cohen, and S. Hamashige, *ibid.*, **78**, 3503 (1956)]. N-Benzyldioxindole-3-propionic acid has been converted to its lactone by refluxing glacial acetic acid, but the free acid did not lactonize spontaneously [G. Hallmann, *Ber.*, **95**, 1138 (1962)].

(9) C. K. Ingold, *J. Chem. Soc.*, **119**, 305, 951 (1921).

(10) Dioxindole-3-acetic acid is a possible intermediate in the enzymatic oxidation of the plant growth hormone indole-3-acetic acid to 3-methyleneoxindole [R. L. Hinman, C. P. Bauman, and J. Lang, *Biochem. Biophys. Res. Commun.*, **5**, 250 (1961)]. Its synthesis by base-catalyzed reaction of dioxindole and chloroacetic acid was also unsuccessful, though this procedure has been used by Hallmann[3] for preparation of the derived ester and nitrile.

(11) H. H. Wasserman, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 364 ff.

TABLE I

SPECTRAL CHARACTERISTICS OF 3-SUBSTITUTED OXINDOLES

No.	Compound	Ultraviolet absorption. $\lambda_{max}^{95\%\ EtOH}$, mμ (ε)				Infrared absorption, μ (KBr) NH region		C=O region	
1	3-Methyloxindole[a]	207 (27,400)	249 (8720)	278 sh (1440)			3.15	5.85	5.97
2	3-Methyldioxindole	208 (32,500)	252 (6450)	287 (1350)		2.94	3.13	5.80 sh	5.85
3	3-Methoxy-3-methyloxindole	208 (24,400)	252 (6350)	289 (1390)			3.02	5.72	5.83
4	3-Bromo-3-methyloxindole[a]	217 (16,900)	229 sh (13,400)	310 (940)			3.12	5.76	5.91
5	5-Bromo-3-methyloxindole[a]	207 (25,000)	254 (12,200)	288 sh (1290)			3.09	5.78	5.98
6	6-Bromo-3-methyloxindole[a]	213 (37,200)	254 (7130)	285 (1960)	293 sh (1540)		3.14	5.83	5.91 sh
7	5-Bromo-3-methyldioxindole	209 (29,400)	258 (10,900)	296 (1420)			3.07	5.79 sh	5.87
8	3-Methyl-3-(phenylthio)-oxindole	207 (23,600)	230 sh (17,400)	287 sh (1590)	258 sh (16,200)		3.12	5.78	5.95
9	3-(Phenylthiomethyl)-oxindole[b]	213 (28,000)	251–252 (14,700)	285 sh (2540)			3.17	5.89	
10	3-Methyl-3-(N-piperidino)-oxindole	207 (31,400)	249 (7700)	282 sh (1640)			3.18	5.86 sh	5.91
11	3-(β-Aminoethyl)oxindole hydrobromide[a]	207 (27,000)	249 (8250)	280 sh (1420)			3.14	5.86 sh	5.91
12	3-(β-Benzamidoethyl)-oxindole[a]	230 (14,900)		280 sh (1800)			3.04	5.92	
13	Oxindole-3-acetic acid[a]	205 (27,600)	247 (8790)	280 sh (1480)			3.01–3.12	5.85	5.90
14	Oxindole-3-propionic acid[a]	207	250 (8500)	280 sh (1400)			3.03	5.77–5.81	5.92
15	Oxindole-3-butyric acid[a]	206 (26,500)	250 (8430)	281 sh (1410)			3.07	5.80	6.00
16	Dioxindole-3-propionic acid	209 (26,500)	251–252 (6090)	288 (1370)		2.88	3.08	5.80 5.91 sh	5.95
17	Dioxindole-3-butyric acid	208 (31,300)	253 (5940)	288 (1350)		2.96	3.08	5.70	5.90
18	3-Bromooxindole-3-acetic acid[a,c]	220 (18,400)	235 sh (13,300)	320 (1000)			3.08	5.75	5.94
19	3-Bromoxindole-3-butyric acid[a]	217 (16,690)	227 sh (14,110)	310 (1000)			3.14	5.80	5.96
20	5-Bromooxindole-3-butyric acid[a]	207 (27,900)	255 (13,000)	290 sh (1310)			3.12	5.74	5.93
21	t-Butyl 3-bromooxindole-3-acetate[a]	218 (15,900)	231 sh (13,500)	317 (880)			3.13	5.77	5.87
22	t-Butyl dioxindole-3-acetate	209 (27,400)	253 (6140)	291 (1400)		2.91 sh 2.99	3.09	5.79	5.96
23	t-Butyl 3-methoxyoxindole-3-acetate	208 (27,600)	253 (5620)	293 (1360)			3.15	5.79	
24	Dioxindole-3-propionic acid lactone	209 (33,500)	253 (4990)	297 (1460)			3.08	5.56, 5.75	
25	Dioxindole-3-butyric acid lactone	208 (31,200)	253 (5680)	292 (1510)			3.13	5.72	5.81
26	α-Acetamido-(dioxindole-3)-propionic acid lactone[a]	d	254 (4780)	298 (1460)		3.01	3.14	5.55, 5.74	6.00
27	3-Methyleneoxindole	d	248 (23,500) 254 (23,500)	289 (2760)			3.13	5.80 5.85	6.09
28	3-Ethylideneoxindole	d	246 (26,800) 249 (26,700)	255 (31,900) 287 (4420)			3.14	5.84 5.87	6.04
29	3-Isopropylidene oxindole	d	250–254 (27,200) 260 (32,000)	291 (6580)			3.17		5.92 6.14
30	t-Butyl isatylidene-3-acetate	d	252 (22,700) 257 (20,900)	312 (7220)			3.14	5.77 5.84	6.07
31	N-Acetyldioxindole-3-propionic acid lactone	219 (15,800)	231 sh (11,400)	275 sh (500)				5.60 5.67 5.84	
32	N-Acetyldioxindole-3-butyric acid lactone	218 (15,200)	232 sh (11,400)	275 sh (500)				5.70 5.81	

[a] Preparation given in ref. 2. [b] Solvent was dioxane. [c] Solvent was ether. [d] Not measured in this region.

yellow solid of about 90% purity [determined by comparison of the ultraviolet absorption spectrum of an isolated and redissolved sample with that of a solution prepared by decomposing pure IIIc at spectrophotometric concentrations ($\sim 10^{-5}$ *M*)]. In color, ultraviolet spectrum and infrared spectrum, it resembles the known, stable 3-ethylidene- and 3-isopropylideneoxindoles,[10] including the >C=C< band near 6.10 μ in the infrared (Table I). It has been further characterized by the addition of sodium bisulfite or hydrosulfite to its aqueous solutions, an operation which is accompanied by a rapid change of the ultraviolet spectrum to that of a simple oxindole, presumably 3-(β-sulfomethyl)oxindole.[10] 3-Ethylidene- and 3-isopropylideneoxindole were also converted to compounds with oxindolic absorption spectra when treated with aqueous bisulfite. At spectrophotometric concentrations, the reaction with 3-methyleneoxindole was instantaneous, whereas

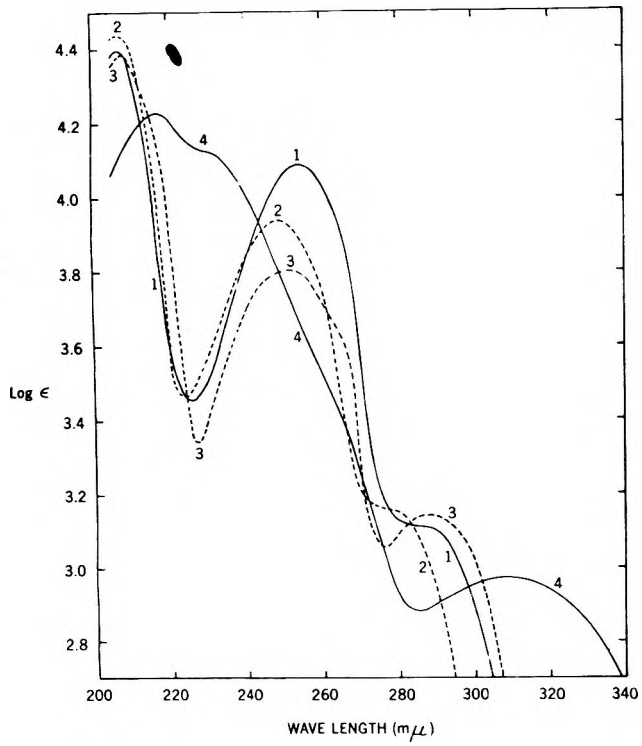
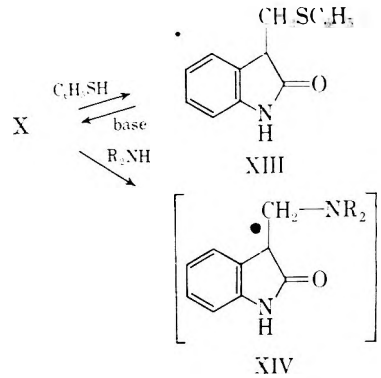


Fig. 1.—Ultraviolet spectra of 3-methyloxindole derivatives in 95% ethanol: 1, 5-bromo-3-methyloxindole; 2, 3-methyloxindole; 3, 3-methoxy-3-methyloxindole; 4, 3-bromo-3-methyloxindole.

reactions of the two higher homologs were complete in 5–10 min. and about 2.5 hr., respectively.[12]

Solid 3-methyleneoxindole underwent no appreciable change during prolonged periods of storage, and the ultraviolet spectra of its solutions in aqueous or ethanolic media underwent very little change over a 24-hr. period if the concentration of methyleneoxindole was 10^{-4} M or less. At concentrations above 10^{-2} M, however, its solutions in a variety of solvents rapidly deposited a high-melting white solid, probably a dimer or higher polymer of 3-methyleneoxindole. The ultraviolet spectrum of this material was that of a simple oxindole while the existence of two peaks near 3 μ in the infrared correspond to those of the OH and NH of a dioxindole (Table I). In these respects it resembled the material obtained in earlier attempts to carry out the Mannich reaction with oxindole,[12-14] in which 3-methyleneoxindole was presumably formed. Melting points of different preparations of the amorphous solid varied considerably, and elemental analyses indicated products containing 1 mole of water/unit of X. Similar spectral and analytical properties were found in products from oxindole and formaldehyde. Products of Diels–Alder dimerization of X analogous to those derived from 2-methylenecyclohexanone,[15] are ruled out by the analysis and the requirement that they contain an indolic chromophore.

As would be expected from its behavior with bisulfite, 3-methyleneoxindole is reactive towards nucleophiles generally. For example, it reacted smoothly with thiophenol in the presence of a trace of piperidine, a reaction which has been observed with other 3-alkylideneoxindoles,[16] yielding 3-(phenylthiomethyl)oxindole (XIII), isomeric with IIc. This product was very sensitive to base and at spectrophotometric concentrations was easily reconverted to 3-methyleneoxindole.



The success of this reaction prompted us to re-examine the problem of the preparation and stability of Mannich bases of oxindole. Although Mannich bases derived from 3-alkyloxindoles are well known,[17] the few attempts[12,13] to prepare these derivatives of oxindole itself have led invariably to amorphous material of the type described above from the spontaneous reaction of 3-methyleneoxindole. Our experiments with compound XIII indicate that a Mannich base would not survive the treatment with a strong base used in the isolation procedures. Accordingly, we have attempted to prepare Mannich bases derived from oxindole by the reaction of 3-methyleneoxindole with a variety of amines, including piperidine and N-methylaniline, with and without a trace of acid present. In all cases the characteristic double-spiked maximum near 250 mμ in the ultraviolet absorption spectrum of 3-methyleneoxindole[10] was replaced by a spectrum characteristic of a simple oxindolic chromophore. Despite considerable care in working up the reaction mixtures, however, no product corresponding to a Mannich base (XIV) could be isolated. Since the products themselves are amines, they may catalyze their own decomposition. These results do indicate, however, that Mannich bases derived from oxindole can exist in solution and they suggest that, by the proper choice of amine, it may be possible to isolate certain members of the class.

A few experiments were also carried out in attempts to prepare the Mannich bases directly from oxindole itself using milder conditions than those of the earlier work. The ultraviolet spectra showed that transformation to a new oxindole had occurred in the reaction mixture, but again no simple product could be isolated.

Spectral Characteristics of Oxindoles.—In the course of the work described in this paper and the preceding one[2] the spectra of a wide variety of oxindoles and di-

(12) The reaction of sodium bisulfite with 3-methoxymethylene-1-methyloxindole can also be explained by addition to the exocyclic double bond. It has been suggested that the product is simply a complex with the inorganic salt [E. Wenkert, A. K. Bose, and T. L. Reid, *J. Am. Chem. Soc.*, **75**, 5514 (1953)], but it seems more likely from our experiments that bisulfite addition to this class of α,β-unsaturated carbonyl compounds is a general reaction.

(13) (a) H. Hellmann and E. Renz, *Ber.*, **84**, 901 (1951); (b) E. Wenkert, J. H. Udelhofen, and N. K. Bhattacharyya, *J. Am. Chem. Soc.*, **81**, 3763 (1959).

(14) A dimer of 3-methyleneoxindole was also reported by L. Horner [*Ann.*, **548**, 117 (1941)], but, since the melting point of the starting material, originally presumed to be oxindole-3-acetic acid, agrees in fact with that of 3,4-dihydroquinolone-3-carboxylic acid, this result must be disregarded.

(15) For leading references, see H. O. House, *J. Org. Chem.*, **26**, 2190 (1961).

(16) T. Wieland and O. Unger, *Ber.*, **96**, 253 (1963).

(17) E. C. Horning and M. W. Rutenberg, *J. Am. Chem. Soc.*, **72**, 3534 (1950).

oxindoles have been determined. These data are summarized in Table I.[18] A point of particular interest in the ultraviolet spectra is the absorption at low wave length (near 208 mμ) of oxindoles, which has not previously been pointed out. This peak is shifted to about 217 mμ by introduction of a bromine at the 3-position (Fig. 1), and the strong absorption here covers the usual oxindole absorption near 250 mμ; the band near 285 mμ is also shifted bathochromically. Oxygen (compound **2**, **3**, **7**, **14**, **15**, **16**, and **17**), nitrogen (**10**), or sulfur (**8**) at the 3-position does not particularly affect the peak at 208 mμ.[19] Acetanilide, which may be considered a parent of the oxindoles, shows peaks at 242 mμ (ε 14,400) and 280 mμ (ε 500), but lacks the peak near 208 mμ. It is interesting that the N-acetyloxindoles (**31** and **32**) show very marked differences from the parent molecules (**24** and **25**), lacking both the peaks at 208–209 and 253 mμ.[3] In this respect the spectra resembled those of the 3-bromooxindoles, but the peak positions at highest wave length do not correspond.

In the infrared spectra, the splitting of the carbonyl peak, observed previously in simple oxindoles,[20] has been noted in a number of examples (**1**–**10**), and appears to be a general effect. In dioxindoles the OH and NH peaks were clearly distinguishable at about 2.95 and 3.1 μ, respectively (**2**, **11**, and **15**).

The n.m.r. spectra of 3-methyloxindole and its 3-bromo derivative are compared with that of skatole (Table II). The proton resonances show the expected relationship.

TABLE II

N.M.R. SPECTRA OF OXINDOLES[a]

Compound	CH_3	NH	Aromatic	CH at C-3
Skatole[b]	7.70		2.82	
3-Methyloxindole[c]	8.45, 8.57	−0.56	2.97	6.68[d]
3-Bromo-3-methyloxindole	7.93	1.24	3.13	
3-Methyl-3-(N-piperidino)oxindole	8.45		2.85[d]	
3-Methyl-3-(phenylthio)oxindole	8.26		2.76[d]	
3-(Phenylthiomethyl)-oxindole	[e]		2.60[d]	[e]

[a] Chemical shifts are given as τ-values (tetramethylsilane as internal standard). Data were obtained with a Varian A-60 magnetic resonance spectrometer. Solvent was deuteriochloroform except where noted otherwise. [b] Taken from L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960). [c] CCl_4. [d] Unresolved multiplet. [e] Complex pattern of at least seven principal lines from τ 6.1–6.9. Hydrogens of side-chain CH_2 are apparently nonequivalent.

Experimental[21]

3-Methyldioxindole (**IIa**).—A mixture of 1.00 g. (4.42 mmoles) of 3-bromo-3-methyloxindole and 0.371 g. (4.42 mmoles) of sodium bicarbonate in 25 ml. of water and 25 ml. of *t*-butyl alcohol was stirred at room temperature for 22 hr. The mixture was then extracted with three 15-ml. portions of ethyl acetate. The extract was dried over sodium sulfate and then concentrated under reduced pressure until a precipitate began to form. After standing overnight at −20°, 0.487 g. of white crystals of 3-methyldioxindole, m.p. 161–162°, were obtained (lit.[22] m.p. 159.5–160.5°). By concentration of the filtrate three additional crops totaling 0.121 g., m.p. 160–162°, were obtained, making the total yield of 3-methyldioxindole 84%.

3-Methoxy-3-methyloxindole (**IIb**).—A solution of 1.00 g. (4.42 mmoles) of 3-bromo-3-methyloxindole and 0.317 g. (4.42 mmoles) of sodium bicarbonate in a mixture of 10 ml. of water and 100 ml. of methanol was stirred at room temperature for 3 days. The solution was concentrated under reduced pressure until cloudy. After cooling, 0.41 g. of crystals, m.p. 121–123°, were collected by filtration. The filtrate was extracted with three 25-ml. portions of ethyl acetate. The extract was washed with saturated salt solution, dried over sodium sulfate, and evaporated. The residual oil was crystallized from an acetone–hexane mixture, yielding an additional 0.25 g. of product melting at 121–122°. The total yield of 3-methoxy-3-methyloxindole was 85%. An analytical sample was obtained as white crystals, m.p. 124.0–124.5° from an acetone–hexane mixture.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.87; H, 6.33; N, 7.88.

3-Methyl-3-(phenylthio)oxindole (**IIc**).—To a solution of 2.26 g. (0.01 mole) of 3-bromo-3-methyloxindole in 50 ml. of *t*-butyl alcohol was added 1.10 g. (0.01 mole) of thiophenol followed by 1.0 ml. of 10 *N* sodium hydroxide. After the mixture had been stirred for 15 min. at room temperature, the white solid that had formed was removed by filtration, and the filtrate was evaporated *in vacuo* at room temperature. The residue was taken up in 20 ml. of toluene, and hexane was added until a white precipitate began to form, which was removed by filtration. From the filtrate was obtained two crops of white crystals of 3-methyl-3-(phenylthio)oxindole, m.p. 151–158°, totaling 0.52 g., which when recrystallized from a mixture of methanol and water gave two crops (0.44 g.) of white crystals, m.p. 158–162°. An additional 0.78 g. of product, m.p. 160.0–161.5°, was obtained from the toluene–hexane mother liquor, giving a total yield of 1.22 g. (48%). An analytical sample, m.p. 161–62°, was obtained by recrystallization from methanol.

Anal. Calcd. for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.49; H, 5.03; N, 5.53; S, 12.36.

3-Methyl-3-piperidinooxindole (**IId**).—To a solution of 1.13 g. (0.005 mole) of 3-bromo-3-methyloxindole in 75 ml. of anhydrous ether was added 1.0 ml. (0.010 mole) of piperidine. The mixture was stirred at room temperature for 1.5 hr. Two crops of piperidine hydrobromide were removed by filtration. From the filtrate were obtained several crops of 3-methyl-3-piperidinooxindole, m.p. 155–160°, totalling 1.1 g. (91% yield). An analytical sample, m.p. 160–161°, was obtained by recrystallization from ether.

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.33; H, 8.24; N, 11.80.

***t*-Butyl Dioxindole-3-acetate** (**VII**).—Prepared from IIId[2] by the procedure used for 3-methyldioxindole, this compound melted at 149–149.5° after recrystallization from an acetone–hexane mixture.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 64.04; H, 6.68; N, 5.44.

***t*-Butyl 3-Methoxyoxindole-3-acetate** (**VIII**).—To a solution of 1.00 g. (3.06 mmoles) of *t*-butyl 3-bromooxindole-3-acetate[2] in 25 ml. of water and 5 ml. of methanol was added 0.257 g. (3.06 mmoles) of sodium bicarbonate. The mixture was stirred for 23 hr. at room temperature and then was concentrated under reduced pressure until crystallization began. The white crystals of *t*-butyl 3-methoxyoxindole-3-acetate, which were filtered and washed with water, weighed 0.69 g. (81%) and melted at 150–151°. An analytical sample, which was obtained by recrystallization from ethanol, then from an acetone–benzene mixture, and finally from an acetone–water mixture, melted at 152–153°.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.15; H, 7.13; N, 5.10.

***t*-Butyl Isatylidene-3-acetate** (**IX**).—A solution of 2.00 g. (6.12 mmoles) of *t*-butyl 3-bromooxindole-3-acetate[2] and 0.618 g. (6.12 mmoles) of triethylamine in 100 ml. of anhydrous ether was refluxed for 7 hr. and then stirred at room temperature for 48 hr. The cream-colored precipitate of triethylamine hydro-

(18) For an earlier discussion of ultraviolet and infrared absorption spectra of oxindoles and 3-alkylideneoxindoles, see ref. 12 and E. Wenkert, B. S. Bernstein, and J. H. Udelhofen, *J. Am. Chem. Soc.*, **80**, 4899 (1958).

(19) A bathochromic shift accompanying introduction of a chlorine at the 3-position of 3-phenyloxindole has been reported by Bruce and Sutcliffe.[3]

(20) A. E. Kellie, D. G. O'Sullivan, and P. W. Sadler, *J. Chem. Soc.*, 3809 (1956).

(21) Melting points and boiling points are uncorrected. Ultraviolet absorption spectra were determined with a Beckman DK-2 recording spectrophotometer, using quartz cells of 1-cm. light path. Infrared spectra were obtained with a Perkin-Elmer 21 recording spectrophotometer equipped with sodium chloride optics.

(22) A. S. Endler and F. I. Becker, *J. Am. Chem. Soc.*, **77**, 6608 (1955).

bromide was removed by filtration and washed with ether. The filtrate was evaporated under reduced pressure. The residue was dissolved in methylene chloride, and hexane was added to the saturation point. Orange crystals were obtained, which after recrystallization from cyclohexane gave 0.623 g. (42%) of *t*-butyl isatylidene-3-acetate, m.p. 133–134°. Since there was evidence of incomplete reaction, all materials from the reaction mixture, except the purified product, were treated with an additional 1.24 g. (12.2 mmoles) of triethylamine in 50 ml. of anhydrous ether. After stirring for 22 hr. at room temperature, the mixture was worked up as before. An additional 0.637 g. of product, m.p. 132–133°, was obtained giving a total yield of 1.26 g. (84%). An analytical sample, obtained as orange needles by recrystallization from cyclohexane, melted at 134–135°.

Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.99; H, 6.35; N, 5.83.

5-Bromo-3-methyldioxindole.—Bromine was added to a solution of 0.29 g. (0.002 mole) of 3-methyloxindole in 13 ml. of *t*-butyl alcohol until an orange-yellow color persisted. After 3 hr. the solvent was removed by evaporation at room temperature and the residue was stirred with a mixture of 10 ml. of water and 10 ml. of *t*-butyl alcohol for 3 days. The solution was concentrated *in vacuo* until precipitation began. Cream-colored crystals, m.p. 240–242° (70 mg., 14%), of 5-bromo-3-methyldioxindole were obtained. An analytical sample, m.p. 241–242.5°, was obtained by recrystallization from 95% ethanol.

Anal. Calcd. for $C_9H_8BrNO_2$: C, 44.66; H, 3.33; Br, 33.01; N, 5.79. Found: C, 44.43; H, 3.00; Br, 33.01; N, 5.80.

Dioxindole-3-butyric Acid Lactone (IVb).—A solution of 1.00 g. (3.36 mmoles) of 3-bromooxindole-3-butyric acid and 0.565 g. (6.72 mmoles) of sodium bicarbonate in a mixture of 25 ml. of water and 55 ml. of methanol was stirred for 2 hr. at room temperature, then acidified to pH 2 with dilute hydrochloric acid, and concentrated under reduced pressure until a precipitate began to form. Two crops of crystals of dioxindole-3-butyric acid lactone were collected, totaling 0.45 g. (61%), m.p. 132–134°. An analytical sample, obtained by recrystallization from water, melted at 134–135°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.12; N, 6.45. Found: C, 65.97; H, 5.16; N, 6.63.

Dioxindole-3-butyric Acid (VIb).—A solution of 2.00 g. of 3-bromooxindole-3-butyric acid in a mixture of 4 ml. of 3 *M* sulfuric acid and 20 ml. of *t*-butyl alcohol (final acid concentration = 0.5 *M*) was stirred for 8 days at room temperature. The solution was diluted with 10 ml. of water, concentrated under reduced pressure until the mixture became cloudy, and then was extracted with three 25-ml. portions of ethyl acetate. The extract was evaporated, and the residue was crystallized from an acetone–benzene mixture. Several crops of dioxindole-3-butyric acid were obtained totaling 1.20 g. (76%), m.p. 169–173°. An analytical sample, m.p. 172–173°, was obtained by recrystallization from an acetone–benzene mixture.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.58; H, 5.53; N, 6.42.

N-Acetyldioxindole-3-butyric Acid Lactone (XIb).—A solution of 0.50 g. (2.13 mmoles) of dioxindole-3-butyric acid in 3 ml. of acetic anhydride was refluxed for 2.5 hr. The solution was diluted with 12 ml. of water and cooled. The solid which formed was recrystallized from an acetone–water mixture, yielding 0.414 g. (75%) of N-acetyldioxindole-3-butyric acid lactone, m.p. 148–151°. An analytical sample obtained by recrystallization from an acetone–water mixture melted at 149–151°.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.64; H, 5.27; N, 5.52.

Hydrolysis of 3-Bromooxindole-3-propionic Acid under Acidic Conditions.—To a solution of 4.73 g. (0.025 mole) of indole-3-propionic acid in 162 ml. of *t*-butyl alcohol, which had been dried over sodium sulfate and treated with Darco (see previous paper[2] for significance of this treatment), was added with stirring under nitrogen at 23–25°, 8.90 g. (0.05 mole) of N-bromosuccinimide over a period of 45 min. After 3 hr. the solution was concentrated *in vacuo* at room temperature to a sirupy residue which was mixed with 100 ml. of anhydrous ether. Two crops of succinimide were removed by filtration. The filtrate was evaporated at room temperature, and the residual sirup was stirred with a mixture of 16 ml. of 1.5 *M* sulfuric acid and 80 ml. of *t*-butyl alcohol for 24 hr. Water (25 ml.) was added, and the mixture was concentrated *in vacuo* until a precipitate began to form. The solid was filtered and upon recrystallization from a benzene–hexane mixture gave two crops totaling 0.98 g. (19%) of impure dioxindole-3-propionic acid lactone, m.p. 120–123° (lit.[2] m.p. 134°), identified by its absorption spectra (Table I). The filtrate from the sulfuric acid–*t*-butyl alcohol solution was then extracted with ethyl acetate, the extract was dried and evaporated, and the residue taken up in a mixture of acetone, benzene, and hexane. A tan solid formed which upon recrystallization from a mixture of acetone, benzene, and methanol gave 1.36 g. (25%) of dioxindole-3-propionic acid, m.p. 182–185° dec. Recrystallization from a methanol–benzene mixture and then from a methanol–acetone mixture raised the melting point to 189–190° (lit.[8] m.p. 195–196°). Although the melting point did not agree with the reported value, the spectra and the reactions described below left no doubt about the structure.

Lactonization of Dioxindole-3-propionic Acid in Sulfuric Acid–*t*-Butyl Alcohol.—A solution of 0.221 g. (1.0 mmole) of dioxindole-3-propionic acid in a mixture of 0.64 ml. of 3 *M* sulfuric acid and 8.2 ml. of *t*-butyl alcohol was stirred at room temperature for 3 days. Then 6 ml. of water was added, and the mixture was concentrated *in vacuo* at room temperature until cloudy. Upon cooling, 0.058 g. of a white solid, m.p. 115–117°, was obtained, which was crude dioxindole-3-propionic acid lactone, as indicated by its ultraviolet spectrum. The filtrate was extracted with three 10-ml. portions of ethyl acetate, and the extract was shaken with three 10-ml. portions of 5% sodium bicarbonate. The quantity of dioxindole-3-propionic acid in the sodium bicarbonate extract was estimated by ultraviolet absorption to be 0.063 g. (29%). The quantity of lactone in the ethyl acetate layer was estimated by ultraviolet absorption to be 0.0039 g., which when added to the crude lactone isolated above gave a total yield of 30% of the lactone. The lactone did not react appreciably with bicarbonate under these conditions.

N-Acetyldioxindole-3-propionic Acid Lactone.—A solution of 0.50 g. of dioxindole-3-propionic acid lactone in 3 ml. of acetic anhydride was refluxed for 2 hr. After cooling and dilution with 12 ml. of water, 0.56 g. (92%) of N-acetyldioxindole-3-propionic acid lactone, m.p. 134–135°, was obtained. An analytical sample, m.p. 134–135° (resolidified and melted at 146–147°), was obtained by recrystallization from a mixture of acetone and water.

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.93; H, 4.65; N, 5.91.

The same product was obtained in 88% yield by treating dioxindole-3-propionic acid with acetic anhydride by the above procedure.

3-Methyleneoxindole (X).—3-Bromooxindole-3-acetic acid (0.587 g., 2.17 mmoles) was dissolved in 15 ml. of 95% ethanol and 260 ml. of water. The solution was immediately extracted with four 50-ml. portions of chloroform. The chloroform extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The yellow solid remaining was further dried in a vacuum desiccator, yielding 0.22 g. (69%) of material which decomposed at 218–232°. The purity was determined to be 91% by comparing the ultraviolet spectrum of a quantitatively prepared solution of the material in 95% ethanol with that of a solution prepared from pure 3-bromooxindole-3-acetic acid (10^{-5} *M*) and a trace of triethylamine. Further purification was not feasible because of the instability of the material in solution.

Anal. Calcd. for C_9H_7NO: C, 74.46; H, 4.86; N, 9.65. Found: C, 69.41; H, 4.84; N, 7.79.

3-(Phenylthiomethyl)oxindole (XVI).—To a solution of one drop of piperidine in 1 ml. of thiophenol was added 0.290 g. of 3-methyleneoxindole, which was 80% pure as determined by ultraviolet spectrum. The thick slurry was stirred under nitrogen for 3.5 hr. at room temperature. After dilution with 5 ml. of *n*-hexane a white solid formed. This solid was isolated by suction filtration and dissolved in 50 ml. of toluene. A small amount of insoluble material was removed by filtration, and to the filtrate *n*-hexane then was added to the saturation point. Two crops of white crystals were obtained, which upon recrystallization from toluene and then from a methanol–water mixture yielded four crops of 3-(phenylthiomethyl)oxindole, totaling 0.24 g. (60%), m.p. 128.0–129.5°. An analytical sample, m.p. 129–130°, was obtained by recrystallization from a methanol–water mixture.

Anal. Calcd. for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.16; H, 5.19; N, 5.94; S, 12.52.

Polymer from 3-Methyleneoxindole.—To a solution of 0.20 g. of 3-bromooxindole-3-acetic acid in 2.5 ml. of 95% ethanol was

added 47.5 ml. of 0.2 *M* acetate buffer (pH 5.0). After about 10 min., a fine white precipitate began to form. After 6 days, 0.039 g. of a cream-colored solid was removed by filtration, but upon drying in a desiccator the solid decomposed to a dark brown solid. The filtrate was concentrated and the white precipitate was isolated by centrifugation. The solid was mixed with water and centrifuged, the clear solution was decanted, and the tan solid was dried in a desiccator. The product melted from 230–270° with gradual decomposition. The ultraviolet spectrum showed λ_{max}^{EtOH} 252 mμ; the infrared, λ_{max}^{Nujol} 2.88, 3.1–3.2, 5.78 μ.

Polymer from Oxindole and Paraformaldehyde.—A mixture of 1.00 g. (7.5 mmoles) of oxindole, 0.23 g. of paraformaldehyde (equivalent to 8 mmoles of formaldehyde), 4 drops of piperidine, and 20 ml. of absolute ethanol was refluxed for 24 hr. A tan solid (0.02 g.) was removed by filtration and the filtrate was evaporated to dryness at room temperature. The residue was dissolved in tetrahydrofuran (THF), and benzene was added to the saturation point. Two crops of a cream solid, m.p. 211–213° dec., totaling 0.28 g., were obtained with λ_{max}^{EtOH} 207 and 251 mμ. The infrared spectrum resembled that of the polymeric product from the decomposition of 3-bromooxindole-3-acetic acid.

A sample of the polymer, m.p. 220–221° dec., which had been recrystallized from tetrahydrofuran–benzene, had the following analysis: C, 67.89; H, 5.99; N, 9.00 ± 1.00.

Notes

The Synthesis and Infrared Spectrum of 3-Deuterioindole

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Whereas exchange of deuterium for hydrogen on the indole nitrogen can be effected in neutral solution by repeated evaporation of solutions of indole and D_2O in a common solvent,[1] exchange at the 3-position requires acid catalysis.[2,3] We have applied this method for convenient syntheses of 1,3-dideuterio- and 3-deuterioindole.[4] Recognition of pronounced differences between the infrared spectra of indole and its 3-deuterio derivatives enabled us to follow the exchange readily and to characterize the isolated products.

Previous work from this laboratory[5] has shown that very rapid exchange of the NH of skatole occurs in dioxane solutions containing 5×10^{-5} *M* sulfuric acid. Very little exchange of the indole NH occurred under comparable conditions during a 2-hr. period. In the presence of 10^{-4} *M* acid, NH exchange occurred but was still slower than exchange in skatole. At this acid concentration no evidence of deuterium at the 3-position of the isolated product was found.[6]

By refluxing a solution of indole in D_2O containing 5×10^{-3} *M* sulfuric acid, exchange of the β-proton was accomplished, yielding 1,3-dideuterioindole. This in turn was converted to 3-deuterioindole by refluxing with water. The last product had an isotopic purity of 87%, as determined by n.m.r. Although the 1,3-dideuterioindole also had a high per cent of deuterium at the 3-position, the nitrogen seldom held more than 60% deuterium, as determined by infrared. Exchange from the nitrogen is a more facile process, and attempts to raise this level by repeated treatments with D_2O were not effective. The same problem was encountered in a recent synthesis of 1,3-dideuterioindole *via* the indole Grignard reagent.[1b] In this case, however, the β-carbon was also only 50% deuterated. The work-up of the Grignard reagent involved basic conditions, which may have promoted exchange[2c] with traces of water inadvertently admitted.

Although the introduction of deuterium produced no visible changes in the CH or CD stretching region near 3.3 μ of the infrared spectrum, probably because the bands are too weak to see with standard equipment, in the C–H bending region deuterium had a very marked effect similar to that reported for other substituents at the 3-position.[7] Of the three characteristic strong peaks at 13.05, 13.45, and 13.85 μ in the indole spectrum, that at 13.05 μ disappeared completely in the deuterated material, and that at 13.85 μ, associated with indoles bearing no substituents at the 2- and 3-positions,[7] was reduced to a weak absorption at 13.70 μ. Had it been possible to obtain isotopically pure product, the last peak would probably have disappeared completely. The band at 13.45 μ, characteristic of indoles unsubstituted in the benzene ring,[7] was unchanged in 3-deuterioindole. New peaks in the deuterated material included a band of moderate intensity at 12.1 μ (830 cm.$^{-1}$), a strong band at 12.4 (808), and what appeared to be an overtone of the former at 6.05 (1660). The absorption at 12.4 μ is in the region characteristic of indoles bearing a substituent at the 3-position.[7]

Thus, the presence of deuterium at the 3-position can be detected by the band at 12.4 μ, and residual C–H at that position can be estimated quantitatively from the

(1) (a) L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960); (b) R. V. Jardine, and R. K. Brown, *Can. J. Chem.*, **41**, 2067 (1963).

(2) (a) M. Koizumi and T. Titani, *Bull. Chem. Soc. Japan*, **13**, 307 (1938); (b) M. Koizumi, *ibid.*, **14**, 453 (1939); (c) The possibility of base-catalyzed exchange at the 3-position is suggested by recent work with 2-methylindole [B. C. Challis and F. A. Long, *J. Am. Chem. Soc.*, **85**, 2524 (1963)].

(3) The occurrence of considerable exchange at the 3-position upon evaporation of solutions of D_2O and indole or 2-methylindole in acetone or ethanol has been reported.[1b] Although this result would be expected in the latter case,[2b] it is difficult to reconcile the indole result with the earlier studies[2a,b] and our own.

(4) The only reported syntheses of C-deuterated indoles are those for 1,3-dideuterioindole (5% isotopic purity at C-3),[1b] 5-deuterioindole, and 2,3,4,5,6,7-hexadeuterioindole [H. Plieninger, R. Fischer, G. Keilich, and H. D. Orth, *Ann.*, **642**, 214 (1961)].

(5) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962).

(6) Indole is considerably more basic than skatole in equilibrium protonation where 3-protonation predominates [R. L. Hinman and J. Lang, *Tetrahedron Letters*, **No. 21**, 12 (1960)]. The differences in exchange rates of the NH proton may reflect differences in basicity of the 1-position.

(7) "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritsky, Ed., Academic Press, New York, N. Y., 1963, pp. 211,212.

absorption at 13.85 μ. Moreover, these effects afford additional proof that deuterium is bonded to carbon. The intense N–D band in N-deuterioindole appeared at 3.95 μ, but no other significant change in the spectrum was observed.

Experimental

3-Deuterioindole.—A mixture of 10 g. of indole and 5 ml. of 0.005 *N* sulfuric acid in D_2O was refluxed under nitrogen for 12 hr., the minimum time required for complete exchange. The solution was cooled and ther. was extracted with dry benzene. The extract was washed twice with D_2O and once with a saturated solution of sodium chloride in D_2O, then was dried over anhydrous calcium sulfate and evaporated. The residual white solid contained about 60% 1,3-dideuterioindole; as indicated by the intensities of the NH and ND peaks in the infrared, the balance was 3-deuterioindole. The mixture was refluxed with 50 ml. of water under nitrogen for a minimum of 3 hr. The mixture was cooled and extracted with benzene. The benzene extract was washed with a saturated salt solution, dried over calcium sulfate, and evaporated. The residual solid was recrystallized twice from a benzene–hexane mixture and then was dissolved in warm hexane. The clear solution, which was decanted from the oil that formed upon standing, was concentrated and cooled. White crystals (0.70 g.) of 87% pure 3-deuterioindole were obtained, m.p. 50.5–51.5°. The purity of the product was determined from the integrated n.m.r. spectrum in carbon tetrachloride by comparison of the areas of the β- and α-H peaks.

The principal peaks of the infrared spectra of indole and 3-deuterioindole, determined in KBr, are given below. Italic values are those which do not appear in the other spectrum. The presence of deuterium on nitrogen made little difference in the spectrum, except for the NH and ND peaks.

Indole.—*2.92* (*vs*), 3.18 (vw), 3.23 (w), 5.15 (w), 5.25 (w), 5.33 (w), 5.47 (w), 5.58 (w), *5.82* (*w*), 5.89 (w), 6.16 (m), 6.30 (w), *6.61* (*w*), 6.68 (w), 6.83 (s), 7.03 (s), *7.35* (*s*), 7.45 (s), 7.80 (m), 8.00 (s), *8.27* (*w*), 8.69 (w), 8.82 (m), 9.15 (s), *9.40* (*s*), 9.87 (w), 9.93 (w), 10.70 (m), *11.13* (*m*), 11.45 (m), *11.60* (*m*), *13.05* (*s*), 13.43 (vs), 13.85 (vs).

Additional Peaks in 3-Deuterioindole.—*6.05* (*w*), *8.49* (*w*), *12.05* (*m*), *12.40* (*s*), *13.72* (*s*).

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Reduction of Some Oxindolylidene Derivatives to 3-Substituted Oxindoles by Sodium Borohydride[1]

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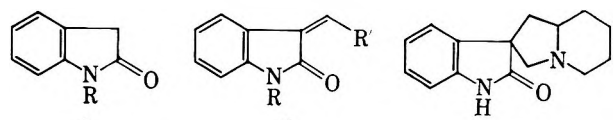
The 3-position of oxindole possesses distinct anionoid character. In 1909, Wahl and Bagard[2a] reported that base- or acid-catalyzed condensation of oxindole (**1**, R = H) with carbonyl compounds led to the formation of oxindolylidene derivatives (**2**). The trivial name "isoindogenides" has been given to the class of compounds with structure **2**. The isoindogenide 3-α-picolylideneoxindole (**2a**) first attracted our attention as a synthetic intermediate for spirooxindole derivatives (**3**).[3] Compounds with the proposed structure **2a** were previously reported by Abramovitch and Hey[4] and by Akkerman and Veldstra.[5] In both cases **2a** was prepared by condensation of isatin with α-picoline, but the two groups gave different melting points for their products.

A reaction between oxindole and 2-pyridinecarboxaldehyde, catalyzed by piperidine, gave a compound whose elemental analysis and spectra accord with constitution **2a**, and the melting point of this compound agrees with the value given by Akkerman and Veldstra. More recently 3-α-picolylideneoxindole (**2a**), which is described as exhibiting strong cholinergic effects, was included in a hydrogenation study of pyridine derivatives, but the method for preparing **2a** was not given.[6] When oxindole and the pyridinealdehyde were condensed in methanol, or when diethylamine was used as the basic catalyst in an open container, the major product was the carbinol (**4**).

Some additions to the class of isoindogenides are reported in Table I and in the Experimental section. In some cases, both oxindole and N-methyloxindole were used. The carbonyl compounds employed (and the products formed) were 2-pyridinecarboxaldehyde (**2a** and **b**), 2-pyrrolecarboxaldehyde (**2c** and **d**), furfural (**2e**), and cyclohexanone.[7]



1 **2** **3**

The scope of sodium borohydride reductions has been greatly expanded beyond the original conception that this reagent was limited to the reduction of carbonyl or imine groups. In particular, there are several reports in which carbon–carbon double bonds of enamines and α,β-unsaturated esters are reduced.[8,9] We found adventitiously that sodium borohydride reduces the 3-*exo* double bond in several isoindogenides.[10] The reaction occurs with a wide variation of substituents. For example, α-picolylideneoxindole (**2a**) is reduced to α-picolyloxindole (**5**)[11] by sodium borohydride, and 3-benzylideneoxindole (**2**, R′ = phenyl) is converted to 3-benzyloxindole (**6**). The proof of structure in the latter case was accomplished by comparing the product of the borohydride reduction with a sample of 3-benzyloxindole prepared by catalytic hydrogenation of benzylideneoxindole.[12] Even with an aliphatic

(1) We gratefully acknowledge a grant in support of this research from the Tennessee Heart Association.

(2) (a) A. Wahl and P. Bagard, *Compt. rend.*, **148**, 716 (1909); (b) W. B. Wright and K. H. Collins, *J. Am. Chem. Soc.*, **78**, 221 (1956); (c) P. L. Julian, E. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 185; (d) W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds," Vol. 8, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1954, p. 142.

(3) R. G. Mason, M. A. Thesis, Fisk University, 1962.

(4) R. A. Abramovitch and D. H. Hey, *J. Chem. Soc.*, 1697 (1954).

(5) A. M. Akkerman and H. Veldstra, *Rec. trav. chim.*, **73**, 629 (1954).

(6) G. N. Walker, *J. Org. Chem.*, **27**, 2967 (1962).

(7) 3-Furfurylideneoxindole has already been described: J. Staněk and D. Rybář, *Chem. Listy*, **40**, 173 (1946).

(8) I. W. Elliott and J. O. LeFlore, *J. Org. Chem.*, **28**, 3181 (1963); J. Szmuszkovicz, "Advances in Organic Chemistry," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 82.

(9) J. A. Meschino and C. H. Bond, *J. Org. Chem.*, **28**, 3129 (1963); M. S. Brown and H. Rapoport, *ibid.*, **28**, 3261 (1963); H. LeMoal, R. Carrié, and M. Bargain, *Compt. rend.*, **251**, 2541 (1960).

(10) These reductions were initiated with the hydrochloride salt of **2a** to establish the structure. The chemistry of these salts will be the subject of a separate communication.

(11) α-Picolyloxindole (**5**) has also been prepared by Walker (ref. 6).

(12) E. Kircher, *Nachr. kgl. Ges. Wiss. Gottingen Math.-Physik. Kl.*, 154 (1921); *Chem. Abstr.*, **17**, 1012 (1923).

TABLE I

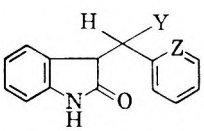
ISOINDOGENIDES[a]

Compound	R	R′	M.p., °C.	Yield, %	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen,— Calcd.	Found
2a	H	2-Pyridyl	205–206	94	$C_{14}H_{10}N_2O$	75.66	75.88	4.51	4.73		
2b	CH_3	2-Pyridyl	159–160	87	$C_{15}H_{12}N_2O$	76.25	76.31	5.12	5.12	11.86	11.74
2c	H	2-Pyrryl	221–222	88	$C_{13}H_{10}N_2O$	74.67	74.35	4.80	4.71	13.33	13.05
2d	CH_3	2-Pyrryl	141–142	83	$C_{14}H_{12}N_2O$	74.98	74.82	5.39	6.65	12.49	12.67
2e	CH_3	2-Furyl	134–135	82	$C_{14}H_{11}NO_2$	74.65	74.40	4.92	4.94	6.22	6.51
2f	H	Styryl	205–206	71	$C_{17}H_{13}NO$	82.57	82.57	5.30	5.59	5.66	5.65
2g	H	2,6-Dimethyl 1,5-Heptadienyl	137–138	64	$C_{18}H_{21}NO$	80.85	80.82	7.92	7.86	5.24	5.50

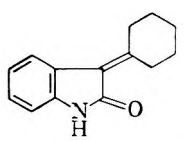
[a] A typical preparation is described for **2a** in the Experimental. Compounds **2f** and **2g** were prepared by azetropic distillation of a benzene solvent rather than in isopropyl alcohol by condensation of oxindole with cinnamaldehyde and citral, respectively.

substituent the reduction is successful under mild conditions. 3-Cyclohexylideneoxindole (**7**) is reduced to 3-cyclohexyloxindole (**8**) in 94% yield. Leucoisoindigo (**10**)[13] can be prepared quantitatively from isoindigo (**9**) on treatment with sodium borohydride in aqueous isopropyl alcohol.

Earlier Lindwall and MacLennan demonstrated that sodium dithionite was capable of reducing 3-phenacylideneoxindole to 3-phenacyloxindole.[14] This reagent is also effective in converting 3-α-picolylideneoxindole (**2a**) to 3-α-picolyloxindole (**5**), but dithionite in hot aqueous methanol did not completely reduce 3-benzylideneoxindole to 3-benzyloxindole under the same conditions.



4, Y = OH; Z = N
5, Y = H; Z = N
6, Y = H; Z = CH



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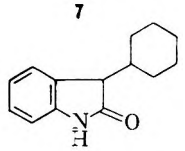

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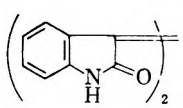

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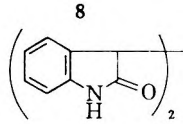

10

Experimental

3-α-Picolylideneoxindole.—To oxindole (10 g.) dissolved in isopropyl alcohol (100 ml.) was added all at once 2-pyridinecarboxaldehyde (10 ml.) and piperidine (2 ml.). The orange solution was boiled 20 min. and cooled. On scratching, there separated orange crystals (15.7 g.), m.p. 203–205°. For analysis a sample, m.p. 205–206°, was recrystallized from aqueous isopropyl alcohol.

3-α-Picolylideneoxindole methiodide was obtained after the base was suspended in dichloromethane and methyl iodide for 5 days. The salt, m.p. 232–233°, crystallized as red needles; infrared spectrum was at 5.88 and 6.22 μ.

Anal. Calcd. for $C_{15}H_{13}IN_2O$: C, 49.47; H, 4.29; N, 7.69. Found: C, 49.57; H, 4.07; N, 7.95.

3-Oxindolyl-2-pyridylcarbinol.—A methanolic solution (30 ml.) of oxindole (2.0 g.) and 2-pyridinecarboxaldehyde (2 ml.) was treated with diethylamine (1 ml.) and boiled 20 min., during which time a precipitate (3.2 g.) formed. The solid, m.p. 180–185°, was recrystallized several times from ethanol to afford pale yellow crystals, m.p. 184–185°.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 70.25; H, 5.06; N, 11.65. Found: C, 70.31; H, 5.06; N, 11.75.

3-α-Picolyloxindole.—To a warm solution of α-picolylideneoxindole (0.5 g.) in 50% aqueous ethanol (20 ml.) was added sodium borohydride (0.25 g.). On further heating for 15 min., the color faded from orange to pale yellow. More water (30 ml.) was added, and the solution was boiled vigorously in an open flask for 5 min. On cooling, a brown oil separated. The aqueous solution was decanted from oil and cooled overnight, whereupon a colorless solid (0.25 g., m.p. 129–131°) precipitated.

The brown oil crystallized from aqueous ethanol as prismatic needles (0.20 g.) that proved identical by melting point and infrared spectra with the reaction product from the aqueous layer. The analytical sample (m.p. 130–131°) was obtained after several recrystallizations from aqueous alcohol or from benzene–ligroin (lit.[6] m.p. 130–132°).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.40; N, 12.50. Found: C, 74.88; H, 5.42; N, 12.11.

The same reduction product was obtained in 67% yield when α-picolylideneoxindole was reduced by sodium dithionite[14] or when the hydrochloride was treated with sodium borohydride.

3-Benzyloxindole. A. By Sodium Borohydride Reduction.—Treatment of 3-benzylideneoxindole (1.0 g.) with sodium borohydride (0.5 g.) in aqueous ethanol gave on dilution with water and chilling 0.9 g. of 3-benzyloxindole, m.p. 129–131°, in two crops. This product proved identical by mixture melting point and infrared spectra with 3-benzyloxindole prepared by catalytic hydrogenation of 3-benzylideneoxindole.

B. By Sodium Dithionite.—To a solution of 3-benzylideneoxindole (0.2 g.) in warm methanol (15 ml.) was added sodium dithionite (0.4 g.) and water (10 ml.). The mixture was shaken and heated to boiling for 15 min. Some of the methanol was boiled off, but the yellow color remained. The cooled solution deposited yellow needles that were identified as starting benzylideneoxindole (0.12 g., 60%). Concentration of the filtrate afforded colorless needles, 0.05 g., m.p. 125–128, that proved to be 3-benzyloxindole by mixture melting point and infrared spectral comparison with an authentic sample.

Cyclohexylideneoxindole.—Oxindole (5 g.) was heated in dry benzene (100 ml.) under reflux conditions together with cyclohexanone (6 ml.) and piperidine (1.5 ml.). The mixture was allowed to reflux 8 hr., and the benzene was distilled. The residual oil was dissolved in hot methanol (20 ml.), filtered, and cooled. An orange solid (4.6 g.) was deposited, m.p. 182–183°. Recrystallization from methanol raised the melting point to 192–193°.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.14; N, 6.57. Found: C, 78.97; H, 6.78; N, 6.81.

3-Cyclohexyloxindole. A. Catalytic Reduction.—A solution of cyclohexylideneoxindole (1.0 g.) in 80% aqueous ethanol (100 ml.) was exhaustively hydrogenated in the presence of 10% palladium on charcoal at 3 atm. After 3 hr., the mixture was filtered, and the filtrate was concentrated to afford colorless needles (0.5 g.), m.p. 167–168°. An analytical sample (m.p. 168–169°) was recrystallized from aqueous methanol.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.21; H, 8.31; N, 6.16.

B. Borohydride Reduction.—A sample of cyclohexylidene oxindole (0.75 g.) was dissolved in hot methanol (40 ml.), and 5 ml. of water was added. Sodium borohydride (0.3 g.) was added to the hot solution, and the solution was boiled 15 min. in an open flask; water was added in small portions to replace the methanol. The colored mixture deposited a light yellow crystalline product (0.71 g.), m.p. 165–167°. Recrystallization from methanol gave colorless crystals, m.p. 168–169°. This product

(13) C. W. Hansen, *Ann. chim.* (Paris), [10]**1**, 94 (1924).

(14) H. G. Lindwall and J. S. MacLennan, *J. Am. Chem. Soc.*, **54**, 4739 (1932).

proved to be identical with cyclohexyloxindole from the catalytic reduction (part A) by mixture melting point and infrared spectral comparison.

Reduction of Isoindigo.—A hot suspension of isoindigo (0.5 g.) in 2-propanol (40 ml.) and water (5 ml.) was treated with sodium borohydride (0.12 g.). Within 10 min. all of the solid had dissolved, and the boiling solution was colorless. More water (20 ml.) was added, and the mixture was kept hot 20 min. longer. The solution was concentrated under reduced pressure to one-third of the original volume, and a solid began to separate. The suspension was reheated and the solid was dissolved by addition of alcohol. On standing, the hot filtered solution deposited colorless crystals, 0.5 g., m.p. 258°. Recrystallization from alcohol raised the melting point to 272–274°. Mixture melting point and infrared spectra showed the product was identical with a sample of leucoisoindigo prepared by zinc–acetic acid reduction of isoindigo.[13]

Long-Range Deshielding by Chlorine

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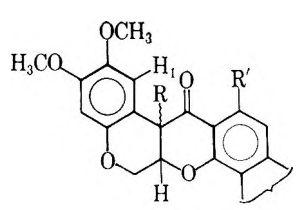
Received December 5, 1963

Long-range shielding and deshielding effects have been known to n.m.r. spectroscopists for some time.[2] Most of the clearly defined examples involve the anisotropy of unsaturated functions. We report herein the observation of an unusually large chemical shift produced by a chlorine atom five bonds distant from the shifted proton.

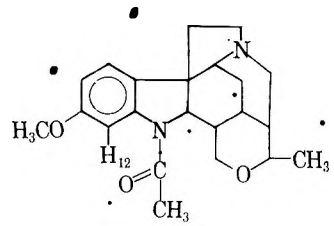
Compounds **2**–**5**, Table I, having R_3 = Cl, all show an absorption in the range τ 0.97–1.20, integrated intensity of one proton. This peak has been assigned to H_4 on the aromatic ring. It appears as the X portion of an ABX system: an intense quartet and two weak combination bands.[3,4] The AB portion of the spectrum, H_2 and H_3, is complicated by overlap and/or coupling to H_1, so that the values for J_{AX} and J_{BX} cannot be obtained. However, the sum $|J_{AX} + J_{BX}|$ = 10.0 c.p.s. can be measured.

Upon reductive removal of the chlorine atom (compound 1) the H_4 peak merges with the H_2 + H_3 resonance at *ca.* τ 2.0.

A long-range deshielding effect, produced by the anisotropy of the carbon–oxygen double bond, previously has been noted for the carbonyl group in formally similar structures. For example, Crombie and Lown[5] have used the shielding of the 1-hydrogen by the 12-carbonyl to assign the geometry of the B/C ring fusion in a series of rotenoids (I). Anet[6] has found that restricted rotation of the N-acetyl group in strychnospermine (II) produces a downfield shift of



I



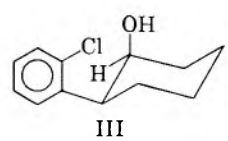
II

the aromatic proton at C-12. At room temperature, rotation of the acetyl group is sufficiently rapid that the two possible environments for C-12 are averaged out. At lower temperatures, that conformation having the carbonyl adjacent in space to C-12 displays the unusual shift. The geometry of this frozen conformation closely resembles that of compounds **1**–**5**.

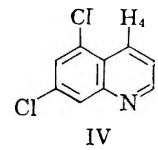
A few reports of such deshielding by chlorine are scattered through the literature. Huitric[7] recently has suggested that, in *cis*-2-(*o*-chlorophenyl)cyclohexanols (III), the *o*-chlorine causes a downfield shift of the 1-hydrogen resonance. However, the shift is smaller by an order of magnitude than that observed in this work (0.1 p.p.m. *vs.* 0.8–1.0 p.p.m.).

The spectrum of 5,7-dichloroquinoline[8] (IV) shows a downfield shift of 0.48 p.p.m. for H_4 when compared to 5,7-dimethylquinoline. In this instance, the chlorine and the shifted proton are *four* bonds apart in a *conjugated* system; a part of the effect may be transmitted through the π-system. Similarly, the indicated aromatic protons of V[9] show a downfield shift of 0.52 p.p.m. when compared to the aromatic protons of 9,10-dihydroanthracene.

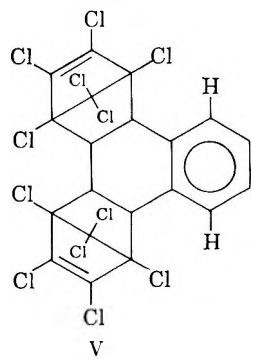
Finally, Osawa and Neeman[10] report chemical shifts for H_4 in the estrones (VIa and b) of τ 2.82 and 3.14, respectively, a difference of 0.32 p.p.m.



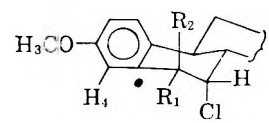
III



IV



V



VIa, R_1 = Cl; R_2 = H
b, R_1 = H; R_2 = Cl

It is possible that the great magnitude of the shift observed in our pyrrolo[1,2-*a*]quinoxalines results from both electrostatic electron withdrawal (a field effect) *and* the anisotropy[11] of the carbon–chlorine bond,[12] rather than the latter alone. Either effect should be enhanced by the close approach of the two atoms;

(1) Allied Chemical Corp. Fellow, 1962–1963; National Science Foundation Predoctoral Fellow, 1963–1964.

(2) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 112 ff.

(3) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 137.

(4) Strictly speaking, H_1 is the X part of an ABCX system; however, since H_1 does not appear to be coupled to H_4, ABX is a reasonable description.

(5) L. Crombie and J. W. Lown, *Proc. Chem. Soc.* (London), 299 (1961).

(6) F. A. L. Anet, *Can. J. Chem.*, **41**, 883 (1963).

(7) A. C. Huitric, *J. Org. Chem.*, **27**, 715 (1962).

(8) F. A. L. Anet, *J. Chem. Phys.*, **32**, 1274 (1960).

(9) Varian Associates, "High Resolution NMR Spectra Catalog," Spectrum No. 338.

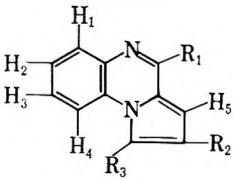
(10) Y. Osawa and M. Neeman, *J. Am. Chem. Soc.*, **85**, 2856 (1963).

(11) Ref. 2, p. 115.

(12) G. S. Reddy and J. H. Goldstein, *J. Chem. Phys.*, **38**, 2736 (1963).

TABLE I[a]

N.M.R. SPECTRA OF PYRROLO[1,2-*a*]QUINOXALINES



Compound	R_1	R_2	R_3	τ-values H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9
1	C_6H_5	CH_3	H	~2.5	7.74	2.6–2.8	2.6–2.8	← 2.02 →				3.29
2	CH_3	H	Cl	7.42	3.30	...	2.27	← 2.71 →			1.16	3.43
3	CH_3	CH_3	Cl	7.48	7.91	...	2.30	← 2.75 →			1.20	3.48
4	C_6H_5	H	Cl	2.60	3.17	...	← 2.13 →				1.02	3.38
5	C_6H_5	CH_3	Cl	2.54	7.73	...	← 2.06 →				0.97	3.19

[a] The preparation of these pyrrolo[1,2-*a*]quinoxalines is described elsewhere [E. C. Taylor and G. W. H. Cheeseman, *J. Am. Chem. Soc.*, 86, 1830 (1964)]; a preliminary account of the synthetic work was presented at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, Abstracts, p. 70Q.

measurements on models give a Cl–H distance of only 2.27 Å.

The variation of the position of the H_1 resonance is also worthy of attention. In compounds **2** and **3**, where R_1 = methyl, H_1 appears at lower field than H_2 and H_3, reflecting its position *ortho* to nitrogen. In compounds **4** and **5**, however, when R_1 = phenyl, H_1 is shifted to higher field, merging with the H_2–H_3 resonance. We attribute this shift to conjugation of the 1-position with the phenyl group; resonance structures can be written which place a formal negative charge at position 1.

All spectra were obtained on a Varian Associates A-60 spectrometer at normal operating temperature. Compounds were run as *ca.* 10% solutions in reagent grade carbon tetrachloride with 1% tetramethylsilane as internal standard. Chemical shifts are considered accurate to ±1 c.p.s., coupling constants to ±0.1 c.p.s.

Acknowledgment.—We wish to thank Dr. Pierre Laszlo for a helpful discussion. This work was supported in part by research grants to Princeton University from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA-02551), and from the American Cancer Society.

Base-Induced Fragmentation of 2-Phenyl-1,3-dioxolane[1]

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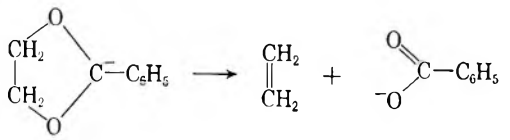
Department of Chemistry, University of Wisconsin, Madison, Wisconsin

Received February 13, 1964

We wish to report a representative of an unexplored and potentially useful class of reactions: 1,3-eliminations of anionic fragments.[2-4]



2-Phenyl-1,3-dioxolane, treated dropwise with phenyllithium in ether at room temperature, rapidly evolved a gas which was collected (80–94% in three separate runs) and shown to be pure ethylene by mass spectrometry. Formally, the reaction proceeds by 1,3-elimination of benzoate anion from the conjugate base of 2-phenyl-1,3-dioxolane. Although benzoic acid was not recovered from the reaction mixture the observed products are consistent with the elimination of lithium benzoate and subsequent reaction with phenyllithium: from one run benzophenone and triphenylcarbinol were recovered in an over-all yield of 85% based on 2-phenyl-1,3-dioxolane.

Experimental

The reaction vessel, a 250-ml. three-necked round-bottomed flask, was fitted with a gas inlet tube, addition funnel with pressure-equalizing side arm, and a condenser. The condenser was connected to a gas buret *via* two traps cooled in a Dry Ice–acetone mixture and a gas sampling tube. The Dry Ice traps prevented ether vapors from reaching the gas buret and thus facilitated the volumetric and mass spectroscopic determinations of gas evolved in the reaction. The entire system was thoroughly flushed with helium, both before and after adding 4.892 g. (32.6 mmoles) of 2-phenyl-1,3-dioxolane[5] to the reaction vessel and 100 ml. of an ethereal solution of phenyllithium (*ca.* 125 mmoles) to the addition funnel. After allowing the volume of the system to equilibrate (*ca.* 1 hr.) the solution of phenyllithium was added dropwise to the reaction vessel until gas evolution ceased. The reaction mixture was stirred (magnetically) continuously and the reaction vessel was immersed in a bath of water at room temperature. Gas evolution ceased when 17 ml. of phenyllithium solution remained unadded. The increase in volume, 769 ml. at 736 mm. and 22°, corresponded to 94% of the theoretical evolution of 1 equiv. of gas. The mass spectrum of the gas (*m/e* = 70 to 12) was indistinguishable (±2%) from a mass spectrum of pure ethylene obtained under the same conditions.

(1) Grateful acknowledgment is made of financial support from the Petroleum Research Fund (Grant 1116-A4).

(2) An interesting and related example was reported by R. L. Letsinger and D. F. Pollart, [*J. Am. Chem. Soc.*, **78**, 6079 (1956)]. They found that treatment of 2-phenyltetrahydrofuran with propyl- or phenyllithium, followed by work-up, yielded ethylene and acetophenone in high yields. Unpublished work with Y. C. Poon has furnished another variation: ethylene glycol sulfite is reduced to ethylene in variable yield (so far not greater than 30%) by metallic sodium or potassium in refluxing xylene.

(3) 1,3-Eliminations of stable and unstable *neutral* molecules are well known and are referred to in the exhaustive documentation of 1,3-additions by R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565 (1963).

(4) The conversion of 1,2-diols to olefins provides an example of immediate synthetic applicability. *Cf.* E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, **85**, 2677 (1963).

(5) H. Hibbert and J. A. Timm, *ibid.*, **46**, 1283 (1924).

Water and then hydrochloric acid were added to the reaction vessel; the mixture was extracted with ether. The ether solution was extracted with 2 *N* sodium hydroxide solution. Work-up of the alkaline aqueous solution yielded 129 mg. of crude phenol, identified by its characteristic odor and infrared spectrum. Work-up of the ether solution yielded 7.121 g. of a yellow oil, the infrared spectrum of which was almost reproduced by a mixture of 80% benzophenone and 20% triphenylcarbinol. (The ratio of intensities of absorption at 6.72 and 6.94 μ can be used for quantitative analysis of such mixtures.)

A portion of the crude product, 0.951 g., was chromatographed on 40 g. of acid-washed alumina (Merck). Oily fractions 4–28, eluted with hexane through 50:50 hexane–benzene, were combined (589 mg.), dissolved in ether–pentane, and cooled to −20°, yielding 557 mg. of benzophenone in three crops, m.p. 46–48°. The yield of benzophenone based on 2-phenyl-1,3-dioxolane is therefore no less than 70%. Crystalline fractions 30–35, eluted with benzene, all showed the characteristic infrared spectrum of triphenylcarbinol. They were combined, yielding 184 mg. with m.p. >150°, corresponding to a yield of triphenylcarbinol based on 2-phenyl-1,3-dioxolane of 15%. Crystallization of the combined triphenylcarbinol fractions from ether–pentane at room temperature yielded 131 mg., m.p. 159–161°, almost indistinguishable from twice crystallized authentic triphenylcarbinol, m.p. 160–162°.

Bisdithiocarbonate and Related Analogs of 2-Aminoethanethiol[1]

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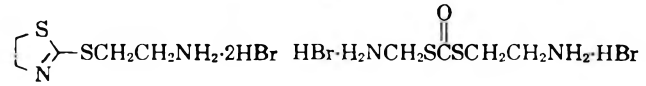
Received January 6, 1964

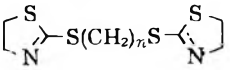
Certain modifications of the mercapto group of 2-aminoethanethiol have resulted in compounds whose radioprotective properties are not dependent *a priori* on simple release of the parent agent.[2] Continued evaluation of such changes may lead to an effective, yet relatively nontoxic antiradiation agent. In this work the excellent method provided by Crawhall and Elliott[3] for the conversion of 2-(alkylthio)-2-thiazolines to the corresponding *S*-alkyl *S'*-2-aminoethyl dithiocarbonate hydrochlorides has been extended to the preparation of several other dithiocarbonate derivatives of 2-aminoethanethiol.

2-(2-Aminoethylthio)-2-thiazoline dihydrobromide (I) was hydrolyzed in refluxing 6 *N* hydrobromic acid to give *S,S'*-bis(2-aminoethyl) dithiocarbonate dihydrobromide (II). The dihydrochloride corresponding

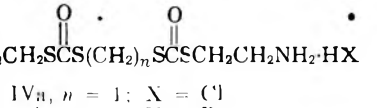


I II

to II had previously been isolated as one of the products of prolonged hydrolysis of 2-thiazolidinethione in refluxing concentrated hydrochloric acid.[4] Hydrolysis of the 2,2'-(alkylenedithio)bis-2-thiazolines (IIIa–e) in 6 *N* hydrochloric (or hydrobromic) acid gave the corresponding *S,S'''*-bis(2-aminoethyl) *S',S''*-alkylene bisdithiocarbonate dihydrohalides (IVa–e). The intermediate bisthiazolines were obtained in good yields from 2-thiazolidinethione and the appropriate dibromoalkane in *N,N*-dimethylformamide with potassium carbonate as acid acceptor, the crude products so obtained being used without further purification. The two lower members of the series, 2,2'-(methylenedithio)bis-2-thiazoline (IIIa) and 2,2'-(ethylenedithio)bis-2-thiazoline (IIIb), were isolated as characterizable solids. Hydrolysis of IIIb was carried out in 6 *N* hydrobromic acid instead of the usual 6 *N* hydrochloric acid, and therefore *S,S'''*-bis(2-aminoethyl) *S',S''*-ethylene bisdithiocarbonate was isolated as the dihydrobromide IVb.

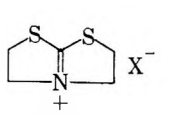


IIIa, *n* = 1
b, *n* = 2
c, *n* = 3
d, *n* = 4
e, *n* = 5

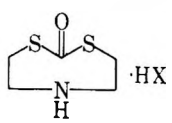


IVa, *n* = 1; X = Cl
b, *n* = 2; X = Br
c, *n* = 3; X = Cl
d, *n* = 4; X = Cl
e, *n* = 5; X = Cl

The preparation of 2,3,5,6-tetrahydrothiazolo[2,3-*b*]-thiazolium chloride (Va) from 2,2'-dichlorodiethylamine and carbon disulfide has been recently described,[5,6] and the structural similarity of Va to the thiazolines described above suggests that it might be converted in hydrochloric acid to the cyclic dithiocarbonate hydrochloride VI. Refluxing a solution of

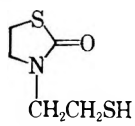


Va, X = Cl
b, X = Br



VI

Va in 6 *N* hydrochloric acid in the usual way resulted in a rather high recovery of unchanged starting material, but prolonged refluxing of a solution of Va in concentrated hydrochloric acid gave in medium yield a distillable nitroprusside-positive oil, whose infrared absorption spectrum is incompatible with the spectra of the dithiocarbonates described above. The identity of the oil as 3-(2-mercaptoethyl)-2-thiazolidinone (VII)



VII

was strongly indicated by a spectral comparison with 2-thiazolidinone itself and confirmed by elemental analyses and iodometric assay. Seto and Ikegami[6] iso-

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2028.

(2) For example: (a) L. Shapira, D. G. Doherty, and W. T. Burnett, Jr., *Radiation Res.*, **7**, 22 (1957); (b) B. Holmberg and B. Sörbo, *Nature*, **183**, 832 (1959); (c) B. Hansen and B. Sörbo, *Acta Radiol.*, **56**, 141 (1961); (d) W. O. Foye, J. R. Marshall, and J. Mickles, *J. Pharm. Sci.*, **52**, 406 (1963); (e) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

(3) J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 3094 (1952).

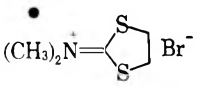
(4) R. J. Gaul and W. J. Fremuth, *J. Org. Chem.*, **25**, 869 (1960).

(5) W. Schulze, G. Letsch, and H. Willitzer, *J. prakt. Chem.*, [4]**19**, 101 (1963).

(6) S. Seto and Y. Ikegami, *Bull. Chem. Soc. Japan*, **36**, 730 (1963).

lated VII from the reaction of Va with water alone and characterized their product as a lead salt. Apparently the hydrolysis of Va proceeds more readily in water alone than in hydrochloric acid, in which the yield of VII may be limited by equilibrium. The thiazolidinone VII has also been proposed as an intermediate in the reaction of Va in sodium hydroxide solution.[5,6]

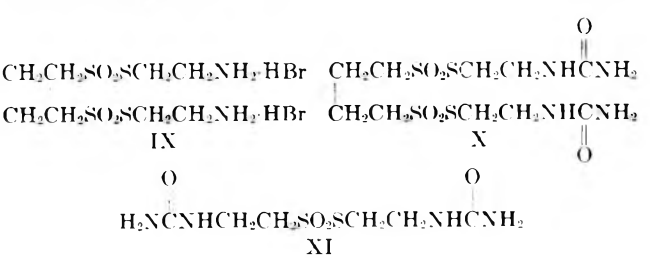
In the preparation of IIIb the formation of the bromide Vb as a by-product was considered a possibility, since ring closure is known to occur by the interaction of similar thioanions and 1,2-dihaloethanes: for example, ring closure (on N-1) occurred in an attempted 2-chloroethylation of purine-6(1*H*)-thione.[7] It was also been observed in this laboratory that the reaction of sodium dimethyldithiocarbamate with either 1-bromo-2-chloroethane or 1,2-dibromoethane gives 1,3-dithiolan-2-ylidenedimethylammonium bromide (VIII), ring closure occurring on sulfur instead of



VIII

nitrogen.[8] The formation of Vb was not observed, even when a favorable ratio of reactants was used.

The 2-aminoethylation of disodium 1,4-butanebisthiosulfonate was accomplished in a manner similar to that already described[9] for the reaction of 2-bromoethylamine hydrobromide and potassium methanethiosulfonate. The product, *S,S'*-bis(2-aminoethyl) 1,4-butanebisthiosulfonate dihydrobromide (IX), is the first bis analog of this type to be reported. The conversion of IX to *S,S'*-bis(2-ureidoethyl) 1,4-butanebisthiosulfonate (X) was brought about by the action of potassium cyanate in water, as was the conversion of *S*-2-aminoethyl 2-aminoethanethiosulfonate dihydrochloride to the corresponding bisureido derivative XI. Similar attempts to prepare the bisureido derivatives of the dithiocarbonates described above gave erratic results. The isolation of pure bisurea from II could not be repeated on a larger scale. Attempted conversions of IVa resulted in cleavage of the dithiocarbonate linkage; products of low nitrogen content were isolated from IVb and IVd. Analyses and infrared absorption spectra of the recrystallized product from IVd suggested formation (at 45 and 90°) of a bisureido biuret from two molecules of the desired bisurea.



IX X

XI

Experimental[10]

S,S'-Bis(2-aminoethyl) Dithiocarbonate Dihydrobromide (II).—A solution of crude 2-(2-aminoethylthio)-2-thiazoline dihydrobromide[11] (3.24 g., *ca.* 10 mmoles) in 6 *N* hydrobromic acid (17 ml.) was refluxed for 4 hr., filtered, and chilled. The white solid that precipitated was dried *in vacuo* over sodium hydroxide and phosphorus pentoxide; the yield of crude II, which decomposed at 229–231° without melting, was 2.09 g. (*ca.* 61%). For analysis a small sample was recrystallized from methanol, ground fine, and dried *in vacuo* over phosphorus pentoxide at 100°; the analytical sample decomposed at 238–239° without melting, ν_{max}^{KBr} 1645 (C=O) and 870 cm.$^{-1}$ (S–C–S).

Anal. Calcd. for $C_5H_{12}N_2OS_2$·HBr: C, 17.55; H, 4.12; S, 18.74. Found: C, 17.84; H, 4.14; S, 18.9.

This procedure carried out on a 0.1-mole scale gave a 58% yield of recrystalllized II in two crops.

General Procedure for the Preparation of 2,2'-(Alkylenedithio)-bis-2-thiazolines (IIIa–e).—To a well-stirred mixture of anhydrous potassium carbonate (29 g., 0.21 mole), 2-thiazolidinethione (25 g., 0.21 mole), and *N,N*-dimethylformamide (75 ml.) was added dropwise over a 1-hr. period a solution of the appropriate dibromoalkane (0.10 mole) in the same solvent (25 ml.) at such a rate that the reaction temperature did not exceed 50°. The resulting mixture was heated at 60–70° for 2 hr., cooled, and poured into water (1 l.). The first two members of the series precipitated as solids, the others as oils.

Crude 2,2'-(methylenedithio)bis-2-thiazoline (IIIa) was obtained as a yellow solid in 94% yield by evaporation of a filtered benzene solution of the precipitate to dryness under reduced pressure. Triturating a 0.5-g. sample in two 2.5-ml. portions of ethanol and drying *in vacuo* gave a 49% recovery of IIIa, m.p. 53–54°, ν_{max}^{KBr} 1565 cm.$^{-1}$ (C=N).

Anal. Calcd. for $C_7H_{10}N_2S_4$: C, 33.57; H, 4.02; S, 51.21. Found: C, 33.83; H, 4.04; S, 51.7.

The precipitate of 2,2'-(ethylenedithio)bis-2-thiazoline (IIIb) was washed with water and dried *in vacuo* (yield 91%), and for analysis a small sample was recrystallized from ethanol as white plates, m.p. 124–126°, ν_{max}^{KBr} 1575 cm.$^{-1}$ (C=N).

Anal. Calcd. for $C_8H_{12}N_2S_4$: C, 36.33; H, 4.57; S, 48.49. Found: C, 36.45; H, 4.63; S, 48.5.

The bisthiazolines that separated as oils were extracted with four 250-ml. portions of benzene; and the benzene extracts, which were washed with three 50-ml. portions of water and dried over magnesium sulfate, were evaporated under reduced pressure, the evaporations being repeated several times after successive additions of ethanol. Finally the oils were dried for 1 hr. at 60° at about 1 mm. 2,2'-(Trimethylenedithio)bis-2-thiazoline (IIIc), 2,2'-(tetramethylenedithio)bis-2-thiazoline (IIId), and 2,2'-(pentamethylenedithio)bis-2-thiazoline (IVe) were thus obtained as crude oils in 90–95% yields, and were used without further purification.

General Procedure for the Preparation of *S,S'''*-Bis(2-aminoethyl) *S',S''*-Alkylene Bisdithiocarbonate Dihydrohalides (IV-a–e).—A suspension of crude 2,2'-(alkylenedithio)bis-2-thiazoline in 6 *N* hydrochloric (or hydrobromic) acid (16.7 ml. per mmole of bisthiazoline) was heated under reflux for 4 hr. The reaction mixture was filtered hot to remove a small amount of insoluble gum and cooled. The solid that precipitated was dried *in vacuo* over phosphorus pentoxide and sodium hydroxide. For analysis small samples were recrystallized from ethanol with Norit treatment; the remaining larger samples, from methanol. These recrystallizations gave fair recoveries (30–70%) of purified products. Typical preparations by this procedure are summarized in Table I.

3-(2-Mercaptoethyl)-2-thiazolidinone (VII).—A solution of unrecrystallized hydrated 2,3,5,6-tetrahydrothiazolo[2,3-*b*]thiazolium chloride[7] (Va, 18 g.) in concentrated hydrochloric acid (21 ml.) was refluxed for 72 hr. The cooled solution was diluted with water (79 ml.) and extracted with three 50-ml. portions of chloroform. The chloroform extract was washed with three 25-ml. portions of water, dried over magnesium sulfate, and evaporated to dryness under reduced pressure; the residue was an oil (7.8 g., $n^{25}D$ 1.5833). Vacuum distillation through a Claisen head gave IX as a colorless oil, b.p. 113–116° (0.3 mm.). The yield was 6.8 g. (50% based on Va as a dihydrate), iodometric assay 98%. Redistillation gave the analytical sample, b.p. 106–108° (0.2 mm.), $n^{25}D$ 1.5828, ν_{max}^{film} 2550 (SH, weak) and 1670 cm.$^{-1}$ (C=O, strong).

Anal. Calcd. for $C_5H_9NOS_2$: C, 36.78; H, 5.55; N, 8.58. Found: C, 36.64; H, 5.69; N, 8.67.

(7) R. W. Balsiger, A. L. Fikes, T. P. Johnston, and J. A. Montgomery, *J. Org. Chem.*, **26**, 3446 (1961).

(8) *Cf.* K. C. Kennard and J. A. VanAllan, *ibid.*, **24**, 470 (1959).

(9) T. P. Johnston and A. Gallagher, *ibid.*, **26**, 3780 (1961).

(10) Melting points were determined with a Mel-Temp apparatus (unless indicated otherwise) and are uncorrected; infrared absorption spectra, with a Perkin-Elmer Model 221 spectrophotometer.

(11) R. C. Clapp, L. Long, Jr., and T. Hasselstrom, *J. Org. Chem.*, **26**, 1666 (1961).

TABLE I

S,S''-BIS(2-AMINOETHYL) *S',S''*-ALKYLENE BISDITHIOCARBONATE DIHYDROHALIDES

Compound	Crude yield, %	M.p.,[a] °C.	ν_{max}^{KBr}, cm.$^{-1}$ C=O[b]	ν_{max}^{KBr}, cm.$^{-1}$ S-C-S[b]	Formula	C, %: Calcd.	C, %: Found	H, %: Calcd.	H, %: Found	S, %: Calcd.	S, %: Found
IVa	57	184–185 dec.	1645	875	$C_7H_{14}N_2O_2S_4 \cdot 2HCl$	23.39	23.51	4.49	4.64	35.69	35.5
IVb	63	240–241 dec.	1640	880	$C_8H_{16}N_2O_2S_4 \cdot 2HBr$	20.78	20.94	3.92	3.59	27.74	27.8
IVc	59	215–216 dec.	1650	875	$C_9H_{18}N_2O_2S_4 \cdot 2HCl$	27.90	28.06	5.20	5.46	33.10	33.1
IVd	51	210–211 dec.	1650	875	$C_{10}H_{20}N_2O_2S_4 \cdot 2HCl$	29.91	29.86	5.52	5.49	31.94	32.1
IVe	55	197–199 dec.	1650	875	$C_{11}H_{22}N_2O_2S_4 \cdot 2HCl$	31.79	31.94	5.82	5.70	30.87	30.6

[a] Varied widely with rate of heating, typical values being reported. [b] Strong absorption; *cf.* ref. 4.

1,3-Dithiolan-2-ylidenedimethylammonium Bromide (VIII).—A solution of sodium dimethyldithiocarbamate hemihydrate[12] (4.00 g., 26.3 mmoles) in methanol (75 ml.) was added dropwise to a solution of 1,2-dibromoethane (4.5 ml., 53 mmoles) in the same solvent (10 ml.) over a period of 15–20 min. The reaction mixture was then stirred for 3 hr., maximum temperature being 31°. The methanol was removed under reduced pressure and the residual yellow solid was triturated in chloroform (100 ml.). The insolubles were removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The white residue after trituration in benzene was dried *in vacuo* at 63° over phosphorus pentoxide, yielding 3.86 g. (64%) of VIII, m.p. 174° (Kofler Heizbank). The same product was obtained from 1-bromo-2-chloroethane, sodium chloride having precipitated from the reaction mixture. The analytical sample was obtained as white prisms, m.p. 174°, by recrystallization from acetonitrile; λ_{max} in mμ ($\epsilon \times 10^{-3}$): 249 (12.2) at pH 1, 249 (12.7) at pH 7, 250 (13.3) in methanol; ν_{max}^{KBr} 1595 cm.$^{-1}$ (C=N, strong). The product isolated was the same when the ratio of dihalide to dithiocarbamate was varied from 1:1 to 4:1, and also when the reaction temperature was increased to 66° by external heating.

Anal. Calcd. for $C_5H_{10}BrNS_2$: C, 26.32; H, 4.42; N, 6.14. Found: C, 26.48; H, 4.59; N, 6.24.

***S,S'*-Bis(2-aminoethyl) 1,4-Butanebisthiosulfonate Dihydrobromide (IX).**—Crude 1,4-butanedisulfonyl chloride[13] (m.p. 76–77°, 17.8 g., about 70 mmoles) was added in portions over a 30-min. period to a cold and well-stirred aqueous solution (100 ml.) of sodium hydroxide (11.2 g.) that had been saturated with hydrogen sulfide at 15°. The resulting mixture was stirred at 5° for 2 hr., the pH changing from 11 to 5, and at room temperature for 4 hr., the pH being maintained at 8 by the addition of 0.2 *N* sodium hydroxide solution (total about 30 ml.). A small amount of solid was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residual solid was extracted with *N,N*-dimethylformamide, first with four 50-ml. portions at room temperature and then with three 50-ml. portions hot. Evaporation *in vacuo* of the combined extracts left a yellow solid, which was rendered white by trituration in 2-propanol. The yield of crude disodium 1,4-butanedisthiosulfonate (20.0 g.) was nearly quantitative.

To a well-stirred suspension of crude disodium 1,4-butanebisthiosulfonate (6.5 g., about 20 mmoles) in *N,N*-dimethylformamide (30 ml.) was added a solution of 2-bromoethylamine hydrobromide (8.61 g., 42.0 mmoles) in the same solvent (20 ml.). The resulting solution was heated at 80–90° for 5 hr. and evaporated to dryness under reduced pressure, the evaporation being repeated several times after successive additions of ethanol. The solid residue was extracted with three 50-ml. portions of methanol to remove sodium bromide, and the methanol-insoluble solid was dried *in vacuo* (8.03 g.). A solution of the crude product in water (100 ml.) was treated with Norit and evaporated to dryness *in vacuo*. Trituration of the white crystalline residue with two 25-ml. portions of methanol left 6.18 g. of IX, m.p. 177–178° dec. An additional 1.30 g., m.p. 176–177° dec., was obtained from the methanol washings, the total yield being about 75%. For analysis a small sample was recrystallized from methanol–ether (m.p. 171–172° dec.).

Anal. Calcd. for $C_6H_{16}N_2O_4S_4 \cdot 2HBr$: C, 19.28; H, 4.45; S, 25.74. Found: C, 19.55; H, 4.52; S, 25.7.

***S,S'*-Bis(2-ureidoethyl) 1,4-Butanebisthiosulfonate (X).**—To a stirred solution of *S,S'*-bis(2-aminoethyl) 1,4-butanebisthiosulfonate dihydrobromide (IX, 2.7 g., 5.5 mmoles) in water (50 ml.) was added dropwise a solution of potassium cyanate (0.89 g., 11 mmoles) in the same solvent (25 ml.). After about 15 min. the solution became cloudy, and solid began to precipitate. The mixture was stirred overnight at room temperature; the solid was collected, washed with water, and dried *in vacuo* over phosphorus pentoxide, yielding 1.8 g. (79%) of crude X, m.p. 177–179° dec. with predarkening. The crude product was recrystallized from water in 84–92% recovery and dried as described above, m.p. 183–184°.

Anal. Calcd. for $C_{10}H_{22}N_4O_6S_4$: C, 28.42; H, 5.25; N, 13.25. Found: C, 28.44; H, 5.21; N, 13.27.

***S*-2-Ureidoethyl 2-Ureidoethanethiosulfonate (XI).**—A solution of potassium cyanate (0.811 g., 10.0 mmoles) in water (5 ml.) was added dropwise to a stirred solution of *S*-2-aminoethyl 2-aminoethanethiosulfonate dihydrochloride[14,15] (1.28 g., 5.00 mmoles) in water (10 ml.). The resulting solution was stirred at room temperature for 5 hr. and then evaporated to dryness under reduced pressure (oil pump) at room temperature, the evaporation being repeated several times after successive additions of methanol. The solid residue was extracted with three 5-ml. portions of *N,N*-dimethylformamide and the combined extracts were evaporated to dryness *in vacuo* at less than 50°. Evaporations were again repeated after successive additions of methanol until the oily residue solidified. Recrystallization from ethanol (100 ml.) gave crude XI as a cream-colored solid, which was dried *in vacuo* (0.62 g., m.p. 115–117° dec. with presoftening). Analytically pure XI, m.p. 151–153° dec., was obtained by diluting a Norit-treated solution of the crude product (250 mg.) in warm methanol (10 ml.) with an equal volume of ether. The recovery (108 mg.) corresponded to an over-all yield of 20%.

Anal. Calcd. for $C_5H_{11}N_3O_3S_2$: C, 26.65; H, 5.22; S, 23.72. Found: C, 26.81; H, 5.25; S, 23.9.

The yield was little improved when the above described procedure was repeated on a 25-mmole scale with omission of the initial ethanol recrystallization. The product, twice recrystallized from 1:1 methanol–ether, melted at 145–146° dec.

Acknowledgment.—The authors are indebted to Mrs. T. N. Carruthers, Jr., and Mr. G. S. McCaleb for preparation of VIII, and to Dr. W. J. Barrett and associates of the Analytical Section of this institute for microanalyses and spectra.

(12) M. Delépine, *Bull. soc. chim. France*, [4]**3**, 650 (1908).

(13) B. Helferich and H. Grünert, *Ber.*, **74B**, 1531 (1941).

(14) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961).

(15) Distillation Products Industries, Rochester 3, N. Y.

The Preparation of Hexaphenylcyclotrisilthiane and of Tetraphenylcyclodisilthiane[1]

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In the course of investigations on the displacement of halogen or amino groups on silicon with sulfhydryl or $-S-SiR_3$ groups, two cyclosilthianes, I and II, have

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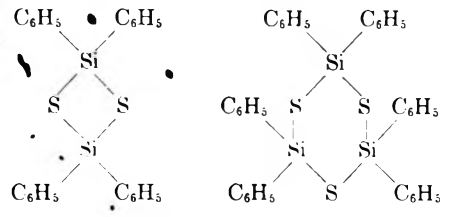

I II

been prepared. A compound with the structure I melting at 145–147° has been reported.[2] Tetraphenylcyclodisilthiane (I) prepared in this work by pyrolysis of II melted at 163–165°. Hexaphenylcyclotrisilthiane (II) has been unreported previously.

The cyclic trimer II was prepared in 55% yield by the reaction of hydrogen sulfide with diphenyldichlorosilane in benzene solution containing a 2:1 mole ratio of pyridine to the silane. Repeated attempts to isolate I from the reaction mixture have been unsuccessful. Compound II was a colorless crystalline solid melting sharply at 188–189°. Elemental analyses and experimentally determined molecular weights were in reasonable agreement with the calculated values. Further, compound II contained no halogen and no hydrogen active in the Zerewitinoff determination and was therefore formulated as cyclic. The molecular weight of II (Table I) was determined by three methods

TABLE I
MOLECULAR WEIGHT DETERMINATIONS

Compound	Formula	Calcd.	Concn., mole/l. in benzene	Exptl. method, found V.p. osmometric: Cryoscopic	Isopiestic
Dimer I	$C_{24}H_{20}S_2Si_2$	428	0.030		383
			0.120		389
			0.100	391[a]	
Trimer II	$C_{36}H_{30}S_3Si_3$	642	0.026		651
			0.074		626
			0.157		632
			0.100	595[a]	
			0.041		653

[a] Average of five determinations.

since this compound is being used in attempts to prepare higher molecular weight linear silthiane polymers by ring opening with subsequent reaction.

Pyrolysis of II in a glass tube at reduced pressure resulted in collection of a crystalline solid in the upper cool part of the tube. Elemental analyses, molecular weight determinations, and infrared spectra support the proposal that I is a cyclic dimer. No material melting near the 145–147° value reported by Moody[2] was isolated. It is possible that I is a crystalline modification of Moody's compound. Polymorphism is common among the corresponding cyclic siloxanes.[3] A mixture melting point of I with II resulted in depression.

The tetramethyl analog of I, tetramethylcyclodisilthiane, has been prepared by thermal rearrangement of hexamethylcyclotrisilthiane.[4] Yokoi[5] has determined bond lengths and angles for these compounds by electron diffraction, and Kriegsmann and Claus[6] have investigated their vibrational spectra and structures.

Young and co-workers[7] have been particularly interested in using infrared data to distinguish ring sizes in various substituted cyclosiloxanes. They have shown that compounds containing six-membered siloxane rings (cyclic trimers) can be distinguished from similarly substituted eight-membered cyclic siloxanes by a characteristic shift in infrared absorption. Our somewhat comparable results with the four- and six-membered cyclic silthianes (I and II) show that vibrational absorption spectra of both have identical bands except for a single shift from 13.45 μ for the dimer I to 13.63 μ for the trimer II. The six-membered cyclosiloxane ring shows a strong band at 9.8–9.9 μ. It is not unreasonable, when one considers the differences in force constants and reduced masses existing with Si–O and Si–S bonds, that the strong absorption of II at 13.63 μ may be characteristic of a six-membered cyclosilthiane ring.

X-Ray powder photographs for I and for II show distinctly different patterns which strongly suggest different compounds (see Table II). The unit cells in each case are large, and the crystal habit for each is probably monoclinic.

TABLE II
X-RAY DIFFRACTION MEASUREMENTS

Compound	Principle X-ray powder photograph lines: Distance, Å.	I (rel.)
Dimer I	9.87	vs
	8.30	m
	6.62	ms
	6.15	m
	4.99	s
	4.72	ms
	4.44	m
	4.25	m
	4.09	mw
	3.54	m
Trimer II	9.60	vs
	8.54	s
	6.83	m
	5.79	ms
	5.21	m
	4.79	m
	4.43	mw
	4.26	m
	3.73	ms

Experimental[8]

Hexaphenylcyclotrisilithiane (II).—In a 1-l. three-neck flask fitted with a thermometer, gas introduction tube, magnetic stirrer, dropping funnel, and reflux condenser was placed 100 ml. of dry benzene and 22.9 g. (0.29 mole) of anhydrous pyridine. The flask was flushed with nitrogen and subsequently anhydrous hydrogen sulfide was bubbled slowly into the solution while redistilled diphenyldichlorosilane (31.63 g., 0.125 mole) was added drop by drop over a period of 0.5 hr. The temperature rose to

(2) L. S. Moody, U. S. Patent 2,567,724 (1951); *Chem. Abstr.*, **47**, 7534f (1953).

(3) J. F. Hyde, L. K. Frevel, H. S. Nutting, P. S. Petrie, and M. A. Purcell, *J. Am. Chem. Soc.*, **69**, 488 (1947).

(4) T. Nomura, M. Yokoi, and K. Yamazaki, *Proc. Japan Acad.*, **29**, 342 (1954).

(5) M. Yokoi, T. Nomura, and K. Yamazaki, *J. Am. Chem. Soc.*, **77**, 4484 (1955).

(6) H. Kriegsmann and H. Clauss, *Z. anorg. allgem. Chem.*, **300**, 210 (1959).

(7) C. W. Young, P. C. Servais, C. C. Currie, and M. J. Hunter, *J. Am. Chem. Soc.*, **70**, 3758 (1948).

(8) Elemental analyses were performed by Elek Microanalytical Laboratories, Torrance, Calif. 90502. All melting points are corrected. Infrared spectra were run on a Baird-Atomic Model KM-1 recording spectrophotometer.

45° during the addition. When the silane introduction was complete, an additional 150 ml. of benzene was added and the temperature was maintained at 50–55° for 2 hr. while slow introduction of hydrogen sulfide was continued. The mixture was filtered from precipitated pyridine hydrochloride in a drybox, the residue was washed once with 50 ml. of hexane (dried over Na), and the wash liquid was combined with the filtrate. Material volatile to 240° was distilled from the filtrate. The pot residue was dissolved in 150 ml. of boiling hexane plus a minimum amount (about 40 ml.) of benzene, filtered, and allowed to cool and crystallize. A total of 11.2 g. of II (m.p. 186–188°) was obtained. A second crop (3.5 g., m.p. 186–188°) was separated by partial concentration of the mother liquor. Total yield of II was 55%. II consisted of colorless, well-formed crystals of density 1.271 g./ml.; infrared bands (KBr pellet) were at 7.00, 9.01, 10.01, 13.63, 14.08, and 14.38 μ.

Anal. Calcd. for $C_{36}H_{50}S_3Si_3$: C, 67.29; H, 4.67; S, 14.96; Si, 13.08. Found: C, 67.35; H, 4.62; S, 14.40; Si, 12.90.

Failure to heat the reaction mixture after introduction of the silane resulted in reduced yields. II was only slowly hydrolyzed by atmospheric moisture, the melting point dropping only 4° after 2 days' standing in an open container in an air-conditioned laboratory.

Tetraphenylcyclodisilithiane (I).—Into a 30 × 2.5 cm. Pyrex tube connected at the top by a ground glass joint to a cold-finger trap cooled by a Dry Ice–ether slurry and then to an oil pump was placed 2.70 g. (0.004 mole) of II. The tube was suspended to a depth of 10 cm. in an electric furnace, the internal pressure was reduced to less than 1 mm., and heating was maintained at 300–315° for 2 hr. During this period, a tan crystalline solid sublimed to the cool upper walls of the tube. This solid was crystallized from 20 ml. of a hexane–benzene mixture (20% benzene by volume). Recrystallization from the same solvent gave 1.40 g. of colorless crystalline I (m.p. 163–165°; density, 1.268 g./ml.). The yield was 52% based on starting II. Remaining in the tube was 0.25 g. of a viscous glass, while 0.3 g. of an unidentified liquid was collected in the cold finger; infrared bands (KBr pellet) were at 7.00, 8.99, 10.01, 13.45, 14.04, and 14.35 μ.

Anal. Calcd. for $C_{24}H_{20}S_2Si_2$: C, 67.29; H, 4.67; S, 14.96; Si, 13.08. Found: C, 65.96; H, 4.88; S, 14.42; Si, 14.43.

A reduced yield of I (about 25%) resulted when the pyrolysis was carried out at atmospheric pressure. Admixture of I with an equal weight of II produced a material with a melting range of 149–171°.

Molecular Weight Determinations.—Molecular weights (Table I) of I and II were determined in benzene using both standard cryoscopic techniques and vapor pressure osmometric equipment.[9] In addition, the molecular weight of II was determined by the isopiestic procedure described by Childs[10] using azobenzene as the reference compound.

X-Ray Diffraction Measurements.—Table II lists principle X-ray powder photograph lines and intensities for the dimer I and the trimer II. Cu $K\alpha$ radiation (Ni filter) was used. Both samples of I and II were recrystallized from a 3:1 mixture of hexane and benzene.

Acknowledgment.—The authors are indebted to Dr. Elihu Goldish for the X-ray diffraction photographs and interpretation and to Dr. John Stern, who built the vapor pressure osmometer.

(9) J. J. Neumayer, *Anal. Chim. Acta*, **20**, 519 (1959).
(10) C. E. Childs, *Anal. Chem.*, **26**, 1963 (1954).

The Synthesis and Thermal Decomposition of 3,3,6,6-Tetramethyl-1,4-cyclohexadiene

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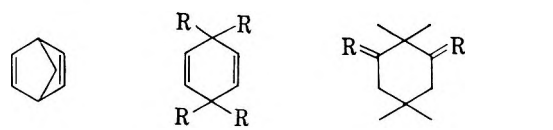
The many unusual properties[1] and reactions[2–10] of norbornadiene (I) have led us to examine other compounds having parallel nonconjugated but interacting double bonds. The simplest hydrocarbon with this structural feature is 1,4-cyclohexadiene (II), which, like I, has an ultraviolet absorption spectrum indicative of interacting π-electron systems.[1,11] Since the chemistry of II is complicated by double-bond isomerization[12] and dehydrogenation to benzene,[13] we decided to synthesize 3,3,6,6-tetramethyl-1,4-cyclohexadiene (III).

Methylation of dimedone[14] gave 2,2,5,5-tetramethylcyclohexane-1,3-dione (IV), which was reduced to a mixture of diols (V) by lithium aluminum hydride and then converted to a crystalline diacetate (VI), m.p. 64–65°,[15] by reaction with acetic anhydride. When pyrolyzed at 350°, the diacetate VI was 10% decomposed and yielded two volatile products, A and B, in a ratio of 10:1, respectively. Pure A, m.p. 7–8°, was obtained by preparative vapor phase chromatography and was identified as III by spectroscopic methods. The infrared and n.m.r. spectra and the v.p.c. retention time of product B proved to be identical with those of authentic *p*-xylene.



I

II, R = H
III, R = CH_3

IV, R = O
V, R = H, OH
VI, R = H, $OCOCH_3$

The infrared absorption spectrum of III exhibits a very strong vinyl hydrogen deformation absorption at 764 cm.$^{-1}$. The corresponding absorption for II is found at a much lower frequency (678 cm.$^{-1}$). The shift may be due to the extensive allylic substitution in III.[16]

The n.m.r. spectrum of III is particularly instructive in that two sharp resonance signals are observed at τ 4.7 and 9.0, with an area ratio of 1:3.1.

The most abundant peaks in the mass spectrum of III are listed in Table I. We tentatively assign the two intense peaks, having *m/e* of 121 and 105, to the relatively stable 1,1,4-trimethylbenzenonium ion[17] and the methyltropylium ion, respectively.

In contrast to the broad envelope of absorption bands

(1) C. F. Wilcox, Jr., S. Winstein, and W. McMillan, *J. Am. Chem. Soc.*, **82**, 5450 (1960).
(2) L. Schmerling, J. Luvisi, and R. Welch, *ibid.*, **78**, 2819 (1956).
(3) S. J. Cristol, G. Brindell, and J. Reeder, *ibid.*, **80**, 635 (1958).
(4) E. F. Ullman, *Chem. Ind.* (London), 1173 (1958).
(5) A. T. Blomquist and Y. C. Meinwald, *J. Am. Chem. Soc.*, **81**, 667 (1959).
(6) H. K. Hall, Jr., *J. Org. Chem.*, **25**, 42 (1960).
(7) C. J. Krespan, B. C. McKusick, and T. L. Cairns, *J. Am. Chem. Soc.*, **83**, 3428 (1961).
(8) G. S. Hammond, A. Fischer, and N. Turro, *ibid.*, **83**, 4674 (1961).
(9) S. J. Cristol, E. Allred, and D. Wetzel, *J. Org. Chem.*, **27**, 4058 (1962).
(10) C. D. Weis, *ibid.*, **28**, 74 (1963).
(11) L. W. Pickett and E. Sheffield, *J. Am. Chem. Soc.*, **68**, 216 (1946).
(12) E. E. van Tamelen, *ibid.*, **77**, 1704 (1955).
(13) D. T. Longone and G. Smith, *Tetrahedron Letters*, **5**, 205 (1962).
(14) R. D. Desai, *J. Chem. Soc.*, 1079 (1932).
(15) This is apparently the diacetate of the *trans* diol (V) reported by A. Allen, R. Sneeden, and J. Colvin [*ibid.*, 557 (1958)].
(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 48.
(17) According to the nomenclature of W. von E. Doering, M. Saunders, H. Boynton, H. Earhart, E. Wadley, W. Edwards, and G. Laber, *Tetrahedron*, **4**, 178 (1958).

exhibited by I and II in the 200–250-mμ region, III shows only intense end absorption, indicating relatively little interaction of the double bonds. In I, the six-membered ring is severely folded (dihedral angle 110°)[1] as a consequence of the methylene bridge; transannular overlap of π-orbitals is thus enhanced on the *endo* side of the molecule. In II, the dihedral angle appears to be about 140°,[18,19] while in III the ring seems to be flattened even more.

TABLE I

MAJOR PEAKS[a] IN THE MASS SPECTRUM OF III

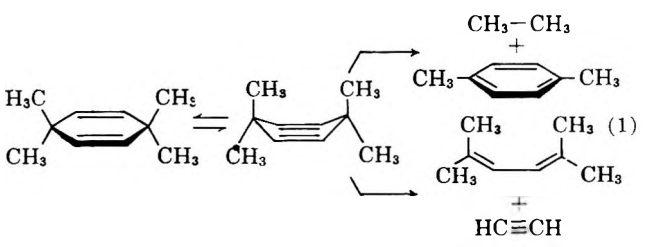
m/e	Relative abundance	m/e	Relative abundance
136 (P)	4.5	91	16.3
122	9.8	79	8.5
121	100.0	77	12.4
119	5.3	65	5.1
106	10.0	53	6.1
105	33.2	51	7.9

[a] Only peaks having $m/e \geq 50$ are considered.

Pyrolysis of the diacetate VI at 410° resulted in complete decomposition, with *p*-xylene as the major product (90%). That the *p*-xylene resulted from subsequent thermal decomposition of III rather than from a unique mode of acetate pyrolysis was shown by experiments in which III itself was pyrolyzed under identical conditions—*p*-xylene was the only product isolated.[20]

Gaseous products from pyrolysis of VI, trapped by liquid nitrogen, were found to contain more ethane than could be reasonably attributed to random combination of methyl radicals. For example, the liquid nitrogen condensate from pyrolysis of a benzene solution of VI at 410° was 1% methane,[21] 44% ethane, 22% ethylene, 9% propane, 18% propylene, and 6% of a C_4 mixture. Consequently we suggest that a primary mode of thermal decomposition of III is an essentially concerted expulsion of ethane.

Fragmentation of III into 2,5-dimethyl-2,5-hexadiene (VII) and acetylene is apparently negligible, since our analytical methods would have detected as little as 1–2% of VII, and authentic VII was shown to survive the pyrolysis conditions unchanged. The absence of this mode of fragmentation is quite reasonable in view of the nearly planar conformation we have assigned to the six-membered ring in III on the strength of its ultraviolet absorption. The only bonds that would overlap well with the π-orbitals during cleavage are those from the ring to the methyl groups. A referee has pointed out that thermal fragmentation of III may proceed from a vibrationally excited nonplanar conformation (eq. 1) and that the previous argument is perhaps an oversimplification. Such a conformation would also be conducive to fragmentation into VII and acetylene; however, the rate of this latter decomposition could well remain much slower than that for ethane expulsion.



(1)

(18) H. Gerding and F. Haak, *Rec. trav. chim.*, **68**, 293 (1949).

(19) F. H. Herbstein, *J. Chem. Soc.*, 2292 (1959).

(20) After our work had been submitted for publication, H. H. Stechl [*Angew. Chem. Intern. Ed. Engl.*, **2**, 743 (1963)] reported that the photodimer of 1,3,3-trimethylcyclopropene was pyrolyzed to durene in 40% yield at 390°. The author suggested a hexamethyl-1,4-cyclohexadiene corresponding to our compound III as an intermediate.

(21) A significant amount of methane may have been lost during the vacuum-line operations that preceeded analysis.

Experimental

The pyrolysis apparatus employed in this work consisted of a 20-mm. Pyrex column packed with 1/16-in. Pyrex helices to a height of 23 cm. This column was fitted with a Hershberg dropping funnel modified so that an inert gas (nitrogen or helium) sweeps through the apparatus as the reactant is slowly added. Control devices for the heating unit (±2°) and gas supply and a series of traps at the bottom of the pyrolysis column complete the system.

Analytical methods consist of gas chromatography using a 12-ft. alumina column and a 6-ft. Apiezon L (30%) column, infrared spectroscopy, mass spectroscopy, and nuclear magnetic resonance spectroscopy. Microanalysis were performed by Spang Laboratory, Ann Arbor, Michigan.

2,2,5,5-Tetramethylcyclohexane 1,3-Diacetate (VI).—Crude 2,2,5,5-tetramethylcyclohexane-1,3-diol (V, 31.7 g.), prepared by reduction of dimethyldimedon (IV)[14] with lithium aluminum hydride (2.5 moles for each mole of diketone) in tetrahydrofuran, was dissolved in 1090 ml. of dry pyridine and treated with 365 ml. of acetic anhydride. After 2 days at room temperature, the reaction mixture was quenched by adding cold methanol and yielded a viscous oil, b.p. 95–100° at 1 mm., which slowly crystallized. Further crystallizations from cold pentane and from aqueous methanol gave colorless needles, m.p. 64–65°, having a raspberry-like odor.

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 65.36; H, 9.40. Found: C, 65.66; H, 9.40.

Pyrolysis of VI. A. Pyrolysis of a pentane solution of VI in a stream of helium at 350° resulted in very little decomposition. Analysis of the crude pyrolysate indicated that roughly 10% of the diacetate had reacted yielding a 10:1 mixture of 3,3,6,6-tetramethyl-1,4-cyclohexadiene (III) and *p*-xylene. These materials were isolated by preparative gas chromatography and identified spectroscopically (see text).

B.—A solution of VI (2.5 g.) in benzene (6 ml.) was slowly passed through the pyrolysis column at 410°. Helium was used as the carrier gas and the effluent was directed through three receivers cooled, respectively, by ice, Dry Ice, and liquid nitrogen. The material trapped in the first receiver was taken up in pentane, washed with dilute sodium bicarbonate, and distilled. Gas chromatographic analysis of the distilled fractions and the pot residue failed to disclose any unreacted VI and indicated *p*-xylene as the major product (50% actual yield) accompanied by traces of III.

The contents of the trap cooled by liquid nitrogen were analyzed by gas chromatography using a 12-ft. column packed with Alcoa activated alumina Grade F-1 and employing Phillips Hydrocarbon Mixture No. 40 as a standard. The results of this analysis are listed in the main part of this paper.

Pyrolysis of III.—A solution of III (200 mg.) in pentane (5 ml.) was pyrolyzed at 410°, the rate of addition and helium flow being identical with that employed in the previous experiment. The crude pyrolysate (90 mg.) proved to be an equimolar mixture of *p*-xylene and pentane.

Acknowledgment.—We are indebted to the National Science Foundation, Undergraduate Research Participation Program, for a grant to Cecelia Dzurella.

Stereiosomerism. II. The Synthesis of Some *cis*- and *trans*-1,3-Cyclopentanedialkanoic Acids[1,2]

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Previously we reported[3] the unequivocal synthesis of the isomeric 1,3-cyclohexanediacetic and dipropionic acids and a large-scale synthesis of *trans*-1,3-cyclohexanedipropionic acid by Wolff–Kishner reduction of 2,6-cyclohexanonedipropionic acid, the *cis* isomer being isolated in only trace quantities. We report here synthesis of the corresponding isomeric cyclopentanediacetic and dipropionic acids (**1a**–**2b**) and a convenient, large-scale synthesis of the *cis*- and *trans*-1,3-cyclopentanedipropionic acids.

Utilizing the readily available *cis*- and *trans*-1,3-cyclopentanedicarboxylic acids,[4a,b] the isomeric diacetic and dipropionic acids were prepared by Arndt–Eistert homologation as described previously.[3] The pertinent data for these compounds are recorded in Table I.

TABLE I

PHYSICAL AND ANALYTICAL DATA OF 1,3-CYCLOPENTANEDIALKANOIC ACIDS

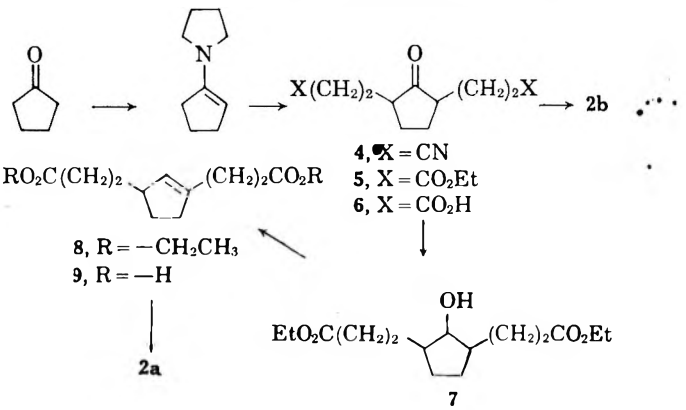
Acid	M.p., °C.[a]	Yield, %[b]	—Calcd., %— C	H	—Found, %— C	H
cis-Diacetic (**1a**)	141–142	23[c]	58.05	7.58	58.06	7.60
trans-Diacetic[e] (**1b**)	152–153	40[d]	58.05	7.58	58.36	7.84
cis-Dipropionic (**2a**)	100–101	26[c]	61.66	8.47	61.53	8.38
trans-Dipropionic (**2b**)	101–102	30[d]	61.66	8.47	61.86	8.55

[a] All samples were recrystallized three times from water. [b] Yields after one recrystallization. [c] Diazald used as diazomethane precursor. [d] DuPont EXR-101 used as diazomethane precursor. [e] R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon [*J. Chem. Soc.*, 1803 (1953)] reported a compound, m.p. 135.5–137.5°, as *trans*-diacetic acid. The mode of their reaction sequence and the accord of **1b** being *trans*-diacetic acid suggests their compound is not *trans*-diacetic acid.

In part I of this series[3] a stereospecific synthesis of the isomeric dipropionic acids (**2a** and **2b**) was developed which utilized the enamine synthesis of Stork and coworkers.[5] In view of the applicability of this method to the cyclohexane series it seemed reasonable to anticipate similar results with the cyclopentane series.

When acrylonitrile was added to the pyrrolidine enamine of cyclopentanone in ethanol a 27% yield of the desired 2,5-cyclopentanonedipropionitrile (**4**), m.p. 66–67°, was obtained[6] along with a high-melting solid. This latter solid material was highly insoluble in most common solvents, its infrared spectrum displayed nitrile and five-ring ketone bands (2245 and 1740 cm.$^{-1}$, respectively), and its elemental analysis was low in carbon and hydrogen for a tripropionitrile adduct. No further investigations are planned for this material.

The ketodinitrile (**4**) was converted directly to the known[7] ketodipropionic acid ester (**5**) in 87% yield by treatment with absolute ethanol and sulfuric acid, followed by addition of water. Hydrolysis of this diester gave the known 2,5-cyclopentanonedipropionic acid (**6**)[7] in 85% yield.



Wolff–Kishner reduction (Huang-Minlon modification[8]) of the ketodinitrile (**4**) or keto diacid (**6**) gave an 86% yield of *trans*-1,3-cyclopentanedipropionic acid (**2b**). As in the case of the reduction of 2,6-cyclohexanonedipropionic acid,[3] the reduction of **4** and **6** appears to be a stereoselective process and, in this case, no *cis* diacid (**2a**) was found.

As noted previously,[3] the Wolff–Kishner reduction of α,α'-disubstituted cyclic ketones appears to yield predominately *trans*-1,3-disubstituted products. The configurations of the ketodinitrile (**4**) or keto diacid (**6**) are not known, but might be presumed *cis*. A further complicating factor is the well-known mobility between conformations of cyclopentane derivatives.[9] Furthermore, before an explanation of this apparent stereoselective reduction may be offered it is also necessary to determine whether a "2-alkyl ketone effect" exists for cyclopentanones and also what effects hydrazone formation and stereochemistry play in the reduction sequence. Such studies are in progress and will be reported elsewhere.

Reduction of the keto diester (**5**) with sodium borohydride in ethanol gave the hydroxy diester (**7**) in 81% yield. This alcohol was dehydrated by refluxing in benzene with *p*-toluenesulfonic acid, the water formed in the reaction being removed by azeotropic distillation, to yield the olefinic diester (**8**). Hydrolysis of the diester gave the olefinic diacid (**9**) in an over-all yield of 54%. The configuration and/or isomeric composition of the hydroxy diester (**7**) could not be reliably determined either by gas–liquid chromatog-

(1) Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) A portion of this work was presented at the Annual Meeting of the Southeastern Regional Section of the American Chemical Society, Nov. 14, 1963, Charlotte, N. C.

(3) T. L. Westman, R. Paredes, and W. S. Brey, Jr., *J. Org. Chem.*, **28**, 3512 (1963).

(4) (a) S. F. Birch, W. J. Oldham, and E. A. Johnson, *J. Chem. Soc.*, 818 (1947); (b) K. T. Pospischill, *Chem. Ber.*, **31**, 1951 (1898).

(5) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(6) Addition of ethyl acrylate to this enamine under conditions expected to yield the diadduct (**5**)[3] consistently gave a material of undetermined structure, b.p. 208° (0.1 mm.).

(7) N. J. Leonard and W. J. Middleton, *J. Am. Chem. Soc.*, **74**, 5114 (1952).

(8) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(9) E. L. Eliel, "The Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc. New York, N. Y., 1962, pp. 248–252.

raphy or analysis of the n.m.r. spectrum.[10] The position of the double bond in the olefinic diacid (**9**) is also not known with certainty since the vinyl proton signal in the n.m.r. spectrum of this compound was not sufficiently resolved for analysis.

Hydrogenation of the olefinic diacid (**9**), using 5% rhodium on alumina and acetic acid as solvent, gave the pure *cis*-dipropionic acid (**2a**) in 86% yield. The apparent stereoselectivity of this reduction suggests that the double bond is in the 1-position since this would allow the 3-alkyl side chain to have a maximum steric effect during the course of the reduction.

Experimental[11]

2,5-Cyclopentanonedipropionitrile (4). A.—The preparation of the pyrrolidine enamine of cyclopentanone followed the general procedure of Stork, *et al.*[5] In general, the enamine was used in crude form and was not distilled.

B.—The crude enamine (from 252 g., 3 moles, of cyclopentanone) was dissolved in 1 l. of absolute ethanol and the mixture was cooled (ice bath), with stirring, and 500 ml. (*ca.* 400 g., 7.5 moles) of acrylonitrile was added dropwise.[12] After the addition was complete the mixture was warmed to room temperature and then refluxed for 5 hr. after which time 250 ml. of water was added and refluxing was continued for an additional hour. The solvent and other volatile materials were removed *in vacuo* (100° at 30 mm.) and a crystalline material formed during the initial reflux period was collected by suction filtration and washed with chloroform.[13] The chloroform wash and an additional 500 ml. of chloroform were added to the liquid reaction product and this resulting solution was washed with three 200-ml. portions of 3 *N* hydrochloric acid, followed by water. After drying over anhydrous magnesium sulfate the chloroform was removed *in vacuo* to yield a thick viscous oil which deposited 106 g. of crystalline 2,5-cyclopentanedipropionitrile after standing several days in the refrigerator. Removal of further liquid from the residual oil (mononitrile?) by distillation up to 180° (0.3 mm.), followed by allowing the viscous residue to stand in the refrigerator overnight, gave an additional 47 g. of the dinitrile. The combined yield of 2,5-cyclopentanonedipropionitrile was 153 g. (27%), m.p. 63–65°, after washing the crystalline material with 50% ethanol, followed by drying in a vacuum desiccator. An analytical sample of this material had m.p. 66–67° after two recrystallizations from 95% ethanol.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.23; H, 7.36; N, 14.56.

The initial crystalline material formed during the reaction was recrystallized twice from acetone, m.p. 178–179°, and submitted for analysis.

Anal. Calcd. for $C_{14}H_{17}N_3O$ (2,2,5-cyclopentanonetripropionitrile): C, 69.11; H, 7.04. Found: C, 68.13; H, 6.49.

2,5-Cyclopentanonedipropionic Acid (6).—2,5-Cyclopentanonedipropionitrile (**4**) (47 g., 0.25 mole) was refluxed for 3 hr. with 500 ml. of concentrated hydrochloric acid. At the end of this period the solution was evaporated to dryness *in vacuo* (steam bath) and the solid residue was triturated with 250 ml. of ethanol. Removal of ammonium chloride by filtration and evaporation of the ethanol yielded 48 g. (85%) of 2,5-cyclopentanonedipropionic acid (**6**), m.p. 121–122.5° after two recrystallizations from dioxane–hexane (lit.[7] m.p. 122°).

***trans*-1,3-Cyclopentanedipropionic Acid (2b) *via* Wolff–Kishner Reduction of 4.**—2,5-Cyclopentanonedipropionitrile (**4**, 57 g., 0.3 mole) was mixed with potassium hydroxide (84 g., 1.5 moles) dissolved in 600 ml. of diethylene glycol. Hydrazine hydrate (85%, 42 ml., *ca.* 1.2 moles) was added and the mixture was refluxed for 1.5 hr. (*ca.* 135°) after which time the condenser was removed and the mixture was heated to 200–220° and maintained at this temperature for about 4 hr., or until the evolution of nitrogen had ceased. After the mixture was cooled, 600 ml. of water was added and this solution was extracted once with ether. The basic, aqueous solution was acidified by the addition of 600 ml. of 6 *N* hydrochloric acid and extracted with five 200-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate followed by removal of the ether to yield 55.0 g. (86%) of *trans*-1,3-cyclopentanedipropionic acid (**2b**), m.p. 96–97° after one recrystallization from water. A mixture melting point of this material with the *trans*-dipropionic acid (m.p. 101–102°) previously prepared *via* the Arndt–Eistert sequence (*vide supra*) was 98–100°. A mixture melting point of this acid with the *cis*-dipropionic acid (**2a**, m.p. 100–101°) was 88–94°. The infrared spectra of the two samples of *trans*-dipropionic acid were identical, except for band intensities.

Following essentially the same procedure as described above, 2,5-cyclopentanonedipropionic acid (**6**) was converted, in comparable yield as above, to the *trans*-dipropionic acid (**2a**).

Diethyl 2,5-Cyclopentanonedipropionate (5).—2,5-Cyclopentanonedipropionitrile (**4**, 140 g., 0.74 mole) was mixed with 170 ml. (*ca.* 3 moles) of absolute ethanol and 300 ml. of dry benzene. Concentrated sulfuric acid (289 g., 3 moles) was added cautiously and the mixture was then refluxed for 12 hr. After cooling to room temperature, the mixture was poured onto 800 ml. of water–ice mixture, the benzene layer separated, and the aqueous solution extracted with ether. The combined ether–benzene extracts were dried over anhydrous magnesium sulfate and the solvent was removed to yield 181 g. (87%) of crude diethyl 2,5-cyclopentanonedipropionate (**5**). Distillation of this material gave pure diethyl ester (**5**), b.p. 170–171° (0.55 mm.), $n^{20}D$ 1.4612 [lit.[7] b.p. 161–162° (0.4 mm.), $n^{20}D$ 1.4633].

Diethyl 2,5-Cyclopentanoldipropionate (7)—To a solution of 48 g. (0.17 mole) of diethyl 2,5-cyclopentanonedipropionate (**5**) in 400 ml. of absolute ethanol, cooled in an ice bath, was added, with stirring, 4 g. (0.1 mole) of sodium borohydride over a 15-min. period. Stirring was continued for an additional 2 hr., the mixture was poured into 800 ml. of ice water and the aqueous mixture was extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate and the solvent then removed to yield an oil. Vacuum distillation of this oil gave 39 g. (81%) of diethyl 2,5-cyclopentanoldipropionate (**7**), b.p. 175–176°(0.55 mm.), $n^{20}D$ 1.4686.

A satisfactory analysis of this material could not be obtained. Similarly, attempts to prepare solid derivatives of this compound also were unsuccessful.

1,3-Cyclopentan-1-enedipropionic Acid (9).—Diethyl 2,5-cyclopentanoldipropionate (**7**, 10 g., 0.035 mole) was dissolved in 50 ml. of dry benzene and 1 g. of *p*-toluenesulfonic acid was added. The mixture was refluxed overnight under a water separator, or until no further water was formed. The benzene solution was then washed with sodium bicarbonate solution, followed by water, and then dried over anhydrous magnesium sulfate. The benzene was then removed *in vacuo* to give an oil which was extracted with pentane to leave behind unchanged alcohol diester (**7**) which is insoluble in pentane. The pentane was removed *in vacuo* to give 8.4 g. (90%) of crude diethyl 1,3-cyclopentan-1-enedipropionate (**8**). The crude diester (**8**, 8.4 g., 0.031 mole) was added to a solution of 7.0 g. (0.125 mole) of potassium hydroxide in 50 ml. of methanol and this mixture was refluxed, with stirring, for 3 hr. After this time, the solution was evaporated to dryness and the residue was dissolved in a minimum amount of water. This basic, aqueous solution was extracted once with ether and then acidified with 6 *N* hydrochloric acid. The acidified aqueous solution was extracted with ether, the ether solution dried over anhydrous magnesium sulfate, and the solvent removed to yield 5.1 g. (77%) of crude 1,3-cyclopent-1-enedipropionic acid (**9**). An analytical sample was obtained by three recrystallizations from water, m.p. 81–82°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.05; H, 7.49.

***cis*-1,3-Cyclopentanedipropionic Acid (2a) *via* Reduction of 9.**—Crude 1,3-cyclopentan-1-enedipropionic acid (**9**, 20.0 g., 0.094 mole), m.p. 77–79°, was dissolved in 200 ml. of glacial acetic acid along with 1.5 g. of 5% rhodium on alumina. Hydrogenation was performed using a modified Paar apparatus at an initial pressure of 30 lb. Hydrogen uptake was complete in *ca.* 3 hr. (0.09 mole hydrogen), the mixture was filtered and poured into 500 ml. of water, and the aqueous solution was extracted with ether. After drying the ether extracts over anhydrous magnesium sulfate, the solvent was removed *in vacuo* to yield crude product, containing traces of acetic acid. The acetic acid was removed by azeotropic distillation with heptane to yield 17.3 g.

(10) *Cf.* also the difficulties encountered in the analysis of similar cyclohexane derivatives, ref. 3.

(11) All melting points are corrected; boiling points are uncorrected.

(12) The addition of acrylonitrile to compounds containing active hydrogen and the generation of considerable heat and caution must be used, particularly for large-scale reactions.

(13) This material is very difficultly soluble in common solvents.

(86%) of crude *cis*-1,3-cyclopentanedipropionic acid (2a) which had m.p. 98–99° after one recrystallization from water. A mixture melting point of this acid with an analytical sample of *cis*-1,3-cyclopentanedipropionic acid (m.p. 100–101°) was 98–99°. A mixture melting point of this acid with an analytical sample of the *trans*-dipropionic acid (2b, m.p. 101–102°) was 87–92°. The infrared spectra of the two samples of *cis*-1,3-cyclopentanedipropionic acid were identical except for band intensities.

The Preparation of o-Amino-Substituted Arylphosphonic Acids[1]

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Twelve years ago we described the preparation of *o*-aminophenylphosphonic acid by the copper-catalyzed reaction between *o*-bromophenylphosphonic acid and aqueous ammonia.[2] Recently, Lukin and Kalinina[3] have reported that they were unable to prepare *o*-aminophenylphosphonic acid by this reaction but obtained instead a 41% yield of *o*-hydroxyphenylphosphonic acid. In their procedure they isolated the phosphonic acid as a copper complex which was converted to the free acid by means of hydrogen sulfide. They reported further that the acid thus obtained gave a negative test for the amino group (by diazotization and coupling) and gave carbon, hydrogen, and phosphorus analyses in reasonable agreement with the theoretical values for *o*-hydroxyphenylphosphonic acid.[4]

In view of the results reported by Lukin and Kalinina, we have re-examined the matter and have found that the phosphonic acid obtained by the procedure they described contains nitrogen and is in fact identical with the *o*-aminophenylphosphonic acid prepared by us in 1952. The properties of *o*-hydroxyphenylphosphonic acid, which has recently been prepared by an unambiguous method,[5] are quite different from those of the material described by the Russian investigators. Thus the *o*-hydroxy compound has m.p. 124–127°, is extremely soluble in water, and gives a purple color with aqueous ferric chloride; by contrast, the acid described by Lukin and Kalinina has m.p. 178–179°, is only moderately soluble in water, and gives an orange-brown color with ferric chloride. Their inability to diazotize their material is surprising, since Miyata[6] has recently obtained an azo compound by diazotizing *o*-aminophenylphosphonic acid (prepared by the amination of *o*-bromophenylphosphonic acid with aqueous ammonia) and coupling the resulting diazonium salt with chromotropic acid.

Although Lukin and Kalinina are therefore mistaken about the identity of the phosphonic acid they obtained, their method of isolation is highly recommended. It is more convenient and gives more consistent results than the tedious isolation procedure we originally described.[2] Other *o*-amino-substituted arylphosphonic acids can also be isolated as copper complexes. Thus we have prepared two new compounds, 2-amino-4-tolyl- and 2-amino-5-tolylphosphonic acids, and found that they form insoluble copper complexes. It is of interest that Lukin, Kalinina, and Zavarikhina[7] have reported that 2-amino-5-chlorophenylphosphonic acid can be isolated as a copper complex; compounds in which the amino group is *meta* or *para* to the phosphono (PO_3H_2) group apparently do not form insoluble copper complexes.[8]

In the course of this work, it was found that *o*-chloro-substituted arylphosphonic acids can be converted to the corresponding *o*-amino compounds under the same conditions used with the *o*-bromo-substituted arylphosphonic acids. This result is of some interest since chloro-substituted anilines (from which the phosphonic acids are made) are usually much less expensive than are the corresponding bromo-substituted anilines.

Experimental[9]

o-Aminophenylphosphonic Acid.—*o*-Bromophenylphosphonic acid[10] (25.7 g.), 18 g. of freshly prepared cuprous oxide, and 400 ml. of concentrated aqueous ammonia were allowed to react under the exact conditions specified by Lukin and Kalinina.[3] On acidification of the reaction mixture to pH 4, a greenish precipitate was obtained, which was removed by filtration and dissolved in 100 ml. of 4 *N* hydrochloric acid. Hydrogen sulfide was then passed into the solution to precipitate copper sulfide. The filtrate from the copper sulfide was decolorized with charcoal and treated with solid sodium carbonate until just alkaline to congo red (pH 3.7). The light gray precipitate thus obtained was washed with cold water and then dried *in vacuo*. The yield was 10.1 g. (58%), m.p. 189–193°. Mixture melting point with authentic *o*-aminophenylphosphonic acid[2] was 190–196°.

Anal. Calcd. for $C_6H_8NO_3P$: N, 8.09; P, 17.89. Found: N, 7.91; P, 17.69.

Some of the reaction conditions described in ref. 3 are not essential to the success of the above preparation. Thus, J. T. Baker reagent grade cuprous oxide is as satisfactory as the freshly prepared material. Furthermore, it is not necessary to pass ammonia gas through the reaction mixture (as Lukin and Kalinina have specified) in order to keep the ammonia concentration constant; equally good results are obtained by simply heating the stirred mixture of phosphonic acid, cuprous oxide, and aqueous ammonia for 18 hr. at 70–80°. It has also been found that *o*-chlorophenylphosphonic acid[11] can be substituted for *o*-bromophenylphosphonic acid in the above reaction.

2-Amino-4-tolylphosphonic Acid.—2-Bromo-4-tolylphosphonic acid[12] (27.6 g.) and 9.0 g. of cuprous oxide were added to 200 ml. of aqueous ammonia (*d* 0.90) in a three-necked flask equipped with a sealed stirrer, a reflux condenser, and a thermometer. The mixture was stirred and heated at 70–80° for 18 hr. The copper complex was isolated as described above and then dissolved in 400 ml. of 4 *N* hydrochloric acid. After the

(1) This work was supported by Research Grant GM-09479 from the National Institutes of Health, U. S. Public Health Service.

(2) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **74**, 753 (1952).

(3) A. M. Lukin and I. D. Kalinina, *Zh. Obshch. Khim.*, **30**, 1597 (1960).

(4) It should be noted that the theoretical values for carbon, hydrogen, and phosphorus do not differ greatly for *o*-aminophenylphosphonic acid and *o*-hydroxyphenylphosphonic acid. The analytical results reported by Lukin and Kalinina are in satisfactory agreement with the theoretical values for *o*-aminophenylphosphonic acid.

(5) L. D. Freedman, G. C. Doak, and E. L. Petit, *J. Org. Chem.*, **25**, 140 (1960).

(6) H. Miyata, *Bull. Chem. Soc. Japan*, **36**, 127 (1963).

(7) A. M. Lukin, I. D. Kalinina, and G. B. Zavarikhina, *Zh. Obshch. Khim.*, **30**, 4072 (1960).

(8) A. M. Lukin and I. D. Kalinina, *Dokl. Akad. Nauk SSSR*, **137**, 873 (1961).

(9) Melting points were determined as previously described [G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **73**, 5658 (1951)]. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(10) G. O. Doak and L. D. Freedman, *ibid.*, **75**, 683 (1953).

(11) G. O. Doak and L. D. Freedman, *ibid.*, **73**, 5658 (1951).

(12) The preparation of 2-bromo-4-tolylphosphonic acid has been previously described [L. D. Freedman, H. Tauber, G. O. Doak, and H. J. Magnuson, *ibid.*, **75**, 1379 (1953)] but was erroneously called "2-Br-5-CH_3-$C_6H_3PO_3H_2$."

copper was removed, the pH of the solution was adjusted to 3.7, whereupon the phosphonic acid crystallized from solution. The crystals were washed with cold alcohol and then dried *in vacuo*. The yield was 4.6 g. (49%), m.p. 213–215°.

Anal. Calcd. for $C_7H_{10}NO_3P$: N, 7.48; P 16.55. Found: N, 7.68; P, 16.60.

2-Amino-5-tolylphosphonic Acid.—2-Chloro-5-tolylphosphonic acid monohydrate[13] (11.2 g.) was treated with cuprous oxide and aqueous ammonia by the procedure described above. The copper complex of the amino acid was isolated, dissolved in 90 ml. of 4 *N* HCl, and then converted to the free acid. The yield was 4.4 g. (47%), m.p. 219–222°.

Anal. Calcd. for $C_7H_{10}NO_3P$: N, 7.48; P, 16.55. Found: N, 7.23; P, 16.21.

Acknowledgment.—The authors wish to acknowledge the invaluable technical assistance given by Mr. Austin C. Cooley.

(13) L. D. Freedman and G. O. Doak, *J. Org. Chem.* **24**, 638 (1959).

Ferrocenylphosphonous Dichloride from Ferrocenylphosphinic Acid. The >PH(O) ⇌ >P(OH) Tautomerism[1]

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The conversion of phosphinic acids (I) to phosphonous dichlorides (III) by treatment with excess phosphorus trichloride has been considered by Frank[3] to be evidence for tautomerism involving form II. Re-

$$\underset{\text{I}}{ArPH(O)OH} \rightleftharpoons \underset{\text{II}}{ArP(OH)_2} \longrightarrow \underset{\text{III}}{ArPCl_2}$$

cently, the existence of such an equilibrium was questioned by Quin and Dysart[4] who found only one inflection in the titration curves of several examples of I including those examined by Frank,[3] and that reaction of the acids with diazomethane failed to give the diesters. They suggested that, in the formation of III, the shift to tricovalent phosphorus involves not I, but the chloro derivative, ArPH(O)Cl.

We have found that the method of Frank[3] is applicable to the conversion of ferrocenylphosphinic acid to ferrocenylphosphonous dichloride. The compound that we have used has an estimated electron density on phosphorus of such a magnitude[5] that Quin and Dysart's hypothesis[4] would predict failure to undergo the tautomeric shift. We suggest that our results, like those of Frank,[3] indicate an equilibrium involving form II, and that the results of Quin and Dysart are not inconsistent with the existence of II.[6]

It is significant that chemical and kinetic evidence point to the existence of a tautomeric equilibrium in a related system.[7,8]

$$(RO)_2P(O)H \rightleftharpoons (RO)_2POH$$

Ferrocenylphosphonous dichloride, a red-orange liquid decomposing on attempted distillation at 0.5 mm., was obtained in 53% yield. Its solubility in *n*-heptane distinguished it immediately from the phosphinic acid which was insoluble in the same solvent. The product was identified by its hydrolysis to the phosphinic acid and conversion to ferrocenylphosphonous dipiperidide, $C_5H_5FeC_5H_4P(NC_5H_{10})_2$. The air-stable dipiperidide, golden platelets with m.p. 106–107°, represents the first known phosphorus amide of ferrocene.

Experimental

Ferrocenylphosphonous Dichloride.[9]—Phosphorus trichloride (3.52 ml., 0.04 mole) was added dropwise over a period of 2 min. to a vigorously stirred slurry of 1.0 g. (0.004 mole) of ferrocenylphosphinic acid[10] in 20 ml. of benzene under nitrogen. The addition of only a few drops of phosphorus trichloride caused a sudden, complete solubilization of the acid. The solution was orange in color, no heat developed, and there was no gas evolution. Almost immediately, immiscible phosphorous acid began to appear as a dark greenish, viscous sirup adhering to the walls of the reaction flask. Stirring was continued for 0.5 hr. at room temperature.

After decantation of the orange solution, benzene and unreacted phosphorus trichloride were removed under reduced pressure (aspirator) on a steam bath. The residue, a red-orange liquid which decomposed on attempted distillation at 0.5 mm., was taken up in *n*-heptane. The orange heptane solution plus a small amount of insoluble yellowish solids were decanted from some red-orange, semisolid material adhering to the bottom of the flask. The solids, probably unreacted phosphinic acid, were removed by filtration. Sensitivity of the dichloride to hydrolysis was indicated when evaporation of films of the filtrate in air gave crystalline phosphinic acid. The solvent was evaporated from the filtrate under a stream of nitrogen leaving 0.6 g. (53%) of red-orange liquid product.

Ferrocenylphosphonous Dipiperidide.—The ferrocenylphosphonous dichloride (0.0021 mole) was dissolved without further purification in 20 ml. of *n*-heptane. The solution, which became somewhat cloudy on standing (probably as a result of some hydrolysis), was added dropwise over a period of 5 min. to a vigorously stirred solution of 0.85 ml. (0.0086 mole) of piperidine in 20 ml. of benzene protected against atmospheric moisture. Cooling was applied with an ice–bath during the addition. The orange solution in the reaction flask soon became cloudy with formation of piperidine hydrochloride. After the addition, the mixture was stirred 2 hr. at room temperature, and then filtered. The filtrate was evaporated to dryness on a steam bath. The residue, a dark orange viscous liquid which became brown-orange in color as it solidified, was extracted three times with boiling heptane, and the insoluble, brown-orange, viscous liquid was discarded. After filtration of the combined orange heptane extracts, evaporation of the solvent under an air stream gave orange crystals together with a yellow viscous liquid which gradually solidified on standing; the yield (crude) was 0.32 g. (39.5%). The product was taken up in boiling ethanol, and the solution was filtered, concentrated, and cooled to give 0.1 g. of product in the form of golden platelets, m.p. 106–107° (uncor.).

Anal.[11] Calcd. for $C_{20}H_{29}FeN_2P$: C, 62.51; H, 7.61; Fe, 14.53; N, 7.29; P, 8.06. Found: C, 62.10; H, 7.52; Fe, 14.52; N, 6.75; P, 7.93.

Further concentration and cooling of the mother liquor yielded no more product. After removal of solvent by evapora-

(1) Abstracted in part from the Ph.D. Dissertation of G. P. Sollott, Temple University, Jan., 1962. For previous publication based on this work, *cf.* ref. 10.

(2) (a) Frankford Arsenal; (b) Temple University.

(3) A. W. Frank, *J. Org. Chem.*, **26**, 850 (1961).

(4) L. D. Quin and M. R. Dysart, *ibid.*, **27**, 1012 (1962).

(5) The electron donor ability of the ferrocenyl group appears to be greater than that of *p*-methoxyphenyl; *cf.* E. M. Arnett and R. D. Bushick, *ibid.*, **27**, 111 (1962).

(6) Quin and Dysart's argument against tautomerism has now been questioned by J. Reuben, D. Samuel, and B. L. Silver, *J. Am. Chem. Soc.*, **85**, 3093 (1963).

(7) G. O. Doak and L. D. Freedman, *Chem. Rev.*, **61**, 31 (1961).

(8) D. Samuel and B. L. Silver, *J. Org. Chem.*, **28**, 2089 (1963).

(9) The method was based on A. W. Frank's procedure A, ref. 3.

(10) G. P. Sollott and E. Howard, Jr., *J. Org. Chem.*, **27**, 4034 (1962).

(11) The analysis was performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

tion, an odor of piperidine was detected in the residue. Moistened indicator paper turned blue on contact with the residue, indicating that alcoholysis had occurred. Crystallization of phenylphosphonous dipiperidide from ethanol has been reported with no indication that alcoholysis occurs, except that the product possesses a piperidine-like odor.[3]

Infrared Spectra of Ferrocenylphosphonous Dichloride and Ferrocenylphosphonous Dipiperidide.—Infrared spectra were obtained from a liquid smear of the dichloride and from a Nujol mull of the dipiperidide, employing a Perkin-Elmer Model 321 spectrophotometer.

Both compounds show asymmetric ring breathing near 1110 cm.$^{-1}$, and in-plane C–H bending near 1005 cm.$^{-1}$,[12] which are characteristic of monosubstituted ferrocenes.[13] The compounds also show ferrocene C–H stretching and out-of-plane C–H bending bands in the regions 3060–3100 and 810–835 cm.$^{-1}$, respectively.[12] A C–C stretching band appears near 1410 cm.$^{-1}$,[12] in the spectrum of the dichloride, but is absent from this region in the spectrum of the dipiperidide. Both compounds absorb near 1310 and 1025 cm.$^{-1}$ in the regions assigned earlier[10] to the ferrocenylphosphorus group. Bands shown by the dichloride at 1164 and 1199 cm.$^{-1}$ and by the dipiperidide at 1150, 1160 (doublet), and 1212 cm.$^{-1}$ are due possibly to ferrocene in-plane C–H bending.[10,11] Other bands appear in the spectrum of the dipiperidide at 850, 890, 932, 1050, and 1115 (doublet with ferrocene band at 1108) cm.$^{-1}$. Bands attributable to P=O or P—O—H are not present in either spectra.

(12) E. R. Lippincott and R. D. Nelson, *J. Am. Chem. Soc.*, **77**, 4990 (1955).

(13) M. Rosenblum and R. B. Woodward, *ibid.*, **80**, 5443 (1958).

(14) G. P. Sollott, H. E. Mertwoy, S. Portnoy, and J. L. Snead, *J. Org. Chem.*, **28**, 1090 (1963).

Dehydro-1,1′-trimethyleneferrocene

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As part of a study of the chemistry of bridged ferrocenes we were led to examine the transformation of α-keto-1,1′-trimethyleneferrocene tosylhydrazone (**2**) under conditions of the Bamford–Stevens reaction.[2] This base-catalyzed reaction has been shown to give initially a diazo compound, which may undergo cationic decomposition in the presence of proton-donor solvents, or in their absence decompose to carbenic intermediates and thence products of hydrogen migration, skeletal rearrangement, or insertion reactions.[3] We were principally interested in the latter mode of this reaction since the action of carbenes on metallocenes has not been widely explored,[4] and the possibility existed that an insertion reaction might lead to a cyclopropane-bridged ferrocene.

The tosylhydrazone (**2**) was readily prepared from the bridged ketone (**1**) by treatment with toluenesulfonylhydrazine under normal reaction conditions. Irradiation of **2** in dimethoxyethane solution in the presence of sodium methoxide failed to give any well-defined products. When decomposition was carried out thermally in dimethoxyethane solution with sodium methoxide, the products were α-methoxy-1,1′-trimethyleneferrocene and the ketone (**1**), while with dimethyl sulfoxide as solvent 1,1′-trimethyleneferrocene (**4**) in addition to **1** was isolated. However, when the tosylhydrazone was subjected to thermal decomposition in cyclohexane solution in the presence of sodium methoxide or preferably sodium hydride, moderate yields of dehydro-1,1′-trimethyleneferrocene (**3**) were obtained. The structural assignment for this substance is supported by its elemental analysis and by its n.m.r. spectrum (peaks at τ 3.96, 6.05, and 7.23, relative intensity 2:8:2),[5] and is confirmed by its conversion to **4** on catalytic hydrogenation. The new compound is the simplest member of a class of ferrocene derivatives possessing an unsaturated three-carbon bridge linking the two rings.[6]

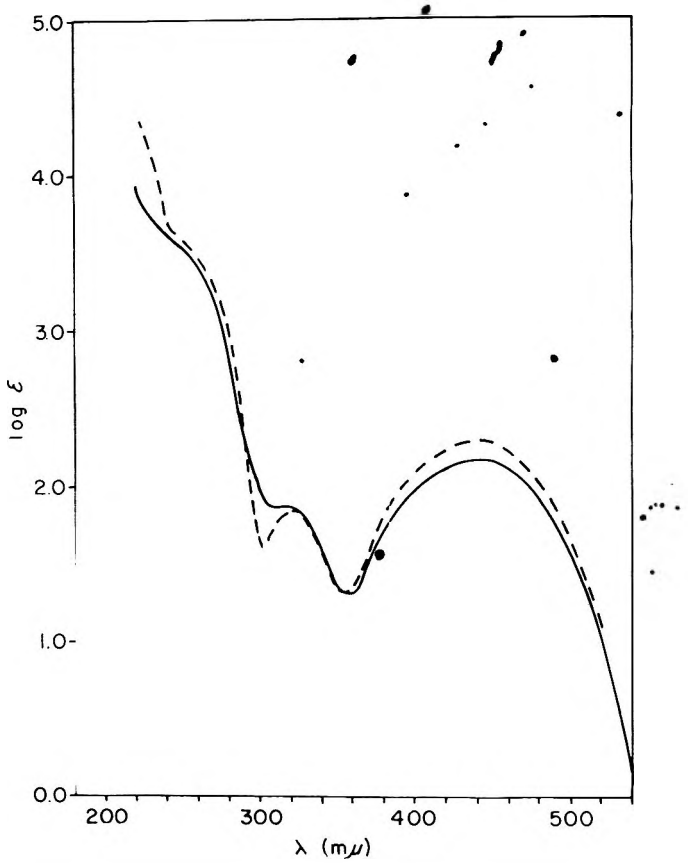


Fig. 1.—Ultraviolet and visible absorption spectra, taken in 95% ethanol: ·····, 1,1′-trimethyleneferrocene (**4**); ———, dehydro-1,1′-trimethyleneferrocene (**3**)

Although the aprotic reaction conditions under which **3** is produced are those favoring the generation of a carbenoid intermediate, no products such as **5** or **6**, which might be expected to be formed from such an intermediate, were detected. In this respect the reaction of **2** more closely resembles the behavior of cyclohexanone and cyclopentanone tosylhydrazones

(1) This research was supported by a grant (RG-5978) from the National Institutes of Health, U. S. Public Health Service.

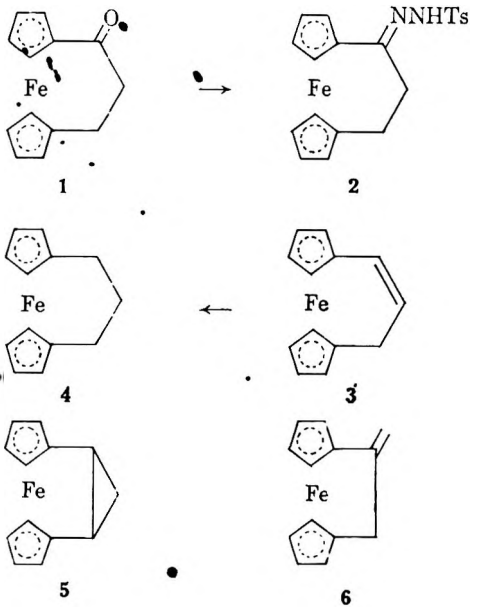
(2) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

(3) (a) L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, **81**, 5512 (1959); **82**, 1002 (1960). (b) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959). (c) P. Clarke, M. C. Whiting, G. Papenmeier, and W. Reusch, *J. Org. Chem.*, **27**, 3356 (1962).

(4) J. H. Richards, K. Plesske, and H. Werner, Abstracts, Symposium on Current Trends in Organometallic Chemistry, University of Cincinnati, Cincinnati, Ohio, June, 1963, p. 77.

(5) Determined in $CDCl_3$ solution at a concentration of approximately 60 mg./ml. and recorded at 60 Mc. with a Varian Model V-4300 spectrometer. Peak positions were calibrated against tetramethylsilane as internal standard by side banding.

(6) For other such compounds, *cf.* M. Rosenblum, A. K. Banerjee, N. Danieli, R. W. Fish, and V. Schlatter, *J. Am. Chem. Soc.*, **85**, 316 (1963); W. Mock and J. H. Richards, *J. Org. Chem.*, **27**, 4050 (1962). K. L. Rinehart, *et al.* [*J. Am. Chem. Soc.*, **84**, 3263 (1962)] had earlier attempted, without success, to prepare dehydro-1,1′-trimethyleneferrocene by dehydration of α-hydroxy-1,1′-trimethyleneferrocene.



than of the corresponding acyclic or small ring carbonyl derivatives which give appreciable amounts of products derived from carbenoid insertion and rearrangement processes.[3a] The possibility that **5** is formed in the reaction, but is rearranged to **3** during chromatographic resolution of the reaction mixture may not, however, be excluded.

A comparison of the ultraviolet spectrum of **3** with that of **4** (Fig. 1) provides a particularly striking demonstration of the absence of conjugation between the ethylenic bond and the cyclopentadienyl ring in **3**.

Experimental

α-Keto-1,1′-trimethyleneferrocene *p*-Toluenesulfonylhydrazone (2).—A solution of 240 mg. (1.0 mmole) of the ketone and 190 mg. (1.0 mmole) of *p*-toluenesulfonylhydrazine in 30 ml. of ethanol containing a few drops of acetic acid was heated on the steam bath for 0.5 hr. On cooling, the hydrazone separated as lustrous golden rods, m.p. 198.5–200.0°, with darkening, yielding 337 mg. (82%). An analytical sample (from ethanol) melted at 201–202°.

Anal. Calcd. for $C_{20}H_{20}FeN_2O_2S$: C, 58.83; H, 4.94; N, 6.86. Found: C, 58.90; H, 4.83; N, 7.02.

Dehydro-1,1′-trimethyleneferrocene (3).—Sodium hydride (180 mg., 7.5 mmoles) was added to a solution of 500 mg. of the tosylhydrazone (1.2 mmoles) in 50 ml. of cyclohexane. The solution was heated at reflux, in an atmosphere of nitrogen, for 12 hr., then cooled, poured into water, and extracted with ether. The combined ether–cyclohexane extract was washed to neutrality and dried over magnesium sulfate. Removal of solvent left a crude crystalline product which was taken up in Skellysolve B and chromatographed on an alumina column. Three bands appeared. The first gave 45 mg. (22%) of **3**, m.p. 100.5–102.5°, after further chromatographic purification followed by sublimation.

The second band afforded 19 mg. of α-keto-1,1′-trimethyleneferrocene (**1**), and the third 120 mg. of starting material. With sodium methoxide as base **3** was obtained in 14% yield.

Anal. Calcd. for $C_{13}H_{12}Fe$: C, 69.68; H, 5.40. Found: C, 70.05; H, 5.28.

Reduction of Dehydro-1,1′-trimethyleneferrocene.—The olefin (25 mg., 0.1 mmole) was taken up in 10 ml. of methanol and hydrogenated at atmospheric pressure and room temperature in the presence of platinum oxide catalyst. At the end of 36 hr., the catalyst was filtered off, solvent was removed, and the product was chromatographed on a short alumina column using Skellysolve B as eluent. In this manner, 11.4 mg. of 1,1′-trimethyleneferrocene, m.p. 100.5–104.0°, was obtained. Its infrared spectrum was identical with that of an authentic sample, and its mixture melting point with a sample of **4** (m.p. 107.5–108.5°) was 105–106°.

A New Phenothiazine Synthesis. The Halogen-Induced Smiles Rearrangement[1]

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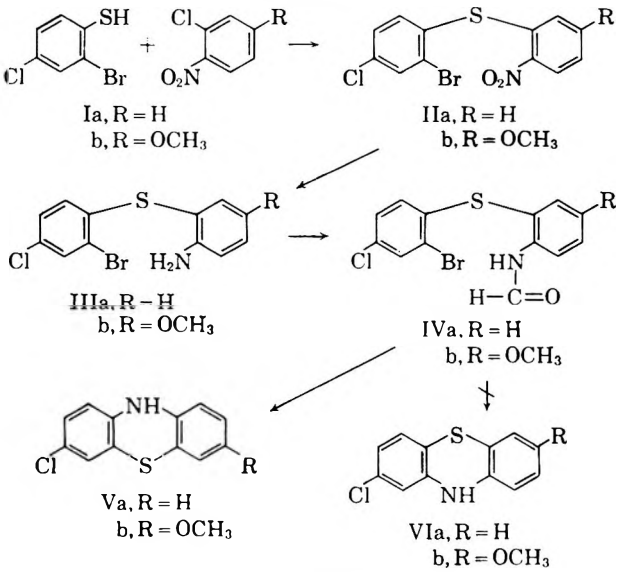
Received March 10, 1964

Bonvicino, Yogodzinski, and Hardy have reported a new Smiles-type rearrangement in which bromo replaces nitro as the activating group.[2] They encountered this rearrangement in the synthesis of phenoxazines by dehydrohalogenation of *o*-bromo-*o*′-alkylaminodiphenyl ethers in benzene in the presence of sodamide. Bonvicino, *et al.*, considered the possibility that the same rearrangement could take place with potassium carbonate in N,N-dimethylformamide (DMF), but they minimized this possibility on theoretical grounds.

Our work on the preparation of the isosteric phenothiazines by dehydrohalogenation of *o*-bromo-*o*′-formamidodiphenyl sulfides (IVa and IVb) has shown that the halogen-induced Smiles rearrangement can indeed take place in DMF–potassium carbonate.

The intermediates (IVa and IVb) were prepared by the routine reaction sequence[3] outlined in Scheme I.

SCHEME I



Cyclizations of IVa and IVb were effected by heating under reflux, in N,N-dimethylformamide, in the presence of anhydrous potassium carbonate and copper–bronze catalyst. Instead of the anticipated 2-chlorophenothiazine (VIa, m.p. 198.5–199.5°)[4–6] and 2-

(1) This rearrangement was first described in our Sixth Progress Report (April 30, 1963) to the Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Md., under Contract SA-43-ph-3758.

(2) G. E. Bonvicino, L. H. Yogodzinski, and R. A. Hardy, Jr., *J. Org. Chem.*, **27**, 4272 (1962).

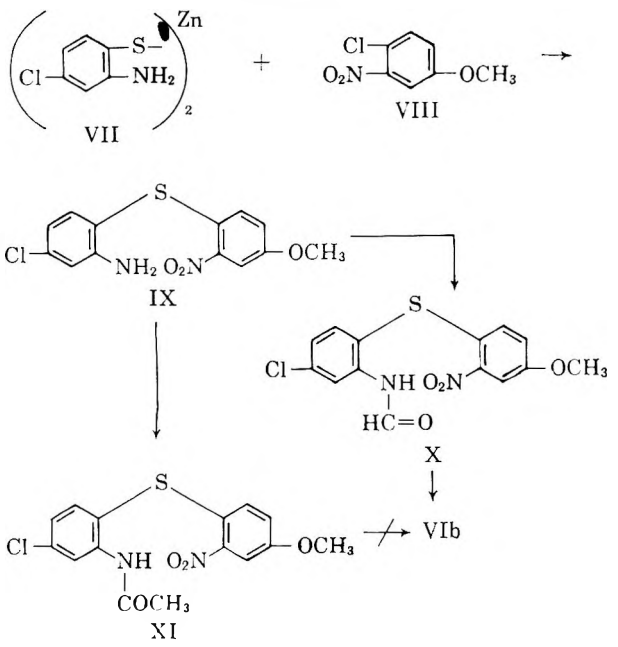
(3) E. A. Nodiff, S. Lipschutz, P. N. Craig, and M. Gordon, *ibid.* **25**, 60 (1960).

(4) P. Charpentier, P. Gaillot, R. Jacob, J. Gaudechon, and P. Buisson, *Compt. rend.*, **235**, 59 (1952).

(5) H. L. Yale, *J. Am. Chem. Soc.*, **77**, 2270 (1955).

(6) We are grateful to Dr. Paul N. Craig of Smith Kline and French Laboratories, Philadelphia, Pa., for samples of 2-chloro- and 3-chlorophenothiazine.

SCHEME II



chloro-7-methoxyphenothiazine (VIb, m.p. 174.5–175°), IVa and IVb yielded, respectively, 3-chlorophenothiazine (Va, m.p. 201–201.5°)[5,6] and 3-chloro-7-methoxyphenothiazine (Vb, m.p. 202–203°).

To permit mixture melting point and infrared comparison, an authentic sample of 2-chloro-7-methoxyphenothiazine (VIb) was prepared as shown in Scheme II.

Adaptations of literature procedures[7-9] provided the 2-nitro-2′-acylaminodiphenyl sulfides (X and XI). Application of the Clarke modification[10] of the Smiles rearrangement to the formamido compound (X) gave a 44% yield of 2-chloro-7-methoxyphenothiazine (VIb). This compound was identical with that obtained by thionation of 3-chloro-4′-methoxydiphenylamine.[11,12]

The Clarke modification was ineffective with the acetamido derivative (XI). Attempts to use standard conditions[9,13] for the conversion of X and XI to VIb were unsuccessful. Starting material, deacylated starting material, and intractable oils were obtained.

Authentic 3-chloro-7-methoxyphenothiazine (Vb) was obtained in very low yield by thionating 4-chloro-4′-methoxydiphenylamine (XII) under very carefully controlled conditions. The major product of this thionation was the dehalogenated compound 3-methoxyphenothiazine. (Similar loss of halogen during thionation of 4-halodiphenylamines has been reported previously.[7,12,14]) Efforts to improve the yield of Vb by eliminating catalyst, by using solvents, and by varying time, temperature, and concentration were to no avail.

The major difference between 2-chloro-7-methoxyphenothiazine and 3-chloro-7-methoxyphenothiazine, in the infrared, lies in the possession by the latter of a single, strong, broad band (12.3 μ) in the region between 12.0 and 13.1 μ.[7] 2-Chloro-7-methoxyphenothiazine has two strong peaks in this region, one at 12.3 and another at 12.6 μ.

Experimental[15]

2-Bromo-4-chloro-5′-methoxy-2′-nitrodiphenyl Sulfide (IIb).—A solution of sodium ethoxide, prepared by adding 1.92 g. (0.084 g.-atom) of sodium metal to 62 ml. of absolute ethanol, was cooled to 10° and treated dropwise with 18.4 g. (0.082 mole) of 2-bromo-4-chlorobenzenethiol.[16] The resulting solution was added to 15.5 g. (0.075 mole) of 3-chloro-4-nitroanisole (Ib)[17] dissolved in 62 ml. of ethanol and the mixture was stirred at room temperature for 20 hr. The yellow solid which separated was washed with water and dried *in vacuo*, m.p. 81–85° (15.6 g., 56%). This material was used in the subsequent reduction without additional purification. An analytical sample was prepared by crystallization from methanol, m.p. 96–97°.

Anal. Calcd. for $C_{13}H_9BrClNO_3S$: C, 41.65; H, 2.40; N, 3.75. Found: C, 41.22; H, 2.58; N, 3.53.

2-Bromo-4-chloro-2′-nitrodiphenyl Sulfide (IIa).—The reaction between 2-bromo-4-chlorobenzenethiol (0.20 mole) and 2-chloronitrobenzene (0.22 mole) was carried out essentially as described for IIb. After heating the reaction mixture under reflux for 3 hr., a 72% yield of IIa was obtained as pale yellow crystals, m.p. 120–121°. Crystallization from ethanol provided an analytical sample, m.p. 123–124°.

Anal. Calcd. for $C_{12}H_7BrClNO_2S$: C, 41.80; H, 2.03; N, 4.07. Found: C, 42.54; H, 2.34; N, 4.09.

2′-Amino-2-bromo-4-chloro-5′-methoxydiphenyl Sulfide (IIIb).—Hydrogen chloride gas was passed into a suspension of 42 g. (0.19 mole) of stannous chloride dihydrate in 192 ml. of glacial acetic acid until the suspension cleared. This solution was added dropwise to a solution of 10 g. (0.027 mole) of IIb in 36 ml. of glacial acetic acid previously heated to 85°. The temperature was maintained at 80–95° during addition and for 1 hr. afterwards. The mixture was allowed to stand at room temperature overnight, cooled with ice, and treated with 1 l. of 10% sodium hydroxide solution. The resulting off-white solid was triturated with 10% sodium hydroxide and extracted with ether. The ether was dried over magnesium sulfate and evaporated under reduced pressure to give 6.3 g. (66%) of tan solid (m.p. 102–106°) sufficiently pure for formylation. An aliquot was crystallized three times from ethanol to yield a tan, crystalline analytical sample, m.p. 107.5–109.5°.

Anal. Calcd. for $C_{13}H_{11}BrClNOS$: C, 45.39; H, 3.19; N, 4.14. Found: C, 45.47; H, 3.26; N, 4.18.

2-Amino-2′-bromo-4′-chlorodiphenyl Sulfide (IIIa).—A suspension of 49.2 g. (0.15 mole) of IIa in 640 ml. of absolute ethanol was warmed to 55° and a solution of 120 g. (0.53 mole) of stannous chloride dihydrate in 64 ml. of concentrated hydrochloric acid was added in several portions. The mixture was heated under reflux for 1 hr., cooled to room temperature, and poured into 2 l. of cold water. The yellow oil which separated on standing was extracted with ether. The ether was dried over magnesium sulfate and concentrated under reduced pressure to leave 44.5 g. of yellow oil. This oil was formylated without additional treatment.

2-Bromo-4-chloro-2′-formamido-5′-methoxydiphenyl Sulfide (IVb).—A mixture of 6 g. (0.017 mole) of IIIb and 60 g. of 90% formic acid was heated under reflux for 6.5 hr. and allowed to stand at room temperature overnight. Tan crystals separated (4.64 g., 72%), m.p. 87–89°. Crystallization from ethanol raised the melting point to 134–137°. The same melting point increase was also produced by maintaining the tan crystals at 85° for 1 hr. The infrared spectra (Nujol) of the high- and low-melting materials were almost identical. Some peaks in the spectrum of the high-melting form were displaced slightly toward longer wave lengths. These differently melting solids were most

(7) E. A. Nodiff and P. N. Craig, *J. Org. Chem.*, **26**, 824 (1961).
(8) K. Florey and A. R. Restivo, *ibid.*, **23**, 1018 (1958).
(9) H. L. Yale, F. Sowinski, and J. Bernstein, *J. Am. Chem. Soc.*, **79**, 4375 (1957).
(10) F. H. Clarke, G. B. Silverman, C. W. Watnick, and N. Sperber, *J. Org. Chem.*, **26**, 1126 (1961).
(11) J. Cymerman-Craig, W. P. Rogers, and M. E. Tate, *Australian J. Chem.*, **9**, 397 (1956).
(12) P. K. Kadaba and S. P. Massie, *J. Org. Chem.*, **24**, 986 (1959).
(13) A. Roe and W. F. Little, *ibid.*, **20**, 1577 (1955).
(14) J. Cymerman-Craig, W. P. Rogers, and G. P. Warwick, *Australian J. Chem.*, **8**, 252 (1955).

(15) Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.
(16) A. J. Saggiomo, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **23**, 1906 (1958).
(17) H. H. Hodgson and F. H. Moore, *J. Chem. Soc.*, 157 (1926).

likely polymorphic forms of IVb. (The presence of polymorphism among diphenyl sulfides has been reported previously.[3]) The analytical sample (ethanol) was a white crystalline solid, m.p. 137–138°.

Anal. Calcd. for $C_{13}H_{11}BrClNO_2S$: C, 45.11; H, 2.95; N, 3.76. Found: C, 44.97; H, 3.28; N, 3.77.

2-Bromo-4-chloro-2′-formamidodiphenyl Sulfide (IVa).—2-Amino-2′-bromo-4′-chlorodiphenyl sulfide (2.0 g., 0.0064 mole) was heated under reflux for 4 hr. with ten times its weight of 90% formic acid. The mixture was poured into 100 ml. of ice–water and the resulting white emulsion was extracted with ether. The ether was dried ($MgSO_4$) and concentrated under reduced pressure leaving an off-white solid. Several crystallizations from ethanol afforded 1.3 g. (60%) of IVa as a white solid, m.p. 139.5–140.5°.

Anal. Calcd. for $C_{13}H_9BrClNOS$: C, 45.31; H, 2.63; N, 4.06. Found: C, 45.51; H, 2.58; N, 4.46.

Cyclization of 2-Bromo-4-chloro-2′-formamido-5′-methoxydiphenyl Sulfide (IVb).—A mixture of 5 g. (0.013 mole) of IVb, 2.1 g. of anhydrous potassium carbonate, 0.05 g. of copper–bronze catalyst,[18] and 125 ml. of DMF was heated under reflux for 2 hr. and allowed to stand at room temperature overnight. An additional trace of catalyst was added and reflux was continued until carbon dioxide evolution stopped (4 hr.). The reaction mixture was filtered, and the filtrate was evaporated to dryness. The residue was extracted with 1.5 l. of boiling ligroin (60–90°) and the extracts were concentrated to give 2.5 g. of blue-gray solid. Repeated crystallization from benzene (Darco G-60) provided 3-chloro-7-methoxyphenothiazine (Vb) as very pale green plates, m.p. 202–203°.

Anal. Calcd. for $C_{13}H_{10}ClNOS$: C, 59.20; H, 3.80; Cl, 13.47; N, 5.31. Found: C, 59.17; H, 3.88; Cl, 13.08; N, 5.30.

Cyclization of 2-Bromo-4-chloro-2′-formamidodiphenyl Sulfide (IVa).—A mixture of 2 g. (0.0058 mole) of IVa, 0.83 g. (0.006 mole) of anhydrous potassium carbonate, 0.1 g. of copper–bronze catalyst,[18] and 20 ml. of DMF was heated under reflux for 11 hr. The mixture was filtered and the filtrate was poured into 300 ml. of cold water yielding 0.96 g. of pale green solid. Crystallization from benzene–petroleum ether (b.p. 20–40°) (Darco G-60) followed by crystallization from pure benzene gave 3-chlorophenothiazine (Va), m.p. 205–206°. The identity of Va was verified by mixture melting point and infrared comparison with authentic samples of 2-chlorophenothiazine[6] and 3-chlorophenothiazine.[6]

2-Amino-4-chloro-4′-methoxy-2′-nitrodiphenyl Sulfide (IX).—To a solution of 13 g. (0.33 mole) of sodium hydroxide in 195 ml. of ethanol was added 50 g. (0.13 mole) of the zinc salt of 2-amino-4-chlorobenzenethiol[19] and a solution of 52 g. (0.28 mole) of 4-chloro-3-nitroanisole[20] in 325 ml. of ethanol. The mixture was heated under reflux for 5 hr. and poured into 2 l. of cold water. The solid was extracted with ether and the extracts were dried over magnesium sulfate, decolorized, and concentrated to give 44.4 g. (55%) of yellow solid, m.p. 129–138°. This material was used directly in subsequent acylations. An aliquot was crystallized from ethanol to provide the analytical sample, m.p. 141–142°.

Anal. Calcd. for $C_{13}H_{11}ClN_2O_3S$: C, 50.22; H, 3.57; N, 9.02. Found: C, 50.20; H, 3.57; N, 9.06.

2-Acetamido-4-chloro-4′-methoxy-2′-nitrodiphenyl Sulfide (XI).—A mixture of 2.5 g. (0.008 mole) of IX, 0.9 ml. of pyridine, and 11 ml. of acetic anhydride was warmed to effect solution. The deep amber solution was allowed to cool, and a trace of undissolved solid was filtered. The filtrate was diluted with a mixture of 10 ml. of methanol and 150 ml. of water. An oil separated which solidified on standing. Crystallization from methanol (Darco G-60) afforded 1.4 g. (49%) of bright yellow crystals, m.p. 150–151°.

Anal. Calcd. for $C_{15}H_{13}ClN_2O_4S$: C, 51.07; H, 3.69; N, 7.94. Found: C, 51.43; H, 3.81; N, 7.40.

4-Chloro-2-formamido-4′-methoxy-2′-nitrodiphenyl Sulfide (X).—The amino derivative (IX) was formylated on a 0.63 mole scale, as described above for the preparation of IVa, to give a 70% yield of X, m.p. 146–147° (ethanol).

Anal. Calcd. for $C_{14}H_{11}ClN_2O_4S$: C, 49.61; H, 3.27; N, 8.27. Found: C, 49.49; H, 3.15; N, 8.50.

2-Chloro-7-methoxyphenothiazine (VIb).—To a boiling solution of X (2.4 g., 0.0071 mole) in 200 ml. of acetone was added, in portions, 1.41 g. (0.021 mole) of powdered 85% potassium hydroxide. After reflux for an additional hour, the mixture was concentrated to 15 ml. and diluted with cold water. Two crystallizations from benzene (Darco G-60) gave 0.79 g. (44%) of VIb, m.p. 174–175°. This sample did not depress the melting point of the compound obtained by thionation of 3-chloro-4′-methoxydiphenylamine.[11,12] The infrared spectra of the two samples were identical.

4-Chloro-4′-methoxydiphenylamine (XII).—A mixture of 93.5 g. (0.50 mole) of *p*-bromoanisole, 101.7 g. (0.60 mole) of *p*-chloroacetanilide, 48.0 g. (0.35 mole) of anhydrous potassium carbonate, and 1.7 g. of copper–bronze catalyst was heated in an oil bath at 210° for 28 hr. The mixture was allowed to cool and extracted with four 300-ml. portions of boiling acetone. The acetone was removed under reduced pressure and the residue was heated under reflux for 4 hr. with a solution of 145 ml. of concentrated hydrochloric acid in 400 ml. of ethanol. The hydrolysis mixture was poured into 2 l. of cold water, basified with 20% sodium hydroxide solution, and extracted with four 300-ml. portions of ether. The extracts were combined, dried ($MgSO_4$), and concentrated. The black residual oil was distilled with a short column to give 70 g. (60%) of XII, b.p. 150–163° (0.1 mm.), m.p. 50–51°.

Anal. Calcd. for $C_{13}H_{12}ClNO$: C, 66.71; H, 5.13; N, 5.95. Found: C, 67.19; H, 5.69; N, 5.88.

3-Chloro-7-methoxyphenothiazine (Vb).—A mixture of 2.3 g. (0.01 mole) of XII, 0.64 g. (0.02 mole) of sulfur, and 0.06 g. of iodine was heated in an oil bath at 140–145° for 45 min. The brown viscous reaction mixture was extracted with ether and the combined extracts were evaporated under reduced pressure to a dark oil. A good recovery of starting material was effected by trituration of the oil with four 25-ml. portions of petroleum ether (b.p. 20–40°). The petroleum ether-insoluble, green, gummy residue was crystallized repeatedly from benzene (Darco) to give 50 mg. of Vb as very pale green glistening plates, m.p. 195–197°. The infrared spectra of this compound and the compound obtained by cyclization of IVb were identical.

Anal. Calcd. for $C_{13}H_{10}ClNOS$: C, 59.20; H, 3.80. Found: C, 59.08; H, 4.06.

Acknowledgment. The authors gratefully acknowledge the assistance of Mr. Klaus Herrle in carrying out some of these preparations.

(18) Arthur S. LaPine and Co., Chicago 29, Ill.

(19) K. J. Farrington and W. K. Warburton, *Australian J. Chem.*, **8**, 545 (1955).

(20) Aldrich Chemical Co., Inc., Milwaukee 10, Wis.

The Synthesis of Thiophene Analogs of Fluorene[1]

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Received March 24, 1964

Sometime ago we measured the dipole moments of the three isomeric dithienyls.[3] The values for 2,2′-dithienyl (0.77 D.), 2,3′-dithienyl (1.07 D.), and 3,3′-dithienyl (0.75 D.) indicated that in solution only the 2,3′-isomer could have a coplanar conformation.

It appeared interesting to measure the equilibrium constants of the dithienyl charge-transfer complexes with some electron acceptors in order to gain additional information about the conformation of these dithienyls.[4]

Truly flat (rigid) analogs of the dithienyls, such as I, II, and III, would also be valuable models in this study.

(1) Part II in the series, "Steric Effects in Heterocyclic Systems." For part I, see H. Wynberg and D. J. Zwanenburg, *J. Org. Chem.*, **29**, 1919 (1964).

(2) Fellow of the Netherlands Organization for Pure Research (Z. W. O.).

(3) H. Wynberg and H. M. J. C. Creemers, *Angew. Chem.*, **75**, 453 (1963).

(4) R. E. Merrifield and W. D. Phillips, *J. Am. Chem. Soc.*, **80**, 2778 (1958).

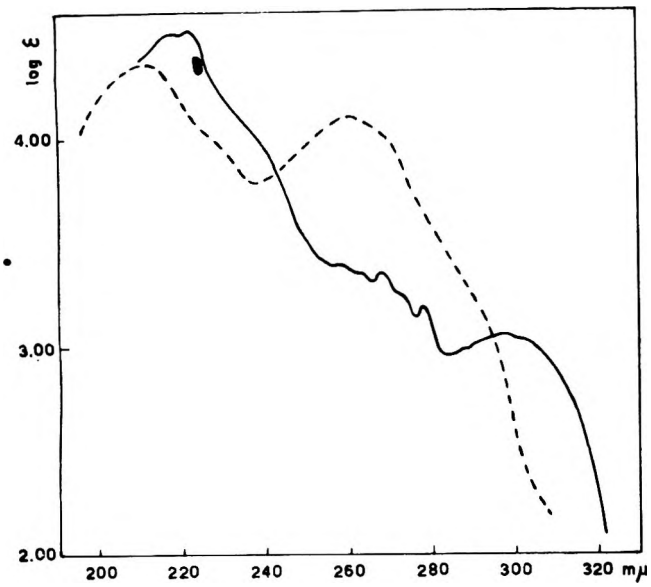
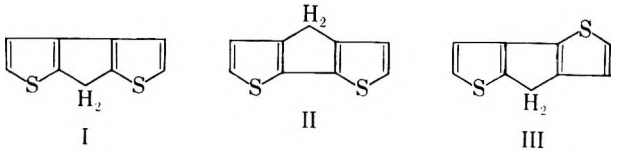
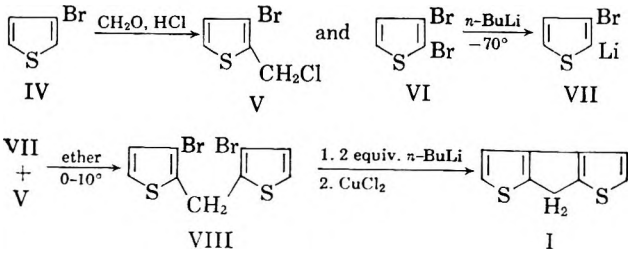


Fig. 1.—Ultraviolet spectra of ———, cyclopenta[1,2-*b*:4,3-*b*′]dithiophene; and – – – –, 3,3′-dithienyl. The solvent was cyclohexane.

This paper reports the synthesis of the first thiophene analog (I)[5] of fluorene related to 3,3′-dithienyl.



After several routes[6] had been tried in vain, the following synthetic scheme proved successful.



Chloromethylation[7] of 3-bromothiophene (IV)[8] gave 3-bromo-2-thenylchloride (V), a lachrymatory liquid, in good yield (72%). The assignment of structure V to the chloromethylated product is based on its conversion by permanganate oxidation to the known[9] 3-bromo-2-thiophene carboxylic acid.

According to the method of Löfgren and Tegnér[10] the 3-bromo-2-thenylchloride was allowed to react with 3-bromo-2-thienyllithium (VII), which was obtained by interconversion of 2,3-dibromothiophene (VI) and *n*-butyllithium at −70°.[11] 3,3′-Dibromo-2,2′-dithienylmethane (VIII) was obtained as a colorless crystalline material in low yield (16%), m.p. 37°.

Ring closure by oxidation of the dilithio derivative[12] in dilute ethereal solution with cupric chloride under ice cooling gave the desired cyclopenta[1,2-*b*:4,3-*b*′]-dithiophene (I) in a reasonable yield (38%).

The cyclopentadithiophene (I) is a colorless solid, m.p. 66–67°. The elementary analysis as well as the ultraviolet and n.m.r. spectra of I is in accord with the structure assigned. Noticeable is the fact that the absorption of the methylene protons (at τ 6.36) is identical with that found for fluorene. The ultraviolet absorption spectrum shows some similarities to that of fluorene with strong maxima at 218 and 223 mμ and characteristic fine structure in the 255–280-mμ region (Fig. 1). This fine structure has been associated with a strained nearly planar structure.[13-15] The 3,3′-dithienyl chromophore (λ_{max} 260 mμ, log ϵ 4.1)[16] no longer dominates the spectrum.

It is worthwhile noting that I, containing a five-membered ring fused to a five-membered heteroaromatic, may well show a Mills–Nixon[1] effect.

Experimental[17]

3-Bromo-2-thenyl Chloride (V).—A rapid stream of hydrogen chloride was passed into a stirred mixture of 57 g. (0.35 mole) of 3-bromothiophene[8] and 15 ml. of concentrated hydrochloric acid during 20 min. while the temperature was maintained at 0–5°. After 38 ml. of 40% aqueous formaldehyde was added dropwise, stirring was continued at 50° for 1 hr. The vigorously stirred mixture was cooled in an ice–salt bath and saturated with hydrogen chloride. The gas stream was stopped and the mixture heated on a water bath for 1 hr. at 80–90°. After cooling, the organic (lower) layer was separated and the aqueous layer extracted with ether. The combined organic layers were washed with 10% sodium bicarbonate solution and with water. After drying over magnesium sulfate, removal of the ether, and fractionation of the residue, there was obtained 53.6 g. (72%) of 3-bromo-2-thenyl chloride (V), b.p. 106.5–107.5° (12 mm.) n^{20}D 1.6059.

Anal. Calcd. for C_5H_4BrClS: C, 28.39; H, 1.90; S, 15.16. Found: C, 28.57; H, 1.90; S, 15.19.

3,3′-Dibromo-2,2′-dithienylmethane (VIII).—*n*-Butyllithium (185 ml. of a 1.33 *N* ethereal solution 0.25 mole) was siphoned under nitrogen into a 1-l. three-necked flask fitted with a mechanical stirrer, reflux condenser, dropping funnel, and low temperature thermometer. After cooling the flask to −70°, 57.2 g. (0.24 mole) of 2,3-dibromothiophene (VI) in 75 ml. of absolute ether was added during 15 min. The solution was stirred for 0.5 hr., whereupon 50 g. (0.24 mole) of 3-bromo-2-thenyl chloride (V) was added with stirring at −30°. After removal of the cooling bath, the mixture warmed spontaneously to reflux with the simultaneous appearance of a yellow precipitate. Refluxing was maintained by occasional warming for 2.5 hr. The mixture was cooled and carefully decomposed by adding 100 ml. of ice–water. The ether layer was washed with salt water, dried over magnesium sulfate, and fractionated. The product, b.p. 150–160° (0.45 mm.), crystallized and was pressed between filter paper. One recrystallization of the crude material from methanol with ice–salt cooling yielded 13 g. (16%) of colorless 3,3′-dibromo-2,2′-dithienylmethane (VIII), m.p. 37–38°. The n.m.r. spectrum showed two doublets at τ_4 3.16 and τ_5 2.92 (J = 5.0 c.p.s),

(5) There are a total of six possible isomers of this kind. Very recently we have prepared a second isomer (II), m.p. 73–74.5°, in this series. A thiophene analog of a substituted fluorenone has recently been reported by M. Y. Poirier, *Bull. soc. chim. France*, 1523 (1963).

(6) One of the most direct routes, *viz.*, *via* chloromethylation of 3,3′-dithienyl furnished polymeric material only. See F. F. Blicke and J. H. Burckhalter, *J. Am. Chem. Soc.*, **64**, 477 (1942).

(7) R. Lukeš, M. Janda, and K. Kefurt, *Collection Czech. Chem. Commun.*, **25**, 1058 (1960).

(8) S. Gronowitz, *Acta Chem. Scand.*, **13**, 1045 (1959).

(9) S. Gronowitz, *Arkiv Kemi*, **7**, 361 (1955).

(10) N. Löfgren and C. Tegnér, *Acta Chem. Scand.*, **6**, 1020 (1952).

(11) P. Moses and S. Gronowitz, *Arkiv Kemi*, **18**, 119 (1961).

(12) When the organometallic intermediate was carbonated instead of oxidized, 3,3′-dicarboxy-2,2′-dithienylmethane was obtained in good yield (54%), demonstrating the formation of the dilithio compound *in situ*.

(13) R. N. Jones, *J. Am. Chem. Soc.*, **67**, 2127 (1945).

(14) H. Suzuki, *Bull. Chem. Soc. Japan*, **32**, 1357 (1959).

(15) C. Eaborn and R. A. Shaw, *J. Chem. Soc.*, 2027 (1954).

(16) H. Wynberg and A. Bantjes, *J. Org. Chem.*, **24**, 1421 (1959).

(17) All melting points are corrected unless otherwise stated. Ultraviolet spectra were recorded on a Zeiss PMQ II spectrophotometer. The n.m.r. spectra were obtained using a Varian Model A-60 spectrometer, in carbon tetrachloride solution with tetramethylsilane as an internal standard. The microanalyses were carried out in the analytical section of our department under the direction of W. M. Hazenberg.

and a singlet at τ_{CH_2} 5.80; ultraviolet spectrum (ethanol), λ_{max} 242 mμ (ε 12,900).

Anal. Calcd. for $C_9H_6Br_2S_2$: C, 31.97; H, 1.78; S, 18.97. Found: C, 32.09; H, 1.88; S, 18.88.

Cyclopenta[1,2-*b*:4,3-*b'*]dithiophene (I).—A solution of 3,3′-dilithio-2,2′-dithienylmethane was prepared at −70° as described above from 4.5 g. (0.013 mole) of 3,3′-dibromo-2,2′-dithienylmethane (VIII) in 80 ml. of absolute ether and 20 ml. of 1.33 *N* ethereal *n*-butyllithium (0.026 mole) in a 250-ml. three-necked flask. The yellow solution was poured under nitrogen in an externally cooled (−20°) dropping funnel, which was attached to a second 500-ml. three-necked flask containing 4 g. (0.03 mole) of anhydrous $CuCl_2$ (dried at 130° for 0.5 hr.) in 20 ml. of absolute ether, maintained under dry nitrogen. While stirring the ice-cooled suspension vigorously the dilithio compound was added dropwise in the course of 1 hr. After stirring at 0° overnight, 40 ml. of 2 *N* hydrochloric acid solution was added and the reaction mixture filtered with suction in order to remove the grayish precipitate of cuprous chloride.

The ether layer was separated and the aqueous phase extracted with ether. The combined ethereal extracts were washed several times with 4 *N* hydrochloric acid, sodium bicarbonate solution, and finally with water. After drying over magnesium sulfate and removal of the solvent, the residue crystallized on cooling. Steam distillation gave 1.5 g. of crude cyclopenta[1,2-*b*:4,3-*b'*]-dithiophene (I). One recrystallization from ethanol yielded 0.9 g. (38%) of pure product, m.p. 66–67°. The n.m.r. spectrum showed two doublets at τ_4 3.05 and τ_5 2.88 (J = 5.0 c.p.s.), and a singlet at τ_{CH_2} 6.36.

Anal. Calcd. for $C_9H_6S_2$: C, 60.61; H, 3.39; S, 35.96. Found: C, 60.56; H, 3.48; S, 35.57.

The n.m.r. spectrum of fluorene (Fa Th. Schuchardt, Germany) under similar conditions gave, in addition to a multiplet between τ 2.3 and 3.0, one sharp singlet at τ 6.36 (>CH_2).

Ultraviolet spectrum (Fig. 1) of I in cyclohexane was λ_{max} mμ (log ε), 218 (4.50), 223 (4.51), 259 (3.38), 264 (3.34), 269 (3.34), 273 (3.24), 279 (3.18), and 298 (3.04).

3,3′-Dicarboxy-2,2′-dithienylmethane.—A solution of 4.5 g. (0.013 mole) of 3,3′-dibromo-2,2′-dithienylmethane (VIII) in 40 ml. of absolute ether was added over a period of 12 min. to 25 ml. of 1.33 *N* ethereal *n*-butyllithium (0.033 mole) cooled to −70° in an apparatus as described above. After 1.5 hr. the mixture was poured onto solid carbon dioxide covered with ether. After standing for 2 hr. the reaction mixture was hydrolyzed with 100 ml. of water and the ether phase extracted with 10% sodium bicarbonate solution. The combined aqueous layers gave on acidification with 4 *N* hydrochloric acid 3.7 g. crude product. Recrystallizations from an 85:15 acetic acid–water mixture (Norit) and finally from acetic acid yielded 1.9 g. (54%) of 3,3′-dicarboxy-2,2′-dithienylmethane, m.p. 257–258° (uncor.). The n.m.r. spectrum in dioxane showed two doublets at τ_4 2.81 and τ_5 2.57 (J = 5.0 c.p.s.), and a singlet at τ_{CH_2} 4.83.

Anal. Calcd. for $C_{11}H_8O_4S_2$: C, 49.23; H, 3.01; S, 23.90. Found: C, 48.96; H, 3.12; S, 23.58.

The Preparation and Pyrolysis of Certain Hexyl Thioacetates

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The addition of thioacetic acid to trisubstituted olefins and subsequent pyrolysis of the resulting esters to chiefly a different isomer has been described by Bailey, Mayer, and Antonucci.[1] This procedure has now been extended to certain mono-, di-, and trisubstituted hexenes.

The addition of thioacetic acid to 4-methyl-1-pentene (I), 3-methyl-2-pentene (III), 4-methyl-2-pentene (VI), and 2-hexene (X) proceeded smoothly to give the corresponding thio esters in 80–81% yields. The thioacetates were pyrolyzed to give mixtures of hexene isomers.

The addition of thioacetic acid to 4-methyl-1-pentene (I) and 3-methyl-2-pentene (III) gave the expected anti-Markownikoff addition product. Predominately one thioacetate was formed in each case. Upon pyrolysis the thioacetate from 4-methyl-1-pentene (II) gave 4-methyl-1-pentene (I), while the thioacetate from 3-methyl-2-pentene (IV)[2] yielded a mixture of 86.0% 3-methyl-1-pentene (V) and 12.6% 3-methyl-2-pentene (III). The observations on thioacetate pyrolysis are in agreement with the assumption that thioacetate pyrolysis parallels acetate pyrolysis with regard to mechanism and product formation.[1,3]

A possible steric effect of the isopropyl group of 4-methyl-2-pentene (VI) upon the addition of thioacetic acid to the double bond was anticipated. If such a steric effect was important, pyrolysis of the resulting thioacetate would be expected to give predominately 4-methyl-1-pentene (I). However, the isopropyl group of VI did not exert an important steric influence upon the addition of thioacetic acid since the gas chromatogram of the thioacetate showed two peaks with approximately equal areas, and the product of pyrolysis was found to consist of a mixture of 60.0% VI and 20.0% each of 2-methyl-2-pentene (IX) and I. The addition of thioacetic acid to 2-hexene (X) was also found to be unselective.

Examination of Table I shows that the efficiency of pyrolysis was affected by temperature and flow rate while the ratio of the product formed was largely independent of these two factors over the temperature range 450–540°. This is in agreement with previous studies on acetate pyrolysis.[4,5]

Experimental[6]

4-Methyl-1-pentene.—Phillips technical grade was used, with no other isomers found by g.c.

4-Methyl-2-pentene.—Phillips technical grade was found to be 56.8% *trans*-4-methyl-2-pentene and 43.2% *cis*-4-methyl-2-pentene by infrared. Phillips Pure Grade and Phillips Pure Grade High Boiling was found to be 100% *trans*-4-methyl-2-pentene by infrared. All grades reacted equally well.

3-Methyl-2-pentene was prepared by the method of Church, Whitmore, and McGrew.[7] They reported the dehydration of 3-methyl-3-pentanol to yield mostly 3-methyl-2-pentene with only a trace of 2-ethyl-1-butene. However, g.c. of the dehydration product obtained in the present work showed it to be a mixture of 16.4% 2-ethyl-1-butene, 30.2% *trans*-3-methyl-2-pentene, and 53.4% *cis*-3-methyl-2-pentene.

(1) W. J. Bailey, R. A. Mayer, and J. Antonucci, Abstracts, 135th National Meeting of the American Chemical Society, Boston, Mass., April, 1959, p. 5-O. W. J. Bailey, U. S. Patent 3,071,364 (Jan. 1, 1963).

(2) The 3-methyl-2-pentene was contaminated with 16.4% 2-ethyl-1-butene, $CH_3CH_2C(C_2H_5)=CH_2$, which would be expected to give, after thioacetic acid addition, $CH_3CH_2CH(C_2H_5)CH_2SAc$. Subsequent pyrolysis would give back 2-ethyl-1-butene. The low over-all yield of olefin (14.0%) from pyrolysis and the small amount of 2-ethyl-1-butene (1.4%) found in the pyrolysate suggested that, under the pyrolysis conditions used, the thioacetate from 2-ethyl-1-butene was not significantly decomposed.

(3) E. E. Royals, "Advanced Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1954, p. 247.

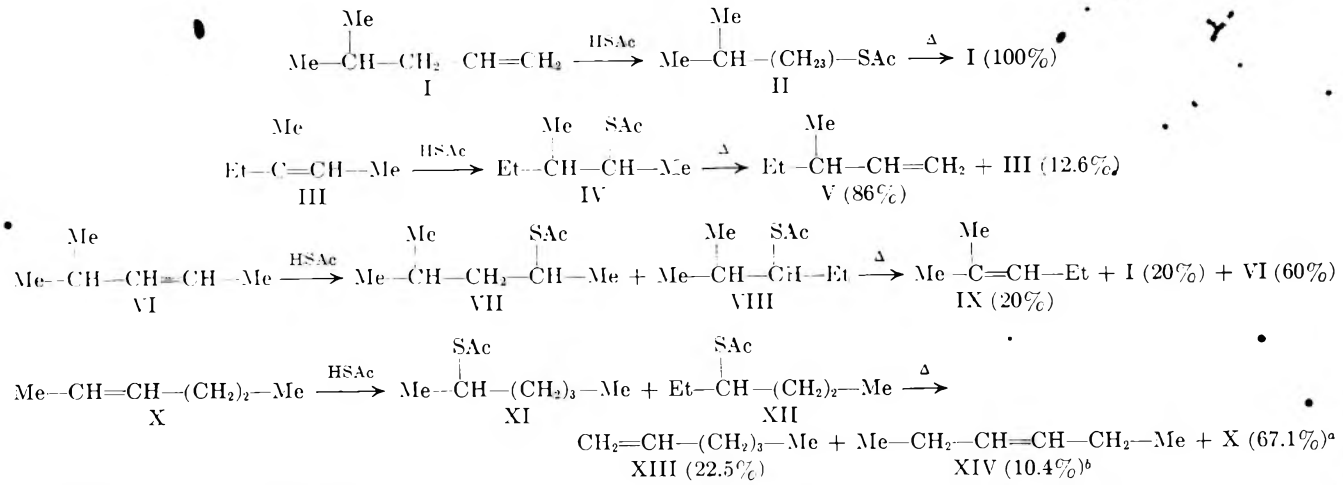
(4) D. H. Froemsdorf, C. H. Collins, G. S. Hammond, and C. H. DePuy, *J. Am. Chem. Soc.*, **81**, 643 (1959).

(5) W. J. Bailey and W. F. Hale, *ibid.*, **81**, 647 (1959).

(6) Elemental analyses were performed by Clark Microanalytical Laboratory, Urbana, Ill.

(7) J. M. Church, F. C. Whitmore, and R. V. McGrew, *J. Am. Chem. Soc.*, **56**, 176 (1934).

CHART I



[a] Maximum value; includes *cis*-3-hexene content. [b] Minimum value; amount of *cis*-3-hexene is not known.

TABLE I

PYROLYSIS OF THIOLACETATES

Thioacetate from	Temp. of pyrolysis, °C.	Flow rate ml./min.	Yield, % Olefin[a]	4-Methyl-1-pentene	4-Methyl-2-pentene	2-Methyl-2-pentene	
4-Methyl-1-pentene	530	1.3	16.3	100			
4-Methyl-1-pentene	450	1.3	0				
4-Methyl-2-pentene	450	1.4	13.2	19.4	64.0	16.6	
4-Methyl-2-pentene	490	3.5	12.9	17.5	65.5	17.0	
4-Methyl-2-pentene	490	2.5	21.0	21.6	63.0	15.4	
4-Methyl-2-pentene	490	1.3	23.0	20.0	60.0	20.0	
4-Methyl-2-pentene	520	1.3	35.0	20.8	59.5	19.7	
4-Methyl-2-pentene	530	1.3	31.0	21.3	60.3	18.4	
4-Methyl-2-pentene	540	4.0	41.5	21.4	59.0	19.6	
				3-Methyl-1-pentene	2-Ethyl-1-butene	*trans*-3-Methyl-2 pentene	*cis*-3-Methyl-2-pentene
3-Methyl-2-pentene	500	3.2	14.0	86.0	1.4	7.1	5.5
				1-Hexene	*trans*-2-Hexene, *cis*-3-Hexene	*cis*-2-Hexene	*trans*-3-Hexene
2-Hexene	500	2.0	52.0	22.5	49.7	17.4	10.4

[a] Based upon charged thioacetate.

3-Methyl-3-pentanol was prepared by the reaction of ethyl magnesium bromide and ethyl acetate in 52% yield, b.p. 120–122°.[7]

2-Hexene.—Phillips technical grade was found to be 28.2% *trans*-2-hexene and 71.8% *cis*-2-hexene by g.c.

Thioacetic Acid.—Matheson Coleman and Bell practical grade was used.

Preparation of the Thioacetates.—An equimolar mixture of the olefin and thioacetic acid was irradiated in a 250-ml. erlenmeyer flask with an incandescent bulb. A brief induction period was followed by a vigorous exothermic reaction. After a forerun of unreacted olefin and thioacetic acid, the thioacetate was collected by distillation through an 18-in. protruded metal column.

The reaction product from thioacetic acid and 4-methyl-1-pentene was obtained in 81% yield, b.p. 90° (21 mm.).

The thioacetate from 4-methyl-2-pentene was obtained in 80% yield, b.p. 78° (23 mm.).

Anal. Calcd. for $C_8H_{16}OS$: C, 59.94; H, 10.08; S, 20.00. Found: C, 60.08; H, 10.16; S, 20.41.

The thioacetate from 3-methyl-2-pentene was obtained in 80% yield, b.p. 81° (20 mm.).

Anal. Calcd. for $C_8H_{16}OS$: C, 59.94; H, 10.08; S, 20.00. Found: C, 59.98; H, 9.55; S, 20.33.

The thioacetate from 2-hexene was obtained in 80% yield, b.p. 84° (20 mm.).

Anal. Calcd. for $C_8H_{16}OS$: C, 59.94; H, 10.08; S, 20.00. Found: C, 59.43; H, 9.90; S, 19.99.

Pyrolysis of the Thioacetates.—The procedure was essentially that of Bailey and Hewitt.[8] In order to achieve uniform flow rates, the thioacetates were pumped from a 100-ml. buret by means of a microbellows pump into the Pyrex pyrolysis tube. The thioacetates were pyrolyzed at the temperatures and flow rates shown in Table I. The pyrolysate obtained was washed with water, dried over anhydrous sodium carbonate, and distilled through an 18-in. protruded metal column. The yields of olefin are shown in Table I.

Analysis.—The hexene samples were analyzed by a Fisher-Gulf partitioner (40-ft. dimethylsulfolane-on-firebrick column, helium flow 60 ml./min., inlet pressure 30 p.s.i.g.). Isomer per cent were calculated by retention time times peak height. No carbon skeleton rearrangement was observed.[3] In the products from 3-methylpentenes all isomers were resolved. In the products from 4-methylpentenes all isomers except *cis*- and trans-4-methyl-2-pentene were resolved. In the products from 2-hexene the following pairs were not separated: 1-hexene and *trans*-3-hexene, *trans*-2-hexene and *cis*-3-hexene. The per cent of 1-hexene was determined by infrared.

(8) W. J. Bailey and J. J. Hewitt, *J. Org. Chem.*, **21**, 543 (1956).

Molecular Rearrangements. III. The Nature of the Darzens Condensation Product from Benzaldehyde and Methyl Dichloroacetate[1]

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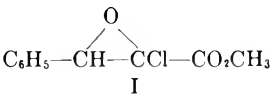
Received February 4, 1964

It has been recently reported[3] that the Darzens condensation of methyl dichloroacetate and benzaldehyde with a suspension of sodium methoxide in dry ether yields the α-chloro epoxide, methyl 2-chloro-2,3-epoxy-3-phenylpropanoate (I). These authors reported that their product was stable to concentrated sulfuric acid at 150° for 5 hr., but was decomposed by base to a dehydrochlorinated polymer. The former observation made us quite skeptical of the assignment of structure from our past experiences with the acid-sensitive nature of α-chloro epoxides.

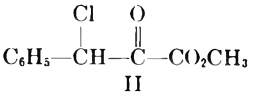


I

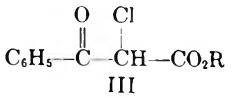
Our interests in the rearrangement and chemistry of α-chloro epoxides[1] prompted us to repeat this Darzens condensation. We have found that a yellow liquid is the only isolable product of the reaction and is obtained in 64% yield. Its chemical and physical properties agree with those reported[3] except for an absorption band at 945 cm.$^{-1}$ which the Russian authors attributed to an epoxide ring vibration. Since benzoic acid has a strong band at 945 cm.$^{-1}$, we believe that this absorption band is due to the acid as a contaminant. We found that the crude product contained this band after only a few aqueous base washings, but after several more base washings and careful fractional distillation, the absorption band was absent from the spectrum.

The infrared absorption spectrum of the yellow liquid product exhibited a single, sharp carbonyl peak at 1724 cm.$^{-1}$. This single carbonyl absorption may have led the Russian investigators to the assumption that only one carbonyl group was present. This need not be the case since pyruvic acid and its esters also exhibit a single, sharp carbonyl absorption.[4]

The nuclear magnetic resonance spectrum of this product was most convincing that the structural assignment was incorrect. An epoxide ring proton with an α-phenyl substituent is expected at approximately τ 6.0. This is observed for the proton of *trans*-2,3-diphenyl-2,3-epoxypropionitrile (τ 5.98), of *trans*-stilbene oxide (τ 6.32), and in styrene oxide (τ 6.17).[5] We, however, observed the proton absorption in the Darzens condensation product at τ 3.85. Since this low τ-value is indicative of a highly deshielded proton and since we have already observed the instability of α-chloro epoxides and their rearrangement to α-chloro ketones, this allows two isomeric α-chloro keto esters for consideration as possible structures for this product. They are methyl chlorophenylpyruvate (II) and methyl α-chlorobenzoylacetate (III, R = CH_3). The single carbonyl in the infrared spectrum is highly suggestive of II rather than III.



II



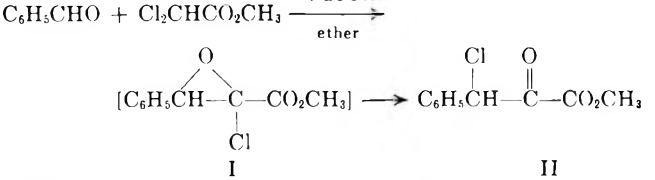
III

We, therefore, carried out independent syntheses of both II and III (R = Et). Methyl chlorophenylpyruvate (II) was prepared by chlorination of methyl phenylpyruvate with lithium chloride and copper(II) chloride in dimethylformamide[6] giving only a 21% yield of the α-chloro ketone (II), whereas sulfuryl chloride chlorination gave a 54% yield of methyl chlorophenylpyruvate (II). Its chemical, physical, and spectral properties were identical with those of the Darzens condensation product.

Treatment of ethyl benzoylacetate with lithium chloride and copper(II) chloride in dimethylformamide gave no reaction; however, treatment with sulfuryl chloride gave a 91% yield of ethyl α-chlorobenzoylacetate (III, R = Et). The nuclear magnetic resonance absorption frequency of the single proton of this compound occurred as a singlet at τ 4.41.

Attempts to prepare the intermediate α-chloro epoxide I by peroxidations of methyl *trans*-α-chlorocinnamate (IV) were carried out. However, treatment of IV with either perbenzoic acid, trifluoroperacetic acid using disodium hydrogen phosphate as base, basic 30% hydrogen peroxide in acetonitrile,[7] or 97% *t*-butyl hydroperoxide using Triton B as base[8] gave no evidence of reaction and only starting material was obtained.

Allowing for the normal mechanism of the Darzens condensation applying to this case with the intermediacy of the α-chloro epoxide I, this then establishes another example of predominant chlorine migration in an epoxide–carbonyl rearrangement and permits the following reaction scheme to be written. It is also of interest to note that none of the alternative product of hydrogen migration, III or its methyl ether, could be isolated from the Darzens condensation. This then infers that chlorine migration is greatly favored, if not exclusively favored, in the rearrangement.



I II

(1) For paper II in this series, see R. N. McDonald and P. A. Schwab, *J. Am. Chem. Soc.*, **85**, 4004 (1963).

(2) This paper comprises a portion of the dissertation submitted by P. A. Schwab to the Graduate School of Kansas State University, Dec., 1963, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) V. F. Martynov and M. I. Titov, *Zh. Obschch. Khim.*, **32**, 319 (1962); *Chem. Abstr.*, **57**, 12,373c (1962).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, p. 141.

(5) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 193.

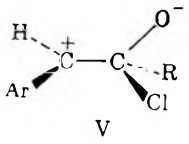
(6) E. M. Kosower, W. J. Cole, G. S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963).

(7) D. H. Rosenblatt and G. H. Broome, *ibid.*, **28**, 1290 (1963).

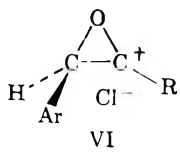
(8) G. B. Payne and P. H. Williams, *ibid.*, **26**, 651 (1961).

This result is of interest in two respects: (1) that chlorine migration accompanies the epoxide–carbonyl rearrangement under basic (or neutral) conditions in the relatively nonpolar solvent, ether, and (2) its mechanistic implications.

Our previous results[1] of chlorine migration in the epoxide–carbonyl rearrangement at the time appeared to be reasonably accommodated by a mechanism involving either a slow ring-opening step to a dipolar structure V (R = Ar′) followed by a fast intramolecular transfer of chlorine, or formation of an ion pair VI (R = Ar′) which collapses intramolecularly to yield the observed α-chloro ketone products. However, in the present case R is equal to carbomethoxy. This



V



VI

would make the ion pair VI less likely, assuming that a single mechanism is operative independent of the nature of Ar and R. Involvement of V, or a modification of it, would also be in line with other ring-opening reactions of epoxides, *e.g.*, bimolecular attack by some nucleophiles,[9] where bond breaking has progressed further than bond making in the transition state of the rate-determining step.

Studies are presently under way which are expected to decide more fully these mechanistic questions.

Experimental[10]

The Reaction of Benzaldehyde and Methyl Dichloroacetate with Sodium Methoxide.—In a 250-ml. three-necked round-bottom flask equipped with a reflux condenser fitted with a drying tube, a mechanical stirrer, and a solid addition apparatus, was placed 30 g. (0.2 mole) of methyl dichloroacetate, 22 g. (0.2 mole) of benzaldehyde, and 100 ml. of anhydrous ether. While stirring at 0°, 15 g. (0.25 mole) of powdered sodium methoxide was added in small amounts. After complete addition, the yellow heterogeneous reaction mixture was allowed to warm up to room temperature and then refluxed for 1.5 hr. After completion of the reaction, water was added to dissolve all the insoluble salts. The ether layer was separated, washed several times with water, and dried over anhydrous magnesium sulfate. After the removal of solvent under reduced pressure, a thick yellow oil remained. This was fractionally distilled collecting 21 g. (64%) of a yellow liquid boiling at 135–137° (6 mm.), n^{20}D 1.5302. This yellow liquid was redistilled through a spinning band column, collecting the fraction boiling at 84–86° (0.03 mm.) [lit.[3] b.p. 135° (6 mm.), n^{20}D 1.5260, 66% yield].

Anal. Calcd. for $C_{10}H_9O_3Cl$: C, 56.49; H, 4.27; Cl, 16.67. Found: C, 56.60; H, 4.35; Cl, 16.58.

The spectral properties of this compound consist of the following: infrared spectrum, 3.3 and 3.4 (vw), 5.8 (s), 6.7 (vw), 6.9 and 7.0 (w), 7.7 (m), 7.9 and 8.0 (m), 9.0 (shoulder), 9.9 (s), 11.5 (m), 13.4 (shoulder), and 14.2 (s) μ; n.m.r. spectrum, τ 2.67 (5), 3.85 (1), 6.30 (3).

Methyl Phenylpyruvate.—In a 250-ml. round-bottom flask fitted with a reflux condenser and a drying tube were placed 26 g. (0.146 mole) of phenylpyruvic acid,[11] 25 ml. of methanol, 60 ml. of ethylene chloride, and 1 g. of *p*-toluenesulfonic acid. This was then refluxed for 15 hr., cooled, washed with a 10% sodium carbonate solution and water, and dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure gave 25 g. of a yellow oil which was recrystallized from Skellysolve B giving 12 g. (45%) of pure methyl phenylpyruvate, m.p. 71–73° (lit.[12] m.p. 75°).

Methyl Chlorophenylpyruvate. A. Using Sulfuryl Chloride.—In a 100-ml. three-necked round-bottom flask fitted with a reflux condenser with a drying tube, an addition funnel, and a magnetic stirrer is placed 14 g. (0.08 mole) of methyl phenylpyruvate in 50 ml. of carbon tetrachloride. While stirring at 45–50°, 11 g. (0.082 mole) of sulfuryl chloride was added dropwise. After addition the reaction mixture was allowed to react for 2.5 hr. This was then washed three times with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure leaving a yellow oil. Fractional distillation afforded 9 g. (54%) of methyl chlorophenylpyruvate boiling at 83–84.5° (0.03 mm.), n^{20}D 1.5361. The infrared and n.m.r. spectra of this compound were identical to the compound obtained by the Darzens condensation reaction.

B. Using the Method of Kosower.[6]—In a 100-ml. three-necked flask fitted with a mechanical stirrer, thermometer, and reflux condenser were placed 18.7 g. (0.11 mole) of copper(II) chloride dihydrate, 2.3 g. (0.054 mole) of lithium chloride, and 30 ml. of dimethylformamide. After heating to 80° while stirring, 8 g. (0.045 mole) of methyl phenylpyruvate was added and this mixture was stirred at 80–90° for 1.5 hr. The dark reaction mixture was diluted with 30 g. of ice followed by sufficient dimethylformamide to dissolve the small amount of precipitated copper(I) chloride. The clear green reaction mixture was extracted with four 50-ml. portions of ether. The ether layers were combined, washed with 100 ml. of water, and dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure gave 5 g. of a light orange oil. Fractional distillation gave 2 g. (21% yield) of the desired product, b.p. 84–85° (0.07 mm.), n^{20}D 1.5282).

Ethyl α-Chlorobenzoylacetate.—This reaction was carried out in the same manner as part A in the synthesis of methyl chlorophenylpyruvate, using the following reactants: 14 g. (0.073 mole) of ethyl benzoylacetate in 50 ml. of carbon tetrachloride and 11 g. (0.082 mole) of sulfuryl chloride. Distillation afforded a clear colorless liquid boiling at 106–108° (0.03 mm.), n^{20}D 1.5318 [lit.[13] b.p. 175–177° (10 mm.), n^{20}D 1.532]. Fifteen grams (91%) of pure ethyl α-chlorobenzoylacetate was obtained.

The spectral properties of this compound were as follows: infrared spectrum, 3.6 (vw), 3.9 (m), 5.7 (s), 6.0 (s), 6.3 and 6.4 (m), 6.7 (vw), 6.8 (w), 6.9 (m), 7.2 (w), 7.3 (m), 7.6 (m), 7.7 (s), 7.9 (s), 8.3 (m), 8.5 (s), 8.6 (m), 8.8 (w), 9.0 (vw), 9.1 (w), 9.3 (vw), 9.8 (m), 10.0 (m), 10.5 (w), 11.4 (w), 12.1 (m), 12.8 (w), 13.0 (w), 13.6 (w), and 14.5 (s) μ; n.m.r. spectrum, τ 1.92–2.14 and 2.40–2.62 (multiplets, 5), 4.41 (1), 5.79 (quartet, 2), and 8.83 (triplet, 3).

2,3-*trans*-Diphenyl-2,3-epoxypropionitrile.—This epoxide was prepared according to Payne and Williams,[8] m.p. 70–71°, 74% yield (lit.[8] m.p. 70–70.5°, 76% yield).

***trans*-Stilbene Oxide.**—This epoxide was prepared according to Reif and House[14]; m.p. 68–69°, 82% yield (lit.[14] m.p. 68–69°, 70–75% yield).

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(9) See J. K. Addy and R. E. Parker, *J. Chem. Soc.*, 915 (1963) and previous papers in their series, and references cited therein.

(10) All melting points were taken on a Kofler hot stage and are corrected. Boiling points are uncorrected. Infrared absorption spectra were determined on a Perkin-Elmer Model 137 double beam recording spectrophotometer. N.m.r. spectra were determined on a Varian A-60 recording spectrophotometer using carbon tetrachloride as solvent (unless otherwise stated) with tetramethylsilane as the internal standard and are singlets unless otherwise noted. Other numbers in parenthesis are the relative integrated areas. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(11) R. M. Herbst and D. Shemin, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 519.

(12) R. Hemmerle, *Compt. rend.*, **162**, 758 (1916).

(13) E. L. Hirst, A. K. Macbeth, and D. Traill, *Proc. Roy. Irish Acad.*, **37B**, 47 (1925); *Chem. Abstr.*, **19**, 2931 (1925).

(14) D. J. Reif and H. O. House, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 860.

Photosensitized *cis–trans* Isomerization of Methyl Oleate

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The photosensitized *cis–trans* isomerization of methyl oleate has been performed using benzophenone as a sensitizer. In a typical experiment a degassed sample of 0.352 *M* methyl oleate dissolved in benzene containing 5.5×10^{-2} *M* benzophenone was photolyzed with 366-mμ light for 1357 min. and 23% *trans* isomer was obtained. The quantum yield for this process was determined to be 0.34; however, the yield decreases as the stationary state is approached.

Since the isolated double bond in methyl oleate absorbs in the vacuum ultraviolet[2] and shows virtually no absorption at 366 mμ, the isomerization is most probably proceeding through the triplet state *via* energy transfer in solution. Recent work[3–5] has established that the triplet state of benzophenone is populated with unit efficiency at 366 mμ.

Benzophenone has been used to photosensitize the *cis–trans* isomerization of a conjugated diene such as piperylene (1,3-pentadiene)[6,7]; however, it was predicted in that work that the sensitized isomerization of an isolated double bond would occur very inefficiently, if at all. This was demonstrated by Hammond and co-workers[7] for the isomerization of a simple unconjugated alkene. Isomerization experiments in the vapor state have been performed with butene-2[8–11]; however, this work was done using 2537-Å. excitation and the triplet state of benzene, which is more energetic than the benzophenone triplet.

The occurrence of this isomerization process *via* the triplet state of methyl oleate is indicative of a low-lying triplet state in this molecule, which may be important in understanding the photooxidation processes that occur in fats and oils.

The direct photolysis of a degassed sample of 0.337 *M* methyl oleate in benzene at 366 mμ for 3114 min. produced no isomerization or significant change in the infrared spectrum. Similarly, the photolysis of 5.5×10^{-2} *M* benzophenone in benzene for 1337 min. indicated no significant changes. This latter result was also recently reported by Bell and Linschitz.[12]

Although the photolysis of benzophenone in benzene produced no significant changes in benzophenone, it was observed that, during the sensitized runs, some benzophenone was consumed, and its disappearance was faster when isomerizing *trans–cis* rather than the reverse. This side reaction is probably due to hydrogen abstraction from the olefin, *i.e.*, $(C_6H_5)_2CO + RH \rightarrow (C_6H_5)_2\dot{C}OH + \dot{R}$. A referee has pointed out that an alternate method for explaining the partial depletion of benzophenone is by addition to the olefin to form an oxetane.[13] In either event, the reaction is in competition with the energy-transfer process which is essential for the isomerization.

The reversibility of the isomerization reaction has been verified by isomerizing methyl elaidate. In a typical experiment, photolysis by degassed 0.152 *M* methyl elaidate in benzene containing 5.5×10^{-2} *M* benzophenone for 1603 min. resulted in 23% oleate, and the quantum yield for this process was determined to be 0.14. Since the isomerization process is reversible, with the rates for the forward and reverse reactions decreasing as the equilibrium state is approached, benzene solution of mixtures of methyl oleate and elaidate were photolyzed in the presence of benzophenone. Results indicate that, when the ratio of *trans* to *cis* isomer is near three, the quantum yield becomes negligibly small; consequently, it appears that the equilibrium state exists with 75% *trans* isomer.

The *cis–trans* isomerization of methyl oleate has been performed using oxides of nitrogen,[14] elemental selenium,[15] and ionizing radiation.[16] Conjugated long-chain fatty acid esters have been isomerized photochemically with iodine[17,18]; however, to the author's knowledge, this is the first unconjugated long-chain fatty acid ester which has been isomerized *cis–trans* in the presence of a photosensitizer. The occurrence of this isomerization reflects the large energy difference between the first excited singlet and triplet in the $\pi \rightarrow \pi^*$ transitions of alkenes.

Since the triplet state energy of methyl oleate is unknown, its determination may be made with different sensitizers as suggested by Hammond, *et al.*[6] The extension of this isomerization method to fatty acid chemistry is an obvious one.

Experimental

The 366-mμ light was isolated from a General Electric BH-6 high pressure mercury lamp by a Farrand UV monochromator. The light intensities were determined with the potassium ferrioxalate actinometer[19] to be approximately 4.7×10^{15} quanta/sec. Photolysis runs were performed at 24.5 ± 0.5° in 1-cm. fused silica cells, with all samples vacuum degassed prior to lamp exposure. Fresh solutions were prepared for each run. At the end of each photolysis experiment, the cell was opened to air and the solution was subjected to infrared analysis for the generation of methyl elaidate at 10.34 μ.[20] It is noteworthy that the fatty acid structure of the ester was not significantly changed during the photolysis. Ultraviolet spectroscopy and gas chromatography (column: 23% ethylene glycol glutarate on 75% 60–80-

(1) Department of Chemistry, St. John's University, Jamaica 32, N. Y.

(2) I. I. Rusoff, J. R. Platt, H. B. Klevens, and G. O. Burr, *J. Am. Chem. Soc.*, **67**, 673 (1945).

(3) G. S. Hammond and W. M. Moore, *ibid.*, **81**, 6334 (1959).

(4) W. M. Moore, G. S. Hammond, and R. P. Foss, *ibid.*, **83**, 2789 (1961).

(5) H. L. J. Bäckstrom and K. Sandros, *Acta Chem. Scand.*, **14**, 48 (1960).

(6) G. S. Hammond, P. A. Leermakers, and N. J. Turro, *J. Am. Chem. Soc.*, **83**, 2396 (1961).

(7) G. S. Hammond, N. J. Turro, and P. A. Leermakers, *J. Phys. Chem.*, **66**, 1144 (1962).

(8) R. B. Cundall and T. F. Palmer, *Trans. Faraday Soc.*, **56**, 1211 (1960).

(9) R. B. Cundall and D. G. Milne, *J. Am. Chem. Soc.*, **83**, 3902 (1961).

(10) S. Sato, K. Kikuchi, and M. Tanaka, *J. Chem. Phys.*, **39**, 239 (1963).

(11) R. B. Cundall, F. J. Fletcher, and D. G. Milne, *ibid.*, **39**, 3536 (1963).

(12) J. A. Bell and H. Linschitz, *J. Am. Chem. Soc.*, **85**, 528 (1963).

(13) E. Paterno and G. Chieffii, *Gazz. chim. ital.*, **39**, 341 (1909); G. Büchi C. G. Inman, and E. S. Lipinsky, *J. Am. Chem. Soc.*, **76**, 4327 (1954).

(14) H. N. Griffiths and T. P. Hilditch, *J. Chem. Soc.* 2315 (1932); *J. Soc. Chem. Ind.* (London), **53**, 75 (1934).

(15) J. D. Fitzpatrick and M. Orchin, *J. Am. Chem. Soc.*, **79**, 4765 (1957).

(16) H. P. Pan, S. A. Boldblith, and B. E. Proctor, *J. Am. Oil Chem. Soc.*, **35**, 1 (1958).

(17) W. E. Tolberg and D. H. Wheeler, *J. Am. Oil Chemists' Soc.*, **35**, 385 (1958).

(18) J. R. Chipault and J. M. Hawkins, *ibid.*, **37**, 176 (1960).

(19) C. G. Hatchard and C. A. Parker, *Proc. Roy. Soc.* (London), **A235**, 518 (1956).

(20) O. D. Shreve, M. R. Heether, H. B. Knight, and D. Swern, *Anal. Chem.*, **22**, 1261 (1950).

mesh Chromosorb W with 2% phosphoric acid) provided an estimate of the purity of the fatty acid esters, the extent of side reactions, and the partial depletion of benzophenone. Gas chromatograms indicated that the isomerization is not accompanied by significant side reactions. A Beckman IR-5A spectrophotometer was used for the quantitative measurements and the length of the sodium chloride cells was determined by counting interference fringes.

The methyl oleate used in this work was better than 99% pure and obtained from the Applied Science Laboratories, State College, Pa. In addition to chromatographic analysis, the purity of the fatty acid ester was estimated by the absence of absorption in the ultraviolet region. At 250 mμ, in isopropyl alcohol, the molar extinction coefficient was 4.5. Methyl elaidate was prepared by esterification of elaidic acid (Chemical Procurement Laboratories, Inc., College Point, N. Y.) with methanol and sulfuric acid. A low-temperature recrystallization in acetone of the prepared ester removed an impurity, which appeared to be eleostearic acid from its ultraviolet absorption. The purity of the elaidate sample was determined to be 99% by gas chromatography and the molar extinction coefficient at 250 mμ, in isopropyl alcohol, was determined to be 4.8.

Baker's analytical reagent grade benzene was used as solvent, and benzophenone (Matheson Coleman and Bell) was recrystallized from ethanol and hexane.

Methyl (Cortison-21-yl 2,3,4-tri-*O*-acetyl-β-D-glucosid)uronate[1]

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In an effort to secure C-21 2-deoxyglycosides of hydrocortisone (11β,17α,21-trihydroxy-4-pregnene-3,20-dione) as potential antiinflammatory agents, we investigated a glycosidation procedure described[3] by Bredereck and co-workers. When, however, 21-tritoxyhydrocortisone (11β,17α-dihydroxy-21-tritoxy-4-pregnene-3,-20-dione, **1**) was treated in the presence of silver perchlorate with various 2-deoxy acylglycosyl halides, the isolation of crystalline products was not realized.

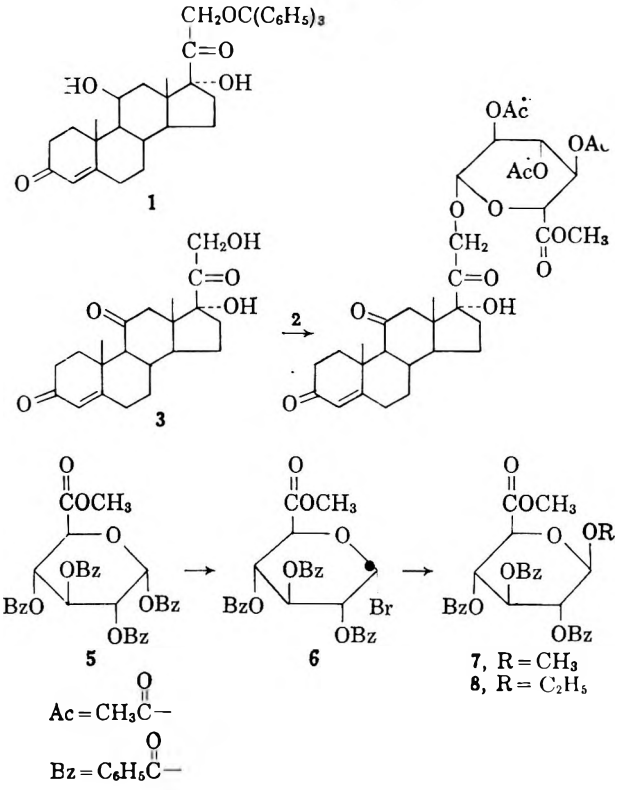
Also investigated was the preparation of some adrenocortical C-21 glucosiduronic acids as possible water-soluble derivatives. Whereas methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate (**2**) coupled readily with cortexone (21-hydroxy-4-pregnene-3,20-dione) to give the desired glucosiduronate in good yield,[4] treatment of hydrocortisone with **2** under identical conditions failed to give crystalline material, even after chromatography of the reaction products on silicic acid.

We next turned our attention to the corresponding methylated and fully acetylated C-21 glucosiduronic acid (**4**) prepared from cortisone (**3**) and previously reported by Wotiz and co-workers.[5] Whereas these workers were able to isolate the crystalline intermediate directly from the reaction mixture, it was necessary for us to chromatograph the material on silicic acid. The crystalline material thus obtained had properties (melting point, rotation) which differed from the data reported by Wotiz for the coupling product (**4**). Also, combustion analysis for our compound (**4**) gave values for carbon and hydrogen closely fitting $C_{34}H_{44}O_{14}$ (the correct molecular formula), while Wotiz' values more nearly correspond to the formula $C_{34}H_{46}O_{14}$ which is the one assigned erroneously to **4** in his paper.

In the absence of further published information, we infer that Wotiz' compound may have been impure (in view of the sharp melting point reported this does not seem likely) or that it possibly represents an incorrectly named coupling product of **2** with some dihydro derivative or cortisone. The synthesis of **4** reported herein represents, then, the first successful coupling of cortisone (**3**) with D-glucuronic acid.

Saponification of **4** yielded amorphous material which could not be crystallized. The material was readily soluble in water giving a solution which was acidic to litmus. It was homogeneous as disclosed by papergrams and, when hydrolyzed by means of β-D-glucuronidase and again chromatographed on paper, showed two spots, exactly coincident in position with cortisone (**3**) and D-glucuronic acid, respectively.

In a further attempt to secure a C-21 glucosiduronic acid from hydrocortisone, we investigated benzoylated derivatives of D-glucuronic acid owing to the superior crystallizing properties of carbohydrate benzoates. Methyl D-glucuronate[6] was readily converted to the tetrabenzoate (**5**), which is provisionally assigned to the α-anomeric configuration because of its strongly positive specific rotation (+125.2°). Treatment of **5** with hydrogen bromide–acetic acid solution gave the expected methyl 2,3,4-tri-*O*-benzoyl-1-bromo-1-deoxy-α-D-glucuronate (**6**), which underwent methanolysis to



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(3) H. Bredereck, A. Wagner, and G. Faber, *Angew. Chem.*, **69**, 438 (1957).

(4) W. W. Zorbach, *J. Org. Chem.*, **23**, 1797 (1958).

(5) H. H. Wotiz, E. Smakula, N. H. Lichtin, and J. H. Leftin, *J. Am. Chem. Soc.*, **81**, 1704 (1959).

(6) W. F. Goebel and F. H. Babers, *J. Biol. Chem.*, **106**, 63 (1934).

give a methyl (methyl 2,3,4-tri-*O*-benzoyl-D-glucosid)-uronate (**7**). Because 1,2-*cis* halides undergo displacement with inversion at C-1, **7** has most likely the β-anomeric configuration.

Several experiments were carried out in attempts to couple hydrocortisone with the bromide (**6**) in the presence of mercuric cyanide but, in each instance, substantial amounts of unreacted hydrocortisone could be recovered. In one case, during a work-up of the reaction mixture using ethanol, methyl (ethyl 2,3,4-tri-*O*-benzoyl-D-glucosid)uronate (**8**) was isolated, indicating that throughout the experiment the bromide (**6**) remained unaffected. Because **8** also is levorotatory, it most probably has the β-anomeric configuration.

Experimental

All melting points were determined using a Kofler hot stage.

11β,17α-Dihydroxy-21-tritoxy-4-pregnene-3,20-dione (**1**).—To a solution of 1086 mg. (3 mmoles) of hydrocortisone in 5 ml. of anhydrous pyridine was added 921 mg. (3.3 mmoles) of trityl chloride. Under exclusion of moisture the solution was heated on a steam bath for 4 hr. and was then dissolved in 300 ml. of ether. After washing successively with 200 ml. of 1 *N* sulfuric acid, 200 ml. of 2% aqueous sodium bicarbonate, and 200 ml. of water, the ether layer was dried over sodium sulfate and was evaporated *in vacuo* at 40° to a sirupy residue. The residue was triturated with 5 ml. of absolute ethanol and, after standing overnight in a refrigerator, there was obtained 1180 mg. (65%) of pure **1**, m.p. 197.5–201° dec., $[\alpha]^{19}D$ +77.1° (*c* 1.188, $CHCl_3$). From the mother liquors an additional 110 mg. of pure **1** was obtained, bringing the total yield to 71%.

Anal. Calcd. for $C_{40}H_{44}O_5$: C, 79.43; H, 7.34. Found: C, 79.35; H, 7.51.

Methyl (17α,21-Dihydroxy-4-pregnene-3,11,20-trion-21-yl 2,-3,4-tri-*O*-acetyl-β-D-glucosid)uronate (**4**).—The coupling of 1500 mg. (3.8 mmoles) of the bromide (**2**) in 70 ml. of anhydrous benzene with 540 mg. (1.5 mmoles) of cortisone (**3**) in the presence of 1450 mg. (5.25 mmoles) of freshly prepared silver carbonate was carried out by an azeotropic distillation technique, directions for which are given[7] by Reichstein and co-workers. After completion of the reaction, the silver salts were filtered and the filtrate was evaporated to dryness giving 1.5 g. of sirupy material which was placed on a column (3 × 48 cm.) of 75 g. of Fisher reagent grade silicic acid. The material which was eluted by dichloromethane methanol (95:5) was collected, and the solution was decolorized with Darco G-60. After filtration and evaporation, the clear sirup was redissolved in methanol and water was added to incipient turbidity. After standing overnight in a refrigerator, the separated crystals were filtered giving 220 mg. (32%) of material melting at 110–118°. Repeated recrystallization from water–methanol gave pure **4**, m.p. 127–129°, $[\alpha]^{18}D$ +103.1° (*c* 0.78, $CHCl_3$), λ_{max}^{MeOH} 239 mμ (log ε 4.1).

Anal. Calcd. for $C_{34}H_{44}O_{14}$: C, 60.34; H, 6.55. Found: C, 60.25; H, 6.82.

Saponification of 4 and Enzymatic Hydrolysis of the Deacetylated Acid.—To a solution of 10 mg. of the protected glucosiduronate (**4**) in 10 ml. of absolute methanol was added 1 ml. of 0.5 *N* sodium methoxide. After standing overnight at room temperature, the solution was made neutral by the addition of acetic acid and was then diluted with an equal volume of water. After treating for 0.5 hr. with 500 mg. of Amberlite MB-1 ion-exchange resin, the solution was filtered and was evaporated to dryness *in vacuo* at 40°. The amorphous residue gave an acid reaction with litmus and did not reduce ammoniacal silver oxide. It was next dissolved in 50 ml. of acetate buffer (pH 5.2) and 250 mg. of β-D-glucuronidase (Nutritional Biochemicals Corp., 60,000–70,000 units/g.) was added. After incubating for 24 hr. at 37°, the solution was cooled and extracted with three 100-ml. portions of ether. After drying over magnesium sulfate, the extract was evaporated and the residue was dissolved in 2 ml. of methanol for paper partition chromatography by an ascending method employing 1-butanol–acetic acid–water (4:1:5). This system appears to be satisfactory for both sugars and corticoids and, when the hydrolysate was chromatographed, there was a good resolution of the material giving two spots, exactly coincident in position with D-glucuronic acid and cortisone (**1**), respectively. The spots were detected using ammoniacal silver nitrate with subsequent drying at 110° for 3 min.

Methyl 1,2,3,4-Tetra-*O*-benzyl-α-D-glucuronate (**5**).—A solution of 19.6 g. (0.094 mole) of sirupy methyl glucuronate[6] in 75 ml. of pyridine was cooled to −10° and 50 ml. of benzoyl chloride (0.425 mole) was added dropwise with stirring. After stirring for an additional 0.5 hr., the mixture was set aside in a refrigerator for 4 days. It was then allowed to warm to room temperature and the excess benzoyl chloride was carefully neutralized by the addition of saturated aqueous sodium bicarbonate. The mixture was added rapidly to 2 l. of ice–water and was set aside in a refrigerator overnight. The gummy mass which separated was dissolved in 300 ml. of chloroform and the solution was washed with 2% aqueous sodium bicarbonate and with water. After drying over sodium sulfate, the extract was boiled down to 100 ml. and was treated with Darco G-60. After filtering, the solution was evaporated to dryness and the residue was redissolved in 300 ml. of ethanol. On the following day the separated material was filtered and was repeatedly crystallized from acetone–water, giving pure **5**, m.p. 183–184°, $[\alpha]^{25}D$ +125.2° (*c* 1.232, $CHCl_3$). Work-up of the mother liquors gave additional material, 30.0 g. (48%) *in toto*, of the glucuronate (**5**).

Methyl 2,3,4-Tri-*O*-benzoyl-1-bromo-1-deoxy-α-D-glucuronate (**6**).—To 50 ml. of a 32% hydrogen bromide–acetic acid solution was added 5.0 g. (8 mmoles) of finely powdered methyl 1,2,3,4-tetra-*O*-benzoyl-α-D-glucuronate (**5**), and the mixture was stirred under the exclusion of moisture for 4 hr. After standing at room temperature for 15 hr., the solution was poured into cold ether and was washed successively with 250 ml. of cold 2% aqueous sodium bicarbonate, and with 250 ml. of ice–water. The ether layer was dried over sodium sulfate and filtered, and then evaporated to dryness at 30°. The residue was redissolved in anhydrous benzene and dry pentane was added to incipient turbidity. After standing in a refrigerator overnight, the separated material was collected by filtration and, after three recrystallizations, there was obtained 2.9 g. (62%) of pure bromide (**6**), m.p. 146–148°, $[\alpha]^{18}D$ +114° (*c* 1.31, $CHCl_3$).

Anal. Calcd. for $C_{28}H_{23}BrO_9$: C, 57.63; H, 3.97; Br, 13.70. Found: C, 56.97; H, 4.20; Br, 13.62.

Methyl (Methyl 2,3,4-tri-*O*-benzoyl-β-D-glucosid)uronate (**7**).—To 150 mg. (0.26 mole) of the bromide **5** was added 10 ml. of anhydrous methanol and the solution was allowed to stand at room temperature for 16 hr. The solution was evaporated to dryness *in vacuo* at room temperature. The solid residue was recrystallized twice from methanol giving 93 mg. (70%) of pure **7**, m.p. 153–154°, $[\alpha]^{19}D$ −3.7° (*c* 0.822, methanol).

Anal. Calcd. for $C_{29}H_{26}O_{10}$: C, 65.16; H, 4.90. Found: C, 64.85; H, 5.13.

Isolation of Methyl (Ethyl 2,3,4-Tri-*O*-benzoyl-β-D-glucosid)-uronate (8) from the Attempted Coupling of the Bromide 6 with Hydrocortisone.—A solution of 362 mg. (1 mmole) of hydrocortisone in 15 ml. of absolute dioxane was treated with 583 mg. of **6** and 253 mg. (1 mmole) of mercuric cyanide according to directions given in a previous paper.[8] After completion of the reaction, the solvent was evaporated *in vacuo* and the resulting sirupy residue was redissolved in 5 ml. of absolute ethanol. After standing overnight, the separated material, which melted at 120–135°, was recrystallized three times from absolute ethanol giving 155 mg. of pure **8**, m.p. 150–152°, $[\alpha]^{19}D$ −5.6° (*c* 0.682, $CHCl_3$).

Anal. Calcd. for $C_{36}H_{28}O_{10}$: C, 65.69; H, 5.14. Found: C, 65.71; H, 5.07.

Acknowledgment.—The authors are indebted to Miss Paula M. Parisius, Microanalytical Laboratory, NIAMD, National Institutes of Health, Bethesda, Maryland, under the direction of Mr. H. G. McCann, for the elemental analyses.

(7) K. Reyle, K. Meyer, and T. Reichstein, *Helv. Chim. Acta*, **33**, 1541 (1950).

(8) W. W. Zorbach, G. D. Valiaveedan, and D. V. Kashelikar, *J. Org. Chem.*, **27**, 1766 (1962).

Acetylenic Amines. X. Piperazines from Substituted N-(2-Hydroxyalkyl)propargylamines

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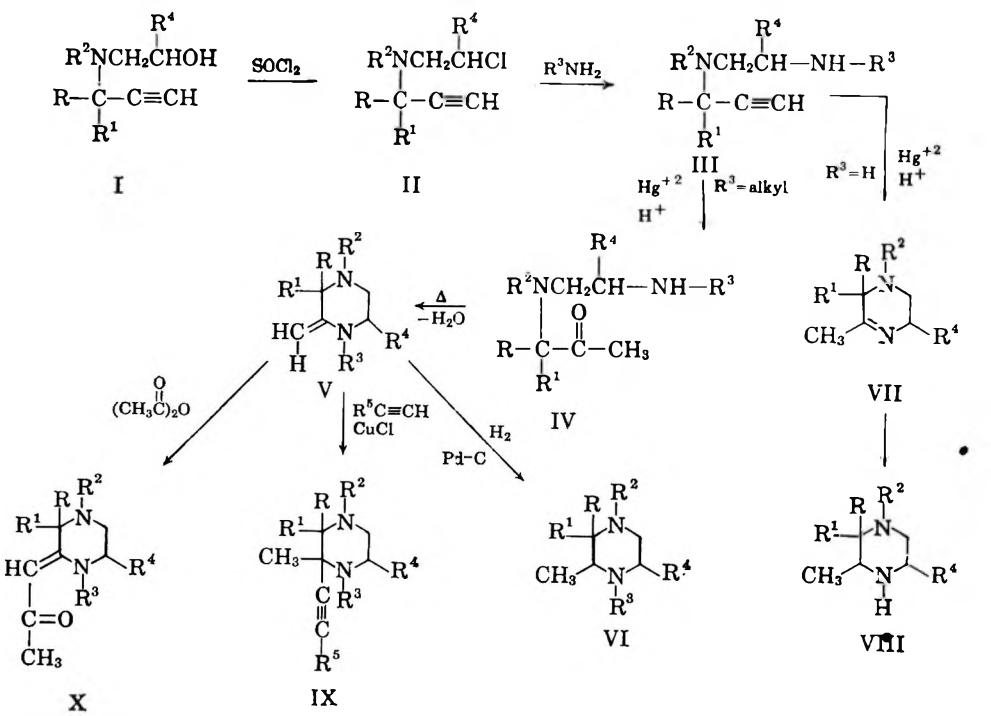
The preparation of 2,2-dimethyl-4-ethyl-3-methylenemorpholine[1] from the acid-catalyzed cyclization of 3-(β-ethylaminoethoxy)-3-methyl-1-butyne suggested the extension of this reaction to the nitrogen analogs, the N-(1,1-dialkylpropargyl)ethylene diamines (III). These compounds should be convertible into methylene piperazines (V) and thence by hydrogenation to substituted piperazines (VI).

The N-(1,1-dialkylpropargyl)ethylene diamines (III) were synthesized from the appropriately substituted β-hydroxyethylamines[1] (I), which have been prepared from readily available 1,1-dialkylpropargylamines.[2,3] Treatment of the amino alcohols (I) with thionyl chloride gave the β-chloroethylamines (II). These were then treated with primary amines to obtain the terminal secondary amines (III, R^3 = alkyl) or with potassium phthalimide followed by replacement with hydrazine[4] to give the primary amino derivatives (III, R^3 = H). (See Scheme I).

SCHEME I



The ethylene diamines, obtained as described above, were treated with mercuric oxide[5] and sulfuric acid in a methanol–water solution. The infrared spectra of the crude reaction products had absorption peaks at 5.8 μ indicating ketone carbonyl functions. Upon distillation, different compounds were produced whose infrared spectra no longer had absorption peaks at 5.8 but new strong peaks at 6.2 μ. These compounds were assigned structure V. The presence of the ketones in the crude reaction products indicates that the cyclization of the ethylene diamines proceeds by hydration of the triple bond. The amino group then adds to the ketone followed by the elimination of water. The cyclization does not proceed by an amine salt addition directly to the triple bond. This mechanism was further evidenced by the unsuccessful cyclization of an ethylenediamine where the R^3 substituent was large (*t*-butyl) and offered steric hinderance to the amine addition to the ketone. Distillation of the reaction products in this case gave only the β-keto alkyl ethylenediamine (IV).

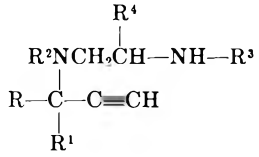
The assignment of structure V was also confirmed by the n.m.r. spectrum[6] of Va (R = R′ = CH_3; R^2 = R^3 = C_2H_5; R^4 = H) which showed unsplit signals at 227 (1H) and 243 c.p.s. (1H) which are ascribed to the vinyl protons; a series of peaks between 140 and 183 c.p.s. (8H) assigned to the protons of the N-methylene groups; an unsplit signal at 76 c.p.s. (6H) assigned to the *gem* dimethyl protons; and triplets centered at 63 (3H) and 66 c.p.s. (3H) assigned to the methyl protons of the ethyl groups.

The hydration and subsequent cyclization was extended to include the aryl and aralkyl groups as the R^3 substituent, giving the substituted methylene piperazines. When N-ethyl-N-[3-(3-methyl-1-butynyl)]-ethylene diamine (IIIa, R = R′ = CH_3; R^2 = C_2H_5; R^3 = R^4 = H) was hydrated and distilled, two different products were possible, the methylene piperazine where

(1) N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **28**, 448 (1963).
(2) G. F. Hennion and R. S. Hanzel, *J. Am. Chem. Soc.*, **82**, 4908 (1960).
(3) N. R. Easton, R. D. Dillard, W. J. Doran, M. Livezey, and D. E. Morrison, *J. Org. Chem.*, **26**, 3772 (1961).
(4) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926).
(5) G. F. Hennion and P. E. Butler, *J. Org. Chem.*, **26**, 3341 (1961).
(6) The machine used was the Varian Associates Model HR60, 60 Mc. Deuteriochloroform was used as the solvent and tetramethylsilane as the internal reference.

TABLE I

ETHYLENEDIAMINES

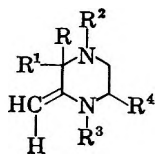


R	R¹	R²	R³	R⁴	B.p., °C. (mm.)	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	CH_3	C_2H_5	H	H	*a*	$C_9H_{20}Cl_2N_2$	47.58	47.62	8.87	9.14
CH_3	CH_3	C_2H_5	C_2H_5	H	70–71 (4)	$C_{11}H_{22}N_2$	72.47	72.28	12.16	12.33
CH_3	CH_3	CH_3	C_2H_5	CH_3	65–67 (4)	$C_{11}H_{22}N_2$	72.47	72.32	12.16	12.39
CH_3	CH_3	CH_3	$CH(3H_3)_2$	H	67 (4)	$C_{11}H_{22}N_2$	72.47	72.85	12.16	12.40
CH_3	CH_3	C_2H_5	$C(CH_3)_3$	H	78–79 (4)	$C_{13}H_{26}N_2$	74.22	73.98	12.45	12.62
CH_3	CH_3	C_2H_5	$-CH_2CH_2C_6H_5$	H	92–95 (0.02)	$C_{17}H_{26}N_2$	79.01	78.87	10.14	10.09
CH_3	CH_3	C_2H_5	C_6H_5	H	105–110 (0.01)	$C_{15}H_{22}N_2$	78.21	78.03	9.62	9.76
$-(CH_2)_6-$		C_2H_5	C_2H_5	H	*b*	$C_{14}H_{28}Cl_2N_2$	56.94	57.16	9.55	9.75

[a] As dihydrochloride, crystallized from ethanol, m.p. 196–198°. [b] As dihydrochloride, crystallized from isopropyl alcohol, m.p. 199–201°.

TABLE II

2-METHYLENEPIPERAZINES



R	R¹	R²	R³	R⁴	B.p., °C. (mm.)	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	CH_3	C_2H_5	C_2H_5	H	71 (4)	$C_{11}H_{22}N_2$	72.47	72.58	12.16	12.33
CH_3	CH_3	CH_3	C_2H_5	CH_3	71–73 (6)	$C_{11}H_{22}N_2$	72.47	72.24	12.16	12.18
CH_3	CH_3	CH_3	$-CH(CH_3)_2$	H	77 (4)	$C_{11}H_{22}N_2$	72.47	72.28	12.16	12.22
CH_3	CH_3	C_2H_5	$-CH_2CH_2C_6H_5$	H	105 (0.05)	$C_{17}H_{26}N_2$	79.02	78.83	10.14	10.05
CH_3	CH_3	C_2H_5	C_6H_5	H	114 (0.01)	$C_{16}H_{22}N_2$	78.21	78.17	9.63	9.78
$-(CH_2)_6-$		C_2H_5	C_2H_5	H	72 (0.3)	$C_{14}H_{26}N_2$	75.61	75.64	11.79	11.92

the double bond was exocyclic or a tetrahydropyrazine where the double bond was in the ring. The infrared and n.m.r. spectra indicated that 4-ethyl-2,3,3-trimethyl-2,3,4,5-tetrahydropyrazine (VII) was obtained. Hydrogenation of the unsaturated piperazines V or VII gave the 2-methylpiperazines (VI or VIII) in 40–80% yields.

The methylene piperazines (V) are readily available stable enamines. Several well-known enamine reactions were performed to obtain piperazines with substituents difficult to obtain by other methods. Phenylacetylene was treated with Va using cuprous chloride as catalyst[7] to obtain 1,4-diethyl-2,3,3-trimethyl-2-phenylethynylpiperazine (IX). The reaction was equally successful using 3-methyl-1-butyn-3-ol and N-3-dimethyl-1-butynyl-3-amine as adducts. Acetylene was reacted with Va in benzene[7] to give a small yield of 1,4-diethyl-2,3,3-trimethyl-2-ethynylpiperazine and some disubstituted acetylenic compound.

When acetic anhydride[8] and Va were refluxed in benzene overnight, 1,4-diethyl-3,3-dimethyl-2-acetonylidenepiperazine was obtained as expected.

(7) K. C. Brannock, R. D. Burpitt, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1462 (1963).

(8) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

Experimental

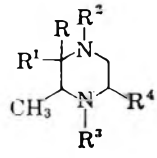
Ethylenediamines (III).—The following general procedure was used. The 1,1-dialkyl-N-(β-hydroxyethyl)propargylamine[1] (0.5 mole) was dissolved in methanol and excess anhydrous hydrogen chloride was added. The methanol and excess acid were removed at reduced pressure and the residue was taken up in 500 ml. of chloroform. At reflux temperature, 1 mole of thionyl chloride was added dropwise to the chloroform solution and reflux was maintained for 3 hr. The chloroform and excess thionyl chloride were removed at reduced pressure; the residue was dissolved in water; the solution was made basic with 50% sodium hydroxide solution and extracted with ether. After drying, the ether solution was distilled, giving the crude β-chloroethylamine (II) as the residue. A mixture of unpurified β-chloroethylamine and primary amine was maintained at reflux temperature for 16 hr. using water or acetonitrile as a solvent. The reaction mixture was treated with excess 20% sodium hydroxide solution and extracted with ether. After drying over magnesium sulfate, the ether solution was concentrated and the residue was distilled giving the ethylenediamine in 60–80% yield, based on starting amino alcohol.

To obtain the primary amino derivative (IIIb, R^3 = H), the β-chloroethylamine was refluxed with potassium phthalimide in ethanol followed by treatment with hydrazine.[4] Upon distillation, the ethylenediamine was obtained in 60–65% yield (see Table I).

2-Methylenepiperazines (V).—The ethylenediamine (0.2 mole) was added dropwise to a mixture of 0.6 mole of 98% sulfuric acid, 60 ml. of water, 60 ml. of methanol, and 5 g. of mercuric oxide.[5] After the addition was complete, the mixture was refluxed 4 hr. with air bubbling slowly into the reaction mixture. After cool-

TABLE III

PIPERAZINES

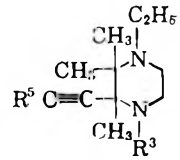


R	R^1	R^2	R^3	R^4	B.p., °C. (mm.)	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	CH_3	C_2H_5	H	H	57 (4)	$C_9H_{20}N_2$	69.17	69.42	12.90	13.14
CH_3	CH_3	C_2H_5	C_2H_5	H	64 (4)	$C_{11}H_{24}N_2$	71.68	71.88	13.13	13.38
CH_3	CH_3	CH_3	C_2H_5	CH_3	*a*	$C_{11}H_{26}Cl_2N_2$	51.35	51.27	10.18	10.43
CH_3	CH_3	CH_3	$CH(CH_3)_2$	H	*b*	$C_{11}H_{26}Cl_2N_2$	51.35	51.46	10.18	10.33
CH_3	CH_3	C_2H_5	$CH_2CH_2C_6H_5$	H	99–100 (0.05)	$C_{17}H_{28}N_2$	78.40	78.55	10.84	10.95
CH_3	CH_3	C_2H_5	C_6H_5	H	90 (0.05)	$C_{15}H_{24}N_2$	77.53	77.47	10.41	10.44
$-(CH_2)_5-$		C_2H_5	C_2H_5	H	67 (0.3)	$C_{14}H_{28}N_2$	74.94	75.10	12.58	12.63

[a] As dihydrochloride, crystallized from isopropyl alcohol, m.p. 225–227°. [b] As dihydrochloride, crystallized from isopropyl alcohol m.p. 223–224°.

TABLE IV

PIPERAZINES



R^1	R	B.p., C. (mm.)	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
C_2H_5	H	*a*	$C_{11}H_{26}Cl_2N_2$	55.51	55.52	9.31	9.50
C_2H_5	C_3H_5	117 (0.008)	$C_{13}H_{28}N_2$	80.23	80.02	9.92	10.03
C_2H_5	$-C(CH_3)_2$ (NHCH$_3$)	80 (0.07)	$C_{17}H_{33}N_3$	73.06	73.32	11.90	12.10
C_2H_5	$-C-(CH_3)_2$ (OH)	73–74 (0.02)	$C_{16}H_{30}N_2O$	72.13	72.32	11.35	11.48
C_6H_5	C_6H_5	145–148 (0.01)	$C_{23}H_{28}N_2$	83.08	82.84	8.49	8.55

[a] As dihydrochloride salt, crystallized from isopropyl alcohol–methyl ethyl ketone, m.p. 190–192°.

ing, the mixture was filtered, and the filtrate was made strongly basic with 50% sodium hydroxide solution and extracted with ether. The ether solution was dried with magnesium sulfate and filtered, and the filtrate was distilled giving the 2-methylenepiperazines in 50–75% yields (see Table II).

4-Ethyl-2,3,3-trimethyl-2,3,4,5-tetrahydropyrazine (VII).—N-Ethyl-N-[3-(3-methyl-1-butynyl)]ethylenediamine was cyclized as described for V and the product was distilled, b.p. 58° (4 mm.).

Anal. Calcd. for $C_9H_{18}N_2$: C, 70.07; H, 11.76. Found: C, 70.03; H, 11.77.

N-[2-(*t*-Butylamino)ethyl]-3-ethylamino-3-methyl-2-butanone (IV).—N-Ethyl-N-[3-(3-methyl-1-butynyl)]-N′-*t*-butylethylene diamine (0.13 mole) was treated with mercuric oxide and sulfuric acid as described for V, and the product was distilled, b.p. 102–104° (7 mm.), giving 15 g. (50%) of colorless oil.

Anal. Calcd. for $C_{13}H_{22}N_2O$: C, 68.37; H, 12.36. Found: C, 68.56; H, 12.61.

2-Methylpiperazines (VI).—The methylenepiperazine (V, 0.1 mole) in 100 ml. of ethanol with 2 g. of 5% palladium on carbon as catalyst was hydrogenated at approximately 40 p.s.i. of hydrogen. The catalyst was filtered and the product was distilled (see Table III). Yields of 60–80% were obtained.

1,4-Diethyl-2,3,3-trimethyl-2-phenylethynylpiperazine (IX).—A mixture of 9.1 g. (0.05 mole) of 1,4-diethyl-3,3-dimethyl-2-methylenepiperazine (Va), 5.1 g. (0.05 mole) of phenylacetylene, and 1 g. of cuprous chloride was stirred in a flask, and the temperature of the reaction mixture rose to 85°. After allowing to cool to 25° (1 hr.), the mixture was filtered and distilled giving 6 g. (42%) of colorless oil boiling at 117° at 0.008 mm. (see Table IV).

1,4-Diethyl-2,3,3-trimethyl-2-ethynylpiperazine and 1,2-Bis[2-(1,4-diethyl-2,3,3-trimethylpiperazino)]ethyne.—A mixture of 0.3 mole of 1,4-diethyl-3,3-dimethyl-2-methylenepiperazine (Va), 4 g. of cuprous chloride, and 300 ml. of benzene was placed in an autoclave and the autoclave was filled with acetylene at 30 p.s.i. The autoclave was warmed at 80° for 2 hr. After cooling, the mixture was filtered and the benzene solution was distilled. A fraction boiling at 89° (4 mm.), 2 g., was collected. The dihydrochloride of the distillate was crystallized from methyl ethyl ketone–isopropyl alcohol (see Table IV). A second fraction boiling at 160–163° (0.3 mm.) was collected, giving 25 g. (43%) of 1,2-bis[(2-(1,4-diethyl-2,3,3-trimethylpiperazino)]ethyne.

Anal. Calcd. for $C_{24}H_{46}N_4$: C, 73.78; H, 11.87; N, 14.34. Found: C, 74.01; H, 12.05; N, 14.23.

1,4-Diethyl-3,3-dimethyl-2-acetonylidenepiperazine (X).—A solution of 0.1 mole of Va and 0.05 mole of acetic anhydride in 100 ml. of benzene was heated overnight at 60°, cooled, washed with cold 10% sodium hydroxide solution, dried over magnesium sulfate, and filtered; the filtrate was distilled. The fraction boiling at 110–112° (0.2 mm.) was collected giving 15 g. (67%) of colorless oil.

Anal. Calcd. for $C_{13}H_{24}N_2O$: C, 69.60; H, 10.78. Found: C, 69.35; H, 11.04.

Acknowledgment.—The microanalyses were performed by Messrs. William Brown, Howard Hunter, George Mackiak, and Alfred Brown. Many of the starting materials were prepared by Mr. Lawrence White. The infrared spectra were obtained by Mrs.

Doris Stephens and Miss Martha Hofmann. The authors wish to thank especially Messrs. Paul Landis and Donald Woolf, Jr., for their invaluable services in interpreting and compiling the infrared and n.m.r. data.

Studies on the Ultraviolet Absorption of Psoralene and Substituted Psoralenes

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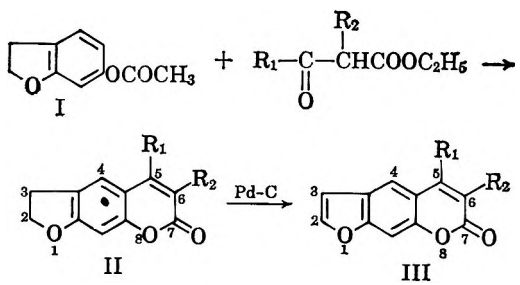
Psoralene, the active principle of *Psoralea corylifolia* Linn., has been widely used in the treatment of leucoderma.[1] Many psoralene derivatives obtained both naturally and synthetically have been studied and the photosensitizing activities have been found to vary according to the position as well as to the nature of the substituent.[2] In view of the demonstration of Pathak and Fellman[3] that there is a correlation between light absorption and photosensitizing activity, it was considered to be interesting to study the ultraviolet absorption spectra of psoralenes substituted at various positions. In this note we have dealt with psoralene derivatives substituted at the pyran ring (*viz.*, 5- and 6-positions).

Different methods employed for the syntheses of psoralene and its derivatives have been reviewed by Esse and Christensen[4] and we have employed 6-acetoxycoumaran (I) as a starting material for our syntheses. Compound I has been prepared according to Horning and Reisner's[5] method by condensing resorcinol and



chloroacetonitrile, acetylating the product, and reducing catalytically the 6-acetoxybenzofuranone with palladized charcoal.• We have also followed the method employed by Davies,[6] *et al.*, for the synthesis of 6-hydroxybenzofuranone from resorcinol and chloroacetyl chloride. Syntheses of substituted psoralenes (III) were accomplished by condensing 6-acetoxycoumaran (I) with an appropriate β-keto ester followed by dehydrogenation of the resulting dihydropsoralene (II) with palladium–carbon in refluxing diphenyl ether.[7]

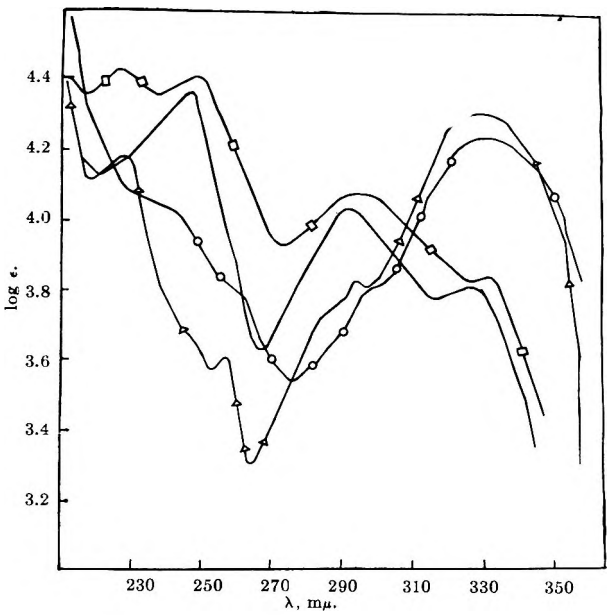


Fig. 1.—Ultraviolet absorption spectra of psoralene, ———; 5-phenylpsoralene (**15**), –□–□–; 5,6-cyclopenteno-2,3-dihydropsoralene (**9**), –△–△–; 5-phenyl-6-methyl-2,3-dihydropsoralene (**7**), –○–○–.

Experimental

Melting points are uncorrected. The compounds were repeatedly crystallized from the solvents until sharp and constant melting points were obtained.

Dihydropsoralenes[5] and psoralenes[7] prepared following the procedure of Horning, *et al.*, are listed in Tables I and II. Natural psoralene as a reference compound was obtained from the seeds of *Psoralea corylifolia* Linn. by the solvent extraction process.[8] The crude product after purification by chromatography and finally by crystallization from benzene, melted at 160–161°.[8]

Absorption was measured with a Uvispek Mark VII photoelectric spectrophotometer, using ethanol as solvent at a concentration of 5–6 mg./l. in the region 200–360 mμ.

Results and Discussion

Important features from the absorption spectra are summarized in Table III. Four types of absorption curves have been observed. One example of each type has been presented in Fig. 1. A study of the data given in Table III will show that substitution of hydrogen at the 5- and 6-positions by the alkyl group in psoralene does not produce any significant change of the absorption pattern; both λ_{max} and log ε remain materially unchanged.

A bathochromic shift as well as increase in log ε value has been observed at a lower wave length when the 5-position of psoralene is substituted by a phenyl group. A new minimum at 221 mμ (log ε 4.26–4.34) and a maximum at 225 mμ (log ε 4.42–4.43) have appeared. The usual minimum at 221 ± 1 has been shifted to 235 ± 1 mμ (log ε 4.24–4.33). The maximum at 245 ± 1 is found at 247–248 mμ (log ε 4.32–4.40), and the characteristic minimum at 265 ± 1 is shifted bathochromically to 270–271 mμ (log ε 3.68–3.91). There is a rather broad band at 297 ± 1 mμ (log ε 3.99–4.06) instead of at

(1) B. Mukherji, *J. Sci. Ind. Res.* (India), **15A**, 256 (1956).

(2) L. Musajoe, G. Rodighiro, and G. Caporale, *Chem. Abstr.*, **48**, 4111 (1954); L. Musajoe, G. Rodighiro, G. Caporale, and C. Antonello, *ibid.*, **53**, 6222[b] (1959).

(3) M. A. Pathak and J. H. Fellman, *Nature*, **185**, 382 (1960).

(4) R. C. Esse and B. E. Christensen, *J. Org. Chem.*, **25**, 1565 (1960).

(5) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **70**, 3619 (1948).

(6) J. S. H. Davies, P. A. McCrea, W. L. Norris, and G. R. Ramage, *J. Chem. Soc.*, 3206 (1950).

(7) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **72**, 1514 (1950).

(8) H. N. Khastagir, P. C. Duttagupta, and P. Sengupta, *Indian J. Appl. Chem.*, **22**, 82 (1959).

TABLE I. 2,3-DIHYDROALKYL AND -ARYL DERIVATIVES OF PSORALENE

Compd. no.	Reactants	Compd. II R1	Compd. II R2	M.p., °C.	Crystn. solvent	Yield, %	Formula	Analysis, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	I + ethyl acetoacetate	CH_3	H	169–170[a]	Ethyl acetate	85[a]	$C_{12}H_{10}O_3$	71.29	71.39	4.95	5.23
2	I + ethyl α-methylacetoacetate	CH_3	CH_3	185–186[b]	Ethanol	50[b]	$C_{13}H_{12}O_3$	72.22	71.92	5.55	5.68
3	I + ethyl α-ethylacetoacetate	CH_3	C_2H_5	144–145[c]	Ethanol	40[c]	$C_{14}H_{14}O_3$	73.04	72.78	6.13	5.93
4	I + ethyl α-isopropylacetoacetate	CH_3	$(CH_3)_2CH$	184–185[d]	Ethanol	25[d]	$C_{15}H_{16}O_3$	73.77	73.58	6.55	6.63
5	I + ethyl α-n-butylacetoacetate	CH_3	$CH_3(CH_2)_3$	89–90	Ethanol	28	$C_{16}H_{18}O_3$	74.42	74.28	6.97	6.92
6	I + ethyl benzoylacetate	C_6H_5	H	200[e]	Ethyl acetate	61					
7	I + ethyl α-methylbenzoylacetate	C_6H_5	CH_3	239–240	Ethyl acetate	15	$C_{18}H_{14}O_3$	77.68	77.35	5.03	5.20
8	I + ethyl α-ethylbenzoylacetate	C_6H_5	C_2H_5	206–207	Ethyl acetate	15	$C_{19}H_{16}O_3$	78.18	78.08	5.50	5.70
9	I + ethyl cyclopentanone-2-carboxylate	$-CH_2$ $>CH_2$ $-CH_2$		185–186	Ethyl acetate	64	$C_{14}H_{12}O_3$	73.68	73.38	5.30	5.24

[a] Lit.[7] m.p. 170°, yield 88%. [b] Lit.[4] m.p. 186°, yield 21%. [c] Lit.[4] m.p. 143–144°, yield 35%. [d] Lit.[4] m.p. 185°, yield 25%. [e] Lit.[7] m.p. 202°.

TABLE II. 5,6-ALKYL AND -ARYL DERIVATIVES OF PSORALENE

Compd. no.	Compd. III R1	Compd. III R2	M.p., °C.	Crystn. solvent	Yield, %	Formula	Analysis, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
10	CH_3	H	185–186[a]	Ethyl acetate	70					
11	CH_3	CH_3	235[b]	Ethyl acetate	50	$C_{13}H_{10}O_3$	72.89	72.69	4.71	4.92
12	CH_3	C_2H_5	178–179[c]	Ethyl acetate	60	$C_{14}H_{12}O_3$	73.68	73.63	5.26	5.30
13	CH_3	CH_3 | CH_3-CH	143[d]	Petr. ether[e]	45	$C_{15}H_{14}O_3$	74.33	73.84	5.78	5.98
14	CH_3	$CH_3(CH_2)_3$	100–101	Ethanol	65	$C_{16}H_{16}O_3$	74.98	74.74	6.25	6.41
15	C_6H_5	H	177[f]	Ethanol	75					
16	C_6H_5	CH_3	160	Ethyl acetate–petr. ether	30	$C_{18}H_{12}O_3$	78.30	77.38	4.35	4.74
17	C_6H_5	C_2H_5	178	Ethanol–petr. ether	30	$C_{19}H_{14}O_3$	78.60	77.96	4.83	4.86
18	$-CH_2$ $>CH_2$ $-CH_2$		234	Ethyl acetate	40	$C_{14}H_{10}O_3$	74.33	73.94	4.42	4.68

[a] Lit.[7] m.p. 187°. [b] Lit.[4] m.p. 236°, yield 45%. [c] Lit.[4] m.p. 179°, yield 55%. [d] Lit.[4] m.p. 145–147°, yield 44%. [e] B.p. 60–80°. [f] Lit.[7] m.p. 178°.

TABLE III. ULTRAVIOLET ABSORPTION DATA OF PSORALENE AND ITS DERIVATIVES[c]

Compd. no.[b]	λ_{min} (log ε)	λ_{max} (log ε)	λ_{min} (log ε)	λ_{max} (log ε)	λ_{min} (log ε)	λ_{max} (log ε)	λ_{min} (log ε)	λ_{max} (log ε)
Psoralene[c]			221 (4.12)	246 (4.37)	266 (3.63)	290 (4.03)	316 (3.77)	328 (3.80)
1	215 (4.10)	225 (4.21)	252 (3.55)	254 (3.57)	264 (3.30)	294 (3.78)		332 (4.26)
2	216 (4.05)	225 (4.10)			266 (3.22)	296 (3.75)		332 (4.22)
3	216 (4.05)	226 (4.11)	254 (3.45)	256 (3.47)	265 (3.21)	295 (3.76)		332 (4.26)
4	216 (4.09)	226 (4.14)	253 (3.56)	255 (3.57)	265 (3.32)	295 (3.80)		332 (4.28)
5	217 (4.01)	226 (4.08)	254 (3.42)	256 (3.45)	265 (3.17)	296 (3.73)		332 (4.23)
6	230 (4.11)	235 (4.13)	255 (3.98)	261 (4.00)	292 (3.61)			337 (4.19)
7					279 (3.55)			335 (4.25)
8					277 (3.37)			335 (4.16)
9	218 (4.10)	227 (4.16)	253 (3.57)	255 (3.60)	265 (3.29)	295 (3.82)		332 (4.30)
10			220 (4.03)	244[d] (4.39)	264 (3.57)	289 (3.99)	312 (3.77)	329 (3.85)
11			221 (4.09)	245 (4.38)	266 (3.68)	290 (4.02)	312 (3.89)	329[e] (3.95)
12			221 (4.13)	245 (4.42)	266 (3.71)	290 (4.06)	312 (3.92)	329[e] (3.99)
13			220 (4.06)	245 (4.30)	266 (3.59)	290 (3.96)	312 (3.85)	329[e] (3.94)
14			221 (4.11)	244 (4.40)	266 (3.65)	290 (4.04)	312 (3.91)	328 (3.98)
15	215 (4.37)	225 (4.43)	236 (4.35)	248 (4.41)	271 (3.91)	298 (4.06)		331 (3.83)
16	221 (4.34)	225 (4.35)	236 (4.32)	247 (4.38)	270 (3.78)	296 (4.05)	317 (3.91)	328 (3.92)
17	222 (4.26)	225 (4.28)	234 (4.24)	247 (4.32)	270 (3.68)	296 (3.99)	318 (3.82)	328 (3.84)
18			222 (4.12)	246 (4.35)	266 (3.62)	298 (4.01)	310 (3.92)	326 (4.00)

[a] Values are in mμ. [b] The numbers of compounds are same as those in Tables I and II. [c] Compound III, $R_1 = R_2 = H$. [d] Twin peak at 422 and 244 mμ. [e] Twin peak at 326 and 329 mμ.

290, and the minimum at 317–318 mμ (log ε 3.82–3.91) corresponds to that of psoralene. A very weak band at 328–330 mμ is also present which corresponds to the similar band of psoralene in this region.

The spectra of 2,3-dihydropsoralenes present very interesting features. Reduction of the furano ring caused the appearance of a band at 226 mμ (log ε 4.08–4.20). This has been considered to be due to the formation of a saturated ether which causes a bathochromic effect, offsetting the effect of the loss of conjugation.[9] The minimum at 221 and maximum at 245 mμ of psoralene is shifted to 253 and 256 mμ (log ε 3.41–3.60), resulting in a very weak band. The very sharp minimum at 265 ± 1 mμ (log ε 3.31–3.32) is characteristic for this group of compounds also. A very small band at 295 ± 1 mμ (log ε 3.75–3.80) is present and the maximum at 332 mμ (log ε 4.22–4.30) though broad is very characteristic.

In case of 5-phenyl-6-alkyl derivatives of dihydropsoralene, the characteristic minimum at 265 is shifted to 277 mμ (log ε 3.37–3.55), whereas in case of 5-phenyl dihydropsoralene, unsubstituted at the 6-position, the minimum occurs at 292 mμ (log ε 3.61). A broad band at above 335 mμ is present in all the three compounds.

Acknowledgment.—The authors are grateful to Mr. P. Bagchi, Director of Research, East India Pharmaceutical Works Ltd., Calcutta, for his kind interest and valuable suggestions, and to Mrs. C. Dutta of Indian Association for the Cultivation of Science, Calcutta, for the analyses.

(9) M. E. Brokke and B. E. Christensen, *J. Org. Chem.*, **23**, 590 (1958).

Alkylation and Metalation of Perylene with *n*-Butyllithium. 1-*n*-Butylperylene

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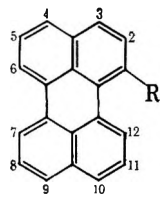
Recently Dixon and Fishman reported that aromatic hydrocarbons undergo alkylation with alkyllithium reagents to form mono- and dialkylated arenes in decalin at elevated temperatures.[2] During the course of metalation studies[3] on perylene (Ia) with *n*-butyllithium, at room temperature, we observed the alkylation reaction. One of the hydrocarbons which was isolated is thought to be 1-*n*-butylperylene and constitutes the first reported substitution of perylene at a position other than position three.

Two monosubstituted *n*-butylperylenes were isolated after column chromatography over alumina. One of these isomers (m.p. 138–139°) has an infrared spectrum which is difficult to distinguish from the spectrum for



Ia, R = H
b, R = *n*-C_4H_9–

the known 3-*n*-hexylperylene.[4,5] The ultraviolet spectrum of this material compares favorably with the spectrum for the known 3-alkylperylenes[6,7] listed in Table I despite the fact that it was isolated in small amount and contained a difficult-to-remove impurity.

The other *n*-butylperylene isomer (13.2%, m.p. 66.5–67.0°) has been assigned the structure 1-*n*-butylperylene (Ib) because its infrared spectrum differs from the spectra of the presumed 2-ethyl- and 2-*n*-hexylperylene in the region of 10–15 μ.[8] Furthermore, comparison of the n.m.r. spectrum of this butylperylene isomer with the spectrum of 3-*n*-hexylperylene shows an appreciable lower field chemical shift of 0.2 p.p.m. for the α-methylene signals.[9] Interestingly, the difference in chemical shift is greater (0.37 p.p.m.) for a comparison of 1-*n*-butylperylene and the presumed 2-ethyl- and 2-*n*-hexylperylene. This deshielding suggests that the *n*-butyl group is not at the 3-position and is predicted for the 1-position because of the increased ring-current effect expected for this position.

The ultraviolet spectrum of the new hydrocarbon bears a closer resemblance to the reported spectrum for 1-methylperylene[7] than for the spectrum of the presumed 2-ethylperylene (see Table II).

The n.m.r. spectrum[9] of 1-*n*-butylperylene exhibits proton signals: (1) at 0.9 and 1.0 p.p.m. from internal tetramethylsilane having an intensity ratio of 1:2.96 (theoretical = 1:2.86); (2) at 2.98 p.p.m. (center of a triplet), intensity ratio of 1:9.9 (theoretical = 1:10);

(1) National Science Foundation Undergraduate Research Participant, spring semester and summer, 1963.

(2) J. A. Dixon and D. Fishman (a) *J. Am. Chem. Soc.*, **85**, 1356 (1963); (b) Abstracts of Papers, Division of Organic Chemistry, 145th National Meeting of the American Chemical Society, Sept. 1963, paper no. 101, p. 54Q.

(3) The solvent was ether–tetrahydrofuran and reaction conditions were chosen to approximate those found to be optimum for metalation in the naphthalene series: H. Gilman and S. Gray, *J. Org. Chem.*, **23**, 1476 (1958).

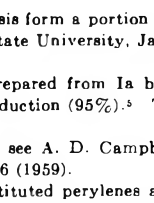
(4) 3-*n*-Hexylperylene (m.p. 141.8–142.6°) was prepared by Wolf-Kishner reduction of 3-*n*-hexanoylperylene. This ketone was secured by alternate syntheses: (a) Friedel-Crafts reaction of I and hexanoyl chloride (62.7%) and (b) the reaction of perylene-3-carbonyl chloride and di-*n*-pentylcadmium (55%).

(5) Details of this synthesis form a portion of the Ph.D. Thesis of H. E. Zieger, The Pennsylvania State University, Jan., 1961; *Dissertation Abstr.*, **22**(1) (1961).

(6) Ethylperylene was prepared from Ia by Friedel-Crafts acetylation (54%) and Wolf-Kishner reduction (95%).[5] The ultraviolet spectrum was obtained in cyclohexane.

(7) For 3-methylperylene see A. D. Campbell, R. S. Elder, and C. W. Emerson, *J. Chem. Soc.*, 3526 (1959).

(8) Only three monosubstituted perylenes are possible and the assumption[5] that was made is that 1,2,3,10,11,12-hexahydroperylene (i) furnished predominantly 5-acylhexahydroperylenes (61–63%) in Friedel-Crafts acylation. Because perylene derivatives secured from these ketones differed from their known 3-position isomers, they had to be either 1- or 2-derivatives of Ia



i

(9) N.m.r. spectra were obtained in carbon tetrachloride at 60 Mc./sec. Data for 2-ethylperylene and 2-*n*-hexylperylene were secured at the Central Research Laboratory of The Socony Mobil Oil Co., Inc., Princeton, N. J., under operating conditions similar to those for 1-*n*-butylperylene. Because of its low solubility, the spectrum of 3-*n*-hexylperylene was obtained in carbon disulfide.

TABLE I

ULTRAVIOLET SPECTRA

3-Ethylperylene[a]		3-*n*-Butylperylene		3-Methylperylene[b]		3-*n*-Hexylperylene[c]	
λ, mμ	log ε	λ, mμ	log ε	λ, mμ	log ε	λ, mμ	log ε
441.8	4.56	442.5	4.83	440	4.53	440.8	4.54
436.3	4.50 (infl.)	437.0	4.73	...	...	...	...
413.8	4.44	413.0	4.58	412.5	4.39	413.8	4.42
392.2	4.07	392.0	4.08	391	4.02	392.0	4.06
		373.0 (infl.)	3.70	370 (infl.)	3.53	371.8	3.63
266.6	3.98	265.0	4.04	268 (infl.)	3.85	266.3	3.88
254.9	4.67	255.1	4.75	254	4.61	254.2	4.59
247.6	4.53	246.5	4.54	246.5	4.45	247.0	4.45
239.7	4.21	227.0	4.28	...	...	227.1	4.26

[a] See ref. 6. [b] See ref. 7. [c] This spectrum was obtained in 95% ethanol for purposes of comparison with the spectrum of 3-methylperylene.

TABLE II

ULTRAVIOLET SPECTRA[a]

2-Ethylperylene[b]		2-Methylperylene[c]		1-Methylperylene[c]		1-*n*-Butylperylene	
λ, mμ	log ε	λ, mμ	log ε	λ, mμ	log ε	λ, mμ	log ε
436.0	4.57	435	4.53	433.5	4.52	427.6	4.60
410.0	4.46	408	4.41	406	4.40	404.0	4.51
388.7	4.13	387	4.08	384	4.10	384.5	4.08
		370 (infl.)	3.90	367 (infl.)	3.70		
264.3	4.10	266 (infl.)	3.97	268 (infl.)	3.88	258.2	4.71
254.4	4.70	253	4.65	258	4.65	251.8	4.52
247.6	4.54	246.5	4.51	245	4.52	...	...
241.1	4.28	208	4.76	208	4.72	...	...

[a] Ethyl- and 1-*n*-butylperylene were taken in cyclohexane; methylperylenes, in 95% ethanol. [b] See ref. 8. [c] See ref. 7.

and (3) at 7.05 to 7.95 p.p.m. (complex aromatic multiplet), intensity ratio 1:1.78 (theoretical = 1:1.82).

Reports of monosubstitution on perylene are few and always refer to electrophilic attack at position three.[5,7,10] Alkylation of perylene with *n*-butyllithium constitutes the first substitution on the perylene ring at a position other than position three. The new hydrocarbon is easily soluble in most common organic solvents at 20°. If this solubility behavior is general for 1-position derivatives, it is not surprising that earlier workers[10] were unable to isolate the small amounts of 1-position substitution products which probably were formed. What is surprising, however, is the amount of alkylation at the hindered 1-position. Substitution at such hindered positions in polynuclear systems has not been reported previously.[11]

The prediction of approximately equal reactivity for positions 1 and 3 in perylene is based on calculated MO reactivity indices.[12] The experimental evidence for such a prediction has been discussed.[13]

Experimental

Melting points were taken on a Nalge–Axelrod apparatus and are corrected.

Perylene.[14]—Perylene was prepared by decarboxylation of 3,4,9,10-perylenetetracarboxylic 3,4:9,10-dianhydride[15] by the method of Neugebauer.[16] The yields of perylene (m.p. 282.5–283.5°) after recrystallization from chloroform ranged from 78–85%. Perylene obtained in this manner was identical in all of its physical properties with a sample obtained from di-β-naphthol[17] using the ring-closing method of Zinke.[18]

***n*-Butyllithium.**—A 0.96 *N* solution of *n*-butyllithium in diethyl ether was prepared using 0.44 g.-atom of lithium and 0.21 mole of *n*-butyl bromide as described by Gilman.[19] The solution was assayed by the Gilman–Haubein method using benzyl chloride.

1-*n*-Butylperylene.—Freshly prepared *n*-butyllithium solution (0.51 mole, 1.19 *N*) was added dropwise during 1 hr. to a 0.025 *M* tetrahydrofuran (THF)[20] solution of perylene (12.60 g., 0.050 mole) under a dry nitrogen atmosphere at 28° with magnetic stirring. Gases were evolved (120 ml.). After 16 hr. of stirring, the reaction mass was added jetwise onto Dry Ice and stirred. Ether and THF were removed by distillation and 14.8 g. of yellow brown solid (dried *in vacuo*) remained. Extraction of this solid with four 125-ml. portions of *n*-hexane left a residue of 7.7 g. (dried *in vacuo*.) The hexane was distilled until the volume became 325–350 ml. Upon cooling at 5°, 0.55 g. of perylene (4.4%) precipitated. Chromatography of the hexane solution over Alumina (250 g. of Alcoa activated, Grade F-20, was used without further activation) yielded 1-*n*-butylperylene (2.035 g., 13.2%, m.p. 66.5–67.0° in the early fractions, 64–65° in later fractions).

Anal. Calcd. for $C_{24}H_{20}$: C, 93.46; H, 6.54; mol. wt., 308. Found: C, 93.40; H, 6.71; mol. wt., 311 (cryoscopic in benzene).

The ultraviolet spectrum was obtained in cyclohexane (see Table II).

Later chromatography fractions furnished 0.04 g. of 3-*n*-butylperylene (m.p. 136.8, 138–139°), identified by comparison of its infrared spectrum with that for 3-*n*-hexylperylene and 3-ethylperylene.[5]

The residue (7.7 g.) was extracted with four 125-ml. portions of hot benzene leaving 3.0 g. of light yellow lithium perylene

(10) (a) N. P. Buu Hoi and C. T. Long, *Rec. trav. chim.*, **75**, 1221 (1956); (b) M. J. S. Dewar and E. Warford, *J. Chem. Soc.*, 3570 (1956).

(11) L. F. Fieser and M. Fieser, "Topics in Organic Chemistry," Reinhold Publishing Co., New York, N. Y., 1963, Chapter 1; (b) M. S. Newman, *J. Am. Chem. Soc.*, **62**, 2295 (1940).

(12) J. Koutecky, R. Zahradnik, and J. Cizek, *Trans. Faraday Soc.*, **57**, 169 (1961); M. J. S. Dewar, *J. Am. Chem. Soc.*, **14**, 3357 (1952).

(13) A. Streitweiser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p. 344.

(14) Perylene used in this work was generously supplied by Professor J. A. Dixon, The Pennsylvania State University.

(15) Decarboxylation conditions for this system are well known; K. Koberle and O. Schlichting, German Patent 703,500 (1941); *Chem. Abstr.*, **36**, 7812 (1941); "Elsevier's Encyclopedia of Organic Compounds, Series III, Carboisocyclic Condensed Compounds," Vol. 14, F. Radt, Ed., 1951, p. 734 S.

(16) German Patent 486,491 (1926).

(17) R. Pummerer, E. Prell, and A. Rieche, *Ber.*, **59**, 2160 (1926).

(18) K. Brass and E. Tengler, *ibid.*, **64**, 1646 (1931); F. Hansgirg and A. Zinke, *Monatsh.*, **40**, 403 (1919).

(19) R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 339 (1951).

(20) Matheson Coleman and Bell THF (b.p. 65.5–66.5°) was distilled first from sodium ribbon into a flask containing lithium aluminum hydride, then directly into the reaction flask containing perylene.

carboxylate salts (infrared spectrum, KBr) undissolved.[21] Impure perylene (1.4 g., 4 %) crystallized from the benzene solution. Chromatography of this solution furnished additional perylene (1.1 g., 9%).

Acknowledgment.—We are indebted to Professor J. A. Dixon, Pennsylvania State University, for securing the n.m.r. spectra and for helpful discussions and encouragement. We are obliged to the City University of New York for a research grant permitting continuation of this investigation.

(21) Investigation of the isomer composition of the methyl esters of the perylenecarboxylic acids by chromatography is in progress.

p-Nitrobenzoic *t*-Butyl Thiolcarbonic Anhydride[1]

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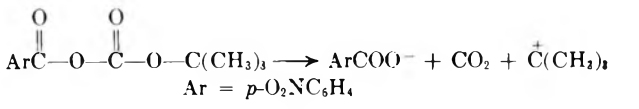
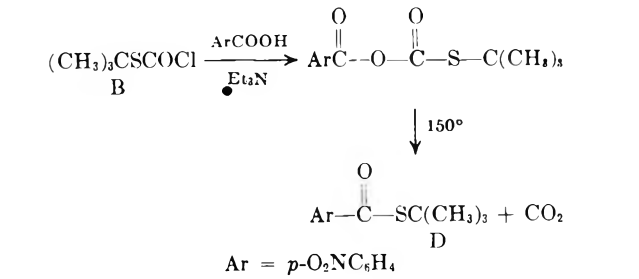
The products formed in the thermal decomposition of *p*-nitrobenzoic *t*-butyl carbonic anhydride[2] (A) indicate that it undergoes alkyl–oxygen cleavage, as shown, rather than the acyl–oxygen cleavage observed with mixed anhydrides with primary or secondary alkyl groups.[3] This note reports the preparation and properties of the sulfur analog of A.



Ar = *p*-$O_2NC_6H_4$

t-Butyl thiolchlorocarbonate (B) was prepared, apparently for the first time,[4] by the action of sodium hydride dispersion on *t*-butyl mercaptan in THF, followed by addition of phosgene in THF. *t*-Butyl thiolchlorocarbonate was distilled *in vacuo* and showed carbonyl absorption[5] at 1770 cm.$^{-1}$; it was converted in the usual way into the crystalline mixed anhydride C, m.p. 86.5–87°, which showed bands at 1730 and 1786 cm.$^{-1}$. The mixed anhydride C was converted by heating at 160° to the *p*-nitrothiolbenzoate D (identified by comparison with a synthetic sample) and carbon dioxide; no other products were observed.



Ar = *p*-$O_2NC_6H_4$

The contrast between the behavior of the sulfur compound C and the oxygen analog A is therefore striking; the former gives no apparent alkyl–sulfur cleavage, and gives high yields of products formed by a single mode of decomposition. The oxygen analog A decomposes at a lower temperature and gives a complex mixture of products, some of which are a result of alkyl–oxygen cleavage.

This pair of sulfur–oxygen analogs illustrates the smaller tendency for alkyl–sulfur cleavage as compared to alkyl–oxygen cleavage, which has been observed in numerous other cases.[6]

Experimental

t-Butyl Thiolchlorocarbonate (B).—*t*-Butyl mercaptan (45 g., 0.5 mole) in anhydrous tetrahydrofuran was added slowly with stirring to a slurry of sodium hydride dispersion[7] (50% in mineral oil; 25 g., 0.5 mole) in tetrahydrofuran and the mixture was refluxed with stirring under nitrogen for 2–4 hr. This suspension was then cooled and added with shaking to phosgene (50 g., 0.5 mole) contained in a flask equipped with stirrer and dry ice condenser and cooled in an ice–salt mixture. Air was carefully excluded during the addition to prevent oxidation of the mercaptide. After additional stirring for 2 hr. at room temperature, the mixture was centrifuged and filtered. The filtrate on distillation *in vacuo* yielded fractions boiling at 50–55° (13 mm.). On redistillation, the product boiling at 30–32° (1 mm.) was collected; this formed a thiocarbamate with aniline which had a melting point that was identical with the literature value[8] (147.5–148°).

Anal. Calcd. for C_5H_9ClOS: C, 39.36; H, 5.94; S, 21.02; Cl, 23.23. Found: C, 39.58; H, 6.18; S, 20.74; Cl, 23.05.

***p*-Nitrobenzoic *t*-Butyl Thiolcarbonic Anhydride (C).**—Dry ether (300 ml.) was chilled to −5° by an ice–salt bath, then *p*-nitrobenzoic acid (1.67 g., 0.01 mole) and *t*-butyl thiolchlorocarbonate (1.53 g., 0.01 mole) were added. The mixture was stirred and 1.01 g. (0.01 mole) of triethylamine in ether was added dropwise. The stirring was continued for 2 hr. more and the resulting mixture was filtered, washed with very dilute acid, with sodium bicarbonate solution and water, and was dried. The ether was evaporated at room temperature at reduced pressure leaving a material which was contaminated with *p*-nitrobenzoic acid; this was removed by extracting the material with carbon tetrachloride in the cold, leaving the mixed anhydride in 80–90% yield. The product was recrystallized twice or thrice from a mixture of carbon tetrachloride and petroleum ether, avoiding strong and prolonged heating. After three crystallizations, the pale yellow needles melted at 86.5–87°. The infrared spectrum contained peaks at 1730 and 1785 cm.$^{-1}$ which are characteristic of mixed carboxylic–carbonic anhydrides.[9] Ultraviolet absorption in cyclohexane showed λ_{max} 254 mμ (ε 26,900).

Anal. Calcd. for $C_{12}H_{13}NO_5S$: C, 50.86; H, 4.62; N, 4.94; S, 11.32. Found: C, 50.92; H, 4.58; N, 4.97; S, 11.24.

Decomposition of the Mixed Anhydride.—In a typical run designed to determine the yield of carbon dioxide, *p*-nitrobenzoic *t*-butyl thiolcarbonic anhydride (0.363 g., 0.00128 mole) was placed in a 10-ml. two-necked flask; through one neck a stream of prepurified nitrogen (free from oxygen and carbon dioxide) was led and the other neck carried an outlet tube and a condenser with an outlet tube. The outlet tube was connected to two microascarite tubes. The sample was heated at 160° for 2 hr. and 0.0595 g. of carbon dioxide was collected (106% of theory). The pot residue was recrystallized from ethanol–water, melted at 75.0°, and did not depress the melting point of an authentic sample of *t*-butyl *p*-nitrothiolbenzoate prepared as below. The infrared spectra of the two were identical.

(1) Aided by Grant G-11240 from the National Science Foundation.

(2) C. J. Michejda and D. S. Tarbell, *J. Org. Chem.*, **29**, 1168 (1964).

(3) E. J. Longosz and D. S. Tarbell, *ibid.*, **26**, 2161 (1961); C. J. Michejda, D. S. Tarbell, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **84**, 4113 (1962).

(4) *t*-Butoxycarbonyl derivatives have been studied extensively by L. A. Carpino [*e.g.*, *ibid.*, **79**, 98 (1957); **82**, 2725 (1960)] and have been used as protecting groups in peptide syntheses.

(5) A. W. Baker and G. H. Harris [*ibid.*, **82**, 1923 (1960)] report that CH_3SCOCl absorbs at 1766 cm.$^{-1}$.

(6) P. N. Rylander and D. S. Tarbell, *ibid.*, **72**, 3021 (1950); B. K. Morse and D. S. Tarbell, *ibid.*, **74**, 416 (1952); D. S. Tarbell, and J. C. Petropoulos, *ibid.*, **74**, 244 (1952); L. A. Carpino, P. H. Terry, and P. J. Crowley, *J. Org. Chem.*, **26**, 4336 (1961); D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 1 (1951).

(7) Obtained from the Metal Hydrides Corp.

(8) E. Dyer and J. F. Glenn, *J. Am. Chem. Soc.*, **79**, 366 (1957).

(9) D. S. Tarbell and N. L. Leister, *J. Org. Chem.*, **23**, 1149 (1958).

t-Butyl *p*-nitrothiolbenzoate (D) was prepared[10] by the action of *p*-nitrobenzoyl chloride on *t*-butyl mercaptan in benzene–pyridine. It melted after several crystallizations from alcohol-water at 74.5–75° and had a carbonyl band at 1670 cm.$^{-1}$ in the infrared; the ultraviolet absorption in cyclohexane showed λ_{max} 258 mμ (ϵ 19700), shoulder at 286 mμ (ϵ 13900).

Anal. Calcd. for $C_{11}H_{13}NO_3S$: C, 55.40; H, 5.47; N, 5.86; S, 13.40. Found: C, 55.40; H, 5.65; N, 6.04; S, 13.27.

(10) *Cf.* R. Adams, E. K. Rideal, W. B. Burnett, R. L. Jenkins, and E. E. Dreger, *J. Am. Chem. Soc.*, **48**, 1758 (1926).

Unsaturated Six-Membered Ring Lactams[1,2]

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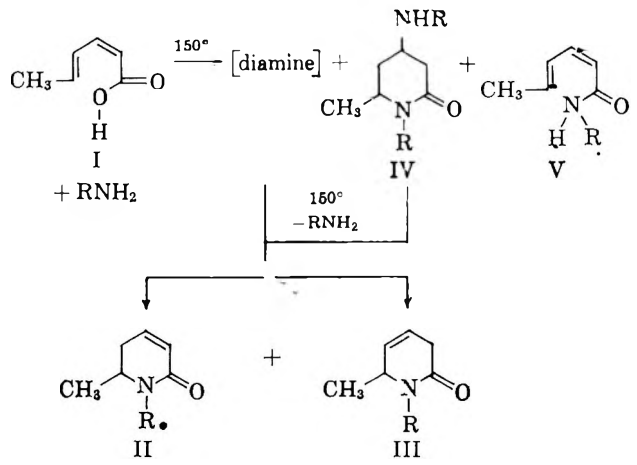
The large number of 3,4-unsaturated lactones which have been found physiologically active[4] prompted our reinvestigation of the synthesis of lactams by the well-known reaction[5–7] between sorbic acid and amines under pressure. Using ammonia,[5] the primary product of this reaction is a diamine which on further heating gives 6-methyl-5,6-dihydro-2(1)-pyridone (II, R = H). The position of the C=C double bond was correctly assumed[5] to be 3,4-, although it was not until much later that the identical compound (II, R = H) was prepared[8] by an exchange reaction between ammonia and 6-methyl-5,6-dihydro-2-pyrone. The 3,4-position of the C=C double bond in this hexenolactone was firmly established[9] and was assumed not to have changed during the exchange. Lithium aluminum hydride reductions[7] of the conjugated lactam analogs of II tend to corroborate the 3,4-position assignment. However, data presented elsewhere[6] indicate that some of the lactams were mixtures of the conjugated II and hitherto unreported unconjugated III isomers, as was evident from triplet absorption in the 6-μ region of the infrared and diminished extinction coefficients in the ultraviolet spectra.

In the present work, reaction of straight-chain alkyl amines with sorbic acid gave mixed conjugated II and unconjugated III lactams in close to 70% yields. The yield of lactam from *p*-anisidine was lower and only the conjugated isomer was isolated. Compounds corresponding to structure IV were also isolated, but were unstable and immediately converted to II and III on distillation or heating above 150°. Intermediate IV was isolated in good yield and purified only when dimethylaminopropyl amine was used. Aqueous isopropyl- and *t*-butylamines yielded no 2-pyridones in this reaction, probably for steric reasons.

Separation of the conjugated and unconjugated dihydro-2-pyridones II and III was effected by careful fractionation. The compounds thus prepared in this study are listed in Table I. Both the conjugated (II) and unconjugated (III) dihydro-2-pyridone structures were firmly established by both infrared and ultraviolet spectra evidence through comparison with model compounds



The ultraviolet spectrum of 6-methyl-5,6-dihydro-2(1)-pyridone (II, R = H) has an absorption peak at 241 mμ (ϵ 1580, previously reported[6] as ϵ 1470). This is comparable to the absorption peak of 1-ethyl-6-methyl-5,6-dihydro-2(1)-pyridone (II, R = C_2H_5) at 250 mμ (ϵ 1570), and that of the model compound, N,N-diethylcrotonamide,[10] λ_{max} 242 mμ (ϵ 6500). The shapes of the absorption curves were also similar. The unconjugated 1-ethyl-6-methyl-1,6-dihydro-2(3)-pyridone (III, R = C_2H_5) showed no absorption peak in the 220–320-mμ region.

Since there is a minimum of strain in the six-membered ring lactams, it was expected that further confirmation of their structures could be gained by comparison with the infrared spectra of model straight-chain amides. N,N-Diethylcrotonamide showed double bond absorption at 6.02 and 6.16 μ, whereas N,N-diethylvinylacetamide showed only one peak in this region, at 6.07 μ. By analogy, the compound assigned structure II showed a doublet at 6.02 and 6.18 μ, whereas the supposed unconjugated structure III showed only one peak at 6.08 μ. Furthermore, N,N-diethylpropionamide, 1-ethyl-6-methyl-2-piperidone, and 6-methyl-2-piperidone all showed a single peak at 6.07–6.08 μ, which is comparable with the absorption of the unconjugated isomer III where the C=C double bond does not interact with the carbonyl group. Identification of the isomers can therefore be made on the basis of either the infrared or ultraviolet spectra.[6] Since the 6.02-μ peak in the conjugated amides was invariably stronger than the 6.18-μ peak, it is reasonable to assume that the 6.02-μ peak was due to carbonyl, since carbonyl absorption is usually stronger than that due to C=C double bonds. The spectra of the saturated pyridones made it clear that the 6.08-μ peak of the unconjugated isomers is at least partly due to the carbonyl group. The unconjugated C=C would not be expected to absorb very strongly and is probably hidden under the 6.08-μ carbonyl peak, which presented a somewhat skew appearance. Upon conjugation the 6.08-μ peak split into the 6.02- and 6.18-μ pair. This unusual shift of the car-

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(2) Taken in part from the Doctoral Thesis of A. J. V., University of Notre Dame, 1954.

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(4) L. J. Haynes, *Quart. Rev.* (London), **2**, 46 (1948).

(5) E. Fischer and F. Schlotterbeck, *Ber.*, **37**, 2357 (1904).

(6) O. E. Edwards and T. Singh, *Can. J. Chem.*, **32**, 683 (1954).

(7) M. Shamma and P. D. Rosenstock, *J. Org. Chem.*, **26**, 718 (1961).

(8) R. Kuhn and D. Jerchel, *Ber.*, **76B**, 413 (1943).

(9) L. J. Haynes and E. R. H. Jones, *Nature*, **155**, 730 (1945).

(10) K. Bowden, E. A. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946).

TABLE I
LACTAMS AND MODEL AMIDES

Compound	B.p. (mm.) or m.p., °C.	$n^{20}D$	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	Ultraviolet, λ_{max}, mμ (ϵ_{max})	Infrared,[a] λ_{max}, μ
6-Methyl-5,6-dihydro-2(1)-pyridone	108–109[b]									241[c,d] (1580)	2.94,[e] 3.13, 5.98, 6.17
6-Methyl-2-piperidone	89–90[f]										2.94,[e] 3.13, 6.07
1,6-Dimethyl-5,6-dihydro-2(1)-pyridone	109–110[c,g] (13)	1.4984									6.02, 6.18
1,6-Dimethyl-1,6-dihydro-2(3)-pyridone	104 (13)	1.4958	$C_7H_{11}NO$	67.15	67.46	8.86	8.88	11.19	11.02		6.07
1-Ethyl-6-methyl-5,6-dihydro-2(1)-pyridone	111–112 (13)	1.4914	$C_8H_{13}NO$	69.02	69.15	9.41	9.44	10.06	10.10	250[h] (1570)	6.02, 6.18
1-Ethyl-6-methyl-1,6-dihydro-2(3)-pyridone	106–107 (13)	1.4985	$C_8H_{13}NO$	69.02	68.87	9.41	9.65	10.06	9.80	252[h] (331)	6.08
1-Ethyl-6-methyl-2-piperidone	105–106 (13)	1.4766	$C_8H_{15}NO$	68.05	67.41	10.71	10.87	9.92	9.80		6.07
1-Propyl-6-methyl-5,6-dihydro-2(1)-pyridone	121–122 (15)	1.4875	$C_9H_{15}NO$	70.56	70.10	9.87	9.82	9.14	9.22		6.02, 6.18
1-Phenyl-6-methyl-5,6-dihydro-2(1)-pyridone	93 (0.05)[g]	1.5728									6.02, 6.16, 6.23
1-(*p*-Anisyl)-6-methyl-5,6-dihydro-2(1)-pyridone	65–66 155–162 (0.2)		$C_{13}H_{15}NO$	71.85	71.66	6.95	6.96	6.45	6.20		5.98,[e] 6.13, 6.19
1-(3′-Dimethylaminopropyl)-6-methyl-5,6-dihydro-2(1)-pyridone	92–95 (0.25)	1.4922	$C_{11}H_{20}N_2O$	67.29	67.47	10.24	10.07	14.27	13.94		6.02, 6.18
1-(3′-Dimethylaminopropyl)-4-(3′-dimethylaminopropylamino)-6-methyl-2-piperidone	167–168 (0.35)	1.4892	$C_{16}H_{34}N_4O$	64.38	64.40	11.48	11.09	18.77	18.51		3.08, 6.10
N,N-Diethylcrotonamide	111 (19)[i]	1.4750								242[h] (6500)	6.02, 6.16
N,N-Diethylvinylacetamide	95 (15)	1.4594	$C_8H_{15}NO$	68.04	68.39	10.71	10.18	9.92	9.96		6.07

[a] Taken in a sandwich cell unless otherwise noted. [b] Reported in ref. 5. [c] Reported in ref. 6. [d] Absolute ethyl alcohol solvent. [e] Nujol mull. [f] Reported in ref. 8. [g] Reported in ref. 7. [h] Isopentane solvent. [i] Reported in ref. 10.

bonyl absorption to lower wave lengths upon conjugation to a C=C double bond is not clearly understood and interference with normal amide absorption[11] seems to be involved.

Experimental

Infrared spectra were determined on a Baird Model AB-1 spectrophotometer. Ultraviolet spectra were measured on a Beckman Model DU quartz photoelectric spectrophotometer. Autoclave reactions were carried out in (a) a 100-ml. capacity stainless steel bomb with an electrically heated jacket, and (b) in a 1-l. capacity stainless steel rocking-type bomb made by the American Instrument Company. Fractionations were carried out in a 0.8 × 30 cm. Podbielniak column with Hasteloy "B" packing. This column was equipped with a Flexopulse timer made by Eagle Signal Corporation, and a Leeds and Northrup iron *vs.* constantan thermocouple. Elemental analysis are by W. Beazley, Micro-Teck Laboratories, Skokie, Ill. Melting and boiling points are uncorrected.

Reaction of Sorbic Acid with Amines.—The method used in this work is essentially that as reported elsewhere[6,7] with only minor variations.

A higher yield of product IV was obtained when relatively anhydrous amines were used. Only in the case of dimethylaminopropylamine was this product (IV) completely identified, since in this case it was relatively stable Heating the products of structure IV at about 150° split out the amine to give the mixed dihydro-2-pyridones.

Aqueous methanol was used in the autoclave reaction with aniline in order to give a homogeneous reaction mixture. Only sorbic acid anilide[12] (V, R = C_6H_5) was obtained when no methanol was added. The yields of 2-pyridones from the aromatic amines were much lower than from the alkyl amines. Aniline gave only a 6.5% yield of pure 1-phenyl-6-methyl-5,6-dihydro-2(1)-pyridone, and *p*-anisidine a 2.3% yield of pure 1-(*p*-anisyl)-6-methyl-5,6-dihydro-2(1)-pyridone (recrystallized from carbon tetrachloride and hexane).

The conjugated isomer predominated in every case where fractional distillation was used. For R = ethyl, the yield of crude mixed isomers was 70%, which upon fractionation gave II (conjugated) and III (unconjugated) in a ratio of about 3:1.

6-Methyl-2-piperidone.—The reduction of 3 g. (0.027 mole) of 6-methyl-5,6-dihydro-2(1)-pyridone (II, R = H) was carried out in 25 ml. of 95% ethanol using 0.1 g. of 10% palladium-on-charcoal catalyst and an initial hydrogen pressure of 40 p.s.i. The theoretical amount of hydrogen was taken up in 7 min. The product was isolated and crystallized from ethyl acetate to give a

(11) R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1260 (1947).

(12) O. Doebner and A. Wolff, *Ber.*, **34**, 2222 (1900).

nearly quantitative yield of 6-methyl-2-piperidone, m.p. 89–90°. Kuhn and Jerchel[8] prepared this compound using a platinum oxide catalyst and report m.p. 84–85°.

1-Ethyl-6-methyl-2-piperidone.—Three grams (0.022 mole) of 1-ethyl-6-methyl-5,6-dihydro-2(1)-pyridone (II, R = C_2H_5) was hydrogenated as above in 15 min. The crude product (2.6 g., 85%) was fractionated on the Podbielniak column to give pure 1-ethyl-6-methyl-2-piperidone (Table I).

This compound was also prepared accidentally in an attempt to N-alkylate 6-methyl-5,6-dihydro-2(1)-pyridone (II, R = H). In this experiment metallic sodium was powdered in the usual manner in toluene. After cooling, an equimolar portion of the lactam (II, R = H) was added; an immediate reaction took place and all of the sodium was used up. Ethyl iodide was added; the mixture was refluxed for 7 hr. and distilled to give a 39% yield of the alkylated and reduced product, 1-ethyl-6-methyl-2-piperidone, as indicated by an identical infrared spectrum, index of refraction, and boiling point.

1-Ethyl-6-methyl-5,6-dihydro-2(1)-pyridone.—Sodamide was prepared in the usual manner using 300 ml. of liquid ammonia, a crystal of ferric nitrate, and 1.3 g. (0.056 g.-atom) of sodium. After addition of 5.6 g. (0.050 mole) of 6-methyl-5,6-dihydro-2(1)-pyridone with stirring the ammonia was allowed to evaporate. Fifty milliliters of dry benzene and 11 g. (0.070 mole) of ethyl iodide were added, and the mixture was refluxed for 3 hr. Distillation yielded 3.4 g. (50%) of a product whose infrared spectrum and boiling point were identical with those of 1-ethyl-6-methyl-5,6-dihydro-2(1)-pyridone which had the correct elementary composition (Table I).

N,N-Diethylvinylacetamide.—In a reaction flask with reflux condenser and gas absorption attachment were placed 25.8 g. (0.30 mole) of vinylacetic acid[13,14] and 41.7 g. (0.35 mole) of thionyl chloride. The reaction started immediately and was allowed to continue overnight. The mixture was refluxed for 0.5 hr. and a solution of 58 g. (0.80 mole) of diethylamine in 100 ml. of dry ether was added slowly with stirring. The precipitate was filtered; the solution was dried over magnesium sulfate and distilled. The crude N,N-diethylvinylacetamide was fractionated through the Podbielniak column to yield 22.7 g. (54%) of high purity material (Table I).

Acknowledgment.—Grateful acknowledgement is given to Dr. Barbara K. Campbell of the Mead Johnson Research Center for her many fruitful suggestions during the course of this work and to Dr. Ernest L. Eliel for generously reading and commenting upon the original manuscript.

(13) A. E. Vogel, "A Textbook of Practical Organic Chemistry," 2nd Ed., Longmans, Green and Co., New York, N. Y., 1951, p. 451.
(14) J. W. Baker and J. B. Holdsworth, *J. Chem. Soc.*, 724 (1945).

Dinitrocarbazoles

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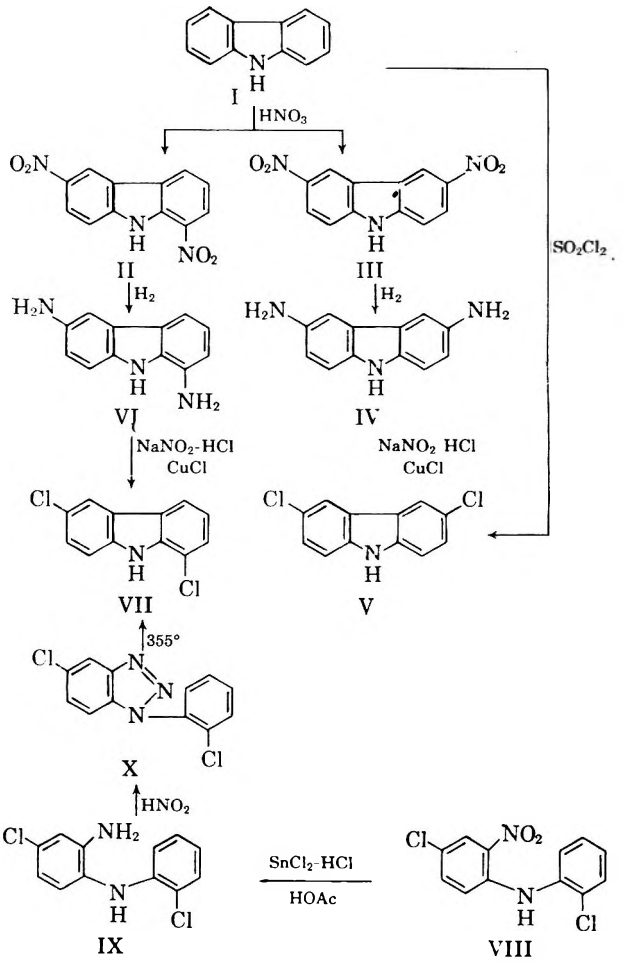
Although it has been recognized that attempts to dinitrate carbazole lead to mixed products,[1] only 3,6-dinitrocarbazole (III) appears to have been isolated from these mixtures. Its melting point has been variously reported as 365–367°,[1] about 360°,[2] 357°,[3] and even as low as 320°.[4] Its structure was assigned by Täuber[5] on the basis of the similarity of its reduction product (IV) with 3,6-diaminocarbazole unambiguously prepared from 2,2′,5,5′-tetraminodiphenyl. Crystal form, solubilities of its salts, and darkening temperatures of the two materials agreed. The isomeric 1,6-dinitrocarbazole (II) appears in the literature only as a speculative structure for a material charring between 300 and 360°.[6] We have found that both 1,6-dinitrocarbazole and 3,6-dinitrocarbazole are present in major amounts in the crude dinitrocarbazole mixture.



Carbazole (I) was nitrated in acetic acid at 75° with 3 equiv. of 70% nitric acid, and, alternatively, by treatment in acetic acid first with 1 equiv. of sodium nitrite and then with 2 equiv. of nitric acid at temperatures up to 100°. Extraction of the crude product from either nitration procedure with alcoholic potassium hydroxide produced two fractions: a red solid residue and a deep red solution. Acidification of the latter precipitated a yellow solid which recrystallized from nitrobenzene as fine yellow needles, m.p. 386–387°. Its reduction and conversion to the dichloride (V) by the Sandmeyer procedure provided a material identical with 3,6-dichlorocarbazole (m.p. 202–203°) prepared from carbazole and sulfuryl chloride,[7] the structure of which has been established by Plant.[8]

Digestion of the alcoholic alkali-insoluble residue with acid and recrystallization from nitrobenzene produced a dinitrocarbazole in glistening golden

(1) H. Schotte and R. Ebert, U. S. Patent 2,392,067 (Jan. 1, 1946).
(2) R. K. Eikhman, V. O. Lukashevich, and E. A. Silaeva, *Org. Chem. Ind. (USSR)*, **6**, 93 (1939); *Chem. Abstr.*, **33**, 7297 (1939).
(3) J. Amemiya, S. Fujii, and T. Horio, *Coal Tar* (Tokyo), **4**, 323 (1952); *Chem. Abstr.*, **48**, 2034h (1954).
(4) R. Oda, Z. Yoshida, and Y. Kato, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **55**, 239 (1952).
(5) E. Täuber, *Ber.*, **25**, 128 (1892).
(6) W. A. Schroeder, B. Keilin, and R. M. Lemmon, *Ind. Eng. Chem.*, **43**, 939 (1951).
(7) G. Mazzara and M. Lamberti-Zanardi *Gazz. chim. ital.*, **26**, II, 236 (1896).
(8) S. G. P. Plant and J. F. Powell, *J. Chem. Soc.*, 937 (1947).

leaflets, m.p. 344–348° Through reduction, diazotization and treatment with cuprous chloride, the corresponding dichlorocarbazole was obtained, m.p. 122.5–124°. 1,6-Dichlorocarbazole (VII), hitherto unreported, was prepared by condensation of 2,5-dichloronitrobenzene with 2-chloroaniline,[9] reduction of the 2′,4-dichloro-2-nitrodiphenylamine (VIII) thus formed to 2-amino-2′,4-dichlorodiphenylamine (IX),[10] diazotization to produce 5-chloro-1-(2-chlorophenyl)benzotriazole (X), and thermal decomposition in the familiar Graebe–Ullmann procedure.[11] This dichlorocarbazole proved identical with the material prepared from the lower melting dinitrocarbazole and thus establishes the structure of the latter compound as the 1,6-dinitro isomer.

It is of interest that roughly the same proportion of the two dinitrocarbazoles was obtained from both nitration procedures, 50–60% of the 3,6- and 30–35% of the 1,6-isomer, though the use of sodium nitrite leads to a higher melting, more readily purified mixture.

Experimental[12]

Nitration of Carbazole.—A slurry of 83.6 g. (0.5 mole) of carbazole in 640 g. of glacial acetic acid, stirred at 30–40°, was treated during 1.5 hr. with 35.3 g. (0.5 mole) of sodium nitrite. After 2 hr. of agitation, most of the solid had dissolved (as 9-nitrosocarbazole), but the addition of an additional 5 g. of sodium nitrite failed to achieve complete solution. During 1.3 hr., 74 g. of 90% nitric acid (1.05 mole) diluted with an equal weight of acetic acid was added with intermittent cooling at 30–40°, and the slurry was stirred at that temperature for an additional 3.5 hr. The mixture was then held at 55° for 1.5 hr., at 65° for 1.5 hr., and at 95° for 2 hr., cooled to 65°, and filtered; the solid was washed with 350 ml. of cold acetic acid and finally with water. The 86 g. of crude product obtained in this way began to soften at 312° and was melted at 354°.

Separation of Isomeric Dinitrocarbazoles.—A 45.5-g. sample of crude dinitrocarbazole was divided into two portions and each was stirred at 50° with 1.5 l. of alcoholic potassium hydroxide (60 g./l.) and filtered. The insoluble red solid residues were combined, digested on a steam bath with dilute hydrochloric acid (whereupon the color changed to yellow), filtered, washed with water, and dried to give 14.4 g. (32%) of 1,6-dinitrocarbazole (II) which recrystallized from nitrobenzene as glistening golden leaflets, m.p. 344–346° (cor.).

Anal. Calcd. for $C_{12}H_7N_3O_4$: C, 56.0; H, 2.7; N, 16.3. Found: C, 55.9; H, 2.7; N, 16.3.

The red alkaline alcoholic solutions were acidified with concentrated hydrochloric acid and the solid yellow precipitates thus formed were combined and washed thoroughly with warm water to remove potassium chloride. The residue of 26.5 g. (58%) was recrystallized from boiling nitrobenzene to give 3,6-dinitrocarbazole (III) as fine yellow needles, m.p. 386–387° (cor.).

Anal. Found: N, 16.4.

3,6-Diaminocarbazole (IV).—Thirty grams of 3,6-dinitrocarbazole (III) in 150 ml. of ethanol containing 3 g. (weight wet with ethanol) of Raney nickel catalyst was reduced under 1000-p.s.i.g. pressure at 100 ± 5° for 6 hr. in a stirred autoclave. The reaction mixture was diluted with water and the solid residue was recrystallized twice from boiling aniline (boneblack) to give 18.3 g. (80%) of IV as tan platelets which softened at 316° and melted at 320–322°. Its dibenzoyl derivative melted at 275–277°. Ziersch, starting from a dinitrocarbazole reported as melting "above 320°," obtained dibenzamidocarbazole of m.p. 270°,[13] while Eikhman[2] obtained m.p. 281° starting from dinitrocarbazole of m.p. "about 360°."

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.1; H, 5.6; N, 21.3. Found: C, 72.9; H, 5.4; N, 21.0.

3,6-Dichlorocarbazole (V).—A 3.2-g. (0.01 mole) portion of 3,6-diaminocarbazole (IV) was slurried in 90 ml. of concentrated hydrochloric acid and tetrazotized at 5–10° by the addition of 2.2 g. (0.032 mole) of sodium nitrite dissolved in the minimum amount of water. The tetrazonium salt solution was filtered and added slowly to a boiling solution of cuprous chloride prepared by treating a hot solution of 15 g. of copper sulfate and 3.9 g. of sodium chloride in 48 ml. of water with 3.3 g. of sodium bisulfite and 2.1 g. of sodium hydroxide in 24 ml. of water, washing the solid with water, and dissolving the cuprous chloride in 40 ml. of concentrated hydrochloric acid. The solution was boiled until foaming from nitrogen evolution subsided, and the greenish yellow product (1.5 g., 39%) was filtered and recrystallized (boneblack) twice from petroleum ether (b.p. 60–110°). This 3,6-dichlorocarbazole, m.p. 200–202.5°, did not depress the melting point of authentic 3,6-dichlorocarbazole (m.p. 201–203°) prepared from carbazole and sulfuryl chloride.[7]

Initial attempts to conduct this Sandmeyer reaction by adding the tetrazonium salt solution to a cold cuprous chloride solution in hydrochloric acid followed by heating were unsuccessful, leading to tarry materials from which 3,6-dichlorocarbazole could not be extracted.

1,6-Diaminocarbazole (VI).—Hydrogenation of 10 g. of 1,6-dinitrocarbazole (II) in a manner similar to that used for 3,6-dinitrocarbazole gave, after recrystallization from xylene, 0.8 g. (10%) of VI as purple-gray needles which darkened at 235° and decomposed around 255°.

1,6-Dichlorocarbazole (VII) from 1,6-Diaminocarbazole.—A 1.6-g. (0.008 mole) portion of 1,6-diaminocarbazole (VI) in 45 ml. of concentrated hydrochloric acid and 20 ml. of water was tetrazotized by the addition at 5–10° of 1.1 g. (0.016 mole) of sodium nitrite dissolved in the minimum amount of water. The tetrazonium salt solution was added at 5–10° to a stirred cuprous chloride solution prepared as above from 5 g. of copper sulfate and dissolved in 8 ml. of concentrated hydrochloric acid. Nitrogen evolution began at once. The reaction mixture was allowed to warm to room temperature and finally heated on the steam bath for 1.5 hr. The dark gummy solid which adhered to the sides of the vessel was dissolved in ethanol, treated with boneblack, diluted with water until quite turbid, and extracted with petroleum ether (b.p. 60–110°). Evaporation of most of the petroleum ether and cooling the solution induced crystallization of VII which recrystallized from petroleum ether as white needles, m.p. 122.5–124°.

2-Amino-2′,4-dichlorodiphenylamine (IX).—One gram of 2′,4-dichloro-2-nitrodiphenylamine (VIII)[9] was dissolved in 50 ml. of acetic acid, the solution was filtered, and to it was added 2 g. of stannous chloride dihydrate and 3 ml. of hydrochloric acid. The solution was heated to boiling and additional increments of stannous chloride totaling 5 g. and hydrochloric acid totaling 7 ml. were added at intervals until, after about 10 min. of boiling, the orange color had disappeared and the solution became greenish yellow. The solution was made strongly alkaline with aqueous sodium hydroxide, and cooled; the solid product was removed by filtration and recrystallized from ethanol to give 0.6 g. (67%) of white needles of IX, m.p. 107–108.5°, lit.[10] m.p. 103°.

Attempted use of Borodkin's sodium sulfide procedure[10] and the use of stannous chloride–hydrochloric acid solution alone[14] were not successful in our hands. In each case unreduced VIII was recovered.

5-Chloro-1-(2-chlorophenyl)benzotriazole (X).—To a slurry of 2.5 g. (0.01 mole) of 2-amino-2′,4-dichlorodiphenylamine (IX) in 35 ml. of hydrochloric acid and 45 ml. of water cooled to 10° was added 0.7 g. (0.01 mole) of sodium nitrite in 25 ml. of water. The slurry turned purple and was stirred for 1 hr after addition of nitrite was complete while the temperature was raised to 45°. The solid product was separated, dissolved in ethanol, treated with boneblack, filtered, and diluted with water while hot. On cooling, 1.3 g. (50%) of glistening white needles of X, m.p. 116–118°, were deposited.

Anal. Calcd. for $C_{12}H_7Cl_2N_3$: C, 54.6; H, 2.7. Found: C, 54.4; H, 2.6.

1,6-Dichlorocarbazole (VII) from 5-Chloro-1-(2-chlorophenyl)-benzotriazole.—A procedure used by Preston, *et al.*,[15] for the

(9) V. F. Borodkin, *Zh. Prikl. Khim.*, **21**, 987 (1948).

(10) V. F. Borodkin, T. V. Malkova, and N. N. Nikolskaya, *ibid.*, **20**, 283 (1947).

(11) C. Graebe and F. Ullmann, *Ann.*, **291**, 16 (1896).

(12) Melting points are uncorrected except where indicated. Elemental analyses were performed by Mr. Frank E. Huber, Jr.

(13) P. Ziersch, *Ber.*, **42**, 3797 (1909).

(14) See J. S. Buck and W. S. Ide, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 130.

(15) R. W. G. Preston, S. H. Tucker, and J. M. L. Cameron, *J. Chem. Soc.*, 500 (1942).

preparation of other carbazoles was used. A 0.5-g. portion of 5-chloro-1-(2-chlorophenyl)benzotriazole (X) was heated in a small open tube for 10 min. at 355° and the residue was dissolved in ethanol and treated with boneblack. The product was precipitated from the ethanolic solution by addition of water and was twice recrystallized from petroleum ether (b.p. 60–110°) to give 0.1 g. (22%) of white crystalline 1,6-dichlorocarbazole, m.p. 123–124°.

Anal. Calcd. for $C_{12}H_7Cl_2N$: C, 61.0; H, 3.0; N, 5.9. Found: C, 60.8; H, 2.9; N, 5.8.

This material did not depress the melting point of the 1,6-dichlorocarbazole derived from 1,6-dinitrocarbazole, thus establishing the structure of the latter compound.

Acknowledgment.—The authors are indebted to the Southern Dyestuff Company Division of Martin-Marietta Corporation for permission to publish this work conducted under their sponsorship.

The Preparation of *trans*-4-*t*-Butylcyclohexene Oxide

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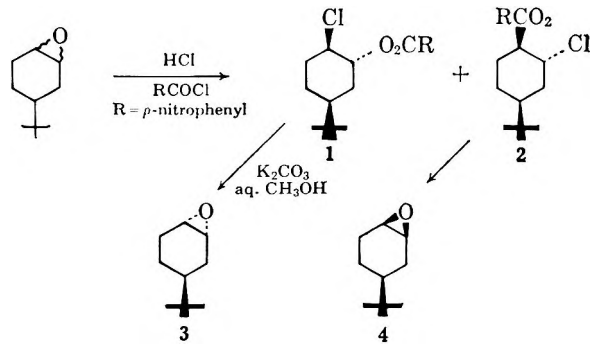
The preparation of isomerically pure liquid epoxides of substituted cycloalkenes has been a major problem in the study of the stereochemistry of oxide ring-opening reactions. Direct fractional distillation is often impossible; *e.g.*, a mixture of *cis* and *trans*-4-*t*-butylcyclohexene oxides on distillation through a 60-cm. spinning band column gives no evidence of fractionation.

Routes to the isomeric 4-*t*-butylcyclohexene oxides have been devised by two groups[1,2]; both sequences are multistep and involve either column chromatography or ion-exchange chromatography which limits their usefulness in large-scale preparations.

We wish to report a simple, rapid method of separating pure *trans*-4-*t*-butylcyclohexene oxide from a mixture with its geometric isomer. Treatment with



anhydrous hydrochloric acid in the presence of *p*-nitrobenzoyl chloride in chloroform solution gave a mixture of chloroesters from which **1** was readily isolated by recrystallization. The identity of **1** follows from C and H analysis, infrared and n.m.r. spectra, expectation of *trans* diaxial opening in formation and from the observation that *trans*-4-*t*-butylcyclohexene oxide is regenerated from it in high yield. While a number of other isomers could conceivably be formed in the initial ring-opening reaction, **1** and **2** must be by far the major products, as the mixed epoxide is recovered in good yield on facile basic hydrolysis of the crude chloro ester mixture.[4]

Recrystallization from methanol of the combined second crops rapidly gave sharp-melting material which appeared to be isomer **2**. However, the reformed epoxide from this material (high yield) was composed of approximately 80% *cis*- (**4**) and 20% *trans*-4-*t*-butylcyclohexene oxide (**3**). Exhaustive recrystallization from aqueous acetic acid gave a poor yield of the chloro ester **2** of approximately 95% purity. This product was used for analysis and n.m.r. spectrum determination.

The procedure described here promises to be of general utility in the separation of epoxides and, with the methods already available[1,3] for stereospecific interconversion of these isomers, offers a straightforward pathway to both *trans* and *cis* forms.

Experimental

4-*t*-Butylcyclohexanol.—A 1-l. high-pressure hydrogenation bomb was charged with 342 g. (2.20 mole) of 4-*t*-butylphenol (recrystallized from aqueous methanol), 300 ml. of glacial acetic acid, and 2.5 g. of 5% rhodium-on-alumina catalyst. At ambient temperature and an average hydrogen pressure of 1800 p.s.i., reduction was complete in approximately 2.5 hr. The product, obtained in essentially quantitative yield, was composed of 60% *cis*- and 40% *trans*-4-*t*-butylcyclohexanol.

4-*t*-Butylcyclohexene was prepared in high yield by the method of Sicher,[2] b.p. 70–72° (20 mm.).

***cis*- and *trans*-4-*t*-Butylcyclohexene Oxide.**—The olefin, 105 g. (0.76 mole), was taken up in 1.5 l. of anhydrous ether, and 160 g. of commercial *m*-chloroperbenzoic acid[5] was added in portions over a period of about 2 hr. Occasional cooling was required. The mixture was allowed to stand 24 hr., washed with 10% sodium sulfite solution and dilute base, and dried over anhydrous magnesium sulfate; the solvent was evaporated. Distillation of the residue gave 107 g. (92%) of the epoxide mixture, b.p. 68–69° (4 mm.).

This mixture, which was identical with that formed by the action of either perbenzoic or monoperphthalic acid on the olefin, was comprised of 60% *cis* and 40% *trans* epoxide.[6]

***trans*-2-Chloro-*trans*-5-*t*-Butylcyclohexyl *p*-Nitrobenzoate.**—The epoxide mixture, 97 g. (0.63 mole) was dissolved in 500 ml. of chloroform, and 140 g. (0.75 mole) of *p*-nitrobenzoyl chloride (recrystallized from petroleum ether, b.p. 90–110°) was added. With magnetic stirring, a slow stream of anhydrous hydrochloric acid was passed into the solution over a period of 6 hr.; the reaction was very slightly exothermic. The chloroform solution was washed with water to remove excess acid and evaporated to give a residue which was taken up in pyridine. A few chips of ice were added to decompose the excess acid chloride, after which the mixture was taken up in ether, washed extensively with 5% hydrochloric acid, then with dilute bicarbonate and water. After drying, evaporation of the ether gave 215 g. of solid material (essentially quantitative crude yield).

Recrystallization was effected from methanol solution, with rapid purification rather than high recovery being stressed. Five recrystallizations gave 24 g. (28%), m.p. 124.5–126°.

Anal. Calcd. for $C_{17}H_{22}ClNO_4$: C, 60.1; H, 6.5. Found: C, 60.4; H, 6.8.

(1) (a) N. A. LeBel and R. F. Czaja, *J. Org. Chem.*, **26**, 4768 (1961); (b) N. L. Allinger, J. Allinger, L. A. Freiberg, R. F. Czaja, and N. A. LeBel, *J. Am. Chem. Soc.*, **82**, 5876 (1960).

(2) J. Sicher, F. Šipoš, and M. Tichý, *Collection Czech. Chem. Commun.*, **26**, 847 (1961).

(3) For a review of the stereochemistry of epoxide-opening reactions, see R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(4) D. Y. Curtin and R. J. Harder, *J. Am. Chem. Soc.*, **82**, 2357 (1960).

(5) FMC Corporation, 85% minimum assay material was used.

(6) Analysis was by vapor phase chromatography.

The n.m.r. spectrum of this material (15%, CCl_4) showed two fairly well-resolved quartets ($J \sim 3$ c.p.s.), as expected for the equatorial protons at C-1 and C-2; these absorptions were centered at 4.29 and 5.33 p.p.m. (tetramethylsilane = 0).

trans-4-*t*-Butylcyclohexene Oxide.—The chloro ester 1, 3.4 g. (0.01 mole), was dissolved in 50 ml. of refluxing methanol. To this solution was added 4 g. of potassium carbonate dissolved in approximately 5 ml. of water. The mixture was refluxed with occasional swirling for 1 hr., after which the contents were taken up in water and extracted twice with pentane. The pentane was dried with potassium carbonate and evaporated; the residue was flash distilled to give 1.4 g. of *trans*-4-*t*-butylcyclohexene oxide (91%). The infrared spectrum was essentially identical with that of the mixed *cis* and *trans* epoxides, and showed no carbonyl absorption. Vapor phase chromatography (DEGS) indicated a purity of >99%.

trans-2-Chloro-*cis*-4-*t*-Butylcyclohexyl *p*-Nitrobenzoate.—The second crops from the three initial recrystallizations of isomer 1 were combined and recrystallized four times from methanol to give 44 g. of material, m.p. 71–72°. This was found to be a mixture of about 80% 2 and 20% 1 by examination of the epoxides obtained on base-catalyzed hydrolysis. Repeated recrystallization from methanol failed to change this ratio appreciably, indicating the probable formation of a mixed compound. Recrystallization from aqueous acetic acid gave poor yields of material with a wide melting point range; 1.5 g. of product, m.p. 60–81°, was obtained after numerous recrystallizations and found to be about 95% 2, 5% 1 by hydrolysis to epoxide. The melting point range is indicative of a eutectic containing a high per cent of 2. Because of the poor yields, additional efforts along these lines were abandoned, and this slightly impure material was used for analysis.

Anal. Found: C, 60.2; H, 6.5.

The n.m.r. spectrum of 2 was very similar to that of 1, two quartets centered at 4.40 and 5.22 p.p.m., indicating again equatorial protons attached to the carbon atoms bearing polar substituents.

Configuration of the Epoxides.—The *trans* epoxide was identified by lithium aluminum hydride reduction, which gives as the major product *trans*-3-*t*-butylcyclohexanol, as expected by diaxial opening of the epoxide. In analogous manner, the *cis* epoxide gave mainly *cis*-4-*t*-butylcyclohexanol. A more extensive discussion of this reaction is reserved for a later communication.

Acknowledgment.—The authors are indebted to the American Chemical Society Petroleum Research Fund for support of this work.

Identification and Separation of the Isomeric 2-Methylpyrazine Mono-N-oxides[1]

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Oxidation of 2-methylpyrazine with an equivalent of hydrogen peroxide in acetic acid was reported by Koelsch and Gumprecht[2a] to lead to two isomeric mono-N-oxides, the 1-oxide (I) and the 4-oxide (II). The 1-oxide was identified[3] by rearrangement with acetic anhydride[4] to yield, after saponification, pyrazine-methanol. The sample thought to have been the 4-oxide, under the same conditions, gave a compound (m.p. 68–69°) assumed to be 5-methyl-2(1H)-pyrazinone.[2b]

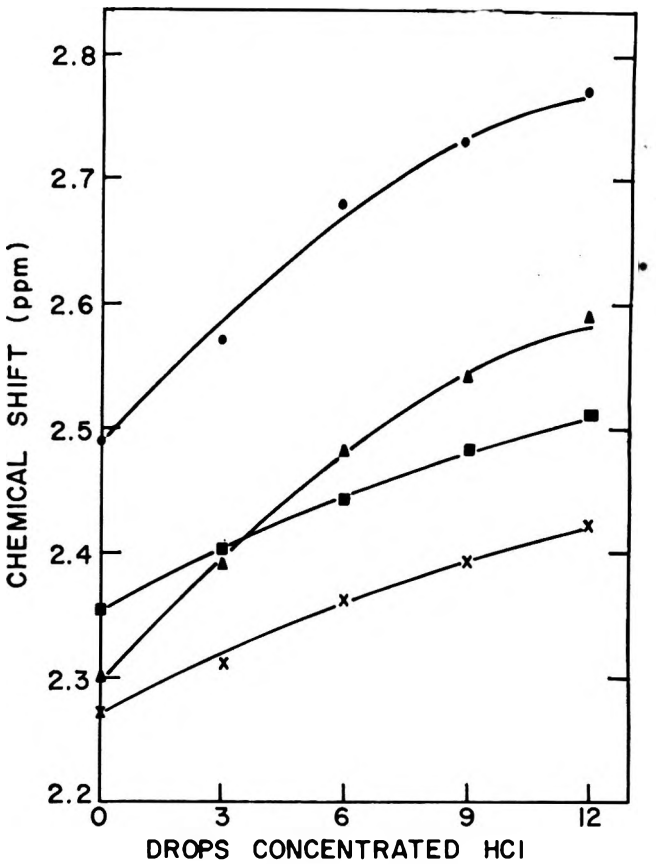
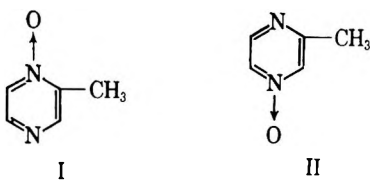


Fig. 1.—Effect of protonation on the chemical shifts for the methyl group in the n.m.r. spectra of pure 2-methylpyrazine 4-oxide (●), 2-methylpyrazine 1-oxide (■), and a eutectic mixture of the 1- and 4-oxides (×, ▲).



I II

Klein and Berkowitz[5a] have questioned the existence of 2-methylpyrazine 1-oxide in concluding that the two samples that they obtained from the mono-N-oxidation were actually polymorphs of the 4-oxide melting at 45 and 80–82°.[5b] Their chemical evidence for polymorphism was the preparation of the same *picrate* from the two samples, and conversion of both in the low yields to 3-chloro-2-methylpyrazine.[6] The exist-

(1) Presented in part at the 4th Omnibus Conference on Experimental Aspects of NMR Spectroscopy, Pittsburgh, Pa., March 2, 1963.

(2) (a) C. F. Koelsch and W. H. Gumprecht, *J. Org. Chem.*, **23**, 1603 (1958). (b) At the time, the authors were unaware of the melting point of 126–128° reported for this pyrazinone by G. Karmas and P. E. Spoerri [*J. Am. Chem Soc.*, **74**, 1580 (1952)].

(3) See also M. Asai, *J. Pharm. Soc. Japan*, **79**, 1273 (1959); *Chem. Abstr.*, **54**, 4607*i* (1960).

(4) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

(5) (a) B. Klein and J. Berkowitz, *ibid.*, **81**, 5160 (1959). (b) Selective N-oxidation at one of the two heteronitrogens in 2-methylpyrazine would be surprising, especially since the formation under the same conditions of both possible mono-N-oxides of 2,6-dimethylpyrazine is reported in this reference. The described separation of the polymorphs by distillation also must be considered unusual since molecular interaction in the vapor phase would not be expected to have a significant influence on orientation in the crystal lattice.

(6) If it is recalled that their higher melting sample melted 10° lower than that reported by Koelsch and Gumprecht, then it would seem likely that their 2-methylpyrazine 1-oxide was contaminated, probably with the 4-oxide.

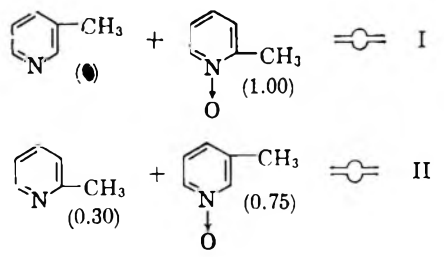


Fig. 2.—Chemical shifts in parentheses of the methyl groups in the n.m.r. spectra of 2- and 3-picolines and their N-oxides (in p.p.m. relative to 3-picoline), and relation of these structures to the 2-methylpyrazine mono-N-oxides.

ence of higher and lower melting forms of isoquinoline N-oxide was cited as precedent.[7]

We now present physico–chemical data for the formation of both 2-methylpyrazine 1- and 4-oxides under mono-N-oxidation conditions. Examination of the n.m.r. spectra of aqueous solutions of samples of these materials, separated in this work by careful fractional crystallization and melting at 90–91° and 44–45°, has shown that the higher melting material contains a single type of methyl group, whereas the lower melting substance contains two types of methyl groups (*y*-intercepts of the three lower curves in Fig. 1). The presence of two methyl group types in the 44–45° sample indicates that it is a eutectic mixture. The composition of the mixture, based on the areas under the methyl group peaks, was 53% of the component with the larger chemical shift and 47% of the other, which essentially agrees with the values of 52 and 47% determined by vapor phase chromatography.

The displacement of the chemical shifts of the methyl groups from each other in the n.m.r. spectrum of the eutectic is only 0.03 p.p.m. Because this difference is very small, it is not possible to relate positively either of the components in the mixture to the pure isomer by comparison of spectra. The minuteness of this difference was predicted by measurement of the positions of the methyl groups in the spectra of 2- and 3-picolines and their N-oxides, followed by summation and comparison of the proper values for relating these structures to the equivalent 2-methylpyrazine N-oxides (Fig. 2). A difference of 0.05 p.p.m. is predicted from these measurements and calculations.

The fact that protonation occurs at the unoxidized nitrogen in mono-N-oxides of pyrazine derivatives[2a,8] was used to resolve more completely the chemical shifts of the methyl groups in the n.m.r. spectrum of the eutectic, and thereby permit relation of one of the components to the pure isomer (Fig. 1). The relation indicates that the component in lower concentration (see above) is identical with the pure isomer melting at 90–91°. The position of protonation also was used to identify the isomers. It is well known[9] that electronic changes occurring in an aromatic system have a more pronounced effect on the chemical shifts of substituents the nearer these groups are to the site of the change. On this basis, the isomer melting at 90–91°, being less affected by protonation than the major component of the eutectic (Fig. 1), is 2-methylpyrazine 1-oxide.[10] This conclusion is in agreement with earlier findings[2a,3] and was further verified by n.m.r. identification of a new sample of pyrazinemethanol prepared from this isomer.

The remaining task was to obtain a pure sample of 2-methylpyrazine 4-oxide for comparison in protonation behavior with the major constituent of the eutectic. The closeness of the melting point (64–67°) of the sample of this component obtained from the vapor phase chromatograph (see Experimental) to that reported by Koelsch and Gumprecht for 5-methyl-2(1H)-pyrazinone and by Asai[3] for the 4-oxide indicated that these materials might be identical. This possibility had been suggested by Asai and Klein[5a] to explain the inconsistent properties of Koelsch and Gumprecht's "pyrazinone." The expected inertness[11] of the 4-oxide to acetic anhydride was used to separate it from the 1-oxide in the eutectic, a process which Koelsch and Gumprecht undoubtedly effected in the preparation of their "pyrazinone." The sample of 2-methylpyrazine 4-oxide, m.p. 69–70°, thus obtained parallels the behavior of the second component of the eutectic on protonation (Fig. 1).

Experimental[12]

Preparation and Fractional Crystallization of 2-Methylpyrazine Mono-N-oxides.—The procedure of Koelsch and Gumprecht[2a] was used to oxidize 386 g. (4.10 moles) of 2-methylpyrazine with 4.00 moles of hydrogen peroxide (as a 30% aqueous solution) in 4700 ml. of acetic acid. The mono-N-oxides were separated from a small amount of 2-methylpyrazine 1,4-dioxide by vacuum distillation, giving 406 g. (90%) of the mixture. The "diamond" procedure[13] of fractional crystallization was performed on five 20-g. portions of this mixture using anhydrous ether as solvent. It was found that treatment of the mother liquors with Darco activated carbon just prior to crystallization of the more soluble fraction increased the ease of crystallization and purity of this fraction. There were obtained from the fractionation 58 g. (29%) of a less soluble fraction, m.p. 90–91°, and 80 g. (40%) of a more soluble fraction, m.p. 44–45°.

Vapor phase chromatography of the two fractions using a tetramethylene adipate column at 170–200° revealed that the higher melting fraction had a purity of 99% in one component, whereas the lower melting fraction contained two components. These two components were trapped from the exit of the column. The more volatile component, present as 47% of the mixture, melted at 90–91°. The less volatile component, forming 52% of the mixture, melted at 64–67°.

N.m.r. Studies.—The n.m.r. spectra of redistilled 2- and 3-picolines and their N-oxides were measured in tetrachloroethylene solution using the Varian Model V-4311 n.m.r. spectrometer. The results of these measurements are shown in Fig. 2.

The Varian A-60 n.m.r. spectrometer was used in the study of the chemical shifts associated with the methyl groups of the isomeric 2-methylpyrazine mono-N-oxides in aqueous solution. The use of field-frequency control in the A-60 greatly facilitated the measurements. It might be thought that the use of a water-soluble internal reference with the conventional spectrometer might be adequate. However, this assumption overlooks the probability of shifts of the reference peak owing to changing pH. Furthermore, unless the time-consuming technique of extrapolation to infinite dilution is used, it is difficult to assess the dif-

(7) M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1956). This reference, in fact, describes isoquinoline N-oxide of different degrees of hydration and, therefore, of different melting points.

(8) J. K. Landquist, *J. Chem. Soc.*, 1885 (1956).

(9) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 258–266.

(10) In the original identification of the isomeric 2-methylpyrazine mono-N-oxides a confusion of samples occurred, leading to an interchange of the melting points reported in ref. 2a.

(11) B. Klein, J. Berkowitz, and N. E. Hetman, *J. Org. Chem.*, **26**, 126 (1961).

(12) Melting points are corrected.

(13) A. Weissberger, "Physical Methods of Organic Chemistry," Vol. III, 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p. 491.

ferent effects of the two structures on the chemical shift of the reference material. The results of the study are shown graphically in Fig. 1; no importance should be placed upon the absolute chemical shifts, since no attempt was made to set the instrument at zero.

Verification of the Compound Melting at 90–91° as 2-Methylpyrazine 1-Oxide (1).—In order to remove the confusion of this material with 2-methylpyrazine 4-oxide,[10] a 22.0 g. (0.20 mole) sample was treated with 58 ml. of acetic anhydride[4] in the manner described by Koelsch and Gumprecht.[2a] Their methods of isolation of the ester and its subsequent saponification were also used. In this way there was obtained 5.7 g. (26%) of pyrazinemethanol as a colorless oil, b.p. 59–60° at 0.23 mm. The n.m.r. and infrared spectra of the sample were indicative of a primary alcohol.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.85; H, 5.45; N, 25.47.

Separation of 2-Methylpyrazine 4-Oxide (II) from the Eutectic Melting at 44–45°.—A mixture of 22.0 g. of the eutectic and 58 ml. of acetic anhydride was boiled under reflux for 1 hr. The resulting dark oil was allowed to stand at room temperature for 5 days. Evaporation of the excess acetic anhydride and acetic acid on a steam bath under reduced pressure left a viscous black oil which, when vacuum distilled, yielded 22.7 g. of a yellow, partially crystalline oil. The crystalline portion was separated by dissolving the mixture in ether at a concentration of 25%, cooling the solution, and decanting the mother liquor. Final purification was performed by recrystallization from ether at room temperature, giving 8.3 g. (73% assuming the eutectic was 52% the lower melting isomer, as indicated by vapor phase chromatography) of 2-methylpyrazine 4-oxide as white crystals, m.p. 69–70°.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.56; H, 5.35; N, 25.51.

(1) Kirtikar and Basu, "Indian Medicinal Plants," Vol. 1, 1918, p. 287.

(2) E. J. Corey, T. H. Topie, and W. A. Wozniak, *J. Am. Chem. Soc.*, **77**, 5415 (1955).

Terpenoids. XLV. Structure and Absolute Configuration of Canarone

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During the course of separation of the constituents of the Black dammar resin (*Canarium strictum* Roxb.),[1] we isolated a small amount of a new monoethynoid sesquiterpene ketone, canarone, $C_{15}H_{24}O$. On the basis of the results described below, it can be represented by structure I and its absolute configuration by the stereoformula IX.

The infrared spectrum of canarone exhibited bands at 1700 cm.$^{-1}$ characteristic of a 2,2-dialkyl cyclohexanone[2] and at 1420 cm.$^{-1}$ due to a $-CO-CH_2-$ grouping. Bands at 3080, 1640, and 890 cm.$^{-1}$ indicated the presence of terminal methylene group. Ultraviolet spectrum showed the absence of a conjugation.

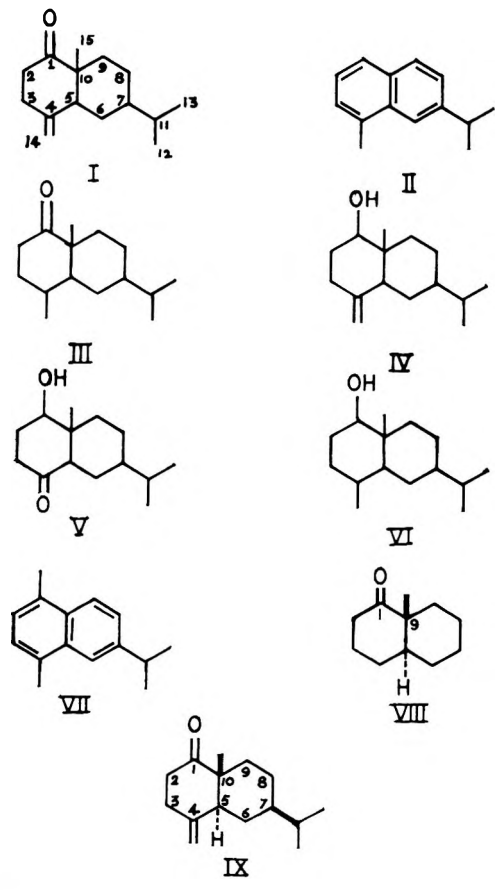
Canarone (I) on lithium aluminum hydride reduction gave canarol (IV), which on selenium dehydrogenation afforded eudalene (II). Canarone should therefore possess a eudalenic skeleton.

Hydrogenation of canarone (I) with Adams catalyst in acetic acid yielded a tetrahydro product, dihydrocanarol (VI), lacking the infrared bands due to ketone and terminal methylene groups, but instead showed an intense band at 3500 cm.$^{-1}$ due to a hydroxyl group.

Hydrogenation of canarol (IV) in acetic acid over Adams catalyst also afforded dihydrocanarol (VI), showing the presence of one double bond in canarol (IV) and hence in canarone (I). In conformity with this, quantitative hydrogenation of canarone over palladium–charcoal catalyst in methanol furnished the saturated ketone, dihydrocanarone (III). Canarone therefore should be a bicyclic ketone.

The position of the carbonyl function at C-1 was fixed by reacting canarone with methyl magnesium iodide and dehydrogenating the resulting tertiary carbinol to furnish 4-methyl eudalene (VII).[3]

Ozonolysis of canarol (IV) yielded formaldehyde as the only volatile component. The nonvolatile portion consisted of the hydroxy norketone (V), which gave a negative iodoform test. In its infrared spectrum, it showed strong absorption bands at 3400 (hydroxyl), 1710 (six-membered ring ketone), 1420 ($-CO-CH_2$), 1360 and 1375 cm.$^{-1}$ (isopropyl). This locates the position of the ethylenic linkage between C-4–C-14 and not in the isopropyl side chain. In further support for this, canarone and all the products derived from it



exhibited a doublet (between 1360 and 1380 cm.$^{-1}$) in the methyl bending region, indicating the presence of a isopropyl group[4] in the hydroxy norketone (V), and hence the location of the exocyclic methylene group at C-4 in canarone (I).

The rotatory dispersion curve (Fig. 1A) of canarone (I) is the same type (+*ve* Cotton effect, $a = +20$), whereas the curve of the hydroxy norketone (V) (Fig. 1B)

(3) G. Buchi, M. S. Wittenau, and D. M. White, *ibid.*, **81**, 1968 (1959).

(4) Infrared spectrum of canarone also showed the presence of bands at 1183 and 1160 cm.$^{-1}$, attributable to isopropyl group [*cf.* H. L. MacMurry and V. Thornton, *Anal. Chem.*, **24**, 318 (1952)].

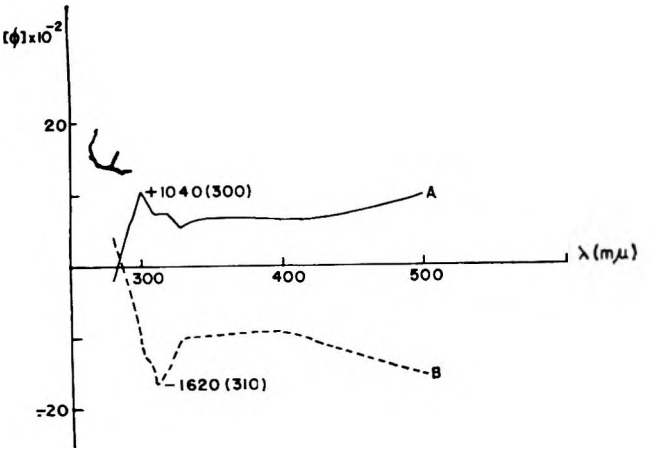


Fig. 1.—Optical rotatory dispersion curves of A, canarone (I); and B, keto alcohol V.

is the antipodal type (*−ve* Cotton effect, $a = -30$) compared to that shown by *trans*-9-methyl-1-decalone (VIII).[5] The molecular amplitude values, *a*, for compounds I and V are in better agreement with those reported[6] for *trans*-1-decalones from the eudesmanic group than from the eremophilane group. The ring fusion in canarone should therefore be *trans*, as shown in the formula of IX. Application of the octant rule[7] also points to a *trans* fusion of the ring.

The customary, β-equatorial configuration is assigned to the C-7 isopropyl side chain in analogy with other eudesmanic compounds. Canarone can therefore be represented by the stereoformula IX.

Experimental[8]

Isolation of Canarone (I).—From the petroleum ether (b.p. 60–80°) extract of the resin (7 kg.), pure ketone (1.8 g.) was isolated by column chromatography over alumina (grade II, 30-fold), followed by regeneration from its semicarbazone (oxalic acid, petroleum ether), b.p. 120–125° (bath) at 1 mm., $n^{28}D$ 1.5020, $[\alpha]D$ +34.78° (*c* 3.45), d^{29}_{29} 0.9819; $\nu_{max}^{liq\ film}$ 3080, 1700, 1640, 1420, 1360, 1375, 1225, 1260, 1183, 1160, and 890 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.00; H, 10.98.

The semicarbazone had m.p. 222–224°.

Anal. Calcd for $C_{16}H_{27}N_3O$: N, 15.15. Found: N, 15.50.

Reduction of Canarone (I) and Dehydrogenation of Canarol (IV).—To a suspension of lithium aluminum hydride (0.9 g.) in dry ether (50 ml.) was added a solution of the ketone (1.03 g.) in dry ether (25 ml.). During addition, the temperature was maintained between 0 and 5° and the solution was then refluxed for 5 hr. The reaction mixture on decomposition in the usual way furnished the secondary alcohol canarol (IV), b.p. 110–115° (bath) at 0.2 mm., $n^{28}D$ 1.5040, $[\alpha]D$ +23.81° (*c* 1.26, ethanol).

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.04; H, 11.74. Found: C, 80.65; H, 11.58.

The secondary alcohol (0.4 g.) was heated with selenium (0.4 g.) at 280° for 7 hr. in a nitrogen atmosphere. The product obtained was filtered through alumina (grade I, 20 g.) and eluted with petroleum ether. The ultraviolet spectrum indicated more than 80% naphthalenic material. It was identified as eudalene (II) through its trinitrobenzene (TNB) derivative, m.p. and m.m.p. 110°, and through its infrared spectrum.

Quantitative Determination of Unsaturation.—Canarone (I, 30 mg.) was hydrogenated in methanol in the presence of palladium on charcoal (5%, 30 mg.); the absorption of hydrogen (3.5 ml. 24°, 710 mm.) amounted to one double bond; $\nu_{max}^{liq\ film}$ 1704, 1420, 1383, and 1366 cm.$^{-1}$.

Hydrogenation of Canarone (I) to Dihydrocanarol (VI).—Canarone (130 mg.) was hydrogenated in acetic acid (20 ml.) using platinum oxide (50 mg.) catalyst. The hydrogenation stopped after absorption corresponding to 2 moles of hydrogen. After removal of the catalyst, the filtrate afforded after the usual processing 90 mg. of dihydrocanarol (VI), b.p. 105–110° (bath) at 0.3 mm., $n^{28}D$ 1.4940, $[\alpha]D$ +8.43° (*c* 1.78); $\nu_{max}^{liq\ film}$ 3450, 1380, and 1370 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{28}O$: C, 80.29; H, 12.56. Found: C, 80.52; H, 12.81.

Hydrogenation of Canarol (IV) to Dihydrocanarol (VI).—A solution of canarol (100 mg.) in acetic acid (20 ml.) was hydrogenated over pre educed Adams' catalyst (50 mg.). The absorption corresponded to 1 mole of hydrogen. The infrared spectrum of the purified product was superimposable with the infrared spectrum of the product obtained by direct hydrogenation of canarone over Adams catalyst, and had identical properties.

Ozonolysis of Canarol (IV) to the Keto Alcohol (V).—Canarol (0.12 g.) in chloroform (10 ml.) was ozonized at −5° to completion. The chloroform was removed *in vacuo* and the ozonide was decomposed with water. The volatile component was identified as formaldehyde by its dimedone derivative, m.p. and m.m.p. 189°. The trap water did not give a test for acetone. The nonvolatile product (60 mg.), purified by filtering through a short column of alumina (grade III), did not give a test for methyl ketone, b.p. 135° (6 mm.); $\nu_{max}^{liq\ film}$ 3400, 1701, 1425, 1375, 1360, 1180, and 1065 cm.$^{-1}$.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 75.04; H, 10.78. Found: C, 76.80; H, 10.6.

Due to the paucity of material a better analysis could not be obtained.

Grignard Reaction on Canarone (I) and Isolation of 4-Methyleudalene (VII) by Dehydrogenation.—The ketone (0.50 g.) in dry ether (20 ml.) was added dropwise to the solution of methyl magnesium iodide (prepared from 0.40 g. magnesium and 2.5 ml. of methyl iodide) in dry ether (50 ml.), and the reaction mixture was refluxed for 12 hr. The product was worked up in the usual way and the derived tertiary alcohol was separated from traces of unchanged ketone by chromatography. The crude tertiary alcohol (0.25 g.) was heated with selenium (0.3 g.) at 290° for 6 hr. The reaction product was extracted with ether and filtered through alumina (grade I, 10 g.). The ultraviolet spectrum of the dehydrogenated product indicated 90% naphthalenic product. It was identified as 1,4-dimethyl-7-isopropylnaphthalene (VII) by its TNB derivative, m.p. 102–103°, lit. m.p. 103–104°.[9]

Anal. Calcd. for $C_{15}H_{18}\cdot C_6H_3N_3O_6$. N, 10.21. Found: N, 10.3.

The parent hydrocarbon regenerated from its TNB complex gave a picrate, m.p. 112–113°, lit. m.p. 113–114°.[3]

Acknowledgment.—We are grateful to Professor W. Klyne of Westfield College, University of London, for optical rotatory dispersion measurements and helpful discussions.

(5) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

(6) C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962).

(7) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 181.

(8) Melting points are uncorrected. Rotations were determined in chloroform solution unless otherwise stated. Infrared spectra were taken by H. Gopinath using a Perkin-Elmer Model 137b spectrophotometer. Ultraviolet spectra were measured in ethanol solution by Miss Prabhu with a DK-2 Beckman spectrophotometer. Analyses were carried out by Mr. Pansare and colleagues.

(9) G. S. K. Rao and S. Dev, *J. Indian Chem. Soc.*, **33**, 561 (1956).

Reactions of Derivatives of 2-Formyl-1-tetralone

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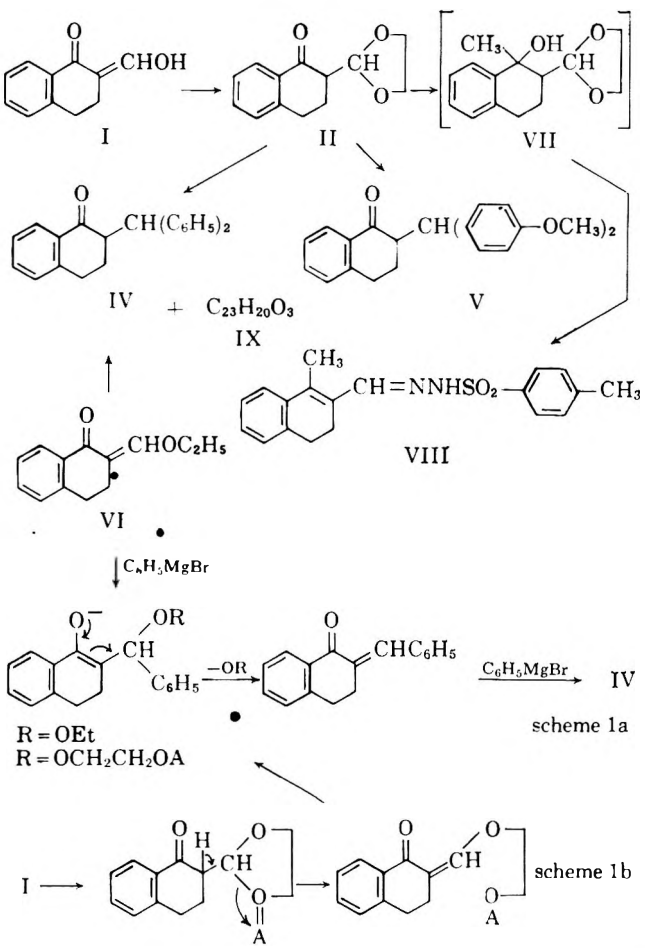
In the course of the preparation of 1-substituted 3,4-dihydronaphthalenes, we had occasion to investigate the reaction of the acetal II with phenylmagnesium bromide.

yl-1-tetralone[1] with 1 equiv. ed this acetal in excellent of a low-field aldehyde proton pectrum of this compound, serves ructure. When the acetal was al- th phenylmagnesium bromide in tetra- ofuran there was obtained in 62% yield a product, m.p. 144–146.5°, which still showed carbonyl absorption in the infrared (1685 cm.$^{-1}$), as well as a small amount of a higher melting ketone (164–165°), IX. The n.m.r. spectrum of the low-melting compound quickly revealed that this was not the product of reaction of II at the 1-carbonyl[2]; there was no band present at low field as would be required by an aldehyde and the integral indicated the presence of fourteen rather than the expected nine aromatic protons. These findings, and the splitting pattern can be accommodated by structure IV. The melting point of this product is in good agreement with that reported for this ketone in the literature.[3] The structure of IX is still unknown: analytical and physical data indicate this to be a diphenyldihydroxy derivative of a tetralone.

Indirect confirmation of the structure of IV comes from the reaction of II with anisylmagnesium bromide. In this case, the yield of product was 82%. The n.m.r. spectrum of this ketone is quite similar to that of IV with the addition of the methoxyl protons. The presence of six of the latter rather than the three which would be expected from the "normal reattion serves to confirm the addition of 2 moles of the reagent. It is of interest in connection with the mechanism of this reaction that the enol ether VI also affords IV with phenylmagnesium bromide, albeit in lower yield. The latter can be rationalized by a 1,4-addition of the reagent to the enol, loss of ethoxide, and again a 1,4-addition (scheme 1a). If it is assumed that the acetal is opened by a Lewis acid component of the Grignard mixture (*e.g.*, $MgBr_2$),[4] an intermediate is at hand which is in effect equivalent to the enol ether. The reaction may then follow a path such as scheme 1b. It is of interest in this connection that the addition of a Grignard reagent to an acetal to afford the ether has been reported.[5]



The reaction of the acetal II with methylmagnesium bromide on the other hand proceeds in a normal manner. The product VII was not isolated as such, but was dehydrated and hydrolyzed in a single step, and the aldehyde was characterized as its *p*-toluenesulfonylhydrazone.

Finally, in order to further characterize V, the compound was treated under ether cleaving conditions with 48% hydrobromic acid in acetic acid. Unexpectedly, the only product which could be isolated from the reaction mixture was α-tetralone. The fact that treatment of IV under the same conditions leads to recovery of better than 50% of starting material leads to the inference that the free phenol may be involved in this unusual scission.

Experimental[6]

2-Formyl-1-tetralone, 2-Ethylene Acetal (II).—A mixture of 18.4 g. of 2-formyl-1-tetralone, 6.6 g. of ethylene glycol, and 0.10 g. of *p*-toluenesulfonic acid in 200 ml. of benzene was heated at reflux with vigorous stirring under a Dean–Stark trap until no more water was evolved (2 hr.). The solution was allowed to cool, washed with aqueous sodium bicarbonate and water, and the solvent was removed *in vacuo*. The residue, a yellow crystalline solid, was recrystallized twice from cyclohexane to afford 20.15 g. of the acetal II, m.p. 61–63.5°. The analytical sample melted at 63.5–65°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.37; H, 6.17.

2-Diphenylmethyl-1-tetralone (IV). A. From 2-Ethoxymethylene-1-tetralone (VI).—A solution of 15.08 g. (0.078 mole) of the enol ether in 150 ml. of ether was added to an ice-cooled solution of phenylmagnesium bromide prepared from 13.5 g. (0.086 mole) of bromobenzene, 2.10 g. of magnesium, and 130 ml. of ether. The mixture was stirred overnight at room temperature, and then ice and 70 ml. of 2.5 *N* hydrochloric acid were added. The organic layer was separated, washed with water, and evaporated to dryness. The residual oil was taken up in 100 ml. of methanol, 5 ml. of 2.5 *N* hydrochloric acid was added, and the mixture was stirred at room temperature. The crystalline solid which separated (6.20 g., m.p. 132–140°) was collected on a filter and recrystallized once from methanol and then from aqueous acetone to afford 4.9 g. of IV, m.p. 144–146.5°, lit.[3] m.p. 147–148°. The infrared (ν_{max} 1685 cm.$^{-1}$) and n.m.r. (14 protons above δ 7.0; doublet at 4.7; multiplets at 3.4, 2.97, and *ca.* 1.9) spectra are in full accord with the structure.

B. From 2-Formyl-1-tetralone, 2-Ethylene Acetal (II).—To an ice-cooled solution of 0.073 mole of phenylmagnesium bromide in 150 ml. of tetrahydrofuran there was added 5.0 g. of the acetal

(1) W. S. Johnson, J. M. Anderson, and W. E. Shelburg, *J. Am. Chem. Soc.*, **67**, 1745 (1945).

(2) The absence of hydroxyl absorption and presence of carbonyl absorption in the infrared spectrum of the product led us first to suppose that loss of acetal and dehydration had occurred during the work-up.

(3) W. D. Garden and F. D. Gunstone, *J. Chem. Soc.*, 2650 (1952).

(4) R. E. Dessey and G. S. Handler, *J. Am. Chem. Soc.*, **80**, 5824 (1958).

(5) E. Späth, *Monatsh.*, **35**, 319 (1914).

(6) The author is indebted to the Upjohn Physical and Analytical Chemistry Department for analyses, ultraviolet, infrared, and n.m.r. spectra. All melting points are uncorrected and were determined on a Thomas–Hoover capillary melting point apparatus. N.m.r. spectra were determined in deuteriochloroform on a Varian A-60 instrument.

II in 100 ml. of tetrahydrofuran. Following 18 hr. of heating under reflux, the mixture was worked up in the same manner as above. The solid product was chromatographed over Florisil (elution with 5% acetone in ligroin) to afford 4.42 g. of crude IV followed by 1.68 g. of a higher melting compound. The former was recrystallized twice from cyclohexane to give 2.88 g. of the ketone IV, m.m.p. (with IV from VI) 146–148°.

The by-product IX was recrystallized from aqueous acetone to a constant melting point of 164–165°, ν_{max} 3375 and 1680 cm.$^{-1}$, λ_{max} 251 (ϵ 10,300) and 290 mμ (1280).

Anal. Calcd. for $C_{23}H_{30}O_3$: C, 80.21; H, 5.85. Found: C, 79.93, 80.63; H, 6.09, 6.21.

1-Methyl-3,4-dihydronaphthalene-3-carboxaldehyde, *p*-Toluenesulfonylhydrazone (VIII).—A solution of 17.84 g. of the acetal II in 400 ml. of tetrahydrofuran was added over 30 min. to an ice-cooled solution of 425 ml. of 2 *M* methylmagnesium bromide in benzene–tetrahydrofuran. Following 18 hr. of heating under reflux, the mixture was again cooled in ice and decomposed with 15 ml. of water followed by 250 ml. of saturated aqueous ammonium chloride. The organic layer was separated and washed with water and brine; the solvent was removed *in vacuo*. There remained 18.59 g. of viscous oil whose infrared spectrum shows no absorption in the carbonyl region.

A solution of 4.0 g. of VII, used as obtained above, and 10 ml. of 2.5 *N* hydrochloric acid in 100 ml. of acetone was stirred for 1 hr. at room temperature and then 1 hr. under reflux. The bulk of the solvent was removed on a rotary evaporator, the residue was dissolved in ether, and the solution was washed with water, sodium bicarbonate, and brine. The solvent was removed *in vacuo* to afford 2.80 g. of the crude aldehyde, ν_{max} 2750 and 1650 cm.$^{-1}$

The crude aldehyde in 50 ml. of ethanol was heated in the presence of 3.0 g. of *p*-toluenesulfonylhydrazine for 6 hr. The solution was allowed to cool and diluted with water. A gum came out which slowly solidified on scratching. This was recrystallized three times from methanol to afford 1.41 g. of the hydrazone VIII, m.p. 156–158° dec.

Anal. Calcd. for $C_{19}H_{20}N_2O_2S$: C, 67.04; H, 5.92; N, 8.23. Found: C, 66.62; H, 6.18; N, 8.28.

2-Di(*p*-methoxyphenyl)methyl-1-tetralone (V).—A solution of 10.0 g. of the acetal II in 200 ml. of tetrahydrofuran was added to an ice-cooled solution of the Grignard reagent prepared from 27.6 g. of *p*-bromoanisole and 5.6 g. of magnesium in 300 ml. of tetrahydrofuran. The reaction was run and the reaction mixture was worked up as above. The crude product was chromatographed over Florisil (elution with 3% acetone in ligroin); the combined crystalline fractions were recrystallized from ligroin to afford 11.13 g. of V, m.p. 105–108°.

A small sample was recrystallized from acetone–ligroin to give V, m.p. 103.5–105°; n.m.r., 12 protons above δ 6.5, doublet at 4.6, singlet 3.75, multiplets at 3.38, 2.95, and 2.0.

Anal. Calcd. for $C_{25}H_{24}O_3$: C, 80.62; H, 6.50. Found: C, 80.09; H, 6.60.

Reaction of 2-Di(*p*-methoxyphenyl)methyl-1-tetralone with Hydrobromic Acid.—A mixture of 2.0 g. of the ketone V and 60 ml. each of 48% aqueous hydrobromic acid and acetic acid was heated overnight at reflux. The volume was reduced to 70 ml. *in vacuo* and then the mixture was diluted with water and extracted with ether. The extracts were washed with aqueous sodium bicarbonate and brine and taken to dryness. The residual oil was chromatographed over Florisil (elution with 3% acetone in ligroin) to afford 0.37 g. (47%) of an oil whose infrared spectrum is identical with that of α-tetralone. The 2,4-dinitrophenylhydrazone of the oil melted at 258° dec., m.m.p. (with authentic α-tetralone 2,4-dinitrophenylhydrazone) 259° dec.

Reaction of 2-Diphenylmethyl-1-tetralone with Hydrobromic Acid.—Two grams of the ketone was treated exactly as above in 60 ml. each of 48% hydrobromic acid and acetic acid. The mixture was diluted with water and extracted with methylene chloride–ether. The oily solid which remained when the extracts were taken to dryness was crystallized twice from cyclohexane to afford 1.06 g. of the ketone, m.p. 141–144°.

Acknowledgment.—The author is indebted to Dr. Philip F. Beal, III, of these laboratories for valuable discussions concerning the n.m.r. spectra of these compounds.

A Synthesis of Polyhydroxy

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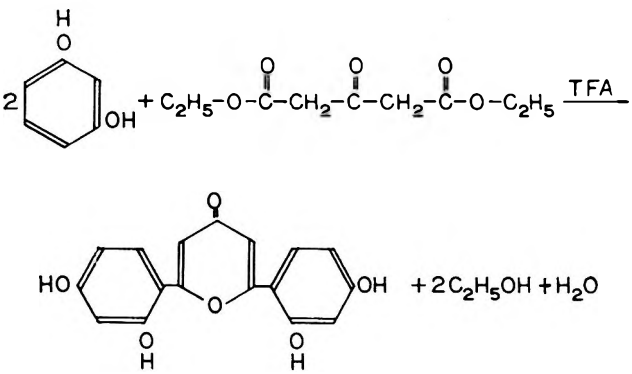
In a previous contribution[1] we have shown that when diethyl acetonedicarboxylate reacts with certain phenols in the presence of trifluoroacetic acid in a mole to mole ratio, ethyl coumarinacetates are formed. However, when the mole ratio is changed to two of the phenol to one of the ester, a polyhydroxy-2,6-diaryl-4-pyrone is produced as shown in the formula below. This reaction provides a one-step general process for the preparation of hydroxydiarylpyrones in acid media, a possibility not available by the method of Soliman and Kholy[2] or other earlier procedures.



I

Table I lists the compounds synthesized along with some pertinent physical data. Table II gives the *p*-nitrobenzoate esters of the members of the series and enumerates some of the spectral characteristics of the compounds. The fluorescence of some of the members of the series is of particular interest because three of them, compounds I, II, and IV, are much more fluorescent than quinine sulfate.

Compound I was selected as a model of the series to be subjected to alkaline degradation as proof of the proposed structures. Degradation in 30% potassium hydroxide[4] produced 2,4-dihydroxybenzoic acid, m.p. 208–210° dec., identical with an authentic sample.

Experimental[5]

Preparation of Members of I–VI Series.—A mixture consisting of 0.2 mole of the phenol, 0.1 mole of diethyl acetonedicarboxylate, and 30 ml. of trifluoroacetic acid was refluxed in the hood for 18 hr. The resulting solutions were diluted with about 150 ml. of water and chilled. The precipitates were filtered and dried in air. The analytical samples were obtained in most cases by recrystallizing the crude compound twice from boiling heptane;

(1) L. L. Woods and J. Sapp, *J. Chem. Eng. Data*, **8**, 235 (1963).
(2) G. Soliman and I. E. Kholy, *J. Chem. Soc.*, 1755 (1954).
(3) R. C. Elderfield, "Heterocyclic Compounds," Vol. 1, John Wiley and Sons, New York, N. Y., 1952, p. 370.
(4) T. A. Geissman, "The Chemistry of Flavonoid Compounds," Macmillan and Co., New York, N. Y., 1962.
(5) Analyses were performed by Dr. Carl Tiedcke, Teaneck, N. J. All melting points were taken on a Fisher-Johns melting point block.

TABLE I

2,6-DIARYL-4-PYRONES FROM DIETHYL ACETONEDICARBOXYLATE

No.[a]	Phenol used	Yield, %	M.p., °C.	Empirical formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Chlorine, %— Calcd.	Found
I	Resorcinol	87	>300	$C_{17}H_{12}O_6$	65.38	64.97	3.87	4.02		
II	4-Chlororesorcinol	90	205–206.5	$C_{17}H_{10}Cl_2O_6$	53.56	54.01	2.64	2.88	18.60	18.29
III	Orcinol	46	>300	$C_{19}H_{16}O_6$	66.66	66.29	4.71	4.93		
IV	Phloroglucinol	100	176–177	$C_{17}H_{12}O_8$	59.30	58.97	3.51	3.82		
V	2,4-Dihydroxyacetophenone	48	149–149.5	$C_{21}H_{16}O_8$	63.63	63.39	4.06	3.89		
VI	2,4-Dihydroxybenzophenone	100	148–149.5	$C_{31}H_{20}O_8$	71.53	71.91	3.87	3.76		

[a] I, 2,6-bis(2,4-dihydroxyphenyl)-4-pyrone; II, 2,6-bis(2,4-dihydroxy-5-chlorophenyl)-4-pyrone; III, 2,6-bis(2,4-dihydroxy-6-methylphenyl)-4-pyrone; IV, 2,6-bis(2,4,6-trihydroxyphenyl)-4-pyrone; V, 2,6-bis(2,4-dihydroxy-5-acetylphenyl)-4-pyrone; VI, 2,6-bis(2,4-dihydroxy-5-benzoylphenyl)-4-pyrone.

TABLE II

Compound used	p-Nitrobenzoate esters of I–VI series[a] Empirical formula	M.p., °C.	—Nitrogen, %— Calcd.	Found	Spectral characteristics of I–VI series — Fluorescence, QRU[b]	Ultraviolet absorption bands in 200–350-mμ range (log ε)[c]
I	$C_{45}H_{24}N_4O_{18}$	161.5–163	6.16	5.98	5.93	284.2 (3.3), 327.0 (3.5)
II	$C_{45}H_{22}Cl_2N_4O_{18}$	174	5.73	5.57	69.20	263.7 (3.5), 332.5 (4.0)
III	$C_{47}H_{28}N_4O_{18}$	189–190.5	5.98	5.84	0.24	263.0 (3.7), 310.5 (4.03)
IV	$C_{69}H_{30}N_6O_{26}$	185–187	6.78	6.60	2.28	273 (3.7), 329 (3.9)
V	$C_{49}H_{28}N_4O_{20}$	159–161	5.64	5.82	0.02	282.5 (4.42), 317.5 (4.5)
VI	$C_{69}H_{32}N_4O_{20}$	175–176.5	5.01	5.20	0.01	264.8 (4.2), 295 (4.5), 329.5 (4.5)

[a] W. J. Hickinbottom, "Reactions of Organic Compounds," 3rd Ed., Longmans, Green and Co., New York, N. Y., 1957, p. 121. [b] QRU = quinine reference unit.[1] [c] Measurements made on a Bausch and Lomb Spectronic-505 in Spectro Grade methanol.

however, II was crystallized once from ethyl acetate, and IV was purified by first taking the compound up in ethyl acetate and precipitating the substance with heptane. The process was repeated for a second purification.

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Acid Hydrolysis of 3-Phenylsydnone-2-N^{15}

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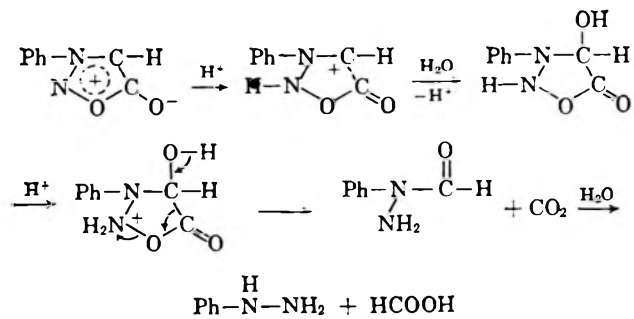
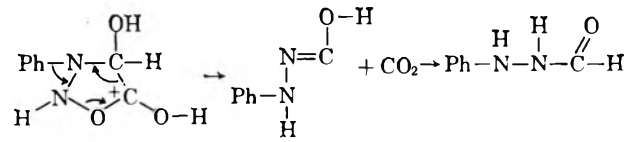
When N-phenylsydnone is hydrolyzed by acid, an internal oxidation-reduction reaction takes place with the formation of phenylhydrazine, formic acid, and carbon dioxide.[2] The mechanism shown below was suggested for this reaction by Baker and Ollis.[3] Aside from the nature of the end products of this hydrolysis, the strongest evidence cited by Baker and Ollis in support of their mechanism is the paper by Kenner and Mackay who reported the isolation of α-acylhydrazines when the hydrolysis was carried out in benzene with stoichiometric quantities of water and hydrochloric acid.[4] However, Kenner and Mackay gave no experimental evidence to support their conclusions and others have not been successful in repeating this work.[5]



$$Ph-N(H)-NH_2 + HCOOH$$

In connection with attempts to prepare isosydnones,[6] the possibility of N → N aryl migration as a step in the acid hydrolysis of sydnones has been raised. This might be pictured as having the second protonation occur on the carbonyl oxygen and having the electron shift in the direction opposite to that postulated.[3]



This hypothesis could be tested readily by labeling one of the nitrogen atoms of the sydnone ring with N^{15} and determining the position of the label in the phenylhydrazine resulting from acid hydrolysis of the labeled sydnone.

This experiment was carried out by using N^{15}-labeled nitrite to prepare 3-phenylsydnone-2-N^{15}. After hydrolysis of the labeled sydnone, phenylhydrazine hydrochloride was isolated and degraded to aniline and am-

(1) (a) Contribution No. 740 from the Chemistry Department, Fordham University, submitted by J. S. in partial fulfillment of the requirements for the M.S. degree. (b) A paper based on this work was presented at the 3rd Annual Metropolitan Regional Meeting of the New York Section of the American Chemical Society, Jan. 27, 1964.

(2) J. C. Earl and A. W. Mackney, *J. Chem. Soc.*, 899 (1935).

(3) W. Baker and W. D. Ollis, *Quart. Rev.* (London), **11**, 15 (1957).

(4) J. Kenner and K. Mackay, *Nature*, **160**, 465 (1947).

(5) I. M. Hunsberger, private communication.

(6) G. Sugerman, "Products Isolated in Unsuccessful Attempts to Prepare Isosydnones," Ph.D. Thesis, Chemistry Department, Fordham University, 1962.

monia by catalytic hydrogenation over palladium black.[7,8]

The isolated ammonia contained 0.80 atom % excess N^{15} while the aniline nitrogen contained only the natural abundance of N^{15}. On repetition of the experiment, the ammonia contained 1.25 ± 0.01 atom % excess N^{15} (expt. 2) and 1.13 ± 0.02 atom % excess N^{15} (expt. 3). The aniline in expt. 3 contained the natural abundance of N^{15}.

As a further check on these results a sample of the labeled sydnone was reduced with zinc and acetic acid to form N-phenylglycine and ammona.[11] When this ammonia was converted to nitrogen[12] and analyzed on the mass spectrometer, it was found to contain 1.30 ± 0.01 atom % excess N^{15} (expt. 2) and 1.19 ± 0.01 atom % excess N^{15} (expt. 3). It is therefore clear that rearrangement cannot occur to an extent greater than 1 or 2% and probably does not occur at all.[13]

The results of these experiments are thus consistent with the mechanism suggested for the acid hydrolysis of sydnones by Baker and Ollis.[3] They, of course, cannot be considered to prove this mechanism but, as is typical of tracer experiments, any alternative mechanism which may be suggested for this reaction must be consistent with the results reported here.

Experimental

N^{15}-Nitroso-N-phenylglycine.—N-phenylglycine (Eastman Organic Chemicals) was dissolved in 1 *N* hydrochloric acid (5 ml./g.), decolorized with charcoal, and precipitated by neutralization of the solution with 5 *N* sodium hydroxide. The precipitated N-phenylglycine was filtered, washed, and dried. The purified N-phenylglycine (5 mmoles) was dissolved in 25 ml. of 1 *N* hydrochloric acid and cooled to 0°. A solution of sodium nitrite (5 mmoles) containing 1% by weight of $KN^{15}O_2$ (Isomet Corp., assay 95.8% N^{15}) in 1 ml. of water was cooled to 0° and added slowly with stirring to the first solution. The oil which formed soon crystallized and was filtered, washed, and dried, m.p. 101–103°, lit.[2] m.p. 102–103°, 75% yield.

3-Phenylsydnone-2-N^{15}.—The above product was treated with acetic anhydride as described by Earl and Mackney,[2] m.p. 135–136°, lit.[2] m.p. 134–135°, 70% yield.

Acid Hydrolysis of 3-Phenylsydnone-2-N^{15}.—One millimole of the above sydnone was heated with 2 ml. of 5 *N* hydrochloric acid on a steam bath for 1 hr. On cooling, phenylhydrazine hydrochloride crystallized out, m.p. 230–235°, lit.[2] m.p. 233–234°, 84% yield.

Reduction of N^{15}-Labeled Phenylhydrazine.—The phenylhydrazine hydrochloride from the previous step was dissolved in 25 ml. of 50% aqueous ethanol and shaken with 0.1 g. of palladium black in an atmosphere of hydrogen at 1 atm. pressure until hydrogen uptake ceased (approximately 16 hr.). The reaction mixture was then acidified with hydrochloric acid, the catalyst was filtered off, and the filtrate was concentrated to a small volume. This sample was then made up to a known volume in a volumetric flask, and aliquots calculated to contain 1 to 2 μmoles of ammonia were taken for analysis by the Conway microdiffusion procedure.[15] Control samples of aniline and phenylhydrazine of similar concentration were analyzed in parallel. The ammonia titrations had to be corrected by subtracting 16% of the total volume of standard acid used in the titration; this allows for the aniline which diffused over in the time taken for quantitative diffusion of ammonia (2 hr.). There was no correction needed for any unreduced phenylhydrazine which may have been present. An aliquot of the hydrogenolysis mixture which contained 1 mg. of nitrogen was steam distilled into 10 ml. of 0.1 *N* sulfuric acid. This distillate which contains the ammonia from phenylhydrazine cleavage was concentrated to approximately 1 ml. and saved for analysis of its N^{15} content.

Isolation of Acetanilide.—Approximately one-half of the sample obtained after reduction of the labeled phenylhydrazine was evaporated to a small volume and treated with acetic anhydride and sodium acetate. Acetanilide was filtered and recrystallized, m.p. 111–113°, lit.[16a] m.p. 114°. Samples (10 to 15 mg.) of the isolated acetanilide were digested by the Kjeldahl procedure[16b] and the ammonia formed was distilled and titrated. This distillate was then evaporated to approximately 1 ml. and saved for mass spectrometric analysis of its N^{15} content.

N^{15} Analysis.—Ammonia samples were converted to nitrogen by use of sodium hypobromite as described by Rittenberg.[12] Aniline which was present in the ammonia samples did not interfere as no nitrogen is liberated when aniline is treated with th reagent. Unchanged phenylhydrazine would interfere, however, as it reacts with sodium hypobromite to liberate nitrogen quantitatively. On the other hand, this makes it possible to analyze phenylhydrazine directly for its N^{15} content when the position of the label does not have to be specified. Natural abundance was determined each day that a set of samples was analyzed, and standard samples of N^{15} ammonia were used for checking the accuracy of the analyses. These measurements were carried out on a Consolidated Electrodynamics Corp. mass spectrometer, Model 21-611.

Acknowledgment—We wish to thank Professor H. B. Waelsch of Columbia University for the loan of the mass spectrometer used in these studies.

(7) H. Rupe and E. Holel. *Helv. Chim. Acta*, **6**, 873 (1923).

(8) It has been established by the work of Holt and Bullock[9] and of Clusius and Hoch[10] that no N → N aryl migration occurs in this reaction. In addition, we prepared 1-phenylhydrazine-2-N^{15} and degraded it by this procedure to demonstrate that no rearrangement occurs under the identical conditions used to degrade the labeled phenylhydrazine obtained by hydrolysis of the labeled sydnone.

(9) P. F. Holt and B. I. Bullock. *J. Chem. Soc.*, 2310 (1950).

(10) K. Clusius and M. Hoch, *Helv. Chim. Acta*, **33**, 2122 (1950).

(11) J. C. Earl, *Rec. trav. chim.*, **75**, 346 (1956).

(12) D. Rittenberg, "Preparation and Measurement of Isotopic Tracers," Edwards, Ann Arbor, Mich., 1946, p. 31.

(13) A somewhat similar reaction in which migration of an aryl group from one nitrogen atom to an adjacent one seemed possible but was not observed is the Rowe rearrangement of a pseudophthalazone to a phthalazone.[14]

(14) W. R. Vaughan, D. I. McCane, and J. G. Sloan, *J. Am. Chem. Soc.*, **73**, 2298 (1951).

(15) E. J. Conway, "Microdiffusion Analysis and Volumetric Error," The MacMillan Co., New York, N. Y., 1958, p. 98.

(16) (a) Handbook of Chemistry and Physics, C. D. Hodgman, Ed., 44th Ed., The Chemical Rubber Publishing Co., Cleveland, Ohio, 1962, p. 768; (b) J. B. Niederl and V. Niederl, "Micromethods of Quantitative Organic Elementary Analysis," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1942, p. 69.

Formation of Copper Phthalocyanine

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The reaction mechanism of the formation of copper phthalocyanine in the phthalic anhydride–urea system remains to be determined. As a first step in the study of the mechanism of this reaction system it was determined that urea does not contribute its carbon to the phthalocyanine molecule in the formation of copper phthalocyanine.[1] As a second step in this study it is established that the α-carbon atom in the maleic anhydride ring in the phthalic anhydride remains in the reaction mass to form copper phthalocyanine, phthalimide, and a relatively small amount of compounds of as yet unknown composition. Phthalic anhydride containing α-C^{14}, *i.e.*, C^{14} in the C-7 position,

(1) S. N. Brumfield, V. W. Foltz, C. M. McGhee, and A. L. Thomas, *J. Org. Chem.*, **27**, 2266 (1962).

TABLE I
RUNS 1–4

Material	Weight, g. Initial	Weight, g. Final	Activity, c.p.m./mg.	Activity, c.p.m./mg. of C^{14}-phthalic anhydride
C^{14}-Phthalic anhydride	0.0012	...	...	...
Phthalic anhydride mix	5.00	...	12.6 ± 0.8	52,500
Reaction mixture	13.89	...	2.3 ± 0.1	26,600
Reaction crude	...	4.8 ± 0.5	11.4 ± 0.5	43,800
Copper phthalocyanine	...	3.5 ± 0.3	16.2 ± 0.3	62,000
Drierite	0	0.6 ± 0.6	0 ± 0	0
Ascarite–Drierite (tower)	0	4.8 ± 3.0	0 ± 0	0
Ascarite–Drierite (tube)	0	0.13 ± 0	0 ± 0	0
Activated charcoal	0	0	0 ± 0	0
Phthalimide condensate from reaction	...	0.5 ± 0.4	9.3 ± 2.7	38,800
Crude–copper phthalocyanine–phthalimide	...	1.0 ± 0.2	0.9 ± 0.2	6300 (max.)
Phthalimide condensate from sublimation	...	1.6 ± 0.4	8.1 ± 0.5	36,300

has now been used in the phthalic anhydride–urea reaction system. The copper phthalocyanine and phthalimide by-product made from this reaction system are radioactive. The carbon dioxide by-product is not radioactive although about 90% of the carbon in the urea is accounted for by weight in the form of carbon dioxide absorbed in Ascarite–Drierite. The remaining 10% of the carbon in the urea may be present as impurity in the form of ammonium carbonate and ammonium bicarbonate in recovered phthalimide (Table I).

Phthalimide is a familiar by-product and monoiminophthalimide[2] has been detected in the reaction mass from the phthalic anhydride–urea system. The presence of diiminophthalimide in the reaction mass has not been reported. Recently, in this laboratory, the presence of phthalonitrile has been detected in the reaction mass.

The fate of phthalic anhydride in this reaction system probably is phthalic anhydride → phthalimide → monoiminophthalimide → phthalocyanine and phthalic anhydride → monoiminophthalimide → phthalocyanine. The monoiminophthalimide may decompose rapidly to form phthalonitrile and water so that phthalonitrile, and not monoiminophthalimide, may be the immediate precursor of phthalocyanine.

The urea molecule is planar.[3] The angle between the two nitrogen atoms and the central carbon atom is 120°. The carbon atoms of phthalic acid are coplanar.[4] The distance between the nitrogen atoms in urea is 2.34 Å. The distance between the α-carbon atoms in phthalic acid is 2.98 Å. The urea molecule would make a "nice fit" into the embrace of the phthalic anhydride molecule to produce phthalonitrile, water, and carbon dioxide. If, on the other hand, the urea molecule and the phthalic anhydride molecule do not meet center-to-center, then the precursors of copper phthalocyanine may include not only phthalonitrile but also phthalimide, ammonia, and carbon dioxide as by-products. Phthalimide, carbon dioxide, ammonia, and water are major by-products.

Experimental

The reaction was carried out in a 300-ml. flask with a nitrogen carrier gas flow of about 1 ml./sec. through the reactor and downstream gas train consisting of two water condensers in series with cooling jacket maintained at 2° to trap sublimed phthalimide, a Drierite tube to trap water, a 50:50 Ascarite–Drierite tower to trap carbon dioxide, an Ascarite tube to test the efficiency of the Ascarite–Drierite tower, an activated charcoal tube to trap carbon monoxide, and a water bubbler.

The reaction mix (61.1 g.) was prepared from which four samples, each weighing 13.89 g., were drawn: 5.00 g. of phthalic anhydride mix, containing 1.2 mg. of carbon-14 phthalic anhydride of stated specific activity of 2.22 mc./mmole, 860 mg. of cuprous chloride, 20 mg. of molybdic trioxide, and 10 mg. of copper. The constituents were weighed on a Mettler balance with a stated sensitivity of about ±0.02 mg. The reaction mixture was ground and blended with mortar and pestle. The reaction mass was heated to temperature in 0.5 hr. and was held at 200° for 6 hr. The reaction product in the 300-ml. flask was weighed and copper phthalocyanine was determined colorimetrically at 430 mμ. It was ground in a mortar and pestle and was heated at 200° for 4 hr. in a 300-ml. flask with nitrogen purge into the flask. The nitrogen was vented to the atmosphere through a water condenser maintained at 2°. The condensate from this sublimation operation and the condensate from the reaction process were combined and weighed. The condensate was a mixture of phthalimide and ammonium carbonates. The residue in the reaction flask contained copper phthalocyanine and reaction by-products. The reaction by-products are soluble in dilute sulfuric acid and copper phthalocyanine is insoluble in dilute sulfuric acid. The residue was purified in 200 ml. of 10% sulfuric acid at 90° for 4 hr. The slurry was filtered over No. 1 Whatman paper and the residue was washed free of acid with about 500 ml. of distilled water. The residue was dried, weighed, and analyzed for copper phthalocyanine, which was in the range 94–98% by weight. To the combined filtrate of 10% sulfuric acid, wash water, and dissolved compounds, now at about pH 2, was added sodium hydroxide to pH 8, at which pH there was considerable flocculation. The slurry was cooled to 15° and was filtered over No. 1 Whatman paper. The residue was pale blue in color; it was dried and weighed. The pale blue residue contained cyanuric acid and sodium sulfate. Cyanuric acid and sodium sulfate were identified by their infrared spectra. The filtrate was evaporated to dryness. The infrared curve of the dry residue from the evaporated filtrate showed it to be sodium sulfate.

The C^{14} phthalic anhydride, phthalic anhydride mix, reaction mixture, reaction crude, phthalimide condensate, and purified copper phthalocyanine were radioactive. The contents of the Drierite tube, Ascarite–Drierite tower, and Ascarite–Drierite tube were weighed and ground. The contents of these three vessels, as well as the activated charcoal tube, gave no count. Determination of radioactivity was made by counting on 100-mg. samples of each of the above items with a Nuclear Corporation Model 2612-P portable radiation survey meter. A 100-mg. sample was placed into a 13-mm. KBr pellet die (Research and Industrial Instruments Co., MK-3). The assembled die was placed in a hydraulic press maintained at 10 mm. for 10 min. at about 120,000 lb./in.^{2}. Vacuum and pressure were removed from the die. The radioactive count was made on the pellet by placing the probe directly over and in contact with the pellet in the die. Background count was made in the same manner but without a pellet in the die. Radioactive count did not depend on the pellet thickness after a minimum thickness was obtained. Radioactive

(2) G. Rosch, W. Wolf, and H. Vollman, U. S. Patent 2,727,043 (Dec. 13, 1955).

(3) J. E. Worsham, Jr., H. A. Levy, and S. W. Peterson, *Acta Cryst.*, **10**, 319 (1957).

(4) W. Nowacki, and H. Jaggi, *Z. Krist.*, **109**, 282 (1957).

counts from 50-mg. pellets and 100-mg. pellets were the same.

It was attempted to determine the composition of the portion of the crude that was not copper phthalocyanine, phthalimide, and cyanuric acid, but without success. This portion of the crude was not identified by its infrared spectrum before or after extractions in water, ethyl alcohol, and α-chloronaphthalene in succession.[1] Its small activity compared with the activity of the other portions of the reaction system indicates that it contained only a small amount of matter derived from the phthalic anhydride.

Four runs were made. Average weights of material and average activity of material with standard deviation are given in Table I. Also, average activity in terms of the C^{14}-phthalic anhydride is presented for each material; this value is calculated from the average weight of the material and the average activity of the material. The average activity in terms of the C^{14}-phthalic anhydride is comparable for all materials except for the portion of the crude that was not copper phthalocyanine, phthalimide, and cyanuric acid, indicating the presence of a small amount of matter derived from phthalic anhydride in this material.

Acknowledgment.—The authors thank Dr. Frank H. Moser, Director of Research, and the Standard Ultramarine and Color Company for permission to publish these results. They thank Oscar L. Harvey, Jr., for his role in carrying out the experiments.

1-(N-Ethoxy)-1-ethylhydrazine

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In light of the current interest in organic derivatives of hydrazine and hydroxylamine we wish to report the preparation and characterization of the first reported N-alkoxyhydrazine. 1-(N-Ethoxy)-1-ethylhydrazine [$C_2H_5ON(C_2H_5)NH_2$] was prepared by the reduction of N-nitrosodiethylhydroxylamine. Of several reducing agents tried, only lithium aluminum hydride gave the desired product.

This basic liquid reduced Fehlings solution, formed a crystalline acid oxalate, and condensed with *p*-nitrobenzaldehyde to give the hydrazone. The infrared and nuclear magnetic resonance spectra confirmed the nature of the new compound. Catalytic reduction of 1-(N-ethoxy)-1-ethylhydrazine acid oxalate in methanol with a platinum catalyst followed by addition of oxalic acid gave ethanol plus the oxalates of ammonia and ethylamine. This again pointed definitely to the correctness of the assigned formula for the new compound.

Experimental

Reduction of N-Nitrosodiethylhydroxylamine with Lithium Aluminum Hydride.—To 19.6 g. (0.17 mole) of N-nitrosodiethylhydroxylamine[1] in 200 ml. of dry diethyl ether at 3–5° was added dropwise, with stirring, a solution of 6.5 g. (0.17 mole) of $LiAlH_4$ in 200 ml. of diethyl ether. The mixture was stirred at room temperature for 3 hr. after the addition was completed, and the complex decomposed with 20 ml. of a 20% potassium sodium tartrate solution. The resulting solid was filtered and extracted continuously with diethyl ether for 50 hr. The combined ether extracts yielded, after drying and fractionation, 6.2 g. of a colorless liquid boiling at 80–81°. This liquid became light yellow on standing in the cold. The infrared spectrum differed considerably from the spectrum of O,N-diethylhydroxylamine, especially in the 10–12-μ region. Selected infrared maxima (NaCl plates) were 3.0, 3.4, 6.1, 9.6, and 11.5 μ. The nuclear magnetic resonance spectrum in $CdCl_2$ showed two triplets closely overlapped at τ 8.3 and two quartets closely overlapped at τ 5.9 in addition to a singlet at τ 7.0.

Anal. Calcd. for $C_4H_{12}N_2O$: C, 46.11; H, 11.63. Found: C, 45.96; H, 11.74.

1-(N-Ethoxy)-1-ethylhydrazonium Oxalate.—The acid oxalate was prepared by the addition of an ethereal solution of the hydrazine to a saturated solution of anhydrous oxalic acid in ether. The precipitated solid was washed with ether and recrystallized from absolute ethanol. The product was a white crystalline solid, m.p. 179–180°.

Anal. Calcd. for $C_6H_{14}N_2O_5$: C, 37.10; H, 7.28. Found: C, 37.51; H, 7.12.

Condensation of 1-(N-ethoxy)-1-ethylhydrazine with *p*-Nitrobenzaldehyde.—A few drops of 1-(N-ethoxy)-1-ethylhydrazine was added to a solution of *p*-nitrobenzaldehyde in methanol containing a drop of glacial acetic acid. Warming for a few minutes gave a yellow solid which, when recrystallized from dimethylformamide, had m.p. 307° dec.

Anal. Calcd. for $C_{11}H_{15}N_3O_3$: C, 55.67; H, 6.38. Found: C, 55.86; H, 6.09.

Reductive Cleavage of 1-(N-Ethoxy)-1-ethylhydrazonium Oxalate with Hydrogen-Platinum.—Crystalline 1-(N-ethoxy)-1-ethylhydrazonium oxalate (0.1 g.) was dissolved in 20 ml. of methanol, and 0.1 g. of brown platinum oxide was added. The mixture was placed in a Parr hydrogenator and shaken for 10 hr. at 50 p.s.i. The platinum was filtered and a small amount of the filtrate was tested for ethanol.[2] A positive test was obtained. The methanol used as solvent was tested in the same manner; it gave a negative test. To the remainder of the methanol solution was added 20 ml. of a saturated solution of anhydrous oxalic acid in ether. On the addition of 50 ml. of dry ether a precipitate formed; it was filtered. This solid was washed with ether and extracted with ethanol. The insoluble portion was found to be ammonium oxalate by infrared spectral comparison. To the ethanol-soluble portion dry ether was added and the precipitated solid was filtered. This solid was recrystallized from methanol–ether, m.p. 148–150°. A mixture melting point with known ethylammonium oxalate showed no depression (m.p. of mixture, 147–149°). The infrared spectrum of the known ethylammonium oxalate was identical with the spectrum of the ethanol-soluble oxalate.

(1) A. B. Boese, Jr., L. W. Jones, and R. T. Major, *J. Am. Chem. Soc.*, **53**, 3530 (1931).

(2) F. Feigl, "Spot Tests in Organic Analysis," Elsevier Publishing Co., New York, N. Y., 1960, p. 358.

The Synthesis of 2,3,9,9a-Tetrahydro-6-hydroxy-5-methoxy-1-methyl-1*H*-benzo[*d*,*e*]quinolin-7(8*H*)-one

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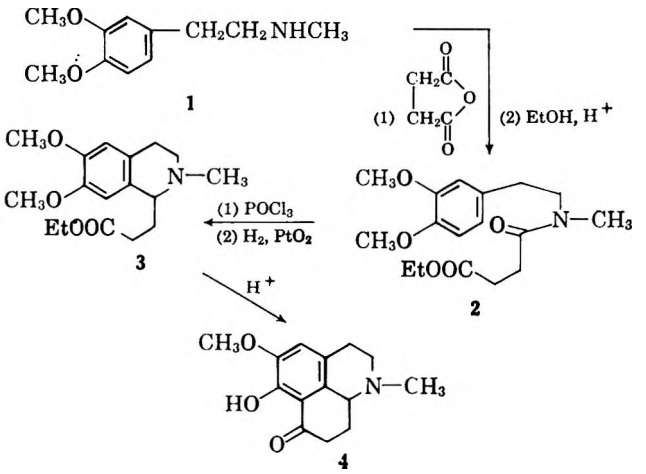
As part of a program on the synthesis of analogs of the aporphine alkaloids in which the D-ring is alicyclic, we have prepared 2,3,9,9a-tetrahydro-6-hydroxy-5-methoxy-1-methyl-1*H*-benzo[*d*,*e*]quinolin-7(8H)-one (**4**). This intermediate contains three rings of the aporphine nucleus and the features necessary for the attachment of the fourth ring by a route such as condensation with methyl vinyl ketone.

(1) M. Shamma and W. Slusarchyk, *Chem. Rev.*, **64**, 59 (1964).

Treatment of N-methyl-3,4-dimethoxyphenethylamine (1) with succinic anhydride followed by esterification gave the ester amide 2. This compound was also formed when the amine 1 was heated with diethyl succinate. Subjection of the ester amide 2 to the conditions of the Bischler–Napieralski[2] reaction gave a dihydro intermediate which after catalytic reduction afforded the tetrahydroisoquinoline 3. The polyphosphoric acid catalyzed cyclization of 3 gave the benzoquinolinone 4. The fact that demethylation had occurred in addition to cyclization was evidenced by the elemental analysis. (See Chart I.)

CHART I



The ether most likely to be cleaved is the one *ortho* to the ketone, since the aromatic ring joins the two in a vinylogous ester relationship. This proposal is verified by the infrared spectrum[3] of 4 which shows bands at 1632 (s) and 3000 (m, broad) cm.$^{-1}$. This is characteristic of an *o*-hydroxyketone chelate such as *o*-hydroxyacetophenone[4] which absorbs at 1638 (s) and 3000 (m, broad) cm.$^{-1}$, but not of *m*-hydroxyacetophenone[5] which shows a normal carbonyl band at 1680 (s) accompanied by free and associated hydroxy bands at 3600 (m, sharp) and 3300 (m, broad) cm.$^{-1}$.

The hydroxy group of 4 was not methylated by treatment with phenyltrimethylammonium hydroxide.[6] Since 4 did not readily undergo methylation, it was decided to discontinue this work.

Experimental[7]

Ethyl N-(3,4-Dimethoxyphenethyl)-N-methylsuccinamate (2). A. From Diethyl Succinate.—A mixture of 195 g. of 3,4-(dimethoxyphenethyl)-N-methylamine[8] and 1 kg. of diethyl succinate was heated at 200° for 4 hr. Distillation gave 156 g. (47%) of a colorless oil, b.p. 195° (0.25 mm.); λ_{max}^{EtOH}, mμ (ε), 229 (8900), 279 (2800).

Anal. Calcd. for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.34. Found: C, 63.04; H, 8.00; N, 4.33.

B. From Succinic Anhydride.—To a slurry of 50 g. of succinic anhydride in 100 ml. of benzene was added a solution of 97.5 g. of 3,4-dimethoxyphenethyl-N-methylamine in 100 ml. of benzene at a rate such that the temperature did not rise above 50°. Stirring was continued for 30 min., and then the solution refluxed for an additional 30 min. The reaction mixture was dissolved in 450 ml. of ethanol containing 3 ml. of sulfuric acid and refluxed for 2 hr. with partial removal of distillate. The ethanol was removed *in vacuo*, and the residue was poured into 200 ml. of ice–water. The mixture was made basic with sodium bicarbonate solution, saturated with sodium chloride, and extracted twice with 250-ml. portions of benzene. The benzene layers were combined, dried over sodium sulfate, and the solvent was removed. Distillation of the residue gave 127 g. (79%) of a colorless oil, b.p. 195° (0.25 mm.).

Ethyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-isoquinolinepropionate (3).—To a refluxing solution of 50.4 g. of phosphorus oxychloride in 90 ml. of toluene was added, over a 30-min. interval, a solution of 97 g. of ethyl N-(3,4-dimethoxyphenethyl)-N-methylsuccinamate in 90 ml. of toluene. Refluxing was continued for an additional 75 min. The reaction mixture was poured into 600 ml. of ice–water, and the temperature was allowed to rise to 25° and held there until there was no exotherm upon removal of the cooling bath. The aqueous layer was made basic with 50% sodium hydroxide solution and extracted three times with 200-ml. portions of chloroform. The chloroform layers were combined and dried over sodium sulfate, and the solvent was removed. The residue was dissolved in 150 ml. of acetic acid, 500 mg. of platinum oxide was added, and the solution was hydrogenated at atmospheric pressure. Hydrogen uptake was constant after 0.20 (65%) equiv. of hydrogen had been absorbed. The catalyst was filtered and the solvent was removed *in vacuo*. Distillation of the residue gave 49 g. (53%) of a colorless oil, b.p. 172–185° (0.25 mm.). Redistillation gave an analytical sample, b.p. 170° (0.25 mm.); λ_{max}^{EtOH}, mμ (ε), 227 (8400), 279 (2600).

Anal. Calcd. for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.52; H, 8.33; N, 4.61.

The **hydrochloride** formed in ether and crystallized from ethanol as a white crystalline solid, m.p. 194–196°.

Anal. Calcd. for $C_{17}H_{26}ClNO_4$: C, 59.38; H, 7.62; Cl, 10.31; N, 4.07. Found: C, 59.57; H, 7.62; Cl, 10.45; N, 3.90.

2,3,9,9a-Tetrahydro-6-hydroxy-5-methoxy-1-methyl-1*H*-benzo[*d,e*]quinolin-7(8*H*)-one (4).—To 96 ml. of 85% phosphoric acid stirred in a nitrogen atmosphere was added 150 g. of phosphorus pentoxide, which resulted in an exotherm to 190°. The temperature was adjusted to 170° and 65 g. of ethyl 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-isoquinolinepropionate added over a 3-min. interval. The temperature was held at 170 to 180° for an additional 8 min. The reaction mixture was rapidly cooled to room temperature, 600 ml. of ice–water was added, and the temperature was held at 25° until complete solution was obtained. The solution was neutralized with 30% sodium hydroxide solution to pH 7.5 (approximate) and extracted with three 100-ml. portions of chloroform. The extracts were combined and dried over sodium sulfate, and the solvent was removed. Trituration of the residue with 70 ml. of petroleum ether (b.p. 30–60°) gave 21.0 g. (38%) of a solid, m.p. 94.5–97.5°. Recrystallization from Skelly solve B gave a light yellow crystalline solid, m.p. 105–105.5°; λ_{max}^{EtOH}, mμ (ε), 227 (16,000), 272 (8100), 364 (3560); $\lambda_{max}^{1\ N\ NaOH}$, mμ (ε), 239 (16,700), 279 (5400), 390 (5800).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.00; H, 7.22; N, 5.86.

The **hydrochloride** formed in methanol and further recrystallization gave a white crystalline solid, m.p. 272°.

Anal. Calcd. for $C_{14}H_{18}ClNO_3$: C, 59.26; H, 6.39; Cl, 12.50; N, 4.94. Found: C, 59.01; H, 6.39; Cl, 12.39; N, 5.10.

(2) For a review of this reaction see W. Whaley and T. Govindachari, *Org. Reactions*, **6**, 74 (1951).

(3) All spectra were measured on a Baird Model 4-55 double beam spectrophotometer equipped with sodium chloride optics. Dilute chloroform solutions were employed such that an increased dilution caused no further shift of the carbonyl absorption frequency. The materials used were obtained from Eastman Kodak.

(4) N. M. Cullinane, R. A. Woolhouse, and V. V. Bailey-Wood, *Rec. trav. chim.*, **80**, 116 (1961).

(5) H. H. Freedman, *J. Am. Chem. Soc.*, **82**, 2454 (1960).

(6) K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Oxford, At the Clarendon Press, London, 1954, p. 60, and references therein.

(7) Melting points are uncorrected. The authors are indebted to Mr. R. Puchalski for the spectral data and Mrs. U. Zeek for analytical determinations.

(8) J. S. Buck, *J. Am. Chem. Soc.*, **52**, 4119 (1930).

Preparation of 1-Carboxybicyclo[4.3.1]dec-3-en-10-one

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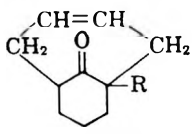
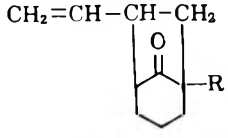
The preparation of bicyclo[4.3.1]dec-7-en-10-one[1] stimulated an interest in the preparation of related bicyclic compounds. Since the dialkylation of malonic ester,[2,3] acetoacetic ester,[4] and ethyl cyanoacetate[4] with 1,4-dihalo-2-butenes has been reported on several occasions, it seemed reasonable that the structurally similar 2-carbethoxycyclohexanone could be used for the preparation of bicyclic compounds.

Dialkylation of malonic ester with 1,4-dihalo-2-butenes has led to two products, 4,4-dicarbethoxycyclopentene and diethyl 2-vinylcyclopropane-1,1′-dicarboxylate,[2,3] depending on whether an allyl shift of the dihalide takes place in the reaction. The cyclopentene derivative is the major product when the *cis* dihalide is used, and the cyclopropane derivative is the major product when the *trans* dihalide is used.[2,3]

It was anticipated, therefore, that dialkylation of 2-carbethoxycyclohexanone with *cis*-1,4-dichloro-2-butene would lead to 1-carbethoxybicyclo[4.3.1]dec-3-en-10-one (Ia), and that the *trans* isomer would give 1-carbethoxy-6-vinylbicyclo[3.2.1]octan-8-one (IIa).



Ia, R = COOEt
b, R = COOH
c, R = H



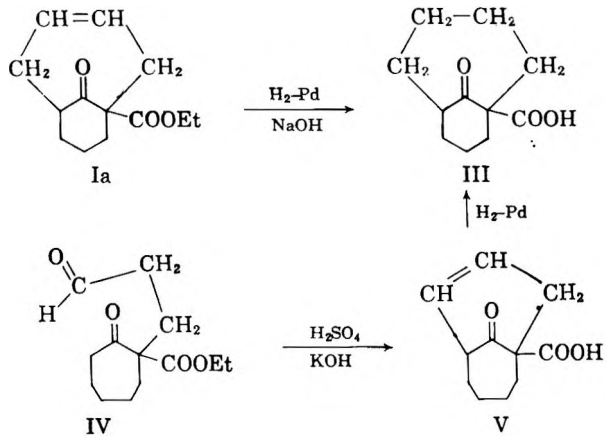
IIa, R = COOEt
b, R = COOH

Furthermore, it was anticipated that a separation of the isomeric products would be possible by virtue of the fact that Ib, the acid obtained from the hydrolysis of Ia, would decarboxylate on heating with quinoline, while IIb, the acid from IIa, would probably not decarboxylate under the same conditions.[5]

It was found, however, that both *cis*- and *trans*-1,4-dichloro-2-butene reacted with 2-carbethoxycyclohexanone to give 1-carbethoxybicyclo[4.3.1]dec-3-en-10-one (Ia) in nearly identical yields. There was no indication of the presence of the isomeric IIa.

The structure was indicated by the infrared and n.m.r. spectra of Ib. Confirmation of the structure, however, was obtained when Ia was converted to 1-carboxybicyclo[4.3.1]decan-10-one (III), and the same acid was obtained by an independent synthesis.

Reduction of Ia, followed by hydrolysis of the resulting saturated ester, gave III. The method Cope and Synerholm used to prepare 1-carboxybicyclo[3.3.1]-nonan-10-one from 2-carbethoxycyclohexanone and acrolein[7] also resulted in the preparation of III, when 2-carbethoxycycloheptanone was used instead of 2-carbethoxycyclohexanone. Since the same product was obtained by the two methods, the structure of III, as well as Ia and Ib, was established.



Ia III IV V

The acid Ib was decarboxylated by heating with quinoline to give bicyclo[4.3.1]dec-3-en-10-one (Ic), an isomer of the bicyclo[4.3.1]dec-7-en-10-one previously reported.[1]

Experimental[8]

Starting Materials.—2-Carbethoxycyclohexanone (Arapahoe Chemicals, Inc.) was fractionated to give a colorless liquid boiling at 77–80° (3 mm.), $n^{23}D$ 1.4821. *trans*-1,4-Dichloro-2-butene (Eastman Yellow Label) was fractionated to give a colorless liquid boiling at 156°, $n^{22}D$ 1.4873, that was completely free of the *cis* isomer.[9] *cis*-1,4-Dichloro-2-butene was prepared by reaction of *cis*-2-butene-1,4-diol (General Aniline and Film Corp.) with thionyl chloride and pyridine in ether.[2] The fractionated product was a colorless liquid boiling at 59° (30 mm.), $n^{22}D$ 1.4871, that was completely free of the *trans* isomer.[9] Acrolein (Eastman Yellow Label) was fractionated twice and used immediately. 2-Carbethoxycycloheptanone was prepared from diethyl oxalate (Eastman White Label) and cycloheptanone[10] (Aldrich Chemical Co.). A colorless liquid boiling at 95° (4 mm.), $n^{22}D$ 1.4701, was obtained.

1-Carbethoxybicyclo[4.3.1]dec-3-en-10-one (Ia). A.—2-Carbethoxycyclohexanone (85 g., 0.5 mole) was added to a solution of sodium (23 g., 1 g.-atom) in 500 ml. of *t*-amyl alcohol. After 30 min. of heating and stirring, the mixture was cooled to room temperature, and *trans*-1,4-dichloro-2-butene (62.5 g., 0.5 mole) was added over 10 min. The mixture was stirred at room temperature for 2 hr. and then refluxed overnight. Filtration of the salt was followed by distillation of the *t*-amyl alcohol. The residue was treated with water, taken up in ether, and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation gave 22.0 g. of liquid boiling at 140–200° (5 mm.) and 36.0 g. of residue. Redistillation gave 17.0 g. of colorless liquid boiling at 130–40° (5 mm.), $n^{22}D$ 1.4940.[11]

B.—When *cis*-1,4-dichloro-2-butene was used, distillation gave 22.5 g. of liquid boiling at 145–200° (3 mm.) and 36.0 g.

(1) R. D. Sands, *J. Org. Chem.*, **28**, 1710 (1963).
(2) K. C. Murdock and R. B. Angier, *ibid.*, **27**, 2395 (1962).
(3) J. Meinwald, P. Gassman, and J. Crandall, *ibid.*, **27**, 3366 (1962).
(4) R. Kierstead, R. Linstead, and B. Weedon, *J. Chem. Soc.*, 1799 (1953).
(5) This prediction is based on the observation that there seems to be a correlation between the sizes of the rings in β-ketobicyclic acids and their ease of decarboxylation. β-Ketobicyclic compounds with at least one seven-membered ring such as 7-methyl-1-carboxybicyclo[4.3.1]dec-7-en-10-one[6] and 1-carbethoxybicyclo[4.3.1]dec-7-en-10-one[1] are readily decarboxylated. 4-Methyl-1-carboxybicyclo[3.3.1]non-3-en-9-one,[6] 1-carboxybicyclo-[3.3.1]-non-3-en-9-one, and 1-carboxybicyclo[3.3.1]nonan-9-one,[7] all with only six-membered rings, are not decarboxylated by heating with quinoline.
(6) V. Prelog, P. Barman, and M. Zimmerman, *Helv. Chim. Acta*, **32**, 1284 (1949).
(7) A. C. Cope and M. E. Synerholm, *J. Am. Chem. Soc.*, **72**, 5228 (1950).
(8) Microanalyses were by Weiler and Strauss, Oxford.
(9) By chromatographic analysis, using an Aerograph A-700 Autoprep with a 10 ft. × 3/8 in. column packed with 20% Dow-710 on acid-washed, 60–80-mesh Chromosorb W.
(10) H. R. Snyder, L. A. Brooks, and S. H. Shapiro, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 531.
(11) Further purification was not attempted because of fear of decarbethoxylation.[5]

of residue. Redistillation gave 19.0 g. of colorless liquid boiling at 140–50° (6 mm), $n^{22}D$ 1.4978.[11,12]

1-Carboxybicyclo[4.3.1]dec-3-en-10-one (Ib).—1-Carbethoxybicyclo[4.3.1]dec-3-en-10-one (25 g.) was refluxed with 10% hydrochloric acid. The hydrolysis mixture was extracted with ether, and the ether extract was washed with sodium bicarbonate solution. Acidification of the sodium bicarbonate solution gave a solid which was recrystallized from toluene to give 3 g. of a pure white solid melting at 146–147°. The ester from the *cis* and that from the *trans* dichloride both gave the same acid (mixture melting point). The 2,4-dinitrophenylhydrazone had m.p. 236–238°. The n.m.r. spectrum indicated the structure to be Ib, not IIb.[13]

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.21. Found: C, 68.12; H, 7.24.

1-Carboxybicyclo[4.3.1]decan-10-one (III). A.—1-Carbethoxybicyclo[4.3.1]dec-3-en-10-one[14] (15 g.) was dissolved in 160 ml. of 95% ethanol containing 1.4 g. of 5% palladium on barium sulfate (Engelhard Industries, Inc.) and agitated at room temperature in the low-pressure hydrogenator under a hydrogen pressure of 32.5 lb./in.^{2} for 23 hr. Filtration of the catalyst and reduced pressure evaporation of the alcohol gave a residue that was refluxed with a solution of 10 g. of sodium hydroxide in 75 ml. of water for 4 hr. The reaction mixture was treated with decolorizing carbon and filtered. The cooled filtrate was washed with ether and then acidified. The resulting oil was taken up in ether, washed with water, and dried over anhydrous magnesium sulfate. The 9 g. of residue from evaporation of the ether was taken up in a bicarbonate solution which was then washed with ether. Acidification gave an oil which was taken up in ether and dried. The solid obtained by evaporation of the ether was recrystallized from methylcyclohexane to give pure white III, melting at 102–103°. The 2,4-dinitrophenylhydrazone had m.p. 189°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 67.36; H, 8.29.

B.—2-Carbethoxycycloheptanone (0.15 mole) was treated with acrolein at −70° according to the method of Cope and Synerholm[7] to give 18.3 g. of crude β-(1-carbethoxy-2-ketocycloheptyl)propionaldehyde (IV), boiling at 165–185° (7 mm.), $n^{21}D$ 1.4774. The 18.3 g. of aldehyde gave 3 g. of crude solid (V) after ring closure and hydrolysis. The 2,4-dinitrophenylhydrazone had m.p. 230° dec.

Anal. Calcd. for $C_{17}H_{18}N_4O_6$: C, 54.54; H, 4.81. Found: C, 54.50; H, 4.88.

When the solid was reduced as above and then recrystallized from methylcyclohexane, a pure white solid melting at 102–103° was formed. There was no depression of melting point when mixed with the acid from A.

Bicyclo[4.3.1]dec-3-en-10-one (Ic).—1-Carboxybicyclo[4.3.1]-dec-3-en-10-one (1.25 g.) was refluxed with 10 ml. of quinoline for 1 hr. The mixture was cooled and treated with ether. The ether solution was washed with water, sodium bicarbonate solution, water, dilute hydrochloric acid, and again with water. The ether solution was dried and evaporated to give 1 g. of brown residue. Distillation of 3.6 g. of the residue isolated 1 g. of white solid from the quinoline still present, b.p. 85° (4 mm.), m.p. 72–73°. The 2,4-dinitrophenylhydrazone had m.p. 175–176°.

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.18; H, 5.45. Found: C, 58.11; H, 5.48.

(12) There were differences in the boiling points and refractive indices of the distillates from the *cis* and *trans* dihalides only because the distillates contained all the same impurities (alcohol, cyclohexanone, 3,4-dichloro-1-butene, *cis*- and *trans*-1,4-dichloro-2-butene, and carbethoxycyclohexanone) in slightly varying amounts.

(13) Carried out and interpreted by Varian Associates, Palo Alto, Calif.

(14) The ester prepared from *trans*-1,4-dichloro-2-butene was used.

The Reaction of Carbyl Sulfate with Pyridine

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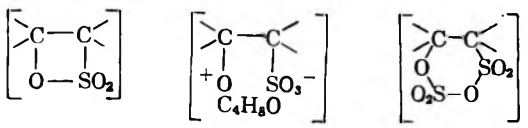
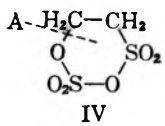
Received February 21, 1964

Bordwell and co-workers studied the mechanism of sulfonation of olefins and concluded that β-sultones (I), or their dioxane-solvated oxonium *ions* (II), and cyclic sulfonate–sulfates (III) are important intermediates when 1 mole of olefin is treated with 1 or 2 moles of sulfur trioxide–dioxane, respectively.[1] The existence of these intermediates, which were isolated in some instances,[2] was supported, for example, by the formation of 2-(1-proto-1-pyridyl)-1-hexanesulfonate[3a] on sequential treatment of 1-hexene with 1 mole of sulfur trioxide–dioxane and excess pyridine, and by the formation of the aniline salt of 2-hydrosulfato-1-hexanesulfonanilide on sequential treatment of 1-hexene with 2 moles of sulfur trioxide–dioxane and aniline.[3b] The reaction of intermediates of type III with tertiary amines was not reported.



I II III

The purpose of our investigation was to conduct a limited study of the reactivity of pure carbyl sulfate (IV) with pyridine. We expected that, if reaction occurred, the most probable reaction would be C–O cleavage at bond A with resultant formation of a betaine salt.[4] Such a reaction would suggest that the



IV

structures of the products formed on sequential treatment of olefins with sulfur trioxide and amines may not clearly differentiate between reaction paths which involve intermediates of structures I, II, and III.

The reaction of IV and pyridine was carried out in ethylene chloride solvent so that the reactive species was IV and not a decomposition product.[5] At room temperature, IV reacted rapidly with pyridine to afford an oily precipitate which gave a crystalline solid in relatively good yield on crystallization from N,N-dimethylformamide. The crystalline product was characterized as the betaine salt, 2-(1-proto-1-pyridyl)-1-ethanesulfonate (V),[3a] by elemental, infrared, and p.m.r. analyses, and by examination of its chemical properties. The product had a high melting point and was soluble in polar solvents. Aqueous solutions of the product were neutral, gave negative tests for

(1) For a summary of the literature on the mechanism of reaction of sulfur trioxide with olefins, see E. E. Gilbert, *Chem. Rev.*, **62**, 549 (1962).

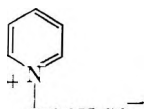
(2) See ref. 1, p. 564.

(3) (a) This nomenclature has been used previously by Professor Bordwell and co-workers. See, for example, F. G. Bordwell, M. L. Peterson, and C. S. Rondestvedt, Jr., *J. Am. Chem. Soc.*, **76**, 3945 (1954). Reference 7 of this paper is reproduced here: "This nomenclature has been suggested by Dr. F. Y. Wiselogle to fill the need for a suitable prefix to designate a substituent which bears a positive charge. "Proto" signifies the addition of a proton; $C_5H_4N^+H$ is then protopyridine and $C_5H_5N^+-$ is the 1-proto-1-pyridyl group. According to this nomenclature a dipolar ion, such as sulfanilic acid, can be given the systematic name *p*-protoaminobenzenesulfonate, rather than p-aminobenzenesulfonic acid, which misrepresents the structure." (b) F. G. Bordwell and M. L. Peterson, *ibid.*, **76**, 3952 (1954).

(4) Betaine-type compounds are defined in this paper as internal salts containing the anion of the sulfonic acid group and a quaternary fully alkylated nitrogen atom.

(5) Infrared analyses of ethylene chloride solutions of IV indicated that decomposition is nil when IV is carefully dissolved in the solvent. Ethylene chloride is a suitable recrystallization solvent for IV.

sulfate anion even after boiling with hydrochloric acid, and liberated pyridine on treatment with warm base. Neutralization equivalent and bromine number determinations carried out according to the method of Bordwell and Peterson[3b] gave the expected values for



V

the betaine salt structure.[6] The infrared spectrum exhibited the two absorption bands which are characteristic of the C=C and C=N vibrations of the N-alkylated pyridine ring.[7] The p.m.r. spectrum exhibited the expected chemical shifts for the two pairs of methylenic protons of V. All of the physical and chemical evidence collected in this investigation supported the betaine salt structure (V) for the reaction product of IV and pyridine.

In other experiments, treatment of IV with equimolar or less than equimolar amounts of pyridine gave V in reduced yields. Attempts to utilize alcohols and water as crystallization solvents for the initial oily precipitate failed. However, V was recrystallizable from methanol after crystallization had been effected from N,N-dimethylformamide. Presumably, the oily precipitate formed initially on treatment of IV with pyridine contains the $-SO_2OSO_3^-$ group which is converted to $-SO_3^-$ by removal of sulfur trioxide to yield V. N,N-Dimethylformamide apparently coordinates with sulfur trioxide to form sulfur trioxide–N,N-dimethylformamide and V.

Thus, our investigation shows that carbyl sulfate (IV) undergoes cleavage at bond A on treatment with pyridine under mild conditions. Cyclic sulfonate–sulfate intermediates (III) will probably react in a similar manner with pyridine or other tertiary heterocyclic amines to yield betaine salts identical with the products formed on treatment of intermediates I or II with the same amine.

Experimental[8]

2-(1-Proto-1-pyridyl)-1-ethanesulfonate.—Carbyl sulfate, 10.0 g. (0.0531 mole), prepared according to the method of Breslow and Hough and recrystallized twice from ethylene chloride,[9] was dissolved in 200 ml. of ethylene chloride by gentle warming on the steam bath. The resulting solution was treated with 19.6 g. (0.25 mole) of pyridine in 80 ml. of ethylene chloride. During the addition, the reaction mixture was maintained at room temperature by external cooling with an ice bath. The exothermic reaction produced an oily precipitate which was separated from unreacted pyridine and solvent by decantation of the supernatant liquid and successive washing of the precipitate with two 100-ml. portions of fresh ethylene chloride and two 100-ml. portions of petroleum ether (b.p. 30–60°). The precipitate was crystallized once from boiling N,N-dimethylformamide to yield 3.5 g. (35.3%) of 2-(1-proto-1-pyridyl)-1-ethanesulfonate as white granular crystals, m.p. 250–255° with sintering at 90°. Evaporation of the mother liquor gave an additional 2.5 g. (25.2%) of product melting at 240°. This product was identical with the first crop of crystals by infrared analysis. Elemental analysis of the first crop gave the results indicated below. The salt was soluble in water and methanol, and insoluble in acetone, ether, petroleum ether, and ethylene chloride.

Anal. Calcd. for $C_7H_9NO_3S$ (mol. wt. 187.21): C, 44.91; H, 4.85; N, 7.48; S, 17.13. Found: C, 44.97; H, 5.03; N, 7.62; S, 17.10.

Aqueous solutions of the salt were neutral and gave negative tests for sulfate anion after boiling with hydrochloric acid for 5 min. Free pyridine was detected by odor on treatment of an aqueous solution of the salt with 1.0 *N* sodium hydroxide solution and warming on the steam bath for a few minutes. The neutralization equivalent was determined by the method of Bordwell and Peterson.[3b] An aqueous solution of the salt was warmed for 30 min. on the steam bath with excess standard sodium hydroxide solution. Back-titration with standard hydrochloric acid solution gave a neutralization equivalent of 177 (calcd. neut. equiv. 187). Determination of the bromine number with an aliquot of the neutralized solution by the bromide–bromate technique gave a value of 86.4 (calcd. 85.3). Another aliquot of the neutralized solution gave a positive test for sulfate anion after sequential treatment with acidic potassium permanganate solution, a few drops of 30% hydrogen peroxide solution to remove manganese dioxide, and barium chloride solution.[10]

The instrument used to record the infrared spectra was a Perkin-Elmer Model 21 recording spectrophotometer. The spectrum of a potassium bromide pellet of 2-(1-proto-1-pyridyl)-1-ethanesulfonate exhibited sharp peaks at 6.1 (strong) and 6.3 μ (weak) in addition to a considerable amount of fine structure beyond 6.5 μ.[7]

The p.m.r. spectrum was measured in deuterium oxide at 60 Mc./sec. and room temperature with a Varian Associates A-60 spectrometer with an internal standard of Tier's salt.[11] The spectrum showed two triplets with relative intensities of 1:1. The triplet at 5.0 p.p.m. was attributed to the methylenic protons β to the sulfonate group, and the triplet at 4.6 p.p.m. was attributed to the methylenic protons α to the sulfonate group.

(6) This type of neutralization equivalent determination is based upon the quantitative reaction of the betaine salt with sodium hydroxide to afford an aqueous solution of pyridine and sodium vinylsulfonate. The bromine number determination, which is carried out with this aqueous solution, is based upon the reaction of bromine with sodium vinylsulfonate, but the numerical value is calculated as grams of molecular bromine consumed/100 g. of original betaine salt.

(7) Infrared spectra have been measured for several betaine sulfonate and sulfate salts. All spectra exhibit the characteristic absorption bands described in the Experimental section. This work will be published shortly.

(8) Melting points are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Neutralization equivalent and bromine number determinations were performed by the Analytical Research and Services Division of The Pure Oil Co., Crystal Lake, Ill.

(9) D. S. Breslow and R. R. Hough, *J. Am. Chem. Soc.*, **79**, 5000 (1957).

(10) Characteristic of α,β-unsaturated sulfonates.

(11) The p.m.r. determination was kindly carried out by Mr. Stuart Armstrong of Varian Associates. Assignments of the chemical shifts were made after examination of several betaine sulfonate and sulfate salts. The results of this examination will be published in a future paper.

Base-Catalyzed Preparation of Methyl and Ethyl Esters of Carboxylic Acids

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Recently[2] the author described a method of making phenacyl esters of carboxylic acids in which dicyclohexylethylamine (DICE) was used as the proton acceptor. Subsequent work has shown that dimethyl sulfate in the presence of this amine rapidly converts carboxylic acids to methyl esters in high yield. The method is simple and rapid, and is useful when the preparation of diazomethane is not feasible or when strongly acidic conditions must be avoided.

(1) A laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) F. H. Stodola, *Microchem. J.*, **9**, 389 (1963).

In the preparation of methyl esters 1 equiv. of the acid, dissolved in methanol or acetone, is heated in an open flask on a steam bath for 15 min. with 1.1–1.2 moles of dimethyl sulfate and 1.3–2.0 moles of DICE. For microscale work proportionately larger amounts of sulfate and amine can be used to facilitate handling. The following acids were methylated in good yield by this procedure: *m*-nitrobenzoic, *m*-hydroxybenzoic, 2,3,5,6-tetramethylbenzoic, 12-hydroxyoctadecanoic, 9,-10,12-trihydroxyoctadecanoic, triphenylacetic, and 9-anthroic. Tetronic acids behave like carboxylic acids, judging from a single experiment with α-methyltetronic acid.

For the preparation of ethyl esters only 1 mole of diethyl sulfate is used per equivalent of acid since excess reagent cannot be removed readily by hydrolysis as is the case with dimethyl sulfate. In this way, phenaceturic acid was converted to the ethyl ester in over 90% yield when heated with DICE for 15 min. in acetone.

Commercially available tris(2-hydroxypropyl)amine, $[CH_3CH(OH)CH_2]_3N$ (Eastman Kodak[3] 1,1′,1″-nitrilotri-2-propanol), was investigated as a possible substitute for DICE in the esterification of larger amounts of acid (*ca.* 0.15 mole). With *p*-nitrobenzoic acid the Eastman amine gave almost a quantitative yield of methyl ester (20% excess amine, 10% excess sulfate, acetone, 95°, 15 min.); under somewhat different conditions (10% excess amine, 20% excess sulfate, methanol, 95°, 15 min.), a 93% yield was obtained with *p*-bromobenzoic acid and with *erythro*-9,10-dihydroxyoctadecanoic acid. Unlike DICE, which can safely be used in 100% excess, the Eastman amine must be restricted in amount since it appears to remove dimethyl sulfate as a quaternary ammonium salt. For example, *erythro*-9,10-dihydroxyoctadecanoic acid gave only a 79% yield with a 100% excess of amine (20% excess sulfate, methanol, 95°, 15 min.); under the same conditions *p*-bromobenzoic acid yielded 83% methyl ester. When the Eastman amine is used for the preparation of ethyl esters a heating time of 1 hr. is recommended.

Experimental[4]

Methyl 2,3,5,6-Tetramethylbenzoate.—To 2.00 mg. of 2,3,5,6-tetramethylbenzoic acid in a microcentrifuge tube were added 10 μl. of dimethyl sulfate, 20 μl. of DICE, and 2 drops of acetone. After 15 min. heating on a steam bath, 2 *N* HCl was added and the crystals (2.05 mg., 96%) were recovered by filtration, m.p. 59.8–60.8° (lit.[5] m.p. 59°).

Methyl 9,10,12-Trihydroxyoctadecanoate.—The β-acid[6] (100 mg., 1 equiv.), dimethyl sulfate (47 mg., 1.2 moles), DICE (0.14 ml., 2 moles), and methanol (0.5 ml.) were heated for 15 min. on a steam bath. The crude methyl ester, obtained by addition of 2 *N* HCl and filtration, was dissolved in methanol, and the solution was made alkaline to phenophthalein by addition of dilute alcoholic NaOH. The alkaline solution was diluted with water and the ester was removed by ether extraction (101 mg., 97%), m.p. 113–115° (hot stage). Slow recrystallization from ethyl acetate gave pure methyl ester in the form of aggregates of needles, m.p. 118.4–119.4°. Mihara and Takaoka[7] reported a melting point of 108–109°.

Anal. Calcd. for $C_{19}H_{38}O_5$: C, 65.86; H, 11.05. Found: C, 65.80; H, 11.05.

Ethyl Phenaceturate.—Phenaceturic acid (193 mg., 1 mmole), diethyl sulfate (154 mg., 1 mmole), DICE (0.35 ml., 1.5 mmoles), and acetone (0.5 ml.) were heated for 15 min. on a steam bath. Addition of 2 *N* HCl gave an oil which crystallized on cooling. Filtration yielded 187 mg. (84%) of ethyl ester, m.p. 79.8–81.3°. Another 20 mg. of ester was obtained by ether extraction of the filtrate. Recrystallization from benzene gave pure ethyl phenaceturate, m.p. 81.3–82.3° (lit.[8] m.p. 82°).

Methyl *p*-Nitrobenzoate.—*p*-Nitrobenzoic acid (16.71 g., 0.10 mole), tris(2-hydroxypropyl)amine (22.95 g., 0.12 mole), dimethyl sulfate (13.87 g., 0.11 mole), and 20 ml. of acetone were heated for 15 min. on a steam bath. About 90% of the acetone was removed in this time. The reaction mixture was cooled to room temperature, and 5 ml. of water was added to decompose excess dimethyl sulfate. After addition of 10 ml. of concentrated HCl, the crystals of methyl ester were removed by filtration (17.81 g., 98%), m.p. 94.5–95.5° (hot stage). A portion (17.70 g.) of the ester was dissolved in ether; the ether was then washed with $NaHCO_3$ and water. Evaporation of the ether gave almost pure methyl ester (17.63 g.), m.p. 95.8–96.8° (lit.[9] m.p. 96°).

Ethyl *m*-Hydroxycinnamate.—*m*-Hydroxycinnamic acid (25.00 g., 0.152 mole), tris(2-hydroxypropyl)amine (34.96 g., 0.182 mole), diethyl sulfate (23.47 g., 0.152 mole), and acetone (25 ml.) were heated for 1 hr. on a steam bath. After addition of water, the ethyl ester was removed by ether extraction. The ether was washed with $NaHCO_3$ solution and finally with water. Removal of ether left 26.84 g. (92%) of ethyl ester, m.p. 62–65° (hot stage). Recrystallization from benzene–hexane gave pure ester, m.p. 67.7–68.7° (lit.[10] m.p. 70–71°).

(3) The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

(4) Melting points were carried out in melting-point tubes and are corrected, unless otherwise noted. The hot-stage melting points were not corrected.

(5) O. Jacobsen, *Ber.*, **22**, 1223 (1889).

(6) This acid (m.p. 139.6–140.6°) had been prepared and carefully purified by J. P. Kass and S. B. Radlove, *J. Am. Chem. Soc.*, **64**, 2253 (1942).

(7) K. Mihara and K. Takaoka, *Yukagaku*, **7**, 88 (1958); *Chem. Abstr.*, **55**, 4357 (1961).

(8) A. Klages and O. Haack, *Ber.*, **36**, 1648 (1903).

(9) H. Henstock, *J. Chem. Soc.*, 216 (1933).

(10) H. Ley, *Z. physik. Chem.*, **94**, 439 (1920).

On 2,5-Dichloropyrazine[1]

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Recently Klein and associates[2] have reported on the action of phosphoroyl chloride on various pyrazine N-oxides. While the experimental results are on the whole in substantial agreement with the ones we had previously reported,[3,4] there is a question concerning the formation of 2,5-dichloropyrazine by treatment of 3-chloropyrazine 1-oxide with phosphoroyl chloride.

We have repeated this reaction following closely the published[2] procedure and we have obtained a liquid (b.p. 84–88° at 25 mm.) that was analyzed by gas–liquid chromatography.[5] Two peaks were obtained and, upon collection of the peak fractions, the first was shown by infrared spectroscopy to be 2,6-dichloropyrazine (λ_{max} 8.41, 8.69, 8.86, 9.99, and 12.1 μ) and the second 2,3-dichloropyrazine (λ_{max} 8.35, 8.67, 9.52, 11.7, and 12.5 μ). Moreover, careful distillation of the reac-

(1) Paper VIII on pyrazine derivatives; Paper VII: G. Palamidessi and F. Chillemi, *Farmaco*, **18**, 566 (1963).

(2) B. Klein, N. E. Hetman, and M. E. O'Donnel, *J. Org. Chem.*, **28**, 1682 (1963).

(3) L. Bernardi, G. Palamidessi, A. Leone, and G. Larini, *Gazz. chim. ital.*, **91**, 1431 (1961).

(4) G. Palamidessi and L. Bernardi, *ibid.*, **93**, 339 (1963).

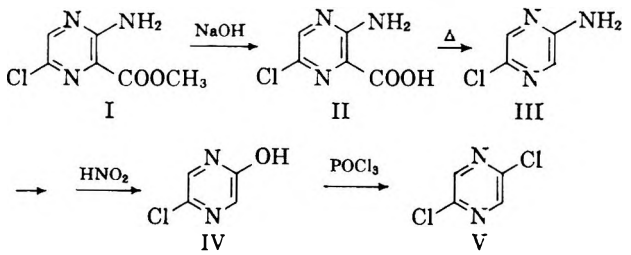
(5) The analyses were performed with a Perkin-Elmer fractometer, column Q, 2 m., 195°.

tion product afforded a first cut that on cooling partly solidified; the crystals were collected and identified as 2,6-dichloropyrazine (melting point, mixture melting point, and infrared spectrum). While the mechanism of formation of this compound is still unclear,[4] its presence in this reaction mixture is definitely proved.

At this point, although our previous results[3] had been, as shown, fully confirmed, it seemed desirable to synthesize a sample of 2,5-dichloropyrazine by a reliable route in order to definitely settle the matter.

Hydrolysis of 3-amino-6-chloromethylpyrazinoate[6] (I) with NaOH gave 3-amino-6-chloropyrazinoic acid (II). Decarboxylation of II in refluxing tetralin afforded, on cooling, an aminochloropyrazine III (m.p. 130–132°) that was definitely different (infrared spectrum and mixture melting point) from both 2-amino-3-chloropyrazine[7] and 2-amino-6-chloropyrazine.[3] It was therefore possible to formulate III as 2-amino-5-chloropyrazine, providing at the same time a rigorous proof of the structure of I, previously reported only in the patent literature.

Treatment of III with sodium nitrite in concentrated sulfuric acid gave 2-hydroxy-5-chloropyrazine (IV) which was converted, by reaction with phosphoroyl chloride, to the required 2,5-dichloropyrazine (V).



Having thus obtained an authentic sample of 2,5-dichloropyrazine, we re-examined the infrared spectrum of the crude mixture of dichloropyrazines formed in the reaction of 3-chloropyrazine 1-oxide and phosphoroyl chloride. All the bands of the spectrum are easily assigned either to 2,3-dichloropyrazine or to 2,6-dichloropyrazine. The conspicuous absorption band at 7.69 μ (which is characteristic of 2,6-dichloropyrazine since it occurs in a region where the two other isomers show no absorption) is completely absent, and we can therefore conclude that no 2,5-dichloropyrazine is formed in the reaction under discussion.

(6) Merck & Co., Inc., Belgian Patent 623,480 (1961).

(7) F. G. McDonald and R. C. Ellingson, *J. Am. Chem. Soc.*, **69**, 1036 (1947).

Experimental

All melting points unless otherwise noted were taken with a Fisher-Johns apparatus and are not corrected. The infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer.

3-Amino-6-chloropyrazinoic Acid (II).—Methyl 3-amino-6-chloropyrazinoate (I, 1 g.) was treated for 1 hr. at reflux temperature with 50 ml. of 2 *N* NaOH. The solution was cooled and acidified with 55 ml. of 2 *N* HCl. The precipitate was collected and dried, giving 0.8 g. of 3-amino-6-chloropyrazinoic acid, m.p. 175–180° dec. A sample was recrystallized from water, m.p. 177–180° dec.

Anal. Calcd. for $C_5H_4ClN_3O_2$: C, 34.59; H, 2.32. Found: C, 34.42; H, 2.47.

2-Amino-5-chloropyrazine (III).—A suspension of 1 g. of 3-amino-6-chloropyrazinoic acid in 10 ml. of tetralin was heated to reflux for 1 hr. On cooling, 0.5 g. of 2-amino-5-chloropyrazine, m.p. 125–126°, separated. A sample was recrystallized from water, m.p. 129–130°.

Anal. Calcd. for $C_4H_4ClN_3$: C, 37.15; H, 3.11. Found: C, 37.08; H, 3.23.

2-Hydroxy-5-chloropyrazine (IV).—Sodium nitrite (0.85 g.) was added, with stirring, at 0° to 4.6 ml. of concentrated sulfuric acid. The cooling bath was withdrawn and the sodium nitrite slowly went into solution. The flask was next cooled again to +5° and a solution of 1.4 g. of 2-amino-5-chloropyrazine in 8 ml. of sulfuric acid was slowly added. After 20 min., the mixture was carefully warmed to 40° and, after an additional 15 min., it was poured onto crushed ice. The solution was repeatedly extracted with ether. The combined organic layers were washed with water and dried over sodium sulfate. After the ether had been removed, the residue was crystallized from cyclohexane; 1 g. of 2-hydroxy-5-chloropyrazine, m.p. 128–129° dec., was collected.

Anal. Calcd. for $C_4H_3ClN_2O$: C, 36.78; H, 2.32. Found: C, 37.0; H, 2.74.

2,5-Dichloropyrazine (V).—2-Hydroxy-5-chloropyrazine (2 g.) suspended in 30 ml. of phosphoroyl chloride was heated at reflux temperature for 2 hr. After cooling, the solution was poured carefully onto 300 g. of crushed ice to destroy the excess phosphoroyl chloride. The solution was extracted with methylene chloride and the combined organic extracts were next washed with water and dried over sodium sulfate. After the solvent had been removed, the crude product was distilled under reduced pressure; 1 g. of 2,5-dichloropyrazine, colorless liquid boiling at 72° (12 mm.), was collected, $n^{25}D$ 1.5575. The product solidified on cooling at 0° and melted sharply at 13–14°. The infrared spectrum showed the following strong characteristic bands: λ_{max} 7.68, 8.71, 9.85, and 11.18 μ.

Anal. Calcd. for $C_4H_2Cl_2N_2$: Cl, 47.61. Found: Cl, 47.76