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Diels-Alder Reactions of 4,5-Dimethylenedioxolanes

J. B. MILLER

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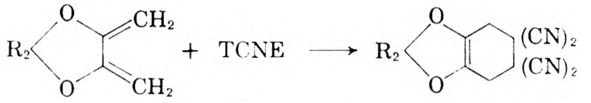
4,5-Dimethylenedioxolane (I) and 4,5-dimethylene-2,2-diphenyldioxolane (II) failed to react with dienophiles other than tetracyanoethylene. The infrared C=C absorption of dialkoxyolefins occurs below 6 μ and shifts to shorter wave lengths with increasing ring strain and thus is similar to that of fluoroalkenes.

The use of 4,5-dimethylenedioxolanes as dienes in the Diels-Alder reaction apparently has not been previously investigated. However, 1,2-dimethylenecyclopentane,[1] 2,3-dimethylenedioxane,[2] and 2,3-dimethoxy(and -diethoxy)butadiene[3] have all been shown to undergo the Diels-Alder reaction. This implies that the five-membered ring and the oxygen atoms in 4,5-dimethylenedioxolanes should not hinder reaction. This implication is strengthened by the data in Table I which indicates a marked similarity between 1,2-dimethylenecyclopentane and I. However, neither I nor II reacted with dienophiles other than tetracyanoethylene (TCNE).[4] The spectra of the tetracyanoethylene adducts are consistent with conventional Diels-Alder products.



I. R=H; II. R=C_6H_5

Thus the near infrared spectra showed no indication of terminal methylene groups, the adduct with I showed no selective ultraviolet absorption, and the nuclear magnetic resonance spectra showed only two types of hydrogen. The 5.73–5.85 μ absorption shown by the tetracyanoethylene adducts is attributed to the olefinic bond by analogy with ketene acetals and fluoroalkenes.

TABLE I

Spectra of Some Butadiene Derivatives

Compound	λ_{max} mμ	log ϵ (solvent)	μ
Butadiene	217[a]	4.32 (hexane)[a]	1.64, 5.5, 6.28
2,3-Dimethoxy-butadiene	225	4.28 (dioxane)	5.5, 6.30
1,2-Dimethyl-enecyclo-pentane	248[b]	4.02 (isooctane)[b]	5.66, 6.15[b]
4,5-Dimethyl-enedioxolane (I)	245	4.06 (dioxane)	1.61, 5.6, 5.95–6.1
4,5-Dimethyl-ene-2,2-diphenyl-dioxclane (II)			1.60, 5.55, 5.95, 6.1

[a] A. E. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy*, E. Arnold Ltd., London, 1954, p. 93. [b] Ref. 1.

Olefinic infrared absorption below 6 μ is well-known for fluoroalkenes (Table II).[5] The reason for this absorption at unusually short wave lengths is not known,[5] but work in progress indicates the important contribution of a mass effect.[6] Dr. Crawford has suggested[6] that the similarity in mass of oxygen and fluorine might be manifested in absorption at unusually short wave lengths for dialkoxyolefins. Thus ketene acetals, $R_1R_2C{=}C$-

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[1] A. T. Blomquist, J. Wolinsky, Y. C. Meinwald, and D. T. Longone, *J. Am. Chem. Soc.*, **78**, 6057 (1956).

[2] R. K. Summerbell and G. J. Lestina, *J. Am. Chem. Soc.*, **79**, 3878 (1957).

[3] J. R. Johnson, W. H. Jobling, and G. W. Bodamer, *J. Am. Chem. Soc.*, **63**, 131 (1941).

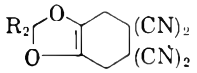
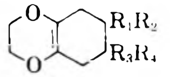
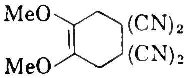
[4] W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Krespan, *J. Am. Chem. Soc.*, **80**, 2783 (1958).

[5] L. G. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen & Co. Ltd., London, 1958, p. 42.

[6] Private communication from Dr. Bryce Crawford, Feb. 16, 1959.

TABLE II

INFRARED ABSORPTION SPECTRA OF OLEFINS

Compound	C=C Absorption, μ	Compound	C=C Absorption, μ
Perfluorocyclobutene	5.56[a] 5.59[b]		5.73[e]
Perfluorocyclopentene	5.7[c]		
Perfluorocyclohexene	5.74[b]		5.81–5.85[f]
Perfluorobutene-2	5.77[b]		
Butene-2	6.06[d]		5.89
Cyclohexene	6.06[d]		
Cyclopentene	6.21[d]		
Cyclobutene	6.37[d]		

[a] J. R. Nielsen, M. Z. El-Sabban, and M. Alpert, *J. Chem. Phys.*, **23,** 324 (1955). [b] R. N. Haszeldine, *J. Chem. Soc.*, 4423 (1952). [c] A. L. Henne and K. A. Latif *J. Am. Chem. Soc.*, **76,** 610 (1954). [d] Ref. 5, p. 387. [e] R = H or C_6H_5. [f] $R_1 = R_2 = R_3 = R_4 = CN$; $R_1 = R_3 = H$, $R_2 = R_4 = CO_2CH_3$; $R_1 = R_3 = H$, $R_2 = R_4 =$ —CO—O—CO—.

$(OR)_2$, are reported to absorb at 6.10 μ ($R_1 = R_2 = H$), 5.97 μ ($R_1 = H$, $R_2 = CH_3$), 5.86 μ ($R_1 = R_2 = CH_3$), and at 6.12 μ ($R_1 = C_6H_5$ $R_2 = H$ or C_6H_5).[7] These results appear to confirm the analogy with the fluoroolefins with the important qualification that the dialkoxyolefin must be at least monosubstituted by alkyl groups to exhibit shifts to below 6 μ. The work of McElvain and Starn[7] also indicates that conjugation acts to nullify, in part, the otherwise expected shift to shorter wave lengths. This is confirmed by examples provided by Yates and Robb.[8]

The effect of oxygen at both ends of an olefinic linkage is of most immediate interest to us in explaining the spectra of the adducts of I and II with tetracyanoethylene. Consistent with the previous remarks concerning ketene acetals, dioxene[9] absorbed at 6.1 μ and 2,3-diphenyldioxene-2 is reported to absorb at 6.06 μ.[10] It was expected that alkyl substitution, however, would cause a shift to shorter wave lengths and several 2,3-dialkyldioxene-2 derivatives were prepared and were found to absorb in the 5.81–5.85 μ region (Fig. 1 and Table II).

Another analogy of dialkoxyolefins with fluoroalkenes is provided by the effect of ring strain (Table II). As ring strain increases, the wave length of C=C absorption increases for hydrocarbons but decreases for fluorocarbons. Similarly, the dialkoxyolefins (with a fused cyclohexane ring as a common feature) showed a decrease in the wave length of C=C absorption in the series open chain > six-membered ring > five-membered ring.

To summarize we suggest that two oxygen atoms attached to a mono- or disubstituted olefin will give rise to C=C absorption below 6.0 μ in the case of monosubstitution and below 5.9 μ in the case of

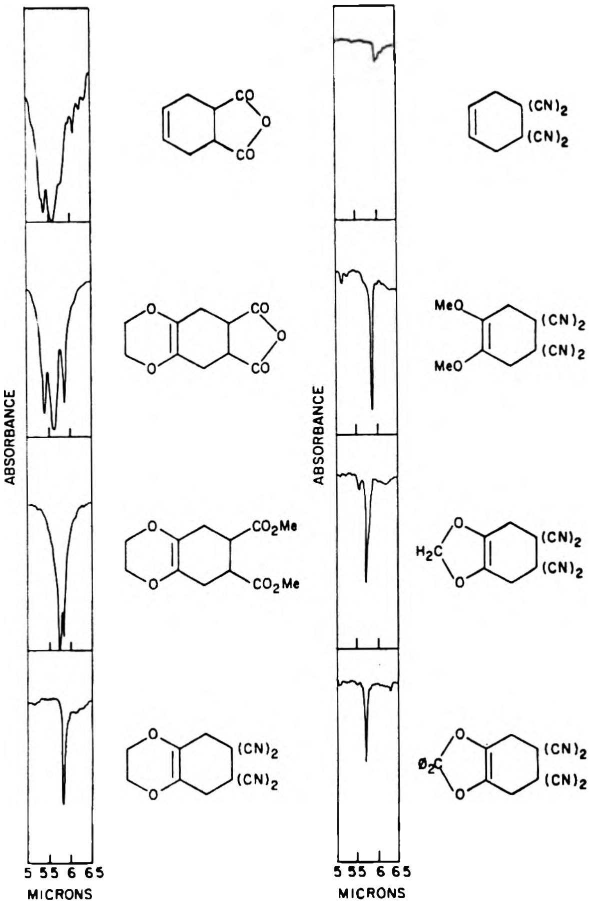


Fig. 1. Infrared spectra of dialkoxy disubstituted olefins

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(7) S. M. McElvain and R. E. Starn, Jr., *J. Am. Chem. Soc.*, **77,** 4571 (1955).

(8) P. Yates and E. W. Robb, *J. Am. Chem. Soc.*, **79,** 5760 (1957).

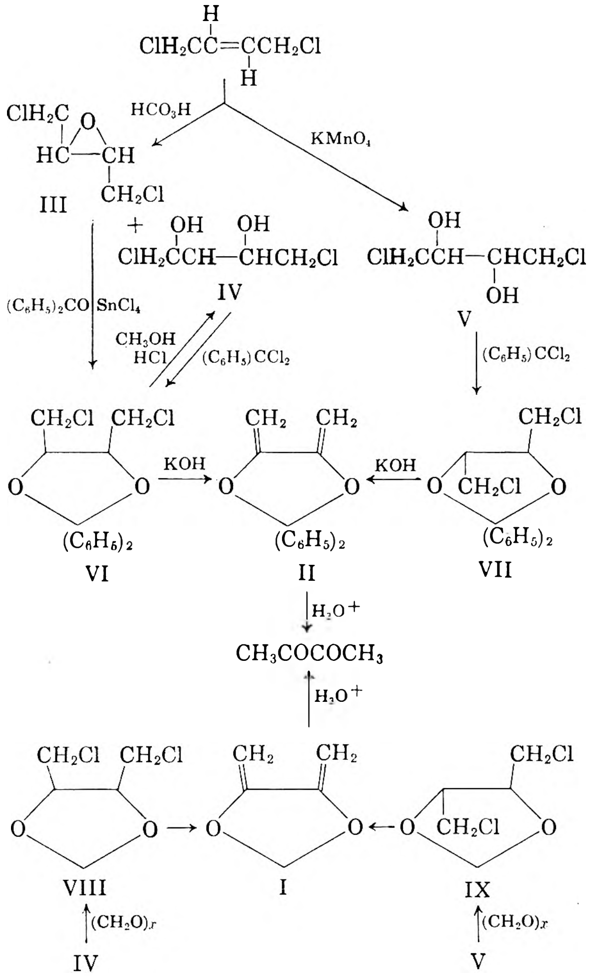
(9) Prepared according to R. K. Summerbell and R. R. Umhoefer, *J. Am. Chem. Soc.*, **61,** 3016 (1939).

(10) R. K. Summerbell and D. R. Berger, *J. Am. Chem. Soc.*, **81,** 633 (1959).

disubstitution. Ring strain where the double bond is endocyclic will decrease, and conjugation will increase, the wave length of absorption.

The preparation of the 4,5-dimethylenedioxolanes (I and II) followed conventional routes and requires only a few comments. The reaction of an epoxide with a ketone to yield a ketal is known,[11] but the stereochemistry has apparently not been elucidated. The preparation of the identical compound (VI) by the reaction of III with benzophenone and by the reaction of IV with dichlorodiphenylmethane showed that the epoxide (III) reacts with inversion. Hydrolysis of VI to yield the glycol (IV) further confirmed that inversion had occurred. Use of acetone in place of benzophenone in the sequence III→VI→IV provided a further example of inversion.

The solvolytic stability of III and IX is noteworthy. Thus III was isolated after long standing in a homogeneous aqueous formic acid solution—conditions which might be expected to lead to solvolysis of the epoxide. Dioxolane is completely hydrolyzed in one hour by a 2% sulfuric acid solution at room temperature[12] but the substituted dioxolane (IX) was recovered after similar treatment for seventeen hours and after refluxing for twenty-one hours with hydrochloric acid (*p*H ≈3) followed by twenty hours refluxing with concentrated hydrochloric acid. However, dioxolane is soluble in 2% sulfuric acid, whereas IX is insoluble in the above hydrolytic media and IX *is* hydrolyzed by methanolic hydrogen chloride in which it is soluble.



EXPERIMENTAL

DL-*Bis(chloromethyl)oxirane* (III) *and meso-1,4-dichlorobutanediol* (IV). The following method is a modification of Owen's procedure[13] for the preparation of IV in 49% yield.

A mixture of 600 ml. of 98% formic acid and 140 ml. of 30% hydrogen peroxide was prepared and maintained at room temperature for 2 hr. It was then cooled to 5° over a period of 1 hr. To this mixture was added dropwise 125 g. (1 mole) of *trans*-1,4-dichlorobutene-2[14] over 3.25 hr. The initially homogeneous reaction mixture became cloudy when somewhat less than one-half of the dichloro compound had been added and remained cloudy even when addition was stopped for 30 min. When addition was complete the reaction mixture was allowed to warm spontaneously to 29° over 45 min. The mixture was then held at −5° for 20 hr. and then at +5° for 12 hr. When allowed to warm spontaneously, the temperature rose to 36° and the mixture became homogeneous. It was then allowed to stand at autogeneous temperature for an additional 27 hr. The solvent was removed under reduced pressure to yield a mixture of liquid and crystals. Steam distillation gave a liquid which was separated from the water, dissolved in ether, dried with sodium sulfate, and filtered. Removal of the solvent under reduced pressure gave 29 g. (21%) of DL-bis(chloromethyl)-oxirane whose infrared spectrum showed no hydroxyl or olefinic bands. Redistillation gave a pure sample, b.p. 78–79° (13 mm.), n_D 1.474(5) (reported[15] b.p. 66–68° [5 mm.], n_D 1.4743).

The pot liquor on standing deposited 13.2 g. of crude *meso*-1,4-dichlorobutanediol, m.p. 129–132° (reported[13,16] m.p. 127°). The mother liquor was neutralized with a mixed cation-anion exchange resin (IR MB-1) and the solvent removed under reduced pressure to yield an additional 7.9 g. of glycol, m.p. 124.5–127° (total yield 13%).

DL-*1,4-Dichlorobutanediol* (V). Following the procedure of Owen[13] 80 g. (0.64 mole) of *trans*-1,4-dichlorobutene-2 was dissolved in 1200 ml. of ethanol and cooled to −15°. To this rapidly stirred solution was added dropwise a solution of 80 g. (0.51 mole) of potassium permanganate and 60 g. (0.50 mole) of magnesium sulfate in 1650 ml. of water. Addition required approximately 3 hr. during which time the temperature was maintained at −30 to −15°. After warming to room temperature, the manganese dioxide was removed by centrifuging. The supernatant liquid was extracted with four 200-ml. portions of ether. The ethereal extracts were dried with sodium sulfate and the solvent was removed under reduced pressure to yield 52 g. of crude glycol, m.p. 75°.

To the manganese dioxide was added a saturated sodium bisulfite solution until a gray slurry was obtained. The slurry

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(11) M. T. Bogert and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **55**, 3741 (1933); T. Bersin and G. Willfang, *Ber.*, **70**, 2167 (1937); G. Willfang, *Ber.*, **74**, 145 (1941).

(12) H. Hibbert and J. A. Timm, *J. Am. Chem. Soc.*, **46**, 1283 (1924).

(13) L. N. Owen, *J. Chem. Soc.*, 241 (1949).

(14) Polychemicals Dept., E. I. du Pont de Nemours & Co.

(15) P. S. Starcher, D. L. MacPeek, B. Phillips, British Patent **794,209**, U. S. Patent **2,861,084**.

(16) W. Reppe *et al.*, *Ann.*, **596**, 141 (1955), R. M. Evans and L. N. Owen, *J. Chem. Soc.*, 239 (1949).

was thinned with water and extracted with three 200-ml. portions of ether. These ethereal extracts when treated as above yielded 5 g. of crude glycol, m.p. 75°, total yield 56%.

In the course of six preparations the reported[13,17,18] melting point, 62–63°, was observed in the first three preparations, whereas the last three gave products melting at 75°.

Once having obtained the higher melting form all attempts to convert it to the lower melting polymorph by recrystallization were unsuccessful. A sample of the higher melting polymorph when vacuum distilled gave a crystalline distillate which melted at 61.3–62.9° when broken into small particles and at 74.9–76.8° after being finely ground. This interconversion on grinding prevented characterizing the polymorphs by means of x-ray diffraction. The identity of the higher melting polymorph was confirmed by preparing the diacetate, m.p. 75.2–76.6° (reported[13] m.p. 76° for the diacetate of the lower melting form), mixed melting point with starting material 55–71°.

The crude glycol contained a trace of impurity which was believed to be a manganese compound [see preparation of DL-4,5-bis(chloromethyl)-2,2-diphenyldioxolane]. This impurity was not removed by recrystallization from benzene–petroleum ether but was removed by distillation. The impurity had no effect on the melting point and was not detected by x-ray fluorescence.

Attempts to use zinc permanganate in place of the potassium permanganate-magnesium sulfate system gave 0–23% yields of product.

meso-4,5-Bis(chloromethyl)-2,2-diphenyldioxolane (VI). a) *From* DL-*bis(chloromethyl)oxirane* (III). To a solution of 5 ml. of stannic chloride in 100 ml. of carbon tetrachloride was added dropwise a solution of 39.5 g. (0.28 mole) of DL-bis-(chloromethyl)oxirane (III) and 58.2 g. (0.32 mole) of benzophenone in 60 ml. of carbon tetrachloride. The reaction mixture became bright yellow and at the end of 55 min. became slightly cloudy. Addition was complete in 70 min. after which the reaction was stirred for an additional hour. Sixty milliliters of 17% potassium hydroxide was added with shaking. The residue was removed by filtration and thoroughly washed with water until no longer basic to litmus to yield 58.9 g. of the dioxolane, m.p. 135–141°.

The water was removed from the filtrate and the organic phase was dried with sodium sulfate. Removal of the solvent under reduced pressure gave an oily crystalline solid. The solid was washed thoroughly with carbon tetrachloride to yield an additional 11.85 g. of the dioxolane, m.p. 135–137°, total yield 78%.

The wash liquor was distilled and after the carbon tetrachloride forerun the following fractions were obtained: 1) b.p. 82–161°, 4.69 g.; 2) b.p. 161–169°, 17.16 g., crystallized on seeding with benzophenone, m.p. 46°; 3) pot residue, 3.42 g. of VI, m.p. 132–134.4° (from cyclohexane and ethanol).

An analytical sample of the dioxolane was prepared by recrystallizing three times from cyclohexane and once from carbon tetrachloride to give a product melting at 139–140.2°, m.w. 291 in benzene, calcd. 323. The sample was then recrystallized from alcohol to give a product having m.p. 139.4–140.4°, m.w. 291 in benzene, ϵ_{max} 459 at 258 mμ (C_2H_5OH).

Anal. Calcd. for $C_{17}H_{16}O_2Cl_2$: C, 63.17; H, 4.99; Cl, 21.94; m.w. 323. Found: C, 63.08; H, 5.08; Cl, 21.84; m.w. 287 (Rast).

b) *From meso-1,4-dichlorobutanediol* (IV). A mixture of 150 ml. of xylene, 7.95 g. (0.05 mole) of *meso*-1,4-dichlorobutanediol, and 11.85 g. (0.05 mole) of dichlorodiphenylmethane was refluxed for 19 hr. Sodium bicarbonate (5.5 g.) was added and the mixture was stirred for 1 hr. Water (100 ml.) was then added and the mixture was stirred for 1 hr. The mixture was then filtered and the residue washed with 50 ml. of ether. The organic layer was separated from the filtrate and washed twice with 50-ml. portions of water. The organic layer was then dried with sodium sulfate to yield a clear, slightly yellow solution. Removal of the solvent under reduced pressure gave slightly yellow crystals which were recrystallized from cyclohexane to yield 6.26 g. of product, m.p. 137.2–139.8°. The mother liquor yielded an additional 9.28 g. of product (total yield 40%).

An attempt to prepare this compound from the corresponding diol (IV) and benzophenone in refluxing benzene using *p*-toluenesulfonic acid as a catalyst gave after 16 hr. essentially no water, a 79% recovery of benzophenone and a 90% recovery of the diol.

c) *Methanolysis.* Methanolysis was effected by suspending 2.96 g. (0.0094 mole) of *meso*-4,5-bis(chloromethyl)-2,2-diphenyldioxolane in 150 ml. of methanol saturated with hydrogen chloride. After standing for 2 days, the solvent was removed under reduced pressure to yield a pasty solid. The solid was slurried with ether, filtered, and washed extensively with ether to yield 0.18 g. of *meso*-1,4-dichlorobutanediol, m.p. 129–130°, mixed melting point with authentic *meso*-glycol 129–130°, yield 12%.

The ether wash was neutralized with 5% sodium bicarbonate solution, dried with sodium sulfate, and the solvent removed under reduced pressure to yield a crystalline solid. The solid was washed by decantation with hot water, dissolved in ether, and the ethereal solution dried with sodium sulfate. Removal of the solvent under reduced pressure gave a slightly yellow oil which instantly crystallized on seeding with benzophenone to yield 0.86 g. of benzophenone, m.p. 40–45°, yield 50%.

DL-*4,5-Bis(chloromethyl)-2,2-diphenyldioxolane* (VII). A mixture of 12.72 g. (0.08 mole) of crude DL-1,4-dichlorobutanediol (m.p. 63.5–66.1°), 15.3 ml. (18.96 g., 0.08 mole) of dichlorodiphenylmethane, and 400 ml. of xylene was refluxed for 19 hr. During the initial warm up period the solution turned yellow and then deep blue. The color then changed to green and after about 3 hr. was greenish-yellow. At the end of the reflux period the solution was bright yellow. (On another occasion, using glycol melting at 55–60°, only a yellow color was observed throughout the reaction.) The solution was filtered to yield a trace of a gray powdery residue. The residue when spotted with 0.1*N* sodium hydroxide turned brown. After drying it was spotted with benzidine which gave a blue color indicating the probable presence of a manganese compound in the glycol starting material.

Removal of the solvent from the filtrate under reduced pressure yielded a bright yellow crystalline slurry which was filtered and washed twice with xylene to yield 19.6 g. of white crystals, m.p. 129.5–132.0°. The filtrate when worked up yielded an additional 3.4 g. (total yield 88%) of brown colored crystals, m.p. 128–129.5°. One recrystallization from cyclohexane, two recrystallizations from carbon tetrachloride, and one recrystallization from ethanol gave an analytical sample, m.p. 138–140°, mixed m.p. with the *meso* isomer 125–130°, ϵ_{max} 479 at 258 mμ (C_2H_5OH).

Anal. Calcd. for $C_{17}H_{16}O_2Cl_2$: C, 63.17; H, 4.99; Cl, 21.94. Found: C, 63.42, 63.45; H, 5.08, 4.99; Cl, 21.51, 21.79.

The *meso* and DL isomers are not readily distinguished by melting point but *are* easily distinguished by their infrared spectra. The *meso* isomer (VI) has bands at 12.0 and 12.4 μ which are not present in the spectrum of the DL isomer (VII). The preference for using infrared spectra rather than physical properties to distinguish between *meso* and DL isomers was also encountered in the case of the 4,5-bis(chloromethyl)dioxolanes (VIII and IX).

4,5-Dimethylene-2,2-diphenyl-dioxolane (II). (a) *Preparation.* To 150 ml. of 2*N* ethanolic potassium hydroxide solution was added 9.75 g. (0.03 mole) of DL(or *meso*)-4,5-bis-(chloromethyl)-2,2-diphenyldioxolane (VI or VII). The solution was refluxed for 4.5 hr. under nitrogen. Dry Ice was then added with shaking followed by 250 ml. of carbon tetrachloride. The solution was filtered and the residue washed

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(17) G. W. Kilmer, M. D. Armstrong, G. B. Brown, and V. du Vigneaud, *J. Biol. Chem.*, **145**, 495 (1942).

(18) M. R. Radcliffe and W. G. Mayes, U. S. Patent **2,445,733**.

with an additional 50 ml. of carbon tetrachloride. Additional Dry Ice was added to the filtrate and the gelatinous precipitate was again filtered. The solvent was again removed from the filtrate under reduced pressure and the amorphous material obtained was dissolved in 100 ml. of carbon tetrachloride. The solvent was again removed under reduced pressure and the residue dissolved in 100 ml. of carbon tetrachloride. Filtration of the solution gave a clear, yellow filtrate. A sample of this filtrate was not basic to wet litmus paper. Removal of the solvent under reduced pressure gave a viscous orange oil which crystallized. This was dissolved in carbon tetrachloride and the solution passed through an F20 alumina[19] column (12 × 2 cm.) and eluted with carbon tetrachloride until the effluent no longer gave a positive bromine test for unsaturation. The effluent had a slightly yellow color and the column contained an immobile colored zone 0–0.5 cm. from the top. The solvent was removed from the effluent under reduced pressure to yield a very slightly yellow, heavy oil which on scratching immediately crystallized with the evolution of considerable heat. The crystals melted at 54–62°, weight 2.53 g., yield 33%.

Further attempts to purify this material by recrystallization and distillation were not successful and an analytical sample was not obtained.

The infrared spectrum of this material showed absorption at 5.5 μ (=CH_2) and a doublet at 6.0 μ. The near infrared absorption spectrum of this compound showed absorption at 1.6 μ characteristic of a terminal methylene group.

A sample of this material was suspended in water containing sulfuric acid and distilled until the distillate was no longer yellow. Addition of hydroxylamine hydrochloride and sodium acetate to the distillate followed by a solution of nickel chloride gave a scarlet red precipitate characteristic of nickel dimethylglyoxime.

(b) *Reaction with tetracyanoethylene.* To a solution of 1.02 g. (0.008 mole) of tetracyanoethylene in 20 ml. of tetrahydrofuran was added 2 g. (0.008 mole) of 4,5-dimethylene-2,2-diphenyldioxolane (II). This experiment was run in triplicate using 1) commercial tetrahydrofuran containing hydroquinone, 2) tetrahydrofuran free of hydroquinone but containing peroxides, and 3) tetrahydrofuran freshly purified and containing neither peroxides nor hydroquinone.

The commercial tetrahydrofuran gave a dark blue solution with tetracyanoethylene which changed to a dark green on adding the diene and then faded to a light green after 2 hr. After 18 hr. there was no further color change. On removing the solvent under reduced pressure a dark green oil was obtained which on trituration with ethanol yielded crystals. These were slurried with ethanol, filtered, and then recrystallized from ethanol to yield 1.56 g. of product, yield 60%, m.p. 164–166°. The tetrahydrofuran free of hydroquinone but containing peroxides gave a greenish yellow solution with tetracyanoethylene which changed to an orange-yellow color on adding the diene. After 2 hr. the solution was light yellow and after 18 hr. dark orange. This solution when worked up as described above yielded 0.15 g. of product, yield 5.8%, m.p. 165–167°. The freshly purified tetrahydrofuran gave a greenish-yellow color with tetracyanoethylene which changed to an orange-yellow color on adding the diene. After 2 hr. the color was dark yellow and no further change occurred on standing for 18 hr. Work up of this solution as described above yielded 1.91 g. of product, yield 74%, m.p. 165–166.6°.

This material after two additional recrystallizations from ethanol and drying overnight at 100° under vacuum over phosphorus pentoxide melted at 175–177°.

Anal. Calcd. for $C_{23}H_{14}N_4O_2$: C, 73.00; H, 3.73; N, 14.81; m.w. 378. Found: C, 72.79; H, 3.53; N, 15.04; m.w. 347 (Rast), 368 (in benzene).

The product (4,4,5,5-tetracyano-1,2-diphenylmethylenedioxycyclohexene-1) did not decolorize bromine in carbon tetrachloride but did decolorize potassium permanganate in acetone. The spectrum of this product showed no terminal methylene group in the 1.6 μ region and had strong sharp absorption at 5.7 μ. The nuclear magnetic resonance spectrum[20] in deuterochloroform was composed of an aromatic hydrogen peak at +99 c.p.s. of relative intensity 2.5 and a ring methylene hydrogen peak at −65 c.p.s. of intensity 1.

(c) *Attempted reaction of II with other dienophiles.* 4,5-Dimethylene-2,2-diphenyldioxolane (II) failed to yield products on attempted reaction with (a) ethylene (600 atm.) in alcoholic potassium hydroxide at 100° for 18 hr., (b) maleic anhydride in refluxing benzene for 2 hr., (c) phenylazomaleianil in benzene for 24 hr., (d) benzoquinone in benzene for 96 hr., (e) fumaronitrile in tetrahydrofuran for 48 hr., and (f) dimethyl acetylenedicarboxylate in refluxing carbon tetrachloride for 16 hr.

meso-4,5-Bis(chloromethyl)dioxolane (VIII). An intimate mixture of 119.3 g. (0.75 mole) of *meso*-1,4-dichlorobutanediol and 24 g. (0.80 mole) of paraformaldehyde was heated until a homogeneous melt was obtained. The mixture was then allowed to cool until solids began to form. An additional 1 g. of paraformaldehyde and 15 ml. of stannic chloride was then added. The mixture was heated on a steam bath for 20 hr. After cooling to room temperature, 350 ml. of 17% potassium hydroxide solution was added with cooling. A two-phase liquid resulted. The organic phase was separated and the water was extracted with three 50-ml. portions of ether. The ether extracts and the organic phase were combined, dried with sodium sulfate, filtered, and then dried with potassium carbonate. Removal of the solvent under reduced pressure gave a liquid which was vacuum distilled. A 16.71 g. forerun, b.p. 38–94° (13 mm.), was obtained whose vapor phase chromatogram indicated 8 components. A second fraction (72.92 g.) was obtained with b.p. 94–101° (13 mm.), n_D 1.482(8)–1.484(2), whose vapor phase chromatogram showed only one component. A brown oily pot residue remained (5.8 g.). A second distillation of the homogeneous fraction gave an analytical sample, b.p. 216–219.5° (762 mm.), n_D^{25} 1.484(7). The infrared spectrum is discussed in the following section.

Anal. Calcd. for $C_5H_8Cl_2O_2$: C, 35.12; H, 4.72; Cl, 41.47; m.w. 171. Found: C, 35.29; H, 4.75; Cl, 41.32; m.w. 168 (Rast).

DL-*4,5-Bis(chloromethyl)dioxolane* (IX). (a) *Preparation.* A mixture of 34.3 g. (0.216 mole) of DL-1,4-dichlorobutanediol and 6.6 g. (0.22 mole) of paraformaldehyde was heated until partially melted. To this was added 4 ml. of stannic chloride and the mixture was heated on a steam bath for 17 hr. The reaction mixture was diluted with 100 ml. of ether and 70 ml. of 17% potassium hydroxide solution was added. This mixture was initially quite viscous but thinned on shaking. The ether layer was separated and the aqueous phase was extracted with two 50-ml. portions of ether. The combined ether extracts were dried with sodium sulfate, filtered, and the solvent removed under reduced pressure. The residual liquid was distilled and after a small forerun, b.p. 40–84° (8 mm.), there was obtained 30 g. (yield 82%) of DL-4,5-bis(chloromethyl)dioxolane, b.p. 84–89° (8 mm.), n_D^{25} 1.477(0). Vapor phase chromatography indicated this material to be homogeneous. A second distillation gave an analytical sample, b.p. 85.5–86.0° (10 mm.), 212–214° (760 mm.), n_D^{27} 1.478(5) [reported[18] b.p. 102° (17 mm.)].

Anal. Calcd. for $C_5H_8O_2Cl_2$: C, 35.12; H, 4.72; Cl, 41.47; m.w. 171. Found: C, 35.25; H, 4.74; Cl, 41.47; m.w. 171 (in exaltone).

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[19] (19) Aluminum Co. of America, East St. Louis, Ill.

[20] (20) We are indebted to Mr. C. B. Matthews, who determined and interpreted the NMR spectra by means of a high resolution NMR spectrometer and associated electromagnet manufactured by Varian Associates, Palo Alto, Calif., operating at 40 Mc. and approximately 10,000 gauss. Spectra were calibrated in terms of displacements in cycles per second (c.p.s.) from the proton resonance of water. Negative frequency displacements indicate resonance occurring at higher field relative to the reference.

The physical properties of *meso*- and DL-4,5-bis(chloromethyl)dioxolane are very similar and the two compounds are not readily distinguished by boiling point or refractive index. Vapor phase chromatography of the pure compounds over didodecyl phthalate on Celite at 190° indicated a slightly greater retention time for the *meso* compound. This difference did not permit, however, a separation of a mixture of the two compounds. The compounds are most readily distinguished by their infrared spectra which although similar do possess distinct differences. The most intense peak in the 7–8 μ region is at 7.7 μ for the DL isomer and at 7.96 μ for the *meso* isomer; in the 12–13 μ region the DL compound has one peak at 12.19 μ and the *meso* isomer has peaks at 12.30 and 12.60 μ; in the 14–15 μ region the DL compound shows no peaks and the *meso* isomer has sharp absorption at 14.59 μ.

(b) *Methanolysis.* Two milliliters of DL-4,5-bis(chloromethyl)dioxolane was dissolved in 35 ml. of methanol saturated with hydrogen chloride. After 16.5 hr. the solvent was removed under reduced pressure to yield a colorless, heavy oil smelling strongly of hydrogen chloride. Seeding with DL-1,4-dichlorobutanediol caused immediate crystallization. The crystals were washed with ether and yielded 1.18 g. of DL-1,4-dichlorobutanediol, m.p. 77–78°, mixed melting point with an authentic sample, 77.0–77.5°.

4,5-Dimethylenedioxolane (I). (a) *Preparation.* A solution of 24 g. (0.6 mole) of sodium hydroxide in 27 ml. of water was added to 200 ml. of 2-(2-ethoxyethoxy)ethanol. To this was added 33.1 g. (0.193 mole) of *meso* (or DL)-4,5-bis(chloromethyl)dioxolane. The mixture was heated and vigorous boiling commenced when the pot reached 113°. Heating was continued until the pot temperature reached 144°, at which point the head temperature was 121°. The two phase distillate was collected over potassium carbonate in an ice-cooled receiver. Fifty milliliters of ether was added and the ether layer was separated from the yellow water phase. The water was extracted with an additional 50 ml. of ether and the combined ether extracts were dried with potassium carbonate to yield a colorless solution. The solution was then decanted and dried with sodium hydroxide which gave a milky solution. The solution was again decanted and lithium aluminum hydride was added. When reaction subsided the mixture was rapidly filtered and then distilled from fresh lithium aluminum hydride. After the ether forerun a fraction, b.p. 75–106.5°, was obtained followed by 4.97 g. of product, b.p. 106.5° (reported[20] b.p. 115–116°), n_D 1.472(6)–1.473(8). Vapor phase chromatography of the product indicated three trace impurities and dissection and weighing of the chromatogram indicated a purity of approximately 99%. The product gave a negative Beilstein halogen test and was more dense than water.

The ultraviolet spectrum of this compound in dioxane gave log ϵ_{max} 4.06 at 245 mμ, in excellent agreement with the value reported for 1,2-dimethylenecyclopentane, log ϵ_{max} 4.02 at 248 mμ.[1] The near infrared spectrum showed strong, sharp absorption at 1.61 μ ($C=CH_2$) and the infrared spectrum showed absorption at 5.6, 11.12, and 11.25 μ ($R_1R_2C=CH_2$) and at 5.95–6.1 μ (a poorly resolved doublet).

The compound when freshly prepared was colorless and had a sweet odor. After exposure to the air for 5–10 min. the liquid turned yellow and smelled strongly of formaldehyde and after exposure overnight it was converted to a yellow glass. Stoppered samples turned yellow but remained liquid over several weeks. The instability of the compound prevented obtaining a satisfactory analysis.

Unsuccessful attempts were made to dehydrohalogenate the starting material using sodium hydride to avoid the formation of water.

(b) *Hydrolysis.* 4,5-Dimethylenedioxolane (0.27 g.) was mixed with 10 ml. of water containing two drops of concd. hydrochloric acid. Shaking for 5 min. gave a yellow solution with a characteristic biacetyl odor and a white amorphous solid. The solution was filtered and treated with hydroxylamine hydrochloride and sodium acetate on a steam bath for several minutes. A nickel chloride solution was added and gave a red precipitate whose infrared spectrum was identical with that of an authentic sample of nickel dimethylglyoxime.[21]

(c) *Reaction with tetracyanoethylene.* To the dark blue solution prepared from 3.96 g. (0.031 mole) of tetracyanoethylene and 35 ml. of commercial tetrahydrofuran (hydroquinone inhibited) was added 3 g. (0.031 mole) of 4,5-dimethylenedioxolane. The reaction mixture became hot and within 1 min. assumed an olive-green color. The mixture was allowed to stand at room temperature for 19 hr. during which time no further change was noted. The solvent was removed under reduced pressure at room temperature to yield an initially dark blue crystalline solid which became light blue on more complete removal of the solvent. The solid was slurried with ethanol, filtered, and washed thoroughly with ethanol to yield a green filtrate which was discarded and a very slightly green crystalline solid, weight 5.9 g., yield 86%.

An analytical sample was prepared by recrystallizing from ethanol-1,2-dimethoxyethane, vacuum sublimation, and two recrystallizations from benzene to yield a white crystalline solid, m.p. 237.2–237.7° dec. (discolored at 220°).

Anal. Calcd. for $C_{11}H_6N_4O_2$: C, 58.40; H, 2.67; N, 24.77; m.w. 226. Found: C, 58.95, 59.06; H, 2.95, 3.09; N, 24.60, 24.87.

An additional recrystallization from benzene gave a solid which was dried under oil pump vacuum over phosphorus pentoxide for 2 days, m.p. 238.5–239.5 dec. Found: C, 58.75; H, 2.61; N, 25.04; m.w. 241, 226 (in acetone).

This compound (4,4,5,5-tetracyano-1,2-methylenedioxycyclohexene-1) showed infrared absorption at 5.7 μ, no terminal methylene group in the near infrared, a simple cutoff in the ultraviolet similar to that found for dihydropyran, and in particular no absorption at 280 mμ (no R_2CO). The NMR spectrum[18] in hexadeuteroacetone was composed of a ring methylene hydrogen peak at −67 c.p.s. of relative intensity 2 and a formal methylene hydrogen peak at +18 c.p.s. of intensity 1.

(d) *Attempted reaction of I with other dienophiles.* 4,5-Dimethylenedioxolane (I) failed to yield products on attempted reaction with 1) maleic anhydride in benzene for 19 hr., 2) dichloromaleic anhydride in benzene for 16 hr., 3) dimethyl acetylenedicarboxylate in benzene for 19 hr., and 4) acrolein (no solvent) for 16 hr.

4,4,5,5-Tetracyano-1,2-dimethoxycyclohexene-1. To a solution of 3.99 g. (0.0311 mole) of tetracyanoethylene in 50 ml. of commercial tetrahydrofuran was added 3.55 g. (0.0311 mole) of 2,3-dimethoxybutadiene.[3] The solution became quite hot and the initial blue color changed to an olive green within 1 min. and to a light green within 5 min. After standing overnight the solvent was removed under reduced pressure at room temperature to yield 7.38 g. of a blue solid, yield 98%. Two recrystallizations from benzene followed by three recrystallizations from ethanol yielded an analytical sample, m.p. 95.2–96.5°.

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.14; m.w. 242. Found: C, 59.68, 59.50; H, 4.11, 4.05; N, 23.22, 23.08; m.w. 253 (Rast).

The infrared spectrum of this compound showed strong, sharp absorption at 5.89 μ. The NMR spectrum[19] in deuterochloroform was composed of a methyl hydrogen peak at −44 c.p.s. of relative intensity 1.5 and a methylene hydrogen peak at −67 c.p.s. of intensity 1.

2,2,3,3-Tetracyano-5,8-dioxaoctalin. To a solution of 12.8 g. (0.10 mole) of tetracyanoethylene in 60 ml. of purified tetrahydrofuran cooled to 10° was added in small portions 13.75 g. (0.123 mole) of 2,3-dimethylene-dioxane,[2] diluted with a equal volume of tetrahydrofuran. A very vigorous exothermic reaction ensued, the solution boiled, and a dark red color was produced which instantly faded after each addition. When addition was complete the solution was light yellow and darkened as the solution cooled to room temperature. After standing for 1 hr. the solvent was removed under reduced pressure to yield a yellow solid. One recrystallization from 1,2-dichloroethane gave 17.56 g. of product, yield 73%, m.p. 196.2–198.4° (sealed tube). An additional recrystallization from 1,2-dichloroethane followed by vacuum sublimation gave an analytical sample, m.p. 198.2–199.4° (sealed tube).

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[21] Kindly provided by Dr. L. G. Donaruma of this laboratory.

Anal. Calcd. for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.33; m.w. 240. Found: C, 60.16, 60.15; H, 3.53, 3.57; N, 23.48, 23.52; m.w. 251, 248 (Rast).

This compound showed strong, sharp absorption at 5.82 μ.

Dimethyl 5,8-dioxaoctalin-cis-2,3-dicarboxylate. A solution of 3.4 g. (0.0162 mole) of 5,8-dioxaoctalin-*cis*-2,3-dicarboxylic anhydride[2] in 100 ml. of methanol was allowed to stand at room temperature for 4 hr. followed by refluxing for 17 hr. To this solution was added an ethereal solution of diazomethane until a permanent yellow color was obtained and the solution was no longer acidic to moist litmus paper. Removal of the solvent under reduced pressure gave a slightly yellow oil. Freezing this oil in a stoppered flask in Dry Ice and allowing to warm spontaneously to room temperature initiated crystallization to give a product, m.p. 77–81°. Recrystallization from boiling methanol-ether (1:1 by volume) gave 3.03 g. of product, yield 73%, m.p. 83°, mixed m.p. 61–65° with a sample of starting material, m.p. 84–85°. Three additional recrystallizations from methanol-ether followed by drying overnight at room temperature over phosphorus pentoxide gave an analytical sample, m.p. 82.0–83.0°.

Anal. Calcd. for $C_{12}H_{16}O_6$: C, 56.25; H, 6.30; sap. eq. 128. Found: C, 56.16, 56.34; H, 6.40, 6.41; sap. eq. 135, 127.

The anhydride starting material showed infrared absorption at 5.4 and 5.61 (—CO—O—CO—) and 5.86 μ. The dimethyl ester showed absorption at 5.72 (—CO_2CH_3) and 5.82 μ.

meso-4,5-Bis(chloromethyl)-2,2-dimethyldioxolane. (a) *Preparation.* To a stirred solution of 5 ml. of stannic chloride in 100 ml. of carbon tetrachloride was added dropwise a solution of 24 ml. of acetone and 39.5 g. of DL-2,3-bis(chloromethyl)oxirane in 75 ml. of carbon tetrachloride. Addition was carried out over 2 hr. and the mixture was then stirred an additional 17 hr. A solution of 20 g. of 85% potassium hydroxide in 80 ml. of water was added with shaking. The organic phase was separated, washed free of base with water, and dried with sodium sulfate. The carbon tetrachloride was removed under vacuum with a hot water bath and the residual bright yellow liquid was distilled through a 15 cm. Vigreux column. The distillate weighed 33.56 g., b.p. 75–92° (10 mm.), n_D^{22} 1.466(2)–1.468(8). A second distillation gave 3 fractions: (a) b.p. 48–88° (8 mm.), n_D^{21} 1.468(2), 8.79 g.; (b) b.p. 88–90° (8 mm.), n_D^{21} 1.468(5), 7.60 g.; (c) b.p. 90–91° (8 mm.), n_D^{21} 1.468(0), 14.25 g. Vapor phase chromatography indicated all fractions contained epoxide starting material, an unidentified component, and the major component (assumed to be product). The chromatograms when dissected and weighed indicated the following approximate percentage compositions: fraction (a), 64.3% product, 33.1% epoxide, 2.5% unknown; fraction (b), 87.8% product, 9.8% epoxide, 2.3% unknown; fraction (c), 97.3% product, 1.0% epoxide, 1.7% unknown. Fraction (c) was analyzed.

Anal. Calcd. for $C_7H_{12}O_2Cl_2$: C, 42.22; H, 6.08; Cl, 35.62 m.w. 199. Found: C, 42.21; H, 6.07; Cl, 35.89; m.w. 194, 209 (in exaltone).

(b) *Methanolysis.* Two milliliters of *meso*-4,5-bis(chloromethyl)-2,2-dimethyldioxolane (fraction C above) was dissolved in 35 ml. of methanol saturated with hydrogen chloride. At the end of 66 hr. the solution was black. The solvent was removed under reduced pressure to yield an amber colored solid. Water (100 ml.) was added with heating and the solution was treated with 0.5 teaspoon of Darco G60. Filtration yielded a very slightly yellow filtrate. Removal of the solvent under reduced pressure gave a white solid, 1.31 g., m.p. 125.5–129.5°, mixed m.p. 127–130° with authentic *meso*-1,4-dichloro-butanediol.

DL-*4,5-Bis(iodomethyl)-2,2-diphenyldioxolane.* Sodium iodide (30 g., 0.2 mole) was mixed with 100 g. of acetonylacetone and heated to 115°. The resulting dark colored solution was cooled to 40° and 16.25 g. (0.05 mole) of DL-4,5-bis(chloromethyl)-2,2-diphenyldioxolane was added. The solution was then heated to 155–165° for 4 hr. during which time the solution turned black and water and 2,5-dimethylfuran were distilled. The black solution was diluted with water and filtered to yield a black, highly crystalline residue. The residue was washed with sodium iodide solution, ether, and carbon tetrachloride. The residue was then washed very thoroughly with hot water, followed again by ether and carbon tetrachloride to yield 7.40 g. of a dark brown, highly crystalline solid, m.p. 191–193°. This solid on ignition liberated iodine and left no residue. The infrared spectrum of this material was nearly identical with the starting material. An analytical sample was prepared by recrystallizing twice from carbon tetrachloride and twice from *n*-butyl alcohol to a constant melting point, 190–191°.

Anal. Calcd. for $C_{17}H_{16}I_2O_2$: C, 40.34; H, 3.19; I, 50.15; m.w. 506. Found: C, 40.32; H, 3.34; I, 49.93; m.w. 512 (Rast).

The ultraviolet spectrum of this compound in methylene chloride showed the expected benzenoid form and absorption at 258 mμ but the ϵ_{max} was three to four times the expected value (400–500) and showed marked changes with concentration: ϵ_{max} 1620 for 1.6 × $10^{-3}M$, 1500 for 3.2 × $10^{-3}M$, 1440 for 7.9 × $10^{-3}M$, 1430 for 8.1 × $10^{-3}M$, 1240 for 15.8 × $10^{-3}M$, and 1170 for 16.2 × $10^{-3}M$.

Acknowledgment. We are grateful to Dr. Bryce Crawford for helpful discussions regarding this work and his own work prior to publication.

WILMINGTON, DEL.

[CONTRIBUTION FROM THE INSTITUTE OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF PISA]

Reaction of *cis*- and *trans*-Stilbene with Peroxybenzoic Acid in the Presence of Trichloroacetic Acid

GIANCARLO BERTI AND FRANCESCO BOTTARI

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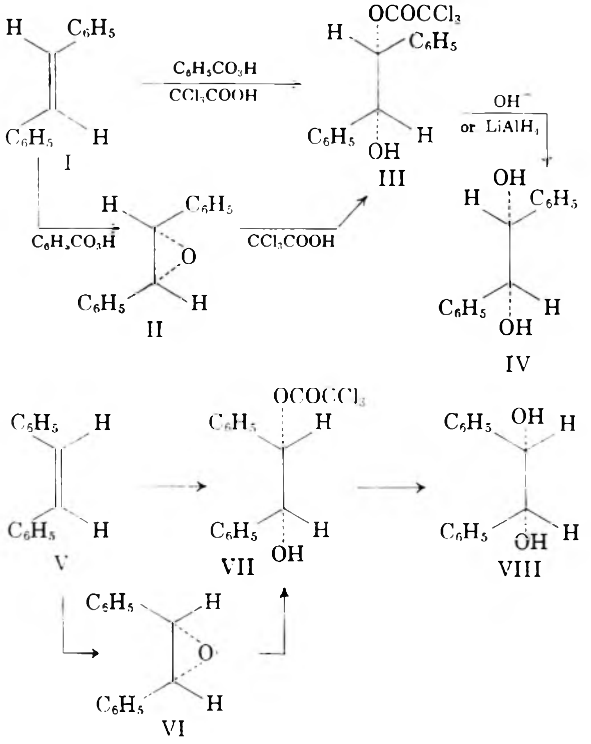
It has been found that the rate of the reaction of peroxybenzoic acid with *cis*- and *trans*-stilbene is considerably increased by addition of trichloroacetic acid, in contrast to previous results with weaker acids. The monotrichloroacetates of the hydrobenzoins are formed by *cis*-addition, in a completely stereospecific way, as the main products of these reactions. The same products were obtained by treating *cis*- and *trans*-stilbene oxide with trichloroacetic acid. The kinetics of these reactions has been studied. The results are discussed, making some suggestions about a mechanism that could explain them. The absolute configurations of the optically active hydrobenzoins have been established.

Previous work[1] on the kinetics of the formation of hydroxy lactones from the stilbene-2-carboxylic acids with peroxybenzoic acid[2] had shown that these reactions are catalyzed by trichloroacetic acid. As these results are in contrast with the fact that the reactions of olefins with peroxyacids are not liable to acidic catalysis,[3] it was thought interesting to investigate the influence of trichloroacetic acid on the reactions of the isomeric stilbenes with peroxybenzoic acid, whose kinetics have been studied extensively.[3c,d] As expected, a very definite catalytic effect was observed in this case, too: reaction rates increased sharply with increasing acid concentrations. The epoxides (II and VI) were not isolated, the diastereomeric hydrobenzoin monotrichloroacetates (III and VII) being obtained instead, as the main products. They were formed in a stereospecific way and isolated in 72 and 44% yields, respectively, starting from *trans*- or *cis*-stilbene. The transformation of these esters into the corresponding hydrobenzoins, both by alkaline hydrolysis and by reduction with lithium aluminum hydride (to avoid inversions), proved their configurations. The fact that the esters obtained from *trans*- and from *cis*-stilbene respectively gave the (±)- and the *meso*-glycol (IV and VIII) showed that the reactions involve *cis*-addition of the OH and CCl_3CO_2 groups to the ethylenic double bonds of the stilbenes.



The same trichloroacetates (III and VII) were obtained in better yields from the stilbene oxides (II and VI) with trichloroacetic acid in benzene. Oily by-products were also formed which contained 15–20% of carbonyl compounds, as shown by precipitation with 2,4-dinitrophenylhydrazine. Fractional crystallization of the 2,4-dinitrophenylhydrazones yielded mainly diphenylacetaldehyde-2,4-dinitrophenylhydrazone and a small amount of benzophenone-2,4-dinitrophenylhydrazone. No reasonable explanation can be given for the presence of the latter compound. No evidence was found for the formation of desoxybenzoin. 2,4-Dinitrophenylhydrazones were not obtained from the by-products of the reactions of the stilbenes with peroxybenzoic and trichloroacetic acid. This cannot be considered as a proof that the formation of the esters (III and VII) follows different routes in the two cases, because the carbonyl compounds could be formed and further transformed by the peroxy acid through a Baeyer-Villiger oxidation.

More stereochemical information was sought through the use of the optically active *trans*-stilbene oxides, which can be obtained easily from (+)- and (−)-*erythro*-α,β-diphenyl-β-hydroxyethyl-

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[1] G. Berti and F. Bottari, *Gazz. chim. ital.*, **89**, 2380 (1959).

[2] G. Berti, *J. Org. Chem.*, **24**, 934 (1959).

[3] (a) J. Boeseken and J. Stuurmann, *Rec. trav. chim.*, **56**, 1034 (1937); (b) S. Medvedev and O. Bloch, *J. Phys. Chem. U.S.S.R.*, **4**, 721 (1933); (c) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955); (d) D. R. Campbell, J. O. Edwards, J. Maclachlan, and K. Polgar, *J. Am. Chem. Soc.*, **80**, 5308 (1958).

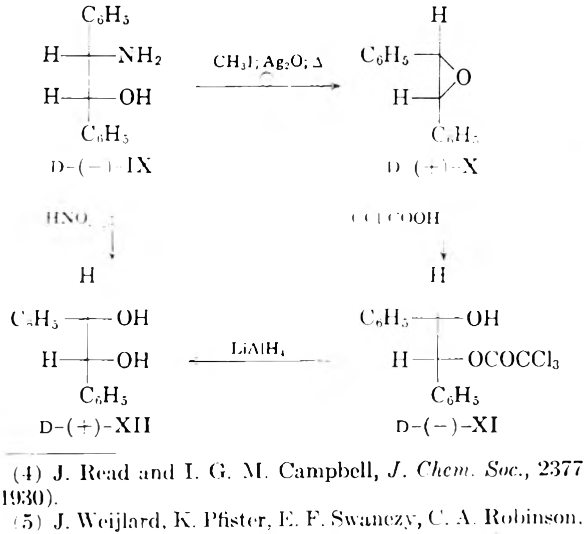
TABLE I

RESULTS OF KINETIC RUNS AT 25°

Run No.	[CCl_3COOH], Mole/L.	[Stilbene], Mole/L.	[$C_6H_5CO_3H$], Mole/L.	Equation[a]	Range of $k_{2.5}$, Mole^{-1} L. Sec^{-1} × 10^2	Trend of $k_{2.5}$	Equation[a]	Range of k_3, Mole^{-1} L. Sec^{-1} × 10^2	Trend of k_3
	trans-Stilbene								
1	0.0333	0.0333	0.0333	Ia	1.18 –1.03	Decr.	Ib	4.67–4.81	Incr.
2	0.0412	0.0412	0.0412	Ia	0.940–0.954	None	Ib	3.17–4.51	Incr.
3	0.0666	0.0333	0.0333	IIa	1.31 –1.21	Decr.	IIb	3.76–3.63	None
4	0.0666	0.3330	0.0333	IVa	1.40 –1.18	Decr.	IVb	3.60–3.27	Decr.
5	0.0665	0.0665	0.0665	Ia	0.915–0.925	None	Ib	2.61–3.19	Incr.
6	0.0746	0.0746	0.0746	Ia	0.980–1.00	None	Ib	2.88–3.47	Incr.
7	0.0814	0.0407	0.0814	IIIa	1.02 –1.09	Incr.	IIIb	2.44–2.95	Incr.
8	0.1110	0.0555	0.0555	IIa	1.29 –1.23	Decr.	IIb	2.82–2.96	Incr.
9	0.1110	0.0555	0.0555	IIa	1.40 –1.31	Decr.	IIb	3.08–3.14	None
10	0.2055	0.1028	0.1028	IIa	1.57 –1.44	Decr.	IIb	2.55–2.45	None
11	0.4590	0.0459	0.0459	Va	2.13 –2.35	Incr.	Vb	2.22–2.46	Incr.
12	0.6070	0.0300	0.0300	Va	2.16 –2.23	None	Vb	1.96–2.02	None
13	0.7938	0.0460	0.0460	Va	2.19 –2.32	None	Vb	1.71–1.84	None
	cis-Stilbene								
14	0.0563	0.0563	0.0563	Ia	1.09 –1.16	Incr.	Ib	3.38–4.04	Incr.
15	0.0814	0.0814	0.0814	Ia	1.05 –1.08	None	Ib	2.81–3.50	Incr.
16	0.4592	0.0563	0.0563	Va	1.74 –2.00	Incr.	Vb	1.82–2.10	Incr.

[a] See Table II.

amine (IX).[4] The (−)-epoxide, derived from (+)-IX, yielded the (+)-trichloroacetate, which was transformed by lithium aluminum hydride into a (−)-hydrobenzoin having the expected specific rotation; this offered a further proof of the stereospecificity of the reaction. The absolute configurations of the α,β-diphenyl-β-hydroxyethylamines are known.[5] Their transformation into the epoxides through the quaternary hydroxides should involve an inversion only on the carbon atom carrying the amino group. Therefore, the (+)-epoxide should have the D-configuration (X), and the (−)-trichloroacetate (XI), as well as the (+)-hydrobenzoin (XII), should belong to the D-series too, unless an extremely unlikely double inversion is involved. The absolute configurations of the hydrobenzoins were not known before, but our findings agree with some results of Read and Steele,[6] who obtained (+)-hydrobenzoin in low yield from the product of the reaction of (−)-*erythro*-IX with nitrous acid. This reaction should proceed without inversion on the β-carbon atom. Therefore, configuration XII must follow for the (+)-glycol.[7]



The opening of an epoxide ring in a *cis* way, although it is contrary to the normal rule, is no longer to be considered as an exception for stilbene derivatives, in the light of several examples in the recent literature of partial or total retention of configuration in the acid-catalyzed cleavage of oxiranes carrying at least one phenyl group on the ring.[8] Ours seems, however, to be the first case of a complete *cis*-stereospecificity in an addition of this type to the two unsubstituted stilbenes and to their oxides. The present reactions have the advantage over similar ones,[3d,9,10] of being faster (a few hours, instead of days), or giving, especially in the *trans* series, pure glycol esters with only one crystallization and in reasonably good yields. They can be interesting as preparative methods, partic-

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(4) J. Read and I. G. M. Campbell, *J. Chem. Soc.*, 2377 (1930).

(5) J. Weijlard, K. Pfister, E. F. Swanezy, C. A. Robinson, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 1216 (1951).

(6) J. Read and C. C. Steele, *J. Chem. Soc.*, 910 (1927).

(7) This matter, however, is not at all clear and is being investigated further, because there is no agreement between the results of Read and Steele, who found that with nitrous acid both the (−)-*erythro* and the (+)-*threo*-diphenylhydroxyethylamines give the same (+)-glycol (XII), and those of Weijlard and co-workers (ref. 5), who showed that the two aminoalcohols have the opposite configurations on the β-carbon; either the latter assumption is wrong, or one of the reactions with nitrous acid gives an inversion on the β-carbon.

(8) For a recent review of this topic, see ref. 17.

(9) B. Witkop and C. M. Foltz, *J. Am. Chem. Soc.*, **79**, 197 (1957).

(10) D. Y. Curtin, A. Bradley, and Y. G. Hendrickson, *J. Am. Chem. Soc.*, **78**, 4064 (1956).

TABLE II

EQUATIONS

No.	Ratio of Concn.[a]	Order	Differential Equations	Integrated Equations
Ia	1:1:0.5	2.5	$\frac{dx}{dt} = k_{2.5}(a - x)^2 \left(\frac{a - x}{2}\right)^{0.5}$	$k_{2.5} = \frac{0.9428}{t}\left[\frac{1}{(a - x)^{1.5}} - \frac{1}{a^{1.5}}\right]$
Ib	1:1:1	3	$\frac{dx}{dt} = k_3(a - x)^3$	$k_3 = \frac{1}{2t}\left[\frac{1}{(a - x)^2} - \frac{1}{a^2}\right]$
IIa	1:1:1	2.5	$\frac{dx}{dt} = k_{2.5}(a - x)^2 \left(a - \frac{x}{2}\right)^{0.5}$	$k_{2.5} = \frac{2}{ta}\left[\frac{\sqrt{a - \frac{x}{2}}}{a - x} - \frac{0.5756}{\sqrt{\frac{a}{2}}}\log\frac{\sqrt{a - \frac{x}{2}} + \sqrt{\frac{a}{2}}}{\sqrt{a - \frac{x}{2}} - \sqrt{\frac{a}{2}}} - \frac{0.2664}{\sqrt{\frac{a}{2}}}\right]$
IIb	1:1:2	3	$\frac{dx}{dt} = k_3(a - x)^2(2a - x)$	$k_3 = \frac{1}{ta^2}\left[\frac{x}{a - x} + 2.303 \log\frac{a - x}{a - \frac{x}{2}}\right]$
IIIa	1:2:1	2.5	$\frac{dx}{dt} = k_{2.5}(a - x)(2a - x)\left(a - \frac{x}{2}\right)^{0.5}$	$k_{2.5} = \frac{2.828}{ta}\left[-\frac{1}{\sqrt{2a - x}} + \frac{1.1513}{\sqrt{a}}\log\frac{\sqrt{2a - x} + \sqrt{a}}{\sqrt{2a - x} - \sqrt{a}} - \frac{0.1742}{\sqrt{a}}\right]$
IIIb	1:2:2	3	$\frac{dx}{dt} = k_3(a - x)(2a - x)^2$	$k_3 = \frac{1}{ta^2}\left[2.303 \log\frac{2a - x}{a - x} - \frac{a}{2a - x} - 0.193\right]$
IVa	high:1:1[b]	2.5	$\frac{dx}{dt} = k_{2.5}[\text{stilbene}](a - x)\left(a - \frac{x}{2}\right)^{0.5}$	$k_{2.5} = \frac{3.256}{t\sqrt{a}[\text{stilbene}]}\left[\log\frac{\sqrt{a - \frac{x}{2}} + \sqrt{\frac{a}{2}}}{\sqrt{a - \frac{x}{2}} - \sqrt{\frac{a}{2}}} - 0.7655\right]$
IVb	high:1:2 [b]	3	$\frac{dx}{dt} = k_3[\text{stilbene}]\,(a - x)\,(2a - x)$	$k_3 = \frac{2.303}{ta[\text{stilbene}]}\log\frac{a - \frac{x}{2}}{a - x}$
Va	1:1:high[b]	2.5	$\frac{dx}{} = k_{2.5}(a - x)^2[(CCl_3COOH)_2]^{0.5}$	$k_{2.5} = \frac{1}{t[(CCl_3COOH)_2]^{0.5}}\left[\frac{1}{a - x} - \frac{1}{a}\right]$
Vb	1:1:high[b]	3	$\frac{dx}{dt} = k_3(a - x)^2[CCl_3COOH]$	$k_3 = \frac{1}{t[CCl_3COOH]}\left[\frac{1}{a - x} - \frac{1}{a}\right]$

[a] [Stilbene]: $[C_6H_5CO_3H]$: $[(CCl_3COOH)_2]^{0.5}$ for the equations of order 2.5; [stilbene]: $[C_6H_5CO_3H]$: $[CCl_3COOH]$ for those of order 3. [b] The concentration of one of the reactants is considered constant, being much higher than those of the other two.

ularly for the optically active hydrobenzoins, which are quite difficult to prepare otherwise.

Kinetic measurements were carried out by following the disappearance of peroxybenzoic acid iodometrically, and in some cases that of stilbene spectrophotometrically. *trans*-Stilbene, which is more easily purified, was used for most determinations, but a few comparative runs were also made with *cis*-stilbene. The results obtained in a series of determinations, with trichloroacetic acid concentrations ranging from 0.033 to 0.79*M* did not fit well into a third order rate expression because, although some single runs gave rather constant values for k_3 up to more than half-life, other ones were much worse; the calculated constants showed a very sharp decrease with increasing acid concentrations (see Table I). In our previous work on the kinetics of the reactions of the stilbene-2-carboxylic acids with peroxybenzoic acid,[1] in which the trichloroacetic acid concentrations remained constant throughout the runs, we had found that the pseudo-second order rate constants were roughly proportional to the square roots of these concentrations. Therefore, the present results were calculated also on the basis of a rate equation of order 2.5:

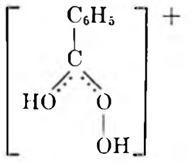
$$-\frac{d[C_6H_5CO_3H]}{dt} = k_{2.5}\ [\text{stilbene}][C_6H_5CO_3H]\ [(CCl_3CO_2H)_2]^{0.5} \quad (1)$$

As the integration of this differential equation is rather complicated, the ratios of initial concentrations of the reactants were chosen in such a way as to give somewhat simpler expressions. Table I shows the values of $k_{2.5}$, as calculated by means of the integrated equations given in Table II. These figures, although they are better for most of the runs than those obtained by third order kinetics, show a tendency to increase with increasing acid concentrations. A comparison of the two series of values ($k_{2.5}$ and k_3), the one increasing while the other decreases, seems to indicate that the order in trichloroacetic acid is not constant, changing between 0.5 and 1. This is confirmed by the fact that for single runs the values of $k_{2.5}$ show mostly a trend to decrease, those for k_3 to increase with time (see Table I, columns 7 and 10), according to what would be expected for rate constants calculated by a rate expression of too low or too high order, respectively.

The kinetic results can be explained, as assumed before,[1] by the hypothesis that trichloroacetic acid, present in part as a dimer, is involved in the rate-determining step. This acid, which is a very strong proton donor in nonpolar solvents, could act as a catalyst for the reaction by protonating the peroxy acid in an equilibrium reaction (2).

$$CCl_3CO_2H + C_6H_5CO_3H \rightleftarrows (CCl_3CO_2^-C_6H_5CO_3H_2^+) \quad (2)$$

The reactive intermediate would therefore be an ion-pair,[11] in which the cation, possibly of the form XIII,


XIII

would be a stronger donor of OH^+ than the peroxybenzoic acid molecule. A rate-determining bimolecular reaction would thus take place between this intermediate and the olefin, which would however be dependent on the trichloroacetic acid concentration, if, as likely, the equilibrium in (2) is reached rapidly and its constant K is small. The over-all kinetics should be third order, with an observed constant $k_3 = Kk_2$, because the concentration of the reactive ion-pair would be given by

$$[(CCl_3CO_2^-C_6H_5CO_3H_2^+)] = K[CCl_3CO_2H][C_6H_5CO_3H]$$

and the rate expression by

$$-\frac{d[C_6H_5CO_3H]}{dt} = Kk_2[\text{stilbene}][C_6H_5CO_3H][CCl_3CO_2H]$$

It is known,[12] however, that trichloroacetic acid is present as a dimer in benzene solutions. Equation (2) should therefore be replaced by the following:[13]

$$(CCl_3CO_2H)_2 + 2\ C_6H_5CO_3H \rightleftarrows 2(CCl_3CO_2^-\ C_6H_5CO_3H_2^+) \quad (3)$$

which would give the rate expression (1), where $k_{2.5} = k_2K^{0.5}$.

The fact that different runs gave results which indicated reaction orders varying between 2.5 and 3 could be explained by assuming that trichloroacetic acid was present only partially, and in different amounts, as a dimer. This could be caused by the presence of small quantities of water, which were hard to avoid, because of the hygroscopicity of the acid and the difficulty in drying completely the peroxy acid solutions without decomposing them. Bell and Arnold[12] found that trichloroacetic acid combines with water to give a 1:1 addition product which is monomeric in dilute benzene solutions, while at higher concentrations (around 0.7*M*), even in the presence of water, all of the acid is present as a dimer. This was confirmed by runs 11 to 13, in which the trichloro-

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(11) A similar hypothesis of a complex formation between peroxyacids and other acids was made by Swern in *Organic Reactions*, 7, 378 (1953). He based his data, however, on acidic catalysis in epoxidation reactions only on cases of different types of oxidations, as pointed out by Lynch and Pausacker (ref. 3c).

(12) R. P. Bell and M. H. M. Arnold, *J. Chem. Soc.*, 1432 (1935).

(13) This trimolecular equation is assumed for the sake of simplicity, but it probably is the resultant of two rapid subsequent bimolecular steps, which should give the same kinetic results.

acetic acid concentrations were much higher than those of the other reactants and were therefore practically constant throughout the reaction: the rate constants were calculated by the second order kinetic equation and divided by the square roots of the dimer concentrations, or by the monomer concentrations, to obtain $k_{2.5}$ or k_3. Constancy was better for $k_{2.5}$.

The discrepancies in some of our results could also be explained by the following sources of errors. 1) Our calculations do not take into account the normal uncatalyzed reaction between the stilbenes and peroxybenzoic acid, which is much slower, but could have some importance in the runs with low catalyst concentration. 2) Decomposition of the peroxyacid by side-reactions (some runs, which were followed both iodometrically and spectrophotometrically, showed that there is a little difference between the rates of disappearance of the peroxy acid and of stilbene, the former being usually somewhat higher). 3) The yields of the esters III and VII are not quantitative; as the side-products do not contain chlorine, the disappearance of trichloroacetic acid is slower than expected. 4) Different lots of trichloroacetic acid were used. 5) The presence of trichloroacetic acid changes the dielectric constant of the solvent; this could affect the rate, particularly at the higher concentrations. Apparently, however, all these possible sources of error are not too important.

The fact that *cis*-stilbene, which in the uncatalyzed reaction with peroxybenzoic acid reacts almost twice as fast as *trans*-stilbene,[3c] seems to be oxidized at about the same rate as the *trans*-isomer in the presence of trichloroacetic acid (see Table I) is not easy to explain in the light of the mechanism discussed above. However, solutions of *cis*-stilbene in benzene slowly developed a pink color, later turning to blue, in the presence of an excess of trichloroacetic acid. This could be due to a protonation of the ethylenic double bond, a reaction that would interfere with the electrophilic attack by the peroxyacid. Washing with alkali after twenty-four hours led to the recovery of a product that still had the ultraviolet absorption spectrum of *cis*-stilbene but only about 80% of its extinction coefficients. Probably a slow transformation into a dimer or polymer takes place, as in the case of the reaction of 1,1-diphenylethylene with trichloroacetic acid.[14] *trans*-Stilbene does not give any color and is recovered unchanged under similar conditions.

The question could be raised as to why acidic catalysis of the reactions of olefins with peroxyacids apparently has not been observed before. The results in the literature are based, however, on tests with relatively weak acids: acetic,[3a] benzoic,[3c,d] and substituted benzoic.[3b] Probably only strong acids can produce ions of type XIII in significant amounts.

An alternative explanation of the catalytic action could be found in an exchange between trichloroacetic and peroxybenzoic acid, with formation of peroxytrichloroacetic acid, certainly a very strong epoxidizing agent. This hypothesis, that could possibly agree with our kinetic results, is, however, very unlikely if one has in mind the results of Hawthorne and co-workers,[15] who found that no such exchange takes place between a strong acid and a weak peroxyacid, and those of Campbell and co-workers,[3d] who did not observe any exchange of C^{14} between benzoic and peroxybenzoic acid.

The present kinetic data do not allow one to distinguish between a reaction path involving slow formation of an epoxide, followed by a rapid reaction with trichloroacetic acid, or direct interaction between a cationic intermediate of the peroxidation and the anion. No precise measurements of the rate of addition of trichloroacetic acid to the epoxides II and VII were made, but it was found, using the optically active *trans*-epoxides, that the half-life at 20° is smaller than one minute and that, therefore, this step could not influence the over-all reaction rate. It appears likely, anyway, that the epoxide does not form at all in the presence of trichloroacetic acid; a cationic intermediate, corresponding to the forms XIVa or XIVb, should react rapidly inside a cage of solvent with the trichloroacetic anion to give the esters III and VII, rather than lose a proton and yield the epoxides. The same intermediates would of course be obtained also from the epoxides and trichloroacetic acid. The differences in the yields of the trichloroacetates obtained from the stilbenes and from the epoxides could well be justified by some side-reactions produced by the peroxybenzoic acid, without assuming different mechanisms in the main reactions. The *cis*-stereospecificity could be explained, as postulated by Brewster[16] for the reactions of *trans*-α-methylstilbene oxide with acetic acid, by a steric course determined by the reciprocal position of anion and cation in the ion-pairs XIV. It is therefore not necessary to assume the formation of a phenonium ion and a double inversion, as suggested by Parker and Isaacs[17] to account for the *cis*-addition of peroxybenzoic acid to the *p*-methoxystilbenes, even if the rearrangement, which in our case produces diphenylacetaldehyde as a side-product, could involve such an intermediate. The same aldehyde, which is not a transformation product of the esters III and VII, was also obtained

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(14) A. G. Evans, N. Jones, and J. H. Thomas, *J. Chem. Soc.*, 1824 (1955).

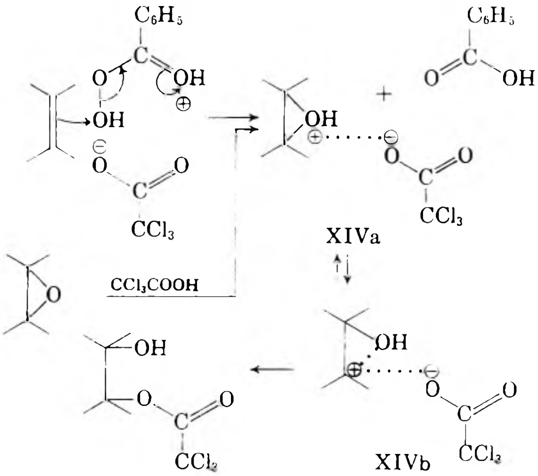
(15) M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *J. Am. Chem. Soc.*, **80**, 6393 (1958).

(16) J. H. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956).

(17) R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 757 (1959).

by House[18] from the stilbene oxides with boron trifluoride and with magnesium bromide.

The present results must be integrated with many more tests, using different solvents, acids, and olefins, before a complete picture of the stereochemistry and mechanism of these reactions is available. We are continuing our work on this line.[19]



EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are not corrected.

Materials. Thiophene-free benzene was distilled over sodium. Commercial *trans*-stilbene, crystallized twice from ethanol, melted at 123.5–124.5°. *cis*-Stilbene was prepared by the method of Buckles and Wheeler[20] and was distilled twice: b.p. 96–98/1 mm., n^{20}_{D} 1.6230. Solutions of peroxybenzoic acid in benzene were prepared by the method of Braun,[21] as modified by Kolthoff and co-workers,[22] dried over magnesium sulfate, then over calcium sulfate, and stored in a refrigerator; kinetic determinations were carried out with solutions not older than 2–3 days. *cis*- and *trans*-Stilbene oxides, prepared from the stilbenes with peroxybenzoic acid and recrystallized once from 70% ethanol, once from petroleum ether, melted at 40–42° and 70–71°, respectively. The optically active forms of *trans*-stilbene oxide were prepared by the method of Read and Campbell,[4] based on the steam-distillation of the quaternary hydroxides obtained from (+)- and (−)-*erythro*-α,β-diphenyl-β-hydroxyethylamine. The (−)-hydroxy amine yielded the (+)-epoxide, m.p. 69–70°, $[\alpha]^{21}_{D}$ +365° (*c* 0.500, benzene), the (+)-hydroxyamine gave the (−)-epoxide, m.p. 69–70°, $[\alpha]^{20}_{D}$ −370° (lit.,[4] m.p. 69–70°, $[\alpha]_{D}$ −374°) Chemically pure trichloroacetic acid was distilled under a pressure of 1 mm.; only center cuts were used.

(±)-*threo-α-Hydroxy-α′-trichloroacetoxybibenzyl* (III). a) A solution of 0.90 g. (0.005 mole) of *trans*-stilbene, 0.006 mole of peroxybenzoic acid, and 0.006 mole of trichloroacetic acid in 60 ml. of benzene stored at room temperature for 2 days, was extracted with 20 ml. of sodium carbonate solution, and was washed with 10 ml. of water. The solvent was distilled and the residue, treated with 20 ml. of boiling petroleum ether (b.p. 40–70°), yielded 1.30 g. (72%) of needles, m.p. 115.5–116.5°.

Anal. Calcd. for $C_{16}H_{13}O_3Cl_3$: C, 53.43; H, 3.64; Cl, 29.58. Found: C, 53.63; H, 3.64; Cl, 28.93.

After elimination of the solvent from the mother liquor, an oil remained which gave only a trace of a precipitate with 2,4-dinitrophenylhydrazine reagent.

b) A solution of 0.98 g. (0.005 mole) of *trans*-stilbene oxide and 0.006 mole of trichloroacetic acid in 60 ml. of benzene, stored overnight at room temperature and treated as described in a), gave 1.40 g. (78%) of needles, m.p. 115.5–116.5°, which were found to be identical with the product from the reaction a). The oil which remained after evaporation of the solvent was dissolved in 20 ml. of ethanol and treated with a reagent prepared from 0.4 g. of 2,4-dinitrophenylhydrazine[23]: a precipitate of mixed 2,4-dinitrophenylhydrazones (0.3 g.), melting between 135 and 165°, was formed. After two crystallizations from ethyl acetate it yielded 0.07 g. of an orange product, m.p. 240–241°. Concentration of the ethyl acetate solutions and dilution with ethanol gave a yellow compound, melting, after recrystallization from ethanol, at 149–151°. The identities of the two products as benzophenone 2,4-dinitrophenylhydrazone and diphenylacetaldehyde 2,4-dinitrophenylhydrazone[18] were established by mixed melting points and comparison of the infrared spectra with those of authentic samples. The above reaction has been carried out several times, with different amounts of trichloroacetic acid and reaction times ranging from 10 min. to several days: the yields of III were quite constant (71–78%).

L-(+)- *and* D-(−)-*threo-α-Hydroxy-α′-trichloroacetoxybibenzyl* (XI). The reaction was repeated by method b), using optically active *trans*-stilbene oxide. A solution of 0.359 g. (0.0018 mole) of the (−)-epoxide, $[\alpha]^{20}_{D}$ −370° and 0.0036 mole of trichloroacetic acid in 25 ml. of benzene was immediately transfered into a 10 cm. polarimeter tube. After 1 min. the observed rotation was −0.50° (calcd. initial value, −5°). After 45 min. it had changed to +0.21° and it remained stable at this value. The solution was washed with sodium carbonate, dried, and evaporated. The residue crystallized from petroleum ether (b.p. 40–70°) as prisms (0.470 g., 71.5%), m.p. 119–120.5°, $[\alpha]^{16}_{D}$ +10.9° (*c* 2.878, benzene). The mother liquor gave, after evaporation, an oily residue of 0.157 g., $[\alpha]^{18}_{D}$ +5.5°. Similarly, starting from 0.332 g. of the (+)-epoxide ($[\alpha]^{21}_{D}$ +365°), 0.441 g. (71%) of product, m.p. 119–121°, $[\alpha]^{18}_{D}$ −11.1 (*c* 2.750, benzene) was obtained, together with 0.09 g. of an oil, $[\alpha]^{17}_{D}$ −5.0°. When equal weights of the two enantiomeric products were crystallized from petroleum ether, optically inactive needles, m.p. 115.5–116.5°, were obtained, which did not depress the melting point of the racemic III.

(±)-*erythro-α-Hydroxy-α′-trichloroacetoxybibenzyl* (VII). *cis*-Stilbene (1.5 g., 0.0083 mole), treated, as described in a) for the *threo*-isomer, with 0.0091 mole of peroxybenzoic acid and with 0.011 mole of trichloroacetic acid, gave, after crystallization from petroleum ether, 1.3 g. (44%) of VII, m.p. 114–115.5° (mixed melting point with the *threo*-isomer, 99–103°).

Anal. Calcd. for $C_{16}H_{13}O_3Cl_3$: C, 53.43; H, 3.64; Cl, 29.58. Found: C, 53.80; H, 3.91; Cl, 29.75.

By method b) 0.005 mole of *cis*-stilbene oxide gave 1.16 g. (64%) of the same *erythro*-ester and an oily residue, which formed 0.37 g. of a mixture of 2,4-dinitrophenylhydrazones.

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(18) H. O. House, *J. Am. Chem. Soc.*, **77**, 3070 (1955).

(19) A referee has pointed out that our hypothesis about the effect of water on the kinetic order of the reactions should be tested by adding small amounts of water to some of the solutions. Work along these lines is being done at present, too, and preliminary results, although quite incomplete from a quantitative point of view, because of the difficulty in obtaining rigorously anhydrous solutions, seem to be in line with our assumptions. The complete results will be published at a later date.

(20) R. E. Buckles and N. G. Wheeler, *Org. Syntheses*, **33**, 88 (1953).

(21) G. Braun, *Org. Syntheses*, **Coll. Vol. I**, 431 (1951).

(22) I. M. Kolthoff, T. S. Lee, and M. A. Mairs, *J. Polymer Sci.*, **2**, 199 (1947).

(23) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, New York, 2nd. ed., 1956, p. 219.

TABLE III

RUN NO. 1

Titrimetric Determination			Spectrophotometric Determination		
Time (sec.)	$Na_2S_2O_3$ (ml. 0.02*N*)	$k_{2.5}$ (mole^{-1} l sec^{-1} × 10^2)	Time (sec.)	Optical density at 320, mμ	$k_{2.5}$ (mole^{-1} l. sec.$^{-1}$ × 10^2)
0	16.65	—	0	1.050	—
2050	15.12	1.18	2090	0.960	1.07
4710	13.68	1.13	4740	.850	1.22
9275	11.82	1.12	9295	.750	1.10
16290	10.12	1.06	16340	.650	1.00
24005	8.80	1.03	24055	.562	1.01

Fractional crystallization of the latter showed that it had about the same composition as that obtained in the reaction of the *trans*-epoxide with trichloroacetic acid. Modifications in the quantities of trichloroacetic acid and in reaction times gave slightly different yields (56–64%) of the *erythro*-ester.

Transformation of the trichloroaceiates into hydrobenzoins. a) *By hydrolysis.* A solution of 0.26 g. of (−)-XI in 4 ml. of ethanol was treated with 2 ml. of a 0.2*M* solution of potassium hydroxide in ethanol and refluxed for 30 min. Water was added and the solution was extracted with ether. The ether extract was dried over magnesium sulfate and evaporated to dryness. The residue (0.14 g., 82%) melted at 145–147°, $[\alpha]_D^{21}$ +91.0° (*c* 1.100, ethanol) [lit.,[24] (+)-hydrobenzoin, m.p. 148–149°, $[\alpha]_D^{20}$ +94.0°]. The same reaction when applied to (±)-III, gave a product, which, after crystallization from water, melted at 92°, from benzene, at 116–118° [lit.,[25] (±)-hydrobenzoin hydrate, m.p. 95–96°, anhydrous. m.p. 119–120°]. The *erythro*-ester (VII), treated in the same way, gave *meso*-hydrobenzoin, m.p. 128–130° (lit.,[25] m.p. 134°).

b) *By reduction with lithium aluminum hydride.* A solution of 0.463 g. of (+)-XI in 10 ml. of ether was slowly added, with stirring, to a slurry of 0.15 g. of lithium aluminum hydride in 20 ml. of ether. The mixture was refluxed for 30 min., then treated with a few drops of ethanol, with water, and with dilute sulfuric acid. The ether layer was dried over magnesium sulfate and evaporated. The residue weighed 0.232 g. (84%), and melted at 148–149°, $[\alpha]_D^{21}$ −94.5° (*c* 0.998, ethanol) (lit.,[24] (−)-hydrobenzoin, m.p. 148–149°, $[\alpha]_D^{20}$ −93.5°). Under similar conditions (±)-III and (±)-VII gave respectively (±)-hydrobenzoin, m.p. 121°, and *meso*-hydrobenzoin, m.p. 134–135°.

Miscellaneous tests. A solution of 0.92 g. of (±)-III and 0.6 g. of trichloroacetic acid in 20 ml. of benzene was refluxed for 30 min. After washing with sodium carbonate and evaporation, 0.81 g. of unchanged starting material was recovered. A test with 2,4-dinitrophenylhydrazine gave a negative result.

A solution of 0.10 g. of (±)-hydrobenzoin and 0.10 g. of trichloroacetic acid was stored for 2 days at room temperature, then refluxed for 30 min. The rotatory power of the solution remained unchanged and 0.094 g. of the starting material was recovered.

A solution of 0.2 g. of *cis*-stilbene and 1.8 g. of trichloroacetic acid in 10 ml. of benzene was stored at room temperature. After about 1 hr. a pink color had developed, which changed to blue after 4 hr. After 24 hr. a sodium carbonate solution was added. The color disappeared after about 1 min. of shaking. The product which was recovered from the benzene solution had the same ultraviolet spectrum as *cis*-stilbene (maxima at 224 and 278 mμ); extinction coefficients were, however, about 20% too low on the whole curve, showing that the material contained only 80% of the stilbene. Under the same conditions *trans*-stilbene did not develop any color and was recovered unchanged.

Kinetics. The kinetic measurements were carried out with benzene solutions at 25.1 ± 0.1°. The reactions, whose results are summarized in Table I, were followed by iodometric titration of the peroxybenzoic acid. A benzene solution of an exactly weighed amount of stilbene in a 50-ml. flask was treated with the calculated volume of a titrated solution of trichloroacetic acid in benzene. The flask was brought to the bath temperature, a preheated titrated solution of peroxybenzoic acid was added, and the volume was made up with preheated benzene. Fractions of 5 ml. were drawn off and the reaction was quenched by stirring with an aqueous solution of 0.5 g. of potassium iodide and 3 ml. of acetic acid. The iodine was titrated with 0.02*N* sodium thiosulfate. The reactions were followed to at least 40% transformation, the faster ones to 60–70%. Parallel runs without trichloroacetic acid were carried out as a control for the method. The second order rate constants for *trans*-stilbene thus found (k_2 = 4.25–4.35) were in fairly good agreement with those of the literature (4.25–4.29[3c]; 4.16–4.21[3d]). The rate constants were calculated using the equations shown in Table II.

In some cases the reactions were also followed by determining the disappearance of the stilbenes spectrophotometrically. Together with the samples for the titrations, others of 2 ml. were drawn off, transfered to test tubes with ground stoppers, containing 2 ml. of 10% sodium carbonate, and shaken. About 1 ml. of the benzene layer was then transfered into another test tube containing some dry magnesium sulfate; 0.09 ml. of this solution was measured exactly with a micro-pipette and brought to 50 ml. with methanol. Optical densities of these solutions were read with a spectrophotometer, at 320 and 330 mμ for *trans*-stilbene and at 315 and 325 mμ for *cis*-stilbene, using as a blank a solution prepared in the same way, but without the stilbene. Preliminary tests had shown that at these wave-lengths and concentrations the compounds II, III, VI, and VII and the reaction products of II and VI with trichloroacetic acid were practically transparent. The results obtained by this second method were usually almost parallel to those obtained by the titrimetric method although there was some tendency, in most cases, to a slightly slower rate of disappearance of the stilbene, than of the peroxybenzoic acid. This effect could, however, be due to the formation of a side-product, which absorbs at the wave lengths used for the determination. Table III shows an example of the values of $k_{2.5}$ obtained by both methods.

Acknowledgment. The authors wish to express their gratitude to Dr. Bruno Macchia for help in the experimental work.

PISA, ITALY

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[24] F. Eisenlohr and L. Hill, *Ber.*, **70**, 942 (1937).

[25] C. Forst and T. Zincke, *Ann.*, **182**, 262 (1876).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

Reaction of Triphenylacetyl Chloride with Organometallic Reagents. Preparation of Alkyl Trityl Ketones

JAMES CASON AND FRANCIS J. SCHMITZ

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Reaction of excess methylmagnesium iodide with triphenylacetyl chloride yields triphenylmethane, triphenylethane, and methyl trityl ketone. There could be detected no ethyl triphenylacetate, previously reported as the principal product of this reaction. It is suggested that the observed reaction products are obtained from an intermediate acylonium ion which either reacts with Grignard reagent to give ketone or decarbonylates to give the triphenylmethyl carbonium ion. Reaction of ethylmagnesium bromide with triphenylacetyl chloride yields no ketone, but a mixture of 2,2,2-triphenylethanol and ethyltritylcarbinol. The latter is believed to arise from reduction by excess Grignard reagent of initially formed ethyl trityl ketone. Methyl, ethyl, and butyl trityl ketones have been prepared in good yield by reaction of triphenylacetyl chloride with the appropriate cadmium reagents.

It has been reported[1] recently that alkyl trityl ketones have not been secured by reaction of the Grignard reagent with triphenylacetyl chloride; in fact, the only ketone of this type whose identity seems authenticated is methyl trityl ketone.[2] Reaction of ethylmagnesium iodide with triphenylacetyl chloride[1] yielded the reduction product 2,2,2-triphenylethanol rather than the previously claimed ethyl trityl ketone,[3] whereas reaction with a large excess of methylmagnesium iodide was reported[1] to result in a 67% yield of ethyl triphenylacetate. Formation of the ester in the latter case was attributed to extraction of halogen from the acid chloride by a Lewis-acid component of the Grignard reagent, and subsequent reaction of the acylonium ion, $(C_6H_5)_3\overset{+}{C}—CO$, with ether solvent. In view of the large excess of Grignard reagent that was employed, this result seems rather surprising, for the Grignard reagent would be expected to react much more rapidly with the acylonium ion than would the ether solvent. Indeed, reaction of organocadmium reagents with acid chlorides has been extensively rationalized[4] on the basis of reaction of an intermediate acylonium ion with the organocadmium reagent or a carbanion released from it.

When reaction of excess methylmagnesium iodide with triphenylacetyl chloride was re-examined during the present investigation, *no ethyl triphenylacetate could be isolated,* nor could this ester (synthesized for reference purposes) be detected in the reaction product by infrared spectroscopy, gas phase chromatography, or column chromatography on alumina. There was obtained a 17–21.5% yield of methyl trityl ketone; however, the major product of the reaction was a mixture of triphenylmethane and triphenylethane. Analysis and separation of the hydrocarbon mixture by gas chromatography indicated 17–21% yields of triphenylmethane and 31–40% yields of triphenylethane. The hydrocarbons were compared (infrared spectra and gas chromatography) with authentic samples.

The products obtained from reaction of methylmagnesium iodide with triphenylacetyl chloride do indeed indicate that the principal reaction path involves extraction of halogen to yield the acylonium ion; however, the fate of this ion does not involve reaction with the ether solvent.[5] Reaction of the acylonium ion with the Grignard reagent (or the methyl carbanion) would yield the trityl ketone, whereas the triphenylmethyl carbonium ion, formed by decarbonylation of the acylonium ion,[6] could lead to hydrocarbon formation. Reaction of the carbonium ion with the Grignard reagent would yield triphenylethane, and use of higher alkylcadmium reagents (see Table I) does lead to the corresponding higher triphenylalkanes. The ether solvent must be the source of the hydrogen required for triphenylmethane formation, possibly by an equilibrium reaction involving extraction of the *alpha* hydrogen from the ether; however, the increased formation of triphenylmethane (Table I) at higher temperature suggests a more complicated reaction path. Extraction of a hydride ion from a phenyl moiety would not be expected. The triphenylmethyl radical can hardly be the intermediate leading to hydrocarbon formation, for triphenylacetyl chloride is stable to heating under reflux in a benzene-ether mixture. Furthermore, there is apparent no reasonable mechanism leading to generation of the triphenylmethyl

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[1] J. L. Greene, D. Abraham, and H. D. Zook, *J. Org. Chem.*, **24**, 132 (1959).

[2] J. L. Greene and H. D. Zook, *J. Am. Chem. Soc.*, **80**, 3629 (1958).

[3] M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice Hall, Inc., Englewood Cliffs, N. J., 1954, p. 763.

[4] A recent report containing references to earlier work is: J. Cason and E. J. Reist, *J. Org. Chem.*, **23**, 1675 (1958).

[5] The origin of the ester reported by the previous investigators seems obscure; however, presence of ethanol in the ether solvent could lead to formation of magnesium ethoxide, which would react with the acylonium ion.

[6] In Friedel and Crafts reactions with trisubstituted acetyl chlorides, alkylations with the tertiary carbonium ion have been observed; for a leading reference, *cf.* E. Rothstein and R. W. Saville, *J. Chem. Soc.*, 1946 (1949).

TABLE I

REACTION OF TRIPHENYLACETYL CHLORIDE WITH ALKYLCADMIUM REAGENTS[a]

Alkyl Group	Ratio of Alkyl Halide to Acid Chloride	Yields, %		
		$(C_6H_5)_3CH$	$(C_6H_5)_3C-R$	$(C_6H_5)_3C-\underset{\underset{O}{\Vert}}{C}-R$
CH_3-	2:1[b]	18	33	12[c]
	2:1	0	21.5	15[c]
	5:1	0	11	73
C_2H_5-	2:1	11	13	39.5
n-C_4H_9-	2:1	11.5	17.5	46
	5:1	8.5	10.5	62.5

[a] Unless otherwise stated, after the cadmium reagent had been formed from the bromide *via* the Grignard reagent, the acid chloride was added at about 10°, then the mixture was stirred for about 1 hr. at room temperature followed by about 20 hr. at 40–43°. [b] After addition of the acid chloride in this run, the mixture was stirred for 1 hr. at about 43°, then for 1 hr. under reflux in benzene solvent. [c] The lower yields of ketone obtained with the 2:1 ratio of methyl bromide are believed due to the volatility of dimethylcadmium and its consequent loss during distillation of ether from the reaction mixture.

carbanion as an intermediate. The hydrocarbons are also formed in cadmium reactions (see Table I), and methyl trityl ketone does not suffer displacement of the triphenylmethyl carbanion on heating with dimethylcadmium under conditions used in the organocadmium reaction with an acid chloride. The ketone is recovered unchanged. Decomposition of the acylonium ion to the carbonium ion is also indicated by the fact that a higher ratio of hydrocarbon is obtained in the organocadmium reaction when it is carried out at higher temperature (Table I).

In view of the unexpected results obtained in our investigation of the reaction of triphenylacetyl chloride with methylmagnesium iodide, the reaction with the ethyl Grignard reagent was also re-examined. In agreement with the previous report,[1] 2,2,2-triphenylethanol was obtained; however, chromatography on alumina separated a second alcohol (infrared spectrum) in somewhat smaller amount than the substituted ethanol. The second alcohol, m.p. 92–93.6°, gave an analysis in agreement with that calculated for ethyltritylcarbinol. The identity of this alcohol was established by oxidation to ethyl trityl ketone and comparison of the latter with an authentic sample. Thus, ethyl trityl ketone appears to have been a primary product of the Grignard reaction, but it was reduced by excess Grignard reagent to the corresponding carbinol. Triphenylacetaldehyde is an improbable intermediate in formation of the carbinol, for the Grignard reagent would not be expected to add to such a highly hindered aldehyde.

As alkyl trityl ketones have proved difficult to synthesize and organocadmium reagents are relatively unaffected by steric hindrance,[7] the reaction of dialkylcadmium reagents with triphenylacetyl chloride was examined. If a large excess of cadmium reagent is utilized, this procedure is a simple and high-yield approach to synthesis of alkyl trityl ketones. Pertinent data are assembled in Table I. It may be noted that a hydrocarbon mixture is also obtained in these reactions, but the amount is reduced by use of excess cadmium reagent and by use of reaction temperatures below 45°. This is consistent with the view that the acylonium ion is the primary intermediate in the reaction. Decarbonylation of this ion is competitive with its reaction with the cadmium reagent or derived carbanion. As reduction products were not encountered, it would seem that the cadmium reagent is free of the reducing action which so often handicaps the Grignard reagent.

EXPERIMENTAL[8]

Triphenylacetic acid. Initial efforts to prepare this acid from commercial triphenylmethyl chloride were unsuccessful because of the presence of triphenylmethylcarbinol, which could not be removed in any convenient manner. The preparation from triphenylmethyl bromide, synthesized by the method which has been described,[9] proceeded smoothly according to a procedure somewhat different from those which have been reported.[1,10]

The Grignard reaction was initiated by addition of about 1 ml. of an ethereal solution of ethylmagnesium bromide to 2.25 g. of magnesium turnings in a stirred solution of 2 g. of triphenylmethyl bromide in a mixture of 20 ml. of ether and 40 ml. of benzene. An additional 8.2 g. of crystalline bromide was added to the stirred solution during about 2 min. After completion of the addition, which caused spontaneous warming, the mixture was heated under reflux with stirring for 1.5 hr. As stirring under reflux was continued, a stream of carbon dioxide was bubbled through the reaction mixture for a period of about 8 hr. Solvent swept out by the stream of gas was replaced periodically with benzene. At the end of the addition period, a yellow precipitate had formed in the brown solution. After addition of 60 ml. of water, followed by 40 ml. of concd. hydrochloric

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(7) J. Cason and R. D. Smith, *J. Org. Chem.*, **18**, 1201 (1953).

(8) Melting points are corrected. Infrared spectra were recorded on a Baird double beam spectrophotometer. Gas chromatography was on silicone grease partitioning agent prepared as described by J. Cason and W. T. Miller, *J. Org. Chem.*, **24**, 1814 (1959). Microanalyses were by the Microanalytical Division, Department of Chemistry, University of California.

(9) W. E. Bachmann, *Org. Syntheses*, **Coll. Vol. III**, 842 (1955).

(10) J. Schmidlin, *Ber.*, **39**, 628 (1906).

acid, the mixture was heated under reflux for 30 min. in order to decompose the complex included in the sticky yellow paste on the walls of the flask.[11] The precipitate containing the triphenylacetic acid was collected by suction filtration of the cooled mixture, washed with water, and then digested on the steam bath with a mixture of 200 ml. of 10% aqueous sodium hydroxide and 400 ml. of water. A gray precipitate was filtered from the cooled alkaline solution,[11] the clear filtrate was acidified with 100 ml. of concd. hydrochloric acid, and the mixture was heated on the steam bath for 2 hr. to coagulate the precipitated acid. The collected and dried product, which amounted to 7.62 g. (83.5%), m.p. 263–267° dec., was used for preparation of the acid chloride.

Triphenylacetyl chloride was prepared by that procedure of Zook and co-workers[1] in which thet hionyl chloride solution was poured into glacial acetic acid, except that a few drops of pyridine were added to the reaction mixture. Pyridine appeared to speed up greatly the rate of formation of acid chloride; crystallization of the product set in rapidly after addition to acetic acid, and there was an improved yield (60–64%) of product, m.p. 128–129°.

Ethyl triphenylacetate, prepared from the acid chloride as has been described,[1] was crystallized from 95% ethanol to yield material, m.p. 117–118°, with carbonyl absorption at 5.81 μ, in carbon tetrachloride solution (lit.,[1] m.p. 116–117°, 116.8–117.8°; absorption at 5.77 μ). This ester is partly separated from methyl trityl ketone by chromatography on alumina with hexane solvent. Some ester is eluted first, followed by a mixture of ester and ketone.

Methyl trityl ketone. (A) *From Grignard reagent.* A Grignard reagent was prepared in an atmosphere of nitrogen from 8.48 g. (58 mmoles) of methyl iodide and 1.22 g. (50.8 mmoles) of magnesium turnings in 40 ml. of ether. To this reagent, cooled in an ice-salt bath, there was added during 5 min. a solution of 0.9 g. (2.94 mmoles) of triphenylacetyl chloride in 15 ml. of ether. The stirred reaction mixture was allowed to warm to room temperature, then heated under reflux for 20 hr. The reaction mixture was decomposed by cautious addition of 20 ml. of a 1:1 mixture of ice and concd. hydrochloric acid. An ether extract of the product was washed with water, sodium hydroxide solution (removal of a red color), and saturated sodium chloride solution, then dried over magnesium sulfate.

The yellow oil remaining after removal of solvent from the ether extract weighed 0.636 g. and solidified on standing. Its infrared spectrum exhibited bands characteristic of methyl trityl ketone, triphenylmethane, and triphenylethane,[12] but no absorption at 5.81 μ, characteristic of ethyl triphenylacetate. Yields for the three products, based on the chromatography data in Table II, were the following: triphenylmethane, 153 mg. (21.3%); triphenylethane, 307 mg. (40.5%); methyl trityl ketone, 181 mg. (21.5%).

In a second run, carried out similarly with 1.7 g. of triphenylacetyl chloride, yields of products in the order listed above were 16.7%, 31.5%, and 17.0%.

TABLE II

CHROMATOGRAPHY OF REACTION PRODUCT FROM METHYLMAGNESIUM IODIDE AND TRIPHENYLACETYL CHLORIDE[a]

Fraction No.	Eluting Solvent	Wt. Eluted, Mg.	Infrared Absorp. in 5–6 μ Region
1	Hexane	253[b]	none
2	Hexane	177[b]	
3	Hexane	30[b]	
4	Hexane	41[c]	
5	Hexane-benzene, 1:1	72[c]	5.88
6	Hexane-benzene, 1:3	35[c]	5.88
7	Hexane-benzene, 1:3	15	
8	Benzene	9	
9	Benzene-ether, 1:1	9	
10	Methanol	0	

[a] The crude reaction product, dissolved in 8 ml. of hexane, was applied to a column of 18 g. of alumina of activity 3, in a 20 mm. i.d. column. Except for the first fraction of 20 ml. of solvent, each fraction represents elution with 25 ml. of the indicated solvent. [b] Fractions 1–3 were taken as the yield of hydrocarbon. Analysis by gas chromatography indicated a ratio of about 2:1 for triphenylethane:triphenylmethane. Chromatography on a 3-m. column at 265°, with helium pressure of about 18 cm. of mercury, gave bands of retention times 22.2 and 27.0 min. The same retention times were observed for authentic samples of the hydrocarbons chromatographed sequentially. Samples of the hydrocarbons separated by gas chromatography gave infrared spectra identical with those of authentic samples. [c] Fractions 4–9 were taken as the yield of ketone. Recrystallization of fractions 4–6 from ethanol yielded 75 mg. of ketone, m.p. 135.5–137°, infrared absorption in carbon tetrachloride 5.88 μ (lit.,[1] m.p. 138°, infrared absorption 5.84 μ).

Methyl trityl ketone. (B) *From cadmium reagent.* A Grignard reagent was prepared in 18 ml. of ether from 0.16 g. of magnesium turnings and excess methyl bromide which had been bubbled through sulfuric acid. This reagent was converted to the cadmium reagent in usual fashion[13] with 0.60 g. of anhydrous cadmium chloride. After distillation of ether and addition of 15 ml. of benzene, there was added at 10° during about 2 min. a solution of 1.0 g. of triphenylacetyl chloride in 5 ml. of benzene. After the cooling bath had been removed, there was no observable exothermic reaction as the mixture warmed to room temperature. The reaction was continued with stirring for 1 hr. at about 43°, then caked solid was scraped from the sides of the flask and the mixture was heated to reflux for 1 hr. As the temperature was raised, sudden boiling occurred and the mixture turned a bright yellow.

The reaction mixture was worked up in a usual fashion for cadmium reactions,[13] and there was obtained 0.54 g. of a yellow oil from which no significant crystallization could be obtained in ethanol. Chromatography on alumina of activity 3 gave a pattern similar to that recorded in Table III. Recrystallization of the methyl trityl ketone yielded material of m.p. 137.5–139°. Yield data are recorded in Table I.

Yield data and conditions for two additional runs are recorded in Table I.

Reaction of ethylmagnesium bromide with triphenylacetyl chloride. The Grignard reagent from 2.14 g. (19.6 mmoles) of ethyl bromide in 14 ml. of ether was added during about 10 min., at 15–20°, to a stirred suspension of 1.0 g. (3.27 mmoles) of triphenylacetyl chloride in 10 ml. of ether. A gray precipitate formed as the Grignard reagent was added. After the mixture had been stirred for 1.5 hr. at room temperature, it was decomposed with ice and acid and worked up essentially as described for the reaction with the methyl Grignard reagent.

The product of the reaction was 0.87 g. of a colorless viscous oil containing some solid. The infrared spectrum showed no absorption in the carbonyl region, but a sharp band at 2.83 μ. Chromatography of this material on 25 g. of alumina of activity 3 gave rather clean-cut separation of two components present in a ratio of about 1:1.3. The first component, *ethyltritylcarbinol*, which was present in the smaller amount, was eluted with hexane. After two crystallizations from hexane, the melting point was 92–93.6°, and there was a sharp absorption band at 2.83 μ.

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[11] In some instances, complex remained undecomposed after this treatment and was a part of the precipitate insoluble in sodium hydroxide. Further digestion on the steam bath of the alkali-insoluble precipitate with 100 ml. of ethanol and 40 ml. of concd. hydrochloric acid liberates the remainder of the product.

[12] The principal absorption bands (μ) for the two hydrocarbons are the following: triphenylmethane, 3.30, 3.34, 3.51, 9.27, 9.68, 13.36, 13.68, 14.33; triphenylethane, 3.30, 3.35, 3.40, 9.71, 13.14, 14.33.

[13] J. Cason and F. S. Prout, *Org. Syntheses*, **Coll. Vol. III**, 601 (1955).

Anal. Calcd. for $C_{22}H_{22}O$: C, 87.4; H, 7.3. Found: C, 87.0; H, 7.3.

The second component, *2,2,2-triphenylethanol* was eluted with 1:1 hexane-benzene. After two crystallizations from hexane, the melting point was 108.8–109.9°, and there was infrared absorption at 2.82 μ, but the spectrum differed substantially in other areas from that of ethyltritylcarbinol. Melting points reported for 2,2,2-triphenylethanol are 103–105°,[1] 104–105°,[14] 107°,[15] and 110.5°.[16]

Chromic acid oxidation of ethyltritylcarbinol. A solution of 32.4 mg. of the alcohol of m.p. 92–93.6°, and of 10.7 mg. of chromic anhydride, in 1 ml. of glacial acetic acid (distilled from permanganate) was allowed to stand at room temperature for about 14 hr. At the end of this period, clear needles had crystallized from the solution. After 10 ml. of water had been added to the reaction mixture the product was collected, washed with water, and dried: wt. 25 mg. (78%), m.p. 122.8–124°. The infrared spectrum of this product was identical with that of ethyl trityl ketone, m.p. 122.5–125° (*cf.* below).

Ethyl trityl ketone was prepared from diethylcadmium and triphenylacetyl chloride according to the procedure described for preparation of methyl trityl ketone. Yield data are recorded in Table I. The ketone, separated by chromatography on alumina of activity 3, was crystallized twice from ethanol to yield material of m.p. 122.5–125°.

Anal. Calcd. for $C_{22}H_{20}O$: C, 88.0; H, 6.7. Found: C. 87.9; H, 6.8.

The hydrocarbon mixture separated by chromatography on alumina was analyzed by gas chromatography and found to exhibit only the band for triphenylmethane and that assigned to triphenylpropane. At 257°, in a 1.6-m. column, under conditions giving retention times of 5.4 and 6.5 min. for triphenylmethane and -ethane respectively, the time for the band assigned to triphenylpropane was 7.8 min.

n-Butyl trityl ketone was prepared in a cadmium reaction carried out similarly to those described for its homologs. Separation of the ketone from the hydrocarbons by chromatography on alumina of activity 3 was somewhat less clean-cut than for the lower homologs, but was satisfactory. Chromatography of a reaction product weighing 765 mg. yielded an initial fraction of 397 mg. of a mixture of ketone and hydrocarbons. Succeeding fractions of ketone contained less than 1% hydrocarbons and weighed 362 mg. The mixture in the initial fraction was analyzed by gas chromatography and found to contain 92 mg. of triphenylmethane, 171 mg. of 1,1,1-triphenylpentane, and 132 mg. of butyl trityl ketone. In a 3-m. column, at 290° and with 21 cm. of helium pressure, retention times for the three compounds, in the order mentioned above, were 15.0, 28.5, and 43 min. For analysis, the ketone was crystallized from ethanol to yield material of m.p. 82.8–83.8°.

Anal. Calcd. for $C_{24}H_{24}O$: C, 87.8; H, 7.3. Found: C, 87.5; H, 7.3.

1,1,1-Triphenylpentane was separated by gas chromatography, in a 3 m. 15 mm. o.d. column, of the first fraction of material separated by chromatography on alumina. After crystallization from ethanol, there was obtained hydrocarbon of m.p. 60–61.2°.

Anal. Calcd. for $C_{23}H_{24}$: C, 92.0; H, 8.0. Found: C, 91.8; H, 8.0.

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[14] S. Weinstein, B. K. Morse, E. Grunwald, K. C. Schrieber, and J. Corse, *J. Am. Chem. Soc.*, **74**, 1119 (1952).

[15] W. Schenk and R. Ochs, *Ber.*, **49**, 610 (1916).

[16] J. Danilow, *J. Russ. Phys. Chem. Soc.*, **51**, 122 (1920).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Factors in Aldol Condensations of Alkyl Acetates with Benzophenone and Reversals by Sodium Amide Versus Lithium Amide. Metallic Cation Effects[1]

CHARLES R. HAUSER AND WILLIAM R. DUNNAVANT[2]

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The condensations of ethyl, isopropyl, and *t*-butyl acetates with benzophenone to form the corresponding β-hydroxy esters were effected by sodium amide in liquid ammonia, but controlled conditions were required with the first two alkyl acetates. Certain of these conditions were the same as those previously used with lithium amide, but certain of them were different. In contrast to lithium amide, sodium amide failed to effect the condensation of ethyl acetate with acetophenone. Four β-hydroxy esters were shown to undergo cleavages with catalytic amounts, and, in certain cases, with equivalent amounts of sodium amide in liquid ammonia but not with lithium amide. Possible reasons for these cleavages are discussed. Metallic cation effects and mechanisms are considered. The condensations are suggested to require the formation of a weaker base.

In a previous investigation[3] it was shown that ethyl and isopropyl acetates can be condensed with benzophenone by means of one equivalent of lithium amide in liquid ammonia to form the corresponding β-hydroxy esters, provided the ketone is added to the reaction mixture soon after the alkyl acetate. Otherwise the alkyl acetate undergoes self-condensation. In the present investigation it was found that these condensations can be effected similarly with one equivalent or slightly more of sodium amide in liquid ammonia provided that, not only is the ketone added immediately after the ester, but also that the reaction mixture is neutralized within a few minutes. Otherwise the

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[1] Supported in part by the Office of Ordnance Research, U. S. Army.

[2] Allied Chemical and Dye Corporation Fellow, 1958–59.

[3] W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, in press.

TABLE I

YIELDS OF β-HYDROXY ESTERS FROM ALKYL ACETATES WITH BENZOPHENONE BY SODIUM AMIDE IN LIQUID AMMONIA

Exp. No.	Alkyl Acetate	Equiv. $NaNH_2$	Ioniz. Time, min.[a]	Cond. Time, Min.	β-Hydroxy Ester	Yield, %
1	Ethyl	1.1	0[b]	5	I	71-73
2	Ethyl	1	0[b]	60	I	0[c]
3	Ethyl	2	0[b]	60	I	72
4	Ethyl	2	15	60	I	0[c]
5	Isopropyl	1	0[b]	5	II	56
6	Isopropyl	1	0[b]	60	II	0[c]
7	*t*-Butyl	1	20	60	III	55
8	*t*-Butyl	1	0[b]	60	III	54
9	*t*-Butyl	2	20	60	III	70

[a] Time allowed after adding the ester to the reagent before adding the ketone. [b] Although the ketone was added immediately after the ester, a few seconds probably elapsed. [c] Benzophenone was recovered in yields of 85-95%.

reaction undergoes reversion (see next section). These condensations, as well as that of *t*-butyl acetate which requires no special conditions with either lithium amide or sodium amide, may be represented by general Equation 1.

$$CH_3COOR \xrightarrow[\text{liq. } NH_3]{MNH_2} MCH_2COOR \xrightarrow[2.\ NH_4Cl]{1.\ (C_6H_5)_2C=O} (C_6H_5)_2C(OH)CH_2COOR \quad (1)$$

M = Li or Na

I. R = C_2H_5
II. R = $CH(CH_3)_2$
III. R = $C(CH_3)_3$

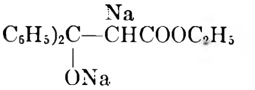
Certain of these condensations were also effected with two equivalents of sodium amide in liquid ammonia. The results are summarized in Table I. The ionization-time column in this Table designates the period allowed for the ionization of the α-hydrogen of the alkyl acetate before adding the ketone, and the condensation-time column the period after adding the ketone. The immediate addition of the ketone after the ester is signified by zero ionization time, although a few seconds probably elapsed in the procedure employed (see Experimental). The resulting reaction mixtures were poured into liquid ammonia solutions of ammonium chloride. This inverse neutralization procedure was employed to minimize the possible cleavages of the β-hydroxy esters.

It can be seen from Table I that good yields of β-hydroxy esters I and II were obtained with one or slightly more than one equivalent of sodium amide when the ionization time was zero and the condensation time only five minutes (exps. 1 and 5), whereas the benzophenone was recovered when the ionization time was again zero but the condensation time was one hour (exp. 2 and 6). Under both conditions the β-hydroxy esters were formed as their sodio salt, for example, I′, but under the latter condition this salt underwent cleavage to regenerate the ketone. Such cleavages are further considered in the next section.

$$(C_6H_5)_2\underset{\displaystyle ONa}{C}\text{—}CH_2COOC_2H_5$$

I′

On the other hand, a good yield of β-hydroxy ester I was realized with two equivalents of the reagent when the ionization time was zero and the condensation time was even one hour (exp. 3). This lack of appreciable cleavage under these conditions may be ascribed to the conversion of monosodio β-hydroxy ester I′ to the disodio derivative I″, which might be expected to be more stable



$$(C_6H_5)_2\underset{\displaystyle ONa}{C}\text{—}\overset{\displaystyle Na}{C}HCOOC_2H_5$$

I″

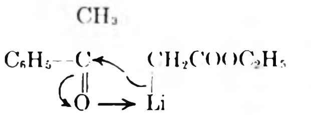
towards cleavage. Although the formation of disodio salt I″ with two equivalents of sodium amide was not established, evidence has previously been obtained[3] that the corresponding condensation of ethyl acetate with benzophenone by two equivalents of lithium amide does produce the analogous dilithio salt.

In contrast to β-hydroxy esters I and II, β-hydroxy ester III was obtained with one equivalent of sodium amide even when the ionization time was twenty minutes, and the condensation time one hour (exp. 7, Table I). This may be attributed to less tendency for the further reaction of sodio *t*-butyl acetate, a low concentration of which is presumably present in equilibrium (see next section). The somewhat better yield of β-hydroxy ester III with two equivalents of sodium amide than with one equivalent (compare exp. 9 with 7 and 8) may indicate that the additional driving force that should be furnished by the conversion of the monosodio β-hydroxy ester to its disodio derivative is required for maximum yield.

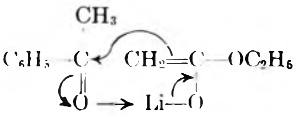
The fact that β-hydroxy ester I was obtained with two equivalents of sodium amide when the ionization time was zero but not when it was fifteen minutes (compare exps. 3 and 4) indicates that an extra equivalent of sodium amide did not exert the type of stabilizing effect on the intermediate sodio ethyl acetate observed previously[3] with an extra equivalent of lithium amide on the intermediate lithio ester. This was substantiated by treating ethyl acetate alone with two equivalents of sodium amide in liquid ammonia for twenty minutes, after which a 12% yield of acetoacetic ester was obtained. Some acetamide might also have formed but none was isolated. Earlier workers have similarly reported only low yields (5–15%) of acetoacetic ester or acetamide from ethyl acetate and sodium amide[4,5] in liquid ammonia[5] or ether.[4]

Since ethyl acetate has now been condensed with benzophenone in 71–73% yields by one or two equivalents of sodium amide in liquid ammonia and converted to acetamide in 10% yield by two equivalents of this reagent,[5] the ratio of attack of this reagent at the α-hydrogen of this ester versus the carbonyl carbon appears to be about 7:1. The ratio might even be higher since the ionization of the α-hydrogen should be reversible, whereas that of acetamide formation would presumably be irreversible.

Although sodium amide effected the aldol type of condensation of ethyl acetate with benzophenone, this reagent (one or two equivalents) failed to bring about the corresponding condensation of this ester with acetophenone, even when the ketone was added immediately after the ester. Instead the intermediate sodio ester evidently effected the ionization of an α-hydrogen of acetophenone to form the sodio ketone, since the ketone was recovered on acidification. The recovered material gave an enol test with ferric chloride indicating the presence of acetoacetic ester or benzoylacetone. Previously[3] ethyl acetate has been condensed in good yield with acetophenone by means of two equivalents of lithium amide, and one equivalent of this reagent would probably be equally satisfactory. This metallic cation effect appears to be attributable to the greater nucleophilic nature of the lithio ester to add to the carbonyl group of the ketone, presumably through coordination at the carbonyl oxygen, as indicated in IVa or IVb.

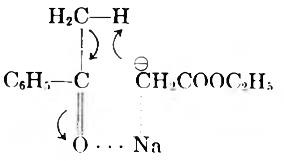


IVa



IVb

The sodio ester, which should coordinate to a smaller degree, functions as the stronger base ionizing the α-hydrogen of the ketone as indicated in V.



V

A similar metallic cation effect has been previously observed in the reactions of lithio and sodio *t*-butyl acetates with acetophenone.[6]

Cleavage of β-hydroxy esters. Although ethyl, isopropyl, and *t*-butyl acetates can be condensed with benzophenone by means of one to two equivalents of sodium amide in liquid ammonia (see Table I), the resulting β-hydroxy esters can be cleaved again by catalytic amounts of this reagent and, in certain cases, even by equivalent amounts. These and certain related results are summarized in Table II. In all of these experiments the reaction mixtures were neutralized inversely to ensure that the cleavage observed had occurred during the four hour period allowed, not during the neutralization.

TABLE II

CLEAVAGE OF β-HYDROXY ESTERS BY ALKALI AMIDES IN LIQUID AMMONIA DURING FOUR HOURS

Exp. No.	β-Hydroxy Ester	Alkali Amide	Equiv.	Benzophenone Yield, %	Recov. β-Hydroxy Ester, %
1	I	Sodium	0.2[a]	26	42
2	I	Sodium	1.25	89	0
3	I	Sodium	2.0	0	94
4	I	Potassium	1.0	71	0
5	I	Potassium	1.2	67	0
6	I	Lithium	0.1	0	96
7	I	Lithium	1.0	0	96
8	I	Lithium	2.0	0	93
9	II	Sodium	0.15	86	0
10	III	Sodium	0.15	82	0
11	III	Sodium	0.5	21	69
12	III	Sodium	1.0	0	91

[a] Neutralized after only five minutes.

First, consideration will be given to the use of catalytic amounts of sodium amide, which effected the cleavages of all three of the β-hydroxy esters studied, I, II, and III, to form benzophenone and presumably the corresponding alkyl acetate (exps. 1, 9, and 10). While only the ketone was isolated, the appropriate fraction of the reaction product from β-hydroxy ester I was indicated by its infrared spectrum to contain ethyl acetate. All of the β-hydroxy esters were probably cleaved completely within much less time than the four hours allowed, since appreciable cleavage of I was observed within five minutes (exp. 1). These reactions are brought about presumably because the neutral ketone and alkyl acetate molecules are more stable thermodynamically than the neutral β-hydroxy ester. The mechanism may be considered to involve a β-elimination of the sodio salt of the β-hydroxy ester, for example, III′, but only that amount of the β-hydroxy ester corresponding to the mole percent of the catalyst employed is first converted to this intermediate. The remainder of the free β-

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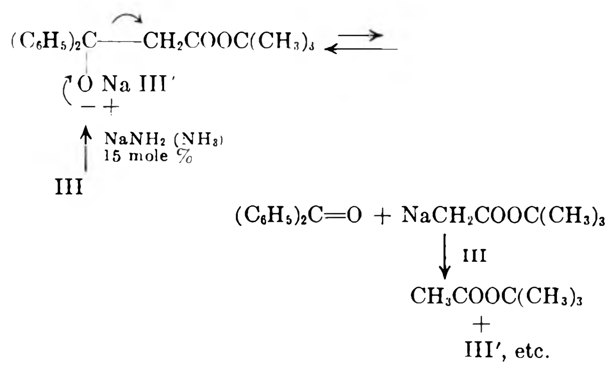
(4) A. W. Titherly, *J. Chem. Soc.*, 81, 1520 (1902).

(5) C. R. Hauser, R. Levine, and R. F. Kibler, *J. Am. Chem. Soc.*, 68, 26 (1946).

(6) C. R. Hauser and W. H. Puterbaugh, *J. Am. Chem. Soc.*, 75, 4756 (1953).

hydroxy ester is gradually converted to this intermediate as it neutralizes the sodio alkyl acetate, a low concentration of which is present in equilibrium (Scheme A).

Scheme A

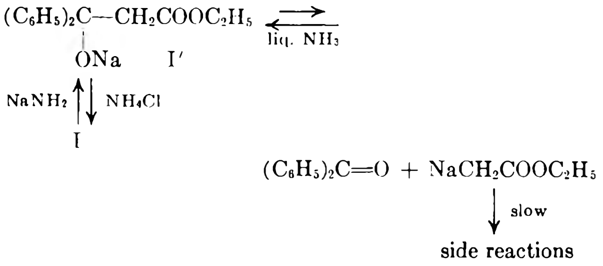

$(C_6H_5)_2C$—$CH_2COOC(CH_3)_3$
O Na III′
NaNH₂ (NH₃) 15 mole %
III
$(C_6H_5)_2C{=}O + NaCH_2COOC(CH_3)_3$
III
$CH_3COOC(CH_3)_3$ + III′, etc.

In agreement with Scheme A, less than half of β-hydroxy ester III underwent cleavage with 0.5 mole % of sodium amide (exp. 11), and essentially none of β-hydroxy ester III was cleaved by one equivalent of the reagent (exp. 12). In this last experiment essentially all of the β-hydroxy ester was immediately converted to its sodio salt III′, leaving none to serve as an acid in the last step.

One of the β-hydroxy esters, I, was also cleaved with a catalytic amount of sodium ethoxide in ethanol. A number of β-hydroxy esters have previously been cleaved with alcoholic alkali alkoxides but an equivalent or more of the reagent has generally been employed.[7] The mechanism would presumably be similar to that shown in Scheme A. However, even with an equivalent of an alkoxide ion, which is a much weaker base than the amide ion, the β-hydroxy ester would probably be converted only gradually to its anion, and the last step may be considered to be effected mainly by the alcohol used as solvent.

Next, consideration will be given to the use of an equivalent or slightly more of sodium amide or potassium amide, which effected the cleavage of β-hydroxy ester I (exps. 2, 4, and 5, Table II) but not that of β-hydroxy ester III under similar conditions (exp. 12). Since both sodio ethyl acetate and sodio *t*-butyl acetate can be condensed in high yield with benzophenone (see Table I), this difference in the relative ease of cleavage of the two resulting sodio β-hydroxy esters I and III appears to be due to the relative tendencies towards side-reactions of the sodio ethyl and sodio *t*-butyl acetates, low concentrations of which are presumably present in equilibrium. In agreement with this, ethyl acetate is known to be converted by sodium amide in liquid ammonia through the sodio ester to its self-condensation product or corresponding acid amide much more readily than *t*-butyl acetate (see previous section). The relationship between the formation and cleavage of sodio β-hydroxy ester I′ may be represented tentatively by Scheme B.

Scheme B

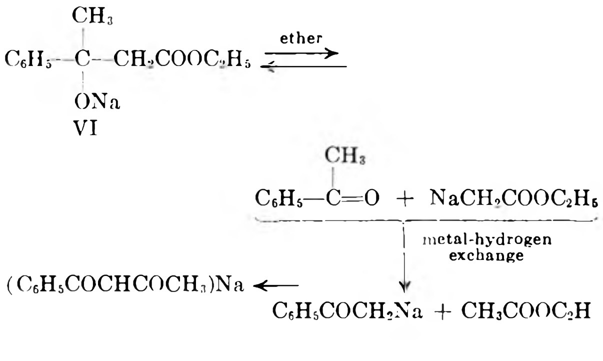

$(C_6H_5)_2C$—$CH_2COOC_2H_5$
liq. NH₃
ONa I′
NaNH₂
NH₄Cl
I
$(C_6H_5)_2C{=}O + NaCH_2COOC_2H_5$
slow
side reactions

However, an attempt to isolate acetoacetic ester or acetamide from the cleavage product of β-hydroxy ester I was unsuccessful. Perhaps these products were converted to derivatives that escaped detection. Actually, only low yields of the β-keto ester and amide have previously been obtained from ethyl acetate and sodium amide[4,5] (see previous section).

The possibility that the β-hydroxy ester I was cleaved by an equivalent of sodium amide because the benzophenone was removed from the equilibrium seems unlikely, since III was not cleaved. In line with this, evidence was obtained that the ketone was not converted to the addition compound $(C_6H_5)_2C(ONa)NH_2$ by reaction with sodium amide, a low concentration of which might have been present in equilibrium. Thus, the suspension resulting from the replacement of the ammonia by ether appeared to contain none of this salt-like product, which should be insoluble in ether (see Experimental).

A better established example of a cleavage by an equivalent of sodium amide brought about because of further reaction of one or both of the products was observed previously[6] with sodio-β-hydroxy ester VI in ether. In this cleavage the ketone and sodio ethyl acetate present in the equilibrium underwent hydrogen-metal exchange followed by Claisen acylation of the resulting sodio ketone (Scheme C). Sodio salt VI was formed from the corresponding β-hydroxy ester and an equivalent of sodium amide.

Scheme C


CH_3
C_6H_5—C—$CH_2COOC_2H_5$
ether
ONa
VI
CH_3
C_6H_5—C=O + $NaCH_2COOC_2H_5$
metal-hydrogen exchange
$(C_6H_5COCHCOCH_3)Na$
$C_6H_5COCH_2Na + CH_3COOC_2H$

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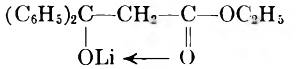
(7) See H. E. Zaugg, *J. Am. Chem. Soc.*, **72**, 3001 (1952).

It can be seen from Table II that, whereas β-hydroxy ester I was cleaved with one equivalent or slightly more of sodium amide or potassium amide, the β-hydroxy ester was recovered after standing with two equivalents of sodium amide under similar conditions (exp. 3). This lack of appreciable cleavage with two equivalents of reagent, which is in agreement with the observation in the previous section concerning the condensation of ethyl acetate with benzophenone (see Table I), may be ascribed to the formation of the relatively stable disodio β-hydroxy ester I″.

It can be seen further from Table II that, in contrast to sodium amide, a catalytic or equivalent amount of lithium amide failed to effect appreciable cleavage of β-hydroxy ester I during four hours, although longer time or more drastic conditions might possibly produce some cleavage. This metallic cation effect appears to be ascribable to less ionization of the lithium-oxygen bond and more chelation in the lithio-β-hydroxy ester VII than in the corresponding sodio-β-hydroxy ester I′.

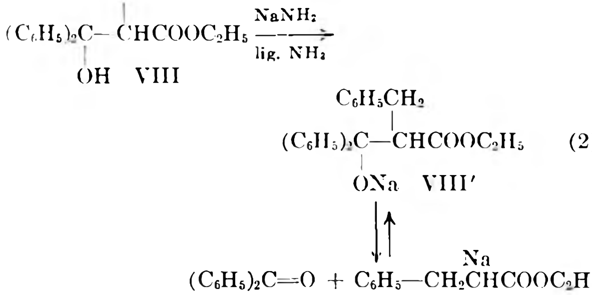


$$\begin{array}{l}(C_6H_5)_2C{-}CH_2{-}C{-}OC_2H_5\\ \qquad\;|\qquad\qquad\;\;\|\\ \quad\;\; OLi \longleftarrow O\end{array}$$

VII

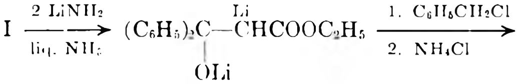
A similar metallic cation effect has previously been observed[6] in ether with sodio-β-hydroxy ester VI and the corresponding lithio-β-hydroxy ester. Although the lithio-β-hydroxy ester failed to cleave appreciably in refluxing ether it was cleaved in refluxing toluene to form benzoylacetone and the self-condensation product of acetophenone.[6]

It should be mentioned that β-hydroxy ester VIII has recently[3] been cleaved by means of 1.25 equivalents of sodium amide in liquid ammonia to form, after inverse neutralization, benzophenone and ethyl hydrocinnamate in high yields. This β-hydroxy ester has now been cleaved similarly with one equivalent of potassium amide. In contrast to sodio β-hydroxy ester III which was stable for at least four hours (see Table II), the sodio or potassio β-hydroxy ester VIII′ establishes an equilibrium with benzophenone and the alkali ethyl hydrocinnamate apparently on the side of the two latter components (Equation 2).



$$\begin{array}{l}\quad C_6H_5CH_2\\ \qquad\quad |\\ (C_6H_5)_2C{-}CHCOOC_2H_5 \xrightarrow[\text{liq. NH}_3]{NaNH_2}\\ \quad\;\; |\\ \quad OH\quad VIII\end{array}
\qquad
\begin{array}{l}\qquad C_6H_5CH_2\\ \qquad\qquad |\\ (C_6H_5)_2C{-}CHCOOC_2H_5\\ \qquad |\\ \quad ONa\quad VIII'\\ \qquad\;\; \downarrow\!\uparrow\\ (C_6H_5)_2C{=}O + C_6H_5{-}CH_2\overset{Na}{C}HCOOC_2H_5\end{array}\quad (2)$$

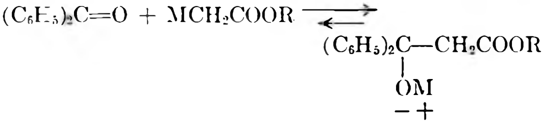
If this position of equilibrium is later established, it could presumably be ascribed to steric factors. Indirect support for this position of equilibrium is our observation that sodio ethyl hydrocinnamate, prepared from the ester and sodium triphenylmethide in ether, failed to yield β-hydroxy ester VIII with benzophenone in this medium even though the reaction mixture was neutralized inversely. The ketone and ester were largely recovered. Actually β-hydroxy ester VIII was obtained, not by an aldol type of condensation,[8] but through the benzylation of the dilithio derivative of β-hydroxy ester I (Equation 3).[3]



$$I \xrightarrow[\text{liq. NH}_3]{2\ LiNH_2} \begin{array}{l}\qquad\qquad\quad Li\\ (C_6H_5)_2C{-}CHCOOC_2H_5\\ \qquad\;\; |\\ \qquad OLi\end{array} \xrightarrow[2.\ NH_4Cl]{1.\ C_6H_5CH_2Cl}$$

VIII (3)

Factors in condensation. The greater thermodynamic stability of the neutral ester and ketone molecules than the neutral β-hydroxy ester (see above) suggests that the addition of the sodio or lithio alkyl acetate to the carbonyl group of benzophenone to form the metallo β-hydroxy ester is dependent on the formation of the more weakly basic anion of this product (Equation 4).[9] Contributing factors may be chelation, especially with the lithio derivative as indicated in VII, and precipitation of the product.



$$(C_6H_5)_2C{=}O + MCH_2COOR \rightleftharpoons \begin{array}{l}(C_6H_5)_2C{-}CH_2COOR\\ \qquad\;\; |\\ \qquad OM\\ \qquad -\,+\end{array}\quad (4)$$

In line with this hypothesis, lithio malonic ester, the anion of which is a weaker base than an alkoxide ion such as that shown in Equation 4, failed to add to the carbonyl group of benzophenone in liquid ammonia during one hour, and the starting compounds were recovered. The lithio malonic ester was prepared by means of an equivalent of lithium amide in liquid ammonia. The condensation failed even in the presence of excess lithium amide, which was employed to effect ionization of the α-hydrogen of the possible condensation product.

Similar observations have been reported by earlier workers. Thus, sodio and lithio malonic esters,[10] prepared by means of sodium and lithium triphenylmethides in ether, failed to add to the carbonyl group of benzaldehyde in this solvent and the malonic ester was recovered. Malonic ester was condensed with benzaldehyde by sodium ethoxide

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(8) The possibility of effecting the aldol type condensation of lithio- or magnesium-bromo ethyl hydrocinnamate with benzophenone seems worthy of consideration. Although the Reformatsky reaction of ethyl α-bromohydrocinnamate with this ketone has apparently not been reported, that with 2-methylcyclohexanone has been achieved; R. Grewe, *Ber.*, **76B**, 1076 (1943).

(9) For similar suggestions in the condensations of sodium diphenylmethide and dialkali phenylacetates with benzophenone see P. J. Hamrick, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, 81, 3146 (1956); P. J. Hamrick, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, 82, 1957 (1960).

(10) G. Wittig, U. Todt, and K. Nagel, *Ber.*, **83**, 110 (1950).

or amines in refluxing ethanol, but the product was benzalmalonic ester (22%).[10] Apparently the dehydration of the intermediate aldol furnished the needed driving force.

Finally, it should be pointed out that the present addition reaction illustrated by Equation 4 is analogous to those of the common organometallic compounds such as sodium diphenylmethide,[9] phenyllithium, and the Grignard reagent with ketones or aldehydes, at least most of which form more weakly basic anions.

EXPERIMENTAL[11]

Condensations of alkyl acetates with benzophenone by sodium amide. Ethyl, isopropyl, and *t*-butyl acetates were condensed with benzophenone by 1–2 equivalents of sodium amide in liquid ammonia[12] to form β-hydroxy esters I, II, and III respectively. The results including failures are summarized in Table I. Some experiments are described in detail below.

A. Experiments with ethyl acetate. In Experiment 1, a solution of 17.6 g. (0.2 mole) of ethyl acetate in an equal volume of ether was added through the addition funnel as rapidly as possible to a stirred suspension of 0.22 mole of sodium amide in 400 ml. of commercial anhydrous liquid ammonia. Since frothing occurred, a reaction vessel having a volume twice that of the amide suspension was used. As the last of the ester passed through the stopcock, a solution of 36.4 g. (0.2 mole) of benzophenone in 70 ml. of anhydrous ether was poured immediately into the addition funnel and allowed to run into the reaction flask as rapidly as possible, the addition funnel being rinsed with a little ether. The resulting white suspension was stirred for 5 min. and was then inversely neutralized by pouring it into a solution of ammonium chloride in liquid ammonia. The ammonia was evaporated to dryness. The residue was stirred with cold water and filtered to yield a white solid, which crystallized from petroleum ether (b.p. 60–90°) to give 38.1 g. (71%) of ethyl β-hydroxy-β,β-diphenylpropionate (I), m.p. 86–87°, reported[13] m.p. 87°.

In Experiment 3, a solution of 17.6 g. (0.2 mole) of ethyl acetate in an equal volume of ether was added rapidly to a stirred solution of 0.4 mole of sodium amide in 400 ml. of liquid ammonia followed immediately by 36.4 g. (0.2 mole) of benzophenone in 70 ml. of ether (see previous experiment). The resulting black solution was stirred for 1 hr. and was inversely neutralized with ammonium chloride. The ammonia was evaporated on the steam bath as 300 ml. of ether was added. Water was added and the aqueous layer was thoroughly extracted with ether. The combined ethereal solution was dried and evaporated to a residue which, upon crystallization from petroleum ether (b.p. 60–90°) gave 38.7 g. (72%) of β-hydroxy ester I, m.p. 85–86°.

B. Experiments with isopropyl acetate. In Experiment 5, a solution of 16.5 g. (0.16 mole) of isopropyl acetate in an equal volume of ether was added rapidly to a stirred suspension of 0.16 mole of sodium amide in 400 ml. of liquid ammonia, followed immediately by 30 g. (0.16 mole) of benzophenone in 70 ml. of ether (see experiment 2 with ethyl acetate). The suspension was stirred for 5 min. and was inversely neutralized with ammonium chloride. The ammonia was replaced by ether. Water was added and the aqueous layer was thoroughly extracted with ether. The combined ethereal solution was evaporated and the residue was crystallized from petroleum ether (b.p. 60–90°) to give 26.1 g. (56%) of isopropyl-β-hydroxy-β,β-diphenylpropionate (II), m.p. 101–102°.

Following removal of II, the filtrate was concentrated and cooled to yield 10.2 g. (34%) of crystalline benzophenone, m.p. 46–47°, reported[14] m.p. 48–48.5°.

C. Experiment with t-butyl acetate. In Experiment 9, a solution of 23.3 g. (0.2 mole) of *t*-butyl acetate in an equal volume of ether was added to a stirred suspension of 0.4 mole of sodium amide in 400 ml. of liquid ammonia. After stirring for 20 min., 36 g. (0.2 mole) of benzophenone in 75 ml. of ether was added. The reaction mixture was stirred for 1 hr. and was inversely neutralized with ammonium chloride. The ammonia was replaced by 300 ml. of ether. Water was added and the aqueous layer was thoroughly extracted with ether. The combined ethereal solution was dried and evaporated. The residue was crystallized from ethanol to give 41.5 g. (70%) of *t*-butyl β-hydroxy-β,β-diphenylpropionate (III), m.p. 92–93°, reported[15] m.p. 92–93°.

Treatment of sodio ethyl acetate with acetophenone. A reaction identical to Exp. 1, Table I (above), with ethyl acetate was carried out, but using 0.2 mole of acetophenone in place of benzophenone. The ethereal residue at the end of the reaction workup was vacuum distilled to give 20.1 g. (84%) of recovered acetophenone, b.p. 88–90°/16 mm, reported[16] b.p. 88.5° at 16 mm. Neither the combined ethereal solution, nor the orange residue obtained upon its evaporation gave a positive enol test.

Repeating this experiment, but using 2 equivalents of sodium amide gave a similar result.

Attempted condensation of ethyl hydrocinnamate with benzophenone. To a stirred suspension of 0.07 mole of sodium amide in 300 ml. of anhydrous liquid ammonia was added 16.8 g. (0.07 mole) of solid triphenylmethane. The deep red solution was stirred for 15 min. and 12.2 g. (0.07 mole) of ethyl acetate in an equal volume of ether was added. The red triphenylmethide color was discharged at the end of the addition and a gray suspension formed. After stirring for 5 min., 12.5 g. (0.07 mole) of benzophenone in 25 ml. of ether was added. The gray suspension was stirred for 1 hr. and was then inversely neutralized with ammonium chloride. The ammonia was replaced by ether and water was added. The aqueous layer was thoroughly extracted by ether. The combined ethereal solution was dried and the solvent was removed. The resulting orange residue was crystallized from petroleum ether (b.p. 60–90°) to give 15.6 g. (93%) of recovered triphenylmethane, m.p. 92–93°, reported[17] m.p. 93–94°. Concentrating and cooling the filtrate precipitated 10.2 g. (82%) of benzophenone, m.p. 46–47°. The remaining filtrate was distilled to give 10.65 g. (85%) of recovered ethyl hydrocinnamate, b.p. 246–248° at 750 mm, reported[18] 247° at 760 mm.

General procedure for cleavages of β-hydroxy esters I, II, *and* III *by alkali amides.* The yields of benzophenone obtained by the cleavage of the β-hydroxy esters and/or the per cent recovery of the β-hydroxy esters upon noncleavage are summarized in Table II.

To a stirred suspension of the appropriate quantity of the alkali amide (see Table II) in 400 ml. of anhydrous liquid ammonia were added 0.05–0.08 mole of the β-hydroxy ester in sufficient ether to effect their solutions. The resulting suspensions were stirred for 4 hr. and were then inversely neutralized by pouring them with stirring into solutions of ammonium chloride in liquid ammonia. The ammonia was then replaced by 300 ml. of ether and water was added. The aqueous layers were extracted thoroughly with ether. The combined ethereal solutions were dried and then evaporated. The resulting residues were then fractionally crystallized from petroleum ether (b.p. 60–90°) to give recovered β-hydroxy ester and/or benzophenone. Since the β-hydroxy ester is only slightly soluble in this solvent, it crystallizes first, reduction of the solvent volume and cooling being required for recovery of the ketone. In each case the identities of the β-hydroxy ester and ketone were verified by comparison of their infrared spectra with those of the respective authentic substances.

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[11] The melting points were taken on a Fisher-Johns melting point apparatus.

[12] For the preparation of the reagent see C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 122 (1954).

[13] H. Rupe and E. Busolt, *Ber.*, **40**, 4537 (1907).

[14] E. Linnemann, *Ann.*, **133**, 1 (1865).

[15] K. Sisido, H. Nozaki, and O. Kurihara, *J. Am. Chem. Soc.*, **74**, 6254 (1952).

[16] C. R. Noller and R. Adams, *J. Am. Chem. Soc.*, **46**, 1889 (1924).

[17] P. Sabatier and M. Murat, *Compt. rend.* **158**, 764 (1914).

[18] W. H. Perkin, *J. Chem. Soc.*, **69**, 1025 (1896).

In a repetition of Experiment 2, Table II, involving β-hydroxy ester I and one equivalent of sodium amide, the ammonia was replaced by ether at the end of 4 hr. and the ethereal suspension, without being neutralized, was filtered through a fritted-glass funnel. Benzophenone (86%) was obtained from the ethereal filtrate in the usual manner following acidification with aqueous hydrochloric acid. The solid on the funnel was shown not to contain a benzophenone–sodium amide addition complex by its noninflammability, and by the fact that its acidification produced no benzophenone.

Cleavage of β-hydroxy ester I by sodium ethoxide. To a solution of 0.0008 mole of sodium ethoxide in 50 ml. of absolute ethanol was added 2.0 g. (0.007 mole) of β-hydroxy ester I. The mixture was allowed to stand at room temperature with occasional shaking for 48 hr. when complete solution was achieved. The solution was poured with stirring into a solution of 5 ml. of concd. hydrochloric acid and 25 ml. of water. Much (50 ml.) of the solvent was removed, and the residue extracted with ether. There was isolated 2.6 g. (85%) of the 2,4-dinitrophenylhydrazone of benzophenone, m.p. 236–238°, reported[19] m.p. 238°.

In a blank experiment with β-hydroxy ester I and absolute ethanol, essentially complete recovery of this compound was realized.

Attempted condensation of malonic ester and benzophenone by lithium amide. To a stirred suspension of 0.1 mole of lithium amide in 400 ml. of anhydrous liquid ammonia was added 16 g. (0.1 mole) of diethyl malonate in an equal volume of ether. The suspension was stirred for 5 min. and 18.2 g. (0.1 mole) of benzophenone in 40 ml. of anhydrous ether was added. After stirring for 1 hr. the suspension was inversely neutralized with ammonium chloride. The ammonia was replaced by 300 ml. of ether. The combined ethereal solution was then evaporated. The resulting residue was vacuum distilled to give 14.8 g. (92%) of recovered diethyl malonate, b.p. 94–98° at 18 mm, reported[20] b.p. 88–89° at 13 mm. Also, 15.9 g. (88%) of benzophenone was recovered, b.p. 186–189° at 15 mm. The benzophenone reaction, after solidification, was crystallized from petroleum ether (b.p. 60–90°) to give crystals of the ketone, m.p. 46–47°.

Repetition of this reaction, but using 2, 3 or 4 equivalents of lithium amide, gave comparable recoveries of the ketone and diester in each case.

DURHAM, N. C.

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(19) N. R. Campbell, *Analyst*, 61, 393 (1936).

(20) H. Reitter and A. Weindel, *Ber.*, 40, 3361 (1907).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT CENTER OF THE FOOD MACHINERY AND CHEMICAL CORPORATION]

α-Oximinoketones. VII. Synthesis of Alkyl 5-Cyano-2-oximinovalerates and DL-Lysine from 2,6-Dioximinocyclohexanone[1]

ARTHUR F. FERRIS, GRANNIS S. JOHNSON,[2] FRANCIS E. GOULD, AND HUGO STANGE

Received January 8, 1960

DL-Lysine monohydrochloride has been prepared in 63% over-all yield from cyclohexanone by a three-step synthesis which involves: (1) nitrosation of cyclohexanone to give 2,6-dioximinocyclohexanone (75%), (2) reaction of 2,6-dioximinocyclohexanone in ethanolic sodium ethoxide with acetic anhydride to give ethyl 5-cyano-2-oximinovalerate (92%), and (3) hydrogenation of ethyl 5-cyano-2-oximinovalerate over Raney nickel in acetic anhydride containing a basic co-catalyst followed by hydrolysis with hydrochloric acid to give DL-lysine monohydrochloride (92%). Discovery that ethanol could be used as solvent for step (2) and Raney nickel as catalyst for step (3) more than doubled the overall yield obtained in previous versions of this synthesis.[3,4]

In two previous papers[3,4] the two similar syntheses of DL-lysine from cyclohexanone outlined below as routes (A) and (B) (p. 1303) were described.

In both syntheses the key reaction was the "partial cleavage" of 2,6-dioximinocyclohexanone to 5-cyano-2-oximinovaleric acid or a derivative. It is readily apparent that conversion of cyclohexanone to lysine *via* this key reaction offers an extremely facile synthesis of this important amino acid, quite possibly more direct than any previously reported. Neither of the previous versions of this synthesis realized its full potential, however, since both suffered from unsatisfactory yields in the steps following the relatively satisfactory initial nitrosation (75% yield). Thus in the first version of the synthesis (route A),[3] the yield in the partial cleavage step was 62% and in the reduction step only 43%, giving an over-all yield of 20%. In the second version (route B),[4] the excellent 88% yield of the partial cleavage was in part offset by the necessity for introducing a separate acylation step (76% yield), so that the over-all conversion of 2,6-dioximinocyclohexanone to ethyl 5-cyano-2-oximinovalerate was 67%.

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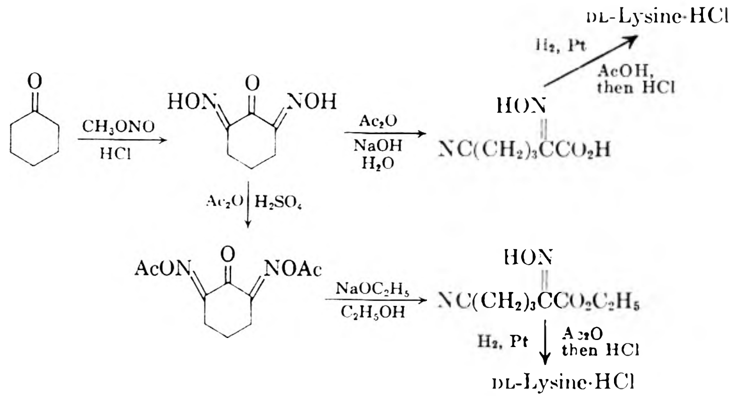
(1) A preliminary account of this work appeared in *Chem. & Ind. (London)*, 996 (1959).

(2) Present address: General Aniline and Film Corp., Linden, N. J.

(3) A. F. Ferris, G. S. Johnson, F. E. Gould, and H. K. Latourette, *J. Org. Chem.*, 25, 492 (1960).

(4) A. F. Ferris, G. S. Johnson, and F. E. Gould, *J. Org. Chem.*, 25, 496 (1960).



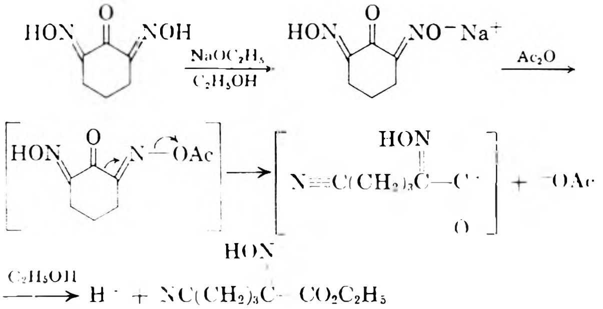
(A)

(B)

Again the reduction step was the least satisfactory, a yield of only 57% being obtained. Although in simplicity and over-all yield (29%) this version probably compares favorably with most reported lysine syntheses, it still did not constitute the superior method which was the goal of this work. The attainment of high yields in the partial cleavage and reduction steps, which would afford such a superior method, was ample incentive for further study of these reactions.

In the course of an examination of the partial cleavage reaction, it was found that high yields could be obtained and isolation of a 2,6-diacyloximinocyclohexanone avoided by a very simple expedient: When 2,6-dioximinocyclohexanone was added to an alcohol containing an equivalent or a little more of strong base, a monosalt appeared to be formed. A completely clear solution was not obtained, but the solid dioxime seemed to go into solution and another solid appeared to come out. When the slurry thus obtained was treated with about an equivalent of acetic or propionic anhydride, very high yields of alkyl 5-cyano-2-oximinovalerates were obtained. Because of its convenience, the combination of sodium ethoxide in ethanol with acetic anhydride as acylating agent was the subject of the most study, and eventually yields as high as 92% were obtained consistently with this system. A number of other combinations of alcohol and strong base also gave good yields with acetic anhydride as acylating agent, including sodium methoxide, magnesium methoxide, and benzyltrimethylammonium hydroxide in methanol, sodium and potassium hydroxide in ethanol, sodium isopropoxide in isopropyl alcohol, and sodium benzylate in benzyl alcohol. In essence, then, it was found that an alcohol could be used instead of water as the solvent for the second order Beckmann rearrangement, with the difference that an ester instead of a carboxylic acid product was obtained. From the standpoint of the lysine synthesis, this was a tremendously important difference, since, unlike 5-cyano-2-oximinovaleric acid, the alkyl 5-cyano-2-oximinovalerates are not cleaved further by acylating agent and base.[4] Thus the use of an alcohol as solvent for the cleavage step retained the simplicity of that step in route A, but avoided the secondary cleavage to glutaronitrile which reduced the yield of 5-cyano-2-oximinovaleric acid in A.

The success of the second order Beckmann rearrangement in alcohols was at first surprising. In typical experiments the mole ratio of alcohol hydroxyl to oxime hydroxyl ranged from 12:1 to 70:1, yet the acid anhydride reacted with the oxime hydroxyl exclusively. It seemed logical to explain this striking selectivity on the basis of ionization of the oxime, since the oxime anion would be expected to be much more effective in attacking the anhydride than the neutral alcohol molecule.[5] Evidence substantiating this hypothesis was obtained when 2,6-dioximinocyclohexanone was slurried in alcohols containing weak bases like pyridine and *n*-butylamine and treated with an equivalent of acetic anhydride. Under these conditions yields of oximino ester were very poor. This is the expected result, since the neutral oxime hydroxyl has no particular advantage over the neutral alcohol hydroxyl in reactivity toward the anhydride. On the basis of all these data, the probable course of the successful reaction with strong base is that shown below:



Interestingly, acid chlorides were much less selective than anhydrides in reacting with the oxime anion in preference to the alcohol. When used in conjunction with sodium ethoxide in ethanol, equivalent amounts of acetyl chloride, benzoyl chloride, and benzenesulfonyl chloride

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(5) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, 1956, p. 300.

gave only 20–40% yields of ethyl 5-cyano-2-oximinovalerate, and substantial amounts of unchanged 2,6-dioximinocyclohexanone were recovered. It is possible that the poor performance of the acid chlorides is the result of their tendency to react, at least in part, by an S$_N$1 mechanism. A situation where reaction with the alcohol by such a mechanism competed with nucleophilic attack by the oxime anion would be expected to give the observed result, namely some selectivity in favor of the oxime anion but not the complete selectivity observed with anhydride where S$_N$2 attack is the only path of reaction.[5]

An effort was made to simplify the preparation of alkyl 5-cyano-2-oximinovalerates still further by preparing 2,6-dioximinocyclohexanone in an alcohol and carrying out the cleavage in the same solvent without isolating the dioxime. Since base is necessary for the cleavage reaction, a base-catalyzed nitrosation[6] was obviously most convenient. When a solution of cyclohexanone in ethanol containing slightly more than an equivalent of sodium ethoxide was treated with ethyl nitrite[6] and then with acetic anhydride, a 50% yield of ethyl 5-cyano-2-oximinovalerate was obtained. When the nitrosation was carried out in ethanol but in the presence of a catalytic amount of hydrochloric acid, and then enough sodium ethoxide was added to neutralize the acid and convert the 2,6-dioximinocyclohexanone to the monosodium salt, treatment with acetic anhydride gave a 64% yield of ethyl 5-cyano-2-oximinovalerate. Neither of these yields is quite as good as the 69% over-all yield obtained by isolating 2,6-dioximinocyclohexanone and then cleaving it in ethanolic sodium ethoxide with acetic anhydride. It should be noted, however, that the simpler processes were not studied in as much detail as the route involving isolation of 2,6-dioximinocyclohexanone.

When the cleavage step had been improved as described above, the only unsatisfactory yield remaining was that in the critical reduction step. An extended search was made in an effort to find a catalyst-solvent system which would permit hydrogenation of ethyl 5-cyano-2-oximinovalerate to lysine without the side reactions which apparently were responsible for the low yields obtained in earlier work.[3,4] In the course of this search the combination of Raney nickel and acetic anhydride was tried. Although Adkins' classic work on catalytic hydrogenation[7] states that this combination cannot be used, recent work[8–10] has indicated that use of this catalyst-solvent system, particularly with the addition of sodium acetate or other weak base,[8,9] enables oximes to be hydrogenated in good yield to acetylated primary amines. The use of the combination of a Raney metal catalyst and an acid anhydride solvent in the hydrogenation of nitriles does not appear to have been reported. Surprisingly, this combination proved to be strikingly more effective in the reduction of ethyl 5-cyano-2-oximinovalerate than the apparently very similar platinum–acetic anhydride system. At 50 p.s.i. and 50°, and with sodium acetate as co-catalyst, hydrogenation usually was complete in about two hours, and lysine monohydrochloride was isolated in 92% yield after hydrolysis of the reaction mixture with hydrochloric acid. With a platinum catalyst, temperatures above 25° led to difficulty, and hydrogenation at 25° and 50 p.s.i. required eight hours and resulted in a yield of only 57%. Further study showed that even more rapid hydrogenation, complete in fifteen minutes, and equally good yields were obtained when strong bases such as sodium hydroxide, potassium hydroxide, or benzyltrimethylammonium hydroxide were used as co-catalysts. Very poor yields of lysine were obtained when no basic co-catalyst was used. The strong base co-catalysts had the additional advantage that the catalyst recovered after their use was as active as fresh catalyst, and could be re-used repeatedly. With a sodium acetate co-catalyst, the activity of the Raney nickel diminished markedly after each use, and was too low to be of practical use after three or four cycles. The platinum catalyst, by way of comparison, was completely inactive after a single use.

When the reaction mixture was worked up by evaporating excess acetic anhydride and the acetic acid formed in the reduction and by precipitating the co-catalyst from the resulting sirup by the addition of ethyl acetate and ether, the previously uncharacterized ethyl ester of *N,N'*-diacetyllysine was obtained in 98% yield. The somewhat lower yield obtained when lysine was isolated as the monohydrochloride was probably the result of mechanical losses in the crystallization step. The ethyl ester of *N,N'*-diacetyllysine was obtained as a viscous sirup which partially crystallized on long standing.

With the completion of the work reported here, the synthesis of lysine from cyclohexanone *via* 2,6-dioximinocyclohexanone reached its final form. The preferred route includes nitrosation of cyclohexanone with methyl nitrite to give 2,6-dioximinocyclohexanone (75%), partial cleavage of 2,6-dioximinocyclohexanone in ethanolic sodium ethoxide with acetic anhydride to give ethyl 5-cyano-2-oximinovalerate (92%), and hydrogenation of ethyl 5-cyano-2-oximinovalerate in acetic anhydride over Raney nickel with a basic co-catalyst

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(6) O. Touster, *Org. Reactions*, **7**, 350 (1953).

(7) H. Adkins, *Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts*, University of Wisconsin Press, Madison, Wis., 1937.

(8) S. I. Lur'e, G. A. Ravdel, and E. S. Chaman, *Zhur. Obshchei Khim.*, **22**, 2011 (1952); *J. Gen. Chem. U.S.S.R. (Eng. Transl.)*, **22**, 2065 (1952).

(9) M. Vignau, *Bull. soc. chim. France*, 638 (1952).

(10) N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.*, **9**, 23 (1955).

(92%). The over-all yield is 63%. With a slight penalty in yield the first two steps can be combined and the isolation of 2,6-dioximinocyclohexanone avoided. In either variation, this sequence of reactions offers probably the simplest and most direct chemical synthesis of lysine presently available.

EXPERIMENTAL[11]

Methyl 5-cyano-2-oximinovalerate. (1) *From sodium methoxide in methanol.* A solution of sodium methoxide in methanol was prepared by dissolving 5.0 g. (0.22 g.-atom) of sodium in 250 ml. of absolute methanol. To this solution was added 31.2 g. (0.20 mole) of 2,6-dioximinocyclohexanone,[3] and the mixture was stirred until most of the dioxime had dissolved. Then 22.0 g. (0.22 mole) of acetic anhydride was added dropwise, the temperature being held at 20–30° by external cooling. When addition was complete, the methanol was evaporated under reduced pressure. The residue was taken up in 500 ml. of ether, and the solid which failed to dissolve (sodium acetate) was removed by filtration. The filtrate was stirred with activated charcoal for an hour and dried over anhydrous magnesium sulfate. Removal of solids and evaporation of solvent under reduced pressure left 25.0 g. (74%) of liquid methyl 5-cyano-2-oximinovalerate, n_D^{25} 1.4779. On long standing this material crystallized to a solid, m.p. 61.5–62°.

Anal. Calcd. for $C_7H_{10}O_3N_2$: C, 49.39; H, 5.92; N, 16.46. Found: C, 49.08; H, 5.95; N, 16.50.

(2) *From magnesium methoxide in methanol.* To a solution of 1.2 g. (0.05 g.-atom) of magnesium metal in 300 ml. of methanol was added 15.6 g. (0.10 mole) of 2,6-dioximinocyclohexanone. While the temperature was maintained at 20–30° by external cooling, 10.2 g. (0.10 mole) of acetic anhydride was added. When addition was complete the cooling bath was removed, and the temperature rose to 40°. After the mixture had cooled to room temperature the solvent was evaporated under reduced pressure, and the residue was taken up in 500 ml. of ether. The solid which failed to dissolve was removed by filtration, and the filtrate was washed with 300 ml. of saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the ether left 11.0 g. (65%) of liquid methyl 5-cyano-2-oximinovalerate. The infrared spectrum of this liquid was identical with that of an authentic sample of methyl 5-cyano-2-oximinovalerate.

(3) *From benzyltrimethylammonium hydroxide in methanol.* To a solution of 8.3 g. (0.05 mole) of benzyltrimethylammonium hydroxide in 300 ml. of methanol was added 7.8 g. (0.05 mole) of 2,6-dioximinocyclohexanone. Most but not all of the solid dissolved on stirring. While the temperature was maintained at 20–30° by external cooling 5.1 g. (0.05 mole) of acetic anhydride was added. The reaction mixture was worked up as described under (2) to give 5.0 g. (59%) of liquid methyl 5-cyano-2-oximinovalerate. The infrared spectrum of this sample was identical with that of an authentic sample.

Ethyl 5-cyano-2-oximonovalerate. (1) *From sodium ethoxide in ethanol.* To a solution of 13.8 g. (0.60 g.-atom) of sodium in 750 ml. of absolute ethanol was added 78.0 g. (0.50 mole) of 2,6-dioximinocyclohexanone. To the resulting slurry was added 61.0 g. (0.60 mole) of acetic anhydride over 30 min., the temperature being held at 20–30° by external cooling. The solvent was evaporated under reduced pressure at 60–70°, and the resulting semisolid mass was taken up in 1000 ml. of ether. The solid which failed to dissolve was removed by filtration, and the ether solution was washed with 1000 ml. of saturated sodium bicarbonate solution. After drying over magnesium sulfate, the ether was evaporated to leave 85.0 g. (92%) of solid ethyl 5-cyano-2-oximinovalerate. A portion of the material was recrystallized from carbon tetrachloride to give a white solid, m.p. 73°. A mixture of this solid and authentic ethyl 5-cyano-2-oximinovalerate[3] melted at 73°.

(2) *From potassium hydroxide in ethanol.* This reaction was carried out as described under methyl 5-cyano-2-oximinovalerate (2), using a solution of 5.6 g. (0.10 mole) of potassium hydroxide in 300 ml. of absolute ethanol, 15.6 g. (0.10 mole) of 2,6-dioximinocyclohexanone, and 10.2 g. (0.10 mole) of acetic anhydride. There was obtained 12.0 g. (65%) of ethyl 5-cyano-2-oximinovalerate. The infrared spectrum of this sample was identical with that of an authentic sample.

Isopropyl 5-cyano 2-oximinovalerate. To 1000 ml. of isopropyl alcohol heated to 60° was added 13.0 g. (0.57 g.-atom) of sodium at 60–70°. When the sodium had dissolved, 78.0 g. (0.50 mole) of 2,6-dioximinocyclohexanone was added, and then, at 50–60°, 58.0 g. (0.57 mole) of acetic anhydride. When heat evolution had ceased, the solvent was evaporated under reduced pressure, and the residue was taken up in 1000 ml. of ether. The material which failed to dissolve was removed by filtration, and the filtrate was washed with 500 ml. of saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the ether left 51.0 g. (51%) of isopropyl 5-cyano-2-oximinovalerate, an oil which crystallized on standing. Recrystallization of a portion of the material from 5:1 cyclohexane–ethyl acetate gave pure white crystals, m.p. 55–56°. The infrared spectrum of this material was identical with that of an authentic sample.[4]

Benzyl 5-cyano-2-oximinovalerate. To a solution of 2.3 g. (0.10 g.-atom) of sodium in 200 ml. of benzyl alcohol was added 15.6 g. (0.10 mole) of 2,6-dioximinocyclohexanone. The mixture was stirred until most of the solid had gone into solution, and then 10.9 g. (0.11 mole) of acetic anhydride was added, the temperature being held at 20–30°. After addition was complete the alcohol was evaporated under reduced pressure, and the residue was taken up in 1000 ml. of ether. The insoluble material was removed by filtration, and the filtrate was evaporated under reduced pressure. Since some product appeared to have remained in the insoluble solid, the filter cake was taken up in water, and the material which failed to dissolve was combined with the residue from the evaporation of the ether filtrate. This procedure gave a total of 14.0 g. (54%) of crude benzyl 5-cyano-2-oximinovalerate, m.p. 125–130°. A portion of the crude solid was recrystallized three times from benzene to give pure benzyl 5-cyano-2-oximinovalerate, m.p. 132–134°. The infrared spectra of the crude and recrystallized materials were identical.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38; Found: C, 63.20; H, 5.52; N, 10.97.

Ethyl 5-cyano-2-oximinovalerate by the one-step procedure. (1) *Base-catalyzed nitrosation.* To a solution of 5.0 g. (0.22 g.-atom) of sodium in 300 ml. of absolute ethanol was added 19.6 g. (0.20 mole) of cyclohexanone. A separate ethyl nitrite generator was charged with 36.0 g. (0.52 mole) of sodium nitrite, 24.0 g. (0.52 mole) of ethanol, and 40 ml. of water, and was connected to the reactor by a tube leading below the liquid level in the reactor. With the generator at 25°, a solution of 40.0 g. (0.40 mole) of sulfuric acid in 40 ml. of water was added dropwise to the nitrite-ethanol solution, thereby generating ethyl nitrite, which passed over into the reactor. The reactor was stirred vigorously and was maintained at 30–40° by external cooling. When all the ethyl nitrite had been admitted, the reactor contents were stirred for an additional 30 min. Then while the temperature was maintained at 20–30°, 24.0 g. (0.24 mole) of acetic anhydride was added dropwise. When addition was complete volatile materials were evaporated under reduced pressure, and the residue was taken up in 500 ml. of ether. The material which failed to dissolve was removed by filtration, and the filtrate was washed with saturated sodium bicarbonate

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(11) All melting points are uncorrected.

solution, decolorized with activated charcoal, and dried over anhydrous magnesium sulfate. Evaporation of the ether left 18.0 g. (50%) of crude ethyl 5-cyano-2-oximinovalerate. Recrystallization of a portion of this material from carbon tetrachloride gave pure ethyl 5-cyano-2-oximinovalerate, m.p. 73–74°. The infrared spectrum of this material was identical with that of an authentic sample.

(2) *Acid-catalyzed nitrosation.* Into a solution of 19.6 g. (0.20 mole) of cyclohexanone and 4 ml. of concd. hydrochloric acid in 150 ml. of absolute ethanol was passed 39.1 g. (0.52 mole) of ethyl nitrite generated as described in the preceding experiment. The reaction temperature was held at 30–40° by external cooling. The mixture was stirred for 30 min. after all the nitrite had been admitted, then a solution of 6.0 g. (0.25 g.-atom) of sodium in 150 ml. of absolute ethanol was added. The basic solution which resulted was held at 20–30° by external cooling while 22.0 g. (0.22 mole) of acetic anhydride was added. When addition was complete volatile materials were evaporated under reduced pressure, and the residue was taken up in 300 ml. of ether. The solid which failed to dissolve was removed by filtration, and the filtrate was washed with saturated sodium bicarbonate solution, decolorized with activated charcoal, and dried over anhydrous magnesium sulfate. The ether was evaporated under reduced pressure to leave 23.0 g. (64%) of crude ethyl 5-cyano-2-oximinovalerate. A portion of this material was recrystallized from carbon tetrachloride to give pure ethyl 5-cyano-2-oximinovalerate, m.p. 73–74°. The infrared spectrum of this compound was identical with that of an authentic sample.

DL-*Lysine monohydrochloride.* (1) *Hydrogenation of ethyl 5-cyano-2-oximinovalerate over Raney nickel with sodium acetate co-catalyst.* A portion of Raney nickel[11] amounting to 3–5 g. was washed twice with 20-ml. portions of ethanol, then twice with 20-ml. portions of acetic anhydride. The washed catalyst and 6.0 g. of anhydrous sodium acetate were then added immediately to a solution of 18.4 g. (0.10 mole) of ethyl 5-cyano-2-oximinovalerate in 120 ml. of acetic anhydride. The resulting mixture was heated to 50° and shaken under hydrogen at an initial pressure of 50 p.s.i. The theoretical amount of hydrogen was taken up in about 2 hr. The catalyst was removed by filtration, and the filtrate was stirred with 80 ml. of water for several hours to decompose the acetic anhydride. Then 180 ml. of concd. hydrochloric acid was added, and the mixture was heated under reflux for 16 hr. The resulting solution was evaporated under reduced pressure to a sirupy mass. The mass was treated with two 50-ml. portions of concd. hydrochloric acid, and evaporated to a sirup after the addition of each portion. The final residue was taken up in 200 ml. of boiling 95% ethanol, and a solution of 10 ml. of pyridine in 20 ml. of ethanol was added. DL-Lysine monohydrochloride began to precipitate almost immediately. To ensure complete precipitation the mixture was held at 5° for 24 hr. At the end of this time 15.6 g. (86%) of DL-lysine monohydrochloride, m.p. 262–264°, was recovered by filtration. Another 1.2 g. was recovered by concentration of the filtrate. The total yield was thus 16.8 g. (92%). The infrared spectrum of this product was identical with that of an authentic sample of DL-lysine monohydrochloride.

(2) *Hydrogenation of ethyl 5-cyano-2-oximinovalerate with benzyltrimethylammonium hydroxide co-catalyst.* A 2–3 g. portion of Raney nickel, washed as described under (1) above, was added along with 1.5 g. of benzyltrimethylammonium hydroxide to a solution of 9.2 g. (0.05 mole) of ethyl 5-cyano-2-oximinovalerate in 60 ml. of acetic anhydride. The resulting mixture was heated and shaken under hydrogen at an initial pressure of 50 p.s.i. until 50° was reached. At this point a vigorously exothermic reaction set in, which raised the temperature to 75° in a few minutes with external heating cut off. The theoretical amount of hydrogen was taken up in 15 min. The reaction mixture was worked up as described under (1) above, halving all quantities of reagents. There was obtained 8.0 g. (88%) of DL-lysine monohydrochloride. The infrared spectrum of this material was identical with that of an authentic sample.

Ethyl ester of N,N'-diacetyllysine. The procedure described under DL-lysine monohydrochloride (1) was followed, except that the sodium acetate was replaced by 3.0 g. of potassium hydroxide. Hydrogen uptake was complete in 15 min., the temperature rising from 50 to 70° during this time with no external heating. The catalyst was removed by filtration, and the acetic acid and acetic anhydride were evaporated from the filtrate under reduced pressure. The viscous sirupy residue was taken up in 100 ml. of ethyl acetate, and the solid which separated was removed by filtration. When 300 ml. of ether was added to the filtrate, it separated into two layers. The ether (upper) layer was separated, and the lower layer was taken up in 50 ml. of ethyl acetate. A small amount of solid separated and was removed by filtration. The filtrate was evaporated under reduced pressure to give 25.2 g. (98%) of sirupy but essentially pure ethyl ester of N,N'-diacetyllysine. The analysis given below was obtained on the sirupy material. On long standing the sirup partially crystallized.

Anal. Calcd. for $C_{12}H_{22}O_4N_2$: C, 55.79; H, 8.59; N, 10.85. Found: C, 55.98; H, 8.57; N, 10.62.

Acknowledgment. The assistance of John E. Zarembo and his staff in carrying out the analyses reported herein and of Herman Adelman and his staff in obtaining and assisting in the interpretation of infrared spectra is gratefully acknowledged.

PRINCETON, N. J.

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(11) Obtained in active form under water from the Raney Catalyst Co., Chattanooga, Tenn.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

Unsymmetrical Tetraalkylmethanes. V.[1] A Study of the Possibility of Rearrangements during Synthesis

NORMAN RABJOHN AND R. J. DEFEO[2,3]

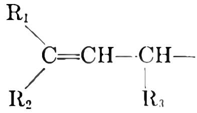
Received January 7, 1960

It has been shown that two alcohols, 5-ethyl-5-methyl-3-decanol and 6-ethyl-6-methyl-4-decanol, which are typical intermediates in a general method of synthesis of tetraalkylmethanes, may be dehydrated over potassium bisulfate to mixtures of olefins without rearrangement of the carbon skeletons.

The previous paper[1] in this series described a general method for the synthesis of tetraalkylmethanes. It was alleged that the dehydration of the intermediate secondary alcohols afforded only mixtures of olefins in which the quaternary carbon atom structure remained intact.

The acid catalyzed rearrangements of a number of related materials have been described,[4] and Mosher and Cox have shown that in the dehydration of 4,4-dimethyl-3-ethyl-2-pentanol, 43% of 4,4-dimethyl-3-ethyl-2-pentene and 57% of 2,4-dimethyl-3-ethyl-3-pentene are obtained. They explained the formation of the latter as due to a 1,3-shift of a methyl group rather than to a series of 1,2-rearrangements.

The present study was undertaken to investigate the possibility of skeletal rearrangements of the initially mentioned carbinols, of the general structure $R_1R_2R_3CCH_2CHOHCH_2R_4$, during dehydration by means of potassium bisulfate. If rearrangements had occurred, mixtures of olefins of the type



$R_1R_2C{=}CH{-}CH(R_3){-}CH_2R_4$

where R_1, R_2 and R_3 may occupy either carbon 1 or 3 would have resulted, which obviously would have led to mixtures of hydrocarbons which were not tetraalkylmethanes.

Since the tetraalkylmethane, 5-ethyl-5-methyldecane, had been prepared[5] previously by a sequence of reactions which did not involve any known rearrangements, it was felt that a comparison of its physical properties with those of the material which would result from the general method of synthesis of tetraalkylmethanes[1] should afford evidence of rearrangements in the process. The latter may be varied so that alkyl groupings of the final hydrocarbons can be introduced in different sequences. Accordingly, it was decided to synthesize the 5-ethyl-5-methyldecane from both 5-ethyl-5-methyl-3-decanol (Route A) and 6-ethyl-6-methyl-4-decanol (Route B). Since the structures of carbonium ions formed during the dehydration of these carbinols would be different, the end products of the reactions would be expected to be dissimilar if rearrangements took place.

To obtain still additional evidence, the 5-ethyl-5-methyldecane was synthesized not only from 2-(β-cyanoethyl)2-ethylhexanol[5] (Route C), but also by two variations of the mixed-Kolbe reaction. In the first of these (Route D), 3-ethyl-3-methyloctanoic acid was coupled with butyric acid, while in the second method (Route E), 4-ethyl-4-methyloctanoic acid was caused to react with butyric acid also to give the desired hydrocarbon directly.

The by-products of the mixed-Kolbe reactions, 6,9-diethyl-6,9-dimethyltetradecane and 5,10-diethyl-5,10-dimethyltetradecane respectively, were of interest since they contain two quaternary carbon atom systems. They are liquids with solidification points below −60°, and have infrared spectra almost identical with that of 5-ethyl-5-methyldecane.

The values for specific gravity, viscosity, refractive index, boiling point, and melting point of the five independently synthesized samples of 5-ethyl-5-methyldecane were all within experimental error of each other, and the infrared spectra appeared to be identical. Samples from Routes A, B, and D were examined by gas chromatography and gave single sharp peaks in their spectra at the same points.

Gas chromatographic studies of 5-ethyl-5-methyl-2(3)-decene (from Route A) and 6-ethyl-6-methyl-3(4-)-decene (from Route B) showed only three distinct peaks in each of their spectra. These apparently were the *cis* and *trans*-beta and *trans*-alpha olefins, with respect to the quaternary carbon atoms. The lack of *cis*, alpha olefins might be explained on the basis of the fact that models of these compounds reveal that the *cis* configurations are

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(1) Paper IV. N. Rabjohn, L. V. Phillips, and R. J. DeFeo, *J. Org. Chem.*, **24**, 1964 (1959).

(2) Abstracted in part from the Ph.D. thesis of R. J. DeFeo, 1958.

(3) Lubrizol Foundation Fellow, 1956–58.

(4) For leading references see W. A. Mosher and J. C. Cox, Jr., *J. Am. Chem. Soc.*, **72**, 3701 (1950); D. J. Cram in M. S. Newman's *Steric Effects in Organic Chemistry*, John Wiley and Sons, New York, 1956, Chap. 5.

(5) N. Rabjohn and H. H. Farmer, *J. Org. Chem.*, **23**, 522 (1958).

highly hindered structures, which suggests that they might be formed with considerable difficulty.

The preceding data support strongly the quaternary carbon atom structures which were assigned to the tetraalkylmethanes described in the previous study.[1]

EXPERIMENTAL[6]

Materials. (a) *Ethyl 2-cyano-3-ethyl-3-methylheptanoate* was prepared from ethyl 2-cyano-3-methyl-2-pentenoate[7] and *n*-butylmagnesium bromide in the presence of cuprous iodide in 70% yield;[8] b.p. 158–160°/17 mm., n_D^{25} 1.4435; lit.,[9] b.p. 160–162°/21 mm., n_D^{25} 1.4435.

(b) *Ethyl 2-cyano-3-ethyl-3-methyloctanoate* was obtained (76%) in a similar fashion from ethyl 2-cyano-3-ethyl-2-pentenoate and *n*-amylmagnesium bromide; b.p. 168–170°/17 mm., n_D^{25} 1.4446; lit.,[9] b.p. 168–170°/20 mm., n_D^{25} 1.4449.

(c) *3-Ethyl-3-methylheptanenitrile* was synthesized in 82% yield by the hydrolysis and decarboxylation of ethyl 2-cyano-3-ethyl-3-methylheptanoate; b.p. 105–107°/17 mm., n_D^{25} 1.4332; lit.,[9] b.p. 112–113°/22 mm., n_D^{25} 1.4328.

(d) *3-Ethyl-3-methyloctanenitrile* was prepared in an analogous manner from ethyl 2-cyano-3-ethyl-3-methyloctanoate; yield, 56%, b.p. 119–121°/17 mm., n_D^{25} 1.4354; lit.,[9] b.p. 127–130°/23–25 mm., n_D^{25} 1.4358.

(e) *3-Ethyl-3-methyloctanoic acid* was prepared in 96% yield by the hydrolysis of 3-ethyl-3-methyloctanenitrile with potassium hydroxide in diethylene glycol; b.p., 158–159°/15 mm., n_D^{25} 1.4427; lit.,[9] b.p. 157–160°/15 mm., n_D^{25} 1.4426.

(f) *4-Ethyl-4-methyloctanoic acid* was obtained from 2-(β-cyanoethyl)-2-ethylhexaldehyde in 73% yield[5]; b.p. 132–135°/2 mm., n_D^{25} 1.4456.

5-Ethyl-5-methyl-3-decanone. A Grignard reagent was prepared from 24.3 g. (1 g.-atom) of magnesium and 109 g. (1 mole) of ethyl bromide in 200 ml. of dry ether. To this was added 91 g. (0.54 mole) of 3-ethyl-3-methyloctanenitrile in 100 ml. of ether. There was obtained 92 g. (86%) of ketone which boiled at 127–129°/15 mm.; n_D^{25} 1.4371.

Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.80; H, 13.21.

5-Ethyl-5-methyl-3-decanol. The reduction of 84 g. (0.42 mole) of 5-ethyl-5-methyl-3-decanone with 19 g. (0.5 mole) of lithium aluminum hydride was carried out in the usual manner. There resulted 82 g. (97%) of alcohol; b.p. 131–132°/15 mm., n_D^{25} 1.4470.

Anal. Calcd. for $C_{13}H_{28}O$: C, 77.93; H, 14.08. Found: C, 77.92; H, 14.13.

5-Ethyl-5-methyl-2(3)-decene. A mixture of 77 g. (0.38 mole) of 5-ethyl-5-methyl-3-decanol and 10 g. (0.07 mole) of potassium bisulfate was heated under reduced pressure at 150–160° for 24 hr. After working up the reaction mixture in the usual way, there was obtained 60 g. (87%) of olefins; b.p. 101–103°/15 mm., n_D^{25} 1.4390.

Anal. Calcd. for $C_{13}H_{26}$: C, 85.63; H, 14.37. Found: C, 85.59; H, 14.21.

6-Ethyl-6-methyl-4-decanone. A Grignard reagent was prepared from 30.4 g. (1.25 g.-atoms) of magnesium and 154 g. (1.25 moles) of *n*-propyl bromide in 250 ml. of dry ether. To this was added 113 g. (0.74 mole) of 3-ethyl-3-methylheptanenitrile. There was obtained 130 g. (89%) of ketone; b.p. 124–126°/15 mm., n_D^{25} 1.4363.

Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.85; H, 13.00.

6-Ethyl-6-methyl-4-decanol. A mixture of 19 g. (0.5 mole) of lithium aluminum hydride and 114 g. (0.58 mole) of 6-ethyl-6-methyl-4-decanone was caused to react in the usual manner to give 105 g. (91%) of the desired carbinol; b.p. 129–131°/15 mm., n_D^{25} 1.4463.

Anal. Calcd. for $C_{13}H_{28}O$: C, 77.93; H, 14.09. Found: C, 77.92; H, 14.13.

6-Ethyl-6-methyl-3(4)-decene. The dehydration of 100 g. (0.5 mole) of 6-ethyl-6-methyl-4-decanol with 10 g. (0.07 mole) of potassium bisulfate afforded 82 g. (90%) of olefins; b.p. 99–100°/15 mm., n_D^{25} 1.4380.

Anal. Calcd. for $C_{13}H_{26}$: C, 85.63; H, 14.37. Found: C, 85.52; H, 14.18.

5-Ethyl-5-methyldecane. Method A. The hydrogenation of 54 g. (0.29 mole) of 5-ethyl-5-methyl-2(3)-decene in 75 ml. of methylcyclohexane with 12 g. of Raney nickel catalyst at 180° and 3200 p.s.i. of hydrogen yielded 45 g. of alkane: b.p. 102–103°/15 mm., n_D^{25} 1.4290; lit.,[5] b.p. 101–103°/18 mm., n_D^{25} 1.4291.

Method B. The above procedure was repeated using 37 g. (0.2 mole) of 6-ethyl-6-methyl-3(4)-decene, 10 g. of Raney nickel catalyst and 75 ml. of methylcyclohexane. There was obtained 31 g. (84%) of an alkane which distilled at 102–103°/15 mm., n_D^{25} 1.4290.

Method C. A mixture of 148 g. (0.75 mole) of 6-ethyl-6-methyl-3-decanone, 105 ml. (1.8 moles) of 85% hydrazine hydrate, 700 ml. of diethylene glycol, 175 g. (2.6 moles) of 85% potassium hydroxide and 150 ml. of water was caused to react in the previously described manner.[5] There was obtained 44 g. (32%) of the desired hydrocarbon; b.p. 101–103°/15 mm., n_D^{25} 1.4291.

Method D. A mixture of 119 g. (0.64 mole) of 3-ethyl-3-methyloctanoic acid, 352 g. (4 moles) of *n*-butyric acid, 500 ml. of petroleum ether (b.p. 60–80°), 2 g. of sodium, which had been dissolved in about 100 ml. of methanol, and sufficient methanol to bring the volume to 1900 ml., was electrolyzed at approximately 5.5 amp. for 29 hr. under the conditions described previously.[10] At the end of this time, the solution was light tan with no odor of butyric acid. Approximately 1 l. of solvent was removed and 132 g. (2 moles) of 85% potassium hydroxide in 500 ml. of water was added. Distillation was continued until another 1 l. of distillate had been collected. At this point, 250 ml. of water and 500 ml. of petroleum ether (b.p. 60–70°) were added, and the layers were separated. The aqueous layer was extracted twice with 500-ml. portions of a petroleum ether–ether mixture, the oil layers were combined, washed twice with water, dried over anhydrous sodium sulfate, and distilled to remove solvent.

The residue was distilled, and the portion which boiled at 95–105°/15 mm. was collected. It was washed three times with 100-ml. portions of cold concd. sulfuric acid and taken up in petroleum ether. The solution was washed with water, 10% sodium bicarbonate solution, water, and dried over anhydrous sodium sulfate. After removing the solvent, the residue was distilled to give 62 g. (51%) of an alkane which boiled at 100–101°/14 mm., n_D^{25} 1.4290.

The high-boiling residue from the distillation of the original reaction mixture was distilled, and that portion, 7 g., which boiled at 170–180°/15 mm. was taken up in petroleum ether washed three times with concd. sulfuric acid, and treated then as above. The residue was distilled to yield 4 g. of the dicoupling product; b.p. 176–178°/15 mm., n_D^{25} 1.4181.

Anal. Calcd. for $C_{20}H_{42}$: C, 85.02; H. 14.98. Found: C, 84.77, H, 14.70.

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[6] All melting points and boiling points are uncorrected. The carbon-hydrogen analyses were performed by Mr. Arthur Mendel of this laboratory and by Drs. Weiler and Strauss, Oxford, England.

[7] A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenberg, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

[8] N. Rabjohn, L. V. Phillips, and R. J. DeFeo, *J. Org. Chem.*, **24**, 1964 (1959).

[9] F. S. Prout, *J. Am. Chem. Soc.*, **74**, 5915 (1952).

[10] N. Rabjohn and H. H. Farmer, *J. Org. Chem.*, **24**, 359 (1959).

Method E. The preceding procedure was followed. A mixture of 119 g. (0.64 mole) of 4-ethyl-4-methyloctanoic acid, 352 g. (4 moles) of *n*-butyric acid, 500 ml. of petroleum ether (b.p. 60–70°), 2 g. of sodium, dissolved in about 100 ml. of methanol, and sufficient methanol to bring the volume to 1900 ml., was electrolyzed at about 5 amp. for 21 hr. There was obtained 29 g. (25%) of an alkane which boiled at 101–103°/15 mm., n_D^{25} 1.4291.

The high-boiling residue was treated as above to give 4 g. of coupling product, b.p. 182–184°/15 mm., n_D^{25} 1.4480.

Anal. Calcd. for $C_{20}H_{42}$: C, 85.02, H, 14.98. Found: C, 85.31; H, 14.87.

Physical constants of 5-ethyl-5-methyldecane. In addition to the constants given above, the following values were determined for each of the five samples of the hydrocarbon: sp. gr. 20/4, 0.7705–0.7707; solidification point, −80°; viscosity in centistokes, 1.71 (100° F.) 1.10 (115° F.), and 0.77 (210° F.); and viscosity index 92.5.

COLUMBIA, MO.

[CONTRIBUTION FROM THE JOHN STUART RESEARCH LABORATORIES OF THE QUAKER OATS CO.]

2-Methoxy-5-methylfuran: Preparation, Properties, and Proof of Structure[1]

EDWARD SHERMAN AND A. P. DUNLOP

Received January 7, 1960

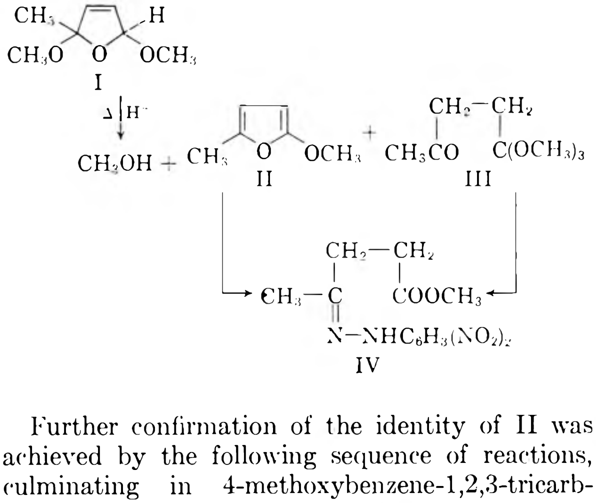
2-Methoxy-5-methylfuran (II) has been prepared in 68% yield by acid-catalyzed pyrolysis of 2,5-dimethoxy-2,5-dihydro-2-methylfuran. Other products obtained in the pyrolysis are methanol (64%), trimethyl ortholevulinate (III) (5–6%) and an unidentified polymer (*ca.* 10% by weight). The structure of II was confirmed by the following sequence of reactions: II + maleic anhydride ⟶ 3-methyl-6-methoxy-3,6-*endo*-oxo-1,2,3,6-tetrahydrophthalic anhydride (V) (84%) ⟶ 3-methyl-6-methoxyphthalic anhydride (VI) (48%) ⟶ the known 4-methoxybenzene-1,2,3-tricarboxylic acid (VII) (85%).

Samples of 2,5-dimethoxy-2,5-dihydro-2-methylfuran (I), prepared by electrolytic methoxylation of 2-methylfuran according to a modification of the method due to Clauson-Kaas *et al.*[2] (ammonium bromide electrolyte), have been found to contain traces of halogen (Beilstein test). Redistillation of stored specimens of I has invariably given rise to small amounts of methanol and a compound, boiling at *ca.* 130°, which from its physical properties and odor appeared to be methyl furfuryl ether.

Finding it practically impossible to explain the formation of methyl furfuryl ether from either methylfuran or I under the conditions of the aforementioned methoxylation or redistillation, we undertook to investigate the true structure of this substance. However, before tackling this problem, it seemed desirable to prepare deliberately the unknown compound in reasonable yield.

On the assumption that hydrogen halide, having its origin in the halogen contamination, was effecting the observed transformation of I, we tested catalytic amounts of strong acids (hydrogen chloride, *p*-toluenesulfonic acid, etc.) in a series of preliminary experiments. Subsequently, the unknown compound (II) was obtained in 68% yield together with a second product (III), by incremental addition of I to hot (*ca.* 250°) dimethyl phthalate containing a few drops of concentrated sulfuric acid, while removing the volatile products continuously by entraining in a gentle stream of nitrogen.

Analysis provided an empirical formula of $C_5H_5O(OCH_3)$, and the infrared spectrum revealed a furan structure for the compound. It was distinguished from the isomeric methyl furfuryl ether by facile formation of an adduct (V) with maleic anhydride, m.p. 111–112.5°, (84.3% yield). Methyl furfuryl ether sluggishly forms a maleic anhydride adduct melting at 97°.[3] From the orientation of substituents in the precursor (I), and the formation of methyl levulinate 2,4-dinitrophenylhydrazone (IV) on treatment with the hydrazine reagent, the structure of the compound was almost unequivocally established as 2-methoxy-5-methylfuran (II).



Further confirmation of the identity of II was achieved by the following sequence of reactions, culminating in 4-methoxybenzene-1,2,3-tricarboxylic acid (VII) which has been described.[4]

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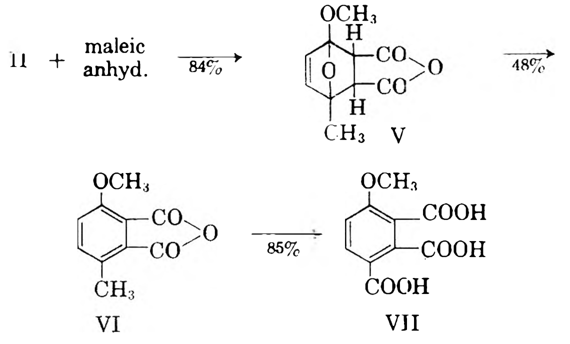
[1] This article, in its entirety, was presented as a portion of a paper of broader scope at the 127th National ACS Meeting in Cincinnati, Ohio, March 1955.

[2] N. Clauson-Kaas, F. Limborg, and P. Dietrich, *Acta Chem. Scand.*, **6**, 545 (1952).

[3] M. G. Van Campen and J. R. Johnson, *J. Am. Chem. Soc.*, **55**, 430 (1933).

[4] D. Gardner, J. F. Grove, and D. Ismay, *J. Chem. Soc.*, 1817 (1954).



V

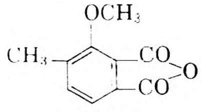
VI

m.p. 188.5–189°

VII

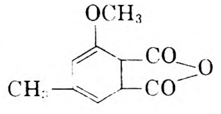
The location of the methoxyl group at a bridgehead of bicyclic adduct (V) was indicated by its facile hydrolysis to a phenolic body.

Structure VI is deduced from the following considerations. There are six isomeric x-methyl-y-methoxyphthalic anhydrides, of which four[5] (VIII–XI) have been described. The isomer (VI) obtained in this study melts much higher than any of these, and, on oxidation, gives a methoxybenzenetricarboxylic acid with the same melting point reported for VII (prepared[4] from 4-methoxy-2,3-dimethylacetophenone). While both VI (as assigned) and XII would give VII on oxidation, XII can be eliminated since it would necessitate a precursor adduct having structure XIIa which cannot give a phenol on *mild* hydrolysis.



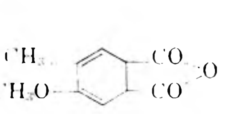
VIII

m.p. [illegible]°[8]



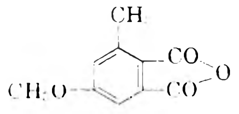
IX

m.p. 167°[illegible]



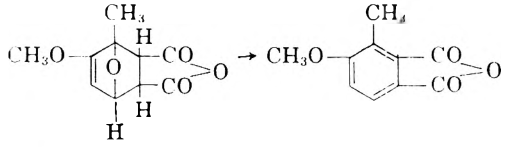
X

m.p. 158.5–159°[10]



XI

m.p. 139°[9]



XIIa

XII

It will be recalled that in addition to II, a second compound (III) was isolated during the acid-catalyzed pyrolysis of I. Compound III has been better prepared by treating I with methanol containing a strong acid catalyst. Analysis indicated an empirical formula of $C_5H_7O(OCH_3)_3$ and infrared spectroscopy disclosed the presence of carbonyl and methyl ketone groups. Reaction with 2,4-dinitrophenylhydrazine reagent yielded IV. Whereas we are convinced that this compound is trimethyl ortholevulinate(III), unequivocal proof awaits its synthesis in an unambiguous manner (*e.g.*, from levulinonitrile). Its preparation from I may be accounted for by way of II as an intermediate.

EXPERIMENTAL[11]

2-Methoxy-5-methylfuran (II). To a 100-ml., three necked, round-bottomed flask, equipped with a dropping funnel, gas inlet capillary, and distilling head connected to a condenser, receiver (containing *ca.* 0.1 g. of anhydrous sodium carbonate), and Dry Ice traps, was added 25 ml. (*ca.* 30 g.) of dimethyl phthalate and 2–4 drops of concd. sulfuric acid. The flask was heated in an oil bath maintained at 250 ± 10° and a slow stream of dry nitrogen was started. 2,5-Dimethoxy-2,5-dihydro-2-methylfuran[2] (I) was added through the dropping funnel at a rate of about 5 sec. per drop until 130 g. (0.9 mole) had been added. The contents of the receiver and traps were combined (141 g.), 25 ml. of fresh dimethyl phthalate added, and fractionated, yielding: 20.4 g. (64%) of methanol, b.p. 63–70°, 68.4 g. (68%) of II, b.p. 120–136°, 8.5 g. (5.4%) of III, b.p. 94–100°/20 mm., and *ca.* 40 g. of dimethyl phthalate. The residue in the reaction vessel, a dark brown, viscous, polymeric material, weighed 13 g. (10% by weight based on I).

For analysis, a portion of the fraction of crude II was distilled once at 90 mm. (b.p. 75°) and again at atmospheric pressure, b.p., 131°; d_4^{25}, 1.0096; n_D^{25}, 1.4525; MR_D (calcd.), 30.06; MR_D (obsd.), 29.99. The infrared spectrum (0.1-cm. cell) indicated peaks at 6.29, 6.98, 7.36, 8.30, 9.86 and 13.70 μ, as compared to reference compounds furan[12] (peaks at 6.33, 6.71, 7.21, 8.41, 10.01 and 13.79 μ), and 2-methoxyfuran[13] (peaks at 6.5, 7.15 and 9.9 μ).

Anal. Calcd. for $C_6H_8O_2$: C, 64.27; H, 7.19; —OCH_3, 27.7. Found: C, 64.40; H, 7.19; —OCH_3, 27.0.

3-Methyl-6-methoxy-3,6-endo-oxo-1,2,3,6-tetrahydrophthalic anhydride (V). A solution of 11.2 g. (0.1 mole) of II, dissolved in 50 ml. of absolute ether, was added to a solution of 10.0 g. (0.1 mole) of maleic anhydride in 50 ml. of absolute ether. On standing at room temperature for 16 hr., there was deposited 15 g. (71.4%) of practically pure adduct (V), m.p. 110–112°. The mother liquor was then concentrated to *ca.* 25 ml. and on chilling yielded an additional 2.7 g. (12.9%) of adduct (after washing with ether).

For analysis, a sample was recrystallized twice from absolute ether, yielding transparent prisms, m.p. 111–112.5°.

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80; neut. equiv., 105.1. Found: C, 57.32; H, 4.88; neut. equiv., 105.0.

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(5) Since the original presentation[1] of this paper, VI has been described[6] (m.p. 185–186°) with reasonable certainty. Isomer XII has also been reported,[6,7] but with some ambiguity.

(6) A. J. Birch and P. Hextall, *Australian J. Chem.*, **8**, 96 (1955); *Chem. Abstr.*, **50**, 884 (1956).

(7) W. Metlesics and F. Wessely, *Monatsh. Chem.*, **88**, 108 (1957); *Chem. Abstr.*, **51**, 12868 (1957).

(8) J. L. Simonsen and M. G. Rau, *J. Chem. Soc.*, 1339 (1921).

(9) A. N. Meldrum, *J. Chem. Soc.*, 99, 1712 (1911).

(10) H. Raistrick and D. J. Ross, *Biochem. J.*, **50**, 635 (1952).

(11) All temperatures are uncorrected. Ultimate microanalyses were by the Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were obtained on a Perkin-Elmer, Model 21, double-beam instrument using sodium chloride sandwich cells.

(12) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determinations of Organic Structures*, D. Van Nostrand Co., Inc., New York, 1949, pp. 46–65.

(13) M. P. Cava, C. L. Wilson, and C. J. Williams, Jr., *Chem. & Ind.* (*London*), 17 (1955).

3-Methyl-6-methoxyphthalic anhydride (VI). A solution of 10.5 g. (0.05 mole) of V, dissolved in 75 ml. of warm glacial acetic acid, was added dropwise over a period of 30 min. to a solution of *ca.* 50 mg. of anhydrous zinc chloride in 20 ml. of boiling acetic anhydride contained in a 100-ml. flask equipped with reflux condenser and dropping funnel. The mixture was refluxed an additional 4.5 hr. and left to cool slowly to room temperature. After 16 hr., 3.6 g. (37.5%) of stout, pale yellow needles of practically pure VI, m.p. 188–189°, had deposited. The mother liquor was then concentrated to *ca.* 25 ml. and on chilling and filtering yielded an additional 1.0 g. (10.4%) of VI.

For analysis, a sample of VI was recrystallized twice from dry benzene; m.p. 188.5–189°.

Anal. Calcd. for $C_{10}H_8O_4$; C, 62.50; H, 4.19; neut. equiv., 96.1. Found: C, 62.60; H, 4.38; neut. equiv., 96.5.

The filtrate (obtained after concentrating and filtering, above) contains at least one more compound which has not been completely characterized. This compound is probably the acetate of a phenolic substance since a positive (violet) ferric chloride test is obtained only after hydrolysis.

4-Methoxybenzene-1,2,3-tricarboxylic acid (VII). VI (1.92 g.; 0.01 mole) was dissolved in 100 ml. of warm 5% potassium hydroxide solution in a tall-form 400-ml. beaker. The solution was vigorously stirred while 90 ml. of 0.35*M* potassium permanganate was added in 5-ml. increments (each addition upon decolorization of the preceding). The reaction mixture was then worked up as described by Buehler *et al.*[14] yielding 2.04 g. (85%) of practically pure VII, m.p. 221–223°.

For analysis, the product was recrystallized first from acetone-benzene and then from acetic acid. To ensure no anhydride contamination, the purified material was boiled with a small amount of water and the excess water removed in a vacuum oven at room temperature. The product was then dried for 1 hr. in the vacuum oven at 60°; m.p. 223.5–224.5°.

Anal. Calcd. for $C_{10}H_8O_7$: C, 50.01; H, 3.36; neut. equiv., 80.1. Found: C, 50.02; H, 3.36; neut. equiv., 80.5.

Trimethyl ortholevulinate (III).[15] To 125 ml. of anhydrous methanol in a 300-ml. flask was added 1.8 g. (0.05 mole) of dry hydrogen chloride and then 68 g. (0.47 mole) of I. The temperature rose rapidly to reflux before the flask could be cooled by a water bath. When the tendency for the temperature to rise on removal of the bath had ceased (*ca.* 30 min.), the reaction mixture was neutralized to *p*H 8 with sodium methoxide in methanol. After filtration and removal of the excess solvent, the product was distilled under vacuum; b.p. 58–65°/1 mm.; yield, 63.9 g. (77%).

For analysis, the material was redistilled and a center-cut taken, b.p. 88.5–89.5°/10 mm.; d_4^{25}, 1.0274; n_D^{25}, 1.4225; MR_D (calcd.), 44.08; MR_D (obsd.), 43.63, pertinent infrared bands (0.2-cm. cell) at 5.88 μ (carbonyl) and 7.02 μ (CH_3 in CH_3CO).

Anal. Calcd. for $C_8H_{16}O_4$: C, 54.53; H, 9.15; $-OCH_3$, 52.8; sapon. equiv., 176.2. Found: C, 54.40; H, 8.95; $-OCH_3$, 52.3; sapon. equiv., 174.1.

Methyl levulinate 2,4-dinitrophenylhydrazone (IV). (*A*). *From* II. II (0.218 g.; 0.00195 mole), treated with 130 ml. of methanol containing 2 g. of 2,4-dinitrophenylhydrazine and 8 ml. of concd. hydrochloric acid, yielded 0.321 g. (53%)[16] of IV; m.p. 136–139°; mixed melting point with pure IV (m.p. 140–141°), 138–141°.

(*B*). *From* III. III (0.202 g.; 0.00115 mole) treated in the same manner as in (*A*) yielded 0.230 g. (64%)[16] of IV; m.p. 133–138°. One recrystallization from methanol raised the melting point to 140.0–140.5°. A mixed melting point with pure IV showed no depression.

Hydrolysis of V. Preliminary information indicates that at least two compounds are formed by the acid or neutral hydrolysis of V. One compound, only slightly soluble in water, has not yet been studied in detail.

Another substance, very soluble in water, has been recovered from the filtrate (after removal of the insoluble material) by extraction with ether. This substance gives a strong phenol test (violet to purple color) with ferric chloride. On treatment with acetic anhydride, it yields a well crystallized acetate which does not give a phenol test until after hydrolysis.

Acknowledgment. The authors gratefully acknowledge the technical assistance of Miss Mary L. Leslie and express their thanks to Dr. Shelbert Smith who determined the infrared spectra.

BARRINGTON, ILL.

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[14] C. A. Buehler, R. B. Specs, and P. A. Sanguinetti, *J. Am. Chem. Soc.*, **71**, 11 (1949).

[15] See also under the preparation of II.

[16] IV is somewhat soluble in methanol. Since no attempt was made to recover the dissolved product, these are only partial yields.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Nitration Studies. XII. Nitrohalogenation of Negatively Substituted Olefins with Mixtures of Dinitrogen Tetroxide and Halogens

G. BRYANT BACHMAN, TED J. LOGAN,[1,2] KENNETH R. HILL,[2] AND NORMAN W. STANDISH[2]

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Mixtures of dinitrogen tetroxide and halogens have been shown to react with olefins to produce compounds with a halogen atom on one carbon atom and a nitrogen-containing group on the other carbon atom of the original double bond. The nitrogen-containing group is $—ONO_2$ when the olefin is ethylene itself or ethylene substituted with electron-supplying groups such as alkyl or acetoxy. It is $—NO_2$ when the olefin is ethylene substituted with electron-withdrawing groups such as halogen or cyano. These two classes of olefins are also distinguished by the orientations of the entering groups. The products seem best explained as resulting from ionic additions induced by electron-supplying groups and from free radical additions induced by electron-withdrawing groups. The mixture of dinitrogen tetroxide and halogen provides a useful tool for determining the relative tendencies of substituent groups to induce ionic *vs.* radical electron displacements in double bonds. The D_i/D_r ratios determined in this way for the olefins investigated correlate well with the known responses of these compounds to acid-catalyzed hydration and to peroxide-catalyzed polymerization.

Recently it was reported[3] that ethylene and its simple homologs react with mixtures of dinitrogen tetroxide and bromine or iodine in liquid phase at ice-bath temperatures to form β-haloalkyl nitrates to the practical exclusion of nitro compounds. The reaction was postulated to proceed by an ionic mechanism initiated by a halonium ion. We now wish to report that halogenated ethylenes under similar conditions react with mixtures of dinitrogen tetroxide and chlorine, bromine, or iodine to form β,β-dihalonitro compounds to the practical exclusion of nitrates. The mechanisms of these reactions will be discussed.

Although several of the dihalonitroalkanes obtained are new, this type of compound has been prepared before by other methods. Thus, Steinkopf and Kuhnel[4] report that nitryl chloride adds to olefins, including the halogenated ethylenes, to give the expected dihalonitro compounds:

$$CH_2{=}CHBr + NO_2Cl \longrightarrow CHBrClCH_2NO_2$$

This synthesis cannot be extended to the use of NO_2Br and NO_2I since these reagents cannot be prepared.[5] The isomers obtained in the additions of NO_2Cl to halogenated ethylenes appear to be the same as those we have obtained in the additions of nitrogen tetroxide and chlorine, but there are differences which indicate that the two syntheses may not proceed by the same mechanism. Yakubovich and Lemke[6] have prepared chloronitro compounds by the reaction of nitrosyl chloride with chloroethylenes:

$$CH_2{=}CHCl + 2NOCl \longrightarrow CHCl_2CH_2NO_2$$

This synthesis appears not to have been extended to the use of nitrosyl bromide although this reagent is known. The related nitrosyl iodide is unknown. A detailed mechanism for the nitrosyl chloride reactions is not given, but it is obvious that it must differ from those of the NO_2Cl and nitrogen tetroxide–chlorine reactions.

Another synthesis leading to dihalonitroalkanes is the reaction of halonitro alcohols with halogenating agents.[4]

$$CH_2OHCHClNO_2 + PCl_5 \longrightarrow CH_2ClCHClNO_2$$

This method appears to have been applied only to the preparation of the product indicated in the above equation. The addition of halogens to nitroalkenes leads to α,β-dihalonitroalkanes only.[7] Such additions appear not to have been attempted with halogenated nitroalkanes. Halogenated alkanes containing tertiary hydrogen atoms have been nitrated.[8a] Other types of halogenated alkanes have not been successfully nitrated, but nitroalkanes have been chlorinated by Riley and McBee.[8b] These authors did not isolate any di- or polyhalonitro alkanes.

Conditions of reactions. The liquid phase nitrohalogenations were all run at ice-bath temperatures to avoid elimination and substitution reactions both of which can become prominent at elevated temperatures. As the number of halogen atoms increased in the starting olefin molecule, the rate of the addition reaction decreased until with tetrachloroethene no products were formed a in reasonable length of time (72 hours). Possibly the use of higher temperatures and sealed tube reactors, as previously employed[4] in NO_2Cl additions to polyhalogenated alkenes, would have led to faster

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(1) Present address: Procter & Gamble Co., Cincinnati, Ohio.

(2) Commercial Solvents Corp. Research Assistant.

(3) G. B. Bachman and T. J. Logan, *J. Org. Chem.*, **21**, 1467 (1956).

(4) W. Steinkopf and M. Kuhnel, *Ber.*, **75**, 1323 (1942). See also Dutch Patent **58,977**, Feb. 15, 1947.

(5) N. V. Sidgwick, *Chemical Elements and Their Compounds*, Oxford University Press, London, Vol. I, 703 (1950).

(6) A. Y. Yakubovich and A. L. Lemke, *J. Gen. Chem. (USSR)*, **19**, 607 (1949).

(7) A. G. Suzie, Ph. D. Thesis, Purdue University, 1939.

(8) (a) M. I. Konovalov, *Zh. russk. khim. obshch.*, **38**, 607 (1906); *Chem. Zentr.*, **77**, II, 1552 (1906); (b) E. F. Riley and E. T. McBee, U. S. Patent **2,337,912** (Dec. 28, 1943).

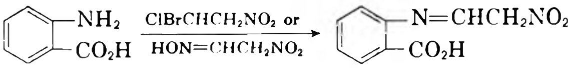
and more complete reactions between our negatively substituted alkenes and nitrogen tetroxide plus halogens, but we preferred to limit our studies to milder conditions for the reasons stated above. Chloroform and carbon tetrachloride solvents were employed exclusively in an effort to avoid the special effects observed with ether,[9] carbon disulfide, and related solvents[10] or the substitution reactions possible with hydrocarbons and other organic solvents. While light was not absolutely excluded, the reaction mixtures were only subjected to dim illumination to avoid photoexcitation of the reactants. Moisture and other polarizing substances were carefully excluded until the reaction mixtures were worked up. All organic products were isolated except for very small amounts of water soluble oxidation products.

Identification of products. The halonitroalkanes were identified by elementary analyses, physical properties, hydrolysis to substituted acetic acids, and conversion to derivatives by reaction with sodium anthranilate.

Primary nitroalkanes have long been known to react with concentrated mineral acids to produce carboxylic acids and hydroxylamine salts of the mineral acids.[11] Other functional groups may also be present without interfering with this process. Thus, Yakubovich and Lemke[6] have shown that 1,1-dichloro-2-nitroethane yields dichloroacetic acid on heating with sulfuric acid. Hawthorne and Strahm[12] have studied the mechanism of the hydrolysis of 1-chloronitroethane and 1-deutero-1-chloronitroethane and shown that these substances are converted to acetic acid, hydrogen chloride, and nitrous oxide (probably). This latter fact has interesting implications relative to previously proposed mechanisms of hydrolysis of primary nitro compounds. Neither isomerization to a hydroxamic acid as suggested by Nenitzescu and Isacescu[13a] nor dehydration to a nitrile oxide as suggested by Noland[13b] can occur when the grouping $\text{—CCl}_2\text{NO}_2$ is present (and may not occur when the grouping —CHClNO_2 is present). Instead the $\text{—CCl}_2\text{NO}_2$ group is probably protonated and then hydrolyzed to carboxyl, hydrochloric acid, and nitrous acid. In any event hydroxylamine salts are not formed as by-products, but oxides of nitrogen are evolved. The solution diazotizes primary aromatic amines and then couples with β-naphthol to form characteristic azo dyes.

This reaction is useful in determining the relative positions occupied by the halogen atoms and the nitro group in halonitroalkanes and in distinguishing these compounds from haloalkyl nitrates which do not give carboxylic acids under these conditions.[3] Usually it is sufficient to reflux the nitro compound with 86–96% sulfuric acid until the mixture becomes homogeneous and then to distill the product. However, in the one example of iodonitroalkane tried the reaction proved to be unsatisfactory. Thus, 1-chloro-1-iodo-2-nitroethane gave copious amounts of free iodine and no identifiable acetic acid. Likewise 1,2,2,2-tetrachloronitroethane gave no trichloroacetic acid. In these cases both ends of the substituted ethane molecule seem to have been hydrolyzed.

The reaction of 1-chloro-2-nitropropane with sodium anthranilate was recently shown[14] to give 2-(2′-nitro-1′-propyl)aminobenzoic acid. This reaction has now been extended to β-halonitroethanes generally and found to be admirably suitable for the derivatization of such compounds (see Table II). It proceeds fairly rapidly at room temperature in aqueous or aqueous-alcoholic solutions containing excess alkali and gives good yields of nicely crystalline solids with characteristic melting points. The reaction involves only those halogen atoms *beta* to the nitro group; α-halogens are usually not affected. If there is but one β-halogen atom the product will contain the group $\text{—NHCH}_2\overset{|}{\underset{|}{\text{C}}}\text{NO}_2$. If there are two β-halogen atoms the group will be $\text{—N=CH}\overset{|}{\underset{|}{\text{C}}}\text{NO}_2$, and if there are three, the group $\text{—NHCO}\overset{|}{\underset{|}{\text{C}}}\text{NO}_2$. Thus, 1-chloro-1-bromo-2-nitroethane yields the same product that is obtained from the reaction of anthranilic acid with methazonic acid.[15]



Here again 1,2,2,2-tetrachloronitroethane gave trouble, and the product seemed to be a mixture from which an analytically pure sample of the expected amide was not obtained by recrystallization. In this case satisfactory results were obtained by treating the chloronitro compound with anthranilic acid in glacial acetic acid. The product had a correct analysis for a derivative containing two anthranilic acid residues. The less reactive

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[9] T. E. Stevens and W. D. Emmons, *J. Am. Chem. Soc.*, **80**, 338 (1958).

[10] G. A. Russell, *J. Org. Chem.*, **23**, 1407 (1958).

[11] H. B. Hass and E. F. Riley, *Chem. Revs.*, **32**, 395 (1943).

[12] M. F. Hawthorne and R. D. Strahm, *J. Am. Chem. Soc.*, **79**, 3471 (1957). See also R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, 2439 (1953).

[13] (a) C. D. Nenitzescu and D. A. Isacescu, *Bull. Soc. Chim. Romania*, **14**, 53 (1932); T. Urbanski, *J. Chem. Soc.*, 3374 (1949). (b) W. E. Noland, J. H. Cooley, and P. A. McVeigh, *J. Am. Chem. Soc.*, **81**, 1213 (1959); W. E. Noland, *Chem. Revs.*, **55**, 153 (1955).

[14] G. B. Bachman and J. P. Chupp, *J. Org. Chem.*, **21**, 465 (1956). See also G. B. Bachman and D. E. Welton, *J. Org. Chem.*, **12**, 208 (1947).

[15] German Patent **347,373**, Jan. 17, 1922.

TABLE I

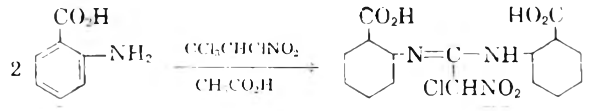
HALONITRATION PRODUCTS

	Reactants				Products					Analyses	
Olefin, moles	Halogen, moles	N_2O_4, moles	Solvent, ml.	Time, hr.	Formula	Conversion, %	B.P., °(mm.)	D_4^T	n_D^T	Calcd.	Found
$CH_2{=}CHCl$, excess	Cl_2, 0.25	0.50	CCl_4, 220	3.0	$CHCl_2CH_2NO_2$[e]	36.0[a]	55(8)	1.432^{25}	1.4663^{20}	C, 16.67 H, 2.10 N, 9.72 Cl, 49.30	C, 17.00 H, 2.41 N, 9.96 Cl, 48.97
	Br_2, 0.50	0.50	$CHCl_3$, 200	12.0	$CHClBrCH_2NO_2$[d]	27.7[a]	41(0.5)	1.861^{20}	1.4980^{20}	C, 12.71 H, 1.59 N, 7.43 X, 29.68	C, 12.47 H, 1.89 N, 7.70 X, 29.80
					$CHClBrCH_2Br$	24.1[a]	44(4)	2.2480^{20}	1.5540^{20}		
	I_2, 0.10	0.20	$CHCl_3$, 600	0.25	$CHClICH_2NO_2$	61.5[b]	dec.				
$CH_2{=}CHBr$, excess	Cl_2, 0.25	0.25	CCl_4, 220	3.0	$CHClBrCH_2NO_2$[d]	41.4[a]	48(1.2)		1.5070^{20}		
					$CH_2ClCHClBr$	32.2[a]	35(3)				
	Br_2, 0.25	0.25	$CHCl_3$, 200	1.0	$CHBr_2CH_2NO_2$	35.0[a]	60(1)		1.5400^{20}	C, 10.40 H, 1.29 N, 6.01 Br, 68.63	C, 10.60 H, 1.56 N, 6.05 Br, 68.33
					$CH_2BrCHBr_2$	58.0[a]	47(2.5)	2.5790^{20}	1.5802^{20}		
$CHCl{=}CHCl$, 1.00	Cl_2, 0.50	0.50	$CHCl_3$, 500	26.0	$CHCl_2CHClNO_2$[d]	7.2[c]	40(3)	1.600^{25}	1.4827^{25}	C, 13.48 H, 1.13 N, 7.85 Cl, 59.63	C, 13.54 H, 1.14 N, 8.19 Cl, 59.69
					$CHCl_2CHCl_2$	2.8[c]	29(1)	1.573^{25}	1.4959^{25}		
$CH_2{=}CCl_2$ 1.00	Cl_2, 0.50	0.50	$CHCl_3$, 500	26.0	$CCl_3CH_2NO_2$	39.7[c]	59(6)	1.608^{25}	1.4845^{25}	C, 13.43 H, 1.12 N, 7.85 Cl, 59.70	C, 13.57 H, 1.33 N, 8.01 Cl, 59.69
					CCl_3CH_2Cl	2.3[c]	123	1.578^{25}	1.4792^{25}		
	Br_2, 0.50	0.50	$CHCl_3$, 500	25.0	$CCl_2BrCH_2NO_2$	24.9[c]	89(11)	1.928^{25}	1.5168^{25}	C, 10.77 H, 0.90 N, 6.28 X, 67.50	C, 11.08 H, 1.15 N, 6.12 X, 67.51
					CCl_2BrCH_2Br[f]	8.8[c]	68(12)	2.240^{25}	1.5448^{25}		
$CHCl{=}CCl_2$, 1.00	Cl_2, 0.50	0.50	$CHCl_3$, 500	29.0	$CCl_3CHClNO_2$[d]	4.7[c]	44(5)	1.670^{25}	1.4921^{25}	C, 11.34 H, 0.48 N, 6.64 Cl, 66.54	C, 11.08 H, 0.65 N, 6.94 Cl, 66.68
					CCl_3CHCl_2[g]	2.3[c]	27(5)	1.659^{25}	1.5095^{25}		
					$CCl_2{=}CClNO_2$[h]	4.2[c]	55(4)	1.655^{25}	1.5032^{25}	C, 13.62 H, 0.00 N, 7.96 Cl, 60.35	C, 13.40 H, 0.00 N, 8.32 Cl, 60.05

TABLE I (*Continued*)

	Reactants				Products					Analyses	
Olefin, moles	Halogen, moles	N_2O_4, moles	Solvent, ml.	Time, hr.	Formula	Conversion, %	B.P., °(mm.)	D_4^T	n_D^T	Calcd.	Found
$CCl_2{=}CCl_2$, 2.0	Cl_2, 1.0	1.0	$CHCl_3$, 500	30.0	None						
$CH_2{=}CHCN$	Cl_2, 0.5	0.5	$CHCl_3$, 500	6.0	$CHNO_2{=}CHCN$[i]	24.5[c]	58(2)	1.294^{28}	1.4877^{25}		
					NH_4Cl	2.8					
$CH_3CH{=}CH_2Cl$	Cl_2, 1.0	1.0	$CHCl_3$, 1000	10.0	$CH_3CH(NO_2)CHCl_2$	23.8[c]	54(3.5)	1.353^{25}	1.4629^{25}	C, 22.98 H, 2.55 N, 8.93 Cl, 45.21	C, 23.15 H, 2.69 N, 9.01 Cl, 44.90
$CH_3C(OCOCH_3){=}CHCH_3$, 0.2											
	Cl_2, 0.1	0.1	CCl_4, 100	2.0	$CH_3COCHClCH_3$	58.0	40(45)				
	Br_2, 0.1	0.1	CCl_4,	2.0	$CH_3COCHBrCH_3$[j]	50.0	52(30)				
	I_2, 0.1	0.1	$CHCl_3$,	2.0	$CH_3COCH_2CH_3$	34.0	76–8				
					$CH_3COCOCH_3$	23.0	86–8				

[a] Based on moles of product/mole of halogen. [b] Calculated from the yield of anthranilic acid derivative. [c] Based on olefin. [d] See Ref. 4. [e] See Ref. 6. [f] H. Van de Walle, *Bull. acad. roy. Belg.*, **1924,** 94; b.p. 65° (13), b.p. 175° dec., D_{15} 2.2695, n_D^{25} 1.5593. [g] J. Timmermen and F. Martin, *J. chim. phys.*, **23,** 733 (1926); b.p. 162.00°, D_{15} 1.68813, D_{30} 1.66530, n_D^{15} 1.50542. [h] The infrared spectra showed absorption peaks for a conjugated nitro group at 6.50 and 7.40 mμ. [i] H. Shechter, F. Conrad, A. Daulton, and B. Kaplan, *J. Am. Chem. Soc.*, **74,** 3052 (1952); b.p. 53° (3.4), n_D^{20} 1.4929, D_4^{20} 1.268. [j] D. H. Hey, E. Jones, J. Catch, and D. Elliott, *J. Chem. Soc.*, **1948,** 272; b.p. 44° (2), n_D^{25} 1.4571.



β-haloalkyl nitrates do not give these reactions with anthranilic acid and may be distinguished from the halonitroethanes by this fact.

The above two reactions are supplementary in determining the structures of the halonitroethanes, since the first of them affects one end of the molecule, *i.e.*, the end containing the nitro group, while the second affects the other end. Consideration of the results shown in Tables I and II together with the analyses and physical constants of the products makes it possible to establish unequivocally the orientations of the entering groups in the additions studied except possibly in the case of the product from trichloroethylene.

By-products. An anticipated by-product in each of these reactions was the halogenated ethane formed by the addition of halogen alone to the double bond. The extent to which this occurred using a 1:1 mole ratio of nitrogen tetroxide:halogen was greatest for bromine and least for iodine. However, this reaction was greatly suppressed by increasing the mole ratio of nitrogen tetroxide:halogen to 2:1. From Fig. 1 it may be seen that the conversion of vinyl chloride to 1,1-dichloro-2-nitroethane based on dinitrogen tetroxide is nearly independent of the nitrogen tetroxide:chlorine ratio, while the conversion based on chlorine increases as this ratio increases. These facts suggest that the rate controlling step in the reaction involves the olefin and the nitrogen tetroxide but not the halogen.

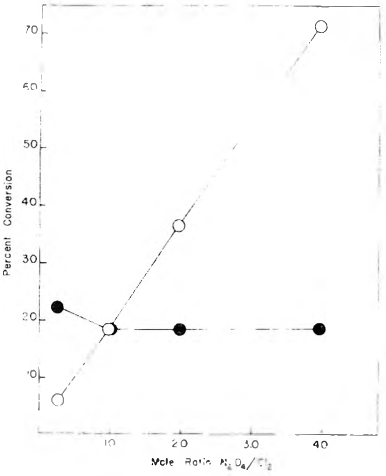


Fig. 1. Effects on conversions to $CHCl_2CH_2NO_2$ of changes in reactant ratios
● Conversions based on N_2O_4
○ Conversions based on Cl_2

As the nitrogen tetroxide:halogen ratio was increased above 1, the amounts of high boiling residues increased. These heavy oils contained higher percentages of nitrogen and oxygen and were un-

TABLE II

IDENTIFICATION OF NITROHALOGENATION PRODUCTS

Compound for Identification	Reagent,[a] Reaction Time	Identifying Product	Solvent for Recrystallization	M.P.°	Conversion, %	Analyses Calcd.	Analyses Found
$CHCl_2CH_2NO_2$	AH_2	A = $CHCH_2NO_2$[b]	C_6H_6	198–199			
	H_2SO_4, 88%, 8 hr.	$CHCl_2CONHC_6H_5$[c]	CH_3CH_2OH	117–118	50		
$CHClBrCH_2NO_2$	AH_2	A = $CHCH_2NO_2$	C_6H_6	198–199			
	H_2SO_4, 88%, 8 hr.	$CHClBrCOOH$[d]		27.5	38.1		
		$CHClBrCONHC_6H_5$	CH_3CH_2OH	119–120		C, 38.66 H, 2.84 N, 5.64	C, 38.43 H, 2.88 N, 5.53
$CHClICH_2NO_2$	AH_2	A = $CHCH_2NO_2$	C_6H_6	198–200			
$CHBr_2CH_2NO_2$	AH_2	A = $CHCH_2NO_2$	C_6H_6	198–199			
	H_2SO_4, 88%, 8 hr.	$CHBr_2COOH$		liq.	25.5		
$CHCl_2CHClNO_2$	AH_2	A = $CHCHClNO_2$	CH_3CH_2OH–$CHCl_3$	200 (dec.)		C, 44.60 H, 3.03 N, 11.50 Cl, 14.60	C, 44.32 H, 3.30 N, 11.19 Cl, 14.88
	H_2SO_4, 88%, 1 hr.	$CHCl_2CONHC_6H_5$[c]	CH_3CH_2OH	117	18.0		
$CCl_3CH_2NO_2$	AH_2	A = $CClCH_2NO_2$	C_6H_6–CH_3OH_2OH	204–205 (dec.)	45.4	C, 44.60 H, 2.91 N, 11.30 Cl, 14.64	C, 44.87 H, 2.89 N, 11.05 Cl, 14.34
$CCl_3CH_2NO_2$	AH_2	$AHCOCH_2NO_2$	CH_3COOH	239 dec.		C, 48.49 H, 3.19 N, 12.55	C, 48.64 H, 3.48 N, 12.30
	H_2SO_4, 88%, 1 hr.	CCl_3COOH[e]		58	78.5		
$CCl_2BrCH_2NO_2$	AH_2	$AHCOCH_2NO_2$	CH_3CH_2OH	239 dec.			
	H_2SO_4, 88%, 1 hr.	$CCl_2BrCOOH$[f]		60–61	27.4	C, 11.57 H, 0.48 X, 72.50	C, 11.92 H, 0.67 X, 72.32
$CCl_3CHClNO_2$	AH_2	A = $C(AH)CHClNO_2$	C_6H_6–CH_3CH_2OH	264 dec.		C, 50.90 H, 3.21 N, 11.12 Cl, 9.31	C, 51.12 H, 3.35 N, 11.40 Cl, 9.20
	H_2SO_4, 88%	dec.					
$CHNO_2{=}CHCN$	AH_2	$AHCH(CN)CH_2NO_2$	CH_3CH_2OH	164 dec.	29.8	C, 51.20 H, 3.86 N, 17.89	C, 50.92 H, 3.80 N, 18.00
	H_2SO_4, 85%, 5 hr.	$CHNO_2{=}CHCONH_2$[g]	C_6H_6	165			
$CH_3CH(NO_2)CHCl_2$	AH_2	A = $CHCH(NO_2)CH_3$	C_6H_6–CH_3CH_2OH	196–197	84.3	C, 54.10 H, 4.86 N, 12.59	C, 53.88 H, 4.78 N, 12.56
$CH_3COCHClCH_3$	$NH_2NHCONH_2$	Semicarbazone[h]	$CH_3CO_2C_2H_5$	138			
$CH_3COCHBrCH_3$	2,4-$(NO_2)C_6H_3NHNH_2$	Hydrazone	C_6H_5–Pet. ether	112			
$CH_3COCH_2CH_3$	2,4-$(NO_2)C_6H_3NHNH_2$	Hydrazone[i]	C_6H_6–Pet. ether	310			

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[a] A is 2-$(COOH)C_6H_4N{=}$. [b] Mixture melting point with product of reaction of methazonic acid and anthranilic acid gave no depression. *cf.* German Patent **347,375** (Jan. 17, 1922). [c] H. Doughty, *J. Am. Chem. Soc.*, **47,** 1097 (1925); m.p. 118°. [d] P. L. Vanderstickele, *J. Chem. Soc.*, **123,** 1227 (1923); m.p. 23.8°. [e] L. Wooten and L. Hammett, *J. Am. Chem. Soc.*, **57,** 2289 (1935); m.p. 58°. [f] R. Neumeister, *Ber.*, **15,** 602 (1882); m.p. 64°. [g] H. Shechter, F. Conrad, A. Daulton, and R. Kaplan, *J. Am. Chem. Soc.*, **74,** 3055 (1952); m.p. 165°. [h] F. H. Curd and A. Robertson, *J. Chem. Soc.*, **1933,** 717. [i] R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 262; m.p. 314–315°.

stable. On attempted distillation under vacuum they evolved gases and more often than not fumed off. Even on standing at room temperatures they decomposed with evolution of gases and deposition of solids in small amounts. Thus the oils from the reactions with 1,1- and 1,2-dichloroethene gave crystals of oxalic acid dihydrate (m.p. 100°). The oil from the reaction of chlorine and nitrogen tetroxide with vinyl chloride deposited dichloroglyoxime[16] (m.p. 199°), a substance capable of causing violent sneezing and swelling of the mucous membranes if small amounts of the powder become dispersed in the air. No other products from these oils were identified, but nitroso compounds were probably present as indicated by the blue or green colors of the small amounts of distillates obtained before decomposition become extensive. Hydrolyses of these oils with 90% sulfuric acid yielded no identifiable products other than oxides of nitrogen and carbon and hydrogen halides.

Mechanisms of the reactions. The reacting state of a molecule may be considered to arise from the resting state through displacements of electrons. In an olefin such displacements may occur ionically (D_i) through displacement of a pair of electrons in one direction, or radically (D_r) through displacement of a single electron in one direction and

$$D_i \quad CH_2{=}CHG \rightleftharpoons \overset{-}{\underset{\cdot\cdot}{C}}H_2{-}\overset{+}{C}HG$$

$$D_r \quad CH_2{=}CHG \rightleftharpoons \underset{\cdot}{C}H_2{-}\underset{\cdot}{C}HG$$

another electron in the other direction. The relative extents to which D_i and D_r occur will depend on the nature of the substituent group G, on the substance with which the olefin is reacting, and on various conditions of the reaction. The influence of G may be seen by comparing the properties of propene (G = methyl) with those of vinyl chloride (G = chlorine). Propene, in which D_i predominates, is more readily attacked by protonium and other cations than it is by free radicals. The reverse is true of vinyl chloride, in which D_r predominates. Thus, propene will dissolve rapidly with hydration in 85% sulfuric acid; vinyl chloride will not. Vinyl chloride will polymerize rapidly in the presence of traces of peroxide; propene will not. Unfortunately, existing data do not permit quantitative comparisons of the relative effects of various other groups.

Similar statements apply to the reacting states of molecules which add to olefins. Thus both nitrogen tetroxide and halogen molecules are able to split ionically or free radically according to their intrinsic natures, the natures of the molecules with which they are reacting, and the conditions.

$$Br\cdot + Br\cdot \leftrightharpoons Br_2 \rightleftharpoons Br^+ + :Br^-$$

$$\begin{tikzcd} NO_2\cdot + NO_2\cdot \arrow[r, leftrightharpoons] & N_2O_4 \arrow[r, rightleftharpoons] \arrow[d, shift left] & NO^+ + :ONO_2^- \\ & NO_2^+ + :NO_2^- \arrow[u, shift left] & \end{tikzcd}$$

Bromine is generally conceded to add to olefins at ordinary temperatures or below by a stepwise process initiated by a bromonium ion. In keeping with this belief is the fact that electron-pair-supplying groups such as alkyl groups facilitate the addition reactions of olefins with bromine. Unfortunately the products of addition would appear to be the same whether the process occurs ionically or free radically and hence give no clue as to the mechanism followed. The situation with nitrogen tetroxide is somewhat more complicated since dissociation can occur in three different ways instead of two. However, as has been pointed out previously,[17] the dissociation of nitrogen tetroxide into NO_2^+ and NO_2^- ions occurs only under the influence of powerful acids and hence may be disregarded for reactions of the types here considered. Of the remaining two types of dissociation one would be expected to lead to dinitro compounds and the other to nitroso nitrates. Unfortunately this simple assumption is complicated by several facts: (1) nitroso groups are easily oxidized to nitro groups by nitrogen tetroxide so that the presence of a single nitro group in the product is no guarantee that addition of a nitro group occurred by a free radical process, and (2) $\cdot NO_2$ must be considered an ambident radical and therefore capable of attaching itself to carbon either at the nitrogen atom to form the $C{-}NO_2$ group or at an oxygen atom to form the $C{-}ONO$ group which may then be oxidized to a $C{-}ONO_2$ group. Hence the presence of a nitrite or a nitrate group in the product is no guarantee that the addition occurred by an ionic process. Finally, (3) the addition may proceed by both the free radical and the ionic processes simultaneously leading thereby to a variety of products. Cases in which a single substance constitutes the bulk of the product in nitrogen tetroxide additions have been the exception rather than the rule.[18]

Some of the complexities mentioned above are suppressed or eliminated in reactions of olefins with equimolar mixtures of nitrogen tetroxide and halogens. Thus there are only two principal products, one formed by the addition of two halogen atoms, the other by the addition of a halogen atom and a nitrogen-containing group. When the substituent group on the olefin is alkyl the nitrogen-containing group is $-ONO_2$ and is located on the carbon holding the alkyl group.[3] When the substituent group is chlorine the nitrogen-containing group is $-NO_2$ and is located on the carbon once removed from the carbon holding the chlorine.

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(16) W. Steinkopf and B. Jurgens, *J. prakt. Chem.*, **83**, 467 (1911).

(17) G. B. Bachman and C. M. Vogt, *J. Am. Chem. Soc.*, **80**, 2987 (1958).

(18) J. L. Riebsomer, *Chem. Revs.*, **36**, 157 (1945).

These differences indicate a difference in the mechanisms of the two reactions. Since the reaction with the alkyl substituted ethylene is difficult to conceive of as other than an ionic reaction initiated by a halonium ion,[3] the reaction with the chlorine substituted ethylene is most probably a radical reaction initiated by an NO_2 radical.

$$ClCH{=}CH_2 + \cdot NO_2 \longrightarrow Cl\underset{\cdot}{C}HCH_2NO_2$$

$$Cl\underset{\cdot}{C}HCH_2NO_2 + Cl_2 \longrightarrow Cl_2CHCH_2NO_2 + Cl\cdot$$

This is in accord with a D_i/D_r ratio of less than 1, as might be expected from other reactions of vinyl chloride. It is also in accord with the orientation of the entering groups, since the reverse orientation would be expected if the reaction were initiated by a halogen atom. Finally it may be noted that nitrogen tetroxide is reported to be 0.15% dissociated[19] to NO_2 radicals at 0° while chlorine and bromine are dissociated to atoms to only a vanishingly small extent at this temperature.[20] Even assuming considerably greater reactivities of halogen atoms relative to NO_2 radicals, the tremendous preponderance of the latter in the mixture would favor their preferential reaction with a D_r-activated olefin.

The absence of substantial amounts of dinitro products indicates a preference of the $Cl\underset{\cdot}{C}HCH_2NO_2$ radicals for combination with chlorine rather than with NO_2 a fact which may be attributed to the greater electrophyllicity of the chlorine. This point provides further reason for assuming a free radical mechanism for the addition. If the first step in the reaction had been the creation of $Cl\overset{+}{C}HCH_2NO$ or $\overset{+}{Cl}CHCH_2NO_2$ cations, the second step should have led to considerable amounts of $ClCH(ONO_2)CH_2NO$ or $ClCH(ONO_2)CH_2NO_2$, since the ONO_2^- anion is about as nucleophilic as the Cl^- anion, as evidenced by the similar degrees of ionization of nitric and hydrochloric acids. In other words the fact that $Cl\cdot$ is considerably more electrophilic than $\cdot NO_2$ while Cl^- is about equally nucleophilic with ONO_2^- is in agreement with a radical mechanism better than with an ionic mechanism for the addition reaction.

The D_i/D_r ratios of other groups. The above arguments apply equally well to the additions of mixtures of nitrogen tetroxide and halogens to olefins substituted by other groups. If we assume validity for the arguments then it is apparent that these mixtures constitute valuable tools for distinguishing radical from ionic mechanisms in addition reactions of olefins and in evaluating D_i/D_r ratios for various substituent groups as being greater or less than 1.

As a working hypothesis for the prediction of D_i/D_r ratios for various groups we have adopted the viewpoint that electron-supplying groups (+I or +E effects as defined by Ingold[21]) promote ionic displacements while electron-withdrawing groups promote radical displacements. In further corroboration of this hypothesis we have treated a vinyl ester with mixtures of nitrogen tetroxide and halogens, then hydrolyzed and obtained halocarbonyl compounds but no nitro compounds.

$$CH_3CH{=}C(CH_3)OCOCH_3 \xrightarrow[0°]{N_2O_4 + X_2} \xrightarrow{H_2O}$$
$$50\text{–}58\%\ CH_3CHXCOCH_3 + HOCOCH_3$$

In this case the electron-supplying properties of the ester oxygen atom seem to have promoted an ionic reaction initiated by halonium ions at the β-position of the double bond. Contrariwise acrylonitrile reacted under similar conditions to give 3-nitroacrylonitrile, which on hydrolysis gave 3-nitroacrylamide.[22] Here the electron-withdrawing cyano group seems to have promoted a reaction initiated by the NO_2 radical at the β-position of the double bond.

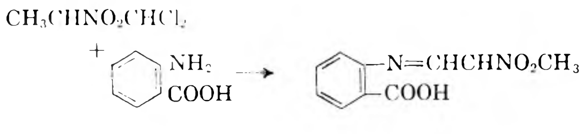
$$CH_2{=}CHCN \xrightarrow[0°]{N_2O_4 + Cl_2} (CH_2NO_2CHClCN) \longrightarrow$$
$$CHNO_2{=}CHCN + HCl$$

$$CHNO_2{=}CHCN + H_2O \longrightarrow CHNO_2{=}CHCONH_2$$

The saturated chloronitronitrile is postulated as an intermediate because copious amounts of hydrogen chloride were evolved during the first distillation of the product.

While the above studies served to indicate the absolute values of D_i/D_r ratios as being greater or less than 1 for various groups, it remained of interest to determine the relative potencies of two different groups with opposite tendencies in electron displacements. To study this effect we chose 1-chloropropene, which may be considered to be ethene substituted on one end by a group (methyl) promoting ionic reaction and on the other end by a group (chlorine) promoting free radical reaction. Treatment of this compound with a mixture of nitrogen tetroxide and chlorine gave a product whose reactions with anthranilic acid and whose analysis showed it to be 1,1-dichloro-2-nitropropane.

$$CH_3\,CH{=}CHCl \xrightarrow[0°]{N_2O_4 + Cl_2} CH_3CHNO_2CHCl_2$$



This result is surprising only because we are accustomed to thinking in terms of ionic displace-

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[19] F. Verhoek and F. Daniels, *J. Am. Chem. Soc.*, **53**, 1250 (1931); C. C. Addison and J. Lewis, *J. Chem. Soc.*, 2837 (1951).

[20] F. Ephraim, *Inorganic Chemistry*, 5th ed., Interscience Publishers, Inc., New York, N. Y., 1958, p. 115.

[21] C. K. Ingold, *Chem. Revs.*, **15**, 225 (1934).

[22] H. Shechter, F. Conrad, A. Daulton, and R. Kaplan, *J. Am. Chem. Soc.*, **74**, 3052 (1952). These authors obtained 2-chloro-3-nitropropionitrile by treating vinyl cyanide with nitryl chloride, and postulated a mechanism involving free radical dissociation of the nitryl chloride.

TABLE III

VAPOR PHASE NITROHALOGENATION OF VINYL HALIDES^{a,b}

	VBr + Br_2	VBr + Cl_2	VCl + Br_2	VCl + Cl_2
Reactor temperature	250	250	325	325
Contact time, seconds	7	7	4	3.6
Mole ratio: VX:X_2:NO_2	3.2:0.3:1.0	9.8:2.3:1.0	11.1:0.3:1.0	7.3:0.5:1.0
Moles VX reacted	4.6	6.9	23.4	5.4
Products, moles				
Nitrohalogenated	0.56^{c}	0.098^{e}	0.126^{g}	0.154^{i}
Halogenated	0.31^{d}	0.28^{f}	0.02^{h}	0.08^{j}
Conversion to nitro compound, percent				
Based on NO_2	3.9	13.9	5.95	22.2
Based on X_2	6.5	3.06	6.73	20.6
Yield of nitro compound, percent				
Based on VX	12.8	20.3	29.2	44.5

[a] The data listed here represent optimum conditions found from many experiments for the temperature, contact time, mole ratios, etc. [b] In this table V is $CH_2{=}CH{-}$ and X is Cl or Br. [c] 1,1-Dibromo-2-nitroethane. [d] 1,1,2-Tribromoethane. [e] 1-Bromo-1-chloro-2-nitroethane. [f] 1,2-Dichlorobromoethane. [g] 1-Chloro-2-bromonitroethane. [h] 1,2-Dibromochloroethane. [i] 1,2-Dichloronitroethane. [j] Trichloroethane.

ments, where methyl is ordinarily more powerful than chlorine. In comparing D_i/D_r ratios, chlorine is evidently more powerful in promoting free radical displacements than is methyl in promoting ionic displacements of the π electrons of the double bonds. The above reaction was remarkable in another respect also; it gave little or no trichloropropane, although chlorine addition is the principal reaction when propene is treated with a mixture of nitrogen tetroxide and chlorine.[3] Apparently the presence of the chlorine atom in 1-chloropropene strongly influences any ionic reaction which may occur and prevents formation of the anticipated dichloride.

Comparison of NO_2Cl with nitrogen tetroxide and chlorine. Although these two reagents appear to give the same products in additions to halogenated ethenes and vinyl cyanide they give different products with other types of olefins. Thus, with simple olefins[23] nitryl chloride gives principally chloronitroalkanes while nitrogen tetroxide and chlorine gives principally dichloroalkanes with small amounts of chloronitroalkanes being obtained only in vapor phase reactions.[24] Nitryl chloride adds to vinyl esters to give products which hydrolyze to nitroketones or nitroaldehydes, while nitrogen tetroxide and chlorine give products which hydrolyze to chloroketones or chloroaldehydes.[25] The products and orientation of entering groups are such as to suggest that NO_2Cl adds as free radicals, the $\cdot NO_2$ and $\cdot Cl$, to double bonds with electron-withdrawing substituents but adds ionically, as NO_2^+ and Cl^-, to double bonds with electron-supplying groups. The reagent nitrogen tetroxide–chlorine is similar in that it adds free radically as $\cdot NO_2$ and $\cdot Cl$ to double bonds with electron-withdrawing substituents, but different in that it adds ionically as Cl^+ and NO_2^- or NO_3^- to double bonds with electron-supplying substituents.

Vapor phase halonitration. In view of the interesting variability in the mechanisms of addition of mixtures of dinitrogen tetroxide and halogens to olefins in the liquid phase, it seemed desirable to investigate these same reactions in the vapor phase. It has already been shown by one of us[24] that simple olefins may be nitrochlorinated in this way. Thus, propene yields 1-chloro-2-nitropropane and 1,2-dichloropropane at 260–275° by an assumed free radical process initiated by chlorine atoms.

Since substituent halogen atoms seem to increase the tendencies of olefins to react by free radical rather than by ionic processes, it seemed likely that vinyl halides would nitrohalogenate somewhat more readily than would propene. Initial experiments were performed with vinyl bromide, nitrogen dioxide, and chlorine. It was found that reaction temperatures could not exceed 255° without liberating bromine by oxidation of the vinyl bromide. However at temperatures below this point the reaction proceeded smoothly and gave 1-bromo-1-chloro-2-nitroethane, the same product obtained in the liquid phase experiments and probably formed by a similar mechanism. Similarly vinyl bromide, nitrogen dioxide, and bromine gave 1,1-dibromo-2-nitroethane. Since reactions in the vapor phase commonly proceed by free radical processes, the isolation of these products in improved yields (over propene[24]) lends support to the previously proposed free radical nature of the liquid phase nitrohalogenation of halogenated olefins. Results of these experiments are summarized in Table III.

It next occurred to us that at still higher temperatures halogen atoms might be formed through thermal dissociation of halogen molecules in sufficient amounts to initiate the addition process and give reversed orientation of the entering groups and hence isomers of the nitrohalogenated compounds obtained at the lower temperatures.

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(23) C. M. Himel, U. S. Patent 2,511,915 (June 20, 1950).

(24) G. B. Bachman and J. P. Chupp, *J. Org. Chem.*, **21**, 465 (1956).

(25) G. B. Bachman and T. Hokama, *J. Org. Chem.*, **25**, 178 (1960).

$$CH_2{=}CHX + NO_2 \xrightarrow[\text{temp.}]{\text{low}} CH_2NO_2CHX\cdot \qquad (1)$$

$$CH_2NO_2CHX\cdot + X_2 \longrightarrow CH_2NO_2CHX_2 \qquad (2)$$

$$CH_2{=}CHX + \cdot X \xrightarrow[\text{temp.}]{\text{high}} CH_2XCHX\cdot \qquad (3)$$

$$CH_2XCHX\cdot + NO_2 \longrightarrow CH_2XCHXNO_2 \qquad (4)$$

X = Cl or Br

Accordingly vinyl chloride was treated at 325° with mixtures of nitrogen dioxide and chlorine or bromine. As expected, the nitrogen-containing products were now 1,2-dichloronitroethane and 1-chloro-2-bromo-1-nitroethane respectively. The The products were identified by analyses, physical properties, acid-catalyzed hydrolysis to halogenated acetic acids, and conversion to derivatives by reaction with anthranilic acid.

The 1,2-dichloronitroethane reacted normally with anthranilic acid to give 2-(2′-chloro-2′-nitroethyl) aminobenzoic acid. It hydrolyzed readily in acid solution to chloroacetic acid. With bases, even aqueous sodium bicarbonate, it dehydrohalogenated and formed in 90% conversion a polymer having a correct analysis for $(-CH_2CCl-NO_2-)_x$. The pure monomer[26] could not be obtained, since it polymerized immediately under basic conditions. Uncatalyzed hydrolysis with steam proceeded rapidly and gave 2-chloro-2-nitroethanol in over 90% conversions.[27] Steam distillation of β-chloronitroalkanes is not generally recommended as a means of purification because of the ease with which such hydrolyses occur.

An attempt to extend the vapor phase study of nitrochlorination to trichloroethene at 325° resulted in the formation of pentachloroethane (26% yield) and dichloroacetic acid (69% yield). Trichloroethene is known to oxidize readily to dichloroacetyl chloride which is easily hydrolyzed to dichloroacetic acid.[28] Such an oxidation evidently supersedes addition of NO_2 under these conditions. It should be noted that although trichloroethene is not inflammable in air it produces flames with NO_2 when ratios of less than about 2.7/1 of C_2HCl_3/NO_2 are heated. Similarly 1,2-dichloroethene gives dangerous mixtures with NO_2. We experienced a violent explosion on one occasion and flames on several occasions while attempting to nitrochlorinate this olefin in the vapor phase. No nitro compound was found from any of these reactions, but we did note that much of the *trans*-1,2-dichloroethene used was isomerized to *cis*-1,2-dichloroethene.

$$CHCl{=}CCl_2 + [O] \longrightarrow CHCl_2COCl \xrightarrow{H_2O} CHCl_2CO_2H + HCl$$

Conclusions. The reactions of mixtures of nitrogen tetroxide and halogens with olefins lead to addition products of remarkable variability in composition and orientation. Substituent groups on the olefin as well as reaction conditions such as temperature and phase determine the types of products formed. These factors influence the relative tendencies of olefins to react by ionic (D_i) *vs.* radical (D_r) mechanisms, and the variability observed can be correlated with the type of mechanism which predominates in any given case. The D_i/D_r ratio for substituent groups in apparently greater than 1 for those groups which supply electrons and less than 1 for those groups which withdraw electrons as judged by the cases we have studied. Further studies of the relative magnitudes of these ratios for various substituents would be valuable in explaining polymerization behavior and other addition reactions of olefins.

EXPERIMENTAL

Addition reactions in liquid phase. The general procedure involved placing weighed quantities of liquid dinitrogen tetroxide, halogen, and solvent in a suitable glass vessel immersed in a salt-ice-water cooling bath and adding the requisite amount of the substituted olefin with stirring as rapidly as possible without causing the temperature to rise above 5°. When the halogen was chlorine a sufficient quantity of solvent was used to hold the gas in solution. Chlorine dissolves in carbon tetrachloride at 0° to the extent of about 8.0 g. per 100 ml. When the halogenated olefin was gaseous (vinyl chloride and vinyl bromide) it was bubbled into the liquid reactants through a gas delivery tube; the liquid olefins were added through a dropping funnel. The reaction rate was fastest and hence the rate of addition of the olefin was slowest for the least highly substituted olefins.

The reaction mixture was worked up by stirring repeatedly with fresh quantities of ice and water until no more material appeared to dissolve, drying and distilling. The water soluble materials were not investigated. The color of the product after washing but before distilling varied from pale yellow to light green; it was usually highly lachrymatory. The 1-chloro-1-iodo-2-nitroethane decomposed on attempted distillation and hence was analyzed and converted to a derivative in its crude form after removal from it of materials volatile at room temperature under 5 mm. pressure.

The above procedure with acrylonitrile, 106 g. (2 moles), dinitrogen tetroxide, 92 g. (1 mole), chlorine, 71 g. (1 mole), and chloroform, 1000 ml., allowed to react for 3 hr. yielded on distillation a product of substitution as well as addition, $C_3H_2Cl_2N_2O_2$, which may have been 2,3-dichloro-3-nitropropionitrile or 2,2-dichloro-3-nitropropionitrile; b.p. 66° (1 mm.) n_D^{25} 1.5049, d_4^{25} 1.441, conversion 7.1%. This product, 4.12 g. (0.03 mole), was dissolved in anhydrous ether, 10 ml., and treated at 0° with sodium acetate, 2.97 g. (0.033 mole), for 1 hr. The mixture was filtered, the solvent removed and the product distilled; b.p. 74° (3 mm.), n_D^{25} 1.5170, d_4^{25} 1.433, conversion 98%. This dehydrohalogenated product may have been 3-chloro-3-nitro-acrylonitrile, or 2-chloro-3-nitroacrylonitrile.

Anal. Calcd. for $C_3HN_2ClO_2$: C, 27.20; H, 0.76; N, 21.08; Cl, 26.80. Found: C, 26.90; H, 0.72; N, 20.66; Cl, 27.16.

The NMR spectrum showed a single peak for hydrogen.

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(26) R. Wilkendorf and M. Trenel, Ber., **57,** 306 (1924) prepared the monomer by pyrolysis of 2-chloro-2-nitroethyl nitrate. They also prepared the polymer.

(27) M. Simonette and G. Favini, *Atti accad. nazl. Lincei, Rend., Classe sci. fis., mat. e nat.*, **14,** 119 (1953); *Chem. Abstr.*, **48,** 2568^d (1954), have studied the kinetics of hydrolysis of the closely related 2-chloronitroethane.

(28) E. H. Huntress, *Organic Chlorine Compounds*, John Wiley and Sons, Inc., 1948, p. 611.

In order to avoid the substitutive halogenation which occurred in the above experiment another run was made in which the nitrogen tetroxide and chlorine were added to the acrylonitrile and chloroform instead of the reverse. Distillation was accompanied by evolution of hydrogen chloride and eventually yielded 3-nitroacrylonitrile as the sole product; b.p. 57° (2 mm.), n_{D}^{25} 1.4877, d_{4}^{25} 1.294, conversion 24.5%. Hydrolysis of this product by heating 3.0 g. (0.03 mole) with 25 ml. of 88% sulfuric acid for 5 hr. at 55°, pouring onto ice, filtering the solid, and recrystallizing from benzene gave 3-nitroacrylamide, m.p. 165°.

Preparation of anthranilic acid derivatives. The reagent was prepared by dissolving anthranilic acid (54.0 g., 0.393 mole) in methanol (166 ml.) and adding this mixture to a solution of sodium bicarbonate (34.0 g., 0.404 mole) in water (100 ml.), warming until all gaseous carbon dioxide was evolved, clarifying with a little decolorizing charcoal, and filtering. The resulting solution was yellow-brown in color and stable enough for use over periods of several months.

The halogenated nitroethane (2.0 g.) was added to the above reagent (10 ml.) and stirred until the solid reaction product appeared. The time required varied from a few seconds to about an hour being somewhat longer with the more highly halogenated compounds. The anthranilic acid derivative was collected, washed with water and recrystallized from a suitable solvent (see Table II).

Better results were obtained with the β,β,β-trichloronitroalkanes by preparing the anthranilic acid derivative in glacial acetic acid. For this purpose 0.01*N* quantities of the chloronitronitro compound and anthranilic acid were dissolved in 30 cc. of glacial acetic acid and allowed to stand at room temperature for 6 hr. The product was filtered and recrystallized from a benzene-ethanol mixture; conversions about 50%.

Hydrolysis of halonitroethanes to halogenated acetic acids. A 0.05-mole sample of the nitro compound and 10 ml. of 88% sulfuric acid were heated together under reflux until homogeneous and then directly distilled at about 1 mm. pressure to recover the substituted acetic acid. The distilled halogenated acetic acids were also converted to their chlorides by warming with thionyl chloride and then to their anilides by reaction with aniline. The melting points of these solid derivatives served to confirm the identity of the acid obtained.

The reaction failed to give the expected product from 1-chloro-1-iodo-2-nitroethane, and free iodine was liberated in copious quantities. It also failed with the tetrachloronitroethane obtained from trichloroethene and gave only gaseous products.

Addition reactions in vapor phase. The techniques employed were similar to those previously described in publications from this laboratory.[29] The reactor system differed however in that it was not immersed in a molten salt bath. Instead the temperature was controlled electrically and automatically with nichrome heating ribbons, thermocouples, and a sensitive relay. Gases were metered through flowmeters of the floating ball type and liquids through a pump of the peristaltic action type. All parts were carefully calibrated and frequently rechecked to ensure accuracy. The greatest difficulty was encountered in metering those reactants which boil a little above or a little below room temperature. Tanks of dinitrogen tetroxide and vinyl bromide had to be immersed in heated water or oil baths to maintain adequate pressures. The di- and trichloroethenes tended to soften the elastic polyethylene tubing used in the peristaltic pump and alter the tubing's effective diameter, thus necessitating frequent replacement. The bromine was vaporized by a stream of nitrogen. Careful control of the temperature and the nitrogen flow rate gave reproducible rates of bromine flow.

In operation the halogen and nitrogen dioxide streams were mixed and then merged with the vinyl halide stream which had been preheated to 250°. This final mixing occurred just before the reactor. Since the vinyl halide made up the bulk of the reactant mixture it quickly raised the temperature of the other reactants to near the reaction temperature.

The products of reaction were condensed in a series of water and Dry Ice condensers and the off gases were passed through a wet test meter. All of the products were analyzed, but since nothing of recognized significance was found beyond that reported in the tables, these data are not included here.

1,2-Dichloronitroethane identification and reactions. The product from the vapor phase reaction of vinyl chloride with nitrogen dioxide and chlorine showed the following constants: b.p. 47.5° (6.5 mm.), d_{20}^{24} 1.483, n_{D}^{20} 1.4680. Steinkopf and Kuhnel[4] report b.p. 124° (10 mm.).

Anal. Calcd. for $C_2H_3NO_2Cl_2$: C, 16.67; H, 2.10; N, 9.72; Cl, 49.30; MR_D 26.78. Found: C, 16.60; H, 2.22; N, 9.61; Cl, 49.18; MR_D 26.93.

The anthranilic acid derivative was *o*-(2-chloro-2-nitroethylamino)benzoic acid, m.p. 139.0–139.5°.

Anal. Calcd. for $C_9H_9N_2O_4Cl$: C, 44.18; H, 3.71; N, 11.45; Cl, 14.49. Found: C, 44.40; H, 3.73; N, 11.31; Cl, 14.42.

Hydrolysis of the dichloronitroethane in 88% sulfuric acid for 8 hr. gave a 74% yield of chloroacetic acid, m.p. 52–54°.

Dehydrohalogenation of the dichloronitroethane was accomplished with a variety of bases. The following procedure gives a good yield of light colored polymer. The product, 14.0 g., was added to a solution of 8.4 g. of sodium bicarbonate in 100 ml. of water at room temperature. After 3 hr. carbon dioxide evolution ceased. The solid polymer (9.2 g., 88% yield) was filtered, washed, reprecipitated from solution in glacial acetic acid with water, and dried. It began to melt at 118°, was a clear liquid at 187°, and became black at 218°.

Anal. Calcd. for $C_2H_2NO_2Cl$: C, 22.34; H, 1.87; N, 13.03; Cl, 32.98. Found: C, 22.60; H, 2.16; N, 12.67; Cl, 32.70.

Uncatalyzed hydrolysis of the dichloronitroethane was accomplished by passing steam through it until the liquid became homogeneous (about 15 min. for a 35-g. sample). Ether extraction and distillation yielded 2-chloro-2-nitroethanol in 92% yield; b.p. 55° (0.4 mm.), n_{D}^{22} 1.4692, MR_D calcd. 23.53, found 23.44.

Anal. Calcd. for $C_2H_4NO_3Cl$: C, 19.14; H, 3.21; N, 11.16; Cl, 28.17. Found: C, 19.06; H, 2.97; N, 11.20; Cl, 28.40.

This alcohol is a colorless, odorless, acidic liquid which turns yellow on standing in the air. It is completely miscible with water, ether, and benzene. We were unsuccessful in our attempts to characterize it by reaction with *p*-nitro- and 3,5-dinitrobenzoyl chlorides, phenyl- and α-naphthylisocyanates, and benzoyl bromide. The procedure of Brewster and Ciotti[30] also failed to yield a derivative.

The distillation residue from the vapor phase nitrochlorination of vinyl chloride gave no anthranilic acid derivative and showed the following properties: $d_{20}^{24.5}$ 1.470, $n_{D}^{24.5}$ 1.4981. It may have been 1,3,4-trichloro-1-nitrobutane, although our data is inadequate to confirm this.

Anal. Calcd. for $C_4H_6NO_2Cl_3$: C, 23.27; H, 2.93; N, 6.78; Cl, 51.52; MR_D 40.88. Found: C, 25.32; H, 3.36; N, 7.40; Cl, 52.00; MR_D 39.83.

Similar residues were found in the other vapor phase nitrohalogenation experiments and increased in amount with increasing mole ratios of vinyl halides in the reactants.

Identification of chloronitro olefins. Gas chromatographic analysis proved to be a most useful tool in determining the purity of products obtained and in detecting the small amounts of chloronitro olefins formed in certain cases. Thus, the chloronitration products from 1,2-dichloroethylene and trichloroethylene gave peaks for the expected saturated chloronitroethanes and other peaks suspected of arising from the corresponding nitroethenes. To check this conclusion the saturated compounds were dehydrohalogenated by treatment with sodium acetate[22] in anhydrous ether, the olefins isolated in pure form, and their chromatographic peaks determined. In both cases the peaks obtained corresponded in elution time to the peaks observed in the original product mixtures. The following example illustrates the procedure employed:

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[29] *J. Org. Chem.*, **17**, 906, 914, 928, 935 (1952); **19**, 312 (1954); **21**, 465, 655 (1956); *Ind. Eng. Chem.*, **46**, 713 (1954).

[30] J. H. Brewster and C. J. Ciotti, *J. Am. Chem. Soc.*, **77**, 6214 (1955).

Sodium acetate, 3.6 g (0.035 mole), was slowly added with stirring to a solution of 1,1,1,2-tetrachloro-2-nitroethane, 6.4 g. (0.03 mole), in anhydrous ether, 15 ml., at 0°. After 1 hr., the solution was filtered to remove excess sodium acetate and sodium chloride, and the ether and acetic acid removed under reduced pressure. Distillation gave 1,2,2-trichloronitroethylene, 4.1 g. (77.5% yield), b.p. 55° (4 mm.).

A Perkin-Elmer Vapor Fractometer with a 2-meter stainless steel column containing Celite packing coated with dodecyl phthalate, a temperature of 140°, and a flow rate of 20 cc. of helium per min. were used to determine the gas chromatographic peaks. Applications of gas chromatography to analysis of nitroparaffin mixtures have been discussed more fully by Bethea and Wheelock.[31]

1-Chloro-2-bromonitroethane identification and reactions. The product from the vapor phase reaction of vinyl chloride with nitrogen dioxide and bromine showed the following constants: b.p. 68° (6.7 mm.), n_D^{20} 1.4970. The anthranilic acid derivative melted at 139–140° and showed a mixture m.p. of 139–140° with the same derivative from 1,2-dichloronitroethane. Hydrolysis with 88% sulfuric acid for 5 hr. gave a 40% yield of bromoacetic acid, b.p. 66–67° (1.0 mm.), m.p. 50°

Nitrohalogenation of the enol acetate of methyl ethyl ketone. (We are indebted to Dr. Takeo Hokama for conducting these experiments.) 2-Buten-2-yl acetate, 23 g. (0.2 mole), was added dropwise in about 2 hr. to a solution of the nitrohalogenating agent (0.2 mole) in 100 ml. of carbon tetrachloride at ice bath temperatures. After stirring for an additional hour the mixture was washed with 10% urea solution, and water, and then dried and distilled. The products were as follows:

Nitrohalogenating Agents	Products (% yld.)	Properties
$N_2O_4 + Cl_2$	3-Chlorobutanone (58)	B.p. 40° (45 mm.)
$N_2O_4 + Br_2$	3-Bromobutanone (50)	B.p. 52° (30 mm.)
NO_2Cl	3-Nitrobutanone (36)	B.p. 56° (2 mm.)

They were further characterized by preparation of derivatives whose properties coincided with those reported in the literature.[32]

LAFAYETTE, IND.

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[31] R. M. Bethea and T. D. Wheelock, *Anal. Chem.*, **31**, 1834 (1959).

[32] G. B. Bachman and T. Hokama, *J. Am. Chem. Soc.*, **81**, 4882 (1959).

[CONTRIBUTION FROM BIOCHEMICAL LABORATORY, COLLEGE OF AGRICULTURE, KYOTO UNIVERSITY]

N-Acylation of Unsubstituted Glycosylamines

KONOSHIN ONODERA AND SHOZABURO KITAOKA

Received January 18, 1960

N-Monoacylation of unsubstituted glycosylamines has been conveniently achieved by the reaction with acid anhydride in *N*,*N*-dimethylformamide or in methanol. *N*-Acetyl-α-D-arabinopyranosylamine, -β-D-xylopyranosylamine, and -β-D-glucopyranosylamine, *N*-benzoyl-β-D-xylopyranosylamine, and a series of *N*-acyl-β-D-glucopyranosylamines with even-numbered fatty acids as the acyl group have been prepared by these methods in good yields.

N-Monoacetylglycosylamines have been prepared by partial hydrolysis of fully *O*-acetylated derivatives of *N*-acetylglycosylamines,[1-4] or by the reaction of unsubstituted glycosylamines and ketene.[5,6] They have also been formed by the action of ammonia on acetylated sugars,[7,8] acetylated aldehydo-sugars,[7,9] or acetylated glycononitriles.[9,10] *N*-Benzoyl-D-mannosylamine, apparently the only reported *N*-monobenzoyl derivative of glycosylamine, has been formed in a small yield by the reaction of D-mannose cyanohydrin hexabenzoate with silver nitrate and methanolic ammonia,[11] the major product of the reaction being *N*,*N*-dibenzoyl-D-mannosylamine. In their studies on the syntheses of purine biosynthesis intermediates, Baddiley, Buchanan, Handschumacher, and Prescott[12] prepared *N*-chloroacetyl-β-D-glucopyranosylamine by the reaction of chloroacetyl chloride and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine and subsequent *O*-deacetylation; the reactions of *N*-benzyloxycarbonylglycyl chloride or *N*-benzyloxycarbonylglycylethyl carbonate with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine and with 2,3,5-tri *O*-benzoyl-D-ribofuranosylamine followed

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[1] H. S. Isbell and H. L. Frush, *J. Research Natl. Bur. Standards*, **46**, 132 (1951).

[2] H. L. Frush and H. S. Isbell, *J. Research Natl. Bur. Standards*, **47**, 239 (1951).

[3] P. Brigl and H. Keppler, *Z. physiol. Chem.*, **180**, 38 (1929).

[4] H. S. Isbell and H. L. Frush, *J. Org. Chem.*, **23**, 1309 (1958).

[5] C. Niemann and J. T. Hays, *J. Am. Chem. Soc.*, **62**, 2960 (1940).

[6] R. Kuhn and G. Krüger, *Chem. Ber.*, **87**, 1544 (1954).

[7] C. Niemann and J. T. Hays, *J. Am. Chem. Soc.*, **67**, 1302 (1945).

[8] L. Zechmeister and G. Toth, *Ann.*, **525**, 14 (1936).

[9] R. C. Hockett and L. B. Chandler, *J. Am. Chem. Soc.*, **66**, 957 (1944).

[10] V. Deulofeu and J. O. Deferrari, *J. Org. Chem.*, **17**, 1087 (1952).

[11] P. Brigl, H. Mühlschlegel, and R. Schinle, *Ber.*, **64**, 2921 (1931).

[12] J. Baddiley, J. G. Buchanan, R. E. Handschumacher, and J. F. Prescott, *J. Chem. Soc.*, 2818 (1956).

TABLE I

N-ACYLGLYCOSYLAMINES

Compound	Method[a]	Yield, %	M.P., °	$[\alpha]_D^b$	Formula	Calculated			Found		
						C	H	N	C	H	N
N-Acetyl-α-D-arabinopyranosylamine[c]	A	59	223–224	−69° (H₂O)	$C_7H_{13}NO_5$	43.99	6.80	7.33	43.65	6.69	7.44
N-Acetyl-β-D-xylopyranosylamine[d]	A	78	213–214	−2° (H₂O)	$C_7H_{13}NO_5$	43.99	6.80	7.33	43.53	6.87	6.94
	B	70	204–212								
N-Acetyl-β-D-glucopyranosylamine[e]	A	84	256	−20° (H₂O)	$C_8H_{15}NO_6$	43.43	6.84	6.33	43.39	6.82	5.94
	B	77	254–256	−16° (H₂O)							
N-Benzoyl-β-D-xylopyranosylamine	A	58	218–219	−10° (H₂O)	$C_{12}H_{15}NO_5$	56.91	5.97	5.53	57.01	5.84	5.08
N-Caprinoyl-β-D-glucopyranosylamine	B	55	254–256	−4° (Pyridine)	$C_{16}H_{31}NO_6$	57.62	9.39	4.21	57.63	9.57	4.09
N-Lauroyl-β-D-glucopyranosylamine	B	66	180–181	+3° (Pyridine)	$C_{18}H_{35}NO_6$	59.78	9.78	3.88	59.56	9.66	3.67
N-Myristoyl-β-D-glucopyranosylamine	B	68	176–178	−3° (Pyridine)	$C_{20}H_{39}NO_6$	61.65	10.11	3.61	61.62	10.19	3.47
N-Palmitoyl-β-D-glucopyranosylamine	B	80	175–177	−9° (Pyridine)	$C_{22}H_{43}NO_6$	63.26	10.39	3.36	63.16	10.20	3.43
N-Stearoyl-β-D-glucopyranosylamine	B	72	172–174	−4° (Pyridine)	$C_{24}H_{47}NO_6$	64.67	10.68	3.14	64.75	10.62	2.86

[a] A: N,N-Dimethylformamide method; B: Methanol method. [b] The temperature was 10° with the pentose derivatives and 15° with the glucose derivatives. [c] The L-isomer was reported[1] to show m.p. 222–224°, $[\alpha]_D^{20}$ +69.7° (H₂O). [d] The reported values[1] are m.p. 213–214°, $[\alpha]_D^{20}$ −0.7° (H₂O). [e] The reported values are m.p. 255°,[5] 257°,[3] 260°,[4] $[\alpha]_D$ −22.4°,[5] −22 → −23°,[3] −22.8°[4] (H₂O).

by partial hydrolyses yielded N-(N′-benzyloxycarbonylglycyl)-β-D-glucopyranosylamine[12] and the anomers of N-(N′-benzyloxycarbonylglycyl)-D-ribofuranosylamine,[13] respectively.

In the light of increasing importance of glycosylamines,[4,14] development of convenient and general methods selectively to N-monoacylate unsubstituted glycosylamines with various acyl groups appeared to be desirable. In the present work, two methods were studied on α-D-arabinopyranosylamine, β-D-xylopyranosylamine, and β-D-glycopyranosylamine, and their N-acetyl derivatives, N-benzoyl-β-D-xylopyranosylamine, and the N-acyl-β-D-glucopyranosylamines with a series of even-numbered fatty acids were prepared. All the compounds obtained in crystalline state are given with physical characteristics in Table I.

The two methods are extensions of the two methods reported recently for the selective N-acylation of D-glucosamine (2-amino-2-deoxy-D-glucose). Kuhn and Haber[15] prepared N-acetyl-β-D-glucosamine by the reaction of acetic anhydride and β-D-glucosamine in N,N-dimethylformamide at −15°, while Inouye, Onodera, Kitaoka, and Hirano[16] obtained N-acyl-D-glucosamines by the acylation with anhydrides of a series of fatty acids in methanolic supersaturated solution of D-glucosamine at room temperature or slightly higher temperatures.

In application of these methods to the N-acylation of unsubstituted glycosylamines, the N,N-dimethylformamide method was found to be more appropriate because glycosylamines are sparingly soluble in methanol and are more labile than glucosamine. The N-acylation of glycosylamines in the methanol method was therefore successful only with relatively more stable amines.

N-Acetylation of glycosylamines in N,N-dimethylformamide was carried out by suspending the glycosylamines in 15 to 25 molar equivalents of dimethylformamide at 0°, adding 1.5 equivalents of cold acetic anhydride with agitation and cooling, and shaking the mixtures for periods required for complete dissolution of the glycosylamines at room temperature. The periods ranged from a few minutes with β-D-glucopyranosylamine to about two hours

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(13) J. Baddiley, J. G. Buchanan, R. Hodges, and J. F. Prescott, *Proc. Chem. Soc.*, 148 (1957).

(14) G. P. Ellis and J. Honeymann, *Advances in Carbohydrate Chem.*, **10**, 95 (1955).

(15) R. Kuhn and F. Haber, *Chem. Ber.*, **86**, 722 (1953).

(16) Y. Inouye, K. Onodera, S. Kitaoka, and S. Hirano, *J. Am. Chem. Soc.*, **78**, 4722 (1956).

with α-D-arabinopyranosylamine. Separation of crystalline *N*-acetylglycosylamines ensued usually immediately after the completion of the dissolution, and the crude yields were 60–80%. Use of larger amounts of acetic anhydride shortened the period before the dissolution but did not improve the yield.

The *N*-acetyl-D-xylosylamine and *N*-acetyl-D-glucosylamine thus obtained showed melting points and optical rotations essentially identical with the reported values for *N*-acetyl-β-D-xylopyranosylamine[4] and *N*-acetyl-β-D-glucopyranosylamine,[3–5] respectively. The infrared spectra potassium bromide of these compounds were identical with those of the compounds[17] prepared by *O*-deacetylation of *N*-acetyltri-*O*-acetyl-β-D-xylopyranosylamine and *N*-acetyltetra-*O*-acetyl-β-D-glucopyranosylamine. *N*-Acetyl-α-D-arabinopyranosylamine is a new compound but the L-enantiomorph is known.[1] The D-isomer here obtained had an identical melting point and an identical value of optical rotation with inversed sign as reported for the L-isomer. The infrared spectrum (potassium bromide) of the D-isomer was essentially identical with the spectrum[17] (potassium chloride) of the L-isomer. These results indicate that the anomeric structures of the original glycosylamines were retained during the *N*-acylation.

Acetylation of the *N*-acetylglycosylamines in pyridine and acetic anhydride gave good yields of the fully acetylated derivatives.

N-Benzoyl-β-D-xylopyranosylamine was prepared in 58% yield similarly by the *N*,*N*-dimethylformamide method. In this case the spontaneous separation of the *N*-benzoyl derivative did not follow the dissolution of β-D-xylopyranosylamine in the mixture of *N*,*N*-dimethylformamide and benzoic anhydride, and additions of ethanol and ether were required for the separation of the crystalline product.

The *N*-acetylation of unsubstituted glycosylamines in methanol was performed as follows: An amount of a glycosylamine was dissolved in 120 to 150 parts of methanol at 50° to make a saturated solution and to this was added with shaking 1.5 parts of acetic anhydride; the mixture was cooled immediately at 0° and kept there overnight. To isolate *N*-acetyl-glycosylamines it was usually necessary to concentrate the solutions to small volumes under reduced pressure before the spearation of crystals took place. The crude yields of the *N*-acetylglycosylamines in this method were similar or somewhat smaller than those in the *N*,*N*-dimethylformamide method. As previously stated, this method was successful only with more stable glycosylamines. *N*-Acetyl-β-D-xylopyranosylamine and *N*-acetyl-β-D-glucopyranosylamine were prepared by this method also. The products showed no depression in mixed melting point with the preparations by the *N*,*N*-dimethylformamide method. An attempt to *N*-acetylate α-D-arabinopyranosylamine gave only a resinous product.

A series of *N*-acyl-β-D-glucopyranosylamines with even-numbered fatty acids were prepared by the methanol method with the use of the respective acid anhydrides. *N*-Caprinoyl-, *N*-lauroyl-, *N*-myristoyl-, *N*-palmitoyl-, and *N*-stearoyl-β-D-glucopyranosylamines were obtained in crystalline form, while the *N*-butyryl, *N*-caproyl, and *N*-capryloyl derivatives were not crystalline.

EXPERIMENTAL

Glycosylamines. Sugars were suspended in 2 to 2.5 parts of anhydrous methanol and into these suspensions was passed anhydrous ammonia at 0° with stirring until complete solutions were obtained. The solutions were kept at 0° for 1 to 4 weeks for satisfactory separation of the glycosylamines. After filtration, washing with methanol, and drying, the products were recrystallized from 100 parts of methanol or from a small volume of water by adding ethanol. The glycosylamines thus obtained and used for subsequent experiments were as follows: α-D-arabinopyranosylamine, a new amine obtained after recrystallizations from methanol in hygroscopic crystals, m.p. 70–85° (gas), $[\alpha]^{10}_{D}$ −52° (*c* 0.68, water). The L-isomer has been reported[1] to melt at 124–125°, $[\alpha]^{20}_{D}$ +86.3° (water). No satisfactory analyses were obtained from this preparation and apparently it was an impure product; β-D-xylopyranosylamine, m.p. 142–143°, $[\alpha]^{10}_{D}$ −18° (*c* 3.3, water). The reported values[4] are m.p. 128–129°, $[\alpha]^{20}_{D}$ −19.6°; β-D-glucopyranosylamine, m.p. 126–128°, $[\alpha]^{12}_{D}$ +22° (c 1.0, water). Reported, m.p. 127–128°,[18] 125–127°,[4] $[\alpha]_{D}$ +20.3°,[18] +20.8°,[4] +22.1°[19] (water).

N-Acetylation of glycosylamines in N,N-dimethylformamide. Suspensions of 0.02 mole of glycosylamines in 0.35 to 0.5 mole of dried *N*,*N*-dimethylformamide were cooled at 0°. To these was added 0.03 mole of acetic anhydride with shaking and cooling. The reaction mixtures were then shaken mechanically at room temperature. The glycosylamines went into solution after various periods of shaking; α-D-arabinopyranosylamine required about 2 hr., β-D-xylopyranosylamine about 1.5 hr., and β-D-glucopyranosylamine a few minutes. Separation of the crystalline *N*-acetylglycosylamines usually occurred rapidly after the dissolution of glycosylamines completed. The mixtures were kept overnight at 0°, and the crystals were collected by filtration and washed with small volumes of cold ethanol and ether, and recrystallized from methanol. The physical characteristics of the *N*-acetyl-glycosylamines thus prepared are given in Table I.

Experiments with D-xylopyranosylamine indicated that employment of larger amounts of acetic anhydride (up to 4.7 moles against 1 mole xylosylamine) shortened markedly the period (up to 20 min.) required for the dissolution of the amine, but the yield of the *N*-acetylated product was identical.

N-Benzoyl-β-D-xylopyranosylamine. Three grams of β-D-xylopyranosylamine were suspended in 18 ml. of *N*,*N*-dimethylformamide and cooled in an ice-bath. To this suspension was added 6.0 g. benzoic anhydride and the mixture was shaken at room temperature for 2 hr., by which time a complete solution had been obtained but no separation of crystals had occurred. The solution was allowed to stand at 0° overnight and to this was added 25 ml. ethanol

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(17) Kindly furnished by Dr. H. S. Isbell.

(18) A. R. Ling and D. R. Nanji, *J. Chem. Soc.*, **121**, 1682 (1922).

(19) J. C. Irvine, R. T. Thompson, and C. S. Garrett, *J. Chem. Soc.*, **103**, 238 (1913).

and then 150 ml. ether to a turbidity which on agitation separated crystals. A small additional volume of ether was added and after standing overnight at 0° the crystals were collected by filtration and washed with small volumes of cold ethanol and ether. The yield was 3.0 g. (58%). Recrystallization from 20 ml. methanol gave needles, m.p. 218–219° dec., $[\alpha]^{10}_{\text{D}}$ +10° (*c* 2, water).

Acetylation of N-acetylglycosylamines in pyridine and acetic anhydride. One gram of an N-acetylglycosylamine was dissolved in 20–30 ml. pyridine and cooled to 0°. To this was added under cooling 5 ml. of cold acetic anhydride. The solution was kept at 0° for 1 hr. and then at room temperature overnight. It was poured into ice-water mixture, extracted with chloroform, and the chloroform extract washed with sodium bicarbonate solution, dilute hydrochloric acid, and water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The fully acetylated products thus obtained and recrystallized from ethanol had the following physical constants: N-Acetyl-tri-*O*-acetyl-α-D-arabinopyranosylamine, m.p. 175–176°, $[\alpha]^{10}_{\text{D}}$ −90° (*c* 1.0, $CHCl_3$). The reported constants[1] for the L-isomer are m.p. 177–178°, $[\alpha]^{20}_{\text{D}}$ +89.6° ($CHCl_3$).

Anal. Calcd. for $C_{13}H_{19}NO_8$: C, 49.21; H, 6.04; N. 4.41. Found: C, 49.31; H, 6.14; N, 4.75.

N-Acetyl-tri-*O*-acetyl-β-D-xylopyranosylamine, m.p. 170–171°, $[\alpha]^{15}_{\text{D}}$ +28° (*c* 1.1, $CHCl_3$); in literature,[4] m.p. 172–173°, $[\alpha]^{20}_{\text{D}}$ +28.5° ($CHCl_3$).

N-Acetyl-tetra-*O*-acetyl-β-D-glucopyranosylamine, m.p. 163°, $[\alpha]^{15}_{\text{D}}$ +17° (*c* 1.0, $CHCl_3$); the reported values[4] are m.p. 163–164°, $[\alpha]^{20}_{\text{D}}$ +17.4° ($CHCl_3$).

N-Acylation of β-D-glucopyranosylamine in methanol. One gram (0.0056 mole) of β-D-glucopyranosylamine was dissolved in 120 ml. of methanol at 50°, and 0.0085 mole of acid anhydrides[16] was added with shaking to this solution followed by immediate cooling in an ice-box where it was allowed to stand overnight. N-Acetyl-β-D-glucopyranosylamine separated in crystalline state on concentration under reduced pressure to about 30 ml. and cooling. For N-butyryl, N-caproyl, and N-capryloyl derivatives, a small volume of ether was added after the concentration to separate precipitates which were hygroscopic and could not be crystallized. Additions of the anhydrides of capric, lauric, myristic, palmitic, and stearic acids were made in acetone or petroleum ether solutions; separation of the N-acyl-β-D-glucopyranosylamines with these acyl groups from the reaction solutions was spontaneous on cooling and needed no concentration. Recrystallization of the N-acyl compounds was effected by dissolving in 2 parts of water and adding 20 parts of ethanol or from methanol.

The N-acetyl-β-D-glucopyranosylamine prepared in the methanol method was identical with the product obtained in the N,N-dimethylformamide method as judged by mixed melting point and infrared spectra. Acetylation of these N-acetylated products in pyridine and acetic anhydride also gave an identical product, N-acetyl-tetra-*O*-acetyl-β-D-glucopyranosylamine.

The N-acetylation in methanol was attempted with α-D-arabinopyranosylamine and β-D-xylopyranosylamine by a similar procedure. The arabinosylamine gave only a resinous product while N-acetyl-β-D-xylopyranosylamine was obtained in crystalline state in a yield of 70%, m.p. 204–212° and mixed melting point with the product by the N,N-dimethylformamide method, 205–212°.

Acknowledgment. We are indebted to Dr. H. S. Isbell, National Bureau of Standards, Washington, D.C., for samples and infrared spectra of some of the N-acetylglycosylamines, to Mr. Zenzaburo Kumazawa for taking the infrared spectra, and to Messrs. Norio Mizutani and Toshio Yamada for technical assistance.

KYOTO, JAPAN

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Reductive Dimerization in Formic Acid

EARLE VAN HEYNINGEN AND DONALD R. CASSADY

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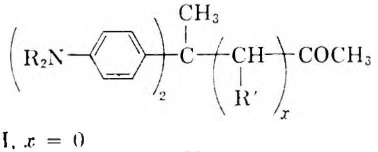
The formation of 1,1,3,3-tetrakis(*p*-dimethylaminophenyl)butane (VII) by the action of formic acid on 1,1-bis(*p*-dimethylaminophenyl)ethylene is reported.

In the course of a program to synthesize compounds similar to Amphenone B (I),[1] an attempt was made to prepare the tetramethylated Amphenone homolog II. Although the attempt was unsuccessful, some rather novel results were obtained.



I. R = H, x = 0
II. R = CH_3, x = 1, R′ = H
III. R = CH_3, x = 1, R′ = $COOC_2H_5$

The first step of the projected synthesis consisted in heating 1,1-bis(*p*-dimethylaminophenyl)ethylene (IV) with acetoacetic ester in 98% formic acid as both solvent and catalyst. It was hoped that the ester III would be formed, which by decarbethoxylation could be converted into the ketone II. This reaction was modeled after a similar reaction by Fosse[2] in which acetoacetic ester and Michler's hydrol were condensed in the presence of acetic acid with the elimination of water to yield a benzhydrylacetoacetic ester. In the synthesis of the ester III the homolog of Michler's hydrol could not be used since all preparations leading to it resulted in the diphenylethylene IV.[3] [In this and all subsequent formulas R is $(CH_3)_2NC_6H_4$–.] This was thought to be of small consequence, however, since the same reactive

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(1) M. J. Allen and A. H. Corwin, *J. Am. Chem. Soc.*, **72**, 117 (1950); R. Hertz, M. J. Allen, W. W. Tullner, *Proc. Soc. Exp. Biol. Med.*, **75**, 627 (1950), **74**, 632 (1950).

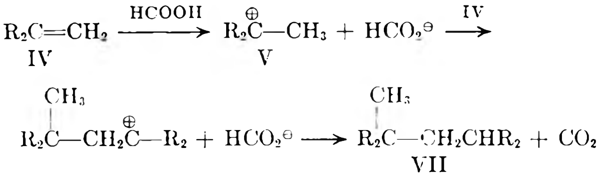
(2) R. Fosse, *Ann. chim.* (*Paris*) [8], 400, 503, 531 (1909).

(3) P. Pfeiffer and R. Wizinger, *Ann.*, **461**, 152 (1928).

carbonium ion intermediate V is formed from either proton addition to the ethylene IV or hydroxyl removal from the carbinol. Formic acid was substituted for acetic acid because it is a somewhat stronger acid and trials with catalytic amounts of acetic acid did not lead to condensations.

A reaction was apparent in formic acid and isolation yielded a new material. This substance was not the anticipated product III, however, for it contained no oxygen by elemental analysis, corroborated by lack of carbonyl absorption in its infrared spectrum, and although a molecular weight determination indicated it was a dimer of IV, the ultraviolet spectrum showed no double bond conjugation with an aromatic ring. The empirical formula, calculated from the analysis, was consistent with a reduced dimer of the starting ethylene IV. A C-methyl determination gave a content of less than half that of the reduced dimer but C-methyl determinations on this type of compound are notoriously low.

From the foregoing evidence and analogous dimerizations in the literature,[4] the product is formulated as structure VII. Several current reports have been made of the dimerization of diphenylethylenes[4] and the reducing action of formic acid and formate has also been the object of recent studies.[5] The ready formation of the carbonium ion V by the action of a relatively weak acid in contrast to the dimerization of most diarylethylenes only by strong acid[6] can be explained by the very strong polarization of the double bond by two *p*-substituent dimethylamino groups. The preferential attack of the ion V on the ethylene IV, rather than on formate to give reduction, may be due to a more favorable reaction rate.[7] The carbonium ion VI would undoubtedly be less reactive (*i.e.*, more highly stabilized) than the carbonium ion V because of its greater bulk and other steric factors, so it would appear reasonable that the relatively small formate ion could effect reduction to the dimer VII in preference to serial attacks of successively generated carbonium ions on the ethylene IV to give polymers.[4a]



$$\underset{\text{IV}}{R_2C{=}CH_2} \xrightarrow{HCOOH} \underset{\text{V}}{R_2\overset{\oplus}{C}{-}CH_3} + HCO_2^{\ominus} \xrightarrow{\text{IV}}$$

$$R_2\overset{CH_3}{\overset{|}{C}}{-}CH_2\overset{\oplus}{C}{-}R_2 + HCO_2^{\ominus} \longrightarrow \underset{\text{VII}}{R_2\overset{CH_3}{\overset{|}{C}}{-}CH_2CHR_2} + CO_2$$

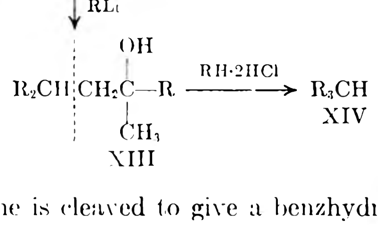
The structure of the reduced dimer VII was supported by the synthesis of its nor-homolog, 1,1,3,3-tetrakis(*p*-dimethylaminophenyl)propane (XI). The synthesis was accomplished by the preparation of β,β-bis(*p*-dimethylaminophenyl)propionic acid by the method of Fosse,[8] conversion of the latter to the ethyl ester and its reaction with *p*-dimethylaminophenyllithium to give the carbinol X. This carbinol was then easily hydrogenolyzed to the propane XI. The ultraviolet spectra of the reduced dimer VII, the carbinol X and the propane XI are uninstructive since they exhibit only the absorption of the *p*-dimethylaminophenylalkyl grouping. The infrared spectra are very similar, in fact, almost identical supporting the like structures for these compounds.

$$\underset{\text{VIII}}{R_2CHCH_2COOH} \longrightarrow \underset{\text{IX}}{R_2CHCH_2COOC_2H_5} \xrightarrow{RLi}$$

$$\underset{\text{X}}{R_2CHCH_2C(OH)R_2} \xrightarrow{H_2} \underset{\text{XI}}{R_2CHCH_2CHR_2}$$

Several attempts were made to synthesize the reduced dimer VII which led to some unanticipated results that are of interest in themselves.

4,4 - Bis(*p* - dimethylaminophenyl)butanone - 2 (XII) was treated with dimethylaniline under hydrochloric acid catalysis as developed by von Braun and co-workers[9] in the expectation of preparing the dimer, but under the usual conditions for this type of reaction only starting material was recovered. The carbinol XIII was then formed in the hope that it might furnish VII but in the von Braun condensation it gave leucocrystalviolet (XIV). Evidently, the bond in XIII crossed by the dotted line is cleaved to give a benzhydryl cation which attacks dimethylaniline yielding the observed product. Attempts to isolate 2,2-bis(*p*-dimethylaminophenyl)propane from the tarry filtrates of this isolation were unsuccessful although its formation would have been anticipated from the proposed mechanism.



$$\underset{\text{XII}}{R_2CHCH_2COCH_3} \xrightarrow{RH\cdot 2HCl} \text{VII}$$

$$\downarrow RLi$$

$$\underset{\text{XIII}}{R_2CH\,\vdots\,CH_2\overset{OH}{\underset{CH_3}{C}}{-}R} \xrightarrow{RH\cdot 2HCl} \underset{\text{XIV}}{R_3CH}$$

The attempted preparation of the next higher homolog of the dimer, 2,2,4,4-tetrakis(*p*-dimethyl-

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(4) (a) A. G. Evans, N. Jones, and J. H. Thomas, *J. Chem. Soc.*, 1824 (1955); (b) A. G. Evans, N. Jones, P. M. S. Jones, and J. H. Thomas, *J. Chem. Soc.*, 2757 (1956); (c) A. G. Evans, P. M. S. Jones, and J. H. Thomas, *J. Chem. Soc.*, 104 (1957).

(5) N. J. Leonard and R. R. Sauers, *J. Am. Chem. Soc.*, **79**, 6210 (1957); R. Stewart, *Can. J. Chem.*, **35**, 766 (1957); S. Bowden and F. F. Watkins, *J. Chem. Soc.*, 1333 (1940).

(6) Unsuccessful attempts were made to dimerize diaryl ethylenes in formic acid when *p*-substituted by hydrogen, methoxyl, or only one dimethylamino group.

(7) E. R. Alexander and R. B. Wildman (*J. Am. Chem. Soc.*, **70**, 1187 (1948)) reduced 1-*p*-dimethylaminophenyl ethanol with triethylammonium formate, so the same would appear possible for the intermediate V.

(8) R. Fosse, *Compt. rend.*, **144**, 643 (1907).

(9) J. von Braun, E. Anton, W. Haensel, and G. Werner, *Ann.*, **472**, 1 (1929).

aminophenyl)pentane, also led to unexpected results. From the reaction of acetylacetone and dimethylaniline in the von Braun condensation, 2,2-bis(*p*-dimethylaminophenyl)propane was obtained as the only isolable product. Again cleavage had occurred with acetic acid probably the other product.

EXERIMENTAL[10]

Preparation of 1,1,3,3-tetrakis(p-dimethylaminophenyl)-butane (VII). Because VII was formed in an attempted synthesis of an Amphenone B homolog, this synthesis is described.

A mixture of 1,1-bis(*p*-dimethylaminophenyl ethylene[3] (2.66 g., 0.01 mole) and 1.3 g. (0.01 mole) of ethyl acetoacetate in 25 ml. of 98–100% formic acid was allowed to stand at room temperature for 12 hr. and then heated on a steam bath for 3 hr. The formic acid was evaporated *in vacuo* and the residue dissolved in ether. The ether solution was washed with water and evaporated. The solid product was recrystallized twice from acetone-methanol. needles, m.p. 149–151°, 0.5 g.

Anal. Calcd. for $C_{36}H_{46}N_4$: C, 80.85 H, 8.67; N, 10.48; C—CH_3, 2.81. Found: C, 81.18; H, 8.55 N, 10.41 C—CH_3, 1.13.

The product possessed an ultraviolet spectrum typical for the unconjugated dimethylaminophenyl grouping, absorption at 262 mμ (ϵ 43,500). The infrared spectrum was typical of compounds containing the 4,4′-bis(dimethylamino)benzhydryl grouping.

The compound formed equally well without the presence of the ethyl acetoacetate. Thus, when 1 g. of the ethylene was refluxed in 10 ml. of formic acid for 3 hr., 0.38 g. of product, m.p. 149–151°, was obtained. When substitution of acetylacetone for ethyl acetoacetate was made, the same reduced dimer was obtained in 0.7 g. yield.

Preparation of 4,4-bis(p-dimethylaminophenyl)butanone-2 (XII). Ethyl bis(*p*-dimethylaminophenyl)carbinylacetoacetate was prepared as described by Fosse[2] by heating 130 g. of ethyl acetoacetate and 270 g. of Michler's hydrol with 7.0 g. of acetic acid as catalyst on the steam bath overnight. Neutralization of the acetic acid with sodium bicarbonate and isolation of the product gave a 350 g. (92%) yield of the acetoacetate.

A solution of 20 g. (0.053 mole) of the product in 200 ml. of absolute ethanol was treated with a solution of 10 g. (0.20 mole) of sodium hydroxide in 50 ml. of water and heated on a steam bath for 15 hr. Dilution with ice-water precipitated the butanone XII, m.p. 124–126°.[11] Recrystallization from ethanol gave the product in 12 g. (0.0387 mole), 74% yield.

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38 H, 8.44 N, 9.03. Found: C, 77.26 H, 8.45 N, 9.12.

Attempted synthesis of 1,1,3,3-tetrakis(p-dimethylaminophenyl)butane (VII). a. *From butanone* XII. A mixture of 12 g. (0.039 mole) of 4,4-bis(*p*-dimethylaminophenyl)butanone-2 (XII), 6.8 ml. of concd. hydrochloric acid and 9.6 g. (0.080 mole) of dimethylaniline was heated in a sealed tube at 130° for 24 hr. The tube was cooled, opened, and the contents poured into excess dilute sodium bicarbonate solution and steam-distilled to remove the unused dimethylaniline. The solid residue was removed by filtration and recrystallized from ethanol to give a 61% recovery of XII, m.p. 125–126°, that had an infrared spectrum identical with an authentic sample.

(b) *From the carbinol* XIII. In a 300-ml. flask, flamed dry, 2.0 g. (0.288 g.-atom) of lithium in strips was treated by dropwise addition in a nitrogen atmosphere with 28.8 g. (0.144 mole) of 4-dimethylaminophenyl bromide in 70 ml. of dry ether. After stirring for several hours, the reaction was filtered through a glass-wool plug into a graduated dropping funnel and the flask rinsed with dry ether. The total volume was 230 ml. Analysis showed that 0.129 mole of reagent was present.

A 30-ml. portion (0.017 mole) of lithium reagent was added to a dry flask under nitrogen and a solution of 4.0 g. (0.0129 mole) of 4,4-bis(*p*-dimethylaminophenyl)butanone-2 (XII) in 300 ml. of dry ether was added dropwise at room temperature. After standing overnight the reaction was refluxed 1 hr. and then poured into excess ammonium chloride solution. The ether layer was separated and the water layer extracted with ether. The combined ether solutions were dried with anhydrous magnesium sulfate and evaporated to dryness in vacuum at room temperature to give an oil smelling of dimethylaniline. The oil did not crystallize and possessed no carbonyl absorption in the infrared at 5–6 μ; it was assumed that all the ketone had reacted. So without purification, the oil was transferred to a bomb tube, 2.7 g. (0.025 mole) of dimethylaniline and 5.4 ml. (0.065 mole) of concd. hydrochloric acid were added and the sealed tube heated at 150° for 18 hr. The reaction mixture was then removed from the tube, treated with a sodium carbonate solution, and extracted with chloroform. The chloroform was removed in vacuum and the residue steam-distilled to remove dimethylaniline. The cooled steam-distilland was extracted with chloroform and the black solution ineffectually treated with activated charcoal. The dark residue from evaporation of the chloroform solution was recrystallized from methanol several times, m.p. 172–173°.

Anal. Calcd. for $C_{25}H_{31}N_3$: C, 80.38; H, 8.37; N, 11.25. Found: C, 80.32· H, 8.16 N, 11.49.

This material agrees in melting point, analysis, and infrared spectrum with leucocrystal violet. It gave a melting point depression with VII. Although this material was obtained in only small amount, an attempt to isolate any other products from the filtrate was unsuccessful.

Preparation of 3,3-bis(p-dimethylaminophenyl)propionic acid (VIII). Fosse[8] has reported this compound but without explicit directions, so the following details are described. In a 100-ml. flask 6.25 g. (0.06 mole) of malonic acid and 16.2 g. (0.06 mole) of Michler's hydrol were mixed intimately and heated on a steam bath for 0.5 hr. and then allowed to stand overnight. Ethanol (50 ml.) was added and the heating continued on the steam bath for 1.5 hr. whereupon a green-white solid formed which was separated by filtration after chilling and washed with ethanol. A crude yield of 14.8 g. (0.0415 mole, 69%) of bis(*p*-dimethylaminophenyl)methylmalonic acid was obtained. The malonic acid was decarboxylated by treatment with 100 ml. of 30% sulfuric acid at 105° for 3 hr. The cooled reaction mixture was neutralized to *p*H 7 with ammonium hydroxide and the solid filtered, washed with water, and recrystallized from ethanol, m.p. 228–230° (lit. m.p. 225–230°), in a yield of 5.9 g. (0.0167 mole), 40% based on the substituted malonic acid.

Preparation of ethyl 3,3-bis(p-dimethylaminophenyl)propionate (IX). A suspension of the propionic acid VIII (5.9 g., 0.0167 mole) in 200 ml. of absolute ethanol was saturated with gaseous hydrogen chloride giving a clear solution. The mixture after standing 5 days at room temperature was slowly poured into 1 l. of saturated sodium bicarbonate solution, adding more solid sodium bicarbonate to maintain basicity. The product was isolated by extraction with ether, the ether extract was evaporated to give a solid which was recrystallized twice from ethanol-water, m.p. 85–87°, 5.3 g. (0.0156 mole), 93%.

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08 H, 8.29; N, 8.23. Found: C, 74.24; H, 8.42; N, 8.10.

Preparation of 1,1,3,3-tetrakis(p-dimethylaminophenyl)-1-hydroxypropane (X). A solution of 8.05 g. (0.0403 mole) of 4-bromodimethylaniline in 20 ml. of dry ether was added

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(10) All melting points and boiling points are uncorrected.

(11) R. Fosse, *Compt. rend.*, 46, 1040 (1908), gives the melting point as 110°.

dropwise with stirring under nitrogen to 0.56 g. (0.0806 g.-atom) of finely-cut lithium strips. The mixture was stirred 0.5 hr. after there was no observable change, the lithium reagent then being filtered through glass wool into another dry flask under nitrogen. Then a solution of 5.3 g. (0.0156 mole) of ethyl 3,3-bis(p-dimethylaminophenyl)propionate in 100 ml. of ether was added to the stirred lithium aryl solution. Two hours after addition the reaction was poured into a saturated ammonium chloride solution. The ether layer was separated and the water layer extracted with chloroform. The combined organic layers were evaporated *in vacuo* and the residue recrystallized from acetone to give the carbinol, m.p. 187–187.5°, in a yield of 4.3 g. (0.008 mole), 51%.

Anal. Calcd. for $C_{35}H_{44}N_4O$: C, 78.32; H, 8.26; N, 10.44. Found: C, 77.98; H, 8.15; N, 10.16.

Preparation of 1,1,3,3-tetrakis(p-dimethylaminophenyl)propane (XI). The propanol X, 2.0 g. (0.00373 mole), was dissolved by heating to boiling in 150 ml. of absolute ethanol, cooled, and reduced in the presence of 1 g. of 5% palladium on charcoal under a pressure of 40 pounds of hydrogen at 40–50°. After 2 hr. there was no further absorption of hydrogen. The cooled solution was filtered and evaporated to dryness *in vacuo* to yield a sticky semisolid. It was recrystallized repeatedly from ethanol, m.p. 180–181°, with prior softening. The yield was low.

Anal. Calcd. for $C_{35}H_{44}N_4$: C, 80.72; H, 8.52; N, 10.76. Found: C, 80.59; H, 8.63; N, 10.87.

Preparation of 2,2,4,4-tetrakis(p-dimethylaminophenyl)pentane. An attempt was made to prepare this compound according to the method of von Braun.[9] A Carius tube was charged with 10 g. (0.1 mole) of acetylacetone, 48.4 g. (0.4 mole) of dimethylaniline and 33.4 ml. of concd. hydrochloric acid, sealed, and heated to 150° for 6 hr. The cooled tube was opened and the viscous contents inverted into an excess of 10% aqueous sodium bicarbonate. The product was extracted with ether, the ether removed, and the residue steam-distilled. The yellow liquid in the distillation flask solidified on cooling; it was extracted with ether, the ether evaporated, and the residue recrystallized from ethanol-water. m.p. 82–83.5°. Although its infrared spectrum was almost identical with that of VII, a molecular weight determination (ebullioscopic in ethanol) established that the product was 2,2-bis(p-dimethylaminophenyl)propane, m.m.p. with authentic sample, 81–83°.

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92; mol. wt., 282. Found: C, 81.03; H, 9.17; N, 9.96; mol. wt., 256.

Acknowledgment. The contributions of the microanalysts, W. L. Brown, H. L. Hunter, R. M. Hughes, and G. M. Maciak and spectroscopists, P. W. Landis and L. G. Howard, are gratefully acknowledged.

INDIANAPOLIS, IND.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, DEPARTMENT OF CHEMISTRY,
UNIVERSITY OF CHICAGO]

Some Syntheses and Structures in the 9,10-Dihydro-9,10-ethanoanthracene Series. II[1a]

EUGENE I. SNYDER[1b] AND ROBERT A. CLEMENT[1c]

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Syntheses of 11-keto-12-hydroxymethyl-9,10-dihydro-9,10-ethanoanthracene, its p-toluenesulfonate ester, and 11-keto-12-methylene-9,10-dihydro-9,10-ethanoanthracene are described, proceeding through the *cis*- and *trans*-11-hydroxy-12-hydroxymethyl-9,10-dihydro-9,10-ethanoanthracenes as intermediates.

In a previous publication[2] we reported synthetic procedures for the preparation of 11-keto-12-hydroxymethyl-9,10-dihydro-9,10-ethanoanthracene (III), 11-keto-12-tosyloxymethyl-9,10-dihydro-9,10-ethanoanthracene (VII), and 11-keto-12-methylene-9,10-dihydro-9,10-ethanoanthracene (IV), along with rigorous structure proofs for these compounds. In this paper we present alternative syntheses of III, VII, and IV which involve different procedures but which are less satisfactory in terms of yields and convenience. The structures concerned are collected in Fig. 1.

RESULTS

Starting material for these transformations was 11-keto-12-carbomethoxy-9,10-dihydro-9,10-ethanoanthracene (I)[2] which was reduced with lithium aluminum hydride to a mixture of the *cis*- and *trans*-11-hydroxy-12-hydroxymethyl-9,10-dihydro-9,10-ethanoanthracenes (II). Treatment of this isomeric mixture with acetone and cupric sulfate effected a clean separation of the racemates, the *cis* diol (IIa) being converted to *cis*-11-hydroxy-12-hydroxymethyl-9,10-dihydro-9,10-ethanoanthracene isopropylidene ketal (V). *trans* Diol (IIb) was recovered from the reaction mixture and *cis* diol (IIa) was obtained by subsequent hydrolysis of the ketal (V). Assignment of configurations to the diols (II) was made on the basis of this selective formation of isopropylidene ketal.

The ketol (III) was conveniently prepared by selective oxidation of the secondary hydroxyl functions in the diol mixture (II) with N-bromo-

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(1) (a) Abstracted from a portion of the Ph.D. dissertation of Eugene I. Snyder, Department of Chemistry, University of Chicago, 1959. (b) National Science Foundation Fellow, 1956–59. (c) Author to whom inquiries should be addressed.

(2) E. I. Snyder and R. A. Clement, *J. Am. Chem. Soc.*, **82**, 1424 (1960).

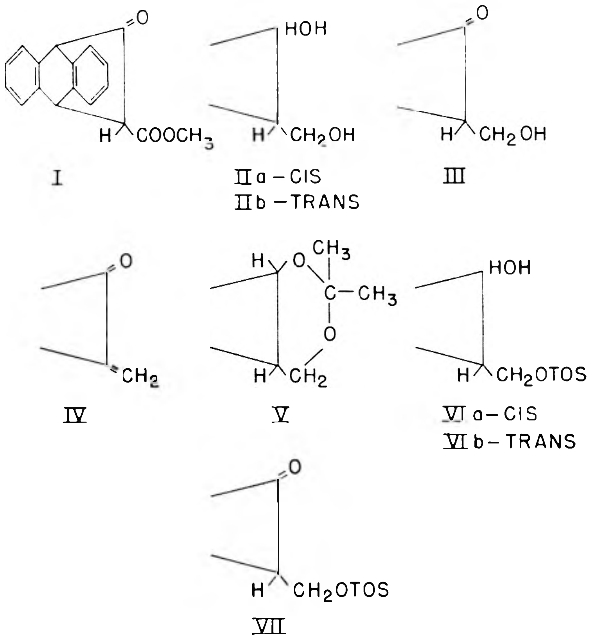

Fig. 1. Some substituted 9,10-dihydro-9,10-ethanoanthracenes. All structures have the 9,10-dihydro-9,10-ethanoanthracene skeleton

acetamide.[3] In an attempt to prepare the keto tosylate (VII), the ketol (III) was treated with tosyl chloride in pyridine. However, the only identifiable product, obtained in poor yield, proved to be the methylene ketone (IV). Presumably, the keto tosylate (VII) was formed but was converted to the methylene ketone (IV) by a subsequent elimination reaction.

The keto tosylate (VII) was successfully prepared, and in comparable yields, by separate oxidations with *t*-butyl hypochlorite[4] of the *cis*- and *trans* - 11 - hydroxy - 12 - tosyloxymethyl-9,10 - dihydro - 9,10 - ethanoanthracenes (VIa and VIb). These latter were prepared from the *cis*- and *trans* diols, IIa and IIb, respectively, by selective tosylations of the primary hydroxyl functions. The separate conversions of the diols IIa and IIb to the common keto tosylate (VII) confirmed their identities as *cis-trans* isomers.

The procedures reported here, although they yielded the desired compounds III, VII, and IV, are inferior to those reported earlier.[2]

EXPERIMENTAL[5]

Reduction of 11-keto-12-carbomethoxy-9,10-dihydro-9,10-ethanoanthracene (I). The keto ester (I)[2] (2.8 g., m.p. 139°) was placed in the thimble of a continuous-return Soxhlet extractor and extracted into a slurry of lithium aluminum hydride (2.0 g.) in boiling ether (300 ml.). After all the keto ester had been extracted from the thimble, the reaction mixture was treated with methanol and then with 10% aqueous sulfuric acid. The aqueous layer was separated, extracted with ether, and the combined ether extracts were dried over magnesium sulfate. After filtration, removal of ether at reduced pressure afforded an oil (2.2 g., 87%) which solidified on being triturated with benzene. This solid, a mixture of the *cis*- and *trans* diols (IIa and IIb), melted over a range, generally 125–135°, and was used directly in subsequent manipulations.

Separation of cis- and trans-11-hydroxy-12-hydroxymethyl-9,10-dihydro-9,10-ethanoanthracenes (IIa and IIb). *cis-11-Hydroxy-12-hydroxymethyl-9,10-dihydro-9,10-ethanoanthracene isopropylidene ketal* (V). The mixture of diols (IIa and IIb) (1.25 g., as obtained directly from reduction) was dissolved in reagent-grade acetone (30 ml.) and stirred at room temperature with cupric sulfate (1.3 g.) for 39 hr. At the end of this time the mixture was filtered and the oil obtained by removal of solvent was dissolved in benzene (5 ml.). After 24 hr., the solid which had appeared was isolated by filtration, the benzene filtrate being preserved for isolation of the ketal (see below). This solid (0.457 g., 36% on diol mixture) was good-quality *trans* diol (IIb), m.p. 151–153°. Two recrystallizations from ethyl acetate afforded *trans-11-hydroxy-12-hydroxymethyl-9,10-dihydro-9,-10-ethanoanthracene* (IIb), m.p. 154.1–154.9°. In the infrared (potassium bromide pellet) IIb exhibited absorption at 3300 cm.$^{-1}$ (hydroxyl), and, among others, at 1045 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.94; H, 6.39. Found: C, 80.98; H, 6.62.

The benzene filtrate obtained from isolation of *trans* diol (IIb) was evaporated to yield, after one recrystallization from methanol, good-quality ketal (V) (0.579 g., 40% on diol mixture), m.p. 146–147°. Several recrystallizations from methanol afforded *cis-11-hydroxy-12-hydroxymethyl-9,10-dihydro-9,10-ethanoanthracene isopropylidene ketal* (V), m.p. 148.0–148.1°.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.15; H, 6.89. Found: C, 81.93; H, 6.84.

The *cis* diol (IIa) was obtained from ketal (V) by ketal exchange. A solution of ketal (V) (0.140 g., m.p. 147°) in absolute methanol (11 ml.) was stirred at room temperature with cupric sulfate (0.14 g.) for 44 hr. Dilution with water, extraction with ether, and removal of the ether at reduced pressure afforded crude *cis* diol (IIa) (0.118 g., 97%), m.p. 141–145°. One recrystallization from benzene raised the m.p. to 149–150°. Additional crystallizations from benzene yielded *cis-11-hydroxy-12-hydroxymethyl-9,10-dihydro-9,10-ethanoanthracene* (IIa), m.p. 150.9–151.0°, m.p. 130–145° on admixture with *trans* diol (IIb). In the infrared (potassium bromide pellet) IIa exhibited a spectrum similar to that of IIb with absorption at 3320 cm.$^{-1}$ (hydroxyl), but lacking absorption at 1045 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.94; H, 6.39. Found: C, 80.76; H, 6.34.

11-Keto-12-hydroxymethyl-9,10-dihydro-9,10-ethanoanthracene (III). A mixture of the diols IIa and IIb (0.830 g., as obtained directly from reduction) was dissolved in absolute methanol (8 ml.) and to the solution were added pyridine (0.8 ml.) and *N*-bromoacetamide (0.621 g.). The solution was kept at room temperature and in the dark for 68 hr., at the end of which time it was diluted with water and treated with sodium bisulfite to decompose the excess *N*-bromoacetamide. The resulting solution was extracted with ether and the ether extract was washed with dilute hydrochloric acid followed by water and dried over magnesium sulfate. Filtration, followed by removal of the solvent, yielded a yellow oil which was chromatographed on 64 g. of Florisil. Elution of the column with 1.5% ether in benzene yielded 0.392 g. (48%) of crude ketol (III) as an oil which solidified on being triturated with carbon tetrachloride to give good-quality ketol (III), m.p. 137.0–137.8°. This material was identical with authentic[2] ketol (III) (m.p. 139.6–140.0°) by the criteria of mixture melting point and infrared spectra.

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[3] T. H. Kritchevsky, D. L. Garmaise, and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 483 (1952); E. P. Olivetto, H. L. Herzog, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 1505 (1953); R. E. Jones and F. W. Kocher, *J. Am. Chem. Soc.*, **76**, 3682 (1954).

[4] C. A. Grob and H. J. Schmid, *Helv. Chim. Acta*, **36**, 1763 (1953).

[5] Melting points are corrected. We are indebted to Mr. William Saschek of this Department for the analyses.

Attempted tosylation of 11-keto-12-hydroxymethyl-9,10-dihydro-9,10-ethanoanthracene (III). *11-Keto-12-methylene-9,10-dihydro-9,10-ethanoanthracene* (IV). A solution of crude ketol (III) (0.455 g., 1.82 mmoles) and *p*-toluenesulfonyl chloride (0.380 g., 1.99 mmoles) in dry pyridine (4 ml.) was kept at room temperature for 40 hr. The solution was then diluted with water, acidified, and extracted with ether.

From the ether extract after drying over magnesium sulfate, filtering, and removing ether, there was obtained an oil which was chromatographed on Florisil. The only identifiable material obtained from the chromatogram was 0.085 g. (20%) of crude methylene ketone (IV), which was eluted with benzene. This material, after one recrystallization from methanol, afforded methylene ketone (IV), m.p. 224.8–225.0°, which was identical with authentic[2] methylene ketone (IV) (m.p. 223.0–224.0°) by the criteria of mixture melting point and infrared spectra.

cis- and trans-11-Hydroxy-12-tosyloxymethyl-9,10-dihydro-9,10-ethanoanthracenes (VIa *and* VIb). A solution of *cis* diol (IIa) (0.530 g., 2.10 mmoles) and *p*-toluenesulfonyl chloride (0.450 g., 2.36 mmoles) in a mixture of dry benzene (7 ml.) and dry pyridine (2 ml.) was kept at room temperature for 17 hr. The mixture was then diluted with water and extracted with ether, the ether extract being washed with dilute hydrochloric acid, then water, and finally being dried over magnesium sulfate. Filtration and removal of solvent yielded a glass which solidified on being triturated with carbon tetrachloride. Recrystallization of this solid from methanol gave 0.319 g. (37%) of the *cis*-hydroxy tosylate (VIa), m.p. 152°. An additional recrystallization from methanol afforded *cis-11-hydroxy-12-tosyloxymethyl-9,10-dihydro-9,10-ethanoanthracene* (VIa), m.p. 152.0–152.2°. In the infrared (chloroform solution) VIa exhibited absorption at 3540 and 3370 cm.$^{-1}$ (hydroxyl) and, among others, at 1365, 1192, and 1180 cm.$^{-1}$ (tosylate).

Anal. Calcd. for $C_{24}H_{22}O_4S$: C, 70.89, H, 5.46. Found: C, 70.72; H, 5.64.

For the preparation of *trans*-hydroxy tosylate (VIb), a solution of the *trans* diol (IIb) (0.177 g., 0.703 mmole) and *p*-toluenesulfonyl chloride (0.156 g., 0.817 mmole) in dry pyridine (6 ml.) was kept at room temperature for 41 hr. The reaction mixture was then processed as above to yield 0.243 g. of crude product which was chromatographed on Florisil. Elution of the column with 5% ether in benzene afforded 0.140 g. (49%) of *trans-11-hydroxy-12-tosyloxymethyl-9,10-dihydro-9,10-ethanoanthracene* (VIb) as a glass which could not be induced to crystallize. In the infrared (chloroform solution) this material exhibited absorption at 3540 cm.$^{-1}$ (hydroxyl) and, among others, at 1367, 1192, and 1178 cm.$^{-1}$ (tosylate); its spectrum was distinct from that of the *cis*-hydroxy tosylate (VIa) and indicated no contamination by VIa.

After elution of the *trans*-hydroxy tosylate (VIb) from the chromatographic column, there was obtained (with 3% methanol in benzene) 0.026 g. (34% recovery) of unchanged *trans* diol (IIb).

11-Keto-12-tosyloxymethyl-9,10-dihydro-9,10-ethanoanthracene (VII). (A). *From cis-11-hydroxy-12-tosyloxymethyl-9,10-dihydro-9,10-ethanoanthracene* (VIa). A solution of *cis*-hydroxy tosylate (VIa) (0.199 g., m.p. 152°), *t*-butyl hypochlorite[6] (0.120 g.) and pyridine (0.139 g.) in chlorobenzene (4 ml.) was permitted to remain at room temperature for 9.5 hr. The solution was then diluted with ether, washed with aqueous sodium bisulfite, water, dilute hydrochloric acid, water, and then dried over magnesium sulfate. After filtration, solvent was removed under reduced pressure to yield the keto tosylate (VII) as a solid which, after one recrystallization from ethanol, melted at 149–150° dec., and amounted to 0.071 g. (36%). Two additional recrystallizations from ethanol afforded material, m.p. 151.0–151.8° dec., which was identical with authentic[2] keto tosylate (VII) (m.p. 152° dec., and 167° dec.) by the criteria of mixture melting point and infrared spectra.

(B). *From trans-11-hydroxy-12-tosyloxymethyl-9,10-dihydro-9,10-ethanoanthracene* (VIb). A solution of *trans*-hydroxy tosylate (VIb) (0.126 g., as obtained from chromatography), pyridine (0.100 g.), and *t*-butyl hypochlorite[6] (0.054 g.) in chlorobenzene (3 ml.) was permitted to remain at room temperature for 16 hr. Isolation procedures as in (A) yielded, after one recrystallization from ethanol, 0.040 g. (32%) of keto tosylate (VII), m.p. 152–153° dec. This material was identical with that obtained in (A) by the criteria of mixture melting point and infrared spectra.

CHICAGO 37, ILL.

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[6] H. M. Teeter and E. W. Bell, *Org. Syntheses*, **32**, 20 (1952).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Chlorides Derived from 1-Ethynylcyclohexanol[1]

G. F. HENNION AND C. A. LYNCH, JR.[2]

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The action of thionyl chloride on 1-ethynylcyclohexanol (I), under a variety of conditions, invariably led to a complex mixture only partially separable by fractional distillation. The following products were identified: unchanged carbinol (I), 1-ethynylcyclohexyl chloride (II), 1-ethynylcyclohexene (III), 1-(α-chlorovinyl)cyclohexene (IV), cyclohexylidenevinyl chloride (V), and 1-(β-chlorovinyl)cyclohexene (VI). The *t*-chloride (II) was always formed in minor amounts only. Cyclohexylidenevinyl chloride (V) is sensitive to thermal and prototropic rearrangement to the isomer (VI) and could not be isolated in high purity. Independent syntheses produced the isomers, II, IV, and VI in satisfactory yield and purity.

Various studies underway in this laboratory require assorted higher *t*-acetylenic chlorides, RR'C(Cl)—C≡CH. Where R and R' are small alkyl groups, the preparations are easily accomplished by reaction of *t*-acetylenic carbinols with concentrated hydrochloric acid.[3] As this method has not proved satisfactory where R and (or) R' are large, other preparative methods have been sought. We wish to summarize now a de-

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[1] Paper no. 72 on substituted acetylenes; previous paper by G. F. Hennion and R. S. Hanzel, *J. Am. Chem. Soc.*, (in press).

[2] Dow Chemical Company Fellow, 1957–58. Abstracted from the Ph.D. Dissertation of C. A. L., Jr.

TABLE I

PRODUCTS OF THE REACTION OF THIONYL CHLORIDE WITH 1-ETHYNYLCYCLOHEXANOL

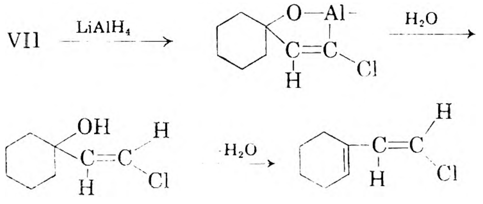
Conditions		Products Found (% of Total)					
Solvent	Temp.	I[a]	II[b]	III[c]	IV[d,e]	V[f]	VI[g]
Pyridine	50–60°	1.2	8.3	5.6	75.0	Absent	9.9
Ether	3°	6.2	6.6	8.9	54.7	Present	23.7
Ether	b.p.	3.2	4.3	16.3	52.5	Present	23.7
Ether	to 85°	30.9	6.4	18.0	31.5	Present	13.1
THF[h]	b.p.	6.7	5.4	4.0	57.6	Present	26.4
Ether-pyridine	3°	11.4	4.6	63.2		20.7	—

[a] 1-Ethynylcyclohexanol (recovered). [b] 1-Ethynylcyclohexyl chloride. [c] 1-Ethynylcyclohexene. [d] 1-(α-Chlorovinyl)-cyclohexene. [e] The figures cited include compound V, if present. [f] Cyclohexylidenevinyl chloride. [g] 1-(β-Chlorovinyl)cyclohexene. [h] Tetrahydrofuran.

tailed study of the reaction of 1-ethynylcyclohexanol (I) with thionyl chloride.

Fortunately, 1-ethynylcyclohexyl chloride (II) can be prepared from I in excellent purity and high yield[3c] by treatment with excess hydrochloric acid containing dissolved cuprous chloride. The yield is very poor in the absence of cuprous chloride.[3b] The reaction of I with thionyl chloride under widely varied conditions produced only minor amounts of *t*-chloride (II) and was more complex than was realized previously.[4,5] Products boiled over a wide range of temperature (*ca.* 40–90° at 12 mm.) and usually could not be separated cleanly by repeated fractional distillation. The infrared spectra of the total distillates were very complex and often revealed the structural features of unchanged carbinol (I), the enyne (III), and the isomeric chlorides (II, IV, V and VI) formulated in Fig. 1. Vapor phase chromatography confirmed the conclusion that the products contained four to six components, depending on experimental conditions.

The isomeric chlorides (II, IV, V and VI) were then prepared by alternative methods as shown in Fig. 1. Pure II was made[3c] from I with hydrochloric acid and cuprous chloride; authentic IV was prepared[6] from the enyne (III) by addition of hydrochloric acid across the triple bond; VI was obtained by the sequence I→VII→VIII→VI. It is noteworthy that VI must have the *trans*-configuration with respect to the exocyclic double bond in view of the scheme shown below.[7] Preparation of pure chloroallene (V) was troublesome, however. The reaction of I with thionyl chloride in cold ether containing pyridine gave a four component product (see Table I, last line) notably rich in V and free of the isomers IV and VI. Removal of unchanged carbinol (I) from this material by percolation through alumina followed by fractional distillation *in vacuo* yielded V in 86% purity as determined by VPC. The distilled sample now contained VI, even though originally absent. It was observed repeatedly throughout this work that the facile thermal and (or) prototropic rearrangement of V to VI virtually precludes the possibility of obtaining V in high purity.



VIII VI

With the exception of V, the compounds listed in Fig. 1 and Table I were thus obtained in excellent purity, permitting characterization by infrared spectroscopy and VPC (retention times). The analysis of the total distilled products of the reaction of 1-ethynylcyclohexanol (I) with thionyl chloride was thus possible. In some instances, however, the presence of *both* IV and V could be established only by infrared examination, as these substances have identical boiling points and VPC retention times (see Table II).

The reaction of 1-ethynylcyclohexanol with thionyl chloride appears to be useful only for the preparation of 1-(α-chlorovinyl)cyclohexene (IV). When the reaction is carried out in warm pyridine, the major product is IV, isolable in acceptable yield and purity as observed earlier[4] (see Table I, line 1). Hurd and Jones[4] postulated that under these conditions I is dehydrated to enyne (III), which adds hydrochloric acid across the triple bond. This mechanism has now been supported by the observation that when thionyl chloride is added to a warm solution of enyne (III) and water (1:1 ratio) in pyridine, IV is indeed produced (70% yield, once distilled, 85% purity by VPC).

The various reaction products are all believed

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(3)(a) G. F. Hennion, J. J. Sheehan, and D. E. Maloney, *J. Am. Chem. Soc.*, **72**, 3542 (1950); (b) G. F. Hennion and E. G. Teach, *J. Am. Chem. Soc.*, **75**, 1653 (1953); (c) G. F. Hennion and K. W. Nelson, *J. Am. Chem. Soc.*, **79**, 2142 (1957).

(4) C. D. Hurd and R. N. Jones, *J. Am. Chem. Soc.*, **56**, 1924 (1934).

(5) Y. R. Bhatia, P. D. Landor, and S. R. Landor, *J. Chem. Soc.*, 24 (1959).

(6) W. H. Carothers and D. D. Coffman, *J. Am. Chem. Soc.*, **54**, 4071 (1932).

(7) R. A. Raphael, *Acetylenic Compounds in Organic Synthesis*, Academic Press, Inc., New York, 1955, p. 30.

TABLE II

VAPOR PHASE CHROMATOGRAPHY, 1-ETHYNYLCYCLOHEXANOL AND REACTION PRODUCTS

Compound	B.P., °C/Mm.	Retention Time, Min.[a]
1-Ethynylcyclohexene (III)	39/12	14
1-Ethynylcyclohexanol (I)	68/11	21
1-Ethynylcyclohexyl chloride (II)	58/12	24
1-(α-Chlorovinyl)cyclohexene (IV)	73/11	45
Cyclohexylidenevinyl chloride (V)	72/11	45
1-(β-Chlorovinyl)cyclohexene (VI)	82/12	49

[a] Silicone oil, G. E. SF-96, 3.05 meter column, 134°, flow rate of 40 ml. of helium per minute.

to originate from the chlorosulfite ester of I as follows: II by the usual S_Ni mechanism; III by elimination of sulfur dioxide and hydrogen chloride; IV by addition of hydrochloric acid to III; V by the S_Ni' mechanism; and VI by prototropic rearrangement of V.

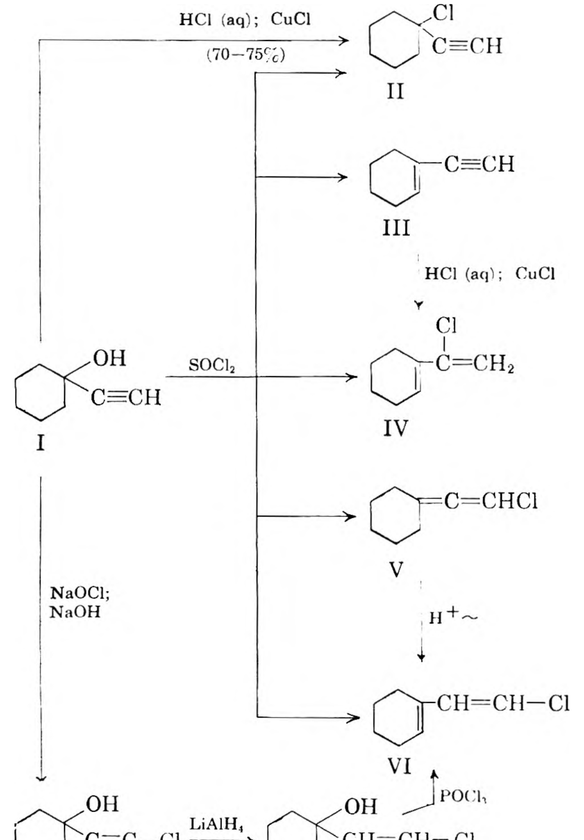

Fig. 1. Preparation of the isomeric chlorides

EXPERIMENTAL

1-Ethynylcyclohexanol (I) was used as received from Air Reduction Company, New York, New York.

1-Ethynylcyclohexene (III), b.p. 39° at 12 mm., n_D^{25} 1.4940, was prepared from I in 75–80% yields.[8] Infrared absorption bands (μ) were observed at 3.05 (vs), 3.40 (vs), 4.77 (m), 6.16 (w), 6.95 (s), 8.80 (s), 10.92 (vs), 11.70 (s), 11.85 (vs), 12.50 (s) and 15.00–15.50 (s).

1-Ethynylcyclohexyl chloride (II), b.p. 58° at 12 mm., n_D^{20} 1.4782, d^{25} 1.009, was prepared in 70–75% yields as previously described.[3c] Infrared bands (μ) were observed at 3.04 (vs), 3.40 (vs), 4.70 (w), 6.90 (vs), 7.74 (s), 7.97 (s), 8.85 (s), 9.95 (s), 11.14 (s), 11.50 (s), 12.40 (vs), 12.80 (vs), 15.00–15.50 (s).

Anal.[9] Calcd. for $C_8H_{11}Cl$: Cl, 24.86. Found: Cl, 24.48, 24.56.

1-(α-Chlorovinyl)cyclohexene (IV), b.p. 73° at 11 mm., n_D^{25} 1.5240, d^{25} 1.041, was prepared from III (60% yield) as described by Carothers and Coffman.[6] Infrared bands (μ) at 3.40 (vs), 6.02 (m), 6.11 (s) 6.25 (vs) 6.93 (s), 8.30 (vs), 9.37 (s), 10.85 (s), 11.50 (vs), 11.69 (vs), 13.70 (s), 14.15 (vs).

1-Chloroethynylcyclohexanol (VII), m.p. 50–51°, was prepared from I in 95% yield by the method of Strauss, Kolleck, and Heyn.[10]

1-(β-Chlorovinyl)cyclohexanol (VIII), b.p. 103–105° at 12 mm., was prepared in 55% yield by minor modification of the procedure of Julia and Surzur.[11] A standardized solution of lithium aluminum hydride in ether (25% excess) was added dropwise with stirring to a solution of 1-chloroethynylcyclohexanol (VII) in cold ether. Stirring was continued for 5 hr. after addition was completed. Hydrolysis was then accomplished with water and aqueous sodium potassium tartrate.

1-(β-Chlorovinyl)cyclohexene (VI) was prepared from VIII by dehydration with phosphorus oxychloride. The latter (40 ml., 0.44 mole) was added dropwise to a well-stirred solution of 32 g. (0.2 mole) of β-chlorovinylcyclohexanol (VIII) in 200 ml. of dry pyridine. The mixture was stirred for 4 hr., poured over crushed ice, and the organic layer was separated. The aqueous layer was extracted with three 100-ml. portions of petroleum ether. The original product and the extracts were combined, washed with dilute hydrochloric acid, with water, finally with saturated sodium bicarbonate solution, and dried over anhydrous potassium carbonate. Distillation yielded three fractions: (a), 0.70 g., b.p. 76–80° at 12 mm.; (b) 7.8 g., b.p. 80–82° at 12 mm., n_D^{25} 1.5304; (c) 3.2 g., b.p. 82–118° at 12 mm. Redistillation of fraction (b) gave 5.7 g., b.p. 82° at 12 mm., n_D^{25} 1.5307, d^{25} 1.036. Infrared bands (μ) were observed at 3.40 (vs), 6.13 (w), 6.27 (s), 6.95 (s), 10.70 (vs), 11.75 (s), 12.0 (vs), 12.80 (vs), 13.1 (vs), and 15.20 (s).

Anal.[9] Calcd. for $C_8H_{11}Cl$: Cl, 24.86. Found: Cl, 24.49.

Cyclohexylidenevinyl chloride (V). Thionyl chloride (purified by the method of Cottle[12]) (39.2 g., 0.33 mole) was added to a stirred solution of 37.2 g. (0.3 mole) of 1-ethynylcyclohexanol (I) and 27.6 g. (0.35 mole) of dry pyridine in 150 ml. of anhydrous ether at 3–5°. Water (100 ml.) was added and the ethereal layer was separated, washed with dilute hydrochloric acid, with saturated sodium bicarbonate, and then dried with anhydrous potassium carbonate. Distillation gave 22 g. of crude product, b.p. 40–71° at 12 mm., n_D^{25} 1.4983. Sixty-four grams of this material (obtained from three runs) was redistilled partially, all material boiling below 46° at 11 mm. discarded (30 g., mostly 1-ethynylcyclohexene). The still residue was dissolved in 50 ml. of petroleum ether and percolated through a column of alumina

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[8] J. C. Hamlet, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 2652 (1951).

[9] Analyses by Midwest Microlab, Inc., Indianapolis, Ind.

[10] F. Strauss, L. Kolleck, and W. Heyn, *Ber.*, **63**, 1868 (1930).

[11] M. Julia and J. M. Surzur, *Bull. soc. chim. France*, 1615 (1956).

[12] D. L. Cottle, *J. Am. Chem. Soc.*, **68**, 1380 (1946).

(80 g., "Alcoa F-20"). The column was washed with petroleum ether and 15-ml. fractions were collected. Each fraction was examined by infrared. The desired product (V) was detected in fractions 7–11, inclusive, free of starting material (I). These fractions were then distilled to yield 3.1 g., b.p. 72° at 11 mm., n^{25}_{D} 1.5229. Redistillation gave 1.04 g. of cyclohexylidenevinyl chloride (V), 86% pure by VPC, b.p. 72° at 11 mm., n^{25}_{D} 1.5235, d^{25} 1.025. The contaminents proved to be III (5.2%), II (1.4%), and VI (7.2%). Infrared bands (μ) at 3.40 (vs), 5.12 (vs), 6.93 (vs), 7.23 (s), 8.15 (vs), 10.28 (vs), 11.17 (s), 11.70 (s), 13.10–13.50 (vs), and 13.90–14.10 (vs). Notably significant are the bands at 5.12 and 13.10–13.50 μ, characteristic of the group C=C=CHCl.[5]

Anal.[9] Calcd. for $C_8H_{11}Cl$: Cl, 24.86. Found: Cl, 24.46. After redistillation, Cl found: 24.70.

Reaction of thionyl chloride with 1-ethynylcyclohexanol in pyridine. The procedure is essentially that of Hurd and Jones.[4] Purified[12] thionyl chloride (108 g., 0.9 mole) was added dropwise to a stirred mixture of 99 g. (0.81 mole) of 1-ethynylcyclohexanol and 78 g. (0.99 mole) of dry pyridine at 50–60°. After addition was complete the mixture was heated at 50–60° for 3 hr. and then cooled to room temperature. Water and petroleum ether (100 ml. of each) were added and the organic layer was separated. After washing and drying with anhydrous potassium carbonate, distillation gave 72 g., b.p. 39–75° at 12 mm., n^{25}_{D} 1.5178. Analysis of the total distillate by VPC (see Table I, line 1) showed that it contained 0.86 g. of recovered I, 5.98 g. of II, 4.04 g. of III, 7.14 g. of VI, and 54.0 g. (47% yield) of 1-(α-chlorovinyl)cyclohexene (IV).

Reaction of thionyl chloride with 1-ethynylcyclohexanol in ether. The procedure is essentially that of Bhatia, Landor, and Landor.[5] A solution of 37.2 g. (0.3 mole) of ethynylcyclohexanol and 39.3 g. (0.33 mole) of purified[12] thionyl chloride in 300 ml. of anhydrous ether was stirred for 1 hr. Most of the ether was then removed by distillation and the residue was heated on the steam bath for 3 hr. After cooling, the mixture was stirred with 100 ml. of saturated sodium bicarbonate solution, dried with anhydrous potassium carbonate, and distilled to give 30 g. of crude product, b.p. 34–82° at 11 mm., n^{25}_{D} 1.4992. Analysis of the total distillate by VPC (see Table I, line 4) indicated the composition to be 9.27 g. of I, 1.92 g. of II, 5.40 g. of III, 3.93 g. of VI, and 9.45 g. of a mixture of IV and V. The infrared spectrum revealed absorption bands for each of these substances.

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NOTRE DAME, IND.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, A'IN SHAMS UNIVERSITY]

Studies on 3-Acylcatechols. II.[1] A New Synthesis of 8-Hydroxyflavone

W. I. AWAD, M. F. EL-NEWEIHY, AND S. F. SELIM

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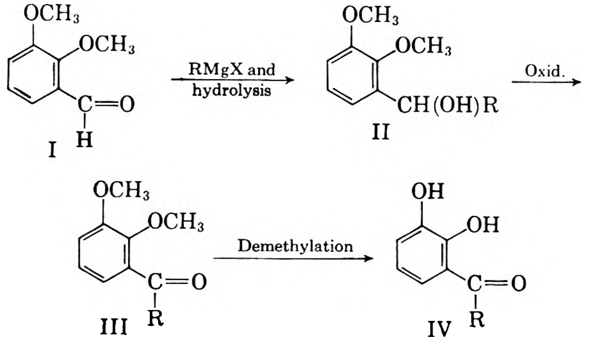
Some 3-acylcatechols are synthesized by an orthodox method. Their infrared spectra are recorded. 2,3-Dihydroxyacetophenone is utilized in the preparation of some chalcones, flavanones, and 8-hydroxyflavone. The latter has also been prepared *via* Claisen condensation of 2,3-dimethoxyacetophenone with ethyl benzoate followed by demethylation and cyclization.

In a previous publication,[1] we used the method described by Krannichfeldt,[2] for the preparation of some 3-acylcatechols[2], according to the following scheme:



In the present work we have prepared 2,3-dihydroxyisovalerophenone (IV. R = $-CH_2CH(CH_3)_2$) 2,3-dihydroxybenzophenone (IV. R = C_6H_5), 2,3,4′-trihydroxybenzophenone (IV. R = p-OHC_6H_4), and 2,3-dihydroxy-4′-chlorobenzophenone (IV. R = p-ClC_6H_4). The first of these compounds (m.p. 48°) is not identical with that reported by Miller, Hartung, Rock, and Crossley[3] (m.p. 93–95°) which they obtained as a by-product of a Fries rearrangement. The structure of our product cannot be questioned on account of the unambiguous method used in its preparation. Furthermore, our product gives a green color with ferric chloride that changes to red by the addition of sodium carbonate solution, a characteristic color test for catechols.[4,5] Moreover, the infrared data (*inter alia*) provides additional proof for the structure of 3-acylcatechols described here. The second

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(1) W. I. Awad, M. F. El-Neweihy, and S. F. Selim, *J. Org. Chem.* **23,** 1783 (1958).

(2) H. V. Krannchfeldt, *Ber.*, **46,** 4017–4018 (1913).

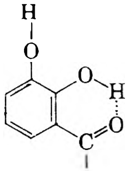
(3) Ellis Miller, Walter H. Hartung, Henry J. Rock and Frank S. Crossley, *J. Am. Chem. Soc.*, **60,** 7 (1938).

(4) Compare Paul Karrer, *Organic Chemistry*, Fourth English Edition, Elsevier Publ. Co., Inc., New York, N. Y., p. 435.

(5) A. Schönberg, W. I. Awad, and G. A. Mousa, *J. Am. Chem. Soc.*, **77,** 3850 (1955).

and third compounds have been prepared by Baker. *et al.*[6]

A comparative study of the infrared spectra of these acylcatechols has been carried out (*c.f.* Table I). 2,3-Dihydroxyacetophenone (IV. R = $-CH_3$) shows in solution a free OH stretching frequency (at 3717 cm.$^{-1}$) and a chelated OH stretching frequency (at 3106 cm.$^{-1}$). It has been previously[7] stated that this compound shows no free OH stretching frequency in the solid state, which led to the conclusion that it exhibits double chelation like that observed with 1,2-dihydroxy-3-aceto-4-cyanonaphthalene.[7] The present measurements show that this conclusion does not hold for 2,3-dihydroxyacetophenone, which in the solid state must possess an intramolecular and intermolecular hydrogen bridge,[8] the latter being destroyed in solution (*cf.* V)



V

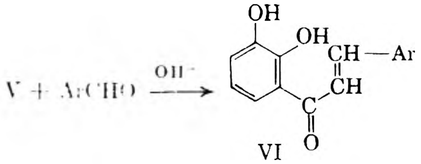
TABLE I[a]

INFRARED SPECTRA OF SOME ACYLCATECHOLS

Name of Compound	Stretching Frequency cm.$^{-1}$ Free OH	Chelated OH	Chelated C=O
2,3-Dihydroxyacetophenone[b]	3717	3106	1633
2,3-Dihydroxypropiophenone[c]	3759	3096	1656
2,3-Dihydroxy-*n*-butyrophenone[c]	3623	3333	1637
2,3-Dihydroxyisovalerophenone[d]	3703	3174	1647
2,3-Dihydroxybenzophenone[d]	3703	3174	1647
2,3-Dihydroxy-4′-chlorobenzophenone[d]	3583	3096	1619

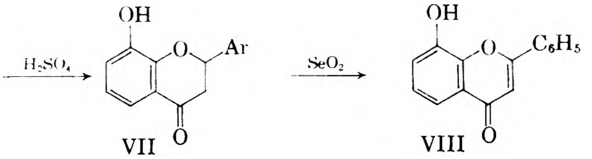
[a] The infrared measurements are carried out in carbon tetrachloride solution using Perkin Elmer Infracord model 137. Cell thickness 1 mm. [b] See ref. 2. [c] See ref. 1. [d] Prepared in this publication.

2,3-Dihydroxyacetophenone has been utilized to prepare some 8-hydroxyflavanones and 8-hydroxyflavones by known method,[9] according to the following scheme:



VI

VIa. Ar = C_6H_5
VIb. Ar = $p\text{-}CH_3OC_6H_4$
VIc. Ar = $p\text{-}ClC_6H_4$

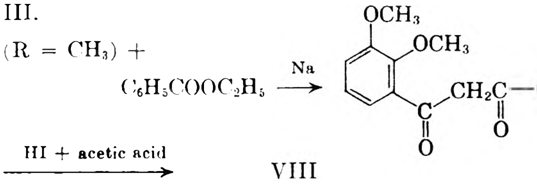


VII VIII

VIIa. Ar = C_6H_5
VIIb. Ar = $p\text{-}CH_3OC_6H_4$
VIIc. Ar = $p\text{-}ClC_6H_4$

VIII was prepared previously by Ruhemann[10] from β-(2-methoxyphenoxy)cinnamic acid and aluminium chloride in benzene, followed by demethylation of the product by hydriodic acid, a method which cannot be easily generalized for the preparation of 8-hydroxyflavones.

8-Hydroxyflavone (VIII) has also been prepared by the Claisen condensation of 2,3-dimethoxyacetophenone and ethyl benzoate in the presence of finely divided sodium metal followed by demethylation and cyclization using hydriodic acid and acetic acid according to the following scheme:



A study of the ultraviolet spectra of flavone and 8-hydroxyflavone (*cf.* Experimental) shows that they absorb at similar wave lengths but the molecular extinction coefficients of the latter are more pronounced in the first two maxima (hyperchrome effect).

EXPERIMENTAL

Microanalyses were carried out by Alfred Bernhardt, Max-Planck Institute; Mülheim (Ruhr), Germany. Melting points are not corrected.

Preparation of 2,3-dihydroxyisovalerophenone (IV. R= C_4H_9). a) *Action of isobutylmagnesium iodide on 2,3-dimethoxybenzaldehyde.* A solution of the aldehyde (I) (10 g.) in anhydrous ether was added dropwise to the isobutylmagnesium iodide (from 13.4 g. isobutyl iodide and 1.8 g. magnesium) while cooling in ice. When the addition was complete, the reaction mixture was treated as described previously[1] and the remaining oil distilled to give II (R = C_4H_9) as a pale-yellow oil b.p. 118–120°/0.5 mm., (yield 9.7 g.).

b) *Preparation of 2,3-dimethoxyisovalerophenone.* The previously described carbinol (9 g.) was added to a mixture of potassium dichromate (18 g.), water (90 ml.) and concd.

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(6) Wilson Baker and A. R. Smith, *J. Chem. Soc.*, 346–348 (1936).

(7) W. I. Awad and M. S. Hafez, *J. Am. Chem. Soc.*, **80**, 6057 (1958).

(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, First Edition, reprinted 1956, London Methuen Co., Ltd., p. 124.

(9) L. F. Fieser and M. Fieser, *Organic Chemistry*, 3rd edition D. C. Heath and Co., Boston, 1956, p. 822. This reference was added by one of the referees.

(10) Ruhemann, B., **46**, 2196 (1913). (*cf.* Beilst. **18** I, 323).

sulfuric acid (8.2 ml.). The reaction mixture was immediately steam-distilled, the distillate extracted with ether, dried (sodium sulfate), and then the ether driven off. III (R = C_4H_9) was obtained as a pale-yellow oil b.p. 130°/3 mm., (yield 5.3 g.).

c) *Demethylation of 2,3-dimethoxyisovalerophenone* (III. R = C_4H_9). The previously described ketone (III. R = C_4H_9) (6 g.) was refluxed with hydriodic acid (sp. gr. 1.71) (25 g.) and an equal volume of glacial acetic acid for 6 hr. The reaction mixture was worked out as described previously.[1] The viscous oil soon solidified on cooling and scratching. It was recrystallized from petroleum ether (b.p. 30–50°) as yellow flakes, m.p. 48°, (yield 4.6 g.). Miller, *et al.* gave m.p. 93–95°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.23; H, 7.25. It gave bluish-green color with alcoholic ferric chloride solution which turned red by adding sodium carbonate solution.[4,5] It also gave a buff coloration with concd. sulfuric acid.

Preparation of 2,3-dihydroxy-4′-chlorobenzophenone (IV. R = p-ClC_6H_4). i) *Action of p-chlorophenylmagnesium bromide on 2,3-dimethoxybenzaldehyde.* A solution of the aldehyde (I) (10 g.) in anhydrous ether was added dropwise, to *p*-chlorophenylmagnesium bromide (from 13.8 g. *p*-chlorobromobenzene, and 1.8 g. magnesium) while cooling in ice. The reaction mixture was treated as in (a) and the carbinol (II. R = p-ClC_6H_4) was obtained as a viscous oil b.p. 220–225°/7–8 mm., (yield 18.1 g.).

Anal. Calcd. for $C_{15}H_{15}O_3Cl$: Cl, 12.71. Found: Cl, 12.22.

ii) *Preparation of 2,3-dimethoxy-4′-chlorobenzophenone.* (III. R = p-ClC_6H_4). The above carbinol (II. R = p-ClC_6H_4) (5 g.) was mixed with the dichromate solution [from potassium dichromate (10 g.), water (50 ml.) and sulfuric acid (4.8 ml.)]. The reaction mixture was treated as in (b). A lemon-yellow oil was obtained, (yield 4.2 g.); b.p. 130–132°/3 mm.

iii) *Demethylation of 2,3-dimethoxy-4′-chlorobenzophenone.* The above ketone (4 g.) was treated as in (c) to give 2,3-dihydroxy-4′-chlorobenzophenone (IV. R = p-ClC_6H_4) in dark-yellow long needles from petroleum ether (b.p. 60–80°) m.p. 115°, (yield 2.9 g.). It gave a dark-green color with alcoholic ferric chloride solution which turned red on adding sodium carbonate solution. It gave an orange-red color with concd. sulfuric acid.

Anal. Calcd. for $C_{13}H_9O_3Cl$: C, 62.78; H, 3.63; Cl, 14.24. Found: C, 62.86; H, 3.87; Cl, 13.96.

Preparation of 8-hydroxyflavone. a) *Preparation of the chalcone* (VIa). To a warm solution of 2,3-dihydroxyacetophenone[2] (IV. R = CH_3) (1 g.) and benzaldehyde (0.5 g.) in ethyl alcohol (12.5 ml.) was added dropwise a solution of sodium hydroxide (30%; 12.5 ml.). The reaction mixture was shaken vigorously for 10 to 15 min. and then diluted with ice-cold dilute acid. It was extracted with ether and the ethereal layer was washed with water, sodium bisulfite solution, and finally with water, dried (sodium sulfate), and the ether was driven off leaving reddish-brown material. This was triturated with a little methanol and filtered. It was recrystallized from ethyl alcohol m.p. 192°, (yield 0.6 g.). It gave no color with alcoholic ferric chloride solution. This proved to be the 8-hydroxyflavanone (VIIa) by melting and mixture melting point (see below).

The methanol mother-liquor contained the chalcone (VIa). It was treated with a little water and left for 48 hr. at 0° where red crystals separated. It was recrystallized from petroleum ether (b.p. 60–80°) as red needles, m.p. 151°, 0.4 g.). It gave a dark-green color with alcoholic ferric chloride solution which turned red by adding sodium carbonate solution.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.28; H, 5.20.

Preparation of 8-hydroxyflavanone from the corresponding chalcone (VIa). The chalcone (0.2 g.) was dissolved in ethyl alcohol (15 ml.) and sulfuric acid was added. The reaction mixture was refluxed for 8 hr. on a water bath. On removal of the ethanol, a yellow crystalline substance was obtained. It was recrystallized from ethyl alcohol, m.p. 192°, (yield 0.16 g.).

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.25; H, 5.17.

c) *Oxidation of 8-hydroxyflavanone by selenium dioxide.* 8-Hydroxyflavanone (VIIa) (1 g.) was mixed with selenium dioxide (1 g.) and freshly distilled isoamyl alcohol (30 ml.). The reaction mixture was refluxed for 12 hr. on an oil bath (160–170°). After refluxing was complete, the reaction mixture was filtered while hot to remove selenium and the filtrate (dark-brown) was subjected to steam-distillation to remove isoamyl alcohol leaving an orange aqueous solution with a solid substance and a sticky mass. It was filtered, dissolved in benzene (charcoal), concentrated, and left to cool. An amorphous solid separated (yield 0.9 g.). It was sublimed to give colorless needles, m.p. 245°; (Ruhemann,[10] m.p. 249–250°). It gave no color with alcoholic ferric chloride solution, (yield 0.35 g.).

Ultraviolet measurements for VIII were: λ_{max} 211, mμ, ϵ_{max} 25,700; λ_{max} 267, ϵ_{max} 31,620; λ_{max} 300, ϵ_{max} 16,600. The ultraviolet measurements for flavone[11] were: λ_{max} 211 mμ, ϵ_{max} 18,840; λ_{max} 252, ϵ_{max} 19,140; λ_{max} 295, ϵ_{max} 24,024. Ultraviolet measurements were carried out in a Beckmann spectrophotometer model D.U. in ethyl alcohol.

Anal. Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 74.97; H, 4.18.

Preparation of 8-hydroxy-4′-methoxyflavanone (VIIb). i) *Preparation of the chalcone* (VIb). To a warm solution of 2,3-dihydroxyacetophenone (1 g.) and *p*-anisaldehyde (0.5 g.) in ethyl alcohol (12.5 ml.) was added dropwise a solution of sodium hydroxide (30%, 12.5 ml.). The reaction mixture was treated as in (a). The methoxychalcone was recrystallized from petroleum ether (b.p. 60–80°) as reddish-brown crystals, m.p. 171°, (yield 0.7 g.). It gave a green color with alcoholic ferric chloride solution which turned red by adding sodium carbonate solution.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.11; H, 5.18. Found: C, 71.41; H, 5.38. ii) *Preparation of 8-hydroxy-4′-methoxyflavanone* (VIIb). The corresponding chalcone (VIb) (0.2 g.) was treated as in (b). The 8-hydroxy-4′-methoxyflavanone (VIIb) was recrystallized from petroleum ether (b.p. 60–80°) as fine yellow needles m.p. 183°, (yield 0.15 g.).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.11; H, 5.18. Found: C, 70.89; H, 5.33.

Preparation of 8-hydroxy-4′-chloroflavanone (VIIc). i) *Preparation of the chalcone* (VIc). To a warm solution of 2,3-dihydroxyacetophenone (1 g.) and *p*-chlorobenzaldehyde (0.5 g.) in ethyl alcohol (12.5 ml.) was added dropwise a solution of sodium hydroxide (30%, 12.5 ml.). The reaction mixture was treated as in (a). The chlorochalcone was recrystallized from petroleum ether (b.p. 60–80°) as brick-red needles, m.p. 141°, (yield 0.6 g.). It gave a red color with concd. sulfuric acid and a dirty green color with alcoholic ferric chloride solution which changed to red by adding sodium carbonate solution.

Anal. Calcd. for $C_{15}H_{11}O_3Cl$: C, 65.57; H, 4.01; Cl, 12.92. Found: C, 65.27; H, 4.35; Cl, 12.85.

ii) *Preparation of 8-hydroxy-4′-chloroflavanone* (VIIc). The corresponding chalcone (VIc) (0.2 g.) was treated as described in (b). The 8-hydroxy-4′-chloroflavanone (VIIc) was recrystallized from petroleum ether (b.p. 60–80°) as fine yellow needles, m.p. 178°, (yield 0.19 g.). It gave no color with alcoholic ferric chloride solution and an orange-red color with concd. sulfuric acid.

Anal. Calcd. for $C_{15}H_{11}O_3Cl$: C, 65.57; H, 4.01; Cl, 12.92 Found: C, 65.04; H, 3.98; Cl, 12.90.

Preparation of VIII *via the Claisen condensation.* 2,3-Dimethoxyacetophenone (5 g.) was mixed with ethyl

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(11) T. S. Wheeler, R. L. Shriner, and D. A. Scott, *Org. Syntheses*, 32, 72 (1952).

benzoate (100 ml.) and finely divided sodium metal (5 g.). The reaction mixture was refluxed on an oil bath (180–200°) for 6 hr. The reaction mixture was then cooled and treated with methyl alcohol (10 ml.) to remove any unchanged sodium, acidified with acetic acid, and left overnight. It was steam-distilled until all the ethyl benzoate was removed and the reaction mixture assumed a yellow color. It was then extracted with ether and worked up as usual. The ether was driven off and a yellow oil was obtained, b.p. 220–225°/2 mm., (yield 8 g.).

The above condensation product (3 g.) was mixed with hydriodic acid (sp. gr. 1.71, 30 ml.) and glacial acetic acid (30 ml.). The reaction mixture was refluxed for 10 hr. It was then poured on ice, extracted with ether, and the ethereal layer was dried (sodium sulfate). The ether was driven off and the remaining oil was triturated with petroleum ether (b.p. 60–80°) until it solidified to an amorphous powder. It was sublimed to give VIII, m.p. 245°, (yield 2.2 g.).

Anal. Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.28; H, 4.22.

ABBASSIA, CAIRO, U.A.R.

[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, NITRO RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

Thiazolethiols and Their Derivatives

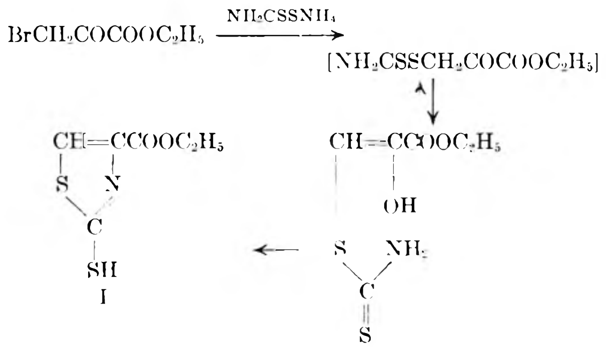
JOHN J. D'AMICO AND THOMAS W. BARTRAM

Received January 13, 1960

Ammonium dithiocarbamate and ethyl bromopyruvate reacted to give ethyl 2-mercapto-4-thiazolecarboxylate (I). Saponification of I gave 2-mercapto-4-thiazolecarboxylic acid. Thirty-four derivatives of I and related thiazolethiols were prepared. Oxidation of I, ethyl-2-mercapto-4-methyl-5-thiazolecarboxylate, or 2-mercapto-4-methyl-5-thiazolecarboxylic acid with hydrogen peroxide under acidic conditions gave the corresponding 4- or 5-substituted thiazoles.

Thiazolethiols and their derivatives have long been established as fundamentally important accelerators for the vlucanization of rubber with sulfur. Among the many derivatives prepared and screened, the thiazolesulfenamides, in particular, 2-(2,6-dimethylmorpholinothio)benzothiazole,[1] *N*-cyclohexyl-2-benzothiazolesulfenamide[2] and *N*-tert-butyl-2-benzothiazolesulfenamide,[3] have shown merit because of their delayed action. As thiazolethiols and their derivatives containing substituents, other than hydrocarbon radicals, in the 4-position have been prepared only in a limited number of examples,[4] it was desirable to prepare the unknown ethyl 2-mercapto-4-thiazolecarboxylate (I) and its derivatives. In addition, our objectives were: 1) the preparation of new derivatives of 5-substituted thiazolethiols and 2-mercaptobenzothiazole and 2) the synthesis of the 4- and 5-substituted thiazoles from the corresponding thiazolethiols. The accelerator activity for these new compounds will be reported in forthcoming patents.

Ammonium dithiocarbamate reacted with ethyl bromopyruvate to give I. The reaction may be represented as:



Saponification of I gave 2-mercapto-4-thiazolecarboxylic acid.

Diethyl 2,2′-dithiobis(4-thiazolecarboxylate) and 2,2′-dithiobis(4-thiazolecarboxylic acid) were prepared by the reaction of I or 2-mercapto-4-thiazolecarboxylic acid with an aqueous solution of ammonium persulfate.

The thiazolesulfenamides II, III, and IV were prepared by the oxidative condensation of I with *tert*-butylamine, cyclohexylamine, or morpholine.

The reaction of an aqueous solution of the sodium salt of I with zinc chloride or cadmium sulfate furnished the corresponding zinc and cadmium salt of I.

The reaction of an acetone solution of the potassium salt of I with β-dimethylaminoethyl chloride gave the desired ethyl 2-(2-dimethylaminoethylthio)-4-thiazolecarboxylate.

4-Ethoxycarbonyl-2-thiazolyl diethyldithiocarbamate was prepared by the reaction of the potassium salt of I with *N*,*N*-diethylthiocarbamoyl chloride.

The reaction of the potassium salt of I with 3-chloro-2,4-pentanedione, ethyl α-chloroacetoacetate, or chloroacetone gave ethyl 2-(1-acetyl acetonylthio)-4-thiazolecarboxylate (V), ethyl 2-(1-ethoxycarbonylacetonylthio)-4-thiazolecarboxylate (VI), and ethyl 2-acetonylthio-4-thiazolecarboxylate (VI), and ethyl 2-acetonylthio-4-thiazolecarboxylate (VII), respectively.

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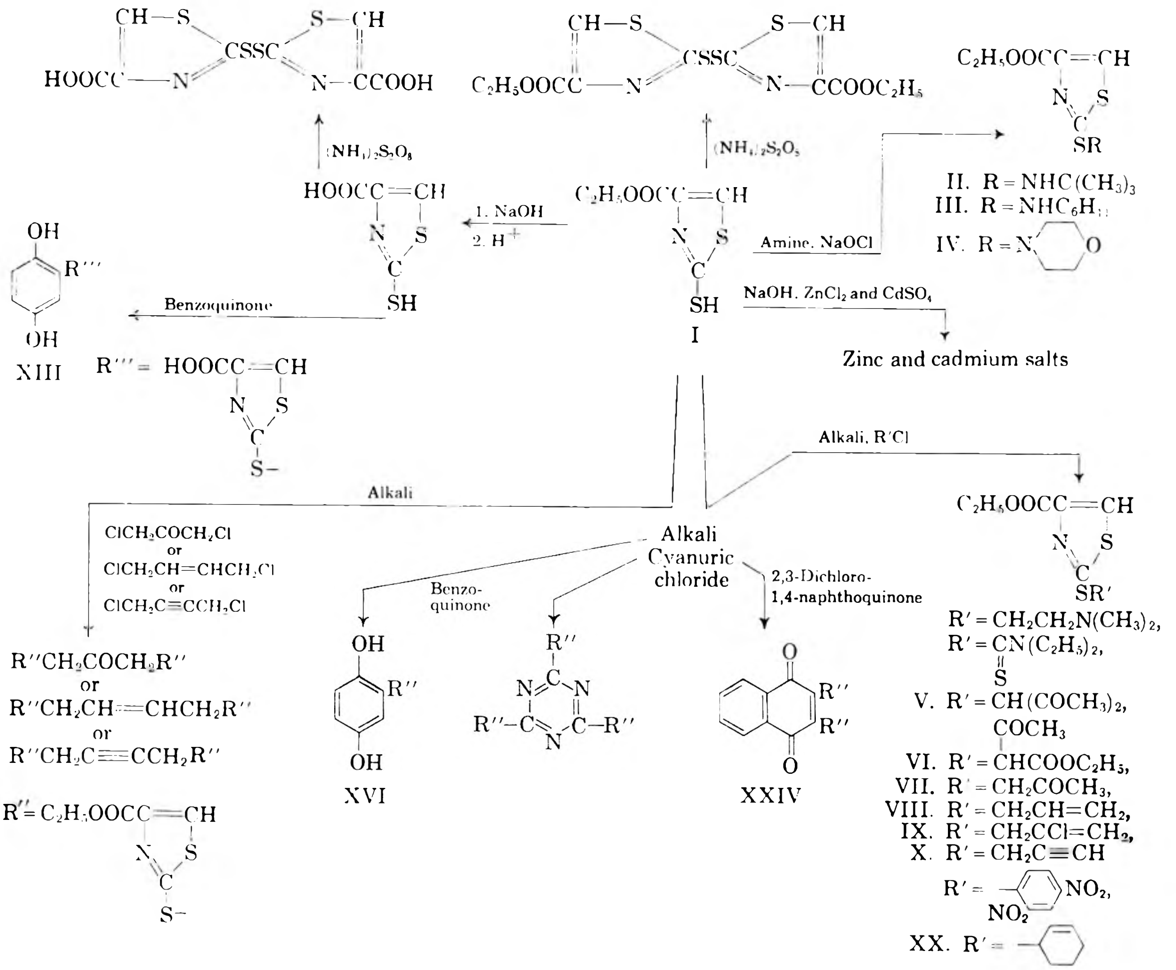
(1) J. J. D'Amico, M. W. Harman, and R. H. Cooper, *J. Am. Chem. Soc.*, **79**, 5270 (1957); U. S. Patent **2,871,239**.

(2) M. W. Harman, *Ind. Eng. Chem.* **29**, 205 (1937); U. S. Patent **2,191,656**.

(3) R. H. Cooper and J. J. D'Amico, U. S. Patent **2,807,620**.

(4) J. J. D'Amico, *J. Am. Chem. Soc.*, **77**, 476 (1955).


(NH4)2S2O8
(NH4)2S2O8
1. NaOH
2. H+
Amine, NaOCl
II. R = NHC(CH3)3
III. R = NHC6H5
IV. R = N O
NaOH, ZnCl2 and CdSO4
Zinc and cadmium salts
I
Benzoquinone
XIII
R‴ = HOOCC=CH N S C S−
Alkali, R′Cl
Alkali
ClCH2COCH2Cl or ClCH2CH=CHCH2Cl or ClCH2C≡CCH2Cl
R″CH2COCH2R″ or R″CH2CH=CHCH2R″ or R″CH2C≡CCH2R″
R″ = C2H5OOCC=CH N S C S−
Alkali
Benzoquinone
Cyanuric chloride
2,3-Dichloro-1,4-naphthoquinone
XVI
XXIV
R′ = CH2CH2N(CH3)2,
R′ = CN(C2H5)2, S
V. R′ = CH(COCH3)2,
VI. R′ = CHCOOC2H5, COCH3
VII. R′ = CH2COCH3,
VIII. R′ = CH2CH=CH2,
IX. R′ = CH2CCl=CH2,
X. R′ = CH2C≡CH
R′ = NO2, NO2
XX. R′ =

Diethyl 2,2′-(2-oxotrimethylene)dithiobis(4-thiazolecarboxylate) was prepared by the reaction of an acetone solution of the potassium of I with 1,3-dichloro-2-propanone.

The reaction of the sodium salt of I with allyl chloride, 2,3-dichloro-1-propene, or 3-bromo-1-propyne furnished ethyl 2-allylthio-4-thiazolecarboxylate (VIII), ethyl 2-(2-chloroallylthio)-4-thiazolecarboxylate (IX), and ethyl 2-(2-propynylthio)-4-thiazolecarboxylate (X), respectively.

Ethyl 2-(2,4-dinitrophenylthio)-4-thiazolecarboxylate was obtained by the reaction of the potassium salt of I with 2,4-dinitrochlorobenzene.

Diethyl 2,2′-(2-butenylene)dithiobis(4-thiazolecarboxylate) and diethyl 2,2′-(2-butynylene)dithiobis(4-thiazolecarboxylate) were prepared by the reaction of the potassium salt of I with 1,4-dichloro-2-butene or 1,4-dichloro-2-butyne.

The potassium salt of I reacted with cyanuric chloride to form 2,4,6-tris(4-ethoxycarbonyl-2-thiazolylthio)*S*-triazine.

Employing the elegant procedure described by Newby[5] *p*-benzoquinone was allowed to react with the appropriate thiazolethiol to give XI through XVI.

5-Chloro-2-mercaptobenzothiazole, 2-mercaptobenzothiazole, 6-ethoxy-2-mercaptobenzothiazole, or I reacted with 3-bromocyclohexene to form 5-chloro-2-(2-cyclohexenylthio)benzothiazole (XVII), 2-(2-cyclohexenylthio)benzothiazole (XVIII), 6-ethoxy-2-(2-cyclohexenylthio) benzothiazole (XIX), and ethyl 2-(2-cyclohexenylthio)-4-thiazolecarboxylate (XX), respectively.

The reaction of 2,3-dichloro-1,4-naphthoquinone with the appropriate thiazolethiol furnished 2,3-bis(2-benzothiazolylthio)-1,4-naphthoquinone (XXI), 2,3-bis(5-chloro-2-benzothiazolylthio)-1,4-naphthoquinone (XXII), 2,3-(6-ethoxy-2-benzothiazolylthio)-1,4-naphthoquinone (XXIII), and diethyl 2,2′-(1,4-dihydro-1,4-dioxo-2,3-naphthylenedithio)bis(4-thiazolecarboxylate)(XXIV), respectively.

Following the procedure described by Buchman,[6] ethyl 4-methyl-5-thiazolecarboxylate (XXV), ethyl 4-thiazolecarboxylate (XXVI), and 4-methyl-5-thiazolecarboxylic acid (XXVII) were prepared by the oxidation of the corresponding thiazolethiols with hydrogen peroxide. H. T. Clarke[7] reported the preparation of XXV by the reaction of thioformamide with ethyl α-chloroacetoacetate; and upon saponification of XXV obtained XXVII. H. Erlenmeyer[8] obtained XXVI by the reduction of ethyl 2 - bromo - 4 - thiazolecarboxylate. These reactions may be represented as:

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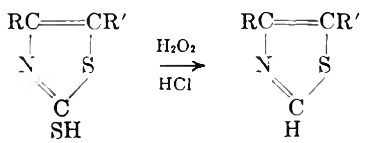
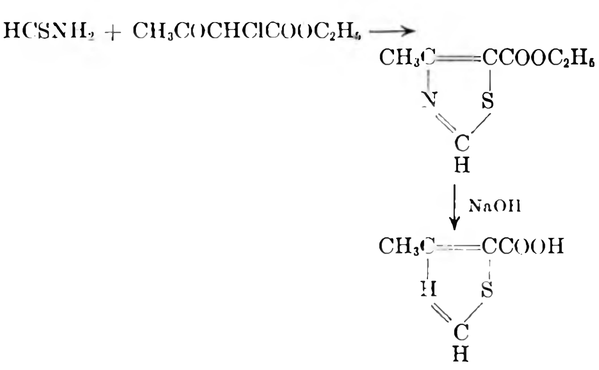
[5] T. H. Newby, U. S. Patent **2,616,871**.

[6] E. R. Buchman, A. O. Reims, and H. Sargent, *J. Org. Chem.* **6**, 764 (1941).

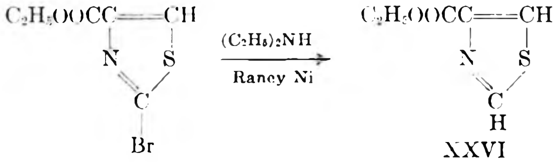
[7] H. T. Clarke and S. Gurin, *J. Am. Chem. Soc.*, **57**, 1876 (1935).



XXV. R = CH_3, R′ = $COOC_2H_5$
XXVI. R = $COOC_2H_5$, R′=H
XXVII. R = CH_3, R′ = COOH



XXVII



XXVI

EXPERIMENTAL[9]

Ethyl 2-mercapto-4-thiazolecarboxylate (I). To a stirred slurry containing 27.6 g. (0.25 mole) of ammonium dithiocarbamate and 150 ml. of ethyl alcohol was added 48.8g. (0.25 mole) of ethyl bromopyruvate[10]; the temperature rose immediately from 22 to 62°. The reaction mixture was stirred for 18 hr. and then heated at 70–80° for 2 hr. After the addition of 300 ml. of water and cooling to 10°, the precipitate was collected by filtration, washed with 200 ml. of cold water, and air-dried at 25–30°. The product, a light tan colored solid, m.p. 117–121°, was obtained in 65.7% yield, m.p. after recrystallization from ethyl alcohol 131–132°.

Anal. Calcd. for $C_6H_7NO_2S_2$: N, 7.40; S, 33.88. Found: N, 7.38; S, 33.98.

2-Mercapto-4-thiazolecarboxylic acid. A solution containing 44 g. (0.23 mole) of I, 74 g. (0.46 mole) of 25% aqueous sodium hydroxide solution and 100 ml. of water was stirred at 70–80° for 2 hr. After cooling to 15°, the solution was made acidic with concd. hydrochloric acid, the precipitate was collected by filtration, washed with 100 ml. of cold water, and air dried at 50°. The product, m.p. 246–250°, was obtained in 93.4% yield. After recrystallization from water it melted at 253–254°.

Anal. Calcd. for $C_4H_3NO_2S_2$: N, 8.69; S, 39.78. Found: N, 8.73; S, 39.64.

Diethyl 2,2′-dithiobis(4-thiazolecarboxylate) and 2,2′-dithiobis(4-thiazolecarboxylic acid). To an agitated suspension of 0.25 mole of either I or 2-mercapto-4-thiazolecarboxylic acid in 300 ml. of water was added dropwise a solution containing 63 g. (0.275 mole) of ammonium persulfate in 147 ml. of water over a 30-min. period at 25–30°. The reaction mixture was stirred for 2 additional hr. The precipitate was collected by filtration, washed with water until the wash water was neutral to litmus, and air-dried at 50°. The former product, m.p. 159–160° after recrystallization from ethyl alcohol, and the latter product, m.p. 267–268°, were obtained in 97.7 and 97.5% yields, respectively.

Anal. Calcd. for $C_{12}H_{12}N_2O_4S_4$: N, 7.44; S, 34.07. Found: N, 7.82; S, 33.78. Calcd. for $C_8H_4N_2O_4S_4$: N, 8.74. Found: N, 8.76.

Thiazolesulfenamides II, III, *and* IV. To an aqueous slurry containing 47.3 g. (0.25 mole) of I, 40 g. (0.25 mole) of 25% aqueous sodium hydroxide, and 50 ml. of water was added dropwise, with agitation, 1.5 to 2.0 moles of amine. After stirring for 15 min., 42 ml. of 25% sulfuric acid was added dropwise. To the resulting slurry was added dropwise at temperatures specified in Table I in 1.5 hr., 167 ml. (13.4 g./100 ml.) (0.30 mole) of aqueous sodium hypochlorite. The stirred reaction mixture was held at these temperatures for 1 hr. longer. The excess oxidizing agent was destroyed by the addition of 4 g. of sodium sulfite. For II the reaction mixture was extracted with 400 ml. of ethyl ether. The ether extract was washed with water until the washings were neutral to litmus and dried over sodium sulfate. Upon removal of the ether *in vacuo* a solid was obtained.

For III and IV the reaction mixture was cooled to 5°, the solid collected by filtration, washed with water until the wash water was neutral to litmus, and air-dried at 25–30°. The data are summarized in Table I.

Zinc and cadmium salts of I. To a stirred solution containing 47.3 g. (0.25 mole) of I, 40 g. (0.25 mole) of 25% aqueous sodium hydroxide, and 800 ml. of water was added in one portion 0.125 mole of zinc chloride or cadmium sulfate dissolved in 500 ml. of water. The reaction mixture was stirred for 2 hr., the resulting solid collected by filtration, washed with water until the washings were neutral to litmus, and air-dried at 50°. The zinc and cadmium salts were obtained in 88.8 and 84.7% yields, respectively.

Anal. Calcd. for $C_{12}H_{12}N_2O_4S_4Zn$: N, 6.34; S, 29.03; Zn, 14.80. Found: N, 6.35; S, 29.30; Zn, 14.25. Calcd. for $C_{12}H_{12}N_2O_4S_4Cd$: N, 5.73; S, 26.23; Cd, 22.99. Found: N, 5.58; S, 26.14; Cd, 22.10.

Ethyl 2-(2-dimethylaminoethylthio)-4-thiazolecarboxylate. To a stirred solution containing 47.3 g. (0.25 mole) of I, 32.2 g (0.50 mole) of 87% potassium hydroxide, and 400 ml. of acetone was added 36 g. (0.25 mole) of β-dimethylamino ethyl chloride hydrochloride. The reaction mixture was stirred at 25–30° for 24 hr. and filtered to remove potassium chloride. The acetone was removed *in vacuo* and the residue was filtered to remove a small amount of impurities. The product, an amber colored liquid, was obtained in 89.5% yield.

Anal. Calcd. for $C_{10}H_{16}N_2O_2S_2$: N, 10.76; S, 24.63. Found: N, 10.78; S, 24.34.

4-Ethoxycarbonyl-2-thiazolyl diethyldithiocarbamate. To a stirred solution containing 47.3 g. (0.25 mole) of I, 16.1 g. (0.25 mole) of 87% potassium hydroxide, and 460 ml. of acetone was added dropwise a solution containing 38 g. (0.25 mole) of N,N-diethylthiocarbamoyl chloride in 200 ml. of acetone. The reaction mixture was stirred for 4 hr. at 25–30° and filtered to remove the potassium chloride. The filtrate was added to 500 g. of ice water and stirred for 15 min. The resulting solid was collected by filtration, washed with water until free of chloride, and air-dried at 25–30°. The product, m.p. 100–105°, was obtained in 69.5% yield. After recrystallization from heptane it melted at 107–108°.

Anal. Calcd. for $C_{11}H_{16}N_2O_2S_3$: N, 9.20; S, 31.60. Found: 9.17; S, 31.63.

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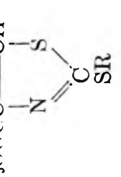
(8) H. Erlenmeyer and C. J. Morel, *Helv. chim. Acta*, **28**, 362 (1945).

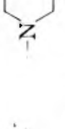
(9) All melting points were taken upon a Fisher-Johns block and are uncorrected.

(10) P. F. Kruse, Jr., N. Geurkink, and K. L. Gust, *J. Am. Chem. Soc.*, 76, 5796 (1954).

TABLE I

THIAZOLESULFENAMIDES C_2H_5OOCC—CH



No.	R	Amine	Mole Ratio, Amine to Thiazole	Reaction Temp., °	% Yield, Crude	M.P. °	Empirical Formula	% N		% S	
								Calcd.	Found	Calcd.	Found
II	$—NHC(CH_3)_3$	*tert*-Butylamine	6:1	30–40	49.4	99–101	$C_{10}H_{16}N_2O_2S_2$	10.76	10.72	24.63	24.55
III	$—NHC_6H_{11}$	Cyclohexylamine	8:1	45–50	42.0	112[a]	$C_{12}H_{18}N_2O_2S_2$	9.78	9.50	22.39	22.36
IV		Morpholine	8:1	45–50	55.3	155–157[a]	$C_{10}H_{14}N_2O_3S_2$	10.21	10.02	23.38	23.50

[a] Recrystallization from heptane.

Ethyl 2-(1-acetylacetonylthio)-4-thiazolecarboxylate (V), *ethyl 2-(1-ethoxycarbonylacetonylthio)-4-thiazolecarboxylate* (VI) *and ethyl 2-acetonylthio-4-thiazolecarboxylate* (VII). To a stirred solution containing 47.3 g. (0.25 mole) of I, 16.5 g. (0.25 mole) of 85% potassium hydroxide, 300 ml. of acetone, and 25 ml. of water was added in one portion 0.25 mole of 3-chloro-2,4-pentanedione,[11] ethyl α-chloroacetoacetate,[12] or chloroacetone. An exothermic reaction set in causing the temperature to rise from 25° to 45° over a period of 5 min. The reaction mixture was stirred for 6 hr. and then added to 500 g. of ice water. After stirring for 0.5 hr. the resulting precipitate was collected by filtration, washed with water until the washings were neutral to litmus, and air-dried at 25–30°. The data are summarized in Table II.

Diethyl 2,2'-(2-oxotrimethylene)dithiobis(4-thiazolecarboxylate). The procedure was the same as described for compounds V, VI, and VII except that 15.8 g. (0.125 mole) of 1,3-dichloro-2-propanone was employed. The product, m.p. 90–95°, was obtained in 90.8% yield. After recrystallization from ethyl acetate it melted at 100–101°.

Anal. Calcd. for $C_{15}H_{16}N_2O_5S_4$: N, 6.48; S, 29.65. Found: N, 6.44; S, 29.72.

Ethyl 2-allylthio-4-thiazolecarboxylate (VIII), *ethyl 2-(2-chloroallylthio)-4-thiazolecarboxylate* (IX), *and ethyl 2-(2-propynylthio)-4-thiazolecarboxylate* (X). To a stirred solution containing 47.3 g. (0.25 mole) of I, 40 g. (0.25 mole) of 25% aqueous sodium hydroxide, and 300 ml. of water was added in one portion 0.25 mole of allyl chloride 2,3-dichloro-1-propene, or 3-bromo-1-propyne. The reaction mixture was stirred at 25–40° for 18 hr. For VIII and IX the reaction mixture was extracted with 400 ml. of ethyl ether. The ether solution was washed with water until the wash water was neutral to litmus and dried over sodium sulfate. The ether was removed *in vacuo*.

For X the stirred reaction mixture was cooled to 0°, the resulting solid was collected by filtration, washed with water until the washings were neutral to litmus, and air-dried at room temperature. The data are summarized in Table III.

Ethyl 2-(2,4-dinitrophenylthio)-4-thiazolecarboxylate. A solution of the potassium salt of I was prepared by mixing 27 g. (0.14 mole) of I, 200 ml. of acetone, 9.4 g. (0.14 mole) of 85% potassium hydroxide, and 5 ml. of water. To this solution at room temperature 28.8 g. (0.14 mole) of 2,4-dinitrochlorobenzene was added and stirred at 25–30° for 6 hr. The reaction mixture was poured into 500 g. of crushed ice. After stirring for 10 min. the solid was collected, washed with water until the washings were neutral to litmus, and air-dried at 25–30°. The product, m.p. 127–129°, was obtained in 95% yield.

Anal. Calcd. for $C_{12}H_9N_3O_6S_2$: S, 18.05. Found: S, 17.70.

Diethyl 2,2'-(2-butenylene)dithiobis(4-thiazolecarboxylate) and diethyl 2,2'-(2-butynylene)dithiobis(4-thiazolecarboxylate). To a stirred solution containing 47.3 g. (0.25 mole) of I, 300 ml. of acetone, 16.5 g. (0.25 mole) of 85% potassium hydroxide, and 25 ml. of water was added 0.125 mole of 1,4-dichloro-2-butene or 1,4-dichloro-2-butyne. An exothermic reaction set in causing the temperature to rise from 25 to 40°. The reaction mixture was stirred at 25–30° for 6 hr. The reaction mixture was added to 500 g. of crushed ice. After stirring for 15 min. the resulting precipitate was collected, washed with water until the wash water was neutral to litmus, and air-dried at 25–30°. The former compound, m.p. 122–123°, after recrystallization from ethyl acetate and the latter compound, m.p. 89–91° after recrystallization from ethyl alcohol, were obtained in yields of 96.6 and 95.5%, respectively.

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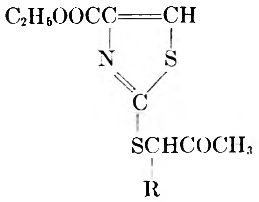
(11) E. R. Buchman and E. M. Richardson, *J. Am. Chem. Soc.*, 67, 395 (1945).

(12) E. R. Buchman and E. M. Richardson, *J. Am. Chem. Soc.*, 61, 891 (1939).

TABLE II

Ethyl 2-(1-acetylacetonylthio)-, Ethyl 2-(1-ethoxycarbonylacetonylthio), and Ethyl 2-acetonylthio-4-thiazolecarboxylate

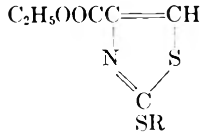


No.	R	% Yield, Crude	M.P., °	Empirical Formula	% N Calcd.	% N Found	% S Calcd.	% S Found
V	$COCH_3$	88.5	99–100[a]	$C_{11}H_{13}NO_4S_2$	4.87	4.88	22.30	22.02
VI	$COOC_2H_5$	86.0	85–86[a]	$C_{12}H_{15}NO_5S_2$	4.41	4.46	20.21	20.40
VII	H	81.9	103–105	$C_9H_{11}NO_5S_2$	5.71	5.69	26.14	25.83

[a] Recrystallization from heptane.

TABLE III

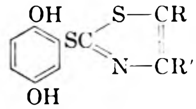
Ethyl 2-(allylthio)-, Ethyl 2-(2-chloroallylthio)-, and Ethyl 2-(2-propynylthio)-4-thiazolecarboxylates



No.	R	% Yield, Crude	M.P., °	Empirical Formula	% N Calcd.	% N Found	% S Calcd.	% S Found	% Cl Calcd.	% Cl Found
VIII	$-CH_2CH=CH_2$	57.6	Liquid	$C_9H_{11}NO_2S_2$	6.11	6.22	27.97	28.28	—	—
IX	$-CH_2CCl=CH_2$	53.3	Liquid	$C_9H_{10}ClNO_2S_2$	5.31	5.38	24.31	24.72	13.44	12.92
X	$-CH_2C\equiv CH$	61.6	62	$C_9H_9NO_2S_2$	6.16	5.91	28.21	28.36	—	—

TABLE IV

Derivatives of *p*-Dihydroxybenzene



No.	R	R′	% Yield, Crude	M.P., °	Empirical Formula	% N Calcd.	% N Found	% S Calcd.	% S Found
XI	$COOC_2H_5$	CH_3	93.5	215–217[a]	$C_{13}H_{13}NO_4S_2$	4.50	4.46	20.60	20.38
XII	$COOCH_3$	CH_3	79.3	216–218[a]	$C_{12}H_{11}NO_4S_2$	4.71	4.72	—	—
XIII	COOH	CH_3	88.7	230–232	$C_{11}H_9NO_4S_2$	4.94	5.10	22.63	22.18
XIV	$CONHC_6H_5$	CH_3	48.0	128–130[a]	$C_{17}H_{14}N_2O_3S_2$	7.82	7.35	17.89	17.87
XV	$CONH_2$	CH_3	65.6	158–160	$C_{11}H_{10}N_2O_3S_2$	9.92	9.72	—	—
XVI	H	COOH	40.2	103–105	$C_{10}H_7NO_4S_2$	5.20	4.86	—	—

[a] Recrystallization from ethyl acetate.

Anal. Calcd. for $C_{16}H_{18}N_2O_4S_4$: N, 6.51; S, 29.79. Found: N, 6.45; S, 29.54. Calcd. for $C_{16}H_{16}N_2O_4S_4$: N, 6.54; S, 29.93. Found: N, 6.31; S, 29.88.

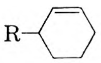
2,4,6-Tris(4-ethoxycarbonyl-2-thiazolylthio)-S-triazine. To a solution containing 47.3 g. (0.25 mole) of I, 400 ml. of acetone, and 16.5 g. (0.25 mole) of 85% potassium hydroxide was added dropwise 15.4 g. (0.083 mole) of cyanuric chloride dissolved in 100 ml. of acetone. After heating at 50–55° for 5 hr. the reaction mixture was added to 500 g. of ice water. After stirring for 15 min., the precipitate was collected, washed with water until free of chloride, and air-dried at 50°. The product, m.p. 217–218°, was obtained in 99% yield.

Anal. Calcd. for $C_{21}H_{18}N_6O_6S_6$: N, 13.08; S, 29.93. Found: N, 12.90; S, 29.40.

Ethyl 2-(2,5-dihydroxyphenylthio)-4-methyl-5-thiazolecarboxylate (XI), *methyl 2-(2,5-dihydroxyphenylthio)-4-methyl-5-thiazolecarboxylate* (XII), *2-(2,5-dihydroxyphenylthio)-4-methyl-5-thiazolecarboxylic acid* (XIII), *2-(2,5-dihydroxyphenylthio)-4-methyl-5-thiazolecarboxanilide* (XIV), *2-(2,5-dihydroxyphenylthio)-4-methyl-5-thiazolecarboxamide* (XV), *and 2-(2,5-dihydroxyphenylthio)-4-thiazolecarboxylic acid* (XVI). A suspension of 27 g. (0.25 mole) of benzoquinone and 185 ml. of methyl alcohol was heated to 50°. The resulting solution was cooled to 0° and to the recrystallized benzoquinone a suspension con-

TABLE V

2-(2-CYCLOHEXENYLTHIO)THIAZOLES



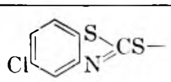
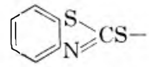
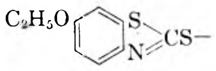
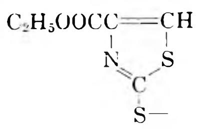
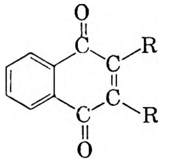
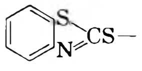
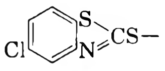
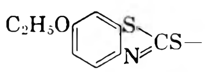
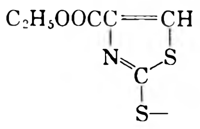
No.	R	State	% Yield, Crude	Empirical Formula	% N		% S	
					Calcd.	Found	Calcd.	Found
XVII		Amber liquid	81	$C_{13}H_{12}ClNS_2$	4.97	4.74	22.76	22.21
XVIII		Amber liquid	91	$C_{13}H_{13}NS_2$	5.66	5.55	25.93	25.39
XIX		Amber liquid	87	$C_{15}H_{17}NO_2S_2$	4.81	4.81	22.00	21.55
XX		Amber liquid	62	$C_{12}H_{15}NO_2S_2$	5.20	4.81	23.81	23.95

TABLE VI

2,3-BIS(2-THIAZOLYLTHIO)-1,4-NAPHTHOQUINONE



No.	R	M.P., °	% Yield, Crude	Empirical Formula	% N		% S	
					Calcd.	Found	Calcd.	Found
XXI		161-162[a]	96.5	$C_{24}H_{12}N_2O_2S_4$	5.73	5.60	26.25	25.85
XXII		223-225[a]	95.2	$C_{24}H_{10}Cl_2N_2O_2S_4$	5.03	5.26	23.00	23.18
XXIII		148-149[a]	97.1	$C_{28}H_{20}N_2O_4S_4$	4.86	4.55	22.24	22.08
XXIV		195-197	80.0	$C_{22}H_{16}N_2O_6S_4$	5.26	5.42	24.08	24.13

[a] Recrystallization from benzene.

taining 0.25 mole of alkyl 2-mercapto-4-methyl-5-thiazolecarboxylate,[13] 2-mercapto-4-methyl-5-thiazolecarboxylic acid,[13] 2-mercapto-4-methyl-5-thiazolecarboxanilide,[14] 2-mercapto-4-methyl-5-thiazolecarboxamide,[15] or 2-mercapto-4-thiazolecarboxylic acid in 300 ml. of methyl alcohol was added in one portion. The stirred reaction mixture was held at 0–10° for 2 hr. and then heated at 60–65° for 15 min. The reaction mixture was filtered at 65° to remove impurities. The filtrate was added to 1500 ml. of hot water and stirred at 60–70° for 1 hr. After cooling to 5° the solid was collected by filtration, washed with 1 l. of water, and air-dried at 25–30°. The data are summarized in Table IV.

5 - Chloro - 2 - (2 - cyclohexenylthio)benzothiazole (XVII), *2 - (2 - cyclohexenylthio)benzothiazole* (XVIII), *6-ethoxy - 2-(2-cyclohexenylthio)benzothiazole* (XIX), *and ethyl 2-(2-cyclohexenylthio)-4-thiozolecarboxylate* (XX). To a stirred solution containing 0.1 mole of 5-chloro-2-mercaptobenzothiazole, 2-mercaptobenzothiazole, or 6-ethoxy-2-mercaptobenzothiazole, 16 g. (0.1 mole) of 25% aqueous sodium hydroxide and 100 ml. of water was added in one portion 16.1 g. (0.1 mole) of 3-bromocyclohexene.[16] The stirred reaction mixture was heated at 80–90° for 8 hr.; and after cooling to 25° was extracted with 300 ml. of ethyl ether. The ether solution was washed with water until neutral to litmus and

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

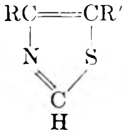
(14) R. A. Mathes, U. S. Patent **2,402,066**.

(15) R. B. Hill and H. W. Kilbourne, U. S. Patent **2,758,046**.

(16) F. L. Greenwood, *J. Am. Chem. Soc.*, **73**, 4495 (1951).

TABLE VII

4- AND 5-SUBSTITUTED THIAZOLES



No.	R	R′	M.P., ° Obtained	M.P., ° Reported	% Yield, Crude	Empirical Formula	% N Calcd.	% N Found	% S Calcd.	% S Found
XXV	CH_3	$COOC_2H_5$	98–99°/3 mm.[a]	140°/12 mm.[7]	51.4	$C_7H_9NO_2S$	8.18	8.16	18.73	18.62
XXVI	$COOC_2H_5$	H	52–54[b]	57[8]	44.6	$C_6H_7NO_2S$	8.91	8.92	—	—
XXVII	CH_3	COOH	255[c]	255[7]	82.9	$C_5H_5NO_2S$	9.78	9.41	22.40	22.73

[a] Boiling point. [b] Recrystallization from heptane. [c] Recrystallization from water.

dried over sodium sulfate. The ether was removed *in vacuo* at a maximum temperature of 80–90°.

To a stirred solution containing 32 g. (0.17 mole) of I, 200 ml. of ethyl alcohol, and 11.1 g. (0.17 mole) of 85% potassium hydroxide was added 27.2 g. (0.17 mole) of 3-bromocyclohexene. An exothermic reaction set in causing the temperature to rise from 25 to 48°. After stirring at 25–30° for 24 hr., 200 ml. of water and 300 ml. of ethyl ether were added. The ether solution was separated, washed with water until the wash water was neutral to litmus, and dried over sodium sulfate. The ether was removed *in vacuo* at a maximum temperature of 80–90°. The data are summarized in Table V.

2,3 - Bis(2 - benzothiazolylthio) - 1,4 - naphthoquinone (XXI), *2,3 - bis(5 - chloro - 2 - benzothiazolylthio) - 1,4 - naphthoquinone* (XXII), *2,3 - bis(6 - ethoxy - 2 - benzothiazolylthio) - 1,4 - naphthoquinone* (XXIII) *and diethyl 2,2′ - (1,4-dihydro - 1,4 - dioxo - 2,3 - naphthylenedithio)bis(4 - thiazolecarboxylate* (XXIV). To a stirred solution containing 0.2 mole of 2-mercaptobenzothiazole, 5-chloro-2-mercaptobenzothiazole, 6-ethoxy-2-mercaptobenzothiazole, or I, 13.2 g. (0.2 mole) of 85% potassium hydroxide, and 400 ml. of acetone, was added in one portion 23.7 g. (0.1 mole) of 2,3-dichloro-1,4-naphthoquinone.

The stirred reaction mixture was heated at 50–56° for 4 hr. and then added to 1500 g. of ice water. After stirring for 15 min., the solid was collected by filtration, washed with water until the washings were neutral to litmus, and air-dried at 25–30°. The data are summarized in Table VI.

Ethyl 4 - methyl - 5 - thiazolecarboxylate (XXV); *ethyl-4 - thiazolecarboxylate* (XXVI) *and 4 - methyl - 5 - thiazolecarboxylic acid* (XXVII). To a stirred slurry containing 0.5 mole of ethyl-2-mercapto-4-methyl-5-thiazolecarboxylate,[13] I or 2-mercapto-4-methyl-5-thiazolecarboxylic acid,[13] and 300 ml. of concd. hydrochloric acid at 50° was added dropwise 170 g. of 30% hydrogen peroxide over a 2-hr. period. During this addition an exothermic reaction set in and the temperature of the stirred reaction mixture was maintained at 50–75° by occasional cooling. The reaction mixture was stirred for an additional hour. For XXV and XXVI the stirred reaction mixture was cooled to 25° and filtered to remove the disulfides. To the stirred filtrate 245 g. of sodium carbonate was added in small portions until the *p*H of 8 was obtained. The stirred reaction mixture was extracted with 700 ml. of ethyl ether. The ether solution was dried over sodium sulfate and the ether was removed *in vacuo*. XXV was purified by distillation *in vacuo* and XXVI was recrystallized from heptane.

For XXVII the reaction mixture was added to 1000 g. of ice water. To this stirred slurry sodium carbonate was added in small portions until a *p*H 3.5 was obtained. The resulting solid was collected by filtration, washed with 400 ml. of water, and air-dried at 50°. The data are summarized in Table VII.

Acknowledgment. The writers wish to acknowledge their indebtness to R. O. Zerbe and D. D. Mullins for assistance rendered during the course of this investigation.

NITRO, W. VA.

[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY OF THE DEPARTMENT OF SURGERY, UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE]

Derivatives of Fluorene. X. Fluorofluorenes. III[1]

T. LLOYD FLETCHER, MOSES J. NAMKUNG, WILLIAM H. WETZEL, AND HSI-LUNG PAN

Received December 31, 1959

Preparation of further monofluoro-2-acetamidofluorenes is described, completing the series for biological testing (carcinogenicity), together with new substances obtained in the course of this work. A further example of monodemethylation in the Schiemann decomposition of a dimethylamino-substituted molecule is observed.

In this paper we describe preparation of the two remaining monofluoro-(6- and 3-)-2-acetamidofluorenes and related compounds. These two, together with the four new isomers already reported, the 1-, 4-, 5- and 8-fluoro-2-acetamidofluorenes,[1,2] have been tested for toxicity and carcinogenicity by Drs. James A. and Elizabeth C. Miller.[3] The 7-fluoro isomer was synthesized and tested earlier.[4]

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[1] *Fluorofluorenes. II., J. Org. Chem.*, 25, 996 (1960). This work has been aided in part by a research grant (C-1744) from the National Cancer Institute, U.S.P.H.S. Part of this material was presented at the Chicago meeting of the American Chemical Society in September, 1958.

[2] T. L. Fletcher, W. H. Wetzel, M. J. Namkung, and H. L. Pan, *J. Am. Chem. Soc.* 81, 1092 (1959).

After submitting our latest report,[1] an article describing some of the products we have prepared has just appeared.[5] Some of these were obtained, admittedly, by methods in which they were minor by-products, very difficult to purify. We began this work with the idea[2] of devising practical syntheses which would give the relatively large amounts required for biological testing. It was stated in the publication[2] that we were embarked on a program of synthesizing the remaining monofluoro 2-acetamidofluorenes. The following and related papers[1,2] outline a quite different approach (from that in ref. 5) to the preparation of these substances.

The diazonium fluoborate of 3-aminofluorenone[6] was decomposed in toluene to give 3-fluorofluorenone. Here, as in previous work,[2] decomposition in sand gave less yield and poorer material. Nitration gave good yields of 3-fluoro-7-nitrofluorenone. Two reductions and acetylation led to the desired *N*-2-(6-fluorofluorenyl)acetamide.

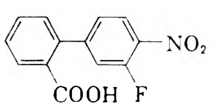
By diazotizing the supposed 3-fluoro-9-oxo-7-fluorenamine in fluoboric acid and decomposing the salt, we obtained 2,6-difluorofluorenone. For comparison the known 2-acetamido-3,7-dinitrofluorene[7] was oxidized, hydrolyzed and deaminated to give 3,7-(2,6-)dinitrofluorenone.[8] The latter was reduced with sodium sulfide to 2,6-diaminofluorenone.[8] Tetrazotization in the presence of fluoboric acid and decomposition gave 2,6-difluorofluorenone, identical with the above (melting point, mixture melting point and infrared spectrum).

N-2-(3-fluorofluorenyl)acetamide was made in two ways. In the better approach we simply nitrated 3-fluoro-7-trifluoroacetamidofluorene,[7] hydrolyzed the product for a few minutes in weak base[7] and deaminated it to give 3-fluoro-2-nitrofluorene. This was reduced and acetylated yielding the desired isomer, identical with the compound, whose structure we had already proved, prepared by the following laborious route.

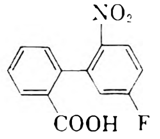
m-Fluoroaniline[9] was nitrated as described[10] giving mostly 3-fluoro-4-nitroaniline and a smaller amount of 3-fluoro-6-nitroaniline. The former was diazotized and treated with potassium iodide and iodine to give 3-fluoro-4-nitroiodobenzene which was coupled with a mixture of methyl *o*-chloro- and *o*-bromobenzoates (see Experimental) and worked up as usual. One of the by-products from symmetrical coupling, 3,3′-difluoro-4,4′-dinitrobiphenyl, was purified by sublimation.

When the crude carboxylic acid fraction of the foregoing reaction mixture was cyclodehydrated in polyphosphoric acid and extracted with alkali, a fluoronitrofluorenone was obtained. This was reduced with stannous chloride in hydrochloric acid (color characteristic of 2-aminofluorenone) and deaminated. The resulting fluorofluorenone was identical with 3-fluorofluorenone which we had already prepared.

A small amount of 1-fluoro-2-nitrofluorenone, the alternate cyclization product, was obtained during the purification of 2-amino-3-fluorofluorene (see I). This was identical[11] with a substance we described previously.[1]



I



II

It was conceivable, though hardly probable, that this minor product had come from a small amount of the lesser nitration isomer, 3-fluoro-6-nitroaniline, which in the subsequent series of reactions (see II) would have given 1-fluoro-4-nitrofluorenone. We therefore synthesized the latter compound, first from pure 3-fluoro-6-nitroaniline, and then from the known 1-amino-4-nitrofluorenone. Both procedures gave the same substance which was different from the by-product of the cyclization to the 2,3-isomer. Furthermore, deamination of the supposed 2-amino-1-fluorofluorenone gave 1-fluorofluorenone.

In another experiment we further confirmed the structure of the main Hodgson nitration product, 3-fluoro-4-nitroaniline, which could lead only to the 2,3- or 2,1-nitrofluorofluorenone. Diazotization of this aniline derivative in fluoboric acid and decomposition in chlorobenzene gave an oil which was fractionated. A yield of 24% of 2,4-difluoronitrobenzene was obtained, establishing the position of the nitro group as either 4- or 6-, with respect to $-NH_2$. Introduction of another nitro group gave the known 1,3-difluoro-4,6-dinitrobenzene (melting point mixture melting point and infrared spectrum). As we had made 1-fluoro-4-nitrofluorenone from the isomer with the nitro group *ortho* ot the amine (6-nitro), the main nitration product must necessarily have been as assumed.

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[3] McArdle Memorial Laboratory, The University of Wisconsin.

[4] J. A. Miller, R. B. Sandin, E. C. Miller, and H. P. Rusch, *Cancer Research*, **15**, 188 (1955).

[5] K. Suzuki, J. H. Weisburger, and E. K. Weisburger, *J. Org. Chem.*, **24**, 1511 (1959).

[6] N. Ishikawa, M. Okazaki, and M. Hayashi, *Yûki Gôsei Kagaku Kyokai-shi*, **15**, 34 (1958); *Chem. Abstr.*, **52**, 5349 (1958).

[7] M. J. Namkung and T. L. Fletcher, *J. Org. Chem.*, **25**, 740 (1960).

[8] N. Ishikawa and M. Hayashi, *Yûki Gôsei Kagaku Kyokai-shi*, **14**, 80 (1956); *Chem. Abstr.* **51**, 8049 (1957).

[9] (a) Purchased in part from L. Light and Company, England, (b) provided in part through the kindness of the Cancer Chemotherapy National Service Center, Bethesda 14, Maryland.

[10] H. H. Hodgson and D. E. Nicholson, *J. Chem. Soc.*, 766 (1941).

[11] See footnote 13 in reference 1.

The preceding is perhaps somewhat more confirmatory than necessary, but as described in the Experimental section we had prepared two derivatives of 4-nitro-3-fluoroaniline, neither of which agreed in melting point with compounds described in the literature,[10] although they both were analytically pure. We are at a loss to explain the discrepancy, but have not had opportunity to pursue the matter further.

Reduction of the 2-amino-3-fluorofluorenone to the corresponding fluorene and acetylation gave the 2,3-isomer, identical with the compound discussed above.

The Schiemann decomposition of 2-*N*,*N*-dimethylaminofluorene-1-diazonium fluoborate was shown[1] to give (31%) 2-*N*-monomethylaminofluorene as the only recognizable product. In the 2,3-series we attempted to confirm structure by making 2 - *N*,*N* - dimethylamino - 3 - fluorofluorene from known 2-*N*,*N*-dimethylamino-3-aminofluorene[12] and also by dimethylation of our supposed 2-amino-3-fluoro isomer. Here again the Schiemann decomposition failed, but gave some 2-*N*,*N*-dimethylaminofluorene with (probably) some *N*-monomethylaminofluorene.

We were curious about the reaction of the corresponding fluorenone. Diazotization in fluoboric acid and decomposition of the salt in boiling xylene led to 2-*N*-monomethylaminofluorenone in small yield.

We also prepared 2,4- and 1,3-difluorofluorenone (the 2,6- isomer was mentioned above). Decomposition of the diazonium fluoborate of 2-fluoro-9-oxo-2-fluorenamine gave an excellent yield of 2,4-difluorofluorenone.

Iodination of *m*-dinitrobenzene with fuming sulfuric acid and iodine[13] gave an improved yield (73%) of the 5-iodo derivative.[14] Reduction to 3-iodo-5-nitroaniline followed by a Schiemann reaction gave 3-fluoro-5-iodonitrobenzene. Further reduction to 3-fluoro-5-iodoaniline, diazonium fluoborate formation, and another decomposition gave us the known 3,5-difluoroiodobenzene. The structure of the latter compound was confirmed by nitration to 3,5-difluoro-2-nitroiodobenzene, identical with a compound obtained from 3,5-difluoro-2-nitroaniline. A specimen of the latter was generously donated.[15] An Ullmann condensation of 3,5-difluoroiodobenzene and a mixture of methyl *o*-bromo- and *o*-chlorobenzoates followed by the usual procedure and cyclodehydration in polyphosphoric acid gave 1,3-difluorofluorenone.

EXPERIMENTAL[16]

3-Fluorofluorenone. A mixture of 33 g. (0.169 mole) of 3-aminofluorenone and 400 ml. of 38% fluoboric acid was heated to form a salt and cooled to 5°. To the mixture, a saturated aqueous solution of 20 g. (0.29 mole) of sodium nitrite was added dropwise with stirring. After stirring a further 30 min., the diazonium salt was filtered and washed with cold 5% fluoboric acid, methanol, and ether and dried, 46 g. (93%), dec. 110°. The salt was decomposed by gently heating a suspension in 3 l. of toluene. We obtained 24.1 g. (72% based on the amine), m.p. 126–127°. One recrystallization from alcohol gave an analytical sample, m.p. 128.5–129°.

Anal. Calcd. for $C_{13}H_7FO$: C, 78.78; H, 3.56; F, 9.59. Found: C, 79.12; H, 3.61; F, 9.64.

3-Fluoro-7-nitrofluorenone. To 35 ml. of fuming nitric acid (d. 1.50) and 35 ml. of glacial acetic acid, 7 g. of 3-fluorofluorenone was added slowly at 35° with stirring. Concentrated sulfuric acid (7 ml.) was then added. The temperature of the mixture rose to 50° and it became a homogeneous solution. The stirring was continued for 10 min., while a light yellow substance precipitated. The reaction mixture was allowed to cool to room temperature, filtered, and washed with a small amount of cold glacial acetic acid and water, and dried, giving 7 g. (80.7%), m.p. 281–283°. An analytical sample was prepared by two recrystallizations from toluene, m.p. 282–283° (lit.,[5] m.p. 276–277°[17]).

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.48; F, 7.81; N, 5.76. Found: C, 64.39; H, 2.41; F, 7.52; N, 5.77.

2-Amino-6-fluorofluorenone. A mixture of 19.2 g. (0.079 mole) of 2-nitro-6-fluorofluorenone, 80 g. (0.35 mole) of stannous chloride dihydrate, 80 ml. of concd. hydrochloric acid, and 40 ml. of ethanol was heated in a beaker. Reaction took place at the boiling point with evolution of gas. The mixture was boiled for 10 min. with stirring, then allowed to cool. The yellow precipitate was filtered, washed with water, and neutralized with aqueous ammonium hydroxide. The deep purple amine was washed with water, dried, and recrystallization raised the m.p. to 218–219°.

Anal. Calcd. for $C_{13}H_8FNO$: N, 6.57. Found: N, 6.49.

N-2-(6-Fluoro-9-oxofluorenyl)acetamide. Acetylation of the foregoing amine gave the amide. One recrystallization from toluene gave an analytical sample, m.p. 277–277.5°.

Anal. Calcd. for $C_{15}H_9FNO_2$: C, 70,58; H, 3.95, N, 5.49. Found: C, 70.54; H, 4.25; N, 5.32.

6-Fluoro-2-fluorenamine. A mixture of 11.7 g. of 2-amino-6-fluorofluorenone, 26 g. of red phosphorus, 35 ml. of 47% hydriodic acid, and 300 ml. of glacial acetic acid was refluxed for 40 hr. The reaction mixture was boiled down to small volume and diluted with 300 ml. of water. This was heated, filtered hot, and the filtrate neutralized with aqueous ammonium hydroxide. The resulting white precipitate was filtered, washed with water, and dried, giving 9.8 g. (90%), m.p. 123–125°. One recrystallization from benzene gave an analytical sample, m.p. 125–126° (lit.[5] m.p. 125–126°[17]).

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.02; N, 7.03. Found: C, 78.65; H, 5.22; N, 7.18.

N-2(6-Fluorofluorenyl)acetamide. The acetylation of the foregoing compound in benzene gave the acetyl derivative, m.p. 203–204° (lit.[5] m.p. 198–199°[17]).

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; F, 7.88; N, 5.81. Found: C, 74.84; H, 4.93; F, 7.66; N, 5.99.

2,6-Difluorofluorenone. (a) A mixture of 3.6 g. (0.017 mole) of 2,6-diaminofluorenone[8] and 30 ml. of 50% fluoboric acid was heated and then cooled to 0° in an ice-salt bath. To the mixture, a saturated aqueous solution of 3 g. (0.044 mole) of sodium nitrite was added dropwise with stirring over a period of 15 min. After a further 15 min. of stirring the diazonium salt was filtered and washed successively with

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[12] T. L. Fletcher and M. J. Namkung, *J. Org. Chem.*, **23**, 680 (1958).

[13] C. F. H. Allen, H. W. J. Cressman, and H. B. Johnson, *Org. Syntheses*, **Coll. Vol. III**, 796 (1955).

[14] B. H. Nicolet, *J. Am. Chem. Soc.*, **49**, 1813 (1927).

[15] Dr. G. C. Finger, Illinois State Geological Survey, Urbana, Illinois.

[16] Melting points are corrected to standards and were taken on a Fisher-Johns block. Analyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

[17] These literature melting points are uncorrected.

10 ml. of 5% fluoboric acid, 10 ml. of methanol, and 10 ml. of ether, and dried, giving 4.2 g. (70%) dec. 130°. Decomposition of the salt in 50 ml. of xylene, filtration, and evaporation of the xylene gave 1.7 g. (47%, based on the amine), m.p. 176–180°. One recrystallization from toluene (Darco) raised the m.p. to 184–185°.

(b) Diazotization of 6-fluoro-9-oxo-2-fluorenamine (2 g.) in a similar manner, in 15 ml. of 50% fluoboric acid and 25 ml. of 85% phosphoric acid, gave 2.9 g. (100%) of the diazonium salt, dec. 180°. Decomposition in *o*-dichlorobenzene gave 1.2 g. (33%) of the difluoro compound, m.p. 170–180°. One recrystallization from toluene (Darco) followed by sublimation under reduced pressure gave an analytical sample, m.p. 185–185.5°. A mixture melting point with the above showed no depression and the infrared spectra were identical.

Anal. Calcd. for $C_{13}H_6F_2O$: C, 72.22; H, 2.79; F, 17.59. Found: C, 72.24; H, 3.04; F, 17.39.

N-2-(6-Fluorofluorenyl)trifluoroacetamide. Trifluoroacetylation of 6-fluoro-2-fluorenamine with trifluoroacetic anhydride[18] in benzene gave this derivative, m.p. 187–188°; after one recrystallization from alcohol, it melted at 187.5–188°.

Anal. Calcd. for $C_{15}H_9F_4NO$: N, 4.74. Found: N, 4.94.

N-2(6-Fluoro-7-nitrofluorenyl)trifluoroacetamide. A solution of 34.8 g. (0.117 mole) of the foregoing compound in 350 ml. of glacial acetic acid was cooled to 60° and 35 ml. of nitric acid (d. 1.42) and 20 ml. of boron trifluoride(diacetic acid complex) were added. The temperature of the mixture rose to 75°, and after 10 min. began to diminish. The mixture was allowed to cool. The precipitate was filtered and washed with alcohol, giving 34 g. (85%), m.p. 286–289°. Two recrystallizations from toluene gave an analytical sample, m.p. 288–289°.

Anal. Calcd. for $C_{15}H_8F_4N_2O_3$: N, 8.23. Found: N, 8.26.

6-Fluoro-7-nitro-2-fluorenamine. To a suspension of 34 g. (0.1 mole) of the foregoing compound in 300 ml. of boiling ethanol 50 ml. of 5% aqueous sodium hydroxide was added. All the solids dissolved and the solution turned dark. After 5 min. of boiling, a dark red precipitate formed. Boiling was continued a further 10 min. and the mixture was cooled. The precipitate was filtered, washed with water, and dried, giving 24 g. (98.5%), m.p. 225–228°. Two recrystallizations from acetone-alcohol (1:1) gave an analytical sample, m.p. 232–233°.

Anal. Calcd. for $C_{13}H_9FN_2O_2$: C, 63.93; H, 3.72; N, 11.47. Found: C, 64.06; H, 3.91; N, 11.50.

2-Nitro-3-fluorofluorene. To a solution of 800 ml. of concd. hydrochloric acid and 14 g. (0.2 mole) of sodium nitrite at 0°, 20.5 g. (0.084 mole) of the foregoing compound was added in small portions with constant stirring. The mixture was stirred at −5° for 1 hr. and 800 ml. of precooled 50% hypophosphorous acid added. A large amount of gas evolved and the color of the solution became lighter. The stirring was continued for 5 hr. at this temperature and the mixture was stored in a refrigerator overnight. It was then warmed on a water bath for 1 hr. and the light brown precipitate filtered, washed with water, and dried, giving 14.9 g., m.p. 125–135°. Recrystallization from ethanol (Darco) gave 12.5 g. (66%), m.p. 131–135°. Recrystallization from benzene and then from ethanol gave an analytical sample, m.p. 134.5–135° (lit.[5] m.p. 134.5–135.5°[17]).

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52; F, 8.30; N, 6.11. Found: C, 68.38; H, 3.45; F, 8.44; N, 6.13.

3-Fluoro-2-fluorenamine. Reduction of 11.5 g. of the foregoing compound in 500 ml. of toluene and 100 ml. of ethanol with Raney nickel and 10 ml. of hydrazine hydrate[12] gave 10.0 g. (96.5%) of the amino compound, m.p. 129–130.5°. A mixture melting point with 3-fluoro-2-fluorenamine was undepressed (lit.[5] m.p. 131–131.5°[17]).

Acetylation gave the amide identical with N-2-(3-fluorenyl)acetamide which is described below.

3-Fluoro-4-nitroaniline. This compound was prepared by both reported methods.[10] After two recrystallizations from benzene it melted at 158.5–159.5° (lit.,[10] m.p. 153°).

3-Fluoro-4-nitro-iodobenzene. Diazotization of 19.8 g. of 3-fluoro-4-nitroaniline and replacement of the diazonium group with iodine (with the use of potassium iodide and iodine) gave 32 g. of crude iodo compound. Recrystallization from ethanol (Darco) gave 28.5 g. (84%), m.p. 118–118.5°.

Anal. Calcd. for $C_6H_3FINO_2$: C, 26.99; H, 1.13; I, 47.54. Found: C, 27.27; H, 1.23; I, 47.33.

3-Fluoro-2-nitro-9-oxofluorenone. An Ullmann coupling procedure using 16.2 g. (0.061 mole) of 3-fluoro-4-nitroiodobenzene with a mixture[19] of 17.1 g. (0.1 mole) of methyl *o*-chlorobenzoate, 21.8 g. (0.1 mole) of *o*-bromobenzoate was run in a 200-ml. round-bottom flask equipped with stirrer, air condenser, and a stoppered wide tube. Activated copper powder[20] (100 g.) was added gradually (1 hr.) through the short tube, removing the stopper as briefly as possible, and with very rapid stirring. The bath temperature was kept at 218° and the stirring was continued 1 hr. after all the copper had been added. After cooling, the mixture was extracted with acetone and the combined extracts from four batches were boiled down to a red oil and hydrolyzed.[21] The green crystalline product was boiled in 600 ml. of water with 120 g. of sodium carbonate (Darco), and the mixture was cooled and filtered. The precipitate was extracted with benzene and the latter was boiled down almost to dryness and the residue extracted with ligroin (d. 0.67–0.69). The residue from ligroin evaporation, 0.94 g., was sublimed under reduced pressure to give 0.52 g. of 3,3′-difluoro-4,4′-dinitrobiphenyl, m.p. 196–198°. Recrystallization from methanol raised the melting point to 197.5–198.5°.

Anal. Calcd. for $C_{12}H_6F_2N_2O_4$: F, 13.56; N, 9.99. Found: F, 13.17; N, 10.10.

The basic filtrate from the separation of the foregoing was heated to boiling and cautiously acidified with concd. hydrochloric acid to give 76.5 g. of green crystals which were mixed with 400 g. of polyphosphoric acid and heated in an oven (155°) for 3 hr. with occasional stirring. The cooled mixture was poured over ice with thorough stirring and filtered. The solid material was boiled in 600 ml. of water with 70 g. of sodium carbonate and, after cooling, filtration gave 4-carboxyfluorenone in the filtrate. Acidification and recrystallization gave 8 g. of 4-carboxyfluorenone, m.p. 222–223°.

The dark yellow residue from this separation was recrystallized from 300 ml. of ethyl acetate (Darco) giving 14.2 g. of yellow crystals, m.p. 220.5–222.5°; a second crop amounted to 3.4 g., m.p. 217–221.5° (total 30%). The combined crops, after recrystallization from ethyl acetate (Darco), gave 15.8 g. of the fluorenone, m.p. 222–223°. As shown in the following paragraphs, this contained some of 2,1- isomer. An analytical sample from chloroform from a further preparation melted at 224–224.5° (lit.[6] 220–221°[17]).

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49; F, 7.81; N, 5.76. Found: C, 64.25; H, 2.63; F, 7.56; N, 5.67. Mol. wt. Calcd.: 243. Found: 235.

2-Amino-3-fluorofluorenone. Reduction of 15.8 g. of the above with stannous chloride and hydrochloric acid[22] gave the amine (13.5 g.) as bright red crystals. Recrystallization from benzene gave a first crop of 9.8 g. (70%), m.p. 163–164.5°. One more crystallization from benzene raised this to

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[18] Provided through the kindness of the Cancer Chemotherapy National Service Center, Bethesda 14, Maryland.

[19] This empirical mixture gave us a better yield than either *o*-halo ester alone, in a considerable number of trials.

[20] See footnote 16 in reference 2.

[21] M. S. Lesslie and E. Turner, *J. Chem. Soc.*, 1760 (1930).

[22] C. C. Arcus and M. M. Coombs, *J. Chem. Soc.*, 3977 (1954).

168–169°. A small sample of this was acetylated and after recrystallization from ethanol it melted at 262–263°.

Anal. Calcd. for $C_{15}H_{10}FNO_2$: C, 70.58; H, 3.95; F, 7.44; N, 5.49. Found: C, 70.74; H, 4.08; F, 7.31; N, 5.60.

The mother liquor from the first crop of the 2,3-fluoroamino compound gave more of that isomer and 1.2 g. (9%) (after benzene recrystallization) of *2-amino-1-fluorofluorenone,* m.p. 129–130.5°, still containing some of the 2.3 isomer (infrared spectrum).

Anal. Calcd. for $C_{13}H_8FNO$: N, 6.57. Found: N, 6.68.

Reduction with phosphorus and 47% hydriodic acid (48 hr.) gave a product which, after several crystallizations proved to be the same compound we have already reported[1] as 1-fluoro-2-fluorenamine. Acetylation gave us the amide, m.p. 187–188° (lit.,[1] m.p. 182–183°, 180.5–181.5°[5,17]).

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67, H, 5.01; F, 7.88; N, 5.81. Found: C, 74.50; H, 5.04; F, 7.70; N, 5.70.

A mixture melting point with the 2,1 isomer that we reported[1] was 186–188° (with slight softening). A mixture of 80% of the 2,1-acetamido isomer[1] with 20% of the 2,3-isomer (see above) melted at 186.5–188°, and a mixture melting point of this combination with the sample melting 187–188° showed no depression. The infrared spectrum[23] was identical with the 2,1-isomer except for hints of five bands all of which could be found in the spectrum of the pure 2,3-isomer.

Deamination of the above 2-amino-1-fluorofluorenone with hypophosphorous acid gave a crude product which was chromatographed on alumina (benzene). The principal substance from the eluate was recrystallized from *n*-heptane, m.p. 110–112°. A mixture melting point with authentic 1-fluorofluorenone showed no depression.

3-Fluoro-2-fluorenamine. Reduction of 3-fluoro-9-oxo-2-fluorenamine (3.6 g.) with phosphorus and 47% hydriodic acid gave 85% of crude product. After two recrystallizations from ligroin (d. 0.72–0.74), the compound melted at 130–131°. A mixture melting point with the compound described above from the alternate method was not depressed (lit.,[5,17] m.p. 131–131.5°).

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.02; N, 7.03. Found: C, 78.51, H, 5.25, N, 7.11.

Acetylation and recrystallization from benzene gave 2-acetamido-3-fluorofluorene, m.p. 198.5–199.5° identical (melting point, mixture and infrared spectrum[23]) with the compound already described (lit.,[5,17] m.p. 194–195°).

Anal. Calcd. for $C_{15}H_{12}FNO$: C 74.67; H, 5.01; F, 7.88; N, 5.81. Found: C, 74.69; H, 5.24; F, 7.81; N, 5.59.

Deamination of 3-fluoro-9-oxo-2-fluorenamine. A small quantity of this ketone was deaminated in the usual way with hypophosphorous acid. The crude product was sublimed under reduced pressure and recrystallized from ethanol, m.p. 125.5–127°. A mixture melting point with 3-fluorofluorenone was not depressed.

1-Fluoro-4-nitrofluorenone. (a) The by-product in the nitration of *m*-fluoroaniline, 3-fluoro-6-nitroaniline,[10] was diazotized and the diazonium group replaced with iodine. This iodo compound, obtained as an oil, was carried through the Ullmann reaction and worked up as described above. After cyclodehydration a small yield of a substance, m.p. 168.5–170° was obtained. A mixture melting point with 1-fluoro-4-nitrofluorenone showed no depression [see (b)].

(b) 1-Amino-4-nitrofluorenone[24] (3.47 g.) was diazotized in fluoboric acid and the dried salt (quant.), dec. 151°, was decomposed in 100 ml. of bromobenzene at a temperature of 130° gradually rising to 155° in 2 hr. The mixture was then boiled (Darco) and filtered. After evaporation of the solvent under reduced pressure, the product was purified by chromatography on alumina (benzene). A fraction, m.p. 160–168°, was recrystallized from acetone and alcohol (1:1) to give 1.05 g. (30%), m.p. 165.5–168°. An analytical sample, m.p. 172.5–173.5°, was prepared by two recrystallizations from ethyl acetate.

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49; F, 7.81. Found: C, 64.05; H, 2.47; F, 7.58.

A mixture with the product in a) gave m.p. 169–170.5° with no prior softening.

Establishment of the structure of the principal nitration product of m-fluoroaniline. Diazotization of the supposed 3-fluoro-4-nitroaniline in fluoboric acid and decomposition of the salt in hot chlorobenzene 90–130° was followed by fractionation, first to remove the solvent; refractionation led to a compound (2,4-difluoronitrobenzene) boiling at 85–86° (11 mm.) which at this stage amounted to 24%, based on the amine. Nitration of the latter (0.30 g.) gave 0.35 g. of 1,3-difluoro-4,6-dinitrobenzene, m.p. 73–74°. A mixture melting point with the authentic material,[9a] m.p. 73–74°, was not depressed. The infrared spectra of the two substances were identical. The main product of nitration must therefore have been as assumed.

Derivatives of 3-fluoro-4-nitroaniline. (a) 3-Fluoro-4-nitrophenol was prepared as reported.[10] m.p. 91.5–92.5° (lit.,[10] m.p. 42°). None of the other three isomeric fluoronitrophenols is reported to melt near 90°.

Anal. Calcd. for $C_6H_4FNO_3$: C, 45.87; H, 2.56; N, 8.92. Found: C, 45.51; H. 2.68; N, 9.04.

(b) *3-Fluoro-4-nitroacetanilide* was also prepared,[10] m.p. 175–176° (lit.,[10] m.p. 140°).

Anal. Calcd. for $C_8H_7FN_2O_3$: N, 14.14. Found: N, 14.13.

2-N,N-Dimethylamino-3-fluorofluorene. 2-Amino-3-fluorofluorene (1 g.) and trimethyl phosphate (0.5 g.) were mixed and heated at 190–195° (bath) for 1.5 hr. The reaction mixture was boiled for 5 min. in a solution of sodium hydroxide (0.9 g.) in water (3 ml.) then cooled. After dilution with water (15 ml.) the solid mass was pulverized, filtered, washed with water, and dried. Recrystallization from ethanol (Darco) gave shiny plates (0.8 g.). Three recrystallizations from methanol gave an analytical sample, m.p. 109–110°.

Anal. Calcd. for $C_{15}H_{14}FN$: C, 79.27; H, 6.21; N, 6.16. Found: C, 79.39; H, 6.04; N, 6.35.

Decomposition of 2-N,N-dimethylamino-3-fluorenediazonium fluoborate. Diazotization of 2-*N*,*N*-dimethylamino-3-fluorenamine[12] in the usual way in fluoboric acid gave a salt (dec. ~130°). This was decomposed in boiling xylene to give 1.6 g. (from 2.9 g. of the amine), m.p. 80–115°. Fractional crystallization from petroleum ether and from methanol finally yielded a small amount of 2-*N*,*N*-dimethylaminofluorene (mixture melting point) and a crude fraction which appeared to be largely 2-*N*-monomethylaminofluorene. We were not able to isolate any material which corresponds to the fluoro derivative described in the preceding paragraph.

2-N,N-Dimethylamino-3-fluorofluorenone. 2-Amino-3-fluorofluorenone (1 g.) was dissolved in trimethyl phosphate (1.3 g.) by heating. The solution was cooled somewhat and powdered anhydrous lithium bromide[25,26] (0.82 g.) was added in one portion. The mixture was shaken and heated under reflux at 120–125° (bath) for a few minutes then at 135–140° (bath) for 1 hr. The bath temperature was raised to 140–145° and heating was continued for 0.5 hr. The pasty reaction mixture was boiled for 20 min. in a solution of sodium hydroxide (0.5 g.) in water (5 ml.) and stirred into cold water. After filtration and washing the dry precipitate weighed 0.9 g. Recrystallization from carbon tetrachloride–methanol gave 0.62 g., m.p. 94.5–95.5°. One more recrystallization from methanol raised the melting point to 95.5–96.5°.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; F, 7.88; N, 5.81. Found: C, 74.54; H, 4.62; F, 7.81; N, 6.00.

2-N,N-Dimethylamino-9-oxo-3-fluorenamine. Reduction[22] of 2-dimethylamino-3-nitrofluorenone[7] (8.05 g.) yielded 2 g.

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(23) Beckman IR-5; potassium bromide disc.

(24) J. W. Cook and J. S. Moffatt, *J. Chem. Soc.* 1160 (1950).

(25) T. L. Fletcher, M. E. Taylor, and A. W. Dahl, *J. Org. Chem.*, 20, 1021 (1955).

(26) See footnote e, Table I, in reference 12.

(28%) of the amine, m.p. 172.5–173.5°. This proved difficult to purify. After several crystallizations from 50% ethanol and from methanol a sample was obtained, m.p. 174–175°.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92. Found: C, 75.21, H, 5.53.

Decomposition of 2-N,N-dimethylamino-9-oxo-3-fluorenediazonium fluoborate. The amine (2 g.) was diazotized in the usual way giving 3.2 g. of the red salt, dec. 124°, which was ground to a powder and decomposed in a xylene (120 ml.) suspension by gradually increasing the temperature to the boiling point (0.5 hr.) and boiling gently for 1.5 hr. with replacement of the solvent lost by evaporation. The mixture was cooled to 0° and the solvent decanted from the purple product. After warming and evaporating, the remaining solvent in a current of air the solid was triturated with 5% ammonium hydroxide solution, which was boiled briefly, filtered, washed, and dried. It was then dissolved in a few ml. of benzene and chromatographed on alumina and was eluted with a 4:1 mixture of benzene and ethanol. The crude product was wide-melting. After crystallizations from benzene (once) and methanol (twice), a sample was obtained melting at 157.5–158.5°. A mixture melting point with authentic 2-N-monomethylaminofluorenone showed no depression.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36, H, 5.30, N, 6.69. Found: C, 80.61; H, 5.10; N, 6.81; F, 0.00.

2,4-Difluorofluorenone. 2-Amino-4-fluorofluorenone (0.5 g., 0.0023 mole) was mixed with 48% fluoboric acid (15 ml.) and cooled to 0°. The mixture was diazotized with a solution of sodium nitrite (0.2 g., 0.0029 mole) in water (1 ml.). After 30 min. of stirring, the diazonium fluoborate was filtered, washed, and dried. It was then mixed with four times its volume of sand and decomposed under reduced pressure at 170–185° (20 min.). The difluoro- compound was extracted with benzene and a small portion was sublimed under reduced pressure at 155–160° giving shiny yellow leaflets, m.p. 144.5–145.5°.

Anal. Calcd. for $C_{13}H_6F_2O$: C, 72.22; H, 2.80; F, 17.58. Found: C, 72.33; H, 2.81; F, 17.36.

The remaining product was chromatographed on alumina (benzene). One recrystallization from aqueous methanol gave 0.35 g., m.p. 143–144°. The total yield was 85–90%.

1,3-Dinitro-5-iodobenzene. This known[14] compound was made by the following improved procedure: In a 2-l. flask, fitted with a reflux condenser, *m*-dinitrobenzene (125 g., 0.745 mole), fuming sulfuric acid (500 ml., 20–30%), and iodine (97 g., 0.382 mole) were mixed. The temperature was allowed to rise slowly, during 1 hr., to 150° (bath) with occasional shaking. White fumes arose from the reflux condenser. Heating was continued (150–155°) until the evolution of white fumes diminished. Occasionally, during the reaction, a little fuming sulfuric acid was added to wash down the sublimed iodine which had collected on the sides of the condenser. The contents were cooled to about 50° and poured over ice cubes with stirring. The mixture was transferred to a mortar and the solid product ground to fine particles. It was then filtered, washed well with water, dried, and recrystallized from 500 ml. of absolute ethanol to give 160 g. (73%) of 1,3-dinitro-5-iodobenzene, m.p. 99–100°. One more recrystallization gave m.p. 99.5–100.5° (lit.,[14] m.p. 99°).

3-Iodo-5-nitroaniline. Sodium sulfide (120 g.) and sulfur (30 g.) were added to 450 ml. of water and warmed until the solution became clear. This was added through a dropping funnel over a period of 1.5 hr. to a boiling, mechanically-stirred solution of 128.3 g. of 1,3-dinitro-5-iodobenzene and 600 ml. of water in a 2-l. beaker. After the addition, the mixture was heated for 0.5 hr. longer with stirring, cooled by adding ice, and the precipitated product filtered off. The latter was boiled for 45 min. in a mixture of 450 ml. of water and 105 ml. of concd. hydrochloric acid. After cooling slightly it was filtered through a sintered glass funnel of medium porosity. The extraction was repeated and the combined filtrates were neutralized with concd. ammonium hydroxide, cooled, and the precipitate recovered by filtration. The dried product was recrystallized from 300 ml. of 95% ethanol (Darco) and boiled down to 150 ml. The first crop, amounting to 40 g., melted at 135.5–139° (35.4%), and was used at this stage in the next step. A second crop yielded 10 g., m.p. 132–135°.

The analytical sample was obtained by two recrystallizations from ethanol, m.p. 140–141°.

Anal. Calcd. for $C_6H_5IN_2O_2$: N, 10.61. Found: N, 10.76.

3-Iodo-5-nitrobenzenediazonium fluoborate. 3-Iodo-5-nitroaniline (35 g., 0.133 mole) was added to 87.5 ml. of 48–50% fluoboric acid diluted with 125 ml. of water. The mixture was stirred magnetically, cooled to 5–10° in an ice bath, and 9.3 g. (0.135 mole) of sodium nitrite in 52 ml. of water was added dropwise over a period of 20 min. It was stirred for an additional 20 min., filtered, and washed successively with 90 ml. of cold 5% fluoboric acid, 26 ml. of cold methanol, and three 50-ml. portions of ethyl ether. The tan product was dried in a desiccator giving 46 g. (95.4% of the diazonium salt, dec. 155–166°.

3-Fluoro-5-iodonitrobenzene. The diazonium salt 50 g. (0.138 mole) was decomposed by mixing with an equal volume of dry sand in a 500 ml. flask heated in a wax bath at 140° under aspirator vacuum. The temperature was slowly raised to 150°, at which point steady decomposition took place during 1 hr. The cooled mixture was then extracted with 95% ethanol. The extracts were combined and boiled with Darco and then filtered. Hot water was added to the boiling filtrate, to the point of cloudiness, to give a crude product, m.p. 64–76°. Combined yields of six such decompositions gave 115 g. The latter was purified by extracting with 350 ml. of 50% aqueous acetic acid. The extract was boiled until only a reddish-brown oil remained and the clear solution allowed to cool and solidify. The yield was 89 g. (40%), m.p. 75.5–78°.

An analytical sample was obtained by recrystallizing once from aqueous ethanol and twice from petroleum ether (b.p. 30–60°), m.p. 77–78.5°.

Anal. Calcd. for $C_6H_3FINO_2$: C, 27.00; H, 1.13; N, 5.25. Found: C, 26.89; H, 1.53; N, 5.05.

3-Fluoro-5-iodoaniline. Two 45-g. batches of 3-fluoro-5-iodonitrobenzene were reduced with stannous chloride and hydrochloric acid in the usual way.[22] After the sodium hydroxide treatment of the crude mixture, the alkaline solution was extracted twice with 500-ml. portions of ether. A small sample of the ether solution was removed, dried, and boiled down to give the amine as an oil. Addition of acetic anhydride gave a product which was recrystallized twice from aqueous ethanol, once from benzene, and once from benzene and cyclohexane (1:1). We thus obtained an analytical sample, m.p. 154–156°, of *3-fluoro-5-iodoacetanilide.*

Anal. Calcd. for C_8H_7FINO: C, 34.43; H, 2.53; F, 6.81; N, 5.02. Found: C, 34.68; H, 2.53; F, 6.79; N, 4.83.

The remainder of the ethereal solution of the free amine was dried and the ether evaporated. During the last part of the evaporation 150 ml. of 50% fluoboric acid were slowly added. After further heating on the steam bath and cooling, crystals were obtained which were dried by suction (110 g., dec. 183–191°). This entire product was added to 110 ml. of 50% fluoboric acid in 100 ml. of water and cooled to 5–10°, diazotizing with sodium nitrite (23.4 g., 0.34 mole) in 50 ml. of water to give a thick pink slurry. After stirring for an additional 45 min., the mixture was filtered, washed with 150 ml. of 5% cold fluoboric acid in several portions, two 35-ml. portions of cold methanol and finally with 50 ml. of ether. After drying, the pink precipitate weighed 64.3 g. (56.5%), dec. 141°.

1,3-Difluoro-5-iodobenzene. The entire amount of the diazonium salt was decomposed in two portions under reduced pressure (17 mm.), each mixed with an equal volume of sand. at a temperature range of 135–160° for 1.5 hr. The crude liquid product, which distilled, was collected in a cooled receiver and amounted to 42 g. This was fractionated to give 36 g. (79%) of 3,5-difluoroiodobenzene, b.p. 58–60° (17 mm.).

Anal. Calcd. for $C_6H_3F_2I$: C, 30.03; H, 1.26; F, 15.83; I, 52.88. Found: C, 30.23; H, 1.17; F, 15.61; I, 52.68.

This substance was reported[27] as obtained from Dr. G. C. Finger.[15] The structure was confirmed by nitration with fuming nitric acid (d. 1.50) and sulfuric acid at −5°. After pouring onto ice and filtering, a 96.5% yield of 3,5-difluoro-2-nitroiodobenzene was obtained, m.p. 66.5–67.5°. An analytical sample was obtained upon recrystallization from petroleum ether (b.p. 40–60°), m.p. 66.5–67.5°.

Anal. Calcd. for $C_6H_2F_2INO_2$: N, 4.92. Found: N, 5.06.

The amine group of 3,5-difluoro-2-nitroaniline[15] was replaced in the usual way with iodine. This was identical with the sample obtained above (melting point and mixture melting point).

1,3-Difluorofluorenone. A mixture of 8 g. of 1,3-difluoro-5-iodobenzene, 11 g. of methyl *o*-bromobenzoate, and 11 g. of methyl *o*-chlorobenzoate was treated (rapid stirring) with 50 g. of activated copper (added gradually) at a temperature of 200–210° over a period of 1.5 hr. Stirring was continued after the addition, for 0.5 hr., at a bath temperature of 215–218°. The product was obtained from the reaction mixture in the usual way with the cyclodehydration step carried out in polyphosphoric acid. A crude yield of 1.65 g. of the ketone was obtained. Chromatography of 0.2 g. of this material through alumina (benzene) gave two zones. From the faster moving band, light yellow leaflets were obtained. Recrystallization from methanol gave 0.09 g., m.p. 188–189°. The same material was also obtained by subliming the crude product at 130–145° (bath) at 1 mm.

Anal. Calcd. for $C_{13}H_6F_2O$: C, 72.22; H, 2.80; F, 17.58. Found: C, 72.44; H, 2.94; F, 17.61.

From the slower-moving band there was obtained 0.03 g. of a yellow compound, m.p. 224.5–225.5°, which did not sublime at 145° (1 mm.).

Anal. Found: F, 10.46.

Further characterization has not been attempted.

SEATTLE 5, WASH.

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[27] H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *J. Am. Chem. Soc.*, **74**, 4809 (1952).

[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY OF THE DEPARTMENT OF SURGERY,
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE]

Derivatives of Fluorene. XI. New Nitrogen Mustards[1]

T. LLOYD FLETCHER AND WILLIAM H. WETZEL

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Some *N*-fluorenyl nitrogen mustards postulated to give more or less tendency for ethylenimmonium ion formation have been designed. The ultraviolet spectra of these and related compounds have been determined, in both neutral and acidic solutions, with a view to studying quaternization (ethylenimmonium ion formation) and in order to correlate these data with possible biological activity. No ethylenimmonium ion formation occurs in most of the compounds reported and protonation of the amine nitrogen is achieved more readily with the amino, dimethylamino, or diethylamino groups than with the mustard group. It is tentatively concluded that a fluorene nitrogen mustard, properly substituted with strong electron donor groups, might exist, at least partially, in the ethylenimmonium ion form.

Prior to this work,[2] only two nitrogen mustard derivatives of fluorene have been reported in the literature, 2-*N*,*N*-di-(β-chloroethyl)aminofluorene[3] and its bromo analogue.

In view of the interesting biological effects of many nitrogen mustards, the variety of biological effects of many substituted fluorenes and the fact that 2-aminofluorene and a number of its derivatives are carcinogenic, we have synthesized a group of *N*,*N*-di-(β-chloroethyl)aminofluorenes and related substances for their own chemical and biological interest and as a background for further specifically tailored nitrogen mustards to be reported on shortly. We were interested in learning the effects of certain changes in the availability of the extra electron pair of the nitrogen atom of the mustard moiety, chemically, spectrally, and ultimately biologically. It was recently suggested[4] that certain structural devices—for example, hydrogen bonding with the electron pair of this nitrogen—would tend to stabilize the β-chloroethylamine form, thus retarding formation of the ethylenimmonium ion and prolonging or potentiating physiological activity of the compound *in vivo*. We felt that this same general purpose could be effected in a series of compounds with the fluorene nucleus properly substituted with electron attracting or electron donating groups. For example, in the case of 2- *N*,*N*-di(β-chloroethyl)amino-7-nitrofluorene the electronegative nitro group would lower the availability of the electron pair on the amine nitrogen and thus inhibit quaternization.

Some of the di-β-hydroxy compounds (See Table I) were prepared by the reaction of ethylene oxide in dilute acetic acid at elevated temperatures and pressures in a bomb. As poor yields resulted with certain amines, the method of bis-β-hydroxyethylation at room temperature[5] was adopted.

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[1] This work was supported in part by a research grant (C-1744) from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

[2] Some of the material was presented at the meeting of the American Chemical Society, New York, September 1957.

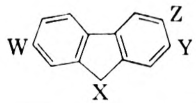
[3] W. Davis, J. L. Everett, and W. C. J. Ross, *J. Chem. Soc.* 1331 (1950).

[4] C. Weatherbee, R. Temple, and W. J. Burke, *J. Org. Chem.* **21**, 1138 (1956).

[5] F. Bergel and J. A. Stock, *J. Chem. Soc.*, 2409 (1954).

TABLE I

PREPARATION OF NITROGEN MUSTARDS



N,N-Di-β-hydroxyethylaminofluorenes											Mole Ratio: Chlorinating Agent/Amine		N,N-Di-β-chloroethylaminofluorenes				
Substituents				Method			Yield, %	Recryst. solvent	M.P.°[b]	G. (Di-β-hydroxy Compound)	PCl$_5$	POCl$_3$	Solvent, ml.	Time, min.	Yield, %	Recryst. solvent	M.P.°[b]
W	X	Y	Z		Time hr.	Temp.[a]											
H[c]	H$_2$	NH$_2$	H	A[n]	2.8	132	52										
H	H$_2$	NH$_2$	H	B[n]	48	—[a]	99	Aq. ethanol	139.5–[d] 141	2	1.2		50	60	49	Abs. ethanol	136–137.5[e]
H[f]	OH, H	NH$_2$	H	B	48		69	Benzene/acetone	158–159	0.5	2.4		27	60	34	Abs. ethanol	118.5–121.5[g]
NO$_2$	H$_2$	NH$_2$	H	B[h]	48		80	Abs. ethanol	181–182	0.5		4.8	—	60	36	Toluene	177–180
H[c]	H$_2$	N(CH$_3$)$_2$	NH$_2$	B	70		49	Ether	112–114		1.2		60	90	27	—[i]	195–196.5 (dec. 180)
NHCOCF$_3$[c]	H$_2$	NH$_2$	H	B	48		62	Chlorobenzene	191.5–193.5	11.4		4.4	—	90	95	Abs. ethanol	159–160.5
NH$_2$[c]	H$_2$	NH$_2$	H	B	60		50	Acetone/abs. ethanol	201.5–204	1.8		5.4	—	60	65	Abs. ethanol	111–113
H[c]	=O	NH$_2$	H	A	5	156	78	—[j]	gum	22	1.3		100	120	40		247–249[k]
H[l]	=O	NH$_2$	Br	A	3	130		Ethanol	127.5[m]–130	0.35	1.3		15	60		Ligroin	135–137[g]

[a] Room temperature unless noted. [b] M.p.'s are corrected to standards. [c] Prepared by the method of T. L. Fletcher and M. J. Namkung, *J. Org. Chem.*, **23**, 680 (1958). [d] Lit. m.p. 137°; J. L. Everett and W. C. J. Ross, *J. Chem. Soc.*, 1972 (1949). [e] Chromatographed before recrystallization, lit. m.p. 138°; see reference in preceding footnote. [f] Prepared by the method of H. L. Pan and T. L. Fletcher, *J. Org. Chem.*, **23**, 799 (1958). [g] Chromatographed before recrystallization. [h] To dissolve the amine (1 g.) it was warmed in a mixture of 40 ml. of acetone, 30 ml. of glacial acetic acid, and 12 ml. of water. Ethylene oxide (8 ml.) was added in portions during a 2-hr. period (40°), then the solution stood at room temperature. Otherwise the procedure is the same as method B. [i] The cooled reaction mixture was shaken with 600 ml. of chloroform and 80 ml. of 2*N* sodium bicarbonate. The chloroform layer was dried and evaporated to yield white crystals which were recrystallized from absolute ethanol and a chloroform–carbon tetrachloride mixture. [j] After the bomb reaction the crude red gum was washed with water, dried, taken up in chloroform, and the filtered solution used directly in the chlorinating step. [k] The cooled reaction mixture was stirred with ice and the chloroform solution separated and dried, after which it was chromatographed (chloroform) and the fractions evaporated to give a red oil which was characterized analytically as the 2,4-dinitrophenylhydrazone. The latter was recrystallized from a chlorobenzene-xylene mixture. [l] Reported by T. L. Fletcher, M. J. Namkung, and H. L. Pan, *Chem. and Ind.*, 660 (1957). [m] The amine (2.5 g.) gave a crude product which was recrystallized from 95% ethanol to give 0.67 g. of starting material. The filtrate was chromatographed (benzene-methanol), and purple crystals (0.35 g.) of the dihydroxy compound (not analyzed) were obtained. [n] For methods A and B see Experimental.

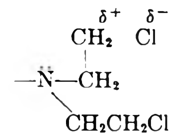
In cases where the amine was insoluble we added acetone to the mixture to effect solution. The yield and quality of the product was in general much better with the latter method. The 9-*N*,*N*-di-(β-hydroxyethyl)aminofluorene was prepared by reaction of 9-bromofluorene with diethanolamine.

In general, if the intermediate hydroxy compound was soluble in chloroform, we chlorinated with phosphorus pentachloride; otherwise, this step was carried out with phosphoryl chloride (see Table I).

Ultraviolet data for these nitrogen mustards and related substances are presented in Table III. It was first found that the spectrum of 2-*N*,*N*-di(β-chloroethyl)aminofluorene was very similar to that of 2-*N*,*N*-diethylaminofluorene and that the spectra in dilute alcoholic hydrochloric acid were changed, and again quite similar to each other. The spectrum of the methiodide of 2-*N*,*N*-diethylaminofluorene was also almost identical with that of the hydrochloride. The change in the spectrum of *N*,*N*-diethylaminofluorene, in going from neutral alcohol to 0.1*N* acidic alcohol (protonized nitrogen), or to the neutral solution of the methiodide (quaternized nitrogen) involved 1) a slight hypsochromic shift (309 mμ to 301 mμ) and 2) the appearance of new peaks (289, 266 mμ in the former case; 289, 267 mμ in the latter).

The spectrum of the analogous nitrogen mustard (Table III; No. 4,4a,5) in neutral solution had a maximum at 300 mμ. In acidic alcohol (0.1*N* concd. hydrochloric acid was added to absolute ethanol) there was no hypsochromic shift, but there was a new peak at 268 mμ and a pronounced shoulder. In more strongly acid solution (0.2*N*) the three characteristic peaks, at 301, 295, and 268 mμ, were observed. Apparently the β-chloroethyl group itself has the same effect in this molecule on the unshared pair of electrons as protonization in the *N*,*N*-diethylamino compound with respect to the small hypsochromic shift.

In the case of the nitrogen mustard, the slight tendency to ionize and the spatial orientation (I) would appear to have altered electronic oscillation enough so that protonization causes no further shift in the 300 mμ band. There is little, if any, ethylenimmonium ion formation, however, as the extra peaks which occur in the spectra of the $N(:H)(C_2H_5)_2^+$ and the $N(:CH_3)(C_2H_5)_2^+$ derivatives are not present in neutral solution. The steric or other effect is sufficient to require stronger (0.2*N*) acid to protonize fully the —$\ddot{N}R_2$ of the mustard.

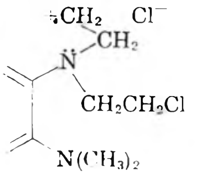


I

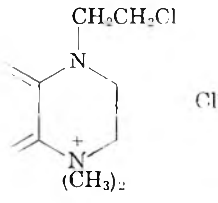
A similar series of spectra of the 7-nitro analogs of the foregoing compounds was studied. It had been observed[6] that the 400 mμ band of the 2-amino-7-nitrofluorene spectrum was hypsochromically displaced to 323 mμ in 0.1*N* alcoholic hydrochloric acid. Presumably, in neutral solution, the unshared electron pair contributed to extended conjugation and a more planar structure; protonization, even in 0.1*N* acid, was sufficient to render the electron pair unavailable for conjugation and the solution became colorless. We obtained the spectrum of this weak amine in more strongly acidic (3*N*) alcohol (Table III; No. 10): no further shift resulted but two shoulders appeared (301, 270 mμ) which were suggestive of the extra peaks found in the spectrum of protonized diethylaminofluorene (and the methiodide). However, in 6*N* acidic alcohol the main absorption (327 mμ) smoothly decreased to a minimum, about 250 mμ, with no hint of shoulders.

With 2-*N*,*N*-di(β-chloroethyl)amino-7-nitrofluorene (Table III; No. 16–19) a more strongly acidic solution (3*N* to 4*N*) was required to show band displacement from the visible part of the spectrum than with the 2-amino-7-nitro- or 2-dimethylamino-7-nitro derivatives. However, spectra of the 7-nitro mustard run at several different acid strengths showed no hint of the complexity observed, even at 0.2*N* acidity, with 2-*N*,*N*-di(β-chloroethyl)aminofluorene.

Thus far 7-*N*,*N*-dimethylamino-2-*N*′,*N*′-di(β-chloroethyl)aminofluorene has been obtained only as a crude oil and we have made no spectral observations. It is of interest, in this connection, that the spectrum of 2-*N*,*N*-dimethylamino-3-*N*′,*N*′-di(β-chloroethyl)aminofluorene (Table III; No. 20,21) is complex, showing four peaks even in neutral alcohol. Solution in acid does not change the absorption appreciably. At first we assumed that this resulted from the strong electron releasing influence of the —$\ddot{N}(CH_3)_2$ group making the unshared electron pair on the mustard group nitrogen sufficiently available for completion of ethylenimmonium ion formation (II). In the absence of sufficient present evidence, including a study of fluorene-3-nitrogen mustard and 3-*N*,*N*-diethylaminofluorene, it seems more likely that the multiple peaks, similar to those observed in the quaternary compounds above, resulted from quaternization of the —$\ddot{N}(CH_3)_2$ nitrogen (III).



II



III

Corresponding data for 7-trifluoroacetamido-2-*N*,*N*-di(β-chloroethyl)aminofluorene is also pre-

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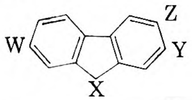
(6) R. B. Sandin, R. Melby, A. S. Hay, R. N. Jones, E. C. Miller, and J. A. Miller, *J. Am. Chem. Soc.*, **74**, 5073 (1952).

TABLE II[a]

ANALYTICAL VALUES OF NITROGEN-MUSTARDS AND RELATED COMPOUNDS

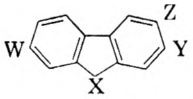


W	X	Y	Z	C		H		Cl		N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
H	H_2	$N(CH_2CH_2OH)_2$	H	75.81	75.65	7.11	7.08			5.20	5.17
H	H_2	$N(CH_2CH_2Cl)_2$	H	66.67	66.51	5.60	5.41	23.15	23.38	4.58	4.52
H	—OH,—H	$N(CH_2CH_2OH)_2$	H	71.56	71.57	6.71	6.59			4.91	4.98
H	—Cl,—H	$N(CH_2CH_2Cl)_2$	H					31.22	30.92	4.11	3.94
NO_2	H_2	$N(CH_2CH_2OH)_2$	H	64.95	64.92	5.77	5.71			8.91	9.10
NO_2	H_2	$N(CH_2CH_2Cl)_2$	H	58.13	57.90	4.59	4.65	20.19	19.99	7.98	7.70
H	H_2	$N(CH_3)_2$	$N(CH_2CH_2OH)_2$	73.04	73.47	7.74	7.76			8.97	9.09
H	H_2	$N(CH_3)_2$	$N(CH_2CH_2Cl)_2$	65.33	65.56	6.35	6.53	20.30	20.32	8.02	7.73
$NHCOCF_3$	H_2	$N(CH_2CH_2OH)_2$	H			5.04	5.16			7.37	7.47
$NHCOCF_3$	H_2	$N(CH_2CH_2Cl)_2$	H	54.69	54.82	4.10	4.39	16.99	16.95	6.71	6.42
H	$=O^b$	$N(CH_2CH_2Cl)_2$	H	55.21	55.14	3.82	3.96	14.18	14.31	14.00[b]	14.12[b]
H	$=O$	$N(CH_2CH_2Cl)_2$	Br	51.16	51.32	3.54	3.52	17.76[c]	17.43[c]	3.51	3.65
$N(CH_2CH_2OH)_2$	H_2	$N(CH_2CH_2OH)_2$	H	67.72	67.98	7.58	7.49			7.52	7.24
$N(CH_2CH_2Cl)_2$	H_2	$N(CH_2CH_2Cl)_2$	H	56.44	56.11	5.42	5.41	31.78	32.02	6.28	6.52
H	H_2	$N(C_2H_5)_2(CH_3)^+I^-$	H	57.00	57.10	5.85	5.87	33.46[d]	32.97[d]	3.69	3.69

[a] Analyses were made by the Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Melting points are corrected. [b] Analyzed as its 2,4-dinitrophenylhydrazone derivative. [c] Bromine analysis. [d] Iodine analysis.

TABLE III

ULTRAVIOLET SPECTRAL DATA[a] FOR REPORTED NITROGEN-MUSTARDS AND RELATED COMPOUNDS



No.	W	X	Y	Z	Concentration[b]	λ_{max}, mμ	ϵ_{max}[c]	$\lambda_{(shoulders)}$, mμ
1	H	H_2	$N(CH_2CH_3)_2$	H	3.33	309	3.46	
						301	1.31	293
2	H	H_2	$N(CH_2CH_3)_2$	H	3.68	289	1.06	226
					(0.1*N* HCl)	266	2.87	219
3	H	H_2	$N(C_2H_5)_2CH_3I$	H	2.5	301	1.29	270
						289	1.10	257
						267	2.53	
4	H	H_2	$N(CH_2CH_2Cl)_2$	H	2.5	300	2.95	340
								340
4a	H	H_2	$N(CH_2CH_2Cl)_2$	H	2.5	301	2.20	290
					(0.1*N* HCl)	268	1.36	279
								273
								220
					2.5	301	2.10	278
5	H	H_2	$N(CH_2CH_2Cl)_2$	H	(0.2*N* HCl)	295	1.87	273
						268	1.82	390
		H				307	0.38	
6	H	$N(CH_2CH_2Cl)_2$	H	H	3.33	297	0.42	285
						260	1.77	254
		·HCl				257	1.74	221
						227	1.10	
7	H	OH	$N(CH_2CH_2OH)_2$	H	2.25	318	2.88	254
		H				322	3.19	241
8	NO_2	H_2	NH_2	H	[e]	400		
						261		
9	NO_2	H_2	NH_2	H	(0.1*N* HCl)[f]	323	2.51	
						234		
10	NO_2	H_2	NH_2	H	3.41	325	2.08	270
					(3*N* HCl)	239	1.11	301
11	NO_2	H_2	NH_2	H	3.41	327	1.96	
					(6*N* HCl)	240	1.01	
12	NO_2	H_2	$—N(CH_3)_2$	H	3.28	492	2.44	
						272	1.65	
13	NO_2	H_2	$N(CH_3)_2$	H	3.28	317	2.53	
					(0.1*N* HCl)	238	1.17	
					3.28	321	2.30	
14	NO_2	H_2	$N(CH_3)_2$	H	(4N HCl)	241	0.98	
15[d]	NO_2	H_2	$—N(CH_3)_2$			491	0.97	
			.MeI[d]	H	0.983	314[d]	0.84	217
						279	0.95	

TABLE III *Continued*

No.	W	X	Y	Z	Concentration[b]	λ_{max}, mμ	ϵ_{max}[c]	$\lambda_{(shoulders)}$, mμ
16	NO_2	H_2	$N(CH_2CH_2Cl)_2$	H	3.44	400	2.56	
						269	1.52	
					3.3	404	2.17	
17	NO_2	H_2	$N(CH_2CH_2Cl)_2$	H	(0.2*N* HCl)	271	1.44	
					3.44	321	2.24	
18	NO_2	H_2	$N(CH_2CH_2Cl)_2$	H	(4*N* HCl)	244	0.88	
					2.064	323	1.94	
19	NO_2	H_2	$N(CH_2CH_2Cl)_2$	H	(6*N* HCl)	245	0.79	
						339	0.64	284
20	H	H_2	$N(CH_3)_2$	$N(CH_2CH_2Cl)_2$	2.5	295	1.20	274
						287	1.00	248
						254	4.14	
					2.5	340	0.64	284
21	H	H_2	$N(CH_3)_2$	$N(CH_2CH_2Cl)_2$	(0.2*N* HCl)	295	1.23	274
						287	1.03	248
						254	4.22	
22	CF_3CONH	H_2	$N(CH_2CH_2Cl)_2$	H	2.5	320	3.39	341
								240
					2.5			345
23	CF_3CONH	H_2	$N(CH_2CH_2Cl)_2$	H	(0.2*N* HCl)	316	2.98	393
								220
					2.5			
24	CH_3CONH	H_2	$N(CH_2CH_2Cl)_2$	H	(4*N* HCl)	312	2.79	283
						293	3.16	220
25	$N(CH_2CH_2Cl)_2$	H_2	$N(CH_2CH_2Cl)_2$	H	2.0	312	3.66	347
								323
					2.5	315	2.31	301
26	$N(CH_2CH_2Cl)_2$	H_2	$N(CH_2CH_2Cl)_2$	H	(0.2*N* HCl)			281
								270
								334
27	$N(CH_2CH_2OH)_2$	H_2	$N(CH_2CH_2OH)_2$	H	1.25	317	4.35	354
						300	1.79	292
					1.25	288	1.53	278
28	$N(CH_2CH_2OH)_2$	H_2	$N(CH_2CH_2OH)_2$	H	(0.1*N* HCl)	267	3.24	272
						262	3.05	252
						258	2.82	227
						220	3.49	
						209	5.45	

[a] These spectra were run on a Beckman DK-1 in 1 cm. silica cells. [b] Expressed as concentration in moles times 10^5, in absolute ethanol. [c] Expressed as ϵ max. times 10^{-4}. [d] The data seem to indicate that this is a mixture containing the unchanged $—N(CH_3)_2$ compound (491 mμ) and possibly the $—N(CH_3)^+{}_3I^-$ molecule (314 mμ). The latter band is observed in the spectrum of the hydrochloride as displaced hypsochromically from 492 mμ.

sented (Table III: No. 22,23,24). There is a slight hypsochromic shift in going from neutral to acid solution, and in strongly acidic alcohol a new peak and shoulders are apparent.

The case of the 2,7-bis(nitrogen mustard) (No. 25,26) is noteworthy and merits further study. When first dissolved in neutral alcohol the solution is colorless. Upon standing, especially in light, a yellow color appears which can be discharged with strong acid. Addition of a solution of this compound, which has been standing in light for a short time, to a solution of diphenylpicrylhydrazyl in alcohol discharges the color of the latter.[7] It is conceivable that, under the influence of light (and free radicals) and the electron releasing influence of the nitrogen mustard group, an equilibrium results which includes some of the compound having an ethylenimmonium ion on one of the rings. This form of the molecule would be stabilized like 2-amino-7-nitrofluorene by a contribution of the quinonoid structure containing the $=\overset{+}{N}<$ group on the other ring.[6]

We hope to make further studies with this 2,7-dimustard compound and with 2-*N*,*N*-di-β-chloroethylaminofluorene having strong electron donating groups at the 7-position. If we can obtain multiple absorption bands, as discussed above, but in neutral solution, we will then presumably have a molecule at least partially in the ethylenimmonium ion state.

EXPERIMENTAL

General preparation of di(β-hydroxyethyl)aminofluorenes. Method A.[3] A ratio of 4 to 9 moles of ethylene oxide to 1 mole of the amine was heated in a stainless steel bomb at 130–156° with 2*N* acetic acid (1 g. of amine to 1 ml. of acetic acid solution) for 2.5–13 hr.; the mole ratios and time depended on the nature of the amine. The bomb pressures ranged from 110–130 p.s.i. The crude product was ground in a mortar with warm water, neutralized with sodium carbonate or ammonium hydroxide solution, filtered, washed well with water, and dried. Usually the di(β-hydroxyethyl)-amino product was recrystallized from ethanol (Darco).

Method B.[5] One gram of the amine and 12 ml. of water were mixed and sufficient warm glacial acetic acid added to effect solution. Ethylene oxide (15 to 20 moles) was added to the cooled solution (30 to 40°). The higher ratio of oxide was used with weak amines and the solution was permitted to stand from 48–70 hr. The resulting mixture was neutralized and the product filtered and recrystallized, usually from 95% ethanol. In general, better yields and purer products resulted from method B.

General procedure for chlorinating di(β-hydroxyethyl)aminofluorenes. Method A. When the amine was soluble in chloroform it was chlorinated in this solvent with a slight molar excess of phosphorus pentachloride in a round bottom flask under reflux (drying tube) for 1 hr. The cooled solution was poured over ice and stirred and the chloroform layer separated, dried, and evaporated on the steam bath. The residue was purified by recrystallization from absolute ethanol or by dissolving in benzene and passing through a short column of alumina and then recrystallizing from absolute ethanol.

Method B. The di(β-hydroxyethyl)amine compound was dissolved in an excess of phosphoryl chloride (1 g. of amine to 2.5 ml. of phosphoryl chloride) in a round bottom flask and the mixture was heated on the hot water bath for 1 hr. under reflux (drying tube). The excess phosphoryl chloride was then distilled under vacuum on the steam bath. The resulting solid was dissolved in acetone and the solution poured over ice, with stirring and subsequent neutralization, to yield the fluorenyl mustard. This was recrystallized, after filtering and drying, usually from absolute ethanol.

9-N,N-Di(β-hydroxyethyl)aminofluorene. To 45 g. (0.184 mole) of 9-bromofluorene was added 37 g. (0.352 mole) of diethanolamine in 20 ml. of absolute ethanol; the mixture was heated for 1 hr. on the steam bath in a 300-ml. flask. This was then boiled on a hot plate for 10 min. with addition of 50 ml. of 95% ethanol. Darco was then added, boiling was continued for a few minutes, and the solution was filtered hot. Boiling water was added to the point of precipitation. A yield of 29 g. of white crystals resulted, m.p. 95–98.5°. Second and third crops gave an additional 16.6 g., m.p. 95–98°, giving a total yield of 91.5%.

An analytical sample was obtained after four recrystallizations from ether, m.p. 97.5–98° (cor.)

Anal. Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.92; H, 7.24; N, 5.42.

9-N,N-Di(β-chloroethyl)aminofluorene hydrochloride. To a suspension of phosphorus pentachloride, 1.93 g (0.0093 mole), in 20 ml. of dry chloroform in a 100 ml. flask equipped with a reflux condenser and a drying tube, 2.1 g. (0.0078 mole) of 9-*N*,*N*-di(β-hydroxyethyl)aminofluorene was gradually added in a few minutes. After refluxing for 1 hr. and cooling, the mixture was poured over ice and stirred. The chloroform solution was separated and evaporated yielding 2.65 g. (quant.) as the hydrochloride salt of the nitrogen mustard. Upon neutralization of a small sample, the amine came out as an oil. After heating the hydrochloride with a little 2*N* hydrochloric acid, the dried product was recrystallized from a chloroform-ether solution four times and once from ethanol to yield a white salt, melting over a range to 138°.

Anal. Calcd. for $C_{17}H_{18}Cl_3N$: Cl, 31.04; N, 4.09. Found: Cl, 31.77; N, 4.27.

2-N,N-Diethylaminofluorene methiodide. This was prepared in the usual way, the analytical sample being obtained after two recrystallizations from absolute ethanol, m.p. 183–184° (see Table II for analyses).

7-Dimethylamino-2-N,N-di-(β-chloroethyl)aminofluorene. Thus far, this has been obtained, as above, only as an oil

SEATTLE 5, WASH.

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[7] C. E. H. Bawn and S. F. Mellish, *Trans. Faraday Soc.*, **47**, 1216 (1951).

[CONTRIBUTION FROM STANFORD RESEARCH INSTITUTE AND VARIAN ASSOCIATES]

Identities of Ethyl Benzoylacetate 2,4-Dinitrophenylhydrazone and Its Derived Pyrazolone. Absolute Configuration of *syn* and *anti* Isomers

ROBERT M. SILVERSTEIN AND JAMES N. SHOOLERY

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Neither ethyl benzoylacetate 2,4-dinitrophenylhydrazone nor its cyclization product, the corresponding pyrazolone, has been correctly identified in the literature. The present work establishes these identities and the absolute configurations of the *syn* and *anti* isomers of the 2,4-dinitrophenylhydrazone. The argument rests on spectrometric evidence for coplanarity in the *anti* form and steric interference with coplanarity in the *syn* form.

The ease and the convenience by which deeply colored, high melting, crystalline 2,4-dinitrophenylhydrazones of aldehydes and ketones may be prepared often make them derivatives of choice for characterization. Unfortunately polymorphism and stereoisomerism occur frequently enough to warrant a *caveat.*[1] Characterization of β-keto esters with 2,4-dinitrophenylhydrazine under the usual strongly acidic conditions presents two additional hazards—decarboxylation, and cyclization to pyrazolones.

In the course of earlier work[2] we treated ethyl benzoylacetate at room temperature with a 2,4-dinitrophenylhydrazine reagent[3] and obtained a product which on recrystallization from acetic acid melted at 163–164° and had a correct analysis for a 2,4-dinitrophenylhydrazone plus a mole of acetic acid of crystallization. Recrystallization from ethanol-ethyl acetate followed by drying at 78° (1 mm.) gave a compound which melted at 164–166° and which gave the expected analytical values for the nonsolvated 2,4-dinitrophenylhydrazone. The infrared ($\lambda_{\max}^{\mathrm{CHCl_3}}$ 3.05 μ and 5.77 μ) and NMR spectra (Fig. 1b) were in accord with the postulated structure. The ultraviolet absorption peak was at 378 mμ.

The identity of the product was of some concern because it was also obtained by treating ethyl thiobenzoylacetate with 2,4-dinitrophenylhydrazine.[2] The literature reported that the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate melted at 222–223°[4] or at 246–247°[5] and absorbed maximally in chloroform at 379 mμ.[5] As a further complication, a more recent report by Khromos-Borisov[6] described the product of reaction between ethyl benzoylacetate and 2,4-dinitrophenylhydrazine as a pyrazolone, m.p. 160–161°.

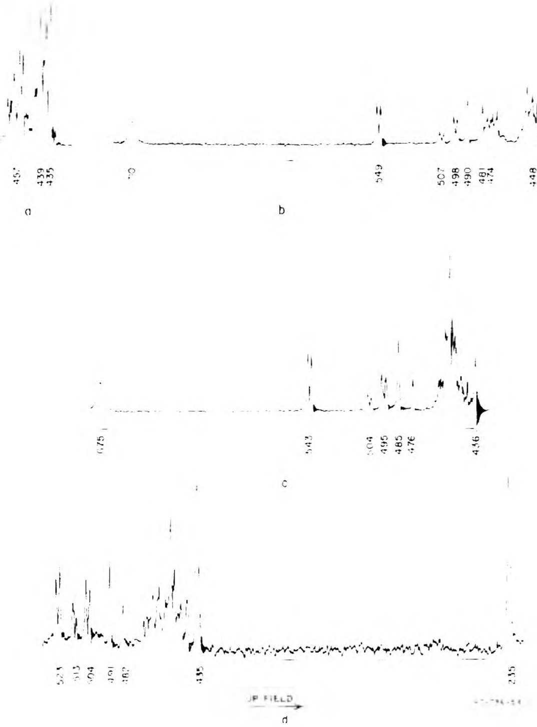

Fig. 1. NMR spectra

a. 2,4-DNP of acetophenone
b. 2,4-DNP of ethyl benzoylacetate (stable)
c. 2,4-DNP of ethyl benzoylacetate (unstable)
d. 1-(2,4-Dinitrophenyl)-3-phenyl-5-pyrazolone

It seems likely that the high melting derivative (246–247°) was the 2,4-dinitrophenylhydrazone of acetophenone resulting from decarboxylation. In fact, the properties of the authentic acetophenone derivative (m.p. 247–248°, $\lambda_{\max}^{\mathrm{CHCl_3}}$ 378 mμ) reported in the same paper[5] were almost identical with those for the compound purported to be the ethyl benzoylacetate derivative. Incomplete decarboxylation probably accounts for the melting point given[4] as 222–223°. The procedure of Khromos-Borisov[6] afforded us a product which melted at 163–164°, gave no melting point depression on admixture with our sample (m.p. 164–166°), and gave an infrared spectrum identical with that of our sample.

Attempts to cyclize the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate under acidic condi-

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(1) For a recent review of 2,4-dinitrophenylhydrazones, see M. E. Umstead (Penn State) Dissertation Abstract Vol. XVII No. 5, Publ. No. 20,982, microfilm 57-1520, University Microfilms, Ann Arbor, Mich.

(2) Z. Reyes and R. M. Silverstein, *J. Am. Chem. Soc.*, **80**, 6367, 6373 (1958).

(3) R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, John Wiley & Sons, New York, N. Y., 1948, p. 171.

(4) N. R. Campbell, *Analyst*, **61**, 391 (1936).

(5) G. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953).

(6) M. V. Khromos-Borisov, *Zhurn. Obshchei Khemii*, **25**, 136 (1955).

tions were unsuccessful; under forcing conditions, the 2,4-dinitrophenylhydrazone of acetophenone (m.p. 247–249°) was obtained. Rapid cyclization to the desired 1-(2,4-dinitrophenyl)-3-phenyl-5-pyrazolone was effected with sodium ethoxide in ethanol at room temperature. The pyrazolone melted at 203–204° and gave the required analytical values. There was no N–H absorption in the 3.0 μ region. The NMR spectrum (Fig. 1d) provided further confirmation for the identity of the pyrazolone.

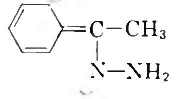
Addition of base to the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate immediately produced the deep magenta color of the anion. Disappearance of the color concomitant with cyclization afforded a convenient measure of rate of reaction. It should also afford a method for determining absolute configuration if the other isomer could be isolated, and if the rate of cyclization were faster than the rate of isomerization. The isomer in which the benzene ring and the 2,4-dinitro-substituted benzene ring are in the *syn* configuration must undergo isomerization prior to cyclization.

There are not very many reported instances of isolation of *syn* and *anti* isomers of 2,4-dinitrophenylhydrazone derivatives, and those usually depended either on the absence of an α-hydrogen as in substituted benzophenones, or on the presence of a group with which the NH group can effect hydrogen bonding and consequent stabilization of one isomer.[1,7] We were also aware that 2,4-dinitrophenylhydrazine derivatives undergo enolization at rates many times greater than those of parent ketones[1]; and the lability of β-keto-esters would argue against the likelihood of isolating both forms of the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate. However, the *syn* and *anti* isomers of the 2,4-dinitrophenylhydrazone acetophenone had been prepared[6] by heating the reactants in the absence of acid. Attempts to use this technique with ethyl benzoylacetate failed, but exposure of a benzene solution of the 2,4-dinitrophenylhydrazone to sunlight over a period of two weeks yielded a small amount of lower-melting (121–122.5°) orange material whose infrared spectrum (in chloroform) differed from that of the starting material only beyond 6 μ, and whose ultraviolet absorption maximum (in chloroform) occurred at 364 mμ—*i.e.*, a hypsochromic shift of 14 mμ. The maximum yield of low melting isomer was 5%. The low melting (unstable) form could be converted to the high melting (stable) form by acid catalysis, and there was virtually no detectable amount of the unstable form at equilibrium.

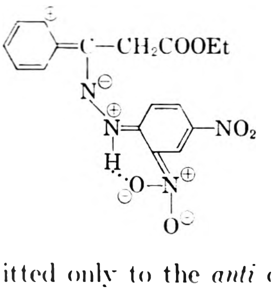
Reaction rate studies were carried out by adding excess sodium ethoxide in absolute ethanol to an absolute ethanolic solution of each isomer, and following the rate at which the absorption peak decreased. A clean pseudo-first-order reaction rate was obtained, and the rate constants for the stable and the unstable forms were identical ($k = 9.40 \times 10^{-3}$ sec.$^{-1}$). Obviously then, isomerization is much more rapid than cyclization, and nothing is learned about absolute configuration.

Molecular models show that coplanarity of both benzene rings and the C=N bond are possible in the *anti* configuration but sterically impossible in the *syn* (*syn* and *anti* refer to the configurations in which the benzene rings are on the same side and opposite sides of the C=N bond, respectively). The 14-mμ hypsochromic shift noted above can thus be taken as presumptive evidence for the syn configuration of the unstable form.

Nuclear magnetic resonance proved to be a remarkably informative tool for observing the effects of coplanarity or the lack of it in the system under consideration. The unsubstituted hydrazone of acetophenone[8] was prepared for orientation purposes. Its NMR spectrum (Fig. 1a) shows that resonance forms such as



contribute strongly to its structure. The shift due to reduction of electron density and magnetic anisotropy effects at the *ortho* positions is greater than that at the *meta* or *para* positions. This accounts for the down-field shifts of absorption peaks corresponding to two protons (multiplet centered on 457 cps.[9]); the remaining three protons show absorption centered on 439 cps. In the spectrum of the stable form (Fig. 1b) of the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate, we find the same two groups of peaks (centered at 474 and 448 cps. respectively) separated by 26 cps. compared with 18 cps. in acetophenone hydrazone. This increased separation would appear to be the result of additional resonance stabilization from a structure such as



which is permitted only to the *anti* configuration. In contrast, the unstable isomer (Fig. 1c) shows practically no separation of *ortho* from *meta* and

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(7) F. Ramirez and A. F. Kirby, *J. Am. Chem. Soc.*, **76**, 1037 (1954). D. Schulte-Frohlinde, *Ann.*, **622**, 43 and 47 (1959). H. van Duin, *Rec. trav. chim.*, **73**, 78 (1954). F. A. Isherwood and R. G. Jones, *Nature* **175**, 419 (1955).

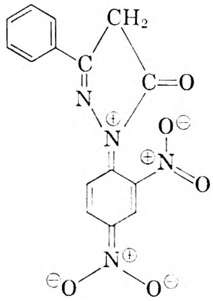
(8) H. Staudinger, *Ber.*, **49**, 1907 (1916).

(9) At 60 mc., relative to internal tetramethylsilane as reference; see Experimental.

para protons in the benzene ring because steric interference in the *syn* configuration between the benzene ring and the NH group prevents the necessary coplanarity.

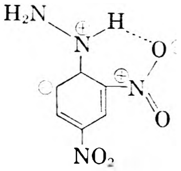
In the stable 2,4-dinitrophenylhydrazone, we also identify the doublet at 549 cps. as the proton between the two nitro groups, the pair of doublets at 507 and 498 cps. as the proton adjacent to one nitro group, and the pair of peaks at 490 and 481 cps. as the third proton on the nitro substituted ring. Looking at the peaks at 710 cps. (Fig. 1b) and at 675 cps. (Fig. 1c), which correspond to the NH proton in the stable and unstable forms respectively, we note that the strong intramolecular hydrogen bonding which leads to this large concentration-independent down-field shift is apparently weakened slightly in the unstable form presumably by steric interference between the benzene ring and the NH group. It will also be noted that, in the unstable form, all three protons on the nitro substituted ring are shifted upfield a few cycles per second. This could be due either to magnetic anisotropy of the adjacent aromatic ring or to decreased importance of electron withdrawing resonance structures.

The spectrum of 1-(2,4-dinitrophenyl)-3-phenyl-5-pyrazolone (Fig. 1d) shows that the doublet absorption peak of the proton between the two nitro groups is shifted upfield considerably (523 cps.) while those of the proton adjacent to one nitro group are shifted downfield slightly (513 and 504 cps.) and the peaks of the third proton are essentially unaffected (491 and 482 cps.). This behavior can be explained by considering the resonance form



which contributes to the structure of this molecule. The nitro group *ortho* to the pyrazolone ring is hindered by the carbonyl group; this would twist it out of the plane of the ring and diminish its tendency to withdraw electrons from the ring. Therefore, the shift of the absorption peak of the proton between the nitro groups would be decreased. On the other hand, if one of the nitro groups were unable to engage in resonance, the other would encounter less competition and should be more heavily involved than usual; this interpretation would account for the downfield shift of the other proton adjacent to it. Evidence for appreciable contribution to the structure by the resonance form having a plus charge in the *ortho* positions of the unsubstituted ring is seen in the moderate downfield shift (*ca.* 465 cps.) of those *ortho* proton peaks. However, steric resistance to complete coplanarity of the three rings is apparent from comparison with the greater shift noted above in the stable form of the 2,4-dinitrophenylhydrazone compound.

The spectrum of 2,4-dinitrophenylhydrazine itself shows essentially the same pattern for the three protons on the nitro substituted ring as was found for the 2,4-dinitrophenylhydrazones. The proton *ortho* to the hydrazine nitrogen is, however, shifted upfield about 18 cps., and this suggests that the resonance structure



is perhaps somewhat more important in this molecule than in the 2,4-dinitrophenylhydrazones.

In view of the discrepancies in the literature[4–6] regarding the identity of the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate and the pyrazolone derived therefrom, we note the presence in the 2,4-dinitrophenylhydrazone spectra of the NH peak (described above) and of the ethoxy proton peaks, CH_2 centered at about 249 cps. and CH_3 at about 75 cps. (off-scale in the Figures). None of these peaks appears in the pyrazolone spectrum. Although tautomeric forms for pyrazolone rings are frequently written,[10] the absence of NH or OH peaks in both the NMR and infrared spectra argues against appreciable equilibrium concentration of these forms in this compound. Furthermore, the ratio of the peak areas of the CH_2 protons (235 cps.) to the peak areas of the protons on the nitro substituted ring is in accord with the structure as written above.

EXPERIMENTAL

Visible and ultraviolet spectra and kinetic data were obtained on a Cary recording spectrophotometer model 14M. Infrared spectra were obtained on a Beckman spectrophotometer model IR 4. The proton nuclear magnetic resonance spectra were obtained on a Varian Associates high resolution 60 mc. spectrometer. Samples were dissolved in deuterated chloroform (traces of chloroform account for the peak at 435 cps.) containing tetramethylsilane as an internal reference standard. Shifts were measured in cycles per second relative to the reference.

Kinetic runs were carried out at 25° as follows: Approximately 5 mg. of the 2,4-dinitrophenylhydrazone was dissolved in 100 ml. of a 20% benzene-80% absolute ethanol solution. To 2 ml. of this solution contained in a 1 cm. cell, 1 ml. of a solution of 1.90 g. of sodium in 100 ml. of absolute ethanol was added with a syringe. The cell was quickly shaken and placed immediately in the spectrophotometer set at the predetermined absorption peak. Log A_0/A_t was

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(10) G. de Stevens, A. Halamandaris, P. Wenk, and L. Dorfman, *J. Am. Chem. Soc.*, 81, 6292 (1959).

plotted against time (sec.). The following tabulation presents crude data from a typical run:

Ethyl Benzoylacetate 2,4-dinitrophenylhydrazone (Stable)

λ_{max} 550 mμ, A_o 2.25

Time, sec.	20	40	60	80	100	120	140
A_t	1.92	1.57	1.28	1.06	0.90	0.75	0.65

2,4-Dinitrophenylhydrazone of ethyl benzoylacetate (stable). To a solution at room temperature of 6.5 g. (33.8 mmoles) of ethyl benzoylacetate in 25 ml. of 95% ethanol was added sufficient reagent (prepared according to Shriner and Fuson[3]) to furnish an equimolar amount of 2,4-dinitrophenylhydrazine. Precipitation occurred within a minute. The precipitate was filtered after 2 hr. at room temperature, washed with ethanol, and recrystallized from ethanol–ethyl acetate. Yield of orange crystals 10.7 g. (85%), m.p. 161.5–163.5°. An analytical sample was recrystallized from glacial acetic acid and air dried, m.p. 163–164°.

Anal. Calcd. for $C_{17}H_{16}O_6N_4 \cdot C_2H_4O_2$: C, 53.0; H, 4.64; N, 13.0. Found: C, 53.3, 53.2; H, 4.82, 4.61; N, 13.2, 13.3.

It was recrystallized from ethanol–ethyl acetate and dried overnight at 78° (1 mm.), m.p. 164–166°. $\lambda_{max}^{CHCl_3}$ 378 mμ (ϵ = 27,500), 241 mμ (ϵ = 16,350); $\lambda_{max}^{CHCl_3}$ 3.05 μ (NH), 5.77 μ (ester C = O). Peaks at 6.93 μ and 9.05 μ are present in the stable, but not present or very weak in the unstable form.

Anal. Calcd. for $C_{17}H_{16}O_6N_4$: C, 54.8 H, 4.33; N, 15.0. Found: C, 54.8; H, 4.50; N, 15.0.

2,4-Dinitrophenyl hydrazone of ethyl benzoylacetate (unstable form). Saturated solutions of the stable form of the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate in benzene were exposed in borosilicate glass flasks to sunlight over a period of 2 weeks. The solvent was removed *in vacuo*, and the residue was extracted with two 5-ml. portions of 95% ethanol. The ethanolic solution was evaporated *in vacuo*, and the residue was recrystallized four times from benzene–petroleum ether (b.p. 65–110°). The best yield was 5% of orange crystals, m.p. 121–122.5°. $\lambda_{max}^{CHCl_3}$ 364 mμ (ϵ = 24,760); 257 mμ (ϵ = 13,380); $\lambda_{max}^{CHCl_3}$ 3.05 μ (NH), 5.77 μ (C = O). A peak at 9.28 μ is present in the unstable form, but absent in the stable.

Anal. Calcd. for $C_{17}H_{16}O_6N_4$: N, 15.0. Found: N, 15.2.

Conversion of unstable to stable isomer. A solution of 2 mg. of the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate in 2 ml. of 95% ethanol containing a droplet (approx. 20 mg.) of concd. hydrochloric acid was boiled for 1 min. Removal of the solvent *in vacuo* left a residue which melted at 160–163° and gave an ultraviolet spectrum identical with that of the stable form. Thermal isomerization was relatively slow; thus a melt held at 140° took about 15 min. to resolidify so that remelting occurred at about 155–161°.

1-(2,4-Dinitrophenyl)-3-phenyl-5-pyrazolone. To a solution of 0.100 g. (0.260 mmole) of the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate in a mixture of 3 ml. benzene and 1 ml. of absolute ethanol at room temperature was added 0.5 ml. of a solution of 2.55 g. of sodium in 100 ml. of absolute ethanol. After 15 min. at room temperature, the solution was acidified with glacial acetic acid, and petroleum ether (b.p. 30–65°) was added until precipitation was complete. The precipitate was recrystallized twice from benzene–petroleum ether. Yield of light yellow crystals was 0.062 g. (71%), m.p. 203–204°. $\lambda_{max}^{CHCl_3}$ 350 mμ (ϵ = 10,800), 300 mμ (ϵ = 16,000); $\lambda_{max}^{CHCl_3}$ 5.86 μ (C = O), no peak at 3 μ.

Anal. Calcd. for $C_{15}H_{10}O_5N_4$: N, 17.2. Found: N, 17.5.

Acknowledgment. The combustion and ultraviolet and infrared data were obtained in the Analytical Section of Standard Research Institute. The authors are indebted to Mr. L. F. Johnson of Varian Associates for the NMR spectra. This work was supported by the Division Research Committee of Stanford Research Institute.

Menlo Park, Calif.

[Contribution from the Department of Chemistry, Duke University]

The Synthesis of 2-Aza-1,2-dihydrodicyclopentadienes[1,2]

CHICITA F. CULBERSON and PELHAM WILDER, Jr.

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The synthesis of the isomeric *endo-* and *exo*-2-aza-1,2-dihydrodicyclopentadienes and several *N*-alkyl derivatives is described.

The facile rearrangement of *endo*-dicyclopentadiene and its 1,2-dihydro derivative (I) to 9-substituted *exo* compounds by addition of halogen acids, sulfuric acid, acetic acid, or formic acid has been fully demonstrated.[3–5] Recently a study of 2-oxa-1,2-dihydro-*endo*-dicyclopentadiene (II) has indicated that under similar conditions, addition of acids to the norbornylene double bond leads to little or no structural rearrangement.[6] An investigation of the effects of a nitrogen atom in the 2-position of 1,2-dihydro-*endo*-dicyclopentadiene upon reactions with acidic reagents[7] has lead to the synthesis of several 2-aza derivatives. Only three *N*-alkylated derivatives of 2-aza-1,2-dihydro-*endo*-

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[1] Presented in part before the Division of Organic Chemistry, 135th National Meeting of the American Chemical Society, Boston, Mass., April 5–10, 1959.

[2] Taken in part from a dissertation submitted by Chicita F. Culberson to the Graduate School of Duke University in partial fulfillment of the requirements for the Ph.D. degree (1959).

[3] P. D. Bartlett and A. Schneider, *J. Am. Chem. Soc.*, 68, 6 (1946).

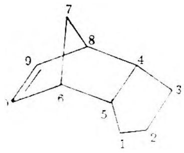
[4] H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, 67, 723, 1178 (1945); *J. Am. Chem. Soc.*, 68, 8 (1946).

[5] P. Wilder, Jr., Chicita F. Culberson, and G. T. Youngblood, *J. Am. Chem. Soc.*, 81, 655 (1959).

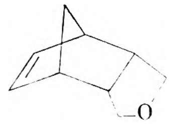
[6] Chicita F. Culberson, J. H. Seward, and P. Wilder, Jr., *J. Am. Chem. Soc.*, 82, 2541 (1960).

[7] P. Wilder, Jr. and Chicita F. Culberson, *J. Am. Chem. Soc.*, 81, 2027 (1959).

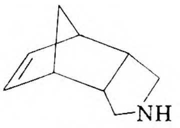
dicyclopentadiene (III) have been previously reported and the isomeric 2-aza-1,2-dihydro-*exo*-dicyclopentadiene (IV) represents the first member of a new heterocyclic ring system. The results



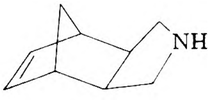
I



II



III

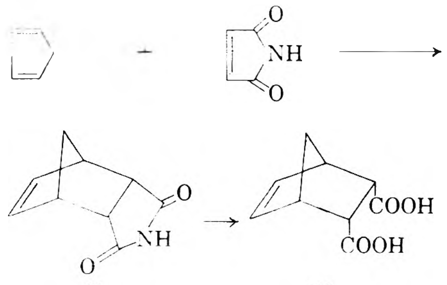


IV

of the synthetic portion of the study of the 2-aza system are presented here. The reactions of 2-aza-1,2-dihydrodicyclopentadiene will be discussed in a subsequent paper.

In 1954 Rice, Ried, and Grogan,[8] studying a number of cyclic amines for testing as hypotensive agents, found that *N*-alkyl derivatives of *endo*-bicyclo[2.2.1]-5-heptene-2,3-dicarboxylic acid imide (V) were readily reduced with lithium aluminum hydride to the corresponding *N*-substituted amines. Nine imides, butyl through dodecyl, were synthesized by treating the anhydride IX with the appropriate amine and then heating the reaction mixture for two hours at 160–170°. Arnold and Searle[9] had previously prepared a large number of *N*-substituted imides by refluxing the anhydride and the amine in an inert solvent while removing the water formed during the reaction. The boiling points of the imides prepared by Rice and also reported by Arnold are not in agreement, and it seemed possible that thermal rearrangement to the *exo* form might have occurred during the two-hour heating at 160–170°. It is shown in the present study, however, that the *N*-hexylamine reported by Rice does not have the *exo* configuration expected if the imide had rearranged during its synthesis.

Although the unsubstituted amine, 2-aza-1,2-dihydro-*endo*-dicyclopentadiene (III) has not been previously reported, the imide (V) from which it is prepared is known. Harvey[10] synthesized the imide by a Diels-Alder addition of maleimide and cyclopentadiene in ether at room temperature. The product, obtained in 93% yield, was hydrolyzed with base to the known *endo-cis*-bicyclo[2.2.1]-5-heptene-2,3-dicarboxylic acid (VI). The Diels-Alder addition was also effected by Blomquist and



V VI

Winslow[11] who showed the identity of this product to that obtained by refluxing the diammonium salt of the *endo-cis* acid VI in acetic anhydride. The same imide was prepared by Morgan *et al.*[12] by heating a mixture of the *endo* anhydride IX and ammonium carbonate to a temperature of 200°. The yield by this method was only 45%, doubtless because some of the product was lost by a reversal of the Diels-Alder addition of maleimide and cyclopentadiene. The reverse Diels-Alder reaction occurs[10] upon heating the imide V above its melting point (187°). The imide was also synthesized by Morgan in 84% yield by directing a stream of ammonia gas over the molten anhydride at 170° and a modification of this method has been used in the present study, maleimide required for the direct Diels-Alder reaction not being readily available.

Lithium aluminum hydride reduction of the unsubstituted imide V, essentially according to the method of Rice *et al.*,[8] yields the secondary amine, 2-aza-1,2-dihydro-*endo*-dicyclopentadiene (III). This amine, purified by repeated vacuum sublimation, is obtained as a soft colorless solid which absorbs carbon dioxide from the atmosphere with extreme rapidity. Because of this instability, a melting point of the pure amine is not a useful identification and an elemental analysis in close agreement with the calculated is difficult to obtain. The compound is more readily identified through its benzenesulfonamide and its picrate, which give good melting points and elemental analyses. The unsaturated secondary amine III is rapidly reduced, over Adams' catalyst at one atmosphere of hydrogen, to 2-azatetrahydro-*endo*-dicyclopentadiene, a compound also easily carbonated and best identified by its benzenesulfonamide or its picrate.

Two *N*-substituted derivatives of 2-aza-1,2-dihydro-*endo*-dicyclopentadiene were synthesized by lithium aluminum hydride reduction of the appropriate imides according to the method of Rice. The *N*-alkylated imides were prepared directly from the unsubstituted imide V by a modification of a method previously used to alkylate the potassium salts of phthalimide[13] and 2,4-thiazolidinedione.[14] A mixture of potassium carbonate, alkyl halide and unsubstituted imide in dimethylformamide, stirred for ten hours at room temperature, yielded the substituted imide. A separate synthesis and isolation of the potassium salt of the imide V was unnecessary. Under these mild conditions thermal rearrangement cannot occur and excellent yields of substituted imides are obtained. The *N*-methyl imide VII which gave a melting point in agreement with that reported by Arnold[9] was smoothly reduced to the corresponding *N*-methyl-2-aza-1,2-dihydro-*endo*-dicyclopentadiene (VIII). This liquid tertiary amine readily forms a methiodide and a picrate and is much more stable toward carbonation than the previously described secondary amines.

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[8] L. M. Rice, E. E. Ried, and C. H. Grogan, *J. Org. Chem.*, **19**, 884 (1954).

[9] H. W. Arnold and N. E. Searle, U. S. Patent **2,462,835** (1949).

[10] S. C. Harvey, *J. Am. Chem. Soc.*, **71**, 1121 (1949).

[11] A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, **10**, 149 (1945).

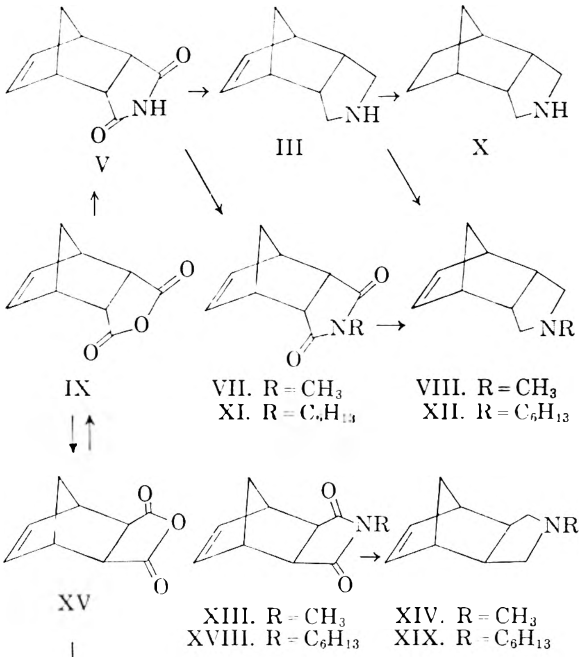
[12] M. S. Morgan, R. S. Tipson, A. Lowy, and W. E. Baldwin, *J. Am. Chem. Soc.*, **66**, 404 (1944).

The *N*-hexyl imide XI prepared at room temperature as described above was reduced with lithium aluminum hydride to the *N*-hexyl amine XII. The physical constants of this amine and the melting point of its methiodide are close to those reported by Rice, and quite different from those of the *exo* isomer described below. Both the *N*-hexyl and the *N*-methyl amines are also obtained in small yield by alkylation of the unsaturated secondary amine III with the appropriate alkyl halides.

To provide further evidence of the *endo* configuration of the amines discussed above the corresponding *exo* isomers were prepared. The *endo* anhydride IX was thermally equilibrated with its *exo* isomer by the method of Craig[15] and the *exo* anhydride was isolated by fractional recrystallization from benzene. Treating the *exo* anhydride with heat and ammonia gas yielded the *exo* imide XVI apparently contaminated with some of the *endo* isomer either because the starting anhydride was not pure or because thermal rearrangement occurred during the reaction. The *exo* imide XVI was purified by fractional recrystallization from water. Reduction with lithium aluminum hydride yielded 2-aza-1,2-dihydro-*exo*-dicyclopentadiene (IV), a liquid which carbonated immediately upon exposure to the atmosphere. The benzenesulfonamide and the picrate of this amine were shown by melting point and mixed melting point to be different from the derivatives obtained from the *endo* amine III. Catalytic reduction of the *exo* amine IV yielded the low-melting solid 2-azatetrahydro-*exo*-dicyclopentadiene (XVII).

The *N*-methyl and *N*-hexyl derivatives of 2-aza-1,2-dihydro-*exo*-dicyclopentadiene (IV) were prepared by lithium aluminum hydride reduction of the *N*-methyl and *N*-hexyl *exo* imides formed from the unsubstituted imide by the same method used to obtain the *endo* isomers.

The purity of the saturated and unsaturated secondary amines (III, X, IV, and XVII) and the *N*-methyl amines (VIII and XIV) was verified by gas chromatography. The secondary amines were passed through a two-meter column of firebrick and polypropylene glycol at 191°. The *N*-methyl amines were tested with a similar column at 150°. Under the conditions used the retention times of the unsaturated secondary amines III and IV were very close and small amounts of one mixed with the other would not have been detectable. But saturating the *endo* isomer decreased the retention time by about one minute while the retention time of the saturated *exo* isomer was increased about one minute. Thus the retention times of the saturated *endo* and *exo* isomers differed by two minutes and since these derivatives were prepared in high yield, their purity helps to establish the purity of the unsaturated amines.



EXPERIMENTAL[16]

endo-Bicyclo[2.2.1]-5-heptene-2,3-dicarboxylic acid imide (V). The imide was prepared by the method of Morgan *et al.*[12] except that a lower reaction temperature was used. A stream of ammonia gas was passed through 300 g. (1.8 moles) of solid *endo* anhydride IX at 120°. The solid melted and the temperature increased to 150° with a vigorous expulsion of water vapor and ammonia. When the melt resolidified, the reaction was allowed to cool and recrystallization of the product from water yielded 262 g. (88%) of the imide; 250 g. in the first crop, m.p. 185–186.5° and 12 g. in the second crop, m.p. 184–186.5°. A small amount of the imide was recrystallized again from water, m.p. 186–187° (reported[12] m.p. 186.5–187°).

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[13] J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2786 (1950).

[14] Chien-Pen Lo and E. Y. Shropshire, *J. Org. Chem.*, **22**, 999 (1957).

[15] D. Craig, *J. Am. Chem. Soc.*, **73**, 4889 (1951).

[16] Melting points and boiling points are uncorrected. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and Drs. Weiler and Strauss, 164 Banbury Road, Oxford, England.

exo-Bicyclo[2.2.1]-5-heptene-2,3-dicarboxylic acid imide (XVI). Ammonia gas was passed through 16.4 g. (0.10 mole) of solid *exo* anhydride XV[15] and the temperature was raised. At about 120° the solid melted and the temperature increased to 130° with a release of ammonia and water after which the melt resolidified. Several recrystallizations from water yielded 9.5 g. (71%) of the *exo* imide, m.p. 163.5–164°; mixed melting point with the *endo* isomer, 135–149°.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.24; H, 5.56. Found: C, 66.06; H, 5.46.

Alkylation of the endo and exo imides V and XVI. (1) With methyl iodide. A mixture of 8.2 g. (0.050 mole) of the unsubstituted imide, 7.2 g. (0.052 mole) of potassium carbonate, 9.0 g. (0.063 mole) of methyl iodide, and 40 ml. of dimethyl formamide was stirred vigorously overnight, diluted to about 400 ml. with water, and extracted with chloroform. The extract was washed with water, 10% sodium hydroxide, and again with water and was then dried over magnesium sulfate. Chloroform was removed under diminished pressure and the product, which solidified on standing, was recrystallized from water.

The *endo* imide V yielded 7.4 g. (85%) of the *N*-methyl derivative VII, m.p. 105–106° (reported[9] m.p. 105–107°).

The *exo* imide XVI yielded 5.9 g. (67%) of the *N*-methyl derivative XIII, m.p. 103–104°; mixed melting point with the *endo* isomer, 75–85°.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26. Found: C, 67.52; H, 6.06.

(2) With hexyl bromide. The imides were alkylated with hexyl bromide by the same method used to form the *N*-methyl derivatives except that 8.2 g. (0.052 mole) of the bromide was used.

The *endo* imide yielded 11.6 g. (94%) of the *N*-hexyl derivative XI, b.p. 137–138°, 0.25 mm., n_D^{24} 1.5023 (reported[8] b.p. 125–130°, 0.3 mm., n_D^{25} 1.4996).

From 4.1 g. (0.025 mole) of the *exo* imide XVI and half quantities of the other reagents indicated above, 5.8 g. (94%) of the *N*-hexyl derivative XVIII was obtained, b.p. 138–139°, 0.20 mm., n_D^{23} 1.5049.

Anal. Calcd. for $C_{15}H_{25}N$: C, 82.13; H, 11.49. Found: C, 81.96; H, 11.29.

The infrared spectra of the *exo* and *endo* *N*-hexyl imides are almost identical in the region 2.0–7.5 μ but are quite different at longer wave lengths, as would be expected.

2-Aza-1,2-dihydro-endo-dicyclopentadiene (III). A solution of 20.0 g. (0.53 mole) of lithium aluminum hydride in 600 ml. of dry ether was stirred rapidly while 32.6 g. (0.20 mole) of solid *endo* imide was added in small portions through a Gooch addition tube. The reaction was refluxed and stirred overnight and then it was immersed in an ice bath and neutralized by cautious addition of water. As soon as the white precipitate began to coagulate, the mixture was filtered rapidly with suction. The ether filtrate was dried over magnesium sulfate and the ether removed yielding 22 g. (82%) of crude *endo* amine III. The product could not be distilled due to solidification and sublimation. A sample was purified by repeated sublimation, m.p. 117–119° with sublimation at about 55°.

Anal. Calcd. for $C_9H_{13}N$: C, 79.95; H, 9.69. Found: C, 79.84; H, 9.81.

A benzenesulfonamide was prepared and recrystallized from 95% ethanol, m.p. 107–108°.

Anal. Calcd. for $C_{15}H_{17}NO_2S$: C, 65.42; H, 6.22. Found: C, 65.26; H, 6.24.

A picrate was prepared, m.p. 196.5–198°.

Anal. Calcd. for $C_{15}H_{16}N_4O_7$: C, 49.45; H, 4.43. Found: C, 49.57; H, 4.19.

2-Azatetrahydro-endo-dicyclopentadiene (X). The *endo* amine III (2.03 g., 0.015 mole) in 50 ml. of absolute ethanol was reduced at room temperature over Adams' catalyst with hydrogen at atmospheric pressure. In less than 25 min. uptake of hydrogen was complete. Solvent was removed under diminished pressure and the residue was taken up in ether and transferred to a sublimation tube. The ether was removed and the product sublimed under reduced pressure yielding 1.84 g. (90%) of the saturated amine X, m.p. 123–124° with sublimation beginning at about 75° and softening at about 105°.

Anal. Calcd. for $C_9H_{15}N$: C, 78.77; H, 11.02. Found: C, 78.91; H, 11.01.

A benzenesulfonamide was prepared and recrystallized from absolute ethanol, m.p. 168–168.5°.

Anal. Calcd. for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90. Found: C, 64.80; H, 6.76.

A picrate was prepared and recrystallized from 95% ethanol, m.p. 215–217° dec.

Anal. Calcd. for $C_{15}H_{18}N_4O_7$: C, 49.18; H, 4.95. Found: C, 49.22; H, 5.03.

Alkylation of the endo amine III *with hexyl bromide. N-Hexyl-2-aza-1,2-dihydro-endo-dicyclopentadiene* (XII). A mixture of 6.75 g. (0.05 mole) of the *endo* amine III, 8.25 g. (0.05 mole) of hexyl bromide, and 2.65 g. (0.025 mole) of sodium carbonate in 25 ml. of absolute ethanol was stirred under reflux for 48 hr. Some ethanol was removed under diminished pressure and the residue was taken up in ether and water. The aqueous layer was acidified with 10% hydrochloric acid and extracted with ether to remove unchanged hexyl bromide. The aqueous solution was then made basic and extracted with ether. This extract was washed with water and dried over magnesium sulfate. Removal of the ether and distillation of the residue yielded 4.1 g. (37%) of the *N*-hexyl amine XII, b.p. 96–97°/0.6 mm., n_D^{30} 1.4872 (reported[8] b.p. 83–85°/0.3 mm., n_D^{25} 1.4873).

A methiodide was prepared and purified by dissolving in absolute ethanol and precipitating with anhydrous ether, m.p. 171–172° (reported[8] m.p. 175°).

N-Hexyl-2-aza-1,2-dihydro-endo-dicyclopentadiene (XII). Ten grams (0.040 mole) of the *N*-hexyl imide XI, reduced with lithium aluminum hydride according to the method of Rice *et al.*,[8] yielded 6.95 g. (78%) of the *N*-hexyl amine XII, b.p. 90–91.5°/0.15 mm.

A methiodide was prepared, m.p. 169.5–170.5°; a mixed melting point with the methiodide of the *N*-hexyl amine obtained by alkylation of the *endo* amine III was not depressed.

Methylation of the endo amine III. *N-Methyl-2-aza-1,2-dihydro-endo-dicyclopentadiene* (VIII). A solution of 6.75 g. (0.05 mole) of the *endo* amine III in 50 ml. of benzene was treated dropwise with stirring with 7.0 g. (0.05 mole) of methyl iodide. After 20 min. the benzene was extracted with water and the aqueous solution made basic with 10% sodium hydroxide and extracted with ether. The ether extract was washed with water and dried over magnesium sulfate. Removal of the ether and distillation of the residue yielded 1.47 g. (20%) of the *N*-methyl amine VIII, b.p. 84–85°/15 mm.

A methiodide was prepared, m.p. 254–256°; a mixed melting point with the derivative of the *N*-methyl amine obtained by reduction of the *N*-methyl imide VII was not depressed.

N-Methyl-2-aza-1,2-dihydro-endo-dicyclopentadiene (VIII). Twenty-seven grams (0.15 mole) of the solid *N*-methyl imide VII was added in small portions to a solution of 13 g. (0.35 mole) of lithium aluminum hydride in 800 ml. of dry ether. After stirring under reflux for 15 hr., the reaction was worked up in the usual way. Distillation of the crude product yielded 20.0 g. (89%) of the *N*-methyl amine, b.p. 80–81°/15 mm., n_D^{23} 1.5050.

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13. Found: C, 80.61; H, 10.13.

From the amine a methiodide was prepared and purified by precipitation from absolute ethanol with anhydrous ether, m.p. 256.5–257.5°.

Anal. Calcd. for $C_{11}H_{18}IN$: C, 45.37; H, 6.23. Found: C, 45.28; H, 6.42.

A picrate was prepared and recrystallized from 95% ethanol, m.p. 222–223° dec.

Anal. Calcd. for $C_{16}H_{18}N_4O_7$: C, 50.13; H, 4.73. Found: C, 50.11; H, 4.75.

2-Aza-1,2-dihydro-exo-dicyclopentadiene (IV). The *exo* amine IV was prepared from the *exo* imide XVI by exactly the same method used to prepare the *endo* isomer. From 20 g. (0.12 mole) of the imide was obtained 11.1 g. (68%) of the *exo* amine IV after one distillation, b.p. 89–90°/16 mm. A sample was further purified by distillation, b.p. 73–74°/7.5 mm.

Anal. Calcd. for $C_9H_{13}N$: C, 79.95; H, 9.69. Found: C, 79.58; H, 9.89.

A benzenesulfonamide was prepared, m.p. 113–113.5°; mixed melting point with the benzenesulfonamide of the *endo* amine III, 86–92°.

Anal. Calcd. for $C_{15}H_{17}NO_2S$: C, 65.42 H, 6.22. Found: C, 65.26; H, 6.26.

A picrate was prepared, m.p. 196.5–198° dec.; mixed melting point with the picrate of the *endo* isomer, 185–193° dec.

Anal. Calcd. for $C_{15}H_{16}N_4O_7$: C, 49.45; H, 4.43. Found: C, 49.60; H, 4.47.

2-Azatetrahydro-exo-dicyclopentadiene (XVII). From 2.03 g. (0.015 mole) of the *exo* amine IV dissolved in 25 ml. of absolute ethanol and reduced at one atmosphere of hydrogen over Adams' catalyst, 1.81 g. (89%) of the saturated amine was obtained after two sublimations. A sample was prepared by resublimation, m.p. 44–45°.

Anal. Calcd. for $C_9H_{15}N$: C, 78.77; H, 11.02. Found: C, 78.78; H, 11.27.

A benzenesulfonamide was prepared, m.p. 100–101°; mixed melting point with the benzenesulfonamide of the saturated *endo* amine X, 98–124°.

Anal. Calcd. for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90. Found: C, 64.64; H, 6.78.

N-Hexyl-2-aza-1,2-dihydro-exo-dicyclopentadiene (XIX). A solution of 4.5 g. (0.018 mole) of the *N*-hexyl imide in anhydrous ether was added slowly to 1.7 g. (0.046 mole) of lithium aluminum hydride in anhydrous ether. The reaction was worked up in the usual way and after one distillation 3.8 g. (95%) of the *N*-hexyl amine, b.p. 94–95°/0.2 mm., was obtained.

Anal. Calcd. for $C_{15}H_{25}N$: C, 82.13; H, 11.49. Found: C, 81.96; H, 11.29.

A methiodide was prepared by dissolving the amine in absolute ethanol and adding excess methyl iodide. After a short time anhydrous ether was added to precipitate the derivative which was purified by redissolving in absolute ethanol and precipitating with anhydrous ether, m.p. 204–206°, mixed melting point with the methiodide of the *endo* isomer XII, 111–163°.

Anal. Calcd. for $C_{16}H_{28}IN$: C, 53.18; H, 7.81. Found: C, 53.06; H, 8.05.

N-Methyl-2-aza-1,2-dihydro-exo-dicyclopentadiene (XIV). From 5.0 g. (0.028 mole) of the *N*-methyl imide XIII reduced with 2.5 g. (0.066 mole) of lithium aluminum hydride in 150 ml. of anhydrous ether was obtained 4.1 g. (98%) of the *N*-methyl amine after one distillation, b.p. 74–77°/14 mm. A sample was further purified by redistillation, b.p. 77–78°/14 mm., n_D^{23} 1.4995.

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13. Found: C, 80.72; H, 10.13.

A methiodide was prepared, m.p. 273.5–274.5°; mixed melting point with the methiodide of the *endo* *N*-methyl amine VIII, 224–253°.

Anal. Calcd. for $C_{11}H_{18}IN$: C, 45.37; H, 6.23. Found: C, 45.59; H, 6.20.

A picrate was prepared, m.p. 225–228° dec.; mixed melting point with the picrate of the *endo* isomer, 222.5–225° dec.

Anal. Calcd. for $C_{16}H_{18}N_4O_7$: C, 50.13; H, 4.73. Found: C, 49.89; H, 4.82.

Gas chromatography: Of the secondary amines. A modified Perkin-Elmer Model 154B vapor fractometer was used. The 6 mm. × 2 m. column was packed with one part Union Carbide polypropylene glycol-1025 on four parts firebrick (Fischer Columpak, 30–60 mesh, acid washed) by weight.[17] The retention times at 191° and 35 ml./min. helium flow are given below:

Amine	Retention Time, Min.
III	7.6
X	6.8
IV	7.3
XVII	8.3

Except for amines III and IV the retention times were sufficiently different to prove the absence of each of the other amines. Since the retention times of the saturated amines are quite different, the analysis of these derivatives helps to establish the purity of the unsaturated amines with respect to each other.

Of the N-methyl amines. A Model 154C Perkin-Elmer vapor fractometer was used. The 6 mm. × 2 m. column contained 1:4 by weight Union Carbide polypropylene glycol-1025 on Johns-Manville Chromosorb W (30/60). At 150° and about 65 ml./min. helium flow the retention times were 8.8 min. for the *endo* isomer VIII and 7.6 min. for the *exo* isomer XIV.

Acknowledgment. The support of this research by a Research Grant (CY-4298 C1) of the National Institutes of Health, Public Health Service, and, in part, by a Grant-in-aid of the Allied Chemical Corp., is greatly appreciated. The authors wish to thank Dr. L. D. Quin for his assistance with the gas chromatographic studies.

DURHAM, N. C.

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(17) This column had been used for some time and the exact proportion of liquid to solid phase was no longer precisely known.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MAINE]

Potential Cancerocidal Agents. I. The Aromatic System of Podophyllotoxin (Part A)[1,2]

GEORGE R. PETTIT AND DAVID S. ALKALAY

Received January 4, 1960

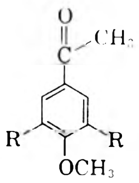
A number of tertiary amines, containing certain structural features of the tumor-damaging natural product podophyllotoxin, have been prepared for cancer chemotherapeutic studies.

The extended (1820–1942) appearance of podophyllum, the dried roots and rhizomes of certain Podophyllum species, in the U. S. Pharmacopoeia was due to its early popularity in this country as a cathartic and cholagogue.[3] Although podophyllum had received some application in early American medicine as a remedy for cancer, it was not until recently that the natural product was shown to be an effective antimitotic agent and actually useful in the treatment of condyloma acuminatum.[3]

The tumor-necrotizing action of podophyllotoxin[3,4] (I), one of the numerous components of podophyllum, is now well established; however, the unfavorable toxicity and water solubility of this substance has limited its usefulness.[5] Consequently, a variety of podophyllotoxin analogs have been prepared in attempts to provide the antitumor activity of I with a molecule presenting more desirable pharmacological properties.[6]

The present investigation was initiated in order to evaluate the effect of incorporating a dialkylaminoalkyl substituent into a molecule containing the oxygenated aromatic system of podophyllotoxin (I). Synthesis of the podophyllotoxin analog illustrated by structure IVa and several related substances appeared to offer an attractive test of this approach to useful antimitotic agents.

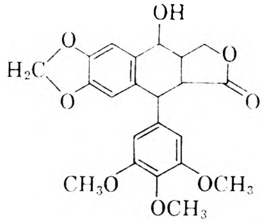
Preparation of the required compounds (IVa–e) was accomplished employing the route illustrated by the generalized formulas II→IV. Conversion of 3,4,5-trimethoxybenzoyl chloride[7] to 3,4,5-trimethoxyacetophenone (IIa), using the malonic ester procedure described by Walker and Hauser,[8] provided the necessary starting material. Condensing 3,4,5-trimethoxyacetophenone with formaldehyde and the appropriate secondary amine



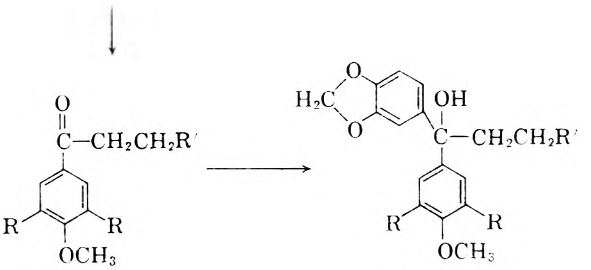
II

IIa. $R = OCH_3$

b. $R = H$



I



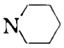
III IV

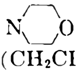
IIIa. $R = OCH_3$, $R' = N(CH_3)_2$

b. $R = OCH_3$, $R' = N(CH_2CH_3)_2$

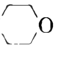
c. $R = OCH_3$, $R' = N(CH_2CH_2OH)_2$

d. $R = OCH_3$, $R' = N(CH_2CH_2Cl)_2$

e. $R = OCH_3$, $R' = N$ 

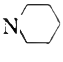
f. $R = OCH_3$, $R' = N$ 

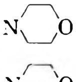
g. $R = H$, $R' = N(CH_2CH_2OH)_2$

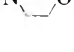
h. $R = H$, $R' = N$ 

IVa. $R = OCH_3$, $R' = N(CH_3)_2$

b. $R = OCH_3$, $R' = N(CH_2CH_3)_2$

c. $R = OCH_3$, $R' = N$ 

d. $R = OCH_3$, $R' = N$ 

e. $R = H$, $R' = N$ 

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[1] Abstracted in part from the Master of Science thesis submitted by D. S. Alkalay to the Graduate School, University of Maine, August 1959.

[2] This investigation was aided by Grant T-79 from the American Cancer Society.

[3] An excellent review of the history, chemistry, and pharmacology of podophyllum has been prepared by J. L. Hartwell and A. W. Schrecker, *Fortschritte der Chemie organischer Naturstoffe*, Vol. XV, L. Zechmeister, ed., Springer-Verlag, Vienna, Austria, 1958, p. 83.

[4] The chemistry of podophyllotoxin has also been reviewed by W. M. Hearon and W. S. MacGregor, *Chem. Revs.*, **55**, 957 (1955).

[5] For example, consult: G. B. Mider, *J. Nat. Cancer Inst.*, **19**, 217 (1957), and H. Seliger, *Krebsarzt*, **10**, 357 (1955).

[6] The following recent studies are pertinent to this subject: E. A. Fehnel and J. E. Stuber, *J. Org. Chem.*, **24**, 1219 (1959); M. Maturová, J. Malinský, and F. Santavý, *J. Nat. Cancer Inst.*, **22**, 297 (1959); J. Rutschmann and J. Renz, *Helv. Chim. Acta*, **42**, 890 (1959).

[7] K. H. Slotta and H. Heller, *Ber.*, **63**, 3029 (1930).

[8] H. G. Walker and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 1386 (1946).

hydrochloride led to the Mannich bases[9] represented by structures IIIa–h.

The recent work of Gensler and Stouffer[10] indicated that employing the lithium derivative of 3,4-methylenedioxybromobenzene would be superior to using the corresponding magnesium Grignard reagent to effect conversion of the intermediate Mannich bases (*e.g.* IIIa) to the tertiary alcohols (IVa–e). The desired products (IVa–e) were indeed readily prepared by allowing a tetrahydrofuran solution of 3,4-methylenedioxyphenyllithium to react at low temperature (Dry Ice–chloroform) with the respective aminoketone (III).

Interest in determining the chemotherapeutic value of several analogous compounds prompted preparation of the *N*-bis(2-hydroxyethyl) aminoketones, IIIc and IIIg, *N*-bis(2-chloroethyl)-amino-3′,4′,5′-trimethoxypropiophenone (IIId) hydrochloride, and α-[2-(*N*-morpholino)ethyl]-α-(*p*-methoxyphenyl)piperonyl alcohol (IVe).

EXPERIMENTAL[11]

β-Bis(2-hydroxyethyl)amino-4′-methoxypropiophenone (IIIg). To a solution composed of *p*-methoxyacetophenone (150 g., 1 mole), diethanolamine hydrochloride (156 g., 1.1 moles), hydrochloric acid (1 ml.) and ethanol (150 ml.) was added 60 g. of paraformaldehyde. After heating for 2 hr. at reflux, a second portion of paraformaldehyde (30 g.) was added and heating was continued an additional hour before concentrating the solution to a viscous yellow oil (460 g.) *in vacuo*. Addition of acetone (2.5 l.) precipitated the crude oily hydrochloride; weight 198 g. after drying (*in vacuo*). An aqueous solution of the hydrochloride was treated with excess sodium carbonate solution and the liquid free base which separated was isolated and added to the chloroform extract of the remaining solution. Removal of solvent from the dry (magnesium sulfate) chloroform solution gave the crude base (IIIg) as an oil which solidified to an oily yellow solid after drying (12 hr. *in vacuo*) and cooling; yield, 114 g. (42.7%), m.p. 25–32°.

A 70-g. sample of crude product (IIIg) from a similar experiment was distilled through a 12-cm. Vigreux column. The main fraction (13 g.) boiled at 126–134° (0.7–0.8 mm.) and solidified during overnight storage. Recrystallization from ethyl acetate gave 11 g. of pale yellow crystals melting at 49–52°. Two additional recrystallizations from the same solvent afforded pure colorless crystals, m.p. 58–59°, γ_{max}^{KBr} 3360 and 1658 cm.$^{-1}$

Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.17; H, 7.81; N, 5.18.

β-Bis(2-hydroxyethyl)amino-3′,4′,5′-trimethoxypropiophenone (IIIc). The crude oily hydrochloride (5.3 g., 34.5%) derived from 3,4,5-trimethoxyacetophenone[8] (8.4 g., 0.04 mole), diethanolamine hydrochloride (5.25 g., 0.04 mole) and paraformaldehyde (3 g.) was converted to the free base IIIc (3.8 g., 29.2%) as described above (*cf.*, IIIg). A portion of the product (2 g.) was distilled through a 12-cm. Vigreux column and the fraction (0.5 g.) boiling at 108–115° (0.07–0.08 mm.) collected, γ_{max}^{pure} 3400 and 1670 cm.$^{-1}$

Anal. Calcd. for $C_{15}H_{25}NO_4$: C, 58.70; H, 7.70; N, 4.28. Found: C, 58.55; H, 7.52; N, 4.21.

β-Bis(2-chloroethyl)amino-3′,4′,5′-trimethoxypropiophenone (IIId) *hydrochloride.* A mixture composed of paraformaldehyde (3.6 g.), bis(2-chloroethyl)amine hydrochloride[12] (14.2 g., 0.08 mole), 3,4,5-trimethoxyacetophenone[8] (16.8 g., 0.08 mole), ethanol (12 ml.), and 1 ml. of hydrochloric acid was heated at reflux during 45 min. A second portion of ethanol (30 ml.) was added and heating continued over a 7-hr. period. The reaction mixture was allowed to cool (room temperature) overnight before collecting the colorless crystalline product; weight 4.4 g. (14%), m.p. 148–150°. Two recrystallizations from ethanol gave pure crystals melting at 151°.

Anal. Calcd. for $C_{16}H_{23}Cl_3NO_4$: C, 47.95; H, 6.04; Cl, 26.54; N, 3.50. Found: C, 47.84; H, 6.15; Cl, 26.40; N, 3.28.

β-N-Piperidino-3,4,5-trimethoxypropiophenone (IIIe). Treating an aqueous solution of *β-N*-piperidino-3,4,5-trimethoxypropiophenone hydrochloride[13] with sodium carbonate solution gave the free base (IIIe) as a colorless solid, m.p. 78–79°. Three recrystallizations from ethanol-water raised the melting point to 81.5°.

Anal. Calcd. for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.22; H, 8.12; N, 4.71.

β-N-Morpholino-3,4,5-trimethoxypropiophenone (IIIf). A mixture of 3,4,5-trimethoxyacetophenone[8] (8.4 g., 0.04 mole) morpholine hydrochloride (5.0 g., 0.04 mole), paraformaldehyde (1.8 g.), ethanol (12 ml.), and 0.3 ml. of hydrochloric acid was heated to reflux. After 1 hr., an additional 1.2 g. of paraformaldehyde and 10 ml. of ethanol were added to the solution and heating continued for a total of 3 hr. The reaction mixture was concentrated to *ca.* one-half its original volume under water-aspirator vacuum and diluted with acetone (100 ml.). The resulting mixture was warmed and then allowed to cool overnight at room temperature. The principal crystalline fraction afforded 8.4 g. melting at 192–197°, while a second crop weighed 0.4 g. and melted at 201–203°; providing a total yield of 74.5%. Three recrystallizations from ethanol gave an analytical sample of *β-N-morpholino-3,4,5-trimethoxypropiophenone hydrochloride* as colorless crystals, m.p. 206–207°.

Anal. Calcd. for $C_{16}H_{24}ClNO_5$: C, 55.57; H, 7.00; Cl, 10.25; N, 4.05. Found: C, 55.80; H, 6.90; Cl, 10.29; N, 4.18.

The free base (IIIf) was obtained as a colorless solid, m.p. 95–96°, from aqueous sodium carbonate solution. Recrystallization from ethanol-water did not change the melting point.

Anal. Calcd. for $C_{15}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.97; H, 7.34; N, 4.30.

α-[2-(Dimethylamino)ethyl]-α-(3,4,5-trimethoxyphenyl)-piperonyl alcohol (IVa). To a stirred solution (under nitrogen) of 3,4-methylenedioxybromobenzene[10,14] (2.7 g., 0.0135 mole) in 15 ml. of anhydrous tetrahydrofuran, cooled to −65° (Dry Ice-chloroform), was added 6.8 ml. of ethereal 2*N* butyllithium.[15] After a 7-min. period had elapsed, an anhydrous solution of *β*-dimethylamino-3,4,5-trimethoxypropiophenone (IIIa, 3.6 g., 0.0135 mole), prepared from the corresponding hydrochloride,[13] in 15 ml. of tetrahydrofuran was added all at once. Stirring was continued an additional 20 min. before removing the cold bath and for 90 min. after cooling was discontinued. The mixture was stored overnight at room temperature before removing (at 30–40°) the solvent *in vacuo*. Ammonium chloride solution was added to the residue and the crude waxy product collected, washed with water, and recrystallized from acetone; yield, 1.9 g. (38%), m.p. 110–120°. Two recrystallizations from acetone-water, followed by one from ether, gave an analytical sample as colorless crystals, m.p. 138.5–139.5°.

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[9] The Mannich reaction has been reviewed by F. F Blicke, *Org. Reactions*, **1**, 303 (1942). A more recent survey has been prepared by K. W. Merz, *Pharmazie*, **11**, 505 (1956).

[10] W. J. Gensler and J. E. Stouffer, *J. Org. Chem.*, **23**, 908 (1958).

[11] Melting points are uncorrected and were observed using the Fisher-Johns apparatus. Boiling points are also uncorrected. The infrared spectra were determined by Messrs. E. Thomas and R. Young of this laboratory. Microanalyses were provided by Dr. A. Bernhardt, Max Planck Institut, Mulheim, Germany.

[12] F. G. Mann, *J. Chem. Soc.*, 461 (1934).

[13] E. Haggett and S. Archer, *J. Am. Chem. Soc.*, **71**, 2255 (1949).

[14] K. N. Campbell, P. F. Hopper, and B. K. Campbell, *J. Org. Chem.*, **16**, 1736 (1951).

[15] H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

Anal. Calcd. for $C_{21}H_{27}NO_6$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.85; H, 6.94; N, 3.79.

α-[2-(Diethylamino)ethyl]-α-(3,4,5-trimethoxyphenyl)piperonyl alcohol (IVb). A sample of this substance was prepared employing the general procedure described above (*cf.*, IVa). The crude product from a solution of 3,4-methylenedioxybromobenzene (3.6 g., 0.018 mole) in anhydrous tetrahydrofuran (30 ml.), ethereal 2*N* butyllithium (9 ml.), and a solution of β-*N*-diethylamino-3,4,5-trimethoxypropiophenone (IIIb, 5.3 g., 0.018 mole), prepared from the hydrochloride derivative[13] in 30 ml. of anhydrous tetrahydrofuran, was recrystallized from ethanol-water; weight 3.5 g. (46.7%), m.p. 77–80°. Four recrystallizations from methanol gave a pure sample of colorless crystals melting at 108°.

Anal. Calcd. for $C_{23}H_{31}NO_6$: C, 66.16; H, 7.49; N, 3.36. Found: C, 66.02; H, 7.60; N, 3.54.

α-[2-(N-Piperidino)ethyl]-α-(3,4,5-trimethoxyphenyl) piperonyl alcohol (IVc). To a solution of 3,4-methylenedioxy bromobenzene (4.02 g., 0.02 mole) in 20 ml. of anhydrous tetrahydrofuran was added 10 ml. of 2*N* ethereal butyllithium followed by β-*N*-piperidino-3,4,5-trimethoxypropiophenone (IIIe, 6.1 g., 0.02 mole) dissolved in anhydrous tetrahydrofuran (100 ml.) as described for the preparation of IVa. Recrystallization of the crude product, 7.1 g. (79%), m.p. 80–100°, from ethanol gave a colorless crystalline analytical sample melting at 146°.

Anal. Calcd. for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.28; N, 3.26. Found: C, 67.41; H, 7.42; N, 3.45.

α-[2-(N-Morpholino)ethyl]-α-(3,4,5-trimethoxyphenyl)-piperonyl alcohol (IVd). This compound was obtained by the procedure outlined for IVa, employing 3,4-methylenedioxybromobenzene (2.21 g., 0.011 mole) in anhydrous tetrahydrofuran (15 ml.), 5.5 ml. of 2*N* ethereal butyllithium and 3.43 g. (0.011 mole) of β-*N*-morpholino-3,4,5-trimethoxypropiophenone (IIIf) dissolved in 140 ml. of tetrahydrofuran. The crude product weighed 3.6 g. (76%) and melted at 156–160°. The analytical sample recrystallized from ethanol-water as colorless crystals, m.p. 161–162°, $\gamma_{\max}^{CHCl_3}$ 3300–2850 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{29}NO_7$: C, 64.02; H, 6.77; N, 3.25. Found: C, 64.48; H, 6.92; N, 3.44.

α-[2-(N-Morpholino)ethyl]-α-(p-methoxyphenyl) piperonyl alcohol (IVe). The crude product prepared as illustrated above (*e.g.*, IVa) from ethereal 2*N* butyllithium (20 ml.), 3,4-methylenedioxybromobenzene (8.04 g., 0.04 mole) in anhydrous tetrahydrofuran (30 ml.), and β-*N*-morpholino-4-methoxypropiophenone[16] (IIIh, 10 g., 0.04 mole) in 80 ml. of anhydrous tetrahydrofuran weighed 13.3 g. (89.5%), and melted at 110–135°. Repeated recrystallization from either ethanol, ethanol-water, or benzene-petroleum ether (b.p. 60–90°) yielded pure colorless crystals, m.p. 143–143.5°, $\gamma_{\max}^{CHCl_3}$ 3300–2850 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77 Found: C, 68.18; H, 6.65; N, 3.92.

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(16) T. Okuda, *Yakugaku Zasshi*, **76**, 1 (1956). *Chem. Abstr.*, **50**, 13029 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MAINE]

Potential Cancerocidal Agents. II. Synthesis of 6,7-Methylenedioxycarbostyril[1]

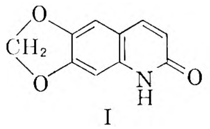
GEORGE R. PETTIT AND MALDA V. KALNINS

Received January 4, 1960

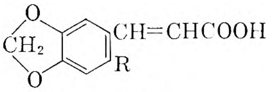
An unequivocal synthesis of 6,7-methylenedioxycarbostyril has been accomplished. Previous reports describing the preparation of this substance have been examined and reinterpreted.

During the course of a continuing search for a substance with useful antitumor activity, it was desirable to prepare 6,7-methylenedioxycarbostyril (I) for biological evaluation.[2]

Although the synthesis of 6,7-methylenedioxycarbostyril (I) had been reported by both Narang[3] and Borsche,[4] certain inconsistencies made questionable the result of each procedure. Reduction of 3,4-methylenedioxy-6-nitrocinnamic acid (IIa) with aqueous ammonia and ferrous sulfate, followed by acidification, had been claimed[3] to yield the carbostyril (I), m.p. 205°. The validity of this conclusion was doubtful in view of the experimental conditions employed and the earlier work of Perkin[5] in which the same reaction sequence had been reported to yield 3,4-methylenedioxy-6-aminocinnamic acid (IIb, brown needles, m.p. 205–207°). However, Narang[3] noted that his product apparently did not contain an amino or carboxylic acid group. Several years later, the room temperature reaction between acetic anhydride and the Schiff



I



IIa. R = NO_2
b. R = NH_2

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[1] This investigation was aided by Grant T-79 from the American Cancer Society.

[2] This work constitutes part of a study concerned with the synthesis of nitrogen compounds based on certain structural features of the tumor-damaging natural product, podophyllotoxin. Consult: G. R. Pettit, and D. S. Alkalay, *J. Org. Chem.*, **25**, 1363 (1960), for the preceding paper in this series.

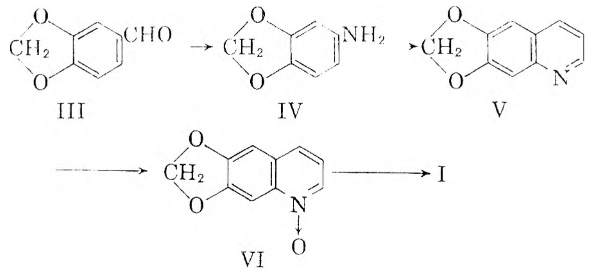
[3] K. S. Narang, J. N. Ray, and T. Das Sachdeva, *J. Indian Chem. Soc.*, **13**, 260 (1936).

[4] W. Borsche and W. Ried, *Ann.*, **554**, 269 (1943).

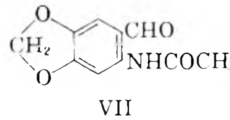
[5] F. M. Perkin, *J. Chem. Soc.*, **59**, 150 (1891).

base VIIIa was found to yield a yellow compound melting at 158–159°, which was again assigned the 6,7-methylenedioxycarbostyril (I) structure.[4]

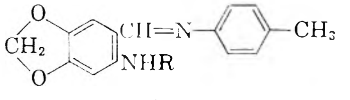
In our hands, reduction of 3,4-methylenedioxy-6-nitrocinnamic acid (IIa) yielded IIb as golden yellow platelets melting at 200–202° dec., readily soluble in dilute sodium bicarbonate. Treating the amino acid (IIb) with hot hydrochloric acid, followed by neutralization, gave a colorless crystalline product melting at 351–353° dec. The infrared spectrum and elemental analysis of the latter compound were clearly in agreement with the 6,7-methylenedioxycarbostyril (I) representation. An unequivocal synthesis of the carbostyril I, therefore, became desirable. The following reaction sequence (III → I) was selected for this purpose. Piperonal (III) was converted *via* its amino derivative (IV) to 6,7-methylenedioxyquinoline (V). Peracetic acid oxidation of V yielded 6,7-methylenedioxyquinoline *N*-oxide (VI) which smoothly rearranged under the influence of boiling acetic anhydride to 6,7-methylenedioxycarbostyril (I). The authentic sample of I, m.p. 351–353°, was identical with the product obtained from the amino acid IIb.



In a reinvestigation of the transformation which occurs when the amine VIIIa is placed in acetic anhydride,[4] it was found that two products could be isolated. Fractional recrystallization of the reaction product from methanol, gave a colorless crystalline compound, m.p. 161–162°, and a pale yellow crystalline substance melting at 186–188°. Elemental analyses and Rast molecular weight determinations suggested empirical formulas $C_{10}H_9NO_4$ and $C_{16}H_{16}N_2O_3$ respectively for these products. This information, combined with the results of an infrared spectral study, implied structures VII and VIIIb. This structural assignment was partially confirmed when it was shown that heating with *p*-toluidine converted the product melting at 161–162° (VII) to the higher melting (186–188°) substance (VIIIb). However, oxidation of the aldehyde VII with either silver oxide or potassium permanganate afforded an acid melting at 239–240°, while 6-acetaminopiperonylic acid (IXa) had been reported by Bogert and Elder[6] to melt at 124–125°. Consequently, an unambiguous synthesis of the acid IXa was undertaken in order to provide an authentic specimen for comparison purposes.

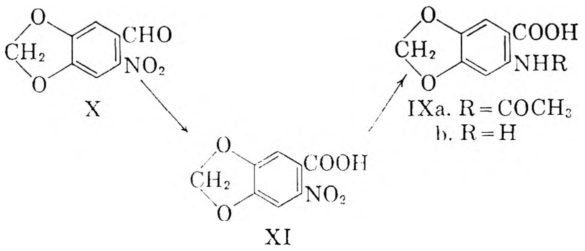


VII



VIIIa. R = H
b. R = COCH$_3$

Oxidation of 6-nitropiperonal (X) led to 6-nitropiperonylic acid (XI) which was reduced with ferrous sulfate, in hot aqueous ammonia solution, to the corresponding amino acid IXb. Treating IXb with warm acetic anhydride gave 6-acetaminopiperonylic acid, m.p. 240–241°. The latter sample (IXa) was identical with the product arising from oxidation of the compound melting at 161–162° (VII).



The room temperature reaction between the Schiffs' base VIIIa and acetic anhydride, therefore, yields the acetanilide derivatives VII and VIIIb. For this reason, it also appears likely that the reaction between the *p*-toluidine derivative of 3,4-dimethoxy-6-aminobenzaldehyde and acetic anhydride may, in fact, yield the corresponding acetanilide derivative and not 6,7-dimethoxycarbostyril as reported by Borsche and Ried.[4]

EXPERIMENTAL[7]

6,7-Methylenedioxycarbostyril (I). A. *From 3,4-methylenedioxy-6-aminocinnamic acid* (IIb). A stirred suspension of 3,4-methylenedioxy-6-nitrocinnamic acid[6,8] (IIa, 70 g.) in 1.2 l. of water containing 750 g. of ferrous sulfate heptahydrate was heated to 80° before adding 600 ml. of 28% ammonium hydroxide. The source of heat was removed and stirring was continued over a 45-min. period. The black colored reaction mixture was filtered through Celite and the filtrate was acidified to *p*H 4 with 280 ml. of hydrochloric acid. The orange-yellow colored crystalline product (IIb) weighed 37 g. (60%) and melted at 180–190° dec. Recrystallization from dimethylformamide-water gave golden-yellow platelets, m.p. 200–202° dec.

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.99; H, 4.41; N, 7.09.

A mixture of 3,4-methylenedioxy-6-aminocinnamic acid (IIb, 5 g.) and 75 ml. of 18% hydrochloric acid was heated at steam bath temperature for 2 hr. The resulting dark brown colored solid was collected and washed successively with dilute sodium bicarbonate solution and water. Recrystallization from acetic acid (Norit-A) afforded colorless crystals of 6,7-methylenedioxycarbostyril (I); yield, 2 g. (44%), m.p. 351–353° dec.

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[6] M. T. Bogert and F. R. Elder, *J. Am. Chem. Soc.*, 51, 532 (1929).

[7] Melting points were observed using open Kimble glass capillaries and are uncorrected. Microanalyses were provided by Dr. A. Bernhardt, Max-Planck Institut, Mülheim, Germany. Infrared spectra were recorded by Mr. E. Thomas, Department of Chemistry, University of Maine.

[8] The general procedure described by J. F. Kefford, *J. Chem. Soc.*, 1209, (1940), provides a convenient method for the preparation of this compound.

B. *From 6,7-methylenedioxyquinoline N-oxide* (VI). Eight milliliters of 30% hydrogen peroxide was added to a solution of 6,7-methylenedioxyquinoline (V, 7 g.)[9] in 50 ml. of glacial acetic acid. After warming the reaction mixture at 70° for 16 hr., it was diluted to 100 ml. with water. The crystalline *N*-oxide (VI) was collected following adjustment of the cool reaction mixture to *p*H 5–6 with aqueous ammonia. Recrystallization from ethanol (Norit-A) gave colorless needles of 6,7-methylenedioxyquinoline *N*-oxide monohydrate melting at 179–180°; yield 4.1 g. (54%).

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.21; H, 4.45; N, 7.22.

A solution of 6,7-methylenedioxyquinoline *N*-oxide (VI, 1.8 g.) in 15 ml. of acetic anhydride was heated at reflux for 5 hr. The reaction mixture was then concentrated *in vacuo*. The rust colored product which separated was collected by filtration and washed with several small portions of water; yield, 1.2 g. (63%), m.p. 350–353° dec. A pure sample (I) recrystallized from acetic acid (Norit-A)–water as colorless crystals melted at 352–353° dec., λ_{max}^{KBr} 5.95, 6.38, 6.69, 6.95, 7.97, 9.63, 10.4, 10.6 and 11.5 μ.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.43; H, 3.81; N, 7.36.

Product I was found by mixture melting point and infrared spectral comparison to be identical with the sample of 6,7-methylenedioxycarbostyril prepared from 3,4-methylenedioxy-6-aminocinnamic acid (IIb).

Acetylation of 6-aminopiperonylidene-p-toluidine (VIIIa). A solution of 6-aminopiperonylidene-*p*-toluidine[4,6] (VIIIa, 2.5 g.) and 5 ml. of acetic anhydride (without prior purification) was allowed to remain at room temperature for 5 days. The orange colored crystalline product was collected and washed with hot methanol. The yellow colored crystalline residue weighed 1.2 g. and melted at 184–186°. Recrystallization from methanol afforded a pure sample of 6-acetaminopiperonylidene-*p*-toluidine (VIIIb) as yellow needles, m.p. 186–188°, λ_{max}^{KBr} 3.05 and 5.90 μ.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$ (284): C, 67.59; H, 5.67; N, 9.85. Found: C, 67.61; H, 5.46; N, 9.65; mol. wt. (Rast), 279.

Cooling the combined methanol washings resulted in the isolation of 0.4 g. of *6-acetaminopiperonal* (VII). The colorless needles melted at 161–162° (lit.,[4] m.p. 161–162°) after recrystallization from methanol; λ_{max}^{KBr} 3.05, 5.88, 5.98, and 6.14 μ.

Anal. Calcd. for $C_{10}H_9NO_4$ (207): C, 57.97; H, 4.38; N, 6.76. Found: C, 57.60; H, 4.32; N, 6.83; mol. wt. (Rast), 198.

When the reaction was carried out employing redistilled acetic anhydride and a 15-min. reaction period, only the Schiff base VIIIb was obtained; while addition of water (1:2 water–acetic anhydride) and extension of the reaction time to 24 hr. led to almost exclusive production of 6-acetaminopiperonal (VII).

The presence of 6,7-methylenedioxycarbostyril (I) was not detected.

6-Acetaminopiperonylidene-p-toluidine (VIIIb). A mixture of *p*-toluidine (0.10 g.) and 0.20 g. of 6-acetaminopiperonal, isolated from the acetylation of VIIIa, was heated at 120° *in vacuo* (water-aspirator for *ca.* 20 min.). Recrystallization from methanol gave yellow needles (0.10 g.), m.p. 186–188°. Mixture melting point and infrared spectral comparison with the substance isolated above, (VIIIb, m.p. 186–188°), established the identical nature of both products.

6-Acetaminopiperonylic acid (IXa). A. *By oxidation of 6-acetaminopiperonal* (VII). A 1.8-g. sample of 6-acetaminopiperonal, prepared as described above (acetylation of VIIIa), 3.1 g. of silver nitrate, and 14 ml. of water was heated to reflux before slowly, and with frequent agitation, adding sodium hydroxide (1.2 g.) in 14 ml. of water. Heating at reflux was continued until the silver mirror dispersed. After the reaction mixture was filtered and the filtrate acidified with dilute hydrochloric acid, the light gray colored crystalline product was collected and recrystallized from methanol. The colorless crystals weighed 1.6 g. (82.5%), m.p. 239–240° dec. The product was shown (mixture melting point and infrared spectral comparison) to be identical with an authentic sample of 6-acetaminopiperonylic acid (IXa) prepared as described below (procedure B).

B. *From 6-aminopiperonylic acid* (IXb). The 6-nitropiperonylic acid[10] employed in this procedure was prepared by silver oxide oxidation of 6-nitropiperonal.[11]

A mixture of 6-nitropiperonylic acid (XI, 8.0 g.) ferrous sulfate (97 g.), water (150 ml.) and 1 ml. of concd. hydrochloric acid was heated to 90° before adding 80 ml. of aqueous ammonia (28%) over a 20-min. period. Heating on the steam bath and stirring were continued for 45 min. The hot reaction mixture was then filtered through Celite and after washing the insoluble material thoroughly with water, the combined filtrate was acidified to *p*H 4.8 with hydrochloric acid. At this point, it was found that the amino acid was still absorbed on the iron oxides. Consequently, the filter cake was suspended (with stirring) in 300 ml. of water and acidified to *p*H 2 with hydrochloric acid. The mixture was filtered and the filtrate adjusted to *p*H 4.8 with aqueous ammonia. The dark colored precipitate was collected, dried, and heated at steam bath temperature with acetic anhydride for 1.5 hr. After cooling, the grayish-brown crystals were collected and recrystallized from methanol (Darco) to give colorless crystals, yield 0.7 g., m.p. 240–241° dec., (*cf.* Ref. 6).

Anal. Calcd. for $C_{10}H_9NO_5$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.97; H, 4.14; N, 6.10.

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[9] A. Sonn and F. Benirschke, *Ber.*, **54**, 1730 (1921).

[10] J. Jobst and O. Nesse, *Ann.*, **199**, 70 (1879).

[11] J. B. Ekeley and M. S. Klemme, *J. Am. Chem. Soc.*, **50**, 2711 (1928).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XXXIV. Nonredox Analogs of Riboflavin. I. Model Studies

ELMER J. REIST, HARLAN P. HAMLOW, IRENE G. JUNGA, R. M. SILVERSTEIN, AND B. R. BAKER

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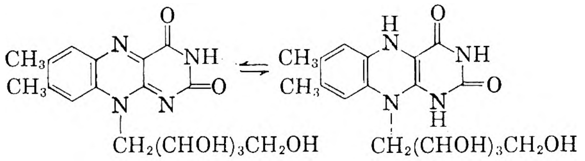
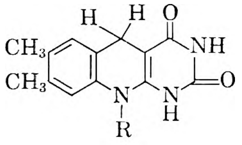
The syntheses of methyl 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylate (XVI) and methyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVI) from 3,4-xylidine (VII) are described. Reaction of XVI with guanidine followed by deamination of the product with nitrous acid gave the desired model compound, 5,10-dihydro-5,5,7,8,10-pentamethylpyrimido[4,5-b]quinoline-2,4(3H,4aH)dione (XXIII). Reaction of XLVI with guanidine afforded 2,10-dihydro-2-imino-7,8,10-trimethylpyrimido[4,5-b]quinoline-4(3H)one (L), which could not be deaminated with nitrous acid.

Riboflavin (I), in its cofactor form, owes its biological activity to its ability to accept electrons and be reduced to the dihydro form (II). Modification or elimination of this redox system could be expected to result in compounds that behave as riboflavin antagonists. Thus, dichloroflavin (7,8-dichloro - 10 - ribitylisoalloxazine), in which the methyl groups were replaced by chloro, has a redox potential of $E_0 = -0.095$ volt as compared to riboflavin with a potential of $E_0 = -0.185$. It has been suggested[2] that dichloroflavin is an antagonist because of this difference in redox potential.

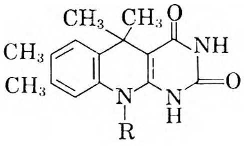
Replacement of the N_5-nitrogen of dihydroriboflavin (1,5-dihydro-7,8-dimethyl-10-ribitylisoalloxazine) by a methylene group, as in III (R = ribityl), would be expected to have a profound effect on the redox potential as compared to riboflavin. Similarly, replacement of the N_5-nitrogen of dihydroriboflavin by an isopropylidene group (IV. R = ribityl) fixes the molecule in the dihydro form, thus eliminating the redox system completely. Although IV is derived from dihydroflavin (II) rather than from riboflavin, the redox enzyme system employing riboflavin coenzymes utilizes both the oxidized and reduced forms; thus analogs of either I or II should be effective antagonists.



I II

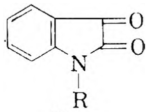


III

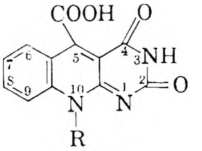


IV

Little is known about the pyrimido[4,5-b]-quinolines, especially those substituted on the 10-position. The synthesis of 2,3,4,10-tetrahydro-2,4-dioxopyrimido[4,5-b]quinoline-5-carboxylic acid (VI. R = H) and 2,3,4,10-tetrahydro-10-methyl-2,4 - dioxopyrimido[4,5 - b]quinoline - 5 - carboxylic acid (VI. R = CH_3) starting with barbituric acid and isatin (V. R = H) or *N*-methylisatin (V. R = CH_3) has been described by King, *et al.*[3] They reported that the 5-carboxyl derivative of VI (R = H) was extremely resistant to decarboxylation, thus negating the use of this approach for the synthesis of compounds such as III.



V



VI

In order to gain more information about this ring system, the 10-methyl group was substituted for the 10-ribityl to obviate any complications introduced by the sugar moiety in the evaluation of a synthetic path to III and IV. The attempted synthesis of these model compounds (III. R = CH_3, and IV. R = CH_3) is the subject of this paper.

3-Methylcrotonoyl chloride, when treated with 3,4-xylidine (VII) in the manner described[4] for aniline and *o*- and *p*-toluidine, gave 3-methyl-3′,4′-crotonoxylidide (VIII) in 84% yield. *N*-Methylation of the anilide (VIII) with methyl iodide and sodium hydride in *N*,*N*-dimethylformamide proceeded smoothly, the N,3-dimethyl-3′,4′-crotonoxylidide (IX) being isolated as a pure distilled liquid in 84% yield. Cyclization of IX

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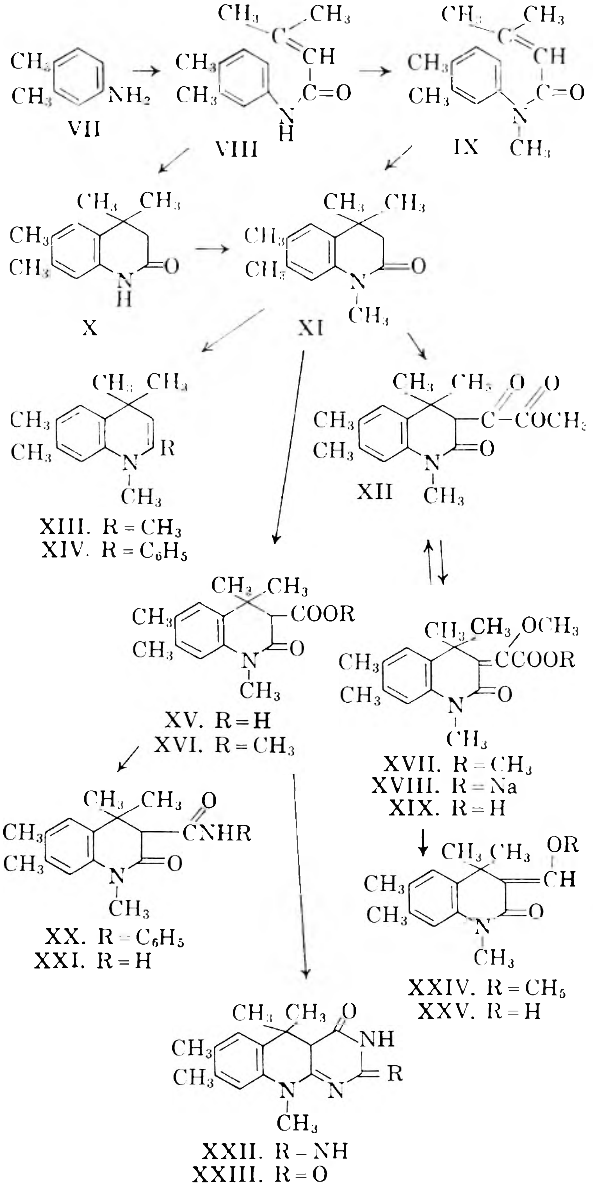
(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. This paper was presented in part at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April 16, 1958; see Abstracts, page 27-M. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* W. A. Skinner, H. F. Gram, and B. R. Baker, *J. Org. Chem.*, **25**, 953 (1960).

(2) R. Kuhn, F. Weygand, and E. F. Möller, *Ber.*, **76B**, 1044 (1943).

(3) F. E. King, T. J. King, and G. B. Thompson, *J. Chem. Soc.*, 552 (1948).

(4) J. Colonge and R. Chambard, *Bull. soc. chim. France*, (5), **20**, 982 (1953).



with aluminum chloride in Skellysolve C[5] afforded the crystalline 3,4-dihydro-1,4,4,6,7-pentamethylcarbostyril (XI) in 82% yield,[6] an over-all yield of 69% based on VIII. The alternative route, in which cyclization of VIII with aluminum chloride is followed by *N*-methylation of the resulting carbostyril (X), gave a 47% yield of XI based on VIII. The difference in yield between the two routes was primarily due to a lower yield in the ring closure of VIII as compared to the ring closure of IX.

Treatment of the carbostyril (XI) with diethyl carbonate and sodium hydride in an effort to prepare ethyl 1,2-dihydro-2-oxo-3-quinolinecarboxylate resulted in recovery of unchanged starting material. Condensation of XI with dimethyl oxalate and sodium hydride at 110–115° for four hours gave the crude glyoxalate (XII) as an oil from which a 22% yield of the crystalline 2,4-dinitrophenylhydrazone of XII could be obtained. In an effort to force this condensation to completion, the reaction was run at 135–140° for four hours. The crystalline product obtained from this reaction in 60% yield was not the expected glyoxalate (XII) but the enol ether ester (XVII), as shown by its analysis and infrared spectrum and its failure to form a 2,4-dinitrophenylhydrazone. The infrared spectrum contained a peak at 6.3 μ, assignable to a vinyl double bond, which was not present in the spectrum of the glyoxalate (XII). Hydrolysis of XVII with dilute hydrochloric acid gave an oil which formed, in low yield, a 2,4-dinitrophenylhydrazone identical with that formed from the glyoxalate (XII). Treatment of the enol ether ester with acetic acid, benzoic acid, or toluenesulfonic acid also gave small amounts of the desired glyoxalate (XII) along with unchanged starting material and the enol ether acid (XIX). Saponification of the enol ether (XVII) formed an alcohol-insoluble sodium salt (XVIII), which showed strong carboxylate bands at 6.23 and 7.17 μ in the infrared. Acidification of XVIII gave the crystalline enol ether acid (XIX), whose infrared spectrum still contained the 6.35 μ band of the vinyl double bond. The normal saponification of the enol ether ester (XVII) is in sharp contrast to the behavior of the glyoxalate (XII) toward alkaline conditions, since the latter is not saponified but the oxalyl residue is cleaved with regeneration of the carbostyril (XI).

When the enol ether acid (XIX) was heated above its melting point at 180–190°, gas was evolved over a period of twenty minutes. When gas evolution had ceased, the residue was crystallized from Skellysolve B[5] to give, not the expected aldehyde enol ether (XXIV), but the enol ether ester (XVII) in 30% yield. The mother liquor gave an oil in 35% yield that appeared to consist of a mixture of the desired aldehyde enol ether (XXIV) and free aldehyde (XXV), as shown by its infrared spectrum, which showed enol ether double bond absorption at 6.22 μ and aldehyde absorption at 3.71 and 5.78 μ. Treatment of the oil with 2,4-dinitrophenylhydrazine gave the dinitrophenylhydrazone derivative of the aldehyde (XXV) in 9% yield. These results could be explained on the basis that some of the enol ether acid (XIX) disproportionated to the enol ether ester (XVII) and the corresponding glyoxylic acid; the latter would be decarboxylated to the aldehyde (XXV). A second possible explanation is that the aldehyde enol ether (XXIV), formed by decarboxylation of the enol ether acid (XIX), transferred its methoxyl group to the enol ether acid (XIX) to generate the aldehyde (XXV) and the enol ether ester (XVII). Heating of the enol ether acid (XIX) in hot quinoline led to a product (or products) whose infrared spectrum showed the presence of carbonyl bands at 5.5 and 5.8 μ, indicative of an anhydride, together with the loss of lactam carbonyl absorption at 6.04 μ, suggesting that some type of skeletal rearrangement had taken place.

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[5] Skellysolve B and Skellysolve C are petroleum hydrocarbon fractions with boiling ranges of 62–70° and 88–99°, respectively. They are supplied by Special Products Division, Phillips Petroleum Company, Bartlesville, Okla.

[6] In this ring closure, there was the possibility of obtaining a mixture of two isomers through closure on either the 2- or 6-position of 3,4-xylidine. Since a sharp melting point was obtained after only two recrystallizations and since subsequent reactions gave readily crystallizable products, it can be assumed either that the reaction was oriented mainly in one direction, or that the isomers are readily separable. Steric considerations suggest that closure on the 6-position of the 3,4-xylidine to give the desired carbostyril (XI) would be favored. This prediction is borne out by the presence in the infrared spectrum of a band at 11.32 μ assignable to the out-of-plane vibrations of the isolated hydrogen atoms of a 1,2,4,5-tetrasubstituted benzene ring.[7] The corresponding absorption for the adjacent hydrogen of a 1,2,3,4-tetrasubstituted benzene ring would fall between 11.6 μ and 12.5 μ.[7]

[7] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 67, 68.

An interesting contrast to the reaction of dimethyl oxalate with the carbostyril (XI) was observed in the reaction of diethyl oxalate with XI under the same conditions. The yields of the ethyl glyoxalate corresponding to XII were low and variable (5–25%) and no detectable amount of the enol ethyl ether corresponding to XVII was observed.

The very nature of the sterically hindered system in the carbostyril (XI) that led to limited success in the introduction of a functional group on C_3 by a Claisen condensation was utilized to introduce a carboxyl at C_3 in the following manner. There are many reports on the synthesis of β-oxo acids by a Grignard exchange reaction in sterically hindered methyl ketones.[8] When a similar type of reaction was attempted on XI with ethylmagnesium bromide, no reaction occurred and starting material was recovered unchanged. Treatment of the carbostyril (XI) with methyllithium gave an almost quantitative yield of 1,4-dihydro-1,2,-4,4,6,7-hexamethylquinoline (XIII), the product to be expected from the normal addition of lithium reagent to the carbonyl, with no detectable amount of the desired lithium salt. Fortunately, reaction of XI with phenyllithium gave the lithium salt of XI, which was treated directly with carbon dioxide to give the desired 3-carboxylic acid (XV) in 24% yield together with considerable quantities of unchanged starting material. In a large-scale run, 1,4-dihydro-1,4,4,6,7-pentamethyl-2-phenylquinoline (XIV), the product to be expected from the normal addition of lithium reagent to the carbonyl, could also be detected.

When the carbostyril-3-carboxylic acid (XV) was heated at its melting point of 150°, there was a smooth evolution of carbon dioxide and the carbostyril (XI) could be recovered, thus proving that the introduction of the carboxyl took place at C_3 without any change in the ring system. Refluxing of the 3-carboxylic acid (XV) with thionyl chloride gave the acid chloride of XV as a sirup. This sirup could be treated with aniline to give the crystalline anilide (XX), or with methanol to give the crystalline methyl ester (XVI). A more convenient synthesis of the methyl ester (XVI) involved the treatment of the acid (XV) with methanol and acetyl chloride[9] to give XVI in 77% yield in one step from the acid; the usual types of esterification proceeded poorly.

The synthesis of 5,10-dihydro-5,5,7,8,10-pentamethylpyrimido[4,5-b]quinoline-2,4(3H,4aH)dione (XXIII) was attempted by the fusion of equal amounts of methyl 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylate (XVI) and urea. The product isolated from the reaction mixture was the 3-carboxamide (XXI). Condensation of XVI with guanidine hydrochloride and sodium methoxide in refluxing *N*,*N*-dimethylformamide resulted in a 54% yield of 5,10-dihydro-2-imino-5,5,7,8,10-pentamethylpyrimido[4,5-b]-quinoline-4(4aH)one (XXII). Deamination of the 2-imine (XXII) with excess sodium nitrite in acetic acid gave a 45–50% yield of a crude product which appeared to contain two components in approximately equal amounts, as shown by paper chromatography using solvent A.[10] Variation of the reaction conditions with respect to solvent, ratio of sodium nitrite to XXII, temperature, or time failed to give a product that was homogeneous, as shown by paper chromatography. The completeness of the reaction was very easily determined by the visual examination of the paper chromatograms of the crude product of the deamination. The starting material (XXII) appeared as a blue fluorescent spot with R_f 0.82, while the two deamination products appeared as yellow fluorescent spots with R_f values of 0.66 and 0.79, respectively.

Since the deamination of XXII under a variety of conditions appeared to have little or no effect on the formation of XXIII with the exclusion of the unknown by-product, efforts were directed toward the separation of this deamination mixture. The essentially complete insolubility of both components in any of the common solvents eliminated the possibility of purification by recrystallization.

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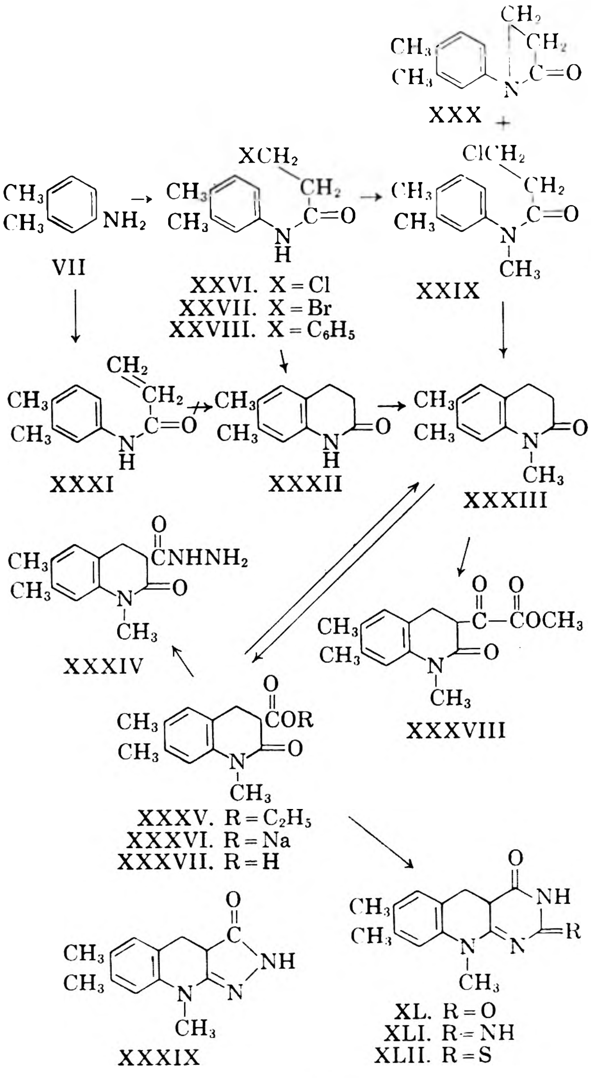
[8] (a) R. Adams and L. O. Binder, *J. Am. Chem. Soc.*, **63**, 2773 (1941); (b) R. Adams, A. W. Anderson, and M. W. Miller, *J. Am. Chem. Soc.*, **63**, 1589 (1941); (c) R. Adams and M. W. Miller, *J. Am. Chem. Soc.*, 62, 53 (1940); (d) R. C. Fuson, W. O. Fugate, and C. H. Fisher, *J. Am. Chem. Soc.*, **61**, 2362 (1939); (e) E. P. Kohler and R. Baltzly, *J. Am. Chem. Soc.*, **54**, 4015 (1932).

[9] K. Freudenberg and W. Jakob, *Ber.*, **74B**, 1001 (1941).

[10] The paper chromatograms were run on Whatman No. 1 paper by the descending technique and spots were located by visual examination under ultraviolet light. The solvent systems used were: A, water saturated butanol; B, butanol–acetic acid–water (4:1:5).

A differential solubility of the two components in concentrated hydrochloric acid made possible the purification of the faster moving of the two components by solution in concentrated hydrochloric acid followed by reprecipitation of the acid-soluble material with water. By this means, a 15% over-all yield of 5,10-dihydro-5,5,7,8,10-pentamethylpyrimido[4,5-b]quinoline-2,4(3H,4aH)-dione (XXIII) hydrochloride was obtained. The hydrochloric acid-insoluble fraction still consisted of a mixture of the two components. Since the by-product was not obtained free of XXIII, its empirical formula could not be determined. Subsequent attempts to repeat this hydrochloric acid separation of XXIII from the by-product were not always successful.

A similar synthetic sequence for the preparation of 5,10-dihydro-7,8,10-trimethylpyrimido[4,5-b]-quinoline-2,4(3H,4aH)dione (XL), starting with xylidine, is outlined in VII→XL. The key intermediate for this synthesis is 3,4-dihydro-1,6,7-trimethylcarbostyril (XXXIII). Many routes to its synthesis from 3,4-xylidine are apparent and a number of these were investigated. Since attempted fusion of 3,4-acryloxylidide (XXXI) with aluminum chloride gave no reaction and starting material was recovered unchanged, the Friedel-Crafts ring closures of the 3-halopropionanilides (XXVI and XXVII) were examined.[11] The condensation of 3,4-xylidine (VII) with 3-chloropropionyl chloride gave the 3-chloropropionamide (XXVI) in 87% yield. Fusion of XXVI with aluminum chloride to give 3,4-dihydro-6,7-dimethylcarbostyril (XXXII) proceeded in a 12% yield. Cyclization of the corresponding 3-bromopropionanilide (XXVII) gave similar yields. Use of Skellysolve C[5] as a solvent in the cyclization of the chloroanilide (XXVI) raised the yield of carbostyril (XXXII) to 27%. Substitution of benzene for Skellysolve C in this reaction[12] led to 3-phenyl-3′,4′-propionoxylidide (XXVIII) instead of the desired carbostyril (XXXII). *N*-Methylation of the dimethylcarbostyril (XXXII) with sodium hydride and methyl iodide in *N*,*N*-dimethylformamide proceeded in 78% yield to 3,4-dihydro-1,6,7-trimethylcarbostyril (XXXIII), a 21% over-all yield from the 3-chloropropionanilide (XXVI).



An effort was made to *N*-methylate the chloroanilide (XXVI) previous to cyclization to the carbostyril, since a similar modification with the 3-methylcrotonanilide (VIII) gave a considerable increase in over-all yield of the carbostyril (XI). One of the by-products to be expected from the methylation of a β-chloroamide such as XXVI is the β-lactam (XXX). That this possible side reaction was a reality was demonstrated by the presence in the infrared spectrum of the *N*-methylation product of a β-lactam carbonyl band at 5.73 μ in addition to the expected amide carbonyl band at 6.04 μ. When the β-chloroanilide (XXVI) was subjected to the basic conditions of the *N*-methylation in the absence of methyl iodide, the β-lactam could be isolated in a pure state. Unfortunately, the mixture of β-lactam (XXX) and trimethylanilide (XXIX) could not be separated by distillation; hence the over-all yield of XXXIII by the cyclization of XXIX as compared to XXVI would not be improved.

Treatment of the trimethylcarbostyril (XXXIII) with dimethyl oxalate and sodium hydride in *N*,*N*-dimethylformamide gave the glyoxalate (XXXVIII), isolated as its 2,4-dinitrophenylhydrazone in 21% yield. There was no evidence for the formation of an enol ether of XXXVIII corresponding to XVII, since the characteristic vinyl double bond of the enol ether of XVII at 6.3 μ in the infrared was absent in the crude product.

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[11] F. Mayer, L. v. Zutphen, and H. Philipps, *Ber.*, **60**, 858 (1927), reported that *N*-methyl-*N*-acrylylaniline failed to cyclize to the dihydrocarbostyril with aluminum chloride. However, they were able to cyclize several *N*-(β-chloropropionyl)anilides.

[12] The use of benzene as a solvent in Friedel-Crafts reactions involving aromatic rings more reactive than benzene has been described by R. Adams, T. A. Geissman, B. R. Baker, and H. M. Teeter, *J. Am. Chem. Soc.*, **63**, 528 (1941).

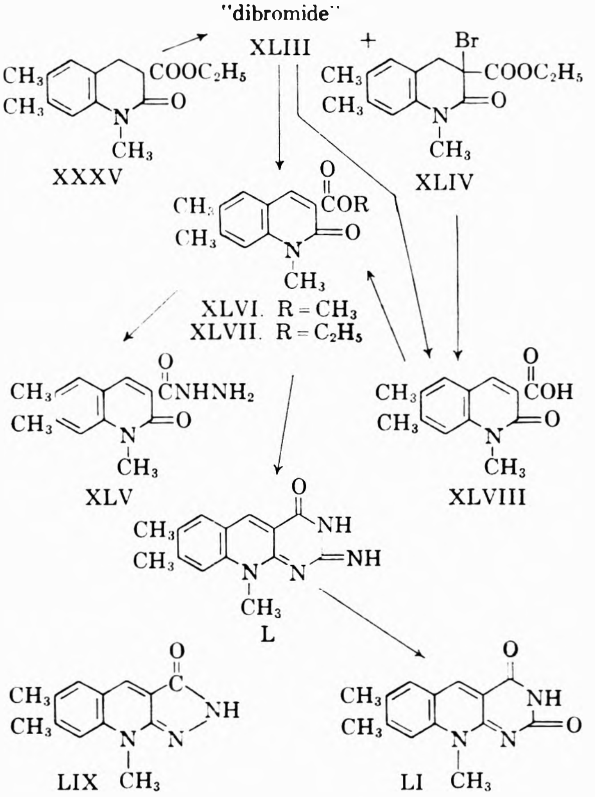
Condensation of XXXIII with diethyl carbonate using sodium hydride in N,N-dimethylformamide afforded ethyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XXXV) in 42% yield. Saponification of the ethyl ester (XXXV) gave a crystalline sodium salt of the acid (XXXVI) containing the expected carboxylate bands in the infrared. Acidification of the sodium salt afforded the crystalline 3-carboxylic acid (XXXVII), m.p. 155°, which could be decarboxylated at 180° back to the starting trimethylcarbostyril (XXXIII), thus showing that no rearrangements had taken place.

The contrast of reactivities and reaction products between the trimethylcarbostyril (XXXIII) and the pentamethylcarbostyril (XI) is notable. The pentamethylcarbostyril (XI) with its sterically hindered 3-methylene groups, fails to react with diethylcarbonate in contrast to the successful conversion of the trimethylcarbostyril (XXXIII) to its 3-carbethoxy derivative (XXXV). Similarly, the pentamethylcarbostyril (XI) reacted with methyl oxalate at 140° to give the glyoxalate enol ether (XVII), whereas the unhindered trimethylcarbostyril (XXXIII) under the same conditions gave only the expected glyoxalate (XXXVIII) with no detectable amounts of the enol ether.

Reaction of ethyl 3-quinolinecarboxylate (XXXV) with hydrazine in boiling ethyl alcohol gave a crystalline compound whose elemental analysis agreed with that to be expected for the carboxylic acid hydrazide (XXXIV). It is conceivable that the product from the reaction of hydrazine and ethyl ester (XXXV) is a hydrate of the ring-closed pyrazolo[3,4-b]quinoline (XXXIX). It has been assigned the structure of the hydrazide (XXXIV), however, on the basis of the similarity of its ultraviolet absorption spectra to that of the ethyl ester (XXXV).

Attempts to convert the ethyl ester (XXXV) to a pyrimido[4.5-b]-quinoline (XL–XLII) by condensation with urea, guanidine, or thiourea under a large variety of conditions were unpromising; either low yields, intractable mixtures (as shown by paper chromatography), or both were obtained. Part of the difficulty appeared to be the further aromatization of the product(s) to compounds such as L–LI. To avoid the aromatization problem, the condensation of a more fully aromatic ester such as ethyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVII) with these agents was investigated.

One of the standard methods for aromatization of a compound such as XXXV to XLVII involves bromination, then dehydrohalogenation. Treatment of the ethyl ester (XXXV) with bromine in carbon tetrachloride gave a sirup that could be separated into two components. The minor component proved to be the expected ethyl 3-bromo-1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLIV), obtained in 23% yield. The main component from the reaction, although crystalline, could not be recrystallized without decomposition and the crude product gave somewhat variable analytical data. The bromine content was consistently high, approaching the value expected for a dibromide of XXXV. Treatment of this 'dibromide' (XLIII) with saturated aqueous sodium bicarbonate gave ethyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVII) in 29% yield based on the ethyl ester (XXXV). In contrast, aqueous sodium bicarbonate had no effect on the monobromo ester (XLIV) and it could be recovered unchanged.



Thermal decomposition of the monobromo ester (XLIV) proceeded with elimination of the elements of the ethyl bromide to give 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid (XLVIII) in 97% yield.[13] Similarly, the 'dibromide' (XLIII) also gave the aromatic acid (XLVIII). The acid chloride, prepared from the acid (XLVIII)

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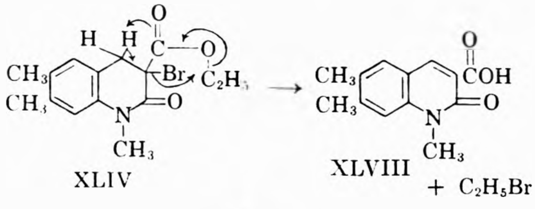
(13) A possible mechanism for the pyrolysis of the bromo ester (XLIV) is illustrated below:



with thionyl chloride, was treated with either methanol, ethanol, or aniline to give the methyl ester (XLVI) (74% yield), ethyl ester (XLVII) (78% yield), and anilide (61% yield), respectively. The ethyl ester (XLVII) prepared *via* the acid chloride of XLVIII was identical in all respects with the ethyl ester prepared by the sodium bicarbonate treatment of the 'dibromide' (XLIII).

Treatment of the ethyl ester (XLVII) with hydrazine hydrate gave a 95% yield of material which again is believed to be the hydrazide (XLV) rather than the pyrazolo[3,4-b]quinoline (LIX), since its ultraviolet spectrum is very similar to that of the carboxylic acid (XLVIII) and the ethyl ester (XLVII). The pyrazolo[3,4-b]quinoline (LIX) with its longer conjugated system of double bonds would be expected to absorb at longer wave lengths than the acid (XLVIII) or ester (XLVII).

Condensation of the methyl ester (XLVI) with guanidine hydrochloride in methanolic sodium methoxide followed by neutralization with acetic acid gave a material which was homogeneous on paper chromatography in solvent B[10] and which analyzed satisfactorily for the acetate salt of 2,10-dihydro-2-imino-7,8,10-trimethylpyrimido[4,5-b]quinoline-4(3H)-one (L). Treatment of L, either as the free base or its acetate salt, with nitrous acid under a variety of conditions gave no reaction as shown by paper chromatography[10] and when the attempted deamination was carried out in acetic acid, the acetate salt of L could be recovered unchanged.

The failure of the 2-imine (L) to react with nitrous acid, compared with the facile reaction with nitrous acid of the 2-imine (XXII) and the many other examples of deamination of 2-aminopyrimidines with nitrous acid and/or mineral acid,[14] is surprising and negates the synthesis of compounds of type LI by this route.

EXPERIMENTAL[10,15]

3-Methyl-3',4'-crotonoxylidide (VIII). To a refluxing solution of 60.7 g. (0.50 mole) of 3,4-xylidine (VII) in 100 ml. of benzene was added dropwise with stirring 29.6 g. (0.25 mole) of 3-methylcrotonoyl chloride[16] in 75 ml. of benzene over a period of 80 min. As the addition proceeded, the aniline hydrochloride precipitated. After the addition was complete, the mixture was stirred under reflux for 1 hr. The mixture was cooled, then the hydrochloride was removed by filtration and washed with four 50-ml. portions of benzene. The filtrate was evaporated *in vacuo* and the brown, viscous residue taken up in 450 ml. of 60% ethanol, heated to boiling, treated with Norit, and filtered. The solution was cooled and an oil separated which crystallized. The solid was collected and washed with 150 ml. of cold 1*N* hydrochloric acid, then with 100 ml. of water. The product, after being dried *in vacuo* over Drierite, weighed 43.0 g. (84%). A small sample was recrystallized from 75% methanol for infrared and elemental analysis, m.p. 102–103°; $\lambda_{max(\mu)}^{KBr}$ 3.01 (NH), 6.05 (C=O), 6.13 (C=C), 12.15 (trisubstituted phenyl).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.8; H, 8.43; N, 6.89. Found: C, 77.0; H, 8.49; N, 6.84.

3,4-Dihydro-4,4,6,7-tetramethylcarbostyril (X). A stirred suspension of 25 g. (0.12 mole) of 3-methyl-3',4'-crotonoxylidide (VIII) in 250 ml. of Skellysolve C[5] was treated with 50 g. of anhydrous, powdered aluminum chloride. The mixture was stirred under reflux for 3.5 hr. The cooled mixture was decomposed with ice and treated with 20 ml. of 6*N* hydrochloric acid. The white, crystalline solid was collected, washed with 25 ml. of Skellysolve *β*,[5] and dried *in vacuo* at 60°; yield 17.2 g. (69%), m.p. 178–180°: $\lambda_{max(\mu)}^{KBr}$ 3.11 (NH), 5.89 (lactam C=O), 11.23 (1,2,4,5-tetrasubstituted benzene).

The analytical sample was prepared from a pilot run by two recrystallizations from 60% ethanol with the use of Norit; white crystals, m.p. 176–178°.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.8; H, 8.43; N, 6.89. Found: C, 76.9; H, 8.36; N, 6.88.

N,3-Dimethyl-3',4'-crotonoxylidide (IX). To a stirred solution of 10.2 g. (0.05 mole) of 3-methyl-3',4'-crotonoxylidide (VIII) in 85 ml. of *N,N*-dimethylformamide was added 1.30 g. (0.054 mole) of sodium hydride. The mixture was cooled in an ice bath while 8.5 g. (0.06 mole) of methyl iodide was added. After several minutes a white precipitate formed. The mixture was heated on the steam bath for 5 min. The *N,N*-dimethylformamide was distilled under reduced pressure and the residue treated with 50 ml. of chloroform. The resulting mixture was washed with two 50-ml. portions of water. The chloroform was removed under reduced pressure and the product was distilled at 96° (0.025 mm.) (bath temperature 110°); yield 9.0 g. (84%), n_D^{20} 1.5506; $\lambda_{max(\mu)}^{film}$ 6.03 (amide C=O), 6.15 (C=C), 7.32 (CH_3), 12.35 (1,3,4-trisubstituted benzene).

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.4; H, 8.81; N, 6.45. Found: C, 77.3; H, 8.86; N, 6.30.

3,4-Dihydro-1,4,4,6,7-pentamethylcarbostyril (XI). (A) A stirred mixture of 1.68 g. (0.0083 mole) of 3,4-dihydro-4,4,6,7-tetramethylcarbostyril (X), 0.24 g. (0.01 mole) of sodium hydride, and 2.13 g. (0.015 mole) of methyl iodide in 15 ml. of *N,N*-dimethylformamide was heated at 50–55° for 1 hr. The solvent was removed *in vacuo* and the residue dissolved in 25 ml. of methylene chloride. The resulting solution was washed with 25 ml. of water, dried over magnesium sulfate, then concentrated *in vacuo*. Distillation at 87–91° (0.050 mm.) (bath temperature 110–115°) yielded 1.28 g. (68.2%) of product that solidified in the receiver, m.p. 48–57°. A 1-g. sample was recrystallized from 2.5 ml. of Skellysolve B,[5] to give 0.5 g. of white crystals, m.p. 54–59°; $\lambda_{max(\mu)}^{KBr}$ 5.97 (lactam C=O), 7.41 (CH_3), 11.32 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.4; H, 8.81; N, 6.45. Found: C, 77.1; H, 8.92; N, 6.83.

(B) To a stirred suspension of 15 g. (0.11 mole) of anhydrous powdered aluminum chloride in 40 ml. of Skellysolve C[5] was added 6.60 g. (0.030 mole) of *N*,3-dimethyl-3',4'-crotonoxylidide (IX) in 15 ml. of Skellysolve C.[5] The mixture was then heated under reflux on the steam bath for 100 min. The mixture was cooled and decomposed by adding ice. The resulting mixture was treated with 20 ml. of 6*N* hydrochloric acid and the Skellysolve C[5] layer separated. The organic solvent was removed *in vacuo*, leaving 6.76 g. of crude product, m.p. 57–60°. The crude material was recrystallized from 15 ml. of Skellysolve B[5]; yield 4.27 g., m.p. 58–60°. The filtrate was treated with Norit and filtered hot. An additional 1.1 g. of colorless crystals was obtained, m.p. 58–60°. The total yield was 5.37 g. (81.5%).

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(14)(a) E. A. Falco and G. H. Hitchings, *Ciba Foundation Symposium on Chemistry of Biology of Pteridines*, Little, Brown and Company, Boston, 1954, p. 183; (b) G. W. Kenner and A. Todd in *Heterocyclic Compounds*, Volume VI, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 278.

(15) Melting points were taken on a Fisher-Johns apparatus and are uncorrected.

(16) L. I. Smith and V. A. Engelhardt, *J. Am. Chem. Soc.*, **71**, 2671 (1949).

The infrared spectrum was identical with that of the carbostyril prepared by method A.

Methyl 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolineglyoxylate (XII). A mixture of 3.0 g. (0.014 mole) of 3,4-dihydro-1,4,4,6,7-pentamethylcarbostyril (XI) and 0.67 g. (0.028 mole) of sodium hydride in 15 g. of dimethyl oxalate and 15 ml. of *N,N*-dimethylformamide was stirred for 4 hr. at 110–115°. The solvent and excess dimethyl oxalate were removed *in vacuo* and the residue was taken up in a solution of 5 ml. of ethanol in 25 ml. of benzene. This solution was diluted with 50 ml. of chloroform and washed with 50 ml. of water. The chloroform solution was dried over magnesium sulfate and concentrated *in vacuo*. A light tan oil weighing 2.65 g. was obtained; $\lambda_{\max(\mu)}^{\text{film}}$ 5.76 (ester C=O), 6.03 (lactam C=O), 11.30 (1,2,4,5-tetrasubstituted benzene).

A 2,4-dinitrophenylhydrazone was prepared by dissolving 0.523 g. (1.72 mmoles) of the residue of XII in 10 ml. of ethyl alcohol, then adding this solution to a freshly prepared solution of 0.4 g. of 2,4-dinitrophenylhydrazine in 2 ml. of concd. sulfuric acid, 3 ml. of water, and 10 ml. of ethyl alcohol. The resulting solution was stirred and heated on the steam bath at 60° for 2 min., then cooled in an ice bath. The yellow solid that precipitated was removed by filtration and dried; yield 0.185 g. (22.3%). The crude 2,4-dinitrophenylhydrazone was recrystallized from 10 ml. of ethyl alcohol with the aid of Norit; yield 0.075 g. of orange-yellow crystals, m.p. 105–113°; $\lambda_{\max(\mu)}^{\text{KBr}}$ 5.82 (ester C=O), 6.05 (lactam C=O), 6.66 (NH and NO_2), 7.47 (NO_2), 8.16 (ester C—O—C).

Anal. Calcd. for $C_{23}H_{25}N_5O_7$: C, 57.1; H, 5.21. Found: C, 57.1; H, 5.33.

Methyl 1,2,3,4-tetrahydro-α-methoxy-1,4,4,6,7-pentamethyl-2-oxo-$\Delta^{\alpha,3}$-quinolinacetate (XVII). A stirred mixture of 2.0 g. (9.2 mmoles) of 3,4-dihydro-1,4,4,6,7-pentamethylcarbostyril (XI) and 0.48 g. (0.02 mole) of sodium hydride in 10 g. of dimethyl oxalate and 10 ml. of *N,N*-dimethylformamide was heated at 130–140° for 4.1 hr. The solvents and excess dimethyl oxalate were removed at 60° and 1 mm. pressure. The residue was treated with 25 ml. of ethanol. This mixture was washed with one 50-ml. and one 25-ml. portion of water. The benzene was removed *in vacuo* at 65°, leaving the crude product as tan crystals; weight 2.71 g. Recrystallization of 2.54 g. of the crystals from 35 ml. of ethyl alcohol and 17 ml. of water gave 1.64 g. (60%) of white needles, m.p. 162–166°; $\lambda_{\max(\mu)}^{\text{KBr}}$ 5.78 (ester C=O), 6.07 (lactam C=O), 6.33 (C=C), 7.65, 8.28 (ester C—O—C), 9.79 (ether C—O—C), 11.28 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.31; N, 4.41. Found: C, 68.2; H, 7.18; N, 4.14.

This compound failed to give a 2,4-dinitrophenylhydrazone even when it was refluxed with the reagent for 1 hr.; the enol ether was recovered unchanged.

Sodium 1,2,3,4-tetrahydro-α-methoxy-1,4,4,6,7-pentamethyl-2-oxo-$\Delta^{\alpha,3}$-quinolinacetate (XVIII). To 0.20 g. (0.63 mmole) of recrystallized enol ether (XVII) was added 1 ml. of 1*N* ethanolic sodium hydroxide. After standing overnight, the mixture was heated on the steam bath for 75 min. under reflux. The cooled solution deposited white, flaky crystals. These were collected, washed with 1 ml. of ethyl alcohol, and dried; yield 0.17 g. (83%). The salt did not melt below 295° and had $\lambda_{\max(\mu)}^{\text{KBr}}$ 6.13 (lactam C=O), 6.25, 7.20 (carboxylate ion), 11.27 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{17}H_{20}NO_4Na \cdot H_2O$: C, 59.5; H, 6.41. Found: C, 58.9; H, 6.42.

1,2,3,4-Tetrahydro-α-methoxy-1,4,4,6,7-pentamethyl-2-oxo-$\Delta^{\alpha,3}$-quinolinacetic acid (XIX). A suspension of 7.42 g. (0.0226 mole) of the sodium salt (XVIII) in a mixture of 50 ml. of water and 50 ml. of chloroform was acidified with 25 ml. of 6*N* hydrochloric acid, then shaken vigorously. The chloroform layer was separated, dried over magnesium sulfate, and concentrated *in vacuo*; yield 5.91 g. (86.5%), m.p. 168–176°. An analytical sample was prepared by recrystallization from Skellysolve B,[5] then from 25% aqueous methanol, m.p. 175–177°.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.3; H, 6.98; N, 4.62. Found: C, 67.4; H, 7.12; N, 4.67.

A similar preparation had $\lambda_{\max(\mu)}^{\text{KBr}}$ 3.8–4.2 (acidic OH), 5.76 (carboxylic acid C=O), 6.10 (lactam C=O), 6.35 (C=C), 9.47 (ether C—O—C), no ester C—O—C at 7.65 or 8.28.

Acid hydrolysis of methyl 1,2,3,4-tetrahydro-α-methoxy-1,4,4,6,7-pentamethyl-2-oxo-$\Delta^{\alpha,3}$-quinolinacetate (XVII). A mixture of 0.06 g. (0.3 mmole) of the recrystallized enol ether (XVII) in 1 ml. of methyl Cellosolve and 2 ml. of 6*N* hydrochloric acid was heated on the steam bath for 1 hr. The solvents were removed *in vacuo*, leaving a colorless oil with $\lambda_{\max(\mu)}^{\text{film}}$ 5.77 (ester C=O), 6.03 (lactam C=O), 7.81, 8.75 (ester C—O—C), no C=C at 6.33.

The above hydrolysis product was dissolved in 1.5 ml. of methanol and 2.0 ml. of 2,4-dinitrophenylhydrazine reagent. The solution was heated on the steam bath for 1 min. and then cooled in an ice bath. Two drops of water were added. The yellow precipitate that formed was collected by filtration, washed with 1 ml. of 50% methyl alcohol, and dried. The yellow solid melted at 70–85°. The infrared spectrum was similar to that of the 2,4-dinitrophenylhydrazone previously prepared from crude XII; $\lambda_{\max(\mu)}^{\text{KBr}}$ 5.85 (ester C=O), 6.05 (lactam C=O), 7.50 (NO_2).

1,2,3,4-Tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxaldehyde (XXV) *2,4-dinitrophenyl hydrazone.* Methyl 1,2,3,4-tetrahydro-α-methoxy-1,4,4,6,7-pentamethyl-2-oxo-$\Delta^{\alpha,3}$-acetate (XIX) (0.512 g., 1.68 mmoles) was heated in a bath at 180–190° for 17.5 min. The solid melted and a gas was evolved. The orange residue weighed 0.427 g. It was dissolved in 7.5 ml. of Skellysolve B[5] and the solution chilled. The yellow crystals that formed were collected on a filter and washed with 2 ml. of Skellysolve B.[5] The crystals weighed 0.210 g., m.p. 135–165°; the infrared spectrum was almost identical with that of methyl 1,2,3,4-tetrahydro-α-methoxy-1,4,4,6,7-pentamethyl-2-oxo-$\Delta^{\alpha,3}$-quinolinacetate (XVII). The filtrate was concentrated *in vacuo*. The orange, viscous residue weighed 0.184 g.; $\lambda_{\max(\mu)}^{\text{film}}$ 3.71 (aldehyde CH, weak), 5.78 (ester and aldehyde C=O), 5.99 (lactam C=O, 6.22 ($>$C=C$<$), 7.43 (CH_3), 11.41 (1,2,4,5-tetrasubstituted benzene).

A solution of 0.163 g. (0.62 mmole) of the above crude aldehyde (XXV) in 2 ml. of ethanol was treated with 10 ml. of 2,4-dinitrophenylhydrazine reagent. Within 1 min. an orange precipitate formed. The mixture was warmed gently on the steam bath for 30 sec., then chilled. The amorphous precipitate was collected, washed with 2 ml. of chilled 60% alcohol, and dried *in vacuo*; yield 0.09 g. (25%, 9% based on XVII), m.p. 135–165°. The infrared spectrum was almost identical with that of a previously prepared analytical sample, m.p. 273–274°; $\lambda_{\max(\mu)}^{\text{KBr}}$ 3.06 (NH), 6.02 (lactam C=O), 6.11 (aryl + NH + NO_2), 7.54 (NO_2), no ester C=O about 5.8.

Anal. Calcd. for $C_{21}H_{23}N_5O_5$: C, 59.3; H, 5.45. Found: C, 59.3; H, 5.22.

1,4-Dihydro-1,2,4,4,6,7-hexamethylquinoline (XIII). To a stirred solution of 0.01 mole of methyllithium prepared from 0.65 ml. (0.011 mole) of methyl iodide and 0.141 g. (0.021 mole) of lithium metal in 11 ml. of ether was added dropwise with stirring a solution of 1.1 g. (0.0050 mole) of 3,4-dihydro-1,4,4,6,7-pentamethylcarbostyril (XI) in 5 ml. of ether. The resulting solution was stirred for 25 min., then poured onto Dry Ice. After the Dry Ice had evaporated, the mixture was diluted with 60 ml. of ether, then re-extracted with 80 ml. of 0.25*N* sodium hydroxide. After a second extraction with 20 ml. of *N* sodium hydroxide, the ether layer was concentrated to dryness *in vacuo* to give 1.07 g. (99%) of a pink, crystalline solid, m.p. 107–120°. After three recrystallizations from Skellysolve B,[5] white crystals were obtained, m.p. 113.5–114.5°; $\lambda_{\max(\mu)}^{\text{KBr}}$ 6.00 (C=C—N), 6.20, 6.59, 6.76 (aryl), 7.22 (CH_3), 11.29 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.7; H, 9.83; N, 6.51. Found: C, 83.2; H, 9.81; N, 6.38.

1,2,3,4-Tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylic acid (XV) *and 1,4-dihydro-1,4,4,6,7-pentamethyl-2-quinoline* (XIV). Phenyllithium (0.01 mole) was prepared from 1.57 g. (0.01 mole) of bromobenzene and 0.153 g. (0.022 mole) of lithium metal in 10 ml. of ether in the usual manner. To the stirred phenyllithium solution at room temperature was added 1.62 g. (0.0075 mole) of 3,4-dihydro-1,4,4,6,7-pentamethylcarbostyril (XI) in 10 ml. of ether. The addition was accompanied by an exothermic reaction. The resulting solution was stirred at room temperature for 25 min., then poured onto powdered Dry Ice. After the Dry Ice had evaporated, the resulting mixture was diluted with 45 ml. of ether and extracted with three 35-ml. portions of saturated aqueous sodium bicarbonate solution. The combined alkaline extracts were acidified with dilute sulfuric acid and extracted with 50 ml. of methylene chloride. The methylene chloride was removed *in vacuo* and the brown, viscous residue (0.65 g.) dissolved in hot benzene. The benzene solution was diluted with an equal volume of Skellysolve B,[5] treated with Norit, and filtered. The chilled filtrate yielded 0.46 g. (23.4%) of white crystals of XV, m.p. 146–148° dec. A sample of a pilot preparation formed white crystals, m.p. 145–147° dec.; a 1:1 ratio of phenyllithium to XI was used and the yield was 7.7%; $\lambda_{\max(\mu)}^{\text{KBr}}$ 3.90 (carboxyl OH), 5.76 (acid C=O), 6.12 (lactam C=O), 7.30 (CH_3, COOH), 11.53 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.9; H, 7.33. Found: C, 69.1; H, 7.39.

A few milligrams of the recrystallized acid (XV) were heated at 160° until the evolution of gases had ceased (about 4 min.). The infrared spectrum of the solid residue was almost identical with that of an analytical sample of 3,4-dihydro-1,4,4,6,7-pentamethylcarbostyril (XI); $\lambda_{\max(\mu)}^{\text{KBr}}$ 5.90 (lactam C=O), 11.35 (1,2,4,5-tetrasubstituted benzene).

In a larger run, the ether solution of nonacidic material was dried, then evaporated to dryness *in vacuo;* 1,4-dihydro-1,4,4,6,7-pentamethyl-2-phenylquinoline (XIV) was obtained as a yellow oil, b.p. 158–160° (0.075 mm.); $\lambda_{\max(\mu)}^{\text{film}}$ 6.02 (C=C—N), 6.18 (aryl), 7.33 (methyl), 11.38 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{20}H_{23}N$: C, 86.6; H, 8.36; N, 5.05. Found: C, 86.0; H, 8.25; N, 5.06.

Methyl 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylate (XVI). (A) A mixture of 5.45 g. (0.021 mole) of 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylic acid (XV) and 10 ml. of thionyl chloride was refluxed for 40 min. The resulting solution was evaporated to dryness *in vacuo* and the last traces of thionyl chloride were removed by the addition and removal *in vacuo* of 10 ml. of dry xylene. A solution of the resulting acid chloride in 20 ml. of methanol was refluxed for 30 min., then evaporated to dryness *in vacuo*. The residue was dissolved in 20 ml. of methylene chloride, then washed with 25 ml. of half-saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, then evaporated to dryness *in vacuo*. The residue was crystallized from 25 ml. of Skellysolve B[5] to yield 4.86 g. (85%) of crystalline solid, m.p. 110–114°. Recrystallization from Skellysolve B[5] raised the melting point to 115–116.5°; $\lambda_{\max(\mu)}^{\text{KBr}}$ 5.78 (ester C=O), 6.01 (lactam C=O), 8.64 (ester C—O—C); $\lambda_{\max(m\mu)}^{\text{abs. alc.}}$ 255 (ϵ 9580).

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.8; H, 7.69; N, 5.09. Found: C, 69.8; H, 7.86; N, 4.85.

(B) To a solution of 10.0 g. (0.038 mole) of 1,2,3,4,-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylic acid (XV) in 100 ml. of methanol was added dropwise with swirling 10 ml. of acetyl chloride. The reaction mixture was refluxed for 30 min., then cooled to room temperature. After the addition of a second portion (5 ml.) of acetyl chloride, the reaction mixture was refluxed for 1 hr. more, then concentrated to dryness *in vacuo*. The residue was dissolved in 100 ml. of benzene. The benzene solution was washed with two 75-ml. portions of saturated aqueous sodium bicarbonate and 75 ml. of water, then dried over magnesium sulfate and evaporated to dryness *in vacuo* to yield 9.30 g. of a white, crystalline solid. Recrystallization from 30 ml. of Skellysolve C[5] gave 8.12 g. (77%) of the methyl ester (XVI), m.p. 110–111°, the infrared spectrum of which was essentially identical with that of the analytical sample of procedure A.

1,2,3,4-Tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxanilide (XX). A solution of 0.26 g. (1.0 mmole) of 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinoline carboxylic acid (XV) in 3 ml. of thionyl chloride was refluxed for 25 min. The excess thionyl chloride was removed *in vacuo* and the residue was dissolved in 7 ml. of acetone, then 0.25 ml. of aniline was added dropwise with stirring. After 20 min., the reaction mixture was poured in 12 ml. of *N* sulfuric acid and the resulting precipitate was filtered and washed with two 10-ml. portions of sodium carbonate solution to give 0.33 g. (97%) of the anilide (XX), m.p. 232–234°.

An analytical sample was obtained by recrystallization of a similar preparation from aqueous ethanol to give white crystals, m.p. 234–236°; $\lambda_{\max(\mu)}^{\text{KBr}}$ 3.02 (NH), 6.03 (amide C=O), 6.47 (amide NH), 13.23, 14.42 (phenyl).

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 75.0; H, 7.19. Found: C, 74.6; H, 7.14.

1,2,3,4-Tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxamide (XXI). A mixture of 1.0 g. (3.65 mmoles) of methyl 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylate (XVI) and 1.0 g. of urea was fused at 235–245° for 13 min. After being allowed to cool to room temperature, the residue was powdered, then triturated with water. The water-insoluble material was filtered, then stirred for 30 min. in 10 ml. of concd. hydrochloric acid. A second 10-ml. portion of concd. hydrochloric acid was added and the suspension was stirred an additional 10 min., then filtered. The filtrate was concentrated to dryness *in vacuo* to yield 0.59 g. (54%) of the crude carboxamide (XXI), m.p. 205–225°. Purification was effected by redissolving the solid in 20 ml. of 6*N* hydrochloric acid, decolorizing with Norit, and filtering. The filtrate was diluted with 10 ml. of water, then cooled to 0° and filtered to yield 0.25 g. of the amide (XXI), m.p. 215–220°; $\lambda_{\max(\mu)}^{\text{KBr}}$ 2.95 (OH, NH), 6.00 (amide C=O).

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.2; H, 7.74; N, 10.8. Found: C, 68.9; H, 7.73; N, 10.6.

5,10-Dihydro-2-imino-5,5,7,8,10-pentamethylpyrimido-[4,5-b]quinoline-4(4aH)one (XXII). A mixture of 0.95 g. (3.45 mmoles) of methyl 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylate (XVI), 0.45 g. (4.75 mmoles) of guanidine hydrochloride, and 0.44 g. (8.15 mmoles) of sodium methoxide in 10 ml. of freshly distilled *N*,*N*-dimethylformamide was heated at 120° for 5 hr. At the end of this time, the mixture was cooled to 60° and 20 ml. of water was added. The suspended solids all dissolved immediately and a crystalline precipitate of the product (XXII) began to separate. The reaction was cooled to 0°, then filtered to yield 0.58 g. (54%) of a cream-colored solid, m.p. >270°. Recrystallization from 30 ml. of methanol gave 0.42 g. of white needles in two crops. This material was homogeneous on paper chromatography in solvent A,[11] with a blue fluorescent spot at R_f 0.82; $\lambda_{\max(m\mu)}^{\text{pH 1}}$ 326 (ϵ 12,700), $\lambda_{\max(m\mu)}^{\text{pH 7}}$ 321 (ϵ 11,600), $\lambda_{\max(m\mu)}^{\text{pH 13}}$ 307 (ϵ 12,850).

Anal. Calcd. for $C_{16}H_{20}N_4O$: C, 67.6; H, 7.09; N, 19.7. Found: C, 67.7; H, 7.10; N, 20.0.

5,10-Dihydro-5,5,7,8,10-pentamethylpyrimido[4,5-b]quinoline-2,4(3H,4aH)dione (XXIII). To a warm (50–60°) solution of 1.0 g. of XXII in 150 ml. of glacial acetic acid was added dropwise with stirring a solution of 8 g. of sodium nitrite in 20 ml. of water. The solution turned a deep yellow. The reaction mixture was left at room temperature for 4 hr., then a second 8-g. portion of sodium nitrite in 20 ml. of water was added and the solution was stored at room temperature for 16 hr. The solution was evaporated to dryness *in vacuo* and the residue was washed with several portions of water to remove the inorganic salts, leaving 0.5 g. of insoluble, yellow solid; paper chromatography in solvent A[10] showed two yellow fluorescent spots with R_f values of 0.66 and 0.79, respectively.

Extraction of 148 mg. of this solid with three portions of concd. hydrochloric acid totaling 7 ml. gave 37 mg. of an insoluble material which still contained a mixture of components as shown by paper chromatography. The acid solution was diluted with 42 ml. of water, then cooled to 0° and filtered to yield 68 mg. of yellow solid that was homogeneous on paper chromatography in solvent A with a yellow fluorescent spot at R_f 0.87. A second reprecipitation from 2.5 ml. of concd. hydrochloric acid and 15 ml. of water gave the analytical sample: $\lambda_{\max(m\mu)}^{\text{pH }1}$ 347 (ϵ 9600), $\lambda_{\max(m\mu)}^{\text{pH }7}$ 342 (ϵ 10,300), $\lambda_{\max(m\mu)}^{\text{pH }13}$ 346 (ϵ 8200).

Anal. Calcd. for $C_{16}H_{19}N_3O_2 \cdot HCl$: C, 59.7; H, 6.26; Cl, 11.0; N, 13.1. Found: C, 60.1; H, 5.85; Cl, 10.8; N, 13.2.

3-Chloro-3′,4′-propionoxylidide (XXVI). To a refluxing solution of 80.1 g. (0.667 mole) of 3,4-xylidine (VII) in 70 ml. of acetone was added, with stirring, a solution of 42.6 g. (0.333 mole) of 3-chloropropionyl chloride in 30 ml. of acetone over a period of 50 min. The solution was stirred under reflux for 1 hr. after the addition was completed. The cooled solution was poured into 500 ml. of 1*N* hydrochloric acid. The oil that separated solidified on cooling the mixture in an ice bath. The solid material was dried *in vacuo* overnight at 55° and recrystallized from 280 ml. of 65% aqueous ethanol with use of Norit; yield 61 g. (87%), m.p. 106–109°. A sample recrystallized for analysis formed white crystals, m.p. 109.5°; $\lambda_{\max(\mu)}^{\text{KBr}}$ 3.03 (NH), 6.04 (amide C=O), 6.46 (amide NH), 12.22 (1,3,4-trisubstituted benzene).

Anal. Calcd. for $C_{11}H_{14}ClNO$: C, 62.4; H, 6.66; Cl, 16.8; N, 6.61. Found: C, 62.7; H, 6.85; Cl, 16.6; N, 6.36.

3,4-Dihydro-6,7-dimethylcarbostyril (XXXII). A mixture of 29 g. (0.104 mole) of 3-chloro-3′,4′-propionoxylidide (XXVI) and 47 g. (0.35 mole) of anhydrous powdered aluminum chloride in 210 ml. of Skellysolve C[5] was heated under reflux with stirring for 2 hr. The stirred mixture was cooled, decomposed with ice, and treated with 30 ml. of 6*N* hydrochloric acid. The white solid was collected on a filter and dried *in vacuo* at 60°; weight 23 g., m.p. 120–150°. The crude product was recrystallized from 65 ml. of ethanol with the use of Norit; yield 7.1 g., m.p. 180–195°. The product was purified further by recrystallization from methanol-ethanol (95 ml.: 15 ml.); yield of pure product, 5.0 g. (30%). The colorless flat needles melted at 199–202°; $\lambda_{\max(\mu)}^{\text{KBr}}$ 3.12 (NH), 5.96 (lactam C=O), 7.25 (methyl); 11.28 (1,2,4,5-tetrasubstituted benzene). The infrared spectrum was identical with that of an analytical sample which had been prepared in 12% yield by the fusion of aluminum chloride with 3-chloro-3′,4′-propionoxylidide (XXVI).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.4; H, 7.48; N, 7.99. Found: C, 75.3; H, 7.71; N, 7.76.

3,4-Dihydro-1,6,7-trimethylcarbostyril (XXXIII). A stirred mixture of 8.9 g. (0.051 mole) of 3,4-dihydro-6,7-dimethylcarbostyril (XXXII) and 1.30 g. (0.054 mole) of sodium hydride in 75 ml. of *N*,*N*-dimethylformamide was warmed gently on the steam bath until most of the sodium hydride had reacted. The mixture was stirred with ice cooling while 3.7 ml. (8.5 g., 0.060 mole) of methyl iodide was added. Stirring was maintained with ice cooling for 15 min. and then the mixture was warmed on the steam bath with occasional stirring for 15 min. more. The solvent was removed *in vacuo* and the residue suspended in 75 ml. of chloroform. The suspension was washed with two 125-ml. portions of water. The chloroform solution, dried over magnesium sulfate, was concentrated *in vacuo*. The residue (8.0 g.) was distilled, b.p. 109° (0.06 mm.) (bath temperature 120–130°): weight 7.55 g. The oil was dissolved in 25 ml. of Skellysolve B[5] and the solution chilled to yield 7.50 g. (77.8%) of white crystals, m.p. 46.5–48.0°. A recrystallized sample melted at 47.5–49.5°; $\lambda_{\max(\mu)}^{\text{KBr}}$ 5.95 (lactam C=O), 11.30 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.2; H, 7.99. Found: C, 76.3; H, 8.01.

1-(3,4-Xylyl)-2-azetidinone (XXX). A stirred solution of 8.64 g. (0.041 mole) of 3-chloro-3′,4′-propionoxylidide (XXVI) in 75 ml. of *N*,*N*-dimethylformamide was treated with 1.1 g. (0.046 mole) of sodium hydride. Hydrogen was evolved and the temperature of the reaction mixture rose to 35°. After 5 min. the vigorous reaction had subsided and the milky suspension was stirred 5 min. at 20°, then 5 min. on the steam bath. The solvent was removed *in vacuo* and the residue was dissolved in 50 ml. of benzene. The benzene solution was washed with two 50-ml. portions of water, dried over magnesium sulfate, and concentrated *in vacuo*. The residue (5.45 g.) distilled at 103–110° (0.15 mm.) (bath temperature 135–180°). The distillate (1.45 g.) was dissolved in 21 ml. of Skellysolve B[5]–benzene (20:1) and chilled. The white crystals were collected; yield 0.52 g. (7.2%), m.p. 101–103°. Recrystallization from benzene–Skellysolve B raised the m.p. to 104–105°; $\lambda_{\max\,\mu}^{\text{KBr}}$ 5.76 (β-lactam C=O), 6.65 (aryl), 7.21 (CH_3), 12.35 (1,2,4-trisubstituted benzene), no amide NH at 3.03 or 6.48.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.4; H, 7.48. Found: C, 75.4; H, 7.57.

3-Chloro-N-methyl-3′,4′-propionoxylidide (XXIX). To a stirred solution of 5.0 g. (0.024 mole) of 3-chloro-3′,4′-propionoxylidide (XXVI) and 5.76 g. (0.30 mole) of methyl iodide in 25 ml. of *N*,*N*-dimethylformamide was added 0.65 g. (0.027 mole) of sodium hydride. Vigorous evolution of hydrogen occurred and the temperature rose to 50°. The mixture was chilled in an ice bath to 20° and an additional 2.28 g. of methyl iodide was added. The stirring with ice-cooling was continued for 15 min. The reaction mixture was poured into 350 ml. of ice water and the aqueous mixture was extracted with two 45-ml. portions of methylene chloride. Concentration of the combined extracts *in vacuo* yielded 3.55 g. of a viscous liquid that distilled at 96–100° (0.05 mm.) (bath temperature 120–130°); weight 1.84 g. From its infrared spectrum the mixture was judged to be about a 2:1 mixture of the expected product (XXIX) and β-lactam (XXX); $\lambda_{\max(\mu)}^{\text{film}}$ 5.73 (β-lactam C=O), 6.04 (amide C=O), 12.13 (1,2,4-trisubstituted benzene), no NH about 3.0.

Methyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolineglyoxylate (XXXVIII) *2,4-dinitrophenylhydrazone*. A stirred mixture of 2.0 g. (0.011 mole) of 3,4-dihydro-1,6,7-trimethylcarbostyril (XXXIII) and 0.54 g. (0.023 mole) of sodium hydride in 7.5 g. of dimethyl oxalate and 7.6 ml. of *N*,*N*-dimethylformamide was heated under reflux for 2.5 hr. The solvent was removed *in vacuo* and the residue was suspended in 35 ml. of benzene. The excess sodium hydride was decomposed with 3 ml. of acetic acid. The resulting suspension was washed with 30 ml. of half-saturated sodium bicarbonate solution. The bicarbonate wash was extracted with 35 ml. of chloroform. The combined organic solutions were washed with 50 ml. of water, dried over magnesium sulfate, and concentrated *in vacuo*, finally at 80° (0.05 mm.). A brown, viscous residue was obtained; weight 2.40 g.; $\lambda_{\max(\mu)}^{\text{film}}$ 5.75 (ester C=O), 6.00 (shoulder, ketone C=O), 6.06 (lactam C=O), 7.91 (ester C—O—C), no enol ether C=C at 6.3.

To a solution of 0.645 g. (2.34 mmoles) of the crude methyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolineglyoxylate (XXXVIII) was added 18 ml. of freshly prepared methanolic 2,4-dinitrophenylhydrazine reagent containing 0.54 g. (2.7 mmoles) of the hydrazine. After several seconds, an orange precipitate formed and the mixture was heated to boiling on the steam bath and then chilled. The precipitate was collected on a filter and washed with 3 ml. of cold methanol. The moist precipitate was suspended in 25 ml. of water and the acid solution was neutralized with saturated sodium bicarbonate solution. The amorphous solid was collected on a filter and dried *in vacuo*; yield 0.22 g. (21%), m.p. about 120–140°. Recrystallization from a mixture of methanol, ethanol, and ethyl acetate yielded a crystalline sample which melted at 252–255° and which was not quite pure; $\lambda_{\max(\mu)}^{\mathrm{KBr}}$ 3.02 (shoulder, NH), 5.78 (ester C=O), 6.02 (lactam C=O), 6.19 (aryl + C=N), 6.65 (aryl + NH + NO_2), 6.93 (NO_2), 11.51 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{21}H_{21}N_5O_7$: C, 55.4; H, 4.65; N, 15.4. Found: C, 54.8; H, 4.74; N, 14.6.

Ethyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XXXV). A stirred mixture of 5.0 g. (0.026 mole) of 3,4-dihydro-1,6,7-trimethylcarbostyril (XXXIII) and 1.3 g. (0.054 mole) of sodium hydride in 12.5 ml. of ethyl carbonate and 12.5 ml. of *N*,*N*-dimethylformamide was refluxed for 1.1 hr. The volatile materials were removed *in vacuo* and the residue was dissolved in 100 ml. of benzene. The benzene solution was washed with 50 ml. of water, dried over magnesium sulfate, then concentrated *in vacuo*. The residue (4.88 g.) was dissolved in a solution of 14 ml. of benzene and 21 ml. of Skellysolve B,[5] then chilled. The crystalline material was collected and washed with 10 ml. of Skellysolve B[5]; yield 1.98 g., m.p. 90–95°. A second crop weighing 0.90 g., m.p. 85–95°, was obtained. The combined yield was 2.88 g. (42%). An analytical sample was prepared from a similar run by several recrystallizations from benzene–Skellysolve B,[5] m.p. 98–100°; $\lambda_{\max(\mu)}^{\mathrm{KBr}}$ 5.78 (ester C=O), 6.00 (lactam C=O), 8.41 (ester C—O—C); $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 1,7,13}$ 258 (ϵ 10,400).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.9; H, 7.33. Found: C, 69.1; H, 7.41.

1,2,3,4-Tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid (XXXVII). A solution of 0.60 g. (2.3 mmoles) of ethyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XXXV) in 6 ml. of 1.25*N* sodium hydroxide solution was refluxed on the steam bath for 1 hr., the resulting solution was chilled, and the white, crystalline sodium salt (XXXVI) was collected; yield 0.46 g. (79%), m.p. 160–165°; $\lambda_{\max(\mu)}^{\mathrm{KBr}}$ 6.04 (lactam C=O), 6.20, 7.00 (carboxylate).

To a suspension of 0.40 g. (1.58 mmoles) of the sodium salt (XXXVI) in 7.5 ml. of water, 5 g. of methylene chloride, and 5 ml. of chloroform was added 2 ml. of 6*N* hydrochloric acid. The mixture was shaken, then the organic layer was separated and concentrated to dryness *in vacuo* to give 0.28 g. (80%) of a white, crystalline solid, m.p. 160–161° dec. (rapid heating). Recrystallization from benzene–Skellysolve B[5] gave white crystals, m.p. 154.5–155.5°, $\lambda_{\max(\mu)}^{\mathrm{Nujol}}$ 5.77 (acid C=O), 6.08 (lactam C=O).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.48; N, 6.01. Found: C, 66.9; H, 6.37; N, 6.03.

Pyrolysis of this acid (XXXVII) at 180° caused a vigorous evolution of gas. After 3.5 min., gas evolution ceased and the infrared spectrum of the resulting product was identical with that of 3,4-dihydro-1,6,7-trimethylcarbostyril (XXXIII); $\lambda_{\max(\mu)}^{\mathrm{film}}$ 5.97 (lactam C=O), 7.42 (CH_3), 11.35 (1,2,4,5-tetrasubstituted benzene).

1,2,3,4-Tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid hydrazide (XXXIV). A solution of 0.50 g. (1.92 mmoles) of ethyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XXXV) in 5 ml. of hydrazine hydrate and 5 ml. of ethanol was heated on a steam bath for 30 min., then poured into 100 ml. of water and kept at 0° overnight. The white, flocculent precipitate was collected, washed with water, and dried *in vacuo*; yield 0.42 g. (91.5%), m.p. 182.5–183.5°; $\lambda_{\max(\mu)}^{\mathrm{KBr}}$ 3.02 (OH, NH), 6.00 (C=O and C=N), 7.39 (CH_3), 11.40 (1,2,4,5-tetrasubstituted benzene); $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 1}$ 257 (ϵ 10,350), $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 7}$ 256 (ϵ 10,550), $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 13}$ 254 (ϵ 12,620).

An analytical sample was recrystallized from benzene, m.p. 178–180°.

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.1; H, 6.93; N, 17.0. Found: C, 63.5; H, 7.21; N, 16.9.

Ethyl 3-bromo-1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLIV) *and 'dibromide'* (XLIII). To a stirred solution of 2.61 g. (0.01 mole) of ethyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XXXV) in 20 ml. of chloroform was added dropwise 0.55 ml. (0.011 mole) of bromine. After an initial induction period of a few minutes, the bromine color was discharged almost immediately after each drop was added. After the addition was complete, the orange solution was stirred for 5 min., then the solvent was removed *in vacuo* with a bath temperature of 30°. Trituration of the resulting yellow oil with 40 ml. of benzene–Skellysolve B[5] (1:1) caused crystallization of the 'dibromide' (XLIII) to occur. The orange-yellow crystals were removed by filtration to yield 1.20 g., m.p. 90°, resolidifying at 110–120° and remelting at 245–248° (the melting point of XLVIII).

The filtrate was cooled at 0° overnight, then filtered to yield 0.78 g. (23%) of almost white monobromide (XLIV), m.p. 120–125°, resolidifying at 130–135° and remelting at 230–240°; $\lambda_{\max(\mu)}^{\mathrm{KBr}}$ 5.70 (ester C=O), 6.03 (lactam C=O, 8.03 8.12 (ester C—O—C), 11.26 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{15}H_{18}BrNO_3$: C, 53.0; H, 5.33; Br, 23.5. Found: C, 53.3; H, 5.53; Br, 20.0. A satisfactory bromine analysis could not be obtained.

From a similar run, 1.00 g. of the dihydro ester (XXXV) and 0.20 ml. of bromine gave 0.55 g. of the 'dibromide' (XLIII), m.p. 90–91°, resolidifying at 125–130° and remelting at 246–248°; $\lambda_{\max(\mu)}^{\mathrm{KBr}}$ 5.78, 5.83 (ester C=O), 6.13 (lactam C=O).

Anal. Calcd. for dibromide of XXXV: Br, 38.2. Found: Br, 37.8.

A solution of 102 mg. of the 'dibromide' (XLIII) in 5 ml. of chloroform was extracted with two 5-ml. portions of saturated aqueous sodium bicarbonate and 5 ml. of water. The aqueous layers were back-extracted with 5 ml. of chloroform. The chloroform layers were combined and dried over magnesium sulfate, then evaporated to dryness *in vacuo* to yield 53 mg. of a yellow oil which crystallized on standing. The infrared spectrum of this material was identical with that of authentic ethyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVII).

Treatment of 101 mg. of the monobromide (XLIV) with saturated aqueous sodium bicarbonate under the same conditions gave a quantitative recovery of the starting monobromide (XLIV).

1,2-Dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid (XLVIII). A flask containing 0.348 g. (1 mmole) of ethyl 3-bromo-1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLIV) was heated at 160° for 5 min. The bromoester melted and evolved a gas, then the melt resolidified. The cream-colored crystalline residue weighed 0.228 g. (98.6% yield), m.p. 235–250°. The crude acid (XLIII) was dissolved in 10 ml. of 1*N* aqueous sodium hydroxide, then was washed with 10 ml. of chloroform. The aqueous layer was diluted with 10 ml. of water, then neutralized with 6*N* sulfuric acid. The cream-colored precipitate was filtered, washed with water, then dried to yield 0.224 g. (97%) of the carboxylic acid (XLVIII), m.p. 250–253°; $\lambda_{\max(\mu)}^{\mathrm{KBr}}$ 5.80 (acid C=O), 6.17 (lactam C=O, C=C), 11.44 (1,2,4,5-tetrasubstituted benzene); $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 1}$ 364 (ϵ 8200), $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 7}$ 353 (ϵ 8450), $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 13}$ 341 (ϵ 7900.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.67; N, 6.06. Found: C, 67.3; H, 5.74; N, 5.97.

Methyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVI). A solution of 2.0 g. (8.65 mmoles) of 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid (XLVIII) in 16 ml. of thionyl chloride was refluxed for 1 hr. The reaction was evaporated to dryness *in vacuo* and the last traces of thionyl chloride were removed by the addition and evaporation *in vacuo* of 10 ml. of dry benzene; $\lambda_{\max(\mu)}^{\mathrm{Nujol}}$ 5.65 (acid chloride C=O).

The yellow, crystalline solid was dissolved in 25 ml. of benzene-methanol (1:1), then refluxed for 10 min. and left at room temperature overnight. Removal of the solvent *in vacuo* gave a crystalline residue which was dissolved in methylene chloride and washed with 10 ml. of saturated aqueous sodium bicarbonate. Evaporation of the methylene chloride *in vacuo* followed by recrystallization of the residue from benzene gave 1.56 g. (74%) of the carbomethoxy derivative (XLVI), m.p. 153–157°, in two crops; $\lambda_{\max(\mu)}^{\mathrm{KBr}}$ 5.76 (ester C═O), 6.11 (lactam C═O and aryl), 6.22 (C═C), 11.32 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.16; N, 5.71. Found: C, 68.6; H, 6.21; N, 5.64.

Ethyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVII) was prepared in 78% yield, m.p. 105,–109°, by the procedure described for the carbomethoxy derivative (XLVI).

Recrystallization from benzene–Skellysolve B[5] raised the melting point to 109–110°; $\lambda_{\max(\mu)}^{\mathrm{KBr}}$ 5.78 (ester C═O), 5.90, 6.07 (lactam C═O); $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 1}$ 359 (ϵ 7400), $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 7}$ 362 (ϵ 7400), $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 13}$ 338 (ϵ 8200).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.5; H, 6.61; N, 5.40. Found: C, 69.2; H, 6.70; N, 5.24.

1,2-Dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid, hydrazide (XLV). A solution of 0.117 g. (4.5 mmoles) of ethyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVII) in 1.2 ml. of methanol was treated with 0.5 ml. of hydrazine hydrate. After about 3 min., a crystalline precipitate separated. The resulting mixture was heated on a steam bath for 1 min., then diluted with 10 ml. of water. The crystalline precipitate was filtered, then dried to yield 0.105 g. (95%), m.p. 215.0–215.5°; $\lambda_{\max(\mu)}^{\mathrm{KBr}}$ 3.07 (NH), 6.02 (C═O); $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 1}$ 365 (ϵ 7370), $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 7}$ 360 (ϵ 8800), $\lambda_{\max(m\mu)}^{\mathrm{pH}\ 13}$ 354 (ϵ 7860).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.6 H, 6.16; N, 17.1. Found: C, 63.7; H, 6.32; N, 17.0.

2,10-Dihydro-2-imino-7,8,10-trimethylpyrimido[4,5-b]-quinoline-4(3H)one (L) *acetate.* A mixture of 290 mg. (3.06 mmoles) of guanidine hydrochloride, 500 mg. (2.04 mmoles) of methyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVI), and 6 ml. of 1*N* methanolic sodium methoxide was refluxed for 3 hr., then cooled and diluted with 25 ml. of water and 5 ml. of saturated aqueous sodium bicarbonate. The precipitate was filtered and washed with water, then dried to give 230 mg. of crude L as a yellow solid.

The acetate salt of L was prepared by heating 50 mg. of the above yellow solid in 30 ml. of 85% acetic acid on a steam bath for 30 min. After being allowed to cool, the supernatent liquid was separated by centrifugation and the solid was dried; yield 48 mg. of yellow solid, m.p. >300°, which was homogeneous on paper chromatography in solvent B[10] with R_f 0.57.

Anal. Calcd. for $C_{14}H_{14}N_4O \cdot HC_2H_3O_2$: C, 61.1; H, 5.77; N, 17.8. Found: C, 61.0; H, 5.62; N, 17.5.

Acknowledgment. The authors wish to thank Dr. Peter Lim for interpretation of the infrared absorption spectra and his staff for the paper chromatography. The authors are also indebted to Mr. O. P. Crews, Jr., and his staff for large-scale preparation of certain intermediates.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

Synthesis and Reactions of Monosubstituted Triptych-Boroxazolidines[1]

ALFRED A. SCHLEPPNIK[2] AND C. DAVID GUTSCHE

Received February 10, 1960

The synthesis of a series of 3-alkyl, 3-aryl, 3-alkoxymethyl, and 3-dialkylaminomethyltriptych-boroxazolidines has been carried out. In addition, several triptychboroxazolidines carrying reactive functional groups at the 3-position have been prepared including the 3-chloromethyl, 3-hydroxymethyl, 3-aminomethyl, and 3-cyanomethyl compounds. Certain of the reactions of the 3-chloromethyl and 3-aminomethyltriptych-boroxazolidines have been investigated with particular reference to the linking of an amino acid moiety to the triptych-boroxazolidine moiety. Although the chloromethyl compound proved to be of limited use in this respect, the aminomethyl compound has provided a boron-containing amino acid, a compound of possible interest in cancer chemotherapy.

The suggestion by Kruger that the neutron-induced disintegration of boron should be applicable to cancer chemotherapy[3] and the demonstration by Christensen *et al.*[4] that some of the amino acids selectively concentrate in certain tumor cells provided the incentive to investigate the synthesis of boron-containing amino acids.[5] The present work involves certain aspects of the chemistry of the triptych-boroxazolidine type of compound[6] and had as its aim the incorporation of this moiety in an amino acid. Triethanolamine borate (I), the simplest triptych-boroxazolidine, was reported first in 1933 in a German patent[7] and investigated in much more detail by Brown and Fletcher[8] and by Hein and Burckhardt.[9] It is with monosubstituted triethanolamine borates that the present paper is concerned, although from the standpoint of a therapeutic agent the triethanolamine borate ring is not the most desirable, as it undergoes fairly rapid hydrolysis. Much more stable is tripropanolamine borate, which has half life in water at 25° of 618 days, over 10^5 greater than the half life of triethanolamine borate.[10] Even in the symmetrically-substituted compound, however, the possibility of diastereoisomers exists (IIa and IIb) and, in fact, Steinberg and Hunter[10] obtained evidence for two species in their tripropanolamine borate preparation, one considerably more rapidly hydrolyzed than the other. The species were not identified, but they may possibly be the two diastereoisomeric forms of II(*a* and *b*). The substitution of another group for one of the methyl groups in II obviously complicates the isomer problem further, and for this reason the initial studies avoided unsymmetrically-polysubstituted triptychboroxazolidines. It had been hoped that both the isomer problem and the hydrolysis problem could be circumvented by using *gem*-dimethyl compounds. Unfortunately, trialkanolamines containing *gem*-dimethyl groups (III) did not yield triptych compounds but gave instead what are thought to be noncyclic borate esters of structure IV. For these reasons the initial work in this laboratory has been conducted on the simplest members of the series, *viz.*, the monosubstituted triptych-boroxazolidines.

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[1] This work was supported, in part, by grant no. CY-3275 from the National Institutes of Health.

[2] Postdoctoral Research Associate 1958–1959.

[3] P. G. Kruger, *Proc. Natl. Acad. Sci.*, **26**, 181 (1940).

[4] H. N. Christensen and T. R. Riggs, *J. Biol. Chem.*, **194**, 57 (1952); H. N. Christensen, T. R. Riggs, H. Fischer, and I. M. Palatine, *J. Biol. Chem.*, **198**, 1, 17 (1952); T. R. Riggs, B. A. Coyne, and H. N. Christensen, *J. Biol. Chem.*, **209**, 395, 413 (1954).

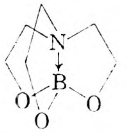
[5] For another recent report of the synthesis of a boron-containing amino acid *cf.* H. R. Snyder, A. J. Reedy, and W. J. Lennarz, *J. Am. Chem. Soc.*, **80**, 835 (1958).

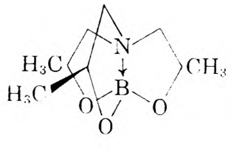
[6] This nomenclature is that suggested in the "Preliminary Report of the Advisory Committee on the Nomenclature of Organic Boron Compounds."

[7] C. A. Rojahn, DRP 582,149 (Cent., 1933, II, 2704).

[8] H. C. Brown and E. A. Fletcher, *J. Am. Chem. Soc.*, **73**, 2808 (1951).

[9] F. Hein and R. Burckhardt, *Z. Anorg. u. Allg. Chem.*, **268**, 159 (1952).


I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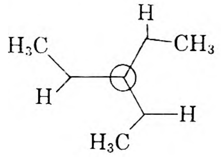
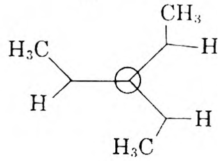

IIa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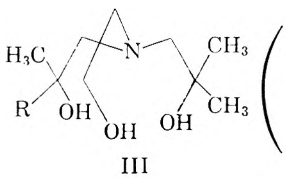
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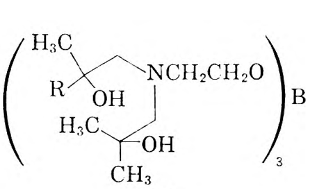
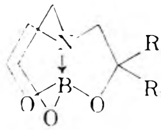
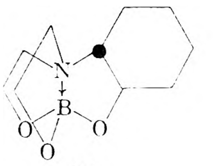
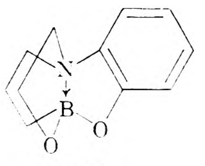

IV

Alkyl and aryl-substituted triptych-boroxazolidines. Although it is possible to obtain the triptych compounds from boric acid and the appropriate trialkanolamine, the preparation proceeds more smoothly and with fewer complications[11] when a boric acid ester is employed. In the present instance, tri-*n*-butyl borate was generally used as the boronating agent, and the *n*-butylalcohol which was formed was removed by distillation. In this fashion compounds of structure V, VI, and VII were prepared, the products in all cases being rather high-melting, crystalline solids soluble in acetonitrile and dimethylformamide, less soluble in chloroform, and insoluble in ether, petroleum ether, dioxane, tetrahydrofuran, etc. The requisite trialkanolamines for compounds of structure V and VI were prepared from diethanolamine and the appropriate epoxide, the reaction being conducted in most cases in chloroform with a trace of water or ethanol as catalyst.[12] The starting material for VII was obtained from *o*-aminophenol and excess ethylene oxide.[13]


V

a. $R_1 = H, R_2 = CH_3$
b. $R_1 = H, R_2 = C_2H_5$
c. $R_1 = H, R_2 = CH{=}CH_2$
d. $R_1 = H, R_2 = C_6H_5$
e. $R_1 = R_2 = CH_3$


VI


VII

Alkoxy-substituted triptych-boroxazolidines. Using boron trifluoride as a catalyst[14] alcohols were condensed with epichlorohydrin to yield 1-alkoxy-2-hydroxy-3-chloropropanes which were then converted to the corresponding epoxides by the action of sodium hydroxide.[15] Using the same sequence of reactions as described above, compounds of structure VIII were prepared. These materials are lower-melting than the alkyl- and aryl-substituted analogs (V, VI, VII) and are soluble in benzene. Of particular interest in this group is 3-diethoxymethyltriptych-boroxazolidine (VIIIe), which was prepared[16] from acrolein diethyl acetal by conver-

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[10] H. Steinberg and D. L. Hunter, *Ind. and Eng. Chem.*, 49, 174 (1957).

[11] As Hein and Burckhardt observed, the use of boric acid often leads to the formation of a low-melting, extremely hygroscopic by-product which makes the purification of the triptych compound difficult. These authors suggested that this by-product was a boric acid salt of the triptych compound. On the basis of the similarity of the infrared spectrum of the by-product with that of the polymer derived from chloromethyltriptych-boroxazolidine (*cf.* later section) and with the knowledge that esters containing free B—OH groups are exceedingly susceptible to hydrolysis, it seems equally likely that the by-product is a cross-linked polymeric boric acid ester containing free B—OH groups.

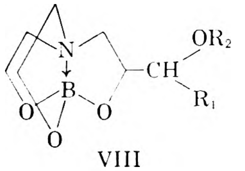
[12] J. W. Headlee, A. R. Collett, and C. L. Lazzell, *J. Am. Chem. Soc.*, 55, 1066 (1949).

[13] I. G. Farben, DRP 296,309 (1927).

[14] *Cf.* E. Levas and H. Lefebvre, *Compt. rend.*, 222, 555, 1439 (1946) for the use of boron trifluoride in similar condensations involving phenols.

[15] H. Flores-Gallardo and C. B. Pollard, *J. Org. Chem.*, 12, 831 (1947).

[16] J. E. Wuller, masters thesis, Washington University, 1957.

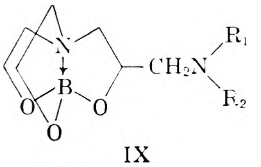


VIII

a. R_1 = H, R_2 = CH_3
b. R_1 = H, R_2 = C_2H_5
c. R_1 = H, R_2 = $CH_2CH{=}CH_2$
d. R_1 = H, R_2 = $CH_2C_6H_5$
e. R_1 = OC_2H_5, R_2 = C_2H_5

sion to the corresponding epoxide *via* the chlorohydrin, reaction of the epoxide with diethanolamine, and boronation with boric acid to VIIIe.

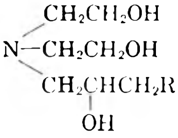
Dialkylamino and alkylarylamino-substituted triptych-boroxazolidines. The action of secondary amines on epichlorohydrin followed by treatment with base[17] yielded 1-dialkylamino-2,3-epoxypropanes. Treatment of these with diethanolamine followed by treatment with tri-*n*-butyl borate provided compounds of structure IX. These materials are moderately high-melting, crystalline solids, soluble in benzene and acetonitrile, distillable in high vacuum without decomposition, and possessing only very weakly basic properties as indicated by failure to form salts with hydrogen chloride and hydrogen bromide and by only a very slow reaction with ethyl iodide.



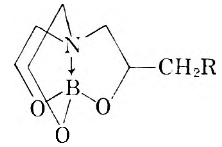
IX

a. R_1 = R_2 = CH_3
b. R_1 = R_2 = C_2H_5
c. R_1 = R_2 = n-C_3H_7
d. R_1 = R_2 = n-C_4H_9
e. R_1 + R_2 = C_4H_8O (morphiline)
f. R_1 + R_2 = C_5H_{10} (piperidine)
g. R_1 = CH_3, R_2 = C_6H_5

Triptych-boroxazolidines substituted with reactive functional groups. The chloromethyl compound (XIa) was obtained from β-chloromethyltriethanolamine (Xa), prepared by the action of diethanolamine on epichlorohydrin. This intermediate. which slowly polymerized as the result of intramolecular quaternization, provided the triptych compound (XIa) in 93% yield if it were subjected soon after preparation to the action of triethyl borate. The hydroxymethyl compound (XIb) was obtained from β-hydroxymethyltriethanolamine (Xb), prepared from 1-chloro-2 3-dihydroxypropane, by the action of tri-*n*-butyl borate. The aminomethyl compound (XIc) was prepared by three routes. the one of choice involving the ammonation of Xa to β-aminomethyltriethanolamine (Xc) followed by boronation with tri-*n*-butyl borate to XIc. Allylamine provided the starting material for two further syntheses of this compound. Conversion to ethyl *N*-allylcarbamate (XIIa) followed by epoxidation to XIIIa and treatment with diethanolamine yielded the trialkanolamine derivative Xd which on hydrolysis provided Xc, convertible to XIc as indicated above. Alternatively, allylamine was converted to benzyl *N*-allylcarbamate (Xd), which was then epoxidized to XIIIb and treated with diethanolamine to yield Xd. Boronation with tri-*n*-butyl borate gave 3-*N*-carbobenzoxyaminomethyltriptych - boroxazolidine (XId) from which the benzyloxy group could be removed by catalytic hydrogenolysis, providing a third synthesis of XIc. The cyanomethyl compound (XIe) was prepared by treating a methanolic solution of β-chloromethyl-triethanolamine (Xa) with a concentrated aqueous solution of potassium cyanide to yield Xe, followed by boronation to XIe.



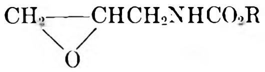
X a. R = Cl
b. R = OH
c. R = NH_2
d. R = $NHCO_2C_2H_5$
e. R = CN



XI a. R = Cl
b. R = OH
c. R = NH_2
d. R = $NHCO_2CH_2C_6H_5$
e. R = CN

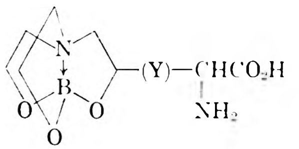
$CH_2{=}CHCH_2NHCO_2R$

XII a. R = C_2H_5
b. R = $CH_2C_6H_5$



XIII a. R = C_2H_5
b. R = $CH_2C_6H_5$

Reactions of triptych-boroxazolidines. The goal of this work, as yet incompletely realized, was to prepare compounds of the general structure XIV where the bridge (Y) between the triptych-boroxazolidine moiety and the amino acid moiety involves a C—C link, an O—C link, or a N—C link. To this end, the compounds XIa and XIc appeared to be promising, and a number of experiments have been carried out with this pair of substances. Unfortunately, the chloromethyl compound (XIa) was ineffectual as a generally-useful alkylating agent. Thus, sodium methoxide or magnesium methoxide in boiling xylene, potassium cyanide in dimethylformamide, cuprous cyanide in pyridine, sodio diethyl malonate,[18] secondary



XIV

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(17) H. Gilman, C. S. Sherman, C. C. Price, R. C. Elderfield, J. T. Maynard, R. H. Reitsema, L. Tolman, S. P. Massie, F. J. Marshall, and L. Goldman, *J. Am. Chem. Soc.*, 68, 1291 (1946).

(18) As the possibility could not be excluded that the anion $B(OR)_3CH(CO_2C_2H_5)_2^-$ would form and interfere with the alkylation, the reaction of sodio diethylmalonate with allyl bromide in the presence of one mole-equivalent of triethyl borate was carried out. A 50% yield of diethyl allylmalonate was obtained, indicating that the failure of XIa to yield a product is probably not due to this difficulty.

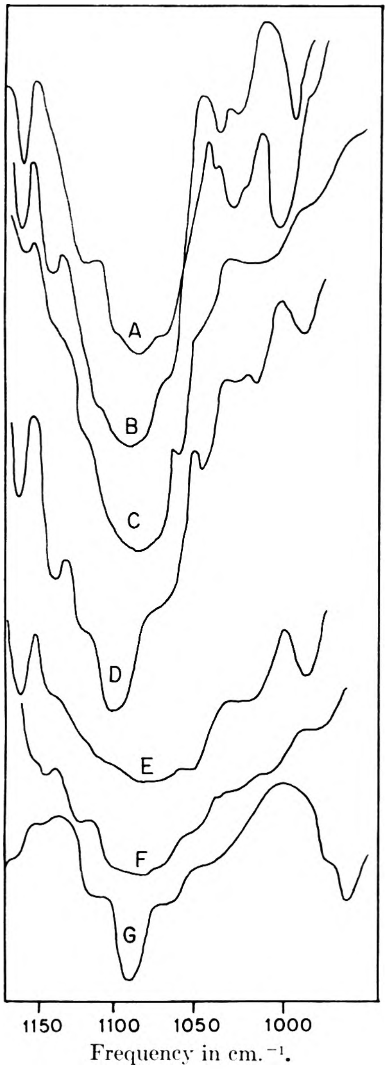
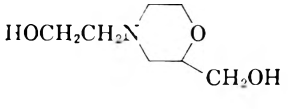


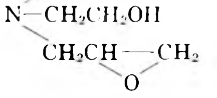
Fig. 1. Infrared spectra of triptychboroxazolidines in 1100 cm.$^{-1}$

Regions: (A) Triptychboroxazolidine (I). (B) 3-Methyltriptychboroxazolidine (Va.) (C) 3-Hydroxymethyltriptychboroxazolidine (XIb). (D) 3-Chloromethyltriptychboroxazolidine (XIa). (E) 2-Cyanomethyltriptychboroxazolidine (XIe). (F) 3-Benzoylaminomethyltriptychboroxazolidine (XVIc). (G) N-(3-triptychboroxazolidinylmethyl)glutamine (XVIIc)

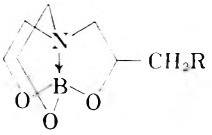
amines in dimethylformamide, and hydrogen in the presence of palladium-charcoal all failed to react with XIa. Sodium methoxide in methanol or sodium ethoxide in ethanol, however, did react with XIa to yield the morpholine derivative XV when a 1:1 ratio of alkoxide to XIa was employed or the alkoxymethylene triptych compound when a 4:1 ratio of alkoxide to XIa was used. A possible explanation for the formation of XV assumes a base-catalyzed alcoholysis to the trialkanolamine (Xa) which may then undergo elimination of hydrogen chloride to form the epoxide XVI. Intramolecular reaction of XVI would yield XV, while intermolecular reaction of XVI with alkoxide ion followed by reboronation could yield VIIIa. Substitution products were also obtained through the action of potassium phthalimide and sodium acetate which led to XVIa and XVIb, respectively. Sodium hydride reacted with XIa, but the product (which appears to be a polymer) was not characterized.



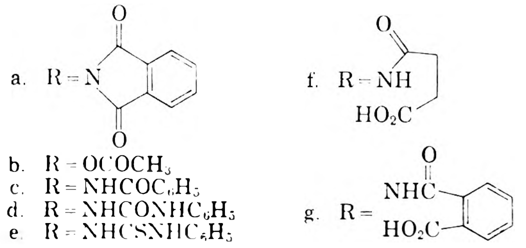
XV



XVI

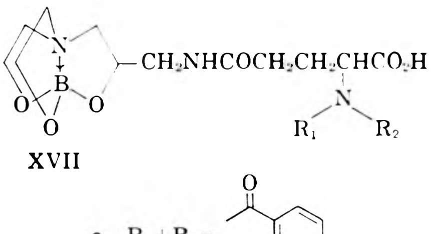


XVI

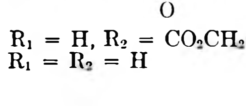


b. R = OCOCH$_3$
c. R = NHCOC$_6$H$_5$
d. R = NHCONHC$_6$H$_5$
e. R = NHCSNHC$_6$H$_5$

The aminomethyl-triptych compound (XIc) was more amenable to reaction than XIa and, albeit with some reluctance, formed derivatives including the N-benzoyl compound (XVIc), the urea derivative from phenylisocyanate (XVId), and the thiourea derivative from phenyl isothiocyanate (XVIe). Succinic anhydride reacted with XIc to yield XVIf, and phthalic anhydride gave, initially, the half amide XVIg which upon heating at 200° was converted to the imide XVIa, identical with the material obtained *via* the chloromethyl compound. An alternate synthesis of XVIa involved the conversion of 3-phthalimido-1,2-epoxypropane to the corresponding triethanolamine derivative followed by boronation. DL-Phthalimidoglutamic acid anhydride reacted with XIc to yield the amino acid derivative XVIIa and with L-N-carbobenzyloxyglutamic acid anhydride to yield the amino acid derivative XVIIb. Catalytic hydrogenolysis of XVIIb furnished the free amino acid XVIIc as a crystalline, low-melting solid but so hygroscopic that an analysis could not be obtained.



XVII



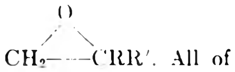
b. R$_1$ = H, R$_2$ = CO$_2$CH$_2$C$_6$H$_5$
c. R$_1$ = R$_2$ = H

The structural assignment is based on the fact that the compound contains boron, gives a positive ninhydrin test, possesses certain bands in the infrared characteristic of the triptych and amino acid moieties, and was prepared by a sequence of reactions which has been shown to lead to such compounds in related instances.

The present investigation has established the fact that the triptych-boroxazolidine moiety may be incorporated as a unit into more complex structures even when the triptych compound is only monosubstituted and thus hydrolytically unstable. It is anticipated that further research in this area will extend the procedures described herein to the use of more highly-substituted triptych compounds leading to the synthesis of substances of greater biological interest and utility.

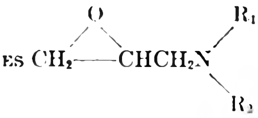
EXPERIMENTAL[19]

Analytical methods. Epoxides containing no basic nitrogen were determined by first treating the sample with a 5% solution of pyridine hydrobromide in glacial acetic acid followed then by titrating with 0.1N perchloric acid in glacial acetic acid using methyl violet as indicator. Epoxides containing basic nitrogen were determined by the method of Durbetaki.[20] Basic nitrogen was determined by titration with 0.1N perchloric acid in glacial acetic acid using methyl violet as indicator.[21] In the case of the triptych-boroxazolidines, which are such weak bases that they do not titrate smoothly with perchloric acid, the following procedure was employed. A 0.2–0.3-g. sample of the compound was dissolved in 50 ml. of 0.1N perchloric acid in acetic acid, and the solution was heated on the steam bath for 15 min. After cooling to room temperature, the excess perchloric acid was back titrated with 0.1N sodium acetate in glacial acetic acid. Boron content was determined by the method of Thomas[22] which involves treating the borate ester with methanol and sulfuric acid, distilling the methyl borate which is formed into a receiver containing water, and titrating the resulting boric acid solution with sodium hydroxide in the presence of mannitol.

Epoxides of the general structure  $CH_2\!-\!-\!CRR'$ (O bridging). All of the epoxides used in the experiments described below in which R and R′ are H, alkyl, aryl, alkoxymethyl, or aryloxymethyl are readily available as items of commerce or *via* syntheses described in the literature. The aminoalkylethylene oxides, listed in Table I, were prepared by adding the appropriate secondary amine to epichlorohydrin[17] and maintaining the temperature over the 4-hr. period of addition at 20–25°. Aqueous sodium hydroxide was then added at such a rate that the temperature was maintained at 25–30°. The resulting epoxide was worked up in the usual way and purified by distillation through a short Vigreux column.

Triethanolamine derivatives of general structure $(HOCH_2CH_2)_2NCH_2C(OH)R_1R_2$. The triethanolamine derivatives listed in Table II were prepared in all cases by the addition of the appropriate epoxide to a chloroform solution of diethanolamine. After the initial exothermic reaction had subsided, the solution was refluxed for several hours and the product then worked up in the usual way and purified by distillation through a short Vigreux column. In the majority of instances a triacetyl derivative of the trialkanolamine was prepared, and in all such cases the analysis for nitrogen agreed closely with the calculated value.

TABLE I

DIALKYLAMINO- AND ARYLALKYLAMINOMETHYLETHYLENE OXIDES  $CH_2\!-\!-\!CHCH_2N(R_1)(R_2)$

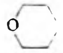
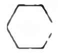
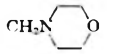
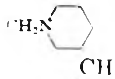
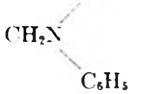
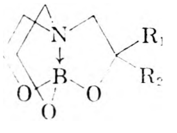
R Groups			Nitrogen, %		Epoxide Oxygen, %	
R_1	R_2	Formula	Calcd.	Found	Calcd.	Found
n-C_3H_7	n-C_3H_7	$C_9H_{19}NO$	8.91	9.01	10.17	10.32
n-C_4H_9	n-C_4H_9	$C_{11}H_{23}NO$	7.56	7.58	8.64	8.53
		$C_7H_{13}NO_2$	9.78	9.92	11.18	11.05
		$C_8H_{15}NO$	9.92	10.01	11.33	11.45
CH_3	C_6H_5	$C_{10}H_{13}NO$	8.58	8.65	9.80	9.79

TABLE II

β-SUBSTITUTED TRIETHANOLAMINES
$(HOCH_2CH_2)_2NCH_2C(OH)R_1R_2$

R Groups			Nitrogen, %	
R_1	R_2	Formula	Calcd.	Found
H	CH_3	$C_7H_{17}NO_3$	8.68	8.71
H	C_2H_5	$C_8H_{19}NO_3$	7.90	7.93
H	$CH{=}CH_2$	$C_8H_{17}NO_3$	8.00	7.90
H	C_6H_5	$C_{12}H_{19}NO_3$	6.22	6.11
CH_3	CH_3	$C_8H_{19}NO_3$	7.90	7.97
H	CH_2OCH_3	$C_8H_{19}NO_4$	7.25	7.39
H	$CH_2OC_2H_5$	$C_9H_{21}NO_4$	6.76	6.90
H	$CH_2OCH_2CH{=}CH_2$	$C_{10}H_{21}NO_4$	6.39	6.25
H	$CH_2OCH_2C_6H_5$	$C_{14}H_{23}NO_4$	5.20	5.20
H	$CH_2OC_6H_5$	$C_{13}H_{21}NO_4$	5.49	5.51
H	$CH_2N(CH_3)_2$	$C_9H_{22}N_2O_3$	13.58	13.23
H	$CH_2N(C_2H_5)_2$	$C_{11}H_{26}N_2O_3$	11.96	11.67
H	$CH_2N(n\text{-}C_3H_7)_2$	$C_{13}H_{30}N_2O_3$	10.68	10.81
H	$CH_2N(n\text{-}C_4H_9)_2$	$C_{15}H_{34}N_2O_3$	9.65	9.71
H		$C_{11}H_{24}N_2O_4$	11.24	11.22
H		$C_{12}H_{26}N_2O_3$	11.37	11.39
H	 $CH_2N(CH_3)(C_6H_5)$	$C_{14}H_{24}N_2O_3$	10.44	10.26

Triptych-boroxazolidines of general structure.



The three methods applicable to the synthesis of triptych-boroxazolidines are illustrated in the preparation of triptych-boroxazolidine (triethanolamine borate) itself.

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[19] All melting points were determined on a Kofler hot stage calibrated against compounds of known melting point. All boiling points are uncorrected. Infrared spectra were determined on a Perkin Elmer Model 21 instrument. We are indebted to Mrs. Franziska Schleppnik for most of the boron and nitrogen analyses.

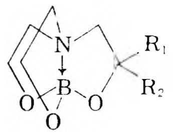
(20) A. J. Durbetaki, *Anal. Chem.*, **30**, 2024 (1958).

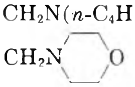
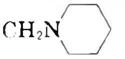
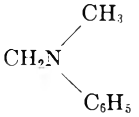
(21) E. F. Hillenbrand and C. A. Pentz, in *Organic Analysis*, Vol. III, Interscience Inc., New York, N. Y., 1956, p. 145.

(22) L. H. Thomas, *J. Chem. Soc.*, 820 (1946).

TABLE III

3-SUBSTITUTED TRIPTYCH-BOROXAZOLIDINES



R Groups		M.P.	Recrystallization Solvent[a]	Formula	Boron, %		Nitrogen, %	
R_1	R_2				Calcd.	Found	Calcd.	Found
H	CH_3	197–198°	a	$C_7H_{14}BNO_3$	6.33	6.26	8.19	8.18
H	C_2H_5	144–145°	a	$C_8H_{16}BNO_3$	5.91	5.93	7.65	7.79
H	$CH{=}CH_2$	155–156°	t	$C_8H_{14}BNO_3$	5.98	5.94	7.75	7.79
H	C_6H_5	228–229°	a	$C_{12}H_{16}BNO_3$	4.64	4.72	6.01	6.27
CH_3	CH_3	178–180°	a–e	$C_8H_{16}BNO_3$	5.91	5.97	7.65	7.65
H	CH_2OCH_3	89–90°	b–p	$C_8H_{16}BNO_4$	5.38	5.26	6.97	7.14
H	$CH_2OC_2H_5$	119–120°	b–p	$C_9H_{18}BNO_4$	5.04	4.79	6.52	6.78
H	$CH_2OCH_2CH{=}CH_2$	73–74.5°	b–p	$C_{10}H_{18}BNO_4$	4.77	4.79	6.17	6.25
H	$CH_2OCH_2C_6H_5$	108–110°	b–p	$C_{14}H_{20}BNO_4$	3.90	3.90	5.05	5.29
H	$CH_2OC_6H_5$	184–186°	b–d	$C_{13}H_{18}BNO_4$	4.11	4.35	5.33	5.23
H	$CH_2N(CH_3)_2$	152–153°	b	$C_9H_{19}BN_2O_3$	5.06	5.21	13.08	12.90
H	$CH_2N(C_2H_5)_2$	136–137°	b–p	$C_{11}H_{23}BN_2O_3$	4.47	4.27	11.57	11.31
H	$CH_2N(n\text{-}C_3H_7)_2$	126–127°	b–p	$C_{13}H_{27}BN_2O_3$	4.01	4.03	10.38	10.40
H	$CH_2N(n\text{-}C_4H_9)_2$	133–134°	b–p	$C_{15}H_{31}BN_2O_3$	3.64	3.85	9.40	9.30
H		189–190°	a–b	$C_{11}H_{21}BN_2O_4$	4.23	4.37	10.92	11.06
H		188–189°	a	$C_{12}H_{23}BN_2O_3$	4.26	4.33	11.02	11.00
H	 $CH_2N(CH_3)(C_6H_5)$	174–175°	a–b	$C_{14}H_{21}BN_2O_3$	3.92	3.98	10.14	10.30

[a] Abbreviations for recrystallization solvents: *a*—acetonitrile, *b*—benzene, *d*—dimethylformamide, *e*—ether, *p*—petroleum ether (b.p. 63–69°), *t*—toluene.

(A) *Boric acid method.* A mixture of 31.0 g. (0.5 mole) of boric acid and 75.0 g. (0.5 mole) of triethanolamine was dissolved, with heating, in 100 ml. of dry dimethylformamide.[23] The water formed in the reaction was distilled off through a short Vigreux column, and after *ca.* 75 ml. of distillate had been collected (head temperature 148°) the solution was cooled to room temperature. The solid fraction was removed by filtration, washed with dimethylformamide, and dried to yield 75.1 g. (96%) of colorless crystals, m.p. 238–239° (reported[7] m.p. 236.5–237.5°).

(B) *Boric ester method.* A 14.9-g. (0.1 mole) sample of triethanolamine was added to 23.0 g. (0.1 mole) of tri-*n*-butyl borate. The initially turbid solution warmed and became clear and then deposited a solid. The butanol was removed by distillation, and the residue was dried to yield 15.7 g. (100%) of colorless crystals, m.p. 235–236°.

(C) *From triacetyltriethanolamine.* Triethanolamine was converted to the triacetate with acetic anhydride in acetic acid,[24] and 13.8 g. (0.05 mole) of this product was treated with 11.5 g. (0.05 mole) of tri-*n*-butyl borate containing 0.1 g. of sodium dissolved in 30 ml. of anhydrous *n*-butyl alcohol. The solution was refluxed for 1 hr., and the butanol and butyl acetate were then removed under reduced pressure. The residue was recrystallized from chloroform–petroleum ether (b.p. 63–69°) to give colorless needles, m.p. 235–236°. The triptych-boroxazolidines listed in Table III were prepared by the boric ester method, and the products were purified by recrystallization, in many cases after prior distillation in a short path apparatus at 0.01 mm. or less.

trans-3,4-Tetramethylenetriptych-boroxazolidine (VI). A 3.0-g. sample of cyclohexene oxide and 3.2 g. of diethanolamine in 30 ml. of chloroform was refluxed for 48 hr. The product consisted of 4.5 g. (74%) of a colorless, very viscous liquid which, upon boronation with tri-*n*-butyl borate gave VI in quantitative yield. Recrystallization from toluene–petroleum ether furnished colorless needles, m.p. 138–139°.

Anal. Calcd. for $C_{10}H_{18}BNO_3$: B, 5.07; N, 6.64. Found: B, 3.69; N, 6.67.

3,4-Dehydro-3,4-benzotriptych-boroxazolidine (VII). Boronation of 4.9 g. of *N,N*-bis(2′-hydroxyethyl)-*o*-aminophenol[13] with 5.8 g. of tri-*n*-butyl borate yielded a brown oil. This was extracted with boiling acetonitrile and the extract evaporated on the steam bath. The resulting semisolid residue was purified by distillation in a short path apparatus to yield colorless crystals, m.p. 155–156°.

Anal. Calcd. for $C_{10}H_{12}BNO_3$: B, 5.28; N, 6.83. Found: B, 5.21; N, 6.99.

3-Chloromethyltriptych-boroxazolidine (XIa). To a stirred and cooled solution of 21.0 g. (0.2 mole) of diethanolamine in 100 ml. of chloroform was slowly added 18.5 g. (0.2 mole) of epichlorohydrin in 50 ml. of chloroform. The mixture was stirred overnight at room temperature, and the solvent was then removed under vacuum to leave 39.6 g. (100%) of β-chloromethyltriethanolamine (Xa) as a viscous, yellow oil. A qualitative test indicated the presence of chloride ion (arising from quaternary compound), and distillation at 0.001 mm. decomposed the material. Consequently, it was used without purification and as soon as possible in the next step which consisted in treating with an equimolar amount of triethyl borate. In a reaction employing 197.5 g. (1 mole) of crude Xa and 146 g. (1 mole) of triethyl borate, the ethanol was slowly distilled through a short column; when the head temperature reached 78°, 200 ml. of dry toluene was introduced and the distillation continued until the head temperature reached 82°. The resulting pale brown solution was cooled, and the white, crystalline product was removed by filtration, washed with dry toluene and petroleum ether, and dried to yield 159 g. (81%) of material, m.p. 149–153°, pure enough for subsequent reactions. Concentration of the mother liquor under reduced pressure and extraction of the residue with hot acetonitrile left a product which was dissolved in hot benzene–petroleum ether (b.p. 33–58°). When this solution was cooled, an additional 24 g. of product was isolated, m.p. 150–153°, bringing the total yield to 171 g. (93%). An analytical sample was prepared by several recrystallizations from benzene–petroleum ether (b.p. 33–58°) and obtained as colorless needles, m.p. 153–155°.

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[23] Technical grade dimethylformamide was dried over calcium hydride and then distilled. The fraction with b.p. 150–151° was collected and stored over calcium hydride in brown bottles.

[24] L. W. Jones and G. R. Burnd, *J. Am. Chem. Soc.*, **47**, 2966 (1925).

Anal. Calcd. for $C_7H_{13}BClNO_3$: B, 5.18; N, 6.70. Found: B, 5.28 N, 7.04.

3-Hydroxymethyltriptych-boroxazolidine (XIb). A solution of 22.1 g. (0.2 mole) of glycerine-α-chlorohydrin[25] and 42.0 g. (0.2 mole) of diethanolamine in 100 ml. of ethanol was refluxed for 4 hr. The solvent was removed under reduced pressure, and the residue was dissolved in water and passed through an Amberlite IRA-400 column in the hydroxy form. The eluate was evaporated under reduced pressure and the residue was distilled in a short path apparatus to yield 22.8 g. (63%) of a viscous, colorless liquid, b.p. 185–205° (3 mm.). A center cut was taken for analysis:

Anal. Calcd. for $C_7H_{17}NO_4$: N, 7.81. Found: N, 7.88.

The tetraacetate was prepared by dissolving 2.0 g. of β-hydroxymethyltriethanolamine (Xb) in 10 ml. of acetic acid and 10 ml. of acetic anhydride and refluxing for 1 hr. The product was purified by distillation in a short path apparatus and obtained as a colorless, mobile liquid, b.p. 160–165° (0.5 mm.).

Anal. Calcd. for $C_{15}H_{25}NO_8$: N, 4.03. Found: N, 4.00. Addition of 8.7 g. of Xb to tri-*n*-butyl borate gave 9.2 g. (100%) of a glassy solid which crystallized after standing at room temperature for 3 months. Trituration with benzene–petroleum ether–acetonitrile removed a small amount of an oily impurity and left colorless crystals which did not have a sharp melting point but sintered over a rather wide range.

Anal. Calcd. for $C_7H_{14}BNO_4$: B, 5.68; N, 7.34. Found: B, 5.71; N, 7.40.

3-Aminomethyltriptych-boroxazolidine (XIc). (*A*) *From Ethyl N-Allylcarbamate* (XII). A solution of 25.8 g. (0.2 mole) of ethyl *N*-allylcarbamate in 200 ml. of methylene chloride was oxidized with peroxytrifluoroacetic acid obtained from 8.2 ml. of 90% hydrogen peroxide (0.3 mole) and 61 ml. of trifluoroacetic anhydride in 50 ml. of methylene chloride.[26] The crude product was distilled through a short Vigreux column to give 22.7 g. (78%) of a colorless liquid, b.p. 95.5–96° (2 mm.).

Anal. Calcd. for $C_6H_{11}NO_3$: Epoxide oxygen, 11.02. Found: Epoxide oxygen, 11.00. A 19.3-g. sample (0.133 mole) of the product described above was dissolved in 50 ml. of chloroform and treated with 13.9 g. (0.133 mole) of diethanolamine. The crude product, 33.2 g. (100%), could not be distilled without decomposition and was used without further purification. A solution of 23.0 g. (0.092 mole) of this material in 50 ml. of 20% hydrochloric acid was refluxed for 4 hr., the solvent and excess acid were removed under reduced pressure, and the residue was dissolved in 100 ml. of water and passed through an Amberlite IRA-400 column in the hydroxyl form. Evaporation of the eluate left a residue which was distilled in a short path apparatus to yield 16.1 g. (98%) of β-aminomethyltriethanolamine (Xc). Boronation of 8.9 g. of Xc with 10.7 g. of tri-*n*-butyl borate yielded 9.3 g. (100%) of a thick, yellow oil Distillation at 185–195° (0.1 mm.) gave a colorless oil which partially solidified after long standing at room temperature. Recrystallization from benzene–acetonitrile–petroleum ether (b.p. 63–69°) gave colorless crystals, m.p 60–66°, and it is this material that is compared (*cf.* below) with subsequent preparations. However, a second recrystallization from chloroform–petroleum ether (b.p. 63–69°) caused a sharp elevation in melting point to 115–116°, presumably another crystalline modification.

Anal. Calcd. for $C_7H_{16}BN_2O_3$: B, 5.70; N, 14.75. Found: B, 5.59; N, 14.87.

(*B*) *From benzyl N-allylcarbamate* (XIIb). A 16.5 g. (0.1 mole) sample of XIIb, prepared from allylamine and carbobenzyloxychloride, was epoxidized with peroxytrifluoroacetic acid[26] to yield 10.0 g. (56%) of a colorless oil, b.p. 150–151° (0.5 mm.).

Anal. Calcd. for $C_{11}H_{15}NO_3$: Epoxide oxygen, 7.72. Found: Epoxide oxygen, 7.88. Treatment of 4.1 g. (0.02 mole) of this material with 2.1 g. (0.02 mole) of diethanolamine yielded 6.2 g. (100%) of β-carbobenzyloxyamidomethyltriethanolamine, a 5.6-g. sample of which was treated with 4.2 g. of tri-*n*-butyl borate. The resulting product was recrystallized from acetonitrile to give 4.0 g. (68%) of 3-carbobenzyloxyamidomethyltriptych-boroxazolidine (XId), m.p. 143–144°.

Anal. Calcd. for $C_{15}H_{21}BN_2O_5$: B, 3.38 Found: B, 3.56. The 3-aminomethyl compound (XIc) was prepared from XId by dissolving 3.3 g. of the latter in 30 ml. of dry dimethylformamide, adding 10% palladium on charcoal catalyst, and hydrogenolyzing for 55 hr. when 90% of the calculated volume of hydrogen had been absorbed. The product was worked up to give 1.8 g. (100%) of colorless crystals, m.p. 63–65°, which did not depress the melting point when admixed with a sample prepared by method A described above.

(*C*) *From β-chloromethyltriethanolamine* (Xa). A solution of crude Xa, prepared as described above from 105 g. of diethanolamine and 94 g. of epichlorohydrin, in 200 ml. of chloroform was added with stirring over a period of 8 hr. to 1 l. of concd. ammonia heated at 60°. After stirring and heating overnight the product was worked up to give 109 g. (62%) of oil, b.p. 195–200° (0.01 mm.).

Anal. Calcd. for $C_7H_{18}N_2O_3$: N, 15.72. Found: N, 15.48. The tetraacetyl derivative of Xc was obtained as a slightly yellow oil, b.p. 175–180° (0.1 mm.).

Anal. Calcd. for $C_{15}H_{26}N_2O_7$: N_{basic}, 4.04. Found: N_{basic}, 3.91. Treatment of Xc with tri-*n*-butyl borate yielded XIc as colorless crystals, m.p. 63–65°, showing no depression in melting point when admixed with material prepared by methods A or B.

3-Cyanomethyltriptych-boroxazolidine (XIe). A solution of 0.2 mole of β-chloromethyltriethanolamine (Xa) in 80 ml. of methanol was cooled in an ice bath and treated, with stirring, with 13 g. (0.2 mole) of potassium cyanide dissolved in a small amount of water, the temperature during the addition being maintained at 10–12°. The solution was allowed to stand at room temperature for 24 hr., and the small amount of solid that had formed was removed by filtration. The filtrate was evaporated, triturated with ethanol, and filtered and evaporated again, and the residue was then treated with tri-*n*-butyl borate and *n*-butyl alcohol until a clear solution resulted. Removal of the *n*-butyl alcohol by distillation left a brown crystalline material which was dissolved in boiling acetonitrile, treated with decolorizing charcoal, and diluted with benzene to cloudiness. Upon chilling in an ice bath the impurities first separated as a black cake adhering to the walls of the flask. Decantation and further cooling then furnished the product as 14.5 g. of colorless crystals, m.p. 149–153°. Recrystallization from benzene–acetonitrile–ether gave colorless needles; m.p. 155–156° $\bar{\nu}^{\text{KBr}}$ 2247 cm.$^{-1}$ (nitrile).

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(25) T. H. Ryder and A. J. Hill, *J. Am. Chem. Soc.*, **52**, 1521 (1930).

(26) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).

Anal. Calcd. for $C_8H_{13}BN_2O_3$: B, 5.41; N_{basic}, 7.00. Found: B, 5.52; N_{basic}, 7.18.

2-Hydroxymethyl-4-(2′-hydroxyethyl)morpholine (XV). An ethanol solution of β-chloromethyltriethanolamine (Xa) prepared from 19.5 g. of epichlorohydrin and 21 g. of diethanolamine, was treated with 13.5 g. of sodium ethoxide in 150 ml. of ethanol. After stirring for 1 hr. and standing overnight at room temperature, the solvent was removed and the residue was distilled from the solid products to yield 12.3 g. of a colorless, viscous liquid, b.p. 145–147° (2 mm.).

Anal. Calcd. for $C_7H_{17}NO_3$: N, 8.60. Found: N, 8.82.

The *diacetate of 2-hydroxymethyl-4-(2′ hydroxyethyl) morpholine* was obtained as a colorless oil, b.p. 120–122° (0.8 mm.).

Anal. Calcd. for $C_{11}H_{21}NO_5$: N, 5.71. Found: N, 5.55.

Reactions of triptych-boroxazolidines. Bromination of 3-vinyltriptych-boroxazolidine (Vc). An 18.1-g. (0.1 mole) sample of Vc was dissolved in 100 ml. of chloroform, cooled in an ice bath, and treated with a solution of 16.0 g. (0.1 mole) of bromine in chloroform. After 2 hr. standing at room temperature 3-(1′,2′-dibromoethyl)triptych-boroxazolidine was isolated as 34.4 g. (100%) of a white powder, analytically pure but without a definite melting point.

Anal. Calcd. for $C_8H_{14}BBr_2NO_3$: B, 3.16; N, 4.08. Found: B, 3.16; N, 4.02.

Sodium methoxide and 3-chloromethyltriptych-boroxazolidine (XIa). A mixture of 1.97 g. (0.01 mole) of XIa and 0.54 g. (0.01 mole) of sodium methoxide in xylene yielded, after refluxing for 5 hr., 1.56 g. of recovered starting material. A similar experiment with magnesium methoxide yielded the same result. However, when a 1.97-g. (0.01 mole) sample of XIa was refluxed with 0.54 g. (0.01 mole) of sodium methoxide in 25 ml. of methanol, sodium chloride precipitated and the product was shown to consist of 2-hydroxymethyl-4-(2′-hydroxyethyl)morpholine (XV) and a very small amount of 2-methoxymethyltriptych-boroxazolidine (VIIIa). A similar experiment employing 4 moles of sodium ethoxide to 1 mole of XIa in ethanol yielded 65% of 2-ethoxymethyltriptych-boroxazolidine (VIIIb) as a colorless solid, m.p. 115–117°, showing no depression in melting point when admixed with VIIIb prepared as described above.

Potassium phthalimide and 3-chloromethyltriptych-boroxazolidine (XIa). A mixture of 3.9 g. of XIa, 2.7 g. of potassium phthalimide, and 50 ml. of dimethylformamide was heated to reflux. From the turbid solution a white solid slowly precipitated. After 3 hr. of refluxing, the mixture was cooled, the precipitate was removed by filtration, and the filtrate was evaporated to leave a residue which crystallized on standing, m.p. 252–260°. Recrystallization from acetonitrile-benzene gave 5.1 g. (81%) of colorless needles, m.p. 258–259°, identical with the material prepared from phthalimidomethyltriethanolamine and tri-*n*-butyl borate (XVIa) The latter material, after recrystallization and distillation in a short path apparatus, melted at 263–264°.

Anal. Calcd. for $C_{16}H_{17}BN_2O_5$: B, 3.42; N, 4.43. Found: B, 3 44; N, 4.55.

Sodium acetate and 3-chloromethyltriptych-boroxazolidine (XIa). A mixture of 7.5 g. of anhydrous sodium acetate, 9.7 g. of XIa, and 50 ml. of dry dimethylformamide was heated with stirring at 120–130° for 4 hr. The cooled mixture was separated from solid material by centrifugation, and the supernatant was evaporated to leave a brown residue. This was dissolved in benzene, filtered, and diluted with petroleum ether whereupon crystals slowly formed, m.p. 92–96°. Distillation and further recrystallization produced a colorless, rather hygroscopic waxy solid; m.p 128–130°, $\bar{\nu}^{\mathrm{KBr}}$ 1742 cm.$^{-1}$ (ester), 1250 cm.$^{-1}$ (acetate). The hygroscopicity of the material precluded the obtention of significant analytical data.

Sodium hydride and 3-chloromethyltriptych-boroxazolidine (XIa). A slurry of 1.2 g. of 50% sodium hydride in mineral oil in dry dimethylformamide was added to a solution of 5 g of XIa in dimethylformamide. Gas was evolved, sodium hydride was consumed, and sodium chloride deposited. After heating at 90–110° for 2 hr., the mixture was worked up to give a glassy residue which after trituration with boiling benzene left a white powder, softening at 150° and decomposing above 200°; $\bar{\nu}^{\mathrm{KBr}}$ strong flat band 1100–1000 cm.$^{-1}$

Anal. Calcd. for $C_7H_{12}BNO_3$: N, 8.69. Found: N, 8.36.

Benzoyl chloride and 3-aminomethyltriptych-boroxazolidine (XIc). A solution of 3.7 g. of XIc in chloroform was treated with 3 ml. of triethylamine followed, with cooling, by 2.8 g. of benzoyl chloride in 10 ml. of chloroform, added dropwise and with stirring. The product was a gum which, after failing to crystallize on long standing, was extracted into boiling benzene. The benzene solution was diluted with petroleum ether to cloudiness and crystals separated very slowly to give 2.0 g. (35%) of XVIc as a colorless solid; m.p. 145–146°, $\bar{\nu}^{\mathrm{KBr}}$ 3251 cm.$^{-1}$ (amide N—H), 1642 cm.$^{-1}$ (carbonyl), 1529 cm.$^{-1}$ (secondary amide).

Anal. Calcd. for $C_{14}H_{19}BN_2O_4$: B, 3.77; N_{basic}, 4.88. Found: B, 3.89; N_{basic}, 5.01.

Phenylisocyanate and 3-aminomethyltriptych-boroxazolidine (XIc). The urea derivative XVId was obtained from XIc and phenylisocyanate as an oil which crystallized after several weeks at room temperature. Recrystallization from dioxane-dimethylformamide gave a 75% yield of colorless crystals, m.p. 205°.

Anal. Calcd. for $C_{14}H_{20}BN_3O_4$: N_{basic}, 4.59. Found: N_{basic}, 4.64.

Phenylisothiocyanate and 3-aminomethyltriptych-boroxazolidine (XIc). The thiourea derivative XVIe was obtained from XIc and phenylisothiocyanate as an immediately crystallizing compound which, after recrystallization from dioxane–petroleum ether (b.p. 63–69°), was obtained as colorless crystals, m.p. 195–196°.

Anal. Calcd. for $C_{14}H_{20}BN_3O_3S$: B, 3.37; N_{basic}, 4.48. Found: B, 3.36; N_{basic}, 4.36.

Phthalic anhydride and 3-aminomethyltriptych-boroxazolidine (XIc). To a solution of 3.7 g. of XIc in chloroform was added 3 g. of phthalic anhydride. An exothermic reaction took place, and a gummy precipitate separated. This was filtered and the filtrate was diluted with petroleum ether (b.p. 33–58°) to give 6.6 g. (100%) of a white powder, m.p. 146–148°, presumed to be the half amide XVIg.

Anal. Calcd. for $C_{15}H_{19}BN_2O_6$: B, 3.24; N, 4.19. Found: B, 2.71; N, 4.48.

When a 0.066-g. sample of XVIg was heated at 200°, it lost water and yielded 0.058 g. of colorless needles, m.p. 263–264°, identical with XVIa obtained as described above.

Succinic anhydride and 3-aminomethyltriptych-boroxazolidine (XIc). In a fashion similar to that used with phthalic anhydride, XIc was converted to XVIf, m.p. 156–158°.

Anal. Calcd. for $C_{11}H_{19}BN_2O_6$: B, 3.79; N_{basic} 4.90. Found: B, 3.39; N_{basic} 4.81.

DL-*Phthalimidoglutamic acid anhydride and 3-aminomethyltriptych-boroxazolidine* (XIc). The reaction of 5.6 g. of XIc with 7.8 g. of DL-phthalimidoglutamic acid anhydride in chloroform yielded a gum which slowly crystallized to 13.4 g. (100%) of XVIIa as a colorless solid, m.p. 48–50°. Attempted recrystallization led to decomposition.

Anal. Calcd. for $C_{20}H_{24}BN_3O_8$: B, 2.43; N_{basic} 3.15. Found: B, 2.33; N_{basic}, 4.28.

L-*Carbobenzyloxyglutamic acid anhydride and 3-aminomethyltriptych-boroxazolidine* (XIc). A solution of 5.6 g. of XIc and 7.9 g. of carbobenzyloxyglutamic acid anhydride in chloroform was allowed to stand at room temperature for several hours and was then diluted with petroleum ether (b.p. 63–69°) causing the precipitation of 13.4 g. (100%) of XVIIb as a gum which crystallized after separation from the solvent, m.p. 84–94°. Purification by recrystallization was not attempted.

Anal. Calcd. for $C_{20}H_{28}BN_3O_8$: B, 2.41; N_{basic}, 3.93. Found: B, 2.21; N_{basic}, 3.90.

A 4.5-g. sample of XVIIb was dissolved in dry dimethylformamide and hydrogenolyzed in the presence of 10% palladium on charcoal. After 4 days the uptake was 220 ml. (calculated 240 ml.), and the product was isolated by removal of the catalyst and the addition of benzene to the filtrate. The material that separated consisted of colorless, fine needles that were so hygroscopic that no significant analytical data for boron and nitrogen could be obtained; m.p. 48–50°, $\bar{\nu}^{KBr}$ 3125 cm.$^{-1}$ (NH_3^+), 1661 cm.$^{-1}$ (amino acid band-I), 1626 cm.$^{-1}$ (amide carbonyl), 1558 cm.$^{-1}$ (CO_2^-), 1513 cm.$^{-1}$ (amide-II band), 1493 cm.$^{-1}$ (amino acid band-II), triptych pattern 1200-950 cm.$^{-1}$ The material gave positive tests for boron and for an amino acid (ninhydrin).

ST. LOUIS, MO.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Structures Related to Morphine. XIV.[1] 2'-Hydroxy-5-methyl-2-phenethyl-6,7-benzomorphan, the 9-Demethyl Analog of NIH 7519 (Phenazocine) from 3,4-Dihydro-7-methoxy-2(1H)naphthalenone

JAMES G. MURPHY, J. HARRISON AGER, AND EVERETTE L. MAY

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3,4-Dihydro-7-methoxy-2(1H)naphthalenone has been converted to 2'-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (V), an interesting intermediate for the synthesis of neuropharmacologic agents. Pyrolysis of V gives a mixture of the base VII and the α,β-unsaturated ketone (VI). Compound VII, readily convertible to the 9-demethyl analog (VIII) of phenazocine (XI) is characterized by its avidity for water or alcohol with simultaneous disappearance of infrared carbonyl absorption in the presence of acids. The *N*-phenethyl compound (VIII) is an effective analgesic in mice.

As reported previously,[2] 2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (XI) is a promising agent for the relief of human pain. Of interest, therefore, was the 9-demethyl analog (VIII) of XI, despite the fact that the related 2'-hydroxy-2,5-dimethyl-6,7-benzomorphan (IX)[3] is only one third as effective in mice as the 9-methyl homolog (XII),[3,4] the corresponding relative of XI.

The most feasible route to VIII appeared to be *via* the *N*-methyl compound IX which hitherto has been prepared either from γ-picoline methiodide in low yield[3] or from phenylacetonitrile in a lengthy sequence.[3,5] Still another possible approach to IX would involve the intermediate bicyclic ketone methobromide (V) which was needed for other investigations as well. The synthesis of V from 3,4-dihydro-7-methoxy-2-(1H)naphthalenone (I) as shown in Fig. 1 was achieved without particular difficulty.

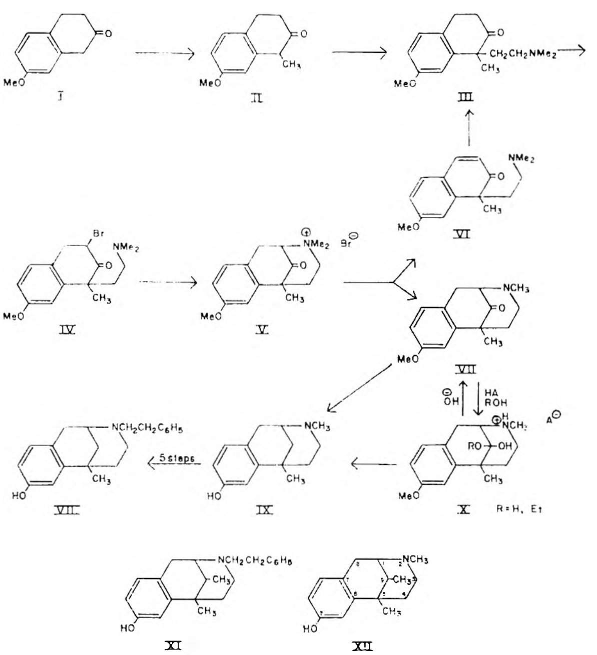

Fig. 1. Synthesis of 2'-hydroxy-5-methyl-2-phenethyl-6,7-benzomorphan, VIII

Methylation of I by the method of Stork[6] gave the 1-methyl compound (II) in 80% yield. Dimethylaminoethylation (sodamide, benzene) of II and bromination of the hydrobromide salt of the resultant III yielded IV hydrobromide which, when neutralized with ammonia, cyclized rapidly to the quaternary compound V. Pyrolysis of V by dry distillation in a high vacuum led principally to tar, the only identifiable product being the α,β-unsaturated ketone VI. However, if the pyrolysis were effected in boiling 1-octanol a 40% yield of the desired base VII could be obtained along with about 15% of VI. The use of either boiling 1-heptanol or 1-hexanol reversed this ratio, giving about 40% of VI and never more than 20% of VII. Hydrogenation of VI (palladium–barium sulfate), the ultraviolet and infrared absorption curves of which were consistent with the structure shown, afforded III. Wolff-Kishner reduction of VII, followed by *O*-demethylation of the product, gave IX. The latter was converted to VII in a five-step process as described previously[2] for similar compounds.

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[1] Paper XIII, J. H. Ager and E. L. May, *J. Org. Chem.*, **25**, 984 (1960).

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[5] E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 257 (1955).

[6] G. Stork, R. Terrell, and J. Smuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

Noteworthy was the disappearance of carbonyl absorption when VII ($\lambda_{\max}^{\text{smear}}$ 5.76 μ) in the presence of water or alcohol was converted to a salt. The hydrochloride, hydrobromide, perchlorate, and picrate salts showed no carbonyl absorption in the infrared but always absorbed in the 3 μ region.[7] Elemental analysis of these salts indicated the presence of the elements of water or alcohol depending upon which was present in the salt preparation. Treatment of the salts with ammonium hydroxide instantaneously regenerated VII with its characteristic carbonyl (5.76 μ) absorption. These facts permit the assignment of formula X for salts of VII, although an ethyleneimmonium structure (containing solvate water or alcohol) resulting from carbonyl-amine proton interaction[8] may be another possibility.

The *N*-phenethyl compound VIII, ED_{50} 0.48 mg./kg. (mice, subcutaneous injection)[9] is twenty times as potent as the *N*-methyl parent (IX),[3] four times as potent as morphine but only about half as effective as phenazocine (XI).[2] The α,β-unsaturated ketone (VI) was analgesically inert.

EXPERIMENTAL

Melting points were taken in a capillary (total immersion thermometers). Microanalyses are by Paula Parisius, Byron Baer, Evelyn Peake, Elizabeth Fath, and W. C. Alford of the institute's service analytical laboratory.

3,4-Dihydro-7-methoxy-1-methyl-2(1H)naphthalenone (II) *semicarbazone.* To 23.4 g. of I[10] and 25 ml. of benzene was added during 5–10 min. (stirring, nitrogen atmosphere) 14 ml. of pyrrolidine. The mixture was refluxed for 45 min. (2.6 ml. of water distilled azeotropically) cooled, and added to 32 ml. of methyl iodide (stirring) so as to cause gentle refluxing. After an additional reflux period of 3–4 hr. 200 ml of water was added and refluxing was resumed. After 30 min. the benzene layer was shaken with a saturated solution of sodium bisulfite, then dried and evaporated at the water pump. Distillation of the residue gave 19.6 g. of II, b.p. 110–115°/0.3–0.4 mm., n_D^{20} 1.5544. A small sample was converted to the semicarbazone (semicarbazide hydrochloride, sodium acetate, alcohol-water) in nearly quantitative yield: plates from 90% ethanol, m.p. 198–200°.

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93. Found: C, 63.14; H, 6.73.

3,4-Dihydro-7-methoxy-1-methyl-1-(2-dimethylaminoethyl)-2(1H)naphthalenone (III) *hydrobromide.* To 5 g. of sodamide in 60 ml. of dry, refluxing benzene (stirring) was added as rapidly as possible 24 g. of II in 60 ml. of dry benzene. After 1 hr. of refluxing 15 g. of 2-chloro-*N,N*-dimethylethylamine in 100 ml. of benzene was added during 1–2 hr. Refluxing and stirring were continued overnight. The benzene was washed twice with water and these washings extracted with ether. The combined ether and benzene extracts were shaken thrice with excess 10% hydrochloric acid. These extracts were made alkaline (ammonium hydroxide) and extracted with ether. The dried (sodium sulfate) extracts were evaporated at the water pump leaving a residue which was distilled at 0.3 mm. (bath temperature 170–180°) through a very short path giving 22.5 g. of crude III. This in 150 ml. of dry ether was acidified with about 22 ml. of 30% hydrobromic acid in acetic acid to give an oil which rapidly crystallized. After decantation (or filtration) the precipitate was slurried with 25 ml. of warm acetone. After keeping at −5° overnight the yield of III hydrobromide was 26.5 g., m.p. 183–188°. It crystallized from acetone in small plates, m.p. 187–190°, $\lambda_{\max}^{\text{nujol}}$ 5.83 μ.

Anal. Calcd. for $C_{16}H_{24}BrNO_2$: C, 56.15; H, 7.07; Br, 23.35. Found: C, 55.88; H, 7.09; Br, 23.57.

3-Bromo-3,4-dihydro-7-methoxy-1-methyl-1-(2-dimethylaminoethyl)-2(1H)naphthalenone (IV) *hydrobromide.* To a stirred refluxing solution of III hydrobromide in 200 ml. of acetic acid was added during 15–25 min. 12 g. (4 ml.) of bromine in 25 ml. of acetic acid. The solution was cooled under a stream of nitrogen and diluted with 300 ml. of ligroin (b.p. 30–60°) and 100 ml. of ether. After thorough cooling at −5°, solvents were decanted through a suction filter and the semisolid residue was stirred with 35 ml. of acetone to the disappearance of all lumps. After cooling overnight at −15°, filtering, and washing the precipitate with cold 2:1 acetone-ether, the yield of IV hydrobromide, m.p. 151–154° dec. was 21 g.[11]; needles from acetone, m.p. 157–158° dec.

Anal. Calcd. for $C_{16}H_{23}Br_2NO_2$: C, 45.63; H, 5.53. Found: C, 45.61; H, 5.83.

2'-Methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (V). Finely divided IV hydrobromide (21 g.), 100 ml. of cold water, 100 ml. of ether, and 6 ml. of concd. ammonium hydroxide were shaken vigorously in a separatory funnel until all but a few small lumps had disappeared. The ethereal layer was transferred quickly to a 250-ml. round bottom flask. The aqueous layer was extracted twice with 25-ml. portions of ether. The combined ethereal extracts were evaporated to dryness at the water pump. The residue and 25 ml. of methanol were warmed to complete crystallization and kept at −5° overnight to give 12.3 g. of V, m.p. 199–203°. The filtrate was evaporated to dryness and the residue was extracted thrice with ether.[12] Crystallization of the residue from 5 ml. of methanol gave an additional 1.0 g. of V. It crystallized from absolute alcohol in feathery crystals, m.p. 204–206°, $\lambda_{\max}^{\text{nujol}}$ 5.75 μ.

Anal. Calcd. for $C_{16}H_{22}BrNO_2$: C, 56.48; H, 6.52. Found: C, 56.31; H, 6.36.

The *methiodide* prepared by aqueous potassium iodide

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(7) With the demethoxy compound[3] corresponding to VII, it was possible, by using dry ether-hydrogen chloride, to obtain a hydrochloride salt showing strong carbonyl absorption at 5.74 μ (in nujol). This was not achieved with VII and usually not with the demethoxy compound.

(8) For a leading reference *cf.* M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 151 (1960).

(9) Test results are from N. B. Eddy, Chief, Section on Analgesics, and staff, by a method reported previously; N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).

(10) B. W. Horrom and H. E. Zaugg, *J. Am. Chem. Soc.*, **72**, 721 (1950); G. B. Diamond and M. D. Soffer, *J. Am. Chem. Soc.*, **74**, 4126 (1952).

(11) Careful addition of ether to the warmed filtrate followed by prolonged cooling (−5°) gave 5.0 g. more of IV hydrobromide. If the intermediate V were desired, the filtrate from the 21 g. of IV hydrobromide was evaporated to dryness and the sirupy residue (10 g.) was cyclized to 3.5 g. of V as described for the 21 g. of IV hydrobromide.

(12) Evaporation of the ether extracts to dryness gave a residue which, in 10 ml. of acetone, was acidified to Congo Red giving from 2–5% of the α,β-unsaturated ketone (VI) as the hydrochloride. Excess ammonium hydroxide or higher cyclization temperatures increased the yield of VI which was identified as described elsewhere in this paper. We are indebted to Hiroshi Kugita, visiting scientist from Osaka, Japan, for this observation.

treatment of V crystallized from 95% ethanol in ellipsoids, m.p. 199–201°, λ_{max}^{nujol} 5.71 μ.

Anal. Calcd. for $C_{16}H_{22}INO_2$: C, 49.62; H, 5.73. Found: C, 49.49; H, 5.96.

Pyrolysis of V *to* VI *and* VII. A mixture of 3.0 g. of V and 13 ml. of 1-octanol[13] was immersed in a bath preheated to 210°, stirred, and refluxed until solution was complete (10–12 min.). After cooling under nitrogen, ether was added. The mixture was extracted thrice with excess 5% hydrochloric acid. Addition of ammonium hydroxide to the combined extracts gave an oil which was dried in ether. Evaporation of the ether and evaporative distillation of the residue at 150–175° (bath temperature)/0.3 mm. gave 1.5 g. of oil. This was dissolved in 10 ml. of acetone, and the solution was filtered from a little solid and acidified to a *p*H of 6–6.5 with hydrogen chloride. After cooling to −15° for 1 hr., 0.25 g. of *7-methoxy-1-methyl-1-(2-dimethylaminoethyl)-2(1H)naphthalenone* (VI) hydrochloride, m.p. 203–206°, was obtained; prisms from alcohol-ether, m.p. 206–208°, λ_{max}^{nujol} 6.01 μ, $\lambda_{max}^{C_2H_5OH}$ 340 mμ (ε 26,400).

Anal. Calcd. for $C_{15}H_{22}ClNO_2$: C, 64.98; H, 7.51; Cl, 11.98. Found: C, 64.66; H, 7.69; Cl, 11.73.

The combined filtrate and acetone-ether washings from the 0.25 g. of VI hydrochloride above were acidified to Congo Red and kept at −15° overnight giving 1.0 g. of the *hydrochloride* (X. R = H, A = Cl) of VII, m.p. 125–128°. It crystallized from alcohol-ether in slim rods, m.p. 130–132°, λ_{max}^{nujol} 2.96, 3.11 μ (no carbonyl absorption).

Anal. Calcd. for $C_{15}H_{21}NO_3 \cdot HCl \cdot H_2O$.[14] C, 56.68; H, 7.61. active H(5), 1.57. Found: C, 56.52; H, 7.61; active H, 1.59.

Treatment of the hydrochloride (X. R = H, A = Cl) with ammonium hydroxide and extraction with ether gave, after evaporative distillation at 0.2 mm. (bath temperature 150°), 2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan (VII), λ_{max}^{smear} 5.76 μ. It gradually becomes discolored on standing.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81. Found: C, 73.02; H, 7.79.

The *hydrobromide* (X. R = H, A = Br) of VII crystallized from acetone in cubes, m.p. 132–134°, λ_{max}^{nujol} 3.1 μ (no carbonyl absorption).

Anal. Calcd. for $C_{15}H_{21}NO_3 \cdot HBr \cdot {}^1/_2H_2O$: C, 50.99; H, 6.56. Found: C, 50.91; H, 6.70.

The *picrate* prepared from VII with alcoholic picric acid crystallized from alcohol acetone in yellow prisms, m.p. 155–157° (gas evolution), λ_{max}^{nujol} 3.1 μ (weak) with no carbonyl absorption. It may be formulated as X (R = C_2H_5, A^- = picrate anion).

Anal. Calcd. for $C_{23}H_{28}N_4O_{10}$: C, 53.07; H, 5.42. Found: C, 53.39; H, 5.57.

Preparation and recrystallization of the picrate from aqueous acetone gave yellow plates, m.p. 120–122°, λ_{max}^{nujol} 2.96 (broad, medium) and no carbonyl absorption. This X (R = H, A^- = picrate anion) is a hemihydrate.

Anal. Calcd. for $C_{21}H_{24}N_4O_{10} \cdot {}^1/_2H_2O$: C, 50.30; H, 5.05; H_2O, 5.40. Found: C, 50.57; H, 5.05; loss in wt. (105–110°), 6.73.

The dried sample showed no absorption in the 3 μ region and relatively weak absorption at 5.71 μ.

Anal. Calcd. for $C_{21}H_{22}N_4O_9$: C, 53.16; H, 4.68. Found: C, 53.62; H, 4.80.

Conversion of VI *to* III. A mixture of 1.0 g. of VI hydrochloride, 0.3 g. of 5% palladium-barium sulfate, and 10 ml. of absolute ethanol absorbed 1.1 molar equivalents of hydrogen during 0.5–1 hr. The filtered solution was evaporated to dryness at the water pump. The residue (III hydrochloride) crystallized from 5 ml. of acetone in a yield of 0.75 g.; rods from ethanol-ether, m.p. 165–168°, λ_{max} 5.82 μ.

Anal. Calcd. for $C_{16}H_{24}ClNO$: C, 64.53; H, 8.12. Found: C, 64.52; H, 8.26.

This hydrochloride was converted to the hydrobromide salt which melted at 187–190° alone or in mixture with the III hydrobromide prepared directly from II. The infrared spectra of the two were identical.

2′-Hydroxy-2,5-dimethyl-6,7-benzomorphan (IX). Two grams of X (R = H, A = Cl) or 2 g. of crude VII, 2 g. of potassium hydroxide, 2 ml. of 95% hydrazine, and 15 ml. of triethylene glycol were kept at 170–175° for 4–5 hr., cooled, and treated with water. Two ether extractions and drying and evaporation of the extracts gave 1.4 g. of sirup. This and 10 ml. of 48% hydrobromic acid were heated under reflux for 20 min. The cooled solution was made alkaline with ammonium hydroxide and extracted thrice with chloroform. The dried (sodium sulfate) chloroform extracts were evaporated at the water pump. The residue crystallized from 5 ml. of acetone to give 1.0 g. (65% based on X, R = H. A = Cl) of IX, m.p. 209–214° which proved to be identical with that described previously.[3]

2′-Hydroxy-5-methyl-2-phenethyl-6,7-benzomorphan (VIII) *hydrobromide.* Methylation of 1.0 g. of IX with ethereal diazomethane containing a little methanol gave 0.9 g. of evaporatively distilled (bath temperature 150–175°, pressure 0.3 mm.) methyl ether. This in 6 ml. of chloroform was added during 45 min. (stirring) to 0.5 g. of cyanogen bromide in 5 ml. of chloroform. The solution was refluxed for 3 hr. and evaporated to dryness at the water pump. The residue and 18 ml. of 6% hydrochloric acid were refluxed for 3 hr. cooled, made alkaline with ammonium hydroxide and extracted with chloroform. The dried chloroform extracts, on evaporation to dryness *in vacuo.* gave 0.7 g. of sirup. This base, 15 ml. of methanol, 5 ml. of water, and 0.8 g. of potassium carbonate were treated (stirring) with 0.8 ml. of phenylacetyl chloride during 5–10 min. The mixture was diluted to 100 ml. with water, extracted with ether, and the ether extracts washed with dilute hydrochloric acid. Evaporation of the dried (sodium sulfate) ether extracts to thorough dryness gave 1.1 g. of crude phenylacetamide derivative which was treated slowly with 15 ml. of 1.3*M* ethereal lithium aluminum hydride (stirring). The mixture was refluxed for 10–15 hr., decomposed with 5 ml. of water, and the ether decanted and dried over sodium sulfate. Acidification of the ether with 33% hydrobromic-acetic acid, decantation, and trituration of the oil with a little acetone gave 0.4 g. of hydrobromide of the methyl ether of VIII, m.p. 376–278°. This material, 4 ml. of 48% hydrobromic acid, and 2 ml. of 33% hydrobromic-acetic acid were refluxed and stirred vigorously for 30 min. and evaporated to dryness at the water pump. A little absolute ethanol was added to the residue and the evaporation repeated. The residue was then decolorized (Norit) in boiling alcohol and the filtrate again evaporated to dryness Trituration of the residue with acetone gave 0.3 g. of VIII hydrobromide, m.p. 220–225°. It crystallized from acetone in blades, m.p. 237–238°.

Anal.[15] Calcd. for $C_{21}H_{26}BrNO$: C, 64.94; H, 6.75. Found: C, 65.00; H, 6.73.

The *base* (VIII) melted at 155.5–156.5°, prisms from methanol-water.

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04: H, 8.20. Found: C, 82.08; H, 8.38.

BETHESDA 14, MD.

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(13) The use of 1-hexanol or 1-heptanol gave 40% of VI and 15% of VII; pyrolysis by dry distillation gave a little VI, no VII, and principally tar.

(14) Evidently X (R = H, A = Cl) is a monohydrate. The hydrate water was indeterminate by loss in weight. All salts (X) prepared of VII could be reconverted to VII with aqueous ammonia. The perchlorate prepared in alcohol absorbed (nujol) at 2.85 and 3.19 μ (no carbonyl band) and melted at 117–121°. Analysis indicated the presence of 1 mole of ethanol. Thus it is formulated as X (R = C_2H_5, A = ClO_4).

(15) After drying (water pump) for 60 hr. at 60–65°.

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Liriodenine, A Nitrogen-Containing Pigment of Yellow Poplar Heartwood (*Liriodendron tulipifera*, L.)

M. A. BUCHANAN AND E. E. DICKEY

Received January 20, 1960

The trivial name "liriodenine" is proposed for a yellow pigment isolated from yellow poplar heartwood. Liriodenine has the composition $C_{17}H_9O_3N$, and a melting point of 282°. Oxidation with chromic acid yields an acid which is decarboxylated at the melting point to form benzo[g]quinoline-5,10-dione. A second pigment containing methoxyl as well as nitrogen was also isolated, but the quantity of this material was not sufficient for proper characterization.

Colorless alkaloids have been reported in the bark of the yellow poplar tree (family *Magnoliaceae*) but they were not well characterized.[1,2] More recently, a lignan diglucoside was isolated from the inner bark.[3] The extractives of the wood, on the other hand, have received but little attention. Yellow poplar heartwood is usually olive-yellow to olive-brown in color, but in trees of rapid growth, the color may be distinctly yellow. On exposure to air and light, the surface darkens. The color of the wood is of some importance in the lumber and is a disadvantage in groundwood pulp prepared from this species.[4,5]

The benzene-soluble extractives of the heartwood consist of a complex mixture of substances, some of which are highly colored. Paper chromatography results in a yellow spot with a bright yellow fluorescence. Attempts to isolate the substance responsible for the yellow spot led to a crystalline pigment, which, however, was not fluorescent. The trivial name "liriodenine" is proposed for this pigment, which melts at 282° and has the composition $C_{17}H_9O_3N$. Liriodenine is basic and is extracted from benzene solution with dilute hydrochloric acid along with a mixture of other colored materials. It is slightly soluble in benzene or chloroform, but is nearly insoluble in ethanol and ether. It is soluble in aqueous acids, and forms a stable rose-colored solution in concentrated sulfuric acid which changes to yellow on addition of potassium nitrate.

The low ratio of hydrogen to carbon in liriodenine suggested the presence of a condensed ring system, but distillation with zinc dust did not form any recognizable products. Tests for methoxyl and methylenedioxy groups were negative. An acetate was not formed under any of the usual acetylating conditions. The absence of hydroxyl groups was supported by the lack of any absorption band in the 3 μ region in hexachlorobutadiene mulls, and by the lack of shift in the ultraviolet spectrum in alkaline ethanolic solution. A monooxime, m.p. 271°, was formed on refluxing with hydroxylamine in pyridine solution, indicating that one of the oxygens was present as a carbonyl group.

Liriodenine was reduced by catalytic hydrogenation to a colorless material which readily reverted to the original material on exposure to air. When warmed with 1% sodium hydroxide containing a small amount of sodium hydrosulfite and some ethanol to promote solubilization, liriodenine formed a blood-red solution which returned to yellow on shaking in the air. It was slowly decolorized to a strongly fluorescent solution by boiling with a mixture of aqueous acetic acid, dilute hydrochloric acid, and tin. The behavior with reducing agents suggested a quinone grouping similar to that present in anthraquinone.

Liriodenine when treated with chromic acid in dilute sulfuric acid solution formed a red-colored insoluble material which was resistant to oxidation and which may have been a chrome lake. In more concentrated sulfuric acid at elevated temperatures, chromic acid oxidation resulted in the formation of water-soluble materials which were not isolated. By proper choice of conditions, it was possible to oxidize liriodenine to a water-insoluble monocarboxy acid $C_{14}H_7O_4N$ with a melting point of 335–336°. The acid decomposed at the melting point with the evolution of gas and the formation of a crystalline sublimate which was identified as benzo[g]quinoline-5,10-dione by comparison with a sample synthesized by the method of Clemo and Driver.[6] The infrared spectra of the two materials were identical, and there was no depression in the mixed melting point.

Identification of the sublimed needles permits a partial formulation of liriodenine as I and the acid obtained on oxidation as II. A melting point of 355–357° has been reported[7] for benzo[g]quinoline-4-carboxy-5,10-dione, and thus it seems likely that the carboxyl group is not in the 4- position.

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(1) J. U. Lloyd and C. G. Lloyd, *Pharm. Rundsch.*, **4**, No. 8, 169 (1886).

(2) P. Morel and P. Totain, *Assoc. franc. avance. sci. Congrés Nîmes*, 41 Session, 810 (1912).

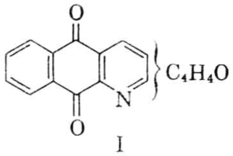
(3) E. E. Dickey, *J. Org. Chem.*, **23**, 179 (1958).

(4) S. D. Wells and J. D. Rue, U. S. Dept. Agr. Dept. Bull. No. 1485, 1927. 101 p.

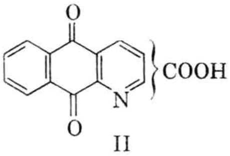
(5) R. M. Kingsbury, F. A. Simmonds, and E. S. Lewis. *Tappi*, **32**, 273 (1949).

(6) G. R. Clemo and G. W. Driver, *J. Chem. Soc.*, 829 (1954).

(7) A. Etienne and A. Staehelin, *Bull. soc. chim. France*, 1954, 748; *Chem. Abstr.* **49**, 9620.



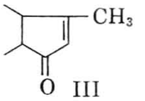
I



II

The benzo[g]quinoline-5,10-dione nucleus was previously demonstrated in the pigment phomazarine isolated form the fungus *Phoma terrestris* Hansen.[8,9] This pigment, like liriodenine, gave only a small amount of unidentified oil on zinc dust distillation and, on hydrogenation, gave a product readily oxidized to the original pigment.

The low ratio of hydrogen to carbon in liriodenine suggests that a fourth condensed ring is present, and the absorption band at 2952 cm.$^{-1}$ suggests the presence of a methyl group. The formation of a monooxime together with the lack of evidence for a hydroxyl group suggest that the third oxygen may be present as a carbonyl group. These conditions would be met by the presence of the ring structure III, but further evidence is needed to elucidate the nature of the fourth ring.



III

After working up the mother liquors to obtain the maximum yield of liriodenine, a chloroform solution was obtained which would not yield additional crystals but which still had a strong yellow coloration.

Evaporation of the solvent gave a dark-colored residue which on repeated crystallization from ethanol gave crystals of a second yellow to orange pigment. This second pigment forms the yellow spot with yellow fluoresence on paper chromatograms. Only small amounts of this pigment have been isolated, and the analytical data have been variable. Analysis for carbon and hydrogen, and estimation of the equivalent weight by titration suggest that the composition may be $C_{20}H_{17}O_5N$ with a molecular weight of 351. On the other hand, a single analysis for nitrogen and two of the methoxyl determinations suggest a molecular weight in the range of 320–330 with three methoxyl groups. At present, the composition of this pigment is still uncertain.

EXPERIMENTAL

Spectra. Infrared spectra (Fig. 1) were determined on potassium bromide wafers with the Perkin-Elmer Model 21 Spectrophotometer. Ultraviolet and visible spectra were determined with a Beckman Model DK-2 Spectrophotometer.

Isolation. Sawdust prepared from yellow poplar heartwood was extracted with 3 l. benzene–95% ethanol 10:1 in a Soxhlet apparatus for 6 hr., and a second charge of sawdust was extracted with the same solvent. The extract from the two charges was concentrated under reduced pressure to about one-half volume. This removed the ethanol and caused the precipitation of some dark-colored material which was separated by filtration. The benzene solution was extracted with five 100-ml. portions of 1% hydrochloric acid. The combined acid solutions were neutralized by careful addition of solid sodium bicarbonate, and the liberated bases were extracted with chloroform. The residue obtained by evaporation of the chloroform was crystallized from chloroform using 4 ml. of solvent per g. of solid. The mother liquor solids were eluted from an alumina column with chloroform, and the eluent from the yellow band was collected. Crystallization of the solids from this fraction gave small amounts of additional yellow crystals. Average yields of the combined crystalline fractions were 0.08% (dry wood basis) from extraction of undried green sawdust, and 0.06% for seasoned lumber.

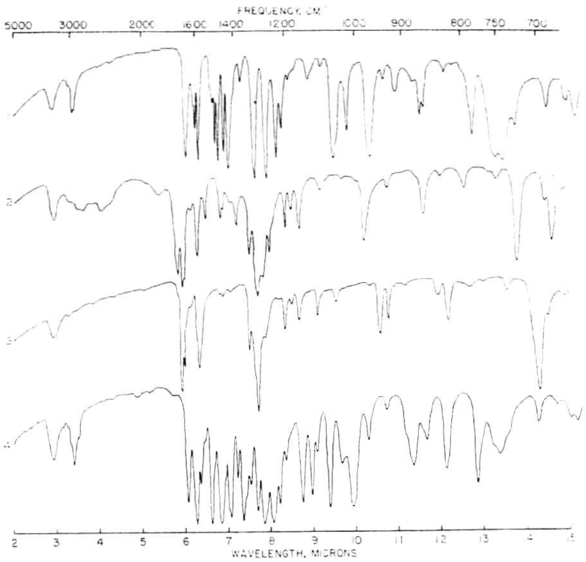


Fig. 1. Infrared absorption curves. I. Liriodenine. II. Acid obtained on oxidation. III. Sublimed needles (benzo[g]-quinoline-5,10-dione). IV. Second yellow pigment

The once crystallized product usually melted in the range of 275–280°. It was purified to a melting point of 282° by further recrystallizations from chloroform, and by chromatography on an alumina column using chloroform as the eluting solvent.

Anal.[10] Calcd. for $C_{17}H_9NO_3$: C, 74.18; H, 3.30; N, 5.09; O, 17.44; molecular weight 275.2. Found: C, 74.17, 73.94; H, 3.28, 3.36; N, 5.07, 5.08; O, 17.52; molecular weight (by an ebullioscopic method using chloroform as solvent) 270.

$\lambda_{\max}^{C_2H_5OH}$ 247.4 mμ (log ε 4.22), 268.2 mμ (log ε 4.13), 309.2 mμ (log ε 3.62), 413 mμ (log ε 3.82). $\lambda_{\min}^{C_2H_5OH}$ 257.9 mμ (log ε 4.08), 291.9 mμ (log ε 3.51), 340 mμ (log ε 3.16), 455–700 mμ (log ε 0.0). $\lambda_{\max}^{0.1N\ \text{HCl in}\ C_2H_5OH}$ 256.7 mμ (log ε 4.33), 277.3 mμ (log ε 4.26), 329 mμ (log ε 3.67), 392 mμ (log ε 3.69), 455 mμ (log ε 3.58). $\lambda_{\min}^{0.1N\ \text{HCl in}\ C_2H_5OH}$ 268.7 mμ (log ε 4.20), 307 mμ (log ε 3.53), 362 mμ (log ε 3.55), 426 mμ (log ε 3.52), 545–700 mμ (log ε 0.00).

Oxime. A 0.257-g. portion of liriodenine purified to a melting point of 280–281° was refluxed for 0.5 hr. with 10 ml. of pyridine and 0.267 g. of hydroxylamine hydrochloride. The crystals dissolved after heating for 10 min. The cooled reaction mixture was stirred into 100 ml. of 2*N* acetic acid. The yellow precipitate was filtered, washed with water, and

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[8] F. Kögl and J. Sparenburg, *Rec. trav. chim.*, **59**, 1180 (1940).

[9] F. Kögl and F. S. Quackenbush, *Rec. trav. chim.*, **63**, 251 (1944).

[10] Except for the first sample of the second pigment, all analyses were by Huffman Microanalytical Laboratories, Wheatridge, Colo.

dried. The yield was 0.267 g. After crystallizing two times from *n*-butanol, the melting point was 271°.

Anal. Calcd. for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47; N, 9.65. Found: C, 69.68; H, 3.34; N, 9.45; residue from combustion 0.5%.

Oxidation with chromic acid. Liriodenine (0.1 g.) was dissolved in 8 ml. of 1:1 (v./v.) concd. sulfuric acid–water by warming, and the solution was diluted with 3 ml. of water. After cooling to room temperature, 0.2 g. of chromic oxide dissolved in 1 ml. of water and 4 ml. of 1:1 sulfuric acid–water was added gradually over a 1-hr. period. After standing at room temperature for 15–16 hr., the solution was diluted with 40 ml. of water and was heated in a steam bath for 1 hr. The final reaction mixture was cooled to room temperature, and the resulting light-colored product filtered and washed with water. The oxidation product was dissolved in dilute ammonium hydroxide and was reprecipitated by acidification with hydrochloric acid. The yield was 0.08 g. The crude product had a melting point of about 330°, and on melting formed a sublimate of yellow crystals. The material was soluble in hot formic, acetic, and nitric acids, but satisfactory conditions for recrystallization were not found. It was purified by dissolving in 2% ammonium hydroxide, heating the solution, and neutralizing with hydrochloric acid. After several such treatments, the melting point was 335–336° on rapid heating.

Anal. Calcd. for $C_{14}H_7O_4N$: C, 66.41; H, 2.79; N, 5.53. Found: C, 66.33; H, 2.83; N, 5.60.

$\lambda_{max}^{C_2H_5OH}$ 254 mμ (log ε 4.49), 325 mμ (log ε 3.50). $\lambda_{min}^{C_2H_5OH}$ 305 mμ (log ε 3.41).

Small amounts of the sublimed needles were obtained by mixing 10 mg. of the oxidation product with 20 mg. of precipitated calcium carbonate and heating in a 3-inch test tube to 335°. After resubliming, the needles melted at 275–277°. Benzo[g]quinoline-5,10-dione synthesized by the method of Clemo and Driver[6] melted at the same temperature, and the mixed melting point was not depressed. $\lambda_{max}^{C_2H_5OH}$ 250 mμ (log ε 4.49), 326 mμ (log ε 3.46). $\lambda_{min}^{C_2H_5OH}$ 304 mμ (log ε 3.55).

Isolation of the second yellow pigment. In the isolation of liriodenine, the mother liquors were rechromatographed on alumina columns by eluting with chloroform as long as additional liriodenine could be crystallized from the material eluted as a yellow band. The mother liquors from these operations still had a very strong yellow color. They were combined, evaporated to dryness, and the solids crystallized from 95% ethanol to give a small amount of orange needles (0.01% dry wood basis). Further crystallizations from ethanol and from benzene gave a constant melting point of 235–236°.

Anal. Found: C, 68.54, 68.01; H, 4.90, 4.96; methoxyl, 33.5, 33.5; equivalent weight by titration, 359, 360.

$\lambda_{max}^{C_2H_5OH}$ 211 mμ (a 91.4), 245 mμ (a 86.5), 273 mμ (a 91.2), 355 mμ (a 30.3).

$\lambda_{max}^{C_2H_5OH}$ 228 mμ (a 62.5), 257 mμ (a 61.2), 318 mμ (a 18.2), λ 500–700 mμ (a 0.0).

The remaining crystals were recrystallized by dissolving in a small volume of chloroform and adding two to three volumes of low boiling petroleum ether. The resulting crystals melted at 235–236°.

Anal. Found: C, 68.60, 68.56; H, 4.77, 4.91; methoxyl, 28.8. Additional crystals melting at 235–236° were obtained from the mother liquors from isolation of the first product by crystallizing the mother liquor solids once from ethanol and once from benzene.

Anal. Found: C, 68.99; H, 4.93; N, 4.30; methoxyl, 28.3.

Acknowledgment. We are grateful to Bruce Sanborn of the West Virginia Pulp and Paper Company for supplying some of the wood, and to L. O. Sell of our Analytical Department for determination and interpretation of the spectra.

APPLETON, WIS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Some New Reactions and Reaction Products of Apogossypol and Desapogossypol[1]

DAVID A. SHIRLEY AND PEGGY W. ALLEY[2]

Received February 5, 1960

The previously unreported desapogossypol was prepared by demethylation of the hexamethyl ether. Desapogossypol was converted to the hexaacetate, to desapogossypolone tetraacetate and to hydrodesapogossypolone octaacetate. The hexalllyl ether of apogossypol has been prepared and carried through a Claisen rearrangement which involved two *ortho-* and two *para*-rearrangements in each molecule. Epoxidation of apogossypolone tetramethyl ether and desapogossypolone tetramethyl ether gave in both cases the corresponding 2,3,2′,3′-diepoxy derivatives.

Gossypol (I), the principal pigment of cottonseed, must be chemically altered or removed during the processing of cottonseed for most uses. There is potentially available about 30,000 tons of gossypol per year from cotton produced in the United States. The large amount of gossypol available, the reactive nature of the molecule, and its deleterious effects in cottonseed processing and utilization are the reasons for a continuing program in these laboratories on the chemistry of gossypol and closely related derivatives. Our earlier work has involved a study of the reduction of gossypol with lithium aluminum hydride[3] and the formation of gossypol anils with a wide variety of primary amines.[4]

Apogossypol (II), apogossypol hexamethyl ether

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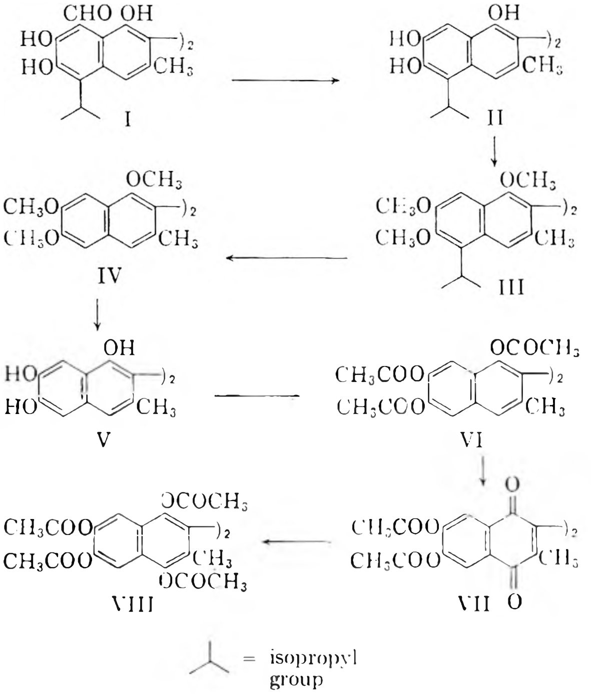
(1) A report of work conducted under contract with the U. S. Department of Agriculture and authorized by the Research and Marketing Act. The contract is being supervised by the Southern Utilization Research and Development Division of the Agricultural Research Service.

(2) Post-doctoral Research Fellow, 1958–59.

(3) D. A. Shirley and W. C. Sheehan, *J. Am. Chem. Soc.*, **77**, 4606 (1955).

(4) (a) D. A. Shirley and W. C. Sheehan, *J. Org. Chem.*, 21, 251 (1956); (b) P. W. Alley and D. A. Shirley, *J. Org. Chem.*, **24**, 1534 (1959).

(III) and desapogossypol hexamethyl ether (IV) are long-known and easily obtainable derivatives of gossypol.[5] Much use was made of these derivatives in work on the structure of gossypol,[6] but the closely related desapogossypol (V) has not been reported. We prepared this latter substance by demethylation of desapogossypol hexamethyl ether using pyridine hydrochloride.[7] Acetylation of desapogossypol with acetic ahydride in pyridine produced the hexaacetate (VI) which upon oxidation with chromic anhydride in acetic acid gave desapogossypolone tetraacetate (VII). Reduction of the binaphthoquinone (VII) with zinc dust in acetic acid[8] produced hydrodesapogossypolone octaacetate (VIII).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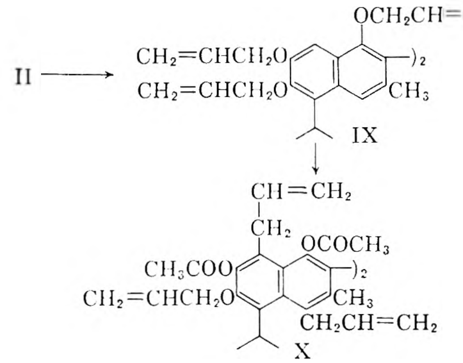
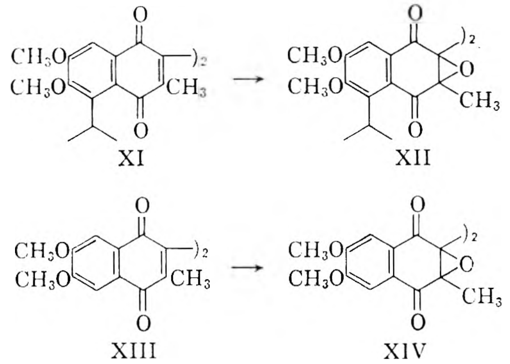
OCOCH₃
CH₃COO
CH₃COO
)₂
CH₃
VI
OCOCH₃
CH₃COO
CH₃COO
)₂
CH₃
OCOCH₃
VIII
O
CH₃COO
CH₃COO
)₂
CH₃
O
VII
= isopropyl group

Apogossypol (II) was converted to its hexaallyl ether (IX) with allyl bromide and potassium carbonate in acetone. The product was a viscous liquid at room temperature which could not be crystallized; however elemental analyses and the infrared spectra were in accord with the indicated structure.

We carried out a Claisen rearrangement of apogossypol hexaallyl ether (IX) in boiling dimethylaniline containing acetic anhydride. It was anticipated that one *para-* and one *ortho-*rearrangement would take place in each half of the molecule. The solid product from the rearrangement could not be obtained in a sharp-melting form, but elemental analyses and the infrared spectrum were in accord with the expected product X from rearrangement followed by acetylation of hydroxyl groups.


II
OCH₂CH=CH₂
CH₂=CHCH₂O
CH₂=CHCH₂O
)₂
CH₃
IX
CH=CH₂
CH₂
OCOCH₃
CH₃COO
CH₂=CHCH₂O
)₂
CH₃
CH₂CH=CH₂
X

1,4-Naphthoquinones undergo epoxidation to give the 2,3-epoxy derivatives.[9] The action of a mixture of 30% hydrogen peroxide and sodium carbonate in an alcoholic solution of apogossypolone tetramethyl ether (XI) yielded the corresponding epoxide (XII) in 83% yield. A similar epoxidation of desapogossypol hexamethyl ether (XIII) to XIV occurred in 40% yield.


O
CH₃O
CH₃O
)₂
CH₃
O
XI
O
CH₃O
CH₃O
)₂
O
CH₃
O
XII
O
CH₃O
CH₃O
)₂
CH₃
O
XIII
O
CH₃O
CH₃O
)₂
O
CH₃
O
XIV

EXPERIMENTAL[10]

Desapogossypol (V). Six grams of pyridine hydrochloride was heated to 190° and 1.4 g. (3.5 mmoles) of desapogossypol hexamethyl ether were added. The mixture was heated under an atmosphere of nitrogen at 195–200° for 10 hr. Water (50 ml.) was added to the cooled reaction mixture, and the white solid removed by filtration and recrystallized (charcoal) from methanol containing a small amount of water. The product was 330 mg. of white crystalline solid which did not melt but started to decompose about 280°.

Anal. Calcd. for $C_{22}H_{18}O_6$: C, 69.83; H, 4.80. Found: C, 69.44, 69.35; H, 4.71, 4.98.

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[5] C. H. Boatner, *Cottonseed and Cottonseed Products*, A. E. Bailey, ed., Interscience Publishers, New York, 1948, pp. 237–9.

[6] (a) Roger Adams and B. R. Baker, *J. Am. Chem. Soc.*, **63**, 535 (1941); (b) D. A. Shirley and W. L. Dean, *J. Am. Chem. Soc.*, **79**, 1205 (1957); (c) J. D. Edwards and J. L. Cashaw, *J. Am. Chem. Soc.*, **79**, 1205 (1957); (c) J. D. Edwards and J. L. Cashaw, *J. Am. Chem. Soc.*, **79**, 2283 (1957); (d) J. D. Edwards, *J. Am. Chem. Soc.*, **80**, 3798 (1958).

[7] M. Gates, *J. Am. Chem. Soc.*, **78**, 1390 (1956).

[8] Roger Adams and D. J. Butterbaugh, *J. Am. Chem. Soc.*, **60**, 2174 (1938).

[9] L. F. Fieser, W. P. Campbell, E. M. Fry, and M. D. Gates, *J. Am. Chem. Soc.*, **61**, 3219 (1939).

[10] Melting points were taken on a Kofler Hot Stage Microscope. Microanalyses are by Weiler and Strauss, Oxford, England. All infrared spectra were obtained by the potassium bromide disk technique on a Perkin Elmer Model 21 infrared spectrophotometer.

The filtrate from the treatment of the above reaction mixture with water was extracted with three 50-ml. portions of ether. The ether was evaporated and the residue crystallized from equal volumes of methanol and water. There was obtained 500 mg. of white crystalline solid which melted at 190–193°. This material is apparently a hydrate of desapogossypol.

Anal. Calcd. for $C_{22}H_{18}O_6 \cdot 1.5H_2O$: C, 65.20; H, 5.18. Found: C, 65.33, 65.19; H, 5.05, 5.14.

Desapogossypol hexaacetate (VI). To a solution of 100 mg. of the desapogossypol hydrate obtained above in 2 ml. of pyridine was added 1 ml. of acetic anhydride. The mixture was heated to boiling and then allowed to stand at room temperature for several hours after which it was poured into crushed ice. After hydrolysis of the anhydride, the precipitated crystals were collected, washed with water, dried, and recrystallized from ethyl acetate–petroleum ether (b.p. 30–60°). There was obtained 123 mg. (74%) of white crystalline product, m.p. 270–274°.

Anal. Calcd. for $C_{34}H_{30}O_{12}$: C, 64.76; H, 4.80. Found: C, 64.75, 64.39; H, 4.98, 4.88.

Desapogossypolone tetraacetate (VIII). To a solution of 200 mg. of desapogossypol hexaacetate in 10 ml. of boiling glacial acetic acid was added with stirring 1.5 ml. of a solution consisting of 40 g. water, 8 g. sulfuric acid, and 5.3 g. chromic anhydride. After heating for 2 min. the mixture was poured into ice and water. The reaction mixture was extracted with ether and the yellow extracts washed with water and the ether evaporated. The residue was dissolved in 15 ml. boiling benzene and petroleum ether (b.p. 60–80°) added to cloud point. Cooling precipitated an oil and the mother liquor was treated with more petroleum ether to a hot cloud point. Cooling precipitated 80 mg. of yellow crystalline solid. This was recrystallized in the same manner as before from ethyl acetate petroleum ether to yield 35 mg. of yellow crystalline product, m.p. 137–140°.

Anal. Calcd. for $C_{30}H_{22}O_{12}$: C, 62.72; H, 3.86. Found: C, 62.20, 62.13; H, 3.97, 4.04.

Hydrodesapogossypolone octaacetate (VIII). Two hundred milligrams of desapogossypol hexaacetate was oxidized as described above. Unrecrystallized product from the oxidation (110 mg.) was dissolved in 5 ml. of acetic anhydride and 0.1 g. of freshly fused sodium acetate added. The mixture was heated under reflux for 15 min. during which time 2.0 g. of zinc dust was added in portions and the color of the solution changed from deep yellow to nearly colorless. The mixture was filtered and excess water added to the filtrate. After standing overnight the semisolid product was crystallized from 95% ethanol yielding 30 mg. of product melting around 150–160°. This was recrystallized from ethyl acetate–petroleum ether (b.p. 30–60°) to give 16 mg. of white crystalline solid, m.p. 245–247°. A second crystallization from the same solvent mixture raised the m.p. to 258–261°.

Anal. Calcd. for $C_{38}H_{34}O_{16}$: C, 61.13; H, 4.59. Found: C, 60.84, 60.94; H, 4.50, 4.52.

Apogossypol hexaallyl ether (IX). A mixture of 5.0 g. (0.011 mole) of freshly prepared apogossypol,[11] 50 ml. of anhydrous acetone, 10.0 g. (0.083 mole) of allyl bromide and 12 g. of freshly ignited and finely powdered potassium carbonate was stirred and heated under reflux for 48 hr. Excess (200 ml.) water was added and the oil which precipitated was separated and extracted with ether. The ether solution was dried, the ether evaporated, and the residual oil dissolved in petroleum ether (b.p. 30–60°). This solution was placed on a 2 × 20 cm. column of 60–100 mesh Florisil adsorbant. This adsorbant is effective in retaining partially alkylated molecules of the gossypol type which contain hydroxyl groups. The column was eluted with petroleum ether (b.p. 30–60°) until the eluate was colorless. Evaporation of solvent left 5.6 g. (74%) of yellow viscous oil. The product could not be crystallized from a wide variety of solvents. Pouring an alcoholic solution of the product into an ice water slurry caused formation of a white solid precipitate which was reconverted to an oil on warming to room temperature. The infrared spectrum of the product showed a sharp band of medium intensity at 6.06 μ characteristic of a nonconjugated carbon–carbon double bond.[12]

Anal. Calcd. for $C_{46}H_{54}O_6$: C, 78.63; H, 7.74. Found: C, 78.67, 78.32; H, 7.90, 7.74.

Claisen rearrangement of apogossypol hexaallyl ether. A solution of 2.5 g. of apogossypol hexallyl ether, 10.0 g. of *N,N*-dimethylaniline, and 5.0 g. of acetic anhydride was heated to a reflux under an atmosphere of nitrogen for 5 hr. The reaction mixture was poured into a mixture of 7 ml. of concd. hydrochloric acid and 100 g. of crushed ice. The precipitated gummy solid was dissolved in hot acetic acid treated with charcoal and the resulting solution poured into an ice water slurry. The precipitated solid weighed 2.5 g. Fractional crystallization from benzene–petroleum ether (b.p. 30–60°) gave a series of fractions ranging in melting point from 115–120° (more soluble) to above 200° (less soluble). All the fractions gave quite similar and clean-cut infrared spectra and similar carbon and hydrogen analytical values. The spectra contained a sharp intense band at 5.63 μ indicative of the presence of acetylated hydroxyl groups in the rearranged product. The carbon–carbon double bond of the allyl groups appeared at 6.00 μ. The product is proposed to be 1,1′,7,7′-tetraacetoxy-3,3′-dimethyl-4,4′,8,8′-tetraallyl-5,5′-diisopropyl-6,6′-diallyloxy-2,2′-binaphthyl (X).

Anal. Calcd. for $C_{54}H_{62}O_{10}$: C, 74.48; H, 7.12. Found: C, 74.25, 74.50; H, 7.32, 7.31.

Claisen rearrangement in the absence of the acetic anhydride was tried in several experiments. Infrared spectra on crude products indicated the presence of rearranged molecules, but attempted purification to sharp melting product was not successful and elemental analytical values were of no value since reactant, intermediate and expected product molecules are isomeric.

Epoxidation of apogossypolone tetramethyl ether (XI). A solution of 80 mg. of apogossypolone tetramethyl ether[8] in 15 ml. of absolute ethanol at 45° was treated with 1 ml. of 30% hydrogen peroxide and 1 ml. of a saturated aqueous solution of sodium carbonate. After 5 min. during which the yellow color of the solution was discharged, the reaction mixture was poured into excess water and the precipitated white solid was crystallized from a mixture of ethanol and water. There was obtained 70 mg. (83%) of white crystalline product. The product melted at 242–245° after a prior melting and resolidification at a lower temperature. The temperature of this first melting varied sharply with rate of heating of the sample. Further recrystallization did not alter the higher melting point. This behavior upon melting may represent a transformation from a less stable to a more stable diastereomeric form among the various possible stereochemical forms of XII. On the basis of the nature of the reaction and elemental analytical values, the product (XII) is designated as 3,3′-dimethyl-5,5′-diisopropyl-6,6′,7,7′-tetramethoxy-2,2′-binaphtho-1,1′,4,4′-quinone-2,3,2′,3′-dioxide.

Anal. Calcd. for $C_{32}H_{34}O_{10}$: C, 66.42; H, 5.92. Found: C, 66.12, 66.45; H, 5.62, 5.78.

Epoxidation of desapogossypolone tetramethyl ether (XIII). A mixture of 0.5 ml. of 30% hydrogen peroxide and 1 ml. of a 10% aqueous sodium carbonate solution was added at 45° to a solution of 40 mg. of desapogossypolone tetramethyl ether (XIII)[8] in 10 ml. of ethanol and 3 ml. of dioxane. The reaction mixture was held at 45° for 1 hr. and its yellow color persisted. An additional 1 ml. of peroxide solution and 1 ml. of sodium carbonate solution were added and the mixture heated to 70°. After a few minutes the yellow

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(11) E. P. Clark, *J. Biol. Chem.*, **78,** 159 (1928).

(12) L. F. Bellamy, *The Infrared Spectra of Complex Molecules,* John Wiley and Sons, New York, N. Y., 1958, p. 36.

color was discharged. The mixture was added to 50 ml. of water and cooled to precipitate 30 mg. of white solid. This was recrystallized once from a mixture of ethanol, dioxane, and water, once from a mixture of benzene and hexane, and once from a mixture of benzene and ethanol to produce 17 mg. (40%) of white crystalline solid dioxide XIV, m.p. 237–241°.

Anal. Calcd. for $C_{26}H_{22}O_{16}$: C, 63.15; H, 4.49. Found: C, 63.35, 62.88; H, 4.64, 4.69.

Acknowledgment. We should like to express our appreciation to the U. S. Department of Agriculture for financial support and to Dr. V. L. Frampton and Mr. T. H. Hopper, Southern Utilization Research and Development Division, New Orleans, La., for their continued interest and aid.

KNOXVILLE, TENN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BRANDEIS UNIVERSITY]

Friedelin and Related Compounds. III.[1,2] The Isolation of Friedelane-2,3-dione from Cork Smoker Wash Solids

VINAYAK V. KANE AND ROBERT STEVENSON

Received February 3, 1960

Friedelane-2,3-dione has been identified as a constituent of "cork smoker wash solids" and characterized as a monoacetate, monobenzoate, monomethyl and quinoxaline derivative. Huang-Minlon reduction of the dione yielded friedelane; a selective reduction gave friedelin (friedelan-3-one).

The nature of the constituents of cork, the bark of *Quercus suber*, has been the subject of considerable investigation, much of which has been reviewed.[3] Of these constituents, friedelin (I) and cerin (II. R = H) were established as triterpenoids by the work of Drake[4–9] and Ruzicka[10,11] and their respective collaborators, and their structure elucidation has been completed.[1,12,13] No fewer than nine di- or trioxygenated friedelanes have recently been isolated from the bark of *Siphonodon australe* Benth.[14,15]

A resin obtained as a by-product in the manufacture of corkboard by steam-baking, known as "smoker wash solids," has been utilized previously[12] as a convenient source of friedelin. Although the isolation of friedelin in a crude state by solvent extraction of this product is exceedingly simple, considerable losses are incurred in the purification and little is known concerning the nature of the contaminants. This paper is concerned with the isolation and identification of friedelane-2,3-dione from this source.

Purification of an extract of this resin by chromatography yielded a fraction, eluted from alumina by chloroform, from which a substance, $C_{30}H_{48}O_2$, was readily crystallized. The characteristic ultraviolet and infrared absorption spectra of this substance indicated that the two oxygen functions were present as an enolized α-diketone system,[16] a conclusion confirmed by formation of a monoacetate, monobenzoate and quinoxaline derivative.

Although it was suspected that the isolated product was friedelane-2,3-dione, the considerable divergence in the empirical constants of the natural product[17] and its derivatives and those reported for the synthetic product[10,12] (see table) necessitated independent characterization.

	This Work	Ref. 10	Ref. 12
Friedelane-2,3-dione	m.p. 274–277° $[\alpha]_D$ +25°	m.p. 265° $[\alpha]_D$ +18°	m.p. 267–269° . . .
Friedelane-2,3-dione enol acetate	m.p. 308–310° $[\alpha]_D$ −22°	m.p. 283–285° $[\alpha]_D$ +3°	. . .
Friedelane-2,3-dione enol benzoate	m.p. 317–319° $[\alpha]_D$ −35°	m.p. 301–303° $[\alpha]_D$ +26°	m.p. 311–313° . . .

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[1] Part I, G. Brownlie, F. S. Spring, R. Stevenson, and W. S. Strachan, *J. Chem. Soc.*, 2419 (1956).

[2] Part II, G. Brownlie, F. S. Spring, and R. Stevenson, *J. Chem. Soc.*, 216 (1959).

[3] For review, see H. Mader, *Encyclopedia of Plant Physiology*, Vol. 10, 282.

[4] N. L. Drake and R. P. Jacobsen, *J. Amer. Chem. Soc.*, **57**, 1570 (1935).

[5] N. L. Drake and S. A. Shrader, *J. Amer. Chem. Soc.*, **57**, 1854 (1935).

[6] N. L. Drake and W. P. Campbell, *J. Amer. Chem. Soc.*, **58**, 1681 (1936).

[7] N. L. Drake and W. T. Haskins, *J. Amer. Chem. Soc.*, **58**, 1684 (1936).

[8] N. L. Drake and J. K. Wolfe, *J. Amer. Chem. Soc.*, **61**, 3074 (1939).

[9] N. L. Drake and J. K. Wolfe, *J. Amer. Chem. Soc.*, **62**, 3018 (1940).

[10] L. Ruzicka, O. Jeger, and P. Ringnes, *Helv. Chim. Acta*, **27**, 972 (1944).

[11] G. W. Perold, K. Meyerhans, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **32**, 1246 (1949).

[12] E. J. Corey and J. J. Ursprung, *J. Amer. Chem. Soc.*, **78**, 5041 (1956).

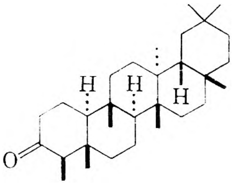
[13] T. Takahashi and G. Ourisson, *Bull. soc. chim. France*, 353 (1956).

[14] J. L. Courtney and R. M. Gascoigne, *J. Chem. Soc.*, 2115 (1956).

[15] J. L. Courtney, R. M. Gascoigne, and A. Z. Szumer, *J. Chem. Soc.*, 2119 (1956).

[16] L. F. Fieser and R. Stevenson, *J. Amer. Chem. Soc.*, **76**, 1728 (1956) report the corresponding spectral data for cholestane-3:4-dione (as its mono-enol) and its acetate in which good agreement is found.

Reduction of the diketone by the Huang-Minlon method gave the hydrocarbon, friedelane, identified by direct comparison with an authentic specimen, and consequently restricted the possible formulations to friedelane-1,2-dione, friedelane-6,7-dione, or friedelane-2,3-dione (III). A decision in favor of III was reached by conversion of the diketone to friedelan-3-one. Treatment of the diketone with lithium aluminum hydride in ether solution, followed by acetylation, gave a keto-acetate. Although the homogeneity of the latter was not established (it clearly differed from cerin acetate II, R = CH_3CO—), it was readily deacetoxylated by zinc dust in acetic acid solution to give friedelan-3-one, identified by comparison with authentic ketone and oxime.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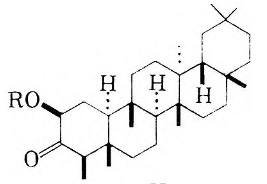
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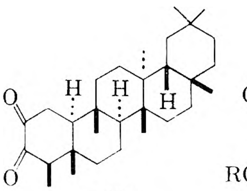
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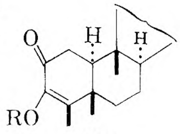
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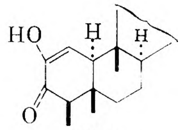
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Friedelane-2,3-dione was first obtained[10] as a minor product of chromic acid oxidation of cerin (II. R = H). It was suggested that of the two enol forms (IIIA) and (IIIB), the dione existed as IIIA, (R = H) since the derived benzoate (IIIA. R = C_6H_5CO—) could also be prepared by oxidation of friedelin enol benzoate. The preparation of the benzoate (IIIA. R = C_6H_5CO—) and regeneration of the dione by gentle alkaline hydrolysis, has been repeated by Corey and Ursprung.[12] Their specimens, kindly supplied by Professor E. J. Corey, were undepressed on mixed melting-point determination with our samples, establishing their essential identity.

The dione was recovered unchanged after treatment with ethereal diazomethane, but was converted to the monomethyl ether by refluxing with boron trifluoride etherate in methanol solution, a method previously used[18] for conversion of cholestane-3,4-dione to 4-methoxycholest-4-en-3-one. The ultraviolet bathochromic shifts found by substitution of an α-methoxyl (+18 mμ) and α-acetoxyl (+5 mμ) in the friedel-3-en-2-one system[19] agree well with the respective corresponding values of (+22 mμ) and (+6 mμ) in the cholest-4-en-3-one system. In their structural studies on the bitter principle, quassin, Robertson and co-workers[20] have drawn attention to the lack of ultraviolet absorption data on enol ethers derived from α-diketones, a chromophore believed present in both quassin and neoquassin. Their observed value of the absorption maximum (264 mμ) due to the methyl ether of the enolized diketone appears rather high when compared with their reported maxima of the derived dione enol (271 mμ) and dione enol acetate (233 mμ) and in view of bathochromic shifts for methoxyl and acetoxyl groups reported here.

EXPERIMENTAL[21]

Isolation of friedelane-2,3-dione. (a) Cork resin (589 g.) was stirred overnight with ethanol (2 × 2 l.), the insoluble residue extracted at room temperature with chloroform (2 × 2 l.), and the chloroform removed to give a light brown solid (124 g.). Much of the color was removed by boiling this extract twice with acetone (500 c.c.) and filtration. The acetone-insoluble residue was crystallized twice from chloroform, the filtrates combined and evaporated to give a solid (53 g.) which was dissolved in a minimum volume of benzene and filtered through a column of alumina (Merck, acid-washed). After elution with benzene (2.5 l.) yielded a white solid (crude friedelin), elution with chloroform (800 c.c.) gave a yellow-brown solid (2.2 g.), two crystallizations of which from chloroform-acetone gave a solid (430 mg.), m.p. 235–268°, λ 5.82, 6.01, 6.03 μ, which was taken up in benzene and chromatographed on a column (20 × 1.5 cm.) of alumina (Woelm, grade 1, almost neutral). The fraction eluted by benzene-chloroform (1:3, 600 c.c.) gave friedelane-2,3-dione as soft needles, m.p. 276–277° (unchanged on recrystallization from chloroform-methanol), $[\alpha]_D$ +25° (*c*, 1.9), λ 276 mμ (ε = 11,500), λ 2.92, 6.01, 6.12 μ.

Anal. Calcd. for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.5; H, 11.0.

(b) Extraction of cork resin (12 g.) with chloroform in a Soxhlet apparatus for 5 hr. yielded a dark brown gum (7.5 g.), a solution of which in benzene was filtered through a column (13 × 1″ diameter) of alumina (Woelm, almost neutral). After elution with benzene (3.5 l.), chloroform (2.5 l.), chloroform-methanol (1:1, 1 l.), chloroform-methanol (1:1, 1 l.) gave a semisolid gum which on three crystallizations from chloroform-methanol gave the dione (60 mg.), m.p. 270–274°, $[\alpha]_D$ +25° (*c*, 1.6).

Friedelane-2,3-dione-3-enol acetate. A solution of friedelanedione (24 mg.) in pyridine (1.5 cc.) and acetic anhydride (1.5 cc.) was heated at 100° for 10 min., diluted with water, and the precipitate (20 mg., m.p. 300–305°) crystallized from chloroform-methanol to give the dione enol acetate as fine needles, m.p. 308–310°, $[\alpha]_D$ +22° (*c*, 1.6), λ 242 mμ (10,600), λ 5.70, 5.90, 6.13 μ. It retains solvent of crystallization tenaciously.

Anal. Calcd. for $C_{32}H_{50}O_3 \cdot CH_3OH$: C, 76.99; H, 10.26. Found: C, 76.85; H, 10.1. Calcd. for $C_{32}H_{50}O_3$: C, 79.62; H, 10.44. Found (after prolonged drying): C, 80.0; H, 10.9.

Friedelane-2,3-dione-3-enol benzoate. A mixture of friedelanedione (25 mg.) in pyridine (0.5 cc.) and benzoyl chloride (0.5 cc.) was warmed to effect solution and allowed to stand overnight. Addition of methanol precipitated a solid (25

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(17) The dione conceivably is an artifact resulting from the oxidation of friedelin or cerin.

(18) R. Stevenson and L. F. Fieser, *J. Amer. Chem. Soc.*, **78**, 1409 (1956).

(19) The ultraviolet absorption maximum reported for friedel-3-en-2-one is 237 mμ (Ref. 12).

(20) K. R. Hanson, D. B. Jaquiss, J. A. Lamberton, A. Robertson, W. E. Savige, *J. Chem. Soc.*, 4238 (1954).

(21) Rotations and infrared absorption spectra were determined in chloroform solution and ultraviolet absorption spectra were determined in 95% ethanol solution.

mg., m.p. 317–319°) which crystallized from chloroform-methanol to give the dione enol benzoate as fine needles, m.p. 317–319°, $[\alpha]_D$ +35° (c, 1.6), λ 231 mμ (16,900), λ 5.77, 5.97, 6.13 μ.

Anal. Calcd. for $C_{37}H_{52}O_3$: C, 81.57; H, 9.62. Found: C, 81.4; H, 9.7.

Huang-Minlon reduction of friedelane-2,3-dione. The dione (104 mg.) was suspended in diethylene glycol (14 cc.), potassium hydroxide (1 g.) and hydrazine hydrate (99–100%; 1.5 cc.) added. The mixture was heated under reflux for 30 min., the condenser removed until the reaction mixture temperature reached 210° and refluxing continued for a further 5 hr. Water (30 cc.) was added, the mixture extracted with chloroform, the extract washed with water, dried (sodium sulfate) and evaporated to give a solid, which crystallized from chloroform-methanol to give friedelane as needles, m.p. and mixed m.p. 251–252°, $[\alpha]_D$ +22° (c, 0.62).

Anal. Calcd. for $C_{30}H_{52}$: C, 87.30; H, 12.70. Found: C, 87.5; H, 12.6.

Friedelane-2,3-dione quinoxaline derivative. A mixture of the dione (50 mg.), o-phenylenediamine hydrochloride (100 mg., freshly sublimed) and sodium acetate (150 mg.) in acetic acid (50 cc.) was refluxed for 2 hr., cooled, poured into water, and the product collected by filtration. Three recrystallizations from chloroform-methanol gave the quinoxaline as slightly yellow small needles, m.p. 248–251°, λ 239 (19,950) and 322 mμ (7,100), lit.,[16] m.p. 244–246°.

Anal. Calcd. for $C_{36}H_{52}N_2$: C, 84.32; H, 10.22. Found: C, 83.8; H, 9.9.

Friedelane-2,3-dione methyl ether. Boron trifluoride etherate (3.5 cc.) was added to a suspension of the dione (50 mg.) in methanol (80 cc.), the mixture refluxed for 2 hr., the resultant solution diluted with water, and the product collected by filtration. Three recrystallizations from chloroform-methanol gave the methyl ether as needles, m.p. 248–251°, $[\alpha]_D$ +27°, +32° (c, 1.4, 1.0), λ 255 mμ (6200), λ 6.00, 6.21 μ.

Anal. Calcd. for $C_{31}H_{50}O_2$: C 81.88; H, 11.08. Found: C, 81.6; H, 11.1.

Conversion of friedelane-2,3-dione to friedelin (friedelan-3-one). A solution of the dione (55 mg.) in ether (35 cc.) was added to lithium aluminum hydride (200 mg.) in ether (50 cc.), the mixture heated under reflux for 15 min. and allowed to stand overnight at room temperature. Working up in the usual way yielded a hydroxy ketone, m.p. 218–221°, from chloroform-methanol, λ 2.90, 5.85 μ. Acetylation by treatment with acetic anhydride and pyridine at 100° gave an acetoxy ketone, m.p. 218–221°, $[\alpha]_D$ −50° as needles from methanol.

Anal. Calcd. for $C_{32}H_{52}O_3$: C, 79.28; H, 10.81. Found: C, 79.1; H, 10.7.

Zinc dust (10 g.) was added portionwise to a solution of the acetoxy ketone (80 mg.) in acetic acid (50 cc.) and the mixture heated under reflux for 22 hr. After filtration and evaporation of the solvent, the residue was extracted with chloroform and the extract washed with water and dried (sodium sulfate). On removal of the chloroform, the residue was dissolved in benzene and chromatographed on alumina (5 g. Woelm, Grade I). Elution with benzene (4 × 50 cc.) gave fractions 14 mg. (m.p. 235–242°), 9 mg. (m.p. 248–255°), 9 mg. (m.p. 248–255°) and 40 mg. (m.p. 244–252°). The last three were combined, recrystallized once from chloroform-methanol and once from ethyl acetate to give friedelin, m.p. and mixed m.p. 255–260° (capillary), 268–270° (vacuum).

It yielded friedelin oxime which, after recrystallization once from benzene and once from dioxane, melted at 287–290°, melting point and mixed melting point with authentic sample, m.p. 297–300° (vacuum).

Acknowledgment. This investigation was supported in part by a research grant (A-3439) from the National Institute of Arthritis and Metabolic Diseases, Public Health Service. We also wish to thank the Research Corporation for the award of a Frederick Gardner Cottrell grant (to R.S.) and acknowledge the aid of an Institutional grant of the American Cancer Society in providing a summer scholarship (to V.V.K.).

WALTHAM, MASS.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. LIX. Conversion of 3β-Acetoxy-5,16-pregnadiene-11,20-dione to Intermediates in the 5-Androstene Series[2]

EDWARD S. ROTHMAN AND MONROE E. WALL

Received January 27, 1960

Beckmann rearrangement of the monoxime of 3β-acetoxy-5,16-pregnadiene-11,20-dione, III, gave 17-acetamino-3β-acetoxy-5,16-androstadiene-11-one, IV. Conditions were found for selective borohydride reduction of the 11-ketone group without attack at the *N*-acetyl enamine function to form, after hydrolysis and reacetylation, 3β-acetoxy-11β-hydroxy-5-androstene-17-one.

There is currently great interest in steroidal compounds which combine the structural features of C-11 oxygenation and the C-5 olefinic bond. This interest arises from the high degree of bioactivity shown by many compounds (in particular 6-fluoro and 6-methyl derivatives) potentially derivable from precursors possessing the Δ^5 and C-11 oxygenation functions.[3] Previously such derivative types were usually prepared by the process of 3-ketalation of 11-oxygenated Δ^4-3-ketones,[3] the

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(1) Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture.

(2) Previous paper in this series, Steroidal Sapogenins. LVIII, A. M. Woodbury, *et al.*, *J. Econ. Bot.*, in press. Presented at 137th national ACS meeting, Cleveland, Ohio, April 1960.

(3) See for example formulation III of A. Bowers, L. Cuéllar Ibanez, and H. J. Ringold, *Tetrahedron*, 7, 138 (1959) and the many references cited by A. Bowers, E. Denot, M. B. Sanchez, L. M. Sanchez-Hidalgo, and H. J. Ringold, *J. Am. Chem. Soc.*, 81, 5234 (1959).

Δ^4 bond migrating to the 5,6 position during the ketalation. The 11-oxygenation of these compounds typically derives from microbiological hydroxylation.[4]

In view of the importance of these derived synthetic hormones, we wish to report the preparation of several Δ^5-11-oxygenated precursory androstene compounds derived by chemical procedures from the steroidal sapogenin, gentrogenin, (botogenin). These derivatives possess the special feature of a 3β-hydroxy-5-ene system as well as 11-oxygenation. Direct microbiological C-11 hydroxylative procedures for preparing such compounds could not have been applied since, in general, an already formed Δ^4-3-ketone system is probably prerequisite for C-11 direct hydroxylation.[4]

In previous papers from this laboratory we had described the preparation of the 12-ketone, gentrogenin,[5,6] its conversion to 11-keto diosgenin, I,[7] and the side-chain degradation of I to yield the key intermediate 3β-acetoxy-5,16-pregnadiene-11,-20-dione, II.[8] More recently the degradation of 11-ketodiosgenin to the 11-oxo-16-dehydro pregnene, II, was carried out using several modifications of our previously described procedure. These variations are presented in detail, as they seem to be generally applicable to degradation of C-ring oxygenated sapogenins.

Conversion of I to the corresponding pseudosapogenin diacetate was carried out by heating in acetic anhydride at 180°.[9] Oxidation of the latter without isolation was accomplished in a one-phase acetic acid-ethylene chloride aqueous chromium trioxide mixture at −5°. For best yields it was necessary to conduct the oxidation at this temperature and to maintain low temperature during the reduction of excess chromic ion with sodium metabisulfite. The oxidation intermediate, 11-ketodiosone, was not isolated. On treatment with refluxing acetic acid,[10] 3β-acetoxy-5,16-pregnadiene-11,20-dione,[8] II, was obtained in 60% yield. The Beckmann rearrangement of Δ^{16}-20 ketosteroid oximes discovered by Tendick and Lawson in 1943, U.S. Patent **2,335,616,** and utilized by Rosenkranz, Mancera, Sondheimer, and Djerassi[11] in unsubstituted C-ring compounds was applied to compound II. Treatment of II with hydroxylamine hydrochloride as in the procedure of Rosenkranz, Mancera, Sondheimer, and Djerassi[11] gave the monoxime, 3β-acetoxy-5,16-pregnadiene-11,20-dione 20-monoxime, III, in 61% yield. On treatment with p-acetamidobenzenesulfonyl chloride, Beckmann rearrangement occurred.[11] The intermediate *N*-acetyl enamine, IV, was obtained in an impure light yellow-orange crystalline form from which a small sample of the pure colorless material was obtained by recrystallization. The impure substance was used without purification in the subsequent steps, as its infrared and ultraviolet spectra were quite similar to those of the pure substance. The ultraviolet maximum of the *N*-acetyl enamine IV, $\lambda_{max}^{CH_3OH}$ 237 mμ, $\epsilon = 7640$, was similar to the absorption values for unacylated enamines reported by Leonard and Locke[12] and similar to that of the 11-desoxy analog of the present compound described by Rosenkranz, Mancera, Sondheimer, and Djerassi.[11] The infrared spectrum of IV with bands at 3450, 1720, 1686, and 1493 cm.$^{-1}$ was in reasonable agreement with published values for the corresponding 11-desoxyamide.[11] On hydrolysis of IV[11] followed by reacetylation, 3β-acetoxy-5-androstene-11,17-dione, V, was obtained in 70% yield. The structure of V is based on analogy with the 11-desoxy compound,[11] on the elemental analysis, and on the infrared absorption spectrum which showed bands at 1707 (11-ketone) and 1740 cm.$^{-1}$ (acetate and 17-ketone).[13]

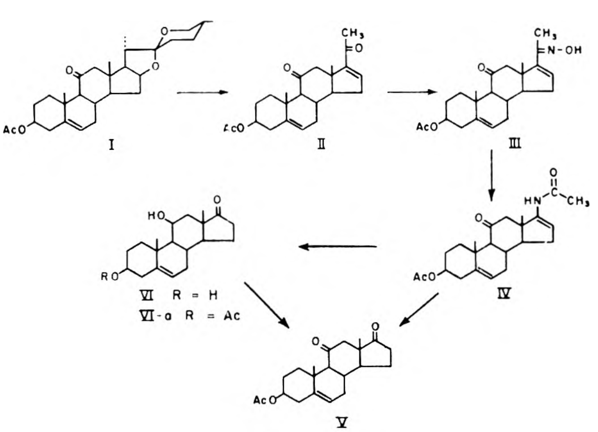

Fig. 1.

We became interested in preparing the intermediate, 3β,11β-dihydroxy-5-androstene-17-one,

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[4] S. H. Eppstein, *et al.*, *J. Am. Chem. Soc.*, **76**, 3174 (1954).

[5] H. A. Walens, S. Serota, and M. E. Wall, *J. Org. Chem.*, **22**, 182 (1957).

[6] M. E. Wall, J. J. Willaman, T. Perlstein, D. S. Correll, and H. S. Gentry, *J. Am. Pharm. Assoc.* (*Sci. Ed.*), **46**, 155 (1957).

[7] E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, **79**, 3228 (1957).

[8] E. S. Rothman and M. E. Wall, **81**, 411 (1959). See also O. Halpern and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 439 (1959) for the 11α hydroxy congener of the compound II.

[9] M. E. Wall and S. Serota, *J. Am. Chem. Soc.*, **79**, 6481 (1957).

[10] A. F. B. Cameron, *et al.*, *J. Chem. Soc.*, 2807 (1955).

[11] G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956).

[12] N. J. Leonard, and D. M. Locke, *J. Am. Chem. Soc.*, **77**, 437 (1955).

[13] After the researches reported in this paper were completed, we noted a report by M. Martin-Smith, *J. Chem. Soc.*, 523 (1958), in which was reported the preparation of V by an unusual route. This worker observed that 3β-acetoxy-17α-hydroxy-5α-pregnane-11,20-dione on chromic acid oxidation gave 3β-acetoxy-5α-androstane-11,17-dione which on further oxidation gave, in low yield, the corresponding 5α-*hydroxy* derivative. On dehydration the latter gave a compound identical in all physical properties and infrared spectrum with V.

VI. From VI one could prepare 11β-hydroxy-4-androstene-3,17-dione[14] which is the starting point for the synthesis of 9α-fluoro-17α-methyl-11β,-17β-dihydroxy-4-androstene-3-one, (halotestin).[15] Hitherto the latter steroids have been available only through the microbiological oxidation of 4-androstene-3,17-dione.[4] Although compound VI might have been prepared from V by forming the 17-monoketal or monoenamine followed by lithium aluminum hydride reduction of the 11-ketone and removal of the protective group, we felt that it might be preferable to retain and utilize the enamine grouping in IV as an already existing blocking group thereby saving two reaction steps. Reasoning that it might be possible to reduce the 11-ketone group without attacking the unsaturated amide linkage, several reduction systems were investigated. Lithium aluminum hydride, in the several solvents tried, seemed to reduce the Δ^{16} double bond, as did sodium borohydride in isopropanol or diethylene glycol dimethyl ether. In these cases the products showed infrared amide, hydroxyl, and NH bands but did *not* show selective ultraviolet absorption near 238 mμ. However, use of sodium borohydride in methanol gave the desired VI, after hydrolysis, in 35% yield. The hydrolysis could be carried out in either acid or basic media but in the latter case was difficult to drive to completion. Structure proof was based on observation of correct analytical values; the infrared absorption spectrum showing a single carbonyl band at 1740 cm.$^{-1}$ (17-ketone); and the fact that monoacylation at C-3 followed by oxidation of VI gave the 11,17-diketone V identical with the diketone directly derived from hydrolysis of IV. Acetylation of VI under mild conditions gave the 3β-acetoxy-11β-hydroxy derivative VIa. In the course of chromatography of the acetylated mother liquors of VIa, 11β-hydroxy-3,5-androstadiene-17-one, VII, was isolated as a by-product. Structure assignment of VII was based on correct analytical values, characteristic ultraviolet spectrum[16] with maxima at 230, 236, and 245 mμ, $\lambda_{\max}^{\mathrm{CH_3OH}}$ 236 mμ, ϵ = 21,900, and infrared spectrum showing bands at 3600 (hydroxyl), and 1743 cm.$^{-1}$ (17-ketone) as well as bands at 3060, 865, 821, and 811 cm.$^{-1}$ characteristic of the conjugated system. Other acid-induced dehydration by-products may have been formed but could not be isolated.

EXPERIMENTAL[17]

3β-Acetoxy-5,16-pregnadiene-11,20-dione, II. One hundred grams of 11-keto-diosgenin acetate,[7] I, were heated with 250 ml. of acetic anhydride containing 0.1% v/v glacial acetic acid for 21 hr. at 180°.[9] After cooling, sufficient water was added to decompose all the acetic anhydride. The volume was brought to 1500 ml. with acetic acid and an equal volume of ethylene chloride was added. The solution was cooled to −8° in an ice-salt bath. To this solution was added a solution of 50.0 g. of chromic acid in 1500 ml. of 90% acetic acid, precooled to +7°. The oxidant was added over a period of 30 min. at such a rate that the temperature did not rise above −2°. The reaction was then allowed to proceed another 30 min. Excess chromium trioxide was then reduced with a solution of 50 g. of sodium metabisulfite in 400 ml. of water, precooled to −4°, and added at such a rate that the temperature did not exceed −2°. To the reduced solution was added 5 l. of 20% sodium chloride solution, and the lower layer consisting of ethylene chloride was drawn off. The aqueous solution was then repeatedly extracted with ether; the combined organic layers were washed with sodium bicarbonate solution until neutral and dried with anhydrous sodium sulfate. The solvents were removed *in vacuo* and the residual glassy 11-keto-diosone refluxed 2 hr. with 1 l. of glacial acetic acid. The acid was removed *in vacuo,* the residue taken up in heptane; the last traces of acetic acid were removed by washing with sodium bicarbonate solution and the heptane was dried with anhydrous sodium sulfate. The crude heptane solution of II was passed through a Florisil[18] column; elution with benzene followed by evaporation of solvent and crystallization from methanol gave 47 g. of II,[8] m.p. 183°, $[\alpha]_{\mathrm{D}}^{25}$ −1.7°.

Conversion of 3β-acetoxy-5,16-pregnadiene-11,20-dione, II, *to its monoxime,* III. A mixture of 6.89 g. of II, 35 ml. of absolute ethanol, 10 ml. of pyridine, and 2.34 g. of hydroxylamine hydrochloride was refluxed for 35 min. On cooling crystals formed and were collected. Dilution of the filtrate with water gave additional crystalline material. The combined crops, after recrystallization from methanol, gave 4.34 g. (61%) of C-20 monoxime, m.p. 214–217°. The analytical sample melted at 217° to a pink liquid $\lambda_{\max}^{\mathrm{CH_3OH}}$ 234.5 mμ, ϵ = 15,200, $[\alpha]_{\mathrm{D}}^{25}$ −24.7°.

Anal. Calcd. for $C_{23}H_{31}O_4N$: N, 3.63. Found: N, 3.58.

17-Acetamino-3β-acetoxy-5,16-androstadiene-11-one, IV. The monoxime III, 4.31 g. in 12.3 ml. of dry pyridine, was treated with 5.27 g. of *p*-acetamidobenzenesulfonyl chloride in 12.3 ml. of pyridine at 0°, and was stirred at 10° for 2 hr. and at 26° for 2 additional hr. The mixture was then stirred into crushed ice whereupon a thick emulsion separated. Extraction with methylene chloride–hexane was carried out, and solid matter collecting at the interface was collected with the organic layer. Evaporation of the solvent *in vacuo* gave an orange syrup which on repeated re-evaporation *in vacuo* with a little methanol was freed of pyridine traces, whereupon the residue spontaneously crystallized. Recrystallization from methanol gave needles, m.p. 220–225° (dark red melt), $[\alpha]_{\mathrm{D}}^{25}$ ± 0; $\bar{\nu}_{\max}^{\mathrm{CHCl_3}}$ 3450 (NH), 1721 (acetate); 1690 (amide + ketone), 1492 cm.$^{-1}$ (NH), $\lambda_{\max}^{\mathrm{CH_3OH}}$ 237 mμ, ϵ = 7,640.

Anal. Calcd. for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.60; H, 8.10; N, 3.61.

3β,11β-Dihydroxy-5-androsten-17-one, VI. The enamine amide, IV, 2.15 g., in 20 ml. of dry methanol (distilled from magnesium turnings) was treated with 235 mg. of sodium borohydride at room temperature for 20 hr. A fresh charge of 225 mg. of sodium borohydride was added and the mixture was again let stand for 20 hr. The suspension was then diluted with methylene chloride and hexane and was shaken with dilute aqueous sodium dihydrogen phosphate to destroy excess reagent. The organic layer was separated and dried with sodium sulfate. An aliquot refluxed with 5% methanolic–aqueous potassium hydroxide for 1 hr. showed persisting infrared bands at 1735 and 1665 cm.$^{-1}$ although their intensity was reduced relative to an untreated aliquot.

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[14] M. E. Herr and F. W. Heyl, *J. Am. Chem. Soc.,* **75,** 5927 (1953).

[15] M. E. Herr, J. A. Hogg, and R. H. Levin, *J. Am. Chem. Soc.,* **78,** 500 (1956).

[16] L. Dorfman, *Chem. Rev.,* **53,** 47 (1953).

[17] We wish to thank S. Serota for determination of optical rotations, R. Kelly for elemental analyses, and C. Leander and A. Smith for spectral determinations.

[18] Specification of brand names of materials used does not imply endorsement over similar commercial products.

The remainder of the material was evaporated to dryness, redissolved in 45 ml. of methanol, 18 ml. of 6N aqueous hydrochloric acid was added and the mixture was refluxed 1.5 hr. The cooled mixture was extracted with methylene chloride–hexane which on concentration gave 720 mg. of crystalline product, m.p. 173–190°. Recrystallization from ether gave blades, m.p. 192–197°. The analytical sample from hexane gave rosettes, m.p. 190–192°, $[\alpha]_D^{25}$ −20.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.62; H, 9.41.

11β-Hydroxy-3,5-androstadiene-17-one, VII. The mother liquors from the preceding preparations were evaporated to dryness, dissolved in benzene, and placed on a short column of Florisil. Elution with benzene gave a noncrystalline orange glassy material followed by 39 mg. of a crystalline fraction. Recrystallization of the latter from methanol and from aqueous methanol gave broad blades having a high vapor pressure near the melting point. The melting point under very slow temperature-rise conditions was 161.5–165°, but a moderate rate of heating on open microscope slide gave the value 178–179°, $[\alpha]_D^{25}$ +52.1°, $\bar{\nu}_{max}^{CS_2}$ 3600 (single sharp), 1743 (v. strong), 821, 811, 865 cm.$^{-1}$, ultraviolet absorption bands occurred at 230, 237, 245 mμ, $\lambda_{max}^{CH_3OH}$ 237 mμ, ϵ = 21,900.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.61; H, 9.30.

Further elution of the column with ether gave 60 mg. of VI.

3β-Acetoxy-11β-hydroxy-5-androstene-17-one, VIa. The 3β,-11β-dihydroxy-17-ketone, VI, 100 mg., was let stand 16 hr. in a mixture of 2 ml. of pyridine and 1 ml. of acetic anhydride. Dilution with water, extraction with ether, and washing the ether free of acetylation mixture with dilute hydrochloric acid and with dilute sodium bicarbonate gave, after evaporation, the required monoacetate. Recrystallization from hexane gave spindles undergoing transition beyond 200°. At 216° the primary crystal forms began to melt before transition of crystal form was completed. Decomposition and reddening supervened, the last crystal of the stable phase disappearing at 231°, $[\alpha]_D^{25}$ −17.1°. The analytical sample melted cleanly at 232°, after undergoing transition, but did not decompose.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.71; H, 8.61.

3β-Acetoxy-5-androstene-11,20-dione, V. (*a*) *From* VIa. 3β-Acetoxy-11β-hydroxy-17-ketone, VIa, 500 mg., was dissolved in 6 ml. of pyridine at 10° and treated with a slurry of 500 mg. of chromium trioxide in 6 ml. of cold pyridine.[19] After standing 16 hr. at room temperature the mixture was diluted with ice water and with ether. Dilute hydrochloric acid was added to make the aqueous phase distinctly acid, and enough dilute sodium bisulfite was added to reduce chromium to the trivalent state. At this point emulsified solid brown matter went into solution and the phases separated cleanly. The organic layer was separated and washed with water, dilute sodium bicarbonate, and saturated sodium chloride. The residue on evaporation gave 500 mg. of colorless crystalline residue, m.p. 163–167°. After crystallizing from methyl acetate and from methanol, the product melted from 172–174°, $[\alpha]_D^{25}$ +38°; Martin-Smith[13] gives m.p. 171°, $[\alpha]_D$ +38°.

Anal. Calcd. for $C_{21}H_{28}O_4$; C, 73.22; H, 8.19. Found: C, 72.81; H, 8.37.

(*b*) *From* IV. A 5-g. sample of the *N*-acetyl enamine, IV, was dissolved in 110 ml. of 5% ethanolic potassium hydroxide and refluxed for 1 hr. The cooled flask contents were diluted with water and extracted with ether. The organic layer was washed with 2*N* hydrochloric acid to remove yellow coloration, with dilute sodium bicarbonate, and with saturated sodium chloride. An aliquot of this material did not show persisting acetate infrared bands. The solvent was evaporated and the residue was acetylated with acetic anhydride–pyridine mixture at room temperature overnight. The product, crystallized from methanol, was obtained in 74% yield and was identical with the sample described in part (a).

Philadelphia 18, Pa.

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[19] G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

Contribution from the Department of Chemistry of Wayne State University]

The Relative Stabilities of *cis* and *trans* Isomers. IX. A Study of the Importance of Conformational Transmission in Determining the Relative Stabilities of Hydrindanones in Steroidal Systems[1]

NORMAN L. ALLINGER and SEYMOUR GREENBERG

Received February 2, 1960

A-nor-5β-androstan-3-one (VIII) and A-nor-D-homo-5β-androstan-3-one (XIV) have been prepared. A comparison of their rotatory dispersion curves, together with the corresponding curves obtained from the epimeric mixtures which resulted when they were treated with base, showed that the strain induced in VIII by the *trans*-C/D fusion and conformationally transmitted to the A/B fusion was not of importance in determining the position of equilibrium at the latter juncture.

The hydrindane and hydrindanone systems, because of their apparent relative simplicity and wide occurrence in nature, have furnished a challenge to conformational analysis to interpret the relative stabilities of the *cis* and *trans* junctures. Although a large amount of work directed at such an interpretation has been carried out,[2] even a qualitative understanding of these systems is lacking in certain cases.

One effect which must in principle influence the stability of a hydrindanone juncture as in the A/B rings of a compound such as VIII and which has not previously been considered in this connection, is the effect of the strained *trans* C/D fusion as relayed

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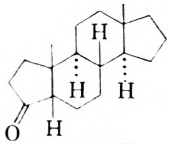
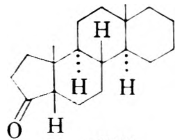
[1] Paper VIII, N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, 25, 922 (1960).

[2] See ref. 1 for summary and references.



VIII



XIV

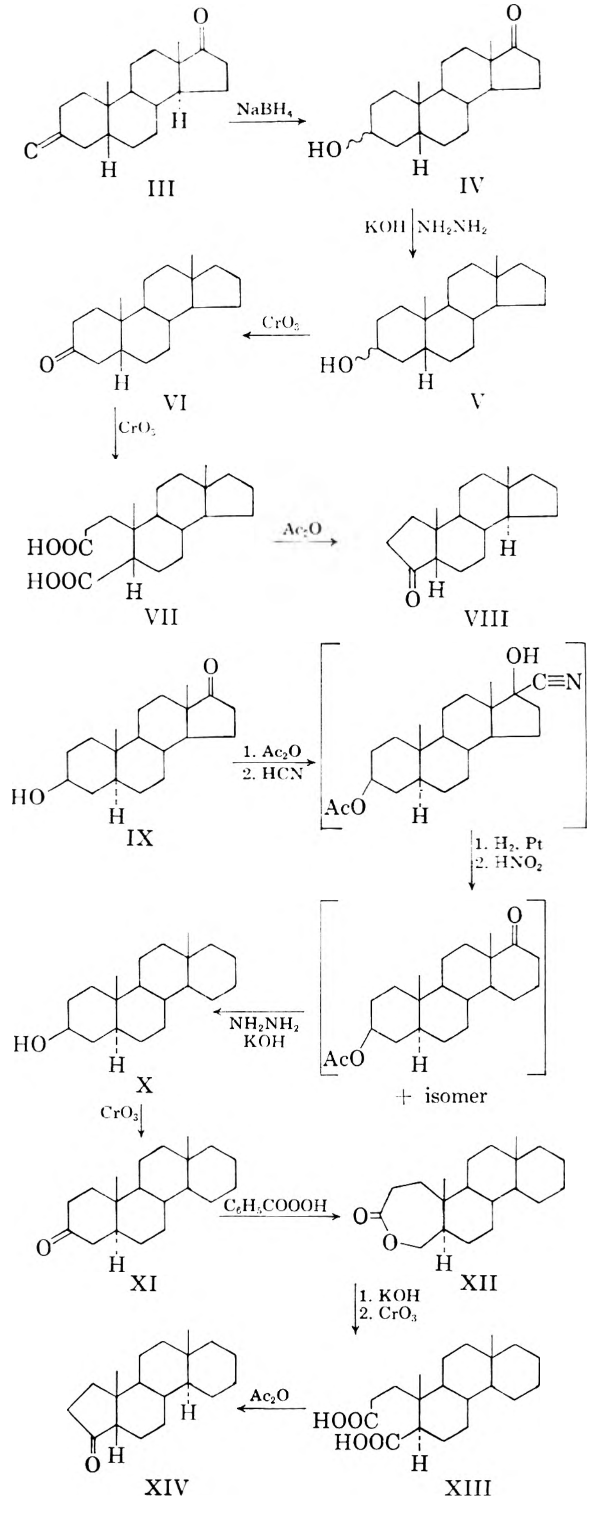
to the A/B fusion by conformational transmission.[3] While an effect of this kind can be assumed to occur, its importance in influencing the stability of the A/B juncture cannot be estimated from available data.

With this type of structure the equilibrium lies very far on the side of the *cis* isomer, compared with other apparently similar compounds and theoretical predictions.[1] If the strained C/D fusion were indeed responsible for the comparatively great stability of the *cis* forms in VIII, then compound XIV should not be analogous to VIII in this respect. An experimental comparison of the equilibrium points between the A/B *cis* and A/B *trans* forms of VIII and of XIV therefore seemed in order.

RESULTS AND DISCUSSION

A-nor-5β-androstane-3-one (VIII) has previously been described in the literature.[4] A new synthesis of it was used in the present work. This synthesis, which is outlined on the flow sheet, began from 5β-androstane-3,17-dione (III). The keto-group at C-3 was selectively reduced with sodium borohydride[5] to give IV. A Wolff-Kishner reduction[6] of IV gave V, which was oxidized[7] to VI and then to VII. This diacid was treated with acetic anhydride[4] which cyclized it to VIII.

The synthesis of XIV began from isoandrosterone (IX). The 3-hydroxyl was acetylated, and the ring expansion[8] was carried out in several steps, by forming the cyanohydrin[4] at C-17, catalytic reduction of the nitrile to the amine, and rearrangement by the Tiffeneau-Demjanov method upon treating the amine with nitrous acid. The resulting keto group was removed by the Wolff-Kishner method,[6] which gave the known D-homo-5α-androstan-3β-ol (X). Chromic acid oxidation of this alcohol yielded the 3-ketone (XI). Perbenzoic acid oxidation[9] of XI yielded a lactone XII, to which the D-homo-4-hydroxy-3,4-seco-5α-androstan-3-oic acid lactone structure was assigned by analogy with the oxidation of cholestan-3-one.



The lactone (XII), upon treatment with alkali, opened to the corresponding hydroxy acid which was oxidized to the dioic acid (XIII) with chromium trioxide. Treatment of XIII with acetic anhydride[4] gave the ketone XIV.

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[3] (a) D. H. R. Barton, A. J. Head, and P. J. May, *J. Chem. Soc.*, 935 (1957). (b) C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 4001 (1958).

[4] L. Ruzicka, V. Prelog, and P. Meister, *Helv. Chim. Acta*, **28**, 1651 (1945).

[5] E. Elisberg, H. Vanderhaeghe, and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 2814 (1952).

[6] Huang-Minlon, *J. Am. Chem. Soc.* **68**, 2487 (1946).

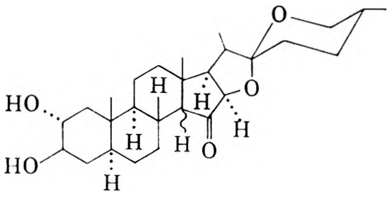
[7] B. Heath-Brown, I. M. Heilbron, and E. R. H. Jones, *J. Chem. Soc.*, 1482 (1940).

[8] (a) R. O. Clinton, R. G. Christiansen, H. C. Neumann and S. C. Laskowski, *J. Am. Chem. Soc.*, **79**, 6475 (1957). (b) M. W. Goldberg and R. Monnier, *Helv. Chim. Acta*, **23**, 376 (1940).

[9] V. Burckhardt and T. Reichstein, *Helv. Chim. Acta*, **25**, 1434 (1942).

The ketones isolated (VIII and XIV) can both be assigned the 5-β configuration (A/B *cis*) on the basis of their rotatory dispersion curves. The curves are nearly identical for the two ketones, and quite similar but epimeric with those of the model compound XV.[10] The alternative 5α structures would be expected to yield curves similar to those found for XVI.[10] The assignments are unambiguous, as the molecular amplitudes are large (over 10,000°) and for VIII and XIV the predicted sign of the Cotton effect is positive, as found, while for the 5α-epimers it would be negative.

If the peracid rearrangement had gone with migration of the other possible alkyl group, then XI would have led eventually to A-nor-D-homo-5α-androstan-2-one instead of to XIV. Qualitatively the Cotton effect curve for this compound would be similar to that of XIV but the amplitudes would differ considerably. Closely similar models (2-keto-A-norcholestane and 3-keto-A-norcholanic acid respectively[10]) have [*a*] + 23,300 and [*a*] + 14,350 respectively. The value for XIV is [*a*] + 12,700 which is additional support for the structure assigned.



XV 14β
XVI 14α

Earlier studies[1] have shown the ease and accuracy of measuring equilibrium constants by means of optical rotations in the ultraviolet. The rotatory dispersion curves of pure VIII and the equilibrium mixture obtained upon treatment of VIII with base were measured and were nearly identical. It can therefore be estimated that the equilibrium mixture contains more than 95% of the 5β epimer under the conditions used. This is a larger percentage than the theory[1] calls for and is analogous to what was found with the previously studied A-nor system. When the curves for XIV and the equilibrium mixture of epimers obtained by treatment of XIV with base were compared, again the equilibrium amount of the 5β epimer was >95%.

Therefore it may be concluded that the equilibrium point in the epimerization at C-5 is not noticeably affected by the presence or absence of a strained C/D fusion, and conformational transmission does not appear to be important in effecting this equilibrium.

EXPERIMENTAL

17β-Acetoxy-5β-androstan-3-one (I). The synthesis of this compound was carried out beginning with testosterone. Hydrogenation of testosterone acetate furnished a mixture of isomers epimeric at carbon 5 from which 17β-acetoxy-5β-androstane-3-one was isolated[11] in 52% yield, m.p. 139–144°; lit.[11] m.p. 143–145°.

5β-Androstane-17β-ol-3-one (II). Compound I, 9.77 g., was heated for 1 hr. in a refluxing solution containing 8.4 g. of potassium hydroxide in 115 ml. of 85% methanol. The reaction mixture was poured into water and extracted with chloroform. The chloroform extracts were dried, the solvent was evaporated, and the residue was crystallized from ether–petroleum ether (b.p. 60–90°) to yield 7 g. (82%) of II in two crops, m.p. 140–143° (lit.[12] m.p. 142–143°).

5β-Androstane-3,17-dione (III). Compound II, 1 g., in 5 ml. of acetic acid was treated with 0.24 g. of chromium trioxide in 10 ml. of 90% acetic acid. The mixture was allowed to stand for 2 hr. at room temperature and was then diluted with 100 ml. of water The resulting solution was kept at 0° overnight and the solid was collected, wt. 0.79 g. (79%), m.p. 122–128° (lit.,[12] m p. 131–132°).

3,4-Seco-5β-androstan-3,4-dioic acid (VII). Sodium borohydride reduction of III according to Elisberg, Vanderhaeghe, and Gallagher[5] gave a mixture of 3α-hydroxy- and 3β-hydroxy-5β-androstan-17-one in 82% yield. Two grams of this material was heated under reflux for 1 hr. with 25 ml. of diethylene glycol containing 1.2 g. of 95% hydrazine and 4 g. of potassium hydroxide. The condenser was then removed and the mixture was allowed to distill until the temperature of the vapors reached 190°. After heating the mixture under reflux for an additional 4 hr. it was cooled, poured into water, neutralized with hydrochloric acid, and the solution was extracted with ether. The ether solution was washed and dried, and the ether was evaporated. The resulting mixture of 3α-hydroxy- and 3β-hydroxy-5β-androstanes was then taken up in 25 ml. of acetic acid and mixed with a solution composed of 10 ml. of 90% acetic acid and 0.5 g. of chromium trioxide. The mixture was allowed to stand at room temperature for 1 hr. and was then poured into water and the solution was extracted with ether. The ether phase was dried and the solvent was evaporated. The residue was found by chromatographic examination still to contain considerable 3-hydroxy-5β-androstane. The crude ketone, 1.3 g., was dissolved in 40 ml. of 90% acetic acid containing 1.5 g. of chromium trioxide, and the solution was heated under reflux for 3 hr.[7] The cooled solution, diluted with 6*N* sulfuric acid, was extracted with ether. The ether layer was then extracted with dilute sodium hydroxide. Extraction of the aqueous phase with ether furnished 200 mg. of neutral material. The basic solution was acidified and extracted with ether. The dried ether extracts gave crude VII, which was recrystallized from ether-pentane, wt. 370 mg. (18%), m.p. 242–245° (lit.[4] m.p. 253–255°).

A-Nor-5β-androstan-3-one (VIII). Compound VII was converted to VIII in 30% yield following the known procedure,[1] m.p. 91–92°, lit.,[4] m p. 89–91°. R. D. in methanol (*c* 0.09): $[\alpha]_{700}$ +98°, $[\alpha]_{589}$ +142°, $[\alpha]_{310}$ +2550°. $[\alpha]_{272.5}$ −1806°, $[\alpha]_{260}$ −1190. After this curve was obtained a drop of 40% aqueous potassium hydroxide was added, the solution was allowed to stand overnight, and the curve was redetermined. The equilibrium curve was very similar to the original one, $[\alpha]_{312.5}$ +2352°, $[\alpha]_{277.5}$ −1638°.

3β-Acetoxy-5α-androstan-17-one. Compound IX, 2.0 g., was converted to the acetate by heating with 2 ml. of acetic anhydride at 60° for 8 hr. The cooled mixture was diluted with water and the mixture was extracted with ether. The ether solution was washed in turn with dilute hydrochloric

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(10) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956). For further details of this rotatory dispersion approach see C. Djerassi, *Optical Rotatory Dispersion Applications to Organic Chemistry*, McGraw-Hill, New York, 1960, p. 41.

(11) Private communication from Dr. O. Mancera of Syntex, S. A.

(12) L. F. Fieser and W.-Y. Huang, *J. Am. Chem. Soc.*, **75**, 4837 (1953).

acid, sodium bicarbonate solution, and water. The solution was dried, the ether was evaporated, and the residue was the crude acetate, 2.2 g. (96%), m.p. 110–114° (lit.[13] m.p. 103–104°).

D-Homo-5α-androstan-3β-ol (X). Compound IX. 2.2 g., was dissolved in 35 ml. of ethanol and the solution was cooled to −5°. Potassium cyanide, 12.8 g., was added and then 9.6 ml. of acetic acid was added during a few minutes with stirring. The mixture was then stirred and allowed to come to room temperature. After standing overnight, the mixture was poured into water. The resulting mixture was extracted with ethyl acetate The organic phase was separated, filtered, treated with charcoal, and the solvent was evaporated. The residue was dissolved in 75 ml. of acetic acid, 0.5 g. of platinum oxide was added, and the nitrile was hydrogenated at atmospheric pressure. The uptake of hydrogen ceased at the theoretical point, and the catalyst was removed by filtration. The bulk of the acetic acid was evaporated at reduced pressure, the residue was dissolved in water and the aqueous solution was filtered through a Celite pad and concentrated to a volume of 50 ml. Two milliliters of acetic acid was then added, the solution was cooled in ice, and an aqueous solution containing 1 g. of sodium nitrite was added. The resulting solution was allowed to stand overnight and the precipitate was collected, washed with water, and dried, wt. 1.4 g. A total of 3.9 g. of this crude material from combined runs was reduced with 3 g. of anhydrous hydrazine using 9 g. of potassium hydroxide in 60 ml. of diethylene glycol as described for the preparation of V. The product was isolated as before, taken up in benzene, and chromatographed on 100 g. of alumina with benzene. Two fractions were obtained, and separately purified by crystallization from benzene-pentane. The first fraction yielded 0.5 g., m.p. 158–163° (lit.[4] for the 3α isomer, m.p. 168–169°), and the second yielded 1.0 g., m.p. 146–150° (lit.[4] for 3β isomer, m.p. 143–143.5°).

D-Homo-5α-androstan-3-one (XI). One gram of D-homo-5α-androstan-3β-ol was oxidized with 0.24 g. of chromium trioxide in 25 ml. of 90% acetic acid by allowing the mixture to stand overnight. The reaction product was isolated by diluting the mixture with water and extracting with ether. The ether extracts were washed and dried; evaporation of the ether gave 0.9 g. (90%) of XI, m.p. 164–166° (lit.[4] m.p. 168.5–170°).

D-Homo-4-hydroxy-3,4-seco-5α-androstan-3-oic acid lactone (XII). Compound XI, 1.37 g., was allowed to stand overnight at 5° in a chloroform solution containing 1.31 g. of perbenzoic acid. The remaining perbenzoic acid was then destroyed by shaking the solution with excess potassium iodide in 5% sulfuric acid followed by sodium thiosulfate. The organic layer was washed and dried and the solvent was evaporated. The residue was crystallized from methylene chloride-hexane and gave 700 mg. of material, m.p. 210–215°, and a second crop, 200 mg., m.p. 205–210°. A sample was recrystallized from hexane several times, m.p. 217–218°.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 77.80; H, 10.31.

D-Homo-3,4-seco-5α-androstan-3,4-dioic acid (XIII). Compound XI, 700 mg., was saponified by heating under reflux in methanol with 2 g. of potassium hydroxide. The cooled solution was diluted with water and extracted with ether. The ether phase was dried, the solvent was evaporated, and the residue was taken up in 30 ml. of acetic acid. To this solution was added 700 mg. of chromium trioxide in 7 ml. of 90% acetic acid. The solution was left at room temperature for several hours, and the product was isolated as described for XI. After crystallization from ethyl acetate there was obtained 330 mg. (43%) of material, m.p. 222–227°. A small sample was recrystallized for analysis, m.p. 224–226°.

Anal. Calcd. for $C_{20}H_{32}O_4$: C, 71.38; H, 9.59. Found: C, 70.96; H, 9.37.

A-nor-D-homo-5β-androstan-3-one (XIV). Compound XIII, 330 mg., was dissolved in 5 ml. of acetic anhydride and the mixture was heated under reflux for 1 hr. The excess acetic anhydride was distilled at reduced pressure, and the residue was heated under reflux for a few minutes at a pressure of 100 mm. The pressure was then lowered to 20 mm. and the mixture was distilled. The distillate was dissolved in ether and the solution was washed first with dilute sodium hydroxide, then with water. The ether solution was dried and the solvent was evaporated. The residue was sublimed to yield XIV, wt. 100 mg., m.p. 118–121°. After chromatography on alumina with hexane-ether, the material was crystallized from hexane, m.p. 124–125°. The compound showed a strong carbonyl band at 5.72 μ in chloroform. R. D. in methanol (*c* 0.09): $[\alpha]_{700}$ +70°, $[\alpha]_{589}$ +130°, $[\alpha]_{312.5}$ +2600°, $[\alpha]_{272.5}$ −2040°, $[\alpha]_{262.5}$ −1640°. After this curve was obtained, a drop of 40% aqueous potassium hydroxide was added to the solution. The basic solution was allowed to stand overnight and the rotatory dispersion curve was redetermined. This curve was nearly identical with the original one, $[\alpha]_{312.5}$ +2620° and $[\alpha]_{272.5}$ −2120°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.33; H, 11.04.

Acknowledgment. The authors are indebted to Dr. Carl Djerassi of Stanford University for obtaining the rotatory dispersion curves reported herein, and for furnishing the compounds used as starting materials in this work, and to the Public Health Service (Grant E-2267) for financial support.

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[13] (a) T. Reichstein and A. Lardon, *Helv.*, **24**, 955 (1941). (b) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953).

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES OF BROWN UNIVERSITY AND THE DEPARTMENT OF CHEMISTRY OF THE RICE INSTITUTE]

The Dipole Moments of Androstan-17-one, Testan-11-one, and Testane-11,17-dione

HAROLD R. NACE AND RICHARD B. TURNER

Received February 19, 1960

The dipole moments of androstan-17-one, testan-11-one, and of testane-11,17-dione derived from dielectric constant measurements of benzene solutions of these compounds at 25° are, respectively, 3.0, 3.0, and 4.1 *D*. The result obtained for testane-11,17-dione is significantly lower than the value of 4.6 *D* calculated for this substance, a discrepancy which is suggestive of an interaction between the two carbonyl groups, postulated previously for 11,17-diketosteroids on the basis of infrared evidence only.

In 1949 Jones, Humphries, and Dobriner[1] observed that the infrared absorption maximum associated with the 17-carbonyl group in 17-ketosteroids is displaced from its normal position (1742–1745 cm.$^{-1}$) to 1748–1754 cm.$^{-1}$ in compounds possessing both an 11- and a 17- carbonyl function. Similar displacements have been observed in 21-acetoxy-20-ketosteroids[1,2] and in 12α- and 12β-acetoxy-11-ketosteroids[3] but not in the structurally related 17β-acetoxy-16-keto derivatives.[4] Although the origins of these shifts are not clearly understood, the suggestion has been made that they result from the interaction of dipolar functions that are proximate in space through a direct field effect.[4,5] This suggestion has prompted us to search for anomalies in the dipole moment of testane-11,17-dione (III) in which the relative position of the two carbonyl groups is fixed by their incorporation in a rigid ring system.

EXPERIMENTAL

The dielectric constants of benzene solutions (25°) of androstan-17-one, testan-11-one, and testane-11,17-dione were determined at 200 kc./sec. using the same capacitance-conductance bridge, test cell, and circuit as employed previously.[6]

Materials. The benzene used in the present work was purified by the method of the previous investigation.[6]

Androstan-17-one. 3β-Benzoyloxyandrostan-17-one[7] (2.2 g. m.p. 220–221°) was pyrolyzed under reduced pressure at 420° for 0.5 hr. The resulting material was taken up in ether, washed with dilute sodium hydroxide, and evaporated to dryness. Separation of the olefinic product from unchanged starting material was accomplished by treatment with methanolic potassium hydroxide, followed by filtration of a petroleum ether solution of the hydrolysate through alumina. Hydrogenation of the crude unsaturated ketone over platinum and subsequent oxidation with chromium trioxide furnished 603 mg. of androstan-17-one, m.p. 118–119°. A pure product, m.p. 121–122°,[8] $\nu_{max}^{CS_2}$ 1745 cm.$^{-1}$, was obtained by recrystallization from aqueous methanol.

Testan-11-one. A mixture of 820 mg. of testane-11,17-dione (prepared as described below), 1.5 g. of potassium hydroxide, 0.5 ml. of 85% hydrazine, and 15 ml. of diethyleneglycol was heated under a reflux condenser at 170° for 0.5 hr. The condenser was then removed and the temperature was allowed to rise to 200°, where it was maintained for a period of 2 hr. The product was isolated by ether extraction and crystallization from aqueous methanol; 403 mg., m.p. 115.5–118.5°. Several recrystallizations from aqueous methanol afforded a pure sample melting at 119–120°, $\nu_{max}^{CS_2}$ 1713 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.99; H, 11.10.

Testane-11,17-dione. 3α-Hydroxytestane-11,17-dione (3.0 g., m.p. 187–188°)[9] was converted into the corresponding benzoate (3.6 g., m.p. 223–225°) by treatment with benzoyl chloride and pyridine. Three recrystallizations from methylene chloride-petroleum ether (b.p. 30–60°) afforded the analytical sample, m.p. 226–227°.

Anal. Calcd. for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 76.29; H, 8.02.

Pyrolysis of the benzoate was carried out under reduced pressure at 400° for 1 hr. The resulting product was hydrogenated over palladized charcoal in a mixture of ethanol and benzene and yielded 1.5 g. of testane-11,17-dione melt- at 139–142°. The analytical sample, m.p. 144–145°, $\nu_{max}^{CS_2}$ 1716, 1751 cm.$^{-1}$, was obtained after two recrystallizations from aqueous methanol.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.06; H, 9.91.

RESULTS AND DISCUSSION

For the dilute solutions studied both the density change, Δd, and the dielectric constant increment, $\Delta\epsilon$, were proportional to the weight per cent solute, W, within experimental error. The average values of $\Delta\epsilon/W$ and $\Delta d/W$ were used to calculate the solute polarization, P_2, and the dipole moment,

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(1) R. N. Jones, P. Humphries, and K. Dobriner, *J. Am. Chem. Soc.*, **71**, 242 (1949).

(2) R. N. Jones, V. Z. Williams, M. J. Whalen, and K. Dobriner, *J. Am. Chem. Soc.*, **70**, 2030 (1948); R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2820 (1952).

(3) D. H. W. Dickson and J. E. Page, *J. Chem. Soc.*, 447 (1955).

(4) L. J. Bellamy and R. L. Williams, *J. Chem. Soc.*, 861 (1957).

(5) R. N. Jones and C. Sandorfy, *Techniques of Organic Chemistry*, IX, "Chemical Aspects of Spectroscopy," ed. A. Weissberger, Interscience Publishers (1956), pp. 462–498.

(6) H. R. Nace and R. B. Turner, *J. Am. Chem. Soc.*, **75**, 4063 (1953).

(7) L. Ruzicka, M. W. Goldberg, and J. Meyer, *Helv. Chim. Acta*, **18**, 210 (1935).

(8) A. Butenandt and H. Dannenbaum, *Z. physiol. Chem.*, **229**, 192 (1934).

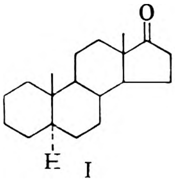
(9) Supplied through the courtesy of Dr. E. B. Hershberg, Schering Corp.

μ, from the relations employed previously.[6] The solute electronic polarization, $P_{E2} = 81.2$, calculated by Kumler,[10] for androstane-3,17-dione was used for testane-11,17-dione, and a value of $P_{E2} = 81.2$ for androstan-17-one and for testan-11-one was derived from the group refractions given by Smyth.[11] Measured solution dielectric constants, ϵ_{12}, densities, d_{12}, and weight per cent values, *W*, are listed in Table I.

TABLE I

Measurements in Benzene at 25°

W	ϵ_{12}	d_{12}
	Androstan-17-one	
1.2013	2.315	0.8738
0.7658	2.301	0.8740
0.5884	2.292	0.8738
0.3199	2.283	0.8726
	Testan-11-one	
1.1573	2.311	0.8741
0.9072	2.307	0.8740
0.7146	2.299	0.8738
0.3329	2.283	0.8722
	Testan-11,17-dione	
1.1473	2.363	0.8751
0.8705	2.324	0.8742
0.7048	2.315	0.8738
0.3952	2.298	0.8732



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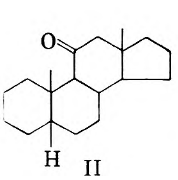
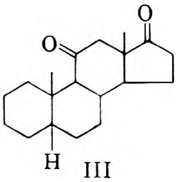


II



III

The values obtained for the dipole moments of the various compounds were: for androstan-17-one (I), 3.0 *D;* for testan-11-one (II), 3.0 *D;* and for testane-11,17-dione (III), 4.1 *D.* For purposes of comparison with the experimental result, the theoretical dipole moment of testan-11,17-dione was calculated as follows. The values of 3.0 *D* obtained for androstan-17-one and for testan-11-one were assumed for the individual moments of the two carbonyl functions in the dione (III), and the angle φ between these groups was derived by measurement of the direction cosines of the carbon-oxygen bonds in a carefully constructed Barton model[12] of testan-11,17-dione, which was mounted in a fixed position with respect to the coordinate system. Use of the relation

$$\cos \varphi = \cos \alpha_1 \cos \alpha_2 + \cos \beta_1 \cos \beta_2 + \cos \gamma_1 \cos \gamma_2$$

gave a value of 81.5° for φ, and the resultant moment calculated for testane-11,17-dione was 4.6 *D.* The discrepancy of 0.5 units between this value and the experimental quantity lies outside the limits of error of the method and provides independent evidence for the interaction theory, which hitherto has been supported by spectroscopic data only.

The precise nature of the phenomenon is, of course, not defined by the dipole moment results. It may involve mutual suppression of polar contributions to the hybrid structures of the carbonyl groups through the field effect, or alternatively an expansion of the carbonyl-carbonyl angle (φ) by dipolar repulsion.[13] The possibility that strains set up by the incorporation of two trigonal carbon atoms in the *trans*-fused C/D ring system may also be involved cannot be dismissed. It is especially worthy of note, however, that both spectroscopic and dipole moment anomalies of appreciable magnitude are observed in a system possessing 1,4-dicarbonyl groups that are nearly orthogonal and in which dipolar interactions should hence be minimal.

Providence, R. I.
Houston, Tex.

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[10] W. D. Kumler, *J. Am. Chem. Soc.*, **67**, 1901 (1945).

[11] C. P. Smyth, *Dielectric Constants and Molecular Structure*, Chemical Catalog Co. (Reinhold Publishing Corp.), New York, N. Y (1931).

[12] D. H. R. Barton, *Chemistry and Industry*, 1136 (1956).

[13] The value calculated for φ from the observed moments of androstan-17-one, testan-11-one, and testane-11,17-dione is 90.4° as compared with 81.5° obtained from the model.

[Contribution from the Organic Chemical Research Section, Lederle Laboratories,
a Division of American Cyanamid Co.]

Absorption Spectra of Steroids in Concentrated Sulfuric Acid. III. Structural Correlations. Analysis of the 300–600 Mμ Region[1]

SEYMOUR BERNSTEIN and ROBERT H. LENHARD

Received January 7, 1960

Certain structural correlations for the spectra of steroids in concentrated sulfuric acid are proposed in the 300–600 mμ region. Generally, hydroxylated steroids will exhibit selective absorption in the 300–600 mμ region. An associated hydroxyl absorption region, 220–278 mμ, has been previously established.[1] 3α- or 3β-Monohydroxylated steroids will probably possess a maximum in the 300–350 mμ region. Some evidence is presented for the selective absorption of the corticoid dihydroxyacetone side chain between 450–549 mμ, especially in the region 474–490 mμ. Selective absorption in the 300–399 mμ region may also be attributed to the ketone function, especially in the region 300–325 mμ. An associated ketone absorption region, 220–278 mμ, has been previously established.[1] Steroids which contain isolated double bonds may be correlated with selective absorption in the 400–449 mμ region.

In the previous paper of this series,[1] certain structural correlations for the spectra of steroids in concentrated sulfuric acid were proposed in the 220–300 mμ region. It is our purpose here to suggest the possibility of additional structural correlations, especially in the 300–600 mμ region of the spectrum. As previously, these observations are based on the analysis of the spectra of 177 compounds.[2]

For convenience, the 300–600 mμ region has been divided into five regions: *A*, 300–399 mμ; *B*, 400–549 mμ (three subdivisions); and *C*, 550–600 mμ. The number of compounds which exhibit selective absorption in these regions are listed in Table I. It will be noted that no compound in our catalog exhibited selective absorption in the 550–600 mμ region.[3] The discussion which follows will be according to the above designated regions.

A. *300–399 Mμ Region*.[4] The following considerations support the proposal that selective absorption in the 300–399 mμ region may be attributed primarily to the ketone and hydroxyl groups. In this connection, let us first examine the spectra of saturated and unsaturated ketosteroids which do *not* contain either an α,β-unsaturated ketone or a hydroxyl group. These compounds may be arbitrarily classified as "non-conjugated" ketones. In Table II are listed 11 such compounds with

TABLE I

Number of Compounds with Maximum[a] in Region 300–600 Mμ

	Region, Mμ (inclusive)	No. of Compounds with Maximum[a,b]
A	300–399	151
B	400–549	211
	400–449	117
	450–499	85
	500–549	9
C	550–600	0

[a] *i.e.*, maximum, plateau, or inflection. [b] A large number of compounds exhibited two or more maxima over the region 300–600 mμ, and were counted accordingly more than once.

TABLE II

Absorption Maxima of Nonconjugated Ketones

Compound (No.)	λ_{max} Mμ ($E^{1\%}_{1\,cm.}$)
Androstane-3,11,17-trione (11)	none [321(18)][a]
Etiocholane-3,11,17-trione (15)	none
Androstane-3,17-dione (18)	302 (595)
Etiocholane-3,17-dione (21)	302 (540)
Δ^7-Allopregnene-3,20-dione (55)	289(132) (I),[b] 322 (209)
Pregnane-3,20-dione (79)	237 (159) (I)
Δ^7-Cholestene-3-one (163)	240 (86), 317 (189)
Cholestane-3-one (165)	312 (152)
Coprostane-3-one (167)	235(91)(I), 316 (146), 477(12)
$\Delta^{7,22}$-Ergostadiene-3-one (172)	238(103), 312 (272)
Ergostane-3-one (177)	240(46), 313 (125)

[a] For all practical purposes, this compound is considered as showing no selective absorption. [b] The symbol, *I* designates an inflection or plateau.

(4) It has already been indicated that α,β-unsaturated ketosteroids exhibit selective absorption between 279–302 mμ (inclusive). Thus, there is in this case a minor overlapping in certain aspects of the structural correlations. It should also be borne in mind that the following chromophores exhibit selective absorption in this region, *i.e.*, 6β-hydroxy-Δ^4-3-ketone ($\cong\Delta^{4,6}$-3-ketone) at about 343–346 mμ (based on three examples); 3β-hydroxy-Δ^5-7-ketone ($\cong\Delta^{3,5}$-7-ketone) at about 355 mμ (based on one example); Δ^4-3,6-diketone at about 348 mμ (based on one example); and, $\Delta^{1,4}$-3-ketone at about 327 mμ (based on one example). In regard to the last chromophore, L. L. Smith and W. H. Muller, *loc. cit.*, have suggested that the combination of selective absorption in the 247–267 mμ region and in the 295–318 mμ region is characteristic of the $\Delta^{1,4}$-3-ketone moiety in the corticoid series.

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(1) Paper II, S. Bernstein and R. H. Lenhard, *J. Org. Chem.*, **19**, 1269 (1954).

(2) This number does not include derivatives such as acetates, when the parent free steroid was available. Also, estrogens, steroid alkaloids, and ethylene ketals are not included.

(3) It is not inferred that there are no steroids which show selective absorption in this region. Recently, L. L. Smith and W. H. Muller, *J. Org. Chem.*, **23**, 960 (1958), have observed a λ_{max} 568 mμ ($E^{1\%}_{1\,cm}$ 132) for $\Delta^{1,4}$-pregnadiene-9β,11β-epoxy-16α,17α,21-triol-3,20-dione 16,21-diacetate.

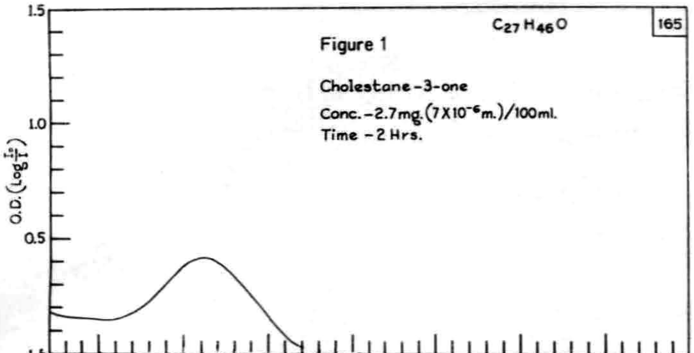

Figure 1

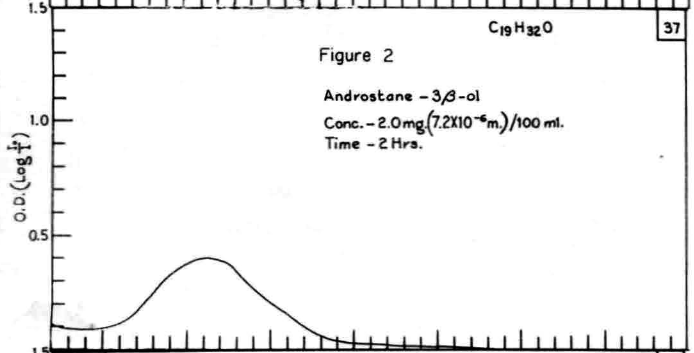

Figure 2

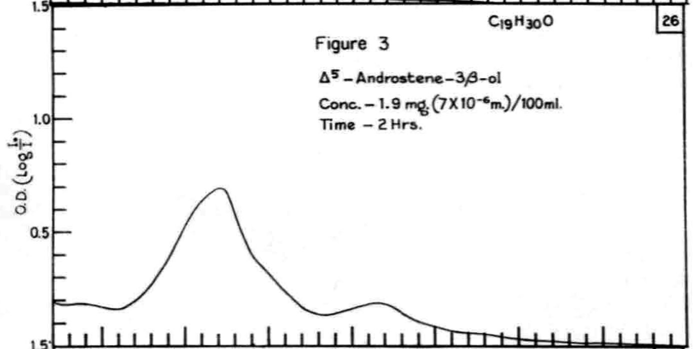

Figure 3

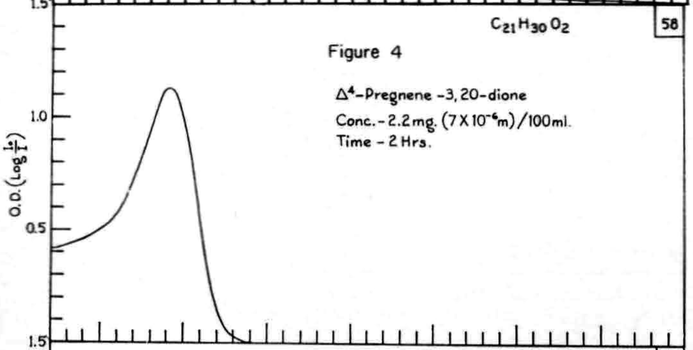

Figure 4

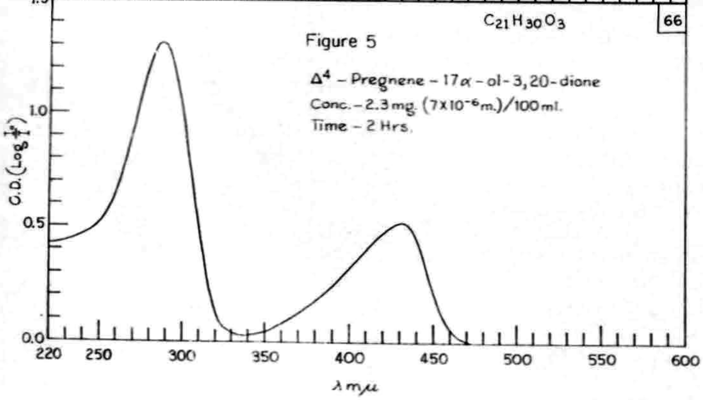

Figure 5

their respective maxima and extinction coefficients.[5] Eight of these compounds exhibit a sizeable absorption maximum between 302–322 mμ (inclusive) ($E^{1\%}_{1\text{ cm}}$ 125–595). Thus, the portion of the spectrum between 300–325 mμ generally represents an additional ketone absorption region to the one already observed, *i.e.*, between 230–278 mμ.[1]

In Fig. 1 is presented the spectrogram of cholestane-3-one (No. 165)[6] which possesses a single maximum at 312 mμ ($E^{1\%}_{1\text{ cm}}$ 152). This illustrates the above correlation in a decisive manner.

The three exceptions to this correlation merit further discussion. Pregnane-3,20-dione (No. 79) exhibits no maximum but only an inflection at 237 mμ, which, however, falls in the lower ketone absorption region. Androstane-3,11,17-trione (No. 11), and its 5β-epimer, etiocholane-3,11,17-trione (No. 15) show essentially no selective absorption, which is in striking contrast to their corresponding 11-deoxo-compounds, androstane-3,17-dione (No. 18), and etiocholane-3,17-dione (No. 21). Thus, the 11-carbonyl group has exerted in some manner (transmissional effect?) a very pronounced influence on the absorption of the 3,17-diketone chromophore. This surprising result is of interest in view of the finding already noted[1] that an 11-ketone group produces an hypsochromic effect on the Δ⁴-3-ketone chromophore.

In Table II it may be observed that if the nonconjugated ketone showed selective absorption in both of the designated ketone regions, the band at the longer wave length invariably possessed the higher extinction coefficient. Therefore, it is believed that the region at approximately 300–325 mμ most likely represents the principal ketone absorption band.[7]

In Table III, there are presented the results of an examination of the absorption bands of 146 compounds which contain hydroxyl groups. The compounds are tabulated according to the number of hydroxyl groups contained in each. Also by each listing there is given the number of combinations or different positions occupied by these hydroxyl groups. Of the 146 hydroxyl-containing steroids 136 (total score of 93%) exhibited selective absorption in the 300–399 mμ region. Although in our catalog of compounds there are 161 compounds which display a band in this region, the overall score of 136/161 or 84% offers a high degree of assurance for the correlation of selective absorption for a hydroxylated steroid in this region.

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[5] Throughout for the purpose of structure correlations, maximum, plateau, and inflection are considered equivalent.

[6] The compound numbers throughout correspond to those employed in Paper I, S. Bernstein and R. H. Lenhard, *J. Org. Chem.*, **18,** 1146 (1953).

[7] In conventional absorption spectroscopy, a nonconjugated ketone will exhibit selective absorption in the 170–200 mμ and 280–300 mμ regions [L. Dorfman, *Chem. Rev.*, **53,** 47 (1953); and, A. Gillam and E. S. Stern, *An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry*, pages 47–51, Edward Arnold (Publishers) Ltd., London, 1954]. Thus, one also finds in sulfuric acid spectroscopy two ketone absorption regions which apparently have resulted by reason of a bathochromic effect of the sulfuric acid solvent.

TABLE III

ABSORPTION MAXIMA OF HYDROXYLATED STEROIDS

Type Compound	No. of Combinations	No. of Compounds Positive/ Total No.	Range
Monoöls	8	90/97	302–399 mμ
Diols	18	32/33	300–391 mμ
Triols	11	11/13	300–398 mμ
Tetrols	2	2/2	330–332 mμ
Pentols	1	1/1	360–378 mμ
		Total score: 136/146 (93%)	300–399 mμ
		Overall score: 136/161 (84%)	

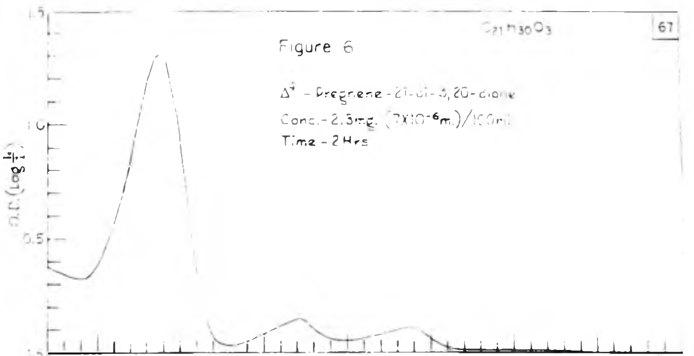
In Table IV 97 monohydroxylated steroids are tabulated according to the location and configuration of the hydroxyl group. A *tentative* conclusion may be stated that most 3α- or 3β-monohydroxylated steroids will show selective absorption in the 300–350-mμ region. This correlation is based on the fact that 63 out of 75 such steroids absorb selectively within this range. Ten C3-monohydroxylated steroids do not conform to this correlation; however, these compounds show selective absorption between 351–399 mμ.

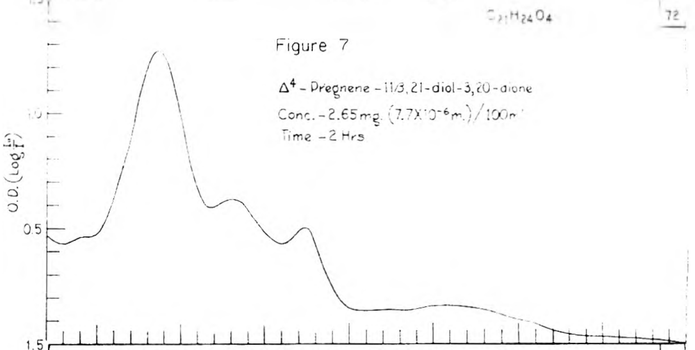
TABLE IV

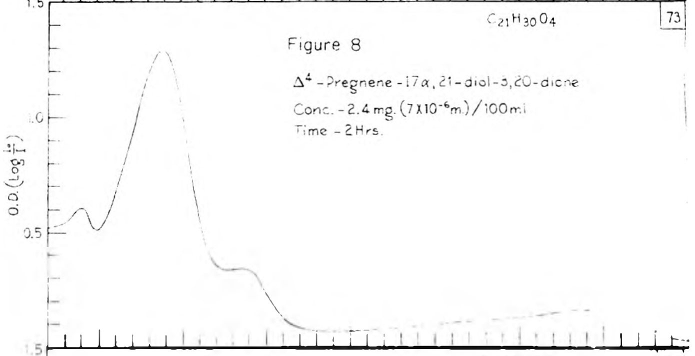
Monoöls	No. Cpds. "Positive"/ Total No.	Range
3α	15/15	11 307–350 mμ 4 351–389 mμ
3β	58/60	52 304–350 mμ 6 351–399 mμ
6β	1/1	344 mμ
11α	3/3	318–381 mμ
11β	2/2	318–380 mμ
17α	1/4	302 mμ
17β	8/10	302–395 mμ
21	2/2	354–372 mμ
Total Score	90/97 (93%)	302–399 mμ

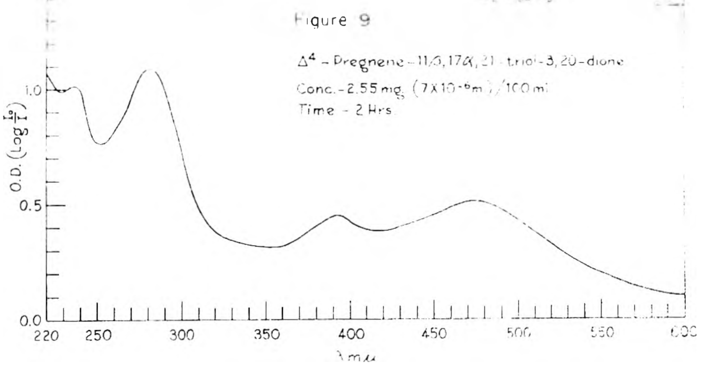
In regard to steroids monohydroxylated at other positions, no such correlation may be stated (or attempted) due to the insufficient number of examples available.

In Fig. 2 is given the spectrogram of androstane-3β-ol (No. 37), with its absorption maximum at 312 mμ, illustrative of the structural correlation of hydroxylated steroids showing selective absorption in the 300–399 mμ region.









B. *400–549 mμ region.* Our catalog contains 67 compounds which contain one to four double bonds and which are not conjugated with a ketone function. In Table V these compounds are tabulated according to the degree of unsaturation. Fifty-nine (88%) of these compounds show selective absorption in the 400–449 mμ region. Thus, it appears that unsaturated (non-conjugated) steroids generally will have selective absorption in this region. However, this correlation must be used with considerable caution as all-told our catalog contains

125 steroids which show absorption in this region. Of this number, 56 contain a hydroxyl function, and three (not really exceptions) contain a Δ^4-3-ketone group with Δ^7- or $\Delta^{7,9(11)}$-double bonds present.

TABLE V

ABSORPTION MAXIMA OF UNSATURATED STEROIDS

Unsaturated Cpds.	No. Cpds. "Positive"/Total No.	Range
Monoenes	35/40	402–449 mμ
Dienes	17/18	405–446 mμ
Trienes	6/8	400–438 mμ
Tetraenes	1/1	433 mμ
	Total Score: 59/67 (88%)	400–449 mμ
	Overall Score: 59/125 (47%)	

The selective absorption of double bonds and hydroxyl groups in this area leads one to believe that both types of compounds in concentrated sulfuric acid give rise to a common species, such as an alkyl hydrogen sulfate.[8] In Fig. 3 is presented the spectrogram of Δ^5-androstene-3β-ol (No. 26) with maxima at 236, 321, and 416 mμ. The 236 and 321 mμ bands may be ascribed to the hydroxyl group, and the 416 mμ band to the Δ^5-double bond (with or without the hydroxyl group?).

In Figs. 4–9 there are presented the spectrograms of Δ^4-pregnene-3,20-dione (No. 58), Δ^4-pregnene-17α-ol-3,20-dione (No. 66), Δ^4-pregnene-21-ol-3,20-dione (No. 67), Δ^4-pregnene-11α,21-diol-3,20-dione (No. 72), Δ^4-pregnene-17α,21-diol-3,20-dione (No. 73), and Δ^4-pregnene-11β,17α,21-triol-3,20-dione (No. 77). With increasing number of hydroxyl functions, the spectrograms become increasingly more complicated in the 300–549 mμ region with a definite trend toward increasing absorption at the higher wave lengths. It appears then that the 400–549 mμ region may also be associated with the hydroxyl function. Moreover, generally hydroxylated steroids will display selective absorption in the 300–549 mμ region. Also it should be noted that absorption in the region 220–278 mμ has been ascribed to the hydroxyl function.[1]

In our catalog there are seven steroids (Nos. 66, 70, 82, 88, 89, 90, and 91) with the 17α-hydroxy-17-acetyl side chain. Also there are three steroids (Nos. 67, 71, and 72) which contain a C17-ketol ($COCH_2OH$) side-chain. All 10 compounds show selective absorption in the 400–499 mμ region (see Figs. 5 and 6).

Also, in our catalog there are twelve steroids (Nos. 54, 73, 74, 75, 76, 77, 103, 113, 122, 141, and 147) which contain the dihydroxyacetone side-chain at C17. It was of interest to examine whether this important grouping displayed some characteristic absorption properties. All twelve show selective absorption (maximum or inflection, $E_{1\,\mathrm{cm}}^{1\%}$ 11-204) between 474–535 mμ. Of these twelve compounds eleven (one exception, No. 147, pregnane-3α,-11β,17α,21-tetrol-20-one-3,21-diacetate, $\lambda_{\max}$ 506 mμ) show selective absorption between 474–490 mμ ($E_{1\,\mathrm{cm}}^{1\%}$ 11-204).[9] It was also interesting to observe that eight out of twelve of the above compounds also show selective absorption in the 338–343 mμ region. ($E_{1\,\mathrm{cm}}^{1\%}$ 93-450), and nine out of twelve show selective absorption in the 233–271 mμ region ($E_{1\,\mathrm{cm}}^{1\%}$ 109-420).

Acknowledgment. We wish to acknowledge the invaluable assistance of Mr. Walter Muller who determined all the spectra. Also we wish to thank Mr. Walter Hearn for the reproductions of the spectrograms.

PEARL RIVER, N. Y.

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(8) R. J. Gillespie and J. A. Leisten, *Quart. Rev.*, **8**, 40 (1954).

(9) L. L. Smith and W. H. Muller, *loc. cit.*, have recorded the spectra (at 15 min., 2 hr., and 20 hr.) of 26 1-dehydrocorticosteroids (with a dihydroxyacetone side-chain) in concd. sulfuric acid. Of this number 18 contain in addition to the $\Delta^{1,4}$-3-ketone function a 16α-hydroxy or acetoxy group. Of the 8 corticosteroids which do *not* contain a 16-oxygenated function, $^3/_8$ (15 min.); $^5/_8$ (2 hr.) and $^7/_8$ (20 hr.) show selective absorption in the 450–549 mμ region. Of the 18 corticosteroids which contain a 16-oxygenated function $^1/_{18}$ (15 min.); $^2/_{18}$ (2 hr.) and $^8/_{18}$ (20 hr.) show selective absorption in the 450–549 mμ region.

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Infrared Spectra of Isotopically Labeled Compounds. II.[1] Compounds Possessing the 2,4-Dimethyl-3-pentyl Skeleton

GERASIMOS J. KARABATSOS[2]

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The infrared spectra of some C^{13} and deuterium labeled diisopropylcarbinols, diisopropylmethanes, 1,1-diisopropylethylenes, diisopropyl ketoximes, and diisopropylcarbinylamines were investigated. The 1236 cm.$^{-1}$ frequency of diisopropylcarbinol is shown to be an O—H deformation and the 1096 cm.$^{-1}$ frequency a skeletal vibration. The 1115 cm.$^{-1}$ frequency of hydrocarbons is a skeletal vibration and the 920 cm.$^{-1}$ a methyl rocking mode. The shifts observed upon O-deuteration of alcohols and oximes are in better agreement with calculations based on the reduced masses of (O—H) and (O—D) than on (H) and (D). The C═N stretch of oximes is less pure than either the C═O stretch of ketones and acids or the C═C stretch of ethylenes. The C—N stretch of aliphatic amines is much less coupled with other vibrations than the C—O stretch of alcohols, and quite different from the C—N stretch of anilines. Examples of displacements to higher wave numbers upon substitution with heavier isotopes are reported.

The infrared spectra of isotopically labeled diisopropyl ketones were reported in the first paper of this series.[1] Evidence was presented there indicating that the 1024 cm.$^{-1}$ frequency of diisopropyl ketone is an uncoupled vibration. Furthermore, it was shown that useful information could be obtained by examining the spectra of compounds isotopically labeled at various atoms. These facts prompted the examination of the infrared spectra of compounds derived from diisopropyl ketone.

This paper reports the spectra of isotopically labeled diisopropylcarbinols, diisopropylmethanes, 1,1-diisopropylethylenes, diisopropyl ketoximes, and diisopropylcarbinylamines. As in the case of diisopropyl ketones the purity of the samples used for infrared analysis was ascertained by vapor phase chromatography. The procedure followed in obtaining the spectra and analyzing them was the same as the one used for the ketones.

The pertinent spectral frequencies, the experimental frequency differences (Δ_ν), and some calculated Δ_ν values of the investigated compounds are presented in Tables I–V. The frequencies of diisopropylcarbinols (Table I) and diisopropyl ketoximes (Table IV) were determined in carbon disulfide. All other frequencies were determined in solutions of carbon tetrachloride, with the exception of the frequencies of the amines in the region of 800 cm.$^{-1}$ which were determined in carbon disulfide.[3] Each spectrum was taken in various concentrations, the range being from 3% to 12%.

DISCUSSION

Diisopropylcarbinols. The infrared spectra of alcohols have been the subject of frequent discussion in the literature,[4-11] due to the uncertainty of band assignment in the 1500–1000 cm.$^{-1}$ region. The most controversial frequencies are the ones in the 1250 cm.$^{-1}$ and 1100 cm.$^{-1}$ regions, assigned either to O—H deformations or to the coupled C—O and C—C stretchings. It appeared reasonable that the spectra of isotopically labeled diisopropylcarbinols might shed some light on the controversy.

The data of Table I show that five frequencies are strongly affected by O-deuteration and unaffected by either C^{13} substitution or C-deuteration. Two of these frequencies, 3610 cm.$^{-1}$ and 3470 cm.$^{-1}$, are the well known O—H stretches of the monomer and its hydrogen bonded complex, respectively.[12] The other three frequencies, 1380 cm.$^{-1}$, 1236 cm.$^{-1}$, and 1117 cm.$^{-1}$, are O—H deformations with one of them perhaps due to the hydrogen bonded complex.

The 1096 cm.$^{-1}$ frequency (1100 cm.$^{-1}$ region frequency of alcohols) is not an O—H deformation as some investigators have suggested. Neither is it a simple C—O stretch or the result of only C—O and C—C coupled stretches. The magnitude and nature of its shifts upon isotopic substitution, 2 cm.$^{-1}$ upon C^{13} substitution, 31 cm.$^{-1}$ upon 2,4-

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[1] Part I. G. J. Karabatsos, *J. Org. Chem.*, **25**, 315 (1960).

[2] Present address: Department of Chemistry, Michigan State University, East Lansing, Mich.

[3] Due to the reactivity of diisopropylcarbinylamine with carbon disulfide the frequencies in the 800 cm.$^{-1}$ region were determined immediately after solution of the amine in carbon disulfide.

(4) H. H. Zeiss and M. Tsutsui, *J. Am. Chem. Soc.*, **75**, 897 (1953).

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(6) H. D. Noether, *J. Chem. Phys.*, **10**, 693 (1942).

(7) A. Borden and E. F. Barker, *J. Chem. Phys.*, **6**, 553 (1938).

(8) E. F. Barker and P. Bosschleter, *J. Chem. Phys.*, **6**, 563 (1938).

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(11) E. L. Eliel, C. C. Price, R. J. Convery, T. J. Prosser, *Spectrochim. Acta*, **10**, 423 (1958).

(12) It is interesting to note that the experimental shifts of both 3610 cm.$^{-1}$ and 3740 cm.$^{-1}$ frequencies, 950 cm.$^{-1}$ and 886 cm.$^{-1}$, respectively, are in better agreement with the shifts calculated from the reduced masses of (O—H) and (O—D), than they are with the shifts calculated from the reduced masses of (H) and (D). It appears that the hydrogen is vibrating against the effective mass of the oxygen, and not against the effectively infinite mass of the whole molecule.

TABLE I

INFRARED SPECTRAL FREQUENCIES OF DIISOPROPYLCARBINOLS[a]

Compound	Wave Number (Cm.$^{-1}$)										$(\mu_2/\mu_1)^{1/2}$[b]
2,4-Dimethyl-3-pentanol	3610	3470	1380	1236	1152	1117	1096	993	977	848	
2,4-Dimethyl-3-pentanol-3-C^{13}	3610	3470	1380	1236	1147	1117	1094	982	966	844	
Δ_ν Experimental[c]					5		2	11	11	4	
Δ_ν Calcd. from (μ_{C-O}) and $(\mu_{C^{13}-O})$					25		24	22	22	19	1.023
Δ_ν Calcd. from (μ_{C-C}) and $(\mu_{C^{13}-C})$					23		21	19	19	17	1.020
2,4-Dimethyl-3-pentanol-O-*d*	2660	2584	1000	915	1143	807	1105	993	982	843	
Δ_ν Experimental[c]	950	886	380	321	9	310	−9		−5	5	
Δ_ν Calcd. from (μ_H) and (μ_D)	1055	1016									1.414
Δ_ν Calcd. from (μ_{O-H}) and (μ_{O-D})	983	944									1.374
2,4-Dimethyl-3-pentanol					1152		1096		977	848	
2,4-Dimethyl-3-pentanol-3-*d*					1145		1097		926	844	
Δ_ν Experimental[c]					7		−1		51	4	
2,4-Dimethyl-3-pentanol-2,4-d_2							1065		941		
Δ_ν Experimental[c]							31		36		

[a] Determined in carbon disulfide solutions. [b] μ_1 is the reduced mass calculated from the unlabeled alcohol and μ_2 the reduced mass calculated from the labeled alcohol. [c] Difference between the frequencies of the labeled compound and the corresponding frequencies of 2,4-dimethyl-3-pentanol. The Δ_ν's between the frequencies of 2,4-dimethyl-3-pentanol-3-C^{13} and 2,4-dimethyl-3-pentanol-O-*d*-3-C^{13} were identical with the Δ_ν's between the frequencies of 2,4-dimethyl-3-pentanol and 2,4-dimethyl-3-pentanol-O-*d*.

dideuteration, and displacement to higher frequencies (1105 cm.$^{-1}$) upon O-deuteration, suggest that it is a complex skeletal vibration characteristic of alcohols. The 1152 cm.$^{-1}$ and 848 cm.$^{-1}$ frequencies are also skeletal vibrations, the latter being equivalent to the 858 cm.$^{-1}$ frequency of diisopropyl ketone.

The spectrum of diisopropylcarbinol shows two strong bands at 993 cm.$^{-1}$ and 977 cm.$^{-1}$ The data of Table I suggest that the 993 cm.$^{-1}$ frequency is a skeletal vibration with no contribution from a C—H mode of either the tertiary or the secondary hydrogens. The 977 cm.$^{-1}$ frequency, having strong C—H contributions, behaves upon O-deuteration like the 1096 cm.$^{-1}$ frequency. Since either one or two strong bands appear in the spectra of many aliphatic alcohols in this region, the possibility of the usefulness of these bands as diagnostic tools, in conjunction with the 1100 cm.$^{-1}$ frequency, is under examination.

Diisopropylmethanes. In the infrared spectra of saturated hydrocarbons the assignment of the 1115 cm.$^{-1}$ and 920 cm.$^{-1}$ frequencies to specific vibrations has been rather difficult, and a great deal of controversy exist in the literature as to which frequency is the skeletal C—C stretch and which is the C—CH$_3$ rocking vibration.[13-17] The data presented in Table II suggest that the 1164 cm.$^{-1}$ frequency of diisopropylmethane (1115 cm.$^{-1}$ region), shifted to 1156 cm.$^{-1}$ upon C^{13} substitution, is a skeletal vibration rather than a methyl rocking mode. On the other hand, the 916 cm.$^{-1}$ frequency (920 cm.$^{-1}$ region) is unaffected by C^{13}, which is compatible with the methyl rocking mode.

TABLE II

INFRARED SPECTRAL FREQUENCIES OF DIISOPROPYLMETHANES[a]

Compound	Wave Number (Cm.$^{-1}$)				$(\mu_2/\mu_1)^{1/2}$
2,4-Dimethylpentane	1164	982	916	867	
2,4-Dimethylpentane-3-C^{13}	1156	972	916	862	
Δ_ν Experimental	8	8		5	
Δ_ν Calcd. from (μ_{C-C}) and $(\mu_{C^{13}-C})$	23	19	18	17	1.020

[a] Determined in carbon tetrachloride solutions.

TABLE III

INFRARED SPECTRAL FREQUENCIES OF DIISOPROPYLETHYLENES[a]

Compound	Wave Number (Cm.$^{-1}$)				$(\mu_2/\mu_1)^{1/2}$
1,1-Diisopropylethylene	1639	1101	1036	891	
1,1-Diisopropylethylene-1-C^{13}	1608	1097	1035	891	
Δ_ν Experimental	31	4	1	0	
Δ_ν Calcd. from (μ_{C-C}) and $(\mu_{C^{13}-C})$	32	22	20	18	1.020

[a] Determined in carbon tetrachloride solutions.

The 982 cm.$^{-1}$ and 867 cm.$^{-1}$ frequencies are assigned to skeletal vibrations, the latter being equivalent to the 858 cm.$^{-1}$ and 848 cm.$^{-1}$ frequencies of diisopropyl ketone and diisopropylcarbinol, respectively.

1,1-Diisopropylethylenes. The infrared spectrum of 1,1 - diisopropylethylene - 1 - C^{13} exhibits few differences from that of 1,1-diisopropylethylene. The 1639 cm.$^{-1}$ frequency, the C=C stretch, is lowered upon C^{13} substitution to 1608 cm.$^{-1}$, a

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(13) N. Sheppard and D. M. Simpson, *Quart. Revs.* (*London*), **7**, 19 (1953).

(14) K. W. F. Kohlrausch and F. Köppl, *Z. Phys. Chem.*, **B26**, 209 (1934).

(15) F. T. Wall and C. R. Eddy, *J. Chem. Phys.*, **6**, 107 (1938).

(16) S. Silver, *J. Chem. Phys.*, **8**, 919 (1940).

(17) N. Sheppard and D. M. Simpson, *J. Chem. Phys.*, **23**, 582 (1955).

TABLE IV

INFRARED SPECTRAL FREQUENCIES OF DIISOPROPYL KETOXIMES[a]

Compound	Wave Number (Cm.$^{-1}$)												$(\mu_2/\mu_1)^{1/2}$
2,4-Dimethyl-3-pentanone oxime	3571	3257	1656	1314	1233	1221	1163	1153	1062	1023	941	865	
2,4-Dimethyl-3-pentanone-3-C^{13} oxime	3571	3257	1629	1309	1232	1214	1151	1152	1050	1015	941	863	
Δ_ν Experimental			27	5	1	7	12	1	12	8		2	
Δ_ν Calcd. from (μ_{C-N}) and $(\mu_{C^{13}-N})$			36				25		23				1.022
Δ_ν Calcd. from (μ_{C-C}) and $(\mu_{C^{13}-C})$			32					20					1.020
2,4-Dimethyl-3-pentanone oxime-O-*d*	2602	2387	1642	1074	990								
Δ_ν Experimental	969	870	14	240	243								
Δ_ν Calcd. from (μ_H) and (μ_D)	1046	954											1.414
Δ_ν Calcd. from (μ_{C-H}) and (μ_{O-D})	972	887											1.374

[a] Determined in carbon disulfide solutions.

shift of 31 cm^{-1}. Calculations based on the reduced masses of (C═C) and (C^{13}═C) predict a shift of 32 cm^{-1}. However, as in the case of diisopropyl ketone, one cannot ascertain the degree of coupling between C═C and C—C without the aid of the spectrum of 1,1-diisopropylethylene-2-C^{13}.

The 891 cm.$^{-1}$ frequency, the ═CH$_2$ bending, behaves upon C^{13} substitution as expected.

Diisopropyl ketoximes. Examination of the data of Table IV reveals that the C═N stretch (1656 cm.$^{-1}$) of diisopropylketone oxime has stronger contributions from other vibrations than either the C═O or C═C stretches of diisopropyl ketone and 1,1-diisopropylethylene; upon C^{13} substitution it is lowered to 1629 cm.$^{-1}$, or shift of 27 cm.$^{-1}$, as compared to 36 cm.$^{-1}$ calculated from the reduced masses of (C═N) and (C^{13}═N). Furthermore, upon O-deuteration it is shifted to 1642 cm^{-1}.

O-deuteration strongly affects five frequencies. The 3571 cm.$^{-1}$ and 3257 cm.$^{-1}$ frequencies are the O—H stretchings of the monomer and its hydrogen bonded complex, respectively.[18] It is interesting to note that two of the O—H deformations,[19] 1314 cm.$^{-1}$ and 1233 cm.$^{-1}$, seem to be coupled with other vibrations, as shown by their shifts, 5 cm.$^{-1}$ and 1 cm.$^{-1}$ respectively, upon C^{13} substitution. It should be further noticed that the magnitude of their shifts upon O-deuteration is much smaller than expected.

The N—O stretch of the oximes is supposed to occur in the 950 cm.$^{-1}$ region.[19] The 941 cm.$^{-1}$ frequency of diisopropyl ketoxime, a very strong band, is most likely the N—O stretch. It should be noticed that it is unaffected by either C^{13} substitution or O-deuteration.

Although certain other frequency changes are observed upon isotopic substitution, assigning of the affected frequencies is not possible from the available data.[20]

Diisopropylcarbinylamines. The C—N stretch of aliphatic amines has not been definitely identified. Colthup[21] suggests that absorptions of aliphatic amines in the 1220–1020 cm.$^{-1}$ region correspond to C—N stretches. In the spectrum of diisopropylcarbinylamine (Table V) the only frequency strongly affected by C^{13} substitution, and the only strong band in the 1220–1020 cm.$^{-1}$ region, is the 1117 cm.$^{-1}$ The experimental shift, 22 cm.$^{-1}$, is in fair agreement with the 24 cm.$^{-1}$ shift calculated from the reduced masses of (C—N) and (C^{13}—N).[22] The extent to which the C—N stretch may be coupled with C—C vibrations cannot be ascertained from the present data. The fact that it is unaffected by either *N*,*N*-dideuteration or C-deuteration at carbon three, indicates that it is not coupled with either N—H vibrations or C—H vibrations of carbon three.

In an attempt to compare the C—N stretch of aliphatic amines with the corresponding stretch of anilines, the spectrum of aniline-N^{15} (a sample of the labeled aniline was kindly provided by Profes-

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(18) As in the case of diisopropylcarbinol the experimental shifts are in much better agreement with calculations based on the reduced masses of (O—H) and (O—D) than (H) and (D).

(19) A. Palm and H. Werbin, *Can. J. Chem.*, **32**, 858 (1954) have assigned the 1265 cm.$^{-1}$ frequency of α-benzaloximes to the O—H bending.

(20) The 1163 cm.$^{-1}$ frequency has the same shape as, but it is weaker than, the 1203 cm.$^{-1}$ frequency of diisopropyl ketone. Since both frequencies show the same shift, 12 cm.$^{-1}$ and 13 cm.$^{-1}$ respectively, upon C^{13} substitution, it is possible that the 1163 cm.$^{-1}$ is the asymmetric C═N stretch. The 865 cm.$^{-1}$ frequency is the same band found in the spectra of diisopropyl ketone (858 cm.$^{-1}$), diisopropylcarbinol (848 cm.$^{-1}$) and diisopropylmethane (867 cm.$^{-1}$). Evidently, it is characteristic of the 2,4-dimethyl 3-pentyl group.

(21) N. B. Colthup, *J. Opt. Soc. Am.*, **40**, 397 (1950).

(22) It is interesting to note that the C—O stretch of diisopropylcarbinol (1096 cm.$^{-1}$) is coupled with other vibrations to a much larger extent than the C—N stretch of diisopropylcarbinylamine.

TABLE V

INFRARED SPECTRAL FREQUENCIES OF DIISOPROPYLCARBINYLAMINES[a]

Compound	Wave Number (Cm.$^{-1}$)						$(\mu_2/\mu_1)^{1/2}$
2,4-Dimethyl-3-pentylamine	1613	1348	1258	1117	919	807[b]	
2,4-Dimethyl-3-pentylamine-3-C^{13}	1613		1258	1095	919	804[b]	
$\Delta\nu$ Experimental				22		3	
$\Delta\nu$ Calcd. from (μ_{C-N}) and $(\mu_{C^{13}-N})$				24			1.022
2,4-Dimethyl-3-pentylamine-N,N-d_2	1118	1348	1258	1117		803[b]	
$\Delta\nu$ Experimental	495					4	
2,4-Dimethyl-3-pentylamine-3-d	1613	1254	1258	1117	919		
$\Delta\nu$ Experimental		94					

[a] Determined in carbon tetrachloride solutions. [b] Determined in carbon disulfide.

sor E. L. Eliel) was examined. The only frequency of aniline affected by N^{15} substitution is a strong band at 1271 cm.$^{-1}$ (carbon tetrachloride solution) which is shifted to 1267 cm.$^{-1}$ The magnitude of the shift, only 4 cm.$^{-1}$, suggested that the C—N stretch of aniline is strongly coupled with other vibrations. Examination of the spectra of aniline-N, N-d_2 and aniline-N, N-d_2-N^{15} showed a displacement of the C—N stretch to 1302 cm.$^{-1}$ and 1298 cm.$^{-1}$, respectively. Such displacements to higher wave numbers upon heavier isotope substitution were observed in the spectrum of diisopropylcarbinol upon O-deuteration (frequencies 1096 cm.$^{-1}$ and 977 cm.$^{-1}$, Table I). That this displacement is common in the spectra of N,N-dideuterated anilines is shown by Table VI.

TABLE VI

CARBON-NITROGEN STRETCH OF ANILINES AND ANILINES-N,N-d_2

Compound	Undeut. Compound (Cm.$^{-1}$)	Deut. Compound (Cm.$^{-1}$)	$\Delta\nu$(Cm.$^{-1}$)
Aniline	1271	1302	31
Aniline-N^{15}	1267	1298	31
2-Bromoaniline	1307	1326	19
4-Bromoaniline	1274	1304	30
2,4,6-Tribromoaniline	1271	1284	13
2-Methylaniline	1269	1307	38
3-Methylaniline	1292	1314	22
4-Methylaniline	1271	1302	31
2-Methoxyaniline	1271	1307	36

One could explain these results by invoking the noncrossing over rule of two vibrations possessing the same symmetry properties. (In the case of anilines the vibrations would be the N—H deformation around 1600 cm.$^{-1}$ and the C—N stretch.) Calculations which would either confirm or refute the above suggestion are under consideration.

EXPERIMENTAL

2,4-Dimethyl-3-pentanol-3-C^{13}. A solution of 2,4-dimethyl-3-pentanone-3-C^{13} (2 g.) in anhydrous ether (20 ml.) was slowly added, at room temperature, to a dispersion of lithium aluminum hydride (0.5 g.) in anhydrous ether (55 ml.) with constant stirring. The product was heated at reflux for 1 additional hr. Cold water (1 ml.), followed by 10% aqueous sodium hydroxide (0.5 ml.), was added and the mixture was allowed to stand overnight. The ether solution was filtered through anhydrous sodium sulfate, the ether evaporated, and the residue (about 2 g.) was vapor phase chromatographed.

2,4-Dimethyl-3-pentanol-O-d. A solution of 2,4-dimethyl-3-pentanol (0.2 g.) in anhydrous ether (5 ml.) was shaken for 15 hr. with heavy water (5 g.). The ether layer was separated, dried over anhydrous sodium sulfate, the ether was evaporated, and the residue was vapor phase chromatographed. 2,4-Dimethyl-3-pentanol-O-d-3-C^{13} was prepared from 2,4-dimethyl-3-pentanol-3-C^{13}.

2,4-Dimethyl-3-pentanol-3-d was prepared by reduction of the ketone with lithium aluminum hydride.

2,4-Dimethyl-3-pentanol-2,4-d_2 was prepared by reduction of the dideuterated ketone with lithium aluminum hydride.

2,4-Dimethylpentane-3-C^{13}. Preparation of this hydrocarbon will be described elsewhere.

1,1-Diisopropylethylene. Preparation of 1,1-diisopropylethylene was achieved by application of the Wittig reaction.[23] Triphenylmethylphosphonium iodide (5 g.)[24] was added to a solution of phenyllithium (1.1 g.) in ether (100 ml.). Stirring was continued for 3 hr. the color of the reaction mixture turning orange-brown. Slow addition of a solution of 2,4-dimethyl-3-pentanone (1.4 g.) in ether (10 ml.) resulted in the discharge of the orange color and the formation of a fine gray-white precipitate. Stirring was continued for 1 additional hr. at room temperature, followed by 3 hr. of steam reflux. The ether layer was separated, washed with 5% aqueous hydrochloric acid, 10% aqueous sodium bicarbonate, and water, and dried over anhydrous magnesium sulfate. The ether was driven off and the residue was vapor phase chromatographed. The yields of 1,1-diisopropylethylene did not exceed 35%. 1,1-Diisopropylethylene-1-C^{13} was prepared by using 2,4-dimethyl-3-pentanone-3-C^{13}.

Preparation of the oximes was accomplished by use of standard methods. Preparation of the amines was achieved by reduction of the corresponding oximes with lithium aluminum hydride (deuteride).[25]

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EAST LANSING, MICH.

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(25) C. R. Walter, Jr., *J. Am. Chem. Soc.*, **74**, 5185 (1952).

[JOINT CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1] AND THE RADIOCARBON LABORATORY, UNIVERSITY OF ILLINOIS]

Labeling Fatty Acids by Exposure to Tritium Gas. II. Methyl Oleate and Linoleate[2]

E. P. JONES,[3] L. H. MASON,[3] H. J. DUTTON,[3] AND R. F. NYSTROM[4]

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Unsaturated fatty acid esters react at room temperature on exposure to gaseous tritium by addition of tritium to a double bond and with little or no substitution of tritium for hydrogen. Evidence for addition to olefinic bonds, rather than substitution for hydrogen, has been obtained from gas-liquid and liquid-partition chromatography of both the tritiated fatty acids and the tritiated products after mild oxidative cleavage. Tritiated fatty acid esters appear on chromatograms at positions of the next less-saturated member of the isologous series. The position of addition of the tritium is deduced from the radioactivity of the monobasic and dibasic acids produced by oxidation.

Tritium labeling of methyl esters of saturated fatty acids by the Wilzbach gas-exposure technique[5] is described in the first paper[6] of this series. The expected substitution of hydrogen by tritium gas was found to take place giving the desired labeled fatty acids with high specific activity and with only small amounts of radiation-induced impurities. Results are presented herein on gas exposure and analysis of two members of the C_{18} unsaturated fatty acid ester series—methyl oleate and linoleate—in which addition to the double bond, not substitution, is found to occur. This discovery not only holds significance to those interested in the labeling of unsaturated fatty acids but shows the need for caution when labeling olefinic compounds by the gas-exposure technique and for establishing the type of labeling which has taken place.[7]

RESULTS

Data on the irradiation and chemical purification of methyl oleate and linoleate are given in Table I. A tritium source containing approximately 1 curie was employed for the irradiation of gram samples of the methyl esters. Activities incorporated in an 18-day period were 8-14 mc. Of this total radioactivity, 76% to 82% was recovered in the purified fatty acid fraction. In agreement with earlier results[6] for saturated fatty esters, little activity remained in the acid aqueous layer after ether extraction. Also activity in the unsaponifiable fraction was found to be due partly to labile tritium exchanged by the ethanol present in the ether layer. The effectiveness of chemical purification procedures in removing labile tritium, and evidence for the structure of the tritiated methyl esters will be given in the following sections.

TABLE I

TRITIUM INCORPORATION AND DISTRIBUTION IN METHYL OLEATE AND METHYL LINOLEATE BY THE GAS EXPOSURE TECHNIQUE

Methyl Ester	Exposure (Days)	Tritium Incorporated (Mc.)	Distribution of Tritium, % Unsaponifiable	Labile	Acid aqueous	Fatty acids
Oleate	18	8.3	14.6	7.7	1.2	76.5
Linoleate	18	14.4	12.9	5.3	0.3	81.5

Methyl oleate. The results of gas chromatography and subsequent liquid scintillation counting of methyl oleate immediately after tritium irradiation are given in Fig. 1. This pattern is similar to that for the saturated ester[6] in showing a small amount of rapidly eluted radioactive material coincident with the solvent peak which is thought to be either residual tritium gas or solvent molecules containing labile tritium. However, the pattern differs from that for the saturated esters in that the major radiochemical peak is eluted prior to the inactive oleate peak. Similar behavior of the major radiochemical component is shown in Fig. 2 for the liquid-partition chromatogram of the oleic acid preparation after saponification, exchange of labile

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(1) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) This paper was presented before Division of Organic Chemistry, 135th National Meeting of American Chemical Society, Boston, Mass., April 5-10, 1959.

(3) Address: Northern Regional Research Laboratory, Peoria, Ill.

(4) Address: Radiocarbon Laboratory, University of Illinois, Urbana, Ill.

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

(6) R. F. Nystrom, L. H. Mason, E. P. Jones, and H. J. Dutton, *J. Am. Oil Chemists' Soc.*, **36**, 212 (1959).

(7) H. J. Dutton and R. F. Nystrom, Proceedings of the Symposium on Advances in Tracer Applications of Tritium, New York, N. Y., October 31, 1958, pp. 8-15.

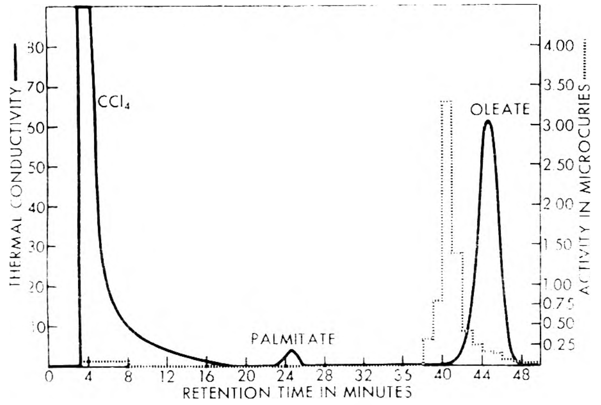


Fig. 1. Gas chromatogram of methyl oleate immediately after exposure to tritium gas

tritium, and acidification. Moreover, this assay technique could be used as a preparative method for isolating radiochemically pure methyl tritiostearate (56 curies per millimole for the addition of T_2 (pure) to C=C). It will become apparent that this shift is not an isotopic effect;[8] rather, the radiochemical peaks in Figs. 1 and 2 are coincident with the positions of methyl stearate and stearic acid, respectively, and the radioactive methyl stearate is produced by the saturation of the double bond in methyl oleate with tritium.

After chemical purification and methylation of the oleic acid by diazomethane (Fig. 3), the effectiveness of our purification procedures can be demonstrated by gas chromatography. The gas analysis shows that labile tritium is absent in the solvent peak, confirms the shift in position of the radiochemical compound compared to inactive methyl oleate, and establishes that the radiochemical product behaves chemically and chromatographically as a methyl ester of stearic acid. In further experiments, the coincidence of this radiochemical peak with that for methyl stearate was established by adding inactive methyl stearate to the tritiated methyl oleate sample.

On periodate-permanganate oxidation of the chemically purified tritiated oleic acid, the acids were separated on a liquid-partition column designed for separating monobasic acids as one peak from the separate peaks of the C_{10}, C_9, and C_9 dibasic acids. Two major peaks corresponding to monobasic acids and azelaic acid were obtained. In Fig. 4 radiochemical activity is coincident with the peak for unresolved monobasic acids and the azelaic acid is inactive.

Subsequent resolution of the monobasic peak on a liquid-partition chromatographic column designed specifically to separate the expected monobasic acids shows (Fig. 5) that the pelargonic acid is also inactive and that the radiochemical activity is coincident with titratable amounts of stearic acid coming from a known methyl stearate impurity in the original untritiated methyl oleate preparation. The radioactivity of this stearic acid and the inactivity of the pelargonic and azelaic acids were confirmed (not shown) by gas chromatography of the mixture of their methyl esters and by radiochemical assay of the fractions.

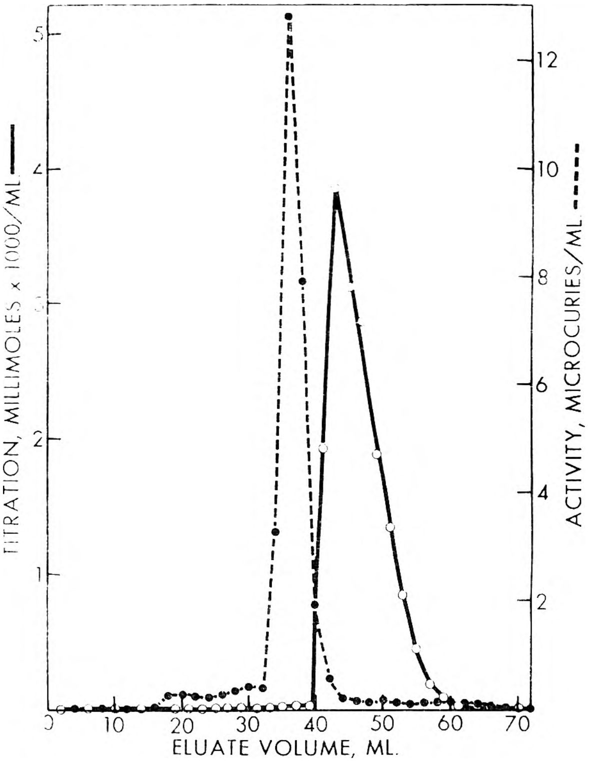
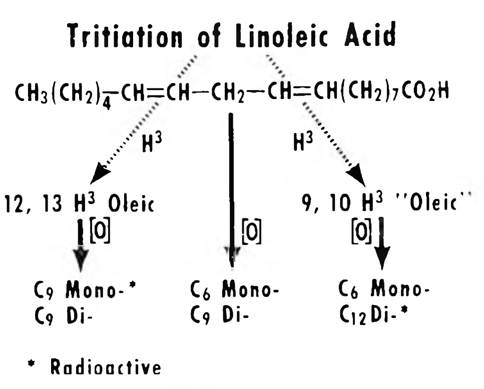


Fig. 2. Liquid-partition chromatogram of a mixture of chemically purified tritiated oleic acid and carrier oleic acid

Methyl linoleate. Gas-chromatographic data for the tritiated methyl linoleate before (Fig. 6) chemical purification show the displacement of the radioactive peak from the inactive parent methyl linoleate to the position expected for methyl oleate. The coincidence of positions for the tritiated linoleate with methyl oleate was confirmed by gas chromatography of a mixture of inactive methyl oleate and tritiated methyl linoleate and by observing coincidence of peaks.

The addition of tritium to methyl linoleate can occur at two positions: the 9,10-double bond and the



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(8) K. E. Wilzbach and P. Riesz, *Science*, 26, 748 (1957).

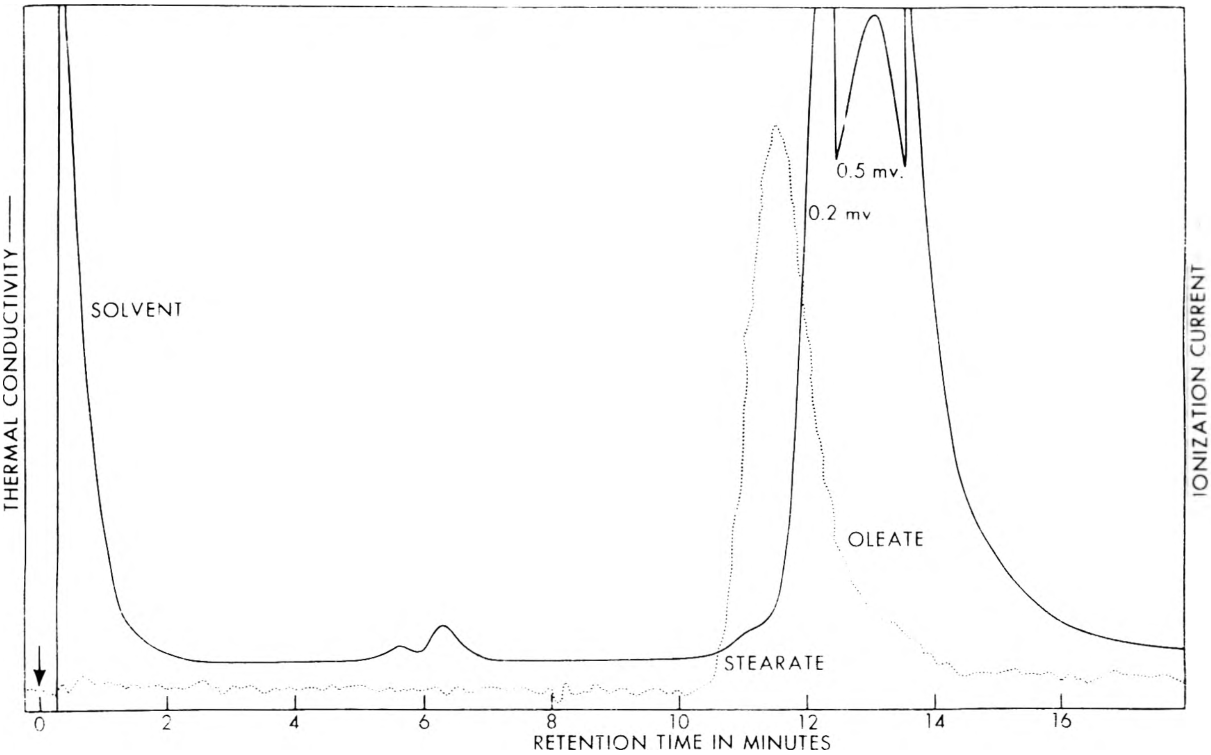

Fig. 3. Gas chromatogram of tritiated methyl oleate after saponification, alcohol exchange, acidification, and methylation

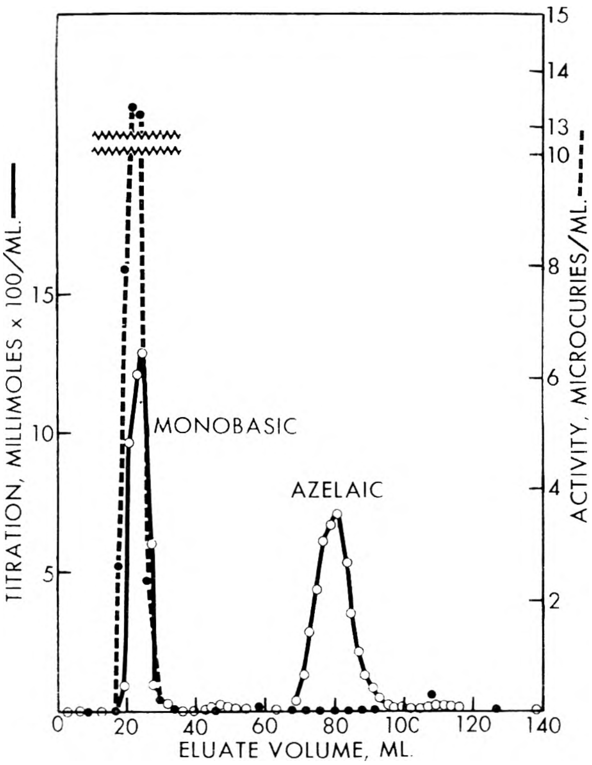

Fig. 4. Partition-chromatogram of mono- and dibasic acids from tritiated oleic acid after oxidative cleavage

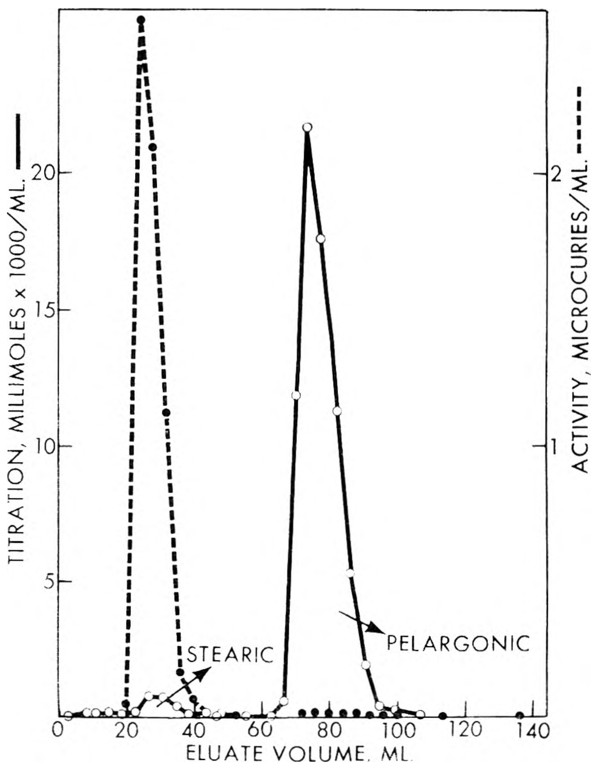

Fig. 5. Liquid-partition chromatogram of the monobasic peak of Fig. 4

12,13-double bond. After oxidation of tritiated methyl linoleate, subanalytical amounts of radioactive pelargonic and radioactive dodecanedioic acid are anticipated. The major constituents expected from the inactive linoleic acid are caproic and azelaic acids. (Malonic acid is not eluted from the chromatogram used.)

Confirmation of the radioactivity of the C_{12} di-

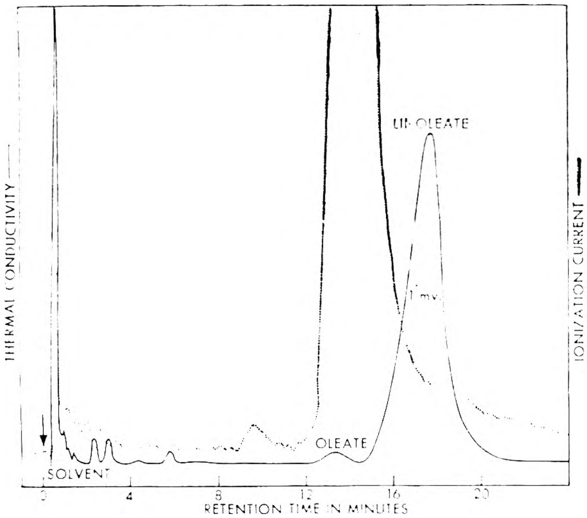

Fig. 6. Gas chromatogram of methyl linoleate after exposure to tritium gas but before chemical purification

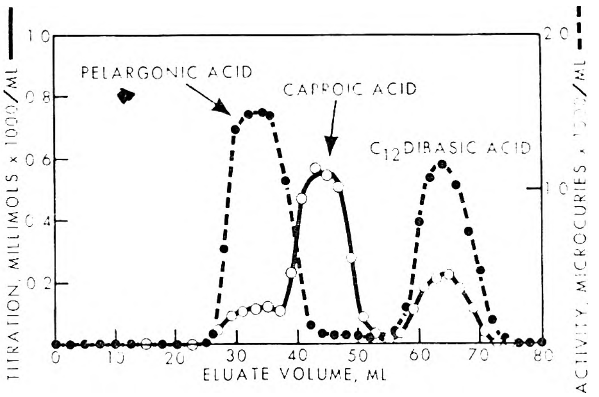

Fig. 8. Liquid-partition chromatogram showing the resolution of the monobasic peak of Fig. 7 (added pelargonic acid and dodecanedioic acids)

basic (dodecanedioic acid) and the C_9 monobasic (pelargonic) acids, as well as the inactivity of the major constituents, caproic and azelaic acids, is found in Figs. 7 and 8. Fig. 7 shows that all radioactivity is in the region of the titrated monobasic peak, and no activity is present in the azelaic or suberic acid peaks; the latter is found in the acidic mixture probably because of the presence of an ester, unsaturated at the C_8 position, in the original methyl linoleate. Similar and confirmatory data by gas chromatography were obtained but are not presented. To separate the two activity peaks associated with the titratable monobasic peak, a special column was designed for better separation of these two acids. In the chromatogram shown in Fig. 8, small amounts of pelargonic and dodecanedioic acids were added to the monobasic acids (peak of Fig. 7) for identification purposes. The chromatogram shows that the monobasic acid fraction is indeed composed of active pelargonic acid, inactive caproic acid, and active dodecanedioic acid. Estimates of the relative activity in the pelargonic and the C_{12} dibasic acids lead to the conclusion that the 12,13 unsaturated carbons are the preferred position of attack by tritium over the 9,10 carbons by a ratio of about 1.4:1.0.

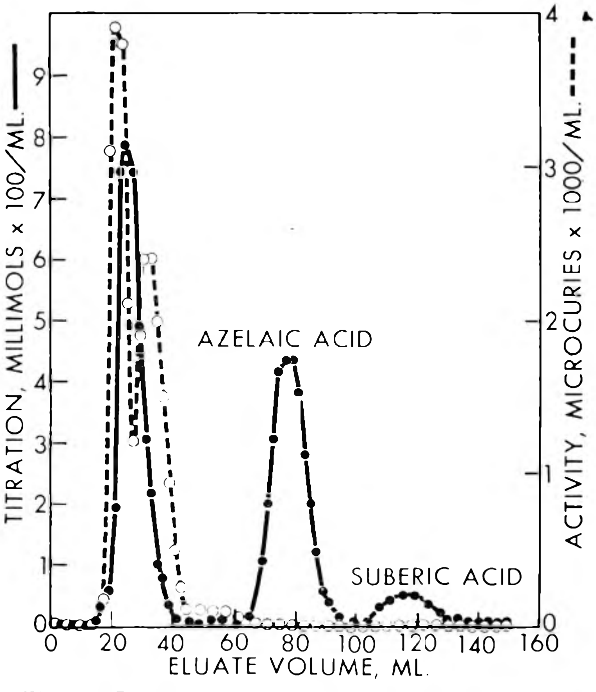

Fig. 7. Liquid-partition chromatograms of the mono- and dibasic acids from tritiated linoleic acid after oxidative cleavage

DISCUSSION

The results of the investigations demonstrate the need for extreme care in establishing the structure of radiochemical products formed by the technique of gas exposure to tritium. The conclusions suggest that addition of tritium may be the generalized or usual reaction for olefinic compounds. It is of considerable interest that exposure of methyl linoleate did not result in the formation of methyl stearate but only one of the two double bonds was reduced.

Separation by chromatography of the radiochemical products from their inactive isologous parent results in isolation of fatty acids of extremely high specific activities. If the addition comprises one hydrogen and one tritium atom, the activity of the labeled product amounts to 28 curies per millimole.

Although the main object of this research was to produce or prepare randomly and substitutively labeled unsaturated fatty acids, it has not been achieved. Instead, labeled octadecanoates and octadecenoates were formed with high specific activities, and they may have many uses where the number and not the position of double bonds is important.

EXPERIMENTAL

Tritiation of methyl oleate. One gram of methyl oleate (Hormel Institute) and 1 curie of tritium gas were placed in a glass tube 25 mm. in diameter and 65 mm. long. This ampoule was rotated to provide continuously renewed thin films of the ester. After 18 days, the excess tritium was removed and the residue was refluxed for 1 hr. with 0.6 ml. of 50% sodium hydroxide diluted with 10 ml. of ethanol. On addition of 25 ml. of water, the unsaponifiable material was removed by extraction with five successive 25-ml. portions of ether. Removal of labile tritium was accomplished by distillation of 1.5 l. of anhydrous ethanol from the soaps in 50-ml. batches. Finally, 9 ml. of $1N$ hydrochloric acid was added and the organic acids extracted with four successive 25-ml. portions of ether.

Gas chromatography of tritiated methyl oleate. Methyl oleate after exposure to tritium gas as well as after tritiation, saponification, alcohol exchange, acidification, and methylation (with diazomethane) was examined for chemical and radiochemical purity by gas chromatography on a 5-ft. Resoflex 296 column at 205° in the "Aerograph" instrument.[9] Simultaneously with the recording of thermal conductivity, an ion chamber–electrometer system recorded radioactivity (ion current) on the gas stream issuing from the thermal conductivity cell.[10] Alternatively radioactivity was determined by trapping the methyl esters in the effluent gas stream in vials containing 15 ml. of scintillation solution for minute intervals and by subsequent assay in the automatic "Tri-Carb Scintillation Spectrometer."[9]

Liquid partition chromatography of tritiated acids. Chemical and radiochemical purity of tritiated fatty acids (after alcohol exchange, *etc.*) was determined by the liquid-liquid partition chromatographic procedure of Nijkamp[11] which employs a methanol-isooctane solvent system on a silicic acid column. Alternate 1-ml. eluate fractions were (a) titrated in a nitrogen atmosphere with $0.2N$ potassium hydroxide to a thymol blue end-point using a Gilmont Microburet, and (b) diluted with 15 ml. of scintillation solution for assay of radioactivity with an automatic "Tri-Carb Scintillation Spectrometer." Quenching of fluorescence by fatty acids and by the chromatographic solvent was negligible.

Degradation of tritiated esters. Oxidative cleavage of the double bonds in the tritiated esters was accomplished by the method of Jones and Stolp[12] after addition of the inactive ester to the tritiated ester. This method involved saponification of the ester, oxidation of the acids as soaps at room temperature with periodate-permanganate solution, and subsequent extraction of all ether-soluble acids in a continuous extractor. Only traces of radioactivity remained in the aqueous layer. Removal of ether gave the acids for chromatographic identification.

Liquid-liquid partition chromatography of monobasic and dibasic acids from methyl oleate. Upper and lower phases of a water-alcohol-benzene mixture at equilibrium comprised the mobile and immobile phases, respectively. Silicic acid was used as the solid support.[12] All monobasic acids emerge as one peak and dibasic acids appear as separate peaks. Alternate 1-ml. eluate fractions were titrated and assayed with the scintillating spectrometer. Monobasic fractions were combined, acidified, and extracted. The acids were identified by the chromatographic procedure of Nijkamp,[1] titrated, and assayed for radioactivity.

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[9] Since the Department of Agriculture does not recommend the products of one company over those of another, the names are furnished for information only.

[10] L. H. Mason, H. J. Dutton, and L. Bair, *J. Chromatog.*, **2**, 322 (1959).

[11] H. J. Nijkamp, *Anal. Chim. Acta.*, **10**, 448 (1954).

[12] E. P. Jones and J. A. Stolp, *J. Am. Oil Chemists, Soc.*, **35**, 71 (1958).

[CONTRIBUTION FROM THE NAVAL STORES RESEARCH STATION[1]

Esters of Some Acids Derived from Terpenes[2]

B. A. PARKIN, JR., AND G. W. HEDRICK

Received December 28, 1959

The preparation of vinyl monomers for use as internal plasticizers for polyvinyl chloride from acids derived from terpenes led to the preparation of six new vinyl esters. Acylpinolic acids were prepared by reaction of pinolic acid with the respective anhydrides and direct reaction with the acids in the presence of an acid catalyst. From the substituted pinolic acids, pinolic acid, pinonic acid, and 3-(1-methyl-1-hydroxyethyl)heptanedioic acid γ-lactone, the new vinyl esters were prepared by vinyl interchange with vinyl acetate in the presence of mercuric sulfate catalyst. Ethyl esters of these acids were prepared by azeotropic removal of water from the reaction mixture with p-toluenesulfonic acid as catalyst. The pinonic and pinolic ethyl and propyl esters have been previously reported. The identity of the ethyl esters obtained by direct esterification and those obtained by catalytic reduction of the vinyl esters was established by means of infrared analyses.

The propyl and allyl esters of pinolic and pinonic acids were prepared by direct esterification in the presence of p-toluenesulfonic acid. Dehydration and rearrangement of pinolic acid in the presence of p-toluenesulfonic acid was observed but not reported in detail.

In the course of investigating terpene derived materials for use in the preparation of polymerizable monomers of interest as internal plasticizers for polyvinyl chloride, vinyl esters were prepared from a number of terpene acids and derivatives of these acids. Two allyl esters were also prepared. For comparison purposes the corresponding ethyl and propyl esters were prepared by reduction of the unsaturated esters and by direct esterification.

The acids involved in this work were pinonic [3 - acetyl - 2,2 - dimethylcyclobutaneacetic acid), pinolic [3-(1-hydroxyethyl)-2,2-dimethylcyclobutaneacetic acid], pinolic acid acetate, pinolic acid propionate, pinolic acid butyrate, 3-(1-methyl-1-hydroxyethyl)heptanedioic acid γ-lactone, pinic acid [3-carboxy-2,2-dimethylcyclobutaneacetic acid], and several monoalkyl pinates. The esters

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[1] One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

[2] Presented at the meeting of the American Chemical Society, Atlantic City, New Jersey, September 13–18, 1959.

TABLE I

ACYLATED PINOLIC ACIDS

Acid	M.P.°	B.P.°, Mm.	Saponification Equivalent		Yield, %	Empirical Formula	Analyses			
							Carbon		Hydrogen	
			Found	Calcd.			Calcd.	Found	Calcd.	Found
Pinolic acid acetate	71–73	126/0.1	113.5	114	60[a]	$C_{12}H_{20}O_4$	63.13	63.23	8.83	8.79
Pinolic acid propionate	—	132/0.1	123.7	123	45[b]	$C_{13}H_{22}O_4$	64.43	64.97	9.15	9.31
Pinolic acid butyrate	—	140/0.1	130.5	130	40[b]	$C_{14}H_{24}O_4$	65.59	65.14	9.44	9.56

[a] Maximum yield from anhydride process; yield generally less than 40%. [b] By catalytic process; yield generally about the same under same conditions.

TABLE II

VINYL ESTERS OF TERPENE DERIVED ACIDS

Acid	B.P.°, Mm.	n_D^{25}	Hydrogenation G./Mole H_2		Yield, %	Empirical Formula	Analyses			
							Carbon		Hydrogen	
			Calcd.	Found			Calcd.	Found	Calcd.	Found
Pinonic	118/5.0	1.4640	210.26	208	69.5	$C_{12}H_{18}O_3$	68.54	68.10	8.63	8.63
Pinolic	114/3.0	1.4669	212.28	208	62.2	$C_{12}H_{20}O_3$	67.89	68.57	9.50	9.50
Pinolic acid acetate	138/2.5	1.45459	254.34	249	61.6	$C_{14}H_{22}O_4$	66.11	66.18	8.72	8.78
Pinolic acid propionate	145/2.0	1.4532	268.34	265	53	$C_{15}H_{24}O_4$	67.18	67.18	9.01	9.16
Pinolic acid butyrate	122/0.1	1.4507	282.37	281	54	$C_{16}H_{26}O_4$	68.05	68.07	9.28	9.41
3-(1-Hydroxy-1-methylethyl)heptanedioic acid γ-lactone	149/0.2	Solid	226.26	227.2	56	$C_{12}H_{18}O_4$	63.13	63.62	7.98	8.08

of the monoalkyl pinates are covered by two publications.[3]

The *cis-dl*-pinonic acid used was prepared by potassium permanganate oxidation of α-pinene.[4] The pinonic acid was reduced to *cis-dl*-pinolic acid by catalytic hydrogenation in alkaline media over platinum oxide catalyst. The procedure is a modification of that given by Delépine and Horeau.[5] 3-(1-Methyl-1-hydroxyethyl)heptanedioic acid γ-lactone was prepared from homoterpenyl methyl ketone, 3-(1-methyl-1-hydroxyethyl)-6-ketoheptanoic acid γ-lactone, *via* the Wilgerodt reaction.[6] The acylated pinolic acids were made from pinolic acid by reaction with acids in the presence of their anhydrides and esterification in the presence of *p*-toluenesulfonic acid with azeotropic separation of the water formed. Physical constants for the three acylpinolic acids prepared are given in Table I. The acylation of pinolic acids is complicated by the ease of dehydration and molecular rearrangement of this compound in the presence of dehydrating agents or strong acids. The behavior of pinolic acid under such conditions is currently under study and results should be published later.

Vinylation of the acids was carried out by the vinyl interchange procedure of Adelman[7] using vinyl acetate and mercuric acetate–sulfuric acid catalyst. Physical constants of the vinyl esters prepared are given in Table II. The vinyl esters were catalytically reduced over 5% palladium on carbon. (Erratic results were obtained when platinum oxide was used.) The identity of the ethyl esters obtained with those prepared by direct esterification was established by infrared analyses. Vinylation of pinonic acid was also accomplished by the Reppe process.[8]

The allyl, ethyl, and propyl esters were prepared by direct esterification over acid catalyst in benzene or chloroform solution. The physical constants of the esters of pinonic acid, substituted pinolic acids, and 3-(1-hydroxy-1-methylethyl)heptanedioic acid lactone are given in Table III. The physical properties of the ethyl, propyl and allyl esters of pinolic acid are given in Table IV. The esters of pinolic acid were characterized by direct methods. Vapor phase chromatography showed only minor impurities, refractive indices of vinyl and allyl reduction products were in good agreement with the indices of the materials produced by direct esterification. and hydrolysis allowed isolation of good yields of unchanged pinolic acid. The ethyl and propyl esters of pinonic and pinolic acids were previously reported by Le-Van-Thoi.[9]

EXPERIMENTAL

The *cis-dl*-pinonic acid used was obtained by oxidation of α-pinene with potassium permanganate.[4]

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[3] J. B. Lewis and G. W. Hedrick, *J. Org. Chem.*, in press.

[4] H. B. Summers, Jr., G. W. Hedrick, F. C. Magne, and R. Y. Mayne, *Ind. Eng. Chem.*, **51**, 549 (1959).

[5] M. Delépine and A. Horeau, *Bull. soc. chim.*, **4**, 31 (1937).

[6] N. J. Halbrook and R. V. Lawrence, unpublished results.

[7] R. L. Adelman, *J. Org. Chem.*, **14**, 1057 (1949).

[8] J. W. Copenhaver and M. H. Bigelow, *Acetylene and Carbon Monoxide Chemistry*, Reinhold Publishing Corp., New York, 1949, p. 59.

[9] Le-Van-Thoi, *Ann. chim.*, **10**, 35–91 (1955).

TABLE III

ETHYL, PROPYL, AND ALLYL ESTERS

Esters	B.P.°, Mm.	n_D^{25}	Molecular Weight		Yield, %	Empirical Formula	Analyses Carbon		Analyses Hydrogen	
			Calcd.	Found			Calcd.	Found	Calcd.	Found
Ethyl pinonate	96–98/1.5	1.4496	212.28	210^a	80–88	$C_{12}H_{20}O_3$	—	—	—	—
Propyl pinonate	125–128/5.0	1.4493	226.30	225^a	76	$C_{13}H_{22}O_3$	68.99	68.66	9.81	9.88
Allyl pinonate	138–139/5.0	1.4611	224.28	220^b	85	$C_{13}H_{20}O_3$	69.61	69.14	8.99	9.05
Ethyl pinolate acetate	76–78/0.5	1.4416	255.32	257^a	75	$C_{14}H_{24}O_4$	65.59	65.77	9.44	9.68
Ethyl pinolate propionate	98–99/0.15	1.4423	270.36	268^a	65	$C_{15}H_{26}O_4$	66.63	66.90	9.69	9.87
Ethyl pinolate butyrate	110–112/0.10	1.4415	284.39	283^a	67	$C_{16}H_{28}O_4$	67.57	67.62	9.92	10.00
Ethyl-3-(1-methyl-1-hydroxyethyl) heptanedioate γ-lactone	122–124/0.25	1.4527	228.28	232^a	69	$C_{12}H_{20}O_4$	62.58	63.10	8.74	8.96

[a] Determined by saponification equivalents. [b] Determined from hydrogenation (g./molo H_2 absorbed).

TABLE IV

PINOLIC ACID ESTERS

Esters	B.P.°, Mm.	n_D^{25}	Molecular Weight Calcd.	Molecular Weight Found	Yield, %
Ethyl pinolate	116–120/1.0	1.4539	214.30	216^a	53.6
Propyl pinolate	153–154/1.0	1.4542	228.33	230^a	69.2
Allyl pinolate	134–137/2.0	1.4619	226.31	225^b	69.5

[a] Determined by saponification equivalents. [b] Determined from hydrogenation (g./mole H_2 absorbed) values.

cis-dl-Pinolic acid.[5] Crystalline, *cis-dl*-pinonic acid (736 g., 4 moles) was dissolved in excess alkali (200 g., 5 moles of sodium hydroxide in 1200 ml. water) and the solution was made up to 2 l. The solution was hydrogenated in a rocking autoclave in the presence of platinum oxide (1.4 g.) at 1500–1800 p.s.i.g. hydrogen pressure. Hydrogen absorption was rapid during most of the run but the last mole was absorbed very slowly. After hydrogen absorption ceased (about one week), the mixture was filtered and the solution acidified by slow dropwise addition of concd. sulfuric acid. The mixture was filtered and the crystalline pinolic acid washed free of sulfuric acid with water and air dried. Some oil, probably *trans*-pinolic acid, precipitated with the crystals, m.p. 91–96°. The melting point can be readily raised to 100–101° by recrystallization from water or ether–petroleum ether mixtures.

cis-dl-Pinolic acid acetate, anhydride method. A solution of *cis-dl*-pinolic acid (46.5 g., 0.25 mole) in glacial acetic acid (70 ml.) was added slowly (3 hr.) to a stirred solution of acetic anhydride (50 ml., 0.53 mole) in glacial acetic acid (50 ml.) heated at reflux. After the addition was completed the mixture was heated for 30 min. longer. Water (20 ml.) was added and the acetic acid was distilled under vacuum. Distillation of the residue gave yields of 30–60%.

cis-dl-Pinolic acid acetate, catalytic method. A solution of *cis-dl*-pinolic acid (186 g., 1 mole) in 400 ml. of chloroform and a solution of 240 ml. glacial acetic acid and 20 g. *p*-toluenesulfonic acid in 200 ml. of chloroform were dried by azeotropic distillation of water with return of chloroform to the solution. The pinolic acid solution was added slowly (4 hr.) to the acetic acid-*p*-toluenesulfonic acid solution heated at reflux and the water formed was removed azeotropically. After the reaction was complete, the mixture was cooled and washed with 200 ml. of water. The wash was extracted with 25–30 ml. of chloroform and the extract combined with the original chloroform solution. The solution was stripped under 30–35 mm. pressure to a pot temperature of about 100°. The residue was washed to remove residual acetic acid, distilled bulb-to-bulb and then through a 2 × 20 cm. column packed with 6 mm. glass helices.

Generally a more crystalline material was obtained by the catalytic procedure. Pinolic acid propionate and butyrate were made by the above procedures but the yields were generally not as good.

dl-3-(1-Methyl-1-hydroxyethyl)heptanedioic acid γ-lactone was prepared from homoterpenyl methyl ketone *via* the Wilgerodt reaction according to the procedure of Halbrook and Lawrence.[6]

cis-dl-Vinyl pinonate. The vinylation procedure followed in each instance is that given by Adelman[7] except that the vinyl acetate to acid ratio was increased from 6:1 to 12:1. *cis-dl*-Pinonic acid (184 g., 1 mole) was placed in a 2-l. flask with 0.5 g. of copper resinate. Vinyl acetate (1110 ml., 12 moles) was distilled into the flask and cooled below 30°. Mercuric acetate (4.0 g., 0.0126 mole) was added and dissolved by stirring the mixture. Sulfuric acid (0.5 ml., 0.0093 mole) was added dropwise with very vigorous stirring. The flask was swept with nitrogen and allowed to stand at room temperature for 3 days. Sodium acetate (2 g., 0.024 mole) was added and the mixture was stirred 30 min. The excess vinyl acetate and most of the acetic acid formed in the reaction were removed by distillation under reduced pressure (25 mm.) to a pot residue temperature of 80°. The residue was then washed with water (2 × 50 ml.) and exhaustively extracted with saturated sodium bicarbonate solution to remove any unchanged acid. After drying over anhydrous sulfate, the residue was distilled to give water-white vinyl pinonate.

The other vinyl esters were prepared by this same procedure except vinyl-3-(1-methyl-1-hydroxyethyl)heptanedioic acid γ-lactone, which crystallized from the dried ether solution, on cooling, m.p. 47.8–48.6°. Distillation of this material generally resulted in considerable loss by polymerization or decomposition. The distilled material super cools and if not seeded may not crystallize.

In the case of vinyl pinolate the reaction mixture was maintained at about 0° during and after addition of the sulfuric acid in order to avoid formation of the vinylidene compound at the hydroxyl group. Inasmuch as the reaction would be expected to be slower at this lower temperature, the reaction time was extended to 5 days.

The vinylation of pinonic acid was accomplished by the Reppe procedure using pinonic acid in toluene with zinc pinonate as a catalyst. The yield of crude product, b.p. 115–150°, 1 mm., 393 g., was 80%. Fractionation of the crude product gave colorless vinyl pinonate (Table II), 50% yield, and 30% yield of a slight amber colored material. The second material was not completely characterized. However, it absorbed two equivalents of hydrogen and had an empirical formula, $C_{14}H_{20}O_3$. Polymers from bulk polymerization with benzoyl peroxide had the appearance of polystyrene foam and were insoluble in common solvents indicating crosslinking had taken place. Obviously two acetylene molecules had reacted with one molecule of pinonic acid. Vinylation of 3-(1-methyl-1-hydroxyethyl)heptanedioic acid γ-lactone by the same procedure was unsuccessful.

Characterization of cis-dl-vinyl pinolate. A 10-g. sample of freshly distilled vinyl pinolate was reduced over 5% palladium on carbon. Alcohol (50 ml., 95%) was used as the solvent and catalyst concentration was about 1%. After the reduction was completed, the solution was filtered and evaporated. Vapor phase chromatography showed the residue to contain ethyl pinolate with minor peaks corresponding to impurities in the vinyl pinolate. Five grams of the material was hydrolyzed by heating on the steam bath for about 4 hr. with excess 6*N* sodium hydroxide. The hydrolysis mixture was extracted with ether to remove the ethanol and the extracted solution was acidified. The acidified solution was extracted with three 15-ml. portions of ether; the ether solution was dried over sodium sulfate, filtered, and evaporated to yield 4.03 g., 91% of crystalline pinolic acid, m.p. 94.8–96.4. Mixed melting point with an equal quantity of 103–104° pinolic acid was 99–102.5°. Allyl and propyl esters also allowed good recovery of pinolic acid on hydrolysis and chromatographed samples showed even less impurities than the ethyl ester.

cis-dl-Ethyl pinonate. cis-dl-Pinonic acid (736 g., 4 moles) was placed in a flask with 95% ethanol (1 l., 17 moles), chloroform (1 l.), and *p*-toluenesulfonic acid (20 g.). The mixture was refluxed through a 2 × 20 cm. protruded metal packed column and the water which separated was removed through a liquid decanter. After separation of water ceased, the mixture was cooled, and treated with water until no further phase separation was noted. The chloroform layer was washed with sodium bicarbonate solution until the wash remained basic to *p*H paper and then dried over sodium sulfate. Evaporation and distillation of the residue yielded water-white ethyl pinonate.

The allyl and propyl esters of pinolic acid were prepared by this method. The ethyl ester, however, (probably because of long heating periods necessary to remove the water) is difficult to obtain in pure form if catalyst concentrations as high as this are used. Azeotropic removal of water from a mixture of pinolic acid ethanol and benzene in the absence of added catalyst has produced the purest *cis-dl*-ethyl pinolate although the yield was only about 50%.

Slow dehydration of the pinolic acid esters will take place if heating is continued beyond the time required to evolve one mole of water.

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OLUSTEE, FLA

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, UNION CARBIDE CHEMICALS CO.]

Synthesis of Some Special Types of Glycidic Esters

PAUL S. STARCHER, FREDERICK C. FROSTICK, JR., AND BENJAMIN PHILLIPS

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Glycidic esters have been found to undergo an ester exchange reaction with a wide variety of alcohols without concomitant destruction of the epoxide function. This exchange reaction was used for the preparation of certain unsaturated glycidic esters and diepoxides which are not readily obtained by other routes. Di-, tri-, and tetraepoxides containing the glycidic ester grouping have also been prepared by epoxidation of the corresponding unsaturated esters with anhydrous peracetic acid. The relative merits of these methods for the synthesis of glycidic esters are discussed.

A previous paper in this series described the preparation of saturated alcohol esters of α,β-epoxy acids by treatment of the esters of α,β-unsaturated acids with peracetic acid.[1] The present paper deals with the synthesis of some special types of glycidic esters, many of which are new, by methods which include 1) an exchange reaction of epoxy esters with alcohols, 2) an extension of the previously described peracetic acid epoxidation,[1] and 3) a combination of methods 1) and 2). Structural considerations govern the choice of method for the synthesis of a given glycidic ester. Other methods for the preparation of glycidic esters include the Darzens method[2] and the treatment of esters of α,β-unsaturated acids with peroxytrifluoroacetic acid.[3]

Esters of α,β-epoxy acids may be exchanged with alcohols under mild conditions without destruction of the oxirane rings. This appears to be a general reaction which works with saturated and unsaturated alcohols and glycols (Table I). Success with the ester exchange reaction depends on carrying it out under mild conditions (60° or below) in the presence of alcoholates of the alkali and alkaline

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TABLE I

GLYCIDIC ESTER SYNTHESES BY ESTER INTERCHANGE

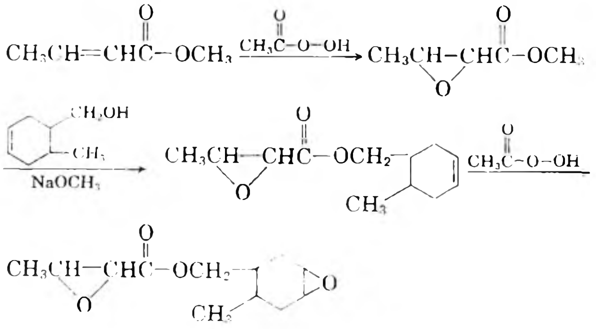
Starting Ester	Moles	Alcohol	Moles	Catalyst	Product Ester	B.P., ° (mm.)	n_D^{30}	Yield, %
Methyl 2,3-epoxybutyrate[a]	1.0	Allyl alcohol	10.0	Na	Allyl 2,3-epoxybutyrate	96–97 (25)	1.4362	37
Methyl 2,3-epoxybutyrate[a]	2.79	Allyl alcohol	16.7	$NaOCH_3$	Allyl 2,3-epoxybutyrate	96–98 (25)	1.4362	58
Ethyl 2,3-epoxybutyrate[b]	1.0	Allyl alcohol	10.0	$Mg(OCH_3)_2$	Allyl 2,3-epoxybutyrate[c]	97 (25)	1.4363	68
Ethyl 2,3-epoxybutyrate[b]	1.0	6-Methyl-3-cyclohexenemethanol	3.0	$NaOCH_3$	6-Methyl-3-cyclohexenemethyl 2,3-epoxybutyrate[d]	117 (2.5)	1.4718	53
Ethyl 2,3-epoxybutyrate[b]	1.0	4-Pentenol	1.92	$NaOCH_3$	4-Pentenyl 2,3-epoxybutyrate[e]	96 (5)	1.4405	33
Ethyl 2,3-epoxy-2-ethylhexanoate[f]	2.0	Allyl alcohol	16.0	$NaOCH_3$	Allyl 2,3-epoxy-2-ethylhexanoate[g]	70 (1)	1.4402	80
Ethyl 2,3-epoxy-2-ethylhexanoate[f]	1.0	6-Methyl-3-cyclohexenemethanol	3.0	$NaOCH_3$	6-Methyl-3-cyclohexenemethyl 2,3-epoxy-2-ethylhexanoate[h]	144 (2.5)	1.4680	44
Ethyl 2,3-epoxybutyrate[b]	1.0	Cyclohexanol	3.0	$NaOCH_3$	Cyclohexyl 2,3-epoxybutyrate[i]	96 (3)	1.4575	41
Ethyl 2,3-epoxybutyrate[b]	20	Ethylene glycol	3.74	$NaOC_2H_5$	Ethylene glycol bis(2,3-epoxybutyrate)[j]	165 (4)	1.4535–42	45

[a] B.p. 84–85° at 49 mm., n_D^{30} 1.4150, d_4^{26} 1.075. Analyzed 99% pure by saponification. Identified by comparison of infrared spectrum with that of ethyl 2,3-epoxybutyrate.[1] Prepared in 61% yield by method of ref. 1 from 3 moles of methyl crotonate and 3.9 moles of peracetic acid at 85–90° for 6 hr. [b] See ref. 1. [c] *Anal.:* 100% pure by saponification; 98% pure by epoxide determination by the pyridine hydrochloride method. Infrared absorption spectrum consistent with that expected. Ref. 4 reports b.p. 100–101° at 26 mm. [d] *Anal.:* 99% pure by saponification; 78% pure by epoxide determination by pyridine hydrochloride method (often not reliable, see ref. 1). calcd. for $C_{12}H_{18}O_3$: C, 68.60; H, 8.57. Found C, 68.64, 68.74; H, 8.79, 8.75. Infrared absorption spectrum consistent with that expected with no evidence of other groups or impurities present. [e] *Anal.:* 99% pure by saponification; 69% pure by epoxide determination by pyridine hydrochloride method. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.63; H, 8.24. Infrared spectrum consistent with that expected. [f] See ref. 1. [g] *Anal.:* 99.6% pure by saponification; 100.2% pure by epoxide determination by addition of HBr. Calcd. for $C_{11}H_{18}O_3$: C, 66.6; H, 9.08. Found: C, 66.76; H, 9.12. This experiment by Dr. D. L. MacPeek. [h] *Anal.:* 100.9% pure by saponification; 51% pure by epoxide determination by pyridine hydrochloride method. Calcd. for $C_{16}H_{26}O_3$: C, 72.2; H, 9.84. Found: C, 72.79; H, 9.99. [i] *Anal.:* 98% pure by saponification. [j] *Anal.:* 99.8% pure by saponification. Calcd. for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.31; H, 6.44. A 15% yield of the monoepoxide, hydroxyethyl 2,3-epoxybutyrate, was also obtained.

earth metals. Such catalysts actively promote ester exchange without causing extensive side reactions of the epoxide ring. In contrast, titanium tetrabutylate and aluminum isopropylate are not useful catalysts, as they do not appear to catalyze the exchange reaction except at higher temperatures where the epoxide rings are destroyed. Acidic catalysts, such as mineral acids, boron trifluoride, and aluminum chloride, attack the epoxide ring excessively even under mild conditions.

Many of the unsaturated alcohol esters of glycidic acids are useful epoxy vinyl monomers.[4,5] We have found the ester exchange method to be a fine and unambiguous synthetic route to these unsaturated esters of glycidic acids (Table I). A saturated alcohol ester of an α,β-unsaturated acid is first epoxidized,[1] and the epoxy ester is then exchanged with an unsaturated alcohol. This procedure avoids several difficulties which are usually encountered in epoxidizing an unsaturated alcohol ester of an α,β-unsaturated acid. For instance, mixtures of monoepoxides or mixtures of monoepoxide and diepoxide may be produced when the epoxidation is not sufficiently selective.[5] In other cases, where the double bond in the alcohol portion is more easily epoxidized than the double bond in the acid portion of the ester, the double bond in the alcohol portion of the ester is selectively epoxidized. For example, allyl crotonate, when treated with approximately an equimolar amount of peracetic acid, yields glycidyl crotonate instead of allyl 2,3-epoxybutyrate.[5] Although the selective epoxidation of allyl 2-ethyl-2-hexenoate to the corresponding glycidic ester (e.g., allyl 2,3-epoxy-2-ethylhexanoate) has been reported,[6] this synthesis is not general, being confined to those esters (usually allyl or vinyl) in which the double bond in the alcohol portion is relatively electron-poor and in which the α,β-double bond in the acid portion is substituted with electron-donating groups.[6]

Di- and polyepoxides constitute an important class of compounds which have widespread use as resin intermediates[7] and as plasticizers and stabilizers for chlorine-containing resins.[8] However, polyepoxides which contain one or more α,β-epoxyacyloxy groups have been very rare. The only diepoxides of which the authors are aware that contain the glycidic ester group are those obtained from the condensation of aromatic dialdehydes or diketones with α-haloesters[9] *via* the Darzens method; *e.g.*, dimethyl 3,3′-*p*-phenylenebis(2,3-epoxybutyrate). We have used the ester-exchange method to prepare diepoxides of a different type from those obtained by the Darzens route. This method lends itself readily to the preparation of diepoxides, either through an intermediate unsaturated glycidic ester or directly by an exchange reaction between a glycidic ester and a glycol. In some cases the exchange method offers the only practical route. For example, treatment of 6-methyl-3-cyclohexenemethyl crotonate with peracetic acid gave 3,4-epoxy-6-methylcyclohexanemethyl crotonate,[5] but further treatment of the monoepoxide resulted only in destruction of most of the epoxy function and a very low yield of diepoxide (Table II). The preparation of 3,4-epoxy-6-methylcyclohexanemethyl 2,3-epoxybutyrate (and many other diepoxy esters) can be accomplished in much better yield by the following reaction sequence in which the ester exchange technique is used:



However, the direct epoxidation method with anhydrous peracetic acid is superior in those cases where there is not too great a disparity in the epoxidation rates of the two unsaturated sites and where neither of the resulting oxirane rings is extremely sensitive to acetic acid under the conditions required for epoxidation (Table II).

In the special case where all of the oxirane rings to be formed are of the glycidic ester type and where the olefinic precursors are highly resistant to epoxidation, the ester exchange method appears to be superior to direct epoxidation. Ethylene glycol bis(2,3-epoxybutyrate) was prepared in 45% yield by exchange of ethylene glycol with ethyl 2,3-epoxybutyrate, while epoxidation of ethylene glycol dicrotonate gave only a 29% yield of the same diglycidic ester (Tables I and II). In both cases the corresponding monoepoxides were also formed. However, suitably substituted α,β-un-

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TABLE II

DIEPOXIDE SYNTHESES BY ESTER EXCHANGE

Starting ester	Moles	Peracetic Acid Solution, Moles	Reaction Time, hrs.	Reaction Temp., °	Product	B.P., ° (Mm.)	n_D^{30}	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Allyl crotonate[a]	1.0	3.14	8	70	2,3-Epoxypropyl 2,3-epoxybutyrate[b]	96–97(1.5)	1.4480	57	53.20	53.90	6.37	6.66
Allyl 2-ethyl-2-hexenoate[a]	2.0	5.0	9	60	2,3-Epoxypropyl 2,3-epoxy-2-ethylhexanoate[c]	114–115(2)	1.4470–1.4478	54	61.66	61.62	8.43	8.58
6-Methyl-3-cyclohexenemethyl 2,3-epoxybutyrate	0.5	0.55	1.75	40	3,4-Epoxy-6-methylcyclohexanemethyl 2,3-epoxybutyrate	142 (1)	1.4734	77	63.70	63.64	7.96	7.76
3,4-Epoxy-6-methylcyclohexanemethyl crotonate[a]	1.0	1.2	6	60–80	3,4-Epoxy-6-methylcyclohexanemethyl 2,3-epoxybutyrate	142 (1)	1.4734	<10	—	—	—	—
6-Methyl-3-cyclohexenemethyl 2-ethyl-2-hexenoate[d]	1.4	4.2	2.25	65	3,4-Epoxy-6-methylcyclohexanemethyl 2,3-epoxy-2-ethylhexanoate[e]	175–180(4)	1.4696–1.4708	63	68.05	67.72	9.28	9.12
Ethylene glycol dicrotonate[f]	1.0	2.5	12	75	Ethylene glycol *bis*(2,3-epoxybutyrate)[g]	165 (4)	1.4335–1.4350	29	52.17	52.40	6.13	6.44
1,5-Pentanediol *bis*(2-ethyl-2-hexenoate)[h]	0.284	0.882	3	75	1,5-Pentanediol *bis*(2,3-epoxy-2-ethylhexanoate)	214–217(2)	1.4540–1.4550	88	65.61	65.90	9.44	9.64
1,1,1-Trimethylolpropane *tris*-(2-ethyl-2-hexenoate)[i]	0.48	2.2	7	50–70	1,1,1-Trimethylolpropane *tris*(2,3-epoxy-2-ethylhexanoate)[j]	Colorless residue product	1.4261	>80	64.91	64.51	9.09	9.09
Pentaerythritol *tetrakis*(2-ethyl-2-hexenoate)[k]	0.50	3.0	5	65	Pentaerythritol *tetrakis*(2,3-epoxy-2-ethylhexanoate)[l]	Pale yellow residue product	1.4696	>80	63.76	62.47	8.68	8.28

[a] See ref. 5. [b] Sapon. equiv. found 157.5 (theory 158.2). [c] Sapon. equiv. found 215 (theory 214.2). [d] Prepared in 88% yield by esterification of 6-methyl-3-cyclohexenemethanol with 2-ethyl-2-hexenoic acid; b.p. 145–146° at 3 mm., n_D^{30} 1.4749, 99.9% pure by saponification. [e] Sapon. equiv. found 282 (theory 282.4). [f] Prepared in 52% yield by esterification of ethylene glycol with crotonic acid; b.p. 108–109° at 2 mm., n_D^{30} 1.4653, 101% pure by saponification. [g] Sapon. equiv. found 115.5 (theory 115.1). A 47% yield of the corresponding monoepoxide, ethylene glycol crotonate 2,3-epoxybutyrate, was also obtained. [h] Prepared by T. F. Carruthers in 71% yield by esterification of 1,5-pentanediol with 2-ethyl-2-hexenoic acid; b.p. 169° at 0.75 mm., n_D^{22} 1.4672, d_{20}^{20} 0.9565, 99% pure by saponification. [i] Prepared in 80% yield by esterification of 1,1,1-trimethylolpropane with 2-ethyl-2-hexenoic acid; b.p. range (one-plate column) 195–240° at 3 mm., n_D^{30} 1.4747. *Anal.* Calcd. for $C_{30}H_{50}O_6$: C, 71.0; H, 9.95; sapon. equiv., 168.9. Found: C, 70.1; H, 9.84; sapon. equiv., 171. [j] The infrared spectrum of this compound gave a strong epoxide band (11.1 μ) and no absorption characteristic of residual unsaturation (6.2 μ). There was a very weak band at 2.9 μ indicating a small amount of epoxide ring opening. [k] Prepared as a residue product by esterification of pentaerythritol with an excess of 2-ethyl-2-hexenoic acid. Product stripped, washed, and dried; n_D^{30} 1.4810, 99.3% pure by saponification. [l] The infrared spectrum of this compound gave a strong epoxide band (11.0–11.1 μ) and very weak bands at 2.9 μ and 6.2 μ indicating very small amounts of epoxide ring opening and residual unsaturation.

saturated esters, such as the 2-ethyl-2-hexenoic esters of 1,5-pentanediol, trimethylolpropane, and pentaerythritol, afford the corresponding di-, tri-, and tetraglycidates in good yield by direct epoxidation with anhydrous peracetic acid (Table II).

EXPERIMENTAL

General procedure for ester exchange. Sodium methoxide (2–10 mole %, based on epoxy ester) was dissolved in the appropriate alcohol (2–10 moles) in a still kettle equipped with a condenser maintained at −5°. Then the ester of the α, β-epoxy acid was added and the reaction mixture refluxed under reduced pressure, the kettle temperature being kept at about 40°. During the period of reflux, the low-boiling alcohol was removed from the still head until no more was obtained. The kettle residue was then cooled to room temperature, the catalyst destroyed with an equivalent of acetic acid, and the mixture filtered, if necessary. The products were isolated by fractional distillation. In some cases metallic sodium, magnesium alcoholate, or other catalyst was substituted for the sodium methoxide. A summary of the results is found in Table I.

General procedure for epoxidation. The techniques were similar to those previously described.[1] In the preparation of di- or polyepoxides an excess of 25–30% peracetic acid solution[10] in either ethyl acetate or acetone was used. The oxidations were continued until the peracetic acid consumption leveled out at its decomposition rate at the temperature employed. The volatile components were removed by feeding the reaction mixture dropwise into a kettle containing ethylbenzene under reflux at 50° under reduced pressure. The solvent, acetic acid, and excess peracetic acid were removed continuously at the still head. After removal of the excess ethylbenzene the epoxides were purified by distillation except in the cases of the trimethylolpropane and pentaerythritol esters. In these cases the epoxy esters were vacuum stripped, diluted with toluene, washed with sodium carbonate solution and water, and dried by vacuum stripping. A summary of the results is found in Table II.

SOUTH CHARLESTON, W. VA.

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[CONTRIBUTION FROM SOUTHERN REGIONAL RESEARCH LABORATORY,[1] UNITED STATES DEPARTMENT OF AGRICULTURE]

Reaction of Epichlorohydrin with Ammonia, Aniline, and Diethanolamine

JOHN B. McKELVEY, BEVERLY G. WEBRE, AND RUTH R. BENERITO

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The reaction of epichlorohydrin with ammonia, aniline, and diethanolamine in various reaction media has been investigated. The hydrochloride of N,N,N-tris(3-chloro-2-hydroxypropyl)amine and N,N,N-tris(2,3-epoxypropyl)amine have been prepared from the crude reaction product of ammonia and epichlorohydrin in a 1:3 mole ratio in methanol. Formation of 1,3-dichloro-2-propanol, when ammonia or ammonium chloride and epichlorohydrin are treated in aqueous medium, has been demonstrated. N-(3-Chloro-2-hydroxypropyl)aniline, N-(2,3-epoxypropyl)aniline, and N,N-bis(2,3-epoxypropyl)-aniline have been isolated. N-(3-Chloro-2-hydroxypropyl)-N,N-bis(2-hydroxyethyl)amine has been prepared and it has been demonstrated that this compound slowly forms a quaternary salt, probably by cyclization.

In the synthesis of polyepoxide finishing agents for cotton, it became necessary to prepare certain N-substituted amine epoxides. The N-(3-chloro-2-hydroxypropyl)amines, obtained by addition of epichlorohydrin to an amine, were dehydrohalogenated to the respective epoxides. An interesting chlorohydroxyamine, N,N,N-tris(3-chloro-2-hydroxypropyl)amine (I), formed by saturating epichlorohydrin with ammonia gas at room temperature in a five-day reaction is mentioned by Fauconnier,[2] but no yields are given. In our experience with this reaction, one is apt to obtain an alcohol-insoluble resin, as it is difficult to know when epichlorohydrin is saturated. Other references to the action of epichlorohydrin and ammonia,[3-10] are concerned chiefly with aqueous ammonia, and frequently the conditions imposed could scarcely be classed as mild. The only compound definitely isolated was 1,3-diamino-2-propanol in the work by Bottoms,[5] who carried out the reaction in the presence of strong alkali. Aqueous solutions of ammonium salts, such as ammonium chloride, have been reported to react with epichlorohydrin.[11,12] The kinetics of the reaction were determined, but no products were isolated. The action of liquid ammonia on epichlorohydrin is not reported in the literature. Neither have the present investigators been successful in isolating and identifying the

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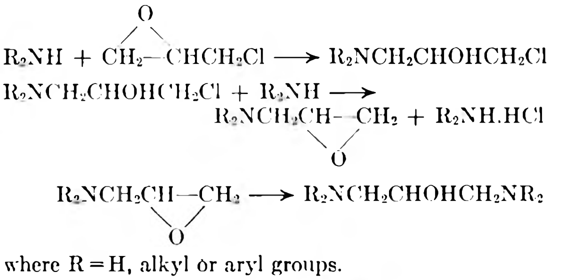
(12) S. Banerjee and H. K. Sen, *J. Indian Chem. Soc.*, **9**, 509 (1932).

products between liquid ammonia and epichlorohydrin. When the reaction was carried out in a Dewar flask in the presence of excess liquid ammonia, only a small amount of a thick yellow liquid whose analysis corresponded to a mixture of the mono- and bischlorohydroxyamines was isolated. When epichlorohydrin and liquid ammonia in a 3:1 mole ratio were treated in a bomb, only a brown, partially water-soluble resin was formed.

From exploratory experiments, it was known to us that 3% aqueous ammonia solubilized epichlorohydrin in a few hours at 25°. Certain condensation products as well as 1,3-dichloro-2-propanol (II), ammonium chloride, and possibly I were easily extracted from the mixture. It was also observed that slow addition of ammonia gas to epichlorohydrin in dioxane solution caused small quantities of ammonium chloride to precipitate. When the gas was slowly passed into a petroleum ether solution of epichlorohydrin, a clear, highly viscous liquid separated within a few hours. This liquid was dehydrohalogenated to yield some *N*,*N*,*N*-tris(2,3-epoxypropyl)amine (III). The reaction was frequently accompanied by ammonium chloride formation. With these facts in mind, it occurred to us that I should be formed if ammonia and epichlorohydrin were allowed to react in a mutual solvent such as a lower aliphatic alcohol in the absence of water. By analogy with the Sturkov reaction,[13] which is concerned with the reaction of epichlorohydrin and aromatic amine hydrochlorides, it was thought that aqueous ammonium chloride should form the desired chlorohydrin.

From aqueous solutions of ammonia or ammonium chloride and epichlorohydrin (1:3 mole ratio) or methanol-water solutions of ammonium chloride and epichlorohydrin (1:4 mole ratio), II could always be isolated in 50 to 80% yields from the ether extract of the reaction mixture. Attempts to isolate chlorohydroxyamines from the extracted aqueous layers were unsuccessful. A pasty white solid which was soluble in alcohol and water but insoluble in acetone or dioxane was obtained. Attempts to dehydrohalogenate this solid, which contained 5.32% nitrogen, resulted in the formation of a resin which was insoluble in water and alcohol. Results of these investigations are similar to the experimental results of Claus[14] with ammonia and epichlorohydrin.

Ammonia or amines are said to add to epichlorohydrin[7,15,16] by the following series of reactions:



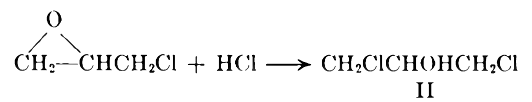
$$R_2NH + \overset{O}{\overbrace{CH_2-CH}}CH_2Cl \longrightarrow R_2NCH_2CHOHCH_2Cl \quad (1)$$

$$R_2NCH_2CHOHCH_2Cl + R_2NH \longrightarrow R_2NCH_2\underset{O}{\underbrace{CH-CH_2}} + R_2NH.HCl \quad (2)$$

$$R_2NCH_2\underset{O}{\underbrace{CH-CH_2}} \longrightarrow R_2NCH_2CHOHCH_2NR_2 \quad (3)$$

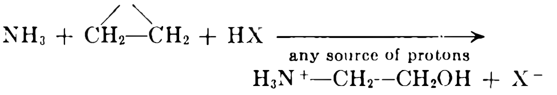
where R = H, alkyl or aryl groups.

To account for the presence of II, it is necessary to consider the presence of the amine hydrochloride. It is well known[17] that epichlorohydrin undergoes hydrolysis easily in the presence of a basic solution to form glycerol and liberate chloride ions. Also, the amine hydrochloride, on hydrolysis, produces some hydrochloric acid which reacts with epichlorohydrin according to the following well established reaction:



$$\overset{O}{\overbrace{CH_2-CH}}CH_2Cl + HCl \longrightarrow \underset{\text{II}}{CH_2ClCHOHCH_2Cl} \quad (4)$$

Removal of the hydrochloric acid by the formation of II leaves the system alkaline. According to Eastham,[18] the reaction between ammonia and ethylene oxide in water can be represented by the following equation:



$$NH_3 + \overset{O}{\overbrace{CH_2-CH_2}} + HX \xrightarrow[\text{any source of protons}]{} H_3N^+-CH_2-CH_2OH + X^- \quad (5)$$

A similar reaction can account for the formation of the di- and triethanolamines.

The present work has been concerned largely with the reaction of ammonia and epichlorohydrin in various solvents in attempts to prepare *N*-(3-chloro-2-hydroxypropyl)amine (IV), and *N*,*N*-bis(3-chloro-2-hydroxypropyl)amine (V) as well as I according to the mechanism of equation (1). Compound IV had not been isolated previously, but its hydrochloride was reported by Gabriel and Ohle[19] and Tomita.[20] Smith,[16a] from kinetic studies in which the products were not isolated, claimed that the main reaction between ammonia and epichlorohydrin is the formation of IV, which is dehydrohalogenated faster than epichlorohydrin to form the amino glycide. Neither compound V nor its hydrochloride had been reported previously. While V has not been isolated in this work, evidence points to its presence in the reaction, because occasionally when distilling III, a somewhat lower boiling epoxide or polymer has been isolated in small quantities. In this investigation, I has not been obtained in the crystalline form (m.p. 92–93° reported by Fauconnier[2]) but rather as an exceedingly viscous liquid which when stripped under vacuum gave a clear plastic solid. The analysis of the crude material points largely to I contaminated with V. Compound III was the main product on dehydrohalogenation.

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[13] I. T. Strukov, *Khim. Farm. Prom.*, No. 2, 11 (1934); through *Chem. Abstr.* **28**, 5421 (1934).

[14] A. Claus, *Ann.*, **168**, 1 (1873).

[15] A. M. Paquin, *Epoxyverbindungen und Epoxyharze*, Springer, 1958, pp. 183–186.

[16] (a) L. Smith and T. Nilsson, *J. prakt. Chem.*, **162**, 63 (1943); (b) L. Smith, S. Mattson, and S. Andersson, *Acta Univ. Lundensis*, **42**, No. 7, 1–18 (1946).

[17] W. J. C. Ross, *J. Chem. Soc.*, 2257 (1950); H. J. Lichtenstein and G. H. Twigg, *Trans. Faraday Soc.*, **44**, 905 (1948).

[18] A. M. Eastham, B. de B. Darwent, and P. W. Beaubien, *Can. J. Chem.*, **29**, 575 (1951).

[19] S. Gabriel and H. Ohle, *Ber.*, **50**, 819 (1917).

[20] M. Tomita, *Z. physiol. Chem.*, **158**, 42 (1926).

The reaction between ammonia and epichlorohydrin appears to take several courses, depending on the amount of water present in the system. Thus, in absolute ethanol, absolute methanol, or petroleum ether, it has been established that I has been formed, because the triepoxy derivative (III) can be prepared from the reaction product, and there is no evidence for the formation of II as a byproduct. Small amounts of ammonium chloride were present. However, when an aqueous medium is used, as in the Strukov reaction, II always occurred and could either be extracted from the aqueous solution or distilled from the mixture. In aqueous medium, about one-third of the epichlorohydrin was used in forming II and the reaction required three to five days for completion.

A number of investigations have been concerned with the aniline-epichlorohydrin reaction,[21–24] but only in recent years[25,26] have relatively mild conditions been used. Homer[26] prepared *N*,*N*-bis-(3-chloro-2-hydroxypropyl)aniline (VI) by a modified Strukov reaction,[13] which required a reaction time of three to five days, and further converted the chlorohydrin to *N*,*N*-bis(2,3-epoxypropyl)-aniline (VII). In this investigation, if dioxane were substituted for part of the water in the solvent medium, the reaction was complete within five hours. One objective of the present work was to obtain *N*-(3-chloro-2-hydroxypropyl)aniline (VIII) and *N*-(2,3-epoxypropyl)aniline (IX), which Homer did not report. The only mention of the latter compound is in the work of Zetzsche and Aeshlimann[23] who isolated a few drops of a liquid having the correct nitrogen content from the mixture of aniline and epichlorohydrin in toluol, which was kept at a high temperature for four days. According to Dains,[24] aniline and epichlorohydrin form no solid or readily purified derivative under mild conditions. In this investigation, when aniline (0.2 mole) and epichlorohydrin (0.3 mole) were treated in aqueous ethanol at the reflux temperature according to the method of Davies and Savige,[25] a mixture of mono- and bischlorohydrins which could not be distilled without decomposition was obtained. We have found that the desired chlorohydrin can be prepared by the reaction of aniline and epichlorohydrin with or without solvents. When aqueous alcohol is used as the solvent medium, about a third of the starting material is converted to water-soluble quaternary compounds, whereas only 5–6% of quaternary compounds is obtained when no solvent is used. The evidence for compound formation was deduced from the sharp increase in viscosity, and decrease in hydrobromic acid titration as performed by the Durbetaki Method.[27]

Little has been reported in regard to the action of epichlorohydrin on the three ethanolamines other than the work of Pierce and Wotiz[28] on diethanolamine. The latter neither isolated nor characterized their reaction products. Exploratory experiments showed that mono-, di-, and triethanolamines react exothermically with epichlorohydrin. The ionic chlorine content of the reaction mixture increases with time even when the reaction temperature has been kept under 30°. Reactions other than those illustrated in Equations 1–5 have been reported, especially with secondary amines, where some form of cyclization has been encountered.[29–31] We have found a similar phenomenon in the exceedingly vigorous reaction between diethanolamine and epichlorohydrin. It was found that initially, the liquid reaction product from the diethanolamine–epichlorohydrin reaction is 20–25% insoluble in chloroform or dioxane and gels on standing. After a week at 25°, practically all the reaction product is chloroform insoluble. The change is quite rapid if dioxane is the reaction medium or if the reaction product is heated in an oven at 70° for a few hours. The decrease in solubility in chloroform has been found to be accompanied by an increase in ionic chlorine content and a decrease in trivalent nitrogen content caused by a quaternization of the desired *N*-(3-chloro-2-hydroxypropyl)-amine. Apparently in the reaction of amines and epichlorohydrin, a considerable variety of products may be obtained by varying temperature, molar ratio of reactants, reaction media, and the basicity of the amine.[32]

EXPERIMENTAL

Preparation of crude N,N,N-tris(3-chloro-2-hydroxypropyl)amine (I) *from ammonia and epichlorohydrin.* To 200 ml. of chilled methanol (1°) in a stoppered flask, ammonia gas or liquid ammonia was added until 4.8 g. (0.282 mole) were absorbed. Then 78.3 g. (0.846 mole) of Fisher[33] reagent

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(21) A. Fauconnier, *Compt. Rend.*, **106**, 605 (1888).

(22) T. Fukagawa, *Ber.*, **68B**, 1344 (1935).

(23) F. Zetzsche and F. Aeschlimann, *Helv. Chim. Acta*, **9**, 708 (1926).

(24) F. B. Dains, R. Q. Brewster, J. S. Blair, and W. C. Thompson, *J. Am. Chem. Soc.*, **44**, 2637 (1922).

(25) W. Davies and W. E. Savige, *J. Chem. Soc.*, 890 (1950).

(26) R. F. Homer, *J. Chem. Soc.*, 3690 (1950)

(27) A. J. Durbetaki, *Anal. Chem.*, **28**, 2000 (1956).

(28) J. S. Pierce and J. J. Wotiz, *J. Am. Chem. Soc.*, **66**, 879 (1944).

(29) R. Rothstein and K. Binovic, *Compt. rend.*, **236**, 1050 (1953).

(30) D. L. Heywood and B. Phillips, *J. Am. Chem. Soc.*, **80**, 1257 (1958).

(31) N. S. Drozdov and O. M. Cherntzov, *J. Gen. Chem. (USSR)*, **4**, 969 (1934); through *Chem. Abstr.*, **29**, 2148 (1935).

(32) J. B. McKelvey, Beverly G. Webre, and E. Klein, *J. Org. Chem.*, **24**, 614 (1959).

(33) Trade names have been used to identify materials used in the work, and such use does not imply endorsement or recommendation by the U. S. Department of Agriculture over other products not mentioned.

grade epichlorohydrin (b.p. 114–116°) were added and the solution was stirred in a water bath overnight at 26°. After 16 hr., the odor of ammonia had disappeared. The final solution (*p*H 8) did not give a precipitate with silver nitrate, but in time a brown mirror formed. Volume reduction in a rotary evaporator yielded 76.7 g. of a clear, glassy solid which did not flow at 25°. It did not crystallize at Dry Ice temperatures nor could it be recrystallized from alcohol or dioxane. It was not soluble in absolute ether or dioxane, but dissolved when a few milliliters of methanol were added to either solvent. No ammonium chloride precipitated from its dioxane solution. The product was quite soluble in water, 15% sodium hydroxide, and dilute hydrochloric acid. It was slightly soluble in acetone or methyl ethyl ketone. It did not form an insoluble picrate or a quaternary salt with methyl iodide. The aqueous solution gave a slight turbidity with silver nitrate and then a silver mirror.

Anal. Calcd. for $C_9H_{18}Cl_3NO_3$: Cl, 36.15. N, 4.75. Found: Cl, 34.84. N, 5.17.

That I is present in the above ammonia-epichlorohydrin reaction product may be proved by the precipitation of its hydrochloride (X) after the crude reaction mixture is treated with excess hydrochloric acid. A 15–25% yield of X, (m.p. 175°) could be obtained by recrystallization of the solvent-free crude hydrochlorides from ethanol or acetone at Dry Ice temperatures.

Anal. Calcd. for $C_9H_{18},Cl_3NO_3.HCl$(X): total Cl, 42.9; ionic Cl, 10.73, N, 4.2. Found: total Cl, 42.2; ionic Cl, 10.86. N, 4.19.

When a 1:1 mole ratio of epichlorohydrin (92.5 g.) and ammonia gas (17 g.) was mixed in methanol, a cloudiness developed in a few days. At the end of 15 days, ammonia could still be detected, and 10.5 g. (0.2 mole) of ammonium chloride had precipitated showing the chloride end of the epichlorohydrin molecule was attacked. Evaporation of the methanol revealed a sticky, white solid which was not investigated.

Preparation of N,N,N-tris(2,3-epoxypropyl)amine (III). When 53.4 g. (0.19 mole) of the above mentioned crude chlorohydrin formed in methanol was agitated for a 0.5 hr. in 150 ml. of dioxane at 25° with 42 g. of powdered 87% potassium hydroxide (0.64 mole), there was obtained after stripping the solvent 37.3 g. (0.2 mole) of a lemon colored oil. Substitution of 98% sodium hydroxide for potassium hydroxide and lowering of temperature to 1–5° resulted in a similar yield of crude oil. When these crude oils were distilled at reduced pressure, they resinified violently, after only a small portion had distilled. Dilution of the crude oils with anhydrous ether or especially carbon tetrachloride caused separation of small amounts of a waxy solid which was insoluble in water and common solvents.

Anal. Found N, 8.1; Cl, 0.0; ash, 0.0.

The undistilled, but solvent treated epoxides showed oxirane oxygen contents of 23%. The purified oils obtained by use of potassium hydroxide and sodium hydroxide could be distilled to give yields of 30 and 56%, respectively, based on the epichlorohydrin.

When 12 g. of the partially purified epoxide was distilled, approximately 6 g. of water-white distillate, b.p. 123–124°, 2 mm., was obtained.

Anal. Calcd. for $C_9H_{15}NO_3$ (III): N, 7.6; oxirane oxygen, 25.9. Found: N, 7.4; oxirane oxygen, 25.8; n_D^{25} 1.4737; d_4^{25} 1.1214.

Compound III was soluble in water, aqueous alkali and acids, carbon tetrachloride, and benzene, but was insoluble in aliphatic hydrocarbons. Within a few weeks, III turned to a hard brown resin insoluble in common solvents. However, it has been kept in a dessicator over phosphorus pentoxide for several months. Methyl iodide and III (4:1 mole ratio) reacted at 26° to form a viscous, water-soluble, noncrystalline mass.

Anal. Calcd. for $C_{10}H_{18}INO_3$: I, 38.8; oxirane oxygen, 14.7. Found: I, 36.9; oxirane oxygen, 12.4.

Preparation of the hydrochloride of N,N,N-tris(3-chloro-2-hydroxypropyl)amine (X). When III was dissolved in dry ether and gassed with dry hydrogen chloride, a brown viscous mass which barely flowed was formed. When a similar experiment was conducted in absolute methanol, a thick viscous mass was formed after evaporation of the solvent.

Anal. Found: N, 4.1; Cl, 36.7.

After long standing, crystals separated from the brown viscous mass. Recrystallization from absolute ethanol yielded white crystals (*X*), m.p. 175°; lit.,[2] m.p. 173°. Pure *X* was soluble in methanol.

Anal. Calcd. for $C_9H_{18}Cl_3NO_3.HCl$ (X): total Cl, 42.9; ionic Cl, 10.72. N, 4.2. Found: total Cl, 42.1; ionic Cl, 10.80 N, 4.2.

Preparation of N,N,N-tris(3-chloro-2-hydroxypropyl)amine (I) *from its hydrochloride* (X). When X was treated with silver oxide, a light yellow oil which solidified within a few days was formed. Analysis of the oil by the method of Durbetaki[27] indicated a trivalent nitrogen content of 18.2% instead of the theoretical 4.75% for I. Hence, silver oxide not only reacted with the ionic chlorine of X but also caused dehydrohalogenation with the resultant formation of epoxide. These results were similar to those obtained by Tomita[20] with compound IV.

Results of potentiometric titrations of X with sodium hydroxide showed that the first rapid reaction was between sodium hydroxide and the ionic chloride and hydrogen ions. The slower reactions were due to the dehydrohalogenation of the chlorohydrins with the resultant formation of epoxides. Therefore, an exact equivalent of sodium hydroxide solution was added to an aqueous solution of X, and the resultant solution was extracted immediately with chloroform. After the chloroform was stripped, a colorless viscous oil was obtained. Continued evacuation at 2 mm. resulted in a waxy solid which did not flow at room temperature.

Anal. Calcd. for $C_9H_{18}Cl_3NO_3$: total Cl, 36.15; ionic Cl, 0.0; trivalent N, 4.75; total N, 4.75. Found: ionic Cl, 0.60; trivalent N, 4.56; total N, 4.38.

Formation of 1,3-dichloro-2-propanol (II) *from epichlorohydrin.* When 92.5 g. epichlorohydrin (1.0 mole) and 5.6 g. of ammonia (0.33 mole) were allowed to react in 300 ml. of water, the time required for complete solution was 3 days at room temperature with stirring. When the clear, colorless, aqueous solution was extracted with ether, 18 g. (0.14 mole) of a colorless liquid resulted (b.p. 172–174°).

Anal. Calcd. for $C_3H_6Cl_2O$: Cl, 55.0. Found: Cl, 54.8.

When 5.35 g. (0.1 mole) of ammonium chloride dissolved in 150 ml. of water (*p*H 5) was agitated with 27.7 g. (0.3 mole) of epichlorohydrin the *p*H rose to 7–8 in 2.5 hr. The epichlorohydrin layer had approximately disappeared in a day, and the solution was homogeneous and colorless in 3 days. The clear liquor which was ether extracted, dried and distilled, yielded 11 g. (0.08 mole) of liquid; b.p. 171–173°; d_4^{25}, 1.3513; lit. b.p. 174°; d_4^{20}, 1.361.

Anal. Calcd. for C_3H_5ClO: Cl, 55.0. Found: Cl, 54.6; N, 0.0.

Reinvestigation of the Strukov reaction. When 17.4 g. (0.1 mole) of *p*-phenetidine hydrochloride (m.p. 235°) was partially dissolved in 150 ml. of water and 27.8 g. (0.3 mole) of epichlorohydrin was added, there resulted a yellow, two-layer mixture. A cloudiness developed within 2 hr., and a deep red to brown-black color developed overnight. After 4.5 days, there resulted a brown oily mass of crystals on the bottom of the flask, while the water layer was a deep pink. The ether extract of the water layer contained 6.4 g. of a red liquid which when distilled yielded 4.0 g. (0.03 mole) of a water-white liquid (b.p. 170–171°).

Anal. Calcd. for II: Cl, 55.0. Found: Cl, 54.5.

A carbon tetrachloride extract of the brown insoluble mass yielded 15 g. of a crystalline solid (m.p. 80°).

Anal. Calcd. for $C_2H_5OC_6H_4N(CH_2CHOHCH_2Cl)_2$: Cl, 22.0. Found: Cl, 21.7.

Some unchanged *p*-phenetidine hydrochloride from the ether extracted water layer was also obtained. The reaction did not go to completion, and on the basis of the phenetidine, a 46% yield of purified *N*,*N*-bis(3-chloro-2-hydroxypropyl)*p*-phenetidine was obtained.

Preparation of N-(3-chloro-2-hydroxypropyl)aniline (VIII). To 9.3 g. (0.1 mole) of Eastman[33] White Label aniline was added 9.25 g. (0.1 mole) of epichlorohydrin in a stoppered flask. After thorough mixing, a 0.1-g. sample of the liquid required 12.72 ml. of 0.0856*N* hydrobromic acid in glacial acetic acid for a Durbetaki[27] titration. A like aliquot was titrated with only 6.40 ml. of the acid after 90 hr. of reaction time. The time of efflux in an Ostwald viscometer was 128.6 sec. at the start and over 12 hr. after a reaction time of 90 hr. The reaction mixture was dissolved in ether and washed with water four times. After the ether solution was dried and stripped, 17 g. of a thick, reddish brown oil was obtained.

Anal. Calcd. for $C_9H_{12}ClNO$: Cl, 19.1; N, 7.5. Found: Cl, 18.9; N, 7.0.

Attempts to distill the oil at 2 mm. resulted in decomposition at 158–160° with formation of a thick, resinous polymer.

Preparation of N-(2,3-epoxypropyl)aniline (IX). To 18.5 g. of epichlorohydrin (0.2 mole) was added 18.6 g. of aniline (0.2 mole) and the reaction mixture was allowed to stand at 25° for 5 days in a stoppered flask. The product was extracted with ether, washed with water, dried, and agitated with 15 g. of powdered potassium hydroxide for 3 hr. at 25°. After filtration and evaporation of the ether, 28 g. remained. On vacuum distillation at 2–3 mm. pressure, 2.3 ml. of a compound which proved to be aniline was collected at 56–58°, and then the temperature rose to 101–103°. A portion of the material resinified in the flask. The fraction collected at 101–103° was redistilled and boiled at 99–101° at 1–2 mm. pressure. A 50% yield was obtained. The product was a light lemon-colored, almost odorless liquid (d_4^{26} 1.1042) and was insoluble in water.

Anal. Calcd. for $C_9H_{11}NO$: N, 9.4; oxirane oxygen, 10.7. Found: N, 9.4; oxirane oxygen, 10.8.

Preparation of N,N-bis(2,3-epoxypropyl)aniline (VII). To a mixture of 100 ml. water and 85 ml. of dioxane were added 25.9 g. of aniline hydrochloride (0.2 mole) and 37.0 g. of epichlorohydrin (0.4 mole). The resulting clear solution deposited a heavy oil in about 4–5 hours. When the oil was dehydrohalogenated with powdered potassium hydroxide in ether, approximately a 50% yield of VII was obtained, b.p. 185–187°, 10–12 mm.; lit. b.p. 165°, 1 mm. In contrast to IX, VII is reasonably stable.

Anal. Calcd. for $C_{12}H_{15}NO_2$: N, 6.8; oxirane oxygen, 15.6. Found: N, 6.7; oxirane oxygen, 15.4.

Preparation of N-(3-chloro-2-hydroxypropyl)N,N-bis(2-hydroxyethyl)amine (XI). According to the procedure of Pierce and Wotiz[28] 42 g. (0.4 mole) of diethanolamine (Union Carbide Chemicals Company)[33] was added to 40 g. (0.44 mole) of epichlorohydrin, after the individual reactants had been chilled to 6°. Agitation in an ice and salt bath kept the temperature from rising above 10–11°, during the vigorous initial exothermic reaction. The material was kept at this temperature for 3 hr., at the end of which time the temperature was increased to 18–20°, and finally, to 26° overnight. After evacuation under a bell-jar, the resultant clear, slightly viscous liquid was soluble in water (*p*H 8) or methanol, and gave a strong chloride ion test. It could not be distilled without decomposition at 2–3 mm. pressure. Only partial solubility resulted when it was mixed with chloroform or dioxane. By the Volhard titration, it contained 2.75% ionizable chlorine (15.5% of the theoretical chlorine content).

Anal. Calcd. for $C_7H_{16}ClNO_3$: total Cl, 18.0; ionizable Cl, 0.0; N, 7.1; trivalent N, 7.1. Found: total Cl, 18.6; ionizable Cl (Volhard), 2.8. N, (Kjeldahl), 6.7; trivalent N (Durbetaki), 7.1.

When 40 g. of the above product was added to 150 ml. of chloroform, approximately 11–12 g. of a turbid liquid separated. The chloroform soluble product (XI) appeared initially in good yield (75%).

Anal. Found: trivalent N (Durbetaki), 6.6.

It slowly quaternized on standing. Attempts to dehydrohalogenate the chloroform soluble portion of XI with powdered caustic only resulted in the formation of a thick, water-soluble, liquid polymer which could not be distilled.

The chloroform insoluble liquid was stripped of excess solvent and analyzed. Now 77% of the total chlorine was ionic, and very little of the nitrogen was in the trivalent state. It would appear reasonable to believe that the chloroform insoluble, waxy solid is the dihydrochloride of 2,5-bis-(2-hydroxyethylaminylmethyl)-*p*-dioxane by analogy to the work of Heywood and Phillips.[29]

Anal. Calcd. for $C_{14}H_{30}N_2Cl_2O_6$: ionizable Cl, 18.06; N, 7.1. Found: total Cl, 19.1; ionizable Cl (Volhard), 14.71; N (Kjeldahl), 6.4; trivalent N (Durbetaki), 0.6.

The formation and identification of such polymers containing quaternary ammonium ions are of interest in the preparation of ion exchange celluloses such as "ECHTEOLA",[34] but are beyond the scope of this investigation.

Acknowledgment. We thank Julian F. Jurgens and Voyce P. Whitley of the Industrial Crops Laboratory for some of the nitrogen and chlorine analyses, and Ralph Berni for the potentiometric titrations.

NEW ORLEANS, LA.

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(34) E. A. Peterson and H. A. Sober, *J. Am. Chem. Soc.*, **78**, 751 (1956).

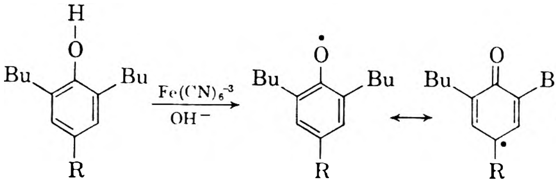
Notes A department for short papers of immediate interest.

Oxidation of Hindered Phenols. X. Effect of 4-Substituents upon the Behavior of 2,6-Di-*t*-butylphenoxy Radicals

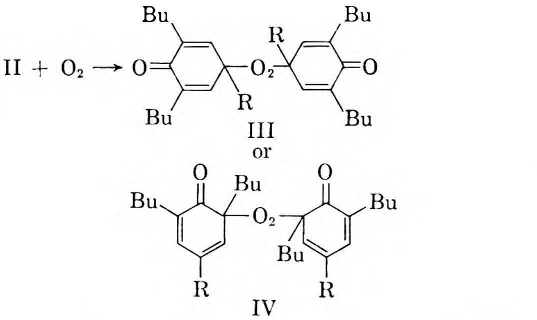
CLINTON D. COOK AND NILES D. GILMOUR

Received January 4, 1960

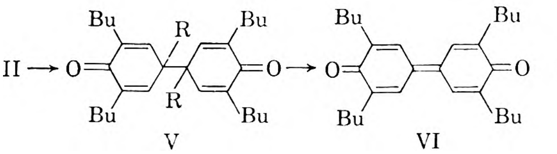
It is now established that the oxidation of trisubstituted phenols having bulky *ortho* substituents may produce phenoxy radicals of considerable stability.[1] As the reactions of such phenoxy radicals vary with the *para* substituent, it was of interest to prepare a series of 2,6-di-*t*-butylphenols having a variety of substituents in the 4-position and to study their behavior in the various reactions typical of phenoxy radicals (Equations 1–3).



(1)



(2)



(3)

Bu = *t*-butyl

Specific compounds are designated throughout the text by symbols after the number, indicating the nature of R. Substituents considered are phenyl, triphenylmethyl, benzhydryl, chloro, bromo, nitro, cyano, benzoyl, acetyl, α-methoxyethyl, and *t*-butyl.

As evidenced by the formation of an intense color on oxidation of the appropriate phenols with an alkaline ferricyanide solution and by subsequent reactions, the following radicals were of at least moderate stability (*i.e.*, capable of existence for at least a few minutes at room temperature): II-C_6H_5 (violet), II-$(C_6H_5)_3C$ (green), II-$(C_6H_5)_2CH$ (blue), II-CN (blue), II-C_6H_5CO (blue), II-CH_3CO (blue), and II-$CH(CH_3)OCH_3$ (blue).[2]

Radicals II-C_6H_5, II-$(C_6H_5)_3C$, II-CN, II-C_6H_5CO, and II-CH_3CO underwent reaction with oxygen much less readily than does 2,4,6-tri-*t*-butylphenoxy[7] (II-*t*-C_4H_9), the rates, as judged by loss of radical color, being in the order II-C_6H_5 > II-$(C_6H_5)_3$ > II-C_6H_5CO > II-CN. II-C_6H_5 reacted with oxygen at not more than one tenth the rate of II-*t*-C_4H_9, and II-CN at not more than one hundredth the rate of II-*t*-C_4H_9. Acceptable yields of peroxides III-C_6H_5 and IV-C_6H_5CO were obtained from the corresponding radicals. Radical II-$(C_6H_5)_3C$ gave an unidentified product which either was not a peroxide of type III or IV or which had a unique mode of decomposition as it did not initiate polymerization of acrylonitrile. The lowered reactivity of these radicals toward oxygen may be due to the increased opportunities for resonance stabilization[8] in the cases of II-C_6H_5, II-CN, and II-C_6H_5CO or in part to a lowered electron density on the *para* carbon. In this respect it is interesting to note that room temperature treatment of the silver salt of tribromophenol with benzene containing a trace of iodine, warming the salt with benzene, or treatment of 2,4,4,6-tetrabromo-2,5-

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(1) For leading references see (a) C. D. Cook and B. E. Norcross, *J. Am. Chem. Soc.* **81,** 1176 (1959); and (b) E. Müller, A. Shick, and K. Scheffler, *Ber.* **92,** 474 (1959).

(2) Since the completion of this work Müller and co-workers have published rather complete descriptions of radicals II-C_6H_5[1b] and II-CN[3a; 3b] and have very briefly mentioned radicals II-$(C_6H_5)_3C$[4a] and II-C_6H_5CO.[4b] Radical II-C_6H_5 was first reported[5] in connection with an EMR study but its chemistry was not defined at that time. Reactions which almost certainly must involve radical II-C_6H_5 have also been reported recently but the radical was not observed directly.[6]

(3) (a) K. Ley, K. Scheffler, A. Rieker, and E. Müller *Z. Naturforsch.* **13b,** 460 (1958).

(3) (b) E. Müller, A. Rieker, K. Ley, R. Mayer, and K. Scheffler, *Ber.* **92,** 2278 (1959).

(4) (a) E. Müller, R. Mayer, and K. Ley, *Angew. Chem.* **76,** 73 (1958).

(4) (b) E. Müller, K. Ley, K. Scheffler, and R. Mayer, *Ber.* **91,** 2682 (1958).

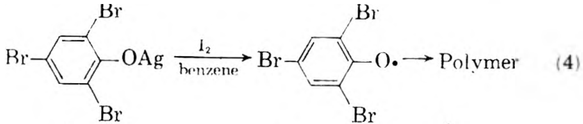
(5) J. E. Wertz, C. F. Koelsch, and J. L. Vivo, *J. Chem. Phys.* **23,** 2194 (1955).

(6) W. R. Hatchard, R. G. Lipscomb, and F. W. Stacy, *J. Am. Chem. Soc.* **80,** 3636 (1958).

(7) C. D. Cook and R. G. Woodworth, *J. Am. Chem. Soc.* **75,** 6242 (1953).

(8) See G. M. Coppinger, *J. Am. Chem. Soc.* **79,** 501 (1957); K. Dimroth, F. Kalk, and G. Neubauer, *Ber.* **90,** 2058 (1957); and ref. 10.

cyclohexadiene-1-one with mercury yields a brilliant blue solution which over a period of an hour or so yields a polymeric material.[9–11] (See Eqs. 4 and 5.) Saturation of such solutions, which presumably contain the 2,4,6-tribromophenoxy radical, with oxygen does not produce a peroxide; nor is there any apparent diminution of the intensity of the blue color. Apparently the tribromophenoxy radical is also relatively unreactive toward oxygen.



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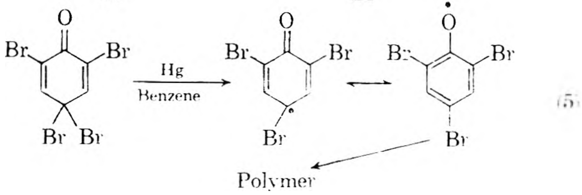
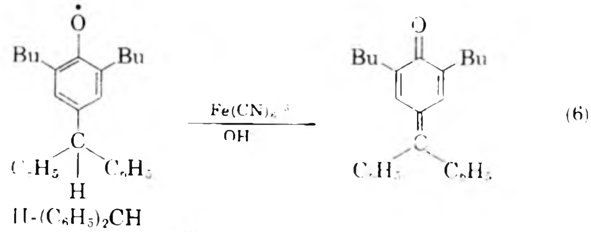
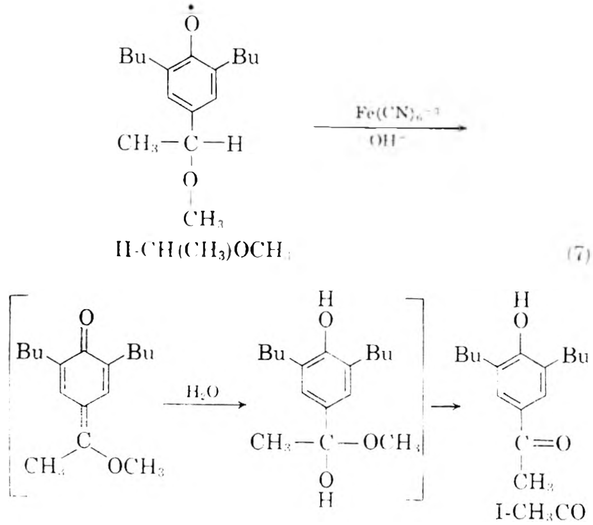


(5)

The phenoxy radicals II-$(C_6H_5)_2CH$ and II-$CH(CH_3)OCH_3$ underwent fairly rapid further oxidation either by disproportionation or with excess alkaline ferricyanide. Radical II-$(C_6H_5)_2CH$ gave the expected[1a] compound, 2,6-di-*t*-butyl-4-benzhydrylidine-2,5-cyclohexadiene-1-one (see Eq. 6), and II-$CH(CH_3)OCH_3$ gave 2,6-di-*t*-butyl-4-acetylphenol (I-CH_3CO), presumably by way of hydration of an intermediate quinonemethide and subsequent cleavage of the hemi ketal (Eq. 7). Further oxidation of I-CH_3CO produced a fairly stable phenoxy radical, II-CH_3CO.



(6)



(7)

Alkaline ferricyanide oxidation of the *p*-chloro (I-Cl) and *p*-bromo (I-Br) phenols gave dimeric products, V-Cl and V-Br, presumably by way of radicals II-Cl and II-Br.[12] The ultraviolet spectrum of V-Cl was almost identical with 1,1′-dihydro-3,5,3′5′ - tetra - *t* - butyl - 2,5,2′5′ - biscyclohexadiene-4,4′-one (V, R = H) produced from 2,6-di-*t*-butylphenol by Kharasch and Joshi.[13] Compound V-Br was an ill-defined, impure solid which evolved bromine on standing at room temperature, on warming, or on solution in ethanol, to produce the corresponding diphenoquinone (VI). Shaking either V-Cl or V-Br with mercury also gave VI. In view of the reversibility of the addition of bromine to 2,4,6-tri-*t*-butylphenoxy (II-t-C_4H_9)[7] these reactions are not surprising. Müller[4] has recently prepared the same compounds (V-Cl and V-Br) by oxidation of I-Cl and I-Br with II-*t*-C_4H_9, and reports identical behavior.

Oxidation of the *p*-nitrophenol (I-NO_2) with alkaline ferricyanide yields directly the diphenoquinone VI. This result is reminiscent of the loss of a carboxyl group on oxidation of 3,5-di-*t*-butyl-4-hydroxy benzoic acid.[14] The ready reversibility of addition of nitrogen dioxide to II-*t*-C_4H_9[7] makes a dimer of type V a very reasonable intermediate. However, all attempts to isolate such a product failed.

EXPERIMENTAL

A. *Preparation of the phenols.* Phenols I-C_6H_5,[15] I-Cl,[16] I-Br,[17] and I-CN[17] were prepared by known methods and had the properties cited in the original literature. Compound I-NO_2 was kindly supplied by H. Shapiro of the Ethyl Corporation, recrystallized from ethanol, m.p. 153–154°.

2,6-Di-t-butyl-4-triphenylmethylphenol (I-$(C_6H_5)_3C$). A solution of 20.6 g. (0.01 mole) of 2,6-di-*t*-butylphenol and 26.0 g. (0.01 mole) of triphenylcarbinol in 75 ml. of glacial acetic acid was treated with 5 ml. of concd. sulfuric acid at room temperature. After 5 hr. the crystals were filtered, washed with water, and recrystallized from ethanol to give 22 g. (50%) of colorless crystals, m.p. 179.5–180°; λ_{max} 284 mμ; ϵ_{max} 2650 (cyclohexane).

Anal. Calcd. for $C_{33}H_{36}O$: C, 88.15; H, 8.07. Found: C, 88.41; H, 8.09.

2,6-Di-t-butyl-4-diphenylmethylphenol (I-$(C_6H_5)_2CH$)—. A solution of 4.0 g. (0.02 mole) of 2,6-di-*t*-butylphenol and 3.6

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(9) Unpublished work with John A. Eberwein.

(10) See W. H. Hunter, A. O. Olson, and E. A. Daniels, *J. Am. Chem. Soc.* **38,** 1761 (1916); W. H. Hunter and G. H. Woolett, *J. Am. Chem. Soc.* **43,** 131 (1921).

(11) G. Staffin and C. C. Price have obtained similar polymers from 2,6-dimethyl-4-bromophenoxy. *Rubber World* **139,** 408 (1958). See also A. S. Hays, H. S. Blanchard, G. F. Endres, J. W. Eustance, *J. Am. Chem. Soc.* **81,** 6335 (1959).

(12) For evidence of the transient existence of a similar reactive phenoxy radical, 2,6-di-*t*-butylphenoxy, see E. Müller, K. Ley, and G. Schlehte, *Ber.* **91,** 2670 (1958).

(13) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.* **22,** 1435, 1439 (1957).

(14) C. D. Cook, E. S. English, and B. J. Wilson, *J. Org. Chem.* **23,** 755 (1958).

(15) G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Am. Chem. Soc.* **67,** 303 (1945).

(16) H. Hart and F. A. Cassis, *J. Am. Chem. Soc.* **73,** 3179 (1951).

(17) L. A. Cohen, *J. Org. Chem.* **22,** 1333 (1957).

g. (0.02 mole) of benzhydrol in 50 ml. of glacial acetic acid was treated with 2.5 ml. of concd. sulfuric acid at room temperature. After 3 hr. the resulting crystals were filtered, washed with water, and recrystallized from *n*-hexane to give 7.5 g. (~100%) of colorless crystals, m.p. 134–134.5°, λ_{max} 284 mμ; ϵ_{max} 2980.

2,6-Di-butyl-4-benzoylphenol (I-C_6H_5CO)—. Aluminum chloride, 13.3 g. (0.1 mole), was added to 40 ml. (0.43 mole) of freshly distilled benzoyl chloride and the flask swirled until complex formation seemed to be complete. Using an ice bath to keep the temperature below 25°, 20.6 g. (0.1 mole) of 2,6-di-*t*-butylphenol was slowly added. The mixture was allowed to stand for an hour in an ice bath, then taken up in benzene and washed with 4*M* sodium hydroxide. Evaporation of the benzene and recrystallization from petroleum ether (b.p. 90–120°) gave 17 g. (55%) of white crystals, m.p. 124–125°. A mixture melting point with an authentic specimen[18] gave no depression.

2,6-Di-t-butyl-4-acetylphenol (I-CH_3CO)—. At 0°, 3.5 g. (0.25 mole) of aluminum chloride was added to 25 ml. of acetyl chloride and, when solution was complete, 4.12 g. (0.02 mole) of 2,6-di-*t*-butylphenol was slowly added. After 45 minutes the mixture was poured into diluted hydrochloric acid containing cracked ice and then extracted with *n*-hexane. Evaporation of the excess hexane gave 3.2 g. (70%) of white crystals, m.p. 145–148°, recrystallized from *n*-hexane, m.p. 147–148°.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74; MW, 248.35; Found: C, 77.39; H, 9.87; MW, 255 (cryoscopic, benzene).

2,6-Di-t-butyl-4-(α-methoxyethyl)phenol (I-CH(CH₃)OCH₃) was prepared by the addition of methanol to 2,6-di-*t*-butyl-4-ethylidene-2,5-cyclohexadiene-1-one according to the method of Cook and Norcross.[1a] The material was obtained in essentially quantitative yields, m.p. 105–105.5° after recrystallization from acetonitrile-water solutions.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.62; MW, 264.39; Found: C, 77.56; H, 10.18; MW, 261 (cryoscopic, benzene).

B. *Preparation of peroxides.* The peroxides were prepared by oxidizing the phenols with a twofold excess of alkaline potassium ferricyanide solution in oxygen-saturated benzene.[7]

Bis(1,5-di-t-butyl-3-benzoyl-2,4-cyclohexadiene-6-one) peroxide (IV-C_6H_5CO)—. Two grams of I-C_6H_5CO gave 0.22 g. (8%) of the above peroxide, m.p. 132–134° dec. after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{42}H_{50}O_6$: C. 77.51; H, 7.74. Found: C, 77.70; H, 7.68.

The ultraviolet spectrum λ_{max} 262 mμ, ϵ_{max} 23,000; λ_{max} 317 mμ, ϵ_{max} 5000 (cyclohexane) indicates that this peroxide has the structure IV-C_6H_5CO.[19] When 0.1% of the peroxide was added to acrylonitrile and the solution warmed to 70° under a nitrogen atmosphere, polymer started to precipitate within 2 min.

Bis(3,5-di-t-butyl-1-phenyl-2,5-cyclohexadiene-4-one) peroxide (III-$(C_6H_5)_3C$)—. Oxidation of 2 g. of I-C_6H_5 for 8 hr. gave 1.8 g. (87%) of light yellow crystals, m.p. 145–147° dec. after recrystallization from acetonitrile; reported,[1b] m.p. 146–148° dec.

C. *Preparation of dimers.* A mixture of 10 g. of potassium ferricyanide, 2 g. of potassium hydroxide, 75 ml. of water, and 50 ml. of benzene was placed in a flask and flushed with oxygen-free nitrogen. A solution of 0.01 to 0.02 mole of the appropriate phenol (I-Cl, I-Br, I-NO_2) in 25 ml. of benzene was rapidly added and the mixture vigorously stirred for 2 to 5 min. The solutions were separated and the benzene layer dried and taken to dryness in a rotary vacuum drier.

1,1′-Dichloro-3,5,3′5′-tetra-t-butyl-bis-2,2′,5,5′-cyclohexadiene-4,4′-one (V-Cl)—. Oxidation of 2.6 g. (0.01 mole) of I-Cl as above gave 2.09 g. (77%) of the above dimer V-Cl, recrystallized from ethyl acetate to m.p. 148.5–150°; reported,[12] m.p. 150–151°; λ_{max} 242 mμ, ϵ_{max} 16,600 (cyclohexane).[20]

Anal. Calcd. for $C_{28}H_{40}O_2Cl_2$: C, 70.13; H, 8.41; Cl, 14.79; MW, 479.51; Found: C, 70.48; H, 8.49; Cl, 14.75; MW, 482 (cryoscopic, benzene). Attempted recrystallization from ethanol or shaking a benzene solution with mercury gave quantitative yields of diphenoquinone (VI) as identified by comparison of ultraviolet spectra and mixture melting points with an authentic specimen.[11]

Oxidation of 2.85 g. (0.01 mole) of I-Br as above gave 2.3 g. (81%) of impure yellow crystals which decomposed over a wide temperature range (110° up) and which decomposed on standing, on solution in polar solvents, or on shaking in benzene with mercury to give the diphenoquinone VI. The material showed an ultraviolet max at 242 mμ, ϵ_{max} = ~25,000 and gave a molecular weight (cryoscopic, benzene) of 538. Calculated for V-Br, 570.6.

Very rapid oxidation of I-NO_2 with limiting amounts of ferricyanide gave only the diphenoquinone VI and unchanged I-NO_2. Use of excess ferricyanide led to quantitative yields of VI.

D. *Other oxidations. 2,6-Di-t-butyl-4-benzhydrylidine-2,5-cyclohexadiene-1-one*—. A solution of 3 g. (0.08 mole) of I-$(C_6H_5)_2CH$ in 25 ml. of benzene was stirred with 20 g. (0.06 mole) of potassium ferricyanide and 10 g. (0.25 mole) of sodium hydroxide in 100 ml. water. The solution turned brilliant blue and gradually faded to deep orange. Removal of the benzene and recrystallization of the residue gave 2.6 g. (87%) of orange crystals, m.p. 178.5–179°, λ_{max} 261 mμ, ϵ_{max} 16,700 (cyclohexane).

Anal. Calcd. for $C_{27}H_{30}O$: C, 87.30; H, 8.15. Found: C, 87.40; H, 8.10.

Oxidation of 2,6-di-t-butyl-4-methylmethoxymethylphenol (I-CH(CH₃)OCH₃) to 2,6-di-t-butyl-4-acetylphenol (I-CH₃CO)—. A solution of 730 mg. (0.0027 mole) of I-$CH(CH_3)OCH_3$ in 20 ml. benzene was oxidized with a solution of 5 g. (0.011 mole) potassium ferricyanide and 1 g. (0.025 mole) of sodium hydroxide in 25 ml. of water. The layers were separated and the benzene layer was washed with water and dried over sodium sulfate. After removal of the benzene 140 mg. (20%) of product was obtained, m.p. 144–147°. Mixed melting point and infrared spectrum showed the sample to be identical with I-CH_3CO.

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DEPARTMENT OF CHEMISTRY
UNIVERSITY OF VERMONT
BURLINGTON, VT.

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(18) T. H. Coffield, A. H. Filbey, G. C. Ecke, and A. J. Kolka, *J. Am. Chem. Soc.* **79**, 5023 (1957).

(19) A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.* 3211 (1953).

(20) Reported for V, R = H, λ_{max} 242 mμ, ϵ_{max} = 15,000 ref. 13.

Hexachloroacetone as a Novel Source of Dichlorocarbene

PANKAJA K. KADABA AND JOHN O. EDWARDS

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Edwards, Evans, and Watson[1] carried out an electrometric study on dilute aqueous solutions of

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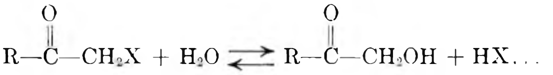
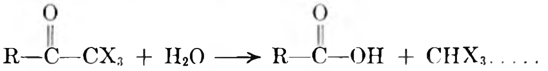
(1) E. G. Edwards, D. P. Evans, and H. B. Watson, *J. Chem. Soc.*, 1942 (1937).

halogenated ketones and discovered the presence of halide ions in the solutions and of chloroform in solutions of hexachloroacetone. They explained these observations as resulting from, not the ionization of ketones, as was thought earlier,[2] but from hydrolyses of two types: an alkyl halide type 1, in the case of mono- and dihalogenated ketones, and a haloform type 11, in the case of polyhalogenated ketones containing the —CX_3 group, which involves attack upon the carbonyl carbon. The



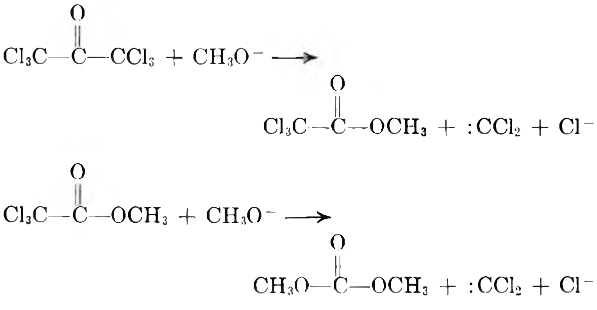
$$R-\overset{\overset{O}{\|}}{C}-CH_2X + H_2O \rightleftarrows R-\overset{\overset{O}{\|}}{C}-CH_2OH + HX\ldots \quad (1)$$



$$R-\overset{\overset{O}{\|}}{C}-CX_3 + H_2O \longrightarrow R-\overset{\overset{O}{\|}}{C}-OH + CHX_3\ldots\ldots \quad (2)$$

electron attractive character of the halogen atoms in $R-\overset{\overset{O}{\|}}{C}-CX_3$ render the carbonyl group highly reactive towards nucleophiles, thereby enabling the —CX_3 to break away with the electron pair by which it was originally linked to the carbonyl carbon. They found this reaction to be prominent in ketones which have three halogens linked to the same carbon atom, and in hexachloroacetone the carbonyl group is so activated that this change occurs to the almost complete exclusion of reaction 1.

From the results of these authors, hexachloroacetone would be expected to yield dichlorocarbene in a nonprotonic medium in the presence of a base like sodium methoxide. Further, the methyl trichloroacetate[3] formed in the first step would then react with more methoxide to yield more dichlorocarbene in a similar manner. Thus, for every mole



$$Cl_3C-\overset{\overset{O}{\|}}{C}-CCl_3 + CH_3O^- \longrightarrow Cl_3C-\overset{\overset{O}{\|}}{C}-OCH_3 + :CCl_2 + Cl^-$$

$$Cl_3C-\overset{\overset{O}{\|}}{C}-OCH_3 + CH_3O^- \longrightarrow CH_3O-\overset{\overset{O}{\|}}{C}-OCH_3 + :CCl_2 + Cl^-$$

of hexachloroacetone, there could result two moles of dichlorocarbene.

The carbene hypothesis has been tested here by the introduction of carbene acceptors and has indeed been found to be the case. Experiments have been carried out using three acceptors. In the first case, a mixture of benzalaniline in dry petroleum ether containing sodium methoxide was treated with hexachloroacetone and the adduct (1,2-diphenyl-3,3-dichloroethylenimine) was obtained as the sole reaction product in 61% yield. Our product had the same melting point reported by Fields and Sandri[4] and underwent rearrangement to the α-chloro-α-phenylacetanilide. In the second case, a mixture of cyclohexene and sodium methoxide in petroleum ether was treated with hexachlorcacetone to yield the expected 7,7-dichlorobicyclo[4.1.0]heptane (dichloronorcarane) in 43% yield based on olefin. There was also obtained a stable, colorless, crystalline solid (10% yield based on hexachloroacetone). Similar results were obtained with 2-methyl-2-butene, the latter also yielding (in addition to 1,1-dichloro-2,2,3-trimethylcyclopropane) the same crystalline compound. The solid melted at 86–87° and contained chlorine. It was insoluble in water but dissolved readily in bases and underwent fast hydrolysis in basic solutions. The solid showed no precipitation with alcoholic silver nitrate and gave a positive carbylamine test. Its infrared spectrum showed a strong absorption at 3525 cm.$^{-1}$ and a weak band at 3225 cm.$^{-1}$ Analysis gave C, 13.98%; H, 0.93% and Cl, 79.65%. All of the above observations are in agreement with the expected behavior of hexachloroisopropyl alcohol; this compound had been synthesized by Geiger, *et. al.*[5] but its chemical properties were not investigated by them. The strongly acidic nature of the hydroxyl group of this compound is explained as due to the presence of two strong electron withdrawing groups on the carbon atom to which the hydroxyl group is attached.

The reduction of hexachloroacetone to form hexachloroisopropyl alcohol occurred exclusively in the reactions wherein olefins were present. This indicated that either the olefin itself, or its dichlorocarbene adduct, is involved in the reduction. However, a mixture of dichloronorcarane and hexachloroacetone in dry petroleum ether containing sodium methoxide. under conditions identical with earlier experiments, failed to yield the alcohol. Also, no reduction was observed (either by isolation or by infrared analysis) when an excess of cyclohexene was treated with hexachloroacetone in the absence of sodium methoxide. The reaction is highly interesting and further investigations should be carried out on the chemistry of this reduction.

The yields obtained with hexachloroacetone as carbene source were not as large as with ethyl trichloroacetate[3] as carbene source. However, hexachloroacetone certainly is a dichlorocarbene source of ready availability at low price and might be desirable as a source of dichlorocarbene for large scale preparations.

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(2) H. B. Watson and E. D. Yates, *J. Chem. Soc.*, 1214 (1932).

(3) W. E. Parham and E. E. Schweizer, *J. Org. Chem.*, **24,** 1733 (1959).

(4) E. K. Fields and J. M. Sandri, *Chem. & Ind. (London)*, 1216 (1959).

(5) M. Geiger, E. Usteri, and Ch. Gränacher, *Helv. Chem. Acta.*, **34,** 1335 (1951).

EXPERIMENTAL

1,2-Diphenyl-3,3-dichloroethylenimine Hexachloroacetone (97%, technical grade, Baker and Adams) (26 g., 0.1 mole), was added with stirring under dry nitrogen, over 1 hr. to a mixture of commercial sodium methoxide (5.4 g., 0.1 mole) (Matheson, Coleman, and Bell) and benzalaniline[6] (9 g., 0.05 mole) in dry petroleum ether (b.p. 37–39°) (200 ml., treated to remove any unsaturation present), cooled in an ice bath. Stirring was continued for 5–6 hr. under nitrogen, with the reaction mixture cooled in ice and water. The flask was then stoppered and kept overnight. It was then filtered and the residue separately treated with water, to remove inorganic materials; the desired product remained, 5 g., m.p. 95–98°. From the petroleum ether solution was obtained another 3 g. of product, m.p. 95–98° (total yield, 61%). Careful crystallization of a sample from petroleum ether gave creamy white crystals, m.p. 98–99° (reported,[4] m.p. 98–99°), identical with the product obtained by using ethyltrichloroacetate[3] in place of hexachloroacetone.

The compound has a characteristic unpleasant odor and precipitates silver chloride from an alcoholic solution of silver nitrate. It undergoes rearrangement in water; the reaction is very slow at room temperature but is complete in 30 min. at 100°, to give α-chloro-α-phenylacetanilide in quantitative yields. The amide was crystallized from acetone–petroleum ether mixture to give colorless crystals, m.p. 148–149° (reported,[4] m.p. 146–148°).

7,7-Dichlorobicyclo[4.1.0]heptane (dichloronorcarane). The reaction was carried out in essentially the same manner as before. It was then poured into cold water, extracted with ether, the ether extracts dried over anhydrous sodium sulphate, and concentrated. The residue was distilled through a short fractionating column and the dichloronorcarane collected at 78–79.5°/15 mm. (reported[7] b.p. 78–79°/15 mm.).

Anal. Calcd. for $C_7H_{10}Cl_2$: C, 50.9; H, 6.1; Cl, 43.0. Found: C, 50.80; H, 5.95; Cl, 43.23.

The oily residue left behind in the distillation flask, on cooling solidified to give hexachloroisopropyl alcohol which crystallized from hexane to give colorless, stout crystals, m.p. 86–87° (reported[5] m.p. 87–87.5°).

Anal. Calcd. for $C_3H_2OCl_6$: C, 13.50; H, 0.76; Cl, 79.75. Found: C, 13.98; H, 0.93; Cl, 79.65.

Four experiments with variation in reactant concentrations gave yields of dichloronorcarane ranging from 34 to 43%. Yields of hexachloroisopropyl alcohol varied from 3% to 10%; the higher values were obtained with short reaction times and with equimolar amounts of hexachloroacetone and sodium methoxide.

1,1-Dichloro-2,2,3-trimethylcyclopropane. Hexachloroacetone (53.0 g., 0.2 mole) was added with stirring over 1.5 hr. under dry nitrogen, to a cold mixture of sodium methoxide (10.8 g., 0.2 mole) and 2-methyl-2-butene (150 ml., excess). The mixture was stirred for 3.5 hr. and worked up in the same manner as above. Fractional distillation yielded the product (b.p. 144°)[7] mixed with small amounts of methyltrichloroacetate (b.p. 154°). The ester was destroyed by refluxing with a 15% aqueous solution of potassium hydroxide (50 ml.) for 15 min., and 1,1-dichloro-2,2,3-trimethylcyclopropane distilled at 69.5°/55 mm., yield 7 g. (23%, (reported[7] b.p. 69–70°/55 mm.).

Anal. Calcd. for $C_6H_{10}Cl_2$: C, 47.1; H, 6.6; Cl, 46.3. Found: C, 46.93; H, 6.66; Cl, 46.60.

From the residue was obtained hexachloroisopropyl alcohol, 4.0 g., m.p. 86–87°, identical in properties with that obtained in the reaction using cyclohexene.

Reaction media. After the above data were obtained, Dr. Francis T. Smyth found that more consistent yields could be obtained if 5 ml. of methanol were added to the petroleum ether solvent.

Acknowledgment. The authors are grateful to the National Institutes of Health of the U. S. Public Health Service for financial aid.

METCALF CHEMICAL LABORATORIES
BROWN UNIVERSITY
PROVIDENCE 12, RHODE ISLAND

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(7) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954).

Hexachloroacetone as a Source of Dichlorocarbene

F. W. GRANT AND W. B. CASSIE

February 18, 1960

Since the original observation of Doering and Hoffman[1] that cyclopropane derivatives are formed by the reaction of chloroform, olefins, and potassium *t*-butoxide, a number of attempts have been made to increase the efficiency of this conversion by varying the base[2,3] and the chlorinated species.[3] Recently, Parham and Schweizer[3] have developed an elegant procedure based on ethyl trichloroacetate as the progenitor of the dichlorocarbene intermediate in this reaction. Yields of cyclohexene adduct of up to 79%, based on trichloroacetate, were obtained using sodium methoxide as the base.

The reaction of sodium methoxide with hexachloroacetone presents a mechanistically similar situation where the latter reagent has the advantage of offering two equivalents of dichlorocarbene per molecule. Preliminary experiments

$$\mathrm{Cl_3CCOCCl_3} \xrightarrow{\mathrm{OR^-}} :\mathrm{CCl_2} + \mathrm{Cl^-} + \mathrm{Cl_3CCOOR}$$

$$\mathrm{Cl_3CCOOR} \xrightarrow{\mathrm{OR^-}} :\mathrm{CCl_2} + \mathrm{Cl^-} + \mathrm{CO(OR)_2}$$

carried out with cyclohexene as the carbene acceptor have resulted in a 59% yield of 2,2-dichlorobicyclo[4.1.0]heptane based on the indicated stoichiometry.

EXPERIMENTAL[4]

2,2-Dichlorobicyclo[4.1.0]heptane. Sodium (5.75 g., 0.25 g.-atoms) was added in portions to 30 ml. of anhydrous methanol. Excess methanol was removed by heating and flushing with dry nitrogen. Hexachloroacetone[5] (26.5 g., 0.10 mole) was added dropwise with stirring to a mixture of the sodium methoxide and 82.0 g. (1.0 mole) of cyclohexene at 0–5°. Stirring was continued for 5 hr. at this temperature

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(1) W. von E. Doering and A. K. Hoffman, *J. Am. Chem. Soc.*, **76**, 6162 (1954).

(2) H. E. Winberg, *J. Org. Chem.*, **24**, 264 (1959).

(3) W. E. Parham and E. E. Schweizer, *J. Org. Chem.*, **24**, 1733 (1959).

(4) Boiling points are uncorrected.

(5) We wish to thank the General Chemical Division of Allied Chemical Corporation for a sample of this material.

and for 10 hr. at 25°. Water was added and the organic layer separated, dried, and distilled. A 19.5-g. (59%) yield of product, b.p. 85–87°/22 mm., was obtained and characterized by comparison of the infrared spectrum with that of an authentic sample.[1]

Acknowledgment. We wish to thank Prof. E. R. Trumbull of Colgate University for making available the infrared spectrophotometer.

Department of Chemistry
Hamilton College
Clinton, N. Y.

Chromic Acid Oxidation of Cyclohexanols to Cyclohexanones

Allen S. Hussey and Robert H. Baker

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Having invested several hours in the preparation of 4-ethylcyclohexanol,[1] we were reluctant to carry out the time-honored oxidation with Beckmann's chromic acid[2] by the usual procedure.[3] This procedure involves the addition of the alcohol in portions,[3] or all at once,[4] to the chromic acid solution and the yields are realatively low (50–70%[1,4]).

By reducing the considerable excess of sodium dichromate commonly used[3] to 20% more than the stoichiometric amount, using the stoichiometric quantity of sulfuric acid, *and adding these reagents in aqueous solution to a warm slurry of 4-ethylcyclohexanol in water*, the yield of 4-ethylcyclohexanone was increased from 70–75%[1] to 90%. A similar procedure increased the yield of 2-methylcyclohexanone from 50–60%[5] to 80% and of menthone, from 85%[3] to 94%.

Infrared spectra indicate the once-distilled products to be somewhat less contaminated by unoxidized alcohol than they are when prepared by the usual procedure,[4,5] and the method has the distinct advantage that it can be used safely to oxidize secondary alcohols in several mole batches. Considerable saving of oxidizing agent is also realized.

It seems quite reasonable to ascribe the improved yield of product to the excess of alcohol over oxidizing agent during the reaction as carried out by this procedure. The carboxylic acid oxidation products, which result from secondary oxidation of the ketone, seldom amount to more than 4–5% of the product.

This procedure is a modification of that developed by Jones and co-workers[6] wherein acetone solutions of unsaturated secondary alcohols maintained below 30° are titrated with standard chromic acid solution (2.67*M* in chromium trioxide, 4.3*M* in sulfuric acid). The latter procedure is the preferred one for alcohols with other easily oxidized functions or for small scale preparations.

EXPERIMENTAL

4-Ethylcyclohexanone. A solution of 120 g. (0.400 mole, 20% excess) of sodium dichromate dihydrate and 135 g. (1.33 mole) of 96% sulfuric acid in 500 ml. of water was added over 40 min. to a well stirred slurry of 128.0 g. (1.00 mole) of 4-ethylcyclohexanol[1] and 200 ml. of water in a 2-l. 3-neck flask fitted with a dropping funnel, condenser, and mechanical stirrer. The mixture became greenish-black within the first 2 min. and the temperature rose from 30° to 68° during the addition of the first half of the oxidizing agent. Immediately after the addition of the reagent was complete, the temperature began to fall and in 25 min. was at 55°. The mixture was cooled, extracted twice with 400 ml. of 3:1 ether-pentane and the extracts were washed several times with water. The dried extracts furnished 113.6 g. (90%) of 4-ethylcyclohexanone which distilled at 109–112°, 50 mm. (n_D^{25} 1.4533) and 4.9 g. of alkali-soluble residue. An infrared spectrum of the product (12% chloroform) showed no hydroxyl absorption at 2.7–3.0 μ.

2-Methylcyclohexanone. By a similar treatment, 114.0 g. (1.00 mole) of 2-methylcyclohexanol and 200 ml. of water gave 89.3 g. (80%) of 2-methylcyclohexanone (b.p. 104–107° at 116 mm.; n_D^{23} 1.4473) when 120.0 g. of sodium dichromate dihydrate and 135 g. of sulfuric acid (96%) in 500 ml. of water were added over 45 min. The temperature rose to 60° and stirring was continued for 20 min. after the addition was complete. A highly purified sample prepared earlier by the alternate procedure[3] had n_D^{23} 1.4472.

l-Menthone. *l*-Menthol (101.7 g., 0.652 mole) and 200 ml. of water were similarly treated, but at an initial temperature of 60°, with 77.7 g. (0.261 mole) of sodium dichromate dihydrate and 88.9 g. (0.870 mole) of 96% sulfuric acid in 400 ml. of water to give 94.0 g. (94%) of *l*-menthone, b.p. 116–119° at 41 mm.; n_D^{23} 1.4490; $[\alpha]_D^{27}$ −28.9° (α_D^{27} −25.6°, neat). The addition of oxidizing agent required 40 min. during which time the temperature was maintained at 65 to 72° by external heat. The mixture was stirred for 40 min. additional time and then was cooled and worked up in the usual way. By the alternate procedure the yield is 82–85%.[3]

Department of Chemistry
Northwestern University
Evanston, Ill.

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(1) W. Ziegenbein, A. Schaeffler, and R. Kaufhold, *Ber.*, **88**, 1906 (1955).

(2) E. Beckmann, *Ann.*, **250**, 325 (1889).

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A Difficulty Encountered in the Use of Methyltriphenylphosphonium Iodide in the Wittig Reaction

Carol H. Collins[1] and George S. Hammond[2]

Received February 24, 1960

In connection with another study, we have attempted to prepare methylenecyclopentane from cyclopentanone by means of the Wittig reaction. Descriptions of procedures generally indicate that any methyltriphenylphosphonium halide may be used to prepare the desired triphenylphosphinemethylene. The halide is usually the bromide,[3] although the chloride has also been used.[4] We have experienced considerable difficulty in the use of the iodide. Four attempts were made, following the procedure of Sondheimer and Mechonlan,[5] but using triphenylmethylphosphonium iodide (prepared from triphenylphosphine and methyl iodide, m.p. 179–180°) instead of the bromide. When attempts were made to filter or centrifuge the precipitate, presumed to be triphenylphosphine oxide, after the completion of the reaction of the reagent with cyclopentanone, a dark green semisolid formed on contact with air or moisture. This interfered with the separation. As a final product, only a rather viscous, dark colored liquid, which showed no olefinic or methylenic bands in an infrared spectrum, could be isolated from the tetrahydrofuran solution.

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[1] Present address: University of Wisconsin, Madison, Wisconsin.

[2] Present address: California Institute of Technology, Pasadena, California.

It is felt that this difficulty is due to the presence of some iodine containing byproduct, as substitution of methyltriphenylphosphonium bromide in the reaction sequence allows the preparation of the desired methylenecyclopentane.

CHEMISTRY DEPARTMENT
IOWA STATE UNIVERSITY
AMES, IOWA

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(3) See the references listed in the following reviews: (a) U. Schollkopf, *Angew. Chem.*, **71**, 260 (1959); (b) J. Levisalles, *Bull. Soc. chim.* (*France*), 1021 (1958); (c) G. Wittig, *Experientia*, **12**, 41 (1956).

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Preparation of Ferrocene from Anhydrous and Hydrated Ferrous Chloride in Alcohol

WILLIAM F. LITTLE, ROBERT C. KOESTLER,
AND ROBERT EISENTHAL

Received February 8, 1960

Two convenient laboratory preparations of ferrocene in high yields have been reported.[1] In the original report of the preparation of ferrocene from anhydrous ferrous chloride and cyclopentadiene in anhydrous aliphatic amine solvents,[2] it was mentioned that low yields of ferrocene could be obtained with ferrous chloride, cyclopentadiene, and sodium methoxide. Lindstrom and Barusch[3] reported that ferrocene can be conveniently prepared in 43% yield from cyclopentadiene, anhydrous ferrous chloride, and sodium ethoxide in ethanol. We wish to submit an experimental procedure for this preparation leading to 90% yield of ferrocene. Since the starting materials are identical in our preparation and that of Lindstrom and Barusch, the principal differences in the two procedures lie in the order of addition of reactants, our use of a 10% excess of base, and a longer reaction time in our preparation. Excess base was found crucial in the observation that commercial hydrated ferrous chloride can also be used in the preparation with a sacrifice in yield:

$$C_5H_{10} + FeCl_2{\cdot}4H_2O + NaOC_2H_5 \xrightarrow[C_2H_5OH]{} C_{10}H_{10}Fe$$

When iron(II) chloride–4-hydrate is used, the addition of slightly more than six moles of sodium ethoxide per mole of ferrous chloride is necessary, and yields up to 30% can be realized. Attempts to remove the hydration water by azeotropic distillation (added benzene) of part of the alcohol from the solution of ferrous chloride prior to the addition of base did not improve the results. Use of potassium hydroxide as the base in place of sodium ethoxide failed to yield any ferrocene.

Commercial anhydrous ferrous sulfate gave no ferrocene by this method, presumably due to the insolubility of ferrous sulfate in alcohol.

EXPERIMENTAL

Use of anhydrous ferrous chloride. To a suspension of 1 mole of ferrous chloride in 400 ml. of dry tetrahydrofuran, prepared in the usual manner[1] from 108 g. of anhydrous ferric chloride and 30 g. of iron powder, was added under nitrogen a solution of sodium ethoxide, prepared by dissolving 50.5 g. (2.2 moles) of sodium in 800 ml. of absolute ethanol. A blue-green precipitate was formed, and to the thick slurry was added with stirring 132 g. (2.0 moles) of freshly distilled cyclopentadiene in one portion. After about 10 min. the slurry had taken on an orange hue and the temperature had risen to 45°. The mixture was stirred for 3 hr. without heat. At the end of this time crystals of ferrocene had precipitated, and 200 ml. of water was added slowly, followed by the addition of 0.5 g. of sodium hydrosulfite and sufficient dilute hydrochloric acid to reduce the small amount of the blue ferrocinium ion formed. Addition of 2 l. of water completed the precipitation of the ferrocene, which was collected by filtration. The crude product was recrystallized from a mixture of 1 l. of petroleum ether (b.p. 90–100°) and about 200 ml. of methylene chloride to yield 138 g. of ferrocene, m.p. 174.5–175.5°, and an additional 29.5 g. melting at 172–174° from evaporation of the mother liquor. The total yield of ferrocene from this procedure was 90%.

Use of hydrated ferrous chloride. A solution of 19.9 g. (0.1 mole) of iron(II) chloride–4-hydrate in 300 ml. of absolute ethanol was prepared and de-oxygenated with nitrogen introduced under the surface of the solution through a fritted disk. A small amount of iron powder was added to reduce any ferric ions present. The mixture was allowed to reflux for an hour and was cooled to room temperature. At the end of the reflux period the solution had turned from

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(1) G. Wilkinson, *Org. Syntheses*, **36**, 31 (1956).

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(3) (a) M. E. Barusch and E. G. Lindstrom, U. S. Patent **2,834,796**, May 13 (1958); *Chem. Abstr.*, **52**, 16366 (1958); (b) E. G. Lindstrom and M. E. Barusch, Abstracts of the 131st Meeting of the American Chemical Society, Miami, Fla., April 7–12, 1957.

green to colorless. To this solution was added with stirring a solution formed by adding 14.9 g. of sodium (0.65 mole) to 500 ml. of absolute ethanol. A greyish white precipitate was formed immediately, and to the slurry was added at once 13.2 g. (0.2 mole) of cyclopentadiene. The mixture was stirred at room temperature for 3 hr. and was then brought to reflux for 3 hr. The volume of the solution, filtered through asbestos, was reduced to 300 ml., and 1700 ml. of water was added. The ferrocene precipitated and after drying weighed 5.6 g. for 30% yield melting at 169–172°.

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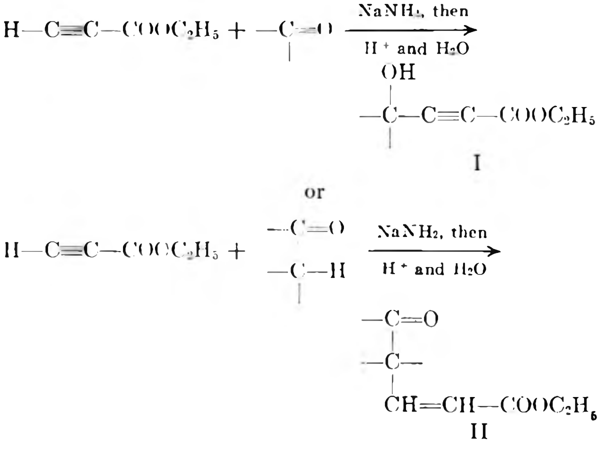
THE VENABLE CHEMICAL LABORATORIES
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, N. C.

Potassium Hydroxide as a Catalyst for the Condensation of Propiolic Acid or Propiolic Esters with Ketones

ELMER K. RAUNIO AND LOUIS P. REMSBERG, JR.[1]

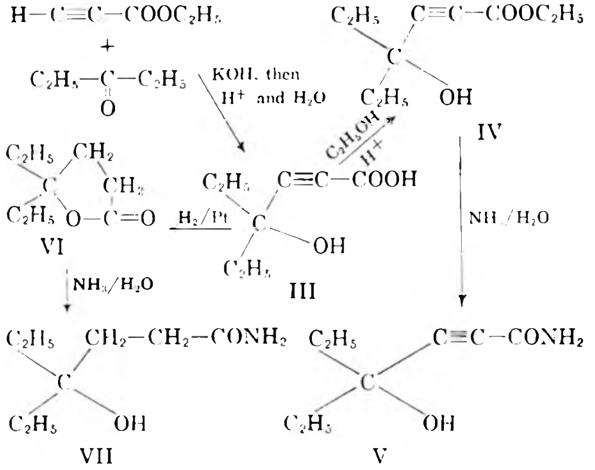
Received January 18, 1960

In previous communications[2,3] we have reported that sodamide in liquid ammonia will bring about the condensation of ethyl propiolate with various cyclic ketones to yield either acetylenic carbinols (I) or esters of substituted acrylic acids (II), depending upon the ketone used.



The ability of potassium hydroxide to bring about analogous condensations of acetylene with ketones is well known.[4] This fact prompted us to try potassium hydroxide as a condensing agent for the condensation of both propiolic acid and of ethyl propiolate with certain ketones. It was found that propiolic acid will add to cyclohexanone in the presence of a solution of potassium hydroxide in aqueous alcohol to yield the acetylenic carbinol.

Furthermore, a suspension of powdered potassium hydroxide in ether brought about the condensation of ethyl propiolate with cyclohexanone in as high yields as were obtained using sodamide in liquid ammonia as the condensing agent.[2] Likewise, a suspension of powdered potassium hydroxide in ether brought about the condensation of the acyclic ketone, diethyl ketone, with ethyl propiolate. In this case the product was isolated as the crystalline 4-ethyl-4-hydroxy-2-hexynoic acid (III).



This acid was further characterized through its crystalline amide (V) which was prepared through the ester (IV). The structure of the acid was established by conversion through the lactone (VI) to the amide (VII) of the known 4-hydroxy-4-ethylhexanoic acid. An authentic sample of this amide was obtained from the lactone which was prepared by the procedure of Hepworth.[5]

In the case of the diethyl ketone and ethyl propiolate, powdered potassium hydroxide in ether gave as good a yield of III, as did sodium hydride in ether. No identifiable condensation product was obtained when the condensation was attempted with sodamide in liquid ammonia as the condensing agent.

EXPERIMENTAL

Condensation of propiolic acid with cyclohexanone. A solution containing 25 g. (0.36 mole) of propiolic acid, 38 g. (0.39 mole) of cyclohexanone, 35 g. (0.52 mole, based on 85% purity) of potassium hydroxide, 5 ml. of water, and 100 ml. of ethanol was allowed to stand at room temperature for 2 days. The solution was refluxed for 10 min., cooled, diluted with 250 ml. of water, and was washed with three portions of ether (washings discarded). The aqueous layer was acidified with sulfuric acid and was extracted with three 35-ml. portions of ether. Removal of the ether under reduced pressure left 50 g. of acidic material from which 18 g. of β(1-hydroxycyclohexane)propiolic acid crystallized upon standing. A recrystallized sample melted at 122–124.5°; reported for β(1-hydroxycyclohexane)propiolic acid: 125°,[6] 123–126°.[2]

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[4] Louis F. Fieser and Mary Fieser, *Organic Chemistry*, third edition, D. C. Heath and Co., Boston, 1956, p. 91.

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Condensation of ethyl propiolate with cyclohexanone and with diethyl ketone. The following procedure was used to condense both cyclohexanone and diethyl ketone with ethyl propiolate. A solution containing 5.0 g. (0.05 mole) of ethyl propiolate and 5.0 g. (0.05 mole) of cyclohexanone was added to a suspension of 4 g. of powdered potassium hydroxide in 50 ml. of ether. The mixture was shaken frequently over a period of 1 hr. and was then poured into cold water. Neutral material was removed by ether extraction; the solution was acidified and extracted with three small portions of ether. After removing the ether from the extract, the residue was kept under a current of air until it crystallized. A 2.77-g. sample of β(1-hydroxycyclohexane)propiolic acid (m.p. 123–126° after recrystallization from benzene-alcohol) was obtained.

The same procedure was used to condense ethyl propiolate (40 g.) with diethyl ketone (35 g.). 4-Hydroxy-4-ethyl-2-hexynoic acid (III) was obtained in 22% yield, m.p. (after repeated recrystallizations from carbon tetrachloride) 79.5–80°.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.60; H, 7.57. The same product was obtained in a 19% yield when sodium hydride was substituted for the potassium hydroxide.

Amide of 4-hydroxy-4-ethyl-2-hexynoic acid. A sample of 4-hydroxy-4-ethyl-2-hexynoic acid was esterified by refluxing with absolute alcohol containing a little concd. sulfuric acid. The ester distilled at 136–139°, 14.5 mm. Upon standing for several days with a saturated ammonia solution, the ester was converted into the crystalline amide; m.p. 107.8–108.3° after recrystallization from chloroform.

Anal. Calcd. for $C_8H_{13}O_2N$: C, 61.93; H, 8.44. Found: C, 61.79; H, 8.64.

Amide of 4-hydroxy-4-ethylhexanoic acid. 4-Hydroxy-4-ethylhexynoic acid (1.35 g.) in 40 ml. of ethanol was shaken with 0.05 g. of platinum oxide under hydrogen (35 p.s.i.) until absorption of hydrogen ceased. After removal of the alcohol from the filtered solution, the lactone of 4-hydroxy-4-ethylhexanoic acid was purified by distillation, b.p., 105–110°, 12 mm. This lactone was allowed to stand with frequent shaking with a saturated solution of ammonia in water. The amide of 4-hydroxy-4-ethylhexanoic acid gradually crystallized from the solution, m.p., 120–121°, after recrystallization from chloroform.

Anal. Calcd. for $C_8H_{17}O_2N$: C, 60.36; H, 10.76. Found: C, 60.57; H, 10.71.

There was no depression in melting point when this amide was mixed with an authentic sample of the amide (prepared from the lactone of 4-hydroxy-4-ethylhexanoic acid which in turn was prepared by the method of Hepworth.[5]

DEPARTMENT OF PHYSICAL SCIENCES
UNIVERSITY OF IDAHO
MOSCOW, IDAHO

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Ketal *versus* Hemiketal Formation for Cyclohexanone and Methanol

D. G. KUBLER[1] AND L. E. SWEENEY[2]

Received December 15, 1959

We have found, in agreement with Lorette, Howard, and Brown,[3] that ketal formation occurs to a significant extent for cyclohexanone and methanol. Lorette *et al.* have shown also that, in general, ketal formation from ketones and alcohols occurs to a significant extent under the proper conditions. Our investigation was started because of the obvious discrepancy between the work of McCoy *et al.*,[4] who also observed ketal formation for these reactants, and of Wheeler,[5] who concluded that hemiketal formation is the predominant reaction even at mole ratios as high as 100:1 of methanol to cyclohexanone.

The approximate equilibrium constant has been determined for ketal formation from cyclohexanone and methanol at three mole ratio levels. The values of K_x were calculated from mole fractions, with the concentrations of all of the constituents having been determined by chemical analysis. The results are shown in Section I of Table I. It is thus seen that K_x is reasonably constant over a rather large mole ratio range.

The yields of ketal, based on chemical analysis are 28, 59, and 71% for the 2:1, 8:1, and 15:1 mole ratio mixtures, respectively. These yields are considerably less than those previously reported by McCoy *et al.*[4] but are in line with the yield (46%) obtained by Lorette *et al.*[3] for a 4:1 mole ratio.

The reaction mixtures, which had been analyzed chemically were then diluted in 1,4-dioxane and the concentrations of cyclohexanone were determined by means of the ultraviolet spectrum (carbonyl absorption). In a similar manner, the analyzed mixtures were diluted in *t*-butyl alcohol and these solutions were analyzed for cyclohexanone by means of the ultraviolet and the infrared spectra. The concentrations of the other constituents of the equilibrium were calculated on the basis of the concentrations of cyclohexanone and the stoichiometry for ketal formation. The values of K_x (mole fraction) are shown in Table I-B (ultraviolet dioxane), Table I-C (ultraviolet *t*-butyl alcohol) and Table I-D (infrared - *t* - butyl alcohol). The values of K_m (molarities) are also shown and are seen to vary by a factor of 10 to 20 as the mole ratio was changed from 15:1 to 2:1.

On the basis of these results we conclude that ketal formation is the predominant reaction whether the reaction is conducted neat or in an inert solvent and K_x is approximately 0.15 at 27° ±5. The results by spectral analysis appear to be somewhat less reliable than the results by chemical analysis

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[1] Author to whom inquiries should be addressed. Present address: Hampden-Sydney College, Hampden-Sydney, Va. Formerly with Union Carbide Chemicals Company, Division of Union Carbide Corporation.

[2] Development Department, Union Carbide Chemicals Company, South Charleston, W. Va.

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TABLE I

EQUILIBRIUM CONSTANT, K_x, FOR KETAL FORMATION FROM METHANOL AND CYCLOHEXANONE

A. K_x for Neat Reaction Mixtures, Chemical Analysis

			Equilibrium Concentrations										
Initial	Reactants[a]		Ketone		Alcohol		Ketal		Water		Total	Total	
Mole Ratio	Ketone	Alcohol	Wt. %	Moles/100 g.	Wt. %	Moles/100 g.	Wt. %	Moles/100 g.	Wt.%	Moles/100 g.	%	Moles/100 g.	K_x
2:1	98.0	61.0	43.2	0.440	28.4	0.886	24.7	0.171	3.31	0.184	99.6	1.68	0.153
8:1	98.0	256	11.1	0.113	61.8	1.93	24.0	0.166	3.06	0.170	100.0	2.38	0.160
15:1	98.0	480	4.77	0.0486	75.3	2.35	17.9	0.124	2.23	0.124	100.2	2.65	0.152

B. K_x by Ultraviolet Analysis in Dioxane[b]

				Equilibrium Concentrations, M							
Initial Mole Ratio	G. Mixture in 100 Ml. Solution	Initial Molarity of Cyclohexanone	Initial Molarity of Methanol	Absorbance	Cyclohexanone	Methanol	Ketal	Water	Total Moles/l.	K_m[c]	K_x
2:1	1.4678	0.0905	0.1810	1.010	0.0641	0.128	0.0264	0.0264	0.245	0.66	0.16
8:1	6.1797	0.1745	1.396	1.145	0.0726	1.192	0.102	0.102	1.469	0.10	0.15
15:1	14.300	0.2475	3.712	1.175	0.0745	3.366	0.173	0.173	3.786	0.036	0.13
C. K_x by Ultraviolet Analysis in t-Butyl Alcohol[d]											
2:1	1.5894	0.0981	0.1962	1.07	0.068	0.134	0.0309	0.0309	0.264	0.78	0.21
8:1	6.1782	0.1744	1.395	1.10	0.070	1.19	0.103	0.103	1.46	0.11	0.16
15:1	14.275	0.2469	3.705	1.07	0.068	3.02	0.179	0.179	3.45	0.052	0.18
D. K_x by Infrared Analysis in t-Butyl Alcohol[e]											
2:1	1.5894	0.0981	0.1962	0.231	0.071	0.142	0.0271	0.0271	0.267	0.51	0.14
8:1	6.1782	0.1744	1.395	0.235	0.072	1.19	0.102	0.102	1.47	0.10	0.15
15:1	14.275	0.2469	3.705	0.222	0.069	3.35	0.178	0.178	3.77	0.041	0.15

[a] One drop of concd. hydrochloric acid was added as a catalyst and the mixtures were maintained under an atmosphere of nitrogen. [b] $\epsilon = 15.77$ at $\lambda_{max} = 287$ mμ with a 1.0 cm. cell. The solutions were balanced against dioxane as a blank. [c] This value is based on molar concentrations. [d] $\epsilon = 15.74$ at $\lambda_{max} = 284$ mμ with a 1.0 cm. cell. The solutions were balanced against t-butyl alcohol as a blank. [e] $\lambda_{max} = 5.83$ μ with a 0.079 mm. sodium chloride cell. The solutions were balanced against t-butyl alcohol as a blank.

but clearly are of the same order of magnitude. The value of K_x is 0.19 calculated from the 46% yield for a 4:1 mole ratio under the conditions used by Lorette *et al.*[3]

We have concluded also that hemiketal existence is negligible for this system. This is based upon the fact that we obtained essentially the same values of K_x for the reaction by chemical analysis and by spectral analysis. The chemical analysis for ketone cannot distinguish between ketone and hemiketal (that is aldehydes and ketones are quantitatively determined by oximation in neutral or basic alcoholic solutions). However, the determination of carbonyl absorption in either the ultraviolet or infrared regions of the spectra should not include hemiketal or hydrated carbonyl.[6] Therefore, the combination of chemical analysis of neat reaction mixtures and spectral analysis for carbonyl in inert solvents should be an excellent method to determine the extent of hemiacetal formation in the presence of acetal for those systems where both equilibria occur to significant extents. We are investigating currently the effects of structure of the carbonyl reactant on the mechanism of this reaction which leads to hemiacetal and acetal in some cases and to acetal only in other cases.

We can only conjecture the reasons as to why Wheeler failed to detect ketal formation. First and foremost it would appear that in some manner his dioxane solutions became contaminated with an appreciable amount of water after having been dried and before the measurements were made. If we assume for the purposes of calculation that the K_x value we obtained is correct, then Wheeler's solutions must have contained approximately 0.5% water (0.25M). With this assumption K_x was calculated for the concentration range he used.[7] The average value of K_x was found to be about 0.14 and was fairly constant over the range.

Calculation of the equilibrium constants for acetal formation should be made on the basis of mole fractions and not molarities. Little is known of the activity coefficients of the equilibrium constituents[6] and the reaction is of the general type,

$$A + 2B \rightleftharpoons C + D$$

for which there is a net decrease in the total number of molecules. Therefore,

$$K_x = \frac{n_C \times n_D}{n_A \times n_B{}^2} \times N \qquad (1)$$

where n_A = moles A, etc., N = total moles, and $K_m = K$ for molar concentrations and is volume (V) dependent.[8] It follows that

$$K_x = K_m \frac{N}{V} \qquad (2)$$

Since K_x appears to remain constant for this system and N is a variable while V is essentially a constant for the reaction conducted in a solvent, then K_m must vary inversely with N.[9] However, we must point out that we did not include the moles of solvent in our K_x calculations. In an approximate calculation of K_x including the moles of solvent for the data of Table I-B, K_x varied from about 6 to 1 to 0.4 as the mole ratio was varied from 2:1 to 8:1 to 15:1. However, the solutions were becoming much more concentrated in this same order and K_x is seen to be approaching the value for the neat reactions. Because of this and because we wanted to compare K_x for the neat reaction mixtures with those for the solvent mixtures we have not included the moles of solvent in our calculations.

To verify further that ketal formation occurred under the conditions similar to those used by Wheeler, a solution of dioxane was prepared which was 3.4M in methanol, 0.14M in cyclohexanone, and 0.1M in hydrochloric acid. After allowing several hours at room temperature for the mixture to equilibrate the acid was neutralized and the mixture was distilled. A fraction was obtained which contained 71.5% 1,1-dimethoxycyclohexane and 24.1% cyclohexanone and represented a 62% yield of the ketal.

Wheeler has applied the ultraviolet method to the determination of the ring size of ketones based on the extents of hemiketal formation.[10] This method would appear to be quite valid except that it is based upon ketal formation and not hemiketal formation.

EXPERIMENTAL[11]

Purification of reagents and solvents. Commercial cyclohexanone was purified by fractional distillation at 50 mm. A series of mid-fractions was collected for which the boiling point was 73° and had n_D^{20} 1.4498 over the range. This material was 98.3% pure by chemical analysis (oximation) and no impurities could be detected by mass spectrometry.

The methanol was AAA grade and was 99.4% pure by chemical analysis (phthalation) and contained a maximum of 0.03% water (Karl Fischer reagent).

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(6) N. C. Melchior, *J. Am. Chem. Soc.*, **71**, 3651 (1949).

(7) K_x values were calculated for ketal formation based on the data for the eight runs shown in Table I of Wheeler's article[5] and assuming the dioxane was 0.25M in water. The values, from top to bottom, were 0.156, 0.160, 0.161, 0.116, 0.125, 0.136, 0.135, 0.131.

(8) S. Glasstone, *Textbook of Physical Chemistry*, 2nd ed., D. Van Nostrand Co., Inc., New York, 1956, p. 822.

(9) We are indebted to Dr. O. D. Bonner of the University of South Carolina for pointing out this relationship to us.

(10) O. H. Wheeler and J. L. Mateos, *Anal. Chem.*, **29**, 538 (1957).

(11) We wish to thank Mr. R. G. Lowther for help in conducting many of these experiments.

A sample of 1,1-dimethoxycyclohexane was prepared as described by McCoy *et al.*;[4] n_D^{20} 1.4395; purity, 99.8% (oximation).

The dioxane was purified by treatment with sodium borohydride to remove peroxides, followed by distillation which provided a material which contained negligible absorption over the range of 250 to 350 mμ. The distillate was then redistilled from lithium aluminum hydride to remove last traces of water. This solvent was not satisfactory for use in the infrared work because it showed some absorption in the carbonyl region (5.8 μ) which was not removed by either the sodium borohydride or lithium aluminum hydride treatment.

t-Butyl alcohol was purified by distillation and was found to be free of carbonyl absorption in both the infrared and ultraviolet region of the spectrum. This material contained less than 0.01% water (Karl Fischer).

Chemical analyses. The determinations of the equilibrium concentrations for the neat mixtures were made by the following methods from Siggia:[12] total carbonyl, as cyclohexanone and 1,1-dimethoxycyclohexane, by the hydroxylamine method (1 hr. reaction time in a steam bath); cyclohexanone by the hydroxylamine-pyridine method (1 hr. reaction time at 27° ±5°); methanol by the phthalic anhydride–pyridine method (5 min. reaction time in a steam bath) and water by the Karl Fischer reagent.

To check the validity of these methods, a synthetic mixture of all components including the catalyst was made having near the equilibrium concentrations for a 2:1 mole ratio mixture (set up for $K_x = 0.172$). The value of K_x based on the analyses of the mixture was 0.157 which compares very well with the values shown in Table I-A. A further check of the methods is furnished by the results shown in Table I-A. In all three cases the total analysis is essentially 100% and the moles of ketal per 100 g. of mixture is essentially equal to the moles of water per 100 g. of mixture.

The values of K_x are considered to be only approximate inasmuch as the samples were not maintained at a constant temperature. In all cases, however, room temperature was 27° ±5°.

Spectral analyses. The ultraviolet measurements were made using a Carey Model 11 spectrophotometer. The solutions were run with either dioxane or *t*-butyl alcohol, as appropriate, in the comparison cell. Solutions of cyclohexanone in dioxane (λ_{max} = 287 mμ, ϵ = 15.77) and *t*-butyl alcohol (λ_{max} = 284 mμ, ϵ = 15.74) followed Beer's law over the concentrations checked in the ultraviolet.

The infrared measurements were made using a Perkin-Elmer Model 21 spectrophotometer. The samples were run in a 0.079 mm. sodium chloride cell and *t*-butyl alcohol was used as a blank. Because these solutions did not follow Beer's law, a curve was constructed for $\log \frac{I_0}{I}$ *versus* the concentration of cyclohexanone in *t*-butyl alcohol. The values used (for λ_{max} = 5.83 μ) were: $\log \frac{I_0}{I}$ = 0.071, 0.136, 0.230, 0.332 for corresponding values of molarity of 0.0205, 0.0407, 0.0710, 0.104.

The solutions which were analyzed spectrally were made from the neat reaction mixtures of Table I-A with the appropriate solvent. The concentrations used are shown in Tables I-B, I-C, and I-D. The solutions were analyzed for cyclohexanone content and rechecked after about an hour—no variations were noted.

THE DEVELOPMENT DEPARTMENT
UNION CARBIDE CHEMICALS COMPANY
SOUTH CHARLESTON, W. VA.

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[12] S. Siggia, *Quantitative Organic Analysis via Functional Groups*, 2nd ed., John Wiley and Sons, Inc., New York, 1957.

Cyanocarbon Chemistry. XVI.[1]
1,1,2,2-Tetracyanocyclopropane

R. M. SCRIBNER, G. N. SAUSEN, AND W. W. PRICHARD

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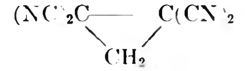
In the course of studies in the field of cyanocarbon chemistry, we have developed four independent syntheses of 1,1,2,2-tetracyanocyclopropane (I). Whereas 3-alkyl- and 3,3-dialkyl-1,1,2,2-tetracyanocyclopropanes have been prepared by earlier workers,[2,3] synthesis of the simplest member of the series has not been reported previously.

1,1,3,3-Tetracyanopropane[4] was brominated by *N*-bromosuccinimide in acetonitrile to give an 89–93% yield of an unstable dibromo derivative, probably 1,3-dibromo-1,1,3,3-tetracyanopropane (II). Addition of a solution of this compound in acetone to aqueous potassium iodide gave a 78% yield of the cyclopropane I. A smaller yield (28%) of I was obtained by reaction of an ethyl acetate solution of the dibromo compound with aqueous potassium cyanide. Proof of the structure of I is based on elemental analysis, molecular weight measurements, and infrared and proton-magnetic resonance spectral analyses.


I

$BrC(CN)_2CH_2C(CN)_2Br$
II

Addition of ethereal diazomethane to a solution of tetracyanoethylene[5] in tetrahydrofuran was accompanied by a vigorous evolution of nitrogen and precipitation of I, isolated in 38% yield after recrystallization. It is of interest that treatment of ethyl diazoacetate with tetracyanoethylene gave neither a cyclopropane nor a pyrazoline. Instead there was obtained an unstable compound, $C_{10}H_6N_6O_2$, that spectral evidence indicated may have been a 4-ethoxycarbonyl-5-tricyanovinyl-1,2,3-tri-

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(1) Paper XV, C. L. Dickenson, *J. Am. Chem. Soc.*, in press.

(2) S. Wideqvist (*Arkiv Kemi, Mineral. Geol.*, **B20**, No. 4, 8 pp. (1945); *Chem. Abstr.*, **41**, 1621 (1947) reports the preparation of 3-alkyl- and 3,3-dialkyl-1,1,2,2-tetracyanocyclopropanes by the reaction of bromomalononitrile and potassium iodide with aldehydes or ketones. The method was unsuccessful when applied to the synthesis of I from formaldehyde. Cf. also S. Wideqvist, *Arkiv Kemi, Mineral. Geol.*, **14B**, No. **37**, 13 pp. (1941); *Chem. Abstr.*, **36**, 79 (1942).

(3) R. P. Mariella and A. J. Roth, III [*J. Org. Chem.*, **22**, 1130 (1957)] report the syntheses of 3-allyl-1,1,2,2-tetracyanocyclopropanes by the action of bromine on alkylidene bis(malononitriles).

(4) O. Diels and B. Conn, *Ber.*, **56**, 2076 (1923).

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

azole,[6] formed by addition of the diazoacetic ester to a carbonitrile group of the tetracyanoethylene.

The third synthesis of I was carried out by modification of a published procedure[2] for the preparation of 3-alkyl-1,1,2,2-tetracyanocyclopropanes by the action of bromomalononitrile and potassium iodide on aldehydes. Use of aqueous formaldehyde in this reaction gave a 68% yield of I.

The most convenient preparation of I (in 85% yield) consisted of adding bromine water to an aqueous solution of malononitrile and formaldehyde in the presence of a trace of β-alanine.

Evidence for the delocalization of the electrons of cyclopropane ring systems[7] made it of interest to determine whether the hydrogen atoms of I were activated by the carbonitrile groups to such a degree that they would undergo reaction commonly associated with "active methylene" compounds. However, I was recovered unchanged after treatment with bromine in carbon tetrachloride, *N*-bromosuccinimide in boiling acetonitrile, selenium dioxide in boiling dioxane, hot sulfuryl chloride (with and without benzoyl peroxide added), and diazotized *m*-chloroaniline. Like the 3-alkyl- and 3,3-dialkyl-1,1,2,2-tetracyanocyclopropanes reported by Wideqvist,[2] I was soluble in 1*M* sodium hydroxide, presumably by saponification of one or more of its carbonitrile groups.

EXPERIMENTAL

1,3-Dibromo-1,1,3,3-tetracyanopropane II). A solution of 10.0 g. (0.07 mole) of 1,1,3,3-tetracyanopropane[4] (m.p. 133–135°) in 140 ml. of acetonitrile was stirred under an atmosphere of nitrogen while 24.8 g. (0.14 mole) of *N*-bromosuccinimide was added in small portions over a period of 15 min. The orange solution was stirred overnight at room temperature and solvent was removed under reduced pressure (25°) to give a white solid. After trituration with successive portions of water and drying at reduced pressure, the solid weighed 19.1 g. (91% yield) and melted at 124–129° dec. This compound was sensitive toward heat and efforts to purify it caused decomposition.

Anal. Calcd. for $C_7H_2Br_2N_4$: Br, 52.94. Found: Br, 51.45.

1,1,2,2-Tetracyanocyclopropane (I). *Method A.* A solution of 3.0 g. (0.01 mole) of 1,3-dibromo-1,1,2,2-tetracyanopropane (II) in 10 ml. of ethyl acetate was added dropwise with vigorous stirring over a period of 35 min. to a solution of 1.37 g. (0.21 mole) of potassium cyanide in 4 ml. of water maintained at −12° to −20°. The solution was stirred for an additional 40 min. while the temperature gradually rose to 15°. The organic layer was separated and washed with water, dried over magnesium sulfate, and evaporated to dryness under reduced pressure. Sublimation of the dark brown residue at 150° (0.03 mm.) gave 0.40 g. (28% yield) of white solid, m.p. 224° dec.[8] The infrared spectrum of this compound in potassium bromide showed the following bands: 3.23, 3.32 (C—H), 4.43 (C≡N), 6.90, 7.01, 8.25, 9.07, 9.88 (cyclopropane?), 13.69 and 14.06 μ. The proton magnetic resonance spectrum of a sample dissolved in deuterated acetone showed a single peak at −108 c.p.s.[9]

Anal. Calcd. for $C_7H_2N_4$: C, 59.16; H, 1.42; N, 39.42; mol. wt., 142. Found: C, 59.39; H, 1.54; N, 39.38; mol. wt. (ebullioscopic in acetone) 138, 136.

A solution of 14.2 g. (0.086 mole) of potassium iodide in 35 ml. of water was added with stirring to a solution of 3.0 g. (0.01 mole) of 1,3-dibromo-1,1,3,3-tetracyanopropane (II) in 15 ml. of acetone. The solution was allowed to stand for 15 min. and then filtered to give, after washing and drying, 1.1 g. (78%) of 1,1,2,2-tetracyanocyclopropane, m.p. 223°.[8] The infrared spectrum of this sample was identical with that of I obtained above.

Method B. A dry solution of 2.8 g. (0.067 mole) of diazomethane in 200 ml. of ether was added in portions (15 min.) with stirring to a solution of 8.5 g. (0.067 mole) of tetracyanoethylene[5] in 100 ml. of dry tetrahydrofuran. After evolution of gas had ceased, the yellow solution was stoppered loosely and allowed to stand for 2 days at room temperature, by which time it had turned bright red in color and had deposited a white solid. Removal of the solid by filtration and recrystallization from benzene-ethanol gave 3.6 g. (38%) of white crystals, m.p. 223–225° dec.[8] The infrared spectrum of this compound was identical with that of I obtained by Method A.

Anal. Found: N, 38.95.

Evaporation of the red ethereal solution remaining after removal of I left 6.5 g. of a dark red solid, m.p. 85–110°, that showed signs of extensive decomposition on standing for several days at room temperature. Attempts to recrystallize this substance and to eliminate nitrogen by boiling in benzene gave no isolable compounds.

Method C. To a solution of 5.2 g. (0.04 mole) of bromomalononitrile in 20 ml. of tetrahydrofuran diluted with 1 ml. of water was added 1.6 g. (0.02 mole) of 37% formalin followed by 6.6 g. (0.04 mole) of potassium iodide in 8 ml. of water. When the exothermic reaction had subsided, the mixture was diluted with a little water and filtered. The precipitate so obtained was washed with dilute potassium iodide solution and then with water, giving 2.2 g. of crude I (68% yield). Recrystallization from methanol (0.7 g./35 ml.) gave needles having an infrared absorption spectrum identical with that of I obtained by Method A.

Anal. Found: C, 59.26, 59.16; H, 1.58, 1.66; N, 39.57, 39.64.

Method D. A solution of 13.2 g. (0.2 mole) of malononitrile in 100 ml. of water was mixed with 8.1 g. (0.1 mole) of 37% formalin in a 2-l. flask equipped with a stirrer and a dropping funnel. Fifty milligrams of β-alanine was added to the solution and a solution of 5.15 ml. (0.1 mole) of bromine in 500 ml. of water was added during 5 min. The colorless solution was warmed to 45°, stirred for 1 hr., and cooled in ice. The white crystalline product removed by filtration weighed 12.0 g. (85%) and was nearly pure I.

Addition of ethyl diazoacetate to tetracyanoethylene. To 10.2 g. (0.15 mole) of tetracyanoethylene[5] dissolved in 125 ml. of dry tetrahydrofuran was added with stirring 20 g. (0.18 mole) of ethyl diazoacetate. After the solution had been allowed to stand for 5 hr. at room temperature, 600 ml. of cyclohexane was added. After 3 days the clear, orange solution was decanted from about 5 g. of black tar and evaporated under reduced pressure (40°). During the evaporation process dark, gummy material precipitated until about two thirds of the original volume of liquid remained, at which time a yellow solid began to precipitate. At this point the clear solution was decanted again from the solid and evaporated to dryness under reduced pressure. Recrystallization of the yellow residue (20 g.) from 500 ml. of benzene–ethyl acetate (12:1) gave 16 g. of yellow amorphous solid, m.p. 120–123°. An analytical sample was prepared by two more crystallizations from benzene, carried out quickly in order to minimize decomposition. Samples stored at room temperature underwent considerable darkening after several days. The infrared spectrum (potassium bromide) showed bands at 2.95 μ (NH), 3.35 μ (CH), 4.45 μ and 4.55 μ (conjugated C≡N), 5.74 μ (ethoxycarbonyl), and 6.25 μ (conjugated C=C or C=N). The ultraviolet spectrum (ethanol) showed absorption peaks at 423 mμ ($\epsilon\lambda_{max}$ 2200), 273 mμ ($\epsilon\lambda_{max}$ 1840), 245 mμ ($\epsilon\lambda_{max}$ 4600) and 215 mμ ($\epsilon\lambda_{max}$ 5330).

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[6] Analogy for such a reaction is to be found in the reaction of diazomethane with methoxycarbonyl cyanide to give a 1,2,3-triazole [*cf.* Thesing and Witzel, *Angew. Chem.*, 68, 425 (1956)]. Methoxycarbonyl cyanide, like tetracyanoethylene, has an electrophilic substituent adjacent to a carbonitrile group.

[7] *Cf.* for example E. N. Trachtenberg and C. Odian, *J. Am. Chem. Soc.*, **80**, 4018 (1958) and G. W. Cannon, A. A. Santilli, and P. Shenian, *J. Am. Chem. Soc.*, **81**, 4264 (1959).

[8] The melting point is strongly dependent on the rate of heating. Samples were placed on a hot stage preheated to 200°.

[9] Obtained by means of a Varian Model 4300 high-resolution spectrometer operating at an R_f field of 56.4 Mc. per second. Spectra were calibrated in terms of displacements in c.p.s. from the proton resonance of water.

Anal. Calcd. for $C_{10}H_6N_6O_2$: C, 49.59; H, 2.50; N, 34.70; mol. wt., 242. Found: C, 50.05; H, 2.66: N (Dumas) 33.56, 33.81; N (Kjeldahl) 24.02, 23.89; mol. wt. (ebullioscopic in acetone) 233, 259.

CENTRAL RESEARCH DEPARTMENT
EXPERIMENTAL STATION
E. I. DU PONT DE NEMOURS & COMPANY, INC.
WILMINGTON 98, DEL.

Improved Preparation of Triphenylmethyl Perchlorate and Fluoroborate for Use in Hydride Ion Exchange Reactions[1]

HYP J. DAUBEN, JR., LEWIS R. HONNEN,[2] AND KENNETH M. HARMON[3]

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The synthesis of tropenium (cycloheptatrienylium) salts by hydride ion abstraction from cycloheptatriene by trityl (triphenylmethyl) carbonium ion[4] has been extended recently to the preparation of a series of substituted tropenium ions,[5] several π-tropenium ion-metal carbonyl complexes,[6,7a] perinaphthenium ion,[7a] triphenylcyclopropenium ion,[7b] and various substituted triphenylmethylcarbonium ions.[7b]

$$R{-}H + (C_6H_5)_3C^+,Y^- \longrightarrow R^+,Y^- + (C_6H_5)_3CH$$

In the course of these studies it was found that when trityl halides were used as the hydride ion abstracting reagents, reaction was slow (except in sulfur dioxide solvent) and halide salts formed frequently had undesirable properties, *e.g.*, tropenium chloride and bromide were quite hygroscopic,[6,8] some substituted tropenium ions reacted with halide ions at their substituent groups,[5] and perinaphthenium halides were found to be only transiently stable.[7a] For these reasons, use of other trityl salts, particularly those with anions of low nucleophilicity, was investigated. Trityl perchlorate and trityl fluoroborate were found to give rapid hydride ion exchange in a number of different solvents and aromatic carbonium ion salt products of unusual stability.[4–7] The consequent need for convenient routes to these trityl salts led to an examination of the known preparative methods, and has resulted in a simplified procedure for the preparation of trityl perchlorate and a convenient new synthesis of trityl fluoroborate.

Trityl perchlorate has been prepared by essentially three different methods: (i) from trityl chloride and silver perchlorate in nitrobenzene on precipitation by benzene addition[9]; (ii) from trityl chloride or triphenylcarbinol in nitrobenzene or ether and 71% perchloric acid, followed by removal of all water by evaporation in a desiccator[9,10]; and (iii) from triphenylcarbinol in acetic anhydride and 71% perchloric acid, the product separating partially from concentrated solution, or by evaporation of dilute solutions in a vacuum desiccator.[10] Method i suffers from the disadvantages of the need for prior preparation of trityl chloride and the use of explosive silver perchlorate, and method ii requires complete removal of water by slow, and potentially dangerous, evaporation. Method iii, on the other hand, employs a convenient starting material and removes the water by reaction with acetic anhydride, but possesses the disadvantage, even when run in concentrated solution, of furnishing conveniently and directly only moderate yields of pure product. However, because of the lower solubility of the salt product in acetic anhydride than in acetic acid, conduct of the reaction of triphenylcarbinol and 71% perchloric acid in an adequate excess of acetic anhydride leads to the direct separation of yellow crystals of trityl perchlorate in 76–92% yield. Circumvention of the evaporation step not only greatly simplifies the preparation but also avoids formation of a dark-colored product that is not satisfactory for most hydride ion exchange reactions; decomposition of substituted tropenium and perinaphthenium perchlorate salt products appears to be strongly influenced by impurities in the trityl salt use in the exchange reaction.

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[1] Supported in part by Office of Ordnance Research, U. S. Army.

[2] Allied Chemical and Dye Corporation Fellow, 1956–1957.

[3] National Science Foundation Predoctoral Fellow, 1956–1958. Present address, Department of Chemistry, Harvey Mudd College, Claremont, California.

[4] H. J. Dauben, Jr., and D. L. Pearson, Abstracts, 126th Meeting, American Chemical Society, New York, N. Y., Sept. 13, 1954, p. 18-O.

[5] (a) H. J. Dauben, Jr., F. A. Gadecki, K. M. Harmon, and D. L. Pearson, *J. Am. Chem. Soc.*, **79**, 4557 (1957); (b) H. J. Dauben, Jr. and K. M. Harmon, Abstracts, 134th Meeting, American Chemical Society, Chicago, Ill., Sept. 9, 1958, p. 35-P; (c) K. M. Harmon, Ph.D thesis, University of Washington, 1958.

[6] H. J. Dauben, Jr. and L. R. Honnen, *J. Am. Chem. Soc.*, **80**, 5570 (1958); Abstracts, 15th Southwest Regional Meeting, American Chemical Society, Baton Rouge, La., Dec. 3, 1959, p. 89.

[7] (a) L. R. Honnen, Ph.D. thesis, University of Washington, 1960; (b) L. L. McDonough, Ph.D. thesis, University of Washington, 1960.

[8] *Cf.* W. v. E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **76**, 3203 (1954).

[9] M. Gomberg and L. H. Cone, *Ann.*, **370**, 142 (1909).

[10] K. A. Hofmann and H. Kirmreuther, *Ber.*, **42**, 4856 (1909).

Trityl fluoroborate has been prepared by Seel[11] from trityl chloride or tritanol and preformed acetyl fluoroborate in chloroform or sulfur dioxide, followed by ether precipitation, or from the chloride with equivalent amounts of acetyl fluoride and boron trifluoride on similar work-up. These related methods give good yields but are inconvenient to use routinely, primarily because of difficulties involved in the preparation of the acetyl fluoride and acetyl fluoroborate reactants. Witschonke and Kraus[12] have employed addition of boron trifluoride to trityl fluoride in benzene for the preparation of the fluoroborate salt but the properties reported for their trityl fluoride and fluoroborate products are probably indicative of the presence of impurities. Similar difficulty in the preparation of pure trityl fluoride has been encountered by others.[5c,13] As neither method provides a convenient route to this salt from readily available reactants, attempts were made to adapt the excess acetic anhydride method to the preparation of trityl fluoroborate. Triphenylcarbinol and 48% fluoroboric acid in acetic anhydride produce trityl fluoroborate but due to its greater solubility, compared with trityl perchlorate, direct separation of the product may not be effected by the use of excess acetic anhydride, and only moderate yields may be realized by addition of large volumes of dry ether. However, conduct of the reaction of tritanol with 48% fluoroboric acid in excess propionic anhydride furnishes directly on cooling yellow crystalline trityl fluoroborate in 95% yield. Trityl fluoroborate prepared by this extremely convenient procedure is very satisfactory for use in hydride ion exchange reactions, and has been used to prepare fluoroborate salts of a number of different types of aromatic carbonium ions.

When first prepared both of these trityl salts are brilliant yellow to orange compounds, depending on crystal size, and both contain traces of acid anhydride solvent, which does not interfere with the hydride ion exchange reaction but may be removed almost completely by trituration with dry ether. Recrystallization of both salts may be effected from minimum quantities of acetonitrile, but recoveries are low unless the mother liquor is recycled. In most organic solvents trityl fluoroborate is appreciably more soluble than trityl perchlorate. Trityl perchlorate keeps well in the dark at deep-freeze temperatures but darkens on exposure to light; the causative factors and the course of this decomposition are not fully known but low yields of 9-phenylfluorene have been isolated from darkened samples.[14] Trityl fluoroborate is much more stable and, once dried, may be stored in a desiccator without protection from light. This increased stability, coupled with the explosive nature of the perchlorate salts of trityl and tropenium ions (particularly when complexed with metal carbonyls[6,7a]), makes trityl fluoroborate the preferred compound for the preparation of aromatic carbonium ion salts by the hydride ion exchange reaction.

For routine preparations it is not necessary to isolate the trityl salt before conducting the hydride ion exchange reaction. For example, tropenium fluoroborate may be prepared in quantity and in good yield (89%) from triphenylcarbinol, 48% fluoroboric acid and cycloheptatriene in essentially a single step by adding cycloheptatriene to the yellow solution of triphenylcarbinol and fluoroboric acid in acetic anhydride until the color is discharged and then flooding with ether to effect separation of the product. Use of acetic, rather than propionic, anhydride in this sequence avoids separation of the trityl fluoroborate and thereby enables rapid and complete hydride ion abstraction on addition of the cycloheptatriene. Caution should be used in extending this simplified procedure to the preparation of tropenium perchlorate as darkened samples result, and impurities are known to increase the shock sensitivity of this explosive product.

Impurities in the triphenylcarbinol reactant markedly affect the color and the stability of the trityl perchlorate or fluoroborate produced by the above methods. Commercially available samples of triphenylcarbinol vary in color from white to yellow and it has been found that only white samples that give colorless solutions in the acid anhydride furnish products with good color and stability. The yellow impurities in commercial triphenylcarbinol usually can be removed by chromatography over alumina using 25% benzene-75% pentane as eluant and subsequent evaporative recrystallization from acetone or benzene. Satisfactory triphenylcarbinol may also be synthesized by a modification of the standard method of preparation of trityl chloride[15] as described in the Experimental.

EXPERIMENTAL

Triphenylcarbinol. The procedure of Hauser and Hudson[15] for the synthesis of trityl chloride was modified and the work-up of the reaction mixture altered so as to effect hydrolysis to the carbinol. Pure white, commercially sublimed aluminum chloride (Baker and Adamson; 425 g., 3.19 moles) was placed in a 5-l. three-necked flask equipped with a mechanical stirrer, a large Allihn condenser, and a 500-ml.

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[11] F. Seel, *Z. anorg. allgem. Chem.*, **250**, 331 (1943).

[12] C. R. Witschonke and C. A. Kraus, *J. Am. Chem. Soc.*, **69**, 2472 (1947).

[13] C. G. Swain and R. B. Mosely, *J. Am. Chem. Soc.*, **77**, 3727 (1955).

[14] On the other hand, it has been reported that surface darkening of trityl perchlorate crystals does not alter their X-ray pattern nor affect conductivity of their solutions (private communication from N. N. Lichtin, Boston University).

[15] C. R. Hauser and R. E. Hudson, Jr., *Org. Syntheses*, **Coll. Vol. III**, 842 (1955).

pressure-equalizing dropping funnel, and thiophene-free benzene (Baker and Adamson Reagent Grade; 1.30 l., 14.6 moles) added with stirring and external cooling in an ice bath. A solution of carbon tetrachloride (Baker Analyzed; 335 ml., 3.48 moles) in benzene (0.50 l., 6.63 moles) was added with continued stirring and ice bath cooling over the period of about 90 min.; adequate cooling must be used to moderate the quite exothermic reaction. Stirring of the dark red reaction mixture was continued for 30 min. in the ice bath and for about 8 hr. at room temperature. The reaction mixture was poured into an enamel bucket half-filled with chopped ice and the bucket heated on a steam cone until all of the red color of the aluminum chloride complex had disappeared. The separated benzene layer was washed thoroughly several times with water and twice with dilute sodium hydroxide, concentrated until almost all solvent had been removed, and allowed to cool to room temperature before placing in a refrigerator to crystallize. Separation of the successive crops by concentration of mother liquors and recrystallization from the recovered benzene by the usual cascade procedure gave four crops of triphenylcarbinol: (i) 249 g., white, m.p. 162.5°; (ii) 243 g., very slightly yellow, m.p. 161.5–162.5°; (iii) 118 g., tan, m.p. 159.5–161.5°; (iv) 34 g., brown, m.p. 152–158°; total yield, 644 g., 77%. Material from the first three crops is satisfactory for the preparation of trityl perchlorate or fluoroborate.

Triphenylmethyl perchlorate. Triphenylcarbinol (20.0 g., 0.077 mole) was dissolved in acetic anhydride (Mallinckrodt Reagent Grade; 225 ml., 2.38 moles) in a 500-ml. round bottomed flask fitted with a drying tube by warming on a steam cone. After cooling to room temperature or slightly below, 71% perchloric acid (Baker and Adamson Reagent Grade; 15 ml., 0.18 mole) was added in portions (0.5 ml.) with cooling at such a rate that the temperature was maintained at or slightly below room temperature to avoid formation of a darkened product; cooling during addition of the first third of the perchloric acid is done best under a stream of tap water to avoid cocrystallization of triphenylcarbinol and trityl perchlorate, after which an ice bath may be used. Separation of the perchlorate salt began during addition of the first few portions of perchloric acid and was completed, after all of the perchloric acid had been added, by cooling in an ice bath for at least 30 min. As moisture in the air rapidly hydrolyzes the product on simple suction filtration, removal of the mother liquor is effected best by use of a large dropper. The moist crystalline residue was rinsed with dry ether (5 × 25 ml.), the ether rinses removed by a dropper, and the yellow crystals of trityl perchlorate dried in the flask by evacuation before transferral to a tightly stoppered amber bottle for storage in a deep-freeze refrigerator; yield, 85% (22.5 g.). Cold, dry ethyl acetate or acetonitrile, followed by dry pentane, also may be used for rinsing without appreciable decrease in yield. The product contains a trace of acetic anhydride impurity, which does not interfere with its use in hydride ion exchange reactions, and may be removed by recrystallization from a minimum volume of hot, dry acetonitrile. Recovery of trityl perchlorate as yellow prisms, m.p. 143° (lit.,[10] m.p. 143–144°), was only 40–50% but may be increased by reuse of the mother liquor as solvent for recrystallization of successive portions. Somewhat larger proportions of the acetic anhydride and perchloric acid reactants may be used to lessen the possibility of cocrystallization of triphenylcarbinol and trityl perchlorate during the reaction; triphenylcarbinol (1.0 g., 0.0038 mole), acetic anhydride (15 ml., 0.16 mole), and 71% perchloric acid (1.25 ml., 0.015 mole) by the above procedure gave a yield of 76% (1.0 g.), and cooling of the mother liquor in a deep-freeze refrigerator furnished an additional 16% (0.21 g.).

A dry solid sample of trityl perchlorate (*ca.* 2 g.) in a stoppered flask exposed to ordinary overhead fluorescent lights for about 2 weeks gradually darkened to a deep red-purple color. The solution resulting from partial dissolution of this darkened sample in acetonitrile (*ca.* 4 ml.) and treatment with pentane (*ca.* 100 ml.) was decanted and evaporated to dryness. Chromatography of a pentane solution of the residue on alumina using pentane as a developer gave as the first fraction, on evaporation, a colorless crystalline residue (85 mg., *ca.* 6%) of 9-phenylfluorene, m.p. 146–146.5° after three recrystallizations from pentane (lit.,[16] m.p. 147–148°); $\lambda_{\max}^{CH_3CN}$, 258(sh), 265, 275(sh), 292, and 303.5 mμ, virtually identical with that reported[17] for 9-phenylfluorene in ethanol. Other materials from the chromatogram were isolated in quantities too small to identify.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.17; H, 5.82. Found: C, 93.85; H, 5.89.

Triphenylmethyl fluoroborate. In a 1-l. round bottomed flask equipped with a drying tube triphenylcarbinol (45 g., 0.17 mole) was dissolved in propionic anhydride (Distillation Products White Label Grade, redistilled; 450 ml., 3.49 moles) by warming on a steam cone. After cooling to about 20° under a water tap, 48% fluoroboric acid (Harshaw Chemical Co.; 45 ml., 0.38 mole) was added in small portions (*ca.* 0.5 ml.) with swirling and cooling under a water tap so as to maintain temperature at 15–25°; excessive heating or excessive cooling (induces cocrystallization of triphenylcarbinol) must be avoided to obtain a satisfactory yield of pure product. Separation of yellow crystals of trityl fluoroborate began well before an equivalent of the acid had been added and was completed, after the remaining acid had been added, by cooling in an ice bath for about 30 min. The bulk of the supernatant liquid was removed by decantation and discarded, as little trityl fluoroborate is recoverable from this mother liquor. Residual amounts of solvent were removed by a large dropper and the mass of crystals triturated with portions of cold, dry ether (25 ml.) until the washings, also removed by a dropper, were colorless (*ca.* 5 washings); prolonged contact with ether should be avoided, as trityl fluoroborate (or perchlorate) slowly abstracts hydride ion from ether to produce triphenylmethane. Rinsing by cold, dry ethyl acetate followed by dry pentane, may also be used, but with slight decrease in yield. Vacuum drying of the moist residue in the flask afforded yellow crystals of trityl fluoroborate (54 g., 95%) suitable for use in hydride ion exchange reactions. Removal of residual traces of propionic anhydride may be effected by recrystallization from a minimum volume of hot, dry acetonitrile with only low recovery (*ca.* 25%) unless a recycling technique is employed; use of a small volume of solvent, removal of the hot solution by a dropper, cooling to effect crystallization, and continued reuse of the saturated mother liquor for recrystallization of successive portions gave greatly increased recovery; yellow prisms, m.p. *ca.* 200° dec.[18] (lit., m.p. 215° dec.,[11] m.p. 195–196°[12]). Recrystallized trityl fluoroborate may be stored in a tightly stoppered bottle or in a desiccator over a good desiccant at room temperature and exposed to light without discoloration or decomposition for a period of at least several months.

Tropenium fluoroborate by in situ technique. Triphenylcarbinol (40 g., 0.165 mole) was dissolved in acetic anhydride (400 ml., 4.23 moles) by heating on a steam cone in a 1-l. round bottomed flask. After cooling to room temperature, 48% fluoroboric acid (25 ml., 0.21 mole) was added

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(16) C. K. Ingold and J. A. Jessop, *J. Chem. Soc.*, 708 (1930).

(17) R. N. Jones, *J. Am. Chem. Soc.*, **67**, 2021 (1945).

(18) Trityl fluoroborate shows no real melting point but decomposition with blackening and gas evolution usually begins around 200°; a sample recrystallized from propionic anhydride showed the highest initial decomposition range, 207–210°. The melting point of 215° dec. reported by Seel[11] is probably somewhat too high, as the melting point given for triphenyl carbinol in the same paper is at least 5° higher than any found in the literature or in the present work.

in portions with external cooling by cold water to maintain this temperature, and then cycloheptatriene (91% cycloheptatriene-7% toluene sample, generously supplied by the Shell Chemical Co.) added with swirling to the solution in an ice bath until the characteristic yellow color of trityl carbonium ion had vanished and precipitation of tropenium fluoroborate had commenced. Dry ether (600 ml.) was added to precipitate the remainder of the salt, and the white microcrystalline product filtered and washed with ether; yield of tropenium fluoroborate, 89% (23.5 g.), m.p. *ca.* 210° dec.,[19] $\lambda_{max}^{96\%\ H_2SO_4}$ 273.5 mμ (ϵ 4320) (lit.[5a]: m.p. >210° dec., $\lambda_{max}^{96\%\ H_2SO_4}$ 273.5 mμ (ϵ 4350)).

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UNIVERSITY OF WASHINGTON
SEATTLE 5, WASH.

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[19] Tropenium fluoroborate also does not show a definite melting point; darkening begins at about 210° and continues to about 260-270° where the last trace of crystal faces disappears and only a crumbled darkened powder remains.

Triphenylmethyl Isothiocyanate

ANTONIO ILICETO, ANTONINO FAVA,
AND UGO MAZZUCCATO

Received January 15, 1960

This report deals with the structure of the product (I) m.p. 138-138.5°, which is obtained in the reaction of triphenylmethyl (trityl) halides (chloride or bromide) with alkali thiocyanates[1-3] or thiocyanic acid.[4] This compound is also referred to in the recent literature[2,5] as trityl thiocyanate. Experimental evidence obtained by us shows that the compound is trityl isothiocyanate.

The infrared absorption spectrum of I shows a complex band with a maximum at 2046 cm.$^{-1}$ (chloroform). Position, intensity, and form of the band are characteristic of isothiocyanates, and not of thiocyanates which show a weaker (by a factor of 10) sharp absorption band around 2150 cm.$^{-1}$ (These two bands have been ascribed to the asymmetric stretching vibration of the isothiocyano- and thiocyano- groups respectively.)[6]

Elbs reports that I can be distilled at high temperature without undergoing any change.[1] Its high thermal stability has been confirmed in an experiment, in which I was heated at 150° for two hours and was recovered unaltered. If I were a thiocyanate, one would expect it to isomerize readily under these conditions. This prediction is based upon the consideration of the thermal isomerization rate of arylmethyl thiocyanates: While benzyl thiocyanate is known to isomerize with great difficulty (repeated distillation at 250°),[7] benzhydryl thiocyanate isomerizes at a measurable rate at 70° (half-time, sixty-six hours in methyl ethyl ketone) and its 4-methyl derivative isomerizes with greater ease (half-time four hours under the same conditions).[8] This and other ancillary evidence (solvent and salt effects) all showing that the isomerization reaction proceeds through an electron deficient transition state, point out that the isomerization is facilitated by increasing the ability of the organic substrate to support a positive charge. The inference therefore is that trityl thiocyanate would isomerize very rapidly. The fact that upon heating, I remains unaltered indicates that it already is an isothiocyanate.

Thioureas can be obtained by the reaction of I with amines. Thus, allylamine reacts with I yielding an adduct which has been proved to be 1-trityl-3-allylthiourea.

Assumption that I is a thiocyanate has led in the past to some misunderstanding about its reactivity toward amines. Such is the case of Swain and Dittmer concerning the 'aminolysis' of I.[5] These workers report that, while aniline rather rapidly reacts with I giving the quaternary ammonium thiocyanate, no reaction is observed with *n*-butylamine, even after months.[9] It has been presently established that *n*-butylamine reacts readily with I, both in the pure state and in cyclohexane solution, to give an adduct which, while not showing any reaction of thiocyanate ion, appears to be 1-trityl-3-*n*-butylthiourea.

The above evidence points out the isothiocyanate structure of I. It must be emphasized, however, that owing to its organic residue, I is an isothiocyanate of a particular nature. The peculiarities of its chemical behavior arise from the stability of the trityl carbonium ion and the consequent cleavage, contrary to most isothiocyanates, of the alkyl carbon-to-nitrogen bond, (1):[10]

$$(C_6H_5)_3C{-}NCS \rightleftharpoons (C_6H_5)_3C^+NCS^- \rightleftharpoons (C_6H_5)_3C^+ + NCS^- \quad (1)$$

Because of this, the reaction of I with a nucleophile may frequently lead to displacement of the thiocyanate ion. In such cases, the familiar reactions of isothiocyanates with nucleophiles (arising from attack on the carbon atom of the —N=C=S group) may be totally absent.

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[1] K. Elbs, *Ber.* **17**, 700 (1884).

[2] C. G. Swain, C. B. Scott, and R. H. Lohmann, *J. Am. Chem. Soc.*, **75**, 136 (1953).

[3] H. Bredereck and E. Reif, *Ber.*, **81**, 426 (1948).

[4] E. Bilmann and N. V. Due, *Bull. Soc. Chim.*, [4], **35**, 384 (1929).

[5] C. G. Swain and D. C. Dittmer, *J. Am. Chem. Soc.*, **77**, 3924 (1955).

[6] For a detailed discussion of the infrared spectra of I and similar isothiocyanates see: U. Mazzuccato, A. Foffani, A. Iliceto, and G. Svegliado; paper presented at the meeting of European Molecular Spectroscopists, Bologna (Italy) Sept. 7-12 (1959).

[7] H. Hennicke, *Ann.*, **344**, 24 (1906).

[8] A. Iliceto, A. Fava, and U. Mazzuccato, *Tetrahedron Letters*, No. 11, 27 (1960).

[9] Swain and Dittmer's statement as to the unreactivity of I towards *n*-butylamine was based solely on the lack of formation of thiocyanate ions.[5]

[10] As expected, the cleavage occurs unimolecularly: This is shown by the solvolysis of I,[2] and by the kinetics of the isotopic exchange between I and labeled thiocyanate ions which is first order in I and zero order in SCN$^-$ (A. Iliceto, A. Fava, and S. Bresadola, to be published).

To put it generally, the outcome of the reaction of I with a nucleophile, N, will ultimately depend upon the competition between displacement, (2), and attack on the isothiocyanate carbon atom, (3):

$$(C_6H_5)_3C^+ + N \longrightarrow \text{products} \qquad (2)$$

$$(C_6H_5)_3C—N=C=S + N \longrightarrow \text{products} \qquad (3)$$

Which course a particular reaction will take depends, in a given medium, on the nature of the nucleophile and, for a given nucleophile, on the reaction medium. (Displacement is expected to be favored in the more polar solvents and in the reaction with the weaker nucleophiles.)

This situation is well illustrated by the reaction of I with different amines in different media: In cyclohexane, *n*-butylamine gives the corresponding thiourea exclusively, while aniline although reacting very slowly, gives displacement of thiocyanate ion. In the absence of solvent, the reaction pattern is not altered, except that the reaction with aniline appears to be considerably accelerated. These findings are consistent with the high nucleophilicity of *n*-butylamine compared with aniline, and the low ionizing power of the media. The high reactivity, towards displacement, of aniline in pure aniline, can probably be ascribed to electrophilic catalysis (due to the relatively high acidity of aniline). On the other hand, the reaction course with *n*-butylamine may be notably altered in a solvent of high ionizing power, such as acetonitrile: in this medium, besides the thiourea, a sizeable amount of ammonium thiocyanate is also formed. Thus the more polar solvent favors the displacement reaction which occurs by way of a rate determining ionization.

In the light of these observations it is not surprising that some aspects of the chemical behavior of I have deceived earlier workers.[11]

EXPERIMENTAL

Solvents and chemicals were commercial reagent grade. Trityl chloride was recrystallized before use,[12] m.p. 111–112°.

Infrared spectra. A Perkin-Elmer double beam Model 21 instrument with sodium chloride optics was used. The solvent was carbon tetrachloride.

Sulfur analysis in the adducts of I *with amines.* To the extent that amines react with I giving either displacement or addition to the carbon-nitrogen double bond, sulfur in the reaction product will either be as thiocyanate ion or thiourea. The adducts were analyzed for thiocyanate ion by exaustively extracting their benzene solution with dilute aqueous alkali and titrating the acidified aqueous extract with standard bromate,[13] using naphthoflavone as end point indicator. Thiourea-type sulfur was determined by weighing silver sulfide precipitated from the ethanolic solution of the adducts by means of ammoniacal silver nitrate.[11]

Triphenylmethyl isothiocyanate (I). To a solution of 2.78 g. (0.01 mole) of trityl chloride in 10 ml. of acetone was added a solution of 1.2 g. (0.012 mole) of potassium thiocyanate in 30 ml. of the same solvent. The mixture, after 4 hr. at room temperature was filtered, evaporated to 8 ml. *in vacuo* and cooled to 0° for a few hours. Two and one half grams of colorless crystals, m.p. 136–138°, separated. Additional product (0.2 g.) was recovered by diluting the mother liquor to 50 ml. with water, and recrystallizing the precipitate from acetone; total yield, 90%; m.p. 138–138.5° after recrystallization from acetone. The ultraviolet spectrum of I is characterized by an absorption band with maximum at 254 mμ; ϵ_{max} 2800.[15]

In an experiment, I was heated at 150° for 2 hr. After this treatment neither its melting point (also in mixture with untreated I) nor its infrared spectrum showed any change.

I reacts with allylamine (for reaction conditions see below, under "reaction of I with *n*-butylamine in cyclohexane") to give 1-trityl-3-allylthiourea, m.p. 177–177.5°. This has been compared and shown to be identical (mixed melting point and infrared spectrum) with a sample prepared from tritylamine and allyl thiocyanate.[5]

N-n-butyltritylamine was obtained from trityl chloride and *n*-butylamine (five-fold excess). After recrystallization from ethanol it melted at 52.5–53.5°.

Anal. Calcd. for $C_{23}H_{25}N$: C, 87.57; H, 7.99; N, 4.44. Found: C, 87.77; H, 7.91; N, 4.40.

N-n-butyltritylamine hydrochloride was obtained by bubbling dry hydrochloric acid into a benzene solution of the amine, m.p. 166–167°.

Anal. Calcd. for $C_{23}H_{26}NCl$: N, 3.98; Cl, 10.07. Found: N, 3.95; Cl, 10.21.

Reactions of I *with n-butylamine: 1-trityl-3-n-butylthiourea.* (a) *In cyclohexane.* The amine (0.146 g., 2.0 mmoles) was treated with I (0.301 g., 1.0 mmole) dissolved in cyclohexane (10 ml.). After filtration and washing with petroleum ether (b.p. 40–60°), an adduct was obtained, m.p. 132–134° (0.355 g., 95% yield).

(b) *Without solvent.* In 1 ml. of amine 0.301 g. (1.0 mmole) of I was dissolved and left at room temperature for 12 hr. Evaporation to dryness gave a quantitative yield of an adduct, m.p. 132.5–133.5°.

Both raw materials obtained under (a) and (b) above, were shown not to contain any appreciable amount of ionizable thiocyanate. Two recrystallizations from acetone gave 1-trityl-3-*n*-butylthiourea m.p. 134–134.5°.

Anal. Calcd. for $C_{24}H_{26}N_2S$: C, 76.95; H, 7.00; N, 7.48; S, 8.56 Found: C, 77.36; H, 7.13; N, 7.25; S, 8.44. Analysis of the thioureic sulfur gave 8.49%.

(c) *In acetonitrile.* A solution of 0.301 g. (1.0 mmole) and 0.146 g. (2.0 mmoles) of I in 4 ml. of acetonitrile was heated at 60° for 1 hr. Thereafter, aliquots of the solution were titrated for thiocyanic and thioureic sulfur giving 20% and 78% of the total sulfur respectively. The remaining solution was added to dilute aqueous alkali and benzene. The benzene layer was evaporated to dryness *in vacuo* and the residue extracted with cyclohexane. The solid residue consisted of pure 1-trityl-3-*n*-butylthiourea. From the cyclo-

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(11) H. L. Wheeler, *Am. Chem. Jour.*, **26**, 345 (1901).

(12) C. R. Hanser and B. E. Hudson, Jr., *Org. Syntheses*, Coll. Vol. III, 846 (1955).

(13) F. P. Treadwell and C. Mayr, *Zeit. anorg. Chem.*, **92**, 127 (1915).

(14) H. Salkowski, *Ber.*, **26**, 2498 (1893); *Houben-Weyl, Methoden der Organishen Chemie*, George Thieme, Stuttgart (1953) Band II, 599; G. Losco and C. A. Peri, *Chimica Industria*, **33**, 557 (1951).

(15) The ultraviolet spectrum of I could support the view that I is an isothiocyanate, as can be seen from the close similarity with the spectra of benzyl and benzhydryl isothiocyanates. Like I, the latter show an absorption maximum in the same region with approximately the same intensity. Benzyl and benzhydryl thiocyanates, on the other hand, show, in that region, absorption of lower intensity without any well defined maximum.

hexane solution N-n-butyltritylamine hydrochloride was precipitated by bubbling in dry hydrochloric acid. After washing with boiling acetone the melting point was 165–166°, undepressed on admixture with an authentic sample.

Reaction of I with aniline. (a) *In cyclohexane.* In 5 ml. of cyclohexane containing 0.093 g. (1.0 mmole) of aniline, 0.150 g. (0.5 mmole) of I was dissolved, sealed in a vial and heated at 80° for 5 hr. After this time the solution showed a slight cloudiness which disappeared on extraction with water. The water layer titrated for thiocyanate ion accounted for 2.8% of the total sulfur. No thioureic sulfur was detected in the cyclohexane layer. This, evaporated to dryness, left a residue which, crystallized form acetonitrile, yielded I, m.p. 136–137°. Accounting for the solubility of I in acetonitrile, 93% recovery of unchanged I was obtained.

(b) *Without solvent.* In 1 ml. of aniline 0.301 g. (1.0 mmole) of I was dissolved under gentle heating. After a few hours at room temperature, the excess aniline was removed *in vacuo.* From the residue taken up in ethanol, N-phenyltritylamine (85%) was crystallized, m.p. 149–150° (lit.,[16] m.p. 149–150°).

CHEMICAL INSTITUTES OF THE FACULTY OF SCIENCE
UNIVERSITIES OF PADOVA AND CAMERINO
VIA LOREDAN 6, PADOVA, ITALY

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[16] M. Gomberg, *Ber.*, **35**, 1829 (1902).

Reaction of Salts of Organophosphorus Acids with Isocyanates[1]

ROBERT B. FOX AND WILLIAM J. BAILEY

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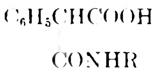
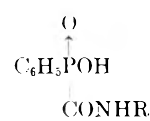
A general analogy in reactivity may be drawn between the α-hydrogen atom of a carboxylic acid and the P-hydrogen atom of a monobasic phosphinic acid, RP(O)H(OH). Reactions involving the carboxyl group and isocyanates are, of course, well known. In addition, Blicke and Zinnes[2] have shown that a carboxylic acid possessing an activated α-hydrogen, such as phenylacetic acid, forms an Ivanov reagent which can be condensed with phenyl isocyanate and the product hydrolyzed to yield N-phenyl phenylmalonamic acid (I). The base-catalyzed condensation involving the phosphorus-hydrogen group in dialkyl phosphonates with isocyanates to give dialkyl carbamoylphosphonates is also well established.[3]

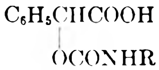
We have found that the tertiary amine salts of phenylphosphinic acid and mandelic acid undergo condensation with isocyanates in the presence of excess amine. Reaction takes place at the P—H and α-O—H groups, respectively, to give salts of the corresponding carbamoyl derivatives (II and III). Tertiary amine half-salts of phosphonic acids condense at the weakly acidic O—H group with the formation of salts of the half-carbamoyl esters (IV), products analogous to those formed from mandelic acid. The acids themselves are readily formed from the salts by treatment with excess mineral acid. These products are obtained in excellent yield, and salt formation therefore appears to be a suitable method for preventing an undesired reaction between an acidic group and an isocyanate. In a single experiment, treatment of phenylphosphinic acid with excess isopropylmagnesium bromide, followed by reaction with phenyl isocyanate, gave a low yield of II after hydrolysis of the bromomagnesium salt. No further investigation of this reaction was carried out, but it is possible that a phosphorus-Ivanov reagent was formed as an intermediate prior to the addition of the isocyanate.


$\mathrm{C_6H_5}\underset{\mathrm{CONHR}}{\mathrm{C}}\mathrm{HCOOH}$

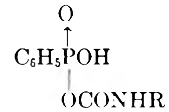
I


$\mathrm{C_6H_5}\overset{\mathrm{O}}{\overset{\uparrow}{\underset{\mathrm{CONHR}}{\mathrm{P}}}}\mathrm{OH}$

II


$\mathrm{C_6H_5}\underset{\mathrm{OCONHR}}{\underset{|}{\mathrm{C}}}\mathrm{HCOOH}$

III


$\mathrm{C_6H_5}\overset{\mathrm{O}}{\overset{\uparrow}{\underset{\mathrm{OCONHR}}{\underset{|}{\mathrm{P}}}}}\mathrm{OH}$

IV

Triethylamine appears to be the most useful salt-forming reagent in this reaction from the standpoint of ease of handling of the products; N-ethylmorpholine and diethylcyclohexylamine gave hygroscopic salts and no reaction involving the phosphorus compound was observed in the presence of pyridine or under Schotten-Baumann conditions. Anilinium and n-butylammonium salts gave only the urea derivatives. Benzene or other hydrocarbons in which the starting salts, prepared *in situ* by mixing equimolar amounts of acid and amine, are somewhat soluble are suitable solvents; an attempted reaction in acetone with phenylphosphinic acid was unsuccessful. Attempts to prepare the triethylamine salt of phenylphosphinic acid in carbon tetrachloride led to a vigorous reaction from which triethylamine hydrochloride precipitated. It is possible that the trichloromethyl derivative has been formed as appears to be the case with dialkyl phosphonates.[4]

EXPERIMENTAL[5]

Triethylammonium phenyl(phenylcarbamoyl)phosphinate. To a stirred two-phased mixture of 14.2 g. (0.1 mole) of phenylphosphinic acid, 50 ml. of triethylamine, and 50 ml. of benzene was added 13.1 g. (0.11 mole) of phenyl isocyanate over a period of 20 min. During the addition, the temperature of the mixture rose to 55° since no external cooling was used. After being stirred for an additional 45 min., the slurry was filtered and the precipitate washed with ether and petroleum ether to yield 34 g. (96%) of crude salt. Recrystallization from hot 2:1 acetone-chloroform solution gave purified material, m.p. 165–167° dec.

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[1] Based on a portion of the doctoral thesis submitted to the University of Maryland in June 1959 by Robert B. Fox; presented in part at the 130th meeting of the American Chemical Society at Atlantic City, N. J., September 1956, Abstracts p. 50–0.

[2] F. F. Blicke and H. Zinnes, *J. Am. Chem. Soc.*, **77**, 4849 (1955).

[3] (a) R. B. Fox and D. L. Venezky, *J. Am. Chem. Soc.*, **78**, 1661 (1956). (b) A. N. Pudovik and A. V. Kuznetsova, *Zhur. Obshcheĭ Khim.* **25**, 1369 (1955). (c) A. N. Pudovik, I. V. Konovalova, and R. E. Krivonosova, *Zhur. Obshcheĭ Khim.*, **26**, 3110 (1956). (d) E. C. Ladd and M. O. Harvey, Canadian Patent **509,034** (1955).

[4] F. R. Atherton and A. R. Todd, *J. Chem. Soc.*, 674 (1947).

[5] All melting points were taken in sealed capillary tubes and are corrected; those accompanied by decomposition gave a gas, but sintering did not take place.

Anal. Calcd. for $C_{19}H_{27}N_2O_3P$: C, 62.96; H, 7.51; P, 8.54. Found: C, 63.31; H, 7.75; P, 8.36.

Triethylammonium phenyl(p-chlorophenylcarbamoyl)phosphinate, m.p. 170–170.5° dec. (from ethanol) was prepared similarly in a 78% yield.

Anal. Calcd. for $C_{19}H_{26}ClN_2O_3P$: C, 57.45; H, 6.60; P, 7.80. Found: C, 57.50; H, 7.13; P, 7.76.

A similar reaction carried out in acetone with phenyl isocyanate gave no precipitate even after being heated under reflux for 2 hr. Concentration of the solution gave an oil which on treatment with water deposited a nearly theoretical yield of diphenylurea. The same result was obtained with pyridine as the base in benzene or by shaking phenyl isocyanate with sodium phenylphosphinate in 10% aqueous sodium hydroxide. The aniline and *n*-butylamine salts without excess amine gave only diphenylurea and *N-n*-butyl-*N'*-phenylurea, respectively.

Phenyl(phenylcarbamoyl)phosphinic acid (II. R = C_6H_5). A filtered solution of 34.7 g. of the crude triethylamine salt of phenyl(phenylcarbamoyl)phosphinic acid in 75 ml. of water was treated with 10.3 ml. of concd. hydrochloric acid. The resulting oil solidified to give 22.4 g. (90%) of the acid; two recrystallizations from hot water afforded colorless needles, m.p. 153.0–153.5° dec.

Anal. Calcd. for $C_{13}H_{12}NO_3P$: C, 59.76; H, 4.64; P, 11.9; neut. equiv., 261.2. Found: C, 60.11; H, 5.42; P, 12.4; neut. equiv., 260.5.

Phenyl(p-chlorophenylcarbamoyl)phosphinic acid, m.p. 161.5–162° dec. (from water, acetone, or methanol) was also prepared in this way in 98% yield.

Anal. Calcd. for $C_{13}H_{11}ClNO_3P$: C, 52.81; H, 3.75; P, 10.5; neut. equiv., 295.7. Found: C, 52.99; H, 4.29; P, 10.4; neut. equiv., 297.4.

Phenyl(2,5-dichlorophenylcarbamoyl)phosphinic acid was prepared without isolation of the intermediate salt. 2,5-Dichlorophenyl isocyanate (9.4 g., 0.05 mole) was added rapidly to a stirred mixture of 7.1 g. (0.05 mole) of phenylphosphinic acid and 5.05 g. (0.05 mole) of triethylamine cooled in an ice bath. After 5 min. the cold reaction mass was taken up in 50 ml. of methanol and the resulting mixture was filtered; the filtrate was diluted with an equal volume of water and the aqueous solution was treated with an excess of concd. hydrochloric acid to precipitate 10.2 g. (62%) of the crude acid, m.p. 141–143°. Two recrystallizations from hot benzene gave analytically pure material, m.p. 153°.

Anal. Calcd. for $C_{13}H_{10}NO_3P$: neut. equiv., 330.1. Found: neut. equiv., 330.2, 329.0.

A filtered aqueous solution of the hygroscopic reaction mass formed from equimolar amounts of phenylphosphinic acid, triethylamine, and *n*-butyl isocyanate was treated with a large excess of hydrochloric acid to precipitate a 71% yield of crude *phenyl(n-butylcarbamoyl)phosphinic acid*. Several recrystallizations from acetone and, finally, one from water afforded a product melting at 95° followed by resolidification and remelting at 116°, which appeared to be the monohydrate of this acid.

Anal. Calcd. for $C_{11}H_{18}NO_4P$: C, 50.95; H, 6.23; neut. equiv., 259.3. Found: C, 50.84; H, 7.01; neut. equiv., 259.

Phenyl(phenylcarbamoyloxy)acetic acid (III. R = C_6H_5). A mixture of 4.56 g. (0.03 mole) of mandelic acid and 3.03 g. (0.03 mole) of triethylamine in 30 ml. of benzene at 30° was treated with 3.57 g. (0.03 mole) of phenyl isocyanate over a 5-min. period. After being heated under reflux for 2 hr., the clear solution was concentrated to give 7.5 g. (67%) of crude salt. This represented only the first crop of material deposited; no attempt at complete recovery was made since subsequent crops came down as oils. Repeated recrystallization of the salt afforded material melting at 122.5–123.5°. Treatment of a filtered hot aqueous solution of the crude salt with excess concd. hydrochloric acid precipitated the urethan of mandelic acid, m.p. 149.5–150.0° dec. (from benzene) (reported m.p. 147–149° dec.[6] and 150–152°[7]).

Anal. Calcd. for $C_{15}H_{13}NO_4$: neut. equiv., 271.2. Found: neut. equiv., 270.5.

Authentic mandelanilide, m.p. 149–150° (from diisopropyl ether), prepared directly from mandelic acid and phenyl isocyanate in the absence of base[6,8] greatly depresses the melting point of the above urethan.

Modified Ivanov reaction. To a solution of isopropylmagnesium bromide heated under reflux (prepared from 0.22 mole of magnesium and 0.26 mole of isopropyl bromide in 150 ml. of diethyl ether) was added 14.2 g. (0.10 mole) of phenylphosphinic acid in 150 ml. of benzene over a 55-min. period. The evolution of a gas was apparent, and near the end of the addition, a black semisolid mass began to form. After being stirred for 1 hr. at 59° the mixture was cooled and 11.9 g. (0.1 mole) of phenyl isocyanate was added rapidly; no gas formation or heat generation was observed during this addition. After the mixture was heated under reflux for 2 hr. and was allowed to stand overnight, the resulting gray solid was broken up and the mixture added to 300 ml. of 10% aqueous ammonium chloride. No products other than diphenylurea were isolated from the organic layer, but treatment of the aqueous phase with concd. hydrochloric acid precipitated 3.5 g. (13.5%) of an acid, m.p. 147–149° dec., which did not depress the melting point of the phenyl(phenylcarbamoyl)phosphinic acid described above.

Triethylammonium phenylcarbamoyl phenylphosphonate. At 25° (water bath) 6.55 g. (0.055 mole) of phenyl isocyanate was added in 15 min. to a slurry prepared from 5.05 g. (0.05 mole) of triethylamine and 7.9 g. (0.05 mole) of phenylphosphonic acid in 150 ml. of dry acetone. After the mixture had been stirred for 1 hr. at room temperature, the precipitate was removed by filtration and washed with ether to give 18.3 g. (97%) of the salt, m.p. 128.5–129.5° dec., without further purification.

Anal. Calcd. for $C_{19}H_{27}N_2O_4P$: C, 60.30; H, 7.18; N, 7.39; P, 8.19. Found: C, 60.29; H, 7.08; N, 7.36; P, 8.18.

When this reaction was carried out at 55°, gases absorbable by Ascarite were formed in an amount approaching the theoretical for carbon dioxide. The fact that sealed tubes containing the pure salt at room temperature developed pressure over a period of weeks indicated considerable instability.

By the above method were prepared samples of very hygroscopic and thermally unstable crude *triethylammonium n-butylcarbamoyl phenylphosphonate*, m.p. 87.5–89° dec. (from benzene) in 69% yield and *triethylammonium phenylcarbamoyl n-butylphosphonate*, m.p. 93–94° dec. in 61% yield.

Phenylcarbamoyl hydrogen phenylphosphonate (IV. R = C_6H_5). A solution of the triethylamine salt of phenylcarbamoyl hydrogen phenylphosphonate in dilute hydrochloric acid (neutral or alkaline solutions of this salt decompose fairly rapidly with the formation of insoluble material) was treated with concd. hydrochloric acid to precipitate a solid which after being washed with diethyl ether gave 13.1 g. of the crude acid, m.p. 71–72° dec. Recrystallization from cold aqueous acetone gave analytically pure material, m.p. 67.5° dec.; upon melting, this substance evolved a gas, resolidified, and then melted at 176–182°.

Anal. Calcd. for $C_{13}H_{12}NO_4P$: neut. equiv., 277.2. Found: neut. equiv., 276, 278 in 50% aqueous acetone.

A sample of this acid was heated at 150° and the evolved gases passed through Drierite. Only carbon dioxide was

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(6) E. Fischer and H. O. L. Fischer, *Ber.*, **47**, 779 (1914).

(7) H. Aspelund, *Acta Acad. Aboensis, Math. et Phys.* **12**, No. 5, 1 (1940).

(8) A. Haller, *Compt. rend.*, 121, 191 (1895).

shown to be present by the infrared spectrum of the gases. Recrystallization of the residue from isopropyl alcohol gave material having an infrared spectrum identical with that of dianilinium diphenylpyrophosphonate.[9]

Phenylcarbamoyl hydrogen n-butylphosphonate, m.p. 84–84.5° dec., neut. equiv., 257, 259 (calcd. 257.1), and *n-butylcarbamoyl hydrogen phenylphosphonate*, m.p. 52.5–55° dec., were prepared similarly.

NAVAL RESEARCH LABORATORY,
WASHINGTON, D. C.

UNIVERSITY OF MARYLAND,
COLLEGE PARK, MD.

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(9) R. B. Fox and W. J. Bailey, in press.

Reactions of Vanillin and Its Derived Compounds. XXIX.[1] 3,3′,4,4′-Tetrahydroxybenzil and Its Reduction

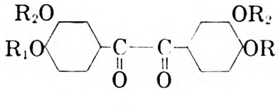
IRWIN A. PEARL, HORACE B. FABER, JR.,
AND WANER C. HOLMAN

Received February 25, 1960

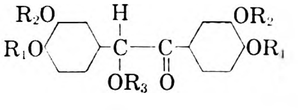
The need for 3,3′,4,4′-tetrahydroxybenzoin for testing in programs on the respiration and scab resistance of potatoes[2] led to a study of the preparation of this compound and other related products. Recent studies on vanillil and its reduction[3,4] indicated that the various monomolecular reduction products of vanillil could be prepared directly from vanillil by the use of various reducing systems. Accordingly, studies were made on the preparation of 3,3′,4,4′-tetrahydroxybenzil from vanillil and its use as a starting material for the preparation of its reduction products.

3,3′,4,4′-Tetrahydroxybenzil (I) was first prepared by Barger and Ewins[5] from piperil by treatment with phosphorus pentachloride followed by hydrolysis and more recently by Schales,[6] who treated 0.5 g. veratril (II) with 100 volumes of hydrobromic acid in acetic acid at 125–135°. The procedure of Schales was applied to vanillil (III) on a relatively large scale, but the melting points of the products obtained from several experiments varied somewhat and did not correspond with reported values for I. Vanillil was then demethylated with pyridine hydrochloride under conditions reported by Erdtman and Lindberg[7] and Hearon, Lackey, and Moyer[8] for the demethylation of conidendrin. Under these conditions the desired I was obtained in good yield. An attempt to demethylate vanillil with aluminum bromide under conditions employed for the production of protocatechualdehyde from vanillin[9] resulted in almost quantitative recovery of the starting material.

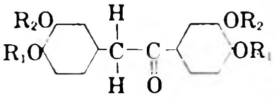
Reduction of I under conditions previously employed for the reduction of vanillil[4] and syringil[10] gave several of the monomolecular reduction products of I, but there appeared to be very little correlation between reduction of I and those of vanillil and syringil. The reduction products were characterized by means of their methyl ethers, acetates, and ultraviolet absorption spectra.



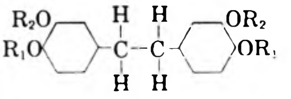
I. $R_1 = R_2 = H$
II. $R_1 = R_2 = CH_3$
III. $R_1 = H; R_2 = CH_3$
IV. $R_1 = R_2 = CH_3CO$



V. $R_1 = R_2 = R_3 = H$
VI. $R_1 = R_2 = CH_3; R_3 = H$
VII. $R_1 = R_2 = R_3 = CH_3CO$



VIII. $R_1 = R_2 = H$
IX. $R_1 = H; R_2 = CH_3$
X. $R_1 = R_2 = CH_3$
XI. $R_1 = CH_3CO; R_2 = CH_3$



XII. $R_1 = R_2 = H$
XIII. $R_1 = H; R_2 = CH_3$
XIV. $R_1 = R_2 = CH_3CO$

EXPERIMENTAL[11]

3,3′,4,4′-Tetrahydroxybenzil (I). A mixture of 50 g. of III[3] and 50 g. of freshly precipitated, dry pyridine hydrochloride in a 500-ml. flask fitted with an air condenser was heated to 160° until complete solution resulted. The temperature was raised to 190–200°, and gentle refluxing was maintained for 2 hr. The clear melt was dissolved in 800 ml. of hot (70°) water, and the resulting solution was heated to boiling and filtered. The filtrate was acidified with 6N hydrochloric acid and allowed to stand at 20° overnight. The resulting dark-colored crystalline precipitate was filtered and washed with a little cold water to yield 40 g. (78%) of crude I dihydrate. The dark crystals were recrystallized from water in the presence of decolorizing carbon and air dried to yield light orange needles of I dihydrate melting first at 125–130° with gas evolution, solidifying, and melting again at 231–234°. Boiling the dihydrate with benzene under reflux and a water-separatory head gave dehydrated crystals melting at 234–236°. Barger and Ewins[5] dried their product in an oven at 110° and obtained the anhydrous product. These authors reported the analysis of the dihydrate from water, but did not report its melting point. The ultraviolet ab-

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(1) For paper XXVIII of this series, see *J. Org. Chem.* **22**, 1266 (1957).

(2) L. A. Schaal and G. Johnson, *Phytopathology* **45**, 626 (1955).

(3) I. A. Pearl, *J. Am. Chem. Soc.* **74**, 4260 (1952).

(4) I. A. Pearl, *J. Am. Chem. Soc.* **74**, 4593 (1952).

(5) G. Barger and A. J. Ewins, *J. Chem. Soc.* **93**, 737 (1907).

(6) O. Schales, *Arch. Biochem. Biophys.* **34**, 56 (1951).

(7) H. Erdtman and B. Lindberg, *Acta Chem. Scand.* **3**, 982 (1949).

(8) W. M. Hearon, H. B. Lackey, and W. W. Moyer, *J. Am. Chem. Soc.* **73**, 4005 (1951).

(9) I. A. Pearl and D. L. Beyer, *J. Am. Chem. Soc.* **75**, 2630 (1953).

(10) I. A. Pearl, *J. Org. Chem.* **22**, 1229 (1957).

(11) All melting points are uncorrected. Ultraviolet spectral data are for solutions in 95% ethanol and were obtained by Mr. Lowell Sell. Analyses were performed by the Analytical Department of The Institute of Paper Chemistry and by Huffman Microanalytical Laboratories, Wheatridge, Colorado.

sorption spectrum was essentially identical with that reported earlier for III[12] and indicated the following maxima: λ_{max} 232 mμ, ϵ 21550; λ_{max} 289 mμ, ϵ 16300; λ_{max} 325 mμ, ϵ 18300.

A solution of 50 g. of III in 500 ml. of boiling glacial acetic acid was treated with 100 ml. of 48% hydrobromic acid, and the mixture was boiled under reflux for 3 hr. and allowed to cool. The reaction mixture was concentrated to one-half volume under reduced pressure, and the residue was diluted with 3 l. of water and allowed to stand overnight. The heavy precipitate was filtered, washed, and air dried to yield 44 g. of product as light yellow crystals. Recrystallization from water gave bright yellow crystals melting at 113° with gas evolution, solidifying, and remelting at 233–235°. Analysis indicated the monohydrate of I. The ultraviolet absorption spectrum was identical with that of the dihydrate.

Anal. Calcd. for $C_{14}H_{12}O_7$: C, 57.54; H, 4.14. Found: C, 57.25; H, 4.57.

Acetylation of either the monohydrate, the dihydrate, or the parent anhydrous I with acetic anhydride in pyridine, and recrystallization from ethanol gave yellow needles of 3,3′,4,4′-tetraacetoxybenzil (IV) melting at 133–134°: λ_{max} 268 mμ, ϵ 21000.

Anal. Calcd. for $C_{22}H_{18}O_{10}$: C, 59.73; H, 4.10. Found: C, 59.73; H, 4.15.

Methylation of any of the three forms of I with dimethyl sulfate and alkali and recrystallization of the product from glacial acetic acid yielded yellow crystals melting at 220–221° and not depressing a mixed melting point with authentic II.[4]

3,3′,4,4′-Tetrahydroxybenzoin (V). A solution of 5 g. of I dihydrate in 200 ml. of hot water was treated with 25 ml. of glacial acetic acid and 5 g. of granulated tin. The mixture was heated on the steam bath for 1.5 hr. and filtered. The precipitate was washed with hot water, and the combined filtrate and washings were concentrated under reduced pressure. After standing at room temperature, the solution deposited 1.2 g. of tan crystals which were recrystallized from water in the presence of decolorizing carbon to yield light tan needles of V hemihydrate melting at 186–188°. The ultraviolet absorption spectrum was identical with that of authentic veratroin (VI) and indicated the following maxima: λ_{max} 232 mμ, ϵ 19750; λ_{max} 281 mμ, ϵ 14780; λ_{max} 325 mμ, ϵ 17250.

Anal. Calcd. for $C_{14}H_{13}O_{6.5}$: C, 58.90; H, 4.46. Found: C, 58.92; H, 4.59.

Acetylation with acetic anhydride in pyridine yielded 3,3′,4,4′-tetrahydroxybenzoin pentaacetate (VII) as colorless needles from ethanol melting at 182–183°.

Anal. Calcd. for $C_{24}H_{22}O_{11}$: C, 59.26; H, 4.56. Found: C, 59.68; H, 4.32.

3,3′,4,4′-Tetrahydroxydeoxybenzoin (VIII). A solution of 5 g. of I dihydrate in 200 ml. of hot water was treated with 10 g. of granulated tin and then slowly with 10 ml. of concd. hydrochloric acid. The mixture was heated on the steam bath 1.5 hr. and filtered. The precipitate was washed with hot water, and the combined filtrate and washings were concentrated under reduced pressure. After standing several days at room temperature the solution deposited 2.2 g. of dark crystals which were recrystallized from water in the presence of decolorizing carbon to yield light tan crystals of VIII monohydrate melting at 196–198° and having the following maxima in its ultraviolet absorption spectrum: λ_{max} 231 mμ, ϵ 18800; λ_{max} 281 mμ, ϵ 11950; λ_{max} 310 mμ, ϵ 8720. The ultraviolet absorption spectrum was identical with that of deoxyvanilloin (IX).

Anal. Calcd. for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.59; H, 5.19.

Acetylation with acetic anhydride in pyridine yielded 3,3′,4,4′-tetraacetoxydeoxybenzoin (X) as light yellow needles from ethanol melting at 127–128° and having the following maximum in its ultraviolet absorption spectrum: λ_{max} 293 mμ, ϵ 26950. The spectrum was essentially identical with that of deoxyvanilloin diacetate (XI).

Anal. Calcd. for $C_{22}H_{20}O_9$: C, 61.68; H, 4.71. Found: C, 61.55; H, 4.74.

VIII was also prepared by reduction of I dihydrate with tin amalgam and hydrochloric acid[13] in either aqueous or dilute ethanolic solution.

3,3′,4,4′-Tetrahydroxybibenzyl (XII). A solution of 5 g. of I dihydrate in 200 ml. of hot water was treated with 10 g. of zinc dust and heated to boiling. The mixture was removed from the source of heat and treated portionwise with 40 ml. of concd. hydrochloric acid. The solution decolorized after the first addition. The mixture was allowed to stand 5 min. after the last addition and filtered hot. The zinc residue was washed with water, and the combined filtrate and washings were concentrated by distillation under reduced pressure. The concentrated solution deposited crystals upon standing at room temperature. The crystals were filtered and recrystallized from water to give 4.0 g. of XII as tan crystals melting at 151–152°. The ultraviolet absorption spectrum had a maximum at 283 mμ (ϵ 6750) and was essentially identical with that of bivanillyl (XIII) except for a slight maximum in the latter at 230 mμ.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.31; H, 6.15.

Acetylation and recrystallization from ethanol yielded 3,3′,4,4′-tetraacetoxybivanillyl (XIV) melting at 148–149° and having the following maxima in its ultraviolet absorption spectrum: λ_{max} 266 mμ, ϵ 1680; λ_{max} 272 mμ, 1660.

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.70; H, 5.33.

Unsuccessful reductions of I. Attempted reductions of I with zinc and ammonium chloride, aluminum and hydrochloric acid, aluminum amalgam and ammonium hydroxide, tin amalgam and hydrochloric acid, sodium borohydride, sodium trimethoxyborohydride in alkaline solution, sodium hydrosulfite in alkaline solution, zinc and sodium hydroxide, and Raney nickel alloy in sodium hydroxide solution under conditions reported previously[4,10,13] resulted in either the recovery of starting material or in the production of highly colored tarry materials from which no crystalline products could be isolated.

THE INSTITUTE OF PAPER CHEMISTRY
APPLETON, WIS.

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[12] I. A. Pearl and E. E. Dickey, *J. Am. Chem. Soc.* **74**, 614 (1952).

[13] I. A. Pearl and W. M. Dehn, *J. Am. Chem. Soc.* **60**, 57 (1938).

Decomposition of Acyl Nitrates. Reaction of Trifluoroacetic Anhydride with Nitric Acid

ROBERT BOSCHAN

Received January 29, 1960

A low yield of fluoropicrin (III) has been obtained from the reaction of trifluoroacetic anhydride (I) with nitric acid at 100°. The formation of this material very likely proceeds *via* the intermediate trifluoroacetyl nitrate (II), which decomposes as shown in a manner similar to that previously postulated in the conversion of alkyl chloroformates to nitrate esters[1] and of dialkyl carbamyl

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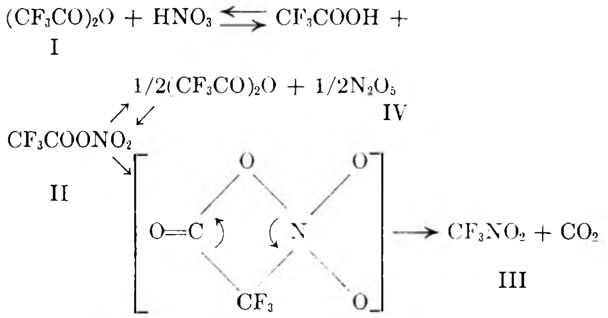
[1] R. Boschan, *J. Am. Chem. Soc.*, 81, 3341 (1959).



chlorides to nitramines[2] by treatment with silver nitrate. Probably the reason for the low yield of III is the reversible conversion to nitrogen pentoxide (IV). The formation of IV from I and nitric acid has been demonstrated previously[3]; IV would certainly decompose very rapidly at 100°, thus preventing the formation of III.

The reactions of perfluorobutyric anhydride and of perfluorosuccinic anhydride with nitric acid were tried, but in neither case was any nitro compound found in appreciable amount. Probably in these cases IV is formed and decomposes too rapidly to allow formation of nitro compounds. Neither of these anhydrides is completely miscible with nitric acid as is I, and this would doubtlessly affect the reversibility of the reaction in which IV is formed.

EXPERIMENTAL

Reaction of trifluoroacetic anhydride with nitric acid. A mixture of 21.0 g. (0.10 mole) of trifluoroacetic anhydride and 6.3 g. (4.20 cc., 0.10 mole) of 100% nitric acid was placed in a hydrogenation bomb liner and inserted in a stainless steel bomb. The heater was turned on, and in less than an hour the reaction mixture was up to 100°. The mixture was maintained at this temperature for about an additional 5.5 hr., and then was gradually allowed to cool to ambient temperature and allowed to remain overnight. The gas was bled into a standard nitrometer tube (240 cc.) and then into a liquid nitrogen trap. Fourteen fillings of the nitrometer tube (total 3360 cc.) were required to bleed all the gas from the bomb. The gases were passed through a molecular sieve vapor phase chromatography column which irreversibly removed carbon dioxide, nitrogen dioxide, and water. A pure sample of fluoropicrin was thus obtained and eluted from the column. Three 5-cc. aliquots of the original gas sample yielded sufficiently pure fluoropicrin to give a good infrared spectrum. The amount of helium (which had been used as carrier gas in the vapor phase chromatograph) and air in the gas sample were determined by mass spectrometry. The weight of the gas sample was measured by weighing the gas sample tube before and after evacuation. From these data it was calculated that 0.815 g. (7.09%) of pure fluoropicrin was obtained in the reaction.

The fluoropicrin was characterized by means of its infrared and mass spectra. The infrared spectrum showed the reported[4] asymmetrical stretch vibration peaks at 6.13 μ and 6.18 μ and the symmetrical stretch vibration peak at 7.78 μ. The entire infrared spectrum was similar to the reported[5] spectrum of 1-chloro-1,1,2,2-tetrafluoro-2-nitroethane. The mass spectrum showed the expected cracking pattern for a compound with the structure trifluoronitromethane.

CHEMISTRY DIVISION
U. S. NAVAL ORDNANCE TEST STATION
CHINA LAKE, CALIF.

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(2) W. P. Norris, *J. Am. Chem. Soc.*, **81**, 3346 (1959).

(3) J. H. Robson, *J. Am. Chem. Soc.*, **77**, 107 (1955).

(4) R. N. Haszeldine and J. Jander, *J. Chem. Soc.*, 4172 (1953).

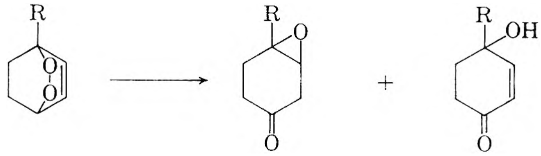
(5) R. N. Haszeldine, *J. Chem. Soc.*, 2525 (1953).

Pyrolysis of 9(11)-Dehydroergosterol Peroxide Acetate

WERNER BERGMANN[1] AND MARTIN B. MEYERS[2]

Received February 17, 1960

The thermal or base-catalyzed treatment of epidioxide rings attached to secondary-secondary or secondary-tertiary carbon atoms ordinarily gives rise to disproportionation into either or both a β,γ-epoxy ketone and/or a keto-allylic alcohol[3]:



Where the epidioxide ring is attached to two tertiary carbon atoms, as in ergosterol peroxide (I), there must be a rearrangement for disproportionation to take place. This is observed when I is refluxed in a hydrocarbon solvent at around 200°. Two major products are formed, ergost-22-ene-5,6α-epoxy-7-one-3β-ol (II) and ergosta-8,22-diene-5,6α-epoxy-3β,7α-diol (III), where the oxygen function has migrated from C_8 to C_7.[4] The assignment of the nuclear double bond to the Δ^8 position was made by oxidation of the 3-monoacetate of III to 3β-acetoxyergosta-8,22-diene-5,6α-epoxy-7-one (IV), which when treated with potassium iodide in glacial acetic acid gave the known 3β-acetoxyergosta-5,8,22-triene-7-one (V). It was thought that further support for the correctness of this assignment could be made by pyrolysis of 9(11)dehydroergosterol peroxide acetate (VI), which by proceeding in analogous manner to ergosterol peroxide (I) would produce the β,γ-epoxy ketone VII and VIII: Basic isomerization of VII should then lead to IV.

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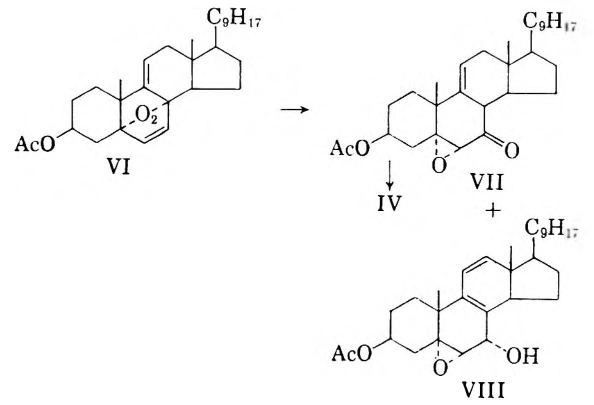
(1) Deceased.

(2) Central Research Laboratories, General Mills, Inc., 2010 East Hennepin Avenue, Minneapolis 13, Minnesota.

(3) (a) W. Bergmann and R. J. Conca, *J. Org. Chem.*, **18**, 1104 (1953); (b) E. J. Agnello, R. Pinson, Jr., and G. D. Laubach, *J. Am. Chem. Soc.*, **78**, 4756 (1956); (c) R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **72**, 339 (1950); (d) T. G. Halsall, W. J. Rodewald, and D. Willis, *Proc. Chem. Soc.*, **1958**, 231.

(4) W. Bergmann and M. B. Meyers, *Chem. & Ind.* (*London*), **1958**, 655; *Ann.*, **620**, 46 (1959).

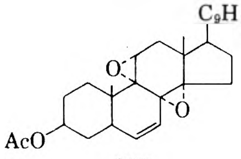


Under conditions sufficient to isomerize I, *i.e.*, one hour refluxing in decane-dodecane mixtures (b.p. 195–200°), VI was recovered unchanged, and prolonged reflux of VI in dodecane (b.p. 214°) in the presence of atmospheric oxygen gave only dark unpurifiable oils. The desired pyrolysis was successfully accomplished by refluxing VI in dodecane under nitrogen for periods of sixty to ninety minutes. Work up of the reaction mixture quickly demonstrated that VI behaves in a highly complex manner on thermal breakdown. On cooling there was deposited a crystalline solid (15–17% yield) (IX). If after filtering IX the mother liquors were allowed to stand three to four weeks, an oil was slowly deposited which amounted to 20–40% by weight of the starting VI. This oil exhibited hydroxyl absorption and a broad band at 5.78 μ in the infrared. Attempts to purify the oil by crystallization or chromatography were unsuccessful. The hydroxyl absorption in this mixture is possibly caused by tertiary hydroxyl groups, as the oil was unchanged after treatment with chromic acid–pyridine complex.

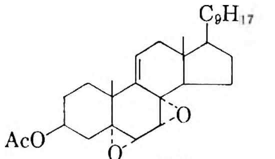
When, after having deposited all insoluble matter, the mother liquors were chromatographed on alumina, elution with 19:1 hexane-benzene yielded about 24% (by weight of starting material) of the deoxygenated 9(11)dehydroergosterol acetate (X). The only previously reported cases of thermal reversal of epidioxide formation have been in the polynuclear aromatic series where, for example, rubrene peroxide loses 80% of its oxygen on heating under vacuum.[5] No detectable amounts of ergosterol are produced on pyrolysis of I; therefore the formation of X must be taken as an indication of the great reluctance of VI to rearrange.

If *Florisil* were substituted for alumina as the absorbent for chromatography of the mother liquors, after the 9(11)dehydroergosterol acetate (X) had been removed, elution with 49:1 hexane-acetone produced a ketone (1.6% yield) which was assigned structure VII (3β-acetoxyergosta-9(11),-22-diene-5,6α-epoxy-7-one as it exhibited $\lambda_{\max}^{\text{KBr}}$ 5.86 μ (α,β-epoxy ketone) and 12.52 μ (epoxide).[6] Elution of VII from unneutralized alumina brought about isomerization of the β,γ-double bond and yielded a compound which was shown to be identical with IV and thus unambiguously establishing the location of the nuclear double bond in III at Δ^8. Continued elution of the Florisil column gave rise to very small amounts of other compounds with ketonic functions.

The compound IX, isolated by cooling of the pyrolysis mixture, showed in the infrared neither hydroxyl or carbonyl absorption other than the original acetate carbonyl but did possess two sharp bands of medium intensity at 5.94 and 6.06 μ, which were also found in the reduction products of IX. These bands were probably not caused by a conjugated dienoid system, as IX exhibited no noticeable absorption in the ultraviolet above 220 mμ. When IX was allowed to react with chromic acid–pyridine complex, starting material was recovered unchanged. Saponification of IX with methanolic potassium hydroxide gave the free alcohol XI which like IX had two bands of medium intensity at 5.89 and 6.02 μ in the infrared. Elemental analyses of IX and XI showed IX to be isomeric with the starting VI and this was supported by a micro-Rast molecular weight determination on IX. Acid treatment of IX gave rise to an unpurifiable hydroxy ketone. The acid sensitivity of IX combined with its stability towards basic reagents is strikingly similar to the properties which Agnello, Pinson, and Laubach[7] reported for 3β-acetoxyergosta-6,22-diene-8,14α:9,11α-diepoxide (XII). When XII was treated with hydrochloric acid in acetone, an amorphous product was obtained, $\lambda_{\max}$ 256 mμ. It therefore seems plausible that IX may have the diepoxide structure XIII:



XII



XIII

Although an intermediate diepoxide is not found on rearrangement of ergosterol peroxide (I) or its acetate, compounds with such structures have been observed in several other rearrangements of epidioxides.[8] The slowly precipitated oil obtained from the pyrolysis may arise from the thermal breakdown of IX, as the diepoxide pseudoascaridole

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(5) W. Bergmann and M. J. McLean, *Chem. Revs.*, **28**, 367 (1941).

(6) *Cf.*, F. Sallmann and C. Tamm, *Helv. Chim. Acta*, **39**, 1340 (1956); R. H. Bible, Jr., C. Placek, and R. D. Muir, *J. Org. Chem.*, **22**, 607 (1957).

(7) E. J. Agnello, R. Pinson, Jr., and G. D. Laubach, *J. Am. Chem. Soc.*, **78**, 4756 (1956).

(8) (a) O. Matic and D. Sutton, *J. Chem. Soc.*, 349 (1953); (b) O. A. Runquist, Ph.D. dissertation, University of Minnesota (1956); (c) C. Dufraisse and J. J. Basselier, *Compt. rend.*, **248**, 700 (1959); (d) G. O. Schenk, *Angew. Chem.*, **64**, 12 (1952); (e) H. Hock and M. Siebert, *Ber.*, **87**, 554 (1954).

gives rise to at least eight different products when held at high temperatures for extended periods.[9]

The presence of at least one epoxide group in IX was shown by its reduction to a diol (XIV) with lithium aluminum hydride; acetylation of XIV by acetic anhydride in pyridine indicated that the reduced epoxide was attached at one end to a tertiary carbon atom as only one of the hydroxyl groups in XIV (presumably the one at 3β) was esterified.

EXPERIMENTAL[10]

Pyrolysis of 9(11)dehydroergosterol peroxide acetate (VI). A. Under a stream of nitrogen, 20 g. of 9(11)dehydroergosterol peroxide acetate[11] was refluxed in 125 ml. of *n*-dodecane for 75 min., then allowed to stand in the refrigerator overnight. Filtration afforded 3.25 g. of *IX*, m.p. 187–195°. A portion of this material (630 mg.) was placed on 15 g. of alumina and eluted with 19:1 benzene-hexane. After recrystallization from methanol, the analytical sample of IX was obtained as plates, m.p. 192–195°; $[\alpha]_D$ +243° (*c* 1.41).

Anal. Calcd. for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46; mol. wt., 468. Found: C, 76.70; H, 9.61; mol. wt., 473 (micro-Rast in camphor).

Saponification of IX was effected by refluxing a solution of 100 mg. of the steroid acetate in a mixture of 0.3 g. of potassium hydroxide, 0.5 cc. of water, and 20 cc. of methanol for 90 min. Water was added to incipient precipitation and cooling gave 72 mg. of a solid (XI), which was recrystallized from aqueous methanol, m.p. 172–175°; $[\alpha]_D$ +274° (*c* 1.04).

Anal. Calcd. for $C_{28}H_{42}O_3$: C, 78.82; H, 9.92. Found: C, 78.75; H, 10.14.

B. In a similar manner 1.0 g. of VI was refluxed 1 hr. in *n*-dodecane under nitrogen. After standing overnight, the solid IX (162 mg., 16%) was removed and the filtrate placed on 30 g. of alumina. Elution with 19:1 hexane-benzene yielded 228 mg. (24%) of 9(11)dehydroergosterol acetate (X), which after recrystallization from methanol melted at 148.5–151°: λ_{max} 310 (ε 10,000), 324 (ε 11,600), and 339 mμ (ε 7300); lit.[12]: m.p. 147.5–149.5°; λ_{max} 311 (ε 10,500), 324 (ε 12,100) and 341 mμ (ε 7500). Further elution of the column produced mixtures.

3β-Acetoxyergosta-9(11),22-diene-5,6α-epoxy-7-one (VII). The final filtrate from part A in the pyrolysis of VI was placed on 300 g. of Florisil and all the 9(11) dehydroergosterol acetate (X) present was removed by elution with 99:1 hexane-acetone. Elution with 49:1 hexane-acetone then gave 325 mg. (1.6%) of VII, m.p. 146.5–149°, which was obtained as small needles after recrystallization twice from methanol, m.p. 149.5–150.5°; $[\alpha]_D$ +29.6° (*c* 1.149).

Anal. Calcd. for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46. Found: C, 76.22; H, 9.65.

3β-Acetoxyergosta-8,22-diene-5,6α-epoxy-7-one (IV). A benzene solution of 50 mg. of VII was placed on 5 g. of unneutralized alumina. After 2 hr. the steroid was eluted with ether and recrystallized from methanol to give material, m.p. 196.5–205°, whose infrared spectrum was identical with that of 3β-acetoxyergosta-8,22-diene-5,6α-epoxy-7-one (IV): lit.[1]: m.p. 209–210°.

Reduction of IX. To a slurry of 1.2 g. of lithium aluminum hydride in 50 cc. of ether there was added 500 mg. of IX. After standing 4 hr. at room temperature, a saturated aqueous solution of ammonium chloride was carefully added. The ethereal layer was separated and the aqueous portion extracted with chloroform. The organic material was combined, dried, and evaporated giving 395 mg. of XIV which on recrystallization from acetone melted at 206–210° dec.; $[\alpha]_D$ +211° (*c* 1.04). Satisfactory elemental analyzes for XIV were not obtained.

One hundred milligrams of XIV was treated overnight with acetic anhydride in pyridine. Workup in the usual manner gave 63 mg. of a solid which was recrystallized from methanol-chloroform and obtained as platelets, m.p. 245.5–248.5°: $[\alpha]_D$ +210° (*c* 1.12); λ_{max}^{KBr} 2.93, 5.75, 5.89, 6.02 μ.

Anal. Calcd. for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46. Found: C, 76.71; H, 9.20.

Reaction of IX *with acid.* To a solution of 100 mg. of IX in 20 cc. of dioxane, there was added a solution of 100 mg. of *p*-toluenesulfonic acid in 2 cc. of water and 3 cc. of dioxane. After standing 18 hr. at room temperature, the reaction mixture was poured into water and extracted with chloroform. The extracts were washed, dried, and evaporated to yield 85 mg. of an oil, which was obtained as an amorphous solid from hexane, m.p. 161–163°; λ_{max}^{KBr} 2.93, 5.74, 5.79 (shoulder), 5.93 μ.

STERLING CHEMISTRY LABORATORY
YALE UNIVERSITY
NEW HAVEN, CONN.

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[9] E. Rick, Ph.D. dissertation, Yale University (1959).

[10] All melting points are corrected. Rotations were measured in chloroform at 25° in a 1 decimeter tube using a photoelectric polarimeter. Infrared spectra were determined in potassium bromide windows. The ultraviolet spectra were determined in absolute alcohol.

[11] A. Windaus and O. Linsert, *Ann.*, **465**, 157 (1928).

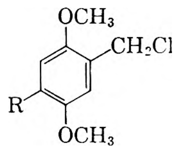
[12] R. Antonucci, S. Bernstein, D. Giancola, and K. J. Sax, *J. Org. Chem.*, **16**, 1159 (1951).

The Synthesis of 2-Chloromethyl-5-alkylhydroquinone Dimethyl Ethers by a Controlled Chloromethylation

GREGORY J. LESTINA AND HOMER W. J. CRESSMAN

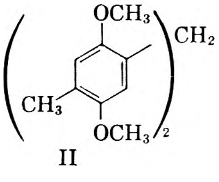
Received February 24, 1960

During the course of our work some hydroquinone dimethyl ethers of Types Ia and Ib were needed.



Ia. R = CH_3
Ib. R = C_8H_{17}

Neither compound had been reported in the literature and a convenient preparation of this class of compounds was not apparent. In fact, an attempt to prepare Ia by the chloromethylation of 2,5-dimethoxytoluene[1] had yielded only 5,5′-methylenebis(toluhydroquinone dimethyl ether) (II).



II

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[1] G. Jacini and T. Bacchetti, *Gazz. chim. ital.*, **80**, 760 (1950).

However, it appeared likely that Ia had been formed as a precursor to II and our experience with the chloromethylation reaction led us to believe that Ia could be obtained in good yield by properly adjusting the reaction conditions.

When 2,5-dimethoxytoluene was slowly added to a chloromethylation mixture at 55–60°, yields of Ia from 55–65% were obtained. This mode of addition of reagent differs from those generally applied[2] in which either all reactants are mixed at once or formalin is added slowly to the reaction mixture.[1] The position of the chloromethyl group was shown by converting Ia to the known 2,5-dimethoxy-*p*-xylene (III).[3]

This technique of chloromethylation, when applied to *n*-octylhydroquinone dimethyl ether gave Ib in comparably good yield, and it is reasonable to assume that other alkyl- or aryl-substituted hydroquinone dimethyl ethers can be chloromethylated with similar ease.

EXPERIMENTAL[4]

5-Chloromethyltoluhydroquinone dimethyl ether (Ia). Gaseous hydrogen chloride was bubbled into a well-stirred mixture of 200 ml. of 35% formaldehyde, 100 ml. of concd. hydrochloric acid, and 400 ml. of dioxane for 15 min. at such a rate that the temperature of the mixture remained between 55–60° with no external heating. To this mixture 152 g. (1.0 mole) of 2,5-dimethoxytoluene was added, dropwise, over a period of 20 min., while the temperature was maintained between 55–60°. When the addition was completed, the passage of hydrogen chloride was stopped. The mixture was cooled and poured into 2 l. of ice water and 300 ml. of ethyl ether. The aqueous layer was extracted twice more with 250-ml. portions of ether. The combined ether extracts were washed with cold water until the washings were neutral to litmus, then dried with anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was distilled through a 4-in. Vigreux column to give 110–130 g. (55–65%) of colorless liquid, b.p. 144–153°/14–16 mm., which solidified on cooling. Recrystallization from acetonitrile gave white crystals, m.p. 61.5–62.5°.

Anal. Calcd. for $C_{10}H_{13}ClO_2$: C, 59.9; H, 6.5; Cl, 17.7. Found: C, 59.8; H, 6.5; Cl, 17.5.

A portion of the residue from the distillation flask was recrystallized from 95% ethanol to give II, m.p. 147–148°.[1]

2,5-Dimethoxy-p-xylene (III). A mixture of 1.0 g. of Ia in 150 ml. of ethyl acetate containing 1.0 g. of 10% palladium on charcoal catalyst was hydrogenated at 45 p.s.i. and 25°. After 1 hr., the mixture was filtered to remove the catalyst and the filtrate evaporated to give a white solid which, after recrystallization from hexane, gave 0.5 g. of white crystals, m.p. 108–109° (lit.[3] m.p. 108°). A mixed melting point with authentic III was not depressed and the infrared spectra of the two were identical.

5-n-Octylhydroquinone dimethyl ether. To a mixture of 2 g. of 10% palladium on charcoal catalyst in 150 ml. of acetic acid was added 26.4 g. (0.1 mole) of 2-*n*-caprylylhydroquinone dimethyl ether.[5] The mixture was hydrogenated at 50 p.s.i. at 25° and hydrogenation was complete overnight. The catalyst was filtered and the acetic acid removed under reduced pressure. The residue was distilled to give 21.3 g. (85%) of slightly yellow liquid, b.p. 128–132°/1 mm., n_D^{25} 1.4979.

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.8; H, 10.4. Found: C, 76.5; H, 10.3.

2-Chloromethyl-5-n-octylhydroquinone dimethyl ether (Ib). The reaction was performed exactly as described for the preparation of Ia. From 100 g. (0.4 mole) of *n*-octylhydroquinone dimethyl ether there was obtained, after distillation, 75 g. (62%) of colorless liquid, b.p. 170–173°/0.4 mm., which solidified on cooling. Recrystallization from acetonitrile gave white crystals, m.p. 51–52°.

Anal. Calcd. for $C_{17}H_{27}ClO_2$: C, 68.3; H, 9.1; Cl, 11.9. Found: C, 68.5; H, 9.0; Cl, 11.8.

Kodak Research Laboratories
Rochester 4, N. Y.

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[2] R. C. Fuson and C. H. McKeever, *Org. Reactions*, **Vol. I,** 63 (1942).

[3] E. Noelting and P. Werner, *Ber.*, **23,** 3251 (1890).

[4] All melting points were measured in capillary tubes and are uncorrected.

[5] J. H. Cruickshank and R. Robinson, *J. Chem. Soc.*, 2064 (1938).

2-Aminothiazolesulfonamides

Carl Ziegler, Eleanor K. Kuhl,
and James M. Sprague

Received November 5, 1959

The sulfonation of 2-acetamidothiazoles with chlorosulfonic acid has been reported by several investigators, but the structure of the resulting sulfonyl chlorides has been a subject of controversy.[1–3]

Backer and co-workers[4,5] considered the products that they obtained from 2-acetamidothiazole and 2-acetamido-4-methylthiazole to be 5-sulfonyl chlorides (I). This assignment of structure by these investigators was based on previous work which proved the point of attack of electrophilic agents, such as nitric acid and bromine, to be the 5 position of the thiazole ring.

However, Postovskii and Belaya,[3] who carried out the reaction under similar conditions, interpreted the reaction as occurring on the acetamido group to yield the acetylsulfamyl chlorides (II). Postovskii[6] later concluded, on the basis of infrared absorption spectra, that this interpretation was in error and that the products were thiazole-5-sulfonyl chlorides.

The amides derived from these sulfonyl chlorides afford a ready solution to the problem. Hydrolysis of the acetyl derivatives that arise from the reaction

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[1] H. E. Faith, *J. Am. Chem. Soc.*, **74,** 5799 (1952); **69,** 2063 (1947).

[2] C. D. Hurd and H. L. Wehrmeister, *J. Am. Chem. Soc.*, **71,** 4008 (1949).

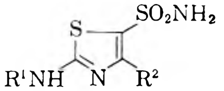
[3] I. Ya. Postovskii and T. S. Belaya, *Compt. Rend. Acad. Sci. U.R.S.S.* **40,** 326 (1943); *Chem. Abstr.* **39,** 1151 (1945).

[4] H. J. Backer and J. de Jonge, *Rec. trav. chim.*, **62,** 158 (1943).

[5] H. J. Backer and J. A. K. Buisman, *Rec. trav. chim.*, **63,** 228 (1944).

[6] I. Ya. Postovskii and T. S. Mamykina, *Zhur. Obshchei Khim.* **23,** 1765 (1953); *Chem. Abstr.* **49,** 300 (1955); S. G. Bogomolov, Yu. N. Sheinker and I. Ya. Postovskii, *Zhur. Obshchei Khim.*, **24,** 539 (1954); *Chem. Abstr.* **48,** 8654 (1954).

TABLE I

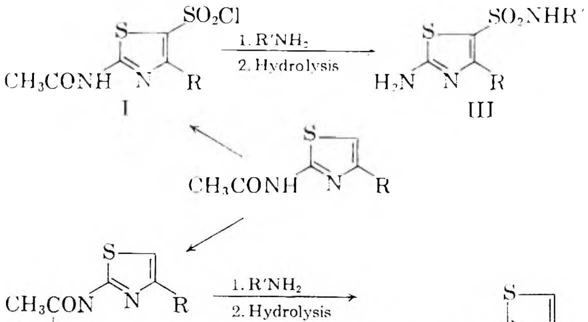


R[1]	R[2]	M.P.° uncorr.	Formula	Analysis[c]						Yield, %
				Calcd.			Found			
				C, %	H, %	N, %	C, %	H, %	N, %	
p-$HO_2CC_6H_4SO_2$	H	297–298	$C_{10}H_9N_3O_6S_3$	33.05	2.50	11.56	32.60	2.70	11.42	50[a]
p-$HO_2CC_6H_4SO_2$	CH_3	298–300	$C_{11}H_{11}N_3O_6S_3$	35.00	2.94	11.14	35.09	3.22	11.06	19[a]
$C_6H_5SO_2$	CH_3	201–203	$C_{10}H_{11}N_3O_4S_3$	36.03	3.33	12.61	36.27	3.49	12.60	54[a]
p-NCC_6H_4CO	CH_3	260–262	$C_{12}H_{10}N_4O_3S_2$	44.70	3.13	17.38	44.89	3.08	17.36	76[a]
$C_6H_5—CH{=}CHCO$	CH_3	244–245	$C_{13}H_{12}N_3O_3S_2$	48.27	4.05	12.98	48.34	4.07	12.96	52[a]
$C_6H_5—CH{=}CHSO_2$	CH_3	239–240	$C_{15}H_{21}N_3O_5S_3$[b]	43.05	4.82	10.04	43.51	4.90	10.07	24[a]
C_3H_7CO	CH_3	166–167	$C_8H_{13}N_3O_3S_2$	36.49	4.98	15.96	36.36	4.83	15.95	33
CH_3CO	C_6H_5[d]	301–303	$C_{11}H_{11}N_3O_3S_2$	44.43	3.73	14.13	44.94	3.90	13.6	30
H	C_6H_5[d]	271 dec.	$C_9H_9N_3O_2S_2$	42.34	3.55	16.46	42.95	3.85	16.17	72

[a] From the amine and the appropriate acid chloride. [b] Solvated with isopropanol. [c] We are indebted to Mr. K. B. Streeter and his associates for the microanalyses. [d] *Cf.* ref. 8.

of the sulfonyl chlorides with ammonia or amines would, in one case, lead to a 2-thiazolylsulfamide (IV), and in the other to a 2-aminothiazole-5-sulfonamide (III). As 2-aminothiazoles can be diazotized and coupled with α-naphthyldimethylamine to give characteristic dyes,[7] III would be expected to undergo this reaction but IV would not.

The work of the previous investigators was repeated in our laboratories and the products subjected to the diazo test. Acid hydrolysis of the acetyl derivatives in all instances (R = H, CH_3 or C_6H_5) yielded products that gave a diazo color; therefore, these products must have the 5-sulfonamide structure III and not the sulfamide structure IV.



In addition to the compounds prepared by Backer *et al.*, the 4-phenyl derivative (R = C_6H_5) was also prepared and found to possess structure III; this compound has been reported by Bas and Rout.[8] Several sulfonyl and acyl derivatives of the aminosulfonamides (III) were prepared through reaction with the appropriate sulfonyl or acyl chloride. The formation of these derivatives under the conditions employed also supports structure III. These compounds are recorded in Table I.

EXPERIMENTAL

Sulfonyl chlorides. The method of Backer *et al.*[4] was used, except that prolonged heating of the chlorosulfonic acid solutions was found unnecessary. Heating longer than 2 hr. on the steam bath did not increase the yield of product.

Sulfonamides. Crude, moist sulfonyl chloride was added to a large excess of liquid ammonia according to the method of Roblin and Clapp.[9] Hydrolysis to the 2-aminothiazole-5-sulfonamides was carried out in acidic medium by the method of Backer.[4] The diazotization and coupling test was carried out as previously described.[7]

Derivatives. Of the compounds listed in Table I, most were prepared by the reaction of a 2-aminothiazole-5-sulfonamide with the appropriate acyl chloride or sulfonyl chloride in pyridine solution.

2-Methylamino-4-methylthiazole, prepared by the method of Burtles *et al.*,[10] was acetylated with acetic anhydride. Subsequent treatment with chlorosulfonic acid gave a crude sulfonyl chloride. This was treated with liquid ammonia to give a low yield (<1%) of 2-acetylmethylamino-4-methylthiazole-5-sulfonamide, m.p. 204–206°.

Anal. Calcd. for $C_7H_{11}N_3O_3S_2$: C, 33.72; H, 4.45; N, 16.86. Found: C, 34.20; H, 4.80; N, 16.84.

MERCK SHARP AND DOHME
RESEARCH LABORATORIES
WEST POINT, PA.

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(7) J. M. Sprague, A. H. Land, and C. Ziegler, *J. Am. Chem. Soc.*, **68**, 2155 (1946).

(8) B. Bas and M. K. Rout, *J. Indian Chem. Soc.*, **32**, 663 (1955).

(9) R. O. Roblin, Jr., and J. W. Clapp, *J. Am. Chem. Soc.* **72**, 4890 (1950).

(10) R. Burtles, F. L. Pyman, and J. Roylance, *J. Chem. Soc.*, 589 (1925).

Potential Anticancer Agents.[1] XXXV. Nonredox Analogs of Riboflavin. II. Synthesis of 3,4-Dihydro-4,4,6,7-tetramethyl-1-(1-D-ribityl)carbostysil

ELMER J. REIST, HARLAN P. HAMLOW, IRENE G. JUNGA, R. M. SILVERSTEIN, AND B. R. BAKER

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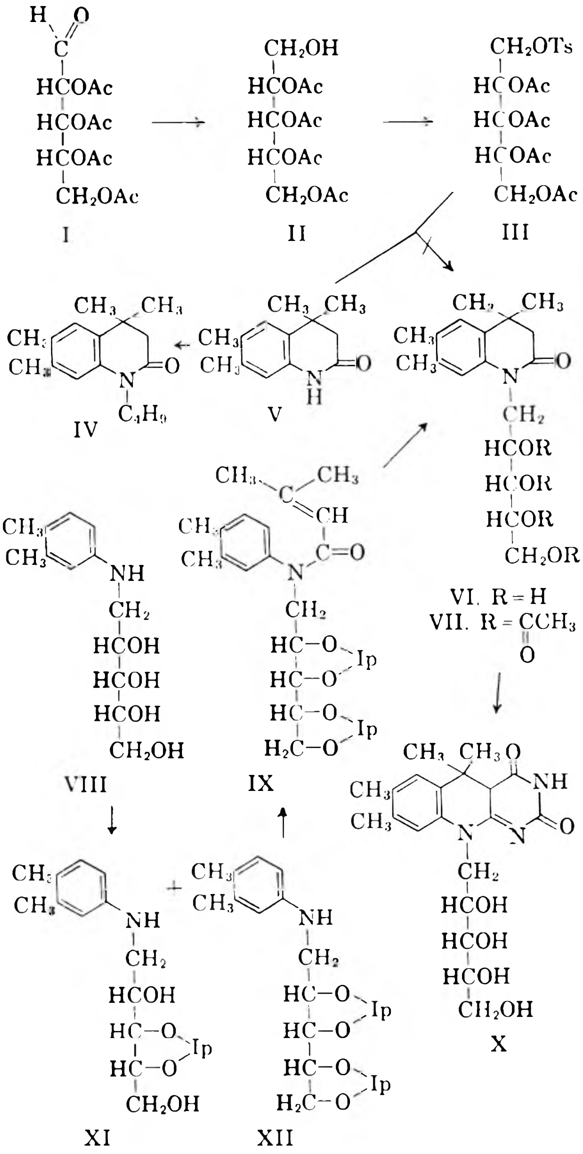
A recent program in these laboratories devoted to the synthesis of antagonists of riboflavin, such as

X, as potential anticancer agents[2] involved the synthesis of 3,4-dihydro-4,4,6,7-tetramethyl-1-(1-D-ribityl)carbostyril (VI) as a key intermediate. One of the more attractive synthetic sequences of VI involves the alkylation of 3,4-dihydro-4,4,6,7-tetramethylcarbostyril (V) with 2,3,4,5-tetra-*O*-acetyl-1-D-(*p*-tolylsulfonyl)ribitol (III). Model studies showed that alkylation of the carbostyril (V) with butyl bromide or butyl tosylate to give the *N*-butyl derivative (IV) proceeded in satisfactory yield.

The synthesis of the 1-tosylate (III) was accomplished in two steps from 2,3,4,5-tetra-*O*-acetyl-D-ribose (I).[3] Hydrogenation of tetraacetyl-D-ribose (I) with Raney nickel in ethyl acetate–acetic acid[4] gave a 76% yield of crude 2,3,4,5-tetra-*O*-acetyl-D-ribitol (II) which could be crystallized in low yield from benzene–Skellysolve B.[6] A more satisfactory procedure consisted of a direct tosylation of the crude tetraacetyl-D-ribitol (II) to give the crystalline 1-tosylate (III) in 39% over-all yield from I.

Several attempts to condense the sodium salt of the carbostyril (V),[2] prepared from sodium hydride, with the tosylate (III) in *N*,*N*-dimethylformamide at 100° were unsuccessful. With a three-hour reaction time, a mixture of tosylate (III) and carbostyril (V) was recovered. Use of a twenty-four hour reaction time brought decomposition of the tosylate (III), recovery of carbostyril (V), and no evidence for the ribityl carbostyril tetraacetate (VII).

An alternative method for the synthesis of the ribitylcarbostyril (VI) commenced with *N*-(1-D-ribityl)-3,4-xylidine (VIII). Since various attempts to accomplish a selective *N*-acylation or *O*-acylation of the ribitylxylidine (VIII) resulted in mixtures of *O*- and *N*-acylated derivatives of VIII, the preparation of the di-*O*-isopropylidene derivative (XII) was investigated; the latter could then presumably be acylated with 3-methylcrotonyl chloride to IX without the complications of *O*-acylation.



Treatment of *N*-(1-D-ribityl)-3,4-xylidine (VIII) with acetone in the presence of alkanesulfonic acid and copper sulfate for three hours gave a crude product which proved to be a mixture of the expected diacetone derivative (XII) and a monoacetone derivative (XI).[7] The monoacetone derivative (XI) could be crystallized in 12% yield. This crystalline material was converted to an *N*,*O*,*O*-triacetate in quantitative yield. The triacetate showed *O*-acetate and *N*-acetate absorption of approximately equal intensity in the infrared, indicating that the carbonyl of the *N*-acetyl has twice the extinction coefficient of the carbonyl of the *O*-acetyl.

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(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center.

(2) For the preceding paper in this series, *cf.* E. J. Reist, H. P. Hamlow, I. G. Junga, R. M. Silverstein, and B. R. Baker, *J. Org. Chem.*, **25**, 1368 (1960).

(3) H. Zinner, *Ber.*, **83**, 418 (1950).

(4) Hydrogenation of I with Raney nickel in dioxane has been described by Fox.[5] Substitution of ethyl acetate–acetic acid as a solvent gives a smoother reaction and avoids possible *O*-acetyl migration caused by the alkaline catalyst.

(5) H. H. Fox, *J. Org. Chem.*, **13**, 580 (1948).

(6) Skellysolve B and Skellysolve C are petroleum hydrocarbon fractions with boiling ranges of 62–70° and 88–99°, respectively. They are supplied by the Special Products Division, Phillips Petroleum Co., Bartlesville, Okla.

(7) The assignment of the 3,4-position for the monoacetone derivative is based on the observation that extended treatment of the ribitylxylidine (VIII) under acetonating conditions failed to drive the reaction any further to completion and the same amount of monoacetone derivative relative to diacetone derivative was obtained. Any 2,3- and/or 4,5-monoacetone derivative would be expected to yield eventually the diacetone derivative (XII).

In a second acetonation reaction, the crude acetonation mixture was distilled to separate the products XI and XII from other by-products. Acetylation of an aliquot of the distillate, followed by infrared examination of the resulting acetate mixture, showed that mono- and diacetone compounds were present in approximately equal amounts, each in 30–35% yield. The pure diacetone derivative was obtained by distillation through a small Vigreux column.

Based on the above information, a more satisfactory technique was developed for the separation of the mono- and diacetone derivatives (XI and XII, respectively), utilizing a solvent partition system of hexane-methanol-water (7:7:2). The hexane layer contained virtually pure diacetone derivative in 37% yield while the aqueous layer contained all the monoacetone derivative essentially free of diacetone derivative. This separation was particularly useful for large-scale separations, since distillation caused considerable decomposition.

Reaction of the diacetone derivative (XII) with 3-methylcrotonyl chloride gave *N*-(2,3:4,5-di-*O*-isopropylidene-1-D-ribityl)-3-methyl-3′,4′-crotonoxylidide (IX) in quantitative yield as a gum. Cyclization of this amide (IX) with anhydrous aluminum chloride in Skellysolve C[6] gave an aluminum chloride complex of the diacetone derivative of the carbostyril (VI). In order to break this complex, it was necessary to use warm, strong acid. Since this acid treatment caused partial deacetonation, the remainder of the acetone blocking groups were removed by refluxing the crude product in methanolic hydrochloric acid. Crystallization from 50% ethanol gave a 20% yield of 3,4-dihydro-4,4,6,7-tetramethyl-1-(1-D-ribityl)-carbostyril (VI). That this compound was the desired carbostyril (VI) and not the uncyclized 3-methylcrotonoxylidide was clearly demonstrated by its infrared spectrum. The product had no band at 6.13 μ characteristic of the double bond in the acyl group of IX. Good evidence for ring closure to a carbostyril (VI) was evidenced by the presence of an N—C band at 7.06 μ which has been present in all the model 1-alkyl-3,4-dihydrocarbostyrils,[2] but absent in their open-chain anilide precursors, including IX.

EXPERIMENTAL[8]

1-Butyl-3,4-dihydro-4,4,6,7-tetramethylcarbostyril (IV). A mixture of 9.0 g. (0.04 mole) of 3,4-dihydro-4,4,6,7-tetramethylcarbostyril (V)[2] and 1.2 g. (0.05 mole) of sodium hydride in 75 ml. of benzene was heated under reflux with stirring for 23 hr. The benzene was removed *in vacuo* and the solid sodium salt suspended in 125 ml. of *N*,*N*-dimethylformamide. The mixture was heated at 100 ± 2° with stirring while a solution of 6.5 g. (0.05 mole) of butyl bromide in 10 ml. of *N*,*N*-dimethylformamide was added dropwise over about 10 min. The suspension cleared as the mixture was heated with stirring for 80 min. The solvent was removed under reduced pressure and the viscous residue extracted with 100 ml. of benzene. The extract was washed with 100 ml. of water, dried over magnesium sulfate, and concentrated *in vacuo*. The residual product (10.4 g., 91%) was recrystallized from 50 ml. of Skellysolve B[6] with the use of Norit; yield 7.1 g. (62%) of colorless crystals, m.p. 62.5–63.5°; $\lambda^{\text{KBr}}_{\max(\mu)}$ 6.04 (amide C=O), 11.36 (1,2,4,5-tetrasubstituted benzene), no NH in 3.0 region.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.7; H, 9.72; N, 5.40. Found: C, 78.4; H, 9.52; N, 5.65.

Similar yields were obtained using *n*-butyl tosylate.

2,3,4,5-Tetra-O-acetyl-D-ribitol (II). A solution of 6.0 g. (0.02 mole) of 2,3,4,5-tetra-*O*-acetyl-D-ribose (I)[3] in 25 ml. of ethyl acetate was treated with 2.2 g. of Norit, heated to boiling, and filtered. The filtrate was treated with 25 ml. of ethyl acetate and 10 ml. of glacial acetic acid. Raney nickel (W-5, 2 g.) was added and the mixture hydrogenated overnight under a pressure of 41 lb. The catalyst was removed by filtration and washed with 25 ml. of ethyl acetate. The filtrate was neutralized with saturated sodium bicarbonate solution. The sodium bicarbonate solution was separated and washed with three 25-ml. portions of methylene chloride. The combined organic solutions were concentrated *in vacuo*. The residue weighed 4.8 g. (80%). The crude product was dissolved in 30 ml. of benzene–Skellysolve B[6] (3:2), treated with Norit, heated to boiling, and filtered. The solvents were removed *in vacuo* and 4.57 g. (76%) of a viscous oil was obtained which was suitable for the preparation of the 1-tosylate (III); $\lambda^{\text{film}}_{\max(\mu)}$ 2.87 (OH), 3.37 (CH), 5.47 (acetate C=O), 8.17, 9.50 (C—O—C).

In a similar run using dioxane as the solvent for the hydrogenation,[5] recrystallization from Skellysolve C[6] gave a 4% yield of colorless needles, m.p. 56–58°, along with a 15% yield of oil which crystallized on standing; $\lambda^{\text{KBr}}_{\max(\mu)}$ 2.90 (OH), 5.70 (acetate C=O), 8.20 (ester C—O—C).

Anal. Calcd. for $C_{13}H_{20}O_9$: C, 48.8; H, 6.30. Found: C, 49.3; H, 6.61.

Fox[5] reported a melting point of 55–57°.

2,3,4,5-Tetra-O-acetyl-1-D-(p-tolylsulfonyl)ribitol (III). A solution of 4.57 g. (0.014 mole) of the crude 2,3,4,5-tetra-*O*-acetyl-1-D-ribitol (II) in 25 ml. of pyridine was cooled in an ice bath with stirring while 3.3 g. (0.02 mole) of *p*-tolylsulfonyl chloride was added in portions. The temperature was kept below 5°. The solution was stirred and cooled in an ice bath for 1.5 hr. protected from moisture, and allowed to warm to room temperature overnight. The brown solution was poured into 300 ml. of ice water. The oil which formed soon solidified to a white solid and was collected on a filter and dried; yield 4.32 g. (63%), m.p. 98–101°. The crude product was recrystallized from 25 ml. of ethanol with the use of Norit; yield 3.44 g. (50%) of white crystals, m.p. 103–104°. This compound had an infrared spectrum identical with that of the analytical sample prepared in a pilot run.

The analytical sample had m.p. 104–105°; $\lambda^{\text{KBr}}_{\max(\mu)}$ 5.75 (acetate C=O), 8.14 (ester C—O—C), 7.38, 8.42, 8.54 (sulfonate).

Anal. Calcd. for $C_{20}H_{26}O_{11}S$: C, 50.6; H, 5.52; S, 6.75. Found: C, 50.8; H, 5.67; S, 7.15.

N-(3,4-O-Isopropylidene-1-D-ribityl)-3,4-xylidine (XI) *and N-(2,3:4,5-di-O-isopropylidene-1-D-ribityl)-3,4-xylidine* (XII). A mixture of 12.0 g. (0.047 mole) of *N*-(1-D-ribityl)-3,4-xylidine (VIII) and 10 g. of anhydrous cupric sulfate in 150 ml. of acetone was cooled to 2–3° in an ice-salt bath, then a solution of 11.5 ml. of ethanesulfonic acid in 20 ml. of acetone was added dropwise with stirring. After the addition was complete, the mixture was stirred with continued cooling for 4 hr., then left at room temperature overnight.

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(8) Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Paper chromatograms were run by the descending technique on Whatman No. 1 paper and the spots were located by visual examination under ultraviolet light. The solvent systems used were *n*-butyl alcohol–methyl ethyl ketone–water (5:3:2) (solvent A) and 5% aqueous disodium phosphate (solvent B).

The reaction mixture was filtered and the filter cake was washed with 20 ml. of acetone. The combined filtrate and washings were poured into 400 ml. of cold 10% aqueous sodium carbonate. The resulting basic mixture was extracted with 300 ml. of methylene chloride. The methylene chloride layer was evaporated to dryness *in vacuo* to give a sirupy mixture of mono- and diacetone derivatives (XI and XII). The crude mixture was partitioned in the solvent system hexane-methanol-water (7:7:2) (336 ml.) to give 5.8 g. (32%) of crude monoacetone derivative (XI) in the methanol-water layer and 5.4 g. (32%) of crude diacetone derivative (XII) in the hexane layer which was satisfactory for the Friedel-Crafts cyclization.

Trituration of the crude monoacetone derivative (XI) with cold hexane caused the sirup to crystallize. Recrystallization from 50 ml. of hexane and 3 ml. of absolute ethanol gave 2.85 g. of a white crystalline material, m.p. 101–102°, the infrared spectrum of which was essentially identical with that of the analytical sample. No effort was made to obtain a second crop.

The analytical sample, prepared from a similar run, melted at 103–104° after two recrystallizations from Skellysolve B[6]–ethanol and had $\lambda^{\mathrm{KBr}}_{\max(\mu)}$ 2.94 (NH, OH), 7.24 (CH_3), 9.50 (C—O—C), 12.34 (1,3,4-trisubstituted benzene).

Anal. Calcd. for $C_{16}H_{25}NO_4$: C, 65.1; H, 8.53; N, 4.74. Found: C, 65.0; H, 8.72; N, 4.39.

To 0.2 g. (0.61 mmole) of crystalline *N*-(3,4-*O*-isopropylidene-1-D-ribityl)-3,4-xylidine (XI) was added a solution of 1 ml. of pyridine and 1 ml. of acetic anhydride. The solution was allowed to stand for 2 days protected from moisture and then was poured into 100 ml. of ice water. The oil which separated was extracted with 50 ml. of methylene chloride. The extract was washed with 50 ml. of 5% sodium bicarbonate solution and 50 ml. of water, and dried over magnesium sulfate. The solution was concentrated *in vacuo;* yield, 0.35 g. of *N,O,O*-triacetyl derivative of XI as a tan, viscous oil which did not crystallize; $\lambda^{\mathrm{film}}_{\max(\mu)}$ 5.74 (acetate C=O), 6.01 (amide C=O), 8.15 and 9.35 (acetate C—O—C). The relative intensities of the amide and acetate carbonyl absorption were almost equal.

A small portion of the crude diacetone derivative (XII) was acetylated in the manner described above for the monoacetone derivative (XI). The infrared spectrum of the *O*-diacetate showed an *O*-acetate/*N*-acetate intensity ratio of 1:17 in the C=O region, indicating less than 5% contamination by the monoacetone derivative.

An analytical sample of the diacetone derivative (XII) was obtained by distillation of the crude material after one partition treatment, b.p. 135–140° (0.025 mm.); $\lambda^{\mathrm{film}}_{\max(\mu)}$ 2.96 (NH), 7.31 (CH_3), 9.31 (C—O—C).

Anal. Calcd. for $C_{19}H_{29}NO_4$: C, 68.0; H, 8.71; N, 4.18. Found: C, 67.9; H, 8.83; N, 4.64.

A small portion of the distilled product was acetylated, using acetic anhydride and pyridine. The infrared spectrum showed only a trace amount of *O*-acetate compared to *N*-acetate.

*3,4-Dihydro-4,4,6,7-tetramethyl-1-(1-*D*-ribityl)carbostyril* (VI). To a stirred solution of 5.3 g. (1.6 mmoles) of *N*-(2,3:4,5-di-*O*-isopropylidene-1-D-ribityl)-3,4-xylidine (XII) in 13 ml. of dry pyridine was added dropwise 2.3 g. (1.9 mmoles) of 3-methylcrotonyl chloride with ice cooling. The addition time was 5 min. A precipitate formed and the resulting mixture was stirred with ice cooling for 2 hr. and then stirred at 30° for 18 hr. protected from moisture. The volatile materials were removed *in vacuo* and the residue dissolved in 50 ml. of methylene chloride. The methylene chloride solution was washed with 50 ml. of saturated sodium bicarbonate solution and concentrated *in vacuo*. The residue was dissolved in a small amount of toluene and then concentrated *in vacuo*. This procedure was repeated several times. The last traces of solvents were removed *in vacuo* at 60° at 0.1 mm. to yield 7.0 g. (theory 6.7 g.) of crude *N*-(2,3:4,5-di-*O*-isopropylidene-1-D-ribityl)-3-methyl-3′,4′-crotonoxylidide (IX); $\lambda^{\mathrm{film}}_{\max(\mu)}$ 6.05 (amide C=O), 6.13 (shoulder, >C=C<), 7.30 (CH_3), 9.37 (C—O—C), no ester C=O in the 5.8 region.

The crude IX (7.0 g., 1.6 mmoles) was dissolved in 80 ml. of Skellysolve C[6] and treated with 8.0 g. (0.060 mole) of powdered, anhydrous aluminum chloride. The mixture was stirred under reflux on the steam bath for 2 hr. The resulting mixture was decomposed with ice and the Skellysolve C decanted from the gummy residue. The residue was suspended in 125 ml. of chloroform and heated to boiling with 100 ml. of 6*N* hydrochloric acid. The mixture was cooled, shaken vigorously, and the chloroform layer separated. The aqueous layer was extracted with 25 ml. of chloroform. The combined chloroform solutions were washed with 3*N* hydrochloric acid, dried over magnesium sulfate, and concentrated *in vacuo;* weight 6.5 g. The infrared spectrum of this material showed that not all of the isopropylidene groups had been removed. The residue was dissolved in 150 ml. of methanol, treated with 6 ml. of 6*N* hydrochloric acid; the solution was heated under reflux on the steam bath for 1 hr. and then concentrated *in vacuo*. The residue (5.72 g.) was dissolved in 110 ml. of hot 50% aqueous ethanol, treated with Norit, filtered, and chilled. The crystals were collected and dried *in vacuo;* yield 0.35 g., m.p. 69–71°. The filtrate was concentrated and a second crop of 0.75 g., m.p. 60–70°, was obtained; total yield 1.10 g. (20.4%). Recrystallization of the first crop from aqueous alcohol with use of Norit gave white crystals that softened at 85°, partially melted at about 100°, then melted at 115–200°; $\lambda^{\mathrm{KBr}}_{\max(\mu)}$ 2.95 (OH), 6.05 (lactam C=O), 8.92, 9.59 (C—O—), 11.37 (1,2,4,5-tetrasubstituted benzene), no C=C at 6.13.

Anal. Calcd. for $C_{18}H_{27}NO_5$: C, 64.1; H, 8.07; N, 4.15. Found: C, 64.5; H, 8.16; N, 4.01.

The filtrate from the second crop was concentrated to obtain a third crop; however, only an oil separated. The infrared spectrum of this oil was similar to that of the product.

Paper Chromatography	R_f in Solvent System A	R_f in Solvent System B
Analytical sample	0.87	0.00
Second crop	0.86	0.00
Oil	0.88	0.58 0.71
Mother liquor	0.00 0.85	0.00

The oil contained little or no product. The mother liquor may have had additional product.

Acknowledgment. The authors wish to thank Dr. Peter Lim for interpretation of the infrared absorption spectra and his staff for the paper chromatography. The authors are also indebted to Mr. O. P. Crews, Jr., and his staff for large-scale preparation of certain intermediates.

DEPARTMENT OF BIOLOGICAL SCIENCES
STANFORD RESEARCH INSTITUTE
MENLO PARK, CALIF.

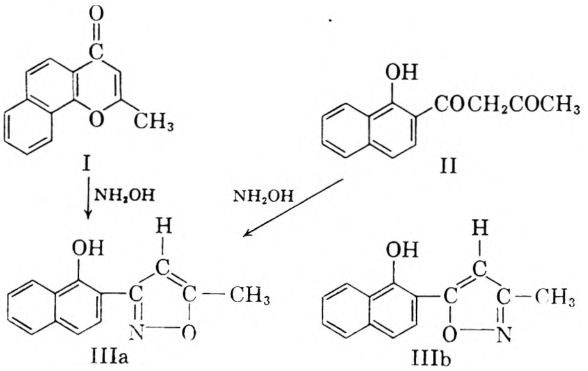
Action of Hydroxylamine, Hydrazine Hydrate, and Phenylhydrazine on 2-Acetoaceto-1-naphthol

ABD ELMAGED AMIN SAMMOUR

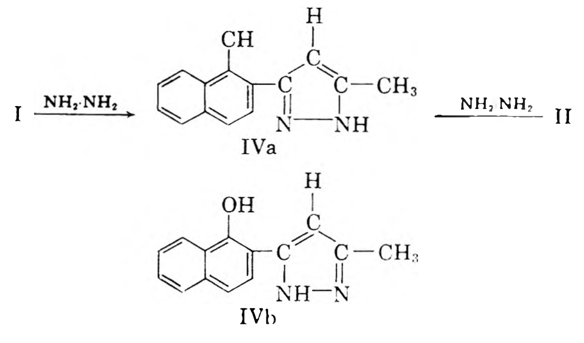
Received November 25, 1959

Recently Schönberg, Fateen, and Sammour[1] have reported the reaction of I with hydroxylamine hydrochloride, hydrazine hydrate, and phenylhydrazine hydrochloride. They have shown that I reacts with hydroxylamine hydrochloride in boiling pyridine to give an isoxazole derivative IIIa or IIIb.

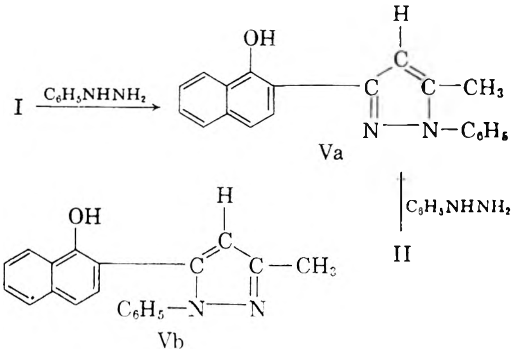
The author has found that 2-acetoaceto-1-naphthol (II) reacts with hydroxylamine hydrochloride in boiling ethyl alcohol leading to the same 2-[5(or 3)-methyl-3(or 5)-isoxazolyl]-1-naphthol (IIIa or IIIb). An alcoholic solution of the product gives a violet color with alcoholic ferric chloride solution. It yields a monobenzoyl derivative. IIIa or IIIb was recovered unchanged when boiled with 10% sodium hydroxide for one hour, followed by acidification with dilute hydrochloric acid. The stability towards alkali was to be expected as, according to Claisen,[2] 3,5-disubstituted isoxazoles are very resistant to alkaline degradation.



The action of hydrazine hydrate on 2-acetoaceto-1-naphthol (II) in alcohol leads to 2-[5(or 3)-methyl-3(or 5)-pyrazolyl]-1-naphthol (IVa or IVb). It is identical with that obtained when hydrazine hydrate is allowed to react with I. The product gives a green color with alcoholic ferric chloride and yields a dibenzoyl derivative.



The reaction of I with phenylhydrazine hydrochloride in pyridine gives a compound Va or Vb which was regarded as a pyrazole derivative· 2-[1-Phenyl-5(or 3)-methyl-3(or 5)-pyrazolyl]-1-naphthol (Va or Vb) was also obtained from the action of phenylhydrazine with 2-acetoaceto-1-naphthol (II) in alcohol. It gives a violet color with alcoholic ferric chloride solution.



EXPERIMENTAL

2-[5(or 3)-Methyl-3(or 5)-isoxazolyl]-1-naphthol (IIIa or IIIb). A mixture of 4 g. of hydroxylamine hydrochloride and 5 g. of 2-acetoaceto-1-naphthol[3] in 50 ml. of ethyl alcohol was refluxed for 4 hr., cooled, and diluted with water. The deposit formed (4.3 g., 85%) was filtered; on crystallization from benzene, it yielded yellowish crystals which were proved by melting point and mixture melting point (181°) and the violet color with alcoholic ferric chloride to be 2-[5(or 3)-methyl-3(or 5)-isoxazolyl]-1-naphthol (IIIa or IIIb). Its monobenzoyl derivative crystallized as colorless crystals from dilute ethyl alcohol (m.p. and mixture m.p. 126°).

2-[5(or 3)-Methyl-3(or 5)-pyrazolyl]-1-naphthol (IVa or IVb). 2-Acetoaceto-1-naphthol (3 g.), hydrazine hydrate (3 ml.), and ethyl alcohol (30 ml.) were heated under reflux for 20 min. and cooled, water was added, and the solid collected, washed, dried (3 g. 97%), and crystallized from benzene as colorless leaflets. The product was proved to be 2-[5(or 3)-methyl-3(or 5)-pyrazolyl]-1-naphthol (IVa or IVb) by melting point and mixture melting point (171°), the deep green color with alcoholic ferric chloride solution and lack of color with concd. sulfuric acid. The dibenzoyl derivative was prepared (Schotten-Baumann method) and crystallized from dilute alcohol as colorless crystals, (m.p. and mixture m.p. 144–145°). It dissolved in concd. sulfuric acid yielding a yellow solution.

2-[-Phenyl-5(or 3)-methyl-3(or 5)-pyrazolyl]-1-naphthol (Va or Vb). 2-Acetoaceto-1-naphthol (2 g.), phenylhydrazine (1 ml.) and ethyl alcohol (20 ml.) were heated under reflux for 2.5 hr., the solution concentrated to half its volume, and water added. The precipitate (1.8 g., 72%) was crystallized from petroleum ether (b.p. 100–120°) giving almost colorless crystals which were proved to be 2-[1-phenyl-5(or 3)-methyl-3(or 5)-pyrazolyl]-1-naphthol (Va or Vb) by melting point and mixture melting point (143°). Its alcoholic solution gives a violet color with alcoholic ferric chloride solution.

DEPARTMENT OF CHEMISTRY
FACULTY OF SCIENCE
A'IN SHAMS UNIVERSITY
CAIRO, EGYPT, U.A.R.

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(1) A. Schönberg, A. Fateen, and A. Sammour, *J. Am. Chem. Soc.*, **78**, 4689 (1956).

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(3) G. Witting, Fr. Bengert, and H. E. Richter, *Ann.*, **446**, 155 (1926).

Amebicides. II. Acyl Derivatives of 2-Amino-1,4-naphthoquinone

Price Truitt, Frank M. Wood, Jr.,[1] and Robert L. Hall[1]

Received March 4, 1960

Buu-Hoï[2] reported that the 1-naphthylamine, *p*-phenylenediamine, 1,5-naphthylenediamine and similar derivatives of 2-chloro-1,4-naphthoquinone were capable of inhibiting the growth of the tubercle bacillus. Calandra and Adams[3] prepared amino derivatives of 2 - chloro - 1,4 - naphthoquinone by treating 2,3-dichloro-1,4-naphthoquinone with amino acids, aminoalkanes aminobenzene, sulfonamide and aminopyridines and found them active against acid-producing bacteria. Thus, it seemed feasible to prepare a number of 2-acylamino-3-chloro-1,4-naphthoquinones to test for biological activity. As these compounds were found to exhibit amebicidal activity, it was logical to replace the 3-chloro with various substituted amino groups to determine the effect of this change on amebicidal activity. This change in structure did indeed enhance the amebicidal activity.

The preparation of 2-amino-3-chloro-1,4-naphthoquinone by the action of ammonia on 2,3-dichloro-1,4-naphthoquinone has been reported by Fries and Ochwat,[4] who also found that this compound was easily acetylated. The activity of the chlorine was greatly enhanced by the acetylation

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(1) Research Fellows of Parke, Davis & Co., 1950–1953.

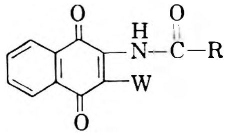
(2) Ng. Ph. Buu-Hoï, *Bull. soc. chim.*, **11**, 578 (1944).

(3) J. C. Calandra and E. C. Adams, *J. Am. Chem. Soc.*, 4804 (1950).

(4) K. Fries and P. Ochwat, *Ber.*, **56B**, 259 (1921); *Ber.*, **56**, 1291 (1923).

TABLE I

2-Acylaminonaphthoquinone Derivatives



	R	W	Yield, %	M.P. °	Formula	Analysis Nitrogen, % Calcd.	Found
1	CH_3	Cl	60	218–219[a]			
2		$—NHC_{14}H_{29}$	95	141–142	$C_{26}H_{38}N_2O_3$	6.57	6.78
3		$—NHC_6H_5$	88	202–204[b]			
4	C_2H_5	Cl	85	190–192[c]	$C_{13}H_{10}NO_3Cl$		
5		$—NHC_{14}H_{29}$	80	124–125	$C_{27}H_{40}N_2O_3$	6.36	6.38
6		—NH(2-Butyl)	88	111–113	$C_{17}H_{20}N_2O_3$	9.33	9.30
7		$—NHC_6H_5$	85	182–183	$C_{19}H_{17}N_2O_3$	8.75	8.67
8		—NH(*p*-Tolyl)	85[d]	165–166[e]	$C_{20}H_{18}N_2O_3$	8.38	8.56
9		—NH(*o*-Tolyl)	90	165 dec.	$C_{29}H_{18}N_2O_3$	8.38	8.39
10	C_3H_7	Cl	90	164–165[f]	$C_{14}H_{12}NO_3Cl$[e]		
11		—NH(1-Butyl)	48	148–149	$C_{18}H_{22}N_2O_3$	8.91	8.83
12		—NH(1-Heptyl)	50	120–122	$C_{21}H_{28}N_2O_3$	7.86	8.07
13		$—NHC_{14}H_{29}$	85	112–114	$C_{28}H_{42}N_2O_3$	6.23	6.16
14		$—NHC_6H_5$	75	207–208	$C_{20}H_{18}N_2O_3$	8.38	8.29
15		—NH(*p*-Tolyl)	89	149–150	$C_{21}H_{20}N_2O_3$	8.04	8.02
16	*i*-C_4H_9	Cl	51	162–163[g]			
17		$—NHC_{14}H_{29}$	50	109–110	$C_{29}H_{44}N_2O_3$	5.98	6.10
18	$C_{11}H_{23}$	Cl	26	133–134	$C_{22}H_{28}NO_3Cl$[h]	3.59	3.51
19		—NH(1-Butyl)	60	124–127	$C_{26}H_{38}N_2O_3$	6.57	6.63
20		—NH(1-Heptyl)	64	108–110	$C_{29}H_{44}N_2O_3$	5.98	6.11
21		$—NH(C_{14}H_{29})$	61	125–126	$C_{36}H_{58}N_2O_3$	4.94	5.11
22	$C_{17}H_{35}$	Cl	54	133–134	$C_{28}H_{40}NO_3Cl$[i]	2.95	3.19
23		—NH(1-Butyl)	33	123–124	$C_{32}H_{50}N_2O_3$	5.49	5.41
24		—NH(1-Heptyl)	66	115–116	$C_{35}H_{54}N_2O_3$	5.07	5.24
25		$—NHC_{14}H_{29}$	51	129–130	$C_{42}H_{20}N_2O_3$	4.30	4.37
26		—NH(*p*-Tolyl)	83	162–163	$C_{35}H_{48}N_2O_3$	5.14	5.34
27	$CHCl_2$	Cl	50	218–219	$C_{12}H_6NO_3Cl_3$[j]	4.40	4.44
28		—NH(1-Butyl)	65	151–152	$C_{16}H_{16}N_2O_3Cl_2$	7.89	7.95
29		—NH(1-Heptyl)	37	141–142	$C_{19}H_{22}N_2O_3Cl_2$	7.05	7.09
30		$—NHC_{14}H_{29}$	54	128–130	$C_{26}H_{36}N_2O_3Cl_2$	5.65	5.97
31		—NH(*p*-Tolyl)	76	203 dec.	$C_{19}H_{14}N_2O_3Cl_2$	7.20	7.16

[a] Reported[4] m.p. 218–219°. [b] Reported m.p. 203°. [c] Reported[6] m.p. 188–189°. [d] Darkened at 94° but regained orange color as the temperature rose above 100°. [e] See ref. 2. [f] Reported[6] m.p. 162–163°. [g] Reported[6] m.p. 161°. [h] Calcd.: Cl, 9.12; found: Cl, 9.31. [i] Calcd.: Cl, 7.51; found: Cl, 7.69. [j] Calcd.: Cl, 33.38; found: Cl, 33.61.

and these workers found that the halogen readily reacted with amines.

Acyl groups were selected for use in this work that ranged from two to eighteen carbons. The dichloroacetyl group was included as a representative as the group is found in chloroamphenicol.[5] Hoover and Day[6] have recently reported the synthesis and use of some 2-acylamino-3-amino-1,4-naphthoquinones in the formation of two substituted 1H-naphthimidazole-4,9-diones.

Although none of the compounds reported in this paper have high amebicidal activity, certain features which correlate this activity with structure are of interest. The lauric acid and stearic acid derivatives, No. 18–26 were inactive in the amebicidal and tubercular tests. Propionic acid and butyric acid derivatives were the most active, and compound No. 9 exhibited the highest activity of any of those tried in the two tests mentioned above. This compound was amebicidal at a dilution of 1:50,000.

EXPERIMENTAL

Acylation of 2-amino-3-chloro-1,4-naphthoquinone. A mixture of 1 mole of 2-amino 3 chloro 1,4-naphthoquinone and 3 moles of the desired acyl halide in 10 parts of dioxane was refluxed for 12 to 15 hr.

A yellow solid separated when the mixture was cooled. This solid was removed and recrystallized from a 50:50 mixture of methanol and dioxane. Most of the acyl derivatives were yellow to tan in color and somewhat light sensitive. The data for these compounds are included in Table I.

2-Acylamino-3-alkyl (or aryl)amino-1,4-naphthoquinones. To a hot solution of 0.01 mole of 2-acylamino-3-chloro-1,4-naphthoquinone in 25 ml. of dioxane was added 0.02 mole of the selected amine. The solution was refluxed for 2 hr., cooled, and filtered. The red product was recrystallized from ethanol. The data for these compounds are given in Table I.

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NORTH TEXAS STATE COLLEGE
DENTON, TEX.

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(5) M. C. Rebstock, H. M. Crooks, J. Controulis and Q. R. Batz, *J. Am. Chem. Soc.*, **71**, 2458 (1949).

(6) J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc.*, **76**, 4148 (1954).

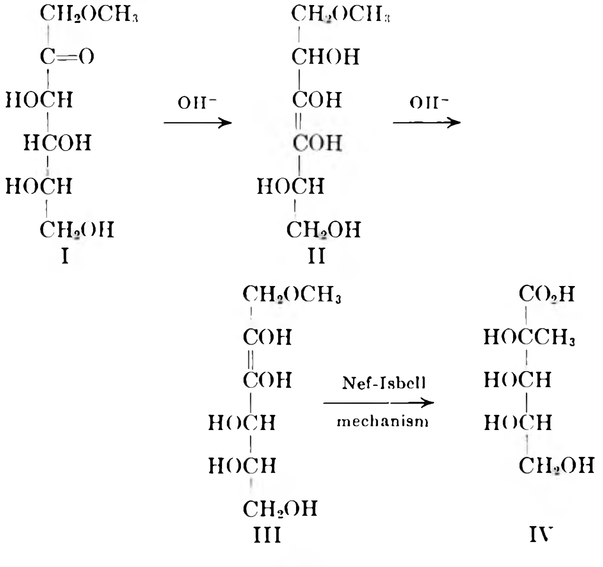
Conversion of 1-*O*-Methyl-L-sorbose to "α"-L-Glucosaccharinic Acid by Alkali

JOHN C. SOWDEN AND IRENE I-LING MAO

Received February 15, 1960

Recent studies by Kenner and his associates have indicated certain general rules, based on the Nef-Isbell mechanism,[1] relating the effects of substitution in a sugar molecule to the course of its conversion to saccharinic acids. For example, treatment of 1-*O*-methyl-D-fructose,[2] 3-*O*-methyl-D-fructose,[3] and 4-*O*-methyl-D-fructose[4] with aqueous calcium hydroxide is reported to lead, respectively, to the preferential formation of the saccharinic, metasaccharinic, and isosaccharinic acid structures.

From the above results, it was to be expected that a new acid of the saccharinic acid class, 2-*C*-methyl-L-*xylo*- or 2-*C*-methyl-L-*lyxo*-pentonic acid, would be the principal product from the treatment of 1-*O*-methyl-L-sorbose with aqueous calcium hydroxide. Accordingly, we have examined the latter reaction in an effort to obtain a reference compound for further studies of alkaline isomerization in the galactose family of sugars. 1-*O*-Methyl-L-sorbose was prepared in amorphous form by methylation of 2,3:4,6-di-*O*-isopropylidene-L-sorbose, followed by hydrolysis of the isopropylidene groups. After reaction of the methylated ketose with aqueous calcium hydroxide, paper chromatography revealed the presence of at least eight components in the product. The mixture was partially separated by column chromatography on powdered cellulose and, although we were unsuccessful in our attempts to isolate and identify either of the two new saccharinic acids indicated above, there was obtained in low yield a crystalline product that proved to be the enantiomorph of the known "α"-D-glucosaccharinic lactone (2-*C*-methyl-D-*ribo*-pentonic γ-lactone[5]).



The unexpected formation of "α"-L-glucosaccharinic acid may be explained by assuming an initial inversion of configuration at C-4 of the 1-*O*-methyl-L-sorbose, I, by way of the 3,4-enediol,[6] II, followed by operation of the Nef-Isbell mechanism on 1-*O*-methyl-L-*erythro*-hexose-2,3-enediol, III. Alternatively, it is conceivable that fragment recombination is involved in the conversion of I to IV.[7]

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[1] H. S. Isbell, *J. Research Natl. Bur. Standards*, **32**, 45 (1944). For a review of the chemistry of the saccharinic acids, including theories of the mechanism of their formation, see J. C. Sowden, *Advances in Carbohydrate Chem.*, **12**, 35 (1957).

(2) J. Kenner and G. N. Richards, *J. Chem. Soc.*, 1784 (1954).

(3) J. Kenner and G. N. Richards, *J. Chem. Soc.*, 278 (1954).

(4) J. Kenner and G. N. Richards, *J. Chem. Soc.*, 1810 (1955).

(5) J. C. Sowden and D. R. Strobach, *J. Am. Chem. Soc.*, **82**, 954 (1960).

EXPERIMENTAL

2,3:4,6-Di-O-isopropylidene-1-O-methyl-L-sorbose. 2,3:4,6-Di-*O*-isopropylidene-L-sorbose[8] (m.p. 77–78°) was methylated by the Haworth procedure according to the general directions of Hibbert and co-workers[9] for the methylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside. The product was isolated from the cooled methylation reaction mixture by extraction with ether. The extract was washed with water, dried over sodium sulfate, and concentrated to a crystalline residue. The crude product (90% yield) was recrystallized from ethanol by the addition of water to give pure 2,3:4,6-di-*O*-isopropylidene-1-*O*-methyl-L-sorbose, m.p. 54–55°, $[\alpha]_D^{22}$ −11° in acetone, *c* 4.

Anal. Calcd. for $C_{13}H_{22}O_6$: C, 56.9; H, 8.08. Found: C, 57.0; H, 8.12.

1-O-Methyl-L-sorbose. A solution of 5 g. of the above product in 50 ml. of 50% ethanol, containing 0.175% of hydrogen chloride, was heated at 80° for 12 hr. The cooled solution was de-ionized over Duolite A-4, decolorized, and concentrated at reduced pressure. The resulting pale yellow sirup, obtained in nearly quantitative yield, showed a methoxyl content of 15.8% (calculated for 1-*O*-methyl-L-sorbose, 16% OCH_3).

Reaction of 1-O-methyl-L-sorbose and calcium hydroxide. A solution of 65 g. of 1-*O*-methyl-L-sorbose in 1200 ml. of oxygen-free water was treated with 55 g. of calcium hydroxide. After 16 days at room temperature, acid production, as determined by successive decationization and titration of aliquots, had practically stopped. The solution was then filtered, saturated with carbon dioxide, again filtered, and passed over Amberlite IR-100 cation exchange resin to remove calcium ions. Decolorization and concentration at reduced pressure then gave 48 g. of a light-colored, acidic sirup.

Samples of the above sirup were subjected to descending chromatography on Whatman no. 1 paper with *n*-butyl alcohol-ethanol–formic acid–water (45:5:1:49 by volume). Spraying the thoroughly dried papers with bromcresol green showed a strong zone at R_f 0.76, whereas spraying with ammoniacal silver nitrate revealed strong zones with R_f values of 0.60, 0.52, 0.43, and 0.28 with weaker zones at 0.66, 0.38, and 0.16. In the same solvent system, the following known compounds showed R_f values as follows: lactic acid, 0.76; "α"-D-glucosaccharinic lactone, 0.52; "α"-D-isosaccharinic lactone, 0.43; "α"-D-galactometasaccharinic lactone, 0.28; 1-*O*-methyl-L-sorbose, 0.27; and L-sorbose 0.12.

Isolation and identification of "α"-L-glucosaccharinic lactone. A sample of the above acidic sirup was extracted continuously with ether for 1 day to remove the bulk of the lactic acid. The residue (1.33 g.) was chromatographed through a column containing 150 g. of Whatman Standard Grade cellulose powder, using the developing solvent mixture described above. Fractions of 5 ml. each were collected and examined by paper chromatography. Fractions 91–99, which showed the presence only of the two components with respective R_f values of 0.43 and 0.52, were pooled and concentrated to yield 0.242 g. of sirup. Crystals appeared in this sirup after several months, and these were used to inoculate the main, sirupy reaction product. After several days, there was obtained 1.0 g. of crude crystals, m.p. 159–161°, R_f 0.52. Recrystallization from water gave pure "α"-L-glucosaccharinic lactone (2-*C*-methyl-L-*ribo*-pentonic γ-lactone), m.p. 162–163°, $[\alpha]_D^{22}$ −93.4° in water, *c* 1. The corresponding constants for "α"-D-glucosaccharinic lactone[10] are m.p. 160–161°, $[\alpha]_D$ +93.5° in water. The infrared spectra of the enantiomorphic lactones were identical.

Anal. Calcd. for $C_6H_{10}O_5$: C, 44.4; H, 6.21; equiv. wt., 162. Found: C, 44.7; H, 6.29; equiv. wt., 161.

Acetonation[7] of "α"-L-glucosaccharinic lactone gave the 2,3-*O*-isopropylidene derivative, m.p. 60–62°, $[\alpha]_D^{22}$ +39.5° in chloroform, *c* 2. The corresponding constants for 2,3-*O*-isopropylidene-2-*C*-methyl-D-*ribo*-pentonic γ-lactone[7] are m.p. 62–63° and $[\alpha]_D^{25}$ −38.4° in chloroform, *c* 3.4. The enantiomorphic acetonated lactones showed identical infrared spectra.

"α"-L-Glucosaccharinic lactone gave a phenylhydrazide with m.p. 164–165° and $[\alpha]_D^{22}$ −50° in water, *c* 1. The reported[11] constants for "α"-D-glucosaccharinic phenylhydrazide are m.p. 167–169° and $[\alpha]_D$ +50.3° in water.

Recrystallization of a mixture of equal parts of α-D- and "α"-L-glucosaccharinic lactones from water gave the racemate, m.p. 155–156°, $[\alpha]_D^{22}$ 0° in water.

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WASHINGTON UNIVERSITY
ST. LOUIS 30, MO.

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[6] Evidence for the participation of the 3,4-enediol in the alkaline isomerization of hexoses is given by J. C. Sowden and R. R. Thompson, *J. Am. Chem. Soc.*, **80**, 1435 (1958).

[7] Evidence for fragment recombination in the formation of "α"-D-glucosaccharinic acid from D-mannose and alkali is given by J. C. Sowden, M. G. Blair, and D. J. Kuenne, *J. Am. Chem. Soc.*, **79**, 6450 (1957).

[8] We are indebted to Dr. J. A. Aeschlimann, Hoffman-La Roche, Inc., Nutley, N. J., for the generous gift of this substance.

[9] T. H. Evans, I. Levi, W. L. Hawkins, and H. Hibbert, *Can. J. Research*, **20**, 175 (1942).

(10) C. Scheibler, *Ber.*, **13**, 2212 (1880).

(11) E. Fischer and F. Passmore, *Ber.*, **22**, 2728 (1889); J. U. Nef, *Ann.*, **376**, 1 (1910).

The Nitrogen Compounds of Petroleum Distillates. XXIX. Identification of 5-Methyl-6,7-dihydro-1,5-pyrindine

H. L. LOCHTE AND A. G. PITTMAN

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In a previous article[1] the isolation of two dihydropyrindines from California petroleum and a new method of synthesis for the methyl-6,7-dihydro-1,5-pyrindines were described. One of the dihydropyrindines from petroleum was identified as 2-methyl-6,7-dihydro-1,5-pyrindine, while the other was assumed to be an isomer with the methyl group located in the cyclopentane ring.

We wish to report the identification of this second dihydropyrindine as 5 - methyl - 6.7 - dihydro - 1,5-

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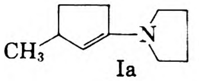
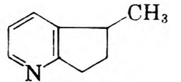
(1) E. L. Lochte and A. G. Pittman, *J. Am. Chem. Soc.*, **82**, 469 (1960).

pyrindine (IIa). This is the first report of the occurrence of this compound from any natural source.

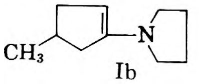
The isomeric 5- and 6-methyl-6,7-dihydro-1,5-pyrindines (IIa and IIb) were synthesized by utilizing the method previously reported for the preparation of methyl-6,7-dihydro-1,5-pyrindines.[1] The reaction of pyrrolidine with 3-methylcyclopentanone resulted in the formation of the enamines Ia and Ib, which in turn were converted to the dihydropyrindines IIa and IIb.



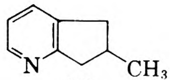
Ia



IIa



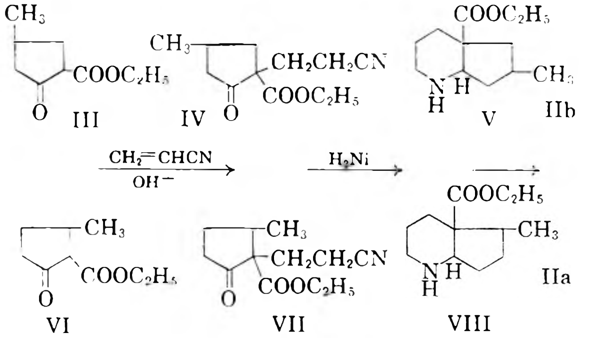
Ib



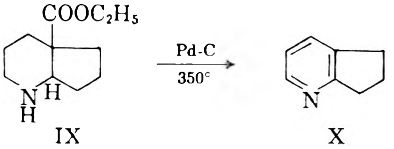
IIb

Separation of the isomers IIa and IIb was accomplished by fractional recrystallization of their picrate derivatives. This operation yielded a picrate melting at 135–136° and another melting at 147–149°. This latter picrate proved identical with the picrate (m.p. 147–149°) of the petroleum base previously isolated.[1]

The position of the methyl group in the two amines obtained *via* the enamine synthesis was established by an alternate synthetic route. Dieckmann has shown[2] that during the base-catalyzed intramolecular cyclization of diethyl β-methyladipate, the product obtained consists mainly of 2-carbethoxy-4-methylcyclopentanone (III), while the isomeric 2-carbethoxy-3-methylcyclopentanone (VI) occurs to a smaller extent. Monocyanoethylation of this product, followed by a reductive ring closure and subsequent dehydrogenation and decarbethoxylation, would then be expected to produce 6-methyl-6,7-dihydro-1,5-pyrindine (IIb) as the major product.



An investigation of the model compound 4a-carbethoxyoctahydro-1,5-pyrindine (IX) to determine the most convenient method of removing the bridge carbethoxy group was initiated. The bridge carbethoxy group could be removed with simultaneous dehydrogenation of the piperidine ring by passing the vapors of the amine slowly over palladium-on-charcoal at 350°. When the mixture of V and VIII, which had been obtained previously, was submitted to this treatment, the product, after conversion to picrate derivatives, was found to consist of an 80:20% mixture of 135–136°:147–149° melting picrates. According to the reasoning outlined above, the picrate which melted at 147–149° corresponds to the derivative of 5-methyl-6,7-dihydro-1,5-pyrindine (IIa), as it is not the major product. Consequently, 5-methyl-6,7-dihydro-1,5-pyrindine is the structure of the petroleum base in question.



EXPERIMENTAL[3,4]

Enamines of 3-methylcyclopentanone (Ia and Ib). The enamine preparation was carried out in the manner previously reported[1] using 80 g. of 3-methylcyclopentanone (0.82 mole) and 125 g. of pyrrolidine (1.8 moles). The 3-methylcyclopentanone was prepared by the oxidation of 4-methylcyclohexanol to β-methyladipic acid by the method of Hartman[5] and cyclization of β-methyladipic acid by distilling with barium hydroxide according to the method of Harries and Wagner.[6]

Monocyanoethylation of Ia *and* Ib. Monocyanoethylation of the crude mixture of Ia and Ib was conducted as before during the monocyanoethylation of cyclopentanonepyrrolidine enamine[1] except that reflux time was continued for 16 hr. After hydrolysis and work-up in the usual manner the product was distilled through a Todd column packed with glass helices yielding 74 g. of colorless liquid (60%), b.p. 97° (0.5 mm.), n_D^{30} 1.4615.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.52; H, 8.61; N, 9.27. Found: C, 71.42; H, 8.68; N, 9.52.

5- and 6-Methyloctahydro-1,5-pyrindine. The ketonitrile mixture obtained in the preceeding preparation was reductively cyclized as before in the preparation of octahydro-1,5-pyrindine.[1] Work-up and distillation gave a colorless liquid, b.p. 88° (29 mm.), n_D^{27} 1.4757.

Anal. Calcd. for $C_9H_{17}N$: neut. equiv. 139.2. Found: neut. equiv. 138.3.

5- and 6-Methyl-6,7-dihydro-1,5-pyrindine (IIa *and* IIb). Dehydrogenation of the mixture of 5- and 6-methyloctahydro-1,5-pyrindine over 30% palladium-on-charcoal in the vapor phase at 310° yielded a colorless liquid, b.p. 207° (753 mm.) n_D^{22} 1.5230.

Anal. Calcd. for $C_9H_{11}N$: neut. equiv. 133.2. Found: neut. equiv. 133.0.

This dehydrogenated product was converted to the picrate derivatives by treatment with a saturated solution of picric acid in 95% ethanol. Fractional recrystallization of

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(2) W. Dieckmann, *Ann.*, **317**, 27 (1901); W. Dieckmann and A. Groeneveld, *Ber.*, **33**, 595 (1900).

(3) All melting points are corrected; all boiling points are uncorrected. Microanalyses were performed at the Huffman Microanalytical Laboratories, Wheatridge, Colo.

(4) Neutralization equivalents were determined by nonaqueous titration by the method of J. S. Fritz, *Anal. Chem.*, 22, 1028 (1950).

(5) W. W. Hartman, *Org. Syntheses*, **Coll. Vol. I,** 19, Note 1. (1941).

(6) Harries and Wagner, *Ann.*, **410,** 36 (1915); see also Thorpe and Kon, *Org. Syntheses*, **Coll. Vol. I,** 192 (1941).

the solid thus obtained from 95% ethanol gave a picrate, m.p. 135–136°, as the major fraction. This picrate was subsequently shown to be the derivative of 6-methyl-6,7-dihydro-1,5-pyrindine (IIb).

Anal. Calcd. for $C_{15}H_{14}N_4O_7$: C, 49.72; H, 3.86. Found: C, 49.73; H, 3.93.

Two grams of this picrate was converted to the free base (IIb) by treatment with concd. ammonium hydroxide. The free base (IIb) was dried over sodium hydroxide and distilled giving a colorless liquid, b.p. 208° (751 mm.), n_D^{23} 1.5239, d_{20}^{20} 1.0007.

Anal. Calcd. for $C_9H_{11}N$: neut. equiv. 133.2. Found: neut. equiv. 132.1.

A *styphnate* derivative of the amine (IIb) was made m.p. 156–157°.

Anal. Calcd. for $C_{15}H_{14}N_4O_8$: C, 47.62; H, 3.70. Found: C, 47.79; H, 3.72.

Another picrate, m.p. 147–149°, was obtained in smaller amounts during the fractional recrystallization mentioned above. This picrate was subsequently shown to be the derivative of 5-methyl-6,7-dihydro-1,5-pyrindine (IIa). A mixed melting point with the petroleum base picrate previously isolated,[1] m.p. 147–149°, showed no depression. The infrared spectra of the petroleum base picrate (m.p. 147–149°) and the synthetic base picrate were identical.

Anal. Calcd. for $C_{15}H_{14}N_4O_7$: C, 49.72; H, 3.86; N, 15.46. Found: C, 49.88; H, 4.08; N, 15.40.

Conversion of 100 mg. of this picrate to the free base (IIa) by treatment with ammonium hydroxide yielded a liquid which, after drying and distillation, boiled at 207–208° (746 mm.).

A *styphnate* derivative of IIa was prepared by adding about 30 mg. of the amine (IIa) to about 1 cc. of a saturated solution of styphnic acid in 95% ethanol. Recrystallization from 95% ethanol yielded small yellow needles, m.p. 172–173.5°.

Anal. Calcd. for $C_{15}H_{14}N_4O_8$: C, 47.6; H, 3.7. Found: C, 47.5; H, 3.8.

6,7-Dihydro-1,5-pyrindine (X) *from 4a-carbethoxyoctahydro-1,5-pyrindine* (IX). One-half gram of the aminoester (IX), prepared according to Albertson,[7] was slowly distilled through 30% palladium-on-charcoal which was held between 350–360°. As before, hydrogen was used as a carrier gas for the vapors. The reaction was complete in 48 hr. The product was converted to a picrate derivative and after two recrystallizations from 95% ethanol gave 0.28 g. (31%) of picrate, m.p. 180–181°. This picrate showed no melting point depression on admixture with an authentic sample of the picrate derivative of X.

Alternate synthesis of 5- and 6-methyl-6,7-dihydro-1,5-pyrindine (IIa *and* IIb). Dieckmann condensation of diethyl β-methyladipate afforded the β-ketoester mixture (III and VI) b.p. 117–119° (16 mm.); (lit.,[2] m.p. 107–108°, 11–12 mm.). This mixture was monocyanoethylated by adding 17 g. of acrylonitrile (0.32 mole) slowly with stirring to 52 g. of the mixture of β-ketoesters (III and VI) (0.30 mole) in 60 g. of 1,4-dioxane containing 4.2 g. of Triton B. The temperature of the reaction mixture was maintained between 30–40° by external cooling during the addition. After 45 min. the addition was complete and the reaction mixture was stirred an additional hour. After adding about 40 cc. of diethyl ether to the reaction mixture it was washed briefly with 5% hydrochloric acid, then once with water. After drying over sodium sulfate, the solvents were removed *in vacuo* and the residue distilled giving 48 g. of colorless material (73%), b.p. 136° (0.5–1 mm.), n_D^{20} 1.4642.

Anal. Calcd. for $C_{12}H_{17}O_3N$: C, 64.57; H, 7.62. Found: C, 64.58; H, 7.73.

The monocyanoethylated product (IV and VII) obtained above was then reductively cyclized as in the preparation of octahydro-1,5-pyrindine.[1] After removal of Raney nickel and ethanol, the product was distilled giving a colorless liquid, b.p. 151° (35 mm.).

Anal. Calcd. for $C_{12}H_{21}NO_2$: neut. equiv. 211.3. Found: neut. equiv. 212.7.

The aminoester mixture (V and VIII) was dehydrogenated and decarbethoxylated in the manner described in the preparation of X. The product obtained by this procedure was chromatographed on a preparative gas chromatographic unit[8] and the amines (IIa and IIb), which occurred as a single peak, were collected. This material was treated with equimolar quantities of picric acid in 95% ethanol. The melting point of the crude picrate mixture which resulted was 121.5–127.5°. This corresponds to an 80:20% mixture of 135–136:147–149° melting picrates according to a previously prepared melting point mixture diagram of the two isomers. After four recrystallizations of a portion of this crude picrate mixture 146 mg. of picrate, m.p. 135–136°, was obtained which did not depress the melting point of the 135–136° melting picrate obtained by the enamine route. The filtrates from the recrystallizations were combined and solvent removed under reduced pressure. After twelve recrystallizations of the crude picrate residue which remained, 24.3 mg. of picrate, m.p. 147–149°, was obtained. This picrate, m.p. 147–149°, showed no melting point depression on admixture with the picrate, m.p. 147–149°, obtained by the enamine route. The filtrates from the last recrystallizations were combined and solvent removed under reduced pressure. The residual crude picrate, after drying, consisted of 106 mg. and melted at 113–117°. According to the melting point mixture diagram of the two isomeric picrates this residue corresponded to a 45:55% mixture of 135–136°:147–149° melting picrates.

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF TEXAS
AUSTIN, TEX.

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[7] N. F. Albertson, *J. Am. Chem. Soc.*, **72**, 2594 (1950).

[8] See ref. 1 for a description of the gas chromatographic apparatus.

Six and Twelve Carbon Fluorocarbon Derivatives of Sulfur Hexafluoride

R. D. DRESDNER, T. M. REED III,
T. E. TAYLOR, AND J. A. YOUNG

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Electrochemical reactions of organic sulfides in anhydrous hydrogen fluoride have received some attention in recent years.[1] This work extends these investigations to include hexyl and phenyl sulfide. As in previous work, the compounds R_fSF_4, $(R_f)_2SF_4$, R_fF and R_f-R_f (where R_f is C_6F_{13} or cyclo C_6F_{11}) were isolated or detected. The yields of isolable product were low for phenyl sulfide. Many of the above products that were liquids at 25° were purified by preparative scale chromatography in one-inch columns packed with hexadecane on an inert support.[2] The products that were solids at 25° were further purified by the method of Tatlow[3] using hot heptane for the recrystallizations.

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[1] (a) A. F. Clifford, H. K. El-Shamy, H. J. Emeleus, and R. N. Haszeldine, *J. Chem. Soc.* 2372 (1953). (b) W. A. Severson, T. J. Brice, and R. I. Coon, 128th Meeting ACS, Minneapolis, Minn., Sept. 11–16, 1955. (c) R. Dresdner, *J. Am. Chem. Soc.* **79**, 69 (1957). (d) F. W. Hoffman, T. C. Simmons, R. B. Beck, H. V. Holler, T. Katz, R. J. Koshar, E. R. Larsen, J. E. Mulvaney, F. E. Rogers, B. Singleton, and R. S. Sparks, *J. Am. Chem. Soc.* **79**, 2424 (1957). (e) R. D. Dresdner and J. A. Young, *J. Am. Chem. Soc.* **81**, 574 (1959). (f) J. A. Young and R. D. Dresdner, *J. Org. Chem.* **24**, 1021 (1959). (g) R. N. Haszeldine and F. Nyman, *J. Chem. Soc.* 2684 (1956).

Freon 112, 1,2-difluoro-1,1,2,2-tetrachloroethane, was an excellent solvent for the solid products and molecular weights were determined by the freezing point depression method in this medium. The molal freezing point constant was determined using perfluorodicyclohexyl as the standard. Raoult's law was observed at concentrations up to 0.06 molal. Semiquantitative purity estimations of all the products reported were determined by vapor phase chromatography using in all cases for the liquids both a polar substrate such as the ethyl ester of Kel-F acid 8114 and a nonpolar substrate such as hexadecane. These were run at various flows of nitrogen carrier gas and at temperatures between 80 and 100°. Very significant changes in purity (as determined by the integrated areas under the various chromatographic peaks) were noted before and after preparative scale purifications on narrow boiling fractions obtained by fractionation. In all cases only minor impurity components, 1–2%, were observed in the purified materials.

Both compounds, hexyl and phenyl sulfide, yielded some extremely high boiling (210–240° at 0.1 mm.) resinous products. One such sample was used to prepare a chromatographic column on which the purity of the purified solid products could be estimated. These products were dissolved in Freon 113 and injected into the unit operated at 200°.

The electrochemical cell and operation procedures were very similar to those described previously[1d,e] although minor alterations were made in the overhead reflux condenser to prevent the perfluorocyclohexane from clogging. Products accumulated at two points: in the cold traps at the end of the gas train and as the less volatile fluorocarbon layer that accumulated at the bottom of the cell. In each operation the cell-retained products were siphoned from the cell into a polyethylene separatory funnel and separated from a small layer of hydrogen fluoride. This fluorocarbon material was neutralized with dilute aqueous sodium bicarbonate, dried, filtered, and fractionated in appropriate equipment.

EXPERIMENTAL

Results from hexyl sulfide. Four hundred and seventy grams of $(C_6H_{13})_2S$ (2.3 moles) was electrolysed at 4.6 volts and at about 10 amperes and yielded 1041 g. of products during 340 hr. of operation. The main product by weight, 411 g., was a mixture of C_6F_{14} isomers, b.p. 57.2–58.0°, m.w. 338, $n_D^{25°}$ 1.2501; reported[4] for n-C_6F_{14}, b.p. 57.32° $n_D^{22°}$ 1.2515. This material was analysed by chromatography using a 40-foot column with hexadecane on inert, acid washed Celite; the main component appeared to present as 75% by weight while another peak representing 20% seemed to be isomeric and about 5% was probably nonisomeric impurity. An aliquot of the material was subjected to preparative scale chromatographic purification in which all but a small amount of the apparent isomeric impurity was removed. The refractive index at 25° of this purified material was 1.2498.

The second largest fraction by weight amounted to 234 g. and boiled between 117.8 and 118.5°. On chromatographic analysis this material demonstrated a main peak of about 74% by weight and seven other impurity peaks. An aliquot of this was purified chromatographically until all but about 1% of the impurities were removed. It had the correct analysis for perfluorohexylsulfur pentafluoride, $C_6F_{13}SF_5$, calcd. MR_D 41.28, mol. wt. 448; observed values: MRp 41.77, n_D^{25} 1.2829, d_D^{25} 1.8910, b.p. 118.2°, m.p. −31.5 to −30.5°, mol. wt. 446.

Anal. Calcd. for $C_6F_{13}SF_5$: F, 76.60; S, 7.18. Found: F, 76.7; S, 6.99.

A fractionation flat was encountered in the vacuum fractionation of the higher boiling materials which condensed to a slush. This occurred at 65° and about 1 mm. The fraction amounted to 100 g. It was filtered at 0°. The residues began to melt at 50°. After several recrystallizations from hot heptane the white crystals reached a constant melting point of 71–72°. A purified sample was analysed chromatographically using a stationary phase of the highest boiling resin recovered from the cell residues. Only about a 2% impurity was detected under the conditions of the tests. Molecular weights of the compounds were determined. About 50 g. of the material, which analysed correctly for perfluorodihexylsulphur tetrafluoride, was recovered, calcd. mol. wt. 746; found mol. wt. 725, 730, m.p. 71–72°.

Anal. Calcd. for $C_{12}F_{30}S$: F, 76.4; S, 4.30. Found: F, 76.8; S, 4.41.

At 85°, 51 mm., a fraction amounting to 51 g. was obtained that by analogy with other work should have been $C_{12}F_{26}$. It had a wide melting range beginning at 10° and showed three equal peaks when it was analysed on the fluorocarbon resin.

Results from phenyl sulfide. Four hundred grams of phenyl sulfide (2.1 moles) electrolysed at 5.1 volts and about 10 amperes yielded 925 g. of products during 267 hr. of operation. The effluent gas product was mainly perfluorocyclohexane, which amounted to 375 g. of crude product, purified by sublimation. The crude material was placed in a large stoppered glass filter funnel. As perfluorocyclohexane condensed on the walls of the funnel the trapped liquid impurities passed through the filter and were removed *via* a stopcock. The process was repeated until no more liquid was collected. The vapor above the subliming solid had a composition of 99.3% of one component, as analysed chromatographically. The purified material had a molecular weight of 300. Three hundred grams was recovered.

A fraction amounting to 30 g. was recovered in the fraction that boiled between 109.5 and 110.5°. Chromatographic purification yielded a product in which the main component was 98.9%. Analysis showed this material to be perfluorocyclohexylsulphur pentafluoride, c-$C_6F_{11}SF_5$, calcd., mol. wt. 408, MR_D 39.08; observed mol. wt. 404, n_D^{25} 1.3041, d_4^{25} 1.9530, MR_D 39.67, b.p. (micro) 110.5°, m.p. glass.

Anal. Calcd. for $C_6F_{16}S$: F, 74.40; S, 7.83. Found: F, 74.00; S, 7.87.

A second fraction was isolated at 88° and 35 mm. which amounted to 117 g. of a slush. The slush was filtered, washed with water and acetone, and dried. The crude material

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(2) T. M. Reed, J. F. Walter, R. Cecil, and R. D. Dresdner, *Ind. and Eng. Chem.* **51**, 271 (1959).

(3) G. B. Barlow and J. C. Tatlow, *J. Chem. Soc.* 4695 (1952).

(4) A. M. Lovelace, W. Postelnek, and D. A. Rausch, *Aliphatic Fluorine Compounds*, Reinhold Publishing Corp., New York, 1958, page 74.

melted at 65.2–67.2°. Chemical analysis showed only a trace of sulfur. The material was recrystallized from boiling heptane several times to a constant melting point of 75.5–76.0°. This agrees with the reported[3] value for perfluorodicyclohexyl. This compound was analysed by vapor phase chromatography using the fluorocarbon resin column and appeared to be 99% one component. The infrared spectrum of a melt agreed exactly with that for perfluorodicyclohexyl as determined by Tatlow.[3] The carbon and fluorine analyses of the compound were within 0.3% of the calculated values.

A final fraction was isolated at 126° and 37 mm. This was a slush amounting to only 12 g. Six grams of crude filtration residue melted at 65–67.5°. It decomposed at 180 to 200° and accordingly could not be analysed by vapor phase chromatography. At lower temperatures the development time was so long that only one broad low peak was obtained. Consequently, the material was recrystallized from hot heptane to a constant melting point of 90–91°. Analysis and molecular weight by the cryoscopic method in Freon 112 indicated that the purified material was the perfluorodicyclohexylsulphur tetrafluoride, $(C_6F_{11})_2SF_4$, mol. wt. 670; observed mol. wt. 660, m.p. 90–91°.

Anal. Calcd. for $C_{12}F_{26}S$: F, 73.73; S, 4.77. Found: F, 73.38; S, 4.81.

In both of the reported operations considerable material boiling well above the highest boiling products reported was obtained. This is not uncommon in low voltage electrolyses in hydrogen fluoride.

Better yields of the cyclic derivatives would probably have been obtained if the starting sulfide had been the cyclohexyl sulfide instead of the phenyl derivative. Further evidence for this statement is apparent from the fact that, in general, unsaturated compounds even though resonance stabilized tend to run poorly in the cells and frequently cause corrosion of the electrodes. Although the corrosion in this case was not as severe as that generally encountered with unsaturated materials, nickel bearing compounds were found in the cell in some quantity. Furthermore, they were observed to react with water quite violently with the evolution of heat and sparks.

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Departments of Nuclear Engineering and Chemistry
University of Florida
Gainesville, Fla.

The Interaction of Some Arylamines with Dowex-50 in 1,2-Dimethoxyethane

Gilbert S. Panson and Robert Ellsworth

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The use of ion exchange resins has been largely limited to aqueous solutions or polar solvents. To a certain extent this is because of the generally higher degree of resin swelling than that which occurs in nonpolar solvents. It is not necessary for a resin to swell in order to exhibit an appreciable ion exchange capacity. However, swelling helps to accommodate larger exchanging particles (molecules or ions).[1] Many organic compounds show limited solubilities in polar solvents or react with them. Studies show that Dowex-50 is effective in removing various aromatic amines from a solution of the amine in anhydrous 1,2-dimethoxyethane.[2] The degree of swelling of the ion exchange resin is, as might be expected, a function not only of the solvent but also of the extent to which the resin is crosslinked. The rate of adsorption of the amine is a function of the steric requirements of the amine as well as the degree of swelling and hence the porosity of the resin. By selectively swelling the ion exchange resin it is possible to get a "molecular sieve" effect where the rate and extent of adsorption is sharply dependent upon the steric requirements of the amine. The use of Dowex-50 in 1,2-dimethoxyethane was decided upon as a result of an investigation of the degree of swelling of Dowex-50 in a number of anhydrous ethers.

As can be seen from an examination of Table I, the resin is not only swollen to a rather high degree in 1,2-dimethoxyethane, but there is also a strong variation of the degree of swelling with the extent of divinylbenzene crosslinkage.

TABLE I

Swelling of Dry Dowex-50 in the Hydrogen Form

Cross linkage (% Divinylbenzene)	Solvent	Max. Swelling, % vol.	Time, hr.
4	Water	215	0.25
4	$CH_3OCH_2CH_2OCH_3$	110	0.5
4	$CH_3(OCH_2CH_2)_2OCH_3$	92	1
4	1,4-Dioxane	100	24
8	Water	115	0.25
8	$CH_3OCH_2CH_2OCH_3$	93	2
8	$CH_3(OCH_2CH_2)_2OCH_3$	80	2
8	1,4-Dioxane	75	24
12	Water	85	0.25
12	$CH_3OCH_2CH_2OCH_3$	60	2
12	$CH_3(OCH_2CH_2)_2OCH_3$	55	2
12	1,4-Dioxane	35	48

It is seen that the degree of swelling decreases with increasing crosslinkage in each case. The rate of swelling in dioxane is slow, requiring forty-eight hours for maximum swelling in the case of the 12% crosslinked resin. The degree of swelling for 1,2-dimethoxyethane and also dimethyl ether of diethylene glycol is appreciable and differs markedly for resins of different crosslinkage. Moreover the time required for attainment of maximum swelling is reasonable.

Table II summarizes the results of the batchwise extraction of some arylamines by Dowex-50 preswollen in 1,2-dimethoxyethane. The amine uptake is stated as milliequivalents of amine adsorbed per gram of resin (dry basis).

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(1) R. Kunin, G. W. Bodamer, *Ind. Eng. Chem.*, **45**, 2577 (1953).

(2) Ansul Ether-121. All glycol ethers were supplied by Ansul Chemical Co., Marinette, Wis.

TABLE II

Adsorption of Some Arylamines at 25° by Dowex-50 in 1,2-Dimethoxyethane (meq./g.)

Amine	Time, hr.								
	1	2	3	4	5	6	24	96	120
				4% Crosslinked Resin					
Aniline	2.1	2.3	2.6	2.7	2.9	—	3.5	3.5	3.5
N,*N*-Dimethylaniline	0.9	1.7	2.3	2.5	2.6	2.7	3.2	3.3	3.3
3,5-Dimethylaniline	1.3	1.5	1.7	2.0	2.1	2.2	3.0	3.3	3.3
2,4-Dimethylaniline	1.1	—	1.5	1.7	1.9	2.2	2.6	2.8	2.8
N-Methylaniline	1.1	1.4	1.5	1.6	—	1.7	2.6	2.7	2.7
2,5-Dimethylaniline	1.1	—	1.4	1.7	1.9	2.0	2.3	2.6	2.6
2,6-Dimethylaniline	0.8	0.9	1.1	1.7	—	—	2.2	2.5	2.6
				8% Crosslinked Resin					
N,*N*-Dimethylaniline	0.9	1.7	2.3	2.5	2.6	2.7	3.1	3.3	3.3
Aniline	0.9	0.9	1.2	1.3	1.4	—	2.4	2.7	2.8
3,5-Dimethylaniline	0.9	1.1	1.3	1.4	—	1.6	2.5	2.6	2.6
2,5-Dimethylaniline	0.8	0.8	1.0	1.1	—	—	2.0	—	2.5
2,4-Dimethylaniline	0.7	—	0.7	0.7	0.9	1.2	1.6	2.1	2.2
2,6-Dimethylaniline	0.5	0.7	0.7	0.8	0.9	—	1.4	1.8	1.8
				12% Crosslinked Resin					
Aniline	0.3	0.8	1.1	1.1	1.2	1.4	1.9	2.4	2.4
3,5-Dimethylaniline	0.5	0.7	1.2	1.3	1.4	—	1.9	2.3	2.3
N,*N*-Dimethylaniline	0.5	0.6	0.7	0.8	0.9	0.9	1.7	2.2	2.3
2,4-Dimethylaniline	0.2	0.3	0.4	0.5	0.6	—	1.0	1.5	1.5
2,5-Dimethylaniline	0.1	0.3	0.4	0.5	0.5	—	1.0	1.5	1.5
2,6-Dimethylaniline	0.2	0.3	0.5	0.5	0.6	—	0.9	1.3	1.4

It is noted that at constant temperature and concentration the rate of adsorption is a function of the resin crosslinkage and the type of methyl substituted amine. The values for the 4% crosslinked resin illustrates the behavior of the resin with the largest pores. Here the amines are adsorbed in the order aniline>3,5-dimethylaniline or *N*,*N*-dimethylaniline, >2,4-dimethylaniline > *N*-methylaniline > 2,5-dimethylaniline > 2,6-dimethylaniline. Apparently steric factors are important although the relative position of *N*,*N*-dimethylaniline may be attributed to difference in base strength. As might perhaps be expected in this case the differences in amine uptake are not well pronounced. The amines fall generally into two groups, aniline, *N*,*N*-dimethylaniline, and 3,5-dimethylaniline in the more strongly adsorbed group and the other amines of the series in a some what less strongly adsorbed group.

The 8% crosslinked resin illustrates the behavior of a resin of intermediate porosity. Here the order of adsorption is *N*,*N*-dimethylaniline > aniline or 3,5-dimethylaniline > 2,5-dimethylaniline > 2,4 dimethylaniline > 2,6-dimethylaniline. The position of *N*,*N*-dimethylaniline with respect to aniline can only be explained on the basis of differences in base strength. The other amines are adsorbed in an order consistent with their relative steric requirements.

The 12% crosslinked resin illustrates the behavior of the resin with the finest pores. The *ortho* methyl-substituted amines apparently do not penetrate the resin to any great extent and are largely adsorbed almost identically. *N*,*N*-Dimethylaniline is adsorbed somewhat less strongly than either of these. Apparently the steric requirements of the two *N*-methyl groups compensate for any enhanced basicity.

EXPERIMENTAL

The resins in the hydrogen form were washed first with the ether to be used in the swelling experiments, then with anhydrous diethyl ether, and then dried *in vacuo* at 60° for at least 72 hr. The ethers were dried over sodium hydroxide, refluxed over sodium borohydride in a nitrogen atmosphere to remove peroxides, and then distilled under nitrogen. The purified ethers were kept over calcium hydride under an atmosphere of nitrogen. All swelling determinations were made dilatometrically at 25°.

The amines used for the batchwise extraction of the arylamines from anhydrous 1,2-dimethoxyethane were of the highest purity available. These were dried over sodium hydroxide and redistilled at reduced pressure. In each case 12 meq. of amine and 1.5 g. (dry weight) of the preswollen resin (the capacity of this resin in water is 5.3 meq. per g.) were present in a volume of 85 ml. The experiments were run in pear-shaped flasks which were well sealed to prevent loss by evaporation and were fitted with mechanical stirrers. The design of the flasks was such as to keep the resin particles well dispersed throughout the solution during the experiments. The flasks were immersed in a thermostat at 25°. Two-milliliter samples of the solution were periodically withdrawn in duplicate, and the concentration of the amine determined potentiometrically as described in the following section. Several blank runs were made with resin and solvent in the absence of amine. Initially, under the experimental conditions used, the acidity due to the resin was negligible. However, this acidity increased slightly over a period of days and since at the same time the concentration of the amine had decreased, a correction had to be made for the values at 120 days. This correction in no case amounted to a titre of more than 0.1 ml. of 0.1N sodium hydroxide per aliquot. A correction also was made for the quantity of amine removed in the course of analysis. The extracted samples were analyzed by titration with 0.1N hydrochloric acid in 1:1 ethylene glycol-isopropyl alcohol solvent.[3] The end points were determined potentiometrically.

Department of Chemistry
Rutgers, The State University of New Jersey
Newark, N. J.

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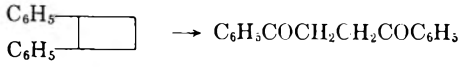
(3) S. Palit, *Ind. Eng. Chem.*, **18**, 246 (1946).

A Dimer of Styrene: 1,2-Diphenylcyclobutane

Irving S. Bengelsdorf[1]

February 19, 1960

The treatment of styrene with refluxing aqueous sulfuric acid yields two dimeric hydrocarbons, the linear, unsaturated 1,3-diphenyl-1-butene, and the cyclic, saturated 1-methyl-3-phenylindan.[2,3] The free radical or thermal polymerization of stryene, on the other hand, leads to high molecular weight polymers. If the thermal reaction is conducted, however, in the presence of polymerization inhibitors such as picric acid,[4] iodine,[5] or *sym*-trinitrobenzene,[5] one again observes the formation of cyclic, saturated dimeric hydrocarbons.[6] These dimers are structurally different from 1-methyl-3-phenylindan. The present paper presents evidence that one of the dimers produced from the free radical inhibited thermal polymerization of styrene is 1,2-diphenylcyclobutane, a head-to-head dimer of styrene. Thus, the chromic oxide oxidation of the dimeric mixture yields 1,2-dibenzoylethane (diphenacyl, succinophenone).[7] This represents the first definite evidence for the preparation[4,5] and presence of 1,2-diphenylcyclobutane.



EXPERIMENTAL

Styrene. Commercial styrene was washed free of inhibitor with aqueous sodium hydroxide, dried, and distilled through a 1-meter packed column at reduced pressure.

Dimerization reaction. A solution of 0.4 g. iodine in 200 g. styrene was refluxed for 16 hr. (146°). Vacuum distillation separated the amber-colored reaction product into 100 g. of recovered monomer, 77 g. solid polymer, and 19 g. liquid oligomer. The latter was washed with aqueous sodium bisulfite and mercury to remove codistilled iodine and then distilled to yield 7 fractions (b.p. 124–160°/0.5 mm., n_D^{20} 1.5864–1.5961).[8]

Fraction 3 (n_D^{20} 1.5913) was submitted for analysis.

Anal. Calcd. for $C_{16}H_{16}$: C, 92.1; H, 7.8; mol. wt. 208; H_2 absorption, 0.00 mole. Found: C, 92.5; H, 7.9; mol. wt. 196 (benzene); H_2 absorption, 0.03 mole.

The infrared spectra of the individual fractions differed from that of the separately prepared sulfuric acid dimer.[2] Significant differences are the presence in the latter of the methyl group absorption at 1376 cm.$^{-1}$ and the *trans*-unsaturation band at 966 cm.$^{-1}$

Oxidation of the dimer. Chromium trioxide (4 g.) was added over a period of 40 min. to a solution of dimer (1 g.) in 40 ml. glacial acetic acid at 50°. The temperature rose to 73° during the oxidation. Extraction with aqueous sodium bicarbonate gave no acidic product. After numerous washings, chromatograms on silica gel, and fractional sublimations of the residue, a small yield of colorless crystals of diphenacyl (m.p. 143–145°, lit.,[9] m.p. 144–145°) was obtained. It gives the described green color in concd. sulfuric acid solution.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.6; H, 5.9. Found: C, 80.9; H, 5.5.

The diketone reacts with 2,4-dinitrophenylhydrazine to yield a brilliant crimson derivative (m.p. 219–221°). This may be the pyridazine which can arise by the condensation of the —$NHNH_2$ function with both carbonyl groups.

Anal. Calcd. for $C_{22}H_{16}N_4O_4$: N, 14.0. Found: N, 14.0.

The *bis*-2,4-dinitrophenylhydrazone of 1,2-dibenzoylethane is reported to be orange-yellow in color and to melt at 250° dec.[10]

Conclusive identification of the oxidation product as 1,2-dibenzoylethane was established by an independent synthesis of the diketone by the zinc dust–acetic acid reduction of 1,2-dibenzoylethylene.[10] The latter was prepared by the Friedel-Crafts condensation of fumaryl chloride with benzene.[11] An attempted synthesis of the diketone involving the sulfur dehydrogenation of the methyl groups of two acetophenone molecules was not successful.

The infrared spectrum (potassium bromide) of the oxidation product was identical with that of the authentic sample of 1,2-dibenzoylethane. Absorption bands are observed at 3060, 2905, 1680, 1598, 1582, 1445, 1396, 1372, 1352, 1256, 1220, 1178, 1074, 1062, 1024, 988, 946, 927, 918, 858, 775, 736, and 692 cm.$^{-1}$

Other reactions. Attempts to isolate definite products from the dimers by (a) ozonization in carbon tetrachloride solution

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(1) Present address: Texas-U. S. Chemical Co., TEXUS Research Center, Parsippany, New Jersey.

(2) M. J. Rosen, *J. Org. Chem.*, **18**, 1701 (1953).

(3) B. B. Corson, J. Dorsky, J. E. Nickels, W. M. Kutz, and H. I. Thayer, *J. Org. Chem.*, **19**, 17 (1954).

(4) F. R. Mayo, *J. Am. Chem. Soc.*, **75**, 6133 (1953).

(5) F. R. Mayo, personal communications.

(6) The author has observed a similar oligomerization of α-methyl styrene in the presence of iodine and ultraviolet radiation.

(7) M. Pailer and U. Müller, *Monatsh-Chemie*, **79**, 615 (1948) have shown that the chromic oxide oxidation of 1,2,3,4-tetraphenylcyclobutane (isolated from the photochemical dimerization of stilbene) yields 1,2-diphenyl-1,2-dibenzoylethane (bidesyl).

(8) A recent personal communication from F. R. Mayo and K. Griggs states that the application of gas chromatographic and infrared techniques reveals that a typical dimer obtained from the iodine-inhibited thermal polymerization of styrene consists of a mixture of 1,2-diphenylcyclobutane, 1-phenylnaphthalene, 1-phenyltetralin, and other components. The 1-phenyltetralin is isolated in greatest yield.

(9) W. Borsche, S. Kettner, M. Gilles, H. Kühn, and R. Manteuffel, *Ann.*, **526**, 1 (1936).

(10) C. F. H. Allen, D. M. Young, and M. R. Gilbert, *J. Org. Chem.*, **2**, 235 (1937).

(11) R. E. Lutz, C. F. H. Allen, and F. P. Pingert, *Org. Syntheses*, Coll. Vol. III, 248 (1955).

at −78°, (b) bromination with N-bromosuccinimide followed by dehydrobromination, (c) nitration with nitric acid–sulfuric acid at 0°, and (d) oxidation with basic aqueous potassium permanganate were unsuccessful in spite of detailed crystallization, chromatographic, and sublimation techniques. These results are in keeping with the now-determined complexity of the dimeric mixture.[8]

Acknowledgments. The author is grateful to Dr. J. R. Ladd and Mr. C. Kamienski for their synthesis of the authentic sample of 1,2-dibenzoylethane.

GENERAL ELECTRIC RESEARCH LABORATORY
SCHENECTADY, N. Y.

Communications TO THE EDITOR

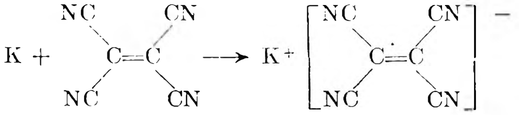
Preparation and Chemistry of Tetracyanoethylene Anion Radical

Sir:

This report describes the synthesis and preliminary study of the chemical properties of the anion radical of tetracyanoethylene (TCNE$^{\cdot-}$). The physical properties of TCNE$^{\cdot-}$, including spectral and electron paramagnetic resonance data, are being reported concurrently.[1]

Work in this laboratory has previously established that TCNE is an unusually strong π-acid, readily giving complexes with a variety of π-bases; *e.g.*, xylene, mesitylene, *etc.*[2] In these complexes there is only partial electron transfer, as indicated by their diamagnetic properties.

Recently, derivatives of TCNE have been synthesized in which there is complete electron transfer, as demonstrated by electron paramagnetic resonance (EPR) studies. For example, reaction of potassium with TCNE in the vapor phase has given a purple solid identified as the ion radical K$^+$TCNE$^{\cdot-}$.[1] The less reactive sodium amalgam and sodium naphthalenide also convert TCNE to Na$^+$TCNE$^{\cdot-}$ at room temperature. Such metals as magnesium, aluminum, zinc, and even copper are oxidized by TCNE in acetonitrile solution at room temperature to form the corresponding metal tetracyanoethylenides. In addition, nickel carbonyl undergoes oxidation and decarbonylation with TCNE to yield Ni(TCNE$^{\cdot-}$)$_2$. Certain anions have also been found to convert TCNE to TCNE$^{\cdot-}$ and the reaction of TCNE with potassium or sodium iodide provides a convenient laboratory synthesis of TCNE$^{\cdot-}$.



$$3KI + 2TCNE \longrightarrow 2K^+TCNE^{\cdot-} + KI_3$$

Tetracyanoethylene (17.0 g., 0.133 mole) and potassium iodide (30.0 g., 0.181 mole) were added to 500 ml. of acetonitrile at room temperature with stirring. The potassium iodide dissolved, and 11.4 g. (51% yield) of K$^+$TCNE$^{\cdot-}$ crystallized from the dark yellow solution. The bronze-colored product was purified by recrystallization from acetonitrile. *Anal.* Calcd. for C_6N_4K: C, 43.10; N, 33.51. Found: C, 43.19; N, 33.43.

K$^+$TCNE$^{\cdot-}$ in the solid state is stable to usual atmospheric conditions for several weeks, and the compound can be heated at 150° in an inert atmosphere for three hours without apparent change. In solution, however, the ion radical is quite sensitive to oxygen and, to a lesser degree, to water. Reaction of K$^+$TCNE$^{\cdot-}$ with water gives a 76% yield of potassium tricyanoethenolate.[3] The action of dilute hydrochloric acid on K$^+$TCNE$^{\cdot-}$ produces an equimolar mixture of TCNE and tetracyanoethane.[4] In addition, TCNE$^{\cdot-}$ is oxidized to TCNE in 65% yield by silver trifluoroacetate.

The studies of the synthesis and properties of TCNE$^{\cdot-}$ are continuing and will be reported shortly.

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CENTRAL RESEARCH DEPARTMENT
EXPERIMENTAL STATION
E. I. DU PONT DE NEMOURS & CO.
WILMINGTON, DEL.

O. W. WEBSTER
W. MAHLER
R. E. BENSON

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[1] The existence of stable metal tetracyanoethylenides was first recognized by Prof. S. I. Weissman, Washington University, St. Louis; see W. D. Phillips, J. C. Rowell, and S. I. Weissman, *J. Chem. Phys.*, in press.

[2] R. E. Merrifield and W. D. Phillips, *J. Am. Chem. Soc.*, **80**, 2278 (1958).

[3] W. J. Middleton, E. L. Little, D. D. Coffman, and V. A. Engelhardt, *J. Am. Chem. Soc.*, **80**, 2795 (1958).

[4] W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Krespan, *J. Am. Chem. Soc.*, **80**, 2783 (1958).