Notes

A department for short papers of immediate interest.

Synthesis and Properties of Triiodoacetic Acid and Its Salts

R. L. Cobb

Received October 30, 1957

In 1893, Angeli reported[1] that the reaction between iodic acid and malonic acid gave triiodoacetic acid and diiodoacetic acid in unspecified amounts. The same method was used in 1938 to prepare the triiodo compound, but no experimental details were given.[2] Recently it was reported that nitrogen triiodide and acetoacetic ester yielded a material thought to be a mixture of diiodoacetamide and triiodoacetamide.[3] In connection with the preparation of triiodoacetic acid for use in another investigation, the reaction of malonic acid with iodic acid has been reexamined, and attempts have been made to determine the conditions which will give optimum yields of triiodoacetic acid.

Under the conditions specified by Angeli,[1] the predominant product is diiodoacetic acid. We have found that the ratio of products (diiodoacetic and triiodoacetic acids) is dependent on the initial ratio of iodic acid to malonic acid. Triiodoacetic acid can be obtained as the major product, in yields of 50–60% based on iodic acid, if an iodic to malonic acid weight ratio of 1.5 is used. Diiodoacetic acid was the major product with reactant weight ratios of less than about 1.2, and the only product isolated when a ratio of 0.6 was used. With reactant weight ratios higher than 1.5, crystallization of triiodoacetic acid from the reaction mixture was accompanied by precipitation of increasingly larger amounts of free iodine. A reactant ratio of 2.0 gave a heavy precipitate of free iodine, and no triiodoacetic acid was isolated. The stability of triiodoacetic acid is involved here, since it was found that it decomposes to free iodine in the presence of concentrated aqueous iodic acid.

The steps in the reaction that lead to the observed products have not been clearly defined. Angeli[1] assumed that the first step in the reaction was formation of diiodomalonic acid, which could react further by simple decarboxylation to yield diiodoacetic acid or by decarboxylation and iodination to give triiodoacetic acid. Willstätter[4] has prepared diiodomalonic acid by the reaction of malonic acid with iodic acid and iodine in anhydrous formic acid as a solvent and noted that it is unstable in water. We obtained a 30% yield of triiodoacetic acid from the reaction of diiodomalonic acid with a suspension of iodine in aqueous idoic acid using charge weights based on Equation 1. The possibility that the use of

$$5CI_2(CO_2H)_2 + 2I_2 + HIO_3 \longrightarrow 5CI_3CO_2H + 5CO_2 + 3H_2O \quad (1)$$

free iodine in the reaction of malonic acid with aqueous iodic acid (Equation 2) would lead to higher yields of triiodoacetic acid was also explored. Good

$$5CH_2(CO_2H)_2 + 6I_2 + 3HIO_3 \longrightarrow 5CI_3CO_2H + 5CO_2 + 9H_2O \quad (2)$$

yields of triiodoacetic acid were obtained by this method, but the product was contaminated by large amounts of unreacted iodine.

Crystalline triiodoacetic acid was found to be quite stable at room temperature, in contrast to a report[2] that decomposition is rapid. The acid decomposes rapidly at higher temperatures, however. Triiodoacetic acid is very soluble in polar organic solvents, but the solutions as a rule are extremely unstable, rapidly developing an iodine coloration. In certain solvents as noted in the experimental section, the acid is stable enough to permit further work, if done rapidly. Triiodoacetic acid is insoluble in water, but aqueous suspensions are quite stable. It is soluble, with rapid decomposition, in dilute (4%) sodium hydroxide, but in more concentrated sodium hydroxide (10–40%) the acid is insoluble and little decomposition is observed. The acid may be partially recovered by rapidly neutralizing a freshly prepared bicarbonate solution.

The lead and sodium salts of triiodoacetic acid were prepared and isolated. Attempts to isolate a calcium salt were unsuccessful, although the calcium salt of diiodacetic acid was prepared.

EXPERIMENTAL[5]

Triiodoacetic acid. A solution of 20 g. of malonic acid in 30 cc. of water was added to an almost boiling solution of 30 g. of iodic acid in 80 cc. of water. The resulting solution was cautiously heated until the evolution of carbon dioxide was vigorous and then cooled immediately by plunging the flask into an ice bath; several small pieces of ice were added to the solution to help moderate the reaction.[6] After the reaction had subsided, the yellow reaction mixture was allowed to stand at room temperature. There was a mildly exothermic reaction, the temperature rising to about 45° with a steady evolution of gas; in about 1.5 hr., the reaction solution was a

(1) A. Angeli, *Ber.*, **26**, 595 (1893).
(2) R. A. Fairclough, *J. Chem. Soc.*, 1186 (1938).
(3) J. F. Fellman, S. H. Wilen, and C. A. VanderWerf, *J. Org. Chem.*, **29**, 713 (1956).
(4) R. Willstätter, *Ber.*, **35**, 1374 (1902).
(5) All melting points are uncorrected.
(6) Particular care must be taken in the heating step, as the reaction may very easily get out of hand and become uncontrollably violent.

bright yellow-orange color. Triiodoacetic acid as golden yellow crystals settled out and was filtered after another hour. Air drying the product served also to remove a small amount of free iodine which was present. Weight 14.3 g. (57.6%), m.p. 135–140° (dec.); reported m.p. 150° (dec.).[1] Other samples of triiodoacetic acid prepared in this manner gave m.p.'s as high as 150–154° (dec.).

Anal. Calcd. for $C_2HO_2I_3$: I, 86.97%; eq. wt. 438. Found: I, 87.5%; eq. wt.[7] 449.

After removal of the triiodoacetic acid, the mother liquor became a dark color and deposited 1.2 g. of iodine; this was removed. By concentration of the solution, a total of 5.4 g. (20.3%) of diiodoacetic acid was isolated as pale yellow needles, m.p. 110–111°; reported[1] m.p. 110°. It was recrystallized from chloroform. Data obtained by varying the reactant ratio were as follows:

Weight Ratio HIO_3/Malonic Acid	Yield, Wt. % Based on Iodine in HIO_3	
	Cl_3COOH	CHI_2COOH
0.60	0	58.6
1.00	19.2	51.8
1.00[a]	39.6	—
1.00[a]	26.4	—
1.26	37.2	30.4
1.50	46.8	28.2
1.50	57.6	20.3
1.50[a]	51.6	28.2
1.75	22.8	21.4
2.00[a,b]	0	14.7

[a] Reaction mixture was kept cold after the initial reaction. [b] A trace of a white solid, m.p. 300°, was isolated.

Diiodomalonic acid. Diiodomalonic acid was prepared by the method of Willstätter.[4] A mixture of 10 g. (0.167 mole) of malonic acid, 6.8 g. (0.10 mole) of iodic acid, and 19.6 g. (0.20 mole) of finely divided iodine in 50 cc. of 90% formic acid was stirred at room temperature 3 hr. The reaction mixture was allowed to stand overnight in a refrigerator and then filtered while cold. The product was dried on a clay plate to allow excess iodine to evaporate, giving 20 g. (58%) of diiodomalonic acid as pale yellow crystals, m.p. 110° (dec.); reported m.p. 119–120° (dec.).[4]

Conversion of diiodomalonic acid to triiodoacetic acid. Ten g. of diiodomalonic acid was added to 20 cc. of water containing 1.0 g. of iodic acid and 2.85 g. of pulverized iodine. The mixture was allowed to stand at room temperature with frequent shaking for 3 hr. A pale yellow solid appeared almost immediately. After standing overnight, the mixture was filtered and the product air-dried 6 days to remove free iodine, giving 3.7 g. (30%) of triiodoacetic acid, m.p. 140–142° (dec.).

Anal. Calcd. for $C_2HO_2I_3$: eq. wt. 438. Found: eq. wt. 450, 439.

Reaction of malonic acid with iodine and iodic acid. A mixture of 10.0 g. (0.096 mole) of malonic acid, 29.3 g. (0.115 mole) of pulverized iodine, and 10.2 g. (0.058 mole) of iodic acid in 250 cc. of water was stirred vigorously. After about 20 min., a yellow solid appeared; in another 15–20 min., evolution of carbon dioxide started with considerable foaming. The reaction was slightly exothermic; the temperature was not allowed to exceed 45° by using a water bath when necessary. A heavy yellow solid appeared after 3.5 hr. After standing overnight in a refrigerator, stirring was resumed for 3 hr. at room temperature. The mixture was filtered and the yellow solid dried on a clay plate in the air to remove excess iodine, giving 17.5 g. (42%, based on malonic acid) of the triiodoacetic acid, m.p. 131–132° (dec.). Other samples of the acid prepared in this manner had m.p. as high as 154–155° (dec.).

Anal. Calcd. for $C_2HO_2I_3$: I, 86.9%. Found: I, 86.4%.

After removal of the triiodoacetic acid, concentration of the mother liquors gave about 7 g. (16%) of diiodoacetic acid, m.p. 108–109° after recrystallization from chloroform.

Preparation of salts of triiodoacetic acid. Calcium salt: A solution of 0.25 g. of calcium acetate in 2–3 cc. of water was added to a freshly prepared solution of 1.00 g. of triiodoacetic acid in 5 cc. of dimethylformamide. Immediately a golden orange solid appeared, accompanied by evolution of a gas. After cooling in an ice bath, the solid was filtered. It decomposed on the filter paper. Similar results were obtained with acetic acid and with a carefully neutralized bicarbonate solution.

Lead salt: A solution of 2.0 g. of lead acetate in 10 cc. of water was added to a freshly prepared solution of 5.0 g. of triiodoacetic acid in 20 cc. of dioxane. After an induction period of a few seconds, a heavy bright yellow solid appeared. This was filtered and washed well with cold water. Drying on the filter in the air for 2 hr. did not change the color of the product. The salt was dried *in vacuo* over phosphorus pentoxide for 4 hr.; 5.1 g. of a light yellow tan product was obtained. On heating in a capillary tube, the product liberated iodine above 90° particularly at 130–140° to 180°, yielding a yellow solid which was stable at 260°.

Sodium salt: Two grams of triiodoacetic acid was dissolved in a solution of 0.4 g. of sodium bicarbonate in 10 cc. of water. Immediately 4 g. of sodium acetate was added to salt out the product and beautiful golden yellow, glistening leaves settled out. These were filtered and air dried, wt. 2.1 g. Upon heating in a melting point tube, the solid started losing iodine at 90°, darkened gradually from 170–180°, and became quite dark colored at 230°. The salt appeared to be relatively stable to air at room temperature.

Preparation of calcium diiodoacetate. Treatment of diiodoacetic acid solution in the same manner as afforded the calcium salts of triiodoacetic acid gave none of the desired salt. It was observed that the salts were more water soluble than the parent acid. Calcium diiodoacetate was obtained as a pale yellow solid in the following manner. Six g. of the acid in 10 cc. of warm water gave a two-phase liquid system. This was neutralized with 1 g. of calcium carbonate. The two layers disappeared and a clear solution resulted until the neutralization point was almost reached, then the calcium salt started crystallizing. Water was added and excess carbonate was filtered off. The solution was concentrated under reduced pressure to 5–10 cc. and cooled to give 4.9 g. of the calcium diiodoacetate, dec. above 200° with liberation of iodine.

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(7) After allowing a sample of the acid to stand several weeks at room temperature, the eq. wt. was redetermined and found to be 451.

Infrared Analysis of a Cyclopropane Polymer

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Received November 14, 1957

In 1939, C. S. Marvel and co-workers reported[2] the preparation of a polymer containing cyclopropane rings by dehalogenation of polyvinyl chloride with zinc.

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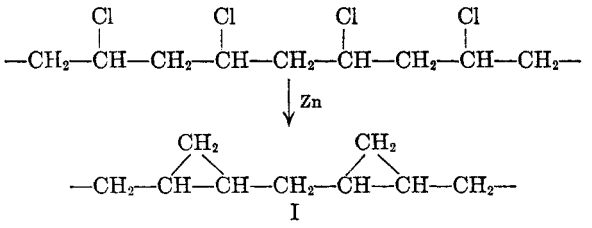
(2) C. S. Marvel, J. H. Sample, and M. F. Roy, *J. Am. Chem. Soc.*, **61**, 3241 (1939).



I

The dehalogenated polymer (I) was shown to be resistant to ozone and permanganate but added chlorine on chlorination. On vigorous nitric acid oxidation, no products could be isolated that would have been characteristic of a dehydrohalogenated polymer.

The preparation of I was repeated in order to obtain additional evidence for the original structure designation and to investigate the position of characteristic cyclopropane bands in a polymer environment. Only 60% of the total chlorine was removed in our experiments, compared to 85% obtained in the previous work; but this seems sufficient for infrared analysis. Films of I were cast directly on salt plates from dioxane solution, dried *in vacuo*, and compared to films of polyvinyl chloride prepared in a like manner. The spectrophotometer was a Perkin-Elmer Model 21 with sodium chloride optics.

Two new bands appeared in I in positions expected from prior band assignments in nonpolymeric cylopropane structures. A band at 9.83μ, characteristic of the nonsymmetrical ring deformations of cyclopropanes[3,4] and a band at 3.2μ, characteristic of the methylene hydrogens of a cyclopropane ring[4,5] confirm the original assignment. Bands associated with carbon-carbon double bonds were either not present or obscured by carbon-chlorine overtone bands between 6.0 and 6.5μ and past 10μ by various skeletal vibrations.

It was not possible to obtain interpretable nuclear magnetic resonance spectra of I because of its low solubility in organic solvents.

RESEARCH DIVISION CONTRIBUTION NO. 258
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(3) J. M. Derfer, E. E. Pickett, and C. E. Boord, *J. Am. Chem. Soc.*, **71**, 2482 (1949).
(4) V. A. Slabey, *J. Am Chem. Soc.*, **76**, 3604 (1954).
(5) S. E. Wiberley and S. C. Bunce, *Anal. Chem.*, **24**, 623 (1952).

Metalation of Cyclopropane by Amylsodium[1]

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Received December 2, 1957

Metalation of hydrocarbons has been observed only when some unsaturation was present, a previous success with decalin[2] having been found due to some impurity.[3] The first experiments with cyclopropane were carried out about ten years ago in the presence of isopropoxide with the expectation that the ring would open to give allylsodium. Thereby an alternative method for the preparation of an Alfin catalyst[4,5] would be provided. The product of this reaction, however, did not cause Alfin polymerization of butadiene. Carbonation yielded an acid which did not resemble vinylacetic but was similar to cyclopropanecarboxylic acid.

Recently cyclopropane was again metalated, but in the absence of an alkoxide, in order to study the absorption spectrum for the cyclopropyl anion. The infrared spectrum showed bands not far from those of cyclopropane itself and entirely distinct from those for allylsodium or amylsodium. Carbonation produced cyclopropanecarboxylic acid which was converted to the known amide for identification.

Although cyclopropane has a formula in which all four valencies for each carbon appear saturated, it still possesses a fair degree of olefinic character according to Coulson and Moffit[6] and Vogel.[7] Accordingly the statements previously made to the effect that some unsaturated system was necessary[8] for metalation of a hydrocarbon and that no indiscriminate removal of hydrogen by a supposedly all-powerful anion[9] took place are still valid.

EXPERIMENTAL

Metalation in the presence of isopropoxide. Amylsodium was prepared[10] from 1 g.-atom of sodium and 0.5 mole of amyl chloride in the usual manner. Isopropyl alcohol (15 ml.) was added and 15 min. later the mixture was saturated with cyclopropane. All operations were under an atmosphere of dry nitrogen and the mixture was continuously stirred at 5000 r.p.m. After a total time of 6.5 hr. the reaction mixture was transferred to a bottle and stored under nitrogen. A portion (20 ml. of suspension) was tested as a polymerizing agent for 30 ml. of butadiene in 180 ml. of pentane, but did not produce the thick gel characteristic for Alfin polybuta-

(1) This work was performed as a part of research projects sponsored by the Reconstruction Finance Corp., Office of Synthetic Rubber, and by the National Science Foundation.
(2) A. A. Morton, J. B. Davidson, T. R. P. Gibb, Jr., E. L. Little, Jr., E. W. Clarke, and A. J. Green, *J. Am. Chem. Soc.*, **64**, 2250 (1942).
(3) A. A. Morton and S. M. Bloom, *J. Am. Chem. Soc.*, **76**, 2976 (1954).
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(5) A. A. Morton, I. Nelidow, and E. Schonberg, Proc. Third Rubber Technology Conference, (1954) 108.
(6) C. A. Coulson and W. E. Moffit, *J. Chem. Phys.*, **15**, 151 (1947); *Phil. Mag.*, **40**, 1 (1949).
(7) E. Vogel, *Fortschr. chem. Forsch.*, **3**, 430 (1955).
(8) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **21**, 93 (1956).
(9) A. A. Morton and A. E. Brachman, *J. Am. Chem. Soc.*, **76**, 2973 (1954).
(10) A. A. Morton, F. D. Marsh, R. D. Coombs, A. L. Lyons, S. E. Penner, H. E. Ramsden, V. B. Baker, E. L. Little, Jr., and R. L. Letsinger, *J. Am. Chem. Soc.*, **72**, 3785 (1950).

diene. No marked polymerization took place within 1 hr. The remainder of the blue-black mixture was carbonated. The carboxylic acid therefrom distilled at 69–86°/1 mm. The neutralization equivalent was 76 and the refractive index was 1.4362. The yield was 1.3 g.

Metalation in the absence of alkoxide. A suspension (250 ml.) of amylsodium was prepared in the usual way[10] from 0.5 g.-atoms of sodium sand and 0.25 mole of amyl chloride, and, next, was saturated with cyclopropane and allowed to stand. The disappearance of amylsodium was followed by infrared measurements[11,12] of a Nujol mull. After one week the bands at 919 and 755 cm.$^{-1}$ characteristic for the amyl anion had become very much weaker. Meanwhile strong absorption bands had appeared at 1155, 1055, 1030, 860, and 810 cm.$^{-1}$, a moderate one at 1570 cm.$^{-1}$ and a weak band at 745 cm.$^{-1}$ These bands are not far from some of those for cyclopropane itself which were very strong at 1434, 1024, and 866, moderate at 1510 and 1188, and very weak at 745 cm.$^{-1}$ The bands are different from those for the allyl ion[12] which are very strong at 1525, 1247, and 600 cm.$^{-1}$

From this reaction mixture a 25-ml. aliquot was evaporated to dryness under reduced pressure. Then the dried residue was heated to 100° for 1 hr. The condensate caught in a nitrogen cooled trap showed an absorption curve identical with that for cyclopropane itself except for contamination from the pyrolysis of some amylsodium which was still present.

The remainder of the reaction mixture was carbonated and the recovered acids fractionated. The fraction of impure acid (4.4 g.), collected at 90°/30 mm., had $n^{26.5}$ 1.4355. The recorded[13] refractive index for cyclopropanecarboxylic acid is n^{25} 1.4359, and boiling point is 105°/48 mm. The amide from the acid chloride and ammonia melted at 124–127° (recorded[14] 124.5–126°).

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(11) E. J. Lanpher, *J. Org. Chem.*, **21**, 830 (1956); *J. Am. Chem. Soc.*, **79**, 5578 (1957).
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A Synthesis of Fluorene-3-carboxylic Acid[1]

D. C. MORRISON

Received December 17, 1957

Alder[2] and coworkers have shown that the sulfuric acid cyclization of phenyl terephthalic acid (diphenyl 2-5-dicarboxylic acid) gives fluorenone-3-carboxylic acid. Their synthesis of the diphenyl dicarboxylic acid, however, presents several difficulties and it was thought that if this acid were more readily available, a convenient route to 3-substituted fluorenes would be at hand. In the present work, the ester of phenyl terephthalic acid was prepared by a one-step process from diethyl terephthalate, though in mediocre yield.

Hey[3] has demonstrated that the free radical decomposition of dibenzoyl peroxide in ethyl benzoate yields a mixture of esters of phenyl benzoic acids. In a similar reaction with diethyl terephthalate, only one isomer is possible due to the symmetry of para di-substituted benzenes. This operation has now been carried out yielding the ester of the desired phenyl terephthalic acid in about 12% yield. The poor yields (expected in this type of reaction) are compensated for by the economy of starting materials. The ester was hydrolyzed under alkaline conditions to the phenyl terephthalic acid which was cyclized by sulfuric acid to the fluorenone-3-carboxylic acid.[2] The latter was purified through its methyl ester as was done by Campbell and Stafford.[4] Reaction of the methyl ester with red phosphorus and hydriodic acid in glacial acetic acid caused reduction and hydrolysis to give fluorene-3-carboxylic acid. This acid was further characterized by its methyl ester.

The route to fluorenone-3-carboxylic acid by oxidation of 3-methyl fluorene by permanganate[5] or by chromic acid[6] gave poor yields of material which was difficult to purify due to its contamination with acids probably produced by further oxidation of the desired acid (with cleavage of the fluorene ring).

EXPERIMENTAL

Melting points are uncorrected.

The better known dimethyl terephthalate was not employed in the reaction as it is a solid at steam bath temperatures. The diethyl terephthalate was made by two days refluxing of the acid with sulfuric acid and ethanol, followed by conventional purification.

Diethyl phenylterephthalate. Diethyl terephthalate (260 g.) was melted and kept at 60–70° while 50 g. of dibenzoyl peroxide were added in portions. The solution was immersed in a bath of boiling water for 4 hr. and then excess diethyl terephthalate was distilled under vacuum directly from the flask. If the temperature during the first hour of the reaction should rise above 100°, the decomposition may become violent. The distillation was carried out at 5 mm. and a forerun of diphenyl was discarded. This was followed by a large amount of recovered terephthalate which could be used again in another run. A similar reaction was done using 357 g. of diethyl terephthalate and 60 g. of dibenzoyl peroxide, and the distillation residues combined with those from the first run. These were now dissolved in ether and the solution extracted with aqueous sodium carbonate and then washed with sodium chloride solution (if water is used, a stable emulsion results). The ether was distilled and the product taken at 140–195°/3 mm. It was redistilled at about 160°/3 mm. The yield was 31.76 g. of a light yellow viscous oil. This is 11.73% based on the peroxide. The yield may perhaps be improved by reaction at higher dilution or by better temperature control. A resinous residue is left in the distillation flask.

Phenyl terephthalic acid. The 31.76 g. of ester was refluxed for 32 hr. with 40 g. of potassium hydroxide in 50% ethanol and the acid isolated as usual, by acidification with hydro-

(1) The work described in this paper was carried out under a research grant (No. C-327) to Prof. D. M. Greenberg, from the National Cancer Institute, U. S. Public Health Service.
(2) K. Alder, K. Heimbach, and K. Neufang, *Ann.*, **586**, 138 (1954); *Chem. Abstr.*, **49**, 5396 (1955).
(3) D. H. Hey, *J. Chem. Soc.*, 1966 (1934).
(4) N. Campbell and W. H. Stafford, *J. Chem. Soc.*, 299 (1952).
(5) D. Vorlander and A. Pritsche, *Ber.*, **46**, 1793 (1913).
(6) O. Kruber, *Ber.*, **65**, 1395 (1932).

chloric acid after removing ethanol. The yield of precipitated acid was 24.29 g. or 94.2%. It was very sparingly soluble in water. After one recrystallization from ether, the acid sintered above 200° and melted at 268–275° and after an additional recrystallization it melted at 277–280° (lit.[2] 277–278°).

Fluorenone-3-carboxylic acid. Alder *et al.*[2] give few details so these were worked out again. The cyclization in sulfuric acid gives yields of 79–87%. It was found to be temperature sensitive and should not be heated over 45° or further reaction occurs. Twenty g. of finely powdered phenyl terephthalic acid was stirred with 180 ml. of concentrated sulfuric acid at 25–30° until all was dissolved. The resulting dark solution was then kept at 40° (internal temp.) for 20–30 min. It was poured into ice water, and the precipitated acid filtered, washed, and dried. A yield of 15.17 g. or 81.9% of acid was obtained which sintered at 265° with melting 270–300°. Hydrolysis of the purified methyl ester and recrystallization from aqueous acetone gave a product of m.p. 299–304° with previous sintering (lit.[4] 304°).

Methyl fluorenone-3-carboxylate. The acid was esterified by refluxing for 1 day a mixture of 8.0 g. acid with 5 ml. concentrated sulfuric acid and 750 ml. of methanol. After the usual isolation, a yield of 7.66 g. or 90% was obtained. Four recrystallizations from aqueous acetone gave a product sintering at 133° and melting at 146–147° (lit.[4] 145°). Recrystallization eliminates any phenyl terephthalate or other impurities. The ester is decomposed by hot concentrated potassium hydroxide solution, giving a dark brown solution, and for hydrolysis, short contact with warm alkali is necessary.

Fluorene-3-carboxylic acid. A solution of 8.24 g. of methyl fluorenone-3-carboxylate in 300 ml. of acetic acid was mixed with 9 g. of red phosphorus and 10 ml. of 47–50% hydriodic acid and the liquid refluxed 45 hr. Most of the solvent was distilled and the residue diluted with 450 ml. of water and ice cooled several hours. The solids were filtered and then extracted with an excess of dilute potassium carbonate solution. The carbonate extract was filtered and acidified and the precipitated acid filtered off, washed, and dried. It weighed 7.18 g. or 98.7%. This preparation melted at 220–230° with previous sintering. Three recrystallizations from acetone-water with a minimum of heating gave a product of m.p. 229.5–231.5° with sintering at 222° (lit.[4] 230 and 231°).

Methyl fluorene-3-carboxylate. 10 g. of the above acid with 8 ml. of concentrated sulfuric acid and 350 ml. of methanol were refluxed 24 hr. and the ester isolated as usual. The light brownish ester was washed with alkali and dried. It was then distilled from a small short-path still at 1 mm. and the solid distillate recrystallized from acetone-water and dried. The yield of white product was 10.1 g. or 94.7%. After four recrystallizations from aqueous acetone, the ester had m.p. 79–80°.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.36; H, 5.36. Found: C, 80.13; H, 5.32.

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Preparation of Diethyl 4-Phosphonovalero-4-lactone

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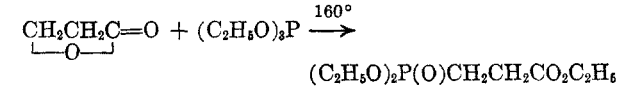
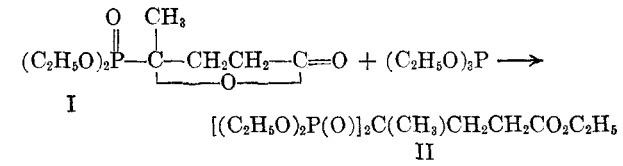
Received January 31, 1958

The preparation of esters of 1-hydroxyalkanephosphonic acids by the base-catalyzed interaction of carbonyl compounds with dialkyl hydrogenphosphonates is well known,[1] but the behavior of 1-ketocarboxylic acids in this reaction does not appear to have been examined hitherto. Interest in such a reaction was provoked during a search for new methods of obtaining methanediphosphonates and related derivatives, *i.e.*, compounds containing a P-C-P bridge.[2]

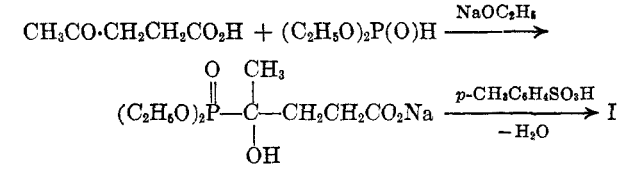
It had been shown,[3] that trialkyl phosphite reacts with a lactone to give predominantly the trialkyl ester of a phosphonocarboxylic acid, *e.g.*:



Such a reaction might be expected to produce a *gem*-bis(dialkyl phosphono)carboxylic ester, II, from a dialkyl phosphonolactone in which the phosphorus atom is joined to the same carbon atom as the oxygen bridge; especially since the presence of the dialkyl phosphono group should enhance the electrophilic power of this atom:



This aspect of the investigations had to be suspended before it was brought to satisfactory completion, but an example of the type of lactone required *viz.* diethyl 4-phosphonovalero-4-lactone, I, was made from levulinic acid by the reactions:



Because of competition from the carboxyl group for the base, more than one equivalent of the latter is necessary to effect interaction, whereas with ordinary ketones a trace suffices. The product, I, is very sensitive to water and alcohols, and could not be isolated in a sufficiently pure condition to warrant quoting a value for the molecular refraction, even after repeated redistillation. It is acknowledged that most 1-hydroxyalkanephosphonates are not stable and easily revert to equilibrium with the components from which they are derived,[4] but one would have expected ring formation in the lactone to prevent this. The triethyl ester obtained by in-

(1) R. L. McConnell and H. W. Coover, Jr., *J. Am. Chem. Soc.*, **78**, 4450 (1956) and references.

(2) Atomic Energy Research Establishment reports C/R 2011; C/R 2012 (1957).

(3) R. L. McConnell and H. W. Coover, Jr., *J. Am. Chem. Soc.*, **78**, 4453 (1956).

(4) V. S. Abramov and N. A. Ilyina, *J. Gen. Chem. (U.S.S.R.)* (Consultants Bureau English Translation), **24**, 121 (1956).

teraction of I with absolute ethanol was even less stable to distillation, but its composition, refractive index, and infrared spectrum were substantially the same as those of the substance produced by the reaction between diethyl hydrogenphosphonate and ethyl levulinate in the presence of a trace of sodium ethoxide.

Two other keto acids were examined. No identifiable product was obtained when pyruvic acid was used in place of levulinic acid although reaction took place; the dimer $[(C_2H_5O)_2P(O)C(CH_3)\text{-}O\text{-}CO]_2$ was sought.

Benzoylformic acid (0.1 mole) in ether reacted readily with dimethyl, diethyl, diallyl, diisopropyl, di-*n*-butyl, di(3,3,5-trimethyl)hexyl, or di-2-phenylethyl hydrogen phosphonates (0.12 mole) in the presence of pyridine (0.12 mole). Subsequent addition of cyclohexylamine (0.1 mole) to the reactions precipitated white crystalline solids with ill-defined melting points, which approximated in composition to the salts with this base of the corresponding phenyl(dialkyl phosphono)glycollic acids, $(RO)_2P(O)C(OH)(C_6H_5)CO_2^-$ $C_6H_{11}NH_3^+$, and which were obtained in yields of 95, 75, 49, 61, 50, 42, and 45%, respectively. Recrystallization from a variety of solvents only had the effect of increasing the melting range and lowering its upper limit.

EXPERIMENTAL

Diethyl 4-phosphonovalero-4-lactone. Sodium (7.9 g., 0.345 mole) was dissolved in ethanol (180 cc.) contained in a 1 liter 3-necked flask fitted with a reflux condenser, a dropping funnel, and a mechanical stirrer. To the cooled solution, diethyl hydrogen phosphonate (45.2 g., 0.328 mole) was added, followed by levulinic acid (38 g., 0.328 mole) in alcohol (50 cc.). The mixture was heated under reflux for 1 hr., the bulk of the alcohol was distilled (180 cc.), and the residue was sucked dry for several hours at the water-pump. Toluene (250 cc.) was then added to the dry product which was dispersed by means of the stirrer and the mixture was heated while toluene (*ca.* 75 cc.) distilled until the boiling point indicated the absence of alcohol.[5] At this stage, *p*-toluenesulphonic acid (59 g., 0.343 mole) in toluene (500 cc.) was added by means of a dropping funnel. The distillation of solvent was continued, while the suspension was stirred to prevent serious bumping, until the boiling point indicated the complete removal of water. The mixture was allowed to cool, was then filtered, and the filtrate was distilled, first at atmospheric pressure to remove toluene and then at low pressure, the fraction b.p. 90–140° (0.1–0.2 mm.) being collected. Redistillation gave 50 g. of almost pure lactone, b.p. 100–104° (0.2 mm.), n_D^{20} 1.442. Yield 64%.

Anal. Calcd. for $C_9H_{17}O_5P$: C, 45.77; H, 7.25; P, 13.11. Found: C, 45.63; H, 7.44; P, 13.00.

Acknowledgment. Thanks are due to Mr. P. J. Fydelor for recording the infrared spectrum of the product which is shown in Fig. 1. It was obtained from a cap layer between rock salt plates in a Hilger H 800 double beam instrument. The absence of an absorption peak in the 2410 cm.$^{-1}$ region characteristic of P-H bond stretching is noteworthy.

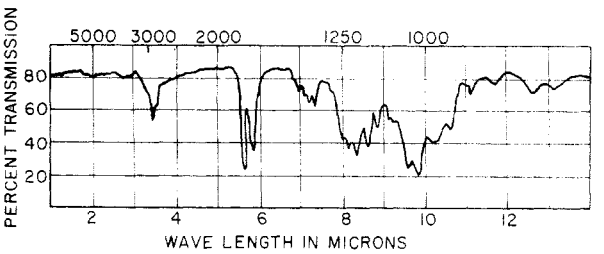


Fig. 1. Infrared absorption spectrum of diethyl 4-phosphonovalero-4-lactone

TABLE I

PRINCIPAL ABSORPTION PEAK ASSIGNMENTS

Cm.$^{-1}$	Assignment
763	P—C
856, 900	C—C=O or C—O—C
1020, 1045	P—O—C
1134	C—O—C
1203	P=O
1252	Epoxy in C—O—C=O
1368, 1393	Multiple —CH_3
1445	Assymetric C—CH_3
1721, 1786	C=O
2900, 2950	Aliphatic C—H

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(5) It is imperative to remove the alcohol completely, otherwise that remaining reacts with the lactone to give triethyl 4-phosphono-4-hydroxyvalerate.

Polar, Resonance, and Steric Effects of the 2:3-Benzo Substituent

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Received February 7, 1958

We have determined the rate constants of (1) acid-catalyzed esterification, in methanol, of benzoic and 1-naphthoic acids, and (2) alkaline hydrolysis(with sodium hydroxide) of methyl and ethyl benzoates and 1-naphthoates in 56% (w/w) acetone-water. Kinetics of esterification, with hydrogen chloride as catalyst, were followed by a method similar to that of Hartman and Borders,[1] a correction for the effect of product water being applied to the rate equation. Tommila and Hinshelwood's[2] method was used in following ester hydrolysis. Results are given in Tables I and II together

(1) R. J. Hartman and A. M. Borders, *J. Am. Chem. Soc.*, 59, 2107 (1937).

(2) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938).

TABLE I

RATE CONSTANTS FOR THE ESTERIFICATION OF ACIDS IN METHANOL

Acid	$k \times 10^4$ (L. mole^{-1} sec.$^{-1}$) 25°	40°	50°	60°	Derived Data E (kcal. mole^{-1})	$\log_{10}B$
Benzoic	2.10	7.05	14.82	30.0	15.01 ± 0.03	7.33 ± 0.02
	2.13	7.06	15.00	30.7		
		7.08	15.12			
		7.13				
1-Naphthoic	0.859	2.78	6.05	12.43	15.15 ± 0.11	7.03 ± 0.07
			6.25	12.55		

TABLE II

RATE CONSTANTS FOR THE ALKALINE HYDROLYSIS OF ESTERS IN 56% (w/w) ACETONE-WATER

Ester	$k \times 10^3$ (L. mole^{-1} sec.$^{-1}$) 15°	25°	40°	50°	Derived Data E	$\log_{10}B$
Ethyl benzoate	1.303	2.98	9.75	19.87	14.44 ± 0.03	8.07 ± 0.02
	1.311	2.99	9.90	19.87		
		3.00				
		3.03				
Ethyl 1-naphthoate	0.436	1.000	3.20	6.73	14.46 ± 0.05	7.61 ± 0.03
		1.005	3.20	6.73		
Methyl benzoate	4.17	9.62	30.6	63.0	14.33 ± 0.01	8.49 ± 0.01
	4.20	9.67	30.8	63.1		
Methyl 1-naphthoate	1.52	3.46	11.33	22.87	14.44 ± 0.04	8.13 ± 0.03
		3.47		23.33		

with the derived values of the Arrhenius parameters E and $\log_{10}B$. Rate constants are accurate to 1%.

Taft[3] has shown that the polar substituent constant (σ^*) of ortho groups in o-substituted benzoates may be evaluated from the equation

$$\log (k/k_0)_B - \log (k/k_0)_A = \sigma^*(\rho_B^* - \rho_A^*)$$

Using the data of Tables I and II and Jaffé's[4] values of ρ for the unhindered m- and p- derivatives, the σ^* value for the 2:3-benzo group relative to hydrogen (the relevant k_0 refers to the reaction of the corresponding unsubstituted benzoic ester) has been evaluated. With this σ^* value, the nonpolar contribution (E_s) to the relative rate, has been evaluated (again relative to hydrogen) using the equation

$$E_s = \log k/k_0 - \sigma^*\rho^*$$

Values for both parameters are given in Table III. These figures are derived using log k values obtained from Arrhenius plots of the data in Tables I and II. It should be noted that Taft's σ^* and E_s values for ortho substituents are relative to the methyl group.

Table IV gives energy factors for the formation and hydrolysis of 1-naphthoic esters at 25°. The values of σ^* and E_s (25°) used are the mean values −0.026 and −0.402, respectively.

(3) R. W. Taft in M. S. Newman *Steric Effects in Organic Chemistry*, John Wiley & Sons, Inc., New York, 1956, Chapter 13.

(4) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

TABLE III

POLAR AND NONPOLAR CONTRIBUTIONS TO RELATIVE RATE

	σ^{*ac}	$E_s{}^a$	σ^{*bc}	$E_s{}^b$
25°	−0.018	−0.401	−0.033	−0.404
40°	−0.019	−0.396	−0.036	−0.399
50°	−0.022	−0.393		

[a] From formation and hydrolysis of methyl 1-naphthoate; [b] from formation of methyl 1-naphthoate and hydrolysis of ethyl 1-naphthoate; [c] mean value and median deviation of the five σ^* values are −0.026 ± 0.004.

At first sight, it would appear, from Table IV, that (1) the polar and nonpolar contributions to the relative heats of activation are both very small and (2) kinetic energy steric effects ($T\Delta\Delta S^\ddagger$) constitute the dominant factor in reducing the rates of reaction of the 1-naphthyl derivatives. However, the nonpolar contribution to the relative heat of activation is a composite of two terms, one due to resonance effects ($\Delta\Delta E\psi^\ddagger$) and the other due to steric strain ($\Delta\Delta E_R{}^\ddagger$). It seems likely that these two effects are of approximately equal magnitude but of opposing sign, so that the total nonpolar contribution is zero. (The steric requirements of the ester transition state would be expected to be at least comparable with those of the transition state for the Menschutkin reaction of quinoline and methyl iodide, for which $\Delta\Delta E_R{}^\ddagger = 1$ kcal.[5]) Upper and lower limits for the rate-increasing resonance effect and hence for the rate-retarding steric strain term may be readily estimated. The loss of resonance energy in passing from ground to

(5) J. Packer, J. Vaughan, and E. Wong, *J. Am. Chem. Soc.*, **80**, 905 (1958).

TABLE IV

ENERGY TERMS (RELATIVE TO BENZOIC ESTERS) FOR 1-NAPHTHOIC ESTER FORMATION AND HYDROLYSIS

Reaction	$\Delta\Delta H\ddagger$[a]	$-2.303\ RT\ \sigma^*\rho^*$[b]	$-T\Delta\Delta S\ddagger$[c]	$-2.303\ RT\ E_s$[d]	$\Delta\Delta H\ddagger + 2.303\ RT\sigma^*\rho^*$[e]
Formation of methyl ester	0.14 ± 0.11	-0.01	0.41	0.54	0.15
Hydrolysis of methyl ester	0.11 ± 0.04	0.06	0.49	0.54	0.05
Hydrolysis of ethyl ester	0.02 ± 0.06	0.06	0.62	0.54	-0.04

[a] Relative heat of activation (ΔE). [b] Relative polar energy of activation ($\Delta\Delta E_0\ddagger$). [c] $2.303\ RT\ \Delta \log B$. [d] Nonpolar contribution to the relative free energy of activation. [e] Nonpolar contribution to the relative heat of activation ($\Delta\Delta H\ddagger - \Delta\Delta E_\sigma\ddagger$).

transition state in the hydrolysis of ethyl benzoate, relative to a simple aliphatic ester, is 6 *k*cal. mole^{-1}.[6] If resonance between the ring and side-chain in a 1-naphthoic ester were completely inhibited owing to the steric effect of the fused ring, then the 1-naphthoate would resemble an aliphatic ester in giving a $\Delta\Delta E\psi\ddagger$ value of -6 *k*cal. mole^{-1}. A lower limit for $\Delta\Delta E\psi\ddagger$ may be estimated from relative pK_a values for benzoic (4.20) and 1-naphthoic (3.69) acids. Resonance interaction between ring and side chain is less in the anion than in the parent acid. Some steric inhibition of such resonance in the case of naphthoic acid leads to a smaller decrease in resonance energy for 1-naphthoic acid ionization than for benzoic acid ionization. If this were the sole reason why 1-naphthoic acid is a stronger acid than benzoic acid, then $\Delta\Delta E\psi\ddagger$ for the ionization of 1-naphthoic acid (relative to benzoic) would be -0.7 *k*cal. mole^{-1} (*cf.* ref. 7). This may be accepted as a lower limit for $\Delta\Delta E\psi\ddagger$ for the ester hydrolysis because in this reaction all resonance interaction is frozen out in the transition state. Thus, the strain in the transition states, for hydrolysis and esterification involving simple 1-naphthoic esters, lies between 0.7 and 6 *k*cal. mole^{-1}.

In view of the small value for σ^* (Table III) it would appear that the relative reactivities of 1-naphthyl and phenyl derivatives will usually be governed more by steric than by polar factors.

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(6) M. M. Kreevoy and R. W. Taft, *J. Am. Chem. Soc.*, 79, 4016 (1957).
(7) Ref. 3, p. 581.

Synthesis of Some New 8,8′-Disubstituted 2,2′-Biquinolines

FRANCIS H. CASE AND JOHN J. LAFFERTY

Received February 10, 1958

It has been shown[1] that when 2,2′-biquinoline is substituted in the 3-position with a methyl or ethyl group the molar absorptivity of the copper (I) complex is greatly reduced. However, substitution of a phenyl group in this position increases the value of the molar absorptivity. It has been proposed that the molar absorptivity and the stability of the complex are a function of the planarity of the biquinoline molecule and the electron density about the nitrogen atoms of the quinoline nuclei. Substitution of any of these substituents in the 3-position introduces a steric factor that causes distortion from planarity of the 2,2′-biquinoline molecule by rotation of the quinoline moieties about the bond between the 2,2′-positions. The stability of the complex and the molar absorptivity should then decrease. The anomalous behavior of 3-phenyl-2,2′-biquinoline was attributed to increased electron density about the nitrogen atoms of the quinoline nuclei by electron donation of the phenyl group. The resulting increased stability of the copper (I) complex would account for the increase in the value of the molar absorptivity of the complex.

To further test this proposal it was decided to prepare 2,2′-biquinolines substituted in the 8,8′-positions with the methyl, ethyl, and phenyl groups. Spatial models of these compounds indicate that formation of the copper (I) complex would require a similar rotation of the quinoline moieties about the bond between the 2,2′-positions of the biquinoline.

The preparation of 8,8′-dimethyl-2,2′-biquinoline from the reaction of 8-methylquinoline with sodium is claimed in the literature.[2] However, it has since been shown[3] that the application of this method to quinoline yields 2,3′-biquinoline and not the expected 2,2′-biquinoline. Although the yields vary widely when the method of Ueda[4] (reductive coupling using palladium and hydrazine) or the Ullmann reaction[5-7] is applied to the corresponding haloquinolines or haloisoquinolines for the preparation of biquinolines or biisoquinolines products of predictable structure are obtained. Application of the method of Ueda to 2-bromo-8-methylquinoline gave a product indicated by analysis to be 8,8′-

(1) G. F. Smith and D. H. Wilkins, *Anal. Chim. Acta*, 10, 139 (1954).
(2) E. Conolly, *J. Chem. Soc.*, 2083 (1925).
(3) K. Ueda, *J. Pharm. Soc. Japan*, 57, 817 (1937); *Chem. Abstr.*, 32, 1265 (1938).
(4) K. Ueda, *J. Pharm. Soc. Japan*, 57, 180 (1937); *Chem. Abstr.*, 33, 608 (1939).
(5) J. G. Breckenridge, *Can. J. Research B*, 28, 593 (1950).
(6) F. H. Case and G. Maerker, *J. Am. Chem. Soc.*, 75, 4920 (1953).
(7) F. H. Case, *J. Org. Chem.*, 17, 471 (1952).

TABLE I

INTERMEDIATE SUBSTITUTED QUINOLINES

	M.P., °C.	B.P., °C.	MM.	Yield, %	Calcd. C	Calcd. H	Calcd. Br	Found C	Found H	Found Br
2-Amino-8-methyl-[a]	84–85	150–155	0.1	41	—	—	—	—	—	—
2-Amino-8-ethyl-	118–119	100–105	0.15	66	76.71	7.02	—	76.90	6.89	—
2-Amino-8-phenyl-[a]	167–168	—	—	63	—	—	—	—	—	—
2-Hydroxy-8-methyl-[a]	218–219	—	—	79	—	—	—	—	—	—
2-Hydroxy-8-ethyl-	137–137.5	—	—	44	76.27	6.40	—	76.25	6.35	—
2-Hydroxy-8-phenyl	127–128	—	—	33	81.45	5.01	—	81.51	5.06	—
2-Bromo-8-methyl-	78–79	140–143	0.3	65	54.08	3.63	—	53.87	3.57	—
2-Bromo-8-ethyl-	26–27	172–175	0.2	80	—	—	33.85	—	—	33.36
2-Bromo-8-phenyl-	—	172–175	0.2	81	63.40	3.55	—	63.40	3.31	—

[a] Preparation previously reported in literature by another method.

dimethyl-2,2′-biquinoline, which melts 56° higher than that reported previously.[2]

The preparation of 8-methyl,[8] 8-ethyl,[9] and 8-phenyl[10] quinolines was effected by variation of the Skraup reaction as described in the literature.

From these, the required 2-aminoquinolines were conveniently prepared by the action of sodamide on solutions of the quinolines in dimethylaniline. This method of preparation was found to be superior to those described in the literature for the methyl[11] and phenyl[12] aminoquinolines.

Attempts to prepare the bromoquinolines from the corresponding aminoquinolines by variations of the Sandmeyer or Craig[13] reaction failed. It was found that the 2-aminoquinolines can be easily diazotized by the methods of Schoutissen[14] or Hodgson and Walker[15] but attempts to prepare the bromo derivatives by the diazonium method were unsuccessful. For this reason the diazonium salts prepared as above were converted to the respective carbostyrils. Of these only the 8-methyl derivative has been previously reported.[16]

From the carbostyrils the three requisite bromoquinolines, previously unreported, were prepared by the method of Kaslow and Lawton.[17]

Application of the Ullmann reaction to 8-ethyl-2-bromoquinoline gave 8,8′-diethyl-2,2′-biquinoline when the copper catalyst was pretreated by the method of Kleider and Adams.[18] With an untreated catalyst none of the desired products could be isolated from the reaction mixture. Application of the Ullmann reaction to 2-bromo-8-methyl and 8-phenylquinoline failed to yield the desired biquinolines. These were obtained in very small yield by the method of Ueda.[4]

These compounds are now being tested and the results will appear in a later publication.

EXPERIMENTAL

2-Amino-8-alkyl and 8-phenylquinolines. A mixture of 0.5 mole of the quinoline, 0.6 mole of sodamide, and 500 ml. of dimethylaniline was stirred and heated at 120–125° for 8–10 hr. The mixture was cooled and treated with 300 ml. of water. The dimethylaniline layer was washed several times with 100-ml. portions of water. The 2-amino-8-phenylquinoline was precipitated by addition of excess petroleum ether (b.p. 30–60°). It was purified by crystallization from benzene.

The 2-amino-8-methyl and 2-amino-8-ethyl quinolines were isolated by vacuum distillation following the removal of the dimethylaniline *in vacuo*. Crystallization of the distillates from benzene-hexane mixtures yielded the pure amines.

8-Alkyl and 8-phenylcarbostyrils. A solution of 0.24 mole of the aminoquinoline in 900 ml. of 85% phosphoric acid was cooled to 0° and diazotized with nitrosylsulfuric acid prepared from 18.6 g. of sodium nitrite in 450 ml. of concentrated sulfuric acid. The temperature was kept below 5° during the addition of the nitrosylsulfuric acid. Stirring was continued for 30 min. after the addition. The diazonium solution was slowly poured into 8 l. of hot water. The solution was heated on the steam bath for 1 hr. and allowed to stand for 15 hr. The *p*H of the solution was adjusted to approximately 5 with aqueous sodium hydroxide solution. The crude carbostyrils separated as semisolid masses which were dissolved in benzene. The benzene solutions were washed with water and evaporated to dryness. The carbostyrils were purified by crystallization from benzene-hexane.

2-Bromo-8-alkyl and 8-phenylquinolines. A mixture of 0.07 mole of the respective carbostyril, 40 g. of phosphorus tribromide, and 26 g. of phosphorus oxybromide was heated at 150–155° for 4 hr. The reaction mixture was poured on ice, made alkaline with aqueous sodium hydroxide solution, and extracted with benzene. The benzene was evaporated and the residual oil distilled *in vacuo*. The final purification of the 8-methyl and 8-ethyl-2-bromoquinolines was accomplished by recrystallization from hexane.

8,8′-Dimethyl-2,2′-biquinoline. A mixture of 10 g. of 8-methyl-2-bromoquinoline, 39.6 g. of 85% hydrazine hydrate in water, 4.5 g. of Pd on calcium carbonate (5% Baker Catalyst), and 300 ml. of 5% ethanolic potassium hydroxide was stirred at reflux for 2 hr. The reaction mixture was

(8) R. Adams and J. Johnson, *Elementary Laboratory Experiments in Organic Chemistry*, Third Ed., Macmillan Co., New York (1945), 351.

(9) R. A. Glenn and J. R. Bailey, *J. Am. Chem. Soc.*, **63**, 640 (1941).

(10) C. E. Kaslow and M. Hayek, *J. Am. Chem. Soc.*, **73**, 4986 (1951).

(11) F. W. Bergstrom, *J. Org. Chem.*, **3**, 233 (1938).

(12) F. W. Bergstrom, *J. Org. Chem.*, **3**, 424 (1938).

(13) L. Craig, *J. Am. Chem. Soc.*, **56**, 231 (1934).

(14) H. A. Schoutissen, *J. Am. Chem. Soc.*, **55**, 4531 (1933).

(15) H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 530 (1935).

(16) O. Fischer, *Ber.*, **35**, 3678 (1902).

(17) C. E. Kaslow and W. R. Lawton, *J. Am. Chem. Soc.*, **72**, 1723 (1950).

(18) E. C. Kleider and R. Adams, *J. Am. Chem. Soc.*, **55**, 4225 (1933).

filtered. The spent catalyst was boiled in benzene and the benzene solution added to the filtrate. After evaporation of the solvent the residue was crystallized from benzene. The yield was 52 mg. (0.8%), m.p. 203–204°.

Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.47; H, 5.67. Found: C, 84.12; H, 5.76.

8,8'-Diphenyl-2,2'-biquinoline. The method of preparation was similar to that used for 8,8'-dimethyl-2,2'-biquinoline. From 6 g. of 8-phenyl-2-bromoquinoline, 71 mg. (1.7%) of purified product was obtained. After crystallization from benzene it melted at 247–248°.

Anal. Calcd. for $C_{30}H_{20}N_2$: C, 88.21; H, 4.94. Found: C, 88.37; H, 4.94.

8,8'-Diethyl-2,2'-biquinoline. A mixture of 7.5 g. of 8-ethyl-2-bromoquinoline and 10 g. of copper powder pretreated by the method of Kleider and Adams[18] was heated for 3 hr. at 210–220°. The reaction mixture was pulverized and extracted with hot concentrated hydrochloric acid. The acid extracts were cautiously neutralized with aqueous sodium hydroxide and then made strongly alkaline with ammonium hydroxide. The mixture was extracted with benzene and the extracts were concentrated to a small volume. The solution was adsorbed on an alumina column. Hexane and hexane-chloroform mixtures were used as eluents with fractions taken at every 20 ml. The residue from evaporation of the solvents was crystallized from benzene yielding 0.156 g. (3.1%) melting at 122–123°.

Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45. Found: C, 84.51; H, 6.41.

Acknowledgment. This work was supported by a grant from the Committee on Research and Publications of Temple University.

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5-Bromoörotic Acid

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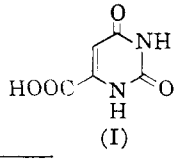
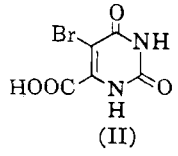
Received February 11, 1958

In the past few years, increased interest in the physiological properties of orotic acid (I) and its derivatives has been apparent. A variety of 5-substituted orotic acids have been investigated, including 5-halogenated derivatives; 5-chloroörotic acid was described by Johnson[1] in 1943, 5-iodoorotic acid has been synthesized and used to elucidate aspects of nucleic acid metabolism,[2] and the effect of 5-fluoroörotic acid on tumor growth has recently been studied.[3] However, no reliable synthesis or description of 5-bromoörotic acid (II) has been available.



(I)



(II)

Several reported attempts to brominate orotic acid directly in aqueous solution resulted in the formation of 5,5-dibromobarbituric acid.[4,5] Behrend[6] suggested that oxidation of 5-bromo-6-methyluracil with hot, fuming nitric acid gave 5-bromoörotic acid, but the yield was very poor and the product was not clearly described.

Although uracil[7] and 6-methyluracil[8] have been brominated in the 5-position in high yield by reaction with bromine in carbon disulfide, we recovered only unchanged starting material when orotic acid was treated with bromine in carbon tetrachloride at 70°. However, reaction with a mixture of aqueous hydrogen peroxide and hydrobromic acid led to a 73% yield of bromoörotic acid. The dihydrate crystallized from aqueous solution, and was converted to the anhydrous compound by heating at 80° *in vacuo* over phosphorus pentoxide. It was recovered unchanged after being boiled with aqueous sodium hydroxide solution, which indicates the stability of the C—Br bond and proves it to be at the 5-position as expected.

Potentiometric titration showed 5-bromoörotic acid to be dibasic, the $-\log$ of the apparent acidic ionization constants being 2.21 and 7.59. The corresponding values for orotic acid itself are 2.40[5,9] (2.8[10,11]) and 9.45,[10,11] while the value for o-bromobenzoic acid is 2.85.[9,12]

Upon heating above its melting point, the acid was smoothly decarboxylated to give a nearly quantitative yield of 5-bromouracil. Conversely, orotic acid itself has only recently been decarboxylated successfully, under drastic conditions, and the yield of the resulting uracil was low.[13]

EXPERIMENTAL[14]

Attempted direct bromination of orotic acid. Orotic acid monohydrate (25.0 g., 0.144 mole) was slurried with 100 ml. dry carbon tetrachloride, and bromine (23 g., 0.144 mole) was added dropwise with stirring. The red mixture was then boiled under reflux for several hours, cooled, and the solid filtered off and washed with carbon tetrachloride. After drying in air, the residue was recrystallized from water to give a quantitative recovery of orotic acid, m.p. 342° (decomp.) (immersed at 340°).

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(3) C. Heidelberger, N. K. Chadhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven, and J. Scheiner, *Nature*, **179**, 663 (1957); R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Am. Chem. Soc.*, **79**, 4559 (1957).
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(12) J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939).
(13) M. R. Atkinson, M. H. Maguire, R. K. Ralph, G. Shaw, and R. N. Warrener, *J. Chem. Soc.*, 2363 (1957).
(14) All melting points were measured in a Vanderkamp block, and are corrected.

Anal. Calcd. for $C_5H_4N_2O_4 \cdot H_2O$: C, 34.5; H, 3.47; N, 16.1. Found: C, 34.7; H, 3.54; N, 16.2.

5-Bromoörotic acid. Orotic acid monohydrate (52 g., 0.30 mole) was suspended in 30% aqueous hydrogen peroxide ("Superoxol") (63 ml., 0.80 mole) at about 0°, and 90 ml. (0.80 mole) 48% aqueous hydrobromic acid was added dropwise with mechanical stirring. The violent reaction was moderated by ice cooling to maintain the temperature below 35°. After addition of the hydrobromic acid was complete, the mixture was allowed to stand overnight. The precipitated solid was isolated by filtration, washed with cold water, and dried to give a 73% yield of crude product.

Recrystallization from water gave pale yellow needles of 5-bromoörotic acid dihydrate, m.p. 288° (dec.) (immersed at 280°).

Anal. Calcd. for $C_5H_3BrN_2O_4 \cdot 2H_2O$: C, 22.2; H, 2.60; N, 10.3. Found: C, 22.8; H, 2.57; N, 10.3.

The anhydrous acid was obtained by drying at 80° over phosphorus pentoxide.

Anal. Calcd. for $C_5H_3BrN_2O_4$: C, 25.6; H, 1.29; N, 11.9. Found: C, 25.6; H, 1.27; N, 12.1.

A sample of 5-bromoörotic acid was boiled for 1 hr. with 10% aqueous sodium hydroxide solution, and was recovered unchanged after acidification, isolation, and drying. Samples of the acid were titrated in approximately 0.01*M* aqueous solution with 0.100*M* sodium hydroxide solution. A Photovolt *p*H meter, equipped with standard glass and calomel electrodes, was employed for these measurements, and the usual precautions were observed. The *p*H of the solutions at 50% of the stoichiometric volume of alkali was taken as pK_a' for each ionizing group. The pK_a' calculated from eight other points on the titration curves was in reasonable agreement with these values. 5-Bromoörotic acid was found to have pK_{a1}' of 2.2_1 and a pK_{a2}' of 7.5_9.

The ultraviolet absorption spectrum of a $10^{-4}M$ solution of 5-bromoörotic acid in deionized water was measured with a Beckman Model DU spectrophotometer. At *p*H 5.6, λ_{max} 279.5 mμ ($\epsilon = 8.75 \times 10^3$), λ_{min} 243 mμ ($\epsilon = 1.02 \times 10^3$) were observed.

5-Bromouracil. A 2.0-g. sample of pure 5-bromoörotic acid was carefully heated to about 300° in a Wood's metal bath until gas evolution ceased. The cooled residue was recrystallized from water to give an almost quantitative yield of 5-bromouracil, m.p. 296° (dec.) (lit. 293°).[7]

Anal. Calcd. for $C_4H_3BrN_2O_2$: C, 25.2; H, 1.58. Found: C, 25.3; H, 1.64.

Acknowledgment. The authors wish to thank Mr. F. G. Bollinger for able assistance and Mr. Quentin Quick and his group for microanalyses.

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Improved Syntheses of Certain Derivatives of 5,6-Dimethoxy-8-aminoquinoline[1]

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Received February 12, 1958

5,6-Dimethoxy-8-(4′-isopropylamino-1′-methylbutylamino)quinoline (SN-9972)[2] [5,6-dimethoxy-8-butylamino(1′-methyl-4′-diethylamino)quinoline and 5,6-dimethoxy-8-(4′-diethylamino-1′-methylbutylamino)quinoline (SN-8233)[2] have recently provided encouraging data when examined against experimental tumors in animals.[3] It therefore became of interest to develop more efficient syntheses than those heretofore available for these substances.

In the preparation of SN-8233 previously reported[4] the key step involves alkylation of 5,6-dimethoxy-8-aminoquinoline with 1-diethylamino-4-bromopentane (as the hydrobromide) at *p*H 4.8.[5] However, even under the optimum conditions the yield of SN-8233, isolated as the oxalate, was only 21% largely because of cyclization of the bromoamine to 1,1-diethyl-2-methylpyrrolidinium bromide.

Shiho[6] has described the condensation of 1-diethylamino-4-ethoxy-3-pentene with 6-methoxy-8-aminoquinoline followed by reduction of the resulting anil to yield pamaquin. Barber and co-workers[7] have successfully condensed the aminoquinoline with 1-diethylamino-4,4-diethoxypentane to yield the same anil which was similarly reduced to pamaquin in high yield. This general method has been adapted, with some modifications, to the preparation of SN-8233 after attempts to effect the direct reductive alkylation of 5,6-dimethoxy-8-aminoquinoline or 5,6-dimethoxy-8-nitroquinoline with 1-diethylamino-4-pentanone as reported by Bergmann[8] failed. It should also be noted that Barber and co-workers[7] were also unable to obtain pamaquin by Bergmann's method.

In the preparation of the requisite intermediates, unexpected complications were encountered in the bromination of 6-methoxy-8-nitroquinoline. When the method described in detail by Elderfield and co-workers,[9] based on a Japanese report,[10] was followed, the expected 5-bromo-6-methoxy-8-nitroquinoline was not obtained. Rather, what appeared to be a perbromide of the desired compound was isolated. This could be readily converted to the 5-bromo compound by treatment with cyclohexene

(1) This work was supported by a Research Grant (CY-2961) from the National Cancer Institute to the University of Michigan.

(2) The prefix SN identifies a compound in F. Y. Wiselogle, *Survey of Antimalarial Drugs*, Edwards Brothers, Ann Arbor, Mich., 1946.

(3) Private communication from Dr. Ralph Jones, Jr., of the University of Miami Medical School.

(4) R. C. Elderfield, V. J. Gensler, J. D. Head, H. H. Hagerman, C. B. Kremer, J. B. Wright A. D. Holley, B. Williamson, J. Galbreath, L. Wiederhold III, R. Frohardt, S. M. Kupchan, T. A. Williamson, and O. Berstein, *J. Am. Chem. Soc.*, **68**, 1524 (1956).

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which underwent bromination as in the analogous reaction with pyridine perbromide.[11] Further, the iron and large excesses of bromine and calcium carbonate used in the earlier preparation[9] were found to be unnecessary, and a simpler procedure which gives the desired bromo compound directly has been worked out.

In the displacement of the bromine in 5-bromo-6-methoxy-8-nitroquinoline by methoxyl, the reaction time has been reduced from 4 days to 20 hr. by employing an excess of sodium methoxide instead of the equivalent amount previously used. Of the two methods for reducing the nitro group in 5,6-dimethoxy-8-nitroquinoline[9,12] catalytic reduction over palladium was manipulatively easier than the stannous chloride reduction, but the product from the latter reaction was easier to purify.

When the preparation of larger amounts of SN-9972 by the method used previously[4] was attempted, cyclization of the amino bromide, 1-isopropylamino-4-bromopentane, prior to alkylation of 5,6-dimethoxy-8-aminoquinoline, likewise was the cause of prohibitively low yields. Accordingly, SN-9972 has been prepared in acceptable yields by reductive alkylation of 5,6-dimethoxy-8-(4-amino-1-methylbutylamino)quinoline (CN-1104)[9] with acetone substantially according to Cope and co-workers.[13]

EXPERIMENTAL[14,15]

5-Bromo-6-methoxy-8-nitroquinoline and its perbromide. A. According to Elderfield et al.[9] To a suspension of 491 g. (2.4 moles) of 6-methoxy-8-nitroquinoline, 183 g. (1.83 moles) of calcium carbonate, and 9.6 g. of iron filings in a refluxing mixture of 2.4 l. of chloroform and 490 ml. of water, 480 ml. (9.4 moles) of bromine was added with stirring. After refluxing for 6 hr. and stirring for 15 hr. at room temperature, the precipitate was collected, washed successively with water and chloroform, and dried to yield 1075 g. of crude perbromide. Crystallization of a sample from benzene-nitrobenzene gave pale orange prisms of the perbromide, m.p. 155–157° (dec.).

Anal. Calcd. for $C_{10}H_7Br_3N_2O_3$: Br, 54.2. Found: Br, 54.2.

A mild exothermic reaction ensued when the crude perbromide was stirred for 15 hr. with 280 ml. of cyclohexene and 2.5 l. of benzene. After heating the mixture to the boiling point and cooling, the precipitate of crude bromo compound (734 g.) was collected. The main contaminant, calcium carbonate, was removed by hot filtration, and crystallization from pyridine gave pure 5-bromo-6-methoxy-8-nitroquinoline (362 g., 53%), m.p. 203.0–205.5°. Reported 204–205°.[9]

B. To a stirred suspension of 40.8 g. (0.2 mole) of 6-methoxy-8-nitroquinoline and 9 g. (0.09 mole) of calcium carbonate in 180 ml. of chloroform and 50 ml. of water, 12.2 ml. (0.24 mole) of bromine was added at such a rate as to maintain a gentle reflux. After refluxing for 1.75 hr., 40 ml. of cyclohexene was added followed, after 5 min., by 12 ml. of 28% ammonium hydroxide. After heating for a further 10 min., the mixture was diluted with 180 ml. of petroleum ether (40–60°) and 140 ml. of water. The product was collected, washed successively with 1:1 chloroform–petroleum ether and water, and dried to yield 49 g. (85%) of crude 5-bromo-6-methoxy-8-nitroquinoline, m.p. 170–195° (dec.). Crystallization from benzene-nitrobenzene gave pale yellow needles of the pure compound, m.p. 205–206°.

1-Diethylamino-4,4-diethoxypentane. A mixture of 222 ml. (1.21 moles) of 1-diethylamino-4-pentanone, 555 ml. of redistilled ethyl orthoformate, 240 g. (1.25 moles) of *p*-toluenesulfonic acid monohydrate, and 870 ml. of absolute ethanol was refluxed for 3 days. The alcohol (about one liter) was distilled off under reduced pressure. After addition of a solution of 61 g. of sodium hydroxide in 500 ml. of water, the mixture was extracted with ether. Removal of the ether from the dried extract and distillation under reduced pressure gave 197 g. (70%) of the ketal, b.p. 127–132° (27 mm.), n_D^{21} 1.433, d_4^{25} 0.86. Reported b.p. 121–122° (22 mm.).[16]

5,6-Dimethoxy-8-(4′-diethylamino-1′-methylbutylamino)-quinoline. (SN-8233). A mixture of 46 ml. (0.17 mole) of 1-diethylamino-4,4-diethoxypentane, 25 g. (0.12 mole) of 5,6-dimethoxy-8-aminoquinoline, and 0.17 g. of ammonium chloride was heated in an oil bath with stirring at 155° for 2 hr. during which the temperature was raised to 182°. Ethanol (16 ml., 81%) distilled. The residue was taken up in 300 ml. of absolute ethanol and shaken with 0.55 g. of prereduced Adams' platinum oxide catalyst at room temperature and 50 lb. hydrogen pressure. After 20 hr. 0.13 mole (77%) of hydrogen had been absorbed. The filtrate from the catalyst was added to a solution of 30 ml. of glacial acetic acid in 750 ml. of water and the resulting mixture was extracted three times with benzene. Removal of the solvent from the dried benzene extracts and distillation of the residue gave 2.0 g. (8%) of unreacted 5,6-dimethoxy-8-aminoquinoline.

The aqueous suspension was made alkaline with sodium carbonate and extracted with four portions of benzene. Removal of the solvent from the dried benzene extracts and distillation of the residue *in vacuo* gave an oily fraction (2 g., 5%), b.p. up to 170° (0.1 mm.) followed by the drug base (28.9 g., 70%) as a yellow oil, b.p. 170–171° (0.1 mm.). Reported b.p. 179–185° (0.3 mm.).[4] The base was converted to the oxalate (96% yield) as previously described.[4] The salt formed yellow prisms, m.p. 132–136°, after recrystallization from absolute ethanol. Reported m.p. 126–128°.[4] When assayed by the Craig countercurrent procedure, the drug base showed an inhomogeneity of 4.6%[17] (*cf.* Fig. 1).

Anal. Calcd. for $C_{22}H_{33}N_3O_5$: C, 60.66; H, 7.64; N, 9.65; $(COOH)_2$, 20.69; drug base, 79.31. Found: C, 61.03; H, 7.34; N, 9.50; $(COOH)_2$, 21.18; drug base, 79.67.

5,6-Dimethoxy-8-(4′-isopropylamino-1-methylbutylamino)-quinoline. SN-9972. When 15 g. (0.045 mole) of 5,6-dimethoxy-8-(4′-amino-1-methylbutylamino)-quinoline[9] was reductively alkylated with acetone according to Cope and co-workers,[13] 13.9 g. (72%) of viscous yellow oil, b.p. 168–173° (0.2 mm.) was obtained. The reported b.p. is 190–195° (0.3 mm.).[4] From this the oxalate, m.p. 143–145° with sintering at 139°, was prepared in 73% yield. The reported m.p. is 138–141°. The drug base showed the presence of 5% inhomogeneity when assayed by the Craig method[17] (*cf.* Fig. 1).

Anal. Calcd. for $C_{21}H_{31}N_3O_5$: C, 59.84; H, 7.42; N, 9.97; $(COOH)_2$, 21.38; drug base, 78.62. Found: C, 59.97, 59.88;

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(14) Melting points and boiling points are uncorrected unless stated otherwise.

(15) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

(16) Van Shelven, British Patent **388,087**, Example 32.

(17) Craig analyses, free base and oxalate determinations were done at Applied Science Laboratories, Inc., State College, Pa.

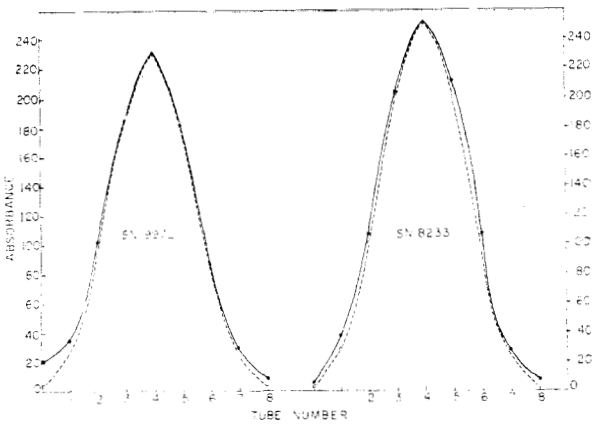

Fig. 1. SN-9972: system of isopropyl ether–*n*-butyl alcohol *vs.* 2*M* (total) citrate buffer at *p*H 3.86; concentration of base, 1.0 mg. per ml. of each phase. SN-8233: system of isopropyl ether–*n*-butyl alcohol *vs.* 2M (total) citrate buffer at *p*H 3.52; concentration of base 0.8 mg. per ml. of each phase. Concentrations determined by absorption at 390 mμ; dashed lines, theoretical; solid lines, experimental

H, 7.14, 7.19; N, 9.99, 10.04; $(COOH)_2$, 21.00; drug base, 79.88.

Acknowledgment. We wish to acknowledge the assistance of Niles Gilmour in the preparation of certain intermediates and that of Elmer Dupre and Anthony Sisti in the preliminary stages of the work.

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Cyclic Sulfides. II. Ring Size and the Ultraviolet Absorption Spectra[1]

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Received February 12, 1958

The measurement of the ultraviolet absorption of ethylene sulfide[1] has now allowed a discussion of the effect of ring size upon the spectra of cyclic sulfides. The data are presented[2] in Fig. 1. Perusal shows that the four membered ring sulfide has the weak absorption band at the longest wave length. It is difficult to offer a complete explanation designating the energy levels and the transitions involved. However, an empirical relationship can be discerned between the electron density and basicity

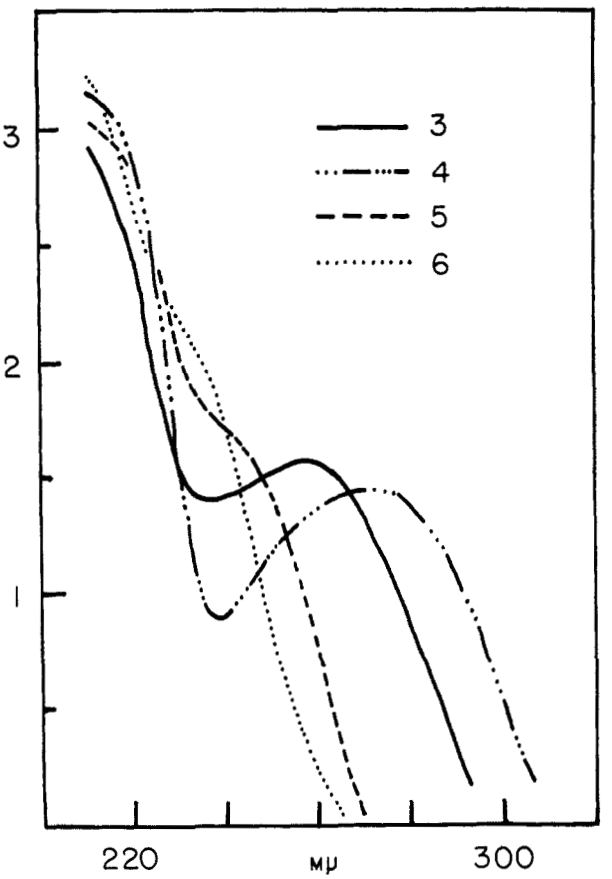

Fig. 1. Spectra of cyclic sulfides in absolute ethanol. Log ε *vs.* λ in mμ. 3 ethylene sulfide, 4 trimethylene sulfide, 5 tetramethylene sulfide, 6 pentamethylene sulfide

of the sulfur atom and the position of the transition in divalent sulfur compounds. The more the electron density on the sulfur, the further the absorption towards longer wave lengths. This can be seen in the following series.

The sulfur atom spectrum[6] serves as the basis for discussion. Hydrogen sulfide[7,8] (λ_{max} hexane 190 mμ log ε 3.2) can be compared with sodium sulfide[9] (λ_{max} 230 mμ log ε 3.8 in aqueous sodium hydroxide). Ethanethiol[7,8] has a band at 195 mμ (log ε 3.15) and an inflection at 225 mμ (log ε 2.2) in ethanol. The sodium salt of 1-*n*-butanethiol[9] in aqueous sodium hydroxide has a band at 240 mμ (log ε 3.7). The spectra of dialkyl sulfides[5] show strong bands in the region 210–215 mμ with inflections near 230 mμ (log about 2). Alkyl groups donate electrons to the sulfur. Unbonded pairs of electrons are needed in divalent sulfur compounds on the sulfur atom to have absorption above 200 mμ.

(1) Part I. R. E. Davis, *J. Org. Chem.*, **23**, 216 (1958).
(1a) National Science Foundation predoctoral fellow, 1955–1957.
(2) The experimental methods have been previously reported.[1] The sulfides were prepared by known procedures: 3 membered ring,[1] 4 membered,[3] 5 membered,[4] 6 membered.[5]
(3) G. M. Bennet and A. L. Hock, *J. Chem. Soc.*, 2496 (1927).
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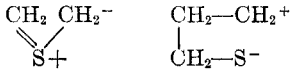
(8) H. Ley and B. Arends, *Z. physik. Chem.*, **B15**, 311 (1932).
(9) L. H. Noda, S. A. Kuby, and H. A. Lardy, *J. Am. Chem. Soc.*, **75**, 913 (1953).

Dimethyl sulfone and triethyl sulfonium chloride[10,11] have no absorption above 200 mμ.

The electron donor abilities of the sulfur atom of cyclic sulfides have been observed to be in the order: 4>5>6>acyclic>3 by the complexing with boron trifluoride.[12] The order of NMR δ-values[13] was found to be 4>3>5>6 for the hydrogens on the carbon adjacent to the sulfur atom. The order of position of the weak band of cyclic sulfides (Fig. 1) is 4>3>5>6.

The explanation of these facts is based on the inherent electronic nature of the ring compounds rather than on steric considerations. The data favor formulas:



as the extreme forms. Each can be obtained as the excited state by consideration of the probable ground state and the geometric properties by molecular orbital treatment. Delocalization of p-electrons has also been used to explain other properties of small ring compounds.[14,15]

The author wishes to thank Profs. M. Carmack and E. A. Fehnel for communicating their unpublished spectral data which are in complete agreement with the data reported.

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Further Reactions of Phenanthraquinone with Diaryldiazomethanes

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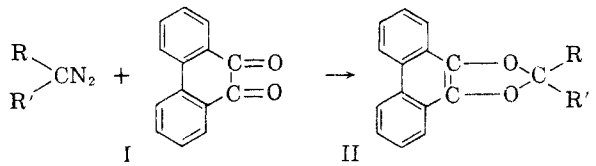
Received February 13, 1958

Schönberg and Mustafa[1] found that the action of diphenyldiazomethane on phenanthraquinone yields a methylenedioxy derivative of type II (R, R′ = C_6H_5) which gives phenanthraquinone when treated with sulfuric acid.

(1) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 746 (1946).

This reaction has now been extended using p,p′-dichlorodiphenyldiazomethane (Ia), o-chlorophenylphenyldiazomethane (Ib), p-nitrophenylphenyldiazomethane (Ic), and p-xenylphenyldiazomethane (Id).[2] The reactions led to the formation of the methylenedioxy derivatives IIa,b,c,d. The hydrolysis of IIa with concentrated sulfuric acid yielded phenanthraquinone.



I. and II:
a, R = R′ = C_6H_4Cl-p
b, R = C_6H_5; R′ = C_6H_4Cl-o
c, R = C_6H_5; R′ = $C_6H_4NO_2$-p
d, R = C_6H_5; R′ = $C_6H_4{\cdot}C_6H_5$-p

EXPERIMENTAL

9,10-(p,p′-Dichlorodiphenylmethylenedioxy)phenanthrene (IIa). To a suspension of phenanthraquinone (0.5 g.) in benzene (20 ml.) was added a benzene solution of p,p′-dichlorodiphenyldiazomethane (prepared from 0.8 g. of p,p′-dichlorobenzophenone hydrazone in 20 ml. of dry benzene). A mild evolution of nitrogen occurred and continued for 10 min. The quinone dissolved and the solution was kept at room temperature overnight. The red oily residue, obtained after evaporation of the benzene, solidified on washing with cold methyl alcohol and was crystallized from ethyl alcohol as yellow crystals, m.p. 185°. It gives, on treatment with concentrated sulfuric acid, a brown color which changes after some time to a green color; yield 0.7 g.

Anal. Calcd. for $C_{27}H_{16}Cl_2O_2$: C, 73.1; H, 3.6; Cl, 16.0. Found: C, 73.7; H, 3.7; Cl, 15.7.

9,10-(o-Chlorophenylphenylmethylenedioxy)phenanthrene (IIb) was obtained from phenanthraquinone (0.5 g.) and o-chlorophenylphenyldiazomethane (prepared from 0.7 g. of o-chlorobenzophenone hydrazone in 20 ml. of dry benzene). It was crystallized from petroleum ether (b.p. 60–80°) as almost colorless crystals, m.p. 207°; yield 0.6 g. It gives a brown then a green color with concentrated sulfuric acid.

Anal. Calcd. for $C_{27}H_{17}ClO_2$: C, 79.3; H, 4.1; Cl, 8.7. Found: C, 79.4; H, 4.2; Cl, 8.4.

9,10(p-Nitrophenylphenylmethylenedioxy)phenanthrene (IIc) was obtained by treating phenanthraquinone (0.5 g.) with p-nitrophenylphenyldiazomethane (prepared from 0.8 g. of p-nitrobenzophenone hydrazone in 20 ml. of dry benzene). It was crystallized from petroleum ether (b.p. 80–100°) as orange crystals, m.p. 225; yield 0.7 g. It gives a brownish purple color with concentrated sulfuric acid.

Anal. Calcd. for $C_{27}H_{17}NO_4$: C, 77.3; H, 4.0; N, 3.3. Found: C, 77.4; H, 4.0; N, 3.5.

9,10-(p-Xenylphenylmethylenedioxy)phenanthrene (IId) was obtained as above, in 60% yield. It was crystallized from petroleum ether (b.p. 80–100°) as yellow crystals, m.p. 170°. It gives an orange color with concentrated sulfuric acid.

Anal. Calcd. for $C_{33}H_{22}O_2$: C, 88.0; H, 5.0. Found: C, 88.0; H, 5.5.

Hydrolysis of IIa. Half a gram of IIa was mixed with concentrated sulfuric acid (3 ml.) and left overnight, whereby a green solution was formed. The solution was poured onto ice,

(2) For the preparation of these diazomethane derivatives compare A. Schönberg, A. Fateen, and A. Sammour, *J. Am. Chem. Soc.*, **79**, 6020 (1957).

neutralized with sodium carbonate, and extracted with ether. The residue, obtained after evaporation of the ether solution, was identified as phenanthraquinone (melting point and mixed melting point determinations).

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Synthesis of 2-Trifluoroacetylpyrrole[1]

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Received February 14, 1958

The reaction of pyrrole and trifluoroacetic anhydride in benzene at near zero temperatures occurred readily and 2-trifluoroacetylpyrrole was obtained in good yield. At higher temperatures a black tar formed rapidly. In contrast, the reaction of the weaker acid, acetic anhydride, and pyrrole was reported by Ciamician and Dennstedt[3] to require heating to give 2-acetylpyrrole.

2-Trifluoroacetylpyrrole was also prepared by treating pyrrole magnesium bromide with trifluoroacetyl chloride at low temperatures but the yield was low. This route was first reported by Oddo[4] who obtained 2-acetylpyrrole from the reaction of pyrrole magnesium bromide and acetyl chloride. More recently Portnoy and Gisser[5] prepared 2-heptafluorobutyrylthiophene by the reaction of thiophene magnesium bromide and heptafluorobutyryl chloride.

Although the fully fluorinated acyl chlorides have been reported to be acylating agents for aromatic compounds in a Friedel-Crafts type reaction,[6] when trifluoroacetyl chloride was added to pyrrole the characteristic "pyrrole red" color formed immediately, then a black tar separated. This occurred with and without aluminum chloride when near zero temperatures were used and either carbon tetrachloride or ether was used as diluent.

EXPERIMENTAL

2-Trifluoroacetylpyrrole. Method 1. A solution of 35 ml. trifluoroacetic anhydride in 300 ml. dry benzene was cooled to about 0°. While the anhydride solution was stirred vigorously, 15 g. pyrrole in 40 ml. benzene was added dropwise over a 2-hr. period. After the addition, the reaction mixture was maintained at about 0° for an additional 4 hr. The reaction mixture was washed with water then dried with anhydrous sodium sulfate. The benzene was removed by distillation and the residue was steam distilled. Trifluoroacetylpyrrole was recovered from the steam distillate by ether extraction: (24 g., 66 wt. % on pyrrole). The crude product was purified by vacuum sublimation and melted 46–47° (uncorr.).

Anal.[7] Calcd. for $C_6F_3H_4ON$: F, 35.9; N, 8.59; mol. wt., 163. Found: F, 34.3; N, 8.67; mol. wt., 163.

Method 2. A solution of 7 g. freshly distilled pyrrole in 50 ml. dry ether was cooled to 3–5° in a flask equipped with stirrer, thermometer, addition funnel, and Dewar-type condenser. Twenty-five ml. of 4*M* methyl magnesium bromide in ether (Arapahoe Special Products, Inc.) was added dropwise during a 1-hr. period while the reaction mixture was stirred and maintained at 3–5°. After the addition of the Grignard reagent, the stirred reaction mixture was maintained cold for 1 hr.

The condenser was filled with an acetone–Dry Ice mixture and the pyrrole magnesium bromide reaction mixture was gassed with 15 g. trifluoroacetyl chloride (10 wt. % excess). The acid chloride addition was completed within 30 min. and the reaction mixture was allowed to warm to room temperature. After the ether was distilled off, the residue was washed with 5 wt. % aqueous NaOH, then steam distilled. The product, recrystallized from ethyl alcohol–water, melted at 45–47° (uncorr.).

The product prepared by both methods was a white solid with a phenol-like odor and was soluble in benzene, ether, and carbon tetrachloride. An infrared spectrogram of a carbon tetrachloride solution of 2-trifluoroacetylpyrrole showed adsorptions at 2.91 microns (NH), 3.03 microns (CH), and 6.0 microns (CO). The phenylhydrazone, prepared by the standard procedure,[8] was a dark liquid which decomposed on heating.

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(1) This investigation was made at the Fluorine Research Center, University of Florida, Gainesville, Fla., under a grant from Minnesota Mining & Manufacturing Co., St. Paul, Minn.

(2) Present address: Celanese Corp. of America, Petroleum Chemicals Research and Development Dept., Clarkwood, Tex.

(3) G. Ciamician and M. Dennstedt, *Gazz. chim. ital.*, **13**, 445 (1883).

(4) B. Oddo, *Gazz. chim. ital.*, **39**, 649 (1910).

(5) S. Portnoy and H. Gisser, *J. Org. Chem.*, **22**, 1752 (1957).

(6) J. H. Simons, W. T. Black, and R. F. Clark, *J. Am. Chem. Soc.*, **75**, 5621 (1953).

(7) Micro-nitrogen determination by Peninsular Chemical Research, Gainesville, Fla. Mol. wt. determined by the melting point depression of *d*-camphor at one arbitrary dilution.

(8) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, 2nd ed., Wiley and Sons, New York, 1940, p. 139.

Preparation of Indazoles and Quinazolines by Catalytic Dehydrogenation

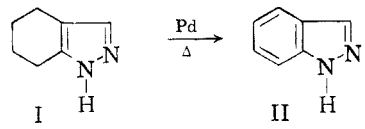
J. PAUL BURNETT, JR., AND C. AINSWORTH

Received March 3, 1958

In a previous publication[1] it was reported that 4,5,6,7-tetrahydroindazole (I) was readily converted to indazole (II) by heating with palladium-on-carbon in decalin. A search of the literature revealed only a few other references[2] to this type of

(1) C. Ainsworth, *J. Am. Chem. Soc.*, **79**, 5242 (1957).

(2) E. C. Horning, M. G. Horning, and G. N. Walker, *J. Am. Chem. Soc.*, **70**, 3935 (1948); H. Adkins and L. G. Lundsted, *J. Am. Chem. Soc.*, **71**, 2964 (1949) and A. Treibs and D. Dinelli, *Ann.*, **517**, 152 (1935).



I II

reaction, namely, the transformation of a tetrahydrobenzo heteroaromatic compound to a benzo heterocyclic material. Two successful related dehydrogenations were recorded,[1] and we now report other examples.

It was found that 1-phenyl-4,5,6,7-tetrahydroindazole was converted in low yield to 1-phenylindazole. When the reaction was applied to the tetrahydroquinazoline system III, the transformation to IV took place in good yield where R was amino and in lower yield where R was aliphatic or aromatic.

III IV

The method was not successful when applied to 2-phenyl-4,5,6,7-tetrahydroindazole, 1-*p*-nitrophenyl-4,5,6,7-tetrahydro-indazole, and 4,5,6,7-tetrahydrobenzo isoxazole.

EXPERIMENTAL

Dehydrogenation—General Procedure. A mixture of 10 g. of the tetrahydro compound, 5 g. of 5% palladium-on-carbon, and 100 ml. of dry decalin was heated under reflux for 2 days. The catalyst was removed by filtration, and the filtrate was concentrated by heating under reduced pressure on a steam bath. The residue was recrystallized from alcohol or petroleum ether.

In this manner 1-phenyl-4,5,6,7-tetrahydroindazole[3] gave 1-phenylindazole,[4] m.p. 80°, yield 20%; 2-amino-5,6,7,8-tetrahydroquinazoline[5] yielded 2-aminoquinazoline,[6] m.p. 200°, yield 45%; 2-phenyl-5,6,7,8-tetrahydroquinazoline[7] formed 2-phenylquinazoline,[8] m.p. 100°, yield 30%; 2-methyl-5,6,7,8-tetrahydroquinazoline (prepared by the general method reported in ref. 7, picrate, m.p. 135°. *Anal.* Calcd. for $C_{15}H_{15}N_5O_7$: C, 47.75; H, 4.01; N, 18.56. Found: C, 47.42; H, 4.36; N, 18.77) gave 2-methylquinazoline,[8] m.p. 40°, yield 10%.

The dehydrogenation procedure was not successful when applied to 2-phenyl-4,5,6,7-tetrahydroindazole,[3] 1-*p*-nitrophenyl-4,5,6,7-tetrahydroindazole (prepared by the general method reported in ref. 3, m.p. 112°. *Anal.* Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.38; H, 5.39; N, 17.34) and 4,5,6,7-tetrahydrobenzoisoxazole.[9]

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(4) W. Borsche and K. Diacont, *Ann.*, **510**, 287 (1934).
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(7) P. C. Mitter and A. Bhattacharya, *Quart. J. Indian Chem. Soc.*, **4**, 149 (1927); [*Chem. Abstr.*, **21**, 3198 (1927)].
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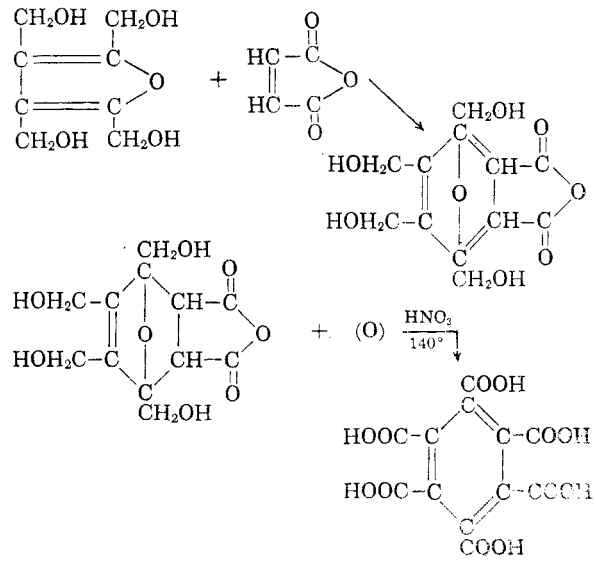
Heterocyclic Tetramethylol Derivatives in the Diene Synthesis

E. C. WINSLOW, J. E. MASTERSON, AND D. A. CAMPBELL

Received March 7, 1958

As a new approach to the laboratory preparation of mellitic acid by the diene synthesis, an attempt was made in this laboratory to add maleic anhydride as a dienophile to the diene system of tetraethyl furantetracarboxylate. The adduct of such a reaction could be hydrolyzed and oxidized to remove the oxygen bridge and produce mellitic acid. Accordingly tetraethyl furantetracarboxylate was prepared by the method of Sutter.[1] Several attempts to bring about the addition of maleic anhydride to this ester were unsuccessful. Attempts were also made to force tetraethyl furantetracarboxylate to react as a diene in the diene synthesis by using different dienophiles. Fumaronitrile, maleonitrile, and dimethylacetylenedicarboxylate were used as dienophiles but no reaction was observed. It was postulated that the dienic character of the tetraester was reduced by pi electron withdrawal from the diene structure of the ring because of the juxtaposition of four ester groupings. If such were the case, the replacement of the four ester groupings on the furan ring by four methylol groups should give some hope of enhancing the dienic character of the ring. The positive inductive effect of the four methylol groups could be relied upon to enhance the pi electron density of the diene system, thus improving its dienic character.

In order to test this theory tetraethyl furantetracarboxylate was reduced to tetramethylolfuran by the use of lithium aluminum hydride. The product, when purified, reacted with maleic anhydride in a



(1) H. Sutter, *Ann.*, **499**, 47 (1932).

typical diene synthesis. The adduct formed by this reaction was subjected to oxidation with concentrated nitric acid to produce mellitic acid.

Because thiophene and its simple derivatives do not react as dienes in a diene synthesis, an attempt was made to see if the positive inductive effect of four methylol groups on the thiophene ring could enhance the dienic character of thiophene sufficiently to enable it to react in a diene synthesis. Tetramethyl thiophenetetracarboxylate was prepared by a method employed by Michael.[2] This was reduced to tetramethylolthiophene by the use of lithium aluminum hydride. This compound failed to react with either maleic anhydride or dimethyl acetylenedicarboxylate in a diene synthesis.

EXPERIMENTAL[3]

Tetramethylolfuran. The tetraethyl ester of furan tetracarboxylic acid was reduced with lithium aluminum hydride to produce tetramethylolfuran. Eleven grams of lithium aluminum hydride were pulverized in a mortar and then suspended in 200 ml. of anhydrous ether in a 1000-ml., three-neck, round-bottom flask, fitted with a reflux condenser and a mechanical stirrer. Thirty-four grams of the tetraethyl ester of furan tetracarboxylic acid were warmed in a water bath to liquefy the ester and a few milliliters of ether were added to keep it in the liquid state. The ester was placed in a small separatory funnel and added drop-wise with caution to the hydride suspension which was cooled in an ice water bath. The rate of ester addition was adjusted to gentle reflux of the reaction mixture. After the ester had reacted, enough water was cautiously added to decompose the excess hydride, after which a large volume of water was added. The resulting aqueous layer contained a thick orange solid in suspension. The water layer was filtered to remove the aluminum and lithium salts and the filtrate, now strongly basic, was adjusted to a *p*H of approximately nine with phosphoric acid. The solution was again filtered, removing lithium and aluminum phosphates, and then evaporated on a steam bath to a volume of about 200 ml. The solution was allowed to go to virtual dryness at room temperature. The residue was treated with 95% ethyl alcohol to extract preferentially the organic portion. The ethyl alcohol was evaporated to 17 g. of a dark brown sirup, representing crude tetramethylol furan. Crystal formation occurred very slowly at a temperature of 0°. These crystals were removed mechanically and recrystallized from water using decolorizing charcoal to yield 8 g. (45%) of white crystals which melted at 123–124°.

Anal. Calcd. for $C_8H_{12}O_5$: C, 51.08%; H, 6.39%. Found: C, 50.93%; H, 6.46%.

Mellitic acid. Mellitic acid was prepared by addition of maleic anhydride to tetramethylol furan followed by oxidation of the adduct with nitric acid. About 5 g. of crude tetramethylol furan were placed in an 8-inch test tube. Four grams of finely ground maleic anhydride were added in the dry state to the test tube. About 5 ml. of dry benzene at a temperature of 23° was added and shaken gently to obtain a homogeneous mixture. During the next 5 min. the reaction temperature rose to 33°. The mixture was allowed to stand for 1 hr. after it returned to room temperature. The mixture was removed as a water suspension and added dropwise through a reflux condenser to 70 ml. of a boiling 1:1 by volume mixture of concentrated nitric and fuming nitric acid. Boiling was maintained for 1 hr. after addition and then the clear yellow solution was evaporated to dryness on a steam bath. The yellow residue was crystallized once from concentrated nitric acid and then from water using decolorizing carbon. White crystals melting at 284–286° were obtained. The yield was not determined because of subdivision of the diene adduct in other purification attempts.

Tetramethylolthiophene. A modification of the reduction technique for the production of tetramethylolfuran was required in the preparation of tetramethylolthiophene because the ester which was used as starting material is relatively insoluble in ether. Lithium aluminum hydride (2.75 g., 0.07 mole) was pulverized and suspended in 300 ml. of absolute ether in a 500-ml. round-bottom flask which was attached to a Soxhlet extraction tube containing tetramethyl thiophenetetracarboxylate (10.0 g., 0.03 mole). The reduction was run at reflux temperature for 12 hr. until no solid remained in the extraction thimble. Water was added to decompose the excess hydride. The reaction mixture was poured into ice water and the ether layer separated from the aqueous mixture. The aqueous portion was filtered with suction, the filtrate was evaporated on a steam bath to dryness, and the residue was extracted with 95% alcohol. The resulting brown solution was evaporated at room temperature to a viscous mass.

The product was isolated by use of Permutit Q cation exchange resin and Dowex 2 anion exchange resin.

Twenty ml. of an aqueous solution of the reaction mixture (5% by volume) was adjusted to a *p*H of approximately four with hydrochloric acid. This solution and the washes were allowed to run through the cation column at the rate of 2.5 ml./minute. After the solution had passed over the resin the column was washed with 50 ml. of distilled water, 20 ml. of 95% ethyl alcohol, and again with 150 ml. of distilled water. The filtrate obtained from the cation column was passed through the anion column at the rate of 2.5 ml./minute. The column was then washed, at the same rate of flow, with 20 ml. of distilled water and 100 ml. of distilled water saturated with carbon dioxide. The filtrate was colorless. The deionized filtrate was evaporated on a steam bath to a volume of 25 ml. and allowed to go to dryness at room temperature. The residue, two grams (33%), was a white substance which melted at 102–103°.

Anal. Calcd. for $C_8H_{12}O_4S$: C, 47.06; H, 5.88; S, 15.69. Found: C, 46.94; H, 5.97; S, 15.98.

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(2) Michael, *Ber.* **28**, 1633 (1895).

(3) All melting points are uncorrected.

Attempts to Copolymerize Pyrene with 1,3-Butadiene and with *p*-Chlorostyrene[1]

C. S. MARVEL AND B. D. WILSON

Received March 14, 1958

Some preliminary experiments on the copolymerization of pyrene with 1,3-butadiene in an emulsion system were reported by Marvel and Anderson.[2] The polymers obtained showed ultraviolet absorption maxima at 342, 301.5, and 260 mμ and on this basis it was concluded that copolymerization had occurred. In this further work on the problem with

(1) The work discussed herein was performed under contract number AF-33(616)-3772 with the Materials Laboratory of Wright Air Development Center, Wright-Patterson Air Force Base, Ohio; Lt. L. E. Coleman and Lt. Paul D. Shaw, project engineers.

(2) C. S. Marvel and W. S. Anderson, *J. Am. Chem. Soc.*, **76**, 5434 (1954).

a better grade of pyrene, the earlier experiments could not be duplicated.

Pure pyrene (m.p. 149.5–150°) was prepared by the zone melting technique[3] and was used in these emulsion copolymerization experiments with 1,3-butadiene and *p*-chlorostyrene. The purified polymers, when analyzed for carbon and hydrogen, proved to be only polybutadiene and poly-*p*-chlorostyrene, respectively. The butadiene polymers did show weak ultraviolet absorption, which appears to be due to small amounts of pyrene which were not removed in the purification. The pyrene contaminations are estimated at 0.031 ± 0.005% in these polymers.

EXPERIMENTAL

Pyrene. A 22-mm. diameter Pyrex tube *ca.* one meter in length was sealed off at one end and filled with 261.5 g. of crude pyrene (Gesellschaft für Teerverwurtung "pure" grade) by melting it to a solid plug *ca.* 81 cm. long. The tube was clamped vertically.

The heater was a 1-cm. long helix of nichrome wire attached to a five volt transformer. The transformer was attached over pulleys to a counterweight. The string connecting the two also was wrapped around a 0.5-inch diameter shaft, which was connected to a one revolution per hour synchronous motor.

The pyrene was heated at such a rate that a 3–5 cm. length was liquid at all times. It was necessary to shield the heater with aluminum foil to protect against air currents in the room. Moving at a rate of 1.6 inches down the tube per hour, the heater required between 19 and 20 hr. per pass. After fifteen passes had been made, the material was removed in fractions, starting from the top of the tube:

Fraction	Approximate Weight, G.	Color (When Melted)	M.P. (°C.) (Corr.)
1	15	Colorless	149.5–150
2	70	Very pale yellow	149 –150
3	90	Pale yellow	148.5–149.5
4	90	Dark	(Discarded)

Fraction 1 was used for all polymerization work.

p-Chlorostyrene. This compound was prepared from *p*-chloroacetophenone, using the procedure of Marvel and Schertz,[4] b.p. 40–41°/2.6 mm., n_D^{20} 1.5649.

Pyrene-butadiene copolymerizations. These copolymerizations were conducted in emulsion in 4-ounce screw-cap bottles sealed with acrylonitrile rubber gaskets. Each charge contained 28 ml. of a 2.86% solution of Office of Rubber Research soap (specification L.M. 2.3.0.5.2), 1.50 g. of pyrene, 7.5 ml. of benzene, 1.5 ml. of a 3% aqueous solution of potassium persulfate, and 13.5 g. of butadiene, in addition to a variable amount of technical lauryl mercaptan (Hooker Electrochemical Co.) as a modifier. The bottles were tumbled end-over-end at 29 revolutions per minute for a specified period in a constant temperature bath at 50 ± 1°. Table I lists the variables for these polymerizations. The polymers were isolated by addition of 5 ml. of a 4.2% solution of sulfuric acid saturated with sodium chloride after first protecting against air oxidation by the addition of 5 ml. of a saturated methanol solution of *N*-phenyl-β-naphthylamine. The polymers were purified by washing well with water, drying, and repeated precipitation (usually ten times) from benzene solution into methanol. The insoluble (cross-linked) material was separated out from the first solution before precipitation by filtration through 200-mesh wire screen. Only samples 10 and 11 showed complete solubility. The elemental analyses shown in Table II are the average of two values. The ultraviolet absorption spectra were obtained with a Cary recording spectrophotometer, Model 11, using solutions in tetrahydrofuran. The solvent was purified by passage through a column of Linde Molecular Sieves, Type 13X.

TABLE I

PYRENE-BUTADIENE POLYMERIZATION VARIABLES

Sample	Modifier, Mg.	Hours Tumbled	Conversion, %[a]	η (0.25% in Benzene)
5	45	88	87.5	[b]
6	45	36	33.1	1.21
7	45	48	46.3	1.65
8	60	37	44.3	1.13
9	60	43	52.6	1.03
10	90	30	42.6	0.350
11	120	30	40.2	0.444

[a] No correction was made for fatty acid or *N*-phenyl-β-naphthylamine inclusion. [b] Essentially only crosslinked material was obtained.

Elemental analysis on the soluble portions of these polymers after purification indicated the materials all to be only polybutadiene (see Table II).

TABLE II

COMPOSITION OF PYRENE-BUTADIENE COPOLYMERS

Sample	Elemental Analysis (Average Values) % C	% H	C/H Ratio
6	88.01	10.97	8.023
7	87.51	10.98	7.970
8	88.52	11.15	7.939
9	88.57	11.10	7.979
10	86.95	10.92	7.962
11	87.48	10.91	8.018
Butadiene	88.82	11.18	7.945
Pyrene	95.02	4.98	19.1

These polymers (5–6 g./l. in tetrahydrofuran) showed weak ultraviolet absorption maxima at 335, 318, 300, 271, and 260 mμ, values differing from those observed by Marvel and Anderson,[2] but very similar to the spectrum of pyrene in ethanol. The spectrum of pyrene in tetrahydrofuran (1.86 mg./l.) showed maxima at 334, 318, 305, 271, 260, and 237 mμ. Using the 335-mμ maximum and assuming Beer's law is applicable, it was calculated that each of these polymers contained pyrene as a contamination in the range of 0.031 ± 0.005 weight per cent. This level of pyrene at the end of the purification process is entirely reasonable.

Pyrene-p-chlorostyrene copolymerization. Only one polymer was prepared, using the same recipe as above, except substituting 15.0 ml. of *p*-chlorostyrene for the butadiene, and using 25 mg. of modifier. The polymerization was of 88 hr. duration and the uncorrected conversion was 107%. The inherent viscosity (0.25% in benzene) was 0.842.

Anal. Calcd. for $(C_8H_7Cl)_x$: C, 69.33; H, 5.09; Cl, 25.58. Found: C, 69.51; H, 5.37; Cl, 25.65. C, 68.90; H, 5.23.

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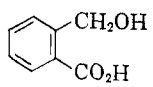
A Reexamination of Phthalide Precursors[1]

PAUL R. JONES

Received March 14, 1958

In the course of a study of the comparative ease of lactonization of various phthalide precursors, it was desired to contrast the chemical properties of *o*-hydroxymethylbenzoic acid (I) and *o*-methoxymethylbenzoic acid (II). While I has long been known,[2] there has been considerable confusion over the physical properties of the ethereal acid II.



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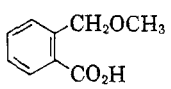

II

Both McGeoch and Stevens[3] and von Braun, Anton, and Weiszbach[4] have reported the preparation of II by treatment of phthalide with alkaline dimethyl sulfate. The recorded melting points of the products, however, were 116–118° and 93–94°, respectively. A melting point of 92–93° was reported by Clemo and Swan[5] for the acid II, which they prepared by an independent route from ethyl *o*-toluate. In another instance[6] a product from metalation and subsequent carbonation of benzyl methyl ether was assigned the structure of *o*-methoxymethylbenzoic acid on the basis of its melting point, 94–95°.

Since the only evidence offered by McGeoch and Stevens for structure II was a neutralization equivalent, it seemed necessary to repeat their work and reexamine the acid product. From combustion analysis, mixture melting point, and a comparison of infrared spectra, it was shown to be *o*-hydroxymethylbenzoic acid (I), which is also formed easily from phthalide by saponification. *o*-Methoxymethylbenzoic acid (II), m.p. 95–96°, prepared for comparison by the method of Clemo and Swan, exhibits a distinctly different infrared spectrum.

The most likely spectral band associated with alcohol or ether C–O stretching is at 1032 cm.$^{-1}$ for I and at 1114 cm.$^{-1}$ for II. While the value for I is considerably higher than that for benzyl alcohol,[7] it is consistent with a similar band at 1032–1033 cm.$^{-1}$ in both *o*-mesitoyl- and *o*-duroylbenzyl alcohol[8]; thus it appears that the bathochromic shift, ordinarily observed as a result of conjugation,[7] is partially counterbalanced by an acyl or carboxy group in the *ortho* position. Analogies for the corresponding assignment in II are to be found in the spectra of ethyl *o*-methoxymethylbenzoate(1115 cm.$^{-1}$) and *o*-duroylbenzyl methyl ether (1110 cm.$^{-1}$).[8]

Chemical evidence for the structure of McGeoch and Stevens' product is the fact that I has been found to be stable under their conditions of alkylation. While it is unusual that dimethyl sulfate is sometimes ineffective as an alkylating agent, it is now clear that their acid should be reassigned structure I.

EXPERIMENTAL[9]

o-Hydroxymethylbenzoic acid (I). Phthalide (10 g.) was heated with 19 g. of sodium hydroxide and 200 ml. of water at 60° for 90 min. After acidification at 5° with dilute hydrochloric acid, the white solid (22 g.) was collected and dried. It was recrystallized from chloroform: ethanol (20:1) in the form of fine needles; m.p. 111–112°.

The infrared spectrum (Nujol mull) contains bands attributable to a primary alcohol (3200 cm.$^{-1}$ broad, 1032 cm.$^{-1}$), to a carboxylic acid group (1670 cm.$^{-1}$ broad), and to *ortho*-disubstituted benzene (740 cm.$^{-1}$).

Attempted methylation of o-hydroxymethylbenzoic acid with dimethyl sulfate. A mixture of 20 g. of the above acid (unrecrystallized), 15 g. of sodium hydroxide, 200 ml. of water, and 25 g. of dimethyl sulfate was heated, with stirring, at 50° for 2 hr. and then stirred an additional 2 hr. By acidification and recrystallization as described above, there was obtained 6 g. (59% based on phthalide) of colorless needles, m.p. 111–112°. A mixture melting point with I showed no depression; and the infrared spectra (Nujol mulls) of the two samples are superimposable.

Attempted direct preparation of o-methoxymethylbenzoic acid (II) *from phthalide.* The procedure, similar to that previously described,[4] was carried out with 10 g. of phthalide, 100 ml. of water, 57 g. of dimethyl sulfate, and 360 ml. of 10% sodium hydroxide. After being washed with ether, the mixture was acidified and the product extracted once with ether and twice with ethyl acetate. By removal of the solvent there was obtained 5.5 g. (48%) of a white solid, m.p. 107–109°. After three recrystallizations from chloroform: ethanol (20:1) the melting point of the *o*-hydroxymethylbenzoic acid (I) was 111.5–112.5°.

Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.17; H, 5.49.

From the filtrate there was recovered 2.2 g. (22%) of phthalide.

o-Methoxymethylbenzoic acid (II). The acid was prepared essentially by the method previously described[5] from 33 g. of ethyl *o*-toluate in an over-all yield of 21%. Intermediates were ethyl *o*-bromomethylbenzoate (not purified) and ethyl *o*-methoxymethylbenzoate (b.p. 246–248°/740 mm.; infrared bands (smear) at 1725, 1267, 1140, 1114, and 742 cm.$^{-1}$). The major modification was the use of *N*-bromosuccinimide in carbon tetrachloride rather than molecular bromine for

(1) This work was supported by a Frederick Gardner Cotrell Grant from the Research Corp. of New York and in part by a grant from the University Research Fund of the University of New Hampshire.

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(9) Infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. Microanalyses were performed at Galbraith Laboratories, Knoxville, Tenn.

bromination of the side chain. The acid, after two recrystallizations from benzene, was in the form of white prisms, m.p. 95.0–96.0°.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.33; H, 6.27.

The infrared spectrum (10% chloroform) of *o*-methoxymethylbenzoic acid contains the typical, broad bands attributable to a carboxylic acid function (3525, 1693 cm.$^{-1}$), as well as a strong band at 1114 cm.$^{-1}$

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An Improved Synthesis of *N*-Phenethylnormorphine and Analogs

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Received March 14, 1958

N-Phenethylnormorphine (Ia) has been prepared[2] by direct phenylethylation of normorphine and exhibits six to ten times the analgesic potency[3] of morphine. We have had occasion to prepare this compound for addiction studies and wish to report an improved method of synthesis.

In this method normorphine was converted to the *N*-phenylacetyl derivative which, without purification, was reduced to the tertiary amine (Ia) with ethereal lithium aluminum hydride.[4] The isolation of Ia from the reduction mixture (in 90% yield based on normorphine) was rendered simple by reason of the low water solubility of its hydrobromide salt.[5] By a similar sequence, norcodeine and dihydrodesoxynorcodeine-D (the latter prepared by cyanogen bromide *N*-demethylation of dihydrodesoxycodeine-D) were transformed into the corresponding *N*-phenethyl derivatives Ib and IIb. There was no complication in isolation of the bases from the reduction mixture since the phenolic hydroxyl is protected in these instances. Hydrobromic acid demethylation of *N*-phenethyldihydrodesoxynorcodeine-D (IIb) gave the phenolic congener (IIa).

The analgesic potency of IIa is five times that of dihydrodesoxymorphine-D (desomorphine), while the effectiveness of Ib and *N*-phenethylnorheterocodeine is twice that of the parent compounds. The duration of action of Ia and the corresponding heterocodiene derivative is about the same as seen in the parent compounds, while Ib and IIb are analgesic twice as long as the *N*-methyl counterparts. In all cases testing was done in mice.

EXPERIMENTAL

Microanalyses and most of the rotations were performed by the Institutes service analytical laboratory, Dr. William C. Alford, director.

N-Phenethylnormorphine (Ia). Normorphine hydrochloride (5 g.),[6] 8 g. of K_2CO_3, 30 ml. of water, and 80 ml. of methanol were treated (stirring) with 6 ml. (2.8 molar equivalents) of phenylacetyl chloride during 0.4 hr. After stirring for an additional 3 hr., the mixture was diluted with water and extracted three times with ethyl acetate. The combined extracts were washed with a little dilute HCl, dried and evaporated to thorough dryness *in vacuo*. The residue and 50 ml. of dry ether were treated (stirring) with 100 ml. of 1.5*M* ethereal $LiAlH_4$ at such a rate as to cause gentle refluxing (10–15 min.). The mixture was refluxed for 15 hr. and treated gradually (vigorous stirring) with 75 ml. of 48% HBr in 130 ml. of water. All inorganic material gradually dissolved leaving a viscous, ball-like mass which, on cooling, crystallized and was easily pulverized. Filtration gave the gummy hydrobromide which, in warm methanol, was converted to the base (Ia) by addition of dilute NH_4OH; yield 5.5 g. (90%), m.p. 250–253° (dec.); thin prisms from absolute ethanol, $[\alpha]_D^{20}$ −117° (c 0.84 in 2:1 $CHCl_3$-MeOH).

Anal. Calcd. for $C_{24}H_{25}NO_3$: C, 76.76; H, 6.71. Found: C, 76.95; H, 6.54.

The tartrate,[1] prepared from the base in refluxing 95% ethanol, melted at 144–147° (froth) alone or in mixture with authentic material[7] and had $[\alpha]_D^{20}$ −68.9° (c 0.99 in 50% by vol. ethanol); reported[1] $[\alpha]_D^{20}$ −67° (solvent not specified).

N-Phenethylnorcodeine hydrobromide (Ib). The reaction of phenylacetyl chloride (1.2 g.) with norcodeine hydrochloride (2 g.) was carried out as described for normorphine above. Reduction of the resultant amide (1.8 g.) with 20 ml. of 1.5*M* ethereal $LiAlH_4$ gave, after addition of 5–10 ml. of water and drying the ethereal filtrate, 1.5 g. of Ib. Acidification of an ether solution of this base with 33% HBr-AcOH yielded an amorphous hydrobromide which crystallized from acetone in prisms; yield 1.5 g., m.p. 273–275°. It was further purified by dissolving it in 225 ml. of boiling 95% ethanol, concentrating the solution to 50–75 ml. and cooling to 0°; m.p. 290–293° (dec.), $[\alpha]_D^{20}$ −97.0° (c 0.58 in MeOH-H_2O, 3:2).

Anal. Calcd. for $C_{25}H_{28}BrNO_3$: C, 63.83; H, 6.00. Found: C, 63.52, 63.46; H, 5.81, 5.95.

N-Phenethyldihydrodesoxynorcodeine-D hydrobromide (IIb). To 2.0 g. of cyanogen bromide (Eastman) in 13 ml. of dry chloroform was added (stirring) during 1 hr. 5.0 g. of dihydrodesoxycodeine-D[8] in 20 ml. of chloroform. The solution was refluxed for 3 hr. and evaporated to dryness *in vacuo*. The residue and 100 ml. of 6% HCl were refluxed overnight. Cooling and basification gave 4.5 g. of crude secondary base which was phenylacetylated as described for normorphine except that 2 molar equivalents of chloride was used. The amide in 50 ml. of dry ether was treated with 50 ml. of 1.5*M* ethereal $LiAlH_4$ during 10–15 min. and the mixture was refluxed overnight. After addition of 20 ml. of water (stirring)

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(5) In another set of experiments in which norheterocodeine was used, almost equally good yields of the *N*-phenethylnorheterocodeine could be obtained in the same fashion.

(6) Supplied by Merck & Co., Inc., *via* Dr. H. F. Fraser, PHS Hospital, Lexington, Ky.

(7) Supplied by Merck & Co., Inc. *via* Dr. Joseph Cochin of this Institute.

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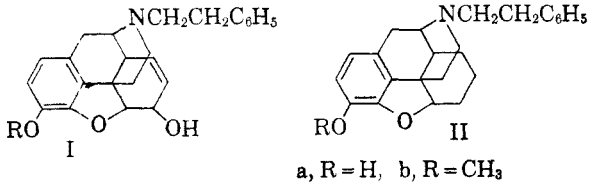
the ether was filtered and dried. The base left from evaporation of the ether was acidified (in acetone) with about 3.0 ml. of 33% HBr-AcOH to give 3.0 g. of IIb hydrobromide, m.p. 243–245°; plates from acetone, m.p. 245–246°, $[\alpha]_D^{26}$ −77.2° (c 1.0 in MeOH).

Anal. Calcd. for $C_{25}H_{30}BrNO_2$: C, 65.79; H, 6.63. Found: C, 65.93; H, 6.60.

N-Phenethyldihydrodesoxynormorphine-D hydrobromide (IIa). Refluxing 2.0 g. of IIb hydrobromide and 12 ml. of 48% HBr for 15 min., cooling and filtering gave a quantitative yield of the IIa hydrobromide, m.p. 285–290°. It crystallized from methanol in plates, m.p. 297–298° (dec.), $[\alpha]_D^{26}$ −74.2° (c 1.0 in MeOH), which analyzed for the hemihydrate; there was, however, no loss in weight of a sample dried for 5 hr. at 135° without vacuum.

Anal. Calcd. for $C_{24}H_{28}BrNO_2 + {}^1/_2\ H_2O$: C, 63.85; H, 6.48. Found: C, 63.92; H, 6.47.



a, R = H, b, R = CH_3

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2-Amino-6-substituted Benzothiazoles as Potential Anthelmintics

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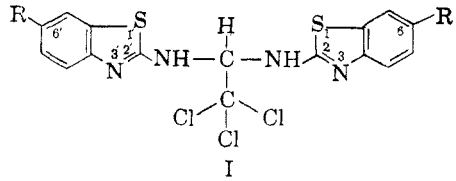
Received March 18, 1958

In an earlier communication Mackie, Stewart and Misra[2] reported the paralysant and lethal action of some benzothiazole compounds toward *Ascaris lumbricoides* and *Fasciola hepatica*. In view of the important physiological properties[3a,b,c] possessed by the 2-amino-6-substituted benzothiazoles, it appeared of interest to prepare the condensation products of these compounds with chloral, of the general structure (I), incorporating a lipoid-solubilizing group (trichloromethyl) which might assist the penetration of the compounds through the cuticle of *Ascaris lumbricoides* and thereby have a deleterious effect on the neuromuscular system of the intestinal nematodes and on other trematodes.



I

Condensation products of aromatic and heterocyclic amines with chloral had previously been reported by Sumerford and Dalton[4] and Nelson *et al.*[5] but no work in this respect seems to have been done with the 2-amino-6-substituted benzothiazoles.

The 1,1-bis(2-benzothiazolylamino)-2,2,2-trichloroethanes of the structure I were prepared by refluxing a benzene solution of the 2-aminobenzothiazole with an excess of freshly distilled chloral for 1.5 hr. on a water bath. The precipitate was filtered, washed with a small volume of dry benzene and recrystallized from a suitable solvent. Under the conditions of the experiment, the condensation did not take place with the 6-nitro, 6-carboxy or 6-carbethoxy-2-aminobenzothiazoles. In the case of 6-chloro-2-aminobenzothiazole, a small amount of its hydrochloride was obtained during reflux along with the unreacted base, while with 2-amino-4,5,6,7-tetrahydrobenzothiazole, the hydrochloride of the base was isolated in good yield. This was presumably due to the partial photochemical decomposition of chloral and the liberation of hydrochloric acid.[6]

The details of the *in vivo* biological activity of these compounds toward the dog hookworms and the ascarid infections in poultry and dogs will be reported later.

EXPERIMENTAL

The 2-aminobenzothiazole and its 6-substituted derivatives were prepared by the known methods.[7-11] The data concerning the new 1,1-bis(2-benzothiazolylamino)-2,2,2-trichloroethanes are listed in Table I. 2-Amino-4,5,6,7-tetrahydrobenzothiazole[12] gave its hydrochloride, which recrystallized in colorless rhomboids from benzene. Yield 50%, m.p. 236–237° (dec.).

Anal. Calcd. for $C_7H_{10}N_2S{\cdot}HCl$, C, 44.09%, H, 5.70%, N, 14.60%. Found C, 43.98%, H, 5.80%, N, 14.89%.

Sprague and Kissinger[13] gave the melting point of the hydrochloride, 249–250°.

(1) Present address: Smith-Mundt Fulbright scholar, Dept. of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan.

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TABLE I

1,1-Bis(2-BENZOTHIAZOLYLAMINO)-2,2,2-TRICHLOROETHANES

R	M.P.	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	% Cl Calcd.	% Cl Found	Yield, %
(a) H	203° (dec.)	$C_{16}H_{11}Cl_3N_4S_2$	44.70	45.20	2.56	2.66	13.03	13.00	24.79	24.65	80
(b) CH_3	180–181° (dec.)	$C_{18}H_{15}Cl_3N_4S_2$	47.21	47.60	3.27	3.34	12.24	12.50	23.27	22.89	51
(c) OCH_3	196–197° (dec.)	$C_{18}H_{15}Cl_3N_4O_2S_2$	44.12	44.30	3.06	3.06	11.44	11.56			82
(d) OC_2H_5	168–169° (dec.)	$C_{20}H_{19}Cl_3N_4O_2S_2$	46.37	46.73	3.67	3.67	10.82	10.73			85
(e) $COO(CH_2)_2-N(C_2H_5)_2$	102–103°	$C_{30}H_{37}Cl_3N_6O_4S_2.2HCl$	45.70	45.93	4.94	4.97	10.65	10.00			75

The analytical samples were: (*a*) recrystallized in colorless needles from benzene; (*b*, *c*, *d*) recrystallized in colorless needles from absolute ethanol–light petroleum (40–60°); (*e*) recrystallized from dry benzene, hygroscopic, decomposes if crystallized from hydroxylic solvents.

Acknowledgments. The author is thankful to Dr. R. C. Shah, Assistant Director, National Chemical Laboratory, Poona(India) for his kind interest in this work, to Dr. B. Mukerji, Director, Central Drug Research Institute, Lucknow (India) for the pharmacological testing of the compounds and to Dr. G. D. Shah for the microchemical analysis.

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An Unusual Reaction of Propargyl Bromide

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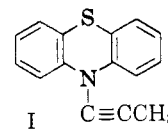
Received March 19, 1958

When an attempt to alkylate phenothiazine with propargyl bromide failed using the customary conditions of sodamide in xylene, the procedure was changed to one using sodium hydride in dimethylformamide. Under these conditions, alkylation occurred to give a 70% yield of product which turned out to be *N*-(1-propynyl)phenothiazine (I) instead of the desired isomeric *N*-(2-propynyl)phenothiazine. Support for the assigned structure includes the presence of disubstituted acetylenic absorption at 4.48 microns in the infrared, and the absence of ≡C—H and >C=C=C< absorption in the 3 and 5.1 micron regions, respectively. However, a disturbing feature of the infrared spectrum is the absence of C-methyl absorption at 7.25μ. Instead, two strong bands appear at 6.87μ and 6.96μ, more characteristic of *N*-methyl absorption. In view of the chemical evidence, it is assumed, nevertheless, that this shift is caused by attachment of methyl to the polar $\rangle N-C\equiv C-$ system.



I

Chemical evidence for structure I was obtained by hydrogenation to known *N*-(*n*-propyl)phenothiazine and by hydrolytic cleavage to unsubstituted phenothiazine.

The anomalous course of this reaction can be rationalized by postulating involvement of the dipolar ion, $\overset{+}{C}H_2C\equiv C^-$, of the type proposed by Hennion and co-workers[1-3] to explain some of the hydrolytic and aminolytic reactions of certain

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tertiary acetylenic chlorides. Resonance stabilization of this ion by the forms, $H:\overset{\cdot\cdot}{\underset{H}{C}}:C:::C: \rightarrow H:C::C::C: \leftrightarrow H:\overset{\cdot\cdot}{\underset{H}{C}}:C:::C$, explains how nucleophilic attack by nitrogen (of the phenothiazine ring) can occur at the acetylenic carbon if one assumes either subsequent or simultaneous attack of a proton or sodium ion at the methylenic carbon atom.

EXPERIMENTAL

N-(1-Propynyl)phenothiazine (I). To a stirred suspension of 7.2 g. (0.3 mole) of sodium hydride in 600 ml. of dry dimethylformamide, protected by an atmosphere of dry nitrogen, was added, in portions, 60 g. (0.3 mole) of phenothiazine. After warming at 50° for an additional 2 hr., the reaction mixture was heated to 70° and a solution of 35.7 g. (0.3 mole) of propargyl bromide in 50 ml. of dimethylformamide was added dropwise. After heating for an additional 2 hr. at 70°, the mixture was stirred overnight at room temperature.

Most of the solvent was removed by distillation at reduced pressure, and the residue was poured into cold water. Insoluble product was taken up in ether, washed with water, and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave an oil (52 g.) which solidified on trituration with hexane. Although purification could be accomplished by recrystallization from hexane, it was conveniently found that passing a benzene solution of the product over a column of alumina gave 48 g. of colorless crystals, m.p. 95–96°.

Anal. Calcd. for $C_{15}H_{11}NS$: C, 75.91; H, 4.67; N, 5.90. Found: C, 75.99; H, 4.70; N, 5.85.

Infrared spectrum (μ): 3.3 (w), 3.37 (w), 3.46 (w), 3.55 (vw), 4.48(m), 5.2 (vw), 5.31 (vw), 5.53 (vw), 5.64 (vw), 6.30 (m), 6.39 (m), 6.77 (m), 6.87 (s), 6.96 (s), 7.18 (vw), 7.28 (vw), 7.58 (s), 7.75 (s), 7.83 (m), 7.97 (s), 8.92 (m), 9.31 (w), 9.68 (m), 10.76 (w), 11.01 (w), 11.21 (w).

Substituting *n*-propyl bromide for the propargyl bromide in the above procedure gave a 65% yield of *N-(n-propyl)-phenothiazine*, b.p. 155–165° (0.8 mm.), m.p. 48–49° (from ethanol) (lit.[4] reports m.p. 49–50°).

Hydrogenation of I. A solution of 10.5 g. of N-(1-propynyl)-phenothiazine (I) in 250 ml. of 95% ethanol was treated with 0.53 g. of platinum oxide catalyst and hydrogenated at 30 lb. pressure and room temperature. After 17 hr., hydrogen absorption was 65% complete. The reaction was then warmed to 60° and reaction was complete in 4 hr. After removal of the catalyst by filtration, the filtrate was concentrated to dryness under reduced pressure. Several portions of benzene were distilled from the residue which was then taken up in 25 ml. of warm absolute ethanol. Heating this solution with charcoal followed by filtering, cooling, and seeding gave, after one more recrystallization from absolute ethanol, 4.2 g. of product, m.p. 47–48°, which did not depress the melting point of *N-(n*-propyl)phenothiazine. Furthermore, the infrared spectrum of the hydrogenation product was qualitatively identical with that of the known reference compound.

Hydrolysis of I. A mixture of 500 mg. of *N*-(1-propynyl)-phenothiazine (I) and 5 ml. of 10% hydrochloric acid was refluxed overnight. However, within 5 min. after the beginning of reflux, the oil turned to a solid. The mixture was concentrated to dryness; the black, crystalline residue was taken up in benzene and dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the benzene solution was passed through an alumina column (20 × 1 cm.). Concentration of the eluate gave 295 mg. of yellow crystals, m.p. 174–176°. Recrystallization from benzene gave 195 mg., m.p. 177–179°.

Anal. Calcd. for $C_{12}H_9NS$: C, 72.32; H, 4.55; N, 7.03. Found: C, 72.46; H, 4.64; N, 6.95.

The product did not depress the melting point of an authentic sample of phenothiazine.

Acknowledgment. The infrared spectra and microanalyses were carried out under the direction, respectively, of Mr. W. F. Washburn and Mr. E. F. Shelberg.

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Decarboxylation of 2-Vinylcyclopropane-1,1-dicarboxylic Acid to the Lactone of 4-Hydroxy-5-hexenoic Acid

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Received March 21, 1958

The synthesis of one of a series of sulfur compounds being prepared in these laboratories involved 3-cyclopentenecarboxylic acid as an intermediate.[1] This acid should readily be obtainable by hydrolysis and decarboxylation of the product of reaction of 1,4-dibromo-2-butene (I) and diethyl disodiomalonate which Skinner *et al.*[2] have described as diethyl 3-cyclopentene-1,1-dicarboxylate. However, the decarboxylation product obtained by this series of reactions did not possess the properties of the required acid. Its properties and infrared spectrum were in fact those to be expected of a vinyl substituted γ-lactone. Decarboxylation at 200° gave only poor yields of this compound, the majority of the product being a higher boiling material, but heating to 170° under a reduced pressure of nitrogen resulted in considerable improvement in the yields of lactone, presumably due to a decrease in the tendency for polymerization.

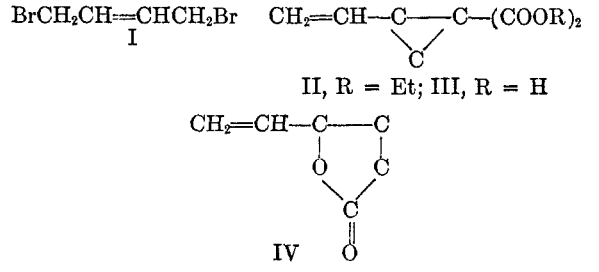
In view of the unexpected course of the preparation, a survey of the literature was made and it was then found that Kierstead *et al.*[3] had reported that condensation of 1,4-dibromo-2-butene and the monosodio-derivative of diethyl malonate gave diethyl 2-vinylcyclopropane-1,1-dicarboxylate (II). Investigation showed that our condensation product had an infrared spectrum not inconsistent with

(1) S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, **22**, 1590 (1957).

(2) G. S. Skinner, G. Limperos, and R. H. Pettebone, *J. Am. Chem. Soc.*, **72**, 1648 (1950).

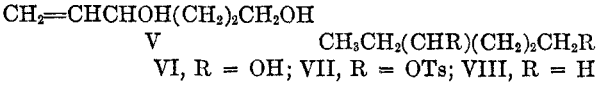
(3) R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 3610 (1952).

its being a vinylcyclopropane diester and that the melting point of the diacid obtained on hydrolysis was in agreement with that quoted[3] for III. It was therefore concluded that a process similar to that described by Kierstead *et al.*[3] had occurred during our condensation and that the product was not the desired cyclopentene compound, but the diester II. Presumably the 3-cyclopentene-1,1-dicarboxylate described by Skinner *et al.*[2] is also in fact this cyclopropane compound.



II, R = Et; III, R = H

IV



V VI, R = OH; VII, R = OTs; VIII, R = H

It seemed likely that the cyclopropane ring of the diacid III had undergone fission during the decarboxylation reaction and that the compound[4] subsequently formed was the lactone of either 4-hydroxy-5-hexenoic acid (IV) or 3-hydroxymethyl-4-pentenoic acid. Examination of the reduction products V–VIII not only confirmed that the cyclopropane ring had been ruptured, but showed that the isolated decarboxylation product was IV, since reduction of the alternative lactone would have given 3-methylpentane instead of *n*-hexane as the final product. It may therefore be concluded that fission of the 3-membered ring occurs in the same position on decarboxylation as on hydrogenation.[3]

EXPERIMENTAL

Microanalyses by Dr. Ing. A. Schoeller, Kronach/Oberfranken, Bambergerstrasse 20, Germany. All melting points are corrected. Infrared spectra are for the liquid state and were obtained using a Grubb Parsons double beam recording spectrometer.

Condensation of 1,4-dibromo-2-butene and diethyl disodiomalonate. 1,4-Dibromo-2-butene (393 g.) was treated (in two batches) with diethyl disodiomalonate as described by Skinner *et al.*[2] Distillation of the product gave 255 g. (65%) of diester (II) b.p. 102–110°/4.5 mm., n_D^{20} 1.4522. Maxima assignable to vinyl (991 and 917 cm.$^{-1}$) and cyclopropane (1031 and 866 cm.$^{-1}$)[5] groups were observed in the infrared absorption spectrum. Skinner *et al.*[2] report b.p. 80–81°/0.5 mm. and n_D^{25} 1.4500 for their material; Kierstead *et al.*[3] give b.p. 69–72°/0.5 mm., n_D^{19} 1.4528 for diethyl 2-vinylcyclopropane-1,1-dicarboxylate.

The lactone of 4-hydroxy-5-hexenoic acid (IV). The above diester (254 g.) was refluxed with aqueous ethanolic potash (KOH, 308 g.; EtOH, 1680 ml.; H_2O, 420 ml.) for 6 hr.; the ethanol was removed by distillation and the residual liquor acidified with hydrochloric acid (600 ml.) and extracted with ether to give the crude diacid (III) (178 g., 93%). A specimen of this, crystallized twice from benzene, melted at 109.5–110.5°. Kierstead *et al.*[3] report m.p. 107–108° for 2-vinylcyclopropane-1,1-dicarboxylic acid.

Anal. Calcd. for $C_7H_8O_4$: C, 53.8; H, 5.2. Found: C, 54.1; H, 5.3.

A small quantity (11.5 g.) of the crude diacid was heated in an oil bath at 200°. Only 3.0 g. (35%) of distillate (b.p. 62–68°/1.7 mm.) was obtained there being a considerable resinous residue. The remainder of the crude diacid was heated in four batches under a pressure of 100 mm. of nitrogen to only 170°. In each instance, when the rate of evolution of carbon dioxide moderated, the nitrogen pressure was reduced to 24 mm. and the material which distilled at about 114° was collected. On redistillation the combined products (103 g.) gave 77.5 g. (62%) of IV, b.p. 108–112°/20 mm. A mid-cut from this distillation, taken as analytical specimen, had n_D^{20} 1.4601 and m.p. −15.5°. Reported[6] for the lactone of 4-hydroxy-5-hexenoic acid b.p. 75°/2 mm. and n_D^{25} 1.4603.

Anal. Calcd. for $C_6H_8O_2$: C, 64.3; H, 7.2. Found: C, 64.0; H, 7.3.

The compound IV could not be esterified by the usual techniques and did not react readily with sodium bicarbonate solution. It rapidly decolorized potassium permanganate solution and bromine water. The infrared spectrum contained bands assignable to a γ-lactone (1779 cm.$^{-1}$)[7] and a vinyl group (990 and 908 cm.$^{-1}$).

1-Hexene-3,6-diol (V). The lactone IV (5 g.) in ether (500 ml.) was reduced with lithium aluminum hydride (3.3 g.) in ether (180 ml.) and the product, b.p. 98–100°/1.8 mm., n_D^{20} 1.4633 was isolated in the usual way;[8] yield 1.8 g. (35%, extraction not completed). Its infrared spectrum showed absorption peaks at 3378 cm.$^{-1}$ (hydroxyl; k = 0.976) and at 990 and 920 cm.$^{-1}$ (vinyl); comparative group analysis using *n*-propyl alcohol (hydroxyl; k = 1.04) as a reference material, indicated the presence of 1.8 hydroxyl groups per molecule.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.0; H, 10.4. Found: C, 61.8; H, 10.5.

1,4-Hexanediol (VI). On hydrogenation at room temperature and atmospheric pressure, the diol V (1.32 g.) in ethanol (15 ml.) absorbed 1 molar equivalent of hydrogen and the product (VI), which was isolated in almost theoretical yield, had b.p. 122–124°/10 mm., n_D^{20} 1.4503 and absorption maxima at 3378 cm.$^{-1}$ (hydroxyl) and 1379 cm.$^{-1}$ (methyl).

Anal. Calcd. for $C_6H_{14}O_2$: C, 61.0; H, 11.9. Found: C, 60.7; H, 11.8.

Di-p-toluenesulfonate of 1,4-hexanediol (VII). The diol VI (0.7 g.) was treated with *p*-toluenesulfonyl chloride and the product VII isolated in the usual way.[9] The crude product (1.1 g., 43%) was crystallized three times from ethanol to give material (0.4 g.) melting constantly at 33–35°.

Anal. Calcd. for $C_{20}H_{26}S_2O_6$: C, 56.3; H, 6.1. Found: C, 56.3; H, 6.4.

Reduction of di-p-toluenesulfonate of 1,4-hexanediol. An ethereal solution of VII (0.3 g. in 0.75 ml.) was reduced with lithium aluminum hydride (0.12 g.) in ether (0.75 ml.), and water (2 ml.) followed by dilute sulfuric acid (H_2SO_4, 0.3 ml.; H_2O, 1.33 ml.) was added dropwise to the reaction mixture. The ethereal layer was removed by means of a hypodermic syringe, and gas liquid chromatography (*n*-hexatriacontane stationary phase at 78°) indicated that the hydrocarbon component was *n*-hexane (retention volume relative

(4) The sharpness of the melting point indicated that the decarboxylation product was essentially one compound.

(5) J. M. Derfer, E. E. Pickett, and C. E. Boord, *J. Am. Chem. Soc.*, **71**, 2482 (1949).

(6) R. R. Russell and C. A. VanderWerf, *J. Am. Chem. Soc.*, 69, 11 (1947).

(7) L. J. Bellamy, *Infrared Spectra of Complex Molecules*, John Wiley and Sons, N. Y., 1954, p. 159.

(8) S. F. Birch and R. A. Dean, *J. Chem. Soc.*, 2477 (1953).

(9) C. S. Marvel and V. C. Sekera, *Org. Syntheses*, Coll. Vol. 3, 366 (1955).

to *n*-pentane: observed 2.46; determined for *n*-hexane, 2.42 and for 3-methylpentane, 2.12). Several further portions were chromatographed and the hydrocarbon fractions were collected in a liquid nitrogen trap as they emerged from the column. The cracking pattern of this material confirmed that it was *n*-hexane.

Acknowledgment. The authors wish to thank the Chairman and Directors of The British Petroleum Company Limited for permission to publish this paper and Messrs. N.G. McTaggart and A.R. West for the determination of the spectroscopic data.

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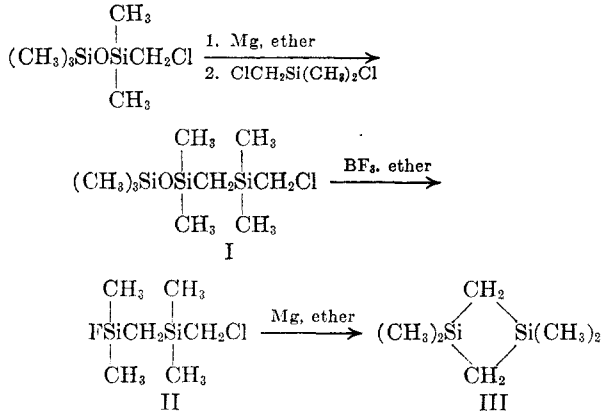
1,1,3,3-Tetramethyl-1,3-disilacyclobutane

W. H. KNOTH, JR., AND R. V. LINDSEY, JR.

Received March 26, 1958

Monosilacyclobutanes have been reported[1,2] only recently and no cyclobutanes containing more than one silicon atom in the ring have been described. Accordingly, it was of interest to prepare such a compound and to compare its properties with those of the monosilacyclobutanes, particularly in view of the reported ease of ring opening of the latter.

1,1,3,3-Tetramethyl-1,3-disilacyclobutane was synthesized in an over-all yield of 25% by a three-step procedure starting with chloromethylpentamethyldisiloxane. The first step, which proceeded



in 73% yield, is analogous to the reported[3] coupling of trimethylsilylmethylmagnesium chloride with chloromethyldimethylchlorosilane. Cleavage of the siloxane linkage with boron trifluoride ethyl etherate gave a 57% yield of II. Cyclization was accomplished in 60% yield by refluxing a solution of II in ether with magnesium turnings.

1,1,3,3-Tetramethyl-1,3-disilacyclobutane is a mobile liquid boiling at 117–119°. It was characterized by elemental analysis, molecular weight determination, and examination of its proton magnetic resonance spectrum, which is in agreement with the assigned structure. The high reactivity of III was demonstrated by its rapid reduction of silver nitrate in alcohol at room temperature, and by its reaction at room temperature with a solution of bromine in carbon tetrachloride. Similar reactions occur with 1,1-dimethyl-1-silacyclobutane and have been shown to involve ring-opening.[4]

EXPERIMENTAL

1-Chloro-2,2,4,4,6,6-hexamethyl-5-oxa-2,4,6-trisilaheptane (I). A Grignard reagent was prepared from chloromethylpentamethyldisiloxane[5] (103 g., 0.52 mole) and magnesium (12.8 g., 0.52 mole) in 250 ml. of ether. To this was added chloromethyldimethylchlorosilane (75 g., 0.52 mole). After the addition, the mixture was heated to reflux and stirred overnight. Saturated ammonium chloride solution was added slowly with stirring until the salts separated to leave a clear, supernatant liquid. The mixture was filtered; the salts were washed with ether; and the ether washings were combined with the filtrate. Distillation gave 103.2 g. (0.38 mole, 73%) of I, b.p. 88–89° (8 mm.).

Anal. Calcd. for $C_9H_{25}ClOSi_3$: C, 40.15; H, 9.31. Found: C, 40.66; H, 9.37.

1-Chloro-4-fluoro-2,2,4-trimethyl-2,4-disilapentane (II). The trisilaheptane (I) (125 g., 0.47 mole) and boron trifluoride ethyl etherate (125 g., 1.06 mole) were mixed and immediately distilled until a head temperature of 125° was reached. The distillation residue was extracted with ether and the extracts were combined with the distillate. This solution was distilled to give 52.5 g. (0.26 mole, 57%) of II, b.p. 173–178°.

Anal. Calcd. for $C_6H_{16}ClFSi_2$: C, 36.36; H, 8.07; Cl, 17.93; Neut. Equiv., 199. Found: C, 36.73; H, 8.29; Cl, 17.85; Neut. Equiv., 195.

1,1,3,3-Tetramethyl-1,3-disilacyclobutane (III). Magnesium (7.2 g., 0.30 mole) and 50 ml. of sodium-dried ether were placed in a 500-ml. flask under an atmosphere of nitrogen. A small amount of II was added and the reaction was started by the addition of three drops of methylmagnesium iodide solution. The reaction mixture was heated to reflux temperature. An additional 225 ml. of ether was added and the remainder of a 58 g. (0.29 mole) sample of II was dissolved in 80 ml. of ether and added over a 95-min. period with rapid stirring. After completion of the addition, stirring and refluxing were continued overnight. Decane (200 ml.) was added and the mixture was distilled rapidly until the head temperature was 170°. Redistillation gave 25 g. (0.17 mole, 60%) of III, b.p. 117–119°, n_D^{27} 1.4380.

Anal. Calcd. for $C_6H_{16}Si_2$: C, 50.00; H, 11.11; Si, 39.00; mol. wt., 144. Found: C, 49.98; H, 11.27; Si, 38.29; mol. wt., 133.

The proton magnetic resonance of this material supports the assigned structure. The product decolorized a carbon

(1) L. H. Sommer and G. A. Baum, *J. Am. Chem. Soc.*, **76**, 5002 (1954).
(2) R. West, *J. Am. Chem. Soc.*, **77**, 2339 (1955).
(3) L. H. Sommer, G. M. Goldberg, J. Gold, and F. C. Whitmore, *J. Am. Chem. Soc.*, **69**, 980 (1947); L. H. Sommer, F. A. Mitch, and G. M. Goldberg, *J. Am. Chem. Soc.*, **71**, 2746 (1949).
(4) L. H. Sommer, private communication.
(5) R. H. Krieble and J. R. Elliott, *J. Am. Chem. Soc.*, **67**, 1810 (1945).

tetrachloride solution of bromine slowly, and reduced alcoholic silver nitrate rapidly as evidenced by the formation of a silver mirror.

CONTRIBUTION NO. 467 FROM THE CENTRAL RESEARCH DEPARTMENT
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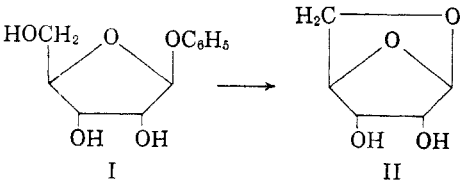
1,5-Anhydro-β-D-ribofuranose from Phenyl β-D-Ribofuranoside

ERIK VIS[1] AND HEWITT G. FLETCHER, JR.

Received April 7, 1958

While the action of strong alkali on aryl glycopyranosides represents a familiar procedure for the synthesis of 1,5-anhydroglycopyranoses[2] and other analogous substances containing this ring system, similar treatment of aryl glycofuranosides has not, to our knowledge, been reported to yield 1,5-anhydroglycofuranoses. In a recent paper,[3] indeed, we stated that an attempt to synthesize 1,5-anhydro-β-D-ribofuranose (II, 1,4-anhydro-α-D-ribopyranose) from phenyl β-D-ribofuranoside (I) had



I II

failed to yield a crystalline product. Subsequent work has now shown, however, that I is converted to II (albeit in low yield) through the action of sodium isopropoxide in 2-propanol.

EXPERIMENTAL[4]

Phenyl β-D-ribofuranoside (158 mg.), prepared as described earlier,[3] was dissolved in 10 ml. of 2-propanol and the solution treated with 6 ml. of 2-propanol in which 32.5 mg. of sodium had been dissolved. The reaction mixture was boiled under reflux for 90 hr., cooled, diluted with a few drops of water and neutralized with carbon dioxide. Solvent was removed *in vacuo* and the residue extracted with acetone. Toluene was added to the extract and the solution concentrated *in vacuo* to a sirup which was freed of the remaining phenol by repeated extraction with benzene. Attempts to crystallize the residue failed and it was therefore benzoylated in the usual fashion to yield a sirup which was partially purified by precipitation from benzene with pentane and then from ethanol with water. On standing for several months at −8° in aqueous ethanol a small deposit of crystalline material was obtained. Recrystallized from methanol this product (*ca.* 15 mg., 6%) showed a double melting point: 132–133° and 146–147°. We reported earlier[3] that 1,5-anhydro-2,3-di-*O*-benzoyl-β-D-ribofuranose melts at 132–133°. Reexamination of the authentic material now reveals that it too shows the double melting point just quoted; a mixture of samples of the compound from the two sources shows the same two melting points. Upon appropriate seeding, either the form with the double melting point or one with the higher melting point only could be obtained from solution.

(1) Chemical Foundation Fellow 1956–58. Present address: Quartermaster Research and Development Center, Natick, Mass.

(2) *Cf.* L. C. Stewart, E. Zissis, and N. K. Richtmyer, *Chem. Ber.*, **89**, 535 (1956).

(3) E. Vis and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **79**, **1182** (1957).

(4) Melting points are corrected.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
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PUBLIC HEALTH SERVICE
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Reciprocal Resolution of DL-Tryptophan and DL-α-Phenylethylamine

LACY R. OVERBY

Received April 11, 1958

Our interests in producing large quantities of L-tryptophan from the DL-form by economically feasible methods prompted a study of known methods and a search for new methods of resolution. The availability of *N*-acetyl-DL-tryptophan as an intermediate in commercial synthesis and the ease of racemization of the undesired D-form[1] indicated that this would be the desirable starting compound. Published methods[1–6] for resolving *N*-acetyl-DL-tryptophan suffer from one or more of the usual disadvantages of resolutions; such as, low yields, time consuming and tedious crystallizations, expensive resolving agents, or handling of large volumes. The method of du Vigneaud and Sealock[1] appeared to offer possibilities for attainment of maximum antipodal purity and for large scale use. The main disadvantage was the scarcity of the desired active form of α-phenylethylamine. DL-α-Phenylethylamine is readily available. If one were able to resolve this with the active forms of acetyltryptophan it would be possible to build up large supplies of optically active acid and base by repetition of the reciprocal resolution.

When one mole of *N*-acetyl-DL-tryptophan was combined with 0.5 mole of (−)- α-phenylethylamine and 0.5 mole of potassium hydroxide in ethanol the sparingly soluble diastereoisomeric salt [LA(−)B]

(1) V. du Vigneaud and R. R. Sealock, *J. Biol. Chem.*, **96**, 511 (1932).

(2) C. P. Berg, *J. Biol. Chem.*, **100**, 79 (1933).

(3) A. C. Shabica, *J. Am. Chem. Soc.*, **71**, 3251 (1949).

(4) Usines Chemiques des Laboratoires Francais, Brit. Patent **745,097**, Feb. 22, 1956; U. S. Patent **2,797,226**, June 25, 1957.

(5) C. Neuberg and I. Mandl, U.S. Patent **2,511,867** (Interchemical Corp.) June 20, 1950.

(6) D. G. Doherty and E. A. Popenoe, Jr., *J. Biol. Chem.*, **189**, 447 (1951).

crystallized in 73% yield and of purity greater than 99% without further recrystallization. The soluble *N*-acetyl-D-tryptophan was racemized with acetic anhydride and again resolved. The acetyl derivative was hydrolyzed to L-tryptophan or reserved for resolution of α-phenylethylamine as needed. The diastereoisomeric (−)-amine salt crystallized from ethanol in 99% purity and 83% yield when the DL-form was mixed with 0.5 equivalent of *N*-acetyl-L-tryptophan and 0.5 equivalent of hydrochloric acid.

Our starting materials were 60.5 g. of (−)-α-phenylethylamine[7] and a plentiful supply of *N*-acetyl-DL-tryptophan and DL-α-phenylethylamine. By alternately resolving acid and base with the available quantities of each several times it was easily shown that 12.5 kg. of acetyl-L-tryptophan and 8.6 kg. of (−)-α-phenylethylamine could be realized after 17 reciprocal resolutions. Thus it is rather easy to work up to quite large scale resolutions with no initial large supply of resolving agent.[8]

These particular experiments were directed toward production of L-tryptophan. Through suitable modifications D-tryptophan and derivatives could be made equally readily, if desired.

EXPERIMENTAL

I. Resolution of acetyl-DL-tryptophan. A. Formation and separation of the diastereoisomers. Acetyl-DL-tryptophan[9] (246 g., 1.0 mole) was dissolved in 500 cc. of hot *N* KOH in 95% 3A ethanol. To the warm solution there was added 60.5 g. (0.5 mole) of (−)-alpha-phenylethylamine.[7] The solution was allowed to cool overnight at room temperature. The yield of crystalline salt [LA(−)B] was 134 g. (73%), $[\alpha]_D^{25}$ + 17.8° (C, 2 in water).[10]

B. Decomposition of the less soluble salt [LA(−)B]. The salt (134 g.) was suspended in about 250 cc. of water and about 50 cc. of benzene. The mixture was made alkaline to phenolphthalein with sodium hydroxide. The aqueous phase was separated and washed three times with 50-cc. portions of benzene. The combined benzene extracts were washed once with water which was combined with the aqueous phase.

C. Preparation of L-tryptophan. The aqueous solution of the sodium salt obtained as in Ib was adjusted with water and 3 equivalents of hydrochloric acid to be 2*N* with respect to acidity. After heating under reflux for 4 hr. the solution was decolorized with carbon and evaporated to dryness under reduced pressure. The residue was extracted with 95% 3A ethanol to separate the tryptophan hydrochloride from the sodium chloride. The alcoholic solution was neutralized with ammonium hydroxide to precipitate the L-tryptophan. This was removed by filtration, washed on the funnel with water followed by alcohol, and dried. The yield was 95%; $[\alpha]_D^{25}$ −31.2° (C, 1 in water).

D. Recovery of acetyl-L-tryptophan. The aqueous solution from Ib was decolorized with activated carbon as necessary and acidified to *p*H 3 with hydrochloric acid. About 96% of the acetyl-L-tryptophan precipitated. This was removed by filtration, washed with water and dried. $[\alpha]_D^{25}$ + 29.1° (C, 1 in H_2O + 1 equivalent NaOH).

E. Decomposition of the more soluble salt and racemization of acetyl-D-tryptophan. The alcoholic solution from Ia was evaporated to dryness and the residue dissolved in about 250 cc. of water and the salt decomposed with NaOH as in Ib. The aqueous solution was decolorized with activated carbon as necessary and 150 cc. of acetic anhydride added. The solution was seeded with *N*-aectyl-DL-tryptophan and kept at 40° overnight, whereupon acetyl-DL-tryptophan crystallized in about 92% yield. After chilling the mixture, the crystalline product was removed by filtration, washed with water, and dried. Specific rotation was zero, m.p. 205–206° (uncorr.). The yield of product was increased to 97% by combining similar filtrates and obtaining additional crops after evaporation of solvent.

II. Resolution of DL-α-phenylethylamine. *N*-Acetyl-L-tryptophan (123 g., 0.5 mole) was dissolved in 250 cc. of warm 95% 3A ethanol. To this solution there was added 0.5 mole of concentrated hydrochloric acid followed by 121 g. (1.0 mole) of DL-α-phenylethylamine (prepared from acetophenone using formamide and formic acid as described by Moore[11]). The solution was seeded and allowed to crystallize at room temperature overnight. The yield of LA(−)B salt was 151 g. (83%), $[\alpha]_D^{25}$ +17.7° (C, 2 in water).[7] The salt was decomposed as in Ia. The (−)-amine was recovered by drying the benzene extracts over sodium hydroxide pellets and distilling the benzene and amine through a short column; b.p. 185–187°, $[\alpha]_D^{25}$ −38.8° to −39.3° (without solvent) depending upon whether the salt was recrystallized before decomposition.

The more soluble material from the original alcohol filtrate was decomposed as in Ie to recover *N*-acetyl-L-tryptophan and the amine rich in the dextro-rotatory form.

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(7) We are indebted to Professor A. W. Ingersoll of Vanderbilt University for this initial supply of active amine.

(8) Although it was not investigated in this study it is also possible to obtain an initial large supply of (−)-α-phenylethylamine through the method of DeWitt and Ingersoll using easily available *N*-acetyldibromo-L-tyrosine, *J. Am. Chem. Soc.*, **73**, 5782 (1951).

(9) Purchased from the Winthrop Chemical Co.

(10) Recrystallization from water increased the specific rotation of the salt to +18.8°, which was unchanged by further crystallization. The over-all yield of salt was reduced to 64%. Unless a product of exceptional antipodal purity was desired recrystallization was normally omitted.

(11) M. L. Moore, *Org. Reactions*, **5**, 321 (1949).

Preparation of 3-(1,1,2-Trifluoro-2-chloroethoxy)propanol and Some of Its Derivatives

J. D. PARK, J. G. ABRAMO,[1] AND J. R. LACHER

Received February 28, 1958

The preparation of ethers of the general formula RO—CF_2—CX_2H where R is an alkyl radical and X is halogen or hydrogen has received a good deal of attention in recent years.[2–4] However, very little has been done in the preparation of ethers of the type, $OH(CH_2)_n$-O-CF_2CX_2H. Coffman *et al.*[5]

(1) Abstracted from a thesis submitted by J. G. Abramo in partial fulfillment of the requirements for the Ph.D. degree, University of Colorado, June 1956.

(2) J. D. Park, D. K. Vail, and J. R. Lacher, *J. Am. Chem. Soc.*, **70**, 1550 (1948).

(3) J. D. Park, C. M. Snow, and J. R. Lacher, *J. Am. Chem. Soc.*, **73**, 861 (1951).

(4) Hanford and Rigby, U. S. Patent 2,409,274 [*Chem. Abstr.*, **41**, 982 (1942)].

(5) D. D. Coffman, M. S. Rausch, G. W. Rigby, P. L. Barrick, and W. E. Hanford, *J. Org. Chem.*, **14**, 747 (1949).

have prepared $HOCH_2CH_2$-O-CF_2CF_2H by the base-catalyzed addition of ethylene glycol to tetrafluoroethylene. The diether, CF_2H-CF_2-O-CH_2CH_2-O-CF_2CF_2H was also isolated. Lawson[6] reported the preparation of $HOCH_2CH_2$-O-CF_2CFClH and Chaney[7] prepared a series of derivatives of 1,1,1,-4,4,4-hexafluorobut-2-yne with ethylene glycol and trimethylene glycol through a base-catalyzed reaction. This paper presents our findings concerning the addition of trimethylene glycol to trifl ıoro-chloroethylene and the preparation of some of its derivatives obtained thereform.

The nucleophilic addition of trimethylene glycol to chlorotrifluoroethylene has been found to proceed in the presence of potassium hydroxide under autogenous pressure. The dispersion of the olefin through the solution of potassium hydroxide and trimethylene glycol under atmospheric conditions was unsuccessful.

Two products were obtained from the pressure reaction in the form of an azeotrope—a mixture of $CFClHCF_2$-$O(CH_2)_3OH$ (I) and $CFClHCF_2$-O-$(CH_2)_3$-OCF_2CFClH (II) which was not separable by ordinary fractional distillation.

Refractive index data later indicated that the mixture had the following composition: 59 mole per cent of I and 41 mole per cent of II.

Separation was achieved by conversion of I to the benzoate followed by purification of the benzoate and subsequent saponification of the benzoate (C_6H_5-$CO_2(CH_2)_3$-O-CF_2CFClH) to the ether-alcohol. The diether II was isolated by oxidation of the azeotrope (in which the ether-alcohol is converted to the ether-acid) and distillation of the solution remaining after extraction of the acid. Another product was obtained from the oxidation mixture, namely $CFClH$-$CF_2OCH_2CH_2$-$COO(CH_2)_3OCF_2C$-$FClH$, which would be expected from the oxidation of an ether-alcohol in an acid medium.

EXPERIMENTAL

The base catalyzed addition of trimethylene glycol to trifluorochloroethylene. A gas-tight 500-ml. Parr hydrogenation bomb was charged with 153 g. (2.0 moles) of trimethylene glycol in which 56 g. (1 mole) of potassium hydroxide had been dissolved. The bomb was then cooled to −78° and charged with 230 g. (2 moles) of trifluorochloroethylene, after which it was rocked for 36 hr. at room temperature. After removal of the unreacted olefin, the bomb was opened and the contents washed with water until neutral to litmus paper, and dried over anhydrous sodium sulfate. Fractionation on a "Helipak"-packed column yielded 175 g. of product distilling at 76–77° at 7-mm. Hg pressure. This product was found to be a mixture of the monoadduct, $CFClH$-CF_2-$O(CH_2)_3$-OH (I) and the di-adduct, $CFClH$-CF_2-$O(CH_2)_3O$-CF_2CFClH (II), which was not separable by simple distillation. The refractive index of this mixture at 20° was found to be 1.3852.

3-(1,1,2-Trifluoro-2-chloroethoxy)-1-propyl benzoate. About 170 g. of the mixture of the mono- and di-ether, I and II, was treated with 120 g. of benzoyl chloride and 100 ml. of pyridine under reflux conditions for about 1 hr. The reaction mixture was washed three times with water and then three times with a 10% solution of sodium hydroxide. Distillation at 3-mm. pressure yielded two fractions with the desired benzoate distilling over at 128–129°; n_D^{20} 1.4710; d_4^{20} 1.313. Molecular refraction: Calcd. for $C_{12}H_{12}O_3F_3Cl$ 62.6. Found, 63.16.

Anal. calcd. for $C_{12}H_{12}O_3F_3Cl$: C, 48.6; H, 4.27, Cl, 12.01. Found: C, 48.79; H, 4.18; Cl, 11.96.

Saponification of $C_6H_5CO_2(CH_2)_3O$-CF_2CFClH. About 53 g. (0.2 mole) of $C_6H_5CO_2(CH_2)_3O$-CF_2CFClH and 22 g. (0.4 mole) of potassium hydroxide pellets were dissolved in 200 milliliters of 75% aqueous ethanol and refluxed for about 0.5 hr. The reaction mixture was then poured into 200 ml. of water and extracted with three 100-ml. portions of ether. The ether fractions were combined and dried over anhydrous sodium sulfate. Distillation in a helix-packed column yielded 15 g. (39%) of $CFClH$-CF_2-$O(CH_2)_3OH$ boiling at 57–58° at 3 mm. of Hg pressure. n_D^{20} 1.3916; d_4^{20} 1.379. Molecular refraction: Calcd. for $C_5H_8O_2F_3Cl$, 33.11. Found, 33.11.

Anal. Calcd. for $C_5H_8O_2F_3Cl$: C, 31.01; H, 4.15; Cl, 18.50. Found: C, 30.8; H, 4.00; Cl, 18.80.

3-(1,1,2-Trifluoro-2-chloroethoxy)propionic acid. About 39 g. of the mixture of the mono- and diether, I and II, was charged to a three-neck flask with 70 g. of magnesium sulfate and 240 ml. of water. To this mixture was added 30 g. of potassium permanganate in 300 ml. of water over a 6-hr. period with constant stirring. The stirring was continued an additional 8 hr. to ensure completeness of reaction after which time, the reaction mixture was then treated with sodium bisulfite until the color of the permanganate was discharged and the manganese dioxide allowed to settle. After filtering and washing the manganese dioxide precipitate, the aqueous solution was treated with 50% sulfuric acid until acid to litmus paper. The aqueous solution was then extracted with 4-250-ml. portions of ether and the ether extracts combined and dried over anhydrous sodium sulfate. Distillation yielded 15 g. of $CHClFCF_2$-$O(CH_2)_2COOH$ boiling at 114–115° at 7 mm. of Hg pressure. n_D^{20} 1.3953; d_4^{20} 1.477. Molecular refraction: Calcd. for $C_5H_6ClF_3O_3$, 33.33. Found, 33.55. Neutralization equivalent: Calcd., 206.6; Found, 208.

The acid-catalyzed oxidation of the mixture of I and II was carried out through the courtesy of Mr. Wayne Severson, Minnesota Mining & Manufacturing Co., St. Paul, Minn.

Isolation of $CFClHCF_2$-$O(CH_2)_2COO(CH_2)_3O$-CF_2CFClH and $CFClH$-CF_2—$O(CH_2)_3OCF_2CFClH$. After the acid had been extracted from the oxidation mixture, distillation of the organic residue gave two main fractions, the first boiling at 73–73.5° (3 mm.) and the second boiling at 136–137° (3 mm.) The physical properties and analyses of the two fractions are given.

(1) $CFClH$-CF_2-$O(CH_2)_3OCF_2CFClH$. B.p. 73–73.5°/3 mm.; n_D^{20} 1.3758; d_4^{20} 1.476. MR_D: Calcd. 47.55; Found, 48.01.

Anal. Calcd. for $C_7H_8F_6Cl_2O_2$: Cl, 23. Found: Cl, 23.1.

(2) $CFClH$-CF_2-$O(CH_2)_2COO(CH_2)_3O$—CF_2CFClH. B.p. 136–137°/3 mm.; n_D^{20} 1.400; d_4^{20} 1.460. MR_D: Calcd. 63.1; Found, 63.1.

Anal. Calcd. for $C_{10}H_{12}F_7Cl_2O_4$: C, 31.42; F, 29.85. Found: C, 31.70; F, 29.90.

Acknowledgment. We wish to express our appreciation to the Minnesota Mining & Manufacturing Co., St. Paul, Minn., and to the Monsanto Chemical Co., St. Louis, Mo., for support of this work in the form of grants-in-aid.

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Synthesis and Properties of Some Fluorinated Ketones[1]

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Received April 15, 1958

Ketones containing one perfluoroalkyl group have been prepared[2] by the reactions of perfluorinated acids with Grignard reagents. In this study, a variety of ketones of the type $Cl(CF_2—CFCl)_n-CF_2-CO-R$ where n = 1, 2, and 3 and R = methyl and ethyl groups were prepared by the action of RMgBr on $Cl(CF_2CFCl)_nCF_2COOH$. Ketones of the type $R_F—CO—R$, where $R_F = -CF_3$ and $-C_2F_5$ and R = methyl, ethyl, and allyl groups, were also prepared by the action of RMgX on R_FCOOH or R_FCOONa. The results are given in Table I.

The formation of secondary alcohols also accompanied the formation of ketones in many cases. These will be reported in a later paper.

EXPERIMENTAL

The method of Dishart and Levine[2b] was used in which three moles of the Grignard reagent was treated with one mole of the fluorinated acid (or salt) at temperatures around 0–15° for about 5–8 hr. The reaction products were hydrolyzed in hydrochloric acid solution, extracted with ether, dried, and then subjected to fractional distillation.

I. Reaction of $CH_2=CHCH_2MgBr$ and CF_3COONa yielded a mixture of $CF_3—\overset{O}{\overset{\|}{C}}—CH_2CH=CH_2$ and $CF_3—\overset{O}{\overset{\|}{C}}—CH=CHCH_3$ (37.1% yield) collected over a temperature range of 55–80°/623 mm. This was dried over P_2O_5, decanted, and then distilled over fresh P_2O_5 whereupon the following fractions were obtained:

Both fractions (A) and (C) gave a positive Baeyer unsaturation test and a positive haloform reaction with concd. sodium hydroxide. Both are strong lachrymators, but found to have no effect on the respiration or blood pressure of a dog. On standing, fractions (A) and (B) reverted almost entirely to fraction (C) as observed by index of refraction, density, and infrared measurements. A 2,4-dinitrophenylhydrazone of fraction (A) with m.p. 140–141° was also prepared (yellow crystals).

Anal. Calcd. for $C_{11}H_9F_3N_4O_4$ (2,4 D.N.P. of Fraction (A)): C, 41.52; H, 2.85; F, 17.91. Found: C, 41.30; H, 2.91; F, 18.03.

Infrared absorption spectra of fraction (A) showed one strong carbonyl peak at 5.64 μ and a very weak one at 5.78 μ; that of fraction (B) showed two strong peaks in the carbonyl region, one at 5.64 μ and another at 5.78 μ; that of fraction (C) showed one strong peak at 5.78 μ with a very weak one at 5.64 μ. Furthermore, fraction (A) and (B) on standing reverted in all properties (index of refraction, density, infrared spectral data) to those of fraction (C). Hence, we propose fraction (A) is comprised almost entirely of $CF_3—\overset{O}{\overset{\|}{C}}—CH_2CH=CH_2$, fraction (B) of a mixture of $CF_3—\overset{O}{\overset{\|}{C}}—CH_2-CH=CH_2$ and $CF_3—\overset{O}{\overset{\|}{C}}—CH=CHCH_3$, and fraction (C) almost entirely of $CF_3—\overset{O}{\overset{\|}{C}}—CH=CHCH_3$. The shift in the carbonyl peak from 5.64 μ to 5.78 μ in going from the β, γ to the α, β isomer is understandable in view of the fact that this results in a shift of the double bond to the conjugate position, hence to greater polarizability of the electrons. Similarly, the higher index of refraction of the α, β isomer over the β, γ isomer is thus accounted for. All three fractions showed strong carbon-carbon double bond absorption at about 6.13 μ. Fraction (A) and (B) also showed absorption in the —OH region (2.85 μ). This might find explanation in the fact that some of the β, γ ketone may exist in the enol form, $CF_3—\overset{OH}{\overset{|}{C}}=CH—CH=CH_2$. This —OH absorption disappears for the α,β ketone where enolization is not possible. This, in effect, substantiates the infrared interpretations of Rausch *et al.*,[2d] who did not obtain and characterize $CF_3COCH_2CH=CH_2$.

Fraction	Component	B.P./ 623 Mm.	n_D^{20}	d_4^{20}	MR_D Calcd.	MR_D Found	Amount, G.
(A)	$CF_3—\overset{O}{\overset{\|}{C}}—CH_2CH=CH_2$	60–61°	1.3544	1.1769	24.83	25.53	5.0
(B)	$CF_3—\overset{O}{\overset{\|}{C}}—CH_2CH=CH_2$ + $CF_3—\overset{O}{\overset{\|}{C}}—CH=CHCH_3$	61–79°	1.3480	—	—	—	11.0
(C)	$CF_3—\overset{O}{\overset{\|}{C}}—CH=CHCH_3$	79–80°	1.3585	1.1891	24.83	25.52	4.0

A higher boiling material still remained from the original distillation, and at a pressure of 33-mm. Hg 8.0 g. of a product boiling at 93.0° was obtained. Analysis showed this fraction to be comprised of a higher polymer of the original ketone, $(C_5H_5F_3O)_n$.

This product was yellow in color and possessed a fairly

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(2) Presented in partial fulfillment of the requirements for the Ph.D. degree at the University of Colorado, 1956. E. I. du Pont de Nemours & Co., Inc., Pre-Doctoral Fellow, 1955–56.

TABLE I

PHYSICAL PROPERTIES OF KETONES PREPARED

Compound	B.P., °C./Mm. Hg	d_4^{20}	n_D^{20}	% C		% F		% Cl		% H		Yield, %
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
$CF_2Cl—CFClCF_2C(=O)—CH_3$	80–81/150	1.4967	1.3685	24.5	25.4	38.78	38.45					23
$CF_2ClCFClCF_2C(=O)—C_2H_5$	106–108/150	1.4607	1.3881	27.82	27.58	36.67	36.37	27.38	26.6	1.94	2.09	8
$Cl(CF_2CFCl)_2CF_2C(=O)—CH_3$	67.5–68.5/9	1.6530	1.3882	23.26	23.67	42.05	42.26					24
$CF_2=CFCF_2CFClCF_2C(=O)—CH_3$	30/10	1.5991	1.3648	28.93	28.94	52.31	52.05					
$Cl(CF_2CFCl)_3CF_2C(=O)—CH_3$	106–107/3	1.7600	1.3938	22.62	23.60	43.73	43.33					22
$CF_3C(=O)—C_2H_4Cl$	86–87/623	1.3932	1.3619	29.93	29.8	35.50	35.12			2.78	2.91	24
$CF_3C(=O)—CH_2CH=CH_2$	60–61/623	1.1769	1.3544	43.48	43.16					3.65	4.0	
$CF_3C(=O)—CH=CH—CH_3$	79–80/623	1.1891	1.3585	43.48	43.30	41.28	41.45			3.65	3.43	37.1
$(C_5F_5F_3O)_n$	93/33	1.3195	1.3886	43.48	43.38	41.28	41.45			3.65	3.84	
$CF_2=CF—C(=O)—C_6H_5$	100–102/5											
$CF_2=CF(C_6H_5)C=NNHC_6H_3(NO_2)_2$-2,4	M.p. 232–234			49.19	49.72	15.56	15.80					

sweet odor. It gave a positive Baeyer unsaturation test, decolorized aqueous bromine solution, and gave a positive haloform reaction with concd. sodium hydroxide.

II. Reaction of CH_2=$CHCH_2MgBr$ and CF_3COOH yielded results similar to that obtained in I. Reaction of C_6H_5MgBr and CF_2=$CFCN$ yielded about 1 g. of material boiling at 100–102° at 5-mm. Hg pressure. This product gave a positive test for unsaturation with 5% permanganate solution and decolorized bromine solution. It formed a 2,4 dinitrophenylhydrazone instantaneously which after two recrystallizations from ethanol-water mixture showed an m.p. 232–234°C.

Anal.: Calculated for $C_{15}H_9F_3N_4O_4$: C, 49.19; F, 15.56. Found: C, 49.72; F, 15.80.

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A Qualitative Test for Mono-, Di-, and Tri-substituted Silanes

HENRY GILMAN, HOUSTON G. BROOKS, JR., AND MARK B. HUGHES

Received May 1, 1958

The reducing properties of Group IVB metal hydrides have been known and recognized for a long time, but only recently has any use been made of this information.

Buchner[1] reported that silane reduced aqueous silver nitrate to metallic silver. Later, Stock and Somieski[2] reported the reduction of iron(III), copper(II), and mercury(II) salts to iron(II), copper (I), and copper(0), and mercury(I) and mercury(0), respectively, the degree of reduction being dependent on the original metal ion to silane ratio in the aqueous solution.

Ruff and Albert,[3] while investigating the properties of silicochloroform, found it also could function as a reducing agent. They report the reduction of chromium(VI) oxide to chromium(III) oxide, sulfur trioxide to sulfur dioxide, sulfur dioxide to sulfur, arsenic(III) to arsenic(0), and antimony(III) oxide to antimony(0), the latter two in the presence of catalytic amounts of sodium hydroxide. Quite similar results are recorded by Besson and Fournier.[4]

Concomitant with these reductions is the evolution of hydrogen gas. Kipping[5] devised a method of quantitative analysis for Si-H compounds which involves measurement of the volume of hydrogen produced. His technique entails the dissolution of the silane in an organic base, such as pyridine or piperidine, and measurement of the hydrogen evolved as the mixture is warmed.

The evolution of hydrogen has also served as a means of monitoring the kinetics of the reaction of Si-H compounds with base. Price[6] examined the rate of hydrolysis of trialkylsilanes in aqueous alcoholic potassium hydroxide, and found his data agreed satisfactorily with a pseudo first order kinetic expression during the first three fourths of the reaction. In a similar study,[7] the effect of substituents on the rate of hydrolysis of triarylsilanes in wet piperidine was found to agree well with the values of Hammett's for carbon compounds. The rates of hydrolysis of triphenylsilane-*d* and triphenylsilane-*t* have also been investigated.[8]

The most recent studies of the reducing power of the Group IVB metal hydrides are those reporting the reduction of fourteen different transition metal salts and seven organic acids with triethylgermane;[9] and the reduction of certain halides and oxides of seven regular group elements and thirteen transitional elements to a lower oxidation state or, in certain cases, to the free element with triethyltin hydride.[10] Another recent publication[11] reports the reaction of Si-H compounds with alcohols in the presence of metallic copper. In light of the low yields reported, there exists the possibility that the reaction is indeed catalyzed by oxides of copper and not the metal itself.

In this laboratory, we have had the occasion to synthesize a large number of partially substituted silanes and, while investigating their chemical and physical properties, have developed a sensitive test for the degree of substitution at the silicon atom. Essentially, the test entails treatment of a mixture of one milliliter of a basic solvent, such as pyridine, and two drops of an approximately 5% aqueous solution of copper(II) chloride with one drop of the silane. Monosubstituted silanes discharge the blue color of the test solution within a few seconds and very rapidly thereafter develop a yellow coloration. Disubstituted silanes are somewhat slower in discharging the blue color, giving a final green coloration. The trisubstituted silanes do not discharge the blue color over a period of three minutes. In all cases where color changes were observed, the aryl compound underwent these changes at a more rapid rate than the similarly substituted alkyl compounds. It is possible to differentiate between monoalkyl and monoarylsilanes using nickel(II) salts. Mercury(II) chloride, potassium permanganate, and silver nitrate, more powerful

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TABLE I

RATE OF REACTION IN PYRIDINE

Oxidant	Color of Complex	Phenylsilane Color	Phenylsilane Time, Sec.	Diphenylsilane Color	Diphenylsilane Time, Sec.	Triphenylsilane Color	Triphenylsilane Time, Min.	*n*-Hexylsilane Color	*n*-Hexylsilane Time, Sec.	Di-*n*-butylsilane Color	Di-*n*-butylsilane Time, Sec.	Triethylsilane Color	Triethylsilane Time, Min.
$CuCl_2 \cdot 2H_2O$	Dk. blue	Green	4	Green	50	Dk. blue	3	Green	6	Green	80	Dk. blue	3
		Yellow	11					Yellow	70				
$Cu(NO_3)_2 \cdot 3H_2O$	Blue	Lt. green	13	Lt. blue	60	Blue	3	Lt. blue	15	Lt. blue	3 (min.)	Blue	3
		Yellow	30					Lt. green	60				
$CuAc_2 \cdot H_2O$	Blue	Brown	2	Green	4								
				Yellow	6	Blue	3	Green	2	Green	50		
				Brown	10			Brown	4	Yellow	60	Blue	3
										Brown	65		
$NiCl_2 \cdot 6H_2O$	Lt. blue	Brown	12	Blue	3 (min.)	Blue	3	Blue	3 (min.)	Blue	3 (min.)	Blue	3
$Ni(NO_3)_2 \cdot 6H_2O$	Lt. blue	Brown	6	Blue	3 (min.)	Blue	3	Brown	40	Blue	3 (min.)	Blue	3
$HgCl_2$	Colorless	Grey	1	Grey	1	Grey	2	Grey	1	Grey	1	Grey	5 (sec.)
$AgNO_3$	Colorless	Brown	1	Brown	2	Brown	5 (sec.)	Brown	1	Brown	2	Brown	6 (sec.)
$KMnO_4$	Deep purple	Brown	2	Brown	2	Brown	5 (sec.)	Brown	2	Brown	2	Brown	5 (sec.)

TABLE II

RATE OF REACTION WITH $CuCl_2$ IN OTHER SOLVENTS

Solvent	Color of Complex	Phenylsilane Color	Phenylsilane Time, Sec.	Diphenylsilane Color	Diphenylsilane Time, Min.	Triphenylsilane Color	Triphenylsilane Time, Min.	*n*-Hexylsilane Color	*n*-Hexylsilane Time, Sec.	Di-*n*-butylsilane Color	Di-*n*-butylsilane Time, Min.	Triethylsilane Color	Triethylsilane Time, Min.
Tetrahydrofuran	Lt. green	Color-less	4	Color-less	3	Lt. green	3	Color-less	9	Lt. green	3	Lt. green	3
		Yellow	30					Yellow	34				
		Turbid	60					Turbid	70				
Ethylene glycol dimethyl ether	Green	Color-less	5	Green	5	Green	3	Color-less	6	Green	3	Green	3
		Yellow	22					Yellow	22				
		Turbid	30					Turbid	32				3
1,4-Dioxane	Lt. blue	Color-less	9	Lt. blue	3	Lt. blue	3	Color-less	13	Lt. blue	3	Lt. blue	
		Yellow	15					Yellow	21				
		Turbid	25					Turbid	30				
Piperidine	Dk. green	Brown	1	Brown	2 (sec.)	Brown	2.5	Brown	1	Brown	10 (sec.)	Dk. green	3

oxidants, give positive tests with trisubstituted silanes. Further differentiations are also possible if the time for color change is observed as well as the final color attained.

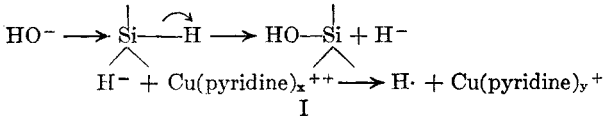
As could be predicted from the previously mentioned kinetic studies,[6,7] there is a slight substituent effect on the rate of reaction. In the tables, the times recorded are for the specific compounds mentioned. However, time variations due to the substituent effect are small when compared with the variations due to degree of substitution at the silicon atom itself and this factor does not, therefore, reduce the applicability of the test. This was demonstrated more precisely when, after testing a total of seventy-two silanes containing either one, two or three hydrogen atoms attached to silicon, all were found to conform to the specifications of this test.[12]

In Table I are listed the various oxidants tested as possible indicators. In addition to those shown, copper(II) sulfate, vanadium(IV) sulfate, nickel(II) sulfate, iron(III) chloride, sodium chromate, chromium(VI) oxide, chromium(III) chloride, and cobalt(II) chloride were also investigated. The first three, all sulfates, and the iron(III) chloride gave precipitates in pyridine which obscured the color changes. The other four compounds underwent little or no color change over the three-minute period.

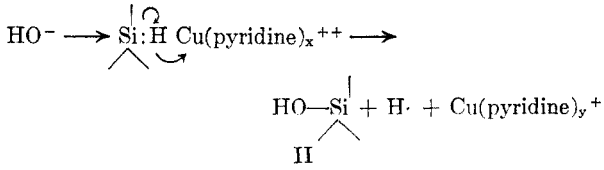
Other polar solvents were investigated as well, and the results, using copper(II) chloride as the oxidant, are assembled in Table II. All are capable of complexing the copper(II) ion somewhat, as evidenced by the various colors observed. It appears that a solvent of basicity and polarity close to that of pyridine is necessary. Piperidine, with its high basicity, is too reactive to be selective; while tetrahydrofuran, ethylene glycol dimethyl ether, and dioxane are not basic and/or polar enough. For intensity of original color and sharpness of color changes, none was as good as pyridine.

Completely nonaqueous systems were investigated also. Suspensions of chloranil, quinone, and azobenzene in pyridine underwent no reaction when treated with the various silanes. However, upon the addition of two drops of water, the evolution of hydrogen was observed and the colors of the solutions were slowly discharged.

These results indicate that hydroxide ion attack on the silane is the first step of the reaction, and the resultant reduction of the oxidant is either by hydride ion in a two step reaction (I) or by a concurrent one electron transfer (II). No attempt



I



II

was made to ascertain which mode of reduction is actually followed.

(12) Some correlations between infrared spectra and the number of hydrogens attached to a silicon atom in organosilanes will be reported later

EXPERIMENTAL

Oxidant solutions. Approximately 5% by weight solutions of all salts were prepared by dissolving 0.5 g. of the hydrated salt in 9.5 ml. of distilled water.

Solvents. All the solvents used were distilled and dried over sodium metal before use, except the pyridine and piperidine. The pyridine employed was a fresh bottle of Baker and Adamson purified grade and the piperidine was Eastman White Label.

Silanes. The times recorded in Tables I and II are for the silanes indicated. In the experiments involving pyridine, the triphenylsilane was added as a 50% by weight solution in pyridine. For the reactions involving other sovents a 50% solution of triphenylsilane in benzene was used for convenience.

Procedure. To one milliliter of the organic solvent was added 2 drops of the oxidant solution and the mixture was shaken until the color became uniform. One drop of the silane or silane solution was then introduced with shaking after which the reaction mixture was allowed to stand while the color changes were observed. The results are summarized in Tables I and II.

Acknowledgment. This work was supported in part by the United States Air Force under Contract AF 33(616)-3150 monitored by Materials Laboratory, Directorate of Laboratories, Wright Air Development Center, Wright-Patterson AFB, Ohio.

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o-(2,4-Dihydroxybenzhydryl)benzyl Alcohol

Max H. Hubacher

Received July 15, 1957

Since *o*-(4,4′-dihydroxybenzhydryl)benzyl alcohol, which Baeyer called phenolphthalol, was found to be a good laxative,[1] it was decided to prepare and test its isomer, the *o*-(2,4-dihydroxybenzhydryl)-benzyl alcohol (VI).

The starting material for its synthesis, the 3-phenyl-3-(2,4-dihydroxyphenyl)phthalide (I) has already been described, but neither of the two methods of preparation is satisfactory. Pech-

(1) M. H. Hubacher, S. Doernberg, and A. Horner, *J. Am. Pharm. Assoc.*, **42**, 23 (1953); O. E. Schultz and L. Geller, *Arch. Pharm.*, **287/59**, 584 (1954); **288/60**, 239 and 244 (1955).

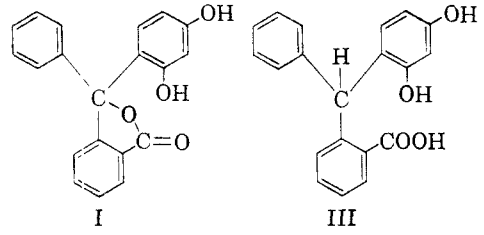
mann's[2] I has a very low melting point and shows color reactions which the pure I does not exhibit. Baeyer's[3] procedure lacks important details, thus giving low yields and erratic results. The procedure described here gives consistent and good yields of pure I.

A second compound (II) melting at 290° is always formed along with I in the reaction between resorcinol and *o*-benzoylbenzoic acid. So far, our investigation has shown that II is not the anhydride of I, as Pechmann[2] thought. This interesting compound is now being investigated further.

The reduction of I leads to the *o*-(2,4-dihydroxybenzhydryl)benzoic acid (III), briefly mentioned by Pechmann.[2] Derivatives of this acid were prepared. One which forms by the elimination of one mole of water on heating of III, is most likely the ϵ-lactone of the α-(2,4-dihydroxyphenyl)-α-(phenyl)-*o*-toluic acid (V), reconverting to III on hydrolysis. This lactone also forms a monoacetyl derivative (Va) and a monomethyl ether (Vb). The latter forms an oily acid on hydrolysis which, on heating to 200°, again yields the monomethylether Vb. Dr. B. Katlavsky of Monsanto Chemical Co., who studied the infrared spectrum of V, reported that V could possibly be a lactone but that the infrared evidence could not in itself confirm or deny this possibility.

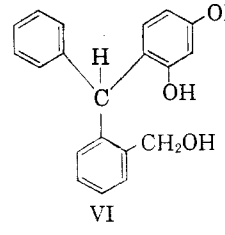
The formation of ϵ-lactones from similarly constituted compounds, such as from 2-carboxy-2′-hydroxydiphenylmethane, has been described by Baker, *et al.*[4]

The *o*-(2,4-dihydroxybenzhydryl)benzyl alcohol (VI) obtained by $LiAlH_4$ reduction of III, was found to possess distinct laxative properties. The pharmacological tests will be described elsewhere.



I

III



VI

EXPERIMENTAL[5]

3-Phenyl-3-(2,4-dihydroxyphenyl)phthalide (I). Attempts to obtain I free from the by-product II, by changing the type of condensing agent, temperature, etc., were unsuccessful. In the absence of a condensing agent, no reaction takes place. Purification of the crude I by precipitation from its alkaline solution by carbon dioxide gives lower yields because it is not as stable in alkaline solution as are most other phthaleins.

A mixture of 22.0 g. (0.2 mole) of resorcinol, 45.2 g. (0.2 mole) of *o*-benzoylbenzoic acid, and 5.0 g. anhydrous zinc chloride was stirred for 2.5 hr. at 120°. Ethanol (150 ml.) was added to the hot, sticky, orange colored reaction mass and refluxed until it had dissolved. The solution, containing some white suspended II, was poured into 1200 ml. slightly acidic water. The precipitated pliable mass was treated with boiling water, hardening slowly on cooling: 53.5–62.3 g. (m.p. 130–148°) of a gray powder was obtained.

This crude I was refluxed with 1600 ml. absolute ether. The insoluble part was II (9.8–15.4 g; m.p. 276–285°). Crystals formed when the ethereal filtrate was evaporated to a volume of 200 ml. These were found to contain one mole solvate ether which was easily lost at 100°.

Anal. Calcd. for $C_{20}H_{14}O_4 \cdot (C_2H_5)_2O$: Ether, 18.9%. Found, loss in weight: 19.2 ± 0.5%.

Additional crystals were obtained by partial evaporation of the filtrate. The total yield of I, dried at 120°, was 30.5–39.0 g., m.p. 195–199° (48–61%). Sometimes, when no crystals are forming, the solvent is evaporated, leaving a gummy residue. On refluxing with chloroform, this residue first dissolves and then crystals containing one mole of chloroform form. These are the solvate crystals described by Baeyer.[3]

Pure 3-phenyl-3-(2,4-dihydroxyphenyl)phthalide (I) melts at 199.0–200.0° (Pechmann[2] 175–176° and Baeyer[3] 198–199°).

Anal. Calcd. for $C_{20}H_{14}O_4$: C, 75.46; H, 4.47; mol. wt. 318. Found: C, 75.34; H, 4.36; mol. wt. 315.

I is very soluble in acetone and ethanol; soluble in absolute ether, but soon crystals containing solvate ether will form in such a solution.

A 0.001-molar solution of I in 0.1*N* sodium hydroxide is of strong reddish orange color[6] which fades slowly when such a solution is exposed to the air, becoming yellow after one week.

A solution of 10 g. of I in 100 ml. *N* sodium hydroxide, heated for 30 min. to 100°, yielded 4.3 g. *o*-benzoylbenzoic acid and 2.2 g. resorcinol. When 5.0 g. of I was stirred in 50 g. molten KOH at 220° for 5 min., benzoic acid and some 2,4-dihydroxybenzophenone were obtained.

The deep orange solution of 0.1 g. of I in 5 ml. concd. sulfuric acid, when heated for 10 min. to 100°, yielded 0.042 g. anthraquinone.

When I was subjected to the oxime splitting of Friedlaender,[7] a small quantity of a compound was obtained, which crystallized from ethanol in needles melting at 163.0–163.5°.

Anal. Calcd. for $C_{14}H_9O_2N$: C, 74.88; H, 4.04; N, 6.27; mol. wt. 223. Found: C, 75.24; H, 3.88; N, 6.85; mol. wt. 228.

A mixture of this compound with 4-phenyl-1*H*-2,3-benzoxazin-1-one (m.p. 162.5–163.0°) prepared by the method of Thorp[8] melted at 162.7–163.1°.

Diacetylderivative of I. Purified by crystallizations from ethanol, it melted at 141.0–141.9° (v. Pechmann 137°).

Anal. Calcd. for $C_{24}H_{18}O_6$: C, 71.63; H, 4.50; —$COCH_3$, 21.40. Found: C, 71.60; H, 4.55; —$COCH_3$, 21.27.

(2) H. v. Pechmann, *Ber.*, **14**, 1860 (1881).
(3) A. Baeyer, *Ann.*, **372**, 91 (1910).
(4) W. Baker, D. Clark, W. D. Ollis, and T. S. Zeally, *J. Chem. Soc.*, 1452 (1952).
(5) All melting points are corrected. Molecular weights were determined by the Signer method as described by E. P. Clark, *Ind. Eng. Chem., Anal. Ed.*, **13**, 820 (1941).
(6) Color designation according to the Munsell Color System *Method of Designating Colors*, National Bureau of Standard Research Paper PR 1239, September 1939.
(7) M. H. Hubacher, *J. Am. Chem. Soc.*, **68**, 718 (1946).
(8) F. H. Thorp, *Ber.*, **26**, 1262, 1795 (1893).

Dimethylether of I. Prepared by heating 3.18 g. of I, 3.8 ml. of methyl iodide, 2.8 g. K_2CO_3, and 50 ml. acetone for 6 hr. at 60°, and recrystallized from ethanol (1 g. in 16 ml.), it formed six-sided plates melting at 157.0–158.5°.

Anal. Calcd. for $C_{22}H_{18}O_4$: C, 76.27; H, 5.20; mol. wt. 346. Found: C, 76.12; H, 5.71; mol. wt. 346.

o-(2,4-dihydroxybenzhydryl)benzoic acid (III). The reduction of I to the acid was best accomplished as follows: 5 g. Raney alloy was added over a period of 20 min. to a stirred solution of 15.9 g. of I in 60 ml. 2.5*N* sodium hydroxide. The temperature rose to 55–60°. As soon as the orange color disappeared, the mixture was filtered to remove the nickel. The light orange filtrate, on acidification, yielded a gummy precipitate which was then treated with hot water. On cooling overnight, it became hard (14.7–15.5 g., m.p. 175–181°).

This acid was purified by dissolving it in absolute ether (1 g. in 30 ml.), and evaporating the filtrate to a small volume (5 ml.). The crystals thus obtained contained one mole of solvate ether, which was lost at 120°. (Calcd. for $C_{20}H_{16}O_4 \cdot (C_2H_5)_2O$: Ether, 18.8%. Found, loss in weight: 19.0 ± 0.3%). The yield, in the form of two crops, was 7.6–10.4 g., m.p. 184–186° (47–65%).

This same acid may be prepared by the zinc dust reduction of I in 80% acetic acid, in which case some V is obtained as the part which is insoluble in 2*N* sodium carbonate.

The pure III melts at 186.9–187.4° (Pechmann,[2] 184°).

Anal. Calcd. for $C_{20}H_{16}O_4$: C, 75.00; H, 5.00; mol. wt. 320. Found: C, 75.03; H, 5.75; neut. equiv. 318.

This acid is very soluble in acetone, ethanol, ethyl acetate, and acetic acid; insoluble in chloroform or benzene. It may also be recrystallized from 20% acetic acid (1 g. in 6 ml.).

I dissolves in concd. sulfuric acid with yellow color, becoming dark green. Its solution in dilute alkalies, initially colorless, slowly turns orange.

Methyl ester of III. Diazomethane, made from 5.2 g. nitrosomethylurea, was distilled into a solution of 8.0 g. of III in 200 ml. pure ether. On evaporation of most of the solvent, white crystals (m.p. 186–194°) formed. Sometimes, an oil is left which, on treatment with benzene, becomes crystalline.

The ester was purified by dissolving it in a large volume of ether and then distilling off most of the ether; or from a mixture of 1 vol. of methanol and 5 vol. of benzene. The pure ester forms white crystals melting at 203.6–204.4°.

Anal. Calcd. for $C_{21}H_{18}O_4$: C, 75.45; H, 5.39. Found: C, 75.24; H, 5.70.

Triacetylderivative of 10-(o,p-dihydroxyphenyl)-9-anthrol (IV). By heating 3.2 g. of III in 5 ml. acetic anhydride and 0.03 ml. of concd. sulfuric acid for 30 min. to 120°, and recrystallizing the crude product from 230 ml. ethanol, 3.1–3.5 g. of IV, m.p. 181–185° were obtained. After crystallizations from ethyl acetate (1 g. in 12 ml.), the pure compound melted at 183.4–184.0°. Solutions of IV in organic solvents exhibit blue fluorescence.

Anal. Calcd. for $C_{26}H_{20}O_6$: C, 72.89; H, 4.67. Found: C, 72.78; H, 4.69.

A mixture of this compound with the acetyl derivatives (m.p. 179–181°) of the condensation product obtained from resorcinol and 9-bromo-10-anthrone by the procedure of Liebermann and Mamlock[9] melted at 182–183°.

The ε-lactone of α-(2,4-dihydroxyphenyl)-α-(phenyl)-o-toluic acid (V). When III (1.60 g.) was heated to 220°, it gave off one mole water (85 mg.) and a trace of carbon dioxide (2 mg.). The resulting compound, obtained in practically quantitative yield, was crystallized from ethanol (1 g. in 12 ml.). It may also be purified by sublimation at 200° and 10 microns pressure. The pure V melts at 242.0–242.5° and dissolves in *N* sodium hydroxide to a colorless solution.

Anal. Calcd. for $C_{20}H_{14}O_3$: C, 79.46; H, 4.76; mol. wt. 302. Found: C, 79.41; H, 4.71; mol. wt. 315.

When a suspension of 0.75 g. of V in 10 ml. of *N* sodium carbonate is refluxed under nitrogen for 5 hr. and the resulting solution is acidified, then III will precipitate out.

Acetyl derivative of V (Va). On heating 1.0 g. of V, 1.5 ml. acetic anhydride, and 0.02 ml. concd. sulfuric acid for 30 min. to 120° and recrystallizing the product from 12 ml. ethyl acetate, 0.78 g. (m.p. 174–175°) was obtained.

This same acetyl derivative is obtained as the main product by direct acetylation of III with acetic anhydride and sodium acetate.

The pure Va melts at 174.6–175.3°.

Anal. Calcd. for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68; mol. wt. 344. Found: C, 76.70; H, 4.73; mol. wt. 345.

The methyl ether of V *or the ε-lactone of α-(2-hydroxy-4-methoxyphenyl)-α-(phenyl)-o-toluic acid* (Vb). A mixture of 3.02 g. of V, 1.4 g. of K_2CO_3, and 50 ml. acetone were heated for 8 hr. on a water bath of 60°. The resulting compound, recrystallized from ethanol (1 g. in 80 ml.), melted at 191.9–192.7°.

Anal. Calcd. for $C_{21}H_{16}O_3$: C, 79.73; H, 5.09; $-OCH_3$, 9.8. Found: C, 79.29; H, 5.25; $-OCH_3$, 10.0.

On heating this methylether with *N* sodium hydroxide, it gradually dissolved. On acidification, an oil separated, which could not be made to crystallize. When heating this amorphous acid to 200°, it was transformed back into Vb.

o-(2,4-dihydroxybenzhydryl)benzyl alcohol (VI). This alcohol was prepared according to the procedure given for phenolphthalol.[10] The extraction thimble was charged with 12.8 g. of III, and the flask with a solution of 5.0 g. of $LiAlH_4$ in 500 ml. pure ether. The thimble content was dissolved during the first 2 to 3 hr. of a total of 24 hr. of refluxing. The quantity of unreacted III was negligible. The oily residue, left after the evaporation of the ether, was dissolved in 200 ml. of 20% ethanol, stirring the solution while slowly cooling. The 10.4–11.2 g. of crystals (m.p. 168–169°; yield 85–91% based on III) were recrystallized from water (1 g. in 450 ml.; recovery 75–81%). The pure VI melts at 169.8–170.4°.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.42; H, 5.92; mol. wt. 306. Found: C, 78.47; H, 6.16; mol. wt. 320.

This alcohol is very soluble in acetone, ethanol, n-butanol, cyclohexanone; soluble in ether; insoluble in chloroform. As expected, its solution in *N* sodium hydroxide is colorless.

Triacetyl derivative of VI. A mixture of 3.06 g. of VI, 6 ml. acetic anhydride, and 0.02 ml. concd. sulfuric acid was heated for 1 hr. to 100°. The 4.1–4.4 g. dry crude acetyl derivative was placed in a thimble and extracted with pure ether. The compound crystallized from the ether in the form of fine white needles after standing for several days at 5° (yield 3.1–3.6 g., m.p. 103–105°). The pure triacetyl derivative melted at 104.1–105.5°.

Anal. Calcd. for $C_{26}H_{24}O_6$: C, 72.22; H, 5.56; mol. wt. 432. Found: C, 72.19; H, 5.29; mol. wt. 422.

Tribenzoyl derivative of VI. To a solution of 1.0 g. of VI in 2 ml. of pyridine was added 2 ml. of benzoyl chloride. The mixture was kept for 0.5 hr. at 120°, and was then poured into ice water. The gummy precipitate, washed free of pyridine, very slowly became crystalline. Recrystallized from a large amount of ethanol, it formed colorless needles, m.p. 141.1–142.2°.

Anal. Calcd. for $C_{41}H_{30}O_6$: C, 79.60; H, 4.89; mol. wt. 618. Found: C, 79.82; H, 5.07; mol. wt. 592.

Acknowledgment. The author is indebted to D. Curtin and A. Horner for experimental assistance.

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(9) C. Liebermann and L. Mamlock, *Ber.*, **38**, 1798 (1905).

(10) M. H. Hubacher, *J. Am. Chem. Soc.*, **74**, 5216 (1952).

2-Chloroprocaine Amide and 2-Chlorothiocaine

DAVID B. REISNER AND MICHAEL G. CORDASCO

Received March 21, 1958

In connection with our investigations on the biological effect of substituting halogens on the benzene ring of procaine and related compounds, we have prepared 2-chloroprocaine amide and 2-chlorothiocaine. These were secured *via* the reaction of 2-chloro-4-nitrobenzoyl chloride with β-diethylaminoethylamine and with β-diethylaminoethanethiol, respectively, and subsequent reduction with iron.

Both, 2-chloroprocaine amide and 2-chlorothioacine, are as active as procaine as local anesthetics. 2-Chloroprocaine amide is approximately four times as potent as procaine amide in blocking artificial fibrillation in the dog.

EXPERIMENTAL[1]

N-(β-Diethylaminoethyl)-2-chloro-4-nitrobenzamide hydrochloride (I). To a solution of 0.25 mole of 2-chloro-4-nitrobenzoyl chloride, secured from the acid and thionyl chloride, in 150 ml. of dry benzene 58 g. of β-diethylaminoethylamine was added with stirring and cooling. The mixture was stirred for 20 min. at room temperature and then allowed to stand overnight at room temperature. It was stirred and heated under reflux for 1 hr., cooled, and poured into a mixture of ice and concd. hydrochloric acid (50 ml.). The aqueous layer was separated and washed with benzene. The aqueous solution was then cooled, made alkaline with sodium carbonate trihydrate (*ca.* 120 g.) and extracted with one 200-ml. and three 100-ml. portions of ether. The combined ether solutions were washed thoroughly with water, dried over anhydrous magnesium sulfate, and saturated with dry hydrogen chloride. The solid was removed by filtration, washed with ether, and air-dried. It weighed 70 g. and melted at 167–170°. Recrystallization from a mixture of ethanol and ether provided an analytical sample melting at 169–170°.

Anal. Calcd. for $C_{13}H_{19}Cl_2N_3O_3$: N, 12.50. Found: N 12.53, 12.35.

N-(β-Diethylaminoethyl)-2-chloro-4-aminobenzamide(2-chloroprocaine amide) dihydrochloride (II). A suspension of 50 g. of powdered iron in 100 ml. of water was heated to 65°, and a warm solution of 20.2 g. of I in 100 ml. of water was added slowly with stirring. The mixture was then stirred and heated for 2 hr. at *ca.* 75° and filtered while hot. The filtrate was chilled, made alkaline with 10% sodium carbonate and extracted with one 300-ml. and three 150-ml. portions of chloroform. The chloroform solutions were combined, washed with water, and dried over anhydrous magnesium sulfate. Ethanol (100 ml.) was added and mixture was treated with dry hydrogen chloride. Ether was added to the cloud point, and after chilling overnight the solid was removed and dried. It weighed 16.2 g. and melted at 190–193°. After recrystallization from ethanol with charcoal, the white crystals melted at 193–195°.

Anal. Calcd. for $C_{13}H_{22}Cl_3ON_3$: N, 12.26; Cl, 31.04. Found: N, 12.26; Cl, 31.04.

Free base (III). An aqueous solution of 25 g. of II was made alkaline with sodium carbonate and extracted with ether. The ether solution was dried over anhydrous sodium sulfate and evaporated to dryness. Recrystallization of the residue (18.7 g.) from ether gave white glistening crystals that melted at 79.5–80.5°.

Anal. Calcd. for $C_{13}H_{20}ClN_3O$: C, 57.86; H, 7.47. Found: C, 57.81; H, 7.50.

Monohydrochloride (IV). This was prepared by mixing a solution of II (3.06 g.) in 50 ml. of methanol and a solution of III (2.70 g.) in 5 ml. of benzene. The product melting at 139.5–141° was recrystallized from a mixture of methanol and ether to provide an analytical sample melting at 142–143°.

Anal. Calcd. for $C_{13}H_{21}Cl_2N_3O$: N, 13.72. Found: N, 13.70, 13.72.

Formate (V). A solution of III (2.70 g.) in 5 ml. of benzene was mixed with a solution of 0.46 g. of 98% formic acid in 5 ml. of isopropyl alcohol and ether was added to induce crystallization. The product weighing 2.40 g. and melting at 99.5–100° was recrystallized from a mixture of ethanol and ether to give an analytical sample melting at 100–100.5°.

Anal. Calcd. for $C_{14}H_{22}ClN_3O_3$: N, 13.31. Found: N, 13.34, 13.37.

N-(β-Diethylaminoethyl)-2-chloro-4-nitrothiolbenzoate hydrochloride (VI). To a solution of 2-chloro-4-nitrobenzoyl chloride, prepared from 12.1 g. of acid and 14.3 g. of thionyl chloride, in 25 ml. of dry benzene a solution of 7.98 g. of β-diethylaminoethanethiol[2] in 20 ml. of dry benzene was added with stirring and cooling. The mixture was stirred 0.5 hr. longer and then allowed to stand overnight at room temperature. It was transferred to a mixture of 150 ml. of water and 50 g. of ice. Ether (50 ml.) and benzene (50 ml.) were added, and mixture was made alkaline with ammonium hydroxide. The organic layer was separated, and the aqueous solution was washed twice with 50 ml. of ether. The combined organic solutions were washed with one 100-ml. and four 50-ml. portions of water, dried over anhydrous magnesium sulfate, and treated with dry hydrogen chloride. The hydrochloride was removed and dried. It weighed 11.85 g. and melted at 120.5–122.5°. After recrystallization from a mixture of ethanol and ether, the melting point was raised to 125–126°.

Anal. Calcd. for $C_{13}H_{18}Cl_2N_2O_3S$: N, 7.93. Found: N, 8.00.

N-(β-Diethylaminoethyl) 2 chloro-4-aminothiolbenzoate (2-chlorothiocaine) hydrochloride (VII). A solution of 2.7 g. of VI (m.p. 120.5–122.5°) in 20 ml. of distilled water was added with stirring to a mixture of 7.5 g. of iron powder and 10 ml. of distilled water preheated to 45°. The resulting mixture was stirred and heated for 1 hr. at 45° and then allowed to stand for 1 hr. at room temperature. While cooling, the *p*H was adjusted to 11 with concd. ammonium hydroxide, and the mixture was filtered. The filtrate was extracted with 50 ml. of ethyl acetate and the sludge was washed with 200 ml. of hot ethyl acetate. The combined ethyl acetate solutions were washed with three 100-ml. portions of water, dried over anhydrous magnesium sulfate, and evaporated to dryness *in vacuo*. Absolute ethanol (10 ml.) and anhydrous ether (50 ml.) were added and solution was charged with dry hydrogen chloride. The crude hydrochloride weighed 1.4 g. An analytical sample, after recrystallization from aqueous ethanol, melted at 218–219°.

Anal. Calcd. for $C_{13}H_{20}Cl_2N_2OS$: N, 8.67; Cl, 21.93. Found: N, 8.60; Cl, 21.82.

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BELLEVILLE, N. J.

(1) All melting points are uncorrected.

(2) N. F. Albertson and R. O. Clinton, *J. Am. Chem. Soc.*, 67, 1222 (1945).

Chromium Trichloride Tetrahydrofuranate[1]

W. Herwig and H. H. Zeiss

Received April 9, 1958

The reaction of anhydrous chromium trichloride and phenylmagnesium bromide in ether[2] or in tetrahydrofuran[3] is necessarily a heterogeneous one owing to the extreme insolubility of this metallic halide in organic solvents. Inorganic salts of chromium are in fact generally insoluble in all nonhydroxylic solvents; and this property presents difficulties in promoting their reactions in organic solvents with organic reagents. We have now found that the trichloride may be made soluble by complexing it with tetrahydrofuran and that its reactions with Grignard reagents proceed rapidly, quantitatively, and homogeneously in this form.

The conversion of anhydrous chromium trichloride into its tetrahydrofuranate is achieved by the continuous extraction with anhydrous tetrahydrofuran of its solid form admixed with catalytic amounts of zinc dust. In this manner the halide is quantitatively extracted by the solvent from which the violet tetrahydrofuranate is crystallized. The zinc metal which is recovered unchanged is considered to behave as a reducing agent, solubilizing chromium in its divalent form, followed by subsequent reduction itself and concurrent formation of $CrCl_3(THF)_3$.[4] The coordinating tetrahydrofuran molecules are very tightly bound in the complex, for they are not lost even upon heating of the complex to 100° at 20 mm., and the tetrahydrofuranate may be kept in the open air several hours without appreciable hydrolysis, since the crystals are only slightly hygroscopic and deliquesce quite slowly to a green hydrate. Consequently, as a reagent it may be stored indefinitely without decomposition so long as it is kept dry.

EXPERIMENTAL

Chromium trichloride tri-tetrahydrofuranate. The tetrahydrofuran (Mathieson, Coleman and Bell, b.p. 64–66°) used in this preparation was purified and dried by refluxing over sodium ribbon with fresh ribbon being added until new ribbon maintained a clean surface after 5 hr. of refluxing. Just prior to use the THF was distilled, treated with fresh sodium ribbon and with lithium aluminum hydride, and then redistilled in a stream of dry, oxygen-free nitrogen (GE lamp grade is suitable for this purpose without further drying and/or purification).

Anhydrous chromium trichloride (Fisher), 12.21 g., mixed with 0.15 g. of zinc dust, is placed in the thimble of a Soxhlet extraction apparatus and then extracted overnight with 140 ml. of boiling THF or until no further color is observable in the cycling liquid (10–15 hr.). After complete extraction only zinc dust remains in the extraction thimble, while the pot flask contains the solution of the tetrahydrofuranate (2.8 g./100 ml. of hot THF) together with the crystalline chromium trichloride tri-tetrahydrofuranate which has crystallized during extraction. Concentration, cooling, and filtration are employed to isolate the crystalline form in essentially quantitative yield.

Anal. Calcd. for $CrCl_3(C_4H_8O)_3$: Cr, 13.88; Cl, 28.39. Found: Cr, 13.42; Cl, 28.57, 28.19.

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(1) Paper VI, "π-Complexes of the Transition Metals"; Paper V, H. H. Zeiss and W. Herwig, *J. Am. Chem. Soc.*, **80**, 2913 (1958).

(2) H. H. Zeiss and M. Tsutsui, *J. Am. Chem. Soc.*, **79**, 3062 (1957).

(3) W. Herwig and H. H. Zeiss, *J. Am. Chem. Soc.*, **79**, 5959 (1957).

(4) This phenomenon has been observed previously in that chromous chloride will cause the trichloride to dissolve in ether: N. V. Sidgwick, *The Chemical Elements and Their Compounds*, Oxford Univ. Press, New York, N. Y., 1950, p. 1012.

Preparation of a New Class of Steroids with Unnatural Configuration. The 19-Nor-5α,10α Series

Richard T. Rapala and Eugene Farkas

Received June 5, 1958

There are four possible steric arrangements of the A/B rings of the 19-nordihydrosteroid nucleus (the *trans-syn-trans* conformation requires a boat form for ring B), all other centers of asymmetry being kept constant. The allo configurational series (5α,10β) was reported by Bowers, Ringold, and Dorfman[1] while the normal series (5β,10β) was described recently from this Laboratory.[2]

This communication reports the synthesis of a third and hitherto unknown series of 19-norsteroids, and evidence is presented which permits assignment of structure and classification as 19-nor-5α,10α-dihydrosteroids.

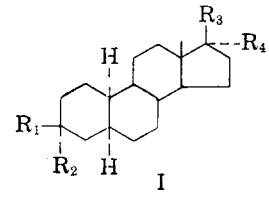
Hydrogenation of 17α - ethinyl - or 17α - ethyl-17β - estradiol with ruthenium dioxide catalyst at elevated pressures afforded a crystalline product, 17α-ethyl-5α,10α-estrane-3β,17β-diol (Ia) (m.p. 143–145°; $[\alpha]_D^{25}$ −20.9° ($CHCl_3$). Found for $C_{20}H_{34}O_2$: C, 78.11; H, 11.27) in excellent yield. Oxidation of this diol with chromic anhydride - pyridine gave 17α-ethyl-5α,10α-estran-17β-ol-3-one (IIa) (m.p. 205–207°; $[\alpha]_D^{25}$ −66.4°. Found for $C_{20}H_{32}O_2$: C, 78.67; H, 10.99).[3] Sodium and pro-

(1) A. Bowers, H. J. Ringold, and R. I. Dorfman, *J. Am. Chem. Soc.*, **79**, 4556 (1957).

(2) R. T. Rapala and E. Farkas, *J. Am Chem. Soc.*, **80**, 1008 (1958).

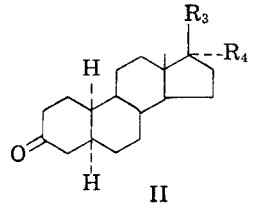
(3) All melting points are uncorrected. We gratefully acknowledge valuable technical assistance by Messr. W. Scanlon, hydrogenation experiments; Messrs. G. M. Maciak, W. L. Brown, and H. L. Hunter, elemental analysis. All rotations are done in methanol unless otherwise specified.

panol reduction of this ketone furnished 17α-ethyl-5α,10α-estrane-3α,17β-diol (Ic) (m.p. 221–223°. Found for $C_{20}H_{34}O_2$: C, 77.93; H, 11.50) (3-monoacetate, m.p. 146–147°; $[\alpha]_D^{25}$ −30.1°. Found for $C_{22}H_{36}O_3$: C, 75.59; H, 10.23) while reduction with sodium borohydride gave the original diol (Ia) (3-monoacetate, m.p. 126–127°. Found for $C_{22}H_{36}O_3$: C, 75.48; H, 10.34).



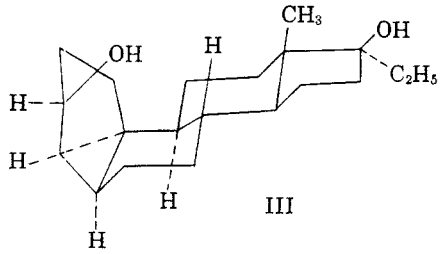
I

(a) $R_1 = R_3 = OH$, $R_2 = H$, $R_4 = C_2H_5$
(b) $R_1 = R_3 = OH$, $R_2 = R_4 = H$
(c) $R_2 = R_3 = OH$, $R_1 = H$, $R_4 = C_2H_5$



II

(a) $R_3 = OH$, $R_4 = C_2H_5$
(b) $R_3, R_4 = O$
(c) $R_3 = COCH_3$, $R_4 = H$
(d) $R_3 = OH$, $R_4 = H$



III

These assignments are supported by the following considerations: (*a*) Assuming a single period of adsorption, catalytic hydrogenation of the benzenoid ring[4] would allow for only two stereochemical products, 5β,10β and 5α,10α. (*b*) Reduction of ketone IIa with sodium - alcohol gave the more stable 3α-alcohol with the equatorial configuration. This is borne out by the fact that the 3 - monoacetate of this diol shows the simple infrared band in the 8μ region typical of equatorial acetoxy steroids.[5] (*c*) Furthermore, the 3 - monoacetate derived from the borohydride reduced ketone and the original diol (Ia) shows a complex band indicative of axial orientation. (*d*) The rotatory dispersion curve of ketone IIa is distinctive and quite different from the curves of the 3-keto allo and the normal estrane series.[2] Using an all chair conformation these results are consistent only with structure III involving an unnatural configuration at C_{10}[6] for the diol Ia.

High yields of 5α,10α-estrane-3β,17β-diol (Ib) (m.p. 179–181°. Found for $C_{18}H_{30}O_2$: C, 77.95; H, 11.09) were obtained from similar hydrogenations (RuO_2) of estrone, β-estradiol or $\Delta^{5:10}$-estraene - 17β - ol - 3 - one. Oxidation with *N* - bromoacetamide gave the corresponding dione, 5α,10α-estrane-3,17-dione (IIb) (m.p. 163-165°; $[\alpha]_D^{25}$ +27.5° (dioxane). Found for $C_{18}H_{26}O_2$: C, 78.66; H, 9.78).

Reduction of 3-hydroxy-17β-acetyl-1,3-5-estratriene gave a diol which upon oxidation yielded the related 5α,10α-dione (IIc)(m.p. 140–142°; $[\alpha]_D^{25}$ −1.0° ($CHCl_3$). Found for $C_{20}H_{30}O_2$: C, 79.22; H, 10.19).

Selective ketalization[7] of diones IIb and IIc followed by reduction and then hydrolysis gave 5α,-10α-estran-17β-ol-3-one (IId) (m.p. 192–194°; $[\alpha]_D^{25}$ −31.1°. Found for $C_{18}H_{28}O_2$: C, 77.95; H, 10.28) and 5α,10α-19-norpregnan-20β-ol-3-one (m.p. 152–154°). Found for $C_{20}H_{32}O_2$: C, 79.02; H, 10.88.

The rotatory dispersion curves[8] of the 3-monoketone derivatives are essentially identical. They differ, however, from the curves of the 3-keto, *cis* A/B (5β,10β) and the *trans* A/B (5α,10β) steroids as well as from the curves of lumistanone A, B, and C.[9]

The results of hydrogenations of 11-oxygenated 1,3,5-estratrienes, equilenin and ring B aromatic steroids to complete the series of 5α,10α analogs of the major classes of natural steroids will be reported shortly.

Added in proof. Careful R. D. determinations of these 3-keto-5α,10α-steroids in methanol, 2-propanol and dioxane confirmed the absence of any Cotton-effect while infrared analysis in methanol showed intense carbonyl absorption. Thus, this is the first example of a monoketosteroid containing the usual asymmetric centers which lacks the Cotton-effect commonly occurring in rotatory dispersion studies.

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(4) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *J. Am. Chem. Soc.*, **64**, 1985 (1942).

(5) D. H. R. Barton, *J. Chem. Soc.*, 1036 (1953).

(6) The only reported unnatural configurations at C_{10} are the C_{10}—CH_3 isomers, lumisterol and pyrocalciferol, and their reduced products. For leading references, see I. M. Heilbron, T. Kennedy, F. S. Spring, and G. Swain, *J. Chem. Soc.*, 869 (1938); J. Castells, E. R. H. Jones, R. W. J. Williams, and G. Meakins, *Proc. Chem. Soc.*, 7 (1958).

(7) E. Oliveto, C. Gerold, and E. B. Hershberg, *J. Am. Chem. Soc.*, **76**, 6114 (1954).

(8) Kindly performed by M. Marsh and J. Carson of these Laboratories. Duplicate curves were obtained from two samples submitted for comparison to Wayne State University through the courtesy of Dr. E. J. Eisenbraun.

(9) We are indebted to Drs. E. R. H. Jones, G. Meakins, and C. Djerassi for making the curves available to us prior to publication.