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AN OPEN LETTER TO YOU . . .

. . and every other ACS member

DEAR MEMBER:

Within the next few weeks, one of your fellow ACS members will be contacting you about a proposal of major importance—a proposal which has considerable bearing not only upon your own professional future, but upon the future of every other chemist and chemical engineer in America as well. In brief, the matter which will be placed before you is this: You will be asked to share according to your ability in the program which is now under way to provide an urgently needed headquarters for the Society in Washington, D. C.

It is our conviction that this program to create an even stronger Society merits your serious consideration for a number of compelling reasons. However, because most of these reasons have been thoroughly explained and discussed in other ACS publications, we should like to place before you only two simple points:

Point 1: A careful study of the history of the chemical profession since the founding of the American Chemical Society clearly indicates that there exists a direct relationship between the fortunes of the profession as a whole and the fortunes of the Society itself. In every instance, the greatest gains in income, prestige, and scientific advancement have occurred close upon the heels of significant gains within the Society.

Point 2: Today, the American Chemical Society has reached what is perhaps the most serious turning point in its 82-year history. Either it continues to move steadily forward—and with it the fortunes of every chemist and chemical engineer—or it begins to fall behind. For unless the Society is provided with a new center for its activities, many of its services will have to be curtailed extensively.

It is our sincere belief that these two points sum up the problem which confronts us today, and for this reason, we ask that you keep them before you in determining what your share in this challenging program will be.

"It's Your Society"—You have heard this phrase before and you will hear it again. But perhaps at no other time in your life will its truth be more clearly demonstrated than in the days which lie ahead.

JOHN H. NAIR	CARL S. MARVEL	E. R. WEIDLEIN
Chairman, Planning Committee	National Chairman	Chairman, Special and Corporate Gifts Committee

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Grignard Reagent Derived from the Ethylene Ketal of ω-Bromobutyrophenone

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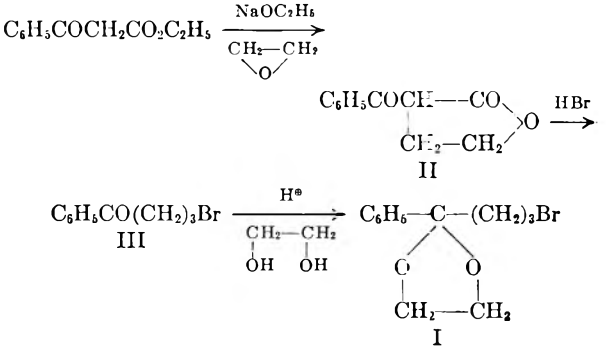
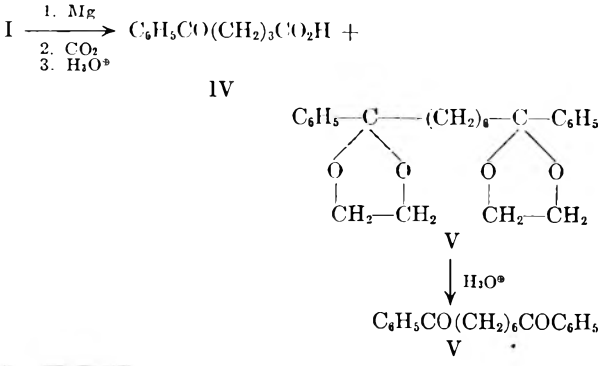
Received August 8, 1957

Reaction of the ethylene ketal of ω-bromobutyrophenone with magnesium followed by carbonation of the reaction mixture yielded a mixture of γ-benzoylbutyric acid and the diketal of 1,6-dibenzoylhexane.

As part of an investigation concerned with synthesis of certain polycyclic aromatic systems, we were led to study methods for the introduction of a γ-benzoylpropyl group. Consideration of one of these methods, use of an organometallic intermediate, resulted in the study of the formation of the Grignard reagent derived from the ethylene ketal of ω-bromobutyrophenone (I) which is reported here. Reaction of the sodium enolate of ethyl benzoylacetate with ethylene oxide produced the lactone II which was converted to the bromide III by treatment with hydrobromic acid. Condensation of the bromide III with ethylene glycol

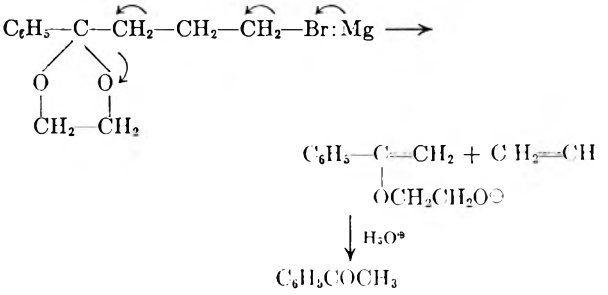


produced the bromo ketal I. The bromo ketal I reacted slowly with magnesium in tetrahydrofuran; carbonation of the resultant reaction mixture followed by hydrolysis produced the known γ-benzoylbutyric acid (IV, 54%) accompanied by the diketal V (23%), the coupling product of I. The structure of the diketal V was established by hydrolysis to form the known diketone VI.



(1) National Science Foundation Predoctoral Fellow, 1956–1957.

Previous studies have indicated that α- and β-halo ketals and acetals do not react with magnesium to form stable Grignard reagents.[2–4] The α-halo ketals and acetals were found to undergo elimination and coupling reactions when treated with magnesium; the similar failure of the β-halo compound may be attributable to the formation of a cyclopropane derivative according to the scheme of Boord and co-workers.[5] One possible side reaction which was anticipated with the γ-bromo ketal I was the cleavage represented in the accompanying equation. This reaction would be analogous to the cleavage of 1,4-dihalides described by Grob and Baumann.[6] However, in no case did we isolate any acetophenone, one of the products expected from this side reaction. Also, no products were isolated which corresponded to either intramolecular or intermolecular attack on the dioxolane ring by the Grignard moiety, although an intermolecular reaction of this type has been observed when acetals and ketals have been allowed to react with Grignard reagents under forcing conditions.[7]



Thus, the preparation of Grignard reagents from γ-halo ketals appears to be a satisfactory synthetic procedure.

(2) J. F. Arens and D. A. Van Dorp, *Rec. trav. chim.*, **65**, 729 (1946).

(3) L. Williman and H. Schinz, *Helv. Chim. Acta*, **32**, 2151 (1949).

(4) K. Ziegler, *Nature*, **176**, 59 (1955).

(5) J. T. Gragson, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Org. Chem.*, **20**, 275 (1955).

(6) C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955).

(7) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, N. Y., 1954, pp. 1041–1045.

EXPERIMENTAL[8]

α-Benzoyl-γ-butyrolactone (II). Ethyl benzoylacetate (194 g., 1.0 mole) was added with stirring to a cold (0°) solution of sodium ethoxide prepared from 23 g. (1.0 g.-atom) of sodium and 1.2 l. of ethanol. Ethylene oxide (44 g., 1.0 mole) was distilled into the cold reaction mixture. After the addition was complete the mixture was allowed to warm to room temperature and stirred under a Dry Ice condenser until all of the ethylene oxide was consumed. After the bulk of the alcohol had been distilled from the mixture under reduced pressure, the residue was neutralized with 5% aqueous sulfuric acid and extracted with ether. The extract was dried over magnesium sulfate, concentrated and distilled through a 30-cm. Vigreux column under reduced pressure. The desired lactone, yield 57.96 g. (33%), b.p. 164° (2 mm.), n_D^{25} 1.5599 [lit.[9] 193–195° (8 mm.)], was accompanied by 85.40 g. (44%) of unchanged ethyl benzoylacetate, b.p. 118° (25 mm.). The lactone, previously described as an oil, crystallized from a benzene–petroleum ether mixture as white needles, m.p. 57–58°. The ultraviolet spectrum of the product has a maximum at 242 mμ (ε 12,800); the infrared spectrum[10] has bands at 1765 cm.$^{-1}$ (C=O of a γ-lactone) and 1680 cm.$^{-1}$ (conj. C=O).

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.29. Found: C, 69.36; H, 5.56.

ω-Bromobutyrophenone (III). A mixture of 9.5 g. (0.05 mole) of α-benzoyl-γ-butyrolactone and 100 g. of 40% hydrobromic acid was heated on a steam bath for 2 hr., cooled and extracted with ether. The extract was dried over magnesium sulfate and concentrated. A solution of the residual oil in petroleum ether deposited 8.8 g. (78%) of the bromo ketone as pale yellow plates, m.p. 34–35° (lit.[9] 36°). The ultraviolet spectrum of the product has a maximum at 242 mμ (ε 9680); the infrared spectrum[10] has a band at 1680 cm.$^{-1}$ (conj. C=O).

ω-Bromobutyrophenone ethylene ketal (I). A solution of 12.55 g. (0.055 mole) of the bromo ketone, 3.0 g. (0.055 mole) of ethylene glycol, 0.1 g. of *p*-toluenesulfonic acid, and 100 ml. of benzene was refluxed until the theoretical amount of water had been separated in a Dean-Starke trap. An additional equivalent of ethylene glycol was added and the solution was refluxed for an additional 4 hr., cooled, washed with 5% aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated. A solution of the residue in petroleum ether deposited 11.46 g. (76.4%) of the bromo ketal as colorless prisms, m.p. 63–65°. The ultraviolet spectrum of the ketal has a maximum at 245 mμ (ε 830) and the infrared spectrum[10] has doublet at 1030 and 1045 cm.$^{-1}$ (C—O of a ketal) with no absorption in the carbonyl region.

Anal. Calcd. for $C_{12}H_{15}BrO_2$: C, 53.15; H, 5.58; Br, 29.47. Found: C, 52.87; H, 5.72; Br, 29.48.

Reaction of ω-bromobutyrophenone ethylene ketal (I) *with magnesium.* To a suspension of 0.66 g. (0.025 mole) of magnesium turnings in 25 ml. of freshly distilled tetrahydrofuran was added, dropwise and with stirring under nitrogen, a solution of 6.8 g. (0.025 mole) of the bromo ketal in 200 ml. of tetrahydrofuran. The resulting mixture was stirred at room temperature for 4 hr. at which time the concentration of Grignard reagent, determined by titration of aliquots from the reaction mixture with standard acid, had become constant. The solution was poured into a slurry of Dry Ice in tetrahydrofuran and the resulting mixture was allowed to warm to room temperature, then treated with cold, dilute hydrochloric acid, and, finally, extracted with ether. Extraction of the ether solution with 10% aqueous sodium hydroxide followed by acidification of the aqueous solution and extraction with ether afforded the crude *γ-benzoylbutyric acid* which was recrystallized from water. The yield of pure acid, m.p. 126–127° (lit.[11] 125–126°), was 2.49 g. (54%). The ultraviolet spectrum of the acid has a maximum at 241 mμ (ε 14,000); the infrared spectrum[10] has a broad band at 3000 cm.$^{-1}$ (associated O—H) as well as bands at 1710 cm.$^{-1}$ (COOH) and 1680 cm.$^{-1}$ (conj. C=O).

The neutral ether solution from the carbonation was dried over magnesium sulfate and concentrated. The residual *diketal of 1,6-dibenzoylhexane* crystallized from a benzene–petroleum ether mixture as colorless plates, m.p. 97–98°, yield 1.1 g. (23%). The ultraviolet spectrum of the diketal has a maximum at 241 mμ (ε 3600); the infrared spectrum[10] exhibits no absorption in the carbonyl region but has a doublet at 1030 and 1040 cm.$^{-1}$ (C—O of a ketal).

Anal. Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.57; H, 7.91.

A solution of 100 mg. of the diketal in aqueous ethanol which contained a few drops of hydrochloric acid was boiled for 30 min. and cooled. The cold solution deposited *1,6-dibenzoylhexane* as white crystals, m.p. 86–87° (lit.[12] 83–85°), yield 70 mg. (94%). The ultraviolet spectrum of the diketone has maxima at 243 mμ (ε 25,400) and 279 mμ (ε 2030); the infrared spectrum[10] has a band at 1680 cm.$^{-1}$ (conj. C=O).

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(8) All melting points are corrected and all boiling points are uncorrected. The ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, model MS. The infrared spectra were determined either with a Perkin-Elmer, model 21, or a Baird, model B, double beam infrared recording spectrophotometer fitted with a sodium chloride prism. The microanalyses were performed by Dr. S. M. Nagy and his associates.

(9) G. V. Chelintzev and E. D. Osetrova, *Compt. rend. acad. sci. U.R.S.S.*, 2, 252 (1935); *Chem. Abstr.*, 29, 6223 (1935).

(10) Determined in chloroform solution.

(11) L. F. Somerville and C. F. H. Allen, *Org. Syntheses*, Coll. Vol. 2, 83 (1943).

(12) L. Etaix, *Ann. chim.* (*Paris*), [7] 9, 389 (1896).

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

Epoxyethers XIII.[1,2] Determination of Stereochemistry

CALVIN L. STEVENS AND THOMAS H. COFFIELD[3]

Received October 14, 1957

A method for the determination of the stereochemical structures of epoxyethers was developed and applied to the epoxyether I. On the basis of this investigation the epoxyether was assigned the *trans* structure.

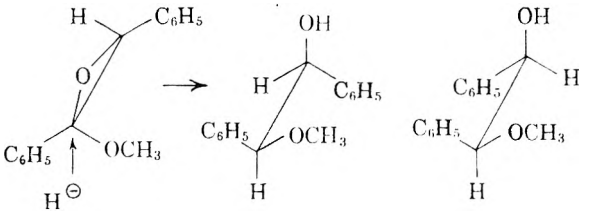
During the course of the investigation of the chemistry of epoxyethers in this laboratory, two solid epoxyethers[4,5] have been isolated from the reaction of *alpha* haloketones with methoxide ion in which both carbon atoms of the epoxide were asymmetric. In each case the product isolated was one of the two possible diastereoisomers as evidenced by the narrow melting point range after repeated recrystallization. In neither case could evidence be obtained for the presence of the other diastereoisomer in the reaction mixture. A consideration of the chemistry of these epoxyethers indicated that a method for the determination of the stereochemistry of the epoxyethers was necessary. The method that was developed in this investigation involved reduction of the epoxyether with hydride ion followed by determination of the stereochemistry of products and assignment of stereochemical structure to the epoxyether on the basis of the assumption that hydride ion attacked the epoxyether with inversion.

The epoxyether chosen for this study was I,[4] since the final products could be related directly to the meso- and DL-hydrobenzoin, which stereochemical structures are known with certainty.

Hydride ion was chosen as the reagent since previous work had indicated attack would occur cleanly at the ketal carbon of the epoxide.[1] Further, since the assignment of the stereochemical structure of the epoxyethers must rest at present upon the prediction of the stereospecificity of the reagent, the known opening of ordinary epoxides by hydride ion with inversion[6] was one stereospecific reaction which was judged likely to proceed with the same stereochemical course in the epoxyether series.

The epoxyether was made in 54% yield by a modification of the procedure previously reported.[4] The product was isolated from the reaction mixture as a low melting solid in substantially pure form. Reduction of the epoxyether with lithium borohydride gave 43% of the monomethyl ether of DL-hydrobenzoin (II) and 1% of the diastereoisomeric monomethyl ether of *meso*-hydrobenzoin (III). In addition, 9% of benzyl phenyl carbinol (IV) was isolated. The three products were separated by a combination of fractional crystallization and chromatography.

Of the two diastereomeric compounds, II is the lower melting and more soluble isomer and presumably would be the less stable and the less favored isomer in a non-stereospecific reaction. Considering the difficulty of purifying II in the presence of small amounts of III, the isolation of 43% of II *vs.* 1% of III indicated that the reaction is almost completely stereospecific and, on the assumption that hydride attacks with inversion, shows the epoxyether I to have the *trans* configuration.



I (*trans*) II (*DL*—derivative) III (*meso*—derivative)

The diastereoisomers II and III had been prepared previously in this laboratory[4] and were used for comparison to prove the stereochemical structures of the products of the reaction. The *p*-nitrobenzoate derivatives of II and III were prepared in *ca.* 60% yield and also were identical with authentic samples.

Since the diastereoisomeric *p*-nitrobenzoate derivatives had a reverse melting point and solubility relationship compared with the parent compounds, the reaction products from the reduction were converted directly to a mixture of the derivatives and then separated. This procedure gave 60% of the crude derivative of II without the aid of chromatography and indicated that the amount of II in the reaction mixture was considerably higher.

Although lithium aluminum hydride had been used previously to reduce epoxyethers to the corresponding methoxy alcohols, lithium borohydride was the only hydride useful for epoxyether I.

(1) The previous paper is "Epoxyethers XII. Reduction with Lithium Aluminum Hydride," *J. Am. Chem. Soc.*, in press.

(2) This work was supported in part by the Office of Ordnance Research, U. S. Army.

(3) U. S. Public Health Service Pre-doctoral Fellow, 1953–1954.

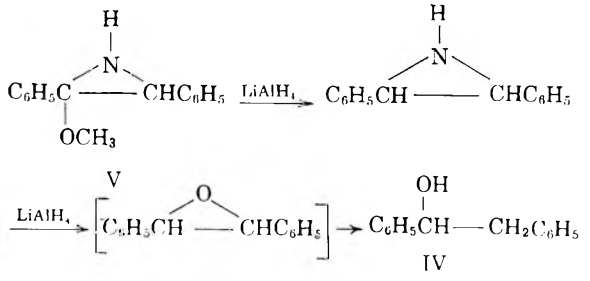
(4) C. L. Stevens, M. L. Weiner, and R. C. Freeman, *J. Am. Chem. Soc.*, **75**, 3977 (1953).

(5) C. L. Stevens and S. J. Dykstra, *J. Am. Chem. Soc.*, **76**, 4402 (1954).

(6) L. W. Trevoy and W. C. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949); P. J. Leroux and H. J. Lucas, *J. Am. Chem. Soc.*, **73**, 41 (1951).

Lithium aluminum hydride reacted rapidly with I to give 75% of benzyl phenyl carbinol. In view of the fact that the nitrogen analog (V) of the epoxyether I is reduced by lithium aluminum hydride to the corresponding ethylene imine,[7] the formation of the carbinol likely involves a similar displacement of methoxide followed by further reduction of the resulting stilbene oxide.

Sodium borohydride was also unsuited as a reagent for this study since the epoxyether was not reduced by this reagent.



EXPERIMENTAL

1,2-Diphenyl-1-methoxyethylene oxide (I). The compound could be conveniently prepared in 54% yield by allowing equivalent amounts of sodium methoxide and desyl chloride to react in absolute methanol solution for two minutes at the reflux temperature. The solution was then cooled to −80° in a Dry Ice–acetone bath and the solid which precipitated was filtered and recrystallized from a petroleum ether–ether mixture, m.p. 56–57°. The product was identical with the product from the previously published procedure,[4] the yield from which was 33%.

Monomethyl ether of DL*-hydrobenzoin (II) by lithium borohydride reduction of I.* A mixture of 1.5 g. (0.068 mole) of lithium borohydride and 75 ml. of dry ether was refluxed for 6 hr. The mixture was then allowed to settle and the clear supernatant solution was decanted and cooled to −60°. The solution was stirred and another cooled solution of 6 g. (0.026 mole) of the epoxyether I in 75 ml. of ether was slowly added. The temperature was allowed to rise to room temperature and the mixture was then stirred an additional two hours. Excess saturated ammonium chloride solution was added and the ether layer separated, dried, and concentrated. The residual oil was crystallized from petroleum ether to give 1.3 g. of II, m.p. 56–57°. Alumina chromatography of the filtrate gave an additional 1.3 g. of II, m.p. 56–57°, 0.07 g. (1%) of the monomethyl ether of *meso*-hydrobenzoin III, and 0.5 g. (9%) of phenyl benzyl carbinol, m.p. 65–66°.

The total yield of II was 2.6 g. (43%) and was shown to be identical with an authentic sample made by independent synthesis.[4]

The *p*-nitrobenzoate derivative of II was prepared by the sodium dispersion method previously described.[1] From 0.5 g. of II was obtained 0.4 g. (50%) of product, m.p. 110–112°. The mixture melting point of this derivative with that obtained from the independently synthesized material was undepressed.

Anal. Calcd. for $C_{22}H_{19}O_5N$: C, 70.01; H, 5.07. Found: C, 70.26; H, 5.15.

The *p*-nitrobenzoate of the diastereoisomer III was prepared in 60% yield by the same method, m.p. 78–80°. The same derivative was obtained from the product of the reaction mixture or from authentic III.

Anal. Calcd. for $C_{22}H_{19}O_5N$: C, 70.01; H, 5.07. Found: C, 69.71; H, 5.02.

In another experiment the crude reaction mixture was converted to the *p*-nitrobenzoate derivative. Reduction of 17.6 g. (0.075 mole) of I as described above gave 16.5 g. of oil after concentration of the ether solution. Before the product began to crystallize from the oil a 2-g. aliquot was converted to the *p*-nitrobenzoate derivative. One recrystallization of the product from petroleum ether gave 2.1 g. (60%) of the *p*-nitrobenzoate of II, m.p. 105–109°. A second recrystallization gave 1.53 g., m.p. 109–111°.

Reduction of I with lithium aluminum hydride. The epoxyether I was reduced with lithium aluminum hydride in the same manner as described for lithium borohydride except that the reduction was started at 0°. From 3 g. of I was obtained 2.1 g. (75%) of phenyl benzyl carbinol, m.p. 65–66°. A mixture melting point with an authentic sample was not depressed.

DETROIT 2, MICH.

(7) M. J. Hatch and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 38 (1953).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

Rearrangement and Condensation of Reissert Compounds with Grignard Reagents. III

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Received August 30, 1957

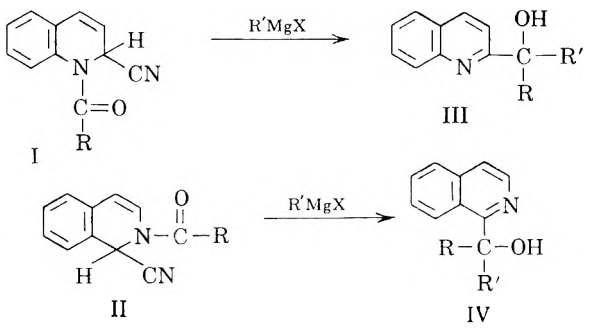
Reissert compounds (1-acyl-1,2-dihydroquinaldonitriles and 2-acyl-1,2-dihydroisoquinaldonitriles) undergo reaction with Grignard reagents in ether-dioxane to form tertiary carbinols containing the 2-quinolyl or 1-isoquinolyl group as one of the substituents bonded to the carbinol carbon atom. The scope of this reaction has been expanded, and evidence has been uncovered which shows that the initial reaction is one between the Reissert compound and RMgX, present in the solid phase of the reaction mixture. A 1-acylisoquinoline or a 2-acylquinoline is formed as an intermediate, and this α-acyl heterocyclic derivative can undergo further reaction to form a salt of the carbinol either with R_2Mg in solution or with RMgX in the solid phase.

1-Acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II) undergo reaction with Grignard reagents to form tertiary alcohols of structures III and IV, respectively.[1,2] It has been established[2] that the mechanism of the reaction in ether-dioxane solution consists of an

(1) W. E. McEwen, J. V. Kindall, R. N. Hazlett, and R. H. Glazier, *J. Am. Chem. Soc.*, **73**, 4591 (1951).

(2) A. P. Wolf, W. E. McEwen, and R. H. Glazier, *J. Am. Chem. Soc.*, **78**, 861 (1956).

initial attack by the anion of the organometallic reagent on the α-hydrogen atom of the Reissert compound (I or II) to form the conjugate base, its intramolecular rearrangement to the α-acyl heterocyclic derivative with expulsion of a cyanide ion, and, finally, condensation of the α-acyl heterocyclic derivative with additional Grignard reagent. The scope of the reaction has now been expanded, and further details of the mechanism of reaction have been uncovered.



I II III IV

EXPERIMENTAL[3]

Diphenylmagnesium. An ether-dioxane solution of this material was prepared according to the procedure of Noller.[4,5] Titration experiments showed the reagent to be 0.5*N* in diphenylmagnesium and less than 0.01*N* in halide ion.

Reaction of 1-benzoylisoquinoline with diphenylmagnesium. A solution of 2.00 g. of 1-benzoylisoquinoline[6] in 15 cc. of anhydrous dioxane was added with mechanical stirring within two minutes to 35 cc. of 0.5*N* diphenylmagnesium solution, the reaction mixture being maintained in an atmosphere of dry nitrogen. An additional 15 cc. of dioxane was added to the homogeneous dark solution and the solution was stirred at room temperature for 10 min. and then heated on a steam bath for 2 hr. The solvents were removed by distillation *in vacuo*, and ice water was added to the residual cake. The mixture was extracted with ether, and the ether solution was extracted with 10% hydrochloric acid. The aqueous acid solution was made alkaline, and ether extraction provided 2.20 g. (79%) of crude diphenyl-1-isoquinolylcarbinol. After two recrystallizations from ethanol, the compound melted at 142–143°, also in admixture with a sample of the carbinol prepared by reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) with phenylmagnesium bromide.[2]

Reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile with diphenylmagnesium. A solution of 10.00 g. of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) in 75 cc. of anhydrous dioxane was added with mechanical stirring within two minutes to 180 cc. of 0.5*N* diphenylmagnesium solution, the reaction mixture being maintained in an atmosphere of dry nitrogen. The homogeneous red solution was treated as described for the previous reaction. After the 10% hydrochloric acid extract had been made alkaline, ether extraction provided only 0.2 g. (0.2%) of crude diphenyl-1-isoquinolylcarbinol.

Concentration of the original ether solution gave 7.5 g. of a mixture of solid and oil. The solid was separated from the oil by filtration and recrystallized from absolute ethanol. There was obtained 5.5 g. (55%) of unreacted 2-benzoyl-1,2-dihydroisoquinaldonitrile. The oil was dissolved in ether and extracted with 6*N* hydrochloric acid. After the acid extract had been made alkaline, ether extraction afforded 1.2 g. (20%) of isoquinaldonitrile, m.p. 86–87° after recrystallization from absolute ethanol. There was no depression of melting point when this compound was mixed with authentic[7] isoquinaldonitrile.

Reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile with 0.49N phenylmagnesium bromide solution. To 180 cc. of a 0.49*N* solution of phenylmagnesium bromide in ether, maintained in a dry nitrogen atmosphere, was added, with mechanical stirring, first 20 cc. of anhydrous dioxane, then a solution of 10.00 g. of 2-benzoyl-1,2-dihydroisoquinaldonitrile in 75 cc. of dioxane. The latter solution was added in a period of about two minutes. The resulting mixture was treated as described above for the diphenylmagnesium reactions. There was obtained 8.22 g. (69%) of crude diphenyl-1-isoquinolylcarbinol, and only 0.3 g. (3%) of unreacted 2-benzoyl-1,2-dihydroisoquinaldonitrile.

Investigation of the two phases in the reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile with 0.49N phenylmagnesium bromide solution. To 72 cc. of a 0.49*N* ethereal solution of phenylmagnesium bromide was added 8 cc. of anhydrous dioxane, the mixture being maintained in a pure nitrogen atmosphere. A solution of 2.00 g. of 2-benzoyl-1,2-dihydroisoquinaldonitrile in 15 cc. of dioxane was added with mechanical stirring over a period of 45 sec., the mixture being maintained at about 25°. The mixture was stirred for 10 min., then filtered in a nitrogen atmosphere. The precipitate was washed with 25 cc. of ether in two portions, and the wash solution was added to the filtrate. The deep red filtrate and the pink precipitate were each heated on the steam bath for an hour, then allowed to stand at room temperature for two hours. The solvents were removed from the filtrate by distillation *in vacuo*, and ice and water were added to the residual cake. The ether solution was treated as described for the previous reactions, and there were obtained 0.68 g. (28%) of crude diphenyl-1-isoquinolylcarbinol and 0.2 g. (10%) of unreacted 2-benzoyl-1,2-dihydroisoquinaldonitrile.

The original precipitate was hydrolyzed with ice water and the resulting mixture extracted with ether. By the usual procedure, 0.28 g. (12%) of crude diphenyl-1-isoquinolylcarbinol was obtained from the ethereal extract.

When the original filtrate plus wash solution was not heated on the steam bath, but instead hydrolyzed immediately, only a trace of diphenyl-1-isoquinolylcarbinol was obtained.

Phenyl-2-thienyl-2-quinolylcarbinol. To an ether solution of 2-thienylmagnesium bromide prepared from 14.2 g. (0.55 g. atom) of magnesium and 93.0 g. (0.57 mole) of freshly distilled 2-bromothiophene was added 250 cc. of anhydrous dioxane, all operations being carried out in a nitrogen atmosphere. A solution of 50.0 g. (0.191 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile[8] in 450 cc. of anhydrous dioxane was added with mechanical stirring over a period of six minutes to the Grignard mixture cooled in an ice bath. Ether was distilled from the red reaction mixture, and the residual dioxane solution was refluxed for one hour, then allowed to stand at room temperature for 12 hr. The dioxane was distilled *in vacuo*, and the residual brown cake was treated with ether, ice, and water. The mixture was extracted with ether in a continuous extractor for 20 hr. The ethereal solution was extracted with 10% hydrochloric acid. The acid solution was made alkaline by addition of sodium hydroxide

(3) All melting points are corrected. Analyses were performed by Weiler and Strauss, Oxford, England, and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(4) C. R. Noller, *J. Am. Chem. Soc.*, **53**, 635 (1931).

(5) C. R. Noller and W. R. White, *J. Am. Chem. Soc.*, **59**, 1354 (1937).

(6) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, **74**, 660 (1952).

(7) J. Padbury and H. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945).

(8) H. Rupe, R. Paltzer, and K. Engel, *Helv. Chim. Acta*, **20**, 209 (1937).

solution. A solid which precipitated was collected by filtration. There was obtained 30.0 g. (49%) of crude phenyl-2-thienyl-2-quinolylcarbinol, m.p. 160.3–161.0° after several recrystallizations from absolute ethanol.

Anal. Calcd. for $C_{20}H_{15}NOS$: C, 75.67; H, 4.76; N, 4.41; S, 10.10. Found: C, 75.90; H, 5.01; N, 4.29; S. 10.10.

The same compound has also been prepared by reaction of 2-thienylmagnesium bromide with 2-benzoylquinoline.[9] A mixed melting point test of the two samples showed no depression, and the infrared spectra of the two samples, taken in chloroform solution, were identical.

Phenyl-2-thienyl-1-isoquinolylcarbinol. This compound, m.p. 136.3–137.8°, was prepared in 40% yield (crude product) from 2-thienylmagnesium bromide and 2-benzoyl-1,2-dihydroisoquinaldonitrile by the same procedure as described above for the preparation of phenyl-2-thienyl-2-quinolylcarbinol.

Anal. Calcd. for $C_{20}H_{15}NOS$: C, 75.67; H, 4.76; N, 4.41; S, 10.10. Found: C, 75.70; H, 4.80; N, 4.55; S, 10.13.

The same compound, as shown by a mixed melting point test and the identity of the infrared spectra in chloroform solution, has been obtained by reaction of 2-thienylmagnesium bromide with 1-benzoylisoquinoline.[9]

Phenyl-p-anisyl-1-isoquinolylcarbinol. By reaction of *p*-anisylmagnesium bromide with 2-benzoyl-1,2-dihydroisoquinaldonitrile in the same manner as described above for the preparation of phenyl-2-thienyl-2-quinolylcarbinol, there was obtained a 34% yield of crude phenyl-*p*-anisyl-1-isoisoquinolylcarbinol. The purified material melted at 124.2–125.3°, also in admixture with a sample of the compound prepared[9] by reaction of *p*-anisylmagnesium bromide with 1-benzoylisoquinoline. The infrared spectra of the two samples were taken in chloroform solution and found to be identical.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.89; H, 5.75; N, 4.10.

Phenyl-p-chlorophenyl-1-isoquinolylcarbinol. This compound, m.p. 133.6–134.6°, was prepared in 43% yield by reaction of *p*-chlorophenylmagnesium bromide with 2-benzoyl-1,2-dihydroisoquinaldonitrile.

Anal. Calcd. for $C_{22}H_{16}NOCl$: C, 76.42; H, 4.66; N, 4.05; Cl, 10.25. Found: C, 76.32; H, 4.88; N, 4.25; Cl, 10.15.

The same compound has been prepared by reaction of *p*-chlorophenylmagnesium bromide with 1-benzoylisoquinoline.[9] A mixed melting point test of the two samples showed no depression, and the infrared spectra, taken in chloroform solution, were identical.

Phenyl-2-thienyl-2-(6-methoxyquinolyl)carbinol. Very crude material was obtained in 23% yield by the reaction of 2-thienylmagnesium bromide with 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile[10] in the usual manner. A pure sample of the carbinol, m.p. 158.3– 159.0°, was obtained after two recrystallizations from toluene and five recrystallizations from absolute ethanol.

Anal. Calcd. for $C_{21}H_{17}NO_2S$: C, 72.62; H, 4.94; N, 4.03; S, 9.23. Found: C, 72.44; H, 5.20; N, 3.81; S, 9.20.

When a portion of the very crude material cited above was subjected to distillation at 0.7-mm. pressure, a small amount of a solid, b.p. 128–132°, was obtained. After several recrystallizations from absolute ethanol, this material melted at 87.0–87.5°. It is thought that this material is probably di-2-thienyl ketone, which is reported[11] to melt at 87–88°.

Anal. Calcd. for $C_9H_6OS_2$: S, 33.00. Found: S, 33.21.

Phenyl-p-anisyl-2-quinolylcarbinol. A mixture of 20.0 g. (0.155 mole) of quinoline, 35.3 g. (0.166 mole) of *p*-methoxybenzophenone, 5.00 g. of aluminum foil, 5.0 g. of mercuric chloride, 5 drops of mercury, and a few mg. of iodine was heated on a steam bath with stirring for 20 min., whereupon a vigorous reaction started. The color of the mixture changed from yellow to dark green. Upon addition of 25 cc. of anhydrous dioxane, enough heat was generated to cause the reaction mixture to reflux. After the mixture had been heated on the steam bath for four hours, it was made strongly alkaline by addition of sodium hydroxide solution. The basic solution was extracted with ether, and the ether solution, in turn, was extracted with 10% hydrochloric acid. The acid extract was made alkaline by addition of sodium hydroxide solution, and unreacted quinoline was removed by steam distillation. The residual aqueous mixture was extracted with ether, and, after evaporation of the ether, there was obtained 12.0 g. (23%) of crude phenyl-*p*-anisyl-2-quinolylcarbinol, m.p. 136.5–137.3° after several recrystallizations from absolute ethanol. A mixed melting point test with the carbinol obtained[9] by reaction of *p*-anisylmagnesium bromide with 2-benzoylquinoline showed no depression. The infrared spectra of the two samples, taken in chloroform solution, were identical.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found:[9] C, 81.12; H, 5.60; N, 4.18.

No phenyl-*p*-anisyl-2-quinolylcarbinol was obtained by reaction of *p*-anisylmagnesium bromide with 1-benzoyl-1,2-dihydroquinaldonitrile under the conditions cited previously for the preparation of phenyl-2-thienyl-2-quinolylcarbinol.

2-Benzoyl-6-methoxyquinoline. To a suspension of 2.4 g. (0.1 mole) of sodium hydride in 200 cc. of anhydrous xylene (mixture of isomers), maintained at 120°, was added, with stirring, in 3–7-g. portions, a total of 29.1 g. (0.1 mole) of 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile during a period of 3 hr. The dark green mixture was heated at 120° for an additional 2 hr., then filtered. The filtrate was washed with water and extracted with 5% hydrochloric acid. A small amount of polymeric material precipitated on addition of the hydrochloric acid, and this material was removed by filtration. The hydrochloric acid solution was made alkaline by addition of sodium hydroxide solution, and a solid which precipitated was collected by filtration. There was obtained 2.9 g. (11%) of crude 2-benzoyl-6-methoxyquinoline, m.p. 116.3–116.7° after several recrystallizations from absolute ethanol. The infrared spectrum of the material was taken in chloroform solution and showed a pronounced carbonyl group absorption peak at 1655 $cm.^{-1}$

Anal. Calcd. for $C_{17}H_{13}O_2N$: C, 77.54; H, 4.98; O, 12.61; N, 5.32. Found: C, 77.40; H, 4.85; O, 12.44; N, 5.31.

Although 2-benzoylquinoline and 1-benzoylisoquinoline are not soluble in 5% hydrochloric acid, 2-benzoyl-6-methoxyquinoline is readily soluble in acid of this concentration, this undoubtedly being due to the base-strengthening effect of the methoxyl group in the 6-position of the quinoline ring.

DISCUSSION

The general procedure for the preparation of 2-quinolylcarbinols of type III and 1-isoquinolylcarbinols of type IV from Grignard reagents and Reissert compounds is to add a dioxane solution of the Reissert compound to the Grignard reagent. It is well known that addition of dioxane to an ether solution of a Grignard reagent causes the precipitation of halide salts, leaving the dialkylmagnesium or diarylmagnesium in solution.[12,13] This poses the question as to which organometallic

(9) K. E. Werth, Master's thesis, Kansas University, 1955.

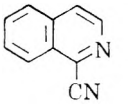
(10) A. Gassman and H. Rupe, *Helv. Chim. Acta*, **22**, 1241 (1939).

(11) L. Gattermann, *Ber.*, **18**, 3012 (1885).

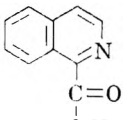
(12) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, N. Y., 1954.

(13) R. E. Dessy, G. S. Handler, J. H. Wotiz, and C. A. Hollingsworth, *J. Am. Chem. Soc.*, **79**, 3476 (1957).

species, RMgX (possibly better formulated as $R_2Mg \cdot MgX_2$[13]) or R_2Mg, is the effective reagent in the various steps of the rearrangement and condensation of Reissert compounds with Grignard reagents. In order to carry out experiments designed to provide information about this matter, a 0.5*N* solution of diphenylmagnesium in ether-dioxane was prepared by Noller's method.[4,5] When a dioxane solution of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, $R = C_6H_5$)[14] was added to the diphenylmagnesium solution, and the resulting *homogeneous* solution treated in a manner analogous to that used for the preparation of 1-isoquinolylcarbinols of type IV from II($R = C_6H_5$) and conventional Grignard reagents, only a 0.2% yield of diphenyl-1-isoquinolylcarbinol (IV, $R = R' = C_6H_5$) was obtained. Isoquinaldonitrile (V) was obtained in 20% yield, and not less than 55% of the starting material, 2-benzoyl-1,2-dihydroisoquinaldonitrile, was recovered. However, a 79% yield of diphenyl-1-isoquinolylcarbinol was obtained by the reaction of 0.5*N* diphenylmagnesium with 1-benzoylisoquinoline (VI), which is known to be an intermediate product in the rearrangement-condensation reaction,[1,2] in ether-dioxane solution under comparable conditions. It should also be stressed that, in a control experiment, the *heterogeneous* reaction mixture resulting from the addition of a dioxane solution of 2-benzoyl-1,2-dihydroisoquinaldonitrile to a 0.49*N* solution of phenylmagnesium bromide in ether gave, after suitable processing, a 69% yield of diphenyl-1-isoquinolylcarbinol.



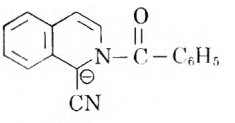
V



VI

In yet another series of experiments designed to provide evidence about the mechanism of the reaction, a solution of 2-benzoyl-1,2-dihydroisoquinaldonitrile in dioxane was added to a 0.49*N* solution of phenylmagnesium bromide in ether. After the reaction mixture had been stirred at room temperature for ten minutes, it was filtered. The filtrate was dark red in color and the precipitate had a pink color. When the filtrate was hydrolyzed immediately, only a trace of diphenyl-1-isoquinolylcarbinol could be isolated. However, when the filtrate was first heated on a steam bath for an hour, then hydrolyzed, diphenyl-1-isoquinolylcarbinol was obtained in 29% yield. It was also found that diphenyl-1-isoquinolylcarbinol could be obtained in 12% yield by heating the pink precipitate on the steam bath for an hour, followed by hydrolysis.

On the basis of the data cited above, plus that given in a previous manuscript,[2] it would appear that a Reissert compound, *e.g.*, 2-benzoyl-1,2-dihydroisoquinaldonitrile, first undergoes reaction with phenylmagnesium bromide in the solid phase of an ether-dioxane slurry of the reagents to form the red colored conjugate base, VII. The resulting salt, of which VII is the anion, is only partially soluble in the mixed solvent, and VII, both in the solid phase and solution, undergoes intramolecular rearrangement to give 1-benzoylisoquinoline (VI) only when heated for an appreciable period of time. Once the intermediate product, 1-benzoylisoquinoline, has been formed, it can undergo reaction with either diphenylmagnesium in solution or with phenylmagnesium bromide present in the solid phase to produce a salt of diphenyl-1-isoquinolylcarbinol



VII

Partly to increase the scope of the rearrangement and condensation reaction between Reissert compounds and Grignard reagents, and partly to provide intermediates for the synthesis[15] of analogs of the well known antihistamine, Dacapryn, a number of new carbinols of types III and IV have been prepared. Also, some of the preparations previously reported[1,2] have been repeated, and yields of carbinols have been considerably improved. With aliphatic Grignard reagents and Reissert compounds, the improvement in yield was brought about by a modification of the older procedure,[2] namely by rapid addition of the Grignard reagent to a dioxane solution of the Reissert compound, without any attempt being made to cool the reaction mixture. In the reaction between phenylmagnesium bromide and 2-benzoyl-1,2-dihydroisoquinaldonitrile, rapid addition of a dioxane solution of the Reissert compound to the Grignard reagent without cooling of the reaction mixture led to a distinct improvement in the yield of diphenyl-1-isoquinolylcarbinol over that previously reported.[2] However, the yields of carbinols produced by reaction of 2-thienylmagnesium bromide with Reissert compounds did not change appreciably whether the reagents were brought together with external cooling in an ice bath or mixed rapidly without any attempt to control the reaction temperature. Attempts to prepare phenyl-*p*-anisyl-2-quinolylcarbinol and phenyl-*p*-anisyl-2-(6-methoxyquinolyl)carbinol by the reaction of *p*-anisylmagnesium bromide with the appropriate Reissert compound failed. There was isolated from both reaction mixtures a compound, m.p. 144.3–144.9°, which had a strong carbonyl absorption peak at 1648 $cm.^{-1}$ in the infrared spectrum taken in chloroform solution. This compound was probably

(14) A. Reissert, Ber., **38**, 3415 (1905).

(15) N. C. Rose, L. R. Walters, and W. E. McEwen, *J. Org. Chem.*, **23**, 341 (1958).

TABLE I

REACTION OF REISSERT COMPOUNDS WITH GRIGNARD REAGENTS

Reissert Compound	Grignard	Product	Yield, %
1-Benzoyl-1,2-dihydroquinaldonitrile	CH_3MgBr	Methylphenyl-2-quinolylcarbinol	81
	2-C_4H_3SMgBr	Phenyl-2-thienyl-2-quinolylcarbinol	49
	p-$CH_3OC_6H_4MgBr$		0
2-Benzoyl-1,2-dihydroisoquinaldonitrile	CH_3MgBr	Methylphenyl-1-isoquinolylcarbinol	83
	2-C_6H_4SMgBr	Phenyl-2-thienyl-1-isoquinolylcarbinol	40
	C_6H_5MgBr	Diphenyl-1-isoquinolylcarbinol	75
	p-$CH_3OC_6H_4MgBr$	Phenyl-p-anisyl-1-isoquinolylcarbinol	34
	p-Cl-C_6H_4MgBr	Phenyl-p-chlorophenyl-1-isoquinolylcarbinol	43
1-Benzoyl-6-methoxy-1,2-dihydroquinaldonitrile	CH_3MgBr	Methylphenyl-2-(6-methoxyquinolyl)carbinol	84
	2-C_4H_3SMgBr	Phenyl-2-thienyl-2-(6-methoxyquinolyl)carbinol	23
	p-$CH_3OC_6H_4MgBr$		0

4,4′-dimethoxybenzophenone, which is reported[16] to have a m.p. of 144°. A compound thought to be di-2-thienyl ketone was also isolated as a by-product from the reaction of 2-thienylmagnesium bromide with 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile. Phenyl-*p*-anisyl-2-quinolylcarbinol was eventually obtained in 23% yield from quinoline and *p*-methoxybenzophenone by application of the Emmert reaction.[17] The results of the various rearrangement and condensation reactions of Grignard reagents with Reissert compounds are summarized in Table I. In each case of the preparation of a hitherto unreported carbinol, the identity of the product was confirmed by comparison with the carbinol obtained by reaction of a Grignard reagent with the appropriate 1-benzoylisoquinoline or 2-benzoylquinoline.[9]

Acknowledgment. This investigation was supported by a research grant, H-2155, from the National Institutes of Health, Public Health Service.

LAWRENCE, KAN.

(16) H. Schnackenberg and R. Scholl, *Ber.*, **36**, 654 (1903).

(17) B. Emmert and E. Pirat, *Ber.*, **74**, 714 (1941).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

Synthesis of Analogs of Decapryn[1]

NORMAN C. ROSE, LEE R. WALTERS, AND WILLIAM E. McEWEN

Received August 30, 1957

Six quinoline and isoquinoline analogs of the prominent antihistamine drug, Decapryn, have been synthesized. The compounds were prepared by reaction of β-dimethylaminoethyl chloride with the sodium or potassium salts of methylphenyl-2-quinolylcarbinol, methylphenyl-2-(6-methoxyquinolyl)carbinol, methylphenyl-1-isoquinolylcarbinol, diphenyl-1-isoquinolylcarbinol, phenyl-2-thienyl-2-quinolylcarbinol and methylphenyl-4-quinolylcarbinol, respectively.

Decapryn (I) is considered[2] to be one of the prominent antihistamine drugs. Although certain compounds containing a quinoline or isoquinoline nucleus have been found to have antihistamine activity,[3–7] no analogs of Decapryn (I) containing a quinolyl or isoquinolyl group in place of the 2-pyridyl group have been reported. Because of this fact, and owing to the recent development of a very convenient synthesis of tertiary carbinols containing a 2-quinolyl or 1-isoquinolyl group bonded to the carbinol carbon atom,[8–10] the preparation of a number of analogs of I was undertaken.

(1) Much of the material in the present paper and all of the data from the preceding paper have been abstracted from the thesis submitted by Norman C. Rose in partial fulfillment of the requirements for the Ph.D. degree, Kansas University, 1957.

(2) B. Idson, *Chem. Revs.*, **47**, 307 (1950).

(3) I. A. Kaye, *J. Am. Chem. Soc.*, **71**, 2322 (1949).

(4) I. A. Kaye, U. S. Patent **2,652,398**; *Chem. Abstr.*, **48**, 10781 (1954).

(5) C. F. Geschickter and M. I. Ruben, U. S. Patent **2,594,418**; *Chem. Abstr.*, **47**, 1193 (1953).

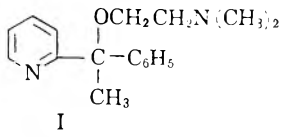
(6) C. F. Geschickter and M. I. Rubin, U. S. Patent **2,549,419**; *Chem. Abstr.*, **47**, 1193 (1953).

(7) S. Ohki, *J. Pharm. Soc. Japan*, **70**, 92 (1950); *Chem. Abstr.*, **44**, 5867 (1950).

(8) W. E. McEwen, J. V. Kindall, R. N. Hazlett, and R. H. Glazier, *J. Am. Chem. Soc.*, **73**, 4591 (1951).

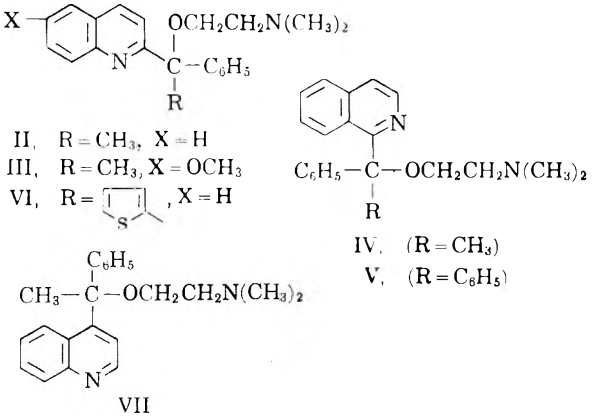
(9) A. P. Wolf, W. E. McEwen, and R. H. Glazier, *J. Am. Chem. Soc.*, **78**, 861 (1956).

(10) N. C. Rose and W. E. McEwen, *J. Org. Chem.*, **23**, 337 (1958).



I

Each of four aminoethers, methylphenyl-2-quinolylcarbinyl β-dimethylaminoethyl ether (II), methylphenyl-2-(6-methoxyquinolyl)-carbinyl β-dimethylaminoethyl ether (III), methylphenyl-1-isoquinolylcarbinyl β-dimethylaminoethyl ether (IV), and diphenyl-1-isoquinolylcarbinyl β-dimethylaminoethyl ether (V), was prepared in quantity sufficient for pharmacological screening. Two additional ethers, phenyl-2-thienyl-2-quinolylcarbinyl β-dimethylaminoethyl ether (VI) and methylphenyl-4-quinolylcarbinyl β-dimethylaminoethyl ether (VII), have also been prepared, but these compounds have not yet been screened.



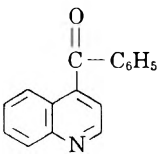
II, R = CH_3, X = H
III, R = CH_3, X = OCH_3
VI, R = thienyl, X = H

IV, (R = CH_3)
V, (R = C_6H_5)

VII

Each of the ethers was prepared by a Williamson reaction. It was found that yields were highest when the sodium or potassium salt of the tertiary carbinol was prepared by addition of the metal to a hot solution of the carbinol in anhydrous toluene, followed by dropwise addition of a toluene solution of β-dimethylaminoethyl chloride to the suspension of the sodium or potassium salt at the reflux temperature of the solvent. The use of sodium amide to form the salts of the carbinols at lower temperatures did not generally give as good results as the procedure cited above.

The carbinols used in the synthesis of ethers II–VI were prepared by the reaction of appropriate Reissert compounds and Grignard reagents.[8–10] The carbinol required for the preparation of VII was obtained by addition of methylmagnesium bromide to 4-benzoylquinoline (VIII), which, in turn, had been prepared by reaction of 4-cyanoquinoline with phenylmagnesium bromide by the method of Kaufmann, *et al.*[11]



VIII

When subjected to pharmacological testing, compound II, in the form of its dihydrobromide trihydrate, compound III, as the dihydrochloride dihydrate and compounds IV and V, as the monohydrochlorides, showed less than 1% "histadyl" (Thenylpyramine, Lilly) action. No outstanding pharmacologic properties of any kind were found for these four compounds.[12]

EXPERIMENTAL[13]

Methylphenyl-2-quinolylcarbinyl β-dimethylaminoethyl ether (II). To a refluxing solution of 20.00 g. (0.08 mole) of methylphenyl-2-quinolylcarbinol in 75 cc. of anhydrous toluene was added 1.84 g. (0.08 g.-atom) of sodium in the form of small chunks over a period of 15 min. The solution was heated under reflux and with mechanical stirring for an additional three hours. A toluene solution of β-dimethylaminoethyl chloride, prepared[14] from 17 g. of the hydrochloride, was added dropwise to the refluxing slurry of the sodium salt over a period of 90 min. The reaction mixture was heated under reflux, with mechanical stirring, for an additional 16 hr. After the reaction mixture had been cooled in an ice bath, it was extracted with 40 cc. of ice water. To the toluene solution was added, with vigorous shaking, sufficient 10% hydrochloric acid to lower the *p*H of the mixture to 5 (universal *p*H paper). The aqueous and toluene layers were separated. The toluene layer, containing most of the unreacted carbinol, was extracted with four 50 cc. portions of 10% hydrochloric acid. The combined 10% hydrochloric acid extract was made alkaline by addition of sodium hydroxide solution, and 8.4 g. (42%) of unreacted methylphenyl-2-quinolylcarbinol was collected by filtration.

The aqueous layer which had been separated from the mixture of *p*H 5 was made alkaline by addition of sodium hydroxide solution. The resulting mixture was extracted with a single 125-cc. portion of low-boiling petroleum ether. Removal of the petroleum ether by distillation left 13.7 g. (93% based on unrecovered carbinol) of crude methylphenyl-2-quinolylcarbinyl β-dimethylaminoethyl ether (II), m.p. 75.3–76.4° after several recrystallizations from 1-butanol and ethanol, respectively.

Anal. Calcd. for $C_{21}H_{24}ON_2$: C, 78.73; H, 7.55; N, 8.75. Found: C, 79.02; H, 7.56; N, 9.01.

Both the hydrochloride and hydrobromide of II proved to be very hygroscopic. Even after the hydrobromide, prepared in ether-ethanol solution, had been dried in a vacuum desiccator over anhydrous calcium chloride, it had a wide decomposition range, 70–95°, and analyzed as a dihydrobromide trihydrate.

Anal. Calcd. for $C_{21}H_{32}N_2O_4Br_2$: C, 47.03; H, 6.02; N, 5.23; Br, 29.81. Found: C, 46.96; H, 5.70; N, 5.10; Br, 30.66.

(11) A. Kaufmann, H. Peyer, and M. Kunkler, *Ber.*, **45**, 3090 (1912).

(12) We are indebted to Dr. Dwight D. Morrison of the Eli Lilly Co. who made the arrangements for the screening of these compounds.

(13) All melting points are corrected and all boiling points are uncorrected. Analyses were performed by Weiler and Strauss, Oxford, England, and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(14) C. Tilford, R. Shelton, and M. Van Campen, Jr., *J. Am. Chem. Soc.*, **70**, 4001 (1948).

Methylphenyl-2-(6-methoxyquinolyl)carbinyl β-dimethylaminoethyl ether (III). This compound, a liquid, b.p. 196–197° (0.25 mm.), was prepared in the same manner as described above for the preparation of II, except that the potassium salt of methylphenyl-2-(6-methoxyquinolyl)-carbinol was used in the reaction with β-dimethylaminoethyl chloride rather than the sodium salt.

Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C, 75.39; H, 7.48; N, 7.99. Found: C, 75.52; H, 7.21; N, 7.68.

The yield of III was 83% based on unrecovered carbinol, or 63% based on starting quantities of reagents.

All attempts to prepare a completely satisfactory solid derivative of III met with failure. Only oils could be isolated on attempted preparation of the chlorobenzylate, picrate, succinate, 2-hydroxy-α-naphthoate, 3-hydroxy-β-naphthoate, methiodide, or bis-1-(2-hydroxy-3-carboxynaphthalene)methylene salt. It was possible to obtain a solid, but extremely hygroscopic, hydrochloride, which, after having been dried in a vacuum desiccator over anhydrous calcium chloride, analyzed moderately well as the dihydrochloride dihydrate of III. A solid chloroplatinate, m.p. 184.0–185.5°, was prepared, but it also could not be obtained in analytically pure form.

Methylphenyl-1-isoquinolylcarbinyl β-dimethylaminoethyl ether (IV). To a mechanically stirred dispersion of 1.55 g. (0.067 g.-atom) of sodium in 85 cc. of anhydrous toluene, maintained at 60°, was added a solution of 16.00 g. (0.062 mole) of methylphenyl-1-isoquinolylcarbinol in 75 cc. of toluene during the course of 30 min. The mixture was stirred for an additional hour at 60° and then was heated to reflux. A toluene solution of β-dimethylaminoethyl chloride, prepared from 13.6 g. of the hydrochloride, was added over a period of an hour to the refluxing mixture. The reaction mixture was refluxed for an additional 15 hr., then worked up as described for the preparation of II. There was obtained 6.3 g. (39%) of recovered methylphenyl-1-isoquinolylcarbinol and 6.0 g. (89% based on unrecovered carbinol) of crude methylphenyl-1-isoquinolylcarbinyl β-dimethylaminoethyl ether (IV), an oil. The oil was dissolved in anhydrous ether, and dry hydrogen chloride was passed into the solution. The monohydrochloride of IV precipitated and was collected by filtration. After several recrystallizations from ethanol–ethyl acetate, the salt had a m.p. of 226–228° (dec.).

Anal. Calcd. for $C_{21}H_{25}ON_2Cl$: C, 70.68; H, 7.35; N, 7.85; Cl, 9.94. Found: C, 70.84; H, 7.05; N, 8.01; Cl, 9.70.

A portion of the hydrochloride of IV was dissolved in water, and the aqueous solution was neutralized by addition of sodium bicarbonate solution. The amino-ether, IV, was extracted from the aqueous mixture with ether. Distillation of the ether left a nearly colorless oil.

Anal. Calcd. for $C_{21}H_{24}ON_2$: C, 78.73; H, 7.55; N, 8.75. Found: C, 78.79; H, 7.71; N, 8.89.

Diphenyl-1-isoquinolylcarbinyl β-dimethylaminoethyl ether (V). This compound was prepared from diphenyl-1-isoquinolylcarbinol and β-dimethylaminoethyl chloride in the same manner as described above for the preparation of IV, with the exception that dispersed potassium was used in place of dispersed sodium. The ether, V, was obtained in 92% yield based on unrecovered diphenyl-1-isoquinolylcarbinol, but in only 24% yield based on the starting quantity of the carbinol. After several recrystallizations from absolute ethanol, the ether, V, m.p. 99.0–99.7°, was obtained as colorless crystals.

Anal. Calcd. for $C_{26}H_{26}ON_2$: C, 81.62; H, 6.85; N, 7.33. Found: C, 81.43; H, 6.64; N, 7.25.

A portion of V was dissolved in anhydrous ether, and dry hydrogen chloride was passed into the solution. The monohydrochloride which precipitated had a m.p. of 197.6–198.4° (dec.) after several recrystallizations from absolute ethanol.

Anal. Calcd. for $C_{26}H_{27}ON_2Cl$: C, 74.52; H, 6.50; N, 6.69; Cl, 8.46. Found: C, 74.24; H, 6.50; N, 6.58; Cl, 8.58.

Phenyl-2-thienyl-2-quinolylcarbinyl β-dimethylaminoethyl ether (VI). The procedure used for the preparation of VI was the same as that used in the preparation of V, except that 0.30 g. of sodium iodide was added to the reaction mixture prior to the addition of the potassium dispersion to the toluene solution of phenyl-2-thienyl-2-quinolylcarbinol. In the eventual work-up of the reaction mixture, a solid precipitated before the *p*H of the mixture reached 5 during the treatment with 10% hydrochloric acid. This solid material proved to be the monohydrochloride of phenyl-2-thienyl-2-quinolylcarbinyl β-dimethylaminoethyl ether. The yield of crude product amounted to 56% based on starting carbinol, or 67% based on unrecovered carbinol. After several recrystallizations from ether-ethanol, the salt had a m.p. of 201.5–202.5° (dec.).

Anal. Calcd. for $C_{24}H_{25}N_2OSCl$: C, 67.83; H, 5.93; N, 6.59; S, 7.54; Cl, 8.34. Found: C, 67.96; H, 6.02; N, 6.50; S, 7.37; Cl, 8.28.

A portion of the salt was dissolved in water, the aqueous solution made alkaline by addition of sodium hydroxide solution, and the mixture extracted with ether. Removal of the ether by distillation left VI, an oil, as a residue.

Anal. Calcd. for $C_{24}H_{24}ON_2S$: C, 74.20; H, 6.23. Found: C, 74.02; H, 6.30.

Methylphenyl-4-quinolylcarbinol. The reaction of 4-benzoylquinoline[11] with methylmagnesium bromide in ether solution under a nitrogen atmosphere gave, after hydrolysis of the reaction mixture, a quantitative yield of crude methylphenyl-1-isoquinolylcarbinol, an oil.

The *picrate* was prepared in ethanol and recrystallized from 95% ethanol. Its m.p. was 220.5–222.0°.

Anal. Calcd. for $C_{23}H_{18}N_4O_8$: C, 57.74; H, 3.76; N, 11.71. Found: C, 57.87; H, 3.47; N, 11.94.

The picrate was decomposed by treatment with lithium hydroxide solution, and the liberated carbinol was extracted from the aqueous mixture with ether. The ether solution was washed with water, and the ether was removed by distillation. The residual, colorless, liquid carbinol was used without further purification for the preparation of VII.

Methylphenyl-4-quinolylcarbinyl β-dimethylaminoethyl ether (VII). This compound was prepared in 11% yield from methylphenyl-4-quinolylcarbinol and β-dimethylaminoethyl chloride by the same method described previously for the preparation of III. The work up was modified as follows:

After the toluene layer had been washed with water to remove salt, it was mixed with just sufficient 10% hydrochloric acid to make the mixture acid to Congo Red paper. Sufficient saturated sodium carbonate solution was then added to make the mixture just basic to Congo Red paper. The aqueous layer was separated from the toluene layer, made alkaline by addition of potassium hydroxide solution and extracted with one large portion of low-boiling petroleum ether. Evaporation of the petroleum ether left crude VII, an oil, b.p. 150–160° (0.3 mm.).

The *dipicrate* was prepared in ethanol and recrystallized from 95% ethanol. Its m.p. was 190.0–191.5°.

Anal. Calcd. for $C_{33}H_{30}N_8O_5$: C, 50.88; H, 3.85; N, 14.39. Found: C, 50.82; H, 3.69; N, 14.16.

A *chloroplatinate* was prepared by addition of a 10% solution of chloroplatinic acid to a solution of VII in 10% hydrochloric acid. The resulting tan precipitate had a m.p. of 212° (dec.) after having been washed with dilute hydrochloric acid and water.

Anal. Calcd. for $C_{21}H_{26}N_2OPtCl_6$: N, 3.83; Pt, 26.74. Found: N, 3.70; Pt, 26.31.

The hydrochloride proved to be very hygroscopic, and no crystalline material could be obtained on attempts to prepare the sulfate, phosphate, or succinate salts.

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LAWRENCE, KAN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF OREGON]

The Reformatsky Reaction in Syntheses of ω,ω-Diarylalkanoic Acids and Related Compounds[1,2]

L. H. KLEMM AND C. M. BOWER[3]

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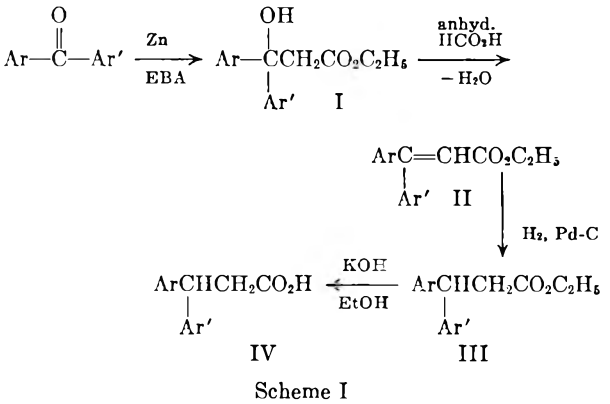
By the sequence of reactions illustrated in Scheme II benzophenone was condensed (Reformatsky reaction) with methyl γ-bromocrotonate (MBC) and thence converted to δ,δ-diphenylvaleric acid (VII) and 9-phenylbenzosuber-5-one (VIII). For structural proof, VIII was reduced to 5-phenylbenzosuberan, identical in infrared spectrum with an authentic sample of this compound prepared from benzosuber-5-one.

3-Methoxy-; 4-methoxy-; 4,4′-dimethoxy-; and 3,4,5,3′,4′-pentamethoxybenzophenones readily underwent Reformatsky reaction with ethyl bromoacetate (EBA) but failed to react significantly with MBC. The hydroxyesters resulting from the reaction with EBA were transformed into β,β-diarylpropionic acids by the general method of Scheme I. For the series starting with 4,4′-dimethoxybenzophenone, the intermediate compound ethyl β,β-bis(4-methoxyphenyl)propionate was also converted to the corresponding δ,δ-diarylvaleric acid XV via Scheme III.

Despite widespread usage of the Reformatsky reaction for condensations involving aldehydes, cycloalkanones, dialkyl ketones, and alkyl aryl ketones, there has been very little investigation of this reaction employing diaryl ketones. In this paper we report the results of our experiments on the Reformatsky reaction between (*a*) benzophenone and various methoxy-substituted benzophenones and (*b*) the bromoesters ethyl bromoacetate (EBA) and methyl γ-bromocrotonate (MBC). An attempt is made to correlate these data with others reported in the literature.

The elegant method of Gardner[4] for production of 4-methoxybenzophenone through benzoylation of anisole by means of benzoic acid in the presence of polyphosphoric acid was repeated and extended to the syntheses of 4,4′-dimethoxybenzophenone (82% yield) and 3,4,5,3′,4′-pentamethoxybenzophenone (60% yield from veratrole and trimethylgallic acid). These ketones, as well as 3-methoxybenzophenone, were treated according to Scheme I.



Scheme I

The Reformatsky condensation with EBA (used in excess) proceeded readily in refluxing benzene in every case. The intermediate hydroxyesters I were successively dehydrated to the unsaturated esters II in good yield by treatment with anhydrous formic acid, hydrogenated to the esters III (presumably in quantitative yield) at low pressure using 30% palladium-charcoal as catalyst and glacial acetic acid as solvent, and hydrolyzed to the acids IV in essentially quantitative yield *via* alcoholic potassium hydroxide. Examination of Table I shows that the yields of hydroxyesters are notably higher in the cases of benzophenone and 3-methoxybenzophenone than they are for the other ketones listed. Such a relationship is consistent with the point of view that the Reformatsky reaction, like the addition of a Grignard reagent to a carbon-oxygen double bond, occurs *via* nucleophilic attack of the halogen-bearing carbon onto the carbonyl carbon. Such attack is hindered by an electron-donating ortho or para methoxy group but is facilitated (if

TABLE I

PERCENTAGE YIELDS FOR REFORMATSKY REACTION OF METHOXY-SUBSTITUTED BENZOPHENONES WITH ETHYL α-BROMOACETATE

Position(s) of Methoxy Substituent(s)	Yield of Hydroxyester (I), %	Over-all Yield[a] of Diarylpropionic Acid (IV), %
None	*ca.* 95[b]	..
2-	60–70[c]	..
3-	95–100[d]	88
4-	78	67
4,4′-	69	56
3,4,3′,4′-	*ca.* 81[e]	...[f]
3,4,5,4′-	*ca.* 70[e]	...[g]
3,4,5,3′,4′-	...[h]	59

[a] From ketone and ethyl α-bromoacetate. [b] H. Rupe and E. Busolt, *Ber.*, **40**, 4537 (1907). The percentage yield given in ref. 5, p. 26 appears to be in error. [c] R. Stoermer and E. Friderici, *Ber.*, **41**, 324 (1908). [d] Estimated. [e] Crude yield of liquid product, see ref. 13. [f] Over-all yield of diarylacrylic acid (from hydrolysis of II) was 59%. [g] Over-all yield of diarylacrylic ester was 39%. [h] Not isolated.

(1) This investigation was supported by research grant No. C-2040 from the National Cancer Institute, Public Health Service. Presented at the Northwest Regional Meeting of the American Chemical Society, Seattle, Wash., June, 1956.

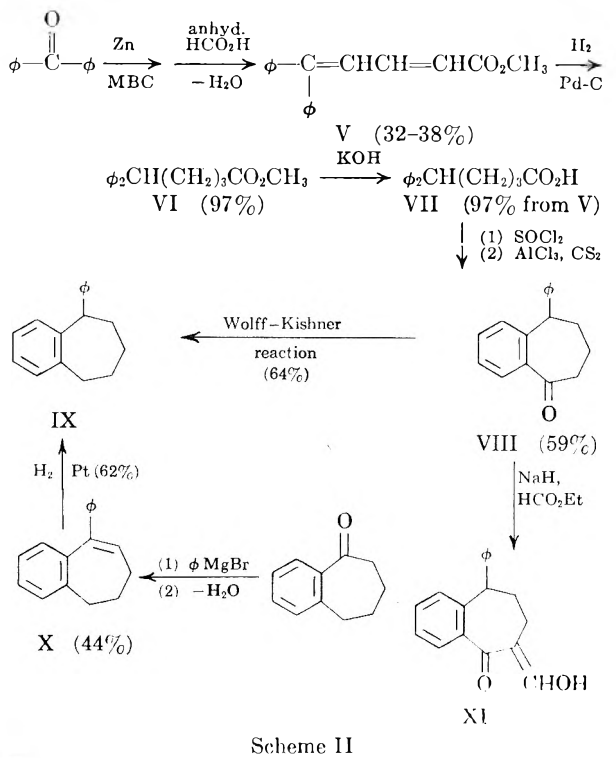
(2) Abstracted from the Ph.D. dissertation of George M. Bower, University of Oregon, June, 1957.

(3) Research assistant, 1954–1956.

(4) P. D. Gardner, *J. Am. Chem. Soc.*, **76**, 4550 (1954).

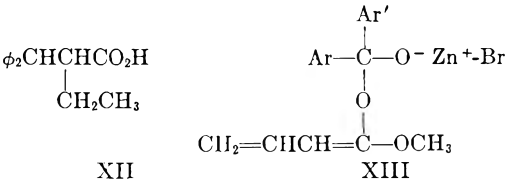
anything) by an electron-withdrawing meta methoxy group. It is apparent that for Ar and Ar′ = phenyl or a methoxy-substituted phenyl group Scheme I represents a suitable synthetic approach to the production of β,β-diarylpropionic acids (and their ethyl esters) as well as of ethyl β,β-diarylacrylates (and the corresponding β,β-diarylacrylic acids). The facile dehydration (even during vacuum distillation) of many Reformatsky hydroxyesters,[5] however, is still occurrent here so that production of esters of type I in high yield and purity is accomplished only in selected cases.

Judging from the preceding results one would anticipate that these diaryl ketones likewise ought to react readily with MBC, though perhaps to give somewhat lower yields than with EBA due to an increasing number of possible side reactions with the former reagent. Indeed, when benzophenone was treated with MBC in benzene-ether and the intermediate product was dehydrated (*cf.* Scheme II) a low yield of the crystalline dienic ester V resulted. Hydrolysis of the ester produced the corresponding dienic acid. Catalytic hydrogenation of V gave the saturated ester VI, hydrolyzable to δ,δ-diphenylvaleric acid (VII), obtained in 31–37% overall yield for the three-step process. In further transformations VII was converted to its acid chloride and cyclized by a high-dilution Friedel-Crafts technique to 9-phenylbenzosuber-5-one (VIII) which was (*a*) formylated with ethyl formate to give XI and (*b*) reduced by the Wolff-Kishner method to 5-phenylbenzosuberan (IX).



Scheme II

In consideration of the observations of Dreiding and Pratt[6] that, depending on reaction conditions, one might get either α- or γ-addition (or both) of MBC to the carbonyl group, it seemed pertinent to ascertain if VII (expected for γ-addition) were, indeed, the correct formulation for the product formed. That the alternative structure XII (expected for α-addition) was inappropriate was indicated by the fact that microanalysis of the compound failed to show the presence of a C-methyl group. Positive evidence for the assignment of



structure VII was then obtained through synthesis of the hydrocarbon IX by an unequivocal route involving dehydration to an alkene (presumably X) of the intermediate carbinol resulting from interaction of phenylmagnesium bromide with benzosuberone and subsequent catalytic hydrogenation of the alkene. The liquid hydrocarbons (IX) from the two pathways exhibited identical infrared absorption spectra which showed no absorption at 7.27 ± 0.05μ (C—methyl deformation) but did show strong absorption at about 13.9μ—perhaps due to —$(CH_2)_4$—deformation.[7]

Attempts to apply the same conditions as used for Reformatsky reaction of MBC with benzophenone to the reaction of MBC with the four methoxy-substituted benzophenones previously found by us to condense readily with EBA, however, gave only very small quantities of crude resinous products (possibly of types V–VII) which were not amenable to purification by distillation or crystallization. Alteration of the refluxing solvent used, the time of reaction, and the molar ratio of MBC to ketone (from a considerable excess of the former to a molar excess of the latter) were of no greater avail. In fact, usually 60–80% of the total original amount of ketone used was recovered from these runs. Stork[8] likewise observed a high (48%) recovery of ketone (plus a 48% yield of Reformatsky product) from interaction of 6-methoxy-1-tetralone with MBC in the molar ratio of 1:2 (ketone:MBC). The low reactivity of our methoxy-substituted benzophenones toward MBC may be the consequence of molecular compound (π-complex) formation between the aryl ring of the ketone and the electron-attracting carbon-carbon double bond of MBC or its zinc derivative. The presence of one or more methoxy groups on the aryl moiety should

(5) R. L. Shriner, *Org. Reactions*, I, 11 (1942). See also ref. 10.

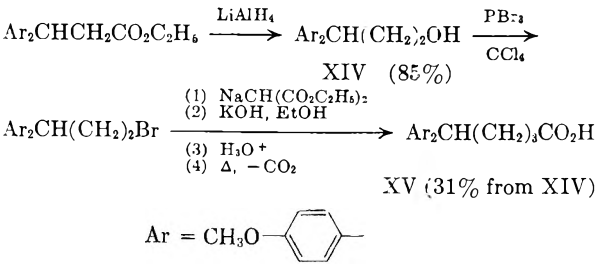
(6) A. S. Dreiding and R. J. Pratt, *J. Am. Chem. Soc.*, 75, 3717 (1953).

(7) F. A. Miller in H. Gilman, *Organic Chemistry*, John Wiley and Sons, Inc., New York, 1953, Vol. III, pp. 143–145.

(8) G. Stork, *J. Am. Chem. Soc.*, 69, 2936 (1947).

greatly enhance such complex formation.[9] From Fisher-Hirschfelder-Taylor models one notes that, especially if the BrZn— end of the complexed MBC (with its alkenic system in planar parallelism to the aryl ring) were to coordinate with the methoxy oxygen, the carbomethoxy group of MBC could easily assume the appropriate stereorelationship for formation of an intermediate (XIII) of the type suggested by Jones, O'Sullivan, and Whiting.[10] On acidification of the reaction mixture one would regenerate the starting ketone. EBA, devoid of a carbon-carbon double bond, ought not give such a molecular compound. The success in reactions (of MBC) with 6-methoxy-1-tetralone and 3,4,5-trimethoxybenzaldehyde (46% yield of Reformatsky product)[6,11] might then be ascribed to the absence in these molecules of a second aryl group, with its attendant effects of steric hindrance to attack at the carbonyl carbon (due to the nonplanarity of benzophenones) and its complexing properties.

Failure to achieve Reformatsky reaction between the methoxy-substituted benzophenones and MBC led us to investigate an alternate pathway for preparation of δ,δ-diarylvaleric acids, pursued only in the case of the starting ketone 4,4′-dimethoxybenzophenone. In this approach the diarylpropionic ester, formed by means of the EBA reaction, was converted to the desired acid XV (15% overall yield from 4,4′-dimethoxybenzophenone) in the manner depicted in Scheme III.



Scheme III

EXPERIMENTAL[12]

4,4′-Dimethoxybenzophenone. Following the general procedure of Gardner[4] an equimolar mixture of anisic acid (57 g.) and anisole (41 g.) was stirred with 540 g. of polyphosphoric acid (Victor Chemical Co.) at 70° for 2 hr. and then poured into ice and water. The precipitate was washed with 500 ml. of 5% aqueous sodium hydroxide and then with water, dried, and recrystallized once from ethanol; yield 75.4 g. (82%) of needles, m.p. 144–146°; reported[13] m.p. 144–145°.

3,4,5,3′,4′-Pentamethoxybenzophenone. By the foregoing procedure a mixture of 41 g. of trimethylgallic acid,[14] 25 g. of veratrole, and 430 g. of polyphosphoric acid gave 36 g. (60%) of slightly tan prisms, m.p. 117–119°; reported m.p. 118°,[15] 119–120°.[16]

Ethyl β-hydroxy-β,β-bis(4-methoxyphenyl)propionate. To a stirred, warmed (to just below ebullition temperature) mixture of 50 g. (0.76 g.-atom) of activated (with hydrochloric acid)[17] 20-mesh zinc, 58.3 g. (0.24 mole) of 4,4′-dimethoxybenzophenone, 400 ml. of anhydrous benzene, and a crystal of iodine there was added over a period of 30 min. (at such a rate as to maintain refluxing) a solution of 70 g. (0.42 mole) of ethyl α-bromoacetate in 20 ml. of benzene. After an additional 15 min. the mixture was treated with *ca.* 200 ml. of 10% acetic acid. The combined organic layer and benzene extracts of the aqueous phase were washed successively with water, excess 1.5% aqueous ammonia, and water, dried (magnesium sulfate), and evaporated. Crystallization of the residue from ethanol gave 55 g. (69%) of needles, m.p. 87–91°. An analytical sample was obtained by recrystallization from ethyl acetate, m.p. 92–93°.

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.07; H, 6.76.

Ethyl β,β-bis(4-methoxyphenyl)propionate. To a warm solution of 14.4 g. of the preceding hydroxyester in 140 ml. of anhydrous benzene was added 20 ml. of anhydrous formic acid. After the transient bright red color had faded (30 sec.) the mixture was boiled for 5 min. and evaporated (air blast). The residual unsaturated ester was hydrogenated in glacial acetic acid (90 ml.) using 2.5 g. of 5% palladium-charcoal and hydrogen at 3.5–4 atm. for 30 min. The liquid from evaporation of the filtered solution crystallized from absolute ethanol to yield 11.4 g. (83%) of saturated ester as plates, m.p. 46–49°. Several recrystallizations of a sample from the same solvent raised the melting point to 49.5–50.5°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.31; H, 7.17.

β,β-Bis(4-methoxyphenyl)propionic acid. Hydrolysis of the preceding saturated ester by refluxing with a 3% solution of potassium hydroxide in 75% ethanol for 1 hr., followed by concentration of the solution, acidification with dilute hydrochloric acid, and filtration, gave a 97% yield of product (m.p. 129–131°); obtained as needles, m.p. 138.5–139.5°, after several recrystallizations from absolute ethanol; reported m.p. 138–139°,[18] 139–141°.[19]

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.57; H, 6.51.

β,β-Bis(4-methoxyphenyl)acrylic acid. Hydrolysis in the foregoing manner of the crude unsaturated ester obtained from dehydration of 5 g. of the preceding hydroxyester gave 4.1 g. (95%) of product (m.p. 141–146°); obtained as needles, m.p. 146.5–147.5°, after several recrystallizations from dilute methanol; reported[18] m.p. 142°.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.09; H, 5.84.

3,3-Bis(4-methoxyphenyl)propanol (XIV). To a stirred suspension of 3.3 g. (0.087 mole) of lithium aluminum hydride in 400 ml. of anhydrous ether was added, at such rate as to maintain gentle refluxing, a solution of 29 g.

(9) L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **75**, 3776 (1953); W. G. Barb, *Trans. Faraday Soc.*, **49**, 143 (1953).

(10) E. R. H. Jones, D. G. O'Sullivan, and M. C. Whiting, *J. Chem. Soc.*, 1415 (1949).

(11) E. C. Horning, M. G. Horning, J. Koo, M. S. Fish, J. A. Parker, G. N. Walker, R. M. Herowitz, and G. E. Ullyot, *J. Am. Chem. Soc.*, **72**, 4840 (1950).

(12) Unless otherwise designated microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. Results on biological tests (conducted in a different laboratory) of selected compounds described in this section will be reported elsewhere.

(13) E. C. Horning and J. A. Parker, *J. Am. Chem. Soc.*, **74**, 3870 (1952).

(14) F. Mauthner, *Org. Syntheses*, **Coll. Vol. I**, 537 (1941).

(15) S. v. Kostanecki and J. Tambor, *Ber.*, **39**, 4022 (1906).

(16) W. H. Perkin and C. Weizmann, *J. Chem. Soc.*, **89**, 1649 (1906).

(17) Ref. 5, p. 16.

(18) F. Bergmann, M. Weizmann, E. Dimant, J. Patai, and J. Szmuskowicz, *J. Am. Chem. Soc.*, **70**, 1612 (1948).

(19) G. A. Holmberg, *Acta Chem. Scand.*, **6**, 607 (1952).

(0.092 mole) of ethyl β,β-bis(4-methoxyphenyl)propionate in 110 ml. of ether. The mixture was refluxed 1 hr. longer, treated first with ethyl acetate and then (cautiously) with 200 ml. of cold 3*N* hydrochloric acid. Combined ethereal solutions (from separation and extraction of the aqueous phase with 150 ml. of ether) were washed thrice with water, dried (magnesium sulfate), and evaporated. The viscous residue crystallized from ether at −5° as needles which were collected by suction-filtration in a cold room at 5°;[20] yield 15 g. (first crop) of m.p. 54–56° and 6.2 g. (second crop) of m.p. 48–52° (85% total). Further recrystallizations of a sample from ether changed the m.p. to 54–55°.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.96; H, 7.44.

The 3,5-dinitrobenzoate[21a] crystallized from benzene–petroleum ether (60–90°) as yellow needles, m.p. 116–117°.

Anal. Calcd. for $C_{24}H_{22}N_2O_8$: N, 6.01. Found: N, 6.15.

δ,δ-Bis(4-methoxyphenyl)valeric acid (XV). To a stirred solution of 55 g. (0.2 mole) of the preceding alcohol in 250 ml. of carbon tetrachloride at −5° was added, over a period of 2 min., 27 g. (0.1 mole) of freshly distilled phosphorus tribromide. Thirty minutes later stirring was stopped. The solution was allowed to stand at room temperature overnight, then warmed to 50° for 20 min. and treated with water. The combined carbon tetrachloride layer and extracts of the aqueous phase were washed repeatedly with water, dried (calcium chloride), and evaporated to leave a slightly yellow viscous liquid bromide. A solution of this liquid in 200 ml. of absolute ethanol was further dried by azeotropic distillation with 20 ml. of anhydrous benzene until the distilling temperature reached 78° and then added to the ethanolic sodiomalonic ester obtained from 4.6 g. (0.2 g.-atom) of sodium, 350 ml. of absolute ethanol, and 32 g. (0.2 mole) of diethyl malonate. The mixture was refluxed for 5 hr. and the decanted (from sodium bromide) supernatant liquid was treated with a solution of 28 g. of potassium hydroxide in 100 ml. of water. After a further 2 hr. of refluxing the mixture was concentrated, diluted with water, washed with ether, and acidified. The resultant immiscible liquid (presumably the monosubstituted malonic acid) which crystallized on standing was evaporatively distilled (with decarboxylation) at 240–270° (1 mm.). Crystallization of the distillate from ethyl acetate gave 19.3 g. (31%) of needles, m.p. 98–101°. Several recrystallizations from the same solvent gave an analytical sample, m.p. 103.5–104°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05; neut. equiv., 314. Found: C, 72.60; H, 7.28; neut. equiv., 314.

Ethyl β-(3,4-dimethoxyphenyl)-β-(3,4,5-trimethoxyphenyl)-propionate. Following the same sequence of transformations as used with 4,4′-dimethoxybenzophenone, the crude hydroxyester from Reformatsky reaction of 15 g. of zinc, 25 g. of 3,4,5,3′,4′-pentamethoxybenzophenone, and 15 g. of ethyl bromoacetate was dehydrated with 50 ml. of anhydrous formic acid and the resultant yellow liquid was hydrogenated (using 200 ml. of hot glacial acetic acid and 2 g. of 30% palladium-charcoal). Crystallization of the liquid product from absolute ethanol gave 18 g. (59% over-all yield) of solid, m.p. 79–81°. Repeated recrystallizations of a sample from the same solvent gave very fine prisms, m.p. 81.5–82.5°.

Anal. Calcd. for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.25; H, 7.04.

β-(3,4-Dimethoxyphenyl)-β-(3,4,5-trimethoxyphenyl)propionic acid. Hydrolysis of the foregoing ester with aqueous ethanolic potassium hydroxide as described above gave a 98% yield of product, m.p. 95–98°. Further purification[22] was effected by two recrystallizations from ethyl acetate displacement by means of benzene-hexane (1:1 by volume) through a column of Mallinckrodt silicic acid, two recrystallizations from benzene-hexane, and drying at 80° for 12 hr. at 1 mm. to a powder, m.p. 128.5–130°.

Anal. Calcd. for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 64.04; H, 6.36.

Ethyl β-hydroxy-β-phenyl-β-(4-methoxyphenyl)propionate. Using the Reformatsky reaction in the aforementioned manner there was obtained (from 15 g. of zinc, 21.2 g. of 4-methoxybenzophenone,[4] and 25 g. of ethyl α-bromoacetate), after one recrystallization from ethanol, 23.5 g. (78%) of needles, m.p. 79–81°. Several recrystallizations of a sample from ethyl acetate changed the m.p. to 79–80°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.08; H, 6.61.

β-Phenyl-β-(4-methoxyphenyl)propionic acid. Successive steps of dehydration, hydrogenation (30% palladium-charcoal), and hydrolysis (according to the previous procedures, but starting with 3 g. of the preceding hydroxyester) gave 2.2 g. (86%) of acid, m.p. 120–122° (without recrystallization), highest reported[19] m.p. 124–125°.

β-Phenyl-β-(3-methoxyphenyl)propionic acid. Repetition of the same transformations on 3-methoxybenzophenone[23] (8.5 g.) as conducted on its isomer 4-methoxybenzophenone produced 9.1 g. (88%) of crude yellow acid, m.p. 92–98°. Several recrystallizations of a sample from ethyl acetate–petroleum ether (90–120°) gave white prisms, m.p. 99–100°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.90; H, 6.18.

δ-Phenylvaleric acid. Following the general procedure of Huang-Minlon[24] a mixture of 10 g. of γ-benzoylbutyric acid,[25] 7.5 g. of sodium hydroxide, 7.5 ml. of 95% hydrazine, and 80 ml. of diethylene glycol gave 8.4 g. (90%) of brown solid, m.p. 51–54°. Recrystallization of a small sample from ether–petroleum ether (30–60°) gave platelets, m.p. 56.5–57.5°; mixture melting point with the product (m.p. 53–56°) from Clemmensen reduction[26] on the same starting material 53–56°.

Methyl δ,δ-diphenylpentadienoate (V). A mixture of 4.4 g. (0.067 g.-atom) of activated 20-mesh zinc (*vide supra*), 20 g. (0.11 mole) of benzophenone, 55 ml. of anhydrous benzene, 35 ml. of anhydrous ether, and a crystal of iodine was treated with a solution of 10 g. (0.056 mole) of methyl γ-bromocrotonate[27] in 25 ml. of benzene, added over a period of 1 hr. An additional 2 g. of zinc was then added. The mixture was stirred and refluxed for 2 hr. longer and then treated with 45 ml. of 2*N* acetic acid. The organic layer was washed with 5% aqueous sodium bicarbonate and then water, dried (sodium sulfate), and evaporated. The residual oil was warmed with twice its volume of anhydrous formic acid for 15 min.[28] The residue from evaporation of the resultant mixture by means of an air-blast was fractionally distilled to give a viscous liquid, b.p. 135–165° (0.8 mm.), which crystallized from methanol; best yield 5.6 g. (38%), av. yield 32%, m.p. 84–86°. Several recrystallizations of a sample from methanol produced needles, m.p. 86–87°.

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(20) Efforts to obtain crystals by filtration at room temperature were unsuccessful.

(21) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, 1956, (a) p. 212, (b) p. 254.

(22) Procedure devised by Dr. C. D. Lind of this laboratory.

(23) L. H. Klemm and T. Largman, *J. Am. Chem. Soc.*, **76**, 1688 (1954).

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

(25) L. F. Fieser and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **70**, 3352 (1948).

(26) A. Ali, R. D. Desai, R. F. Hunter, and S. M. M. Muhammad, *J. Chem. Soc.*, 1013 (1937).

(27) Prepared by the method of K. Ziegler A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann, [*Ann.*, **551**, 80 (1942)] as modified by H. Schmid and P. Karrer [*Helv. Chim. Acta*, **29**, 573 (1946)]. It was found advisable to use recrystallized (obtained as white plates from water) *N*-bromosuccinimide in this preparation.

(28) Sometimes dehydration was effected merely by heating at 125°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 82.00; H, 6.11.

δ,δ-Diphenylpentadienoic acid. Acidification of the solution obtained by refluxing the preceding ester with a slight excess of 2% methanolic potassium hydroxide for 2 hr. gave a quantitative yield of product, m.p. 176–186°. Several recrystallizations of a sample from toluene gave needles, m.p. 190–191°.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 82.02; H, 5.90.

Methyl δ,δ-diphenylvalerate (VI). A solution of 15 g. of methyl δ,δ-diphenylpentadienoate in 150 ml. of glacial acetic acid was shaken with 3 g. of 5% palladium-charcoal for 10 min. under hydrogen at 3.5–4-atm. pressure. The filtered solution (negative permanganate test) was distilled to give 14.7 g. (97%) of colorless liquid, b.p. 145–150° (0.5 mm.).

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 81.39; H, 7.51.

δ,δ-Diphenylvaleric acid (VII). Hydrolysis of the preceding saturated methyl ester in the manner used for the dienic ester produced a quantitative yield of product, m.p. 89–92°. Several recrystallizations of a sample from 60% ethanol gave needles, m.p. 92.5–93.5°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.23; H, 7.30; C-methyl,[29] none.

9-Phenylbenzosuber-5-one (VIII). In an adaptation of published[30] high-dilution Friedel-Crafts intramolecular acylations, a solution of δ,δ-diphenylvaleryl chloride [prepared from 10 g. (0.039 mole) of the foregoing acid and 8 ml. of thionyl chloride] in 250 ml. of purified[31] carbon disulfide was added (*via* the attachment described by Leonard and Sentz)[32] over a period of 10 hr. to a stirred, refluxing mixture of 750 ml. of carbon disulfide and 2.7 g. of anhydrous aluminum chloride. At 3-hr. intervals 2.7-g. portions of aluminum chloride (total used 10.8 g., 0.081 mole) were added. After 12 hr. the dark red mixture was treated with water and filtered. The benzene solution of the residual oil from distillation of the organic layer was washed with excess 10% aqueous potassium carbonate and then with water, dried (magnesium sulfate), and evaporated. Evaporative distillation of the residue at 190–200° (0.5 mm.) gave 5.47 g. (59%) of ketone. Several recrystallizations of a sample from dilute ethanol gave needles, m.p. 71.0–71.5°.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found:[29] C, 86.82; H, 6.99.

The oxime[21b] was obtained in the form of prisms from benzene–petroleum ether (30–60°), m.p. 152.5–153.5°.

Anal. Calcd. for $C_{17}H_{17}NO$: N, 5.57. Found: N, 5.47.

δ-Phenylbenzosuberan (IX). (*a*) *From 9-phenylbenzosuber-5-one.* The diluted mixture from the Huang-Minlon reaction[24] on 2 g. of the preceding ketone was extracted with benzene. Distillation of the water-washed and dried (magnesium sulfate) extract yielded 1.2 g. (64%) of light yellow liquid, b.p. 132–135° (1 mm.). A re-distilled sample for infrared analysis was obtained almost colorless, b.p. 149–150° (2 mm.). After long standing it yielded prisms, m.p. 41–45°.

(*b*) *From benzosuber-5-one.* To the ice-cold Grignard reagent from 0.4 g. of magnesium (16 mg.-atoms), 2.4 g. (15 mmoles) of bromobenzene, and 75 ml. of ether was slowly added a solution of 2 g. (8.5 mmoles) of benzosuber-5-one (obtained by cyclization of δ-phenylvaleric acid with polyphosphoric acid)[33] in 20 ml. of ether. The mixture was stirred in the cold for 30 min. and then refluxed for 1 hr. Hydrolysis, collection of carbinol, and dehydration with formic acid followed the method of Klemm and Ziffer[34] to give, after fractional distillation at 1.5 mm., 0.4 g. of colorless ketonic liquid (presumably recovered starting material), b.p. 95–110°, and 1 g. (44%) of permanganate-reducible liquid (presumably *δ-phenylbenzosuber-5-ene*, X), b.p. 115–135°.

A solution of 0.9 g. of the preceding alkenic fraction in 25 ml. of glacial acetic acid was shaken with 0.1 g. of Adams' platinum oxide under hydrogen at 4 atm. pressure for 2 hr. (whereupon the solution no longer reduced permanganate). Distillation of the filtered solution yielded 0.56 g. (62% from the alkene) of colorless liquid, b.p. 115° (0.6 mm.). A sample for analysis was redistilled at 149–150° (2 mm.).

Anal. Calcd. for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.51; H, 8.34.

The infrared absorption spectra[35] of the products from (*a*) and (*b*) were identical; strong to very strong bands at 3.26–3.52 (C—H stretching), 6.24 and 6.71 (phenyl), 6.90 (CH_2-deformation), *ca.* 13.35 (ortho disubstituted benzene), *ca.* 13.9 (tetramethylene deformation), and *ca.* 14.35μ.

6-Hydroxymethylene-9-phenylbenzosuber-5-one (XI). A mixture of 2.36 g. (0.01 mole) of 9-phenylbenzosuber-5-one, 1.48 g. (0.02 mole) of ethyl formate, and a few ml. of anhydrous benzene was stirred and warmed with 0.5 g. (0.02 mole) of sodium hydride in an atmosphere of nitrogen. Vigorous evolution of gas occurred. The red pasty contents were diluted with 10 ml. of benzene, stirred at 50° for 1.5 hr., and treated successively with 3 ml. of glacial acetic acid and 30 ml. of water. The benzene layer was separated, washed with water, and extracted with 100 ml. of 10% aqueous sodium carbonate. Acidification of the alkaline extract gave 2.1 g. of solid, recrystallized once from ethyl acetate, m.p. 101.5–102.5°. Several recrystallizations of a sample from benzene–petroleum ether (60–90°) gave prisms, m.p. 102–102.5°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.46; H, 6.12.

EUGENE, ORE.

(29) Analyzed by Clark Microanalytical Lab., Urbana, Ill.

(30) G. D. Hedden and W. G. Brown, *J. Am. Chem. Soc.*, **75**, 3744 (1953); R. Huisgen and W. Rapp, *Ber.*, **85**, 826 (1952); W. M. Schubert, W. A. Sweeney, and H. K. Latourette, *J. Am. Chem. Soc.*, **76**, 5462 (1954).

(31) L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed., D. C. Heath and Co., New York, 1941, p. 365.

(32) N. J. Leonard and R. C. Sentz, *J. Am. Chem. Soc.*, **74**, 1704 (1952).

(33) W. J. Horton and F. E. Walker, *J. Am. Chem. Soc.*, **74**, 758 (1952).

(34) L. H. Klemm and H. Ziffer, *J. Org. Chem.*, **20**, 182 (1955).

(35) Obtained by Samuel P. Sadtler and Son, Inc., Philadelphia, Pa. See spectrum No. 67257 in their catalog.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF OREGON]

Syntheses of 3,3′-Dimethoxybenzophenone. *Para* Substitution in Acylation of the Organocadmium Reagent from *m*-Haloanisoles[1,2]

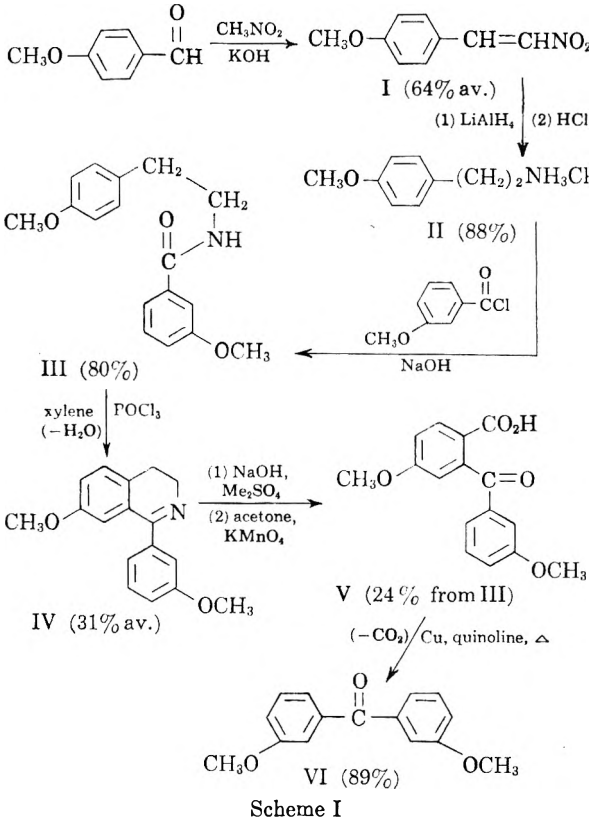
L. H. KLEMM, ROGER MANN,[3] AND C. D. LIND[4]

Received September 10, 1957

3,3′-Dimethoxybenzophenone (VI) has been prepared in 10% over-all yield from either (*a*) *p*-anisaldehyde (by the unequivocal Scheme I) or (*b*) benzophenone (Scheme II). The structure of the product from (*b*) was established by comparison of its 2,4-dinitrophenylhydrazone with that from procedure (*a*) and by Beckmann rearrangement of its oxime to 3-methoxy-*N*-(3-methoxyphenyl)benzamide (XI), identical with an authentic synthetic specimen.

Treatment of the organocadmium compound from either *m*-iodoanisole or *m*-bromoanisole with *m*-methoxybenzoyl chloride gave *ca.* 20% yield of liquid ketone from which was isolated the crystalline derivative of 3,4′-dimethoxybenzophenone 2,4-dinitrophenylhydrazone, identified by comparison with an authentic sample. Infrared analysis of the ketone (obtained from *m*-bromoanisole) showed it consisted of *ca.* 35% "normal product" (VI) and 65% "rearranged product," 3,4′-dimethoxybenzophenone.

For use in further studies we desired a convenient synthesis of 3,3′-dimethoxybenzophenone (VI) of unequivocal structure. Three alternative procedures were investigated in this regard. The first of these (Scheme I) was an adaptation of the method of Gensler and Samour[5] for a different series. Thus the ω-nitrostyrene I, formed by condensation of *p*-anisaldehyde with nitromethane, was reduced with lithium aluminum hydride in ether to the amine hydrochloride II. II was converted to the amide III by means of the Schotten-Baumann reaction. Bischler-Napieralski cyclization of III to the dihydroisoquinoline IV proved difficult (presumably because electrophilic substitution must occur meta to a deactivating methoxy group)[6,7] but could be effected in low yield using phosphorus oxychloride in refluxing xylene. More strenuous conditions proved even less suitable due to the formation of increased yields of tar. The crude liquid resulting from treatment of IV with alkaline dimethyl sulfate was oxidized directly to the crystalline acid V. Decarboxylation of V produced the desired ketone VI, b.p. 144–145° (0.3 mm.), in an over-all yield of 10% for the six-step process. As an added indication that the structural assignment for VI was appropriate for the final product, it was found that the 2,4-dinitrophenylhydrazone exhibited (*a*) an absorption maximum at 385–387 mμ (log ε 4.48), consistent with the values predicted (λ_{max} *ca.* 387 mμ, log ε *ca.* 4.5) on the basis of observations by Johnson,[8] and (*b*) a m.p. of 191–192°, the same as reported by Buchta and Weidinger[9] (whose prep-



Scheme I

(1) This investigation was supported (in part) by research grant No. CY-3097 from the National Cancer Institute, Public Health Service. Presented at the Northwest Regional Meeting of the American Chemical Society, Spokane, Wash., June, 1957.

(2) Abstracted in part from the M.A. thesis of Roger Mann, University of Oregon, June, 1957.

(3) Research Fellow, 1957.

(4) Research Associate, 1956–1957.

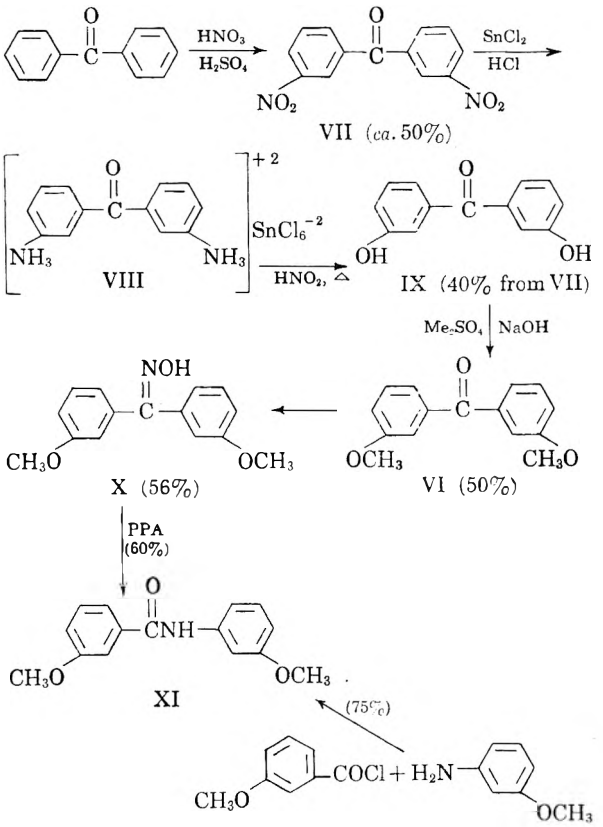
(5) W. J. Gensler and C. M. Samour, *J. Am. Chem. Soc.*, **73**, 5555 (1951).

(6) W. M. Whaley and W. H. Hartung, *J. Org. Chem.*, **14**, 650 (1949).

(7) See W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **VI**, Chap. 2 (1951); and discussion of the mechanism of the Morgan-Walls reaction (a special type of the more general Bischler-Napieralski reaction) by E. Ritchie, *J. Proc. Roy. Soc. N. S. Wales*, **78**, 147 (1944).

(8) G. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953). Note the absence of an effect on the observed λ_{max} due to the presence of an unconjugated 3-methoxy group but the bathochromic shift caused by a conjugated 4-methoxy group in the series of 2,4-DNP's reported by Johnson: benzophenone $\lambda_{max}^{CHCl_3}$ 387 mμ (log ε 4.51); 3-methoxybenzophenone 387 (4.47); 4-methoxybenzophenone 396 (4.47); 4,4′-dimethoxybenzophenone 400 (4.46). It might also be noted that log ε is approximately 4.5 in all cases.

(9) E. Buchta and H. Weidinger, *Ann.*, **580**, 83 (1953).



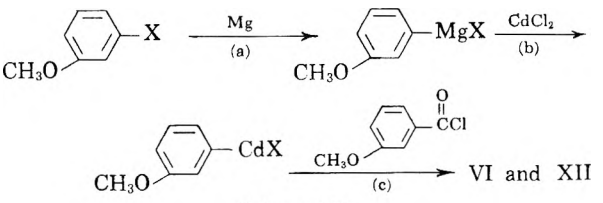
Scheme II

aration served only as a means of locating the positions of carbon-carbon double bonds in a tetraanisylhexadiene and not as a suitable synthetic procedure for VI).

The second approach (Scheme II) was a modification of the method of Valette[10] by which he had produced a dimethoxybenzophenone of doubtful structure. This involved the successive steps of nitration according to the method of Barnett and Matthews,[11] reduction of the nitro compound with stannous chloride in hydrochloric acid, hydroxydeamination of the crude salt VIII to give IX, and methylation of IX to form VI in *ca.* 10% over-all yield for the four-step process.

Two different procedures were used to establish the structure of the Valette dimethoxybenzophenone. First, it formed a 2,4-DNP identical (as based on melting point and mixture melting point) with that from Scheme I. Second, it was converted to a crystalline oxime which underwent Beckmann rearrangement in the presence of polyphosphoric acid to the amide XI, identical (as based on melting point, mixture melting point, and infrared spectrum) with an authentic specimen produced by Schotten-Baumann reaction between *m*-anisidine and *m*-methoxybenzoyl chloride.

Proof of the structure of the Valette dimethoxybenzophenone apparently also serves to establish the structures of VII, VIII, IX, X, and the free diamine obtainable from VIII. Since the Barnett and Matthews nitration procedure involves separation through crystallization of VII from other nitration products formed simultaneously, it is necessary to perform a careful fractionation before carrying out the reduction step in order to be assured of the isomeric purity of the resultant VI. Nonetheless as a preparative method for VI, Scheme II is much to be preferred over Scheme I on the bases of facility of carrying out the reactions as well as time and expense involved.



Scheme III

Scheme III was an adaptation of the method of Klemm and Largman[12] (for preparation of *m*-methoxybenzophenone) whereby *m*-methoxybenzoyl chloride would be reacted with the organocadmium compound from a *m*-haloanisole (rather than from bromobenzene). Use of *m*-iodoanisole in this fashion, however, yielded only 17% of liquid product from which no crystalline oxime could be obtained. Moreover, the dinitrophenylhydrazone A, m.p. 211–212° (dec.), λ_{max} 396 mμ (log ε 4.45), depressed the melting point of the *bona fide* derivative from Schemes I and II upon admixture therewith. Repetition of the synthesis using *m*-bromoanisole instead of *m*-iodoanisole gave similar results, *viz.* 20–24% yield of liquid which showed the expected percentage of methoxy groups for a dimethoxybenzophenone but gave a 2,4-DNP identical (as based on melting point, mixture melting point, and ultraviolet spectrum) with A. It thus appeared likely that our ketonic products from Scheme III contained at least an appreciable percentage of some isomer other than VI. On the basis of the λ_{max} found and the belief that no migration of the methoxy group should occur in the *m*-methoxybenzoyl moiety of the acid chloride, we tentatively assigned A the structure of *3,4′-dimethoxybenzophenone 2,4-dinitrophenylhydrazone*. That this was indeed the correct assignment followed from the fact that *bona fide* 3,4′-dimethoxybenzophenone (XII), prepared in 60% yield by interaction of anisole and *m*-methoxybenzoic acid in the presence of polyphosphoric acid, formed a 2,4-dinitrophenylhydrazone derivative identical with A (as based on melting point, mixture melting point, ultraviolet and infrared spectra). Comparison of the infrared spectrum of the free ketone, B, from the *m*-bromoanisole reaction with the spec-

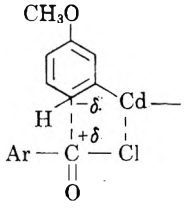
(10) M. Valette, *Bull. soc. chim. France*, [4] **47**, 289 (1930).

(11) E. deB. Barnett and M. A. Matthews, *J. Chem. Soc.*, **125**, 767 (1924).

(12) L. H. Klemm and T. Largman, *J. Am. Chem. Soc.*, **76**, 1688 (1954).

tra of standard mixtures of VI and XII indicated that B contained *ca.* 35% VI ("normal product") and 65% XII ("rearranged product").

Consideration of Scheme III for the organocadmium reaction of a *m*-haloanisole indicates there are three steps (*a*)–(c) in which a molecular rearrangement might plausibly occur. That step (*a*) is free of rearrangement is indicated by the results of Inagaki[13] and of Votocek and Matejka.[14] The former treated isatin with *o*-, *m*-, and *p*-methoxyphenylmagnesium iodides (respectively) and obtained three different crystalline products. Oxidation of these products by means of alkaline hydrogen peroxide gave *o*-, *m*-, and *p*-anisic acids, respectively. The latter workers reacted *m*-methoxyphenylmagnesium iodide with 4,4′-dimethylaminobenzophenone to give the carbinol which was reduced to bis(4-dimethylaminophenyl)-3-methoxyphenylmethane, identical with the product formed by condensation of *m*-methoxybenzaldehyde with *N*,*N*-dimethylaniline. Recent studies by Dauben and Collette[15] indicate that the rearrangement is associated with step (*c*) and not with step (*b*). Perhaps lending assistance to the consummation of such rearrangement would be the formation of a pseudo five-membered ring, as illustrated schematically by XIII. The donation of electronic charge by the methoxy group of the organocadmium reagent to the para position of the benzene ring is considered especially pertinent to this rearrangement.



XIII

EXPERIMENTAL[16]

3,3′-Dihydroxybenzophenone (IX). A mixture of 125 g. (0.46 mole) of 3,3′-dinitrobenzophenone,[11] 625 g. (2.76 moles) of C.P. stannous chloride dihydrate, and 835 ml. of concentrated hydrochloric acid was stirred at 70° for 6 hr. The yellow crystalline benzophenone-3,3′-diammonium chlorostannate was collected by filtration with a sintered glass funnel and suspended in 835 ml. of fresh concentrated hydrochloric acid. Beneath the surface of the cooled (3°) suspension was added over a period of 1 hr. a solution of 64 g. (0.93 mole) of sodium nitrite in 210 ml. of water. After an additional hr. of stirring at 0° the mixture was quickly filtered by means of a cold sintered glass funnel and the resultant bright yellow precipitate (tetrazonium salt) was added (cold) in small portions of 2.4 l. of boiling 1*N* sulfuric acid containing 10 drops of General Electric "Antifoam 60."[17] After the addition of 1 g. of Norit to the red solution the mixture was filtered hot. On cooling, the filtrate deposited a light tan powder, yield 39.6 g. (40%), m.p. 157.5–159.5°, reported[18] m.p. 163–164°.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.70; H, 4.92.

3,3′-Diaminobenzophenone. For purposes of identification a small amount of the preceding chlorostannate was suspended in water, brought to *p*H 3, and treated with hydrogen sulfide. The filtered (to remove stannic sulfide) solution was basified with sodium hydroxide. The resultant precipitate was washed with water and recrystallized from 20% ethanol as light yellow, fine needles, m.p. 148–149°; reported[19] m.p. 150.5°.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.13; H, 5.82; N, 13.22.

4-Methoxy-β-nitrostyrene (I). This compound, m.p. 85–87.5°, prepared according to the method of Rosenmund,[20] showed strong allergenic properties[21] (contact dermatitis) toward Mr. Mann.

2-(4-Methoxyphenyl)ethylammonium chloride (II). In a manner similar to the second method described by Erne and Ramirez[22] for reduction of 2,3,4-trimethoxy-β-nitrostyrene there was added slowly (over a period of 3 hr.) a solution of 36 g. (0.201 mole) of I in 1.2 l. of anhydrous ether to a stirred refluxing mixture of 27 g. (0.71 mole) of lithium aluminum hydride in 2 l. of ether. After 2 more hr. of refluxing the reaction mixture was cooled thoroughly (ice-salt bath), and treated *very cautiously*[23] with 1.5 l. of 2*N* sulfuric acid, added in small portions over a period of 2 hr. by means of a long stem funnel reaching beneath the surface of the ether. The layers were separated and the ethereal layer was extracted with a slight excess of 2*N* sulfuric acid. The combined aqueous layer and extracts were basified cautiously with 33% aqueous sodium hydroxide until a milky emulsion resulted (*p*H > 10) and extracted thrice with ether. The white chalky precipitate which resulted from passing anhydrous hydrogen chloride into the dried (solid potassium hydroxide) combined ethereal extracts was collected and dried in air, yield 33.3 g. (88%), m.p. 203–210° (dec.), reported[20] m.p. 207°. For analysis a sample was recrystallized thrice from absolute ethanol to give silvery plates, m.p. 212–214° (dec.).

Anal. Calcd. for $C_9H_{14}ClNO$: Cl, 18.9. Found:[24] Cl, 19.2.

(13) S. Inagaki, *J. Pharm. Soc. Japan*, **59**, 7 (1939).

(14) E. Votocek and J. Matejka, *Ber.*, **46**, 1755 (1913).

(15) In a private communication, Prof. W. G. Dauben reports that he and J. W. Collette "have shown that the cadmium reagent is normal and that the two products arise by competitive reactions of the acid chloride."

(16) Unless otherwise stated, all microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.; ultraviolet spectra were obtained by means of a Beckman DU instrument; and infrared spectra, by means of a Perkin-Elmer 112-C instrument.

(17) A preparation containing 30% silicone solids in aqueous suspension. In the absence of this agent considerable tar was produced.

(18) L. Gattermann and H. Rüdt, *Ber.*, **27**, 2293 (1894).

(19) P. J. Montagne, *Ber.*, **48**, 1027 (1915).

(20) K. W. Rosenmund, *Ber.*, **42**, 4778 (1909).

(21) I was identified as an active allergen through a series of patch tests made on the various compounds of Scheme I at the University of Oregon infirmary. The procedure is discussed by F. A. Patty, *Industrial Hygiene and Toxicology*, Interscience Publishers, Inc., New York, 1948, pp. 360–365.

(22) M. Erne and F. Ramirez, *Helv. Chim. Acta*, **33**, 912 (1950).

(23) Though this method of destroying unreacted lithium aluminum hydride was reported by Erne and Ramirez and gave no serious consequences in our hands, nonetheless we were unable to modify the manner of addition in such a way as to prevent violent reaction on contact of the acid with the hydride. It is *strongly recommended* that in future work a milder agent (perhaps ethyl acetate) be used to destroy at least a large part of the hydride before any acid is added.

(24) Analysis by R. Mann using the Mohr method.

N-(4-Methoxyphenylethyl)-3-methoxybenzamide (III). To a cooled, stirred mixture of 10 g. (0.25 mole) of sodium hydroxide, 250 ml. of water, and 18.8 g. (0.1 mole) of II was added dropwise (over a period of 1 hr.) 17.1 g. (0.1 mole) of freshly distilled *m*-methoxybenzoyl chloride. The reaction mixture was stirred overnight and filtered with suction. The white curdy precipitate was washed with water, aspirated for several hr., and dried in air, yield 22.7 g. (80%), m.p. 94–95°. For use in cyclization the product was dried further at room temperature *in vacuo* overnight in the presence of phosphorus pentoxide. A small sample, recrystallized four times from 60% ethanol, was obtained as platelets, m.p. 94.5–95°.

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 72.17; H, 6.50; N, 4.61.

1-(3-Methoxyphenyl)-7-methoxy-3,4-dihydroisoquinoline (IV). (*a*) *Cyclization with phosphorus oxychloride in xylene.* A solution of 4.35 g. of preceding amide in 35 ml. of anhydrous reagent xylene (mixed isomers, Matheson Co.) was treated with 12 ml. of freshly distilled phosphorus oxychloride, refluxed for 5 hr., cooled in ice, and cautiously treated over a period of 2 hr. with *ca.* 350 g. of chipped ice. The aqueous phase was separated, washed with benzene (discarded), basified with 20% aqueous sodium hydroxide, and extracted twice with benzene. Evaporation of the combined, dried (magnesium sulfate) benzene extracts by means of an air blast left a pale yellow liquid; best crude yield 1.77 g. (43%), av. crude yield 31%. Two distillations of the combined crude products from several runs gave a yellow liquid, b.p. 172–173° (0.6 mm.).

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.08; H, 6.60; N, 5.70.

Treatment of 1.62 g. of the crude liquid with 10 ml. of methyl iodide[25a] gave 1.45 g. (25% from the amide) of *methiodide*, m.p. 228–235° (dec.). Five recrystallizations from absolute ethanol gave bright yellow needles, m.p. 226–230° (dec.).

Anal. Calcd. for $C_{18}H_{20}INO_2$: C, 52.81; H, 4.93; N, 3.42. Found: C, 53.03; H, 5.16; N, 3.70.

(*b*) *Cyclization by other methods.* Dropwise addition (over a period of 8 hr.) of a solution of 4 g. of amide in 750 ml. of anhydrous xylene to a refluxing solution of 25 ml. of phosphorus oxychloride in 500 ml. of xylene gave 0.83 g. (14%) of methiodide. Refluxing for 3.5 hr. a mixture of amide, reagent grade phosphorus pentoxide, phosphorus oxychloride, and xylene as per the general procedure of Whaley and Hartung[6] gave an 11% yield of methiodide. Attempts to use phosphorus oxychloride in toluene,[26] phosphorus oxychloride plus phosphorus pentachloride in benzene, or phosphorus oxychloride plus polyphosphoric acid[27] gave only minute quantities of liquid product.

2-(3-Methoxybenzoyl)-4-methoxybenzoic acid (V). A mixture of the crude dihydroisoquinoline resulting from cyclization of 28.1 g. of amide III by procedure (a), 570 ml. of 20% aqueous sodium hydroxide, and 41.5 ml. of dimethyl sulfate was stirred and heated on a steam bath for 24 hr. The ethereal extracts of the cooled mixture were combined and washed first with 4% hydrochloric acid and then with water, dried (magnesium sulfate), and evaporated *in vacuo* at room temperature. A solution of the residue [9.2 g., presumably of 2-(3-methoxybenzoyl)-4-methoxystyrene] in 700 ml. of acetone was refluxed for 1.5 hr., during which time 21.0 g. of C.P. potassium permanganate was added in 10 equal portions. Following dissipation of the permanganate color, the acetone was removed by distillation and a slurry of the residue in 360 ml. of water was treated with sulfur dioxide until the brown color of manganese dioxide had disappeared. The yellow-white precipitate remaining was collected by filtration and dissolved (by warming for 15 min.) in 120 ml. of 2% aqueous sodium hydroxide. Acidification with dilute hydrochloric acid of the filtered alkaline solution gave 6.7 g. (24% from the amide) of nearly white solid, m.p. 168–170°. A sample for analysis was obtained as small prisms, m.p. 172–173°, after three recrystallizations (one with Norit) from ethanol.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 67.36; H, 5.08.

3,3'-Dimethoxybenzophenone (VI). (*a*) *From decarboxylation of V.* A mixture of 7.45 g. of the preceding ketoacid, 18.6 g. of fine copper powder (J. T. Baker, precipitated), and 140 ml. of synthetic quinoline was heated in a reflux apparatus (bearing an attachment for measurement of evolved carbon dioxide by displacement of dilute hydrochloric acid) to a temperature where evolution of gas was first noted. The temperature was maintained constant for 30 min. (94% completion as adjudged by gas evolution) and then raised to refluxing for 15 min. The filtrate from the cooled reaction mixture was diluted with 700 ml. of ether, washed first with excess 5% hydrochloric acid and then with excess 2% aqueous sodium hydroxide, dried (magnesium sulfate), and evaporated. Distillation of the residue gave 5.6 g. (89%) of pale yellow liquid, b.p. 145–160° (0.4 mm.). Redistillation gave an analytical sample, b.p. 144–145° (0.3 mm.).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.30; H, 5.87.

The *2,4-dinitrophenylhydrazone*,[25b] recrystallized four times from ethyl acetate, was obtained as bright orange microcrystals, m.p. 191–192°, $\lambda_{max}^{CHCl_3}$ 385–387 mμ (log ε 4.48); reported[9] red-orange crystals, m.p. 191–192°.

Anal. Calcd. for $C_{21}H_{18}N_4O_6$: C, 59.71; H, 4.30; N, 13.27. Found: C, 59.46; H, 4.28; N, 13.61.

(*b*) *From methylation of* IX. A mixture of 3.43 g. of 3,3'-dihydroxybenzophenone (*vide supra*), 1.7 g. of sodium hydroxide, 30 ml. of water, and 8.0 g. of dimethyl sulfate was heated on a steam bath for 1 hr. The ethereal extract of the cooled mixture was washed with 5% aqueous sodium hydroxide, dried (magnesium sulfate), and evaporated. Distillation of the residue therefrom gave 1.94 g. (50%) of yellow liquid, b.p. 157–159° (0.5 mm.); reported[10] b.p. 230–235° (20 mm.).

The *2,4-dinitrophenylhydrazone*[25b] was recrystallized as in part (*a*), m.p. 190.5–191°, mixture melting point with 2,4-dinitrophenylhydrazone (m. p. 191–191.5°) from part (*a*) was 190.8–191.5°.

3,3'-Dimethoxybenzophenone oxime (X). Using the pyridine method of Shriner, Fuson, and Curtin[25c] 1 g. of 3,3'-dimethoxybenzophenone (from methylation) was converted to the oxime, recrystallized as tablets from 50% methanol, yield 0.59 g. (56%), m.p. 82–83°, reported[10] m.p. 86–87°.

Anal. Calcd. for $C_{15}H_{15}NO_3$: N, 5.44. Found: N, 5.15.

3-Methoxy-N-(3-methoxyphenyl)benzamide (XI). (*a*) *By Schotten-Baumann reaction.* A mixture of 4.6 g. (0.027 mole) of *m*-methoxybenzoyl chloride, 3.1 g. (0.025 mole) of *m*-anisidine, and 20 ml. of 10% aqueous sodium hydroxide (0.05 mole) were shaken vigorously in a stoppered flask for 10 min., diluted, and filtered. The collected solid was washed well with water and recrystallized from methanol to give 4.75 g. (75%) of needles, m.p. 91.5–93.5°. Recrystallization of a small sample from the same solvent gave a m.p. 92.5–93.5°.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.20; H, 6.23; N, 5.61.

(*b*) *By Beckmann rearrangement.* A mixture of 0.5 g. of oxime X and 15 g. of polyphosphoric acid was stirred and heated on a steam bath for 10 min. and then poured into 75 ml. of water. The ethereal extract thereof was washed with water and evaporated. The residue was recrystallized from 70% methanol, yield 0.3 g. (60%) of needles, m.p. 91.5–

(25) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, (a) p. 228, (b) p. 219, (c) p. 254.

(26) Method of R. D. Haworth, W. H. Perkin, and J. Rankin, *J. Chem. Soc.*, 125, 1686 (1924).

(27) Method of H. R. Snyder and F. X. Werber, *J. Am. Chem. Soc.*, 72, 2962 (1950).

92.5°, mixture melting point with crude compound from (*a*) 91.5–93°.

The infrared spectra (Nujol mulls) of compounds from parts (*a*) and (*b*) were identical.

3,4'-Dimethoxybenzophenone (XII). A mixture of 3.8 g. (0.025 mole) of *m*-methoxybenzoic acid, 2.7 g. (0.025 mole) of anisole, and 25 g. of polyphosphoric acid was stirred and heated at 65° for 2 hr. and then poured into 100 ml. of water. The ethereal extract thereof was washed with water, dried (magnesium sulfate), and evaporated. Distillation of the residue yielded 3.6 g. (60%) of pale yellow liquid, b.p. 158–164° (0.5 mm.), which partially solidified on standing.

The *2,4-dinitrophenylhydrazone*[25b] was obtained as bright orange microcrystals from ethyl acetate, m.p. 205.5–207° (dec.), $\lambda_{max}^{CHCl_3}$ 396 mμ (log ε 4.47).[28] The m.p. was raised to 214–215° (dec.) on repeated recrystallization from the same solvent.[29]

m-Iodoanisole. To the cold solution prepared by diazotization of 10.5 g. (0.085 mole) of *m*-anisidine in 6–8% sulfuric acid[30] was added dropwise (over 30 min.) a warm (40°) solution of 17.5 g. (0.105 mole) of potassium iodide in the same solvent. A small amount of sodium bisulfite was added and the mixture was steam distilled. The product was collected as a slightly pink liquid, b.p. 76–78° (0.5 mm.), yield 9.1 g. (46%).

Dimethoxybenzophenones via the organocadmium process. (*a*) *From m-iodoanisole.* Following the general procedure of Dauben and Tilles[31] the cold (ice bath) Grignard reagent from 17.3 g. (0.074 mole) of *m*-iodoanisole, 1.8 g. (0.075 g.-atom) of magnesium, 38 ml. of anhydrous ether, and 13 ml. of anhydrous benzene was treated with 7.33 g. (0.04 mole) of anhydrous cadmium chloride and then refluxed for 2.3 hr. until a negative Gilman test[32] was obtained. The ether was replaced by benzene, a solution of 10.2 g. (0.06 mole) of freshly distilled *m*-methoxybenzoyl chloride in 15 ml. of benzene was added, and the mixture was refluxed overnight and processed essentially according to published directions;[33] yield 2.4 g. (17%) of yellow liquid, b.p. 140–170° (0.3 mm.).

From treatment of the preceding distillate with 2,4-dinitrophenylhydrazine reagent[25b] and four recrystallizations of the resultant precipitate from ethyl acetate there were obtained bright red-orange microcrystals of *3,4'-dimethoxybenzophenone 2,4-dinitrophenylhydrazone*, (A) m.p. 211–212° (dec.); $\lambda_{max}^{CHCl_3}$ 396 mμ (log ε 4.45).

Anal. Calcd. for $C_{21}H_{18}N_4O_6$: C, 59.71; H, 4.30; N, 13.27. Found: C, 59.81; H, 4.34; N, 13.29.

A mixture m.p. of A with a sample of the DNP of XII (m.p. 210–211.6°[c]) was 210–211.8°.

(*b*) *From m-bromoanisole.* In fashion similar to that of part (*a*) the Grignard reagent from 1.65 g. (0.069 g.-atom) of magnesium, 10.7 g. (0.057 mole) of *m*-bromoanisole,[34] 35 ml. of anhydrous benzene, and 35 ml. of anhydrous ether was treated at room temperature with 7.5 g. (0.041 mole) of anhydrous cadmium chloride and allowed to stand overnight, whereupon a Gilman test on the mixture was negative. After replacement of the ether by benzene and addition of 9.9 g. (0.058 mole) of *m*-methoxybenzoyl chloride, the mixture was stirred and refluxed for 2 hr. and then poured into 200 ml. of 10% aqueous ammonium chloride. The combined organic layer and benzene extracts of the aqueous phase were washed first with 10% aqueous sodium bicarbonate and then with water, dried (magnesium sulfate), and evaporated. Fractional distillation of the residue gave 6.0 g. of unreacted acid chloride and 2.7 g. (20%) of yellow liquid, b.p. 162–172° (1.2 mm.).

Anal. Calcd. for $C_{15}H_{14}O_3$: CH_3O, 25.6. Found:[35] CH_3O, 25.4.

Repetition of the procedure except with use of twice the amount of cadmium chloride gave a yield of 24%.

The infrared spectrum of the preceding distillate appeared to be a composite of those of VI and XII. Comparison of the first of these with spectra of synthetic mixtures of VI and XII containing 50%, 65%, and 75% (respectively) of XII showed virtual identity thereof only with the spectrum from 65% XII–35% VI.

From treatment of the distillate with 2,4-dinitrophenylhydrazine reagent[25b] and three recrystallizations of the resultant precipitate from ethyl acetate there were obtained brown-orange microcrystals of *3,4'-dimethoxybenzophenone 2,4-dinitrophenylhydrazone*, m.p. 205–207° (dec.),[29] identical with XII·2,4-dinitrophenylhydrazone (m.p. 205.5–207°) as based on mixture melting point, ultraviolet spectrum, and infrared spectrum.

EUGENE, ORE.

(28) Spectrum obtained by means of a Beckmann DK-2 instrument.

(29) The maximum value of the melting point for samples dried by an infrared lamp was 207°; while that for samples simply dried in air was 212° or 215°.

(30) *Cf.* diazotization procedure for *o*-anisidine by J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y., 1950, pp. 182–183.

(31) W. G. Dauben and H. Tilles, *J. Org. Chem.*, **15**, 785 (1950).

(32) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

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

(34) S. Natelson and S. P. Gottfried, *J. Am. Chem. Soc.*, 61, 1001 (1939).

(35) Analysis by Judith H. Lind.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Ortho Substitution Rearrangement and Certain Related Reactions in the Naphthalene Series Catalyzed by Sodium Amide[1]

CHARLES R. HAUSER, DONALD N. VAN EENAM, AND PHILLIP L. BAYLESS

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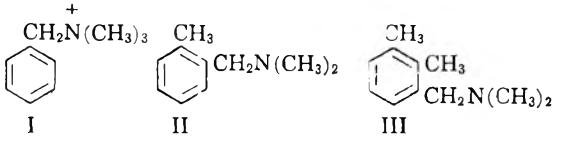
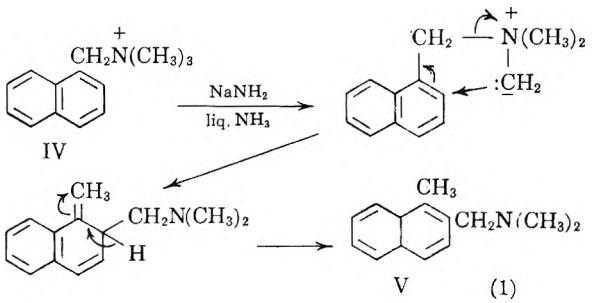
The 1- and 2-naphthylmethyltrimethylammonium ions underwent with sodium amide in liquid ammonia the ortho substitution rearrangement to form 1-methyl-2-dimethylaminomethyl- and 2-methyl-1-dimethylaminomethylnaphthalenes, respectively. The methiodide of the former tertiary amine failed to undergo with this reagent further rearrangement which would have involved the 3-position. The methiodide of 2-methyl-1-dimethylaminomethylnaphthalene underwent partly the first phase of the ortho substitution rearrangement to form an *exo*-methylenamine, and partly a Stevens type of 1,2-shift to give a β-arylethylamine. Mechanisms are considered.

The benzyltrimethylammonium ion (I) has previously[2] been rearranged by sodium amide in liquid ammonia to form tertiary amine II (96%), and the methiodide of this amine, further rearranged to give tertiary amine III (67%). Still further rearrangements around the aromatic ring have also been effected.[2]



I II III

In the present investigation a study was made of this ortho substitution type of rearrangement in the naphthalene series. The 1-naphthylmethyltrimethylammonium ion (IV) underwent the rearrangement to form tertiary amine V in good yield. The mechanism for this reaction, which involves the β-position of the naphthalene nucleus, may be represented by equation 1.



IV V (1)

Whereas the rearrangement of quaternary ion I was complete within a few minutes, that of IV proceeded much more slowly possibly because of the low solubility of the latter quaternary ammonium salt in the liquid ammonia. In Table I are summarized the yields of tertiary amine V obtained from IV on varying the time and equivalents of sodium amide. The maximum yield (75%) of V was realized after five hours employing two equivalents of sodium amide.

TABLE I

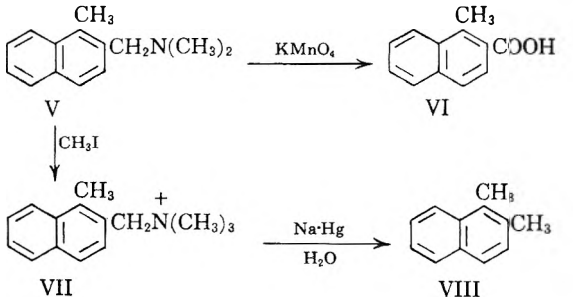
INFLUENCE OF TIME AND OF EQUIVALENTS OF SODIUM AMIDE ON YIELD OF AMINE V FROM QUATERNARY ION IV

$NaNH_2$, Equivalents[a]	Time, Hr.	Amine V, Yield, %	Recov. IV, %
2	1	29	61
2	3	68	27
2	5	75	17
2	8	71	6
1	3	53	31
1.3	3	62	27

[a] One equivalent of quaternary ion IV was 0.15 mole.

The structure of the rearranged amine was established as V by a permanganate oxidation to form 1-methyl-2-naphthoic acid (VI), and by an Emde reduction of the methiodide (VII) to give 1,2-dimethylnaphthalene (VIII) (Scheme A).

Scheme A



V VI VII VIII

Whereas the methiodide of amine II in the benzene series was further rearranged to amine III, the methiodide of amine V (formula VII) apparently failed to undergo with sodium amide in liquid ammonia further rearrangement around the naphthalene ring. Instead of another distillable tertiary amine, only tarry material was obtained. This is not surprising in view of the well known

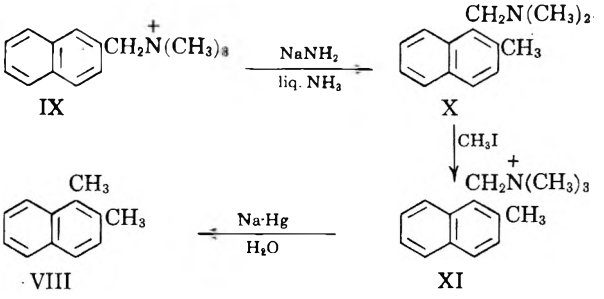
(1) Supported by the Office of Ordnance Research, U. S. Army and by Eli Lilly and Co.

(2) S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

deficiency in double bond character at the 2,3-position of the naphthalene nucleus.[3]

The 2-naphthylmethyltrimethylammonium ion (IX) underwent the *ortho* substitution rearrangement to form tertiary amine X in 84% yield. This rearrangement into the α-position of the naphthalene nucleus was anticipitated. The structure of the product was established by an Emde reduction of the methiodide (XI) to give 1,2-dimethylnaphthalene (VIII) (Scheme B).

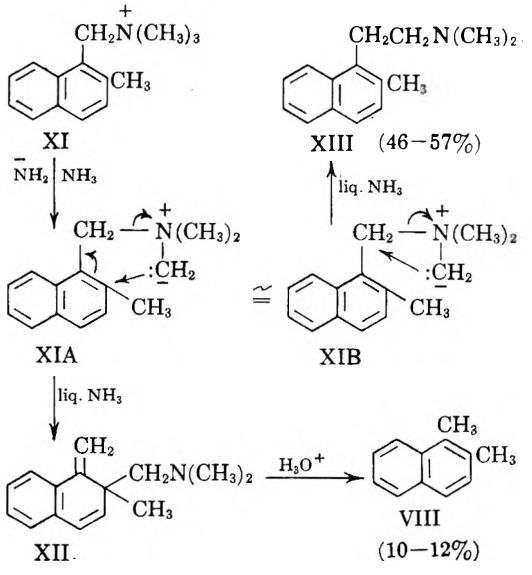
Scheme B



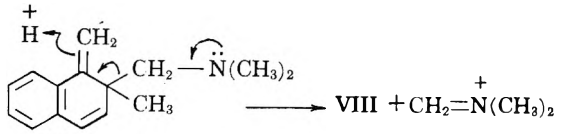
IX X VIII XI

The methiodide of rearranged tertiary amine X (formula XI) underwent two courses of reaction with sodium amide in liquid ammonia, both courses involving the same intermediate carbanion XIA-B (Scheme C).

Scheme C

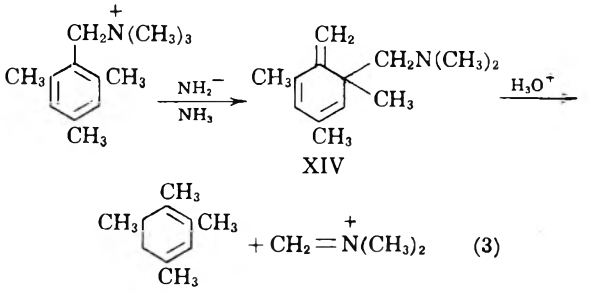


It can be seen from Scheme C that the intermediate carbanion rearranged partly to *exo*-methylenamine XII but mainly to β-arylethylamine XIII. The former product arose from a first-phase *ortho* substitution rearrangement (indicated in XIA) and the latter, from a Stevens type of 1,2-shift (indicated in XIB). The *exo*-methylenamine (XII) was identified by decomposition with hydrochloric acid to form 1,2-dimethylnaphthalene (VIII), the dimethylmethyleniminium ion being eliminated (Equation 2).



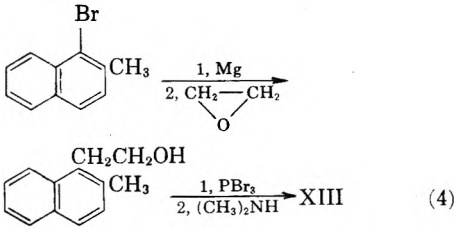
XII (2)

The formation of a similar *exo*-methylenamine (XIV) and its acid-induced decomposition has recently[4] been realized in high yields starting with the 2,4,6-trimethylbenzyltrimethylammonium ion (Equation 3).



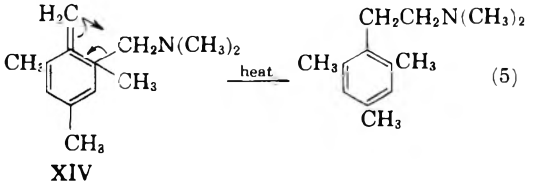
(3)

The β-arylethylamine (XIII), which was the main product from the rearrangement of quaternary ion XI (Scheme C), was identified by an independent synthesis from 2-methyl-1-bromonaphthalene (Equation 4).



(4)

It might appear that β-arylethylamine XIII arose from the thermal isomerization of *exo*-methylenamine XII during distillation, since such a thermal isomerization has been observed to occur readily with *exo*-methylenamine XIV (Equation 5).



XIV (5)

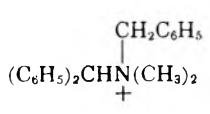
However, whereas *exo*-methylenamine XIV underwent some thermal isomerization on distillation under reduced pressure even at 50°, *exo*-methylenamine XII appeared to undergo relatively little isomerization on distillation at 80–87° or at 137–145°. Moreover, the yield of β-arylethylamine XIII was not decreased when the ether solution of

(3) See for example, R. C. Fuson, *Advanced Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 600-603.

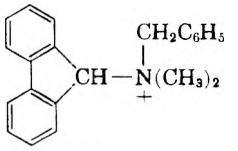
(4) C. R. Hauser and D. N. Van Eenam, *J. Am. Chem. Soc.*, 79, 5512 (1957).

the reaction products from the rearrangement of quaternary ion XI was shaken with hydrochloric acid, and the products then distilled. In fact the best yield (57%) of XIII was obtained under these conditions, the yield of 1,2-dimethylnaphthalene (VIII) being only 12%. This treatment with acid undoubtedly converted all of *exo*-methylenamine XII to the latter product.

It should be pointed out that the Stevens type of 1,2-shift indicated in XIB predominates apparently because the first phase of the ortho substitution rearrangement is somewhat hindered. In fact 1,2-shifts have been observed[5] with sodium amide in liquid ammonia only with relatively complex quaternary ammonium ions such as XV and XVI; in these quaternary ions the benzhydryl and fluorenyl hydrogens are mainly ionized and the benzyl group is rearranged.



XV



XVI

The 1,2-shift indicated in XIB appears to be the first example brought about by sodium amide in liquid ammonia in which the carbanion of a methyl group is involved. This carbanion is presumably present in equilibrium with a predominant carbanion, that resulting from the ionization of a methylene hydrogen of quaternary ion XI. The latter type of carbanion has been observed to undergo the Stevens 1,2-shift of a methyl group only at relatively high temperatures.[5]

EXPERIMENTAL[6]

1-Naphthylmethyltrimethylammonium chloride (IV). To a solution of 216.0 g. (1.22 mole) of 1-chloromethylnaphthalene, b.p. 128–140° at 5 mm. (reported b.p. 128–133° at 5 mm.),[7] in 500 ml. of absolute ethanol there was added with swirling 100 g. (1.69 moles) of liquid anhydrous trimethylamine during 30 min. The flask was immersed in an ice bath occasionally to minimize loss of trimethylamine. After standing at room temperature for 5 hr., 1 liter of anhydrous ether was slowly added to precipitate the quaternary ammonium chloride (IV), which was collected on a funnel, washed with ether, and dried *in vacuo* in a desiccator. The somewhat hygroscopic salt melted at 226–227°; yield 93%. Its picrate, after three recrystallizations from water, melted at 161–162°.

Anal. Calcd. for $C_{20}H_{20}N_4O_7$: C, 56.07; H, 4.71; N, 13.08. Found: C, 56.09; H, 4.71; N, 12.99.

Rearrangement of IV to 1-methyl-2-dimethylaminomethylnaphthalene (V). This reaction was carried out in a 1-l. three-necked flask equipped with a Dry Ice reflux condenser and sealed stirrer, the quaternary salt (IV) being kept dry by adding it from a 250-ml. Erlenmeyer flask connected to the third neck of the flask through Gooch tubing. The yields of rearranged tertiary amine V and of recovered quaternary salt IV on varying the time and equivalents of sodium amide are summarized in Table I. A typical experiment is described below.

To a rapidly stirred suspension of 0.30 mole of sodium amide in 500 ml. of liquid ammonia there was added during approximately 5 min. 35.4 g. (0.15 mole) of finely powdered quaternary salt IV. The resulting bright red reaction mixture, which gradually became deep blue during 3.5 hr., was stirred for 5 hr. and then decomposed by the addition of excess solid ammonium chloride. The liquid ammonia was evaporated on the steam bath as 600 ml. of dry ether was added. The resulting ether suspension was filtered, and the solvent removed from the filtrate. The residual oil was distilled *in vacuo* to give 22.3 g. (75%) of 1-methyl-2-dimethylaminomethylnaphthalene (V), b.p. 157–159° at 10 mm., n_D^{25} 1.5928 (leaving 1.7 g. of residue).

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.35; H, 8.54; N, 7.08.

The picrate, after three recrystallizations from 95% ethanol, melted at 190–190.5°.

Anal. Calcd. for $C_{20}H_{20}N_4O_7$: C, 56.07; H, 4.71; N, 13.08. Found: C, 56.17; H, 4.98; N, 13.38.

The solid obtained by filtration of the ether suspension described above was extracted twice with minimum amounts of hot acetonitrile, and the extracts were combined. Dry ether was added, and the resulting precipitate was collected on a funnel, and dried *in vacuo*. There was recovered 6.0 g. (17%) of crude quaternary salt IV, m.p. 212–214°.

Oxidation of amine V to form 1-methyl-2-naphthoic acid (VI). This reaction was carried out essentially as described previously[2] for the oxidations of polyalkylbenzyldimethylamines.

To 0.5 g. of amine V suspended in 15 ml. of water and 1.0 ml. of 15% sodium hydroxide there was added in small portions during 3 hr. 1.0 g. of finely powdered potassium permanganate. After stirring 2 hr. longer at room temperature, the reaction mixture was filtered. The clear filtrate was acidified to give 0.2 g. of 1-methyl-2-naphthoic acid (VI), m.p. 176–177.5°. One recrystallization from benzene raised the melting point to 178–178.5° (reported m.p. 178°).[8]

Methiodide of tertiary amine V (VII). To a solution of 12.4 g. (0.062 mole) of tertiary amine V in 50 ml. of absolute ethanol there was added with swirling 14.2 g. (0.10 mole) of methyl iodide, the flask being cooled occasionally by immersion in an ice bath. After standing at room temperature for 1 hr. (some crystalline product separated), 200 ml. of ether was added to precipitate the quaternary ammonium salt, which was collected on a funnel washed with ether, and dried *in vacuo*. There was obtained 20.2 g. (95%) of 1-methyl-2-naphthyl methyltrimethylammonium iodide (VII), m.p. 237–238°, dec., with darkening at 200°.

Anal. Calcd. for $C_{15}H_{20}NI$: C, 52.81; H, 5.92; N, 4.11. Found: C, 52.68; H, 5.99; N, 4.41.

Reduction of methiodide VII to form 1,2-dimethylnaphthalene (VIII). The general procedure of Emde[9] for the reduction of benzyl-type quaternary ammonium salts to hydrocarbons was followed.

To a stirred solution of 17.1 g. (0.05 mole) of 1-methyl-2-naphthylmethyltrimethylammonium iodide (VII) in 400 ml. of water heated on the steam bath, was added gradually (10 minutes) 200 g. of 5% sodium amalgam, and the stirring continued until all the sodium had reacted (*ca.* 12 hr.). After cooling, the oily reaction mixture was extracted with ether, dried, and the product distilled *in vacuo* to afford 7.5 g. (96%) of 1,2-dimethylnaphthalene (VIII), b.p. 138–

(5) C. R. Hauser, R. M. Manyik, W. R. Brasen, and P. L. Bayless, *J. Org. Chem.*, **20**, 1119 (1955).

(6) Melting and boiling points are uncorrected. Microanalyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(7) O. Grummitt and A. Buck, *Org. Syntheses*, **24**, 30 (1944).

(8) F. Mayer and O. Schnecko, *Ber.*, **56**, 1408 (1923).

(9) H. Emde, *Ber.*, **42**, 2590 (1909).

138.5° at 15 mm., n_D^{25} 1.6127 (reported b.p. 135–136° at 14 mm., n_D^{20} 1.6135).[10]

The picrate of this hydrocarbon, after crystallization from 95% ethanol, melted at 130.5–131° (reported m.p. 131°).[11]

2-Naphthylmethyltrimethylammonium chloride (IX). This salt was prepared in three steps in 71% over all yield from 2-naphthoic acid.

This acid (0.58 mole) was reduced with 0.725 mole of lithium aluminum hydride in 2 l. of ether employing the Soxhlet extractor as described by Nystrom and Brown.[12] After 6 hr., the reaction mixture was decomposed with water, followed by 20% sulfuric acid. One recrystallization of the product from ligroin (b.p. 60–90°) gave a 99% yield of 2-hydroxymethylnaphthalene, m.p. 80.5–81° (reported m.p. 80°).[13]

This carbinol (0.57 mole) was treated with 0.76 mole of thionyl chloride in 400 ml. of dry toluene (refluxed 3 hr.) to give a 73% yield of 2-chloromethylnaphthalene, b.p. 125–132° at 2 mm., m.p. 47–48° (reported b.p. 170° at 20 mm., m.p. 47°).[13]

A solution of 73.1 g. (0.41 mole) of this chloride in 750 ml. of absolute ethanol was treated with 75 g. (1.25 mole) of trimethylamine during 20 min., and the product precipitated with 1 l. of ether after several hours at room temperature, as described in the preparation of isomeric quaternary ammonium salt IV. There was obtained 94.3 g. (98%) of 2-naphthylmethyltrimethylammonium chloride (IX), m.p. 205–206°. The picrate of this somewhat hygroscopic salt, after three recrystallizations from water, melted at 160–161°.

Anal. Calcd. for $C_{20}H_{20}N_4O_7$: C, 56.07; H, 4.71; N, 13.08. Found: C, 56.03; H, 4.89; N, 13.10.

Rearrangement of IX to 2-methyl-1-dimethylaminomethylnaphthalene (X). This reaction was carried out with 94.3 g. (0.40 mole) of 2-naphthylmethyltrimethylammonium chloride (IX) and 0.80 mole of sodium amide in 1200 ml. of liquid ammonia (addition period, 20 min.) as described above for the rearrangement of IV. The resulting deep red reaction mixture, which gradually became blue-green, was decomposed with ammonium chloride after 2 hr. There was obtained 66.5 g. (84%) of 2-methyl-1-dimethylaminomethylnaphthalene (X), b.p. 152–153° at 10 mm., n_D^{25} 1.5927 (leaving 4.0 g. of residue).

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.59; H, 8.79; N, 6.92.

The *picrate*, recrystallized three times from 95% ethanol, melted at 204–205°.

Anal. Calcd. for $C_{20}H_{20}N_4O_7$: C, 56.07; H, 4.71; N, 13.08. Found: C, 56.23; H, 4.71; N, 13.09.

Also, there was recovered by means of acetonitrile extraction (see above) 7.8 g. (8%) of crude IX, m.p. 193–197°.

Methiodide of tertiary amine X (XI). This salt (m.p. 184–185°, dec., with darkening at about 150°) was obtained in 98% yield from 66.5 g. (0.334 mole) of 2-methyl-1-dimethylaminomethylnaphthalene (X) and 95 g. (0.67 mole) of methyl iodide in 200 ml. of absolute ethanol as described for VII. The melting point of the white, crystalline product was not raised by recrystallization from absolute ethanol-ether.

Anal. Calcd. for $C_{15}H_{20}NI$: C, 52.81; H, 5.92; N, 4.11. Found: C, 52.62; H, 6.16; N, 4.06.

Reduction of methiodide XI to form 1,2-dimethylnaphthalene (VIII). This reaction was carried out with 20.5 g. (0.06 mole) of methiodide XI and 250 g. of 5% sodium amalgam in 450 ml. of water as described for the reduction of methiodide VII. There was obtained 8.9 g. (95%) of 1,2-dimethylnaphthalene (VIII), b.p. 139–140° at 15 mm., n_D^{25} 1.6127. The picrate melted at 129.5–130.5°. This melting point was not depressed on admixture with the picrate of 1,2-dimethylnaphthalene obtained as described above.

Two courses of reaction of methiodide XI with sodium amide. Finely powdered quaternary ammonium salt XI (51.2 g., 0.15 mole) was rapidly added to a suspension of 0.30 mole of sodium amide in 700 ml. of liquid ammonia as described for the rearrangement of IV. The reaction mixture, which at first was grey-violet but soon changed to bright green, was decomposed after one hour with ammonium chloride and the ammonia replaced by absolute ether. The mixture was filtered, and the solvent removed from the filtrate. The residual oil was distilled through a 7-cm. Vigreux column to give 20.2 g. of distillate, b.p. 80–104° at 0.4 mm., leaving 8.7 g. of tarry residue. Fractionation of this distillate through a 40-cm. Podbielniak type column gave (*1*) 3.1 g., b.p. 137–145° at 10 mm., 80–87° at 0.4 mm., and (*2*) 14.8 g., b.p. 168–169° at 10 mm., n_D^{25} 1.5808. Fraction (2) was identified as 2-methyl-1-(β-dimethylaminoethyl)naphthalene (XIII); yield 46%.

Anal. Calcd. for $C_{15}H_{19}N$: C, 84.45; H, 8.98; N, 6.57. Found: C, 84.43; H, 9.16; N, 6.37.

The *picrate*, recrystallized three times from 95% ethanol, melted at 174.5–175.5°.

Anal. Calcd. for $C_{21}H_{22}N_4O_7$: C, 57.01; H, 5.01; N, 12.66. Found: C, 57.27; H, 5.17; N, 12.77.

Fraction (*1*) appeared to consist mostly of *exo*-methyleneamine XII (10%), since it gave with excess 12*N* hydrochloric acid during 12 hr. 2.0 g. (10%) of 1,2-dimethylnaphthalene (VIII), identified by its picrate, m.p. and mixed m.p. 129–130°. The acidified aqueous solution from the decomposition of XII evidently contained the dimethylmethyleniminium ion, since formaldehyde and dimethylamine were detected after hydrolysis with 50% sodium hydroxide.

The experiment was repeated with 34.1 g. (0.10 mole) of 2-methyl-1-naphthylmethyltrimethylammonium iodide (XI) and 0.20 mole of sodium amide in 500 ml. of liquid ammonia. After the ammonia had been replaced by ether and the precipitated salts removed by filtration, the ethereal solution of products was shaken with 200 ml. of 12*N* hydrochloric acid for 1 hr. Water was added and the two layers separated. The ethereal layer was washed with water and dried over magnesium sulfate, and the solvent was removed. The residue was distilled giving 1.8 g. (12%) of 1,2-dimethylnaphthalene (VIII), b.p. 127–129° at 10 mm., n_D^{25} 1.6129, leaving 1.1 g. of residue. This aromatic hydrocarbon was identified through its picrate, m.p. and mixed m.p. 129–130°.

The aqueous acid layer (and washings) was cooled and made alkaline with cold 50% sodium hydroxide solution (odor of formaldehyde detected). The resulting oil was taken up in ether, and the ethereal solution was washed with water and dried over magnesium sulfate. The solvent was evaporated and the residual oil distilled to give 12.1 g. (57%) of 2-methyl-1-(β-dimethylaminoethyl)naphthalene (XIII), b.p. 167–168.5° at 10 mm., n_D^{25} 1.5807, leaving 4.2 g. of dark residue. The picrate melted at 174–175°.

Independent synthesis of β-arylethylamine XIII. This amine was synthesized in three steps from 2-methyl-1-bromonaphthalene.

This halide[14] (33.2 g., 0.15 mole) was converted to its Grignard reagent with 3.8 g. (0.156 g.-atom) of magnesium turnings in 50 ml. each of dry ether and benzene (refluxed 1.5 hr.), and this reagent treated at −10° with 13.2 g. (0.30 mole) of ethylene oxide in 40 ml. of dry ether, following the directions of Wilds[15] for the preparation of β-1-naphthylethanol. After standing for 2 hr. at room tempera-

(10) O. Kruber and W. Schade, *Ber.*, **68**, 11 (1935).

(11) R. P. Linstead, A. F. Millidge, S. L. S. Thomas and A. L. Walpole, *J. Chem. Soc.*, 1146 (1937).

(12) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 2549 (1947).

(13) N. Campbell, W. Anderson, and J. Gilmore, *J. Chem. Soc.*, 819 (1940).

(14) See R. Adams and L. O. Binder, *J. Am. Chem. Soc.*, **63**, 2773 (1941).

(15) A. L. Wilds, *J. Am. Chem. Soc.*, **64**, 1421 (1942).

ture, the reaction mixture was decomposed with water and 6*N* hydrochloric acid. There was obtained 14.0 g. (50%) of 2-methyl-1-(β-hydroxyethyl)naphthalene, b.p. 122–124° at 0.3 mm., n_D^{25} 1.5967, as a pale yellow, viscous liquid.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.90; H, 7.59.

The *picrate*, after two recrystallizations from 95% ethanol, melted at 126.5–127.5°.

Anal. Calcd. for $C_{19}H_{17}N_3O_8$: C, 54.94; H, 4.13; N, 10.12. Found: C, 55.14; H, 4.14; N, 9.98.

To a solution of 13.0 g. (0.07 mole) of this alcohol in 30 ml. of dry chloroform was added dropwise a solution of 13.5 g. (0.05 mole) of phosphorus tribromide in 10 ml. of dry chloroform.[16] After refluxing 1.5 hr., the solvent was removed, and 100 g. of ice added. The resulting product was taken up in ether, and the ethereal solution washed three times with saturated sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed, and the residue distilled to give 7.8 g. (45%) of 2-methyl-1-(β-bromoethyl)naphthalene, b.p. 119–121° at 0.5 mm., n_D^{25} 1.6014.

Anal. Calcd. for $C_{13}H_{13}Br$: C, 62.66; H, 5.26. Found: C, 62.89; H, 5.34.

This bromide (7.0 g., 0.028 mole) and 20 ml. of absolute methanol were placed in a 125-ml., amber-colored, screw-cap bottle, and 13.5 g. (0.30 mole) of liquid anhydrous dimethylamine added with stirring. The bottle was closed, and allowed to stand in the dark at room temperature for one week. The solvents were evaporated, and the residue made strongly alkaline with 50% sodium hydroxide. The product was taken up in ether, and the ethereal solution washed with water and dried. The solvent was removed, and the residue distilled to give 4.25 g. (72%) of 2-methyl-1-(β-dimethylaminoethyl)naphthalene (XIII), b.p. 165–168° at 10 mm., n_D^{25} 1.5806. After two recrystallizations from 95% ethanol, the picrate of this amine melted at 174–175°. This melting point was not depressed on admixture with the picrate of the tertiary aromatic amine obtained from the rearrangement of XI.

DURHAM, N. C.

(16) See P. Cagniant, C. Mentzer, and N. P. Buu-Hoï, *Bull. soc. chim. France*, [5], **10**, 145 (1943)

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

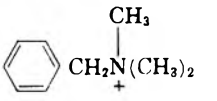
Rearrangement of the Methiodide of *N,N*-Dimethylaminomethylferrocene by Potassium Amide in Liquid Ammonia[1]

CHARLES R. HAUSER, JACQUE K. LINDSAY, AND DANIEL LEDNICER

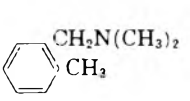
Received August 27, 1957

The methiodide of *N,N*-dimethylaminomethylferrocene was found to undergo with potassium amide in liquid ammonia a rather novel type of Stevens 1,2-shift involving the migration of the ferrocylmethylene group to form the β-ferrocylethylamine. The structure of the product was established by the conversion of its methiodide to vinylferrocene by further treatment with potassium amide and by two independent syntheses. Mechanisms are considered.

The benzyltrimethylammonium ion (I) has previously been shown to undergo with sodium amide or potassium amide in liquid ammonia the ortho substitution rearrangement to form tertiary amine II in 96% yield.[2]

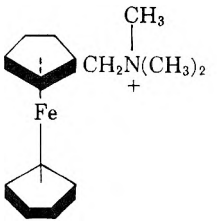


I

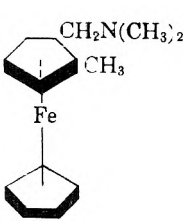


II

Since the ferrocene nucleus has been observed to possess certain aromatic properties,[3] the corresponding quaternary ammonium ion (III) in the ferrocene series might be expected to exhibit this type of rearrangement to form tertiary amine IV.

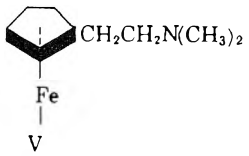


III



IV

However, it was found in the present investigation that quaternary ion III is rearranged by potassium amide in liquid ammonia to form the β-ferrocylethylamine (V) in yields of 40 to 50%.[4] This rearrangement was realized in lower yield with sodium amide.



V

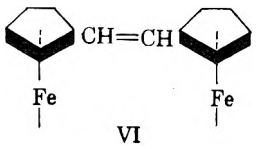
Also there was obtained a neutral by-product (10–20%) which is tentatively assigned structure VI. Such dimeric olefins have been produced as by-products in certain rearrangements of quaternary ammonium ions.[2]

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

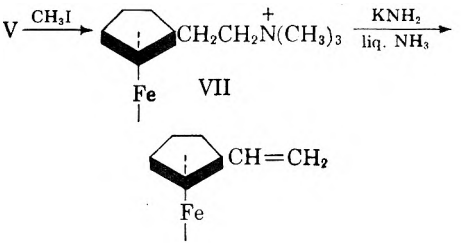
(3) See P. L. Pauson, *Chem. Revs.*, **9**, 391 (1955).

(4) This rearrangement in which structure IV was assumed for the product was reported in a communication by C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **21**, 382 (1956). Preliminary evidence for structure V was reported in a later communication by C. R. Hauser, J. K. Lindsay, D. Lednicer, and C. E. Cain, *J. Org. Chem.*, **22**, 717 (1957).



VI

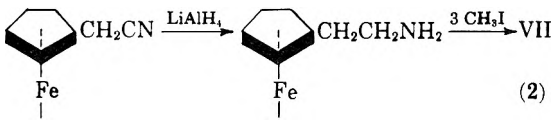
The structure of the rearranged tertiary amine was established as V by the further treatment of its methiodide (VII) with potassium amide, in which vinylferrocene was produced in good yield (Equation 1).



(1)

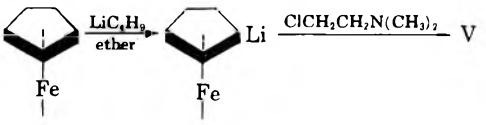
Incidentally this β-elimination of trimethylamine from methiodide VII to form vinylferrocene was observed in low yields with aqueous sodium hydroxide, sodium in ethanol, and sodium amalgam in water. These two last experiments were carried out in attempts to effect reduction to a nonnitrogenous compound.

The structure of the rearranged amine from quaternary ion III was confirmed as V by two independent syntheses. The first synthesis involved the reduction of ferrocylacetonitrile and the exhaustive methylation of the resulting primary amine as described elsewhere[5] (Equation 2). The over-all yield in this sequence was 43%.



(2)

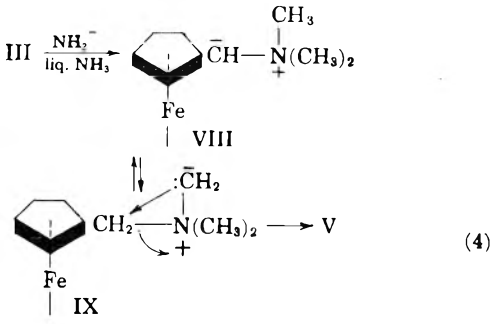
The second independent synthesis involved the metalation of ferrocene with butyllithium and the alkylation of the resulting lithio derivative with β-dimethylaminoethyl chloride (Equation 3).



(3)

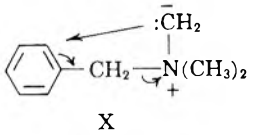
Although the yield was low (about 3%), tertiary amine V was the only isolable basic product. This is in line with the observation of earlier workers[6] who reported less than a 10% yield of a mixture of mono- and dibasic carboxylic acids on carbonation of the metalated intermediate.

The mechanism of formation of the β-ferrocylethylamine V from quaternary ion III is considered to involve the Stevens type of 1,2-shift of the methyleneferrocene group within carbanion IX, which presumably is in equilibrium with the predominant carbanion VIII (Equation 4).



(4)

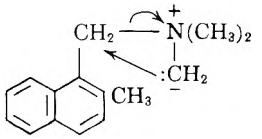
This rearrangement of carbanion IX is rather novel since corresponding methyl carbanions in the benzene series undergo the ortho- substitution rearrangement,[2,7] in which the benzene nucleus functions as an electron acceptor (aromatic nucleophilic substitution). For example, methyl carbanion X, which is structurally analogous to IX, rearranges exclusively to the *ortho*- substituted tertiary amine (II).[2]



X

This difference in the course of reaction of carbanions IX and X indicates that the ferrocene nucleus has less tendency to function as an electron acceptor than the benzene nucleus and/or that the methyleneferrocene group undergoes the 1,2-shift more easily than the benzyl group.

Only one other example of the Stevens 1,2-shift within a methyl carbanion to form a β-arylethyldimethylamine appears to have been observed. This involved carbanion XI in which there is an *o*-methyl substituent.[8]



XI

In connection with the present work it was shown that the product obtained from the rearrangement of quaternary ion III was not tertiary amine XII which might have arisen from the Stevens 1,2-shift of a methyl group within carbanion VIII. This tertiary amine was synthesized

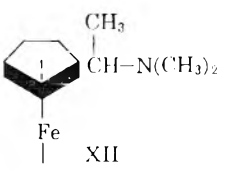
(5) D. Lednicer, J. K. Lindsay, and C. R. Hauser, *J. Org. Chem.*, in press.

(6) R. A. Benkeser, D. Goggin, and G. Schroll, *J. Am. Chem. Soc.*, **76**, 4025 (1954).

(7) C. R. Hauser and A. J. Weinheimer, *J. Am. Chem. Soc.*, **76**, 1264 (1954).

(8) C. R. Hauser, D. N. Van Eenam, and P. L. Bayless, *J. Org. Chem.*, **23**, 354 (1958).

recently in another investigation.[9] Apparently the 1,2-shift of a methyl group, which is the more common Stevens rearrangement at higher temperatures, has not been observed in liquid ammonia.[10]



XII

EXPERIMENTAL[11]

Rearrangement of the methiodide III. The quaternary salt III,[12] (38.5 g., 0.1 mole) was added to a well stirred solution of 0.2 mole of potassium amide in 500 ml. of liquid ammonia over the period of 1 hr. Each addition was followed by a transitory red color. At the end of an additional 3 hr. excess ammonium chloride was added to the brown reaction mixture and the ammonia was replaced by ether. The residue was removed by filtration and washed well with ether. The ether was evaporated from the combined filtrates to afford a clear amber oil. Distillation of this oil at 0.3 mm. gave a small forerun, b.p. 70–90°, of 4.0 g. and 10.5 g. (41%) of a fraction b.p. 101–103°. A sample of the latter was redistilled at 0.35 mm. to afford the tertiary amine V b.p. 103–104°, n^{25}_{D} 1.5805.

Anal. Calcd. for $C_{14}H_{19}NFe$: C, 65.38; H, 7.45; N, 5.45; Fe, 21.72. Found: C, 65.16; H, 7.40; N, 5.74; Fe, 21.39.

In a number of runs, the yield of amine ranged from 40 to 50%.

The *picrate* of the amine was prepared in the usual way and recrystallized from ethanol to a constant m.p. of 179–180° (dec.).

Anal. Calcd. for $C_{20}H_{22}O_7NFe$: C, 49.40; H, 4.56; N, 11.52; Fe, 11.49. Found: C, 49.48; H, 4.55; N, 11.48; Fe, 11.62.

The forerun of the distillation was dissolved in ether and the solution washed with *N* hydrochloric acid followed by saturated sodium bicarbonate and water. On removal of the solvent a brown solid remained. This was recrystallized from ethanol to give old gold colored plates m.p. 39–40° having a strong camphoric odor. This compound (VI) shows strong absorption at 1100 cm.$^{-1}$ and 1000 cm.$^{-1}$ and weak absorption at 1620 cm.$^{-1}$, suggesting mono substituted rings, and a double bond.

Anal. Calcd. for $C_{22}H_{20}Fe_2$: C, 66.71; H, 5.09; Fe, 28.20. Found: C, 66.81; H, 5.22; Fe, 28.46. Mol. wt. calcd. for $C_{22}H_{20}Fe_2$: 396. Found[13]: 425, 414, 392, 408.

Methiodide VII of the rearrangement product. To an ice cooled solution of 11.35 g. (0.045 mole) of the tertiary amine V in 15 ml. of methanol, there was added 10 ml. of methyl iodide. Heat was evolved and a crystalline solid gradually came out. At the end of 1 hr. ether was added and the solvent removed by filtration to afford 16.08 g. (91%) of methiodide VII m.p. 248–250° (dec.).[14]

Anal. Calcd. for $C_{15}H_{22}NIFe$: C, 45.14; H, 5.56; N, 3.51; Fe, 13.99. Found: C, 45.18; H, 5.65; N, 3.29; Fe, 13.81.

The infrared spectrum of this salt (which shows the bands at 811, 1002, and 1108 cm.$^{-1}$ characteristic of monosubstituted ferrocenes)[3] and that of an authentic sample prepared from ferrocyclacetonitrile[5] are superimposable (as potassium bromide pellets).[15]

A sample of the methiodide was treated with saturated alcoholic picric acid to afford the quaternary picrate m.p. 150–152°. The mixed melting point of this with a freshly prepared sample of the authentic quaternary picrate[5] m.p. 150–152° was 150–152°.

β-Elimination of methiodide VII to vinylferrocene. Over the period of 30 min. 20.0 g. (0.05 mole) of the yellow quaternary salt was added to a stirred solution of 0.1 mole of potassium amide in 250 ml. of liquid ammonia. After an additional 3 hr. stirring, excess ammonium chloride was cautiously added and the ammonia allowed to evaporate. The residue was washed several times with ether; the washes were combined and the solvent removed. The gummy orange solid, m.p. 45–52°, (10.1 g.), which remained was recrystallized from ethanol to afford vinylferrocene[16] m.p. 56°.

Anal. Calcd. for $C_{12}H_{12}Fe$: C, 67.96; H, 5.70; Fe, 26.34. Found: C, 68.10; H, 5.90; Fe, 26.13.

The infrared spectrum of this compound is superimposable upon one of authentic vinylferrocene[17] m.p. 52–53°.

Tertiary amine V from ferrocene and β-dimethylaminoethyl chloride. A solution of 0.75 mole of butyllithium (prepared from 102.8 g. of butyl bromide and 12.9 g. of lithium) in 500 ml. of ether was added to a vigorously stirred, ice-cooled, solution of 93 g. (0.5 mole) of ferrocene[18] in 1.5 l. of ether. The reaction mixture was slowly (1 hr.) brought to reflux temperature, heated for 5 hr., and then stirred at room temperature for 23 hr.[6] At the end of this time a solution of 81 g. (0.75 mole) of the freshly prepared[19] amino halide in 100 ml. of ether was added to the reaction mixture, at such a rate that gentle refluxing ensued. After heating for 3 hrs. the reaction was allowed to stand overnight. Water (500 ml.) was then cautiously added and the organic layer separated. The ethereal solution was subsequently extracted with three 100 ml. portions of *N* hydrochloric acid. The latter were combined, clarified by filtration, and made alkaline with 20% sodium hydroxide. Extraction of the alkaline suspension with ether followed by drying and finally evaporation of the solvent from the extracts afforded 20 g. of basic products as an oil. Distillation of this at 0.4 mm. afforded 4.0 g. of tertiary amine V b.p. 110–112°. No other readily distillable material was observed.

The picrate of this product, m.p. 177–179°, did not depress the m.p. of picrate of the rearrangement product (V).

A sample of the amine was converted to the methiodide in the manner described above. This salt formed a quaternary picrate, m.p. 150–152°, which when mixed with that of the rearrangement product melted at 150–152°.

DURHAM, N. C.

(9) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **22**, 906 (1957).

(10) See C. R. Hauser, R. M. Manyik, W. R. Brasen, and P. L. Bayless, *J. Org. Chem.*, **20**, 1119 (1955).

(11) Analyses are by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected.

(12) J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355 (1957).

(13) Molecular weight determination by Dr. C. Tiedcke, Teaneck, N. J.

(14) This melting point varies with the rate of heating.

(15) When the spectra are run as Nujol mulls, samples of both the authentic salt and that obtained from rearranged amine exhibit spectra when both are crystallized from water which are different from those of samples crystallized from methanol-ether. In each case the absorbtions of each pair are identical to each other.

(16) F. S. Arimoto and A. C. Haven, Jr., *J. Am. Chem. Soc.*, **77**, 6295 (1955).

(17) We are indebted to Dr. R. L. Pruett of Lindy Air Products Co. for a sample of this compound.

(18) We are indebted to Linde Air Products Co., Tonawanda, N. Y. (Dr. R. L. Pruett) for a generous sample of this compound.

(19) K. A. Slotta and R. Behnish, *Ber.*, **68**, 757 (1935).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE AND THE LOS ALAMOS SCIENTIFIC LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

Some Oxygen-Containing Heterocycles as Liquid Scintillator Solutes

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Derivatives of dibenzofuran, dibenzo-*p*-dioxin, and xanthene have been screened as liquid scintillator solutes. The first of these appears to offer the most promise. The results suggest that methoxy derivatives increase the relative pulse height.

Continuing our general survey[1] of aromatic systems as liquid scintillator solutes, we have prepared and screened a few selected heterocycles containing oxygen as the only hetero atom (Table I). The compounds tested have many of the desirable properties of good solutes, and a remarkable variety is available by extension of the synthetic methods employed.

TABLE I

PRIMARY-SOLUTE RELATIVE PULSE HEIGHTS

No.	Compound	Relative Pulse Height
1.	Dibenzofuran	0.10
2.	3-Dimethylaminodibenzofuran[a]	0.79
3.	4,6-Dimethoxydibenzofuran[b]	0.24
4.	2,8-Dimethoxydibenzofuran[c]	0.27
5.	2-Hydroxy-8-methoxydibenzofuran[c]	0.21
6.	2,8-Diaminodibenzofuran[d]	0.14
7.	2-Methoxy-3-carbomethoxydibenzofuran[e]	0.13
8.	2,2′-Bidibenzofuran[f]	0.14
9.	6,6′-Dimethoxy-2,2′-bidibenzofuran[f]	0.46
10.	Tri-4-dibenzofurylcarbinol[d]	0.13
11.	1,2,3,4-Tetrahydro-6-methoxy-4-oxobenzo-[b]naphtho[1,2-d]furan[e]	<0.10
12.	1,2,3,4-Tetrahydro-7-methoxy-1-oxocyclo-octa[klm]dibenzofuran[e]	<0.10
13.	Dibenzo-*p*-dioxin[g]	<0.10
14.	2-Phenyldibenzo-*p*-dioxin[h]	0.40
15.	1,1′-Bidibenzo-*p*-dioxin[h]	0.15
16.	2,2′-Bidibenzo-*p*-dioxin[h]	0.59
17.	1-(2-Dibenzo-*p*-dioxinyl)-1,2-diphenyl-ethanol[h]	<0.10
18.	2-(α-Phenylstyryl)dibenzo-*p*-dioxin[h]	<0.10
19.	Spiro(fluorene-9,9′-xanthene)[i]	<0.10
20.	Spiro(9,10-dihydroanthracene-9,9′-xanthene)[i]	<0.10
21.	9,9′-Spirobixanthene[i]	<0.10
22.	2-Biphenylyl phenyl ether[j]	0.16
23.	4-Biphenylyl phenyl ether[j]	0.16
24.	2-Biphenylyl 4-biphenylyl ether[j]	<0.10

[a] W. H. Kirkpatrick and P. T. Parker, *J. Am. Chem. Soc.*, **57**, 1123 (1935). [b] H. Gilman and L. C. Cheney, *J. Am. Chem. Soc.*, **61**, 3149 (1939). [c] H. Gilman, J. Swiss, H. B. Willis, and F. A. Yoeman, *J. Am. Chem. Soc.*, **66**, 798 (1944). [d] J. Swislowsky, *Iowa State Coll. J. Sci.*, **14**, 92 (1939). [e] S. Avakian, doctoral dissertation, Iowa State College, Ames, Iowa, 1944. [f] H. B. Willis, *Iowa State Coll. J. Sci.*, **18**, 98 (1943). [g] H. Gilman and J. J. Dietrich, *J. Am. Chem. Soc.*, **79**, 1439 (1957). [h] See Experimental. [i] R. G. Clarkson and M. Gomberg, *J. Am. Chem. Soc.*, **52**, 2881 (1930). [j] Kindly supplied by Dow Chemical Co.

The relative pulse heights (RPH) of the limited number of dibenzo-*p*-dioxin derivatives screened are low and seem to reflect a suspected generalization, *i.e.*, values will always be higher for compounds having a direct union of two aromatic rings than for those in which the rings are joined through an oxygen atom. The biphenyl linkage in dibenzofuran will presumably make all of its derivatives superior to corresponding dibenzo-*p*-dioxin derivatives. This principle is remarkably evident when comparing 4-biphenylyl phenyl ether (compound 23, RPH 0.16) and *p*-terphenyl (RPH 0.97). The generalization also appears to hold for preliminary work with carbazole and phenoxazine.

As previously noted[1] there is again a remarkably high response for the lone dimethylamino derivative tested (compound 2). In hopes of finding some reflection of this effect in structurally similar methoxy derivatives, a number of these compounds were also screened. The most remarkable (and as yet unexplainable) value obtained from the methoxy derivatives investigated is certainly that of compound 9 which gives a response so much higher than compound 8 (0.46 and 0.14, respectively). It is also noteworthy that all the methoxy derivatives tested give some response, although only compound 9 has more than two benzene rings. It would surely be unwarranted to generalize on the basis of so few examples, but these values are encouraging.

The fact that the values obtained from these methoxy derivatives are consistently good, along with the excellent values for dialkylamino derivatives, suggests that these groups result in a shortening of the lifetime of the excited state and thus provide a greater probability that fluorescence will occur before a radiationless transition.[2] The effect of methoxyl and dialkylamino groups on the lifetime of the excited state is not known with certainty, but all previous reports of solutes with substituent groups on an aromatic ring seem to indicate a rough parallel with the activation or deactivation of the aromatic system toward electrophilic substitution. Perhaps there is some significance in the fact that phenols and aryl amines give markedly lower values than the corresponding alkylated compounds.

(1) For leading references see: H. Gilman, E. A. Weipert, T. Soddy, and F. N. Hayes, *J. Org. Chem.*, **22**, 1169 (1957).

(2) D. G. Ott, F. N. Hayes, E. Hansbury, and V. N. Kerr, *J. Am. Chem. Soc.*, **79**, 5448 (1957).

The dibenzo-*p*-dioxin derivatives reported herein are the first of these compounds screened as scintillators. The values recorded in Table I indicate that further work on this heterocycle is promising only in the case of the 2-substituted derivatives (compare, for example, compounds 15 and 16). Compound 18 would make it seem that any further aromatic systems should be linked directly to the heterocycle (see compound 14) rather than through a vinyl side chain.

Of some interest are the two general methods employed in the experimental section to prepare phenyl and styryl derivatives of heterocycles. Amino derivatives are converted by three relatively convenient steps to phenyl derivatives. The described modification of the Gomberg reaction obviates the isolation of intermediates and leads to a single isomer. The condensation of benzylmagnesium chloride with aromatic aldehydes or ketones, followed by dehydration of the resulting carbinol, gives good yields of styryl or β-substituted styryl derivatives. In this case also, isolation of the carbinol is unnecessary since dehydration by the Lucas reagent, as developed by Crawford and Nelson,[3] can be effected conveniently using a benzene solution of the crude carbinol.

The values reported in Table I were measured in the pulse height analyzer previously described,[4] and all were measured at a concentration of 3 g./l. in toluene except 6, 9, 10, 15, and 16 which, due to limited solubility, were measured as saturated solutions. All values are relative to 2,5-diphenyloxazole which is assigned the arbitrary value of 1.00.

EXPERIMENTAL[5]

1,1'-Bisdibenzo-p-dioxin. A mixture of 4.0 g. (0.015 mole) of 1-iododibenzo-*p*-dioxin[6] and 4 g. of copper bronze was heated in an oil bath at 250° for 5 hr.[7] After cooling, the reaction mixture was pulverized, extracted with hot benzene, and filtered. Concentration of the benzene followed by dilution with ethanol produced 0.9 g. of product melting at 215–218°. Further recrystallization from ethanol-benzene afforded 0.6 g. (22%) of white plates, m.p. 217–219°.

Anal. Calcd. for $C_{24}H_{14}O_4$: C, 78.69; H, 3.82. Found: C, 78.36, 78.50; H, 4.24, 4.28.

2,2'-Bisdibenzo-p-dioxin. A mixture of 4.0 g. (0.015 mole) of 2-iododibenzo-*p*-dioxin[8] and 5 g. of copper bronze was heated at 240–250° for 4 hr.[7] After cooling, the reaction mixture was pulverized, extracted with hot benzene, and chromatographed on alumina. The eluate was concentrated and diluted with ethanol to produce 0.7 g. of product melting at 225–230°. One further recrystallization from glacial acetic acid afforded 0.6 g. (22%) of white plates melting at 227–230°.

Anal. Calcd. for $C_{24}H_{14}O_4$: C, 78.69; H, 3.82. Found: C, 78.40, 78.49; H, 4.08, 4.07.

2-Phenyldibenzo-p-dioxin. Nitrous fumes[9] were slowly bubbled through a solution consisting of 4.0 g. (0.016 mole) of 2-acetamidodibenzo-*p*-dioxin,[6] 130 ml. of glacial acetic acid, and 20 ml. of acetic anhydride at 10° for 2.5 hr.[10] The yellow-green solution was poured into a liter of ice water, and the precipitated yellow solid was filtered off. This solid was air dried and then stirred for 8 hr. with 200 ml. of dry benzene. After 8 hr. at room temperature, the solution was warmed for 1 hr. and the bulk of the benzene distilled. The concentrated benzene solution was chromatographed on alumina and the eluate was evaporated. Two recrystallizations of the residue from ethanol produced 0.7 g. (16%) of white plates, m.p. 108–110°. The infrared spectrum showed bands characteristic of 1,2,4 trisubstitution, 1,2 disubstitution, and monosubstitution.

Anal. Calcd. for $C_{18}H_{12}O_2$: C, 83.08; H, 4.61. Found: C, 82.64, 82.71; H, 4.64, 4.72.

1-(2-Dibenzo-p-dioxinyl)-1,2-diphenylethanol. An excess of benzylmagnesium chloride was added to a stirred solution of 5.76 g. (0.02 mole) of 2-benzoyldibenzo-*p*-dioxin[6] in 100 ml. of diethyl ether over a period of 15 min. After addition, which caused gentle reflux, the reaction mixture was refluxed for 2 hr. and then hydrolyzed with saturated ammonium chloride. The ether layer was separated, dried over sodium sulfate, and evaporated. The residual 6 g. of crude material was recrystallized three times from ethanol-water to give 4.5 g. (60%) of white needles, m.p. 141–142°.

Anal. Calcd. for $C_{26}H_{20}O_3$: C, 82.10; H, 5.26. Found: C, 82.12, 82.15; H, 5.22, 5.48.

2-(α-Phenylstyryl)dibenzo-p-dioxin. A mixture of 3.5 g. (0.009 mole) of 1-(2-dibenzo-*p*-dioxinyl)-1,2-diphenylethanol, 45 ml. of benzene, and 15 ml. of Lucas reagent was refluxed for 2 hr. The benzene layer was separated and washed with dilute sodium carbonate solution. Evaporation of the benzene left an oil which solidified when boiled with petroleum ether (b.p. 60–70°). Three recrystallizations of this material from ethanol-water afforded 1.1 g. (33%) of white needles, m.p. 123–125°.

Anal. Calcd. for $C_{26}H_{18}O_2$: C, 86.18; H, 4.97. Found: C, 86.18, 86.19; H, 4.83, 5.08.

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AMES, IOWA

(3) H. M. Crawford and H. B. Nelson, *J. Am. Chem. Soc.*, **68**, 134 (1946).

(4) F. N. Hayes, D. G. Ott, V. N. Kerr, and B. S. Rogers, *Nucleonics*, **13**, No. 12, 38 (1955).

(5) All melting points are uncorrected.

(6) J. J. Dietrich, doctoral dissertation, Iowa State College, Ames, Iowa, 1957.

(7) D. A. Shirley, *Preparation of Organic Intermediates*, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 122.

(8) H. Gilman and J. J. Dietrich, *J. Am. Chem. Soc.*, **79**, 1439 (1957).

(9) J. Haworth and D. Hey, *J. Chem. Soc.*, 361 (1940).

(10) W. E. Bachman and R. A. Hoffman, *Org. Reactions*, *II*, p. 249 (1949).

[CONTRIBUTION NO. 228 FROM THE GOODYEAR TIRE AND RUBBER RESEARCH LABORATORY]

Preparation of Symmetrical Diaryl Disulfides Containing Side Chains Terminated by Halogen or by Tertiary Amino Functions

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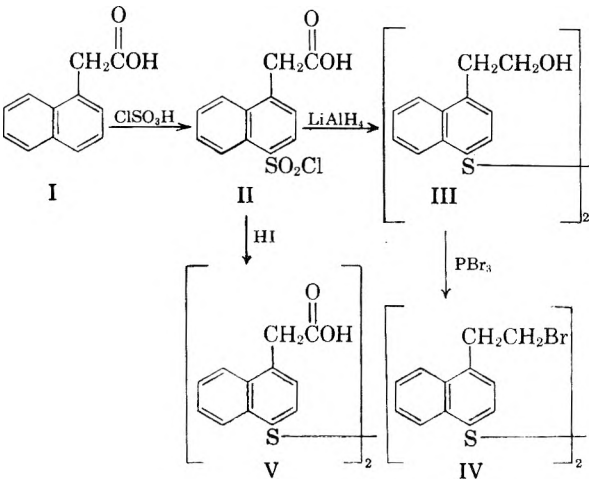
Various methods of preparation for a number of new symmetrically substituted diaryl disulfides containing (*a*) such side chain halogen or pseudo halogen-containing functions as ω-haloalkyl-, ω-haloacyl-, and ω-tosyloxyalkyl-, *e.g.*, bis(4-β-bromoethyl-1-naphthyl) disulfide, bis(4-γ-chloropropoxy-1-naphthyl) disulfide, bis(2-chloroacetamidophenyl) disulfide, bis(4-β-tosyloxyethoxy-1-naphthyl) disulfide, and bis(2-chloroacetophenyl) disulfide, and (*b*) such side chain tertiary amino functions as the isonicotinoyl-, ω-4-pyridylalkyl-, or ω-dimethylaminoalkyl, *e.g.*, bis(2-isonicotinamidophenyl) disulfide, bis[2-β-(2′,4′-pyridylethylthio)propionamidophenyl] disulfide, and bis(4-β-dimethylaminoethoxycarbonyl-2,6-xylyl) disulfide, are described. Chain transfer constant values of a number of these diaryl disulfides (as determined for bulk styrene polymerization at 50°) as well as other physical properties and data relating to the preparation of these disulfides and their intermediates are recorded.

It has been well established that linear polystyrene molecules containing one arylthio (ArS-) group at each chain end, can be prepared by a bulk polymerization process in which a diaryl disulfide modifier as well as an initiator is included in the polymerization recipe.[1] In previous papers, syntheses for a number of symmetrical, substituted diaryl disulfides which have proven to be chain transfer agents for bulk styrene polymerization systems, and sometimes for emulsion diene-containing polymerization systems have been reported.[1-4] This known group of substituted diaryl disulfides included two bis(haloalkylaryl) disulfides, namely bis(2-chloromethylphenyl) and bis-(2-bromomethyl-phenyl) disulfides.[1] One of the prime objectives of the present work was the expansion of the field of symmetrical, side-chain-halogen-substituted diaryl disulfides to include compounds with varying degree of halogen activity, and with chain transfer activity in a range suitable for efficient modification (molecular weight control by chain transfer reaction) of bulk and emulsion polymerization systems. This objective has been attained. A series of symmetrical, haloacyl-, haloalkyl-, and tosyloxylalkyl-substituted diaryl disulfides with fairly high modifier activity [with a range of transfer constant (*C*) values of 0.7 – 2.7[5]] whose halide functions have a wide range of activity toward alcoholic silver nitrate, solutions of sodium iodide in acetone, or tertiary amines, has been prepared.

Four methods for introduction of ω-haloalkyl groups (with alkyl carbon chain longer than one carbon atom) into diaryl disulfide systems have proven successful. Only one of these methods involves direct substitution of the haloalkyl group on the aromatic nucleus. Synthesis of a compound so substituted, bis-(4-β-bromoethyl-1-naphthyl) disulfide (IV), is indicated schematically:



1-Naphthalene acetic acid (I) was chlorosulfonated to the 4-sulfonyl chloride[6] II. This compound was

(1) R. M. Pierson, A. J. Costanza, and A. H. Weinstein, *J. Polymer Sci.*, 17, 221 (1955).

(2) A. J. Costanza, R. J. Coleman, R. M. Pierson, C. S. Marvel, and C. King, *J. Polymer Sci.*, 17, 319 (1955).

(3) E. J. Quinn, G. P. Scott, C. King, and C. S. Marvel, "Sterically Hindered Aromatic Disulfides," Copolymer Report No. 3757 to Office of Synthetic Rubber, F.F.C., 1955. [See reference (30) concerning availability of this publication.]

(4) C. S. Marvel, T. H. Shepherd, C. King, J. Economy, and E. D. Vessel, *J. Org. Chem.*, 21, 1173 (1956).

(5) The *C* values, obtained by measurement of parameters in bulk styrene polymerizations run at 50°, using azoisobutyronitrile as initiator, in accordance with the method of F. R. Mayo, *J. Am. Chem. Soc.*, 65, 2324 (1943), were determined by Mr. Albert J. Costanza under conditions fully described in (1).

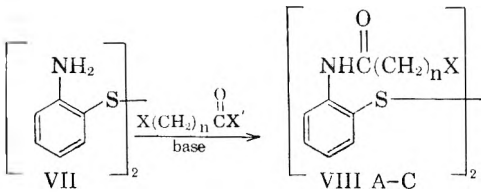
(6) Although indisputable evidence for assignment of the position of the sulfur atom in II at the para position is not presented, known facts about the orientation of the chlorosulfonyl groups of related compounds prepared under similar conditions would indicate that our assumption is well founded: (*a*) The 1-alkoxynaphthalenes chlorosulfonate almost quantitatively at the 4-position.[7] (*b*) Treatment of 1-benzylnaphthalene with chlorosulfonic acid in nitrobenzene yielded the 4-sulfonic acid as the sole product.[8] (c) Treatment of 1-methylnaphthalene with chlorosulfonic acid at low temperature yielded the 4-sulfonic acid as the predominant product as well as a small amount of isomeric sulfonic

reduced with lithium aluminum hydride. The reduction product, upon hydrolysis, proved to be bis(4-β-hydroxyethyl-1-naphthyl) disulfide (III) rather than the expected hydroxyethyl thiol.[11a] Compound III was converted to the dibromide IV. The sulfonyl chloride II was selectively reduced to bis(4-carboxymethyl-1-naphthyl) disulfide (V)[11b] with hydriodic acid.

Although bis(4-β-hydroxyethylphenyl) disulfide (VI) was successfully prepared from β-4-aminophenyl-ethanol by the Leuckart xanthate method,[12] a pure dibromide could not be isolated from the reaction mixture of this diol with phosphorus tribromide.

Three methods, other than that already described, leading to syntheses of bis (ω-haloalkylated) diaryl disulfides were developed, all leading to better over-all yields of desired dihalides. However, none of these routes led to synthesis of compounds containing haloalkyl groups directly substituted on aromatic rings, but rather to compounds containing haloalkyl groups linked to aromatic rings *via* oxygen or nitrogen bridges.

A simple example of such a synthesis involving a nitrogen bridge is as follows:



VIII A, n = 1, X = Cl, X′ = Cl
VIII B, n = 1, X = Br, X′ = Br
VIII C, n = 2, X = Br, X′ = Cl

Upon treatment of bis(2-aminophenyl) disulfide (VII) with chloroacetyl chloride in the presence of glacial acetic acid and aqueous sodium acetate[13] at 25°, an 87% yield of bis(2-chloroacetamidophenyl) disulfide (VIII A) was obtained. In a similar manner, the bis(2-bromoacetamido) analog VIII B was prepared. Compound VIII A was also prepared, in poor yield of pure compound, by treatment of VII with chloroacetyl chloride in anhydrous benzene-pyridine system. In this case, the reaction product proved to be a sharp melting, difficultly separable mixture of VIII A with a compound (IX) having the empirical formula $C_{16}H_{13}Cl_3N_2O_2S_2$. Compound IX, isolated by many fold fractional crystallizations of the reaction product with ethanol, was believed to be the unsymmetrical compound, N-chloroacetyl, *N′*-dichloroacetylbis(2-aminophenyl) disulfide. It is believed that presence of IX in the reaction product was caused by presence of dichloracetyl chloride in the chloracetyl chloride reagent. Nevertheless, the yield of bis(2-β-bromopropionamidophenyl) disulfide (VIII C) obtained by haloacylating VII in the benzene-pyridine system was much better than that obtained by the use of the buffered acetate system.

Another member of this family of bis(haloacylamidoaryl) disulfides, namely bis(4-chloroacetamido-1-naphthyl) disulfide (X), was prepared by a more circuitous route. α-Naphthylamine was chloroacetylated to α-chloracetnaphthalide (XI),[14] which was chlorosulfonated to the 4-sulfonyl chloride (XII).[15] By reduction of this sulfonyl chloride with 50% hydriodic acid,[16] the desired disulfide X was obtained.

Data pertaining to the synthesis, physical properties, and polymerization transfer constants of these bis(haloacylamidoaryl) disulfides may be found in Table I.

Attempts to replace the chlorine atoms of VIII A with either the methylthio or *n*-butylthio function, or with the amino function, all resulted in formation of the same non-halogen containing

acids.[9] (*d*) Stewart[10] proved that the only sulfonyl chloride obtained by treatment of cinnamic acid with this reagent was 4-chlorosulfonylcinnamic acid and felt certain that the sulfonyl chloride he obtained from phenylacetic acid was also a para-sulfonyl chloride.

(7) E. H. Huntress and F. H. Carten, *J. Am. Chem. Soc.*, **62**, 511 (1940).

(8) K. Dziewonski and S. Dziecelewski, *Bull. intern. acad. Polonsci.*, 1927A, 273; *cf. Chem. Abstr.*, 22, 2164 (1928).

(9) V. Vesely, F. Stursa, H. Olejnicek and E. Rein, *Collection Czechoslov. Chem. Commun.*, **1**, 493 (1929); *cf. Chem. Abstr.*, **24**, 611 (1930).

(10) J. Stewart, *J. Chem. Soc.*, **121**, 2555 (1922).

(11) (a) Similar experiences were observed when (i) the compound obtained upon acidification of the alkaline hydrolysis product of the (4-β-hydroxyethylphenyl) ester of ethylxanthic acid proved to be bis(4-β-hydroxyethyl phenyl) disulfide (VI) rather than the mercaptan, and when (ii) the hydrolysis product obtained from the reaction of 1-naphthylmagnesium bromide with an atom equivalent of sulfur contained a 70:30 ratio of mercaptan to disulfide. Evidently, the $LiAl^{+4}$ and $MgBr^{+1}$ mercaptides of aryl thiols as well as their alkali and ammonium mercaptides are sensitive to air oxidation; (b) Bis(4-carboxymethoxy-1-naphthyl) disulfide, m.p. 215.0–215.9° in white flakes from aq. HOAc, with (*C*) value of 1.79, was prepared (49%) similarly (Calcd. for $(C_{12}H_9O_3S)_2$: S, 13.74; N.E., 233. Found: C, 13.5, 13.6; N.E. 237) from the intermediate, 4-carboxymethoxy-1-naphthalene sulfonyl chloride, m.p. 177.7–178.7°, in white crystals from 15:1 benzene-nitrobenzene, prepared in turn (69%) by chlorosulfonating 1-naphthoxyacetic acid by the general method of Huntress,[7] at 0°, using 3 moles $ClSO_3H$ per mole of carboxylic acid. Calcd. for $C_{12}H_9ClO_6S$: Cl, 11.79; S, 10.66. Found: Cl, 11.7, 11.7; S, 10.5, 10.7.

(12) (a) R. Leuckart, *J. prakt. Chem.*, [2] 41, 189 (1890); (b) D. S. Tarbell and D. K. Fukushima, *Org. Syntheses*, **Coll. Vol. III**, 809 (1955).

(13) A reagent combination used effectively by W. A. Jacobs and M. Heidelberger, *J. Am. Chem. Soc.*, 41, 1450 (1919), in chloroacetylating various anisidines and phenetidines.

(14) D. Tommasi, *Bull. soc. chim.*, [2] 20, 19 (1873).

(15) This compound was prepared under essentially the same conditions used by L. N. Goldyrev and I. Ya. Postovskii, *J. Appl. Chem. U.S.S.R.*, 11, 316 (1938) for preparation of 4-chlorosulfonyl-1-acetnaphthalide.

(16) A method developed by A. Ekbom, *Ber.*, 24, 335 (1891) for preparation of aryl disulfides from sulfonyl chlorides, and modified by L. Bauer, and J. Cymerman, *J. Chem. Soc.*, 3434 (1949) who developed a homogeneous reaction system by utilization of glacial acetic acid solvent.

TABLE I

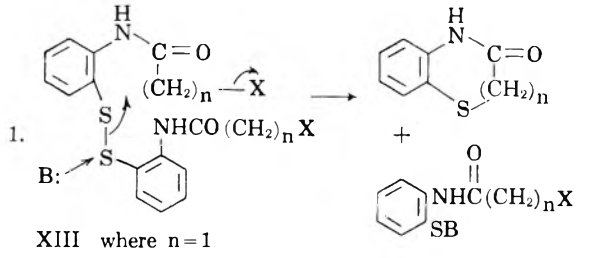
BIS(ω-HALOACYLAMIDOARYL) DISULFIDES

Bis-disulfide[a]	Crude Yield,[b] %	M.P.,[c] °C.	Halogen, % Calcd.	Halogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Transfer Constant (C)
2-Chloroacetamidophenyl (VIII A)	87	133.2–133.7[d]	17.79	17.67 17.77	6.98	7.14 7.07	15.97	16.13 16.09	5.3
2-Bromoacetamidophenyl (VIII B)[e]	74	157.4–157.7[f]	32.61	31.43 31.44			13.08	13.10 12.83	3.8
2-β-Bromopropionamidophenyl (VIII C)	79	155.1[f]	30.83	30.90 30.75	5.40	5.50 5.64	12.37	12.57 12.51	7.3
4-Chloroacetamido-1-naphthyl (X)	68	203.5[g]					12.79	12.29 12.39	0.0[h]

[a] All disulfides are white crystalline products. [b] Yields are based on product of less than 3° melting range. [c] Corrected melting points of analytical samples. [d] 85% Aq. ethanol. [e] Calcd. for carbon and hydrogen, %: 39.20; 2.88. Found: 39.05; 39.40; 2.91, 3.04. [f] Absolute ethanol. [g] Dioxane-chlorobenzene. [h] Compound so insoluble in styrene and in most solvents suitable for use in transfer constant determination that it did effect a reduction of molecular weight of polystyrene obtained from a bulk styrene polymerization below that obtained in the control polymerization.

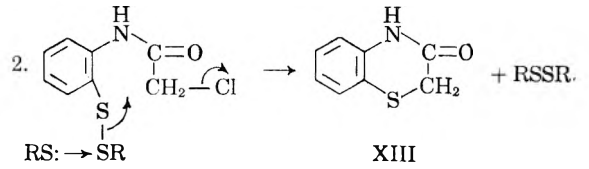
compound of empirical formula C_8H_7NOS, believed to be identical with 3-keto-2,3-dihydro-1,4-benzothiazine (XIII)[17] previously prepared by Unger.[18]

An attempt to hydrolyze the halide functions of VIII C resulted in formation of another non-halogen-containing compound believed to be the known bicyclic fused six-seven membered compound 2,3-dihydrobenzothiazepin-4(5)-one (XIV).[19] A suggested mechanism for cyclization of VIII A and VIII C to the bicyclic compounds XIII and XIV in the presence of various bases is illustrated.



XIII where n = 1
XIV where n = 2

B: = RS^-, OH^-, or HCO_3^-



XIII

In view of the fact that formation of XIII from VIII A was almost quantitative when sodium methyl- or sodium butyl-mercaptides were used, step 2, which like step 1 involves a pair of S_N2 reactions, is suggested to account for a theoretical yield based upon 100% rather than upon 50% cyclization of substituted arylthio units.

(17) See A. M. Patterson and L. T. Capell, *The Ring Index*, Rheinhold Publishing Corp., New York, 1940, Nos. 955 and 956.

(18) O. Unger, *Ber.*, **30**, 607 (1887), prepared this compound from 2-mercaptoaniline and bromoacetic acid.

(19) (a) F. Mayer and C. Horst, *Ber.*, **56B**, 1415 (1923); (b) W. H. Mills and J. B. Whitworth, *J. Chem. Soc.*, 2738 (1927).

A method of preparation of bis(ω-haloalkylated) diaryl disulfides in which the haloalkyl function is joined to the aromatic ring by an ether linkage was developed. The second and third steps of this method are identical to that used for preparation of X. First, a phenol or naphthol is converted to the ω-haloalkyl aryl ether by treatment of the phenolic compound with the appropriate α, ω-dihaloalkane in presence of aqueous alcoholic alkali by an adaptation of the Williamson method.[20] The resultant haloethers were chlorosulfonated by the method of Huntress.[7] The chlorosulfonyl derivatives of the naphthyl haloalkyl ethers were assumed to have the same orientation of chlorosulfonyl groups as those assigned to the chlorosulfonation products of the analogous methoxy- and ethoxy-naphthalenes by Huntress, *i.e.*, the 1-naphthyl haloalkyl ethers were considered to chlorosulfonate at the 4-position, the 2-naphthyl haloalkyl ethers at the 1-position at 0°. The chlorosulfonyl group of a product obtained by chlorosulfonation of 5-β-bromoethoxy-1,3-xylene was assigned to the 2-position (*para* to the ether function) analogous to the assignment given to a chlorosulfonation product by Marvel *et al.*[4] obtained similarly from ethyl 3,5-dimethylphenoxyacetate (5-carbethoxymethoxy-1,3-xylene). The ω-haloalkoxy aromatic sulfonyl chlorides were reduced selectively to the respective bis(ω-haloalkoxyaryl) disulfides by means of the previously mentioned hydriodic acid reduction method.[16]

In a similar manner, 1-β-tosyloxyethoxynaphthalene (XV), prepared by tosylation of 2-α-naphthoxyethanol, was chlorosulfonated, and the 4-sulfonyl chloride reduced to bis(4-β-tosyloxyethoxy-1-naphthyl) disulfide (XXX). Data pertinent to the preparation and properties of the ω-haloalkyl or β-tosyloxyethyl aryl ethers, the ω-haloalkoxy- or β-tosyloxyethoxy- aromatic sulfonyl chlorides, and the bis(ω-haloalkoxy- or β-

(20) C. S. Marvel and A. L. Tanenbaum, *Org. Syntheses*, Coll. Vol. I., 435 (1941).

TABLE II

ω-HALOALKYL OR β-TOSYLOXYETHYLARYL ETHERS

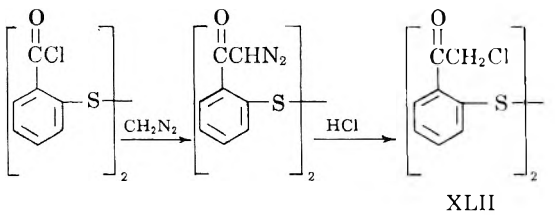
Ether	Crude Yield, %	B.P., °C./Mm.	n_D^{25}	M.P.,[a] °C.	Recryst. Solvent	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1-β-Tosyloxyethoxynaphthalene (XV)	52			98.7–99.2	EtOH	66.65	66.56 66.47	5.30	5.18 5.13			9.36	9.03 9.02
1-β-Bromoethoxynaphthalene (XVI)[b]	50	167–170/3.2	1.6286	34.0–35.0	n-C_6H_{14}	57.39	57.68 57.75	4.42	4.49 4.41	31.83	31.79 31.88		
2-β-Bromoethoxynaphthalene (XVII)[c]	62			94.8–96.0	EtOH								
1-β-Chloroethoxynaphthalene (XVIII)[d]				37.0–38.0	EtOH	69.71	69.40 69.25	5.37	5.27 5.20	17.16	16.32 16.39		
2-β-Chloroethoxynaphthalene (XIX)[d]				82.7–83.3	95% EtOH (2B)	69.71	69.35 69.25	5.37	5.29 5.27	17.16	16.77 16.37		
1-γ-Chloropropoxynaphthalene (XX)[e]	49	153.4–156.0/1.0	1.5997							16.07	15.56 15.80		
5-β-Bromoethoxy-1,3-xylene (XXI)[f]	41	124–132/15											
5-β-Bromoethoxy-3-ethyltoluene (XXII)	35	106.7–108.1/0.8	1.5359							32.86	31.32 31.08		

[a] Corrected melting points of analytical samples. [b] Prepared by W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 441 (1915), as a solid m.p. 25°, b.p. 154–156°/0.8 mm. [c] A. Wohl and E. Berthold, *Ber.*, **43**, 2179 (1910), obtained 40% yield of this compound, recryst. to m.p. 96° from absolute ethanol. [d] Prepared by treating a mixture of 1- and 2-β-hydroxyethoxynaphthalenes with thionyl chloride and pyridine, fractionally distilling, and fractionally recrystallizing the mixture of chlorides. W. R. Kirner and G. H. Richter *J. Am. Chem. Soc.*, **51**, 3409 (1929), and G. R. Clemo and W. H. Perkins, Jr. *J. Chem. Soc.*, **121**, 646 (1922), prepared these chlorides previously. C. and P. report the melting points for the 1-β-and 2-β-isomers as 28° and 83°, respectively. [e] W. R. Kirner and G. H. Richter (see reference d) obtained this chloride in 54% yield of yellow oil b.p. 167–181°/1 mm., n_D^{20} 1.6025. [f] W. S. Gump and E. J. Nikawitz, *J. Am. Chem. Soc.*, **72**, 3847 (1950), report this bromide as an oil b.p. 120–121°/5 mm., n_D^{20} 1.5405; P. Hey, *Brit. J. Pharm.*, **7**, 117 (1952), reports it as an oil b.p. 99°/1 mm., n_D^{20} 1.5426.

tosyloxyethoxyaryl) disulfides is given in Tables II, III, and IV, respectively.

Although the crude yields of the bis(haloalkoxynaphthyl) disulfides approached theoretical values, on basis of the yields of iodine formed during the hydriodic acid reduction process (as determined roughly by back titrating with sodium thiosulfate), presence of impurities in the reaction products made them very tacky and difficult to purify by fractional crystallization.

Only one of the several schemes devised for synthesis of a bis(haloketoaryl) disulfide proved completely successful. Bis(2-chloroformylphenyl) disulfide was prepared by the following indirect route:



XLII

Bis(2-chloroformylphenyl) disulfide,[21] was converted to the bis(diazoketo) compound by treatment with diazomethane. The latter compound was treated *in situ* with hydrogen chloride gas to form the bis chloroketone (XLII).

Several previous attempts to prepare bis(chloroacetaryl) disulfides by a more direct route, namely by treatment of symmetrical, alkyl-substituted diphenyl disulfides with chloroacetyl chloride under Friedel-Craft conditions, were only partially successful. For example, a crude chloroacetylated di-2,6-xylyl disulfide (XXXIX), obtained as a viscous sirup, and which appeared to contain a 73:27 ratio of dichloroacetylated to monochloroacetylated product, was obtained under very mild chloracetylation conditions (reaction at 25°). The product could not be separated into pure crystalline fractions by elution chromatography using a 1:1 mixture of activated silicic acid/Hi-Flow Supercell. In addition to the complications introduced by formation of dissymmetrical haloacetylation products and positional isomers, the tendency of the diaryl disulfides to undergo a reductive S-haloacylation even under mild conditions made the problem insurmountable. In several instances, pure thiol haloesters such as phenylthiol chloro-

(21) R. List and M. Stein, *Ber.*, **31**, 1569 (1898).

TABLE III

ω-HALOALKOXY- OR β-TOSYLOXYETHOXYAROMATIC SULFONYL CHLORIDES

Sulfonyl chloride[a]	Crude Yield,[b] %	M.P.,[c] °C.	Recryst. Solvent	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
4-β-Tosyloxyethoxy-1-naphthalene (XXIII)	58	109.6–110.2	$CHCl_3$/ n-C_6H_{14}							14.54	14.44 14.67
4-β-Bromoethoxy-1-naphthalene (XXIV)	81	120.8	Ditto or gl. HOAc	41.21	41.60 41.75	2.89	3.01 2.92			9.17	9.03 8.93
4-β-Chloroethoxy-1-naphthalene (XXV)	85	102.3–103.3	80% aq. HOAc					23.24	23.15 23.13		
4-γ-Chloropropoxy-1-naphthalene (XXVI)	78	127.0 128.0	n-C_7H_{16}/ C_6H_6					22.22	21.95 22.03	10.04	9.95 10.16
2-β-Bromoethoxy-1-naphthalene (XXVI)	14	120.9–121.9	gl. HOAc					33.00	32.38[d] 32.52[d]	9.17	9.30 9.27
2-β-Chloroethoxy-1-naphthalene (XXVIII)	17	122.7 123.9	i-PrOH					23.24	23.14	10.50	10.58
4-β-Bromoethoxy-2,6-xylene (XXIX)	51	70–71	n-C_6H_{14}	36.70	36.30	3.68	4.09			9.80	9.91
4-γ-Bromo-n-propoxy 1-naphthylene (L)	33	132.3–133.6	gl. HOAc or n-C_7H_{16}/ C_6H_6					31.73	30.50[d] 30.62[d]	8.81	9.06 9.20

[a] All sulfonyl chlorides are white crystals, except XXIV and XXVI which are yellowish white crystals, and XXIX and L which are yellow crystalline compounds. [b] Yields are based on products of less than 3° melting range. [c] Corrected melting point of analytical sample. [d] Assuming that a 1:1 atomic ratio of Br:Cl is present.

acetate (XL),[22] and a product believed to be 4-chloroacetomesitylthiol chloroacetate (XLI), were isolated as sharp-melting crystalline products from haloacylation reaction products of diphenyl disulfide[23] and dimesityl disulfide,[24] respectively.

An attempt to couple diazotized p-amino-α-chloroacetophenone with sodium disulfide led only to formation of an organic solvent-insoluble substance.

Various attempts to prepare ω-haloesters of symmetrical hydroxy-substituted diaryl disulfides proved unsuccessful. The chloroacetate of 1-naphthol (XXXVIII) could not be chlorosulfonated by the method of Huntress.[7]

Attempts to haloacylate 4,4′-dithio-1-naphthol[26] with chloroacetyl chloride, bromoacetyl bromide or β-bromopropionyl chloride, either in the presence or absence of such catalysts as pyridine or phosphorus oxychloride, did not lead to pure crystalline products.

An attempt to prepare a bis haloester from bis(2-hydroxymethylphenyl) disulfide[1,2] by treatment of this diol with chloroacetyl chloride in benzene solution, resulted in formation of a crude uncrystallizable product containing an average of 2.2 chloroacetyl groups per disulfide molecule. (It may be that some S-chloroacylation as well as the desired O-chloroacylation occurred.)

The novel methods of preparation of diaryl disulfides containing substituents introduced by electrophilic substitution, developed by Kharasch and Swidler,[27] and by Tarbell and Herz,[23] could not be applied directly to preparation of diaryl disul-

(22) C. E. Dalgliesh and F. G. Mann, *J. Chem. Soc.*, 559 (1947), prepared this compound as a solid, m.p. 45°, by chloroacetylating thiophenol.

(23) A. H. Herz and D. S. Tarbell, *J. Am. Chem. Soc.*, 75, 4657 (1953) observed a similar cleavage of diphenyl disulfide by acetyl chloride in presence of aluminum bromide with isolation of phenylthiol acetate as the major product as well as a very low yield of p-bromophenylthiol acetate. The crude product XXXIX did give the transfer constant 0.72 (a value close to that of di-2,6-xylyl disulfide itself—0.69[1]) although XL has absolutely no modifier activity, and was considered to be essentially a nuclearly acylated diaryl disulfide.

(24) A sample of dimesityl disulfide was prepared for us, under the supervision of Professor C. S. Marvel at the University of Illinois, Urbana, Ill., by a method indicated in reference (2). Since that time, Prof. Marvel's group has prepared this compound by two somewhat different methods as indicated in reference (3).

(25) An adaptation of a method used by D. S. Tarbell and A. H. Herz, *J. Am. Chem. Soc.*, 75, 1668 (1953) to prepare bis(4-acetophenyl) disulfide.

(26) Prepared by the method of T. Zincke and J. Ruppersberg, *Ber.*, 48, 129 (1915).

(27) N. Karasch and R. Swidler, *J. Org. Chem.*, 19, 1704 (1954).

TABLE IV
BIS(ω-HALOALKOXY- OR β-TOSYLOXYETHOXYARYL) DISULFIDES

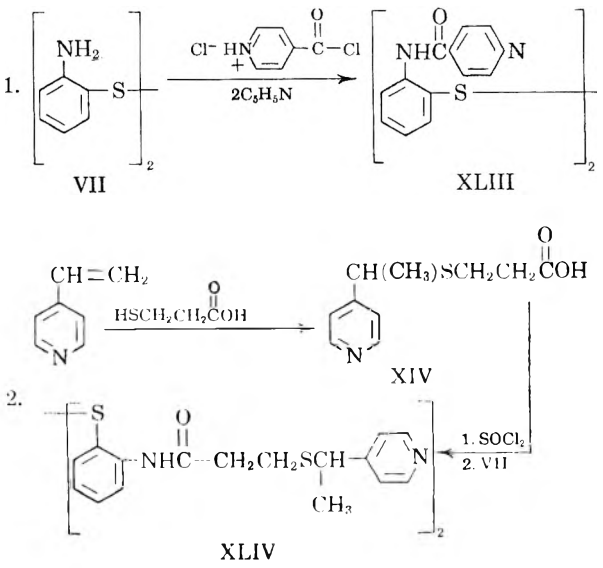
Bis-disulfide[a]	Crude Yield,[b] %	M.P.,[c] °C.	Recryst. Solvent	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Transfer Constant (C)
4-β-Tosyloxyethoxy-1-naphthyl (XXX)	75	141.2–142.6	*i*-PrOH or gl. HOAc	61.10	60.80 60.65	4.59	4.43 4.38			17.17	17.42 17.16	1.81
4-β-Bromoethoxy-1-naphthyl (XXXI)	41	99.2–100.2	*i*-PrOH					28.32	28.52 28.49	11.36	11.56 11.50	1.46
4-β-Chloroethoxy-1-naphthyl (XXXII)	68	90.5 91.3	EtOH/ *i*-PrOH					14.92	14.68 14.82	13.49	13.50 13.51	1.57
4-γ-Chloropropoxy-1-naphthyl (XXXIII)	60	100.1–100.9	*i*-PrOH					14.09	13.93 13.82	12.74	12.70 12.66	1.40
2-β-Bromoethoxy-1-naphthyl (XXXIV)	88	144.6	Cyclohexane or gl. HOAc					28.32	27.66 27.71	11.36	10.93 11.17	2.88
2-β-Chloroethoxy-1-naphthyl (XXXV)	83	155.4–156.4	EtOH/ *i*-PrOH					14.92	14.81 14.77	13.49	13.74 14.07	2.60
4-β-Bromoethoxy-2,6-xylyl (XXXVI)	82	104.8–106.5	*n*-C_6H_{14}	46.15	46.15	4.65	4.64					0.73
4-γ-Bromo-*n*-propoxy-1-naphthyl (LI)	53	104.5–105.5	*i*-PrOH					26.98	26.6 26.9	10.82	10.57 10.78	1.42

[a] Above disulfides are all bright yellow crystalline compounds when in purest form, XXXIV and XXXV being needlelike crystals, and compounds, XXXI, XXXV, and XXXVI being more of a lemon shade as compared with a plain yellow color for the others. [b] Yields are based on products of 5° melting range or better. [c] Corrected melting point of analytical sample.

fides containing labile halogen because of the fact that both methods involve cleavage of mixed aryl sulfide intermediates by strong bases.

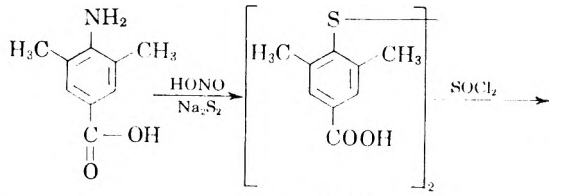
A second objective of this project was the preparation of symmetrical, substituted diaryl disulfides containing tertiary amino groups. Three such compounds were prepared as follows. Bis(2-isonicotinamidophenyl) disulfide (XLIII) was prepared by acylating VII with isonicotinyl chloride hydrochloride.[23]

Bis[2 - β - (α′ - 4′ - pyridylethyl)propionamido phenyl] disulfide (XLIV), a sirup with theoretical amine content (on basis of perchloric acid titration), was prepared by treating VII with an acid chloride obtained from the addition product of 4-vinylpyridine with β-mercaptopropionic acid. The intermediate carboxylic acid was assigned the configuration β[-(α′-4′-vinyl)ethylthio]propionic acid (XLV) on basis of a prominent band in the infrared absorption spectrum at 1734 cm.$^{-1}$,[29] indicating presence of a terminal methyl group (indicating that mercaptan addition was in accordance with Markownikoff's rule). The third and last bis(tertiary-amino-substituted) diaryl disulfide, bis(4-β-dimethylaminoethoxycarbonyl-2,6-xylyl) disulfide (XLVI), was prepared by treating bis(4-chloroformyl-2,6-xylyl) disulfide (XLV-III), prepared in turn from the new diacid, bis(4-carboxy-2,6-xylyl) disulfide (XLIX), by treatment with β-dimethylaminoethanol:

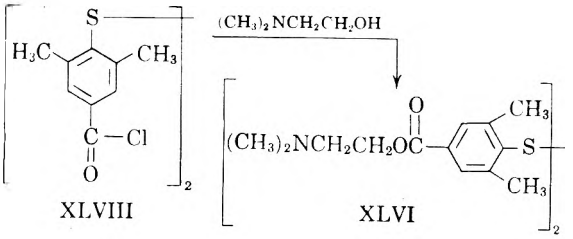


(28) E. Späth, *Ber.*, 59, 1429 (1926).

(29) Determined by Mr. Dexter E. Woodford at this laboratory.



3. XLIX



XLVIII XLVI

EXPERIMENTAL[30]

4-Chlorosulfonyl-1-naphthalene acetic acid (II). To 583 g. (5.0 moles) of chlorosulfonic acid (Eastman Kodak pract. grade), kept at 0–5°, was added slowly 186 g. (1.00 mole) of 1-naphthaleneacetic acid (Matheson, Coleman and Bell Co.). As the reaction proceeded, hydrogen chloride gas was evolved. After 6 hr. at 0°, followed by 12 hr. at room temperature, reaction mixture was warmed to 40–45° for 4 hr. The dark, viscous sirup was poured onto ice and 107 g. of yellow-brown precipitate collected. This solid was recrystallized twice from benzene to 91 g. (32%) of white needles, m.p. 174–175°.

Anal. Calcd. for $C_{12}H_9ClO_4S$: Cl, 12.45; S, 11.26. Found: Cl, 12.40, 12.64; S, 11.37, 11.26.

Bis(4-β-hydroxyethyl-1-naphthyl) disulfide (III). To a stirred suspension of 7.6 g. (0.20 mole) of lithium aluminum hydride (Metal Hydrides Inc.) in 600 ml. of anhydrous ethyl ether (dried over sodium), a solution of 25.2 g. (0.0877 mole) of II in 400 ml. of this ether was introduced dropwise. After addition of all reagent, the system was refluxed for another 8 hr. The reaction mixture was carefully hydrolyzed with water and then with dilute acid. By extracting the yellow solid, m.p. 101–110°, so obtained with ether, and recrystallizing the solid so isolated from benzene/*n*-hexane mixture, 3.8 g. (21%) of fine yellow crystals, m.p. 115–117°, containing 95% of theoretical disulfide,[37] having *C* value 1.95, was obtained.

Anal. Calcd. for $(C_{12}H_{11}OS)_2$: C, 66.33; H, 4.17; S, 14.75. Found: C, 65.60, 65.50; H, 4.28, 4.23; S, 14.84, 14.99.

Bis(4-β-bromoethyl-1-naphthyl) disulfide (IV). To a mixture of 600 mg. (0.0015 mole) of IV in 50 ml. benzene (C.P.) at 10°, was added a solution of 140 mg. phosphorus tribromide in 20 ml. of this benzene, dropwise, with stirring. The reaction mixture was allowed to stand for 3 hr. at 10°, then warmed to 40°. Upon removal of benzene *in vacuo*, the sirup residue was dissolved in a minimum of ethanol. The dibromide crystallized from this solution upon standing overnight, in 90 mg. (13%) quantity of white crystals, m.p. 113–115°.

Anal. Calcd. for $(C_{12}H_{10}BrS)_2$: Br, 30.02. Found: Br, 28.87, 28.99.

Bis(4-carboxymethyl-1-naphthyl) disulfide (V). To 7.0 g. (0.025 mole) of II was added 90 ml. glacial acetic acid and 30 ml. of 50% hydriodic acid. The mixture was well shaken, and allowed to stand for 24 hr. at room temperature. To the darkened reaction mixture was added 300 ml. of ice cold 10% sodium thiosulfate solution. By extracting the resultant yellow precipitate with hot benzene 2.05 g. (38%) of yellow fluffy powder, m.p. 187–189°, with *C* value 2.24, was obtained.

Anal. Calcd. for $(C_{12}H_9O_2S)_2$: C, 70.90; H, 5.45; S, 15.77. Found: C, 69.45; H, 5.60; S, 15.02.

Bis(4-β-hydroxyethylphenyl) disulfide (VI). A 24.0 g. (0.175 mole) quantity of 4-β-hydroxyethylaniline, m.p. 110–111°, (isolated from a mixture of *o*- and *p*-β-hydroxyethyl-anilines obtained from Eastman Kodak Co. by fractional crystallization) was diazotized, the diazonium solution treated with potassium ethyl xanthate, and the xanthate ester hydrolyzed in accordance with the mercaptan synthesis procedure of Tarbell and Fukushima.[12b] Upon acidifying the alkaline hydrolysis system with 6*N* sulfuric acid, and cooling the system to 0°, an orange solid was obtained. This solid, when recrystallized from a hot absolute ethanol/*n*-hexane solution by cooling to −78°, yielded 5.46 g. (20.5%) of pale yellow platelets, m.p. 86–96°. By recrystallizing this product from 725 ml. of aqueous 40% ethanol, 3.83 g. of flaky white crystals (14.4%), m.p. 94.8–95.2°, was obtained. Although this compound did not dissolve in concentrated ammonium hydroxide, nor dilute sodium hydroxide, and would not form a silver or lead mercaptide, it could be reduced with sodium sulfite solution to a compound which did react with silver nitrate to form a mercaptide. The *C* value of VI was 0.09. On basis of titration for disulfide content,[37] 94.4% of theoretical disulfide was accounted for.

Anal. Calcd. for $(C_8H_9OS)_2$: C, 62.71; H, 5.92; S, 20.93. Found: C, 62.45, 62.70; H, 6.12, 6.13; S, 20.48, 20.31.

Bis(2-haloacylamidophenyl) disulfides (VIII A-C). VIII A. To a solution of 20.0 g. bis(2-aminophenyl) disulfide (VII) (0.0806 mole of American Cyanamid Co. product) in 450 ml. glacial acetic acid was added 100 ml. of saturated sodium acetate solution. The solution was cooled to 0°, and treated with 16.0 ml. of chloroacetyl chloride (Eastman Kodak white label), dropwise with stirring over a 20-min. period. The system, now containing a voluminous white precipitate, was diluted with one volume of cold water, and the precipitate collected, washed, and dried on a clay plate. The 34.7 g. (87%) of crude product, m.p. 126.5–129°, was recrystallized from 85% ethanol to white needles, m.p. 130.2–130.9°, (77%), and this product recrystallized for analysis to m.p. 133.2–133.7°.

VIII B. By treating VII with bromoacetyl bromide in the same manner, a 74% yield of greenish white bis(2-bromoacetamidophenyl) disulfide (VIII B), m.p. 140.5–143.5, was obtained. By recrystallizing this product twice from absolute ethanol a white, needle-like product, m.p. 157.4–157.7°, was obtained.

VIII C. A 57% yield of VIII C was obtained by treating VII with β-bromopropionyl chloride (Matheson, Coleman and Bell Co.) in this manner. However, if VII was treated with two mole equivalents of this acyl chloride in a benzene solution containing two mole equivalents of pyridine, a 79% yield of VIII C was obtained.

Isolation of IX. By treating a mixture of 60 g. of VII in benzene solution, two equivalents of chloroacetyl chloride (Eastman Kodak pract. grade), and two equivalents of solid sodium bicarbonate at reflux for 2 hr., cooling the system, and washing it with water, hydrochloric acid, water, bicarbonate solution, water, drying the benzene solution, and removing benzene *in vacuo*, 87.5 g. of a mixture of VIII A and IX was obtained. By recrystallizing from hot absolute ethanol, 32.8% of orange colored needles, m.p. 144.7–146.2°, was obtained. By repeatedly recrystallizing the most insoluble fraction six more times from ethanol, a 100-mg. crop of white needles, m.p. 151.7–152.8°, was obtained.

Anal. Calcd. for $C_{16}H_{13}Cl_3N_2O_2S_2$: C, 44.13; H, 3.01; Cl,

(30) Melting points of all compounds reported herein are corrected. Element analyses were determined by Messrs. Wellman W. Dietz and William C. Hukari of this laboratory or by Clark Microanalytical Laboratory, Urbana, Ill. Amine content of compounds XLIII, XLV, and XLVI was determined by titrating benzene solutions of these compounds with perchloric acid in acetic acid to a methyl violet end point. Disulfide content was determined by a sodium sulfite–silver nitrate titration method. (See reference 37).

24.42; N, 6.43; S, 14.71. Found: C, 44.25, 44.24; H, 2.83, 3.09; Cl, 24.27, 24.08; N, 6.55, 6.36; S, 14.84, 14.94.

4-Chloracetamido-1-naphthalenesulfonyl chloride (XII). By treating 1-naphthylamine (Du Pont tech. grade) in benzene solution with a mole equivalent each of chloroacetyl chloride and pyridine at reflux, and working up the product an 85% yield of crude α-chloroacetnaphthalide (XI), m.p. 153–159°, was obtained. This product was recrystallized from absolute ethanol to a 58% yield of pure XI, as white needles m.p. 163.6–166.8°, (recrystallized for analysis to m.p. 166.4° as compared with m.p. 161° reported for XI by Tommasi[14]).

Anal. Calcd. for $C_{12}H_{10}ClNO$; Cl, 16.14; N, 6.38. Found: Cl, 15.95, 16.01; N, 6.41, 6.25.

To a flask containing 200 ml. of chlorosulfonic acid maintained at 0°, was added 38.7 g. of XI, m.p. 166.1–166.4°, in small portions, with stirring, over a 20-min. period. This solution was warmed to 60°, and maintained at this temperature for 1 hr. to complete hydrogen chloride evolution. The solution, after being cooled, was poured onto ice water, and the resultant precipitate collected, washed, and dried. The 53.3 g. (95.3%) of product was recrystallized from 600 ml. hot chlorobenzene to 23.1 g. (41.3%) of tan needles, m.p. 180–182°. An analytical sample, recrystallized to tiny yellow needles, m.p. 184–185°, had an equivalent weight (on basis of halogen hydrolyzed with piperidine and titrated potentiometrically with silver nitrate solution) of 157 (theoretical eq. wt. is 159).

Anal. Calcd. for $C_{12}H_9Cl_2NO_3S$: Cl, 22.29; S, 10.08. Found: Cl, 22.33, 22.53; S, 10.25, 10.06.

Bis(4-chloroacetamido-1-naphthyl) disulfide (X). To 9.55 g. of XII, (0.0302 mole) m.p. 184–185°, was added 180 ml. of glacial acetic acid, and 30 ml. of 50% hydriodic acid. This slurry formed a gel upon standing 1 hr. at room temperature. The gel was mixed thoroughly, and allowed to react at this temperature for another 23 hr. Upon addition of 300 ml. of a 10% solution of hydrated sodium thiosulfate in water, the resultant precipitate was collected, washed, and dried. The 6.5 g. of product was separated into a 1.76 g. fraction, m.p. 195–198, and 1.57 g. of less soluble fraction, m.p. 204–205°, by recrystallizing from hot glacial acetic acid. By recrystallizing both fractions separately from dioxane/chlorobenzene solutions, and combining fractions, 1.67 g. of solid, m.p. 203.0–203.5°, (0.00334 mole or 22.1%) was obtained. This compound contained 100% of theoretical disulfide on the basis of the sodium sulfite/silver nitrate titration method. The product was insoluble in most organic solvents, and only slightly soluble in hot glacial acetic acid, hot chlorobenzene, or hot dioxane.

Anal. Calcd. for $(C_{12}H_9ClNOS)_2$: S, 12.79. Found: S, 12.29, 12.39.

Treatment of VIII A *with sodium alkyl mercaptides and with ammonium hydroxide.*

A. By treating 10.0 g. (0.0250 mole) VIII A with a solution of 4.51 g. (0.0500 mole) butyl mercaptan in 200 ml. methanol to which 1.15 g. (0.0500 g. atom) sodium has been added, at reflux for 1.5 hr., and pouring reaction mixture into one volume of cold water, 8.2 g. of white crystals, m.p. 181.2°, was obtained (8.25 g. is theoretical yield for 0.0500 mole of 3-keto-2,3-dihydro-1,4-benzothiazine (XIII) whose m.p. has been reported as 179°[18]). The compound gave a negative Beilstein test, and negative tests for mercaptan or disulfide functions.

B. By treating another 0.0250 mole of VIII A similarly with 0.0500 mole of sodium methyl mercaptide, 7.88 g. (95.5% yield on basis of XIII as a product) of white flaky crystals, m.p. 178.2–180.2°, was obtained as in A.

C. By treating 20.1 g. (0.0500 mole) VIII A with 400 ml. of 29% ammonium hydroxide (d = 0.90), in an autoclave for 4 hr. at average temperature of 90°, 8.5 g. of gray crystals, m.p. 180.0–181.2°, was isolated (52% yield on basis of XIII as product). This product, when recrystallized twice from aqueous ethanol, gave white needles, m.p. 181.3–181.5°, whose melting point was undepressed upon admixture with product obtained in A.

Analysis of product A. Calcd. for C_8H_7NOS: C, 58.16; H, 4.27; S, 19.41. Found: C, 58.75, 58.80; H, 4.46, 4.57; S, 19.14.

Treatment of VIII C *with aqueous sodium bicarbonate.* To 1.90 g. (0.00375 mole) of VIII C was added an aqueous solution of 0.61 g. (0.0073 mole) of sodium bicarbonate dissolved in 20 ml. of water. After refluxing the mixture for 40 min., and adding 10 ml. absolute ethanol, the mixture was refluxed for an additional 2 hr. Upon cooling, 0.40 g. (25% based on XIV) of white flaky crystals was formed. By recrystallizing this product from 8 ml. of absolute ethanol, 0.19 g. of white flakes, m.p. 213–214°, was obtained. This product also gave a negative Beilstein test, and contained neither mercaptan nor disulfide [compare with melting point reported for 2,3-dihydro-1,5-benzothiazepin-4(5)-one (XIV)—215–216°[19]].

Anal. Calcd. for C_9H_9NOS: C, 60.32; H, 5.06; N, 7.82. Found: C, 60.30, 60.42; H, 5.33, 5.21; N, 7.42.

1-β-Tosyloxyethoxynaphthalene (XV). This compound was prepared by tosylating 1-β-hydroxyethoxy-naphthalene according to one of the methods described by Tipson.[31]

A 17.1-g. quantity (0.0910 mole) of 1-β-hydroxyethoxynaphthalene, m.p. 40–43°, (obtained from reaction of 1-sodionaphtholate with ethylene bromohydrin) was added in small portions to a stirred solution of tosyl chloride (Eastman Kodak pract. grade) in 72 ml. of dry pyridine precooled to −10°, in brine. When addition was completed, the reaction mixture was allowed to stand for 20 min. at −10°. A solution of 210 ml. of 5*N* sulfuric acid, cooled to 0°, was added to it. By rubbing the oil, which now separated from the system, against the flask wall with a glass rod, a white crystalline solid was obtained. The washed, dried solid weighed 22.4 g., had m.p. 77–87°. By recrystallizing this product from 340 ml. of hot methanol, 13.9 g. (40.7%) of white platelets, m.p. 98.7–99.2°, was obtained.

4-β-Bromethoxy-1-naphthalenesulfonyl chloride (XXIV). This compound, as well as the other ω-haloalkoxy aromatic sulfonyl chlorides, and 4-β-tosyloxyethoxy-1-naphthalene sulfonyl chloride, whose preparations are indicated in Table III, was prepared by chlorosulfonation of the respective haloether or tosyloxy ether by an adaptation of the method of Huntress[7] as follows: A solution of 24.0 g. (0.096 mole) of 1-β-bromethoxynaphthalene (XVI), m.p. 33.9–35.1°, in 90 ml. of chloroform solution, was cooled in an ice salt bath. To it was added, dropwise, with stirring, 22.2 g. (2.00 equivalents) chlorosulfonic acid. During this time, a white precipitate of sulfonic acid formed, and redissolved. The mixture was allowed to warm to room temperature, and stand at this temperature, with stirring, for 20 min. The reaction mixture was poured onto 400 g. of cracked ice. After addition of more chloroform and some brine to the system, it was filtered free of 3.6 g. of the sulfonic acid precipitate. After separating liquid phases of the filtrate, washing, and drying the chloroform phase, and removing chloroform, 27.1 g. (80.7%) of sulfonyl chloride, m.p. 118.7–120.7°, was isolated as light yellow crystals. By recrystallizing from either hot glacial acetic acid or hot isopropanol, large yellow needles, m.p. 120.2–120.7°, were obtained.

Bis(4-β-bromethoxy-1-naphthyl) disulfide (XXXI). The general procedure of Bauer and Cymerman[16] was followed in reducing the aromatic sulfonyl chlorides listed in Table III to the corresponding disulfides with this exception. Since the substituted naphthalenesulfonyl chlorides were not soluble in a glacial acetic acid/50% hydriodic acid mixture, enough benzene was added to this mixture to make a homogeneous ternary system in which these sulfonyl chlorides were soluble. Only 4-β-bromethoxy-2,6-xylnesulfonyl chloride (XXXVI) did not require benzene as a component of the reduction system.

A solution of 49.4 g. (0.142 mole) XXIV, m.p. 119.7–

(31) R. S. Tipson, *J. Org. Chem.*, 9, 235 (1944).

120.7°, in 420 ml. benzene, was treated with 1085 ml. of glacial acetic acid and 189 g. of 47.7% hydriodic acid (a fresh, yellow colored Eastman Kodak white label grade solution or 5.00 mole equivalents of hydriodic acid per mole of XXIV). The reaction mixture, which turned brown immediately, was shaken, and allowed to stand at room temperature for 23 hr. To this was added 1170 ml. of an aqueous solution containing 123 g. of sodium thiosulfate pentahydrate (enough thiosulfate to decolorize all iodine). The layers were separated, the aqueous layer extracted with more benzene, and the washed, dried benzene extract distilled *in vacuo*, leaving 40.6 g. of residual golden sirup. An extract of 39.4 g. of this sirup in 1170 ml. hot isopropyl alcohol dissolved all product except 4.2 g. of gummy residue. The decantate, upon cooling, yielded a mixed crop of waxy rosettes, and very fine yellow crystals. The precipitate, when collected, crushed, rinsed with cold isopropanol, *n*-hexane, and desiccated, weighed 22.3 g. (56.1%), of m.p. 89–93°. By recrystallizing this product from 240 ml. of hot isopropanol, 16.3 g. (40.9%) of lemon yellow crystals, m.p. 99.2–100.2°, was obtained. The equivalent weight of disulfide (on basis of disulfide titration method) was 565. (Theoretical eq. wt. is 564.4). The product can be recrystallized from hot glacial acetic acid also.

Ethyl 4-γ-chloropropoxy-1-naphthalene sulfonate (XLVII). In attempting to recrystallize 4-γ-chloropropoxy-1-naphthalenesulfonyl chloride (XXVI), m.p. 124.1–125.6, from 16 parts of hot absolute ethanol, the melting of the product was lowered to 92–98°. By recrystallizing this crystallizate from ethanol several times more, a crop of long, coarse, white needles, m.p. 102.2–103.3, of the ethyl sulfonate (XLVII) was obtained. Since it is known that the β-chloroethoxynaphthalenes XVIII and XIX can be recrystallized from hot ethanol without solvolysis, it is considered very unlikely that an ethyl ether rather than an ethyl ester was obtained from XXVI.

Anal. Calcd. for $C_{15}H_{17}ClO_4S$: Cl, 10.78; S, 9.75. Found: Cl, 10.51, 10.15; S, 9.79, 9.76.

Reaction of diphenyl disulfide with chloroacetyl chloride. A. A solution of 34.4 g. (0.158 mole) of diphenyl disulfide (Eastman Kodak white label) in 100 ml. of dry carbon disulfide was added dropwise, over a 20-min. period to a mixture of 44.0 g. (0.330 mole) anhydrous aluminum chloride (Merck Co.) and 39.3 g. (0.348 mole) chloroacetyl chloride, precooled to 0°. After the addition was complete, the system was removed from the ice bath, and allowed to react for an additional 40 min. The mixture was poured onto 500 g. of crushed ice, containing 50 ml. of concentrated hydrochloric acid. The gummy product which appeared was extracted with chloroform, and the extract washed, and dried. Upon removal of solvent at below 27° *in vacuo*, 39.09 g. of brown gum was isolated (indicating that a maximum of 16.6% of dichloracetylated product was present). By dissolving the gum in 38 ml. acetone, adding nine volumes of isopropanol, and cooling to −78°, a 1.0-g. fraction of white crystalline phenyl thiol chloroacetate (XL), having m.p. 43.0–43.5°, (compare with m.p. 45° by Dalgliesh and Mann[22]) was obtained.

Anal. Calcd. for C_8H_7ClOS: Cl, 18.99; S, 17.17. Found: Cl, 19.09, 19.11; S, 17.17, 17.01.

B. By combining the same ratio of reagents used in A in a different manner, *i.e.*, by adding the aluminum chloride and then the chloracetyl chloride to the solution of disulfide, allowing the mixture to warm to 46°, and to react at reflux for 2.25 hr., and distilling the gum isolated from the hydrolyzate, an oil, b.p. 127–145°/9 mm., was obtained. Upon cooling the distillate, white crystals of m.p. 43° were formed (27%).

Preparation of 3-chloroacetomesitylenethiol chloroacetate (XLI). A solution of 2.195 g. dimesityl disulfide[24] in 3 ml. of dry carbon disulfide was added, dropwise, with stirring, to a mixture containing 4.4 mole equivalents of anhydrous aluminum chloride, and 4.0 mole equivalents of chloroacetyl chloride in 10 ml. of dry carbon disulfide, cooled in an ice bath. There was no evolution of hydrogen chloride gas at 0°. The reaction mixture was refluxed for 20 min. at 46°, causing considerable evolution of hydrogen chloride. By cooling the mixture, hydrolyzing the product, and working it up in the usual manner, 3.0 g. (91% of dichloroacetylated product on a weight basis) of viscous brown oil was obtained. By triturating this product with much petroleum ether, 1.045 g. (32%) of white crystalline product, m.p. 112–114.5° was obtained. By recrystallizing the product from 2:3 chloroform/*n*-hexane white crystals, m.p. 118.5–119.5°, were obtained. The product was not a mercaptan, and had no activity as a polymerization modifier.

Anal. Calcd. for $C_{13}H_{13}Cl_2O_2S$: Cl, 23.31; S, 10.53. Found: Cl, 23.58; S, 10.34.

Bis(2-chloroacetophenyl) disulfide (XLII). An ethereal solution of diazomethane was prepared from 2.5 g. of *p*-tolylsulfonyl methyl nitrosoamide by the method of DeBoer and Backer[32] by treatment with caustic potash solution. To the ethereal diazomethane solution, was added, slowly, a solution of 1.00 g. of bis(2-chloroformylphenyl) disulfide,[18] m.p. 153–155°, in warm dry benzene. After the initial vigorous reaction had subsided, the mixture was allowed to stand for 1 hr. After excess diazomethane and some solvent was removed *in vacuo*, 20 ml. of benzene was added to the concentrated bisdiazoketone solution. Upon introduction of hydrogen chloride gas to the system, white crystals of bischloroketone formed. The product, weighing 0.46 g. (43%), had m.p. 183–185°, and was recrystallized to m.p. 184–185°. This compound had a *C* value of 0.14.

Anal. Calcd. for $(C_8H_6ClOS)_2$: C, 52.00; H, 3.26. Found: C, 52.00, 52.25; H, 3.36, 3.31.

Bis(2-isonicotinamidophenyl) disulfide (XLIII). To 17.8 g. (0.100 mole) of isonicotinyl chloride hydrochloride, prepared by the method of Späth[28] from isonicotinic acid (Reilly, Tar and Chem. Co.), was added 50 ml. of dry benzene, and 8.0 g. (0.10 mole) of dry pyridine. To this system was added, dropwise, with stirring, a solution of 12.4 g. (0.0500 mole) VII in 150 ml. of benzene, over a 0.5-hr. period. The mixture was refluxed for 0.5 hr., cooled, poured into ice water, and the yellow precipitate collected. The solid was washed successively with sodium bicarbonate solution, water, dilute hydrochloric acid, more water, more bicarbonate, and more water, and dried on a clay plate. A diamide sample weighing 16.0 g. (70.0%) of compound, m.p. 185.0–186.5°, was obtained. By recrystallizing the product from absolute ethanol, white crystals, m.p. 185.5–186.5°, were obtained. The equivalent weight of product (on basis of amine titration) was 228 (theoretical eq. wt. is 229.2). This compound had a *C* value of 3.6.

By preparing the compound by the method used by Hook to prepare bis(2-nicotinamidophenyl)disulfide,[33] a 35% yield of product, m.p. 185° was obtained.

Anal. Calcd. for $(C_{12}H_9N_2SO)_2$: C, 62.84; H, 3.95; N, 12.21; S, 13.97. Found: C, 62.40; 62.55; H, 3.99, 3.96; N, 12.23, 11.89; S, 24.11, 24.01.

4-[α-(β'-Carboxyethylthio)ethyl]pyridine (XLV). Upon mixing 34.4 g. (0.328 mole) of 4-vinylpyridine (Reilly Tar and Chem. Co. product stabilized with *p-t*-butyl-catechol) and 38.7 g. (0.328 mole) of 90% β-mercaptopropionic acid (B. F. Goodrich Co.), great evolution of heat was observed, and the reaction mixture solidified. After washing the solid with water, then benzene, and drying it on a clay plate, 53.4 g. (73.1%) of white crystals, m.p. 154.0–155.0, was obtained. The melting point of a sample recrystallized for analysis was 154.0–154.5°.

Anal. Calcd. for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; S, 15.17. Found: C, 56.55, 56.45; H, 6.13, 6.12; S, 15.10, 15.15.

Bis[2-β-(α'-4'-pyridylethylthio)propionamidophenyl] disulfide (XLIV). To 5.00 g. (0.0474 mole) of XLV, m.p. 154.0–155.0°, was added 50 ml. of chloroform followed by 5.64 g.

(32) T. J. DeBoer and H. J. Backer, *Rec. trav. chim.*, **73**, 229 (1954).

(33) E. O. Hook, U. S. Patent 2,502,150 (1950).

(0.0474 mole) of thionyl chloride. After refluxing the mixture for 15 min. on a hot water bath, excess thionyl chloride and chloroform were removed by distillation *in vacuo*. To the oily residue was added a solution of 2.94 g. of VII in 70 ml. of chloroform, and 7.77 g. (0.948 mole) of anhydrous sodium acetate. The mixture was refluxed on a hot water bath for 1 hr., washed twice each with sodium bicarbonate solution and water, and the chloroform extract dried, and evaporated to dryness. The residue was a brown sirup weighing 7.12 g. (61%), giving an equivalent weight of 314 (on basis of titration of amine function, indicating that 99% of theoretical amine was present). The *C* value of this compound was 5.0.

Bis(4-carboxy-2,6-xylyl) disulfide (XLIX). A 2.54 g. (0.0154 mole) quantity of 4-aminomesitylenic acid, m.p. 249–254°, (prepared by a series of reactions from mesitylene, *via* nitromesitylene,[34] 4-nitromesitylenic acid,[3,35] and 4-amino-mesitylenic acid[36]) was treated with 3.08 ml. of concentrated hydrochloric acid and 50 ml. of water. The slurry was cooled to 0°, and diazotized by addition of an ice cold solution of 1.06 g. sodium nitrite in 10 ml. of water (to a starch-iodide paper end point), in small portions. The diazonium solution was decanted from 0.32 g. of unreacted amino acid, and added, dropwise, to a solution containing 4.9 g. of sodium disulfide nonahydrate, 0.52 g. sulfur, 0.61 g. sodium hydroxide, and 8 ml. water, kept at 5°. After addition of diazonium-salt was complete, the system was allowed to warm to room temperature, and to stand at this temperature for 2 hr. The system was acidified with 2.8 ml. of concentrated hydrochloric acid, and the precipitate filtered. The crude solid was extracted with aqueous sodium carbonate, and the extract reacidified. By recrystallizing the product from hot 85% ethanol, 1.40 g. (50%) of very fine yellow crystals, m.p. 286.5–287.5°, was obtained. A sample, recrystallized for analysis from absolute ethanol at −78°, was a white power of m.p. 281–282°. The compound was insoluble in cold *n*-hexane or cold benzene, but soluble in cold ethanol or hot chloroform. The compound, which gave negative tests for mercaptan, had a *C* value of 2.11.

Anal. Calcd. for $(C_9H_9O_2S)_2$: C, 59.64; H, 5.02; S, 17.69. Found: C, 59.95, 59.80; H, 5.10, 5.17; S, 17.60.

Bis(4-chloroformyl-2,6-xylyl) disulfide (XLVIII). By treating 1.23 g. of XLIX, m.p. 288–290°, with 40 ml. of thionyl chloride at reflux for 3 hr., removing excess thionyl chloride and some benzene, a sirup was obtained. By adding a few ml. of benzene followed by addition of some *n*-hexane, a yellow precipitate was obtained. When collected, rinsed with hexane, and desiccated, the product, weighing 0.37 g. (27%), m.p. 162.9–164.4°, having a sweet sharp odor, was obtained.

Bis(4-β-dimethylaminoethoxycarbonyl-2,6-xylyl) disulfide (XLVI). By treating 0.98 g. (0.0027 mole) of XLIX with thionyl chloride just as in the previously described preparation of XLVIII, a crude sirupy form of XLVIII was obtained. This sirup was dissolved in 20 ml. of dry benzene. To this was added a solution of 0.48 g. (0.0054 mole) β-dimethylaminoethanol (Eastman Kodak white label) in benzene. After refluxing the mixture for 1 hr., during which time a hydrochloride precipitated, the benzene was removed, *in vacuo*, and the residue dissolved in water. Solid potassium carbonate was added to this solution until maximum coagulation of gum had been achieved. The gum was extracted with ether, the extract washed twice with brine, dried over anhydrous sodium sulfate, and the ether removed. The residual 0.50 g. of brown sirup (37%), having an equivalent weight of 262 (on basis of amine content, indicating 96% of theoretical amine content, theoretical eq. wt. being 252), gave a *C* value of 2.2.

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(34) G. Powell and F. R. Johnson, *Org. Syntheses*, Coll. Vol. II, 449 (1943).

(35) Emerson, *Am. Chem. J.*, 8, 269 (1868).

(36) H. L. Wheeler and C. Hoffman, *Am. Chem. J.*, 44, 119 (1910).

(37) This disulfide assay method, as reported by G. E. Meyer, R. J. Coleman, and R. M. Pierson, "Behavior of Some Bis-Type Modifiers in Emulsion Butadiene Polymerization," Copolymer Report No. 3635 to Office of Synthetic Rubber, F.F.C., 1954, (a publication distributed by the Dept. of Commerce, Office of Technical Services as indicated in Public Bulletin 118310s, and available from the Library of Congress, Photoduplication Service, Publication Board Project, Washington, D.C.), is based upon the newly discovered fact that diaryl disulfides are cleaved quantitatively by treatment with sodium sulfite, generally to one mole of sodium mercaptide and one mole of Bunte salt, and in special cases to two moles of sodium mercaptide. The mercaptide content is then determined by potentiometric titration with standardized silver nitrate solution by a modification of the method of M. W. Tamale, L. B. Ryland and V. C. Irvine, *Ind. Eng. Chem. Anal. Ed.*, **13**, 618 (1941), substituting a silver electrode sensitized by treatment with ammoniacal, alcoholic dodecyl mercaptan for the prescribed silver sulfide electrode.

[CONTRIBUTION FROM THE WILLIAM H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY AND THE RESEARCH LABORATORIES OF THE WILLIAM S. MERRELL COMPANY]

A Study of the Chemistry of Pyrophthalone and Related Compounds

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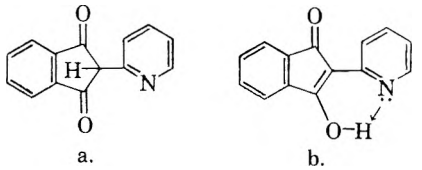
The synthesis and reactions of pyrophthalone and related compounds has been investigated. Pyrophthalone, 2-(2′-pyridyl)-1,3-indanedione, and certain other 2-substituted-1,3-indanediones have been shown to exist in a chelated enol form by chemical evidence and a comparison of infrared spectra. However, the carbonyl group was reactive toward organometallic compounds to form 2-hetero-3-arylindan-1-on-3-ols from which the elements of water could be eliminated to form the corresponding 2-hetero-3-arylindenone. The indanediones and the indenones were reduced by sodium borohydride, catalytically, and in one case, by Clemmensen's method to yield a variety of hydrogenated products.

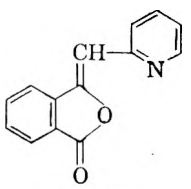
This work was undertaken to provide, for pharmacological testing, a series of new 2-substituted-1,-3-indanediones in which the substituent groups are heterocyclic residues. These structures suggested possible activity as anticonvulsants and estrogenic antagonists. Perhaps the best known of such substances is pyrophthalone itself, I.



a. b.

I

Pyrophthalone was first synthesized by Jacobsen and Reimer[1] and later by von Huber[2] by the condensation of α-picoline with phthalic anhydride. These workers correctly assumed the indanedione structure for their product, although the phthalide-type structure, LIV, was suggested by von Huber for a low-melting product he obtained at one time.



LIV

In an attempt to repeat von Huber's work, Eibner[3,4] isolated only one product, a high melting compound, I. When treated with alcoholic sodium methoxide, phthalides produce a red color and rearrange, but these phenomena were not observed with Eibner's product. On the basis of these data, Eibner assumed von Huber's low melting product to be impure pyrophthalone having the symmetrical structure shown in I above. In our work, derivatives of phthalide were not encountered. Furthermore, an infrared spectrum of pyrophthalone shows a diminished carbonyl band at 6.04μ and a band at 8.4μ attributed to an NH stretching. In many instances, the compounds decolorized potassium permanganate solution, produced a color with ferric chloride, and failed to form picrates. These data are indicative of a chelated enolic system, Ib, for compounds analogous to pyrophthalone.

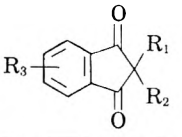
DISCUSSION

2-Substituted-1,3-indanediones. Table I lists the methods for the synthesis of 2-substituted-1,3-indanediones and the physical data pertaining to these compounds. For the most part, the 2-substituted-1,3-indanediones were synthesized by condensing phthalic anhydride with an alkyl heterocycle. The reactive hydrogens were usually restricted to those on a methyl group although, occasionally, reactive methylene groups were found to condense, as in 2-ethylpyridine and 2-benzylpyridine. Attempts to condense phthalic anhydride with either ethyl 2-pyridyl acetate or 2-[β-(*N*-piperidylethyl)]pyridine failed.

The most reactive methyl groups are those on carbon adjacent to a ring nitrogen. Thus, the product from 2,3- and 2,4-, and 2,5-dimethylpyridine consistently contained the 2-pyridyl nucleus. In no case was a product formed where both methyl groups had reacted. Furthermore, 2-methylquinoline condensed readily, whereas 4-methylquinoline was unreactive. It is interesting to note that though 2-methylpyridine readily condensed to form pyrophthalone, 2-methylpyrazine resembled toluene in being quite unreactive toward phthalic anhydride. An analogous situation arises in comparing 2-methylquinoline and 2-methylquinoxaline. The former was very reactive, (more so than 2-methylpyridine), while the latter was unreactive. Methyl groups at the 2-position of cyclic structures containing hetero-atoms in both the 1- and 3- positions were sufficiently reactive to form condensation products readily; thus, 2-methylbenzimidazole, 5-chloro-2-methylbenzimidazole, and 2-methylbenzothiazole formed 2-substituted-1,3-indanediones readily. Although reactive,

(1) E. Jacobsen and C. L. Reimer, *Ber.*, **16**, 2602 (1883).
(2) H. von Huber, *Ber.*, **36**, 1653 (1903).
(3) A. Eibner and H. Merkel, *Ber.*, **37**, 300 (1904).
(4) A. Eibner and K. Hofmann, *Ber.*, **37**, 3023 (1904).

TABLE I—SUBSTITUTED 1,3-INDANEDIONES

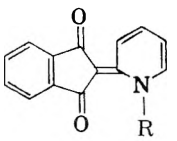


Compound	R_1	R_2	R_3[i]	Method	Yield (%)	M.P. °C.	M.P.° C. (lit.)	Analyses C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
I	2-Pyridyl	H-	H-	A	7.2	289–291	280[2]						
				B	39.9	290–292							
				C	43.1	285–290							
				D[a]	18	287–290							
				E	28	288–291							
II	2-(6-Methylpyridyl)	H-	H-	C	12	218–219	210–211[3]						
III	2-(5-Ethylpyridyl)	H-	H-	A	31	235–237		76.47	76.17	5.21	5.05		
				C	21	235–237							
IV[k]	2-Pyridyl	Br-	H-	F	—	152–154	157[3]						
V	2-(3-Methylpyridyl)	H-	H-	C	2.1	178–180		75.50	75.64	4.67	4.60		
VI	2-(4-Methylpyridyl)	H-	H-	C	11	259–260	262[5]						
VII[b]	2-Pyridyl	CH_3-	H-	D[b]	15	137–138		75.9	75.7	4.64	4.65	10.4	10.3
VIII	2-Pyridyl	H-	4-NO_2	C	3.2	315–316						10.45	10.34
IX	2-(6-Methylpyridyl)	H-	4-NO_2	A[c]	14	293–294						9.98	10.16
X	2-Pyridyl	H-	5-NO_2	A	17	352–355		62.7	61.4	2.95	3.15	10.4	9.87
XI[l]	2-Pyridyl	ϕ-	H-	D[h]	52	152–153		80.3	80.2	4.37	4.63		
				D[i]	49	152–153							
XII	2-Quinolyl	H-	H-	C[e]	42	241–242	241[6]						
XIII	2-Benzothiazoyl	H-	H-	A[d,f]	51	350–360		68.8	69.0	3.23	3.18	5.02	5.04
XIV	2-(5-Chlorobenzimidazoyl)	H-	H-	C[e]	61	No m.p. up to 480						9.44	9.45
XV	2-Benzimidazoyl	H-	H-	G[g]	67	No m.p. up to 500	No m.p. up to 350[g]						

[a] Benzene used as a solvent. [b] Toluene used as a solvent for a reflux period of 16 hr. The product was extracted with dilute hydrochloric acid and reprecipitated by neutralization with sodium hydroxide solution. Picrate: m.p. 216–218°C; *Anal.* Calcd.: N, 12.0; found: N, 11.6. [c] Heated to reflux only until solid began to appear. [d] No catalyst employed. [e] Phosphoric acid used as a catalyst. [f] Product was insoluble in all solvents; purified by washing with boiling 95% ethyl alcohol. [g] Author[7] reports product to be slightly soluble in glacial acetic acid but insoluble in all other solvents. In this work, the product was found to be soluble in concentrated sulfuric acid from which it could be reprecipitated unchanged, upon dilution. [h] Refluxed for 63 hr. [i] Toluene used as a solvent, mixture refluxed for 10 hr. [j] Phthalones with R_3 substituents are derived from the corresponding phthalic anhydrides. [k] Hydrobromide salt: m.p. 305°C. *Anal.* Calcd. for $C_{14}H_9O_2Br_2N$: Br, 42.3. Found: Br, 41.8. [l] Picrate: m.p. 189–190°C., *Anal.* Calcd. for $C_{26}H_{16}O_9N_4$: N, 10.6. Found: N, 10.9.

2-methylbenzoxazole gave a product which could not be characterized.

Compounds which reacted with phthalic anhydride readily condensed with substituted phthalic anhydrides to form indanediones substituted in the benzene ring; thus, 2-methylpyridine condensed readily with 3-nitro-, 4-nitro-, and 4,5,6,7-tetrachlorophthalic anhydride while 2,6-dimethylpyridine condensed with 3-nitrophthalic anhydride.



LVI

Little success was had in the preparation of *N*-substituted pyrophthalones (structure LVI).

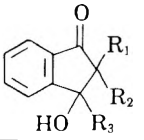
Using the method of Kuhn and Bär[5] for the synthesis of *N*-methylpyrophthalone from dimethyl sulfate and the sodium salt of pyrophthalone, there resulted, in good yield, a compound melting at 223–225° which reverted to pyrophthalone on attempted reduction with Raney nickel W-6. Kuhn and Bär[5] reported a melting point of 165°. An attempt to form *N*-benzylpyrophthalone from benzyl chloride and the sodium salt of pyrophthalone afforded no product at all.

Products of reaction with organometallic compounds. Table II lists the products of reaction of phthalone-type molecules with organometallic compounds. For the most part, organolithium compounds were employed but in one case, the reaction of pyrophthalone with benzylmagnesium

(5) R. Kuhn and F. Bär, *Ann.*, **516**, 155 (1935).
(6) J. Ogilvie, U. S. Patent, **1,963,374**.
(7) J. van Alphen, *Rec. trav. chim.*, **59**, 289 (1940).
(8) A. Scholze, *Ber.*, **38**, 2806 (1905).

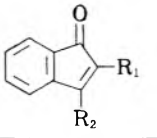
TABLE II

A. Products of Reaction With Organometallic Compounds[i]



Compound	Reactant	R_1	R_2	R_3	Method	Yield (%)	M.P.	Analyses C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
XVI	I	2-Pyridyl	H-	C_6H_5-	H	80	142–143	79.99	78.08	4.70	4.95		
XVII	I	2-Pyridyl	H-	*p*-CH_3O-C_6H_4-	H	70	156–157	76.12	75.88	5.17	5.35		
XVIII	I	2-Pyridyl	H-	*p*-$CH_3C_6H_4$-	H	92	150	79.99	79.70	5.39	5.43		
XIX	I	2-Pyridyl	H-	*m*-CH_3-C_6H_4-	H	75	130d	79.99	80.00	5.39	5.40		
XX	I	2-Pyridyl	H-	*o*-$CH_3C_6H_4$-	H	70	145–155	79.99	79.90	5.39	5.36		
XXI	I	2-Pyridyl	H-	*p*-ClC_6H_4-	H[c]	80	150–160	71.55	69.80	4.17	4.90	Cl 10.58	Cl 9.57
XXII[d]	XII	2-Quinolyl	H-	C_6H_5-	H	100	164	79.78	77.80	4.71	5.01		Ash
XXIII	XIII	2-Benzothiazoyl	H-	C_6H_5-	H	89	No m.p. up to 360	73.95	70.60	4.20	4.22	3.88	11.00
XXIV	XIV	2-(5-Chlorobenzimidazoyl)	H-	C_6H_5-	H	49	No m.p. up to 510					7.48	9.66[k]
XXV	I	2-Pyridyl	H-	$C_6H_5CH_2$-	I	68	100–120						
XXVI	XV	2-Benzimidazoyl	H-	C_6H_5-	J	94	235 (100d)					8.23	7.45
		Name											
XXVII	[h]	2-(2′-Pyridyl)indan-2-ol			H[c]	10	119–120	79.58	79.40	6.20	6.23	6.63	6.80
XXVIII	[i]	1-(2′-Pyridyl)indan-1-ol			H[c]	33	78–80					6.63	6.49
XXIX	XXXI	1,3-Diphenyl-2-(2′-pyridyl)-1-inden-3-ol			H	28	237–238	86.4	85.9	5.30	5.49	3.87	3.79
					H[a]	78	237–238						
XXX	XI	1,2,3-Triphenyl-2-(2′-pyridyl)indane-1,3-diol			H	90	107					3.08	3.02

B. Products of Dehydration of Carbinol Intermediates

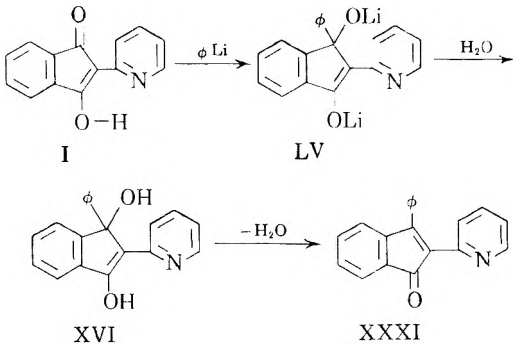


Compound	Reactant	R_1	R_2	Method	Yield (%)	M.P.	Analyses C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
XXXI[f]	XVI	2-Pyridyl	C_6H_5-	J	100	130–131	84.8	84.9	4.62	4.92		
				K	82	129–131						
XXXII	XVII	2-Pyridyl	*p*-$CH_3OC_6H_4$-	J	100	155–156	80.52	80.06	4.83	4.70		
XXXIII	XVIII	2-Pyridyl	*p*-$CH_3C_6H_4$-	J	100	155–156	84.83	84.95	5.08	5.07	4.71	4.66
XXXIV	XIX	2-Pyridyl	*m*-$CH_3C_6H_4$-	J[b]	100	107–110	84.83	84.30	5.08	5.10	4.71	4.87
XXXV	XX	2-Pyridyl	*o*-$CH_3C_6H_4$-	J	100	121–122	84.83	85.20	5.08	5.51	4.71	4.59
XXXVI	XXI	2-Pyridyl	*p*-ClC_6H_4-	J	100	136–138	75.59	75.15	3.78	4.40	11.18 Cl	11.10 Cl
XXXVII[g]	XXII	2-Quinolyl	C_6H_5-	K	96	220(125[d])	86.5	81.6	4.50	4.95	4.20	3.94
XXXVIII	XXIII	2-Benzothiazoyl	C_6H_5-	K	100	169–170	77.9	77.4	3.83	3.91	4.13	4.14
XXXIX[e]	XXV	2-Pyridyl	$C_6H_5CH_2$-	K	54	65–100 (gum)						
XL	XXVI	2-Benzimidazoyl	C_6H_5-	K	100	255–257	81.95	81.75	4.38	4.33	8.74	8.81

[a] A benzene solution of the phthalone was added to the ether solution of the phenyllithium. The mixture was then treated with dilute hydrochloric acid, and the solid was recrystallized from *n*-amyl alcohol. [b] Prepared by thermally decomposing the carbinol in boiling nitroethane. [c] Organolithium prepared by the method of Gilman, Langham, and Moore[9] using *n*-butyllithium and the corresponding halo compound. [d] Product decolorized $KMnO_4$, and did not form a 2,4-dinitrophenylhydrazone, but formed a picrate which melted at 205°C. [e] A picrate derivative of the gummy residue melted at 209–211°C, but analyzed poorly. Anal. Calcd. for $C_{27}H_{18}O_8N_4$: C, 61.6; H, 3.44; N, 10.64. Found: C, 61.5; H, 3.77; N, 9.50. [f] Picrate, m.p. 198–199°C; oxime, m.p. 185–186°C; 2,4-dinitrophenylhydrazone, m.p. 295–299°C (d). [g] Picrate, m.p. 205°C. [h] The reactant was 2-indanone. [i] The halide used to prepare the organometallic compound was the bromide corresponding to R_3 except for the compound XXXV, where the chloride was used. [j] Reactant was 1-indanone. [k] Some ash present.

(9) H. Gilman, W. Langham, and F. W. Moore, *J. Am. Chem. Soc.*, 62, 2327 (1940).

chloride, a product was obtained which was a gum and difficult to characterize. The sequence of reactions involved may be illustrated by the reaction of pyrophthalone with phenyllithium:



Control experiments have indicated that two moles of organometallic compound are required for one mole of phthalone, and for this reason, we write the dilithiated intermediate above, LV. Hydrolysis of the reaction mixtures always resulted in the formation of an indanol, XVI, which is shown above in the enolic form for reasons previously stated. The carbinols so produced could be isolated, but since they dehydrated readily, purifications and characterizations were difficult and sometimes impossible. Dehydration of the carbinols could be done either thermally, that is by heating above the melting point of the carbinol, or by treating the carbinol with concentrated hydrochloric acid. In either case, a pure indenone, XXXI, could usually be isolated.

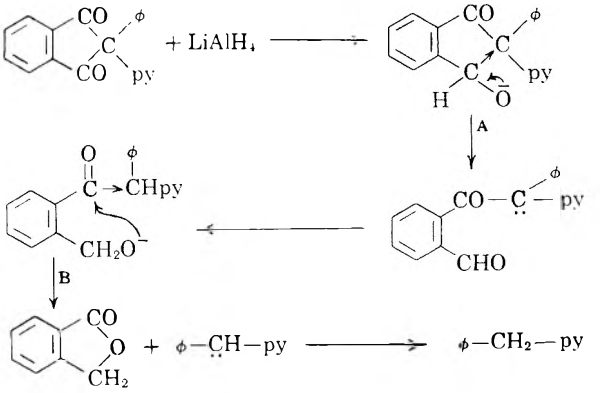
In a few cases, a second mole of phenyllithium added to the phthalone. In the reaction of 2-phenylpyrophthalone (XI) with phenyllithium, the product isolated was 1,2,3-triphenyl-2-(2′-pyridyl) indanediol (XXX), indicating the addition of two moles of organometallic compound to the molecule. In addition, 3-phenyl-2-(2′-pyridyl)indenone (XXXI), reacted with phenyllithium to form 1,3-diphenyl-2-(2′-pyridyl)-1-inden-3-ol (XXIX).

The indenones differed markedly from their parent indanedione. They were usually more intensely colored, had lower melting points, and were more soluble in organic solvents and hydrochloric acid solutions. Since they were unable to enolize, they could not chelate, and it was usually possible to form derivatives such as picrates, oximes, and occasionally, 2,4-dinitrophenylhydrazones. They generally decolorized potassium permanganate solutions, and infrared spectra indicated the presence of a carbonyl group in the molecules.

The addition of organometallic compound to the indandione generally proceeded smoothly and the carbinol and the indenone produced by dehydration of the carbinol were solids. Occasionally, however, the indenone would form as a gum which could not be crystallized and when this occurred, characterization was virtually impossible. Such was the case, for example, in the reaction of pyrophthalone with *n*-butyllithium, benzylmagnesium chloride, or methyllithium.

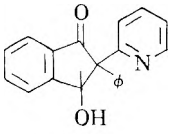
Reduction products. Reductions of pyrophthalone-type compounds were done: 1. catalytically, 2. with sodium borohydride, and 3. in one instance, using Clemmensen's method. These products are listed in Table III.

The Clemmensen reduction was attempted on 2-phenylpyrophthalone and 3-phenyl-2-(2′-pyridyl)indenone (XXXI). The 2-phenyl derivative reduced nicely to give 60% yield of 2-phenyl-2-(2′-pyridyl)-indan-3-on-1-ol, XLVII. The 3-phenyl derivative (XXXI) could not be reduced by this method, although catalytically, or with sodium borohydride, it afforded a variety of products depending upon the conditions (Table III). Attempted reduction of 2-phenylpyrophthalone with lithium aluminum hydride gave 2-benzylpyridine and phthalide. A probable mechanism for the formation of these substances follows:



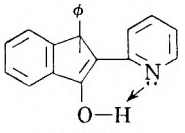
Step A is a reversal of the aldol condensation and Step B is a reversal of the Claisen ester condensation. Both of these reactions are well known to be equilibrium reactions.

A Wolff-Kishner reduction on 2-phenylpyrophthalone gave an unidentified product, melting at 252–255°.



XLVII

Vigorous catalytic hydrogenation not only reduced indene double bonds, but occasionally reduced part or all of the heterocyclic ring substituent. Thus, 3-phenyl-2-(2′-pyridyl)indenone, XXXI, was reduced with Raney nickel W-6 to give 3-phenyl-2-(2′-pyridyl)indanone. This compound was demonstrated to exist in a chelated enol form XLI, by

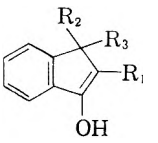


XLI

TABLE III

REDUCTION PRODUCTS

A. INDENES



Compound	Reactant	R_1	R_2	R_3	Method	Yield (%)	M.P.	Analyses C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
XLI	XXXI	2-Pyridyl	H-	C_6H_5-	L[c]	60	187–188	84.0	83.8	5.61	5.39		
					L[d]	30	188–189						
					N	49	188–189						
XLII	XXXI	2-(3,4,5,6-Tetrahydropyridyl)	H-	C_6H_5-	L[f]	36	213	83.1	83.1	6.59	6.62	4.84	5.07
					L[g]	46	212–213						
XLIII	XXXVII	2-(3,4-Dihydroquinolyl)	H-	C_6H_5-	N	86	275	85.5	85.8	5.64	5.58	4.15	4.07
XLIV	XIII	2-Benzothiazoyl	H-	HO-	N	100	345–348	68.3	68.5	3.91	3.73		
XLV	XXXVIII	2-Benzothiazoyl	H-	C_6H_5-	N	50	151–152	77.4	77.6	4.37	4.55		
XLVI[i]	XXXIII	2-Dihydropyridyl[h]	H-	*p*-CH_3-C_6H_4-	N	43	183–184	84.0	84.2	6.00	5.95	4.67	4.64

B. INDANES

Compound	Reactant	Name	Method	Yield (%)	M.P.	Analyses C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
XLVII	XI	2-Phenyl-2-(2′-pyridyl)indan-3-on-1-ol	M	60	186–187	79.6	78.3	4.98	5.11	4.65	4.70
XLVIII[b]	XXXI	3-Phenyl-2-(2′-piperidyl)indan-1-ol	L[a]	15	180–181	81.86	82.4	7.91	8.08		
XLIX	XXXI	3-Phenyl-2-(2′-piperidyl)indan-1-ol	L[a]	39	206–208	81.86	81.94	7.91	7.84		
L	XXX	1,2,3-Triphenyl-2-(2′-piperidyl)indane-1,3-diol	L[e]	71	135–136	83.3	83.0	6.73	7.17		
LI	I	2-(2′-Piperidyl)indane-1,3-diol	L[j]	11	230–232(d) as B·HCl	62.31	62.42	7.47	7.49		
LII	XI	2-Phenyl-2-(2′-piperidyl)indane-1,3-diol	L[l]	8	184–186	77.62	77.61	7.49	7.64		
LIII	I	2-(2′-Piperidyl)hexahydroindane-1,3-diol	L[k]	41	196–199	65.00	65.82	10.10	10.01		

[a] Conditions: 3.3 g. phthalone in 30 ml. absolute ethanol containing three molar equivalents of dry HCl, 20 mg. platinum oxide, 2100 lbs/in², 24 hr. [b] Acetic anhydride reacted with the reduced compound to produce the *N*-acetyl-*O*-acetyl derivative, m.p. 166–167°. Anal. Calcd. for $C_{24}H_{27}O_3N$: C, 76.4; H, 7.17. Found: C, 76.2; H, 7.32. We believe XLVII and XLIX to be optical isomers. [c] Conditions: 5.7 g. phthalone in 250 ml. absolute ethanol, 0.2 g. Raney nickel W-6, 2 atm., 78 hr. The product did not form a 2,4-dinitrophenylhydrazone or picrate, but gave a dark green color with ferric chloride. A repeat synthesis using three molar equivalents of dry HCl in absolute ethanol gave a 46% yield. [d] Conditions: 10 g. phthalone in 30 ml. dioxane, 2.0 g. Raney nickel W-6, 2 atm., 16 hr. A 10% yield of an unidentified product was also obtained; this compound was insoluble in ethanol and melted at 148–149°. [e] Conditions: 1.5 g. phthalone in 25 ml. of dioxane, 2 g. Raney nickel W-6, 122 atm., 24 hr., 125°. [f] Conditions: 5.6 g. phthalone in 30 ml. of dioxane, 2 g. Raney nickel W-6, 2000 lbs/in², 42 hr. 125°. [g] Conditions: 28.3 g. phthalone in 300 ml. of dioxane, 10 g. Raney nickel W-6, 153 atm., 20 hours, 108°. [h] Exact location of the dihydropyridyl ring hydrogens is not known at present. [i] Picrate: m.p. 193–195°. [j] Conditions: 6 g. phthalone in 50 ml. of CH_3OH, 2.7 ml. concentrated HCl, 0.5 g. platinum oxide at 60 lbs/in². [k] Conditions: 7.5 g. phthalone in 100 ml. of glacial HOAc, 0.8 g. platinum oxide, 2 hr. [l] Conditions: 2 g. phthalone, 50 ml. 80% HOAc, 0.4 g. platinum oxide.

an infrared spectrum which showed -OH and -NH stretching at 2.7μ and 3.05μ respectively, a peak for -NH bending at 6.4μ, a peak for -OH at 7.5μ, and a broad peak for -OH deformation at 9.1–9.3μ.

Furthermore, the compound produced a green color with ferric chloride and did not form a picrate or a 2,4-dinitrophenylhydrazone. This same product was synthesized by a reduction of the parent compound with sodium borohydride. Under

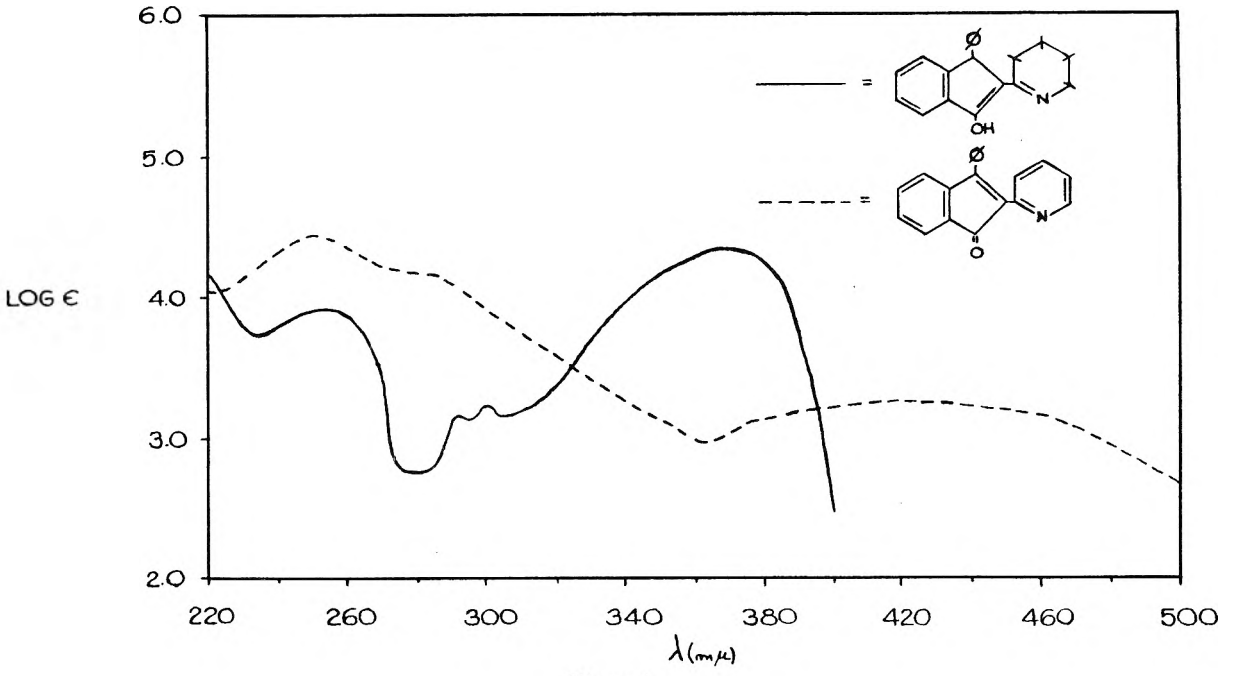
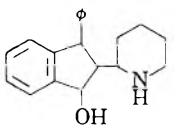
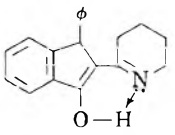


Figure 1

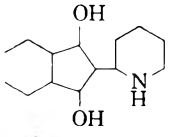
more vigorous conditions, 3-phenyl-2-(2′-pyridyl) indenone, XXXI, was reduced to 3-phenyl-2-[2′-(3′,4′,5′,6′-tetrahydropyridyl)]indenone, XLII, which was also shown to have a chelated enol structure by the same methods as described above. Further evidence for the assignment of XLII as the structure of the compound was found in a comparison of the ultraviolet and visible absorption spectra (Fig. 1) of both the parent compound and the reduced product. The similarity in the curves is indicative of analogous chains of conjugation. The small hypsochromic shift at the longer wavelengths is as expected by a slight decrease in the length of the conjugated chain brought about by the partial reduction of the pyridine ring. Under still more vigorous conditions, the compound was reduced to 3-phenyl-2-(2′-piperidyl)-indanol, XLVIII, which was acetylated at the piperidine nitrogen and the indanol oxygen by refluxing with acetic anhydride. A higher melting isomer (XLIX) of XLVIII was isolated under slightly different conditions and it is believed that these are optical isomers. In one instance, pyro-



XLVIII



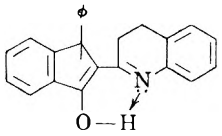
XLII



LIII

phthalone itself was completely reduced to a saturated diol (LIII).

Sodium borohydride reduced the 3-phenyl-2-substituted indenones more readily than it reduced the 2-substituted indanediones. Thus, pyrophthalone and 2-(2′-quinolyl)indanedione were not reduced by sodium borohydride while the corresponding 3-phenyl-2-(2′-substituted)indenone was reduced readily by this reagent. The reduction product of 3-phenyl-2-(2′-pyridyl)indenone was discussed above. In the case of 3-phenyl-2-(2′-quinolyl)-indenone, analysis showed that four hydrogen atoms were added to the system. Unlike the parent compound, the reduction product did not decolorize potassium permanganate solutions, did not form a picrate, and was insoluble in hydrochloric acid solutions. Furthermore, it gave no ferric chloride test[10] and did not form a 2,4-dinitrophenylhydrazone. There was little difference in the ultraviolet and visible spectra (Fig. 2) of the starting material and the reduced product, indicating that the chain of conjugation in each is essentially the same. On this basis, the most likely structure of the reduced product is XLIII.



XLIII

The reduction of 3-(*p*-tolyl)-2-(2′-pyridyl)indenone with sodium borohydride yielded a compound which contained a partially reduced pyridyl ring. The product produced a green color with ferric chloride, decolorized potassium permanganate, did not form a 2,4-dinitrophenylhydrazone, did form a picrate, and, by analysis, appeared to be a tetrahydro derivative. These data indicate an enolic system which could be weakly chelated to the ring nitrogen, thus, the compound must have

(10) The spectra (see Fig. 2) indicated the presence of an enolic system in spite of the negative ferric chloride test.

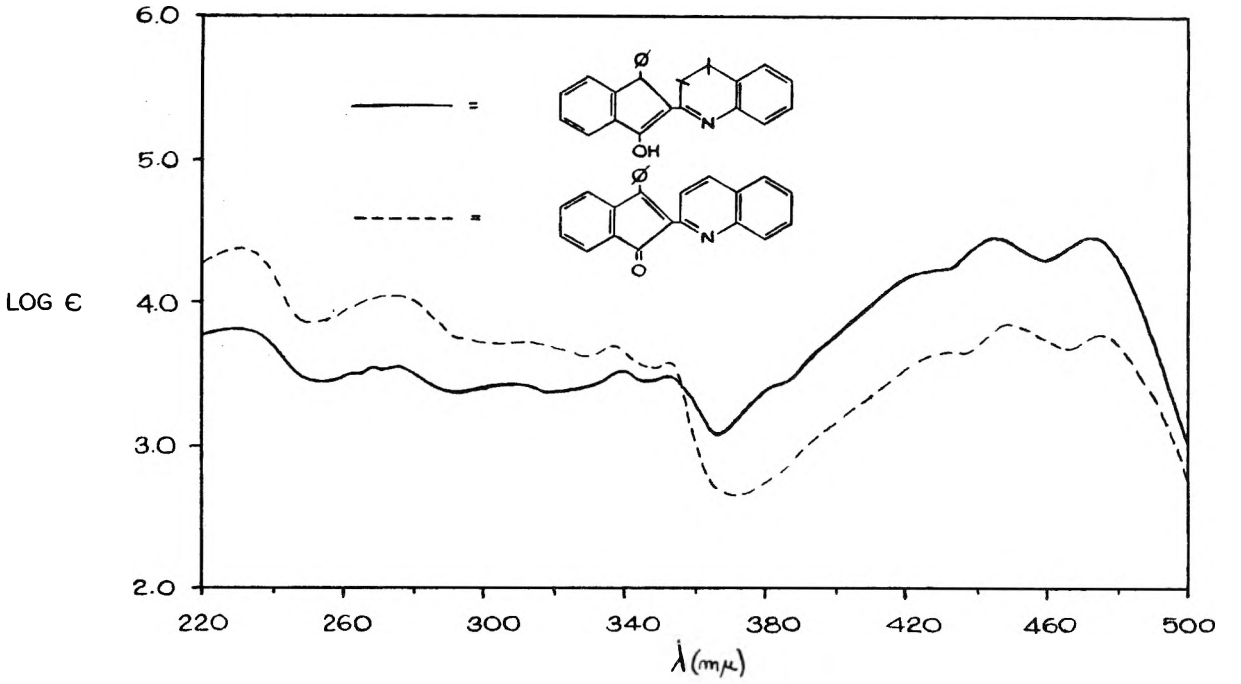
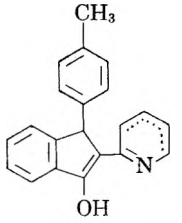


Figure 2

been partially reduced in the heterocyclic ring. The location of the ring hydrogens is as yet uncertain, but the compound can be considered as the enol form of 3-(*p*-tolyl)-2-(2′-dihydropyridyl)indanone, XLVI.

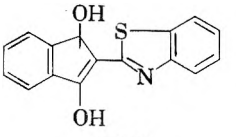


XLVI

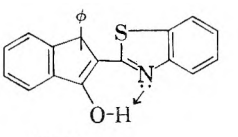
The reduction of 2-(2′-benzothiazoyl)indandione with sodium borohydride gave a quantitative yield of 2-(2′-benzothiazoyl)indan-3-on-1-ol, XLIV. The product was insoluble in all solvents and could not be completely characterized; however, previous experience indicates this compound probably is in the enol form and chelated to one of the heteroatoms of the benzothiazole ring. The 3-phenyl-2-(2′-benzothiazoyl)indenone was reduced to form a compound which was soluble in most organic solvents, but did not dissolve in concentrated hydrochloric acid solutions as did the parent compound. Furthermore, it gave no color with ferric chloride, and formed no picrate. These data indicate the ring nitrogen to be chelated with the hydroxyl group on the five-membered ring, and the product has been assigned structure XLV.

Attempts to reduce 3-phenyl-2-(2′-benzimidazoyl)indenone and 2-[2′-(5′-chlorobenzimidazoyl)]-indanedione with sodium borohydride, failed.

Results of Pharmacological Testing. After extensive screening, seven of the compounds under consideration were found to have antiarthritic activity. These are XVII, XXXI, XXXII, XXXIII, XXXIV, XXXVI, and XXXVII. It is interesting to note that six of these are indenones and that the remaining compound (XVII) is a carbinol precursor to an indenone (XXXII).



XLIV



XLV

EXPERIMENTAL

Method A. H von Huber[2] employed an equimolar mixture of phthalic anhydride and the active methyl compound and heated with a catalytic amount of zinc chloride for 5 hr. at 200°.

Method B. A modification of Method A. A two-molar quantity of active methyl compound was used and the mixture was heated in a sealed tube.

Method C. The method of J. Ogilvie[6] is a modification of Method A employing a solvent. The reactants and catalyst were dissolved in a quantity of nitrobenzene (approximately equal in weight to the phthalic anhydride employed), and the solution was refluxed for 6 hr. The mixture was cooled and the solid phthalone was filtered, washed with ether, and recrystallized from a suitable solvent such as nitroethane, nitrobenzene, or ethanol.

Method D. In this procedure, phthalyl chloride in benzene was used in place of phthalic anhydride.[2]

Method E. A modification of Method C, employing phosphoric acid as a catalyst.

Method F. The phthalone was dissolved in glacial acetic acid, and a half-molar quantity of bromine (based on the phthalone) added dropwise with stirring. Stirring was continued for 10 min. after complete addition of the bromine. The solution was filtered, the solid was slurried with cold

water, and 5% sodium hydroxide solution was added until the slurry was slightly basic. The product was then filtered, washed, and dried.

Method G. J. van Alphen[7] heated phthalic anhydride and an equimolar amount of 2-methylbenzimidazole at 200°C for 2 hr. The mixture was washed with hot water, hot ethanol, and hot glacial acetic acid until the washings were clear. The product was only slightly soluble in glacial acetic acid, but was reprecipitated from concentrated sulfuric acid by dilution with water.

Method H. The organolithium compound was prepared from the halide corresponding to R_3. The molar ratio of lithium to halide to phthalone was 4:2:1. The lithium was cut into small pieces and added to 35 times its weight of absolute ether. A 0.5*M* solution of the halide in absolute ether was added to the lithium-ether mixture with stirring, and at such a rate as to maintain gentle reflux of the ether. After the lithium had reacted completely, the phthalone was added as a powder at such a rate as to maintain gentle reflux. After complete addition of the phthalone, the mixture was stirred with gentle reflux until a negative Gilman test indicated complete reaction of all the organometallic compound. A solid usually precipitated during the course of the reaction. The reaction vessel was surrounded by an ice bath and an equal volume of a dilute solution of ammonium chloride was slowly added to the reaction mixture with stirring. The solid present dissolved and a new solid precipitated as more ammonium chloride solution was added. Stirring was continued for 0.5 hr. after addition of the hydrolysis solution. The solution was filtered, and the solid carbinol was washed with water and dried.

Method I. The Grignard reagent was prepared according to the method of Gilman and Meyers.[11] In this work, the molar quantity of Grignard employed was four times the molar quantity of the phthalone used. The phthalone was added as a solid to the Grignard solution and the mixture was refluxed for 1 hr. The product worked up as described in Method H.

Method J. The dried carbinol, as prepared by Method H or I was heated above its melting point until effervescence ceased, and the melt was uniform in color. It was purified by recrystallization from an ethanol-water solution.

Method K. The dried carbinol, as prepared by Method H or I, was dissolved in concentrated hydrochloric acid. A great deal of effervescence occurred and the solution became a deep red. The solution was stirred for 15 min., cooled with an ice bath, and neutralized with sodium hydroxide solution. The solid which separated was the dehydrated carbinol, which was filtered, washed with 10% sodium bicarbonate solution, and dried. The product was purified by recrystallization from an ethanol-water solution.

Method L. Reference to the specific reaction conditions is given in Table III. After completion of the reaction, the solution was filtered away from the catalyst, and the solvent was removed by distillation under reduced pressure. The solid residue was purified by recrystallization from a suitable solvent such as ethanol or nitroethane.

Method M. The following quantities were used for every mole of phthalone: 598 g. mossy zinc, 47.9 g. mercuric chloride, 30 ml. concentrated hydrochloric acid, and 720 ml. water. The materials were mixed and shaken vigorously for 10 min., and the liquid phase was then decanted. To the residue of amalgamated zinc was added 450 ml. water, 598 ml. concentrated hydrochloric acid, and 1 mole of the phthalone. An oil separated, and therefore, 450 ml. water, and 598 ml. concentrated hydrochloric acid were again added, and thereafter, 59.8 ml. concentrated hydrochloric acid was added every hour for 5 hr., and the solution was refluxed overnight. On cooling, a solid separated which was slurried with sodium hydroxide solution until the mixture remained basic. The product was then washed with water, and recrystallized from a suitable solvent such as ethanol or nitroethane.

Method N. The phthalone was added as a solid to a 0.2*M* solution of sodium borohydride in tetrahydrofuran. The molar ratio of phthalone to borohydride was 1:1. The mixture was stirred, and a volume of a 0.5*M* solution of lithium chloride in tetrahydrofuran was added slowly, the volume chosen was such that there was present a 1 molar equivalent of lithium chloride, based on the quantity of the phthalone used. The mixture was allowed to stir 24 hr. at room temperature, after which it was slowly added to a beaker filled with ice and a few milliliters of concentrated hydrochloric acid. The hydrolysis mixture was stirred during the addition and stirring was continued until the vigorous reaction ceased. The solid which formed was filtered, washed with 10% sodium hydroxide solution, dried, and recrystallized from a suitable solvent such as ethanol or nitroethane.

Acknowledgment. The authors wish to express their appreciation to Dr. M. G. Van Campen, Dr. G. L. Krueger, and the William S. Merrell Company for the financial support of this work, and to Dr. V. B. Fish who performed the analyses. Preliminary work on this project was supported by the Vale Chemical Co. to whom the authors express their thanks.

BETHLEHEM, PA.

(11) H. Gilman and C. H. Meyers, *Org. Syn.*, 4, 59, (1925).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

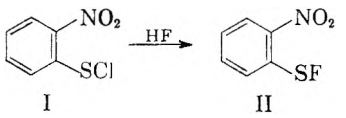
Derivatives of Sulfenic Acids. XXIX. Bis(2,2′-fluorosulfonyl)azobenzene *via* 2-Nitrobenzenesulfenyl Chloride and Hydrogen Fluoride[1]

DAVID L. CHAMBERLAIN, DAVID PETERS, AND NORMAN KHARASCH

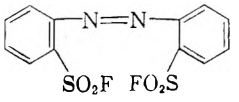
Received August 19, 1957

The reaction of 2-nitrobenzenesulfenyl chloride (I) with liquid hydrogen fluoride was studied as a possible route to 2-nitrobenzenesulfenyl fluoride (II). Besides tars, and a small amount of an unidentified, colorless product (found when carbon tetrachloride was used as diluent), there was formed 5–15% of the bright-red bis(2,2′-fluorosulfonyl)azobenzene, III. The proof of structure of III is given and related preparative details are reported.

Introduction. Concurrently with attempts to prepare 2,4-dinitrobenzenesulfenyl fluoride and *p*-toluenesulfenyl fluoride,[2] reaction 1 was studied as a possible route to 2-nitrobenzenesulfenyl fluoride, II. It was found that I and liquid hydrogen fluoride react vigorously,[3] but none of the desired sulfenyl fluoride could be found. Besides much tar, there was also formed a crystalline, bright-red solid, whose structure was not immediately apparent to us, but which now has been shown to be bis(2,2′-fluorosulfonyl)azobenzene, III.



I II



III

The yield of III seems not to depend greatly on the conditions of the reaction, ranging from 5 to 15% by working in liquid hydrogen fluoride at −70°, 0°, or room temperature, or in the presence or absence of organic solvents.[4] In our experience, the most convenient procedure is to work at −70°, using a polyethylene flask, magnetic stirrer, and without adding an organic solvent.

Evidence for structure III. Since the elementary analysis (C,H,N,S,F) for the red compound agreed for 2-nitrobenzenesulfenyl fluoride (II), it was first considered [*Cf.* footnote 3 of ref. (2)] that this might be the structure of the product. Further study of its physical properties, such as solubility and spectra, and an initial study of its chemical properties, however, showed that the new fluorine compound was distinct from the sulfenyl chloride (I) or the corresponding sulfenyl bromide (*o*-NO_2-C_6H_4SBr), which resemble each other closely. Furthermore, although the low solubility of the new fluorine compound made determination of the molecular weight difficult, the molecular weight (Rast method, in camphor) indicated a dimeric structure, whereas the sulfenyl fluoride would not be expected to be a dimer.[5] Structure II was therefore ruled out of consideration.

The azo structure for III was foreshadowed by the observation that the red fluoride added hydrogen (H_2, Raney nickel) to form a colorless product that was suspected to be a hydrazo compound. Since an azo group could also be responsible for the observed color, and because there was some precedent for oxidation-reduction reactions between the bivalent sulfur moiety of sulfenyl deriv-

(1) We are indebted to Research Corporation for a grant which permitted initiation of this project. The study was completed under sponsorship of the United States Office of Scientific Research, Air Research and Development Command (Project OSR-30-19). It is published for technical information only and does not necessarily represent recommendations or conclusions of the sponsoring agency. For references to earlier papers of this series, *Cf.* Part XXVI, *J. Chem. Ed.*, **33**, 585 (1956) and *J. Org. Chem.*, **22**, 1673, 1701 (1957).

(2) D. L. Chamberlain and N. Kharasch, *J. Am. Chem. Soc.*, **77**, 1041 (1955). As recorded in this reference, all attempts, to date, to synthesize sulfenyl fluorides have failed, with the possible exception of CF_3-$(CF_2)_{11}$-SF, which is claimed in U. S. Patent **2,519,983**, but no supporting data for the structure of the product are given [*cf. Chem. Abstr.*, **45**, 51 (1951)].

(3) H. J. Emeleus and H. G. Heal, *J. Chem. Soc.*, 1126 (1946), recorded that there was no reaction in this instance. With other aromatic sulfenyl chlorides, however, they observed extensive reactions, giving tars, disulfides (in some cases), and higher fluorides. The latter were presumed to arise through disproportionations of the initially formed sulfenyl fluorides, ArSF.

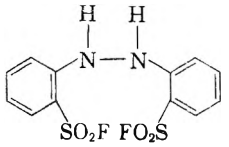
(4) When carbon tetrachloride was used as a diluent for the reaction, a small amount of an unidentified, colorless, low-melting solid (*cf*, experimental) was also observed. This product has also been noted by H. H. Szmant, who had occasion to carry out the reaction of 2-nitrobenzenesulfenyl chloride and liquid hydrogen fluoride, using carbon tetrachloride as diluent (private communication from H. H. S. to N. K.). An investigation of this product is being made in this laboratory.

(5) In the absence of conclusive evidence, the possibilities of structures as ArS(Cl)-S(Cl)Ar, for the products of reaction of chlorine with bis(aryl) disulfides had to be considered. However, in the case of 2,4-dinitrobenzenesulfenyl chloride, *e.g.*, the molecular weight was 234.6 (found, by the cryoscopic method, in benzene; *vs.* 234 calcd. for the monomer). *Cf.* N. Kharasch and C. M. Buess, *J. Am. Chem. Soc.*, **71**, 2726 (1949).

atives and adjacent nitro groups,[6] it appeared that the reaction of 2-nitrobenzenesulfenyl chloride with liquid hydrogen fluoride might involve a novel conversion, leading to a structure like III. That III is, indeed, the structure of the product was then confirmed as follows.

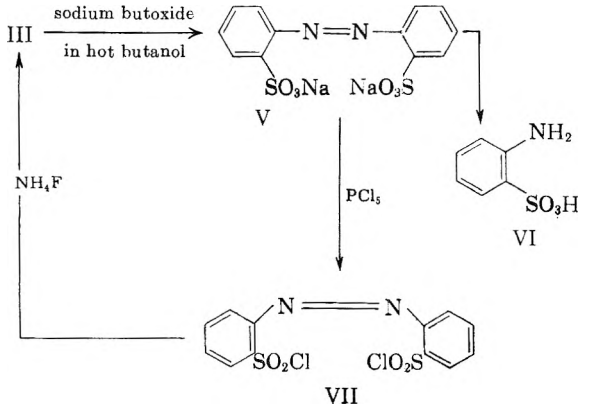
(1) Fig. 1 shows the ultraviolet absorption spectra of azobenzene, the new fluoride (hereafter referred to as III) and bis(2,2′-chlorosulfonyl)azobenzene.[7] The near identity of all three curves leaves little doubt, if any, that an azo group must be present in the new fluorine compound. For comparison, the spectra of 2-nitrobenzenesulfenyl chloride and 2-nitrobenzenesulfenyl bromide are also shown in Fig. 1.

(2) The derivative obtained by hydrogenation (as mentioned above) was also obtained by reducing III by various methods, *e.g.* with stannous chloride. On oxidation, even by exposure to air, the colorless reduction product readily reverted to III. Since we conclude that III is the correct structure of the red compound, IV is the logical one for the product of reduction.



IV

(3) Under severe solvolytic conditions (treatment with a solution of sodium *n*-butoxide, in *n*-butyl alcohol, at reflux) III gave a red water-soluble sodium salt, V, which was characterized as the di(*S*-benzylthiuronium) salt, m.p. 228–229°. The *ortho* relation of the azo and sulfonate functions in V was then confirmed by catalytic reduction to orthanilic acid (VI). Compound V was also converted to VII; and original III was obtained from



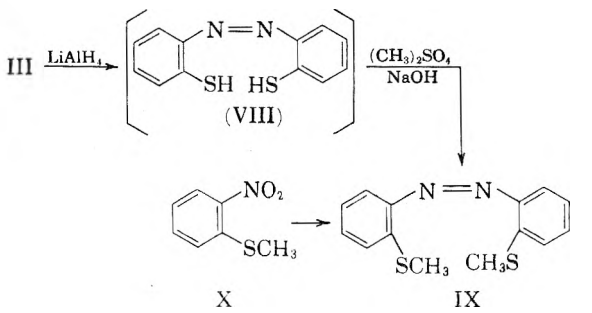
(6) The conversion of 2-nitrobenzenesulfenyl chloride to orthanilic acid was observed by Zincke and Farr, *Ann.*, **391**, 55 (1912). Similarly, Kharasch, King, and Bruice found that methyl 2,4-dinitrobenzenesulfenate, may be converted, by treatment with hot hydrochloric acid solutions, to 2-amino-4-nitrobenzenesulfonic acid.

(7) The preparation of this compound is described further in the text and in the experimental part.

VII by reaction with ammonium fluoride in acetone.

Since no rearrangement of V is expected under alkaline conditions, the cycle of reactions, III→V→VII→III, confirms that the only change effected in the reaction of III with sodium butoxide is conversion of $-SO_2F$ to $-SO_2ONa$. Fairly drastic conditions were required for the hydrolysis of the fluorosulfonyl groups, as anticipated for III on the basis of the known hydrolytic stabilities of sulfonyl fluorides.[8] The inertness of III to solvolytic reactions is further illustrated below.

(4) Alkaline reduction of 3-nitrobenzenesulfonic acid is known to yield the salts of the bis-3,3′-azobenzenedisulfonic acid.[9] While we confirmed this conversion, the extension to the similar synthesis of V, from *o*-nitrobenzenesulfonic acid, could not be effected. Because of this failure to achieve the independent synthesis of V, the sequence of reactions, III→IX, as well as the alternate synthesis of IX from X, by the recorded method of Brand[10] were carried out. These reactions confirm the presence of an azo group in III and also show that it is situated *ortho* to the sulfur function.



X IX

Compound VIII was not isolated, as such, but was methylated directly to IX.

(5) The infrared spectra of the fluoride, III, and of azobenzene were examined. The most striking feature of the spectrum of the fluoride is the presence of two strong bands, at 1209 cm.$^{-1}$ and 1394 cm.$^{-1}$, which are absent in the spectrum of azobenzene. These are the sulfone bands, which generally occur[11] at 1120–1160 cm.$^{-1}$ and 1350–1400 cm.$^{-1}$, and which are known, from the Raman spectra, to occur in sulfonyl fluorides[12] at 1167–1197 cm.$^{-1}$ and at 1402–1412 cm.$^{-1}$ The assignment of infrared absorptions for the azo group has not yet been made with sufficient assurance;[13] hence, no conclusion as to the presence

(8) J. Simons, *Fluorine Chemistry*, Vol. I, Academic Press, New York, N. Y. (1950), p. 178.

(9) Dr. Mahrenholtz and Dr. Gilbert, *Ann.*, 202, 331 (1880); cf. also, S. Stern and A. Taub, *J. Am. Pharm. Assoc.*, **28**, 1032 (1939); and H. Limpricht, *Ber.*, **11**, 1046 (1878).

(10) K. Brand, *Ber.*, **42**, 3463 (1909).

(11) R. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., 1954, p. 279.

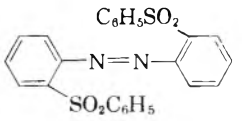
(12) N. S. Ham and A. M. Hamble, *Australian J. Chem.*, 6, 135 (1953).

(13) R. J. W. Le Fevre, M. F. O'Dwyer, and R. L. Werner, *Australian J. Chem.*, 6, 341 (1953).

of this group was drawn from the infrared spectrogram.

A few other points related to III are noted below. (*a*) Bis(2,2′-fluorosulfonylazobenzene) is a very stable substance. It sublimes, without decomposing, near its melting point (259–260°, uncorr.), is completely inert to water and mineral acids, and may be recrystallized, without loss, from hot concentrated nitric acid. It is not affected by bromine and does not react with sodium sand, in refluxing toluene. Treatments of III with cold chromic acid, cold sulfuric acid, or potassium permanganate are also without effect; but hot sulfuric acid or hot mixtures of nitric and sulfuric acids, attack III. Similarly, solvolysis of the fluoride does not occur appreciably by attempted reactions with boiling methanol, aniline, and several other nucleophilic reagents. It dissolves only with difficulty, without reacting, in a large volume of boiling acetone, from which it crystallizes (on rapid cooling) in fine, orange needles, m.p. 256–257° (uncorr.); or, on slow cooling, in heavy, deep-red cubes (1–2 mm. in length), which melt somewhat higher (258–259° and 259–260°, both melting points having been observed on different samples). The inability of the several powerful oxidants, mentioned above, to attack the azo linkage reflects a lowered reactivity of this azo group, compared to other azo compounds. This is probably related mainly to the powerful electron-withdrawing effect of the *ortho*-fluorosulfonyl groups in III.

(*b*) Treatment of III with benzene and boron trifluoride, under Friedel-Crafts conditions, gave only unreacted III; but with aluminum chloride as catalyst, the corresponding bis(2,2′-benzenesulfonyl)azobenzene, XII, was obtained. The assignment of structure XI is based on analysis, mode of synthesis and the ultraviolet spectrum and makes the reasonable assumption that no rearrangement of the substituent -SO_2F groups occurs in the conversion to XI. It is likely that the chloride, VII, corresponding to III, is an intermediate in the synthesis of XI, since the reactions of sulfonyl fluorides with aluminum chloride[14] are known to give sulfonyl chlorides. From steric considerations, the *trans* structure of XI can scarcely be doubted. On empirical grounds, also, there is little doubt that all the azo compounds reported in this paper are the *trans* isomers, but their geometry has not been established independently.



EXPERIMENTAL[15]

Synthesis of bis(2,2′-fluorosulfonyl)azobenzene, III. A 500-ml. polyethylene bottle, fitted with a magnetic stirrer and cooled in an acetone-solid carbon dioxide bath was placed in a good hood. Hydrogen fluoride (200 ml.) was added and to this was introduced 11.0 g. (0.06 mole) of powdered 2-nitrobenzenesulfenyl chloride. The yellow suspension turned red as the reaction mixture was warmed to room temperature. After standing about 12 hr., to vent the hydrogen fluoride, the black, semi-solid residue was extracted with cold acetone. Evaporation of the extracts gave magnificent red needles of the fluoride (0.5 g.), m.p. 259–260°. Further extraction of the black tar with hot acetone, using chromatographic or crystallizing procedures, failed to yield any identifiable material. Since the red fluoride (III) was inert to concentrated nitric acid, an attempt to "burn off" the impurities by boiling with nitric acid was made, but no additional III was obtained.

The preparation was repeated several times, using up to 160 g. (0.84 mole) of I. The yield of III was 14.5 g. (10.6% yield), from 160 g. of the sulfenyl chloride and the yields in various runs were from 5% to 15%, based on 2 moles I → 1 mole III.

Anal. Calcd. for $C_{12}H_8O_4F_2N_2S_2$: C, 41.61; H, 2.33; F, 10.97; N, 8.09; S, 18.52; mol. wt., 346. Found (on different samples, in different analytical laboratories): C, 41.38, 41.71, 42.40; H, 2.45, 2.54, 1.97; F, 9.61, 9.44, 10.50; N, 8.42, 8.76; S, 18.29, 18.54. Mol. wt. (Rast method, in camphor): 333.

The product (III) was too insoluble in convenient solvents to permit determination of the molecular weight by usual cryoscopic or isothermal (Signer) methods.

With carbon tetrachloride as a diluent in the above reactions, III resulted in low yield and a white, waxy product of low melting point was also found. Thus: Hydrogen fluoride (100 ml.), forming the upper layer, was added to 100 ml. of carbon tetrachloride. The mixture was stirred in a polyethylene flask, at room temperature and a solution of I (5 g., 0.025 mole in 100 ml. carbon tetrachloride) was added. As judged through the opaque flask, the carbon tetrachloride layer appeared cream colored, the interface was green, and the hydrogen fluoride layer was violet. The hydrogen fluoride was evaporated overnight and its removal completed with a stream of nitrogen.

The carbon tetrachloride layer and a red, oily solid were then homogenized by adding acetone, the solution was treated with charcoal and the solvents were removed *in vacuo* until only 25 ml. of solution remained. On cooling, the mass set to a semi-solid and was extracted with low-boiling petroleum ether, leaving a 100 mg. residue of III. Evaporation of the petroleum ether solution yielded a white, waxy solid, m.p. 55–57°, apparently identical with the product described by Szmant (*cf.* footnote 4).

An attempted reaction with nitromethane as solvent gave no III. The attempt to prepare III, using 48% hydrogen fluoride, also failed. Instead, hydrolysis products of I (the disulfide and thiolsulfonate ester) were encountered.

Bis(2,2′-fluorosulfonyl)azobenzene is insoluble in ether, and almost completely insoluble in benzene, ethylene chloride, and chloroform. It is moderately soluble in hot acetone, ethyl acetate, and pyridine and quite soluble in *N,N*-dimethylformamide. Crystallization from a large volume of acetone, with rapid cooling, gave fine orange needles of III. Slow or spontaneous crystallization from hot acetone gave deep-red rectangular crystals, 1–1.5 cm. long and 1–2 mm. wide. The melting point varied slightly with the crystal form; the orange crystals melted at 256–257° and the larger red crystals at 258–259°.

The ultraviolet spectra of 2-nitrobenzenesulfenyl chloride (I) and the corresponding bromide were determined in purified dioxane[16] and that of III was made in dioxane, as well as in ethylene chloride, using a Beckmann DU quartz

(14) M. W. Renoll, *J. Am. Chem. Soc.*, 64, 1489 (1942).

(15) Melting points are not corrected; they were made in glass capillaries, in a liquid bath.

(16) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Organic Compounds*, John Wiley and Sons, New York, N. Y., 1951, p. 12.

spectrophotometer. The ultraviolet spectra of VII, bis(2,2′-chlorosulfonyl)azobenzene and of azobenzene were determined in ethylene chloride. The ultraviolet spectra of the sulfenyl chloride, I, the corresponding bromide, and III were also determined in concentrated sulfuric acid, but the spectra varied with time and are not recorded here. The infrared spectrum of I was obtained on a Nujol mull, with a Perkin-Elmer double beam instrument.

Reduction of III *to bis-2,2′-fluorosulfonylhydrazobenzene*, IV. The fluoride, III, 500 mg., was dissolved in 100 ml. of absolute ethanol, about 1 g. of Raney nickel catalyst was added, and the mixture shaken with hydrogen at 45 p.s.i. for 2 hr. The Raney nickel was separated and the colorless filtrate was concentrated, cooled, and the crystals collected. Recrystallization from 95% ethanol gave excellent white crystals of IV, m.p. 156–157°.

Anal. Calcd. for $C_{12}H_{10}O_4F_2N_2S_2$: C, 41.38; H, 2.87; N, 8.04; S, 18.30. Found: C, 41.77; H, 3.18; N, 7.81. On a different sample: C, 41.83; H, 2.84; N, 8.26.

On standing in the open air for extended periods, or on treatment with dilute nitric acid at room temperature, the reduced compound (assigned structure IV) quantitatively reverted to III.

Treatment of III *with sodium n-butoxide in n-butyl alcohol.* III (1.0 g.) was added to a cold solution of 400 mg. of sodium in *n*-butyl alcohol (30 ml.). The resulting red solution was boiled for 30 min., during which time a red-orange precipitate formed. This was collected (1.150 g. crude material). The red product was very soluble in cold water. Acidification of the solution caused no precipitate to form nor was a change in color noted with change of *p*H. The product was completely insoluble in nonpolar solvents and could be purified only with difficulty from a large volume of absolute ethanol. The latter treatment removed a buff-colored solid and gave a yellow-orange powder, presumed to be the still somewhat impure and possibly solvated disodium salt of V.

Anal. Calcd. for $C_{12}H_8O_6N_2Na_2S_2$ (V): C, 37.31; H, 2.07; N, 7.25; S, 16.53; Na, 11.92. Found: C, 37.20; H, 4.2; N, 6.85; S, 15.83; Na, 11.10.

The red sodium salt darkened and decomposed at 290–310° and left a residue on ignition. To characterize the product more fully, the neutral aqueous solution of the sodium salt was treated with a cold aqueous solution of *S*-benzylthiuronium chloride. The resulting orange precipitate was crystallized from hot water and from aqueous methanol, giving a product which melted at 228–229°. Melting was accompanied by decomposition to a black oil.

Anal. Calcd. for the di-*S*-benzylthiuronium salt of 2,2′-azobenzenedisulfonic acid, $C_{28}H_{30}O_6N_6S_4$: C, 49.55; H, 4.6; N, 12.46; S, 19.0. Found: C, 49.54; H, 4.62; N, 12.46; S, 18.0.

Treatment of the acidified, aqueous solution of the disodium salt of V with zinc metal gave a colorless solution; and diazotization of this solution, then coupling with alkaline β-naphthol, gave a deep red dye, which was not investigated further. Presumably, the dye stems from orthanilic acid (see below).

Conversion of V *to the disulfonyl chloride* (VII). The orange disodium salt (V), 830 mg., was triturated with 1.0 g. of phosphorus pentachloride. The excess phosphorus pentachloride was hydrolyzed with water and the organic material was extracted with benzene. The benzene extract was passed through a column of silica and the first fractions eluted from the column were evaporated, giving a solid, which was recrystallized from a mixture of benzene and low-boiling petroleum ether. The product, 400 mg. was lavender in color and melted at 167–168°.

Anal. Calcd. for $C_{12}H_8O_2Cl_2N_2S_2$ (VII): C, 38.0; H, 2.10; N, 7.37; Cl, 18.68. Found: C, 39.15; H, 2.18; N, 7.20; Cl, 17.23.

Treatment of a small quantity of VII with ammonium fluoride, in acetone, gave a product which corresponded (m.p. and spectra) to III, thus completing the cycle III → V → VII → III.

Reduction of the disodium salt, V, *to orthanilic acid,* VI. The disodium salt, V, 600 mg., was dissolved in 50 ml. of water. About 500 mg. of Raney nickel catalyst was added and the mixture shaken with hydrogen at 45 p.s.i. for 2 hr. The colorless solution was separated from the catalyst and the filtrate was concentrated to 10 ml. and acidified with hydrochloric acid, causing precipitation of a white product (200 mg.). Treatment of the latter with diethylamine gave the diethylammonium salt of orthanilic acid, m.p. 177–178°. There was no depression of melting point on admixture of an authentic specimen of the salt, which melted at 176–178°, and is recorded[17] to melt at 177–178°.

Repetition of the reduction, using 700 mg. of salt V, gave 250 mg. of free orthanilic acid (characterized as the diethylammonium salt).

Bis(2,2′-methylmercapto)azobenzene, IX. To prepare methyl 2-nitrophenyl sulfide (X), bis(2-nitrophenyl)disulfide (13 g., 0.04 mole)[18] was refluxed for 30 min. with a soln. prepared from 5.6 g. (0.02 mole) of sodium sulfide nonahydrate and 4 g. (0.1 mole) of sodium hydroxide, in 45 ml. of 95% ethanol and 25 ml. of water. The dark reaction mixture was diluted with water (100 ml.), filtered, warmed to 45° and shaken with dimethyl sulfate (10 g., 0.08 mole). After cooling, the precipitated methyl 2-nitrophenyl sulfide (7.3 g., 0.04 mole) was collected and crystallized from 95% ethanol. It melted at 87° (lit.,[10] 85–87°).

Conversion of methyl 2-nitrophenyl sulfide (X) *to* IX. To a refluxing solution of X (1.5 g., 0.09 mole), in 20 ml. 95% ethanol, was added a solution of 1.5 g. sodium hydroxide in 5 ml. water. Zinc dust (2.6 g.) was added in portions to the hot solution and the mixture refluxed 15 min. Filtration and cooling of the filtrate gave a first crop of red product, and concentration of the mother liquor gave more product. The combined crude products were taken up in 95% ethanol (100 ml.), the solution filtered to remove zinc salts and the filtrate concentrated to give IX (830 mg., 0.006 mole), m.p. 155° (lit.[10] 156–158°).

To confirm the structure of IX, it was cleaved with sodamide to the disodium salt of VIII and remethylated to IX. Compound IX (1.0 g.) was added to a solution of sodamide, prepared from 1.0 g. sodium and 150 ml. of liquid ammonia, and the ammonia was evaporated. The residue was treated with water, to give a violet-red aqueous extract, and a residual orange solid. The latter was insoluble in carbon tetrachloride, ethyl acetate, and acetone and is presumably a polymeric disulfide of VIII, formed by partial oxidation. The violet-red solution and orange residue were refluxed with 1.0 g. of sodium sulfide nonahydrate for 30 min. and the mixture was diluted with water and filtered, to give a small amount of solid residue and a deep red filtrate. The latter was warmed to 50° and shaken with 1.0 g. of dimethyl sulfate. An orange emulsion formed immediately, and on cooling there precipitated 0.06 g. of IX, m.p. and mixture m.p. with IX (made alternately, as above) 155°. The above procedure was patterned on the work of Hughes and Thompson.[19]

Conversion of III *to* IX. Bis(2,2′-fluorosulfonyl)azobenzene, 700 mg., was added to a refluxing slurry of lithium aluminum hydride (1.0 g.) in 250 ml. of ether. A colorless solution was obtained after 1 hr., but it was noted that a pink color developed on cooling and that this color change was reversible with heating and cooling. Treatment of the alkaline reaction mixture with water and dilute sulfuric acid gave a yellow precipitate. This was extracted from the acidic solution with ether, leaving a trace of a greenish solid, and forming a red ethereal solution. The ethereal solution was shaken with 50 ml. of 10% aqueous sodium hydroxide

(17) S. Morita and M. Sugahara, *J. Chem. Soc., Japan, Pure Chem. Sect.*, **72**, 621–623 (1951). *Chem. Abstr.*, **46**, 6039 (1952).

(18) *Org. Syntheses*, **Coll. Vol. I**, 220 (1941).

(19) Hughes and Thompson, *Proc. Royal Soc. New South Wales*, **83**, 269 (1949).

solution, to give a deep purple aqueous layer and a colorless ethereal solution. To assure complete reduction, the aqueous purple layer was refluxed, as in the preceding experiment, with sodium sulfide nonahydrate (1.0 g.) for 30 min. The deep red solution which resulted was shaken, at 50°, with 1.0 g. of dimethyl sulfate. The cooled solution gave *ca.* 50 mg. of a pale-orange material, which still contained a trace of inorganic salts, for it did not melt completely, even at 290°. Recrystallization from ethylene chloride removed the colorless, inorganic impurity and left bis(2,2′-methylmercapto)azobenzene, m.p. and mixture m.p. with an authentic specimen,[10] 154–155°. The remaining material from the reduction of III was present as a water soluble compound and was not examined.

Synthesis and characterization of 3,3′-azobenzenedisulfonic acid. *m*-Nitrobenzenesulfonyl chloride (22 g., 0.1 mole) was refluxed with a solution of potassium hydroxide (28 g., 0.5 mole) in 240 ml. water, to give a clear yellow solution. Stirring and refluxing for 2 hr., while portions of zinc dust were added, gave a clear, colorless solution, from which the excess zinc was removed by filtration. The filtrate was refluxed for 2 hr., while a stream of air was passed through the solution, whereby a deep red solution resulted. The dissolved zinc salts were precipitated as the carbonates, by adding carbon dioxide, and the precipitate was collected. The red filtrate was evaporated, yielding the crude orange-red potassium salt (14.3 g.). Two recrystallizations from water gave an analytical sample.

Anal. Calcd. for $C_{12}H_8O_6K_2N_2S_2$: C, 34.28; H, 1.90; N, 6.67; S, 15.24; K, 18.57. Found: C, 33.90; H, 2.37; N, 6.92; S, 15.48; K, 18.30.

Reduction of the water solution of the potassium salt with hydrogen and Raney nickel, at 45 p.s.i., gave a colorless solution which, on concentration and acidification, gave a white precipitate. The diethylammonium salt of the latter melted at 143–145°, without purification. The reported melting point of the diethylammonium salt of metanilic acid is 148°.[17]

To assure the structure of the above salt it was converted to a series of derivatives, as follows:

Bis(3,3′-azobenzene)disulfonic acid (potassium salt), 1.0 g., was mixed with 1.0 g. phosphorus pentachloride and the mixture warmed several minutes. After hydrolysis of the excess phosphorus pentachloride, the red precipitate was recrystallized from methyl acetate and low-boiling petroleum ether mixture. The product melted at 171–172° (Mahrenholtz and Gilbert[9] record a melting point of 166°).

Anal. Calcd. for $C_{12}H_8O_4Cl_2N_2S_2$: C, 37.89; H, 2.1; N, 7.37; S, 16.84; Cl, 18.68. Found: C, 37.93; H, 2.20; N, 7.55; S, 17.23; Cl, 18.95.

The *diethyl ester of 3,3′-azobenzenedisulfonic acid* was prepared by refluxing the dichloride in ethanol for 1 hr., precipitating the product with water and recrystallizing from a mixture of methyl acetate and low boiling petroleum ether. The product melted at 107–108° (Mahrenholtz and Gilbert[9] give 100°).

Anal. Calcd. for $C_{16}H_{18}O_6N_2S_2$: C, 48.24; H, 4.52; N, 7.02; S, 16.08. Found: C, 48.28; H, 4.65; N, 7.02; S, 16.13.

The *S-benzylthiuronium salt*, prepared from the dipotassium salt (above) of 3,3′-azobenzenedisulfonic acid, melted at 217–218°, but was not analyzed. It is presumably the di-*S*-benzylthiuronium salt.

Attempts to prepare 2,2′-azobenzenedisulfonic acid and derivatives. In contrast to the above experience with the *meta* isomer, similar attempts to prepare the *ortho* isomer (2,2′-azobenzenedisulfonic acid) by reduction of the salts of 2-nitrobenzenesulfonic acid with zinc dust, in alkaline solution, did not yield the desired compound. The attempted conversion of bis(2,2′-methylmercaptoazobenzene) to the sulfonyl chloride, VII [bis-2,2′-chlorosulfonylazobenzene] by chlorination in wet acetic acid, was also not successful.

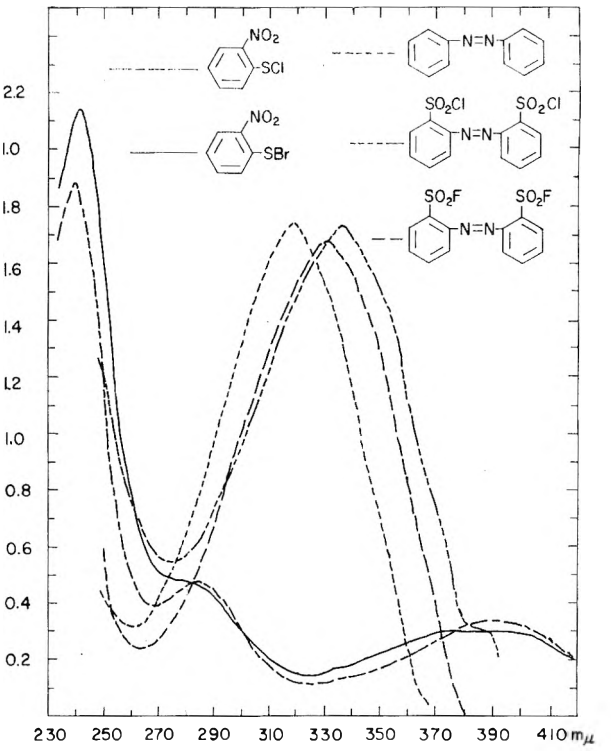


Fig. 1. The ultraviolet spectra of azobenzene, bis(2,2′-chlorosulfonyl)azobenzene and bis(2,2′-fluorosulfonyl)benzene, in dioxane, and of 2-nitrobenzene, in dioxane, and of 2-nitrobenzenesulfenyl chloride and 2-nitrobenzenesulfenyl bromide, in ethylene chloride

Bis(2,2′-benzenesulfonyl)azobenzene, XI. III (250 mg.) was dissolved in a mixture of 25 ml. of nitrobenzene and 10 ml. of benzene. One gram of aluminum chloride was added and the reaction mixture heated, under anhydrous conditions, on the hot plate for 2 days. It was then decomposed on ice, the organic layer was separated, dried, diluted with low-boiling petroleum ether, and passed through a column of activated silica. Elution with benzene gave a yellow eluate, from which no solid material could be recovered. Elution with acetone gave a red eluate, which yielded orange crystals. These were recrystallized from acetone, yielding 153 mg. of product, m.p. 250° and giving a 20° m.p. depression on admixture with bis(2,2′-fluorosulfonyl)-azobenzene, III, m.p. 256–257°.

Anal. Calcd. for XI, $C_{24}H_{18}O_4N_2S_2$: C, 62.34; H, 3.9; N, 6.20. Found: C, 62.40; H, 4.23; N, 6.06.

A qualitative trace of the ultraviolet absorption spectrum of this product, in dioxane solution, showed that it was very similar to the azo compounds whose spectra are reported in Fig. 1.

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Condensation of Some Trifluoromethyl Ketones with Secondary Amines and Formaldehyde

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Condensation of trifluoroacetone with the methylols of piperidine, morpholine, and diisobutylamine produced the hydrates of 1,1,1-trifluoro-3-piperidinomethyl-4-piperidino-2-butanone, 1,1,1-trifluoro-3-morpholinomethyl-4-morpholino-2-butanone, and 1,1,1-trifluoro-3-di(isobutyl)aminomethyl-4-diisobutylamino-2-butanone, respectively.

1,1,1-Trifluoro-4-piperidino-2-butanol, was prepared by the reduction of *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine with sodium borohydride to *N*-(β-hydroxy-γ,γ,γ-trifluorobutyryl)piperidine, followed by the reduction of the latter by lithium aluminum hydride.

Trifluoromethyl ethyl ketone, trifluoromethyl *n*-butyl ketone, and *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine condense with piperidine and formaldehyde to form the hydrates of 1,1,1-trifluoro-3-piperidinomethyl-2-butanone, 1,1,1-trifluoro-3-piperidinomethyl-2-hexanone, and *N*-(α-trifluoroacetyl-β-piperidinopropionyl)piperidine, respectively.

The syntheses of some trifluoromethyl ketones of the structure $CF_3COCHRCH_2NR_2$ and the corresponding alcohols were attempted as starting materials for the future preparation of local anesthetics.

No reaction occurred between trifluoroacetone, paraformaldehyde, and the hydrochlorides of piperidine, morpholine, and diethylamine. Trifluoroacetone reacted with either formaldehyde and diethylamine, dimethylamine, di-*n*-propylamine and di-*n*-butylamine, or the methylols of these amines to form in each case an unstable oily product and an unstable amorphous solid. The structures of these products could not be determined, although all contained fluorine.

Trifluoroacetone and the methylols of piperidine, morpholine, and diisobutylamine gave in each case a single crystalline product which, on the basis of varied evidence, appears to be the hydrate of a product resulting from the substitution of two dialkylaminomethyl groups for two hydrogens on the methyl group of the trifluoroacetone molecule and can be assigned the following general structure.

$$CF_3C(OH)_2CH(CH_2NR_2)_2$$

Compound I, R_2N is piperidino, $C_5H_{10}N$—

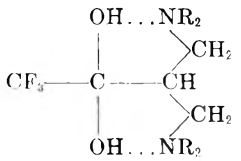
Compound II, R_2N is morpholino, OC_4H_8N—

Compound III, R_2N is diisobutylamino, $(C_4H_9)_2N$—

Acetone has previously been condensed with two moles each of dimethylamine and formaldehyde to form a corresponding but unhydrated product.[2]

After repeated attempts no product corresponding to a dialkylaminoethyl trifluoromethyl ketone could be isolated from the Mannich condensation.

Compounds I, II, and III gave indecisive chemical tests for the presence of the carbonyl group and this was attributed to internal hydrogen bonding as represented herewith:



Samples of compound I and II, prepared by the deposition of the crystals on the salt window from a chloroform solution, gave a strong infrared band at 3.03 microns corresponding to the absorption of associated hydroxyls.[3] No carbonyl absorption appeared in the infrared spectra of these two samples. If a sample of compound I was prepared by melting the sample on the salt window, the associated hydroxyl band disappeared and a carbonyl band appeared at 5.7 microns. It was concluded that the heating of compound I to its melting point served to remove a molecule of water, converting the carbonyl hydrate to the free ketone.

The preparation of 1,1,1-trifluoro-4-piperidino-2-butanol (IV) was eventually accomplished by the following series of reactions. Treatment of ethyl γ,γ,γ-trifluoroacetoacetate with piperidine gave *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine V which was reduced to *N*-(β-hydroxy-γ,γ,γ-trifluorobutyryl)piperidine VI by means of sodium borohydride. Reduction of VI with lithium aluminum hydride afforded the amino alcohol IV.[4] The stepwise reduction of V to IV was undertaken because attempts to accomplish this reduction directly by

$$CF_3COCH_2CO_2C_2H_5 \xrightarrow{C_5H_{10}NH} CF_3COCH_2CONC_5H_{10} \xrightarrow{NaBH_4}$$
V

$$CF_3CHOHCH_2CONC_5H_{10} \xrightarrow{LiAlH_4} CF_3CHOHCH_2CH_2NC_5H_{10}$$
VI IV

(1) Inquiries should be addressed to this author.

(2) C. Mannich and O. Salzmann, *Ber.*, **72**, 506 (1939).

(3) H. M. Randall, R. G. Fuson, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand Company, Inc., New York, N. Y., 1949, p. 20.

(4) A number of tertiary amines prepared by the reduction of tertiary amides by lithium aluminum hydride are listed in Table VI of Chapter 10 of *Org. Reactions*, **VI**, Roger Adams, Editor in Chief, p. 505 (1951).

use of lithium aluminum hydride were unsuccessful. An alternate method for preparing VI was investigated by allowing ethyl β-hydroxy-γ,γ,γ-trifluorobutyrate to react with piperidine. A small yield of the expected amide VI was realized, accompanied by the formation of the salt piperidinium β-hydroxy-γ,γ,γ-trifluorobutyrate, the structure of which was proven by its independent synthesis from β-hydroxy-γ,γ,γ-trifluorobutyric acid and piperidine.

Unlike *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine, (V),*N*-(acetoacetyl)piperidine was reduced successfully to 4-*N*-piperidino-2-butanol by lithium aluminum hydride. The hydrochloride and the benzoate hydrochloride of the resulting amino alcohol were proved to be identical with these derivatives of the amino alcohol obtained by Mannich and Hof[5] by reducing the condensation product of acetone, formaldehyde, and piperidine.

The reaction of formaldehyde and piperidine with trifluoromethyl ethyl ketone, trifluoromethyl *n*-butyl ketone, and *N*-(γ,γ,γ-trifluoroacetoacetyl)-piperidine V gave the expected hydrated Mannich bases VII. These substances are apparently *gem*

$$CF_3COCHRCH_2NC_5H_{10}\cdot H_2O$$
VII

diols with a structure similar to that proposed for the hydrated "disubstituted" Mannich bases obtained from trifluoroacetone. The assignment of *gem*-diol structures to these hydrates receives support from their failure to undergo carbonyl reactions under the usual conditions. The Mannich base derived from V, *N*-(α-trifluoroacetyl-β-piperidinopropionyl) piperidine [VII, R=CON(C_5H_{10})] exhibited low stability. An attempt to recrystallize it from boiling aqueous methanol caused its decomposition to *N*-(α-trifluoroacetylacryloyl)piperidine hydrate VIII. The structure of the latter was confirmed by its synthesis from *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine V and formaldehyde in the presence of sodium hydroxide.

$$\text{VII (R = CONC}_5\text{H}_{10}) \longrightarrow \underset{\text{VIII}}{CF_3COC(=CH_2)CONC_5H_{10}\cdot H_2O} \xleftarrow{NaOH} \underset{\text{V}}{CF_3COCH_2CONC_5H_{10}} + CH_2O$$

1,1,1-Trifluoromethyl-3-piperidinomethyl-2-butanone hydrate (Compound VII, R=CH_3) was reduced by sodium borohydride to 1,1,1-trifluoromethyl-3-piperidinomethyl-2-butanol (Compound IX) which was then converted to the hydrochloride of its *p*-nitrobenzoate ester. Reduction of 1,1,1-trifluoromethyl-3-piperidinomethyl-2-hexanone hydrate (Compound VII, R = *n*-propyl) with sodium borohydride produced 1,1,1-trifluoromethyl-3-piperidinomethyl-2-hexanol (Compound X). The latter was also obtained as the *p*-aminobenzoate ester and as the hydrochloride of this ester.

(5) C. Mannich and W. Hof, *Arch. Pharm.*, 265, 589 (1927).

EXPERIMENTAL[6]

1,1,1-Trifluoro-3-piperidinomethyl-4-piperidino-2,2-butanediol (Compound I). One-tenth mole of *N*-methylolpiperidine was prepared by adding 8.5 ml. of cold 37% aqueous formaldehyde solution to 8.5 g. (0.1 mole) of piperidine in 17 ml. of water and maintaining the mixture at 0° for 1 hr. Then 11 g. (0.1 mole) of trifluoroacetone[7] was added to the resulting *N*-methylolpiperidine with cooling by a Dry Ice–Cellosolve bath. The reaction flask was fitted with a Dry Ice reflux condenser and the cooling bath was removed. The flask was permitted to stand (with occasional shaking) at room temperature for about 30 min. A heavy precipitate formed which was twice recrystallized from acetone, m.p. 93–95°. A yield of 15.5 g. (48%) was obtained.

Anal. Calcd. for $C_{15}H_{27}F_3N_2O_2$: C, 55.7; H, 8.34; N, 8.64; mol. wt., 324; neut. equiv., 162. Found: C, 55.5; 55.6; H, 8.14, 8.46; N, 8.15; 8.44; mol. wt. (cryoscopic, benzene), 352, 350; neut. equiv., 167.4, 166.

If this diol is treated with 2,4-dinitrophenylhydrazine hydrochloride in methanol, followed by addition of methanolic KOH, a slight muddy red color appeared. If a blank test was run a greenish black color appeared which faded rapidly, while acetone gave a deep red color.

A determination of the number of active hydrogens in this diol by means of the Zerewitinoff test indicated 2^+ per mol.

Further, when this diol was esterified using the Schotten-Baumann technique a small amount of a viscous product, insufficient to characterize, was obtained. This product did give a positive hydroxamic acid test which is indicative of an ester.

1,1,1-Trifluoro-3-morpholinomethyl-4-morpholino-2,2-butanediol (Compound II). This compound was prepared in the same fashion as compound I above by substituting *N*-methylolmorpholine for the *N*-methylolpiperidine. The resulting crude product was twice recrystallized from methyl ethyl ketone, m.p. 83.5–87°. A yield of 13 g. (36%) was obtained.

Anal. Calcd. for $C_{13}H_{23}F_3N_2O_4$: C, 47.6; H, 7.03; N, 8.55. Found: C, 47.7; H, 7.6; N, 8.55.

1,1,1-Trifluoro-3-di(isobutyl)aminomethyl-4-diisobutylamino-2,2-butanediol (Compound III). This compound was prepared in the same fashion as compound I above by substituting the methylol of diisobutylamine for the *N*-methylolpiperidine. The crude product was obtained as an oil which crystallized on standing. The latter was recrystallized twice from acetone and melted at 79–81°. The yield was 8 g. (20%).

Anal. Calcd. for $C_{21}H_{43}F_3N_2O_2$: C, 61.9; H, 10.55; N, 6.55. Found: C, 61.3; H, 10.44; N, 6.8.

N-(γ,γ,γ-*trifluoroacetoacetyl)piperidine* (V). The apparatus used was similar to that described for the preparation of benzoylacetanilide.[8] A boiling mixture of 184 g. (1 mole) of ethyl γ,γ,γ-trifluoroacetoacetate[9] in 200 ml. of dry xylene was treated with 76.5 g. (0.9 mole) of dry piperidine, added dropwise, and the reaction mixture was refluxed for 30 min. Vacuum concentration and fractionation gave 147 g. (73%) of yellow oil, b.p. 119–120°/7 mm. (n_D^{27} 1.4647, which solid-

(6) Microanalyses for C, H, and N by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(7) A. L. Henne and R. L. Pelley, *J. Am. Chem. Soc.*, **74**, 1428 (1952).

(8) C. J. Kibler and A. Weissberger, *Org. Syntheses*, **Coll. Vol. III**, 108 (1955).

(9) A. L. Henne, M. S. Newman, L. L. Quill, and R. A. Staniforth, *J. Am. Chem. Soc.*, 69, 1819 (1947).

ified on cooling. After recrystallization from petroleum ether (b.p. 30–60°) it had m.p. 27.4–30.0° (corr.)

Anal. Calcd. for $C_9H_{12}F_3NO_2$: C, 48.43; H, 5.42. Found: C, 48.23; H, 6.07.

The *2,4-dinitrophenylhydrazone* was recrystallized from aqueous methanol, m.p. 114.5–115.5° (corr.).

Anal. Calcd. for $C_{15}H_{16}F_3N_5O_5$: C, 44.67; H, 3.99. Found: C, 45.13; H, 3.94.

The *copper chelate* was recrystallized from aqueous methanol, m.p. 207.0–207.5° (corr.).

Anal. Calcd. for $C_{18}H_{22}CuF_6N_2O_4$: Cu, 12.5. Found: Cu, 12.6.

N-(β-hydroxy-γ,γ,γ-trifluorobutyryl)piperidine (VI). To a stirred solution of 44.6 g. (0.2 mole) of V in 200 ml. of ether was added, in small portions and with cooling, 4 g. (0.1 mole) of sodium borohydride, after which stirring at room temperature was continued for 1.5 hr. Unreacted borohydride was removed by filtration, and the filtrate was treated with 20 ml. of 5% HCl with stirring at room temperature for 1.5 hr., then freed of solids by filtration. The organic layer was washed, dried, and concentrated, giving 36 g. (79%) of product. The analytical sample, recrystallized from benzene–petroleum ether, had m.p. of 109.4–109.8° (corr.).

Anal. Calcd. for $C_9H_{14}F_3NO_2$: C, 48.00; H, 6.27. Found: C, 47.89; H, 6.58.

1,1,1-Trifluoro-4-piperidino-2-butanol (IV). A solution of 31.5 g. (0.14 mole) of VI in 100 ml. of dry tetrahydrofuran was added to 8.7 g. (0.24 mole) of lithium aluminum hydride in 200 ml. of ether. The product was isolated according to the procedure of Micovic and Mihailovic[10] and fractionated to give 19 g. (64%) of material, b.p., 94° (14 mm.), n_D^{24} 1.4232, d_4^{24} 1.151.

Anal. Calcd. for $C_9H_{16}F_3NO$: C, 51.18; H, 7.64; M.R., 46.43; neut. equiv. 211.2. Found: C, 51.19; H, 8.39; M.R., 46.73; neut. equiv. 211.2.

The *phenylurethan* was recrystallized from petroleum ether, m.p. 93.0–93.6° (corr.).

Anal. Calcd. for $C_{16}H_{21}F_3N_2O_2$: C, 58.17; H, 6.41. Found: C, 58.56; H, 6.76.

The *methyl p-toluenesulfonate* was recrystallized from ethyl acetate–methanol, m.p. 122.8–124.0° (corr.).

Anal. Calcd. for $C_{17}H_{26}F_3NO_4S$: C, 51.37; H, 6.59. Found: C, 51.88; H, 7.03.

The *p-nitrobenzoate hydrochloride* was recrystallized from acetone-methanol, m.p. 191–193° (corr.).

Anal. Calcd. for $C_{16}H_{19}F_3N_2O_4 \cdot HCl$: Cl, 8.94. Found: Cl, 8.87.

The *p-aminobenzoate* was prepared from the latter by hydrogenation using PtO_2 as catalyst, followed by neutralization with concd. NH_4OH. After recrystallization from aqueous methanol, it had m.p. 103.0–103.8° (corr.).

Anal. Calcd. for $C_{16}H_{21}F_3N_2O_2$: C, 58.13; H, 6.41; neut. equiv., 165. Found: C, 59.05; H, 6.81; neut. equiv., 167.

Ethyl β-hydroxy-γ,γ,γ-trifluorobutyrate. This ester has been previously prepared by other methods.[11,12] The reduction was performed in a manner similar to that described for the preparation of VI by treating a solution of 49 g. (0.26 mole) of ethyl γ,γ,γ-trifluoroacetoacetate in 50 ml. of ether with 3.8 g. (0.1 mole) of sodium borohydride. Fractionation afforded 34 g. (69%) of product, b.p. 80–83° (14–15 mm.), n_D^{25} 1.3732 (reported[12] b.p. 81–83°/15 mm., n_D^{25} 1.3720).

The *phenylurethan*, melted at 67–69° (reported[12] m.p. 70.0–70.5°).

Reaction of ethyl β-hydroxy-γ,γ,γ-trifluorobutyrate with piperidine. A boiling solution 49.5 g. (0.22 mole) of ethyl β-hydroxy-γ,γ,γ-trifluorobutyrate in 75 ml. of dry xylene was treated with 27 g. (0.32 mole) of dry piperidine. The mixture was refluxed for 2 hr., decolorized with Nuchar and vacuum concentrated, producing 20 g. of crude solid product which was isolated by filtration. This product was extracted with water. The water insoluble fraction was recrystallized from benzene and gave 3.6 g. of VI. The aqueous extract was treated with benzene to remove traces of VI, evaporated to near dryness at reduced pressure and dried by azeotropic distillation with benzene, giving 12 g. of piperidinium β-hydroxy-γ,γ,γ-trifluorobutyrate which, after recrystallization from benzene, had m.p. 100.8–101.8° (corr.).

Anal. Calcd. for $C_9H_{16}F_3NO_3$: C, 44.44; H, 6.63; neut. equiv., 243. Found: C, 44.46; H, 6.62; neut. equiv., 243.

The melting point of this salt was not depressed by admixture of the compound obtained by treatment of β-hydroxy-γ,γ,γ-trifluorobutyric acid[12] with piperidine.

4-(N-piperidino)-2-butanol. *N*-(acetoacetyl)piperidine[13] was first prepared by the following procedure:

A solution of 65 g. (0.5 mole) of acetoacetic ester in 70 ml. of xylene was heated to 145°. To this solution was added 34 g. (0.4 mole) of piperidine in small portions. Heating was continued for 45 min. and after vacuum fractionation 55 g. (88%) of product was collected, b.p., 126–128° (4 mm.).

This product was reduced by the method of Uffer and Schlitter[14]:

A one-liter three-necked flask equipped with a dropping funnel, mercury sealed stirrer, and a Y tube fitted with a reflux condenser was charged with 500 ml. of dry ether and was swept out with dry nitrogen. Twenty-five grams (0.66 mole) of lithium aluminum hydride was added while the flow of nitrogen was maintained. Then a solution of 59 g. (0.35 mole) of *N*-(acetoacetyl)piperidine in 50 ml. of dry ether was admitted to the reaction mixture during a period of 1 hr. The reaction mixture was stirred for 30 min. after the last of the ketoamide was added, and then was refluxed for 24 hr. On cooling, water was added very cautiously and the mixture was stirred and allowed to stand at room temperature to ensure complete decomposition of the excess hydride. To the resulting slurry, 10% sulfuric acid was added until all the white precipitate dissolved. The acid solution was separated from the ether and the latter was extracted once with 50 ml. of 10% sulfuric acid. The combined acid solutions were then made strongly alkaline with 10*N* sodium hydroxide and extracted twice with 100-ml. portions of ether. The ether extracts were dried over anhydrous $MgSO_4$ and distilled. A total of 25 g. (45% of theory) of product boiling at 103° (11 mm.) was obtained.

The hydrochloride of the resulting amino alcohol was prepared and was recrystallized from alcohol and acetone, m.p., 145°. The benzoate hydrochloride, recrystallized from acetone, melted at 192°. Mixed melting point determinations were run with each derivative, using the hydrochloride and the benzoate ester hydrochloride prepared from an authentic sample of 4-(*N*-piperidino)-2-butanol prepared by the method of Mannich and Hof.[5] In neither case was any depression of the melting point observed.

1,1,1-Trifluoro-3-piperidinomethyl-2-butanone hydrate (VII R = CH_3). Trifluoromethyl ethyl ketone[15] (12.6 g., 0.1 mole) was treated with 8.5 g. (0.1 mole) of piperidine and 10 ml. of 37% formalin with cooling. Addition of water and chilling produced 21 g. (87%) of product which was recrystallized from aqueous ethanol and had m.p. 98–100°.

Anal. Calcd. for $C_{10}H_{16}F_3NO \cdot H_2O$: C, 49.78; H, 7.52. Found: C, 50.12; H, 8.45.

The *picrate*, recrystallized from aqueous methanol, had m.p. 105–107°.

(10) V. M. Micovic and M. L. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

(11) H. M. Walborski and M. Schwarz, *J. Am. Chem. Soc.*, **75**, 3241 (1953).

(12) E. T. McBee, O. R. Pierce, and D. D. Smith, *J. Am. Chem. Soc.*, **76**, 3722 (1954).

(13) P. W. Vittum, K. P. Griffin, and A. Weissberger, U. S. Patent 2,378,266; *Chem. Abstr.*, **39**, 3743 (1945).

(14) A. Uffer and E. Schlitter, *Helv. Chim. Acta*, **31**, 1397 (1948).

(15) A. Sykes, J. C. Tatlow, and C. R. Thomas, *Chem. & Ind. (London)*, 630 (1955).

Anal. Calcd. for $C_{16}H_{19}F_3N_4O_8 \cdot H_2O$: C, 40.85; H, 4.50. Found: C, 41.44; H, 5.26.

1,1,1-Trifluoro-3-piperidinomethyl-2-hexanone hydrate (VII, R = *n*-propyl). Trifluoromethyl *n*-butyl ketone[16] (15.4 g., 0.1 mole) was treated with 8.5 g. (0.1 mole) of piperidine and 10 ml. of 37% formalin, yielding 23 g. (85%) of product. After recrystallization from aqueous methanol it melted at 82–84°.

Anal. Calcd. for $C_{12}H_{20}F_3NO \cdot H_2O$: C, 53.55; H, 8.24. Found: C, 54.09; H, 8.74.

The *picrate*, recrystallized from aqueous methanol, had m.p. 93–95°.

Anal. Calcd. for $C_{18}H_{23}F_3N_4O_8 \cdot H_2O$: C, 43.37; H, 5.06. Found: C, 43.81; H, 5.53.

N-(α-trifluoroacetyl-β-piperidinopropionyl)piperidine hydrate (VII, R = $CON(C_5H_{10})$). A solution of 5 g. (0.22 mole) of N-(γ,γ,γ-trifluoroacetoacetyl)piperidine V in 20 ml. of 95% ethanol was cooled to 10° and treated with 1.9 g. (0.22 mole) of piperidine and 2.2 g. (0.22 mole) of 30% formalin with cooling and shaking. There was obtained 6.8 g. (90%) of product which, after recrystallization from ether–petroleum ether (b.p. 30–60°), had m.p. 96–98°.

Anal. Calcd. for $C_{15}H_{23}F_3N_2O_2 \cdot H_2O$: C, 53.25; H, 7.45; neut. equiv., 338. Found: C, 53.35; H, 7.39; neut. equiv., 339.

The *picrate*, after washing with ether, had m.p. 92–93°.

Anal. Calcd. for $C_{21}H_{26}F_3N_5O_9 \cdot H_2O$: C, 44.44; H, 4.97; neut. equiv., 567. Found C, 44.41; H, 4.96; neut. equiv., 566.

An attempt to recrystallize the Mannich base from hot aqueous methanol caused its decomposition to VIII.

N-(α-trifluoroacetylacryloyl)piperidine hydrate (VIII). A solution of 5 g. (0.22 mole) of *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine V in 15 ml. of methanol, to which ten drops of 15% NaOH had been added, was cooled to 20° and treated with 3 g. (0.03 mole) of 30% formalin, added dropwise with vigorous shaking. After heating the mixture to 50° and shaking vigorously for 5 min., 5 ml. of water was added and the mixture was cooled, affording 4 g. (70%) of product which was recrystallized from aqueous methanol, m.p. 138.4–140.0°.

Anal. Calcd. for $C_{10}H_{12}F_3NO_2 \cdot H_2O$: C, 47.43; H, 5.57. Found: C, 48.05; H, 5.38.

1,1,1-Trifluoro-3-piperidinomethyl-2-butanol (IX). To a solution of 5 g. (0.023 mole) of 1,1,1-trifluoro-3-piperidinomethyl-2-butanone hydrate (compound VII, R = CH_3) in 100 ml. of ether was added in small portions 0.38 g. (0.01 mole) of sodium borohydride. Stirring was continued for 1.5 hr. Unreacted borohydride was removed by filtration and the filtrate was treated with a solution of 2 g. of sodium hydroxide in 50 ml. of water and the mixture was stirred vigorously for 1 hr. The water layer was separated and extracted with ether and the combined ether extracts were dried over magnesium sulfate. Upon distillation of the ether extracts 2.5 g. (50%) of a colorless oily liquid, b.p. 79–81° (4 mm.), was obtained.

p-Nitrobenzoate hydrochloride. Recrystallized from a chloroform–petroleum ether solution, m.p. 206–208° (corr.).

Anal. Calcd. for $C_{17}H_{22}O_4F_3N_2Cl$: C, 49.69%; H, 5.39%. Found: C, 49.51%; H, 6.18%.

1,1,1-Trifluoro-3-piperidinomethyl-2-hexanol (X). A procedure was employed similar to that described above for the preparation of 1,1,1-trifluoro-3-piperidinomethyl-2-butanol (IX). When 10 g. (0.037 mole) of 1,1,1-trifluoro-3-piperidinomethyl-2-hexanol hydrate (Compound VII R = *n*-propyl) was reduced, a colorless oily liquid was obtained. B.p. 92–95° (4 mm.). Yield 4.7 g. (47%).

p-Aminobenzoate. Repeated attempts to purify the *p*-nitrobenzoate derivative of the above alcohol by recrystallization failed. Seven grams (0.016 mole) of the crude *p*-nitrobenzoate hydrochloride in 100 ml. of ethyl alcohol was reduced using 150 mg. of Adams' platinum catalyst and 0.048 mole of hydrogen. After reduction was complete the catalyst was removed by filtration. After many repeated attempts at crystallization of the *p*-aminobenzoate hydrochloride had failed, an alcohol solution of this ester hydrochloride was neutralized with sodium hydroxide, whereupon the color of the solution changed from yellow to a deep orange brown. Upon addition of water a nearly colorless precipitate formed. This was recrystallized from an aqueous alcohol solution and melted at 92–94°. Yield 3.8 g. (63%).

Anal. Calcd. for $C_{19}H_{27}F_3N_2O_2$: C, 61.27%; H, 7.31%. Found: C, 61.42%; H, 7.82%.

p-Aminobenzoate hydrochloride. To 1.4 g. (0.0035 mole) of the free ester was added exactly 37.8 ml. of 0.0924*N* HCl. A white precipitate remained which was washed several times with water and was then dried. It melted at 223–225° (corr.).

Anal. Calcd. for $C_{19}H_{28}F_3N_2O_2Cl$: C, 55.81%; H, 6.89%. Found: C, 55.91%; H, 7.29%.

Acknowledgment. We extend our thanks to Dr. W. C. Fernelius of Pennsylvania State University for suggesting this problem and to Samuel P. Sadtler and Sons, Inc., Philadelphia, who prepared and assisted us in interpreting the infrared spectra.

SYRACUSE 10, N. Y.

(16) K. T. Dishart and R. Levine, *J. Am. Chem. Soc.*, **78**, 2268 (1956).

[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Preparation of Some Substituted α,β-Diphenylacrylic Acids and Related Derivatives

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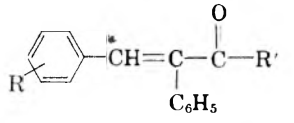
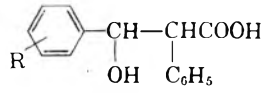
The preparation of a number of compounds related to ethyl β-(3,4-methylenedioxyphenyl)-α-phenylacrylate is described.

A part of the insecticide research program under way in this laboratory is concerned with the synthesis of insect toxicants, synergists, repellents, and attractants. The search for these compounds originally was conducted on an empirical basis, for no relationship between chemical constitution and biological activity was known. However, with the synthesis of many compounds and their subsequent

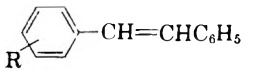
screening against insects, structural leads have been uncovered. These leads, when utilized in the synthesis of additional compounds, have produced a much higher percentage of biologically active compounds than were obtained by the empirical approach.[1] Some esters of tropic acid, for example,



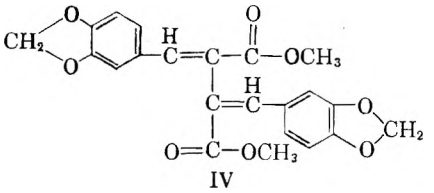
Ia, R = 3,4-CH_2O_2, R′ = OC_2H_5
Ib, R = 3,4-CH_2O_2, R′ = OH
Ic, R = *o*-OCH_3, R′ = OCH_3
Id, R = *p*-OCH_3, R′ = OC_2H_5
Ie, R = *o*-OCH_3, R′ = OH
If, R = 3,4-CH_2O_2, R′ = OCH_3
Ig, R = 3,4-CH_2O_2, R′ = $N(C_2H_5)_2$
Ih, R = *p*-OCH_3, R = $N(C_2H_5)_2$



IIa, R = *p*-OCH_3
IIb, R = 3,4-CH_2O_2



IIIa, R = *p*-OCH_3
IIIb, R = 3,4-CH_2O_2



IV

were found useful as repellents,[2] and a related compound, ethyl β-(3,4-methylenedioxyphenyl)-α-phenylacrylate, Ia,[3] was synthesized and proved to to be an excellent synergist for pyrethrum when tested against lice. With the biological information available on this compound, it was of interest to synthesize compounds related to it and to determine the effect of structural variations on biological activity. The preparation of these compounds is described herein. As indicated by melting point data,[4] the reported acrylic acids are *trans* compounds.

Our attention was first directed toward the synthesis of *beta*-(*p*-methoxyphenyl)tropic acid, IIa. A related compound, *beta*-(3,4-methylenedioxyphenyl)tropic acid, IIb, had previously been prepared in good yield.[3] Most attempts to prepare IIa in a pure state failed, because the compound partially dehydrated on recrystallization from alcohol. However, a pure product was obtained which melted at 136–138° (dec.). When treated with acetic anhydride and sodium acetate at 100°, IIa dehydrated and decarboxylated simultaneously to give the stilbene, IIIa. This decarboxylation was not anticipated, since IIb, when similarly treated, gave the acrylic acid, Ib, in 97% yield,[3] and not 3,4-methylenedioxystilbene, IIIb. Curiously, IIIb was obtained in quantitative yield when the crude chrysanthemumic ester of *alpha*-benzylpiperonyl alcohol was distilled.

Methoxy analogs of Ia (Ic through Ie) were prepared in the same manner as described for the methylenedioxyphenyl compounds.[3] Hydrogenation of these acrylates under pressure with a nickel-kieselguhr catalyst[5] gave the propionates in quantitative yield. The acrylamides were made in the usual way from the acid chlorides. Treatment of 2,3-dipiperonylidenesuccinic acid[6] with methanol and sulfuric acid at 100° gave the dimethyl ester, IV, in high yield.

EXPERIMENTAL

β-(p-Methoxyphenyl)tropic acid (IIa) was prepared as previously described, for the methylenedioxyphenyl compounds,[3] from anisaldehyde and phenylacetic acid. The crude product, yield 43%, was rather difficult to purify because it partially dehydrated when recrystallized from hot ethanol-water (1:1) in the usual way. A pure product was obtained, however, in the following manner.

The crude tropic acid was added to a warm (50°) 50% aqueous alcohol solution with rapid stirring until solution was effected. On cooling precipitation occurred and the isolated crystals when dry melted at 136–138° (dec.).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.47; H, 6.02.

β-(o-Methoxyphenyl)-α-phenylacrylic acid (Ie) was prepared as previously described for the methylenedioxyphenyl compound;[3] recrystallized from ethanol-water (3:1); m.p. 185–187°; yield 59%.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.86; H, 5.80.

3-(o-Methoxyphenyl)-2-phenylacrylic acid, methyl ester (Ic) was prepared by refluxing the acid with 5% methanolic hydrogen chloride; recrystallized from methanol; m.p. 100–101°; yield 86%.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.69; H, 6.14.

3,4-Methylenedioxystilbene (IIIb) was produced in quantitative yield when the crude chrysanthemumate of *alpha*-benzylpiperonyl alcohol[7] was distilled at 145–180° at 0.2 mm. pressure in a short-path still; recrystallized from 95% ethanol; m.p. 93–94° (lit. 95–96°).[8]

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.04; H, 5.41. Found: C, 79.91; H, 5.32.

4-Methoxystilbene (IIIa) was prepared from beta-(*p*-methoxyphenyl)tropic acid.[3] The acid, 89 g., acetic anhydride, 200 ml., and anhydrous sodium acetate, 50 g., were stirred on the steam bath at 100° for 4 hr. The mixture, while hot, was poured into 1 kg. of cracked ice and water with stirring. After standing overnight, the mixture was filtered and the crystals were washed with cold water;

(1) S. A. Hall, N. Green, and M. Beroza, *J. Agr. Food Chem.*, **5**, 663 (1957).

(2) W. V. King, *U. S. Dept. Agr. Handbook* **69**, (1954).

(3) B. H. Alexander and W. F. Barthel, *J. Org. Chem.*, **22**, 1647 (1957).

(4) C. R. Hauser and M. Patterson, *Org. Reactions*, **I**, 252 (1942).

(5) L. W. Covert, R. Connor, and H. Adkins, *J. Am. Chem. Soc.*, **54**, 1651 (1932).

(6) R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 1985 (1938).

(7) W. F. Barthel and B. H. Alexander, *U. S. Dept. Agr.*, **ARS-33-42**, Procedures C and E (1957).

(8) B. B. Dey and K. K. Row, *Quart. J. Indian Chem. Soc.*, **1**, 277–87 (1925).

recrystallized from 95% ethanol; m.p. 135–136° (lit. 132°)[9]; yield 75%.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.94; H, 6.93.

β-(p-Methoxyphenyl)-α-phenylacrylic acid, ethyl ester (Id) was prepared in the usual way by refluxing the acid with 5% ethanolic hydrogen chloride; recrystallized from ethanol; m.p. 48–50°; yield 51%.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.79; H, 6.30.

3-(p-Methoxyphenyl)-2-phenylpropionic acid, ethyl ester (Id dihydro) was prepared by hydrogenation of the acrylate (Id), 35 g., ethanol, 120 ml., and nickel-kieselguhr catalyst,[5] 5 g. at 2000 p.s.i. and at 130° for approximately 1 hr.; recrystallized from 95% ethanol; m.p. 57–59°; yield quantitative.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.60; H, 7.29.

3-(o-Methoxyphenyl)-2-phenylpropionic acid, methyl ester (Ic dihydro) was prepared in the same manner as the ethyl ester (described above); b.p. 147–155°/0.5 mm., n_D^{25}° 1.5538; yield quantitative.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 76.01; H, 6.86.

3-(3,4-Methylenedioxyphenyl)-2-phenylpropionic acid, methyl ester (If dihydro) was prepared as described above; b.p. 162–195°/0.2 mm., n_D^{25}° 1.5636; yield quantitative.

(9) M. S. Kharasch and H. G. Clapp, *J. Org. Chem.*, **3**, 355–60 (1938).

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.81; H, 5.67. Found: C, 71.06; H, 5.94.

3-(3,4-Methylenedioxyphenyl)-2-phenylpropionic acid, ethyl ester (Ia dihydro) was prepared as described above; b.p. 161–190°/0.2 mm., n_D^{25} 1.5552; yield quantitative.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.10; H, 6.41.

2,3-Dipiperonylidenesuccinic acid, dimethyl ester (IV) was prepared by refluxing 2,3-dipiperonylidenesuccinic acid,[6] 83 g., sulfuric acid, 50 g., and methanol, 1 l., for 6 hr. The product was isolated in the usual way; recrystallized from ethanol; m.p. 181–182°; yield quantitative.

Anal. Calcd. for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42. Found: C, 63.83; H, 4.70.

N,N-Diethyl-β-(3,4-methylenedioxyphenyl)-α-phenylacrylamide (Ig) was prepared in the usual way by reacting the acid chloride with diethylamine; recrystallized from 95% ethanol; m.p. 128–129°; crude yield quantitative.

Anal. Calcd. for $C_{20}H_{21}NO_3$: N, 4.33. Found: N, 4.07.

N,N-Diethyl-β-(p-methoxyphenyl)-α-phenylacrylamide (Ih) was prepared as described above; recrystallized from ethanol-water (4:1); m.p. 68–70°; crude yield quantitative.

Anal. Calcd. for $C_{20}H_{23}NO_2$: N, 4.53. Found: 4.77.

Acknowledgment. All microanalyses were performed by Kathryn Gerdeman, of the Chemistry Department, University of Maryland.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

A Preparation and Certain Properties of 2-Carbomethoxy-*N*-methylgranatonine

STEPHEN P. FINDLAY*

Received September 25, 1957

The preparation of racemic 2-carbomethoxy-*N*-methylgranatonine is described, and certain of its physical and chemical properties are compared with those of racemic 2-carbomethoxytropinone.

Succindialdehyde combines with methylamine and the half methyl ester (II) of β-ketoglutaric anhydride (I), the principal product being racemic 2-carbomethoxytropinone (VI and its mirror image).[1] The readiness with which this variation of Robinson's biological synthesis[2,3] occurs made it seem probable that an analogous condensation in which glutaraldehyde, now obtainable commercially,[4] was used in the place of succindialdehyde would give racemic 2-carbomethoxy-*N*-methylgranatonine (3 - keto - 2 - carbomethoxy - 9 - methyl - 9 - azabicyclo[3.3.1]nonane)(III) with comparable ease; and it was thought that this compound, which has not been reported before, would permit some instructive comparisons with racemic 2-carbomethoxytropinone and that it might constitute a valuable intermediate in the synthesis either of analgesics like cocaine and psicaine[5] or of certain derivatives of cyclooctane or of both.

By this procedure 2-carbomethoxy-*N*-methylgranatonine (III) was indeed obtained, but the yield realized (*ca.* 25%) was disappointing, being no greater than half that of 2-carbomethoxytropinone.[1] The large quantities of colored by-products likewise isolated, are, because of their solubility in aqueous alkali, very probably β-keto esters also. It is pertinent here to note that, although *trans* fusion of the rings in the reaction leading to 2-carbomethoxytropinone (VI) is almost certainly

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(1) S. P. Findlay, *J. Org. Chem.*, **22**, 1385 (1957).

(2) R. Robinson, *J. Chem. Soc.*, **111**, 762 (1917).

(3) R. Willstätter, H. Wolfes, and R. Mader, *Ann.*, **434**, 111 (1923).

(4) K. Alder and H. A. Dortmann, *Chem. Ber.*, **86**, 1544 (1953).

(5) *The Merck Index*, Sixth Edition, Merck & Co., Inc., Rahway, N. J., 1952, p. 803.

impossible, some *trans* combination of the piperidine rings formed in this reaction is at least conceivable and that in instances in which ring strain is non-existent, as in the synthesis of the analogous 1,2,6-trimethyl-4-piperidone, both the *cis* and *trans* isomers are obtained.[6] However, in this reaction no evidence of the formation of *trans* isomer was found. It is worth noting also that the phenomena observed in connection with the preparation of each of these two compounds resemble those recorded by McElvain and Adams of the amino β-keto ester, ethyl isogranatonine carboxylate (VII).[7]

Certain of the physical properties of racemic 2-carbomethoxy-*N*-methylgranatonine indicate it to be a mixture: in the anhydrous form, obtained by sublimation, it melts over a considerable range (97.3–101.8°), and in chloroform solution this modification has absorption maxima characteristic of both keto and enol structures. Its solubility in both polar and non-polar solvents is considerable, and it readily forms a hydrate when its solution in acetone is diluted with water. In all these respects it resembles 2-carbomethoxytropinone closely.[1] On the other hand, its picrate, prepared in methanol, was not converted to another modification by recrystallization from acetone.[1]

The ultraviolet absorption spectra indicate that in absolute alcoholic solution the proportion of 2-carbomethoxy-*N*-methylgranatonine existing as the enol tautomer is considerably greater than that of 2-carbomethoxytropinone (Table I). It is noteworthy that the location of the absorption maximum and the molar extinction coefficient, both of which are different for the two compounds in absolute alcohol, have both become the same or nearly so in 50% aqueous acetic acid. Presumably in this solvent the two esters are enolized entirely.

TABLE I

	Racemic 2-Carbomethoxytropinone	Racemic 2-Carbomethoxy-*N*-methylgranatonine
Melting points		
Anhydrous form	102–104°[1]	97.3–101.6°[a]
Hydrated form	93–96°[1]	98–100.5°[a]
Picrate salt	168°[1] and 176°[1]	207°[a]
Absorption spectra		
Absolute alcohol	255 mμ (ε = 6190)[1]	253 mμ (ε = 8930)[a]
50% Aq. acetic acid	248 mμ (ε = 9727)[a]	248 mμ (ε = 9420)[a]

[a] This investigation.

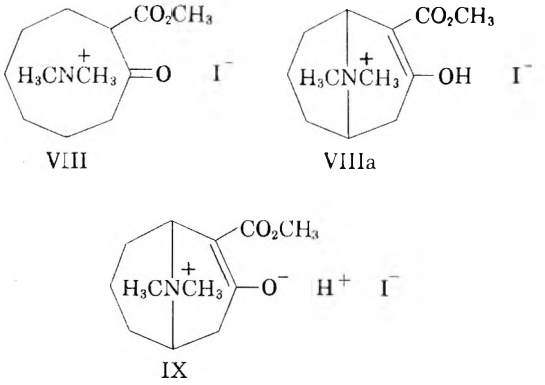
Methyl iodide combines with racemic 2-carbomethoxy-*N*-methylgranatonine in acetone solution to give a derivative having the composition of the methiodide, $C_{12}H_{20}INO_3$. This substance is soluble in cold aqueous potassium carbonate, but the resulting solution does not yield 2-carbomethoxy-2,7-cyclooctadienone (IV) or 2,7-cyclooctadienone (V) either at room temperature or on heating. The apparent pronounced stabilization of an essentially labile compound through combination with methyl iodide arises probably from the formation of an inner salt like that present in phenolbetaines which makes the Hofmann Degradation of phenolic alkaloids difficult also[8] and, together with its tendency to lose hydrogen iodide (see Experimental section), suggests that this substance has structure IX rather than structure VIII or VIIIa. The methiodide has absorption maxima at 221 mμ (ε = 15,600) and at 247 mμ (ε = 8,600) in absolute alcohol, and at 228 mμ (ε = 15,930) and approximately at 250 mμ in aqueous solution. These are due presumably to the iodide ion[9] and to the α,β-unsaturated ester linkage.

(6) C. Mannich, *Arch. Pharm.*, **272**, 323 (1934).

(7) S. M. McElvain and R. Adams, *J. Am. Chem. Soc.*, **45**, 2738 (1923); see also, R. H. F. Manske and H. L. Holmes, *The Alkaloids*, Vol. I, Academic Press, Inc., New York, 1950, p. 188.

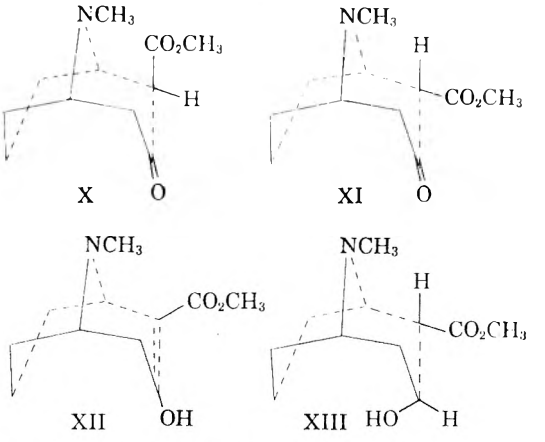
(8) *Cf.*, L. F. Small and R. E. Lutz, *The Chemistry of the Opium Alkaloids*, United States Government Printing Office, Washington, D. C., 1932, pp. 147 and 268.

(9) For iodide in aqueous solution λ_{max} = *ca.* 226.5 mμ (ε = 18,200) [A. D. Awtrey and R. E. Connick, *J. Am. Chem. Soc.*, **73**, 1842 (1951)].



By recrystallizing the L-bitartrate of the racemic base from water a small yield of one antipode of 2-carbomethoxy-*N*-methylgranatonine as the L-bitartrate salt, $C_{15}H_{23}NO_9 \cdot 2H_2O$, was obtained pure or nearly pure: $[\alpha]_D^{20}$ +43.4° in water. In analogy with (+)-(2-carbomethoxytropinone) (VI), the L-bitartrate of which is less soluble in water than that of the (−)-antipode,[1] the basic moiety of this L-bitartrate should have the absolute configuration or three-dimensional structures of formulas, X-XII, representing the enol form and the two possible keto forms of the base.

Catalytic hydrogenation[1] of this antipode in aqueous acetic acid should result in the two optically active 2-carbomethoxy-*N*-methylgranatolines (XIII and its C_2 epimer) having an axial C_3-hydroxyl group (tropine or α configuration),[10-12] whilst hydrogenation with sodium amalgam[3] should afford the two optically active 2-carbomethoxy-*N*-methylgranatolines having an equatorial C_3-hydroxyl group (pseudotropine or β configuration).[10,11,13] Benzoylation of these esters should furnish analogues of the cocaines[3,12,13] and hydrolysis hydroxyamino acids closely related to the ecgonines.[3,12-14]



This investigation will not be continued.

(10) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).
(11) G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953).
(12) S. P. Findlay, *J. Org. Chem.*, **21**, 711 (1956).
(13) S. P. Findlay, *J. Am. Chem. Soc.*, **76**, 2855 (1954).
(14) A. Einhorn and A. Marquardt, *Ber.*, **23**, 468 (1890).

EXPERIMENTAL[15]

Materials. Glutaraldehyde, supplied and used as a 25% solution in water, was a gift of the Carbide and Carbon Chemicals Company. Fisher C.P. methylamine hydrochloride and Mallinckrodt A.R. L-tartaric acid (the common or naturally occurring antipode) were employed.

Racemic 2-carbomethoxy-N-methylgranatonine (3-keto-2-carbomethoxy-9-methyl-9-azabicyclo[3.3.1]nonane) (III). β-Ketoglutaric anhydride[1,16] (13.5 g., 0.105 mole) was dissolved in Fisher absolute methanol (100 ml.) at 0°. This mixture was kept one hour at room temperature and poured into another consisting of methylamine hydrochloride (10.0 g., 0.148 mole), 4*N* aqueous sodium hydroxide (25 ml.), and water (850 ml.). To the resulting solution glutaraldehyde (40 g. of a 25% aqueous solution, 0.100 mole) was immediately added. The evolution of carbon dioxide soon became noticeable, and after 2 to 3 hr. the initially rather pale yellow solution had acquired an orange hue.

After 24 hr. at room temperature the orange reaction mixture was filtered from some flocculent matter and the filtrate brought to *p*H *ca.* 4 with 6*N* sulfuric acid, an observable evolution of carbon dioxide being thus brought about. A little potassium bicarbonate, anhydrous sodium sulfate (50 g.), and more potassium bicarbonate (15 g. altogether) were successively dissolved in this mixture, which was then extracted with chloroform (6 × 100 ml.). The dried (sodium sulfate) extracts were concentrated on the steam bath and then *in vacuo* to a thick, orange brown oil (18.5 g.) having a greenish fluorescence. Seeded with material from a previous preparation, long, delicate filaments grew gradually from the upper walls of the flask to the surface of the red liquid which during the course of several weeks was slowly converted thereby to a semi-circle of mounds consisting of slender prisms mixed with reddish-brown liquid impurities.

By leaching with boiling ligroin (b.p. 60–71°) (2 × 100 and 50 ml.) from the reddish-brown by-products and removing the solvent from the yellow leachings *in vacuo*, an oil (8.0 g.) was isolated which, when mixed with absolute methanol (5 ml.) and seeded with anhydrous 2-carbomethoxy-*N*-methylgranatonine, slowly solidified. This material was purified by distillation about 90°/1 mm.: 5.1 g. (24%) of pale yellow solid melting at 98.7–101.6°.

Another preparation conducted essentially as the foregoing except that the temperature was maintained about 0° for 24 hr. gave *ca.* 5.5 g. of the β-keto ester.

The above-mentioned brown, ligroin-insoluble by-products (10.5 g.) were soft at 60° but solid at room temperature. This mixture was dissolved in a solution of potassium hydroxide (2.2 g.) in methanol (25 ml.) and precipitated at 0° therefrom with carbon dioxide. The recovered, brick-red solid could not be sublimed *in vacuo*, and attempted recrystallization from aqueous acetone gave only a small yield of yellow solid. The ligroin-insoluble fraction was not further investigated.

Physical properties of racemic 2-carbomethoxy-N-methylgranatonine. A small amount (*ca.* 0.1 g.) of the filaments (m.p. 102–104°) described above were sublimed about 90°/1 mm. The nearly colorless sublimate adhered tenaciously to the cold finger, readily acquired an electric charge, and melted over a considerable range, 97.3–101.8°.

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.11. Found: C, 62.28; H, 8.06.

The sublimed base (1.0 g.) was dissolved in hot acetone (5.0 ml.); and, after cooling the solution somewhat, water (1.0 ml.) was added. The crystals which soon began to precipitate were collected after a day and washed with acetone: rosettes of colorless, minute, broken prisms, m.p. 98–100.5°.

(15) The melting points herein recorded are corrected and were observed in Pyrex capillaries.
(16) R. Kaushall, *J. Indian Chem. Soc.*, **17**, 138 (1940).

Anal. Calcd. for $C_{11}H_{17}NO_3 \cdot 1^1/_2H_2O$: C, 55.44; H, 8.46. Found: C, 55.33; H, 8.44.

In chloroform solution the anhydrous base did not absorb near 3.0 μ but did so at 5.76 μ, 5.87 μ, and 6.03 μ, band locations characteristic of unconjugated ester, unconjugated ketone, and conjugated ester groupings, respectively. The band intensities in the 5.5–6.5 μ region were measured about 10 min. after making up the chloroform solution and again about 2 hr. later. No change of intensities was noticed. In Nujol it did not absorb appreciably near 3.0 μ, or 5.75 μ, or 5.85 μ; but it did have a strong band at 6.04 μ. The sesquihydrate absorbed strongly in the 3-μ region and at 6.0 μ in Nujol; but, like the anhydrous modification, it had no bands near 5.75 μ and 5.85 μ.

In absolute alcohol the β-keto ester had an absorption maximum at 253 mμ (ϵ = 8930) and in aqueous acetic acid (50% by weight) at 248 mμ (ϵ = 9420). In the latter solvent a sample of anhydrous racemic 2-carbomethoxytropinone[1] absorbed at 248 mμ (ϵ = 9727).

The anhydrous base dissolved readily in alcohols, acetone, and chloroform, and also in water. It was less soluble in ether and in ligroin.

Racemic 2-carbomethoxy-N-methylgranatonine hydropicrate. Sublimed racemic 2-carbomethoxy-*N*-granatonine (0.42 g.), dissolved in warm methanol (6 ml.), was added to a hot solution of picric acid (0.46 g.) and methanol (5 ml.). Yellowish orange grains of the picrate melting at 204.5–205° precipitated at once. Recrystallized from methanol, it was obtained as stout prisms, m.p. 207° (bubbling), the salt discoloring several degrees below the fusion point. From acetone it separated as minute cubes which melted also at 207° but did not discolor below this temperature. The sample from acetone was dried 18 hr. at room temperature *in vacuo* over potassium hydroxide for analysis.

Anal. Calcd. for $C_{17}H_{20}N_4O_{10}$: C, 46.36; H, 4.58. Found: C, 46.60; H, 4.51.

Racemic 2-carbomethoxy-N-methylgranatonine methiodide. Sublimed racemic 2-carbomethoxy-*N*-methylgranatonine (2.0 g.), dissolved in acetone (25 ml.), was mixed with methyl iodide (2.0 ml.); and the resulting solution was left 1 hr. at room temperature. The crystals which began to precipitate almost immediately were then collected, washed with acetone, and dried overnight *in vacuo* over potassium hydroxide: 3.05 g. (91%) of yellowish white methiodide melting above 300°, which is low in iodine, presumably through loss of hydrogen iodide, as in the case of pseudoecgonine methiodide.[13]

Anal. Calcd. for $C_{12}H_{20}INO_3$: C, 40.80; H, 5.71; I, 35.93. Found: C, 41.06; H, 5.54; I, 35.35. Kept overnight the mother liquors deposited an additional small amount of methiodide.

In absolute alcohol the methiodide had absorption maxima at 221 mμ (ϵ = 15,600) and at 247 mμ (ϵ = 8600) and the indication of a weak maximum at 335 mμ. The proximity of the first two maxima makes the molar extinction coefficients, especially the second, probably not very accurate. In water it absorbed strongly at 228 mμ (ϵ = 15,930), and a shoulder on the longer wave length side of this maximum indicated another, hidden maximum about 250 mμ.

The methiodide (0.73 g.) was suspended in water (10 ml.) in which it did not completely dissolve, and saturated aqueous potassium carbonate (10 ml.) was added. The resulting clear solution was shaken 70 min. with ether (75 ml.). From the dried (sodium sulfate) ethereal phase a negligible residue was obtained. The aqueous phase was heated at 100° 1.5 hr. during which interval a moderate turbidity developed. Kept overnight at 0°, the mixture deposited no crystalline material. It was made mildly acidic with 6*N* aqueous sulfuric acid and extracted with ether (4 × 25 ml.). Evaporation of the dried (sodium sulfate) extracts again resulted in the recovery of a negligible residue. Throughout these operations the color of the aqueous phase changed very little or not at all.

Resolution of racemic 2-carbomethoxy-N-methylgranatonine. Sublimed racemic 2-carbomethoxy-*N*-methylgranatonine (4.84 g.) and L-tartaric acid (3.31 g.) were dissolved in water (12 ml.). Exposed to air the solution became more viscous, but no crystals formed. After a day the evaporated water was replaced, and the solution was left once more exposed to air. During the next day or so crystals slowly separated. These were recrystallized from water (2.0 ml.): 0.95 g., $[\alpha]_D^{20}$ +42.1° (c, 2, water).[17] Recrystallized again from water the L-bitartrate dihydrate as colorless needles was obtained: 0.2 g., $[\alpha]_D^{20}$ +43.4° (c, 2, water).[17]

Anal. Calcd. for $C_{15}H_{23}NO_9 \cdot 2H_2O$: C, 45.33; H, 6.85. Found: C, 45.07; H, 6.92.

Dried to constant weight at 57° *in vacuo alto* the salt underwent a weight loss of 9.53% (theoretical loss for two moles of water: 9.07%), and the residue appeared to be anhydrous.

Anal. Calcd. for $C_{15}H_{23}NO_9$: C, 49.30; H, 6.42. Found: C, 49.71; H, 6.60.

The bitartrate is extremely soluble in water and appears to crystallize much more slowly from solution after seeding than the 2-carbomethoxytropinone bitartrates.[1] From the mother liquors the base slightly enriched in one antipode was recovered by adding excess potassium bicarbonate and extracting with chloroform.

Spectral measurements. The infrared measurements were made with a Perkin-Elmer (Model 21) double beam spectrophotometer having sodium chloride optics. The ultraviolet absorption spectra were determined by a Cary Recording Spectrophotometer (Model 11).

Acknowledgment. The analytical data herein recorded were determined principally by Miss Paula M. Parisius of the Institute's Microanalytical Services Laboratory directed by Dr. William C. Alford. Mr. Harold K. Miller measured the infrared absorption spectra and Mrs. Charles I. Wright the ultraviolet absorption spectra.

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(17) This measurement was by Mrs. Evelyn G. Peake of This Institute.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WEST VIRGINIA UNIVERSITY]

Azabenzazulenes. III.[1] 1-Azanaphth[1,2-*b*]azulene

CHESTER W. MUTH AND EDWARD S. HANRAHAN[2]

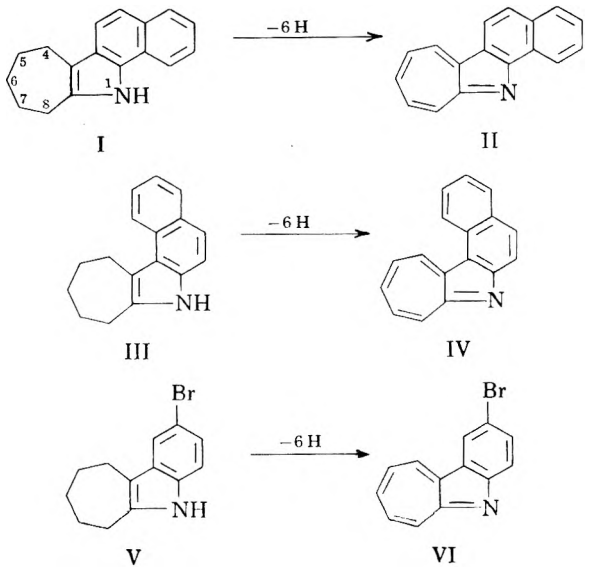
Received August 2, 1957

The foregoing azanaphthazulene as well as 1-azanaphth[2,1-*b*]azulene[3,4] has been prepared by the dehydrogenation of the appropriate indole.

It is desirable to study modifications of azulene since it is a chromophore the number of which is extremely limited. The list of reported azazulenes[4,5] is small.

1-Azanaphth[1,2-*b*]azulene (II) has been prepared from 1,4,5,6,7,8-hexahydro-1-azanaphth[1,-2-*b*]azulene (I) by both catalytic and chloranil dehydrogenations. Also, 1-azanaphth[2,1-*b*]azulene (IV) has been prepared from 1,4,5,6,7,8-hexahydro-1-azanaphth[2,1-*b*]azulene (III) by the catalytic method by us and by the chloranil method of Treibs *et al.*[3] We were not able to convert III to IV with chloranil in boiling xylene; Treibs[3,4] has not reported the solvent used in converting III to IV. We observed that boiling *n*-amyl alcohol was a better solvent than boiling xylene for converting I to II. For the preparation of II, the chloranil method is superior to the catalytic method.

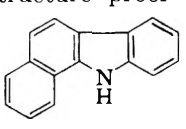
Attempts to dehydrogenate 1,4,5,6,7,8-hexahydro-1-aza-(4′-bromo)benz[*b*]azulene (V) by either the chloranil or catalytic methods yielded little if any VI. The compound corresponding to V without bromine has been dehydrogenated by both the catalytic[6] and chloranil[7a,b] methods.



The structure proofs for II and IV are based on elemental analyses, visible, ultraviolet, and infrared spectra, and hydrogenations to the indole precursors, I and III, respectively. Also, for II and IV the methiodides were prepared and found to have satisfactory elemental analysis. For IV the proper neutral equivalent was found and the perchlorate formed during the neutral equivalent determination gave the proper elemental analyses.

It is to be noted that the structures of II and IV are dependent on the structures of indoles I and III, respectively. Indoles I and III were made in one-step processes in glacial acetic acid from cycloheptanone and 1- and 2-naphthylhydrazine hydrochlorides, respectively. Indolization with 1-naphthylhydrazine might occur at the 2-position or a six-membered ring would form if attack were made at the 8-position. Since the ultraviolet spectrum of I is different from those of III and V which are similar there was some doubt as to which structure to assign to I. Also, indolization with 2-naphthylhydrazine might occur at the 1- or 3-positions.

The structures of I and III were confirmed by the very close similarity of their spectra (Table I) with those of 1,2-benzo-5,6,7,8-tetrahydrocarbazole[8] (VII) and 3,4-benzo-5,6,7,8-tetrahydrocarbazole[8] (VIII), respectively. Compound VIII was made from cyclohexanone and 1-naphthylhydrazine and compound VIII was made from cyclohexanone and 2-naphthylhydrazine. The structure proof for VII[8] has been based on its dehydrogenation to 1,2-benzocarbazole (IX) which was prepared by Kym.[9] Kym's structure proof for IX, although



IX

(1) Paper II, C. W. Muth, W. L. Sung, and Z. B. Papanastassiou, *J. Am. Chem. Soc.*, **77**, 3393 (1955).

(2) We wish to thank the Research Corporation for its support of this work. Abstracted in part from the M.S. thesis of Edward S. Hanrahan presented at West Virginia University, 1956. Presented in part before the West Virginia Academy of Science, Keyser, W. Va., April 1957.

(3) W. Treibs, W. Kirchof, W. Ziegenbein, and H. Piffko, *Angew. Chem.*, **65**, 542 (1953).

(4) W. Treibs, W. Kirchof, and W. Ziegenbein, *Fortschritte der Chemischen Forschung*, Springer, Berlin, 1955, p. 401.

(5) C. W. Muth, D. O. Steiniger, and Z. B. Papanastassiou, *J. Am. Chem. Soc.*, **77**, 1006 (1955).

(6) A. G. Anderson and J. Tazuma, *J. Am. Chem. Soc.*, **74**, 3455 (1952).

(7a) W. Treibs, R. Steinert, and W. Kirchof, *Ann.*, **581**, 54 (1953). (b) D. Lloyd, *Chem. & Ind. (London)*, 921 (1953).

(8) W. Borsche, *Ann.*, **359**, 49 (1908).

(9) O. Kym, *Ber.*, **23**, 2458 (1890).

his structure was found to be correct, was not convincing. For that reason, carbazole IX was prepared by an unambiguous route: the dehydrogenation of 1,2-benzo-3,4-dihydrocarbazole (X).[10] Carbazole IX so prepared is identical with the product obtained by the dehydrogenation of 1,2-benzo-5,6,-7,8-tetrahydrocarbazole (VII) as shown by mixed melting point, elemental analysis, infrared and ultraviolet spectra. *Therefore the previously assigned structure for VII has been confirmed, the structure of I is proved, and as a result the structure of II is also established.* The structure for hydrocarbazole VIII was firmly established by Huisgen,[11] consequently the structure for III and IV are correct.

The broad maximum in the visible absorption spectrum, which is typical of azabenzazulenes, is at longer wave lengths for II and IV than for 1-azabenz[*b*]azulene,[6] 1-azadibenz[*bf*]azulene[5] or 1-azadibenz[*bh*]azulene.[5,7a] Inspection of the spectra of II and IV (Table I) shows that II is absorbing less in the violet and more in the red region than is IV. This is in agreement with the purple color of II and the more reddish color of IV.

TABLE I

ULTRAVIOLET AND VISIBLE SPECTRA DATA[a]

Compound	Wave Length in mμ (Log ε)
I	Min. 240 (3.80), shoulder 260–265 (4.56), max. 270 (4.85), shoulder 285–295 (4.0), min. 330 (3.08), max. 335 (3.17), min. 347 (2.68), max. 350 (2.88).
VII	Min. 241 (4.01), shoulder 258–266 (4.48), max. 270 (4.78), shoulder 285–295 (3.9), min. 328 (3.21), max. 332 (3.27), min. 345 (2.91).
III	Max. 229 (4.47), min. 241 (4.36), max. 251 (4.40), min. 256 (4.34), max. 258 (4.36), min. 264 (4.20), max. 268 (4.26), min. 277 (3.26), max. 314 (4.01), min. 318 (3.99), max. 321 (4.04), min. 326 (4.00), max. 329 (4.02), min. 333 (3.91), max. 336 (4.04).
VIII	Max. 230 (4.48), min. 245 (4.38), max. 248 (4.40), min. 254 (4.36), max. 256 (4.38), min. 262 (4.25), max. 266 (4.34), min. 275 (3.46), max. 312 (4.02), min. 317 (3.96), max. 320 (4.01), min. 325 (3.93), max. 335 (3.99).
V	Max. 235 (4.24), min. 255 (3.24), max. 290 (3.80).
II	Min. 238 (4.01), max. 258 (4.26), min. 280 (4.15), max. 315 (4.67), min. 320 (4.65), max. 328 (4.68), min. 335 (4.45), max. 342 (4.55), min. 355 (3.98), max. 358 (3.99), min. 365 (3.87), max. 377 (3.96), min. 382 (3.89), max. 388 (3.99), min. 400 (3.00), max. 404 (ε 1890), min. 430 (ε 88), max. 560 (ε 748), min. 590 (ε 625), max. 610 (ε 638).
IV	Min. 243 (3.96), max. 275 (4.22), min. 278 (4.20), max. 301 (4.50), min. 310 (4.41), max. 324 (4.48), min. 330 (4.45), max. 342 (4.50), min. 368 (3.74), max. 380 (3.91), min. 390 (3.65), max. 395 (3.92), min. 404 (3.58), max. 415 (ε 10,825), min. 450 (ε 113), max. 540 (ε 414).

[a] All spectra were determined in cyclohexane with a Beckman quartz spectrophotometer, Model DU.

(10) E. Ghigi, *Gazz. chim. ital.*, **60**, 194 (1930); *Chem. Abstr.*, **24**, 3797 (1930).

(11) R. Huisgen, *Ann.*, **559**, 101 (1948).

EXPERIMENTAL[12]

1,4,5,6,7,8-Hexahydro-1-azanaphth[1,2-b]azulene (I). The method of Rogers and Corson[13] was used except the hydrazine hydrochloride was employed in place of the hydrazine. From 10.0 g. (0.051 mole) α-naphthylhydrazine hydrochloride (Eastman Kodak Co.) and 5.6 g. (0.050 mole) cycloheptanone (n_D^{25} 1.4595) in 37 g. of glacial acetic acid was obtained 8.65 g. of reddish-brown prisms, m.p. 143–146°. After recrystallization from 95% ethanol the yield was 6.02 g. of light red prisms, m.p. 145–148°. A portion of this material (4.55 g.) was twice chromatographed on alumina (45 × 150 mm. column). Chloroform was the solvent and developer; development was continued until a dark-brown zone neared the bottom of the column. The effluent on evaporation yielded 3.88 g. of light-brown prisms, m.p. 149–150°. Recrystallization of this material from 95% ethanol gave 3.07 g. (34%) of light-brown prisms, m.p. 152–153°. Absolute ethanol was used for crystallizing the analytical sample, m.p. 152–153°.

Anal. Calcd. for $C_{17}H_{17}N$: C, 86.8; H, 7.22; N, 6.01. Found: C, 86.7; H, 7.36; N, 5.96.

The ultraviolet spectrum for model compound, 1,2-benzo-5,6,7,8-tetrahydrocarbazole (VII)[14] was found to be almost superimposable on the spectrum of I except for a slight hypsochromic effect. The infrared spectrum was taken in chloroform and showed strong absorptions in μ at 2.9, 3.4, 7.2, 12.4, and 13.5. An absorption at 8.4 μ differentiated the spectrum of I from that of VII which had an absorption at 8.55 μ which I did not have.

1-Azanaphth[1,2-b]azulene (II). (*a*) *Palladium on charcoal dehydrogenation.* The apparatus, reagents, and technique for the dehydrogenation of 1,4,5,6,7,8-hexahydro-1-azanaphth-[1,2-*b*]azulene (I) to yield II were similar to those used by Anderson, *et al.*,[6,15] for the preparation of 1-azabenz[*b*]-azulene except that 1.5 g. of I was added to the dehydrogenation apparatus during 2 hr. The reaction temperature was 360–370°. The yield was 72 mg. (5%) of violet needles, m.p. 190–191°. A second run gave a 15% yield. The analytical sample was crystallized from benzene-petroleum ether mixture.

Anal. Calcd. for $C_{17}H_{11}N$: C, 89.0; H, 4.83; N, 6.11. Found: C, 89.0; H, 4.90; N, 6.17.

Hydrogenation of the foregoing product in absolute ethanol with 45 p.s.i. of hydrogen in the presence of platinum oxide immediately produced a colorless solution which yielded a substance which was proved to be I by mixed melting point and ultraviolet spectrum.

The methiodide derivative was prepared in benzene from 45 mg. of II and an excess of methyl iodide. The solution was warmed and shaken intermittently for 15 min. and then allowed to stand at room temperature for several days. The yield was 70 mg. (93%) of dark red flakes, m.p. 303–304° (corr.).

Anal. Calcd. for $C_{18}H_{14}NI$: C, 58.2; H, 3.80; N, 3.77. Found: C, 58.4; H, 3.99; N, 3.89.

(*b*) *Chloranil dehydrogenation.* Hexahydronaphthazulene (I) (1.18 g. 0.0051 mole) was dissolved in 25 ml. of boiling *n*-amyl alcohol. As 3.83 g. (0.0156 mole) of recrystallized chloranil was added in portions during 45 min. the solution became blue immediately and as more chloranil was added the solution became a dark reddish-brown color with suspended solid which caused bumping. An additional 15 ml. of amyl alcohol was added in an unsuccessful effort to pre-

(12) All temperatures are uncorrected unless otherwise indicated. All elemental analyses were done by Galbraith Laboratories, Knoxville, Tenn.

(13) C. U. Rogers and R. B. Corson, *J. Am. Chem. Soc.*, **69**, 2910 (1947).

(14) We wish to thank Mr. Raymond Clutter for preparing this compound and recording its ultraviolet spectrum.

(15) A. G. Anderson, J. A. Nelson, and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4980 (1953).

vent bumping. The total heating time was 1 hr. The reaction mixture was made homogeneous by adding methylene chloride and then the basic fraction was isolated as described;[7a] yield 190 mg. (18%) of violet needles, m.p. 189–191°, which did not require chromatography or recrystallization for purification. This product was the same as the one obtained by *method a* as shown by mixed melting point, ultraviolet, and visible spectra.

When a run lasting 2.5 hr. was made in boiling xylene, the yield of II after chromatography and recrystallization from benzene-petroleum ether mixture was about 3%.

1,4,5,6,7,8-Hexahydro-1-azanaphth[2,1-b]azulene (III). The procedure, reagents, and quantities were the same as for the preparation of I except that 2-naphthylhydrazine hydrochloride (Eastman Kodak Co.) was used in place of the 1-isomer. The yield of light-brown needles, m.p. 114–115°, once recrystallized from 95% ethanol was 9.70 g. (83%). The analytical sample was crystallized from absolute ethanol.

Anal. Calcd. for $C_{17}H_{17}N$: C, 86.8; H, 7.22; N, 6.01. Found: C, 86.8; H, 7.57; N, 5.71.

The ultraviolet spectrum of model indole 3,4-benzo-5,6,7,8-tetrahydrocarbazole[14] (VIII) was found to be very similar to that for III except for a slight hypsochromic shift. The infrared spectrum in chloroform was very similar to the infrared spectra for I and VIII. The spectrum for III showed slight maxima at 8.45 and 9.24 μ which were not present for VIII and the latter showed maxima at 7.92, 9.09, and 11.22 μ which were not in the spectrum for III.

1-Azanaphth[2,1-b]azulene (IV). Hexahydronaphthazulene (III) (1.70 g., 0.007 mole) was dehydrogenated by the same technique as was used for the preparation of II by *method a*. Methylene chloride was used to collect the reaction mixture as well as the solvent and developer in the chromatography. The yield of raspberry-red needles, m.p. 201–202°, (lit.[4] m.p. 201°) obtained by crystallization from benzene was 228 mg. (7%).

Anal. Calcd. for $C_{17}H_{11}N$: C, 89.0; H, 4.83; N, 6.11; neut. equiv., 229.3. Found: C, 89.6; H, 4.46; N, 5.83; neut. equiv., 228.9.

As the neutral equivalent was taken with perchloric acid in glacial acetic acid a reddish-orange flocculent solid, m.p. 282–283° (corr.) (73%) formed.

Anal. Calcd. for $C_{17}H_{12}O_4NCl$: C, 61.9; H, 3.67; N, 4.25. Found: C, 62.3; H, 3.81; N, 4.27.

The methiodide derivative for IV, m.p. 329–331° (corr.), (63%) was prepared as was the methiodide for II.

Anal. Calcd. for $C_{18}H_{14}NI$: C, 58.2; H, 3.80; N, 3.77. Found: C, 58.1; H, 3.80; N, 3.59.

Hydrogenation of IV, under conditions similar to those used for II, produced III as shown by mixed melting point and ultraviolet spectra.

1,2-Benzocarbazole (IX). The chloranil method of Barclay and Campbell[16] was used for the dehydrogenation of both 1,2-benzo-5,6,7,8-tetrahydrocarbazole (VII) and 1,2-benzo-3,4-dihydrocarbazole (X).[10,17] The desired product (IX) was readily obtained from the latter but with much difficulty from the former. From VII the product was purified by chromatography (alumina), sublimation, and finally by crystallization from benzene. The white purified products were identical as shown by mixed melting point, ultraviolet, and infrared spectra. The authentic material, m.p. 229–230° (corr.), (lit.[9] 225°) obrained from X had a slightly more narrow melting range than the other product.

Anal. Calcd. for $C_{16}H_{11}N$: C, 88.4; H, 5.10; N, 6.45. Found: C, 88.3; H, 5.19; N, 6.34.

MORGANTOWN, W. VA.

(16) B. M. Barclay and N. Campbell, *J. Chem. Soc.*, 530 (1945).

(17) We wish to thank Mr. Edward A. Pacofsky for the preparation of this compound and Mr. Paul Brown for its dehydrogenation as well as the infrared spectra for this paper.

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

Halopropargyl Alcohols and Ethers[1]

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The following compounds have been prepared and characterized: 2,3-dibromo-2-propen-1-ol, 3-bromo-3-chloro-2-propen-1-ol, 1,1-dibromo-3-ethoxy-1-propene, 1,1-dibromo-3-phenoxy-1-propene, 1-bromo-1-chloro-3-ethoxy-1-propene, 1-bromo-1-chloro-1-propene, 1,3-dibromo-1-chloro-1-propene, 3-bromo-2-propyn-1-ol, 3-chloro-2-propyn-1-ol, 1-bromo-3-ethoxy-1-propyne, 1-bromo-3-phenoxy-1-propyne, 1-chloro-3-ethoxy-1-propyne. The stereochemistry of the addition of bromine to *cis*- and *trans*-1-chloro-1-propene followed by dehydrohalogenation is discussed.

There are only fragmentary reports in the literature on the preparation of halopropargyl alcohols. Lespieau[2] prepared 3-bromo-2-propyn-1-ol by the hydrolysis of the corresponding acetate which in turn was formed by the reaction between 1,3-dibromopropyne and potassium acetate. The yields were very low and the alcohol was impure. 3-Bromo-2-propyn-1-ol has now been prepared by the dehydrobromination of 2,3-dibromo-2-propen-1-ol by potassium amide in liquid ammonia and by the dehydrobromination of 3,3-dibromo-2-propen-1-ol using potassium hydroxide in glycerol.

2,3-Dibromo-2-propen-1-ol was prepared by the addition of bromine to propargyl alcohol in carbon tetrachloride. Apparently only one geometrical isomer was formed and it is assumed to have the *trans* (Br,Br) configuration formed by *trans* addition of the bromine to the triple bond. Several attempts were made to dehydrobrominate this alcohol using alcoholic potassium hydroxide. The yield of 3-bromo-2-propyn-1-ol was very low because of the multiplicity of by-products. The follow-

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(2) R. Lespieau, *Ann. chim.*, (7)11, 232 (1897).

ing were isolated and identified: propargyl alcohol, acetylene, potassium formate (as formic acid), and bromine.

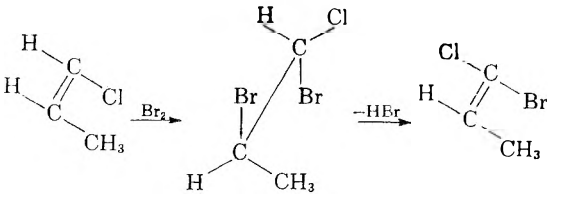
The organic products can be accounted for by the initial production of 3-bromo-2-propyn-1-ol followed by its reaction with potassium hydroxide to form propargyl alcohol. Propargyl alcohol has been reported to decompose to form acetylene and the salt of formic acid in the presence of a strong base.[3] Apparently the formic acid is not formed from formaldehyde by a Cannizzaro reaction, for methanol was not detected in this or previous work.

2,3-Dibromo-2-propen-1-ol was dehydrobrominated successfully by potassium amide in liquid ammonia. Because the yield was low (20%), the dehydrobromination of 3,3-dibromo-2-propen-1-ol was investigated. The 3,3-dibromo-2-propen-1-ol was obtained by the alkaline hydrolysis of 1,1,3-tribromo-1-propene which was made by the reaction between 1,1-dibromo-1-propene and N-bromosuccinimide.[4] The dehydrobromination was effected by the use of 20% potassium hydroxide in glycerol to give a 19% yield of 3-bromo-2-propyn-1-ol.

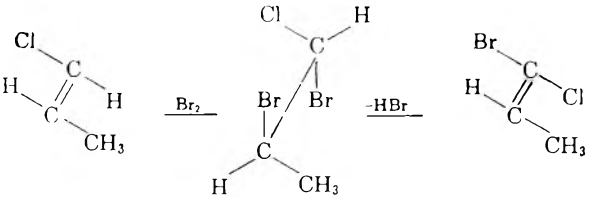
The ethyl ether of 3-bromo-2-propyn-1-ol was obtained as a by-product (16%) in the reaction between 1,1,3-tribromo-1-propene and sodium ethoxide in ethanol to form 1,1-dibromo-3-ethoxy-1-propene. 1-Bromo-3-phenoxy-1-propyne was obtained in a 17% yield by the dehydrobromination of 1,1-dibromo-3-phenoxy-1-propene. The dibromo-ether was prepared by treatment of 1,1,3-tribromo-1-propene with sodium phenoxide.

3-Chloro-2-propyn-1-ol was prepared from 1-chloro-1-propene by the addition of bromine to form 1,2-dibromo-1-chloropropane[5] which was dehydrobrominated by potassium acetate to 1-bromo-1-chloro-1-propene.[6] The 1-chloro-1-propene was a mixture of the two isomers and contained a high percentage of the *trans* isomer.

The possibility of producing both isomers of 1-bromo-1-chloro-1-propene from the separate isomers of 1-chloro-1-propene was investigated. *Trans* addition of bromine to *cis*-1-chloro-1-propene should give a stereoisomeric 1,2-dibromo-1-chloropropane which on *trans* elimination of the elements of hydrogen bromide should give the *trans* (H,Br) isomer.



The *trans* isomer of 1-chloro-1-propene should give the *cis*(H,Br) isomer of 1-bromo-1-chloro-1-propene.



The *trans*-1-chloro-1-propene used contained 10% *cis*-1-chloro-1-propene while the *cis* isomer was 99+% pure. Addition to the *cis* isomer was appreciably slower than to the *trans* isomer.

The greater eclipsing effect of bromine compared to chlorine is evident in the dehydrobromination reaction. The addition product from *cis*-1-chloro-1-propene dehydrobrominated less readily to produce *trans*-1-bromo-1-chloro-1-propene(H,Br) than the product from the *trans* isomer to give *cis*-1-bromo-1-chloro-1-propene(H,Br). The extent of the difference in reactivity of the two isomers was determined only in a qualitative manner.

The dehydrohalogenation of the 1-bromo-1-chloro-1-propene from *cis*-1-chloro-1-propene gave only 1-chloro-1-propyne as would be expected with the hydrogen atom and bromine atom in a *trans* position.[7] The unreacted 1-bromo-1-chloro-1-propene, however, had an infrared spectrum identical with that of the product from *trans*-1-chloro-1-propene. The 1-bromo-1-chloro-1-propene from 90% *trans*-1-chloro-1-propene also gave 1-chloro-1-propyne as the only product. *cis*-1-Bromo-1-chloro-1-propene(H,Br) would not be expected to dehydrobrominate by *cis* elimination of the elements of (H,Br) and the reason why *trans*-1-bromo-1-chloro-1-propene(H,Br) is more resistant to dehydrobromination than the *cis*(H,Br) isomer is not known. Apparently either the assignment of configuration is incorrect or the elimination reaction is not the conventional E_2. These possibilities are being investigated.

The *cis*(H,Br) isomer of 1-bromo-1-chloro-1-propene was brominated to 1,3-dibromo-1-chloro-1-propene using *N*-bromosuccinimide. The 1,3-dibromo-1-chloro-1-propene appeared to be produced as a single isomer which isomerized at room temperature in the presence of light. Similar compounds (1,3-dibromopropene) have been observed to isomerize under these conditions.[8] Hydrolysis of the 1,3-dibromo-1-chloro-1-propene appeared to give a single isomer of 3-bromo-3-chloro-2-propen-1-ol which did not isomerize. This alcohol was dehydrobrominated to 3-chloro-2-propyn-1-ol in a 19% yield.

The reaction of 1,3-dibromo-1-chloro-1-propene with sodium ethoxide in ethanol formed a single

(3) L. Henry, *Ber.*, **8**, 398 (1875); A. F. Thompson and C. Margnetti, *J. Am. Chem. Soc.*, **64**, 573 (1942); L. F. Hatch and A. C. Moore, *J. Am. Chem. Soc.*, **66**, 285 (1944).

(4) L. F. Hatch and S. D. Zimmerman, *J. Am. Chem. Soc.*, **79**, 3091 (1957).

(5) M. Reboul, *Ann. chim.*, (5) **14**, 462 (1878).

(6) B. K. Mereshkowsky, *Ann.*, **431**, 231 (1923).

(7) S. J. Cristol, *J. Am. Chem. Soc.*, **69**, 338 (1947).

(8) L. F. Hatch and K. E. Harwell, *J. Am. Chem. Soc.*, **75**, 6002 (1953).

TABLE I

PHYSICAL PROPERTIES OF HALOPROPARGYL ALCOHOLS AND ETHERS AND RELATED COMPOUNDS

Compound	B.P., °C. (Mm.)	Index of Refraction			Density			Analysis			
								Bromine		Chlorine	
		20/D	25/D	30/D	20/4	25/4	30/4	Calcd.	Found	Calcd.	Found
$CHBr{=}CBrCH_2OH$	56–58 (1)[a,b]	1.5799	1.5778	1.5754	2.2226	2.2108	2.2035	74.0	74.3 74.3		
$BrC{\equiv}CCH_2OH$	41–42 (1.5)	1.5162	1.5146	1.5119	1.7601	1.7584	1.7544	59.2	58.7 58.7		
$CBr_2{=}CHCH_2OC_2H_5$	58–59 (5)	1.5100	1.5070	1.5050	1.7406	1.7329	1.7264	65.5	65.1 65.6		
$BrC{\equiv}CCH_2OC_2H_5$	50–53 (18)	1.4702	1.4665	1.4670	1.3877	1.3806	1.3683	48.8	48.2		
$CHBrClCHBrCH_3$	59.0 (10)[c]	1.5415	1.5390	1.5360	2.0493	2.0371	2.0254	67.6	67.3	15.0	15.0
$CBrCl{=}CHCH_3$[d]	52–53 (113)	1.4870	1.4841	1.4810	1.6120	1.6024	1.5933	51.4	51.3	22.8	22.8
$CBrCl{=}CHCH_3$[e]	33–34 (55)	1.4864	1.4836	1.4810	1.6030	1.5964	1.5870				
$CBrCl{=}CHCH_2Br$[f]	62.5 (10)	1.5702[f]	1.5680	1.5649[f]	2.1182[f]	2.1099[f]	2.1017[f]	68.4	68.1	15.1	15.0
$CBrCl{=}CHCH_2OH$	45.5–46.0 (1)	1.5281	1.5263	1.5242	1.7908	1.7869	1.7785	46.6	46.5 46.7	20.7	20.6 20.7
$ClC{\equiv}CCH_2OH$	50.5–51.0 (13)	1.4708	1.4690	1.4669	1.2389	1.2342	1.2307			39.2	39.2 39.3
$CBrCl{=}CHCH_2OC_2H_5$	57.5–58.0 (10)	1.4820	1.4799	1.4779	1.4496	1.4422	1.4367	40.6	40.5 40.6	17.8	17.7 17.7
$ClC{\equiv}CCH_2OC_2H_5$	49.5–50.0 (56)	1.4365	1.4340	1.4315	1.0386	1.0368	1.0349			29.9	29.7 29.8
$CBr_2{=}CHCH_2OC_6H_5$	105–107 (1)	1.5936	1.5912	1.5890	1.7400	1.7344	1.7298	54.8	54.2 54.9		
$BrC{\equiv}CCH_2OC_6H_5$	89–93 (2)		1.564			1.415					

[a] R. Lespieau [*Ann. chim.*, [7]**11**, 262 (1897)] gives a b.p. of 205–208° (760 mm.). [b] M.p. 29.5–30.0°. [c] M. Reboul [*Ann. chim.*, [5]**14**, 453 (1878)] gives b.p. 177–177.5°. [d] Prepared from *cis*-1-chloro-1-propene. [e] Prepared from *trans*-1-chloro-1-propene. [f] Thought to be one isomer (*trans*-H, Br). Mangold (D. J. Mangold, Ph.D. Dissertation, The University of Texas, 1954) gives b.p. 39.0–42.0 (5 mm.); n_D^{25} 1.5675.

isomer of 1-bromo-1-chloro-3-ethoxy-1-propene and a small amount of 1-chloro-3-ethoxy-1-propyne. The 1-bromo-1-chloro-3-ethoxy-1-propene was dehydrobrominated to give a 23% yield of 1-chloro-3-ethoxy-1-propyne and no 1-bromo-3-ethoxy-1-propyne. This is in agreement with the results of the dehydrohalogenation of the 1-bromo-1-chloro-1-propenes.

All of the allylic bromides are lachrymators and the allylic alcohols are vesicants. Either the bromochloro olefinic ether or the chloro acetylenic ether caused severe dermatitis.

The infrared spectra[9] of the various compounds are in agreement with the assigned structures. It was not possible to assign definite geometrical configuration from the spectra because the compounds did not possess a hydrogen atom on each of the carbon atoms associated with the double bond.

EXPERIMENTAL

The physical properties and analysis of the compounds prepared during this investigation are given in Table I unless otherwise noted.

3-Bromo-2-propyn-1-ol. This alcohol was prepared from 2,3-dibromo-2-propen-1-ol and 3,3-dibromo-2-propen-1-ol.

From 2,3-dibromo-2-propen-1-ol. 2,3-Dibromo-2-propen-1-ol was prepared in an 87% yield by the addition of bromine to propargyl alcohol in carbon tetrachloride at −15°. Apparently only one isomer was formed and it is assumed to have the *trans* configuration.

Several attempts were made to dehydrobrominate 2,3-dibromo-2-propen-1-ol using alcoholic potassium hydroxide. The following alcohols were used: methyl, ethyl, *n*-propyl, and *n*-butyl. The maximum yield (9%) of 3-bromo-2-propyn-1-ol was obtained using *n*-propyl alcohol. Appreciable quantities of propargyl alcohol, acetylene, and potassium formate were identified as by-products. Bromine was observed during the course of the dehydrobromination reaction but was not identified further. Potassium phenoxide in ethanol gave the same results as alcoholic potassium hydroxide.

2,3-Dibromo-2-propen-1-ol was dehydrobrominated to 3-bromo-2-propyn-1-ol in a 20% yield using potassium amide in liquid ammonia. The operating conditions, mainly salt formation, were partly responsible for the low yield. A 25% yield of propargyl alcohol was obtained.

From 3,3-dibromo-2-propen-1-ol. 1,1,3-Tribromo-1-propene was obtained in a 78% yield by treatment of 1,1-dibromo-1-propene with *N*-bromosuccinimide.[4] It was hydrolyzed to 3,3-dibromo-2-propen-1-ol (72% yield) using a 10% solution of sodium carbonate at 80° for 10 hr.[4] The 3,3-dibromo-2-propen-1-ol was dehydrobrominated to 3-bromo-2-propyn-1-ol using a 20% solution of potassium hydroxide in glycerol. The reaction was carried out at 2 mm. pressure on a steam bath. The bromoacetylenic alcohol distilled as formed and was collected in a cold trap. Distillation under nitrogen gave a fraction boiling at 41–42° (1.5 mm.); lit.[2] b.p. 80–83° (12 mm.). *3,5-Dinitrobenzoate of 2,3-dibromo-2-propen-1-ol:* m.p. 117.5–118°.

Anal. Calcd. for $C_{10}H_6O_6N_2Br_2$: N, 6.33. Found: N, 6.84, 6.82.

3,5-Dinitrobenzoate of 3-bromo-2-propyn-1-ol: m.p. 115–116°.

Anal. Calcd. for $C_{10}H_5O_6N_2Br$: N, 8.51. Found: N, 8.52, 8.51.

(9) Obtained through the courtesy of the Monsanto Chemical Co. and William F. Hamner, Texas City, Tex.

1-Bromo-3-ethoxy-1-propyne. This ether was prepared in a 16% yield when equimolar quantities (1 mole) of 1,1,3-tribromo-1-propene and sodium ethoxide in ethanol were refluxed for 5 hr. There was a 47% yield of 1,1-dibromo-3-ethoxy-1-propene.

1-Bromo-3-phenoxy-1-propyne. This ether was prepared by the dehydrobromination of 1,1-dibromo-3-phenoxy-1-propene. The 1,1-dibromo-3-phenoxy-1-propene was synthesized in a 55% yield from 1,1,3-tribromo-1-propene and sodium phenoxide in ethanol in a manner similar to that used for the preparation of 1,1-dibromo-3-ethoxy-1-propene. The 1,1-dibromo-3-phenoxy-1-propene was dehydrobrominated to 1-bromo-3-phenoxy-1-propyne (17% yield) using potassium hydroxide in glycerol and a procedure similar to the one used for the preparation of 3-bromo-2-propyn-1-ol.

3-Chloro-2-propyn-1-ol. 3-Chloro-2-propyn-1-ol was prepared by a series of reactions which started with the low temperature (−40°) addition of bromine to a commercial mixture of 1-chloro-1-propenes (Columbia Organic Chemicals, Columbia, S. C.). The reaction time was 16 hr. and the yield of *1,2-dibromo-1-chloropropane* was 83%. This material had the following physical properties: b.p. 57.5° (10 mm.); n_D^{20} 1.5385, n_D^{25} 1.5361, n_D^{30} 1.5338; d_4^{20} 2.0397, d_4^{25} 2.0325, d_4^{30} 2.0251. Lit.[5] b.p. 177.0–177.5°.

Anal. Calcd. for $C_3H_5Br_2Cl$: Br, 67.6; Cl, 15.0. Found: Br, 67.3; Cl, 15.0.

The 1,2-dibromo-1-chloropropane was dehydrobrominated to *1-bromo-1-chloro-1-propene* using potassium acetate and the procedure of Mereshkowsky.[6] A 69% yield was obtained and the product had the following physical properties: b.p. 58.5° (198 mm.); n_D^{20} 1.4868, n_D^{25} 1.4838, n_D^{30} 1.4809; d_4^{20} 1.6009, d_4^{25} 1.5920, d_4^{30} 1.5847.

Anal. Calcd. for C_3H_4BrCl: Br, 51.4; Cl, 22.8. Found: Br, 51.3; Cl, 22.8.

The 1-bromo-1-chloro-1-propene was brominated to *1,3-dibromo-1-chloro-1-propene* in a 55% yield using *N*-bromosuccinimide and the usual procedure. The product appeared to have been produced as a single isomer but to have isomerized to a small extent on standing in the light at room temperature. The physical properties given in Table I are for freshly distilled material.

The 1,3-dibromo-1-chloro-1-propene was hydrolyzed to *3-bromo-3-chloro-2-propen-1-ol* using a 10% solution of sodium carbonate at 75° for 18 hr. The reaction products were worked up in the usual manner and a 70% yield of 3-bromo-3-chloro-2-propen-1-ol was obtained. This alcohol was dehydrobrominated to 3-chloro-2-propyn-1-ol using a 25% solution of potassium hydroxide in decyl alcohol at 75° for 2 hr. under 5 mm. Hg pressure. The pressure was reduced to 0.5 mm. Hg and the remaining product and unreacted dihalo alcohol were flashed to a cold trap. Conventional treatment of this material gave a 19% yield of 3-chloro-2-propyn-1-ol. *3,5-Dinitrobenzoate of 3-bromo-3-chloro-2-propen-1-ol:* m.p. 78.0–78.5°.

Anal. Calcd. for $C_{10}H_6O_6N_2BrCl$: N, 7.67. Found: N, 7.60, 7.75.

3,5-Dinitrobenzoate of 3-chloro-2-propyn-1-ol: m.p. 86.0–86.5°.

Anal. Calcd. for $C_{10}H_5O_6N_2Cl$: N, 9.84. Found: N, 9.70, 9.72.

1-Chloro-3-ethoxy-1-propyne. This ether was prepared by the dehydrobromination of 1-bromo-1-chloro-3-ethoxy-1-propene. 1-Bromo-1-chloro-3-ethoxy-1-propene was prepared by a Williamson synthesis from 1,3-dibromo-1-chloro-1-propene and sodium ethoxide in ethanol. The temperature was held at 35° for 2 hr. and at 50° for 1.75 hr. The yield of 1-bromo-1-chloro-3-ethoxy-1-propene was 35%. About a 2% yield of 1-chloro-3-ethoxy-1-propyne was obtained.

1-Bromo-1-chloro-3-ethoxy-1-propene was dehydrobrominated using a 10% solution of potassium hydroxide in decyl alcohol at 60° for 2 hr. under 10 mm. Hg pressure. At the end of the reaction period the remaining material was

flashed to the cold trap at 1 mm. pressure. The products were worked up in the usual manner to give a 23% yield of 1-chloro-3-ethoxy-1-propyne.

cis-1-Bromo-1-chloro-1-propene (H,Br). Bromine was added to a mixture of 90% *trans*-1-chloro-1-propene and 10% *cis*-1-chloropropene (0.77 mole) in carbon tetrachloride (400 ml.) at −10° over a period of 1 hr. followed by 3 hr. at the same temperature. The reaction mixture was worked up in the usual manner and distilled to give a 75% yield of 1,2-dibromo-1-chloropropane boiling at 56° (9 mm.). The physical properties of this compound were the same as those obtained for the 1,2-dibromo-1-chloropropane from *cis*-1-chloro-1-propene and its infrared spectrum was essentially the same.

This 1,2-dibromo-1-chloropropane (0.17 mole) and potassium acetate (0.51 mole) in acetic acid (100 ml.) were heated for 16 hr. at reflux temperature. Work up of the reaction mixture gave a 30% yield of 1-bromo-1-chloro-1-propene. A 56% yield was obtained by using potassium hydroxide (12%) in glycerol at 80° and a pressure of 113 mm. Under these conditions the product flashed to a cold trap as soon as formed. Physical properties of this material are given in Table I.

The *cis*-1-bromo-1-chloro-1-propene (H,Br) was dehydrobrominated by dropping it into a 12% solution of potassium hydroxide in glycerol under nitrogen at a temperature of 76°. There was a 26% conversion and a 25% yield of 1-chloro-1-propyne boiling at 31–31.5° (755 mm.). The identity of the 1-chloro-1-propyne was checked by comparing its infrared spectrum with that of an authentic sample.

trans-1-Bromo-1-chloro-1-propene (H,Br). *cis*-1-Chloro-1-propene with a boiling point of 30.5° at 733 mm. pressure (n_D^{20} 1.4061) was obtained from Columbia Organic Chemicals Co. The material had been purified by distillation through a 100-plate column at a reflux ratio of 100:1. The distillation was made by Arthur Rose, Applied Science Laboratories, Inc., State College, Pa. Gas chromatography indicated a purity of 99+%.

Bromine was added to the *cis*-1-chloro-1-propene in a manner similar to that used for the *trans*-1-chloro-1-propene. Sixty-three hours were required to effect the addition. A 70% yield of 1,2-dibromo-1-chloropropane was obtained. The physical properties were essentially the same as those of the 1,2-dibromo-1-chloropropane from *trans*-1-chloro-1-propane (Table I).

It was not possible to dehydrobrominate this compound with potassium acetate in acetic acid in a manner similar to that used for the bromine addition product of *trans*-1-chloro-1-propene. *trans*-1-Bromo-1-chloro-1-propene(H,Br) was obtained by using potassium hydroxide in glycerol and the same procedure as that used for the production of *cis*-1-bromo-1-chloro-1-propene(H,Br) from the 1,2-dibromo-1-chloropropane from *trans*-1-chloro-1-propene. A 60% yield was obtained.

This 1-bromo-1-chloro-1-propene was not dehydrohalogenated by potassium hydroxide in glycerol under the same conditions used to dehydrobrominate the 1-bromo-1-chloro-1-propene from *trans*-1-chloro-1-propene. It was dehydrobrominated by powdered potassium hydroxide at 130° to give a 33% yield of 1-chloro-1-propyne. No 1-bromo-1-propyne was detected. The unreacted 1-bromo-1-chloro-1-propene was shown by its infrared spectrum to be the same as that of the isomer from *trans*-1-chloro-1-propene.

Infrared spectra. The infrared spectra were obtained using a Baird Associates Double-Beam Recording Infrared Spectrophotometer equipped with sodium chloride optics. The following are the principal bands in microns.

cis-1-Chloro-1-propene: 3.41; 6.10; 6.92; 7.23; 7.60; 10.68; 13.2–13.3; 14.4–14.7.

trans-1-Chloro-1-propene: 3.41–3.45; 6.12; 6.94; 8.09; 10.55; 10.8–10.9; 12.6.

1,2-Dibromo-1-chloropropane (from cis-1-chloro-1-propene): 3.33; 6.91; 7.25; 7.30; 7.99; 8.30; 8.53; 9.51; 9.96; 11.21; 13.08; 13.4–13.9; 14.7.

1-Bromo-1-chloro-1-propene (from cis-1-chloro-1-propene): 3.41; 5.61; 6.17; 6.91; 7.25; 7.87; 9.04; 10.02; 10.2–10.3; 10.73; 11.7–12.1; 12.3–12.4; 14.20.

1-Bromo-1-chloro-1-propene (from trans-1-chloro-1-propene): 3.46; 6.22; 6.97; 7.30; 7.91; 9.10; 10.3–10.4; 11.9–12.1; 12.4.

2,3-Dibromo-2-propen-1-ol: 2.92–3.10; 3.21; 3.41; 3.50; 6.20; 6.90; 8.00; 8.15; 9.4–9.8; 10.42; 12.56; 14.0–14.2.

3-Bromo-3-chloro-2-propen-1-ol: 3.0–3.1; 3.40; 3.48; 6.21; 6.9–7.1; 7.4; 8.2; 9.5–9.9; 11.9–12.2.

1-Bromo-1-chloro-3-ethoxy-1-propene: 3.40; 3.50; 6.21; 6.92; 7.18; 7.42; 7.90; 8.9–9.1; 12.0–12.1.

1,1-Dibromo-3-ethoxy-1-propene: 3.34; 3.47; 6.21; 6.92; 7.31; 7.43; 7.87; 8.29; 9.0–9.1; 9.8; 11.25; 11.9; 12.5–12.8.

1,1-Dibromo-3-phenoxy-1-propene: 3.28; 3.41; 3.48; 6.12; 6.25; 6.68; 6.85; 7.29; 7.70; 8.0–8.3; 8.52; 9.27; 9.63; 9.8; 10.05; 11.32; 11.9; 12.5–12.7; 13.2–13.3; 14.54.

3-Chloro-2-propyn-1-ol: 3.0–3.1; 3.42; 3.48; 4.48; 6.9–7.1; 7.40; 8.18; 9.9–10.1.

3-Bromo-2-propyn-1-ol: 2.9–3.1; 3.43; 3.51; 4.52; 6.9–7.1; 7.41; 8.18; 9.4–9.6; 10.1–10.3; 12.6–12.7.

1-Chloro-3-ethoxy-1-propyne: 3.38; 3.48; 4.45; 6.92; 7.18; 7.42; 7.95; 8.9–9.1; 11.9; 15.1.

1-Bromo-3-ethoxy-1-propyne: 3.35; 3.47; 4.50; 6.72; 6.93; 7.31; 7.42; 7.94; 8.9–9.2; 9.76; 10.01; 11.88.

1-Bromo-3-phenoxy-1-propyne: 2.99; 3.24; 3.39; 3.44; 4.46; 6.22; 6.67; 6.86; 7.25; 7.70; 7.92; 8.1–8.3; 8.49; 9.23; 9.5; 9.7; 10.08; 11.28; 11.99; 12.82; 13.1–13.3; 14.54.

AUSTIN, TEX.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES OF THE ETHYL CORPORATION]

Catalytic Graphite Inclusion Compounds. II. Potassium Graphite as an Alkylation Catalyst

H. PODALL AND W. E. FOSTER

Received July 8, 1957

Potassium graphite has been found to catalyze both the nuclear and side-chain alkylation of aromatic hydrocarbons with ethylene.

While attempting to catalyze the polymerization of ethylene with potassium graphite, KC_8,[1] in benzene and in toluene, it was found that alkylation of these hydrocarbons occurred instead. A study was therefore undertaken of the potassium graphite-catalyzed alkylation of aromatic hydrocarbons with olefins. The results are shown in Table I.

(1) H. E. Podall, W. E. Foster, and A. P. Giraitis, *J. Org. Chem.*, **23**, 82 (1958).

TABLE I

CATALYTIC ALKYLATION OF AROMATICS USING POTASSIUM GRAPHITE (KC_8) CATALYST

Solvent or Substrate	KC_8 (g.)	Temp. Time	Pressure, C_2H_4 (psig)	Products
Benzene 0.28 mole	1.4	102–112° 2–3 hr.	700	1.7 g. *sec*-butylbenzene, 2.6 g. higher monosubstituted benzenes + *m*-disubstituted benzene, 0.6 g. residue
Benzene 0.34 mole	3	200° 20 hr.	900	9.6 g. liquid, b.p. > 150°, containing 23% *sec*-butylbenzene and 19% diphenyl
Benzene 0.23 mole	2	250° 26 hr.	150	None
Toluene 0.24 mole	9	120–130° 7–9 hr.	800	16.4 g. 3-phenylpentane (50% conversion) + 5–10 g. higher boiling material
Toluene 0.24 mole	2	150–155° 30 hr.	970	28% toluene recovered, 34% conversion to *n*-propylbenzene (48% yield), 12% conversion to 3-phenylpentane (17% yield) and 0.7 g. high-boiling material
Isopropylbenzene 0.18 mole	2	200° 24 hr.	700	21.9 g. liquid, b.p. 172–267° (corr.), contain- tert-amylbenzene (42% conversion) and 11% unreacted isopropylbenzene, 3.9 g. residue

It was found that ethylene was readily absorbed in benzene in the presence of catalytic amounts of potassium graphite at 100–110°. This temperature was considerably lower than that required for the polymerization of ethylene in the presence of potassium graphite in aliphatic hydrocarbons. Workup of the reaction mixture yielded about 3 grams of alkylated benzene per gram of potassium. *Sec*-butylbenzene was the predominant product (35% by weight) with higher monoalkylbenzenes and some *m*-dialkylbenzene as the remainder. No significant quantity of ethylbenzene could be detected. This contrasts with the results obtained with organosodium catalysts by Pines and Mark.[2] Apparently with KC_8 as catalyst, the ethylbenzene immediately reacts further with ethylene.

In an effort to obtain a higher conversion of benzene to *sec*-butylbenzene, a run was made at 200° and an ethylene pressure of 900 psig. It was found that although the yield of products boiling above benzene increased to 11 grams per gram of potassium, the product now contained only 23% *sec*-butylbenzene. The remainder consisted of 19% of a rather surprisingly pure white solid [b.p. 257–260° 760 mm. (corr.), m.p. 66.5–68.5°] and higher monoalkylbenzenes. The white solid was identified as diphenyl from its mixed melting point and infrared spectrum.[3]

In an effort to decrease the chain growth leading to higher monoalkylbenzenes, another run was made at 250° and an ethylene pressure of only 150 p.s.i.g.[4] No significant reaction occurred. Apparently under these conditions the initiation and/or propagation reactions were too slow to compete with the termination reactions.

An attempt was made to alkylate benzene with isobutylene using the KC_8 catalyst at 200°, 330 p.s.i.g. A high yield of *tert*-butylbenzene was expected, since it does not contain α-hydrogens to lead to transmetallation and further alkylation. It was found, surprisingly, that no reaction occurred; only benzene and isobutylene were recovered from the reaction mixture.[5]

Reaction of ethylene with KC_8 in toluene gave alkylation of the side chain. A 50% conversion of toluene to 3-phenylpentane was obtained together with some higher alkylbenzenes. It has been reported by Pines and coworkers[6] that the alkylation of toluene with ethylene is effectively catalyzed by the use of a mixture of sodium and a "promoter" such as anthracene or *o*-chlorotoluene. They suggest that the reaction occurs *via* an organosodium compound, which is formed *in situ*.

The use of KC_8 as a catalyst for the side-chain alkylation of toluene was apparently novel and rather interesting because of its high catalytic activity. A "promotor" was not required.[7] In an effort to increase the conversion of toluene to 3-phenylpentane, another reaction was carried out at a somewhat higher temperature, 150° instead of 120°,

(2) H. Pines and V. Mark, Abstracts of Papers, 127th Meeting AMERICAN CHEMICAL SOCIETY, Cincinnati, Ohio, March 29 to April 7, 1955, p. 21N.

(3) Diphenyl might arise from the coupling of phenyl radicals formed by a radical-transfer reaction.

(4) Data obtained for the KC_8 catalyzed polymerization of ethylene (see ref. 1) indicate that an increase in temperature and a decrease in the ethylene pressure both tend to decrease the chain length of the resulting polymer.

(5) The absence of any reaction here might be interpreted as being due either to the unreactivity of isobutylene towards phenylpotassium (which may be formed from the interaction of benzene with KC_8), or to the unreactivity of isobutylene towards KC_8. In the latter case, it would be assumed that the first step in the alkylation of benzene involves formation of an *alkyl*-potassium compound, from the olefin and KC_8, and that the latter transmetallates benzene.

(6) H. Pines, J. A. Vesely, and V. N. Ipatieff, *J. Am. Chem. Soc.*, **77**, 554 (1955).

(7) It has been found in our laboratories that sodium or potassium alone is considerably less effective than potassium graphite as an aromatic alkylation catalyst.

and with a smaller concentration of suspended KC_8 catalyst. Surprisingly, the main product now was *n*-propylbenzene instead of 3-phenylpentane; the product mixture contained a 48% yield of *n*-propylbenzene, a 17% yield of 3-phenylpentane, and a small quantity of higher alkylated products. The product distribution in the side-chain alkylation of toluene is thus apparently quite sensitive to changes in the reaction conditions.

In order to establish the generality of the KC_8 catalyzed side-chain alkylation reaction, an attempt was made to ethylate isopropylbenzene with ethylene. A 42% conversion to *tert*-amylbenzene was obtained.

It thus appears that the potassium graphite inclusion compound, KC_8, is a powerful and effective catalyst for the side-chain alkylation of aromatic hydrocarbons with ethylene and possibly with other olefins. It appears to be particularly useful for side-chain ethylations of aromatic hydrocarbons, containing at least one α-hydrogen, leading to highly branched alkylbenzenes.

EXPERIMENTAL

Materials. The materials used were all C.P. reagents and/or were rectified followed by drying with sodium ribbon.

General procedure[8]*—ethylation of isopropylbenzene.* Two grams of KC_8 and 25 ml. of isopropylbenzene (dried over sodium ribbon) were charged into a 100 ml. Magne-Dash autoclave. The system was purged and then pressurized with ethylene to 300 p.s.i.g. It was then heated to 200° and and repressurized to 700 p.s.i.g. with ethylene. The reaction was carried out for 24 hr. at 200°. The system was then cooled to room temperature, quenched with 50 ml. of water, and filtered. The organic layer was red-brown in color. On rectification it gave 2.3 g. of isopropylbenzene (11% recovery), 21.9 g. of fractions b.p. 172–267°/760 mm. (corr), and 3.9 g. of residue, b.p. >267°/760 mm. (corr). The fractions of b.p. 172–267° contained principally a pure fraction of *tert*-amylbenzene, b.p. 192°/760 mm; the total *t*-amylbenzene, estimated from an analysis of the rectification data, amounted to 11.1 g, or a 42% conversion. The graphite filter cake, 3.3 g., was extracted with 100 ml. of *m*-xylene for 6 hr. in a Soxhlet extractor. The extract was then cooled to room temperature, and about 25–50 ml. of 2B ethanol was added to precipitate a very small quantity of a gelatinous white solid. This material was not investigated.

The alkylations of benzene and toluene were carried out by similar procedures, except for the temperature and time employed (see Table I).

Acknowledgment. The authors wish to thank Dr. R. L. Hudson and Mr. J. B. Sigrest for the infrared and rectification work, respectively.

BATON ROUGE 1, LA.

(8) See ref. 1 for procedure used to prepare KC_8.

[CONTRIBUTION FROM AVERY LABORATORY, THE UNIVERSITY OF NEBRASKA]

An *O*-Aroylglycollate and Carboxylic Anhydrides from the Attempted *C*-Aroylation of Methyl Diazoacetate[1]

J. H. LOOKER AND DONALD N. THATCHER[2]

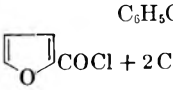
Received August 2, 1957

3,5-Dinitrobenzoyl chloride reacts with methyl diazoacetate containing water to give methyl *O*-(3,5-dinitrobenzoyl)glycollate. Under similar conditions, α- and β-naphthoyl chloride, and *o*-iodobenzoyl chloride give carboxylic anhydrides. Possible mechanisms are discussed.

In a previous communication from this laboratory,[3] it was shown that reduction of methyl benzoyldiazoacetate affords DL-*erythro*-β-phenylserine (allophenylserine) in good yield. Extension of this reaction would require synthesis of additional aroyldiazo esters. The present paper describes the attempted synthesis of the latter class by the action of four aromatic carboxylic acid chlorides on methyl diazoacetate, prepared in the usual manner and used without distillation.

Previous work indicates that benzoyl bromide reacts smoothly with methyl diazoacetate (I) to give the crystalline methyl benzoyldiazoacetate,[4] whereas benzoyl chloride gives with I an oily product which was not identified.[4] In other instances, acid chlorides react with I to give the acyl- or aroyldiazo ester. Thus several aliphatic acid chlorides give liquid diazo esters,[4] and α-furoyl chloride[5] gives the crystalline methyl α-

$$C_6H_5COBr + 2\,CHN_2COOCH_3 \longrightarrow C_6H_5COCN_2COOCH_3 + CH_2BrCOOCH_3 + N_2$$



$$+ 2\,CHN_2COOCH_3 \longrightarrow$$

I

$$+ CH_2ClCOOCH_3 + N_2$$

(1) Taken in part from a portion of a thesis submitted by Donald Nixon Thatcher in partial fulfillment of requirements for the Ph. D. degree, 1954.

(2) Du Pont Teaching Assistant, 1953–1954.

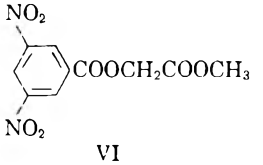
(3) J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **22**, 1233 (1957).

(4) H. Staudinger, J. Becker, and H. Hirzel, *Ber.* **49**, 1978 (1916).

(5) T. Reichstein and H. J. Morsman, *Helv. Chim. Acta*, **17**, 1120 (1934).

furoyldiazoacetate. The crystallinity of diazo esters is important in projected arylserine syntheses, since such esters are readily and safely purified by crystallization techniques. The purification of liquid diazo esters by vacuum distillation is hazardous unless very low pressures are used.[4] Because acid chlorides are more accessible than the bromides, the possibility of obtaining aroyldiazo esters from 3,5-dinitrobenzoyl chloride (II), α-naphthoyl chloride (III), β-naphthoyl-chloride (IV), and *o*-iodobenzoyl chloride (V) has been investigated.

Reaction of II with I gave in 68% yield a colorless product which contained neither diazo group[6] nor halogen.[7] Analysis and molecular weight determination indicated a formula of $C_{10}H_8N_2O_8$, and infrared spectral data indicated the possible presence of two ester groups. These data led to the speculation that the product was methyl *O*-(3,5-dinitrobenzoyl)glycollate (VI). An independent synthesis of VI by the method of Einhorn and Seuffert[8] indicated that this conjecture was correct. 3,5-Dinitrobenzoic acid also reacts with I to give VI, but in only 18% yield.



VI

The acid chlorides III, IV, and V take a different course in reacting with I. On the basis of combustion analyses and presence of infrared maxima in the region 1760–1790 cm.$^{-1}$, which are attributed to the anhydride carbonyl function,[9] the products are considered to be carboxylic anhydrides. In addition, α- and β-naphthoic anhydrides thus prepared gave melting pionts in reasonable agreement with the literature values. Apparently, *o*-iodobenzoic anhydride has not been previously reported.

It becomes evident that three reaction paths are shown by acid chlorides in reaction with I containing water: formation of the aroyldiazo ester,[5] of the *O*-aroylglycollate, and of the carboxylic anhydride. Although the present work is not sufficiently detailed to permit formulation of precise mechanisms, several interpretations of the general reaction course in terms of current theory[10] are possible and are presented. Formation of the aroyldiazo ester has been explained previously by assuming a diazonium betaine intermediate.[11]

In this study, two procedures were employed: reaction of the acid chloride with I in methyl acetate, and with I without added solvent. In either procedure, water could be present. Methyl diazoacetate was not distilled, and although the procedure employed called for drying of the ethereal extracts of I, the residual diazo ester was not dried after solvent removal. Storage at 0–5° also could lead to condensation of considerable quantities of water. Methyl acetate, which was used as received, undoubtedly contained water, and possibly methanol and acetic acid from hydrolysis as well. The presence of water appears important, since it is probable that the acid chlorides are hydrolyzed in the presence of methyl diazoacetate, which acts as a base. One possible route leading to the glycollate is considered in Chart I.

CHART I

(1) $ArCOCl + 2H_2O \longrightarrow ArCOOH + H_3O^+ + Cl^-$; Ar = 3,5-Dinitrophenyl

(2) $ArCOOH + H_2O \rightleftharpoons ArCOO^- + H_3O^+$

(3) $\{:N\equiv\overset{+}{N}-\overset{-}{\underset{\cdot\cdot}{C}}H-COOOCH_3 \longleftrightarrow$ I

$\overset{-}{\underset{\cdot\cdot}{N}}=\overset{+}{N}=CH-COOCH_3\} +$

$H_3O^+ \rightleftharpoons \overset{\cdot\cdot}{N}\equiv\overset{+}{N}-CH_2-COOCH_3 + H_2O$ VII

(4) (a) $ArCOO^- + VII \longrightarrow ArCOOCH_2COOCH_3 + N_2$

or (b) $VII \longrightarrow N_2 + {}^+CH_2COOCH_3$

${}^+CH_2COOCH_3 + ArCOO^- \longrightarrow ArCOOCH_2COOCH_3$ VI

In simplest terms, Chart I depicts an oxonium ion-catalyzed reaction of 3,5-dinitrobenzoic acid with methyl diazoacetate. The irreversible formation of hydronium ion in Step (1) would be important, since 3,5-dinitrobenzoic acid alone in reaction with I gave a low yield of VI. The dissociation of the acid in Step (2) may be of great importance or none, depending on the importance of the ion in Step (4). The reaction of diazoacetic esters with

(6) This statement is based on analytical data and on the absence of a band in the infrared absorption spectrum in the region 2000–2200 cm.$^{-1}$ For detailed infrared spectral data, see ref. (3), footnotes (13), (14), (15), and (16).

(7) The possibility of halogen being present was considered, in view of the ready reaction of diazoketones with hydrogen chloride liberated in the course of the reaction. However, aroyldiazo esters are unusually stable toward acid, a possibility which has been previously discussed by F. Arndt and J. Amende [*Ber.* **61**, 1123 (1928)]. See also ref. (4).

(8) A. Einhorn and R. Seuffert, *Ber.* **43**, 3000 (1910).

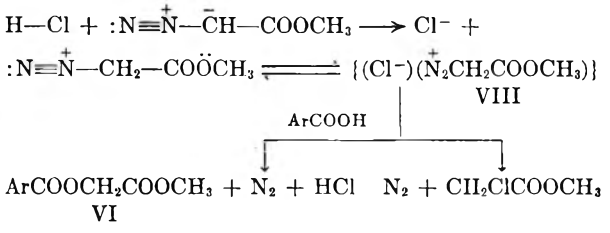
(9) F. Miller in *Organic Chemistry*, Vol. III, edited by H. Gilman, John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 140–141, 143–150.

(10) Of several important review articles over the chemistry of aliphatic diazo compounds, three can be cited for their coverage of the theoretical area: (a) B. Eistert (translated and revised by F. W. Spangler) in *Newer Methods of Preparative Organic Chemistry*, Interscience, New York, N. Y., 1948, p. 513; (b) R. Huisgen, *Österr. Chem. Ztg.*, **55**, 237 (1954); (c) R. Huisgen, *Angew. Chem.*, **67**, 439 (1955). Recent papers of interest include (d) J. D. Roberts, C. M. Regan, and I. Allen, *J. Am. Chem. Soc.*, **74**, 3679 (1952) and preceding papers; (e) D. Y. Curtin and S. M. Gerber, *J. Am. Chem. Soc.*, **74**, 4052 (1952); (f) R. W. Taft, Jr., and D. J. Smith, *J. Am. Chem. Soc.*, **76**, 305–7 (1954).

(11) B. Eistert, *Ber.*, **68**, 208 (1935).

hydronium ion in Step (3) is well known.[12] The formation of VI could involve either a displacement of nitrogen from the diazonium ion VII as in step (4)(a), or a dissociation to carbonium ion and subsequent coupling as in step (4)(b).[13] Utilization of carboxylate anion is largely a matter of convenience. Attack of diazonium or carbonium ion on the undissociated acid also could give VI [alternative Step (4)]. Inasmuch as the solvent system employed cannot be clearly defined, it is difficult to determine the extent to which it would support ionization. If the mechanism is indeed ionic, it is obvious that other molecules in addition to water could carry the proton: *e.g.*, methanol or acetic acid in the methyl acetate used. The fate of chloride ion is not indicated. Presumably it reacts with diazonium ion [from regenerated hydronium ion in Step (2) or alternative Step (4) and excess I] to give methyl chloroacetate and nitrogen.

A somewhat different approach to the problem of mechanism would assume that methyl diazoacetate effects proton transfer without any intermediate formation of appreciable quantities of hydronium ion, or even in the absence of water. Such a mechanism could be important if the solvent system is aprotic or becomes aprotic during the course of the reaction. The key step in such a mechanism would be reaction of molecular hydrogen chloride (from hydrolysis of the acid chloride) with I to give initially diazonium and chloride ions. It is conceivable that the latter would be associated in the ion-pair VIII, of limited but finite stability. Reaction of VIII with undissociated acid would give VI, nitrogen and hydrogen chloride, while the competing decomposition of VIII would give methyl chloroacetate and nitrogen. The whole problem of mechanism in the present study is intimately associated with the larger problem of specific and general acid catalysis of reactions of diazoacetic ester,[14] and is regarded as incompletely solved.



In explaining the formation of carboxylic anhydrides, the discussion will be restricted to the sequence in Chart I. Rates appear important. In formation of VI it appears likely that Step (1) is fast to give a large number of hydronium ions, which react rapidly to give a correspondingly large number of diazonium ions. The latter would react readily with carboxylic acid molecules or carboxylate ions to give the glycollate VI. If, however, the rate of hydrolysis of the acid chloride is slow, reaction of carboxylic acid molecules or carboxylate ions with unreacted acid chloride, in presence of the base methyl diazoacetate, would be statistically favored. A more detailed analysis is not obvious from data in the present study. The practical problem of purity of the acid chlorides may have a profound effect on the reaction course and also must be considered.[15]

The reactivity of methyl diazoacetate can be correlated to some extent with that of diazomethane. The catalytic activity of water, alcohols, and certain salts in reactions of the latter compound has long been recognized as important.[16] Very recently, interesting accounts of the basic activity of diazomethane in promoting ester interchange have been recorded.[17] It is apparent from the present study that methyl diazoacetate also is capable of acting as a useful base, and may prove important in synthesis of other reactive intermediates.

EXPERIMENTAL[18]

Source and purity of reagents. All acid chlorides except β-naphthoyl chloride were of the purest grade (White Label) available from the Eastman Kodak Co., and were used without additional purification. β-Naphthoyl chloride was practical grade, and also was used without purification. Glycine methyl ester hydrochloride was obtained from the Dow Chemical Co. Methyl acetate was obtained from several different companies, none of whom offered the reagent grade solvent, and was used as received.

Methyl diazoacetate. This substance was prepared from glycine methyl ester hydrochloride by the method of Womack and Nelson.[19] The residual ester from ether removal was used without further purification, and was stored in a refrigerator between runs.

Methyl O-(3,5-dinitrobenzoyl)glycollate. A. From reaction of 3,5-dinitrobenzoyl chloride with methyl diazoacetate. A 5-g. quantity of 3,5-dinitrobenzoyl chloride was dissolved in *ca.* 30 ml. of methyl acetate and the resulting solution added slowly to 4.5 ml. of methyl diazoacetate. Gas evolution commenced immediately. After standing at room temperature

(12) See ref. (10), especially b, c, and d; also L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, N. Y., 1940, p. 288.

(13) An interesting recent discussion of this general problem is presented by A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, 79, 2888 (1957).

(14) For a detailed discussion of this rather difficult problem, see ref. (10) (d).

(15) Recent studies in this laboratory indicate that interaction of very pure I and freshly recrystallized II and V affords the aroyldiazo ester in satisfactory yield (J. H. Looker and C. H. Hayes, unpublished observations).

(16) H. Meerwein and W. Burneleit, *Ber.*, 61B, 1840 (1928). These authors cite several studies by other workers indicating the importance of catalysts of various types.

(17) T. Wieland and R. K. Rothhaupt, *Chem. Ber.*, 89, 1176 (1956); H. Bredereck, R. Sieber, L. Kamphenkel, and R. Bamberger, *Chem. Ber.*, 89, 1169 (1956).

(18) All melting points are uncorrected, and are expressed in °C. Infrared spectra of Nujol mulls were recorded with a Perkin-Elmer Model 21 spectrophotometer, using sodium chloride prisms. Analyses for nitrogen content were performed by D. N. T. by the Dumas Method. Carbon-hydrogen analyses and molecular weight determinations were run by either Clark Microanalytical Laboratories, Urbana, Ill., or by Micro-Tech Laboratories, Skokie, Ill.

(19) E. B. Womack and A. B. Nelson, *Org. Syntheses*, 24, 56 (1944).

for 24 hr., the reaction mixture was placed in a refrigerator for one week. The crystalline material present was collected by filtration and recrystallized twice from methanol-methyl acetate; yield 4.2 g. (68%), m.p. 131–132°.

Anal. Calcd. for $C_{10}H_8N_2O_8$: C, 42.26; H, 2.84; N, 9.86; mol. wt., 284. Found: C, 42.00; H, 2.83; N, 9.66; mol. wt. (Rast), 272, 286.

B. From reaction of sodium 3,5-dinitrobenzoate with methyl chloroacetate. Reaction of methyl chloroacetate and sodium 3,5-dinitrobenzoate in aqueous methanol containing sodium iodide according to the general method of Einhorn and Seuffert[8] gave an 82% yield of methyl *O*-(3,5-dinitrobenzoyl)-glycollate, m.p. 131–132°, no depression upon admixture with the compound prepared as in *A*. The infrared spectra of the products prepared by the two methods were identical, and possessed absorption bands at 1745 (ester carbonyl), 1725 (ester carbonyl), 1535, 1350, 1225, 1160, and 719 cm.$^{-1}$

C. From reaction of 3,5-dinitrobenzoic acid with methyl diazoacetate. 3,5-Dinitrobenzoic acid (5 g., 0.024 mole) was dissolved in 30 ml. of methyl acetate and added to 10 ml. of methyl diazoacetate (0.11 mole) at 5°. No immediate evolution of gas was noticed. The reaction mixture was allowed to stand for 24 hr. at room temperature, then for two weeks at 0°. At the end of this time a crystalline product was collected and recrystallized from methanol-methyl acetate; yield, 1.2 g. (18%), m.p. and mixed m.p., 131–132°.

α-Naphthoic anhydride. To 5.6 g. (0.056 mole) of methyl diazoacetate at 5° was added a 5-g. quantity (0.026 mole) of α-naphthoyl chloride. Gas evolution commenced immediately. After standing at 0–5° for one week, the crystalline product then present was collected by filtration and recrystallized twice from methanol-methyl acetate; yield 2.8 g. (66%), m.p. 147–148° [lit.[20] m.p., 148°]. The infrared absorption spectrum showed a prominent band at 1762 cm.$^{-1}$, attributed to the anhydride carbonyl group.[9]

(20) W. F. Bruce, *J. Am. Chem. Soc.*, 60, 2277 (1938).

Anal. Calcd. for $C_{22}H_{14}O_3$: C, 80.96; H, 4.32. Found: C, 80.67; H, 4.33.

β-Naphthoic anhydride. To 5.6 g. (0.056 mole) of methyl diazoacetate at 5° was added a 5-g. quantity (0.026 mole) of β-naphthoyl chloride, dissolved in *ca.* 30 ml. of methyl acetate. After standing at 0–5° for three weeks, the crystalline product then present was collected by filtration and recrystallized from methanol-methyl acetate; yield, 2.0 g. (48%), m.p. 137–138° [lit.[21] m.p. 134°]. The infrared spectrum displayed a prominent absorption maximum at 1775 cm.$^{-1}$, due to the carboxylic anhydride carbonyl group.[9]

Anal. Calcd. for $C_{22}H_{14}O_3$: C, 80.96; H, 4.32. Found: C, 80.67; H, 4.31.

o-Iodobenzoic anhydride. To 4 ml. (0.045 mole) of methyl diazoacetate at 5° was added a 5-g. quantity (0.019 mole) of liquid *o*-iodobenzoyl chloride (warmed if necessary). Gas evolution commenced immediately. After standing at room temperature one day and at 0° for one week, the crystalline product then present was collected by filtration and recrystallized from methanol-methyl acetate; yield, 3.0 g., (66%), m.p. 76–77°. The infrared absorption spectrum showed a strong maximum at 1790 cm.$^{-1}$

Anal. Calcd. for $C_{14}H_8O_3I_2$: C, 35.20; H, 1.69. Found: C, 35.50; H, 1.75.

Acknowledgment. The support of this investigation by the Research Corporation of New York through a Frederick Gardner Cottrell Grant to The University of Nebraska is gratefully acknowledged.

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(21) I. Heilbron, *Dictionary of Organic Compounds*, Vol. III, Oxford University Press, New York, N. Y., 1953, p. 559.

[CONTRIBUTION NO. 1016 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Chemistry of Pyrazine and its Derivatives. I. The Hypohalite Oxidation of Acetonyl- and Phenacylpyrazine[1]

JOHN D. BEHUN[2] AND ROBERT LEVINE

Received August 5, 1957

Acetonylpyrazine has been oxidized with potassium hypochlorite solution to give a mixture of what is believed to be dichloromethylpyrazine (III) (78%) and acetic acid (36%). Similarly, phenacylpyrazine gives a mixture of III (37%) and benzoic acid (56%). The reaction of III with methanolic sodium methoxide gave a 79% yield of the dimethyl acetal of pyrazinealdehyde.

As part of an extensive study of the chemistry of pyrazine and its derivatives, we have prepared a series of ketones in high yields by acylating the side chain of methylpyrazine with a variety of esters using sodium amide in liquid ammonia as the condensing agent.[3] Acetonylpyrazine and phenacylpyrazine are two of the ketones which were prepared by this method.

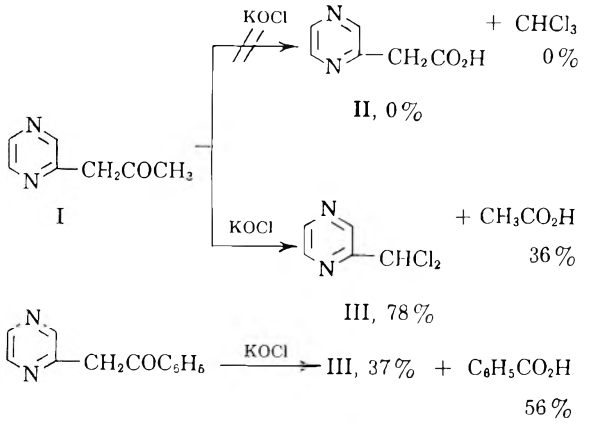
It was of interest to treat acetonylpyrazine, I, with potassium hypochlorite as a possible route to the previously unreported pyrazineacetic acid (II). However, none of the desired acid was obtained. Instead, what is believed to be dichloromethylpyrazine (III) (78%) and acetic acid (36%) were isolated. When phenacylpyrazine was treated similarly, a mixture of III (37%) and benzoic acid

(1) This work was performed under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(2) This paper is based on part of the thesis to be presented by John D. Behun to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

(3) J. D. Behun and R. Levine, page 9N of the Abstracts of the 130th meeting of the American Chemical Society, Atlantic City, N. J., September 16–21, 1956; the details of these acylations will be published shortly.

(56%) was obtained. The reactions involved are shown in the following scheme.



Although preliminary attempts to hydrolyze III to pyrazinealdehyde have failed, the hydrolysis study is being continued. However, it was found that III could be converted to the dimethylacetal of pyrazinealdehyde in 79% yield by reaction with methanolic sodium methoxide.

The study of the hypohalite oxidation of a variety of active hydrogen compounds which was initiated several years ago is being continued.[4,5]

EXPERIMENTAL[6]

Oxidation of acetonylpyrazine by potassium hypochlorite. An aqueous solution of potassium hypochlorite was prepared according to the method described in the literature.[7] Thus, a solution containing 30 g. of potassium carbonate and 5 g. of potassium hydroxide, dissolved in 40 ml. of water, was added to 50 g. of Pittchlor (commercial bleach) in warm water.

To this rapidly stirred solution, 19.0 g. (0.14 mole) of acetonylpyrazine was added over a 15-min. period. The reaction temperature rose to 50° during the addition of the acetonylpyrazine and a white precipitate formed. Stirring was continued for an additional hour and then the unreacted hypochlorite was destroyed by adding sodium bisulfite solution. The mixture was made weakly acidic with dilute hydrochloric acid and was filtered to remove the inorganic solids which were present. The filter cake was triturated with ether and filtered and the ether washings were combined with the ether extracts of the filtrate. The combined ether phases were dried over anhydrous sodium sulfate and the solvent was then removed by distillation at atmospheric pressure. Distillation of the residue gave 3.0 g. (35.8%) of acetic acid, b.p. 110–118° at atmospheric pressure. A sample of this acid was converted to acetanilide, m.p. 113–114° alone and when mixed with an authentic sample. The residue was distilled *in vacuo* to give 17.8 g. (78%) of dichloromethylpyrazine, b.p. 87–90° at 10 mm.

Anal. Calcd. for $C_5H_4N_2Cl_2$: C, 36.84; H, 2.47: N, 17.19; Cl, 43.50. Found: C, 36.78; H, 2.39; N, 17.11; Cl, 42.77.

Oxidation of phenacylpyrazine with potassium hypochlorite. Using the procedure described above, phenacylpyrazine (10.0 g., 0.05 mole) was oxidized by potassium hypochlorite to give dichloromethylpyrazine (3.0 g., 37%) and benzoic acid (3.4 g., 56.2%), m.p. 121–122° alone and when mixed with an authentic sample.

Preparation of the dimethyl acetal of pyrazinealdehyde. Commercial sodium methoxide (3.0 g., 0.05 mole) was added to dichloromethylpyrazine (7.1 g., 0.044 mole), which was dissolved in 50 ml. of anhydrous methanol. The reaction was very exothermic and it was necessary to cool the mixture in an ice bath. After the reaction mixture had come to room temperature, it was refluxed for two hours, cooled to room temperature and then poured onto ice. The mixture was extracted with several portions of chloroform. Removal of the solvent at atmospheric pressure gave a liquid residue which is a lachrymator and a skin irritant. This residue was dissolved in 40 ml. of anhydrous methanol. Then, additional sodium methoxide (3.0 g., 0.05 mole) was added and the mixture was refluxed for three hours. Finally, the mixture was processed as described above and the residue was distilled *in vacuo* to give 5.1 g. (79.2%) of the dimethyl acetal of pyrazinealdehyde, b.p. 90–94° at 10 mm.

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54. Found: C, 54.65; H, 6.49.

PITTSBURGH 13, PA.

(4) M. W. Farrar and R. Levine, *J. Am. Chem. Soc.*, **71**, 1496 (1949).

(5) R. Levine and J. R. Stephens, *J. Am. Chem. Soc.*, **72**, 1642 (1950).

(6) The methylpyrazine, which was used in this study, was generously supplied by Wyandotte Chemicals Corp.

(7) M. S. Newman and H. L. Holmes, *Org. Syntheses*, **Coll. Vol. II**, 428 (1943).

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, TOKYO UNIVERSITY]

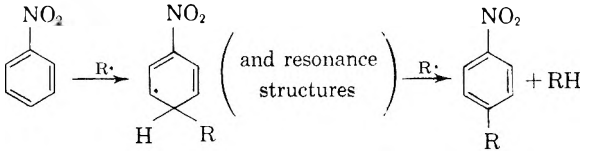
Reactions of Nitro Compounds with 1-Cyano-1-methylethyl Radicals Produced by the Decomposition of α,α'-Azobisisobutyronitrile

NACKI INAMOTO AND OSAMU SIMAMURA

Received July 31, 1957

1-Cyano-1-methylethyl radicals attack the nitro group of nitrobenzene, *m*-dinitrobenzene and tetranitromethane yielding hydrogen cyanide, acetone, and, in the case of the first two compounds, *N*-phenyl- and *N*-(*m*-nitrophenyl)-*O*,*N*-bis(1-cyano-1-methylethyl)hydroxylamines. Nitromethane does not react with this radical. The importance of this reaction in the mechanism of retardation of vinyl polymerization by nitro compounds is pointed out.

Aromatic nitro compounds are effective retarders or inhibitors of the free-radical polymerization of vinyl compounds.[1–5] Price and Durham have postulated for the retarding action of aromatic nitro compounds a mechanism shown in the following scheme, in which R· denotes a growing polymer radical.



In support of this mechanism, they found that the elements of nitro compounds used as retarders were incorporated in the polymer molecule produced. Further support for the mechanism is that the nuclear methylation of nitro compounds occurs readily in the reaction with various reagents[6] which are believed to produce methyl radicals on decomposition.

An alternative mechanism involving an attack by a radical on the nitro group has been suggested by Hammond and Bartlett[4] on the basis of their observations on the benzoyl peroxide-initiated polymerization of allyl acetate:

$$ArNO_2 + R\cdot \longrightarrow Ar{-}\overset{+}{N}\!\!<\!\!\begin{matrix}O^-\\ OR\end{matrix}$$

$$Ar{-}\overset{+}{N}\!\!<\!\!\begin{matrix}O^-\\ OR\end{matrix} + R\cdot \longrightarrow ArNO + ROR$$

In connection with the retarder action of nitro compounds their reactions with simple aliphatic radicals seem to be of interest. Hammond and Ravve[7] investigated the reaction of triphenylmethyl with nitrobenzene with the result that the former reacted only by abstracting oxygen from the nitro group, whereas Gingras and Waters[8] reported that 1-cyano-1-methylethyl radicals did not react detectably in boiling toluene solution with 1,3,5-trinitrobenzene and 2,4-dinitrochlorobenzene.

We have now examined reactions of nitrobenzene, *m*-dinitrobenzene, nitromethane, and tetranitromethane with 1-cyano-1-methylethyl radicals, which are generated by thermal decomposition of α,α'-azobisisobutyronitrile and which could be regarded as models of growing polymethacrylonitrile radicals. It has been found that the 1-cyano-1-methylethyl radical can indeed react with the nitro group.

The decomposition of α,α'-azobisisobutyronitrile in nitrobenzene at 100° gave a small amount each of hydrogen cyanide, acetone, and a crystalline compound, $C_{14}H_{17}N_{30}$, m.p. 93–94°, besides tetramethylsuccinonitrile and 2,3,5-tricyano-2,3,5-trimethylhexane, the usual products. The crystalline compound was identified as *N*-phenyl-*O*,*N*-bis(1-cyano-1-methylethyl)hydroxylamine, which was also obtained from nitrosobenzene and α,α'-azobisisobutyronitrile in boiling toluene according to Gingras and Waters.[8] The amount of the acetone isolated from the reaction mixture as the 2,4-dinitrophenylhydrazone corresponded to 3.4% of 1-cyano-1-methylethyl radicals to be generated from the azonitrile used, and that of the disubstituted phenylhydroxylamine to 2.8%.[9]

Similarly, when α,α'-azobisisobutyronitrile and *m*-dinitrobenzene were boiled in toluene, the evolution of hydrogen cyanide was noticed and acetone was produced together with a yellowish crystalline compound, $C_{14}H_{16}N_4O_3$, m.p. 159–159.5°. This compound was thought to be *N*-(*m*-nitrophenyl)-*O*,*N*-bis(1-cyano-1-methylethyl)hydroxylamine on

(1) S. G. Foord, *J. Chem. Soc.*, 48 (1940).

(2) C. C. Price and D. A. Durham, *J. Am. Chem. Soc.*, 65, 757 (1943).

(3) C. C. Price, *J. Am. Chem. Soc.*, 65, 2380 (1943); C. C. Price and D. H. Read, *J. Polymer Sci.*, 1, 44 (1946); G. V. Schulz, *Chem. Ber.*, 80, 232 (1947).

(4) G. S. Hammond and P. D. Bartlett, *J. Polymer Sci.*, 6, 617 (1951); *cf.* also P. D. Bartlett and H. Kwart, *J. Am. Chem. Soc.*, 72, 1051 (1950).

(5) J. W. Breitenbach, *Z. Elektrochem.*, 60, 286 (1956).

(6) L. F. Fieser, R. C. Clapp, and W. H. Daudt, *J. Am. Chem. Soc.*, 64, 2052 (1942); R. B. Sandin and W. B. McCormuck, *J. Am. Chem. Soc.*, 67, 2051 (1945).

(7) G. S. Hammond and A. Ravve, *J. Am. Chem. Soc.*, 73, 1891 (1951).

(8) B. A. Gingras and W. A. Waters, *J. Chem. Soc.*, 1920 (1954).

(9) The percentage yields reported in this paper are all based on 1-cyano-1-methylethyl radicals to be generated from the azonitrile used, it being assumed that one molecule of the latter gives two of the former radicals.

the basis of elemental analysis and by analogy with the formation of the corresponding product from the reaction in nitrobenzene. The amounts of the acetone and trisubstituted hydroxylamine isolated were, respectively, 4.6% and 2.2% of 1-cyano-1-methylethyl radicals generated.

When α,α'-azobisisobutyronitrile was added to boiling nitromethane, neither hydrogen cyanide nor acetone was detected and tetramethylsuccinonitrile and 2,3,5-tricyano-2,3,5-trimethylhexane were obtained in yields of 77.5% and 16%, respectively, on the basis of 1-cyano-1-methylethyl radicals generated. If the latter compound is produced by disproportionation of 1-cyano-1-methylethyl radicals followed by attack of the same radical on the resulting methacrylonitrile,[10] the yield of 16% corresponds to consumption of 21.5% of 1-cyano-1-methylethyl radicals; therefore, 99% of the radical produced is accounted for. Thus, 1-cyano-1-methylethyl radicals do not appear to attack nitromethane.

Unlike nitromethane, tetranitromethane was found to react with 1-cyano-1-methylethyl radicals in toluene at 100° affording 4% of acetone.

It is inferred from the results mentioned above that 1-cyano-1-methylethyl radicals attack an oxygen atom of the nitro group eventually to produce a nitroso compound and a 1-cyano-1-methylethoxy radical. The exact mechanism of the attack by the radical is unknown. The radical may abstract the oxygen atom directly (Equation 1) or alternatively it may add primarily to the oxygen atom as postulated originally by Hammond and Bartlett[4] to give an intermediate radical as shown below, the latter decomposing subsequently into a nitroso compound and a 1-cyano-1-methylethoxy radical (Equation 2).

$$ArNO_2 + (CH_3)_2\dot{C}(CN) \longrightarrow ArNO + (CH_3)_2C(CN)O\cdot \quad (1)$$

$$ArNO_2 + (CH_3)_2\dot{C}(CN) \longrightarrow \left[Ar\dot{N}O\,OC(CH_3)_2CN \leftrightarrow Ar\dot{N}O^-\,OC(CH_3)_2CN \text{ etc.} \right] \longrightarrow ArNO + (CH_3)_2C(CN)O\cdot \quad (2)$$

The nitroso compound thus formed combines with two 1-cyano-1-methylethyl radicals to yield a trisubstituted hydroxylamine (Equation 3).[8] The 1-cyano-1-methylethoxy radical gives rise to acetone and hydrogen cyanide probably either through the formation of acetone cyanhydrin (Equation 4) or through decomposition similar to that of *tert*-butoxy radicals (Equation 5).

$$ArNO + 2\,(CH_3)_2\dot{C}(CN) \longrightarrow Ar{-}N(C(CH_3)_2CN){-}O{-}C(CH_3)_2CN \quad (3)$$

$$(CH_3)_2C(CN)O\cdot \xrightarrow{\text{Hydrogen donor}} (CH_3)_2C(CN)OH \longrightarrow (CH_3)_2CO + HCN \quad (4)$$

$$(CH_3)_2C(CN)O\cdot \longrightarrow (CH_3)_2CO + \cdot CN \quad (5)$$

$$\cdot CN \xrightarrow{\text{Hydrogen donor}} HCN$$

In the case of tetranitromethane, the formation of 1-cyano-1-methylethoxy radicals can be considered certain, as was evidenced by the isolation of acetone; but the fate of an intermediate from tetranitromethane is as yet unknown. As evolution of some nitrogen dioxide was observed in the course of the reaction, it is possible that the decomposition took place into nitric oxide and nitrogen dioxide. Neither tris(1-cyano-1-methylethyl)hydroxylamine[8] nor α-nitroisobutyronitrile,[11] both of which should have been formed from 1-cyano-1-methylethyl radicals and nitric oxide or nitrogen dioxide, respectively, could be detected, however. It is also unknown why nitromethane does not react with radicals whereas tetranitromethane does.

There is a rough parallelism between the amount of acetone produced in the present reaction and the retarder efficiency of nitro compounds in the polymerization.[1,5] One nitro group in an aromatic compound gives a strong retardation, and the retarding effect is much stronger with two nitro groups. While tetranitromethane is a strong retarder,[5] nitromethane is ineffective in retarding both thermal[5] and benzoyl peroxide-initiated[2] polymerization of styrene or effective only to a limited extent, if at all, in the peroxide-induced short-chain polymerization of allyl acetate.[4] It may thus be concluded that the nitro compound takes part in the retardation by reacting with growing polymer radicals as shown in formulas 1, 2, and 3. In the case of aromatic nitro compounds with a replaceable hydrogen atom in the nucleus the mechanism postulated by Price and Durham[2] cannot be excluded.

EXPERIMENTAL

Reaction of nitrobenzene with α,α'-azobisisobutyronitrile. α,α'-Azobisisobutyronitrile (5.34 g.) was added little by little during 2 hr. to 20 g. of nitrobenzene heated on a boiling water bath and the heating was continued for a further 12 hr. Evolution of nitrogen took place, and hydrogen cyanide was detected by its odor and the Berlin blue reaction. The reaction mixture was distilled with steam, and tetramethylsuccinonitrile was separated from the distillate. On addition of an alcoholic solution of 2,4-dinitrophenylhydrazine to the aqueous distillate 0.53 g. of 2,4-dinitrophenylhydrazone of acetone, m.p. 126°, precipitated. The oily residue of the steam distillation was extracted with ether, the ether re-

(10) A. F. Bickel and W. A. Waters, *Rec. trav. chim.*, 69, 1490 (1950).

(11) J. F. Tilney-Bassett and W. A. Waters, *Chem. & Ind. (London)*, 957 (1956).

moved from the extract and the residue dissolved in petroleum ether. This solution, after standing in a refrigerator, gave 0.45 g. of *N*-phenyl-*O*,*N*-bis(1-cyano-1-methylethyl)-hydroxylamine, m.p. 93–94° (recrystallized from aqueous alcohol) with no depression on admixture with a sample prepared from nitrosobenzene according to Gingras and Waters.[8]

Anal. Calcd. for $C_{14}H_{17}N_3O$: N, 17.28. Found: N, 16.94%.

The insoluble part in petroleum ether gave, on filtration, 70 mg. of 2,3,5-tricyano-2,3,5-trimethylhexane, m.p. and mixed m.p. 81–82°.

Reaction of m-dinitrobenzene with α,α′-azobisisobutyronitrile. To a solution of 6.72 g. of *m*-dinitrobenzene in 20 cc. of toluene heated on a boiling water bath 6.56 g. of α,α′-azobisisobutyronitrile was added in small portions over 2 hr., and the mixture was heated for a further 3 hr. to complete the reaction. Hydrogen cyanide was evolved during the reaction. The reaction mixture was subjected to steam distillation and after recovery of tetramethylsuccinonitrile, acetone was isolated as 2,4-dinitrophenylhydrazone (0.85 g.) from the distillate. The residue from the steam distillation was extracted with ether, the ether removed and the residue was treated with petroleum ether. An insoluble part in this solvent was extracted with benzene and evaporation of the benzene gave 0.5 g. of *N*-(*m*-nitrophenyl)-*O*,*N*-bis(1-cyano-1-methylethyl)hydroxylamine, m.p. 159–159.5° (from benzene).

Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.44; mol. wt., 288. Found: C, 58.62; H, 5.88; N, 19.3%; mol. wt. (Rast), 278.

Reaction of nitromethane with α,α′-azobisisobutyronitrile. α,α′-Azobisisobutyronitrile (8.2 g.) was added gradually during 2 hr. to nitromethane (30 g.) under reflux and the refluxing was continued for a total of 6 hr. No hydrogen cyanide was detected in the nitrogen evolved during this period. The reaction mixture was distilled through a Vigreux column and the recovered nitromethane was shown to contain no acetone. On slow sublimation at 100° of the solid residue from the distillation, 5.27 g. of tetramethylsuccinonitrile was obtained. The residue was extracted with ether and evaporation of the ethereal solution gave 1.09 g. of 2,3,5-tricyano-2,3,5-trimethylhexane, m.p. 81–82°.

Reaction of tetranitromethane with α,α′-azobisisobutyronitrile. To a solution of 4.0 g. of tetranitromethane in 15 cc. of toluene heated on a boiling water bath, 5.0 g. of α,α′-azobisisobutyronitrile was added in small portions during 2 hr. and the mixture was heated for a further 6 hr. Some nitrogen dioxide was evolved. The reaction mixture was distilled with steam and acetone was isolated as 2,4-dinitrophenylhydrazone (0.6 g.) from the distillate after separation of tetramethylsuccinonitrile. No tractable products could be isolated from the viscous residue from the steam distillation.

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Oxidation of *n*-Octane with White Fuming Nitric Acid[1]

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The heterogeneous reactions of *n*-octane with white fuming nitric acid at −5°, 4°, and 27° have been investigated, using infrared spectroscopy as the main analytical tool. The effect of added phosphorus pentoxide, nitrogen pentoxide, sulfuric acid, and water was studied. The vigor of the reaction is a function of both the temperature and the concentration of nitrogen pentoxide. It is suggested that the nitrogen pentoxide in the white fuming nitric acid is responsible for its higher reactivity compared with the reactivity of aqueous nitric acid.

The principal products formed from the low temperature reaction include initially an alkyl nitrate (presumably 2-octyl nitrate) and subsequently 2-octanone. At higher temperatures carbon-carbon scission occurs and a mixture of carboxylic acids is obtained.

The reaction of white fuming nitric acid with alkanes is of interest as a model, controllable system for certain hypergolic (spontaneous ignition) reactions. The liquid phase heterogeneous reaction of *n*-octane with white fuming nitric acid has been investigated in order to determine the initial attack involved and the course of the reaction.

Previous work on the liquid phase reactions between alkanes and nitric acid has involved mainly aqueous solutions of nitric acid. The nitration of *n*-octane carried out by Konovalov[3] at 130° (sealed tube) with dilute nitric acid (sp. gr. 1.075) produced a fair yield of 2-nitrooctane. Worstall[4] reported the formation of primary mono- and dinitrooctanes in the reaction of this hydrocarbon with a mixture of nitric acid (sp. gr. 1.42) and sulfuric acid at the reflux temperature. The use of fuming nitric acid (sp. gr. 1.52) resulted in extensive oxidation of the hydrocarbon.

The literature yields the following generalizations concerning the liquid phase reactions of alkanes and nitric acid. Dilute nitric acid is preferable for nitration,[5] concentrated nitric acid favors oxidation and polynitroalkane formation,[3] while fuming nitric acid leads to both vigorous oxidation and polynitration.[4,6] Tertiary carbon atoms are nitrated most readily.[7] In the light of the above data and of Hass' signal successes with

(1) This work was conducted under Office of Naval Research Contract Nonr-630(00).

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(3) Konovalov, *J. Russ. Phys. Chem. Soc.*, **25**, 472 (1893).

(4) R. A. Worstall, *Am. Chem. J.*, **20**, 202 (1898).

(5) N. Levy and J. D. Rose, *Quart. Rev.*, **1**, 358 (1947).

(6) F. E. Francis and S. Young, *J. Chem. Soc.*, **73**, 928 (1898).

(7) W. Markovnikov, *Ber.*, **32**, 1441 (1899).

vapor phase nitration of alkanes,[8] it has generally been assumed that alkanes undergo reaction with nitric acid only under vigorous conditions. The present investigation shows that alkanes will react with white fuming nitric acid at room temperature or below.

It should be noted that the research cited above was directed toward the synthesis of nitroalkanes and not to the complete elucidation of the reaction between alkanes and nitric acid. Considerable confusion has arisen because of the failure of previous workers to specify the identity of the nitric acid used. Even the designation of the specific gravity of the nitric acid is of little use for concentrations of acid above 90%, in which region the density of the acid changes little with composition.

Recent spectroscopic and cryoscopic investigations of the nature of analytically anhydrous nitric acid have demonstrated the presence of 1–2% nitrogen pentoxide.[9] The presence of nitrogen pentoxide results in a significant difference in the reactivities of white fuming nitric acid and of aqueous nitric acid on alkanes as shown in the present work. In this connection the work of Titov and Shchitov[10] is of major significance. They studied the reactions of nitrogen pentoxide with cyclohexane, *n*-heptane, and *n*-octane in carbon tetrachloride solution. The principal products of these reactions were alkyl nitrate and nitroalkane. They also observed that the addition of a mixture of phosphorus pentoxide and "anhydrous" nitric acid to cyclohexane in carbon tetrachloride solution gave similar results.

In the present work, infrared spectroscopic analysis has been utilized in order to investigate the products present at low conversions of the reaction of *n*-octane and white fuming nitric acid in order to determine the initial oxidation product as well as the further sequence of oxidation products.

EXPERIMENTAL

Materials. *n*-Octane was obtained from the Matheson Co., n_D^{20} 1.3964. 2-Octyl nitrate was synthesized according to the method of Ferris,[11] n_D^{20} 1.4261. 2-Octyl nitrite was synthesized according to the method of Kornblum and Oliveto,[12] n_D^{20} 1.4089. 2-Octanone, obtained from the Eastman Kodak Co., was purified by means of the bisulfite addition compound, n_D^{20} 1.4142. 2-Octanol was an Eastman Kodak Co. product, n_D^{20} 1.4261. White fuming nitric acid was obtained from the General Chemical Division of Allied Chemical and Dye Corp., and was found by titration with standard base to contain 102–103% nitric acid. Cerate ion analysis of a similar sample of white fuming nitric acid indicated the concentration of nitrogen dioxide to be 0.02–0.03 g./ml.[13]

General procedure. One volume of the hydrocarbon was added cautiously by means of dropping funnel to two volumes of white fuming nitric acid contained in a 125-ml. Erlenmeyer flask which was equipped with a reflux condenser and magnetic stirrer, and submerged in a small water bath. The liquid, heterogeneous mixture was stirred vigorously at a constant rate for 0.25–5 hr., and poured over ice. The oil layer was separated, washed twice with water, and dried over anhydrous sodium sulfate; the reaction mixture was then submitted for infrared analysis. It was shown that this treatment did not affect any of the postulated products of the reaction.

Runs were made routinely at 27 ± 2° and 4 ± 1°. The 27° runs were conducted in a water bath; the 4° runs although conducted in an ice bath, did not attain 0° because of heat transfer from the magnetic stirrer. Occasionally the violence of a reaction raised the internal temperature to 50° or more. An ice-salt mixture was employed to obtain a temperature of −5 ± 2° and a circulating water bath maintained a temperature of 19 ± 1°.

Reactions were run using white fuming nitric acid alone, as well as white fuming nitric acid with added phosphorus pentoxide (Mallinckrodt Chemical Co.), nitrogen pentoxide, sulfuric acid (Baker and Adamson, 96% sulfuric acid), and water. The phosphorus pentoxide was added to the nitric acid at 0° prior to the introduction of the hydrocarbon. The nitric acid–nitrogen pentoxide mixture was prepared from a sample of distilled nitrogen pentoxide,[13] formed from the reaction of white fuming nitric acid and phosphorus pentoxide.

All infrared spectra were determined using a Perkin-Elmer Double Beam Recording Infrared Spectrophotometer Model 21 employing matched 0.1-mm. cells with sodium chloride windows. The analytical data and summary of the runs are given in Table I.

RESULTS

Effect of nitrogen pentoxide. The reaction of white fuming nitric acid with *n*-octane produced, in general, oxidation products although a small amount of nitration was observed. It was observed that the most vigorous stage of reaction at 27° occurred with the addition of the first few milliliters of hydrocarbon to the nitric acid. This implied the presence of some substance in the nitric acid which produced a vigorous reaction and which was consumed rapidly. The assumption that this substance was nitrogen pentoxide accounted for this rapid diminution of rate.

Several experiments bore out this theory. There was a remarkable reduction in total reaction in going from *ca.* 100% acid to 97.5% and 95% acids. On the other hand, by adding nitrogen pentoxide as such to the white fuming nitric acid, or by adding phosphorus pentoxide which forms nitrogen pentoxide according to the equation:

$$P_2O_5 + 6HNO_3 \longrightarrow 3N_2O_5 + 2H_3PO_4$$

the amount of total reaction was markedly increased. These results are presented in Table I, Runs 8–12. It should be noted that the 27° runs utilizing additional nitrogen pentoxide or

(8) H. B. Hass and E. Riley, *Chem. Revs.*, **32**, 373 (1943).

(9) C. K. Ingold and D. J. Millen, *J. Chem. Soc.*, 2612 (1950). R. J. Gillespie, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2552 (1950).

(10) A. I. Titov and N. V. Shchitov, *Doklady Akad. Nauk S.S.S.R.*, **81**, 1085 (1951).

(11) A. F. Ferris, K. W. McLean, I. G. Marks, and W. D. Emmons, *J. Am. Chem. Soc.*, **75**, 4078 (1953).

(12) N. Kornblum and E. P. Oliveto, *J. Am. Chem. Soc.*, **69**, 465 (1947).

(13) We acknowledge the assistance of Dr. George Gibson in these experiments.

TABLE I

OXIDATION OF *n*-OCTANE WITH WHITE FUMING NITRIC ACID

Run	*n*-Octane Ml.	Oxidant: White Fuming HNO_3, Ml.	Oxidant: Other	Temp., °C.	Time, Hr.	Overall Reaction, %[h]	Infrared Product Analysis-Mole, %[a,f]: RCO_2H[b]	$RCOR$[c]	$RONO_2$[d]	RNO_2[e]	
1	7	12.5	P_2O_5[m]	−5	1.25	13	0	0	100	0	
2	5	10		4	2.0	3	0	68	25	7	
3	5	5	H_2SO_4[l]	4	0.25	0.7	0	0	100	0	
4	14	25	P_2O_5[m]	4	1.5	26	0	0	99	1	
5	14	25	P_2O_5[m]	4	4.0	29	9	67	18	6	*j*
6	3	6	N_2O_5[n]	4	2.0	14	0	50	37	13	
7	5	10		19	2.0	2	63	1	20	6	
8	8	20	H_2O (5%)	27	3.0	0.06	89	0	0	0	
9	8	20	H_2O (2.5%)	27	5.0	0.28	84	0	0	6	
10	1	2		27	6.0	2.2	77	0	0	8	*g,o*
11	3	6	N_2O_5[n]	27	2.3	5.5	48	0	0	14	*i*
12	3	6	P_2O_5[m]	27	2.5	7.3	65	0	0	10	*o,i*
13	5	12	$NaNO_2$	27	1.0	0	0	0	0	0	*o*
			Oxidation of Intermediate Compounds								
14	2-Octanol	4		4	0.25	—	0	91	7	2	*j*
15	2-Octanone	2		27	2.0	76	57	24	0	1	*g*
16	2-Octyl Nitrate	5		4	1.0	31	0	28	69	3	*j*
17	"Octyl" Nitrate	9		4	2.0	31	0	28	69	3	*k*

[a] The product analyses are expressed in mole % of the total water-insoluble product. The product analyses are reproducible to ±5%. Several assumptions were made in the calculations: (1) the validity of Beer's Law in these systems; (2) the validity of the standards (the standards were chosen to reproduce individual absorption peaks but do not imply that the products had the identical structure except for functional groups) (see footnotes *b–f*); (3) the independence of the extinction coefficient of a given functional group from the structure of the rest of the molecule. [b] Calculated from the 1712 cm.$^{-1}$ absorption peak using *n*-heptanoic acid (in *n*-octane) as standard. [c] Calculated from the 1724 cm.$^{-1}$ absorption peak using 2-octanone as standard. [d] Calculated from the 1642 cm.$^{-1}$ absorption peak using 2-octyl nitrate as standard. [e] Calculated from the 1560 cm.$^{-1}$ absorption peak using 2-nitrooctane as standard. [f] In reactions carried out at 19° and 27° (runs 7–12 and 15), another component was detected by infrared analysis, having an absorption band at 1604 cm.$^{-1}$ This substance may be an alkyl nitrite (2-octyl nitrite shows absorption peaks at 1643 and 1604 cm.$^{-1}$) or a polynitro compound in which the absorption band of the nitro group has been shifted to the 1604-cm.$^{-1}$ region. A. I. Titov and M. K. Matveeva, *Doklady Akad. Nauk, S.S.S.R.*, **83**, 101 (1952) and Sbornik Statei, *Obshchei Khim. Akad. Nauk, S.S.S.R.*, **1**, 246 (1953) report the formation of cyclohexyl nitrite from cyclohexane and nitric acid or nitrogen oxides. It is possible that the sample of white fuming nitric acid used in the present experiments contained enough dissolved nitrogen dioxide to account for the formation of alkyl nitrite in these cases. [g] The water-insoluble carboxylic acid fraction was identified in the following fashion. The reaction product, washed with water was extracted with dilute aqueous sodium bicarbonate. The acrid material obtained from acidification of the bicarbonate extract was distilled *in vacuo* (b.p. 80–85°/3 mm.). The neutralization equivalent of the fraction from Run 11 was 116 ± 1 and from Run 16 was 121 ± 1. *p*-Toluides of each of these acid samples melted in the range of 58–62°, considerably lower than the toluides of pentanoic, hexanoic, or heptanoic acids. [h] The over all % reaction is the percentage of the reactant found as the total water-insoluble product. The abnormally low yields found in some of the higher temperature runs are probably due to extensive disruption producing water-soluble products which were not isolated. The percentages are reproducible to ±5%. [i] An experiment fourfold as large produced an uncontrollable reaction evolving heat and copious fumes of nitrogen dioxide. [j] The ketone was isolated by stirring the reaction product (washed free of carboxylic acid with sodium bicarbonate) for several hours with a strong, aqueous solution of Girard's Reagent T. The aqueous phase was acidified with hydrochloric acid, warmed gently for an hour on a steam bath, and extracted with ether. The ketone was recovered from the ether extract, and converted into a 2,4-dinitrophenylhydrazone, m.p. 57–58°, after recrystallization from ethanol. A mixture of this sample and an authentic sample melted at 57–58°. [k] A solution of what was presumably an octyl nitrate in *n*-octane was prepared from the reaction of *n*-octane with 100% nitric acid and phosphorus pentoxide at −5° according to Run 1. Its infrared spectrum was identical with that of authentic 2-octyl nitrate from 1000–4000 cm.$^{-1}$ [l] The molar ratio of the sulfuric acid to the nitric acid was 4:1. [m] The molar ratio of the octane to the phosphorus pentoxide was 1:1 in runs 5 and 6; and 1:0.8 in runs 13 and 4. [n] The molar ratio of the nitrogen pentoxide to the nitric acid was 1:10. [o] Nitrogen dioxide was liberated.

phosphorus pentoxide were accompanied by vigorous evolution of nitrogen dioxide and boiling of the reaction mixture.

Main oxidation products. At 4° or lower, with a reaction time of 1.5 hr. or less, using mixtures of phosphorus pentoxide and nitric acid (Runs 4 and 1) an alkyl nitrate is almost the sole product. At 4° nitric acid alone produced a mixture of alkyl nitrate and ketone with the latter predominating (Run 2). At 19° the main products of the oxidation with nitric acid were carboxylic acid, ketone, and alkyl nitrate (Run 7). At room temperature the reaction of nitric acid and *n*-octane gave mainly carboxylic acid (Run 10).

The alkyl nitrate exhibited an infrared spectrum identical with that of authentic 2-octyl nitrate. However, the infrared spectra of other octyl nitrates are practically indistinguishable from that

of 2-octyl nitrate. It may be concluded that the alkyl nitrate produced is an octyl nitrate or mixture of octyl nitrates. The ketone produced in the oxidation was isolated and identified as 2-octanone. The water-insoluble carboxylic acid fraction produced in the oxidation was isolated and shown to have an average molecular weight equivalent to that of hexanoic acid, probably a mixture of pentanoic, hexanoic, and heptanoic acids, since the *p*-toluidide of this fraction melted lower than the toluidides of either one of the individual acids.

In order to demonstrate the hypothesis of a stepwise reaction involving the sequence: alkane → alkyl nitrate → ketone → carboxylic acid, the following experiments were performed. 2-Octyl nitrate was treated with nitric acid producing 2-octanone which was isolated and identified (Runs 16 and 17). 2-Octanone was treated with nitric acid producing a (water-insoluble) carboxylic acid fraction whose neutralization equivalent was 121 ± 1, indicating approximately equal amounts of hexanoic and heptanoic acids (Run 15).

DISCUSSION

Reaction path. Using the previous data, the following reaction scheme can be postulated

$$\text{Alkane} \longrightarrow \begin{matrix}\textit{Sec.}\text{-Alkyl Nitrate}\\ \text{or}\\ \textit{Sec.}\text{-Alcohol}\end{matrix} \longrightarrow \text{Ketone} \longrightarrow \begin{matrix}\text{Carboxylic Acid} + CO_2\\ \text{or}\\ \text{2-Carboxylic Acids}\end{matrix}$$

This scheme satisfies all the data presented above and implies that the nitroalkane(s) be considered as by-products.

The decision as to whether the alcohol or alkyl nitrate is the initial oxidation product proved difficult. Under one set of reaction conditions nitrate was detected exclusively. 2-Octanol was converted to nitrate although the reverse was not observed, probably owing to the lack of water in the reaction mixture. Both 2-octanol (Run 14) and 2-octyl nitrate were converted to 2-octanone. These experiments do not permit an unambiguous assignment of the roles of alkyl nitrate and alcohol. The results can be explained by (1) the primary formation of alcohol with subsequent esterification to alkyl nitrate and oxidation to ketone; or (2) the primary formation of alkyl nitrate followed by oxidation to ketone. It should be pointed out that the chromic acid oxidation of alcohols has been demonstrated to proceed through an ester intermediate.[14]

The oxidation of ketone to acid involves the rupture of a carbon-carbon bond and may result in the formation of two carboxylic acids or of one carboxylic acid and carbon dioxide. There was some ambiguity in the identification of the carboxylic acid fraction. Since the only ketone isolated was 2-octanone, there might seem to be justification to assume that the water-insoluble carboxylic acids produced would be those derived from 2-octanone, namely hexanoic and heptanoic acids. However, there is no reason to exclude the formation of other octanones. Therefore, the carboxylic acid fraction could conceivably contain all normal alkanoic acids containing two to seven carbon atoms.

Mechanism of the initial attack. It has been shown that the ease of attack of an alkane by white fuming nitric acid is directly related to its nitrogen pentoxide content. This result is consistent with the results of Titov and Shchitov[10] on the facile oxidation of alkanes with nitrogen pentoxide. It is possible that the nitrogen pentoxide reaction occurs by a primary dissociation into NO_2 and NO_3 radicals or into the nitronium cation and the nitrate anion. If it is assumed that the oxidation occurs in the nitric acid phase, attack by an ionic species such as nitronium ion is indicated since Millen demonstrated that nitrogen pentoxide exists as nitronium nitrate in 100% nitric acid.[9] However, it is more probable that the oxidation process occurs in the hydrocarbon phase, and in such a situation, it is probable that the species that attacks the alkane is the NO_3 radical as postulated by Titov and Shchitov. It has been demonstrated by Ogg[15] that nitrogen pentoxide dissociates in the gas phase according to the equilibrium:

$$N_2O_5 \rightleftharpoons NO_2 + NO_3$$

In a nonpolar organic solvent such as *n*-octane this equilibrium would also be expected to exist. Titov and Shchitov have demonstrated that the initial attacking agent in the N_2O_5 oxidation in an organic solvent is the NO_3 radical by means of kinetic studies, the effect of solvent on the rate of oxidation and the effect of N_2O_4 on the rate of the reaction and on the relative product formation. It is reasonable to extrapolate this hypothesis to the present two-phase system involving white fuming nitric acid and *n*-octane. It should be noted that gas phase nitration and other substitution reaction of alkanes normally proceed by free radical mechanism;[16] the reactions under study appear to be members of the same mechanistic family.

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(14) F. H. Westheimer and N. Nicolaides, *J. Am. Chem. Soc.*, **71**, 25 (1949).

(15) R. A. Ogg, Jr., *J. Chem. Phys.*, **18**, 573, 770 (1950).

(16) H. E. DeLaMare and W. E. Vaughan, *J. Chem. Ed.*, **34**, 10, 64 (1957).

[CONTRIBUTION FROM THE RICHARD B. WETHERILL LABORATORY OF PURDUE UNIVERSITY]

Relative Rates of the Aluminum Chloride-Catalyzed Benzoylation of the Monoalkylbenzenes in Nitrobenzene Solution. Importance of Carbon-to-Carbon Hyperconjugation in Alkyl Substituents[1,2]

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A convenient procedure has been developed for following the rates of the aluminum chloride-catalyzed benzoylation of aromatics in nitrobenzene solution. Applied to the monoalkylbenzenes, RC_6H_5, this procedure gives the relative rates: R = Me, 1.00; Et, 0.89; *i*-Pr, 0.82; *t*-Bu, 0.69. In toluene 92% of the total reaction involves substitution in the *para* position. Consequently these results indicate that the rate of substitution *para* to the alkyl group decreases in the order, Me > Et > *i*-Pr > *t*-Bu. This order agrees with that predicted from the σ^+ constants for these alkyl groups and indicates that carbon-to-carbon hyperconjugation in these alkyl groups must play a dominant role in controlling the rates of the benzoylation reaction in the *para* position.

Apparently conflicting results have recently appeared in the literature with regard to the relative influence of methyl and *t*-butyl groups in activating the *para* position of the aromatic ring toward electrophilic substitution. Thus, bromination in the *para* position occurs more readily in toluene than in *t*-butylbenzene.[5,6] This is the order which would be predicted on the basis of the σ^+ constants which were recently proposed to correlate aromatic substitution.[7]

On the other hand, the rate of nitration in the *para* position has been reported to be greater for *t*-butylbenzene than for toluene.[8]

We recently examined the aluminum chloride-catalyzed benzoylation of toluene in nitrobenzene solution.[9] The reaction proceeds at a convenient rate and substitution involves the *para* position predominantly (92%). For this reason the reaction appeared eminently suitable for examining further the effect of alkyl substituents upon the rate of substitution in the *para* position. Accordingly, we undertook to determine the rates of benzoylation of methyl-, ethyl-, isopropyl- and *t*-butylbenzene.

Results. The original procedure[3] for following the benzoylation reaction involved hydrolyzing aliquots of the solution to convert unreacted benzoyl chloride to benzoic acid, followed by isolation and measurement of the benzoic acid. This procedure exhibited satisfactory precision, but proved to be very time-consuming.

Consequently, an alternative procedure was developed. In this method, aliquots of the reaction mixture were treated with water under carefully controlled conditions to remove aluminum chloride and hydrogen chloride without affecting the contained benzoyl chloride. The latter was then determined by utilizing a pyridine-catalyzed hydrolysis, followed by titration of the pyridine hydrochloride and benzoic acid formed in the hydrolysis.

Identical results were realized by both procedures. However, the latter procedure was far more convenient and it was adopted for the present rate determinations.

To test the reproducibility of the reaction, we redetermined the rates of benzoylation of benzene and toluene. With each reactant at 0.400 *M*, we obtained 3.5 order rate constants of 0.00620 $l.^{2.5}$ $mole^{-2.5}$ $min.^{-1}$ for benzene and 0.975 $l.^{2.5}$ $mole^{-2.5}$ $min.^{-1}$ for toluene, in excellent agreement with the values 0.00615 and 0.943 observed previously.[9] The ratio, $k_{toluene}/k_{benzene}$ is 154, as compared with the rate ratio 151 based upon both the rate data and the observed half-lives of the reactions.[9]

Since the rate constants vary with the initial concentration of the aluminum chloride, the four monoalkylbenzenes were determined using a constant initial concentration of 0.200*M* for each of the three reactants. The rate constants are summarized in Table I.

A series of measurements made with one particular preparation of aluminum chloride yielded values of the individual rate constants somewhat higher than those reported in Table I. However, the relative rates calculated from these rate constants (set B, Table I) were in satisfactory agreement with the other values (set A, Table I). These higher rate constants appeared to be due to the presence of traces of ferric chloride in the aluminum

(1) Directive Effects in Aromatic Substitution. XIX.

(2) Based in part upon a thesis submitted by F. R. Jensen in partial fulfillment of the requirements for the Ph.D. degree.

(3) Post-doctorate research assistant on a project supported by the Atomic Energy Commission, 1956; Canteens Services Trust Fund (Australia) Post-graduate Scholar, 1956–57.

(4) Research assistant on a project supported by the Atomic Energy Commission, 1953–54; National Science Foundation Predoctoral Fellow, 1954–55.

(5) E. Berliner and F. Berliner, *J. Am. Chem. Soc.*, **72**, 222 (1950).

(6) P. W. Robertson, P. B. D. de la Mare, and B. E. Swedlund, *J. Chem. Soc.*, 782 (1953).

(7) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **79**, 1913 (1957).

(8) H. Cohn, E. D. Hughes, M. H. Jones, and M. A. Peeling, *Nature*, **169**, 291 (1952).

(9) H. C. Brown and H. L. Young, *J. Org. Chem.*, **22**, 719, 724 (1957).

TABLE I

RATE CONSTANTS FOR THE ALUMINUM CHLORIDE-CATALYZED BENZOYLATION OF THE MONOALKYLBENZENES IN NITROBENZENE SOLUTION AT 25°

Aromatic	Rate Constants[a] $k_{3.5}$ ($l.^{2.5}$ mole$^{-2.5}$ min.$^{-1}$) Duplicate	Values	Mean	Relative Rates A	B[c]	C[d]
Benzene	0.0144[b]			1/154		1/151[e]
Toluene	2.23	2.18	2.20	1.00	1.00	1.00
Ethylbenzene	1.86	1.84	1.85	0.84	0.93	0.89
Isopropylbenzene	1.80	1.78	1.79	0.81	0.83	0.82
t-Butylbenzene	1.58	1.53	1.55	0.71	0.67	0.69

[a] Concentrations: [ArH] = [C_6H_5COCl] = [$AlCl_3$] = 0.200*M*. [b] Calculated from the toluene rate at 0.200*M* and the $k_{toluene}/k_{benzene}$ ratio obtained with each component 0.400*M*. [c] Relative rates obtained with aluminum chloride containing traces of ferric chloride. [d] Average relative rates. [e] Ref. (9).

chloride used as catalyst. It has been noted that minor amounts of ferric chloride in the aluminum chloride can have a marked accelerating effect upon the rate of the acylation reaction.[10]

Average values for the relative rates are summarized as set C in Table I.

Discussion. The benzoylation of toluene results in the formation of 7.2% *ortho*, 1.1% *meta* and 91.7% *para* substitution. Unfortunately, similar data for the isomer distribution in the benzoylation of the other monoalkylbenzenes are not now available. However, it is well known that the extent of *ortho* substitution decreases with the increasing steric requirements of the alkyl group. Thus the per cent of the *ortho* isomer decreases in nitration from 58.5% for toluene, to 45.0% for ethylbenzene, to 30.0% for isopropylbenzene, to 15.8% for *t*-butylbenzene.[11]

Fortunately, the benzoylation reaction is one of large steric requirements with but 7% substitution in the *ortho* position of toluene and no significant error would be introduced by ignoring the extent of substitution in the *ortho* (and *meta*) positions. However, it probably involves a smaller uncertainty to estimate that the extent of *ortho* substitution decreases linearly with the degree of branching of the alkyl group. On this basis, the *ortho* substitution has been estimated as 5% for ethyl-, 2.5% for isopropyl- and 0% for *t*-butylbenzene.[12]

In this way the *para* partial rate factors have been calculated for the benzoylation reactions. The results are summarized in Table II with related values for other reactions.

The marked difference in the σ^+ values for *m*- and *p*-*t*-butyl was considered to require a large, hyperconjugative contribution from the *p*-*t*-butyl group.[13-15] The small increase in the values of the σ^+ constants with increasing branching of the alkyl groups was considered to mean that each carbon-to-carbon bond was slightly less effective in hyperconjugation (a factor of 0.8 was indicated) than a corresponding carbon-to-hydrogen bond.[14] The satisfactory linear agreement between the log of the *para* partial rate factors and the σ^+ constants (Fig. 1) indicates that hyperconjugation must also be playing a dominant role in determining the relative reactivity of the *para* positions in the benzoylation reaction.

The σ^+ constants clearly predict that the partial rate factors for substitution in the *para* position should decrease more or less regularly with increasing branching of the alkyl group. Such a decrease is observed for benzoylation, for the uncatalyzed bromination in acetic acid (Br_2), and the perchloric acid-catalyzed bromination with hypo-

TABLE II

Para PARTIAL RATE FACTORS FOR THE MONOALKYLBENZENE

Reaction	Alkylbenzene, RC_6H_5 R = Me	Et	i-Pr	*t*-Bu
σ^+ Constants[a]	−0.306	−0.291	−0.276	−0.250
Benzoylation[b]	830	755	715	615
Bromination (Br_2)	2420[c]			775[d]
Bromination (Br^+)	59[e]			38.5[f]
Nitration[g]	58			75

[a] Ref. 7. [b] Present study. [c] H. C. Brown and L. M. Stock, *J. Am. Chem. Soc.*, **79**, 1421 (1957). [d] Ref. 6. [e] P.B.D. de la Mare and J. T. Harvey, *J. Chem. Soc.*, 36 (1956). [f] P. B. D. de la Mare and J. T. Harvey, *J. Chem. Soc.*, 131 (1957). [g] Ref. 8.

(10) L. F. Martin, P. Pizzolato, and L. S. McWaters, *J. Am. Chem. Soc.*, **57**, 2584 (1935).

(11) K. L. Nelson and H. C. Brown, *J. Am. Chem. Soc.*, **73**, 5605 (1951); H. C. Brown and W. H. Bonner, *J. Am. Chem. Soc.*, **76**, 605 (1954).

(12) Acetylation of *t*-butylbenzene has been reported to yield 0% *ortho*, 1.8% *meta* and 98.2% *para*. J. C. Butler, L. L. Ferstandig, and R. D. Clark, *J. Am. Chem. Soc.*, **76**, 1906 (1954).

(13) N. N. Lichtin and P. D. Bartlett, *J. Am. Chem. Soc.*, 73, 5530 (1951).

(14) H. C. Brown, J. D. Brady, M. Grayson, and W. H. Bonner, *J. Am. Chem. Soc.*, **79**, 1897 (1957).

(15) For an alternative interpretation, see W. M. Schubert, *et al.*, *J. Org. Chem.*, 21, 119 (1956), and *J. Am. Chem. Soc.*, **79**, 910 (1957).

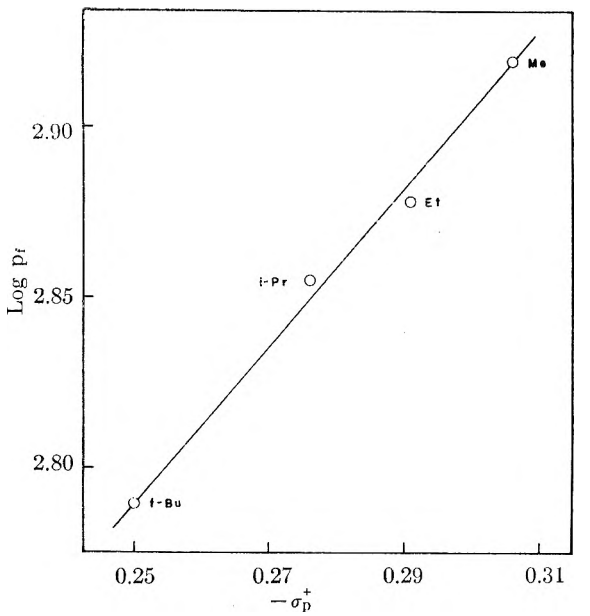

Fig. 1. Relationship between the *para* partial rate factors for the benzoylation reaction and the σ_p^+ constants

bromous acid (Br^+).[16] However, the nitration results of Hughes and his coworkers[8] constitute a serious exception to this correlation between the σ^+ constants and the partial rate factors. This exception appears deserving of a renewed scrutiny.

EXPERIMENTAL

Materials. The nitrobenzene, benzoyl chloride, and aluminum chloride were carefully purified by the procedures previously described.[9] Benzene, toluene, ethyl-, isopropyl- and *t*-butylbenzene were carefully purified commercial samples. Purities, as established by cooling curves, were 99.5% or better.

Analytical procedure. Considerable time was devoted to the development of a convenient analytical procedure which would permit accurate determination of the unreacted benzoyl chloride. Since careful attention to detail is required for accurate results, the procedure will be fully described.

A 5-ml. sample was pipetted from the reaction vessel into a 125-ml. separatory funnel which contained 15 ml. of distilled water and 20 ml. of ice chips. The pipet was a fast delivery pipet and its delivery volume with nitrobenzene had been accurately determined. The separatory funnel was vigorously shaken for 20 seconds in order to stop the reaction and to bring the hydrogen chloride and aluminum chloride into the water layer. After allowing the solution to settle, the nitrobenzene was drained off and the aqueous layer extracted twice with 2 ml. portions of chloroform. Ten milliliters of ice water was added to the combined extracts, the mixture was shaken, 2 drops of phenolphthalein in acetone was added to the water layer, and then the water layer was neutralized with 0.03*M* sodium hydroxide.

Sufficient 85% pyridine-15% water mixture (neutralized to the phenolphthalein end point) was added to make the solution homogeneous. The solution was covered and allowed to stand for a definite time interval, 10 min. being sufficient to hydrolyze the acid chloride completely. The pyridine hydrochloride and benzoic acid formed were titrated with standard base to the phenolphthalein end point. During the titration, sufficient neutralized 95% ethanol was added to maintain the homogeneity of the solution.[17]

The results obtained in one experiment were checked by a procedure which has been previously reported.[9] In this procedure the sample from the reaction solution was hydrolyzed in base, the solution acidified, the benzoic acid extracted with ether, the ether evaporated, ethanol and water were added, and then the benzoic acid was titrated with standard base.

The results obtained by the two analytical procedures are given in Table III.

TABLE III

COMPARISON OF THE RESULTS OBTAINED USING DIFFERING ANALYTICAL PROCEDURES

Time,[b] min.	Unreacted Benzoyl Chloride[a] Method A[c]	Method B[d]	Difference
3.6	0.2263	0.2398	0.0035
10.0	.1916	.1961	.0045
19.2	.1571	.1604	.0033
28.8	.1372	.1413	.0041
38.7	.1230	.1258	.0028
47.7	.1139	.1183	.0044
57.4	.1051	.1097	.0046

[a] Reaction mixture: $[C_6H_5CH_3] = [C_6H_5COCl] = [AlCl_3] = 0.309$ M, in nitrobenzene solution. [b] The samples were removed from the same reaction mixture at the times indicated. [c] Method A: pyridine-catalyzed hydrolysis. [d] Method B: isolation of benzoic acid, ref. (9).

The values given for Method B (isolation of benzoic acid) were not corrected for the usual small blank measurements. Such corrections would largely eliminate the present small differences in the two sets of data. The accuracy of the two methods is seen by comparing the differences which are always in the same direction. The samples were taken simultaneously using two pipets which were alternated from sample to sample. Since the pipets did not deliver exactly the same volume the differences are alternately low and high. The analytical data reported in Table III by method B were obtained by Dr. H. L. Young.

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(16) The mercuration reaction also appears to exhibit the hyperconjugative order. H. C. Brown and C. W. McGary, Jr., *J. Am. Chem. Soc.*, **77**, 2310 (1955). Unfortunately, isomer distributions other than for toluene are not presently known. Moreover, reliable estimate of the *para* partial rate factors could not be made in the manner utilized for the benzoylation reaction, since mercuration results in relatively large amounts of substitution in both the *ortho* and *meta* positions. Consequently, the mercuration reaction was not included in Table II. We hope to obtain accurate experimental data on the isomer distribution for this reaction shortly.

(17) Pyridine has been used previously in analytical procedures to assist in the hydrolysis of acid halides. D. Klamann, *Monatsh. Chem.*, **83**, 719 (1952) and references cited therein.

[CONTRIBUTION FROM THE RICHARD B. WETHERILL LABORATORY OF PURDUE UNIVERSITY]

Relative Rates of the Aluminum Chloride-Catalyzed Benzoylation of the Methylbenzenes in Nitrobenzene Solution[1,2]

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The rates of the aluminum chloride-catalyzed benzoylation of benzene and the polymethylbenzenes have been measured in nitrobenzene solution at 25° and compared with the relative rates calculated from the partial rate factors for the benzoylation reaction. Relatively large discrepancies are observed between the calculated and experimental rates, particularly in the case of the more reactive derivatives. Possible reasons for the discrepancies are examined. Intense colors are developed by nitrobenzene solutions containing aluminum chloride and certain of the polymethylbenzenes. It is suggested that the discrepancies in part arise from the presence of ternary nitrobenzene-aluminum chloride-polymethylbenzene complexes.

It was originally suggested by Condon that the reactivities of the polymethylbenzenes could be calculated from the partial rate factors obtained from rate data for benzene and toluene and the observed isomer distribution in toluene.[5] Excellent agreement has been realized in applying this procedure to the mercuration[6] and bromination of the methylbenzenes.[7]

We recently determined the partial rate factors for the aluminum chloride-catalyzed reaction of benzoyl chloride with toluene in nitrobenzene solution[8] and developed a convenient procedure for following the reaction rate.[9] Accordingly, it appeared desirable to apply this procedure to the determination of the rates of benzoylation of the polymethylbenzenes and a comparison of the observed and calculated reaction rates.

Results. The rates of reaction of benzoyl chloride with the methylbenzenes were measured in nitrobenzene solvent at 25° using equimolar concentrations of benzoyl chloride, aluminum chloride, and the aromatic hydrocarbon. The reactions were followed by determining the amount of residual benzoyl chloride using the technique described in the preceding paper.[9]

The benzoylation reaction appears to be first order in aromatic, and first order in benzoyl chloride, but of complex order with respect to aluminum chloride. At any given aluminum chloride concentration, the kinetics of the reaction with benzene follow a third order expression, but the third order constant decreases with increasing concentration of aluminum chloride. The corresponding reaction with toluene appears to agree more closely with a seven-halves order rate law.[8]

The kinetics of the present compounds proved to be similar to toluene—they followed a seven-halves order rate expression quite closely.

In order to minimize the effects of the difficulties, the rate constants were measured with all components at equal concentrations: 0.200*M* for the less reactive derivatives and 0.100*M* for the more reactive compounds. Toluene and *m*-xylene were

TABLE I

RATE CONSTANTS FOR THE ALUMINUM CHLORIDE-CATALYZED REACTION OF BENZOYL CHLORIDE WITH THE METHYLBENZENES IN NITROBENZENE SOLUTION AT 25°

Aromatic	Rate Constants, $k_{2.5}$ ($l.^{2.5}$ mole$^{-2.5}$ min.$^{-1}$) 0.400M[a]	0.200M[a]	0.100M[a]
Benzene	0.00632[b]		
	0.00607[b]		
Toluene	0.964[b]	2.23[b]	4.95
	0.950[b]	2.18[b]	4.90
o-Xylene		19.8	
		19.4	
m-Xylene		54.4	134
		56.8	119
p-Xylene		2.07	
		2.00	
Hemimellitene			413
			438
Pseudocumene			238
			248
Mesitylene			3,940
			4,050
Prehnitene			1,150
			1,120
Isodurene			6,820
			6,530
Durene			349
			352
Pentamethylbenzene			4,370
			4,510

[a] [ArH] = [C_6H_5COCl] = [$AlCl_3$] at molar concentrations indicated. [b] From Ref. (9).

(1) Directive Effects in Aromatic Substitution. XX.

(2) Based in part upon a thesis submitted by F. R. Jensen in partial fulfillment of the requirements for the Ph.D. degree.

(3) Post-doctorate research assistant on a project supported by the Atomic Energy Commission, 1956; Canteens Services Trust Fund (Australia) Post-graduate Scholar, 1956–57.

(4) Research assistant on a project supported by the Atomic Energy Commission, 1953–54; National Science Foundation Predoctoral Fellow, 1954–55.

(5) F. E. Condon, *J. Am. Chem. Soc.*, **70**, 1963 (1948).

(6) H. C. Brown and C. W. McGary, *J. Am. Chem. Soc.*, **77**, 2311 (1955).

(7) H. C. Brown and L. M. Stock, *J. Am. Chem. Soc.*, **79**, 1421 (1957).

(8) H. C. Brown and H. L. Young, *J. Org. Chem.*, **22**, 719, 724 (1957).

(9) H. C. Brown, B. A. Bolto, and F. R. Jensen, *J. Org. Chem.*, **23**, 414 (1958).

examined at both concentrations to permit reduction of the data to a single scale of relative reactivities.

The observed rate constants are summarized in Table I.

Whereas in the case of benzene and toluene the reaction solutions were pale yellow, very similar in color to solutions of aluminum chloride in nitrobenzene itself, the more highly alkylated aromatics produced much more intensely colored solutions, varying from orange-yellow for hemimellitene, to red-orange for isodurene, to dark red for pentamethylbenzene.

This phenomenon was examined further by preparing solutions in nitrobenzene of the aromatic hydrocarbon and aluminum chloride, 0.2*M* in each component. The observations are summarized in Table II.

TABLE II

COLORS EXHIBITED BY SOLUTIONS OF ALUMINUM CHLORIDE AND METHYLBENZENES IN NITROBENZENE[a]

Aromatic	Color of Solution	Calcd. Relative Rate / Obsd. Relative Rate
Benzene	Pale yellow	1.0
Toluene	Yellow	1.0
p-Xylene	Darker yellow	0.7
o-Xylene	Orange-yellow	1.0
m-Xylene		2.3
Pseudocumene		3.0
Durene		0.7
Mesitylene		3.4
Hemimellitene	Yellow-orange	3.5
Prehnitene	Light red-orange	5.9
Isodurene	Red-orange	6.7
Pentamethylbenzene	Dark red	25

[a] [ArH] = [$AlCl_3$] = 0.2*M*.

Discussion. The observed relative rates for the benzoylation reaction, $k_{toluene}/k_{benzene}$ = 151, and the observed isomer distribution in toluene, 7.2% *ortho*, 1.1% *meta*, and 91.7% *para*, yield the partial rate factors: o_f 32.6, m_f 5.0, p_f 831. Utilizing these rate factors, the relative rates of benzoylation of the methylbenzenes have been calculated. These calculated values are summarized in Table III along with the observed values of the relative rates.

In the case of the mercuration and bromination reactions, excellent agreement was realized between the observed reaction rates and those calculated from the partial rate factors. However, in the present case serious discrepancies exist between the observed and calculated rates (Fig. 1).[10]

We have carefully reviewed the experimental technique for following the benzoylation rates. Although some of these reactions are exceedingly fast, introducing the possibility of an appreciable error in the measurement of the rate constants, we do not believe that the large discrepancies between the observed and calculated values can be attributed to this cause. We have been able to check our measurements of the rate constants with a reproducibility of ±5% and, even in the case of the very fast reactions, we doubt that the uncertainty can be very much larger than this.

In the case of the mercuration reaction, we observed certain minor discrepancies which pointed to an enhanced steric effect when the position undergoing substitution is flanked by two methyl groups, particularly when these are buttressed by additional methyl substituents. However, the present data show good agreement between the observed and calculated rates for durene (with buttressed double-*ortho* substituents) and a very large discrepancy for the related structure, pentamethyl-

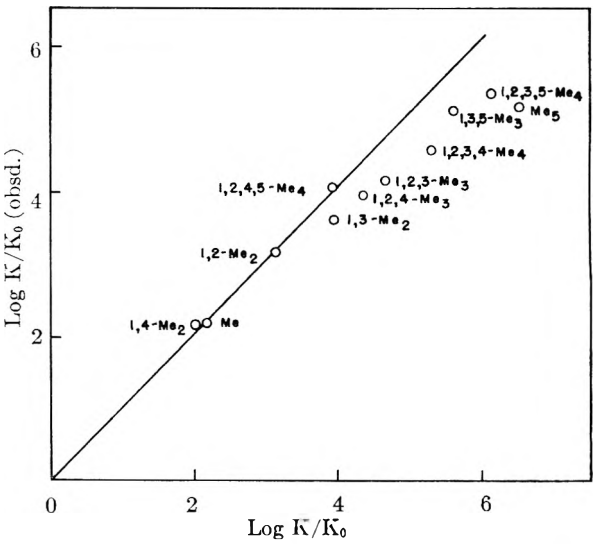

Fig. 1. Comparison of observed and calculated relative rates of the aluminum chloride-catalyzed reaction of benzoyl chloride with the methylbenzene

TABLE III

OBSERVED AND CALCULATED RELATIVE RATES FOR THE ALUMINUM CHLORIDE-CATALYZED BENZOYLATION OF THE METHYLBENZENES IN NITROBENZENE AT 25°

Aromatic	Relative Rate Observed	Relative Rate Calculated[a]
Benzene	1.00	1.00
Toluene	154	151
o-Xylene	1,360	1,440
m-Xylene	3,910	9,210
p-Xylene	142	108
Hemimellitene	13,300	48,600
Pseudocumene	7,600	23,700
Mesitylene	125,000	442,000
Prehnitene	35,500	225,000
Isodurene	212,000	1,470,000
Durene	11,000	8,850
Pentamethylbenzene	139,000	3,690,000

[a] Calculated from the factors: o_f 32.6; m_f 5.0; p_f 831 (ref. 8).

(10) To obtain a graphical estimate of the marked difference in the agreement realized in these three reactions, compare Fig. 1 with the corresponding diagrams for the mercuration and bromination reactions. H. C. Brown and L. M. Stock, *J. Am. Chem. Soc.*, 79, 5175 (1957).

benzene. Consequently, this factor cannot be responsible for the large discrepancies observed.

We also considered the possibility that the rate of transfer of aluminum chloride from nitrobenzene to benzoyl chloride might become a factor in the very fast reactions and thereby account for the observed drop below the calculated values. In these solutions the aluminum chloride is presumably associated with the nitrobenzene as a 1:1 addition compound, with a minor amount of the aluminum chloride associated with the benzoyl chloride.

$$C_6H_5NO_2{\cdot}AlCl_3 + C_6H_5COCl \rightleftharpoons C_6H_5NO_2 + C_6H_5COCl{\cdot}AlCl_3$$

The available evidence indicates that such transfers are very fast. If so, the rate of transfer would not be involved in the measured rate of reaction. However, in the case of the very fast benzoylations there exists the possibility that the rates of these reactions may be comparable to the rate of transfer and result in a decrease in the observed rate from that calculated from the partial rate factor.

On the basis of the available evidence, we cannot completely eliminate this possibility as a factor. However, we believe that it cannot be the entire answer and can, at most, only account for a portion of the effect. Were this a factor in the fast reactions, it should also be present in durene. Yet the agreement between the calculated and observed rates for durene is good. On the other hand, relatively large discrepancies exist for *m*-xylene and pseudocumene, which react at rates comparable to that for durene.

Previously, in studying the aluminum chloride-catalyzed reaction of 3,4-dichlorobenzyl chloride with aromatics in nitrobenzene solution, we encountered certain peculiarities which we attributed to the formation of ternary complexes of aluminum chloride, nitrobenzene, and the aromatic hydrocarbons.[11] In the present case we also encountered the intensely colored solutions characteristic of such complexes.

Solutions of aluminum chloride and the aromatic hydrocarbon in nitrobenzene were prepared at 0.2*M* and the colors which developed were compared (Table II). Benzene and toluene yield solutions whose colors differed but little from those of binary aluminum chloride-nitrobenzene solutions. However, the colors deepened with the more highly methylated aromatics and a rough correlation was observed between both the shift in the color and its intensity and the magnitude of the discrepancy between the observed and calculated rates (Table II).

It is not possible on the basis of such qualitative evidence to conclude that the discrepancy is due to this factor. However, it is apparent that the formation of complexes within the reacting solution involving a portion of both aluminum chloride-nitrobenzene and the aromatic hydrocarbon might well result in a decrease in the equilibrium concentration of the benzoyl chloride-aluminum chloride complex which is believed to be responsible for the benzoylation reaction, with a resulting decrease in the experimentally observed rate.

We are attempting to test this possibility by examining in more detail the interactions of aluminum chloride in nitrobenzene solution with benzoyl chloride and with aromatic hydrocarbons individually. However, it appears that the aluminum chloride-nitrobenzene system possesses a number of complicating characteristics which render it undesirable for studies directed to the quantitative determination of rates of aromatic substitution. Consequently, we are examining other solvents which may permit the determination of benzoylation rates free of the difficulties encountered with nitrobenzene as the medium.

EXPERIMENTAL

Materials. The nitrobenzene, benzoyl chloride and aluminum chloride were purified as previously described.[8]

The aromatic hydrocarbons were obtained from stocks available in the laboratory.[6,7] All compounds had been carefully purified and had been shown to possess minimum purities of at least 99.5% purity by cooling curve measurements.

Analytical procedure. The analytical procedure was the same as reported previously for the benzoylation of the alkylbenzenes in nitrobenzene[9] except with the more reactive compounds, where it was feared that contacting the solution with the immiscible water layer might not be sufficiently effective to stop the reaction instantly. Therefore, for mesitylene, pentamethylbenzene, and 1,2,3,5-tetramethylbenzene, a more rapid procedure for halting the reaction was devised. Standard solutions of the hydrocarbon in nitrobenzene and of benzoyl chloride and aluminum chloride in nitrobenzene were prepared. Aliquot portions of these solutions were brought together, using fast delivery pipets. The reactions were stopped by pouring 10 ml. of a 0.5*M* benzophenone solution in chlorobenzene into the reaction vessel. The ready miscibility of the benzophenone solution with that of the reaction mixture permitted the instant coordination of the aluminum chloride by the benzophenone and the practically instantaneous halting of the reaction. The samples were then worked up in the manner previously described.

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(11) H. C. Brown and M. Grayson, *J. Am. Chem. Soc.*, **75**, 6285 (1953).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PITTSBURGH AND THE RICHARD B. WETHERILL LABORATORY OF PURDUE UNIVERSITY]

An Extended Table of Hammett Substituent Constants Based on the Ionization of Substituted Benzoic Acids

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It is recommended that a return be made to the use of the dissociation constants of substituted benzoic acids as a basis for evaluating Hammett substituent constants. A survey of the available data has been made and the substituent constants have been tabulated. The approximate precision of these values is discussed.

More than twenty years ago Hammett pointed out certain parallelisms between the magnitude of reaction rate constants in a homologous series and equilibrium constants of various substituted compounds in other homologous series.* Using the ionization of benzoic acids as a standard reaction, he expressed this relationship in the now well known form:

$$\log \frac{k}{k^\circ} = \rho\sigma \quad (1)$$

where k = a rate (or equilibrium) constant for a *meta* or *para* substituted aromatic compound (2)

k° = the rate (or equilibrium) constant for the unsubstituted aromatic compound (3)

ρ = a constant for the specific reaction and taken as unity for the ionization of benzoic acids (4)

σ = a constant for a given substituent = log K − log K° where K is the ionization constant for a substituted benzoic acid in water at 25° C and K° is the ionization constant for benzoic acid itself. (5)

The choice of the standard reaction was dictated by the relative availability of numerous and highly accurate values, largely by Dippy and his co-workers, for the ionization constants of substituted benzoic acids. Fortunately, σ values for most of the more common substituents could thus be directly established. Some σ values, however, were obtained by indirect means. After a ρ value for a particular reaction had been established, based upon the σ values obtained from the ionization of benzoic acids, it was possible to calculate σ values for groups whose rate constants (or equilibrium constants) for that particular reaction were known, even though the ionization constants for the corresponding benzoic acids were not known. The σ values calculated in this manner might be considered to be "secondary standards" or "secondary" σ values. When these "secondary" σ values were used in calculating ρ values for other reactions, and further σ values obtained from these reactions, the σ values so derived (which might be termed "tertiary" σ values) were found to be dependent on the precise order in which the process of establishing ρ values and secondary σ values was carried out. Partially to circumvent this difficulty Jaffé proposed a redefinition of the substituent constant as "the value of σ which best fits the entire body of experimental data." (The ρ value would presumably still be set as 1.000 for the ionization of the benzoic acids.)

Jaffé himself has pointed out the shortcomings of his redefinition. "It makes substituent constants dependent on the body of knowledge available at the time of their evaluation, and implies that they should be revised at frequent intervals. Moreover, the evaluation of such substituent constants requires the formidable task of fitting the entire available data by some suitable statistical procedure. Such computation is not feasible without the use of electronic computing equipment."

Both Hammett and Jaffé include such "secondary" and "tertiary" values in their compilations. In some cases relatively large discrepancies have been shown to exist between these derived σ constants and those based upon more recently available dissociation constants. In other cases the values listed exhibit relatively large differences between very similar, closely related groups.

Our attention was drawn to this problem in the course of our efforts to extend the Hammett treatment to electrophilic reactions through the development of a set of electrophilic (σ^+) substituent constants.[21,65] Excellent agreement had been observed previously between the σ_m^+ and the σ_m values.[21] However, in extending our determination of σ^+ values to additional groups, we observed a number of discrepancies between the σ_m values listed in the compilations of Hammett[40] and of Jaffé[47] and the experimental σ_m^+ values. In almost every case where a major discrepancy was encountered the σ_m value proved to be a "secondary" or "tertiary" constant. In large part the discrepancies could be eliminated by re-evaluating the σ_m values, utilizing dissociation constants now available in the literature.

As a result of our experience, we wish to recommend a return to Hammett's original definition for σ, *i.e.*, the difference in pK_a values of benzoic acid

* Because of the large number of references to which attention must be called repeatedly throughout the paper, it has appeared more convenient to list them together at the end of the paper.

and a substituted benzoic acid. The ambiguity inherent in the development of "secondary" and "tertiary" σ values may be avoided by using for the establishment of ρ values only σ values obtained from the thermodynamic dissociation constants of benzoic acids in water at 25°. This does not rule out the evaluation and consideration of "secondary" σ values, but it would eliminate their use in determining ρ or in evaluating further σ values.

Jaffé's proposed redefinition of the σ constant would be useful in applying the Hammett equation primarily as an empirical tool for the correlation of rate and equilibrium data. However, recently, there has been evidenced considerable interest in examining the inductive and resonance components of the Hammett substituent constants in an effort to attain a better theoretical understanding of the influence of structure on chemical behavior.[65,86] For such theoretical studies, it appears more desirable that unambiguous values of the σ constants be available, together with a realistic estimate of the probable precision with which the individual constants are established by the experimental measurements. The availability of such data should facilitate both an understanding of the factors controlling the observed effects of the substituents and of the theoretical basis for deviations from the Hammett equation which lie outside the precision of the experimental measurements.

In a recent publication we had surveyed the literature on the effects of structure on the dissociation of acids and bases.[20] Consequently, with this preliminary survey available, it appeared desirable to gather together all of the available data to provide the basis for a critical appraisal of unambiguous values for the σ constants.

THE σ VALUES

The pK_a values of benzoic acid as determined by various investigators are given in Table I.

TABLE I

pK_a VALUES OF BENZOIC ACID AT 25°

Classical and Apparent	Conductance (Thermodynamic)	Potentiometric (Thermodynamic)
4.222[8,66]	4.200[19]	4.213[16]
4.164[92]	4.203[34]	4.228[18]
4.165[79]	4.203[35]	4.202[51]
4.183[83]	4.185[46]	4.175[55]
4.177[a,63]	4.215[76]	4.175[57]
4.174[10]	4.201[78]	4.202[35]
4.16, 4.15[90]	4.196[49,91]	4.188[35]
3.995[b,94]	4.205[53]	4.202[35]
Average	4.201 ± 0.005	4.198 ± 0.012

[a] $\mu = 0.03$. [b] $\mu = 0.1$ at 20°.

The constants listed under the heading of classical or apparent pK_a values are those determined from the Ostwald dilution law,[67] or from the midpoint of a pH titration[39] or by other methods which do not adequately take into account the activity, rather than concentration, of the species present. As has been noted by Dippy,[26] these pK values tend to be lower than the thermodynamic values, approaching the latter at high dilution. Since there is often a variation in the dilution at which the different substituted benzoic acids have been measured, the σ values calculated from the classical constants will reflect this variation. Of perhaps even greater importance is the failure of many early workers to establish the purity of their compounds.[26]

Inspection of the thermodynamic pK_a values in Table I indicates that the precision of the conductance method is slightly greater than the various potentiometric methods.* Furthermore, it is usually recognized as desirable to have a single set of values from one laboratory since procedural or systematic errors may to some extent cancel when σ values are obtained by Equation 5. The dissociation constants obtained by Dippy and co-workers are the most extensive set available and these values were obtained by conductance methods.[26-34] Accordingly, it appears reasonable to continue to use values obtained by Dippy and co-workers where such values are available. Thermodynamic dissociation constants obtained by other workers may be used as a check on the reliability of the data.

In Table II are listed the original σ values, based upon the dissociation constants of Dippy and co-workers, as well as a comparison with other values based upon both thermodynamic and classical dissociation constants. Agreement with other thermodynamic values at 25° is seen to be approximately ±0.01 unit, while the average deviation of the remaining data is ± 0.04.

Table III gives additional σ values, based upon data of Dippy *et al.* Also given in this Table are σ values from other data on ionization of benzoic acids in water and values of σ from Hammett and from Jaffé. These values of Hammett were not based on benzoic acid ionization, while the values of Jaffé represent assignments from all reactions of that particular substituent known to him at the time.

Major discrepancies are apparent between Jaffé's values and those based on Dippy's measurements for p-C_6H_5O and m-OH. The value due to Dippy *et al.* of σ for p-OH appears to be slightly low (by comparison with other thermodynamic data at 25°) and a value of −0.37 might reasonably be assigned to this group. For the p-CN group good agreement is found among the thermodynamic data and a σ value of 0.660 may be safely assigned to this group. With the m-CN group there is a surprising disagreement in thermodynamic values; an average value of 0.56 will be adopted.

The σ-constants in Tables II and III which were derived from the thermodynamic dissociation constants of the benzoic acids may be considered to be accurate to within ~0.02 units. Only these values, of those reported in this survey, should be used to establish ρ values.

SECONDARY SIGMA VALUES

Within recent years a large amount of data has become available on the ionization of substituted benzoic acids in 50% (by volume) ethanol measured with the glass electrode.† Using the σ values from Tables II and III, the data of Roberts and his co-workers (H, 5.80;[74] p-CH_3, 6.00;[74] p-CH_3O, 6.12;[74] p-Br, 5.35;[72] m-Br, 5.22;[72] m-OH, 5.61;[73] m-NO_2, 4.66;[72] p-NO_2, 4.53;[72] p-CN, 4.70[71]) and the data of Bordwell and Cooper (m-CH_3CO, 5.21;[14] p-CH_3CO, 5.10[14]), a value of ρ of 1.522 was calculated for the ionization of benzoic acid in 50% aqueous ethanol, with log K° = 5.761. (The calculations were made assuming σ to be more pre-

* It is of interest to note that some of the variation in the values obtained by the conductance method lies in the value assigned to the limiting mobility of the hydrogen ion.[91]

† The pK values obtained with a quinhydrone or hydrogen electrode in 50% alcohol appear to be significantly lower than those obtained with the glass electrode.[17]

TABLE II

σ VALUES ORIGINALLY DERIVED FROM THE DISSOCIATION CONSTANTS OF BENZOIC ACIDS

Group	Substituent Constants, σ			
	Hammett's values[43]	Derived from thermodynamic data at 25°	Derived from thermodynamic data, not at 25°	Derived from classical and apparent data
p-CH_3O	−0.268[34]		−0.22,[22] −0.29[52]	−0.28,[94] −0.27,[66] −0.25[90] −0.31,[79] −0.26[68]
p-*t*-C_4H_9	−0.197[27]			−0.194[83]
p-CH_3	−0.170[31]			−0.18,[79] −0.20,[92] −0.07[66] −0.19,[10] −0.20[90]
p-*i*-C_3H_7	−0.151[27]			−0.11[10]
p-C_2H_5	−0.151[27]			
m-CH_3	−0.069[31]			−0.08,[79] −0.09[92] −0.07,[66] −0.08,[90] −0.20[90]
p-F	0.062[33]		0.16[58]	
m-CH_3O	0.115[31]		0.12[52]	0.14,[68] 0.15 to 0.24[90]
p-Cl	0.227[33]	0.227,[16] 0.203[78]		0.06,[84] 0.20,[94] 0.16[90]
p-Br	0.232[33]	0.211[16]		0.23[90]
m-F	0.337[31]		0.35[58]	
m-I	0.352[31]			0.31,[79] 0.37[90]
m-Cl	0.373[33]	0.386,[16] 0.379[78]		0.36,[84] 0.46[90]
m-Br	0.391[31]	0.395[16]		0.25,[84] 0.38[90]
m-NO_2	0.710[31]			0.72,[79,10] 0.76,[66,90] 0.80[90]
p-NO_2	0.778[31]	0.771[16]		0.82,[66] 0.76,[90] 0.73[94] 0.78,[10] 0.80[64]

TABLE III

NEW σ VALUES BASED ON THE IONIZATION OF BENZOIC ACIDS

Group	Substituent Constants, σ					
	Hammett's values[a,4]	Jaffé's values[a,47]	Values based on Dippy's data	Derived from other thermodynamic data at 25°	Derived from thermodynamic data not at 25°	Derived from classical and apparent data
p-C_6H_5O		−0.028	−0.320[32]			
p-OH		−0.357	−0.327[29]	−0.369[16]	−0.28[58]	−0.32[66,90]
				−0.37[77]	−0.32[22]	−0.37[95]
					−0.39[52]	−0.38[92]
					−0.41[62]	
					0.09[1]	
3,4($CH)_4$[b]	0.170		0.042[30]			0.053[8]
						0.051[59]
						0.024[25]
m-OH		−0.002	0.121[29]		0.04[52]	0.07,[92] 0.00[84]
					0.14[58]	0.03,[95] 0.16[66]
					0.30[1]	
						0.05 to 0.22[90]
m-C_6H_5O			0.252[32]			
m-CH_3CO	0.306		0.376[28]			
p-CH_3CO		0.516	0.502[28]			
m-CN	0.678			0.615[16]		0.52[66]
				0.520[54]		0.60[93]
p-CN		0.628		0.662[16]		
				0.651[54]		
				0.666[55,89]		0.66[93]

[a] Not derived from benzoic acid ionization data. [b] β-Naphthyl.

cisely known than p*K*′. The correlation coefficient is 0.995.) Using these values in Equation 1, the σ values given in Table IV have been calculated. The σ values of Hammett and of Jaffé have been listed for comparative purposes, many of the σ values of the latter have been based in part on the ionization data in 50% alcohol.

The variation of p*K*′ values of benzoic acid itself in 50% alcohol obtained with the use of the glass electrode, *i.e.*, 5.70 (at 20°)[36] 5.73,[14] 5.75,[72] 5.80,[74] is probably typical of the precision of these data. Direct comparison of the σ values derived from the p*K*′ in 50% alcohol with those obtained in water using the glass electrode may be made in the cases of the groups $(CH_3)_3Si$, PO_3H^-, and CH_3SO_2. Such comparison indicates that the σ values in Table IV are probably reliable to approximately ±0.1 unit. Solvation effects may be the source of some difference in σ in water and 50% alcohol.

Ionization data for substituted benzoic acids in other concentrations of aqueous alcohol may be used to obtain σ values for other groups. Thus Chatt and Williams[23] have shown that in the *para* position the groups $(CH_3)_3Si$, $(C_2H_5)_3Si$, $(CH_3)_3Ge$, $(C_2H_5)_3Ge$, $(CH_3)_3Sn$, and $(C_2H_5)_3Sn$ have p*K*′ values within ±0.03 of that of benzoic acid itself

TABLE IV

σ-VALUES CALCULATED FROM THE APPARENT DISSOCIATION CONSTANTS AT 25° OF BENZOIC ACID IN 50% (BY VOLUME) ETHANOL

Group	Substituent Constants, σ			
	Hammett's values[43]	Jaffé's values[47]	Derived from pK′ values in 50% alcohol	Derived from classical and apparent pK_a values in water
p-$(CH_3)_3SiCH_2$			−0.210[a,36]	
m-$(CH_3)_3SiCH_2$			−0.157[a,36]	
m-$(CH_3)_3Si$		−0.121	−0.157[74]	−0.04[5]
p-$(CH_3)_3Si$		−0.072	−0.026[74]	−0.07[5]
p-CH_3S	−0.047		0.014,[14] −0.026[b,4]	
p-C_2H_5S			0.034[b,4]	
p-CH_3CONH		−0.015	0.053[12]	−0.06[66]
p-i-C_3H_7S			0.067[b,4]	
m-CH_3S		0.144	0.152[14]	
p-PO_3H^-		0.238	0.263[48]	0.25[48]
m-CH_3CONH			0.270[12]	0.15[66]
m-PO_3H^-			0.309[48]	0.17[48]
p-CH_3CO_2			0.309[12]	−0.16[66]
m-$C_2H_5O_2C$		0.398	0.369[73]	
m-CH_3COS			0.388[12]	
m-CH_3CO_2		0.315	0.395[12]	0.22,[66] 0.31[84]
m-CF_3		0.415	0.428[75]	0.41[85]
p-CH_3COS			0.441[12]	
p-$C_2H_5O_2C$		0.522	0.451[73]	
p-CH_3SO		0.567	0.493[13]	
m-CH_3SO		0.551	0.520[13]	
p-SCN		0.699	0.520[12]	
p-CF_3		0.551	0.540[75]	
m-CN	0.678		0.598[71]	See Table III
m-CH_3SO_2		0.647	0.645,[14] 0.658[56]	0.56[66]
p-CH_3SO_2		0.728	0.710,[14] 0.756[56]	0.68[56]
p-$(CH_3)_3N^+$		0.859	0.881[70]	0.77[50]
m-$(CH_3)_3N^+$		0.904	1.012[70]	0.75[24]

[a] 18°. [b] 32°.

TABLE V

σ VALUES ESTIMATED FROM DISSOCIATION OF BENZOIC ACID IN AQUEOUS ALCOHOL AT VARIOUS CONCENTRATIONS

Group	Substituent Constants, σ			Concentration of Ethanol
	Hammett's values[43]	Jaffé's values[47]	Estimated values	
m-NH_2	−0.161		−0.07 to −0.20	55:45 Ethanol-water and 50(vol)% ethanol
m-C_2H_5		−0.043	−0.07	55:45 ethanol-water
p-$(C_2H_5)_3Si$			0.0	60.1 wt. % ethanol
p-$(CH_3)_3Ge$			0.0	60.1 wt. % ethanol
p-$(C_2H_5)_3Ge$			0.0	60.1 wt. % ethanol
p-$(CH_3)_3Sn$			0.0	60.1 wt. % ethanol
p-$(C_2H_5)_3Sn$			0.0	60.1 wt. % ethanol
p-CH_3Se			0.0	30 (vol.) % ethanol
m-CH_3Se			0.10	30 (vol.) % ethanol
p-SH			0.15	48.9% ethanol
m-SH			0.25	48.9% ethanol
p-C_6H_5	+0.009		−0.01	50% butylcellosolve[a]
m-C_6H_5	+0.218		0.06	50% butylcellosolve[a]

[a] Ionic strength 0.05 in lithium chloride.

in 60.1 weight % ethanol. Accordingly all of these groups may be assigned a σ value of 0.0 ± 0.1. Likewise, the data of Baker, Barrett, and Tweed[3] show that in 30% by volume aqueous alcohol the pK′ of CH_3S and CH_3Se substituted benzoic acids lie within 0.01 unit of each other. Accordingly, the σ value assigned to m-CH_3Se should be the same as that assigned to m-CH_3S and likewise the σ of p-CH_3Se should be the same as p-CH_3S. The data of Baker *et al.* further indicate that the σ value for m-CH_3O should be greater than m-CH_3S (by ∼0.02 units), *i.e.*, the σ value for m-CH_3S in Table IV is probably high by ∼0.05 units.

From the pK′ values of Schwarzenbach and Rudin[80] for the isomeric hydroxy and mercapto benzoic acids in 48.9% alcohol the σ value of the p-SH group should be about 0.03 unit greater than that of m-OH. From this σ for p-SH may be set at ∼0.15 ± 0.1. The σ value for m-SH

TABLE VI

σ VALUES FROM CLASSICAL AND APPARENT IONIZATION CONSTANTS OF BENZOIC ACIDS IN WATER

Group	Substituent Constants, σ		
	Hammett's values[43]	Jaffé's values[47]	Derived from classical ionization constants
p-$(CH_3)_2N$	−0.205	−0.600	−0.83[50]
p-CH_3NH		−0.592	−0.84[50]
p-NH_2	−0.660		−0.66 to −0.70,[90] −0.70,[81] −0.62,[2] −0.73[45] −0.72,[50] −0.6,[44] −0.66,[61] −0.98[92]
p-C_2H_5O	−0.25		−0.07,[68] −0.57,[52] −0.24[22]
p-n-C_3H_7O		−0.268	−0.55,[52] −0.25[22]
p-n-C_4H_9O		−0.320	−0.32[22]
p-i-C_3H_7O		−0.286	−0.45[52]
p-n-$C_5H_{11}O$		−0.340	−0.34[22]
m-t-C_4H_9		−0.120	−0.10[83]
m-CO_2^-		0.104	−0.05 to −0.14,[90] +0.021,[63] −0.10,[9] −0.10[88] 0.075[87]
p-CO_2^-		0.132	0.16 to −0.05,[90] −0.05,[95] +0.04[88]
p-AsO_3H^-		−0.09	−0.02[69]
m-SO_3^-			0.05[96]
p-SO_3^-		0.381	0.09[98]
p-I	0.276		0.18[90]
m-C_2H_5O	0.150		0.186,[68] 0.05[52]
m-n-C_3H_7O			0.03[52]
m-i-C_3H_7O			0.08[52]
m-n-C_4H_9O			−0.02[52]
m-CO_2H	0.355		0.38,[66] 0.46,[99] 0.28,[88] 0.18,[87] 0.42[63]
p-CO_2H	0.728		0.66,[90] 0.51,[58] 0.36[88]
m-NH_2SO_2			0.46[97]
p-NH_2SO_2		0.621	0.62,[82] 0.53[97]
m-IO_2		0.70	0.70[15]
p-IO_2		0.76	0.76[15]
p-$(CH_3)_2S^+$			0.90[11]
m-$(CH_3)_2S^-$			1.00[11]

should be about 0.1 higher, giving a σ value for this group of $\sim$0.25 ± 0.1.

Beringer and Sands[6] report the same pK′ value for m-C_2H_5 and m-CH_3 benzoic acid in 55:45 ethanol-water, hence the σ value for m-C_2H_5 may be set at −0.07. Beringer and Sands also report a pK′ for m-aminobenzoic acid of about the same magnitude as m-methylbenzoic acid, while in 50 volume % alcohol Bright and Briscoe[17] report a pK′ for m-aminobenzoic acid which is slightly more than that of p-methylbenzoic acid.* From these data the σ value of m-NH_2 should lie in the range −0.07 to −0.20. Hammett's value of −0.161 (derived from ester hydrolysis at 30° in 87.83% alcohol) is within this range.[43]

Finally, from the pK′ values at 25° of benzoic acid (5.65), m-phenyl- (5.57) and p-phenylbenzoic acids (5.66) in 50% aqueous butylcellosolve, ionic strength 0.05 in lithium chloride (ρ = 1.32), the σ values of m-C_6H_5 and p-C_6H_5 can be estimated as +0.06 and −0.01 respectively. These estimates are summarized in Table V.

VALUES FROM CLASSICAL IONIZATION CONSTANTS

The σ values presented in Table VI are based on classical and apparent pK values of the benzoic acids in water, or on thermodynamic values at temperatures other than 25°. The reliability of the data varies widely.

There are two sets of thermodynamic pK$_a$ values of the p-n-alkoxybenzoic acids at 20° available. Those of Cavil, Gibson, and Nyholm[22] have been used by Jaffé to establish the σ values of the n-C_4H_9O and n-$C_5H_{11}O$ groups. The precision of the pK data was given as ±0.1. The data of Jones and Speakman[52] give σ values which differ considerably from those of Cavil *et al.* and which give σ values for the higher p-n-alkoxy groups which differ considerably from that of p-CH_3O. Accordingly, it is believed that the data of Cavil *et al.* are to be preferred. For the *meta* alkoxy groups Jones and Speakman indicate greater precision, but again the rather wide variation of values from that for m-CH_3O indicates that the σ values for these derivatives are probably questionable. An approximate σ value of 0.1 is assigned to these groups.

Thermodynamic pK$_a$ data for p-aminobenzoic acid give a value of −0.66 for the p-NH_2 group in excellent agreement with the value assigned to this group by Hammett. This may be somewhat fortuitous, since Willi and Meier estimate that 9.5% zwitterion exists in this system.[94] For the p-$NHCH_3$ and p-$N(CH_3)_2$ groups the classical data of Johnson[50] has been used to obtain σ values. Comparison of the value assigned to p-NH_2 from Johnson's calculations on Winkelbleck's data makes it appear that these values are probably larger than they should be by 0.05 to 0.10 units.

The excellent agreement of the σ-value for p-t-C_4H_9 (see Table II) from the conductance data of Shoesmith and Mackie[83] with that of Dippy *et al.* makes it seem reasonable to place limits of ±0.03 on the σ value of m-t-C_4H_9 in Table VI.

Comparison of the numerous values in Tables II and III from the data of Vandenbelt *et al.* with those of Dippy *et al.* indicates a probable limit of ±0.1 in the accuracy of the σ value for p-I.

* The pK value of m-aminobenzoic acid in water is not used here in assigning a σ value since in water the "neutral" species exists to a large extent as the zwitterion. According to Ebert[37] the ratio of zwitterion to uncharged species is given by $K_I/K_E - 1$ where K_I is the first acid dissociation constant of the amino acid and K_E is the ionization constant of an alkyl ester of the amino acid. From the data of Cumming[24] the ratio of zwitterion to uncharged species in water is thus approximately 2.2. In alcoholic solution the pK of the amino group decreases while that of the carboxyl group increases, greatly reducing the ratio of zwitterion to uncharged species.

TABLE VII

SUMMARY OF HAMMETT SUBSTITUENT CONSTANTS, σ, BASED ON IONIZATION OF SUBSTITUTED BENZOIC ACIDS[a]

Group	Meta			Para		
	σ	Estimated limits of uncertainty	Table	σ	Estimated limits of uncertainty	Table
—CH_3	**−0.069**	0.02	II	**−0.170**	0.02	II
—CH_2CH_3	−0.07	0.1	V	**−0.151**	0.02	II
—$CH(CH_3)_2$				**−0.151**	0.02	II
—$C(CH_3)_3$	−0.10	0.03	VI	**−0.197**	0.02	II
—C_6H_5	0.06	0.05	V	−0.01	0.05	V
—3,4(CH)$_4$				**0.042**	0.02	III
—CF_3	0.43	0.1	IV	0.54	0.1	IV
—CN	**0.56**	0.05	III	**0.660**	0.02	III
—$COCH_3$	**0.376**	0.02	III	**0.502**	0.02	III
—$CO_2C_2H_5$	0.37	0.1	IV	0.45	0.1	IV
—CO_2H	(0.37)	0.1	VI	(0.45)	0.1	VI
—CO_2^-	−0.1	0.1	VI	0.0	0.1	VI
—$CH_2Si(CH_3)_3$	−0.16	>0.1	IV	−0.21	>0.1	IV
—$Si(CH_3)_3$	−0.04	0.1	IV	−0.07	0.1	IV
—$Si(C_2H_5)_3$				0.0	0.1	V
—$Ge(CH_3)_3$				0.0	0.1	V
—$Ge(C_2H_5)_3$				0.0	0.1	V
—$Sn(CH_3)_3$				0.0	0.1	V
—$Sn(C_2H_5)_3$				0.0	0.1	V
—NH_2	−0.16	0.1	V	−0.66	0.1	VI
—$NHCH_3$				−0.84	0.1	VI
—$N(CH_3)_2$				−0.83	0.1	VI
—$NHCOCH_3$	0.21	0.1	IV	0.00	0.1	IV
—$N(CH_3)_3^+$	0.88	>0.2	IV	0.82	>0.2	IV
—NO_2	**0.710**	0.02	II	**0.778**	0.02	II
—PO_3H^-	0.2	>0.1	IV	0.26	>0.1	IV
—AsO_3H^-				−0.02	>0.1	VI
—OCH_3	**0.115**	0.02	II	**−0.268**	0.02	II
—OC_2H_5	0.1	0.1	VI	−0.24	0.1	VI
—$O(CH_2)_2CH_3$	0.1	0.1	VI	−0.25	0.1	VI
—$OCH(CH_3)_2$	0.1	0.1	VI	−0.45	0.1	VI
—$O(CH_2)_3CH_3$	0.1	0.1	VI	−0.32	0.1	VI
—$O(CH_2)_4CH_3$	0.1	0.1	VI	−0.34	0.1	VI
—OC_6H_5	**0.252**	0.02	III	**−0.320**	0.02	III
—OH	**0.121**	0.02	III	**−0.37**	0.04	III
—$OCOCH_3$	0.39	0.1	IV	0.31	0.1	IV
—SCH_3	0.15	0.1	IV	0.00	0.1	IV
—SC_2H_5				0.03	0.1	IV
—$SCH(CH_3)_2$				0.07	0.1	IV
—SH	0.25	0.1	V	0.15	0.1	V
—$SCOCH_3$	0.39	0.1	IV	0.44	0.1	IV
—SCN				0.52	0.1	IV
—$SOCH_3$	0.52	0.1	IV	0.49	0.1	IV
—SO_2CH_3	0.60	0.1	IV	0.72	0.1	IV
—SO_2NH_2	0.46	0.1	VI	0.57	0.1	VI
—$S(CH_3)_2^+$	1.00	>0.1	VI	0.90	>0.1	VI
—SO_3^-	0.05	>0.1	VI	0.09	>0.1	VI
—$SeCH_3$	0.1	0.1	V	0.0	0.1	V
—F	**0.337**	0.02	II	**0.062**	0.02	II
—Cl	**0.373**	0.02	II	**0.227**	0.02	II
—Br	**0.391**	0.02	II	**0.232**	0.02	II
—I	**0.352**	0.02	II	0.18	0.1	VI
—IO_2	0.70	0.1	VI	0.76	0.1	VI

[a] Values in bold faced type are σ constants based on thermodynamic constants in water at 25°. It is recommended that the reaction constants, ρ, be based on these σ constants.

The σ values for the *m*- and *p*-IO_2 groups are from the data of Bothner-By and Medalia[15] obtained at 50°. The original authors indicate a ρ for dissociation at this temperature of 1.09 and report σ values of 0.63 and 0.69 respectively for the meta and para substituents. The original authors' values are probably better assignments of σ, but the ρ is probably due more to systematic errors rather than a real change (*cf.* Briegleb's data[16] and the variation of ρ with T assigned by Jaffé[47]). From the precision of Bothner-By and Medalia, limits of ±0.06 may be assigned to their values of σ or of ~ ± 0.12 to the values in Table VI.

In similar fashion, the σ values for *m*- and *p*-NH_2SO_2 given in Table VI are 0.09 units lower than those reported by Zollinger and Wittwer.[97] Since the measurements were made in a medium of ionic strength of 0.1, and the ρ value apparently differs from unity, the values assigned by the original authors may be more accurate than those given in Table VI.

There is considerable variation in the σ values assigned to the *m*- and *p*-CO_2H groups on the basis of p*K* data (corrected for a statistical factor of 2 in K_a). Accordingly it seems reasonable to assign values to these groups by resorting to the practice of assuming the electrical effects of the carboxyl group are approximately equal to those of carbalkoxy groups. Hammett's value for *m*-CO_2H thus receives support from Table IV (σ for *m*-$C_2H_3O_2C$ is 0.37); however, his value for *p*-CO_2H may be questioned (σ for *p*-$C_2H_5O_2C$, 0.45).

Again, for the *m*- and *p*-CO_2^- groups there is considerable variation, however the average σ for *m*-CO_2^- is -0.1 while that of *p*-CO_2^- group is 0.0. The σ value of these groups, as well as those of the remaining groups which bear a charge, are subject to large activity corrections and accordingly limits of somewhat larger than 0.1 appear reasonable.

SUMMARY

Hammett σ values have been compiled from the literature data of the ionization of benzoic acids. Hammett's original values given in Table II and further values from the data of Dippy *et al.* in Table III (with the exception of *p*-OH) are probably reliable within approximately 0.02 unit. The values in Table IV are based on ionization of benzoic acids in 50% ethanol and approximate limits of ± 0.1 have been set here. Table V contains estimates of σ from ionization data in various concentrations of ethanol and the limits may be set somewhat in excess of 0.1. Table VI contains σ values from classical ionization data with widely varying limits of error to the values assigned to σ.

For convenience in utilization, the individual σ values have been summarized in Table VII, together with an estimate of the probable uncertainty. Reference is given to the particular table which lists both the individual measurements and the literature references. The σ values based on thermodynamic data are shown in bold faced type. According to the recommendation advanced here, only these values should be used for the calculation of ρ. All other σ constants are derived values.

It is apparent from this survey that additional precise thermodynamic dissociation constants for the ionization of substituted benzoic acids are greatly to be desired.

(1) C. T. Abichandani and S. K. K. Jatkar, *J. Indian Inst. Sci.*, **21A**, 417 (1938).
(2) A. Albert and R. Goldacre, *Nature*, **149**, 245 (1942).
(3) J. W. Baker, G. F. C. Barrett, and W. T. Tweed, *J. Chem. Soc.*, 2831 (1952).
(4) V. Baliah, Sp. Shanmuganathan, and R. Varadachari, *J. Phys. Chem.*, **61**, 1013 (1957).
(5) R. A. Benkeser and H. R. Krysiak, *J. Am. Chem. Soc.*, **75**, 2421 (1953).
(6) F. M. Beringer and S. Sands, *J. Am. Chem. Soc.*, **75**, 3319 (1953).
(7) E. Berliner and E. A. Blommers, *J. Am. Chem. Soc.*, **73**, 2479 (1951).
(8) H. G. Bethmann, *Z. physik. Chem* , **5**, 399 (1890).
(9) N. Bjerrum, *Z. physik, Chem.*, **106**, 219 (1923).
(10) S. Bodforss, *Z. physik. Chem.*, **102**, 40 (1922).
(11) F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **78**, 87 (1956).
(12) F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **78**, 854 (1956).
(13) F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **79**, 717 (1957).
(14) F. G. Bordwell and G. D. Cooper, *J. Am. Chem. Soc.*, **74**, 1058 (1952).
(15) A. A. Bothner-By and A. I. Medalia, *J. Am. Chem. Soc.*, **74**, 1402 (1952).
(16) G. Briegleb and A. Bieber, *Z. Elektrochem.*, **55**, 250 (1951).
(17) W. L. Bright and H. T. Briscoe, *J. Phys. Chem.*, **37**, 787 (1933).
(18) H. T. Briscoe and J. S. Peake, *J. Phys. Chem.*, **42**, 637 (1938).
(19) F. G. Brockman and M. Kilpatrick, *J. Am. Chem. Soc.*, **56**, 1483 (1934).
(20) H. C. Brown, D. H. McDaniel, and O. Hafliger, in E. A. Braude and F. C. Nachod, ed., *Determination of Organic Structures by Physical Methods*, Academic Press, Inc., New York, 1955, Chap. 14.
(21) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **79**, 1913 (1957).
(22) G. W. K. Cavill, N. A. Gibson, and R. S. Nyholm, *J. Chem. Soc.*, 2466 (1949).
(23) J. Chatt and A. A. Williams, *J. Chem. Soc.*, 4403 (1954).
(24) A. C. Cummings, *Proc. Roy. Soc.* (*London*), **A78**, 103 (1906).
(25) C. G. Derick and O. Kamm, *J. Am. Chem. Soc.*, **39**, 395 (1917).
(26) J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939).
(27) J. W. Baker, J. F. J. Dippy, and J. E. Page, *J. Chem. Soc.*, 1774 (1937).
(28) L. G. Bray, J. F. J. Dippy, and S. R. C. Hughes, *J. Chem. Soc.*, 265 (1957).
(29) L. G. Bray, J. F. J. Dippy, S. R. C. Hughes, and L. W. Laxton, *J. Chem. Soc.*, 2405 (1957).
(30) J. F. J. Dippy, S. R. C. Hughes, and J. W. Laxton, *J. Chem. Soc.*, 1470 (1954).
(31) J. F. J. Dippy and R. H. Lewis, *J. Chem. Soc.*, 644 (1936).
(32) J. F. J. Dippy and R. H. Lewis, *J. Chem. Soc.*, 1426 (1937).
(33) J. F. J. Dippy, F. R. Williams, and R. H. Lewis, *J. Chem. Soc.*, 343 (1935).
(34) J. F. J. Dippy and F. R. Williams, *J. Chem. Soc.*, 1888 (1934).
(35) H. S. Dunsmore and J. C. Speakman, *Trans. Faraday Soc.*, **50**, 236 (1954). The value quoted here is based on molarity rather than molality as given by the original authors.
(36) C. Eaborn and S. H. Parker, *J. Chem. Soc.*, 939 (1954).
(37) L. Ebert, *Z. physik. Chem.*, **121**, 385 (1926).
(38) D. H. Everett and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **35**, 1380 (1939).
(39) S. Glasstone, *Textbook of Physical Chemistry*, 2nd ed., D. Van Nostrand Company, New York, 1946, p. 1003.
(40) L. P. Hammett, *Chem. Revs.*, **17**, 125 (1935).
(41) L. P. Hammett, *J. Am. Chem. Soc.*, **59**, 96 (1937).
(42) L. P. Hammett, *Trans. Faraday Soc.*, **34**, 156 (1938).
(43) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, 1940, Chap. VII.
(44) L. J. Harris, *Biochem. J.*, **24**, 1080 (1930).
(45) B. Holmberg, *Z. physik. Chem.*, **62**, 726 (1908).
(46) D. J. G. Ives, *J. Chem. Soc.*, 731 (1933).
(47) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).
(48) H. H. Jaffé, L. D. Freedman, and G. O. Doak, *J. Am. Chem. Soc.*, **75**, 2209 (1953).
(49) G. H. Jeffery and A. I. Vogel, *Phil. Mag.*, **18**, 901 (1934).
(50) J. Johnson, *Proc. Roy. Soc.* (*London*), **A78**, 103 (1906).
(51) A. V. Jones and H. N. Parton, *Trans. Faraday Soc.*, **48**, 8 (1952).
(52) B. Jones and J. C. Speakman, *J. Chem. Soc.*, 19 (1944).

(53) S. S. Joshi and D. N. Solanki, *J. Indian Chem. Soc.*, 14, 323 (1937).
(54) M. Kilpatrick and R. D. Eanes, *J. Am. Chem. Soc.*, 65, 589 (1943).
(55) H. D. Kirschman, B. Wingfield and H. J. Lucas, *J. Am. Chem. Soc.*, 52, 23 (1930).
(56) H. Kloosterziel and H. J. Backer, *Rec. trav. chim.*, 71, 295 (1952).
(57) I. M. Kolthoff and W. Bosch, *J. Phys. Chem.*, 36, 1695 (1932).
(58) R. Kuhn and A. Wassermann, *Helv. Chim. Acta*, 11, 31 (1928).
(59) K. Lauer, *Ber.*, 70B, 1288 (1937).
(60) N. N. Lichtin and H. P. Leftin, *J. Am. Chem. Soc.*, 74, 4207 (1952).
(61) A. M. Liquori and A. Ripamonti, *Gazz. chim. ital.*, 85, 578 (1955).
(62) B. N. Mattoo, *Trans. Faraday Soc.*, 52, 1462 (1956).
(63) W. R. Maxwell and J. R. Partington, *Trans. Faraday Soc.*, 33, 670 (1937).
(64) S. M. Neale, *Trans. Faraday Soc.*, 17, 505 (1922).
(65) Y. Okamoto, and H. C. Brown, *J. Org. Chem.*, 22, 485 (1957).
(66) W. Ostwald, *Z. physik. Chem.*, 3, 419 (1889).
(67) W. Ostwald, *Z. physik. Chem.*, 2, 901 (1888).
(68) W. Pip, doctoral dissertation, quoted in reference 82.
(69) D. Pressman and D. H. Brown, *J. Am. Chem. Soc.*, 65, 540 (1943).
(70) J. D. Roberts, R. A. Clement, and J. J. Drysdale, *J. Am. Chem. Soc.*, 73, 2181 (1951).
(71) J. D. Roberts and E. A. McElhill, *J. Am. Chem. Soc.*, 72, 628 (1950).
(72) J. D. Roberts, E. A. McElhill, and R. Armstrong, *J. Am. Chem. Soc.*, 71, 2923 (1949).
(73) J. D. Roberts and W. T. Moreland, Jr., *J. Am. Chem. Soc.*, 75, 2267 (1953).
(74) J. D. Roberts and C. M. Reagan, *J. Am. Chem. Soc.*, 75, 4102 (1953).
(75) J. D. Roberts, R. L. Webb, and E. A. McElhill, *J. Am. Chem. Soc.*, 72, 408 (1950).
(76) C. K. Rule and V. K. LaMer, *J. Am. Chem. Soc.*, 60, 1974 (1938).
(77) E. E. Sager, M. R. Schooley, A. S. Carr, and S. F. Acree, *J. Research Natl. Bur. Standards*, 35, 521 (1945).
(78) B. Saxton and H. F. Meier, *J. Am. Chem. Soc.*, 56, 1918 (1934).
(79) Schaller, quoted in reference 38.
(80) G. Schwarzenbach and E. Rudin, *Helv. Chim. Acta*, 22, 360 (1939).
(81) G. Schwarzenbach, A. Willi, and R. O. Buch, *Helv. Chim. Acta*, 30, 1303 (1947).
(82) H. Scudder, *The Electrical Conductivity and Ionization Constants of Organic Compounds*, D. Van Nostrand Co., New York, 1914.
(83) J. B. Shoesmith and A. Mackie, *J. Chem. Soc.*, 300 (1936).
(84) L. D. Smith and H. C. Jones, *Am. Chem. J.*, 50, 39 (1913).
(85) F. Swarts, *Bull. acad. roy. Belg.*, 35, 395 (1898).
(86) R. W. Taft, Jr., in M. S. Newman, ed., *Steric Effects in Organic Chemistry*, John Wiley and Sons, New York, 1956, Chap. 13.
(87) B. J. Thamer, *J. Phys. Chem.*, 59, 450 (1955).
(88) B. J. Thamer and A. F. Voigt, *J. Phys. Chem.*, 56, 225 (1952).
(89) E. P. Valby, and H. J. Lucas, *J. Am. Chem. Soc.*, 51, 2718 (1929).
(90) J. M. Vandenbelt, C. Henrich, and S. G. Vandenberg, *Anal. Chem.*, 26, 726 (1954).
(91) A. I. Vogel and G. H. Jeffery, *Chem. & Ind. (London)*, 53, 779 (1934).
(92) G. F. White and H. C. Jones, *Am. Chem. J.*, 44, 197 (1910).
(93) S. Widequist, *Arkiv. Kemi*, 2, 383 (1950).
(94) A. V. Willi and W. Meier, *Helv. Chim. Acta*, 39, 318 (1956).
(95) A. V. Willi and J. F. Stocker, *Helv. Chim. Acta*, 38, 1279 (1955).
(96) H. Zollinger, W. Büchler, and C. Wittwer, *Helv. Chim. Acta*, 36, 1711 (1953).
(97) H. Zollinger and C. Wittwer, *Helv. Chim. Acta*, 39, 347 (1956).

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Kinetics of the Reaction between a Vinyl Fluoride and Sodium Ethoxide

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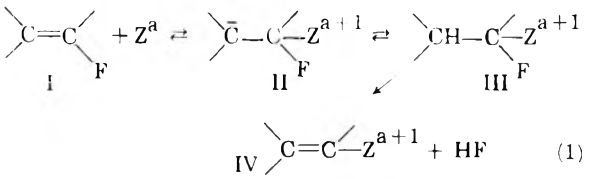
The synthesis of 1,1-diphenyl-2-fluoroethylene is reported. This vinyl fluoride is converted to 1,1-diphenyl-2-ethoxyethylene by sodium ethoxide in ethanol. At 99.75° the kinetics are second-order, first-order with respect to each reactant, and the rate is 270 times faster than that of 1,1-diphenyl-2-chloroethylene. The results are consistent with an addition-elimination mechanism.

The unexpectedly high reactivity of fluorine attached to unsaturated carbon atoms toward nucleophilic substitution has been observed by a number of workers.[1-6] For example, piperidine reacts with 2,4-dinitrofluorobenzene more rapidly than with the other 2,4-dinitrohalobenzenes.[1] Also, the vinylic fluorine atoms of perfluorocyclobutene can be replaced by ethoxide more readily than the allylic ones.[2] These observations probably rule out an S_N2 displacement mechanism that

(1) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Am. Chem. Soc.*, 79, 385 (1957).
(2) J. D. Park, M. L. Sharrah, and J. R. Lacher, *J. Am. Chem. Soc.*, 71, 2337 (1949).
(3) K. E. Rapp, R. L. Pruett, J. T. Barr, C. T. Bahner, J. D. Gibson, and R. H. Lafferty, Jr., *J. Am. Chem. Soc.*, 72, 3642 (1950).
(4) R. L. Pruett, J. T. Barr, K. E. Rapp, C. T. Bahner, J. D. Gibson, and R. H. Lafferty, Jr., *J. Am. Chem. Soc.*, 72, 3646 (1950).
(5) N. B. Chapman and R. E. Parker, *J. Chem. Soc.*, 3301 (1951).
(6) N. B. Chapman, R. E. Parker, and P. W. Soanes, *Chem. & Ind. (London)*, 148 (1951).

involves some carbon-fluorine bond fission in the transition state on two grounds. First, the carbon-fluorine bond is less readily cleaved than the other carbon-halogen bonds.[1,7-10] Second, substituents attached to unsaturated carbon atoms ordinarily undergo nucleophilic substitution less readily than those attached to saturated carbon.[11-14]

It has been pointed out that "C—F bond-breaking cannot have made significant progress in the transition state of any substitution in which fluorine is the most rapidly replaced of the halogens."[1] Furthermore, additions to the double bond of vinyl fluorides are common.[3,4,15-23] Therefore, an addition-elimination mechanism, summarized in Equation 1, has been suggested for the nucleophilic displacement of vinyl fluorine.[3,21] In Equation



(1)

1, the addition is written in two steps as previously suggested,[20] and Z^a represents a nucleophilic agent with charge a. It is also possible that the anion II is directly converted to product (IV) by loss of a fluoride ion.

In order to test this mechanism, a study was made of the kinetics of the reaction between 1,1-diphenyl-2-fluoroethylene and sodium ethoxide in ethanol. The progress of the reaction was followed by periodic determinations of the sodium ethoxide concentration. Three runs, in which the ratio of the initial concentration of olefin to that of ethoxide ranged from 0.69 to 2.5, were carried out. Second-order rate constants were calculated in the usual way,[24] and the results are tabulated in Table I. A typical run is summarized in Table II. If an excess of olefin is used (run 3, Table I), the ethoxide concentration reaches zero after 1.1×10^6 seconds, showing that the reaction is essentially irreversible. The data indicate that the kinetics are second-order, first-order with respect to olefin and with respect to ethoxide. In a separate experiment, the product of the reaction was isolated and identified as 1,1-diphenyl-2-ethoxyethylene.

TABLE I

SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF 1,1-DIPHENYL-2-FLUOROETHYLENE WITH SODIUM ETHOXIDE IN ETHANOL AT 99.75 ± 0.05°

Run	Initial Concn. of $NaOC_2H_5$ (M)	Initial Concn. of Olefin (M)	10^5 k (l. Mole^{-1} Sec.$^{-1}$)
1	0.0952	0.1036	4.62 ± 0.09[a]
2	0.1617	0.1112	4.38 ± 0.18
3	0.0740	0.1860	4.31 ± 0.16

[a] Mean deviation.

TABLE II

RATE OF THE REACTION BETWEEN 0.1860M 1,1-DIPHENYL-2-FLUOROETHYLENE AND 0.0740M SODIUM ETHOXIDE IN ETHANOL AT 99.75 ± 0.05°

Time (10^4 Sec.)	Titer[a]	10^5 k (l. Mole^{-1} Sec.$^{-1}$)
0	6.15	
2.16	5.13	4.58
4.32	4.38	4.39
6.48	3.69	4.53
8.64	3.30	4.22
10.80	2.87	4.22
15.48	2.15	4.17
23.67	1.39	4.08
		4.31 ± 0.16[b]

[a] Milliliters of 0.0602M hydrochloric acid needed to titrate a 5-ml. sample. [b] Mean deviation.

A similar run was carried out with 1,1-diphenyl-2-chloroethylene, but the reaction rate was too low to make measurement convenient at the temperature (99.75°) used for the fluorine analog. After 1.19×10^6 seconds, the ethoxide concentration had decreased from 0.1370 M to 0.1324M (the initial olefin concentration was 0.1826M.) This yields a second-order rate constant of 1.66 ×

(7) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 167.
(8) D. N. Glew and E. A. Moelwyn-Hughes, *Proc. Roy. Soc.* (*London*), 211A, 254 (1952).
(9) B. V. Tronov and E. A. Krüger, *Zhur. Russ. Fiz.-Khim. Obshchestva*, 58, 1270 (1926); *Chem. Abstr.*, 21, 3887[9] (1927).
(10) N. B. Chapman and J. L. Levy, *J. Chem. Soc.*, 1673 (1952).
(11) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 141-142.
(12) L. F. Fieser and M. Fieser, *Organic Chemistry*, 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1956, p. 152.
(13) J. B. Conant, W. R. Kirner, and R. E. Hussey, *J. Am. Chem. Soc.*, 47, 488 (1925).
(14) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, 49, 273 (1951).
(15) J. D. Park, W. R. Lycan, and J. R. Lacher, *J. Am. Chem. Soc.*, 73, 711 (1951).
(16) J. D. Park, M. L. Sharrah, W. H. Breen, and J. R. Lacher, *J. Am. Chem. Soc.*, 73, 1329 (1951).
(17) J. D. Park, D. K. Vail, K. R. Lea, and J. R. Lacher, *J. Am. Chem. Soc.*, 70, 1550 (1948).
(18) W. E. Hanford and G. W. Rigby, U. S. Patent 2,409,274 (1946).
(19) P. Tarrant and J. A. Young, *J. Am. Chem. Soc.*, 75, 932 (1953).
(20) W. T. Miller, Jr., E. W. Fager, and P. H. Griswold, *J. Am. Chem. Soc.*, 70, 431 (1948).
(21) J. T. Barr, K. E. Rapp, R. L. Pruett, C. T. Bahner, J. D. Gibson, and R. H. Lafferty, Jr., *J. Am. Chem. Soc.*, 72, 4480 (1950).
(22) P. Tarrant and H. C. Brown, *J. Am. Chem. Soc.*, 73, 1781 (1951).
(23) E. T. McBee and R. O. Bolt, *Ind. Eng. Chem.*, 39, 412 (1947).
(24) A. A. Frost and R. G. Pearson, *Kinetics and Mechanism*, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 17.

10^{-7} l. mole^{-1} sec.$^{-1}$, which is smaller than the rate constant for the reaction of the fluoroolefin by a factor of about 270. This observation demonstrates that the S_N2 mechanism does not play an important role in the reaction of the fluoroolefin.[1]

All of the present results support the mechanism given in Equation 1 for the reaction of the fluoroolefin. This mechanism is applied to the present system in Equations 2–5.

$$(C_6H_5)_2C{=}CHF + OC_2H_5^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (C_6H_5)_2C^-{-}CH(OC_2H_5)F \quad (2)$$

$$(C_6H_5)_2C^-{-}CH(OC_2H_5)F + C_2H_5OH \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} (C_6H_5)_2CH{-}CH(OC_2H_5)F + OC_2H_5^- \quad (3)$$

$$(C_6H_5)_2C^-{-}CH(OC_2H_5)F \xrightarrow{k_3} (C_6H_5)_2C{=}CHOC_2H_5 + F^- \quad (4)$$

$$(C_6H_5)_2CH{-}CH(OC_2H_5)F + OC_2H_5^- \xrightarrow{k_4} (C_6H_5)_2C{=}CHOC_2H_5 + C_2H_5OH + F^- \quad (5)$$

We feel that the process corresponding to k_{-2} (Equation 3) is probably not important in the present case. The anion resulting from such a reaction could become involved in reactions corresponding to k_{-1}, k_2, and k_3. The combination of processes k_{-2} and k_{-1} is an ethoxide-catalyzed removal of the elements of ethanol, which lacks precedent.[25] Processes k_{-2} and k_3 constitute a two-step dehydrohalogenation, and it has been clearly demonstrated that one-step dehydrohalogenations (Equation 5) are favored[26] unless (a) the fragments to be eliminated can not assume a *trans* configuration,[27] (b) the hydrogen is strongly activated,[28] or (c) a base stronger than ethoxide ion is used.[29] Thus, the process corresponding to k_{-2} can probably be followed only by its reverse process (k_2), and since k_2 is undoubtedly much larger than k_{-2} (*i.e.*, the equilibrium of Equation 3 lies far to the right), process k_{-2} is not important in the overall reaction.

The observed second-order kinetics are consistent with a mechanism consisting only of equations 2 and 4; *i.e.*, it is not necessary that 1,1-diphenyl-2-fluoro-2-ethoxyethane be involved at all. The kinetics are also in agreement with a mechanism that involves the α-fluoroether (Equations 2, 3, and 5) provided that the rate of formation of the α-fluoro ether is considerably faster than or considerably slower than the conversion of α-fluoroether to 1,1-diphenyl-2-ethoxyethylene [*i.e.*, provided that $k_1k_2/(k_{-1} + k_2) \gg k_4$ or $k_1k_2/(k_{-1} + k_2) \ll k_4$].

(25) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, pp. 420–472.

(26) Ref. 7, pp. 168–173.

(27) S. J. Cristol and D. D. Fix, *J. Am. Chem. Soc.*, **75**, 2647 (1953).

(28) H. L. Goering, D. I. Relyea, and K. L. Howe, *J. Am. Chem. Soc.*, **79**, 2502 (1957).

(29) C. R. Hauser, *J. Am. Chem. Soc.*, **62**, 933 (1940).

The 1,1-diphenyl-2-haloethylenes used for the kinetic studies were prepared by dehydration of the corresponding 1,1-diphenyl-2-haloethanols, which in turn were synthesized by the reaction of ethyl haloacetate with phenylmagnesium bromide. To our knowledge, this method represents a new approach to the synthesis of the rather inaccessible[30] simple (*i.e.*, containing no halogen atoms except one vinylic fluorine) vinyl fluorides.[31]

EXPERIMENTAL[32]

Ethyl fluoroacetate. Ethyl fluoroacetate was prepared by the method of Bacon *et al.*[33] Our yield was improved by mechanically stirring the mixture during the reaction. Even with stirring, only 15.0 g. (21%, lit.[33] 45%) of product, b.p. 114–117° (lit.[33] 117.5°), was obtained from 110 g. of ethyl bromoacetate and 129 g. of anhydrous potassium fluoride.

1,1-Diphenyl-2-fluoroethanol. An ethereal solution of phenylmagnesium bromide was prepared from 10.0 g. of magnesium, 30.0 g. of bromobenzene, and 200 ml. of ether. The solution was freed from solid impurities by decantation, and a solution of 6.1 g. of ethyl fluoroacetate in 200 ml. of ether was added to it over a period of one hour. During the addition, which was done in an atmosphere of dry nitrogen, the mixture was stirred and maintained at $-65 \pm 10°$ by cooling with a Dry Ice–acetone bath. After the addition, the mixture was allowed to warm to −11°, and a solution of 15 g. of ammonium chloride in 200 ml. of water was added slowly with stirring. The ether layer was separated and dried with sodium sulfate. The solvent was removed and the residue was fractionated at reduced pressure. The fraction boiling at 130° (2 mm.) soon solidified, and recrystallization from hexane yielded 4.8 g. (41%) of white crystals, m.p. 71.8–72.6°.

Anal. Calcd. for $C_{14}H_{13}OF$: C, 77.76; H, 6.06. Found: C, 77.86; H, 6.35.

1,1-Diphenyl-2-fluoroethylene. A solution of 1.55 g. of 1,1-diphenyl-2-fluoroethanol in 50 ml. of dry benzene was heated at reflux with 1.59 g. of phosphorus pentoxide for 2.75 hr. The solution was decanted and the solvent removed; distillation of the residue yielded 0.83 g. (55%) of a colorless liquid, b.p. 102–103° (2 mm.).

Anal. Calcd. for $C_{14}H_{11}F$: C, 84.82; H, 5.59. Found: C, 84.74; H, 5.98.

The product decolorized solutions of bromine and potassium permanganate. Oxidation with alkaline permanganate[34] gave a product which yielded a 2,4-dinitrophenylhydrazone melting at 240° (lit.[35] for benzophenone 2,4-dinitrophenylhydrazone, 239°) and did not depress the melting point of an authentic sample of benzophenone 2,4-dinitrophenylhydrazone.

1,1-Diphenyl-2-chloroethanol. An ethereal solution of phenylmagnesium bromide, prepared from 17 g. of magnesium,

(30) A. L. Henne in R. Adams, *Organic Reactions*, John Wiley and Sons, Inc., New York, N. Y., 1944, Vol. II, pp. 53 and 66–67.

(31) For other methods of synthesizing simple vinyl fluorides, see ref. 30 and E. T. McBee and W. R. Hausch, *Ind. Eng. Chem.*, **39**, 418 (1947); O. W. Cass, U. S. Patent 2,442,993 (1948); D. D. Coffman and R. D. Cramer, U. S. Patent 2,461,523 (1949); F. B. Downing, A. F. Benning, and R. C. McHarness, U. S. Patent 2,480,560 (1949); P. R. Austin, U. S. Patent 2,585,529 (1952).

(32) Temperatures are uncorrected. Analyses were carried out by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(33) J. C. Bacon, C. W. Bradley, E. I. Hoegberg, P. Tarrant, and J. T. Cassaday, *J. Am. Chem. Soc.*, **70**, 2653 (1948).

(34) Ref. 11, p. 250.

(35) Ref. 11, p. 318.

85 g. of bromobenzene, and 150 ml. of ether, was added, dropwise, and with stirring, to a solution of 20 g. of ethyl chloroacetate in 200 ml. of ether which was cooled by an ice bath. Ice water (200 ml.) was added. The ether layer was separated, washed with water, dried with magnesium sulfate, and fractionated. The fraction distilling at 140° (2 mm.) solidified in the receiver, and yielded 9.0 g. (24%) of white crystals, m.p. 63.4–65.0° (lit.[36] 64–65°), on recrystallization from hexane.

1,1-Diphenyl-2-chloroethylene. A mixture of 6.4 g. of 1,1-diphenyl-2-chloroethanol, 6.0 g. of phosphorus pentoxide, and 50 ml. of dry benzene was heated at reflux for 1 hr. Distillation yielded 4.3 g. (70%) of a colorless liquid, b.p. 138–139° (5 mm.) [(lit.[37] 189° (39 mm.)].

Anal. Calcd. for $C_{14}H_{11}Cl$: C, 78.32; H, 5.16. Found: C, 78.23; H, 5.25.

The product was unsaturated and yielded benzophenone (identified as the 2,4-dinitrophenylhydrazone) on cleavage with alkaline permanganate.[34]

(36) H. Gilman and C. C. Wanser, *J. Am. Chem. Soc.*, **73**, 4030 (1951).

(37) W. T. Buttenberg, *Ann.*, **279**, 324 (1884).

Rate determinations. Solutions of sodium ethoxide in ethanol were prepared by adding sodium to absolute ethanol. The reaction solutions were prepared by diluting weighed samples of 1,1-diphenyl-2-haloethylene with ethanol containing sodium ethoxide in volumetric flasks at 25°. These solutions were heated at 99.75 ± 0.05° in ampoules, and the sodium ethoxide concentrations were determined periodically by titrating 5-ml. aliquots with standard hydrochloric acid, using phenolphthalein as the indicator.

1,1-Diphenyl-2-ethoxyethylene. A solution of 3.0 g. of 1,1-diphenyl-2-fluoroethylene in 70 ml. of absolute ethanol which was 0.64*M* in sodium ethoxide was heated at 99.75° for 118 hr. Water (500 ml.) was added, and the mixture was extracted with four 100-ml. portions of ether. The ether was removed, and distillation of the residue yielded a colorless liquid, b.p. 136–138° (2 mm.) [lit.[47] 178–182° (18 mm.)].

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 86.02; H, 7.09.

The product decolorized bromine and potassium permanganate solutions, and permanganate oxidation[34] gave benzophenone, identified as the 2,4-dinitrophenylhydrazone.

South Hadley, Mass.

[Contribution from the Department of Chemistry, Duke University]

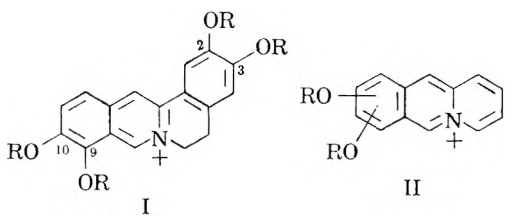
Aromatic Cyclodehydration. XXXVII[1,2] Quinolizinium Derivatives Related to the Protoberberine Alkaloids

C. K. BRADSHER and JAMES H. JONES

Received August 16, 1957

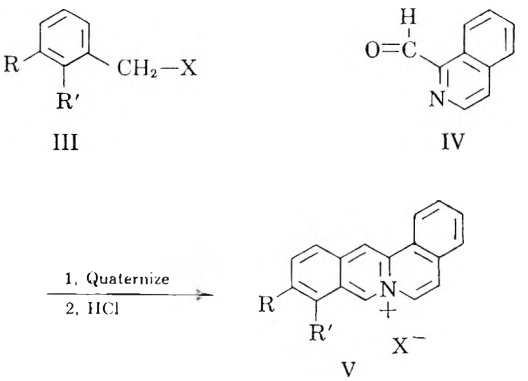
It has been found that isoquinoline-1-carboxaldehyde may be substituted for picolinic aldehyde in the acridizinium ion synthesis, affording a new method for the synthesis of the benz[*a*]acridizinium system (V). Salts of three new alkoxybenz[*a*]acridizinium ions have been synthesized.

In earlier model experiments[3] directed toward the synthesis of the protoberberine alkaloids (I), it was shown that salts produced by the reaction of alkoxybenzyl halides with picolinic aldehyde can be



I II

cyclized in the presence of hydrochloric acid to yield alkoxyacridizinium salts (II). It seemed likely that if 1-isoquinoline aldehyde (IV) were used instead of picolinic aldehyde a route to benzo[*a*]acridizinium salts (V) would be afforded.



III IV V

The aldehyde (IV), available by the selenium dioxide oxidation of 1-methylisoquinoline,[4] was found to quaternize with benzyl bromide satisfactorily. Cyclization of the crude salt gave the expected benzo[*a*]acridizinium bromide (V, R = R′ = H; X = Br) in 52% yield. This new salt (V) might be regarded as the parent substance of all of the protoberberine alkaloids and could be referred to as a "dehydroprotoberberinium" salt. By the use of alkoxybenzyl halides several alkoxybenzo[*a*]acridizinium salts were produced (Table I).

(1) For the previous communication of this series see *J. Am. Chem. Soc.*, **80**, 930 (1958).

(2) This investigation was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health. Abstracted in part from a dissertation to be submitted by James H. Jones in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Duke University.

(3) C. K. Bradsher and James H. Jones, *J. Am. Chem. Soc.*, **79**, 6033 (1957).

(4) R. S. Barrows and H. G. Lindwall, *J. Am. Chem. Soc.*, **64**, 2430 (1942).

TABLE I

BENZO[*a*]ACRIDIZINIUM SALTS (V)

R	R′	Yield, %	M.p., °C.[a] Bromide	Perchlorate	Picrate
H	H	52	257–258	234–235	277
CH_3O	H	78	235 dec.	276 dec.	283 dec.
CH_3O	CH_3O	53[b]		265–267	212
O—CH_2—O		66[c]		318–320	274–275

[a] The melting points reported are for analytical samples. [b] The product could not be isolated as the bromide. The yield reported is that of the perchlorate. [c] Crystallized from the cyclization mixture as the chloride, m.p. 309° dec.

While all of the salts described in Table I are new, they do not represent the first examples of fully aromatic benzo[*a*]-acridizinium salts. At least one earlier example is extant,[5,6] probably the earliest known instance of a compound having the aromatic quinolizinium[7] nucleus.

EXPERIMENTAL[8]

Benzo[a]acridizinium bromide (V, R=R′=H; X=Br). Two grams of isoquinoline-1-carboxaldehyde was refluxed with 2.05 g. of benzyl bromide and 3 ml. of methanol on the steam bath for 2 hr. Concentrated hydrochloric acid (60 ml.) was added and refluxing maintained for an additional 4 hr. The solvent was removed by vacuum evaporation and the residual oil washed with ether. Crystallization of the residue from propyl alcohol gave 2.0 g. (52%) of reddish-yellow crystals, m.p. about 250°. The analytical sample melted at 257–258°, λ max, 260, 270, 296, 309, 346, 364, 383, 403, 475, 507 mμ, min., 239, 265, 287, 304, 338, 355, 370, 391 mμ.

Anal. Calcd. for $C_{17}H_{12}BrN$: C, 62.21; H, 4.30; N, 4.27. Found: C, 61.85; H, 4.29; N, 4.22.

The *perchlorate* formed well-defined reddish crystals from ethanol, m.p. 234–235°.

Anal. Calcd. for $C_{17}H_{12}ClNO_4$: C, 61.92; H, 3.68; N, 4.25. Found: C, 61.76; H, 3.92; N, 4.59.

The *picrate*, m.p. 277°, was prepared in ethanol.

Anal. Calcd. for $C_{23}H_{14}N_4O_7$: C, 60.24; H, 3.08; N, 12.21. Found: C, 60.21; H, 3.04; N, 12.59.

10-Methoxybenzo[a]acridizinium bromide (V, R=OCH_3, R′=H, X=Br). Isoquinoline-1-aldehyde (3.0 g.), *m*-methoxybenzyl bromide[3,9] (3.8 g.) and methanol (4 ml.) were heated together on the steam bath for 2.5 hr., 90 ml. of concentrated hydrochloric acid added, and heating continued for 2 hr. The product, isolated in the usual way, afforded 5.1 g. (78%) of fine yellow crystals from ethanol, m.p. about 230°. The analytical sample consisted of clusters of microscopic yellow crystals, which melted at 235° dec., λ_{max} 270, 296, 309, 323, 345, 397, 417 mμ; min., 243, 286, 319, 370, 380, 405.

Anal. Calcd. for $C_{18}H_{14}BrNO$: N, 3.91. Found: N, 4.09.

The *perchlorate* was obtained from ethanol as fine yellow needles, m.p. 276° dec.

Anal. Calcd. for $C_{18}H_{14}ClNO_5 \cdot {}^1/_2H_2O$: C, 58.61; H, 4.06; N, 3.80. Found: C, 58.82; H, 3.86; N, 4.00.

The *picrate* was prepared in ethanol solution as a yellow solid, m.p. 283° dec.

Anal. Calcd. for $C_{24}H_{16}N_4O_8$: C, 57.72; H, 3.23; N, 11.22. Found: C, 57.99: H, 3.25; N, 11.56.

9,10-Dimethoxybenzo[a]acridizinium perchlorate (V, R=R′=OCH_3; X=ClO_4). The quaternary salt was formed from 2 g. of isoquinoline aldehyde, 2.94 g. of 2,3-dimethoxybenzyl bromide[3,10] and cyclized as in the case of the 10-methoxy analog. Since the oil which remained after removal of the hydrochloric acid could not be crystallized, it was treated with perchloric acid to give 2.5 g. (53%) of brown crystals, m.p. 265–267°. The analytical sample consisted of irregular clusters of orange-brown microscopic needles which melted at 265–267°; λ_{max} 259, 317, 332, 473, and 504 mμ; min., 245, 294, 400, 450, 482 mμ.

Anal. Calcd. for $C_{19}H_{16}ClNO_6$: C, 58.60; H, 4.14; N, 3.60. Found: C, 58.88; H, 4.26; N, 3.65.

The *picrate* separated from ethanol solution as yellowish brown crystals, m.p. 212°.

Anal. Calcd. for $C_{25}H_{18}N_4O_9$: N, 10.81. Found: N, 11.01.

9,10-Methylenedioxybenzo[a]acridizinium chloride (V, R—R′=OCH_2O, X=Cl). Quaternization of 2,3-methylenedioxybenzyl bromide[3,11] (2.74 g.) with 2.0 g. of isoquinoline aldehyde in the presence of methanol (2 ml.) was carried out as in the previous cases, but the cyclization was effected by refluxing the mixture with acid for only 0.5 hr. The product separated from the reaction mixture as fine red crystals which were recrystallized from ethanol as very small elongated rectangular plates, m.p. 304° dec.; yield 2.98 g. (66%). The analytical sample melted at 309° dec., λ_{max}, 229, 262, 284, 328, and 340 mμ, min., 244, 275, 300, 335 and 363 mμ.

Anal. Calcd. for $C_{18}H_{12}ClNO_2 \cdot {}^1/_2H_2O$: C, 67.81; H, 4.11; N, 4.40. Found: C, 67.75; H, 4.16; N, 4.79.

The *perchlorate* crystallized from ethanol as bright red crystals m.p. 318–320°.

Anal. Calcd. for $C_{18}H_{12}ClNO_6$: C, 57.84; H, 3.24; N, 3.75. Found: C, 57.81; H, 3.47; N, 3.85.

The *picrate*, prepared in ethanol solution, was bright red, m.p. 274–275°.

Anal. Calcd. for $C_{24}H_{14}N_4O_9$: C, 57.38; H, 2.81; N, 11.15. Found: C, 57.15; H, 2.83; N, 11.16.

DURHAM, N. C.

(5) W. Schneider and K. Schroeter, *Ber.*, **53B**, 1459 (1920).

(6) W. Schneider and O. Böger, *Ber.*, **54B**, 2021 (1921).

(7) *Chemical Abstracts* nomenclature.

(8) All analyses were by Micro-Tech Laboratories, Skokie, Ill. All melting points were taken on the Fisher-Johns block and are uncorrected. The ultraviolet absorption spectra were measured in 95% ethanol solution using a Warren Spectracord spectrophotometer and 1-cm. quartz cells.

(9) E. Späth, *Monatsh*, **34**, 1965 (1913).

(10) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, 127, 1434 (1925).

(11) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, 105, 1456 (1914).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF SWARTHMORE COLLEGE]

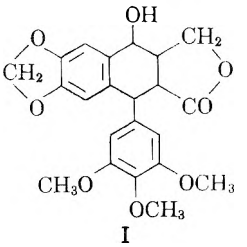
Quinoline Analogs of Podophyllotoxin. I. Preliminary Experiments. Syntheses of Some 4-Phenylquinoline Derivatives[1]

EDWARD A. FEHNEL

Received September 20, 1957

A number of 4-phenylquinoline derivatives showing structural resemblances to podophyllotoxin have been synthesized for evaluation as potential antitumor agents.

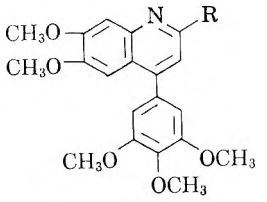
The discovery of tumor-damaging properties in podophyllotoxin (I) and some related naturally occurring lignans[2] has prompted the preparation



I

by several groups of investigators of a number of synthetic podophyllotoxin analogs for evaluation as potential antitumor agents. Most of the work which has been reported thus far has been concerned with the replication of all or part of the carbon-oxygen skeleton of the natural product and has involved the preparation of derivatives of butyrolactone,[3] 1,2,3,4-tetrahydronaphthalene,[4] 1-phenyl-1,2,3,4-tetrahydronaphthalene,[5] and 1-phenylnaphthalene.[6] More recently, Reeve and Paré have reported tumor-damaging activity in a 1-phenyldihydroisoquinoline derivative showing a close structural resemblance to podophyllotoxin.[7]

It seemed of interest to explore the possibility that certain quinoline analogs of podophyllotoxin might exhibit antitumor activity. Since the methylenedioxy moiety of podophyllotoxin may be replaced by two methoxyl groups without loss of activity[8] and since this modification simplified the synthetic procedure by permitting the use of somewhat more readily available starting materials, our initial experiments were concerned with the preparation of a series of 4-phenylquinoline derivatives of type II. The route to these products is



II

(R = H, CH_3, CHO, COOH)

outlined in the accompanying reaction diagram.

1-(3,4,5-Trimethoxyphenyl)-1,3-butanedione (III), prepared by a Claisen condensation between 3,4,5-trimethoxyacetophenone and ethyl acetate in the presence of sodium, was condensed with 3,4-dimethoxyaniline to give the anil IV or, more probably,[9] its tautomer V. Cyclodehydration of this product in cold concentrated sulfuric acid provided 6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)quinaldine (VI) in 76% over-all yield from III. Treatment of VI with selenium dioxide in dioxane gave a mixture of the aldehyde VII and the acid VIII, the latter being obtainable in excellent over-all yield either by isolating the aldehyde and oxidizing it further with hydrogen peroxide in acetone or, more simply, by subjecting the crude mixture of VII and VIII to the action of this reagent. Decarboxylation of the acid VIII occurred readily at temperatures slightly above its melting point, yielding 6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)quinoline (IX).

All attempts to reduce VI, VIII, and IX to the corresponding 1,2,3,4-tetrahydroquinoline derivatives by the usual methods (catalytic hydrogenation over platinum black or palladium-charcoal, electrolytic reduction at a lead cathode, chemical reduction with tin and hydrochloric acid) were unsuccessful and resulted only in recovery of unchanged starting material. The action of sodium on an ethanolic solution of IX yielded a reduction product having a composition corresponding to the

(1) This investigation was supported by research grant C-2726 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) See the excellent review by W. M. Hearon and W. S. MacGregor, *Chem. Revs.*, **55**, 957 (1955), which includes numerous references to articles dealing with the pharmacology of these compounds.

(3) N. L. Drake and W. B. Tuemmler, *J. Am. Chem. Soc.*, **77**, 1204 (1955).

(4) K. N. Campbell, J. A. Cella, and B. K. Campbell, *J. Am. Chem. Soc.*, **75**, 4681 (1953).

(5) G. N. Walker, *J. Am. Chem. Soc.*, **75**, 3390, 3393 (1953).

(6) W. Reeve and H. Myers, *J. Am. Chem. Soc.*, **75**, 4957 (1953).

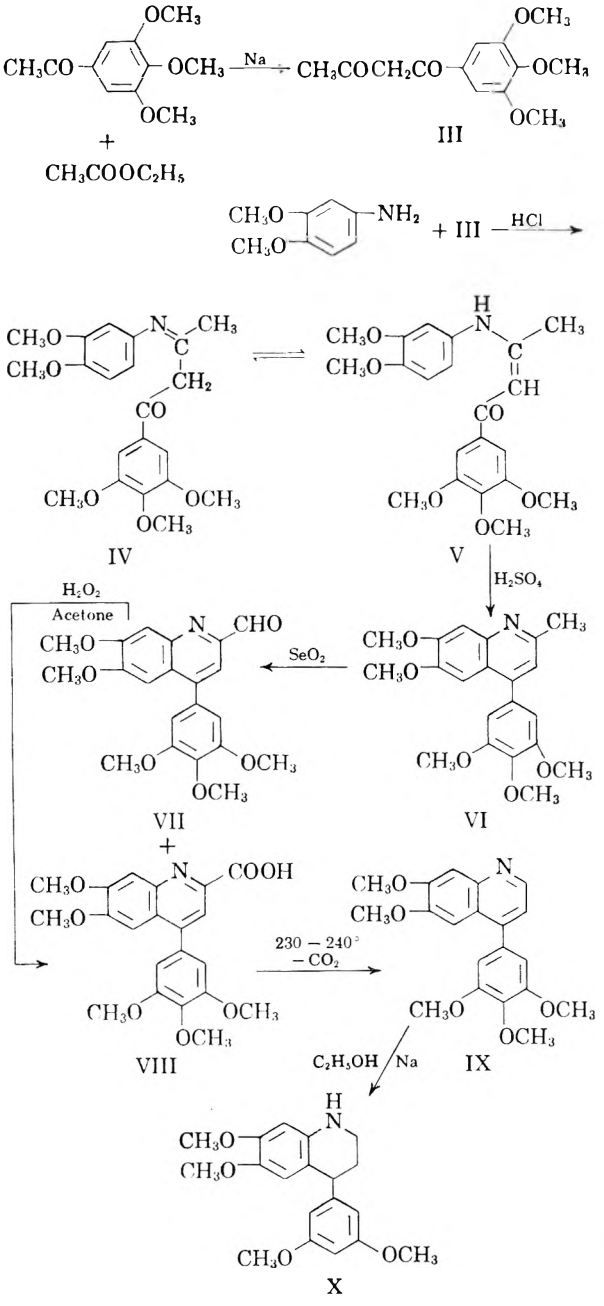
(7) W. Reeve and P. J. Paré, *J. Am. Chem. Soc.*, **79**, 675 (1957).

(8) *Cf.* sikkimotoxin, which is 1-hydroxy-2-hydroxymethyl-6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid lactone; reference in footnote 2.

(9) *Cf.* F. Lions, *J. Proc. Roy. Soc., N. S. Wales*, **71**, 242 (1938); *Chem. Abstr.*, **32**, 7460 (1938).

formula $C_{19}H_{23}NO_4$ rather than to the desired $C_{20}H_{25}NO_5$. Since the central methoxyl group of the *vic*-trimethoxyphenyl moiety is known to be subject to hydrogenolysis under these conditions,[10] the product may be provisionally assigned structure X. Further study of the anomalous reduction behavior of this series of compounds is planned.

The preparation of 6,7-dimethoxy-4-phenylquinaldehyde (XI) and 6,7-dimethoxy-4-phenylquinaldic acid (XII), which were obtained during exploratory experiments with the readily accessible 6,7-dimethoxy-4-phenylquinaldine, is described in the Experimental part. Pharmacological data for compounds described in this paper will be reported elsewhere.



(10) See, for example, the discussion in J. Houben, *Die Methoden der Organischen Chemie*, 3rd ed., Verlag Georg Thieme, Leipzig, 1925, vol. 2, p. 235.

EXPERIMENTAL[11]

1-(3,4,5-Trimethoxyphenyl)-1,3-butanedione (III). About 20 ml. of a solution of 20.3 g. (0.097 mole) of 3,4,5-trimethoxyacetophenone[12] in 100 ml. of freshly purified[13] anhydrous ethyl acetate was added to 6.8 g. (0.30 g.-atom) of sodium sand in a nitrogen atmosphere. The mixture was stirred, and after the exothermic reaction had begun the remainder of the ketone solution was added dropwise at such a rate as to maintain refluxing (*ca.* 15 min.). Stirring and refluxing were continued for another 4 hr. After standing at room temperature overnight, the reaction mixture was diluted with 200 ml. of water, acidified with 30 ml. of acetic acid and extracted with three 150-ml. portions of chloroform. The combined chloroform extracts were washed once with 100 ml. of water and were then extracted with four 80-ml. portions of 10% aqueous sodium hydroxide. Acidification of the combined alkaline extracts with 55 ml. of acetic acid provided a yellow solid precipitate, which was collected, washed with water, dried, and recrystallized from aqueous methanol to yield 16.9 g. (69%) of pale yellow crystals, m.p. 97–99°. Further recrystallization from aqueous methanol gave colorless leaflets melting at 101–102°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.88; H, 6.39. Found: C, 61.82; H, 6.38.

β-(3,4-Dimethoxyanilino)-3,4,5-trimethoxycrotonophenone (V). A mixture of 16.8 g. (0.067 mole) of III and 10.2 g. (0.067 mole) of 3,4-dimethoxyaniline was heated in a boiling water bath until a clear amber melt was obtained. Four drops of 6*N* hydrochloric acid was then added and heating was continued until the mixture solidified (*ca.* 5 min.). The resultant yellow solid was pulverized and dissolved in *ca.* 300 ml. of boiling methanol. On cooling this solution, 21.1 g. (82%) of bright yellow crystals, m.p. 143–144°, were obtained. Dilution of the mother liquor with an equal volume of water and recrystallization of the resultant precipitate from fresh methanol provided an additional 2.3 g. of product of comparable purity; total yield 23.4 g. (90%). Recrystallization from methanol raised the m.p. to 145–146°.

Anal. Calcd. for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.51; N, 3.62. Found: C, 65.30 H, 6.26; N, 3.61.

6,7-Dimethoxy-4-(3,4,5-trimethoxyphenyl)quinaldine (VI). Finely powdered V (17.4 g.) was added in small portions with vigorous stirring over a 20-min. period to 90 ml. of cold concentrated sulfuric acid. The resultant yellow solution was poured onto 160 g. of cracked ice, and 300 ml. of concd. ammonium hydroxide was then added cautiously while stirring and cooling in an ice bath. The gummy suspension was heated to boiling for 5 min., and the precipitate was then collected, washed with water, and recrystallized from aqueous methanol to give 15.4 g. (93%) of almost colorless needles, m.p. 152–154°. Treatment of this material with Nuchar and further recrystallization from aqueous methanol or benzene-cyclohexane provided colorless crystals which melted at 153–154°; λ_{max}^{EtOH} 236 mμ (log ε 4.63), 320 mμ (log ε 4.00), 334 mμ (log ε 4.03).

Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.52; H, 6.47; N, 3.74.

The *methiodide* of VI was prepared by dissolving 0.70 g. of VI in 5 ml. of benzene, adding 1.60 g. of methyl iodide, and allowing the mixture to stand at room temperature for several months. The yellow precipitate was collected, washed with benzene, and dried to give 0.60 g. (62%) of

(11) Microanalyses are by the Clark Microanalytical Laboratory, Urbana, Ill.

(12) E. C. Horning, J. Koo, and G. N. Walker, *J. Am. Chem. Soc.*, **73**, 5826 (1951).

(13) L. F. Fieser, *Experiments in Organic Chemistry*, 3rd ed., D. C. Heath and Co., Boston, 1955, p. 287.

yellow crystals, m.p. 220–225° with decomposition beginning above 205°. Recrystallization from absolute ethanol raised the m.p. to 228–230° (dec.).[14]

Anal. Calcd. for $C_{22}H_{26}INO_5$: C, 51.67; H, 5.13. Found: C, 51.83; H, 5.21.

Selenium dioxide oxidation of VI. A mixture of 7.97 g. (0.0216 mole) of VI, 3.00 g. (0.0270 mole) of selenium dioxide,[15] 27 ml. of purified[16] dioxane, and 2.2 ml. of water was refluxed for 6 hr., after which the hot reaction mixture was filtered to remove the precipitated selenium. On cooling, the dark red solution deposited crude *6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)quinaldic acid* (VIII) in the form of orange crystals, which were collected, washed with dioxane, and dried; yield 4.46 g. (52%), m.p. 205–210° (dec.) with previous sintering. Repeated recrystallization of this material from ethanol and from dioxane provided silky yellow needles of the pure acid, m.p. 224–225° (dec.).

Anal. Calcd. for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; neut. equiv., 399. Found: C, 62.93; H, 5.58; neut. equiv., 399.

After removal of the crude acid, the dioxane filtrate from the above oxidation reaction was diluted with *ca.* 200 ml. of water and allowed to stand overnight. The resultant yellow precipitate was collected, washed with water, and dried to give 3.30 g (40%) of *6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)quinaldehyde* (VII), m.p. 176–178°. Recrystallization from ethanol gave pale yellow crystals which melted at 179–180°.

Anal. Calcd. for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52. Found: C, 65.78; H, 5.54.

Hydrogen peroxide oxidation of VII. A mixture of 4.12 g. (0.0108 mole) of VII, 120 ml. of acetone, and 10 ml. (0.088 mole) of 30% hydrogen peroxide was refluxed for 2 hr. and allowed to stand overnight. The precipitate was then collected, washed with a little acetone, and dried to give 3.70 g. (86%) of yellow powder, m.p. 222–224° (dec.) alone and when mixed with the acid VIII obtained above.

6,7-Dimethoxy-4-(3,4,5-trimethoxyphenyl)quinoline (IX). Small (1 to 2 g.) samples of the acid VIII were heated on an oil bath at 230–240° for 10 min. and were then extracted repeatedly with 10-ml. portions of boiling cyclohexane until the extracts no longer deposited solid material on cooling. The yellow solid thus obtained was collected, washed with petroleum ether, and dried. Yields varied from 60% to 78% in three runs; the combined yield from 3.44 g. of VIII was 2.17 g. (71%) of yellow microcrystalline powder, m.p. 136–139° with previous sintering. Recrystallization from cyclohexane provided pale yellow needles melting at 140–141°.

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96. Found: C, 67.71; H, 5.74.

Sodium-ethanol reduction of IX. Nine grams of sodium was added in small pieces over a 90-min. period to a refluxing solution of 2.15 g. of IX in 60 ml. of absolute ethanol, and refluxing was continued for another 3 hr. About 30 ml. of water was then added cautiously to the boiling mixture, the condenser was set for distillation, and another 60 ml. of water was added gradually to the boiling mixture while *ca.* 70 ml. of distillate was collected. The residual aqueous solution was cooled, extracted several times with ether, and the combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether solution to dryness on the steam bath left a pale yellow tacky sirup, which slowly crystallized to an almost colorless waxy solid, m.p. 90–94°; yield 1.09 g. Recrystallization of this material from cyclohexane and from aqueous ethanol provided a white microcrystalline powder which melted at 101–103°; λ_{max}^{EtOH} 310 mμ (log ε 3.58).

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04. Found: C, 69.22, 69.50; H, 7.01, 6.94.

Selenium dioxide oxidation of 6,7-dimethoxy-4-phenylquinaldine. A mixture of 5.58 g. (0.020 mole) of 6,7-dimethoxy-4-phenylquinaldine,[17] 2.22 g. (0.020 mole) of selenium dioxide,[15] 15 ml. of purified [16] dioxane, and 1.5 ml. of water was refluxed for 6 hr., after which the hot reaction mixture was filtered to remove the precipitated selenium (1.51 g., 96%). On cooling, the dark red filtrate deposited crude *6,7-dimethoxy-4-phenylquinaldic acid* (XII) as an orange solid, which was collected, washed with a little ether, and recrystallized from a relatively large volume of ethanol to give 1.14 g. (18%) of yellow needles, m.p. 180–181° (dec.). Further recrystallization from ethanol raised the m.p. to 182–183° (dec.).

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89. Found: C, 70.04; H, 4.91.

Concentration of the dioxane filtrate on the steam bath afforded a viscous red oil which slowly solidified. The dark colored solid was taken up in boiling ethanol, water was added to the hot solution until a slight turbidity appeared, and the solution was allowed to stand for several days. The orange waxy solid (1.5 g., 26%) thus obtained was recrystallized repeatedly from aqueous ethanol and finally from cyclohexane to give yellow crystals of 6,7-dimethoxy-4-phenylquinaldehyde, which melted at 121–123°, then resolidified and remelted at 136–137°.

Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.16. Found: C, 73.25, 73.23; H, 5.27, 5.39.

The *p-nitrophenylhydrazone* of this product, prepared in the usual way,[18] was obtained as a red-orange microcrystalline powder, m.p. 260–261°.

Anal. Calcd. for $C_{24}H_{20}N_4O_4$: C, 67.28; H, 4.71. Found: C, 67.33; H, 4.93.

SWARTHMORE, PA.

(14) Melting point taken on Fisher-Johns apparatus preheated to 220°.

(15) H. A. Riley and A. R. Gray, *Org. Syntheses*, **Coll. Vol. II**, 510, note 2 (1943).

(16) L. F. Fieser, *Experiments in Organic Chemistry*, 3rd ed., D. C. Heath and Co., Boston, 1955, p. 285, method (a).

(17) Prepared in 77% yield from 3,4-dimethoxyaniline and 1-phenyl-1,3-butanedione according to the directions of Lions.[9] After recrystallization from aqueous methanol, the product was obtained in the form of colorless needles, m.p. 141–142°; λ_{max}^{EtOH} 238 mμ (log ε 4.64), 334 mμ (log ε 4.03).

(18) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, 1956, p. 219.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Alstonia Alkaloids. VIII. Synthesis of Tetra- and Pentacyclic Quaternary Carboline Analogs of Alstoniline by Fischer Indole Ring Closure.[1,2,3]

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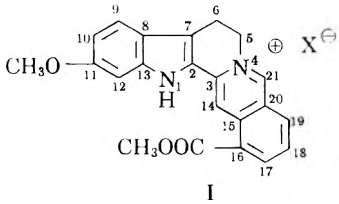
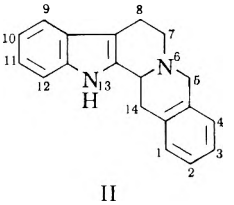
Synthesis of a series of penta- and tetra-cyclic β-carbolines by application of the Fischer indole synthesis to 1-keto-1,2,3,4-tetrahydroquinolizinium salts is described. Nitration and sulfonation of 3-methylisoquinoline has been shown to occur primarily at the 5 position.

The structure of alstoniline, a minor alkaloid of *Alstonia constricta*, F. Muell., has been shown to be represented by I.[6,7] The unsaturation of the ring



I



II

system of alstoniline is unique among the naturally occurring pentacyclic β-carbolines and appears to offer certain advantages from the synthetic point of view which are absent in other members of this general class of substances. Thus, the lack of an asymmetric center eliminates configurational problems and the possibility of introduction of functional groups into the molecule combined with the possibility of varying the degree of unsaturation in Rings C, D, and E are attractive from the standpoint of the synthesis of compounds which may possess hypertensive or tranquilizing properties. In the present communication we wish to report an investigation of the synthesis of tetra- and pentacyclic quaternary β-carbolines by application of the Fischer indole synthesis to ketones derived from pyridine and isoquinoline.

When this work was started no reports of the synthesis of tetra- or penta-cyclic quaternary β-carbolines in which Ring C is saturated and Ring D (and Ring E) is aromatic had appeared. The synthesis of sempervirine in which Rings C and D are aromatic, by Woodward and McLamore[8] represents the only reported example of the synthesis of a quaternary carboline of this type by methods other than those involving dehydrogenation of saturated systems. After the present investigation was substantially complete, Sugasawa, Terashima, and Wanaoka[9] described the synthesis of 6,7-dihydro-12*H*-indolo[2.3-*a*]quinolizinium bromide by a different route than the one here reported.

Several examples of the application of the Fischer indole synthesis to the preparation of compounds related to the pentacyclic β-carbolines but with ring C open have appeared.

Julian and coworkers[10] prepared tetrahydroyobyrine by cyclization of the phenylhydrazone of *n*-propyl-3-isoquinolyl ketone and analogs of alstoniline with Ring C open have been prepared by the same general route.[11] Clemo and Swan[12] have synthesized II by ring closure of the phenylhydrazone of the appropriate tricyclic ketone.

In order to gain experience in the application of the Fischer method attention was first turned to the synthesis of substances related to alstoniline but which did not carry the carbomethoxy group in position 16.[13] The general synthetic scheme followed for the preparation of these compounds is represented by the sequence illustrated. 3-Methylisoquinoline (III) was oxidized to isoquinoline-3-carboxaldehyde (IV) with selenium dioxide essentially according to Teague and Roe.[14] Reaction of IV with

(1) For paper VII in this series see H. Boaz, R. C. Elderfield, and E. Schenker, *J. Am. Pharm. Assoc. Sci. Ed.*, **46**, 510 (1957).

(2) This work was supported in part by Research Grant H-1733 from the National Heart Institute of the Public Health Service.

(3) Portions of this paper are taken from doctoral dissertations submitted by Jeanne M. Lagowski, Orville L. McCurdy, and Stephen L. Wythe.

(4) Eli Lilly Fellow in Chemistry 1954–55.

(5) Eli Lilly Fellow in Chemistry 1952–53.

(6) R. C. Elderfield and S. L. Wythe, *J. Org. Chem.*, **19**, 683 (1954).

(7) R. C. Elderfield and O. L. McCurdy, *J. Org. Chem.*, **21**, 295 (1956).

(8) R. B. Woodward and W. M. McLamore, *J. Am. Chem. Soc.*, **71**, 379 (1949).

(9) S. Sugasawa, M. Terashima, and Y. Wanaoka, *Pharm. Bull., Pharm. Soc. Japan.*, **4**, 16 (1956).

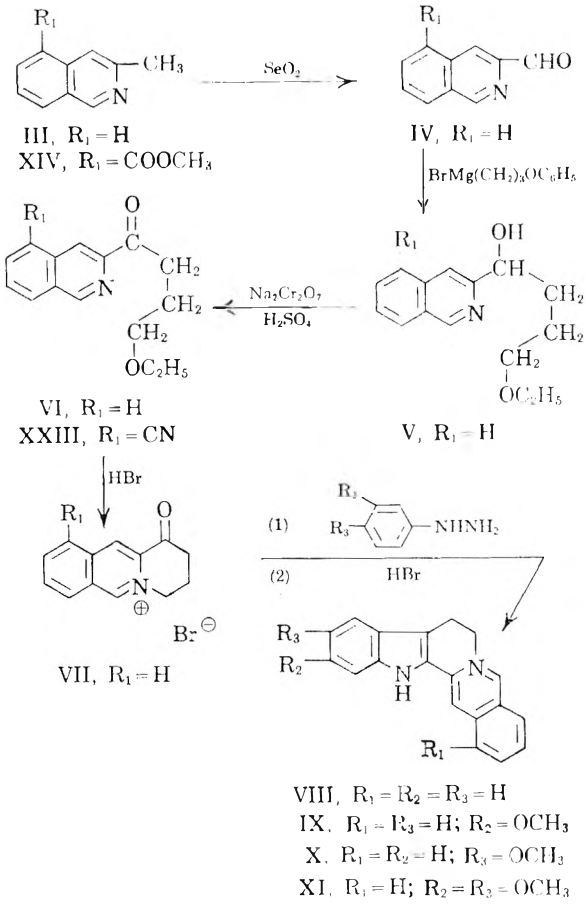
(10) P. L. Julian, W. J. Karpel, A. Magnani, and E. W. Meyers, *J. Am. Chem. Soc.*, **70**, 180 (1948).

(11) R. C. Elderfield and S. L. Wythe, *J. Org. Chem.*, **19**, 693 (1954).

(12) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 617 (1946); 487 (1949).

(13) The numbering in the skeleton represented by alstoniline (I) is confusing. Common practice has led to the adoption of the numbering scheme shown in I for alkaloids derived from the parent system. On the other hand the systematic name, benzo[g]indolo[2.3-*a*]quinolizine and the numbering system shown in II is approved by the Ring Index. In this paper the system shown in II will be used.

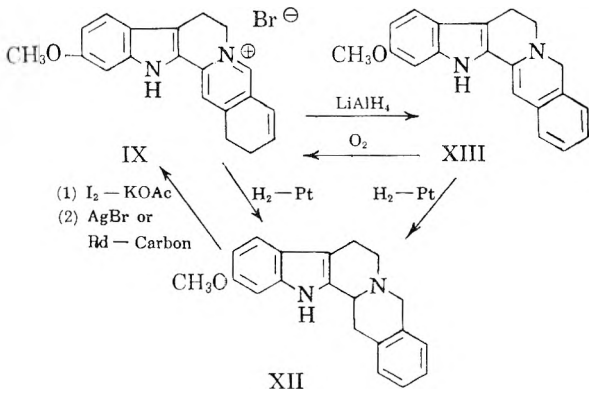
(14) C. E. Teague, Jr., and A. Roe, *J. Am. Chem. Soc.*, **73**, 688 (1951).



γ-ethoxypropylmagnesium bromide gave γ-ethoxypropyl-3-isoquinolinemethanol (V) which was in turn oxidized to the ketone (VI). Treatment of VI with hydrobromic acid resulted in cleavage of the ether and cyclization to give 1-keto-1,2,3,4-tetrahydrobenzo[*b*]quinolizinium bromide (VII). Reaction of VII with phenylhydrazine, *m*- and *p*-methoxyphenylhydrazine, and 3,4-dimethoxyphenylhydrazine gave the corresponding phenylhydrazones which were cyclized with hydrobromic acid to give 7,8-dihydro-13*H*-benzo[*g*]indolo[2.3-*a*]quinolizinium bromide (VIII) and the 11-methoxy (IX), the 10-methoxy (X), and the 10,11-dimethoxy (XI) derivatives of VIII, respectively.

Ring closure of the *m*-methoxyphenylhydrazone of VII can conceivably lead to the formation of two isomers. However, no evidence for the presence of a second isomer was noted. It thus appears that this ring closure follows the general rule in quinoline and indole syntheses involving a methoxyl group *meta* to the ring nitrogen that closure occurs exclusively *para* to the methoxyl group.[15]

The colors of the indoloquinolizinium bromides are of some interest. VIII and IX are orange, X is yellow, and XI is brick red. The ultraviolet spectrum of IX is nearly identical with that of alstoniline hydrochloride whereas the spectra of X and XI differ considerably from the spectrum of IX. A similar effect of the position of methoxyl substituents on the ultraviolet spectra of other indoles has been noted previously.[16] Catalytic reduction of VIII gave 5,7,8,13,13*b*,14-hexahydrobenzo[*g*]indolo[2.3-*a*]quinolizine (II) which has previously been prepared by a number of routes.[12,17,18] Conversion of VIII to II furnishes a convenient proof for the structure assigned to VIII. Further, certain of the reactions undergone by IX furnish confirmation for the unsaturated system previously assigned to alstoniline. Thus, IX was reduced to 11-methoxy-5,7-,8,13,13*b*,14-hexahydrobenzo[*g*]indolo[2.3-*a*]quinolizine (XII) which is analogous to tetrahydroalstoniline. The ultraviolet curves of tetrahydroalstoniline and XII are very similar.



Dehydrogenation of XII with iodine and potassium acetate or catalytically with palladium resulted in aromatization of ring D and regeneration of IX. An analogous dehydrogenation of II has been noted by Swan.[19] Inasmuch as alloyohimbane, in which rings C, D, and E are saturated, undergoes dehydrogenation in Ring C to give tetradehydroalloyohimbane[20] it appears that the tetrahydroisoquinoline ring system is dehydrogenated more readily to an isoquinoline than the tetrahydro-β-carboline is to a carboline. Dehydrogenation of XII to IX was accomplished also slowly with air. Reduction of IX with lithium aluminum hydride gave a dihydro compound, presumably XIII, by reduction of the quaternary azomethine linkage. XIII was readily oxidized back to IX by atmospheric oxygen and absorbed one mole of hydrogen on catalytic reduction to give XII. It is noteworthy that neither the free bases of XII or XIII underwent oxidation by air to give a compound of the type of alstoniline oxide.[7] The influence of the carbomethoxyl group in alstoniline in promoting formation of alstoniline oxide is some-

(15) C. Mentzer, *Compt. rend.*, 222, 1176 (1946); L. Bradford, T. J. Elliot, and F. M. Rowe, *J. Chem. Soc.*, 437 (1947); W. O. Kermack, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 119, 1602 (1921).

(16) N. Neuss, H. E. Boas, and J. W. Forbes, *J. Am. Chem. Soc.*, 76, 2463 (1954).

(17) J. Jost, *Helv. Chim. Acta*, 32, 1297 (1949).

(18) K. T. Potts and Sir Robert Robinson, *J. Chem. Soc.*, 2675 (1955).

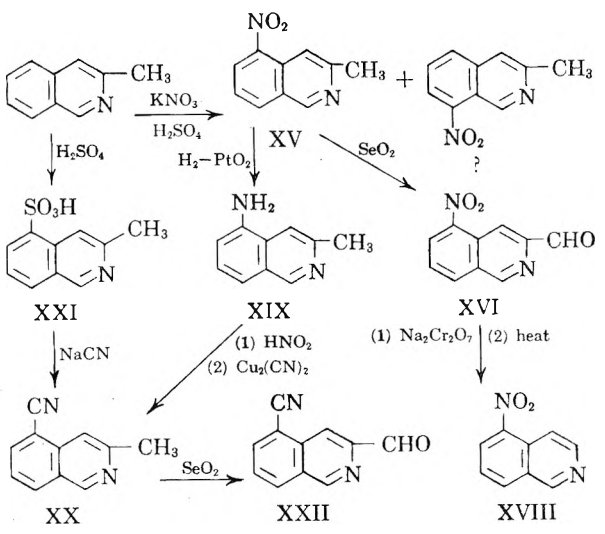
(19) G. A. Swan, *J. Chem. Soc.*, 1720 (1949).

(20) A. LeHir, M. M. Janot, and R. Goutarel, *Bull. soc. chim. France*, 1027 (1953).

what unexpected. It is known that a nitro group in the 5 position of isoquinoline promotes pseudo base formation by increasing the electrophilic strength of the carbon atom at the 1 position.[21] A similar effect of the electron-attracting carbomethoxyl group may be operative in alstoniline.

For the synthesis of alstoniline itself, substantially the same series of reactions as those used for the synthesis of IX was contemplated. Rather than starting from III, the isoquinoline, XIV, carrying a carbomethoxyl group or some group potentially convertible to a carbomethoxyl group was required. Two routes to the desired intermediate were explored.

Isoquinoline itself nitrates in the 5 position[22] and a methyl group in the 3 position would not be expected to alter the orientation appreciably. Bergstrom and Patterson[23] nitrated 3-methylisoquinoline with fuming nitric and sulfuric acids and obtained a major and a minor product but did not prove the structure of either. On nitration with potassium nitrate in sulfuric acid 3-methylisoquinoline gives a major product, m.p. 109–110°, and a minor one, m.p., 85–90°. The major product was shown to be the desired 3-methyl-5-nitroisoquinoline (XV) as follows. Oxidation with selenium dioxide gave 5-nitroisoquinoline-3-carboxaldehyde (XVI) which was not purified but rather was oxidized in the crude state to 5-nitroisoquinoline-3-carboxylic acid (XVII) with sodium dichromate in dilute sulfuric acid. Oxidation of XV stepwise in this fashion gives much better over-all yields of XVII than direct one-step oxidation. When heated above its melting point XVII gave 5-nitroisoquinoline (XVIII) identical with a known sample. The lower melting nitro compound is presumably 3-methyl-8-nitroisoquinoline although its structure was not proved. A route was thus opened to the desired potential isoquinolinecarboxylic acid.



Catalytic reduction of XV over platinum oxide gave 5-amino-3-methylisoquinoline (XIX) from which a poor yield of 5-cyano-3-methylisoquinoline (XX) was obtained on application of the Sandmeyer reaction. Substitution of nickel cyanide[24] for cuprous cyanide did not improve the yield of XX. In view of the discouraging yield of XX, attention was devoted to the preparation of XX from 3-methylisoquinoline-5-sulfonic acid (XXI). Sulfonation of 3-methylisoquinoline occurs in the 5 position as shown by conversion of the sulfonic acid (XXI) to XX on fusion with sodium cyanide. Although the yield of XX by this route is only about 15%, it still is to be preferred to the Sandmeyer procedure.

Oxidation of XX with selenium dioxide gave 5-cyanoisoquinoline-3-carboxaldehyde (XXII). At this point the reaction of XXII with γ-ethoxypropylmagnesium bromide was attempted paralleling the similar reaction of IV. It was hoped that the aldehyde group of XXII would react selectively faster with the Grignard reagent than the cyano group.[25] The cyano group could then be converted to the carbomethoxyl group at some later stage of the reaction sequence. However, oxidation of the crude reaction product failed to yield any of the desired 5-cyano-3-isoquinolyl-γ-ethoxypropyl ketone (XXIII).

The Grignard reaction of γ-ethoxypropylmagnesium bromide was then attempted on isoquinoline-3-carboxaldehyde-5-carboxylic acid which was in turn prepared by hydrolysis of the cyano group in XXII. The thought was that an extra mole of reagent would merely react with the hydrogen of the carboxyl group which would then be regenerated during decomposition of the Grignard addition compound. Oxidation of the crude reaction product with dichromate did, indeed, give a poor yield of the desired ketone as the 2,4-dinitrophenylhydrazone. However, the yields in this series of reactions were so discouragingly low that this approach was abandoned.

In another attempt to obtain the ketone (XXIII) the acid chloride of 5-cyanoisoquinoline-3-carboxylic acid was brought into reaction with both γ-ethoxypropylmagnesium bromide and γ-ethoxypropylcadmium chloride. In neither case could any XXIII be isolated from the reaction products.

We have also investigated the application of the general synthesis discussed above to the preparation of quaternary tetracyclic β-carbolines preparatory to the preparation of such compounds carrying various functional groups in the molecule. Specifically, 6,7-dihydro-12*H*-indolo[2.3-*a*]quinolizinium bromide (XXIV) has been prepared as follows.

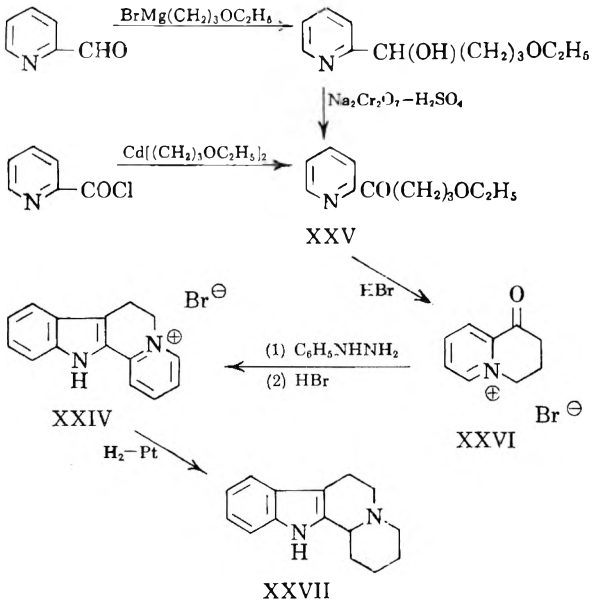
(21) R. C. Elderfield, *Heterocyclic Compounds*, Vol. 4, John Wiley and Sons, Inc., New York, 1952, p. 469.

(22) F. T. Tyson, *J. Am. Chem. Soc.*, **61**, 183 (1939).

(23) F. W. Bergstrom and R. E. Patterson, *J. Org. Chem.*, **10**, 479 (1945).

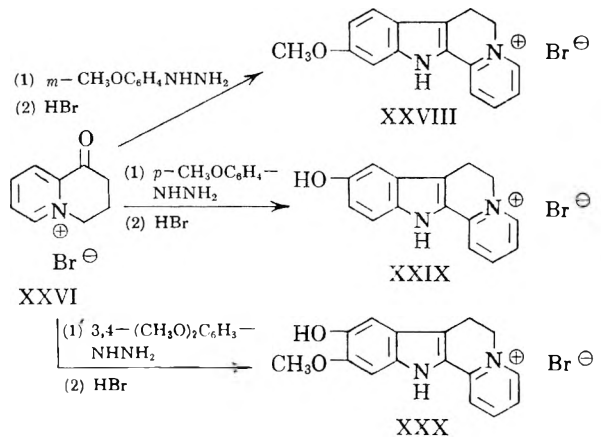
(24) J. A. McRae, *J. Am. Chem. Soc.*, **52**, 4550 (1930).

(25) H. Gilman, *Organic Chemistry, An Advanced Treatise*, 2nd Ed., Vol. 2, John Wiley and Sons, Inc., New York. 1943, p. 501.



The ketone (XXV) was prepared both from pyridine-2-carboxaldehyde *via* the carbinol and from picolinic acid chloride and di(γ-ethoxypropyl)cadmium, a method which failed with an isoquinoline aldehyde. Catalytic hydrogenation of XXIV gave 1,2,3,4,6,7,12,12*b* - octahydroindolo[2.3 - *a*]quinolizine (XXVII) which had previously been prepared by other methods.[26,27] While this work was in progress, Sugasawa, Terashima, and Wanaoka[9] reported the synthesis of XXIV by another method. The physical constants for XXIV reported by them are in agreement with ours.

When the ketone (XXVI) was subjected to the Fischer indole synthesis with *m*-methoxy-, *p*-methoxy- and 3,4-dimethoxyphenylhydrazine, certain departures from the behavior displayed by the isoquinoline ketone (VII) were noted. Reaction with *m*-methoxyphenylhydrazine, proceeded normally to give 6,7-dihydro-10-methoxy-12*H*-indolo[2.3-*a*]-quinolizinium bromide (XXVIII).



(26) L. H. Groves and G. A. Swan *J. Chem. Soc.*, 650 (1952).

(27) W. A. Reckhow and D. S. Tarbell, *J. Am. Chem. Soc.*, **74**, 4961 (1952).

However during the course of the analogous reaction with *p*-methoxyphenylhydrazine the ether was cleaved. The product, 6,7-dihydro-9-hydroxy-12*H*-indolo[2.3-*a*]quinolizinium bromide (XXIX), gave analytical data consistent with loss of a methyl group. No ether absorption was present in the infrared spectrum but a hydroxyl band was. Similarly, with 3,4-dimethoxyphenylhydrazine, XXVI underwent cleavage of one methoxyl group to give 6,7-dihydro-9-hydroxy-10-methoxy-12*H*-indolo[2.3-*a*]-quinolizinium bromide (XXX). The structure of XXX is assigned on the basis of analytical data, the infrared spectrum, which showed both hydroxyl and methoxyl absorption, and summation of the ultraviolet curves of XXVIII and XXIX[28] (Fig. 1).

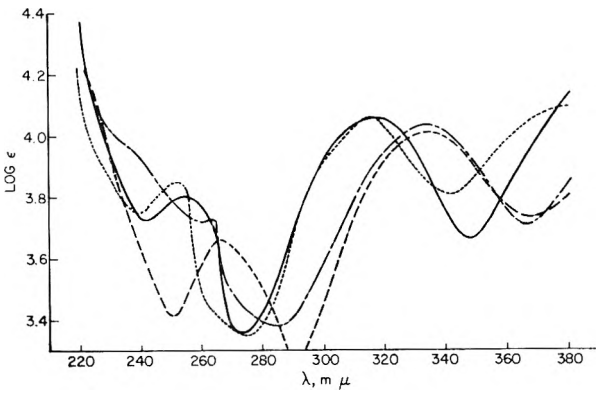


Fig. 1. Ultraviolet absorption curves. ——— 6,7-Dihydro-9-hydroxy-12*H*-indolo[2,3-*a*]quinolizinium bromide (XXIX), - - - - 6,7-Dihydro-10-methoxy-12*H*-indolo[2,3-*a*]quinolizinium bromide (XXVIII), ... 6,7-Dihydro-12*H*-indolo[2,3-*a*]quinolizinium bromide (XXIV), ——— 6,7-Dihydro-9-hydroxy-10-methoxy-12*H*-indolo[2,3-*a*]quinolizinium bromide (XXX).

A possible explanation for this difference in behavior in the two series may be found in the fact that whereas, in the isoquinoline series, the quaternary salts crystallized from the reaction mixture, the analogous salts derived from the pyridine derivatives remained in solution and were therefore subject to the action of hydrobromic acid for the entire reaction period.

EXPERIMENTAL[29,30]

γ-Ethoxypropyl-3-isoquinolinemethanol (V). A solution of 40 g. of isoquinoline-3-carboxaldehyde[11] in 1200 ml. of absolute ether was added gradually with stirring to the Grignard reagent prepared from 50 g. of γ-ethoxypropyl bromide[31] and 8.4 g. of magnesium turnings in 400 ml. of absolute ether. It was necessary to activate the magnesium

(28) See ref. 16 for another example of the summation of ultraviolet absorption in the indole series.

(29) All melting points are corrected unless otherwise noted. Boiling points are uncorrected.

(30) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. or by Mrs. Anna Griffin, University of Michigan.

(31) L. I. Smith and J. A. Sprung, *J. Am. Chem. Soc.*, **65**, 1276 (1943).

with methyl iodide for the successful preparation of the Grignard reagent. After addition of the aldehyde the mixture was stirred at room temperature for 16 hr., then cooled in an ice bath and decomposed with 1 l. of saturated ammonium chloride solution. The ether layer was separated, washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent left the carbinol as a dark red viscous oil which could not be crystallized. It was used without purification for the next step.

For characterization a picrate was prepared in ethanol. It formed bright yellow crystals, m.p. 122–123°, on recrystallization from absolute ethanol.

Anal. Calcd. for $C_{21}H_{22}N_4O_9$: C, 53.2; H, 4.7. Found: C, 52.8; H, 4.6.

γ-Ethoxypropyl-3-isoquinolyl ketone. (VI). To a stirred solution of 35 g. of the above carbinol in 175 ml. of concentrated sulfuric acid and 1 l. of water a solution of 26.8 g. of sodium dichromate dihydrate in 175 ml. of water was added slowly at room temperature. After stirring for 18 hr. the solution was made basic with sodium hydroxide, the precipitate was collected, dried, and extracted in a Soxhlet extractor. The alkaline filtrate was also extracted with ether. The combined ether extracts were concentrated somewhat and extracted with 10% hydrochloric acid. The acid extract was made basic with sodium hydroxide and the brown precipitate was collected, dried, and extracted in a Soxhlet extractor with 40–60° petroleum ether to yield 15.2 g. of crystalline ketone. After recrystallization from petroleum ether it melted at 79–81°. The yield from isoquinoline-3-carboxaldehyde was 24%.

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.1; H, 6.9. Found: C, 73.8; H, 7.0.

1-Keto-1,2,3,4-tetrahydrobenzo[b]quinolizinium bromide. (VII). A solution of 15.2 g. of the ketone (VI) in 100 ml. of 48% hydrobromic acid was refluxed for 3 hr. After cooling, the hydrobromic acid was removed under reduced pressure. Addition of ether to a solution of the residue in absolute ethanol precipitated white crystals. In some runs cyclization did not occur in the acid solution and a compound, m.p. 157°, which is probably γ-bromopropyl-3-isoquinolyl ketone, was isolated. This was converted to VII by refluxing it in absolute ethanol with ether. VII melted at 244° and the yield was quantitative.

Anal. Calcd. for $C_{13}H_{12}BrNO$: C, 56.1; H, 4.4. Found: C, 55.8; H, 4.7.

Phenylhydrazone of VII. A mixture of 3 g. of VII, 3 g. of phenylhydrazine, and 50 ml. of absolute ethanol was refluxed for 30 min. On cooling 3.5 g. (88%) of the phenylhydrazone of VII separated. On recrystallization from absolute ethanol it formed orange needles which darkened at 285° and melted at 351° (dec.).

Anal. Calcd. for $C_{19}H_{18}BrN_3$: C, 62.0; H, 4.9; N, 11.4. Found: C, 61.9; H, 4.8; N, 11.2.

m-Methoxyphenylhydrazone of VII. This was prepared in 76% yield from 7.5 g. of VII and 4 g. of *m*-methoxyphenylhydrazine as in the preceding case. It crystallized from absolute ethanol as clusters of small orange-yellow needles, m.p. 254° (dec.).

Anal. Calcd. for $C_{20}H_{20}BrN_3O$: C, 60.3; H, 5.1; N, 10.5; Br, 20.1. Found: C, 60.3; H, 5.3; N, 10.3; Br, 20.3.

7,8-Dihydro-13H-benzo[g]indolo[2.3-a]quinolizinium bromide. (VIII). A rapid stream of hydrogen bromide was passed into a solution of 2 g. of the phenylhydrazone of VII in 200 ml. of 95% ethanol. After 30 min. a yellow precipitate formed. Passage of hydrogen bromide was continued for an additional 20 min. and the mixture was cooled. The precipitate was collected and recrystallized from absolute ethanol yielding 1.7 g. (89%) of light orange needles, m.p. 350–351° (dec.).

Anal. Calcd. for $C_{19}H_{15}BrN_2$: C, 65.0; H, 4.3; N, 8.0. Found: C, 65.2; H, 4.5; N, 7.8.

11-Methoxy-7,8-dihydro-13H-benzo[2.3-a]quinolizinium bromide. (IX). This was prepared from 5 g. of the *m*-methoxyphenylhydrazone of VII in 500 ml. of methanol as in the preceding case. The yield of bright orange needles, m.p. 311–312° (dec.) after recrystallization from absolute ethanol, was 4.5 g. (94%).

Anal. Calcd. for $C_{20}H_{17}BrN_2O$: C, 63.0; H, 4.5; N, 7.4. Found: C, 62.9; H, 4.7; N, 7.5.

10-Methoxy-7,8-dihydro-13H-benzo[2.3-a]quinolinizium bromide. (X). The intermediate phenylhydrazone was not isolated. A mixture of 4 g. of VII, 2.2 g. of *p*-methoxyphenylhydrazine and 100 ml. of methanol was refluxed for 30 min. After cooling hydrogen bromide was passed through the mixture as in the above cases. The yield of yellow needles, m.p. 326–327° (dec.) after recrystallization from absolute ethanol, was 3.6 g (65%).

Anal. Calcd. for $C_{20}H_{17}BrN_2O$: C, 63.0; H, 4.5; N, 7.4. Found: C, 62.8; H, 4.7; N, 7.4.

10,11-Dimethoxy-7,8-dihydro-13H-benzo[2,3-a]quinolizinium bromide (XI). This was prepared by the same method as was X without isolation of the phenylhydrazone from VII and 3,4-dimethoxyphenylhydrazine. The yield of light red needles, m.p. 306–307° (dec.), was 54%.

Anal. Calcd. for $C_{21}H_{19}BrN_2O$: C, 60.7; H, 5.6; N, 6.8. Found: C, 60.8; H, 5.6; N, 6.8.

5,7,8,13,13b,14-Hexahydrobenzo[g]indolo[2.3-a]quinolizine hydrochloride. A suspension of 1.0 g. of VIII in 100 ml. of methanol was shaken with 100 mg. of Adams' platinum oxide catalyst at room temperature and atmospheric pressure. After uptake of 2 equivalents of hydrogen in 15 min. during which the color of the solution changed from orange to light yellow-green, hydrogen absorption ceased. The catalyst was filtered off under nitrogen and the filtrate was concentrated at reduced pressure to 30 ml. After addition of 30 ml. of water, addition of a few drops of sodium hydroxide solution precipitated the free base. The yield of white needles, m.p. 190° (dec.) after recrystallization from ethyl acetate, was 0.8 g. (90%). The reported m.p. is 196–197°,[12] 192°[17] and 188–189° (dec.).[18]

The hydrochloride precipitated when dry hydrogen chloride was passed into a solution of the free base in methanol. It forms yellow platelets, m.p. 282–284° (dec.). The reported m.p. is 288° (dec.),[12] 290° (dec.),[17] and 288–289° (dec.).[18]

Anal. Calcd. for $C_{19}H_{18}N_2 \cdot HCl$: C, 73.4; H, 6.2; N, 9.0. Found: C, 73.0; H, 6.2; N, 8.8.

11-Methoxy-5,7,8,13,13b,14-hexahydrobenzo[g]indolo[2.3-a]quinolizine hydrochloride. (XII). Reduction of IX as in the preceding case gave XII as clusters of tan crystals, m.p. 230° after recrystallization from ethyl acetate. The yield was 93%. In the presence of air and moist catalyst XII oxidizes rapidly to orange products. The hydrochloride of XII, m.p. 248° (dec.), formed long white needles from methanol.

Anal. Calcd. for $C_{20}H_{20}N_2O.HCl$; C, 70.6; H, 6.2; N, 8.2. Found: C, 70.4; H, 6.6; N, 8.1.

Dehydrogenation of XII. A. with iodine. A warm solution of 1.4 g. of potassium acetate and 0.7 g. of iodine in 20 ml. of absolute ethanol was added to 140 mg. of XII in 4 ml. of absolute ethanol. The mixture was warmed on the steam bath for 5 min. during which a copious orange precipitate formed. This was collected and suspended in 50 ml. of hot water. Sulfur dioxide was passed through the suspension for 10 min. After cooling, the solid was collected and recrystallized from absolute ethanol to give 120 mg. of the iodide corresponding to IX as orange-red needles, m.p. 310° (dec.).

The above iodide was converted to the bromide (IX) by refluxing it with 1 g. of freshly prepared silver bromide in 150 ml. of ethanol and 50 ml. of water. Evaporation to dryness and recrystallization of the residue from ethanol after filtering from silver salts gave IX, m.p. 312° (dec.). The infrared spectrum was identical with that of an authentic sample of IX.

B. with palladium. A solution of 700 mg. of maleic acid and 500 mg. of XII in 150 ml. of hot water was refluxed with 250 mg. of 20% palladium-on-charcoal under nitrogen for 22 hr. The filtrate from the catalyst was concentrated under

nitrogen until crystallization began. After cooling, the precipitate was collected, suspended in 75 ml. of methanol, and treated with dry hydrogen bromide. The precipitate dissolved and, on cooling, 340 mg. of IX, m.p. 311–312° (dec.), separated. The ultraviolet spectrum was identical with that of an authentic sample of IX.

C. with air. A slow stream of air was passed through a refluxing solution of 500 mg. of XII and 2 ml. of 48% hydrobromic acid for 4 days. On concentration and cooling 80 mg. of IX, m.p. 311–312° (dec.), separated. It was further identified by ultraviolet and infrared spectra.

Action of lithium aluminum hydride on IX. (XIII). To a stirred suspension of 1 g. of IX in 100 ml. of absolute ether 0.76 g. of lithium aluminum hydride was slowly added. Reduction occurred immediately and the color of the suspension changed from orange to light yellow-green. After refluxing for 2 hr. excess hydride was destroyed by cautious addition of 10 ml. of ethyl acetate. After addition of 50 ml. of 5% hydrobromic acid, the ether was removed in a stream of nitrogen leaving a white precipitate which slowly began to turn orange even under nitrogen. Part of the precipitate was filtered and hydrogenated in methanol over platinum oxide. One equivalent of hydrogen (calculated on the amount of XII isolated) was absorbed. After working up, 380 mg. of XII, m.p. 230°, was obtained. Identification was by mixture m.p.'s and identity of the infrared spectrum with that of an authentic sample of XII.

The other portion of the suspension was allowed to stand exposed to air and the precipitate rapidly turned orange. The precipitate was collected and recrystallized from ethanol yielding 350 mg. of IX, m.p. 311–312°. The ultraviolet and infrared spectra were identical with those of a known sample of IX.

10-Methoxy-5,7,8,13,13b,14-hexahydrobenzo[g]indolo[2,3-a]quinolizine hydrochloride. Reduction of X over platinum oxide by the same procedure as that used in the reduction of IX gave 90% of the quinolizine hydrochloride, m.p. 275–277° (dec.).

Anal. Calcd. for $C_{20}H_{20}N_2O.HCl$: C, 70.6; H, 6.2; N, 8.2. Found: C, 70.8; H, 6.5; N, 8.5.

3-Methyl-5-nitroisoquinoline. (XV). This procedure was adapted from one for the preparation of 5-nitroisoquinoline.[32] A solution of 55 g. of potassium nitrate in 300 ml. of concentrated sulfuric acid was added with stirring to a solution of 72 g. of 3-methylisoquinoline in 400 ml. of concentrated sulfuric acid, chilled in an ice-salt bath, at such a rate that the temperature of the mixture did not exceed 4°. The addition required 2.5 hr. The solution was stirred for an additional 2 hr. during which it was allowed to come to room temperature. It was then poured into a mixture of 4 l. of water and 4 kg. of chopped ice. After neutralization by cautious addition of ammonia, the suspension was cooled and the solid was collected and recrystallized from ethanol yielding 28 g. of yellow needles, m.p. 105–108.5°. The mother liquor was concentrated and water was added to the hot solution to the point of incipient crystallization. On cooling, 14 g. of needles, m.p. 105–108°, separated. A third crop, m.p. 102–107°, obtained by the same procedure weighed 18 g., and finally, a fourth crop, m.p. 85–90°, weighed 2.5 g. The total recovery was 85 g. (90%). The first crop on recrystallization from ethanol gave pale yellow needles, m.p. 109.5–110.5°, in good recovery. Additional material was obtained from the first three fractions. Bergstrom and Patterson[23] nitrated 3-methylisoquinoline by a different procedure and obtained 55% of a nitro derivative, m.p. 108–110°, and 14% of a second isomer, m.p. 90–91°.

Oxidation of 3-methyl-5-nitroisoquinoline. A solution of 3.16 g. of the major product, m.p. 109.5–110.5°, of the above nitration in 30 ml. of nitrobenzene was added slowly with stirring to a suspension of 2.2 g. of selenium dioxide (purified by sublimation) in 100 ml. of nitrobenzene. During the addition the suspension was slowly brought to boil. After the addition was complete the mixture was refluxed for 1 hr. during which the color changed from yellow to deep red-brown. After cooling the solution was washed successively with 50 ml. of 5% sodium hydroxide solution and 100 ml. of water and then extracted with several portions of 10% hydrochloric acid until the extracts gave no precipitate with alcoholic 2,4-dinitrophenylhydrazine reagent. The acid extracts were combined and made basic with sodium hydroxide solution, chilled, and the solid was collected. The filtrate was extracted with ether. Removal of the ether left a solid residue which was combined with the first filter cake and recrystallized from 90–100° petroleum ether with carbon. The first crop, m.p. 165–172°, weighed 0.7 g. A second crop, m.p. 159–163°, weighed 0.6 g. Both crops gave positive tests with 2,4-dinitrophenylhydrazine. Recrystallization raised the m.p. to 173–178°. The aldehyde (XVI) was not purified further since the contaminant, 3-methyl-5-nitroisoquinoline was not attacked in the next step and could easily be separated from the resulting acid.

A solution of 0.5 g. of sodium dichromate heptahydrate in 5 ml. of water was added to a solution of 0.45 g. of the crude aldehyde (XVI) in 15 ml. of water and 5 ml. of concentrated sulfuric acid. After standing 2 hr., the solution was diluted with 50 ml. of water, filtered, and brought to *p*H 4 with ammonia. After boiling a few minutes, the solid was collected. The combined filter cakes, m.p. 260–263° (dec.), weighed 200 mg. The material was dissolved in 10% sodium hydroxide solution, the solution was extracted with ether, and the acid was precipitated with acetic acid.

When the above acid was heated above its melting point carbon dioxide was evolved and a yellow volatile product distilled and solidified, m.p. 102–104°. After recrystallization from water it was identified by m.p. (108–110°) and mixture m.p.'s as 5-nitroisoquinoline.

5-Amino-3-methylisoquinoline (XIX). Reduction of XV in methanol over platinum oxide catalyst at room temperature and atmospheric pressure gave a quantitative yield of 5-amino-3-methylisoquinoline, m.p. 213–216°. Bergstrom and Patterson[23] report m.p. 219.5–221° for the amine prepared by reduction with stannous chloride.

3-Methylisoquinoline-5-sulfonic acid. (XXI). 3-Methylisoquinoline (28.6 g.) was added slowly with cooling to 110 g. of 50% fuming sulfuric acid and the mixture was allowed to stand at room temperature for 48 hr. After pouring onto 500 g. of ice and water and standing until crystallization was complete, the sulfonic acid was collected. It formed white needles, m.p. 420–430° (dec.), after recrystallization from water. The yield was 39 g. (88%).

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.8; H, 4.1; S, 14.4. Found: C, 53.8; H, 4.1; S, 14.4.

5-Cyano-3-methylisoquinoline. (XX). *A. from 5-amino-3-methylisoquinoline.*[33] A solution of 8.3 g. of 5-amino-3-methylisoquinoline in 56 ml. of concentrated hydrochloric acid and 120 ml. of water was chilled to 0°. A chilled solution of 4.9 g. of sodium nitrite in 25 ml. of water was added slowly and the resulting solution was allowed to stand 5 min. It was then cautiously neutralized with sodium carbonate and added slowly with stirring to a chilled solution of 11.4 g. of potassium cyanide and 10.2 g. of cuprous cyanide in 80 ml. of water. The solution was allowed to come to room temperature and stirred overnight. It was necessary to add a few drops of octyl alcohol to prevent excessive foaming. The mixture was steam distilled for 24 hr. using a combination steam distillation and liquid-liquid extraction apparatus[34] with chloroform as the extractant. The chloroform extracts were exhaustively extracted with 10% hydrochloric acid. The combined acid extracts were made basic with sodium hydroxide solution, chilled and 1.2 g. (15%) of XX

(32) Private communication from Dr. R. L. Shriner.

(33) *Cf.* L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **62**, 1640 (1940).

(34) A. I. Vogel, *Practical Organic Chemistry*, 2nd Ed., Longmans, Green and Co., Ltd., London, 1951, p. 223.

separated. After recrystallization from 90–100° petroleum ether it melted at 127–129°.

Anal. Calcd. for $C_{11}H_8N_2$: 3, 78.5; H, 4.8. Found: C, 78.3; H, 4.7.

B. from 3-methylisoquinoline-5-sulfonic acid. An intimate mixture of 56 g. of XXI, 12 g. of sodium cyanide, 32 g. of potassium cyanide, and 10 g. of anhydrous sodium acetate was placed over 10 g. of anhydrous sodium acetate in a 500-ml. Monel metal flask. The flask was connected to a condenser set downward for distillation which was in turn connected to a filter flask chilled in ice and connected to an aspirator. The metal flask was heated with a Meker burner at water pump pressure and the nitrile distilled and partially solidified in the condenser. The distillate was extracted with ether and the extract was dried over anhydrous potassium carbonate. Distillation of the residue after removal of the ether gave a forerun of 1.5 g. of 3-methylisoquinoline, b.p., 65–70° (0.07 mm.), m.p. 52–53°, followed by 6.4 g. of XX, b.p. 115–120° (0.05 mm.). After recrystallization from methanol it formed white needles, m.p. 128°. The m.p. was not depressed on admixture with XX prepared from 5-amino-3-methylisoquinoline thus proving that sulfonation had occurred in the 5 position.

5-Cyanoisoquinoline-3-carboxaldehyde. (XXII). A solution of 12 g. of XX in 150 ml. of nitrobenzene was added slowly to a suspension of 10.8 g. of freshly prepared and sublimed selenium dioxide in 850 ml. of nitrobenzene at 180° with stirring. After refluxing for one hour, the solution was cooled and extracted with three 300 ml. portions of 10% hydrochloric acid. After extraction of the combined acid extracts with ether they were made basic with ammonia. The precipitated aldehyde was collected and recrystallized from benzene–petroleum ether. The yield of fine white needles, m.p. 208–210°, was 5.3 g. (41%). Analytical data indicated that partial hydrolysis of the cyano group had occurred since the carbon figures were consistently low.

Anal. Calcd. for $C_{11}H_6N_2O$: C, 72.5; H, 3.3. Found: C, 71.6; H, 3.3.

A 2,4-dinitrophenylhydrazone, m.p. 275–276° (dec.) was prepared. Again the analytical data were unsatisfactory. However, the acid prepared by hydrolysis of the nitrile gave satisfactory figures.

Isoquinoline-3-carboxaldehyde-5-carboxylic acid. A solution of 5.3 g. of XXII in 50 ml. of 48% hydrobromic acid was refluxed for 3 hr. After cooling the *p*H of the solution was adjusted to 5 and it was extracted with ether in a continuous extractor. The aldehydo acid was recrystallized from dioxane giving 5.2 g. (89%) of long white needles, m.p. 249–250° (dec.). It retained 0.5 mole of dioxane of crystallization.

Anal. Calcd. for $C_{11}H_7NO_3 \cdot 0.5\ C_4H_8O_2$: C, 63.7; H, 4.5; N, 5.7. Found: C, 63.9; H, 4.3; N, 5.8.

γ-Ethoxypropyl-5-carboxyisoquinolyl ketone. γ-Ethoxypropylmagnesium bromide (prepared from 8.35 g. of γ-ethoxypropyl bromide in 50 ml. of absolute ether) was added slowly to a stirred solution of 3.5 g. of the above aldehydo acid in 300 ml. of dry tetrahydrofuran. A copious yellow precipitate formed immediately. After refluxing for 5 hr., the mixture was cooled and hydrolyzed with saturated ammonium chloride solution. The tetrahydrofuran was removed by distillation and, after adjusting the *p*H to 5, the solution was extracted with ether. After drying the extract over anhydrous magnesium sulfate, removal of the solvent left about a gram of viscous oil. This was dissolved in a mixture of 5 ml. of concentrated sulfuric acid and 30 ml. of water and a solution of 2 g. of potassium dichromate in 15 ml. of water was added. After 18 hr. at room temperature the *p*H was adjusted to 5 and the solution was extracted with ether. After drying over anhydrous magnesium sulfate, removal of the ether left a viscous oil. This was refluxed with 200 mg. of 2,4-dinitrophenylhydrazine in absolute ethanol for 30 min. On cooling 70 mg. of a 2,4-dinitrophenylhydrazone, m.p. 249° (dec.) after recrystallization from ethanol, crystallized.

Anal. Calcd. for $C_{22}H_{21}N_5O_7$: C, 56.5; H, 4.5; N, 15.0 Found: C, 56.6; H, 4.6; N, 14.9.

γ-Ethoxypropyl-2-pyridinemethanol. To a solution of γ-ethoxypropylmagnesium bromide prepared from 53.4 g. of γ-ethoxypropyl bromide and 8.0 g. of magnesium in 400 ml. of absolute ether a solution of 30.4 g. of freshly distilled pyridine-2-carboxaldehyde, b.p. 63° (14 mm.), in 500 ml. of absolute ether was added with powerful stirring as rapidly as possible. A gummy yellow precipitate formed almost immediately. After stirring and refluxing, for 2 hr., the complex was hydrolyzed by boiling with 400 ml. of 15% ammonium chloride solution for 1 hr. The ether layer was separated and the aqueous layer was extracted with four 250-ml. portions of ether. After drying over anhydrous magnesium sulfate, removal of the ether left a brown oil which was distilled through a 13-cm. Vigreux column at reduced pressure to give 34.2 g. (62%) of very hygroscopic yellow oil, b.p. 121–126° (1.5 mm.). An analytical sample, b.p. 130° (4 mm.), n_D^{29} 1.5002, was analyzed immediately after distillation. The infrared spectrum showed bands at 3400 cm.$^{-1}$ (OH) and 1100 cm.$^{-1}$ (saturated —O—).

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.7; H, 8.8. Found: C, 67.7; H, 8.5.

The picrate, m.p. 92–93°, formed yellow rhomboids from ether.

Anal. Calcd. for $C_{17}H_{20}N_4O_9$: C, 48.1; H, 4.7. Found: C, 47.9; H, 4.8.

γ-Ethoxypropyl-2-pyridyl ketone, (XXV). *A. by oxidation of the carbinol.* To a solution of 24.8 g. of γ-ethoxypropyl-2-pyridinemethanol in 123 ml. of concentrated sulfuric acid and 740 ml. of water was added slowly a solution of 24.6 g. of sodium bichromate dihydrate in 123 ml. of water. After standing 24 hr. at room temperature, the solution was made strongly basic with sodium hydroxide and filtered on a large Buchner funnel. The air-dried filter cake was extracted with ether in a Soxhlet extractor for 10 hr. The aqueous filtrate was exhaustively extracted with ether. Removal of the solvent from the combined dried ether extracts left a brown oil which was distilled at reduced pressure under nitrogen through a 13-cm. Vigreux column to give 12.3 g. (50%) of very hygroscopic colorless oil, b.p. 109–114° (1.3 mm.). An analytical sample, b.p. 114° (1.2 mm.), n_D^{29} 1.4978, was analyzed immediately after distillation. The ketone, or solutions of it, cause a very irritating skin eruption.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8. Found: C, 68.1; H, 8.2.

The infrared spectrum of XXV indicates that it exists in the enol form to a considerable extent. It shows strong bands at 1700 cm.$^{-1}$ (C=O) and at 1100 cm.$^{-1}$ (saturated —O—). There are less intense bonds at 3400 cm.$^{-1}$ (OH), 1580 cm.$^{-1}$ (aromatic absorption), and 990 cm.$^{-1}$ (vinyl or trans C=C). Further, XXV gave a dark green color with ferric chloride in ethanol.

The *p*-nitrophenylhydrazone, m.p. 94–96°, formed fine, orange needles from dilute methanol.

Anal. Calcd. for $C_{17}H_{20}N_4O_3$: C, 62.2; H, 6.1; N, 17.1. Found: C, 62.2; H, 6.2; N, 17.1.

B. via the cadmium reagent. Picolinic acid chloride was prepared by heating 5.0 g. of picolinic acid with 19 ml. of freshly distilled thionyl chloride under reflux for 20 min. The excess thionyl chloride was removed under reduced pressure; 20 ml. of dry benzene was added to the residue and removed by distillation. The dark green residue was dissolved in 25 ml. of absolute ether and used directly without further purification.

To a solution of γ-ethoxypropylmagnesium bromide prepared from 1.6 g. of magnesium and 13.3 g. of γ-ethoxypropyl bromide in 100 ml. of absolute ether was added 13.1 g. of anhydrous cadmium chloride. After stirring for 30 min. the above ethereal solution of picolinic acid chloride was added dropwise with stirring. The mixture was stirred and refluxed for 3 hr. After cooling, the complex was hydrolyzed by stirring with a solution of 10 g. of ammonium chloride and 10 ml. of concentrated hydrochloric acid in 50 ml. of water for

5 hr. The ether layer was separated and the aqueous layer was refluxed for an additional 5 hr., made basic to litmus with sodium hydroxide and extracted with four 50-ml. portions of ether. Removal of the ether from the dried combined extracts and distillation under reduced pressure gave 1.15 g. (15% based on picolinic acid) of XXV. The refractive index and infrared spectrum were identical with those of the ketone prepared by procedure A

1-Keto-1,2,3,4-tetrahydroquinolizinium bromide (XXVI) A mixture of 12.25 g. of XXV and 255 ml. of 48% hydrobromic acid was refluxed for 3 hr. Removal of the acid left a red-brown oil. The product was very difficult to purify if the excess hydrobromic acid was not completely removed at this point. The oil was heated under reflux with 20 ml. of absolute ethanol for 8 hr. Concentration of the solution under reduced pressure and dropwise addition of absolute ether to the concentrate induced crystallization of XXVI. After chilling for several hours, the product was filtered in a dry atmosphere, washed with 2 ml. of anhydrous ether, and desiccator dried. The yield of very hygroscopic bromide was 6.3 g. (48%). An analytical sample crystallized as light tan needles, m.p. 204.5–206° (dec., uncorr.) with preliminary darkening, from absolute ethanol–anhydrous ether.

Anal. Calcd. for $C_9H_{10}BrNO$: C, 47.4; H, 4.4; N, 6.1. Found: C, 47.4; H, 4.4; N, 6.1.

The *p*-nitrophenylhydrazone crystallized as fine orange needles, m.p. 291–292° (uncorr.) after sintering at 280°, from absolute ethanol.

Anal. Calcd. for $C_{15}H_{15}BrN_4O_2$: C, 49.6; H, 4.2. Found: C, 49.6; H, 4.1.

The phenylhydrazone (85% yield) formed fine yellow-orange needles, m.p. 264–265° (dec.), from absolute ethanol.

Anal. Calcd. for $C_{16}H_{16}BrN_3$: C, 56.6; H, 5.1; N, 13.2. Found: C, 56.4; H, 5.2; N, 13.3.

6,7-Dihydro-12H-indolo[2.3-a]quinolizinium bromide (XXIV). A stream of dry hydrogen bromide was bubbled through a solution of 0.71 g. of the phenylhydrazone of XXVI in 50 ml. of absolute ethanol at such a rate that gentle refluxing was maintained. The color changed from golden yellow to yellow-green. The mixture was concentrated under reduced pressure, chilled, and the precipitate was collected in a dry atmosphere and dried in a desiccator. The yield was 0.60 g. (91%). The bromide formed bright yellow needles from absolute ethanol and melted at 335–337° (dec., uncorr.). Sugasawa and coworkers[9] report m.p. 327–330° (dec.) for XXIV prepared by another method.

Anal. Calcd. for $C_{15}H_{13}BrN_2$: C, 59.8; H, 4.4; N, 9.3. Found: C, 59.8; H, 4.3; N, 9.3.

The ultraviolet spectrum of an ethanolic solution of XXIV showed maxima at 252 (log ϵ 3.85), 315 (log ϵ 4.06), and 385 (log ϵ 4.09) mμ and minima at 240 (log ϵ 3.75), and 275 (log ϵ 3.35), and 340 (log ϵ 3.80) mμ.

Hydrogenation of XXIV. *1,2,3,4,6,7,12,12b-octahydroindolo-[2.3-a]quinolizine.* (XXVII). A solution of 0.254 g. of XXIV in 80 ml. of absolute methanol containing 3 drops of ammonium hydroxide was shaken with 0.1 g. of platinum oxide under hydrogen at room temperature and atmospheric pressure. Three equivalents of hydrogen were absorbed in 20 min. and the color changed from red to colorless. The filtrate from the catalyst was made basic with 5% sodium carbonate solution and concentrated to dryness under reduced pressure. The yellow residue was extracted with ether. Recrystallization of the residue after evaporation of the ether from hexane (Norite) gave 0.18 (95%) of stout, white needles, m.p. 153–154°. Reported m.p.'s for XXVII prepared by other routes are 148–151°[27] and 147–147.5°.[26] The m.p. of XXVII was not depressed on admixture with an authentic sample,[35] and the infrared spectra of the two samples were superimposable.

The ultraviolet spectrum of an ethanolic solution of XXVII showed maxima at 226 (log ϵ 4.58), 283 (log ϵ 3.91), a shoulder at 290 (log ϵ 3.84), and a minimum at 247 (log ϵ 3.42) mμ. Groves and Swan[25] report a maximum at 279 (log ϵ 3.89) and a minimum at 247 (log ϵ 3.33) mμ.

10-Methoxy-6,7-dihydro-12H-indolo[2.3-a]quinolizinium bromide. XXVIII. The *m*-methoxyphenylhydrazone of XXVI, prepared in and recrystallized from absolute ethanol, formed fine orange-yellow needles, m.p. 261–262° (dec.).

Anal. Calcd. for $C_{16}H_{18}BrN_3O$: C, 55.2; H, 5.2; N, 12.1. Found: C, 55.1; H, 5.0; N, 11.9.

Cyclization was effected by passing dry hydrogen bromide through a solution of 0.75 g. of the above phenylhydrazone in 60 ml. of absolute ethanol for 1 hr. Concentration of the mixture and chilling gave 0.63 (86%) of XXVIII. It formed yellow-orange needles, m.p. 306–307° (dec., uncorr.), from absolute ethanol.

Anal. Calcd. for $C_{16}H_{15}BrN_2O$: C, 58.0; H, 4.6; N, 8.5. Found: C, 58.0; H, 4.7; N, 8.4.

9-Hydroxy-6,7-dihydro-12H-indolo[2.3-a]quinolizinium bromide. (XXIX). The *p*-methoxyphenylhydrazone of XXVI, prepared in and recrystallized from absolute ethanol, formed orange needles, m.p. 269–271° (dec., uncorr.) after darkening at about 255°.

Anal. Calcd. for $C_{16}H_{18}BrN_3O$: C, 55.2; H, 5.2; N, 12.1. Found: C, 55.3; H, 5.1; N, 12.1.

Cyclization was carried out as in the case of XXVIII. XXIX formed fine orange needles, m.p. 304–306° (dec. uncorr.) after darkening at 290°, from absolute ethanol. The yield of very hygroscopic material was 61%.

The infrared spectrum taken as a Nujol mull showed a weak band at 3400 cm.$^{-1}$ (OH) and there were no prominent bands in the region associated with an ether linkage (1100 cm.$^{-1}$).

Anal. Calcd. for $C_{16}H_{16}BrN_2O$: C, 58.0; H, 4.6; N, 8.5. Calcd. for $C_{15}H_{13}BrN_2O$: C, 56.8; H, 4.1; N, 8.8. Found: C, 56.6; H, 4.3; N, 8.7.

9-Hydroxy-10-methoxy-6,7-dihydro-12H-indolo[2.3-a]-quinolizinium bromide. (XXX). The 3,4-dimethoxyphenylhydrazone of XXVI, prepared as in the preceding cases formed brown-orange needles, m.p. 265° (dec., uncorr.), after softening and darkening at 255°.

Anal. Calcd. for $C_{16}H_{20}BrN_3O_2$: C, 54.0; H, 5.3; N, 11.1. Found: C, 54.0; H, 5.4; N, 11.1.

Cyclization was accomplished as in the preceding cases to give 67% of XXX as fine red-orange needles, m.p. 302–303° (dec., uncorr.) after darkening at 290°. The compound is very hygroscopic.

The infrared spectrum (Nujol) showed a weak band at 3400 cm.$^{-1}$ (OH) and a stronger band at 1100 cm.$^{-1}$ (ether).

Anal. Calcd. for $C_{17}H_{17}BrN_2O_2$: C, 56.5; H, 4.7; N, 7.8. Calcd. for $C_{16}H_{15}BrN_2O_2$: C, 55.3; H, 4.4; N, 8.1. Calcd. for $C_{15}H_{13}BrN_2O_2$: C, 54.0; H, 3.9; N, 8.4. Found: C, 55.2; H, 4.6; N, 8.2.

The ultraviolet spectra for XXVIII, XXIX, and XXX are shown in Fig. 1.

ANN ARBOR, MICH.

(35) We wish to thank Dr. D. S. Tarbell of the University of Rochester for a generous sample of XXVII.

[CONTRIBUTION FROM THE PHARMACEUTICAL LABORATORY, MEDICAL SCHOOL, KEIO-GIJUKU UNIVERSITY]

Santonin and Related Compounds. XIII. Attempted Preparation of *trans*-3,5-Diketo-α-sant-Δ¹-enic Acid[1,2]

MASAITI YANAGITA AND HARUO OGURA

Received August 6, 1957

Preparation of the acid (III) mentioned in the title was attempted by three different methods, but all proved unsuccessful. First, epimerization of the *cis*-Δ¹-diketo acid (I) into the *trans* isomer (III) could not be effected under the mild conditions employed. The second method, involving lactone-opening and subsequent oxidation of *trans*-Δ¹-dihydrosantonin (VI), gave not the desired acid (III), but an unidentified product. The third attempt of dehydrobromination of the 2-bromo-*trans*-diketo acid (IX) furnished only the enol lactone (XII) under rearrangement. Similar treatment of the bromide (XIII) of the *cis*-diketo acid (IV, R = H) resulted in a mixture of the Δ¹-diketo acid (I) and the same enol lactone. A possible explanation for the position of bromination in some pairs of the *cis* and *trans* series of 3-decalone systems is proposed.

In paper XII of this series,[1] we described the preparation of *cis*-3,5-diketo-α-sant-Δ¹-enic acid[3] (I) by selective hydrogenation of 3,5-diketo-α-santa-Δ¹,⁴-dienic acid (II) with zinc and ethanol. It seems of interest to prepare the *trans* isomer (III) of I for comparison of their behavior in some reactions, especially toward isomerization to santonic acid with alkali.[1]

It was reported[4] that the interconversion of *cis*- and *trans*-3,5-diketo-α-santanic acids (IV and V, both R=H) by isomerization was readily effected by warming with dilute alkali. Under similar conditions, isomerization of *cis*-Δ¹-diketo acid (I) into the *trans* isomer (III), which was expected to be more stable, was attempted. After careful examination of the reaction mixture, most of the starting acid was recovered and the *trans* acid could not be isolated. It is noteworthy that the *cis* configuration at the ring juncture in I is more resistant toward alkaline isomerization than the saturated *cis*-diketo acid (IV, R=H).

As a possible second route to the *trans* acid (III), the lactone opening and subsequent oxidation of *trans*-Δ¹-dihydro-α-santonin (VI) came under consideration. It had been disclosed from the authors' laboratory[5] that the 2-bromide of *trans*-tetrahydro-α-santonin (VII, R=Br) on collidine treatment gave only a low yield of the Δ¹-dihydro compound (VI) as the sole product isolated. In order to improve the reported result, dehydrobromination of the bromide (VII, R=Br) was performed with lithium chloride and dimethylformamide, which reagents are known to be effective in the dehydrohalogenation of α-halo-3-ketosteroids.[6,7] When the reaction was conducted under the conditions favorable for dehydrobromination of the bromoketosteroids,[6] the known chloro compound (VII, R=Cl)[8,9] was formed in a good yield. Since the halogen in α-chloro-3-ketosteroids was dehydrochlorinated by these reagents only at higher temperatures than the bromo analogs,[6,7] the bromide (VII, R=Br) was treated with these reagents at a higher temperature, in view of possible intermediate formation of the above chloro compound. There was indeed obtained a halogen-free mixture, but the desired Δ¹- compound could not be isolated from it. As mentioned previously with the 2-chloro-3-ketosteroids,[10] this chloro compound showed resistance toward hot collidine, but was readily reduced with zinc and ethanol to the parent ketone (VII, R=H). The location of the chlorine at the 2- position, which is not evident from the previous work,[8] can be given by the mode of its formation. It involves the above replacement reaction of halogens in the 2-bromo compound (VII, R=Br) where the location of bromine was confirmed,[11] and the direct chlorination of VII (R=H) with chlorine which possibly parallels 2-bromination with bromine.[5,11] Based on the ultraviolet spectrum, the

(1) Paper XII, M. Yanagita and H. Ogura, *J. Org. Chem.*, **22**, 1092 (1957).

(2) This work was supported in part by the Grant in Aid for Scientific Research from the Ministry of Education of Japan.

(3) For the definition of the nomenclature employed and the numbering system used in this paper, see W. G. Dauben and P. D. Hance, *J. Am. Chem. Soc.*, **77**, 606 (1955). The term *cis-trans* refers to the configuration at the juncture of six-membered rings, corresponding to γ- and α-tetrahydrosantonins in our previous papers of this series, and the term α-β represents the α- and β-santonin series, which are epimers at the methyl group of the 11- position.

(4) A. Tahara, *J. Org. Chem.*, **21**, 442 (1956).

(5) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955).

(6) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

(7) J. J. Beereboom and C. Djerassi, *J. Org. Chem.*, **19**, 1196 (1954).

(8) E. Wedekind and K. Tettweiler, *Ber.*, **64**, 387 (1931).

(9) Since completion of this experimentation, a communication by W. Cocker and T. B. H. McMurry [*J. Chem. Soc.*, 4549 (1956)] appeared describing the same result. However, these authors obtained, in an unspecified yield, the chloro compound, the melting point of which was about 30° lower than that reported previously[8] and given in the present work. Unfortunately, the previous work[8] was overlooked by these authors.

(10) J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 3500 (1953).

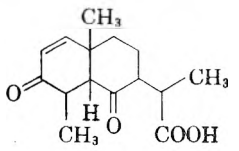
(11) Unpublished work.

chlorine in VII (R = Cl) was previously assigned an equatorial conformation,[9] and this was further evidenced by the shift (24 cm.$^{-1}$) in carbonyl absorption from the tetrahydroketone (VII, R = H) to the chloro compound (VII, R = Cl).[12]

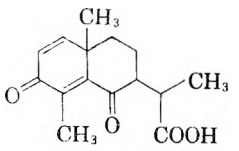
Two possible mechanisms were suggested by Holysz[6] for dehydrobromination of the 4-bromo-3-ketosteroids of the natural series (rings A/B: *cis*) into the Δ^4- compound with lithium chloride and dimethylformamide. The one involves an intermediate formation of a displacement product with an axial chlorine at the 4- position, a favorable conformation for ionic elimination. The other, which is considered more plausible, is a concerted mechanism with a transition state involving a six-membered ring between the bromide and the reagents. The above reaction of the bromo compound (VII, R = Br) with lithium chloride does not seem to follow either of the mechanisms of Holysz. It is reasonable to consider that the substitution of bromine by chlorine in VII (R = Br) gives an intermediate compound with axial chlorine, which, contrary to the case of steroids, may be immediately inverted to the stable equatorial position.

Attempt was made to transform the Δ^1-*trans*-dihydro compound (VI) into the desired *trans*-Δ^1-3,5-diketo acid (III) by lactone-opening and subsequent oxidation under similar conditions as described for the conversion of VII (R = H) to the corresponding diketo acid (V).[4] There was isolated, in low yield, unidentified crystals, which showed none of the characteristics expected of III, and was not further investigated.

The third line of approach to III involved the bromination-dehydrobromination of the *trans*-diketo acid (V) in the usual manner. The starting material (V) has been previously prepared by the two different methods, both of which are unsuitable for our purpose. Thus, the hydroxy acid, prepared from the *trans*-tetrahydro compound (VII, R = H) by lactone opening, was reported to give a rather poor yield of V on oxidation with chromium trioxide. Another method, consisting in hydrogenation of the methyl ester of $\Delta^{1,4}$-diketo acid (II) followed by hydrolysis to the free acid,[13] appears tedious. It has been found now that direct hydrogenation of the $\Delta^{1,4}$-diketo acid (II) itself over Raney nickel in the presence of potassium carbonate in dilute methanol resulted in 80% yield of V in a sterically pure state.

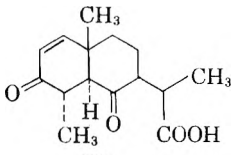


I

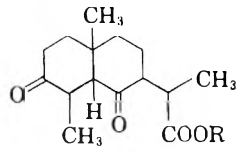


II

(12) E. J. Corey, *J. Am. Chem. Soc.*, 75, 2301 (1953).
(13) H. Matsumura, I. Iwai, and Ohki, *J. Pharm. Soc. Japan*, 75, 1043 (1955).



III



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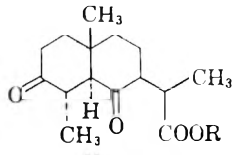
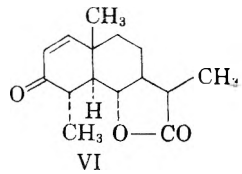
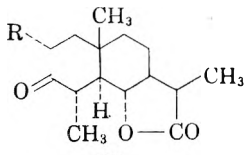


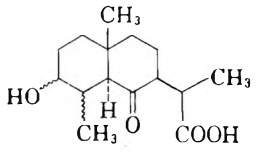
V



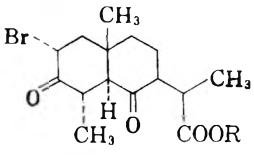
VI



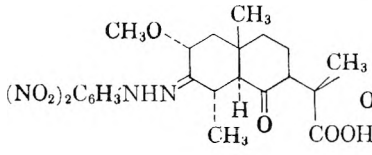
VII



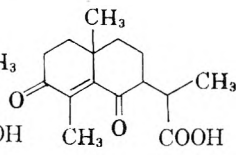
VIII



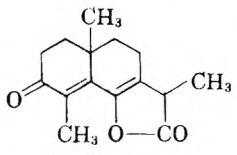
IX



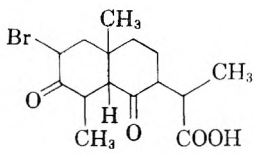
X



XI



XII



XIII

On hydrogenation of II with platinum black in acetic acid, a hydroxy acid (VIII) was formed in 78% yield, which was oxidized to the *trans*-diketo acid (V), indicative of the *trans* fusion of VIII. This hydroxy acid was unaffected by warm hydrochloric acid (no lactone formation) and did not give a 2,4-dinitrophenylhydrazone. These results show that in this hydrogenation, the keto group at the 3- position in II was highly selectively reduced to the hydroxy group, while the severely hindered keto group at the 5- position was preserved, as in the case of the saturated 3,5-diketo acids (IV and V, both R = H).[4] The hydroxy acid,[4] previously obtained by hydrogenation of V (R = H), is isomeric but not identical with VIII, probably being different in the configuration at the 3- and/or 4- positions.

Treatment of the *trans*-diketo acid (V) with one mole of bromine in chloroform afforded a monobromo compound (IX, R = H), as the single product, in 90% yield. Similar bromination of the methyl ester of V led to the ester of the mono-

bromide (IX) in low yield. To establish the position of bromine, the monobromide (IX, R=H) was treated with Brady's reagent[14] to give the 2,4-dinitrophenylhydrazone of the methoxyl derivative (X). This hydrazone proved identical with the same derivative of the methoxyl compound, prepared from 2-methoxy-*trans*-tetrahydro-α-santonin (VII, R=OCH_3) by lactone-opening and subsequent oxidation with chromium trioxide. Compound VII (R=OCH_3) had previously been obtained from the 2-bromo compound cited above (VII, R=Br) by reaction with Brady's reagent followed by hydrolysis.[5] Accordingly, the monobromide of the *trans*-diketo acid (V) must possess the 2-bromo structure (IX), excluding the possibility that the bromine may be located at other positions α to the keto groups. An equatorial orientation of the bromine in IX, which was rendered likely by conformational analysis,[12] was indicated by the shift in carbonyl absorption (12 cm.$^{-1}$) from the diketo acid (V) to IX.[12]

Dehydrobromination of the bromodiketo acid (IX) was carried out with hot collidine, forming 1.02 moles of the collidine salt. Unexpectedly, there was obtained a neutral brown oil, along with a lesser amount of acidic product. From the latter fraction, the desired Δ^1- compound (III) could not be isolated. The neutral oil, which refused to crystallize, was converted to 2,4-dinitrophenylhydrazone. Use of lithium chloride and dimethylformamide in place of collidine furnished a similar result, but the two fractions were obtained in higher yields.

It had been announced[15,16] that *rac*-Δ^4-3,5-diketo acid (XI) was converted, on heating by itself, to the enol lactone (XII) as yellow crystals, the melting point of which was variable. On repetition, it was found that the yield of XII was somewhat raised by conducting the pyrolysis at a lower temperature. Similar formation of enol lactone may be expected to take place in the above reaction of the bromide (IX) with a base. Indeed, analogous treatment of XI with lithium chloride and dimethylformamide at a high temperature furnished a neutral brown sirup, which was converted to its 2,4-dinitrophenylhydrazone. The latter was shown to be identical with the derivative of crystalline enol lactone (XII) and also with that of the neutral oil obtained above from the bromide (IX). Consequently, it is obvious that the dehydrobromination of the bromide (IX) with bases is attended with rearrangement to give the Δ^4- compound, as the sole product isolated.

Another interesting method for preparing the enol lactone (XII) has been reported involving selective hydrogenation of the enol lactone of the $\Delta^{1,4}$-diketo acid (II) over Raney nickel in the presence of pyridine in ether solution.[16] In the present work, it was found that hydrogenation of the $\Delta^{1,4}$-enol lactone into XII in a comparable yield was also achieved by using palladium-charcoal as a catalyst in acetone in the absence of a base. Similarly, the $\Delta^{1,4}$-diketo acid (II) itself can be reduced to the Δ^4-diketo acid (XI) in a fair yield. The latter was further hydrogenated with zinc and ethanol to the *cis*-diketo acid (IV, R=H), providing evidence for the location of the double bond between the keto groups in XI.

Since, as described above, the bromo-*trans*-diketo acid (IX) behaved abnormally on dehydrobromination, the *cis* isomer (XIII) was subjected to the same sequence of reactions. Bromination of the *cis*-diketo acid (IV) took place less readily than that of the *trans* isomer (V). Collidine treatment of the *cis*-monobromide (XIII) resulted in the formation of 0.97 mole of collidine salt, and the isolation of the *cis*-Δ^1-diketo acid (I), the normal product, in a low yield. In addition, a lesser amount of the enol lactone (XII) was isolated from the neutral fraction, as its 2,4-dinitrophenylhydrazone. Use of lithium chloride and dimethylformamide gave both products in better yields. In this case, however, there is a possibility that the bromide of the *cis*-diketo acid (IV, R=H) might be isomerized to the bromide of the more stable *trans*-isomer (V, R=H) on treatment with hot collidine, producing the unsaturated enol lactone (XII). Reported facile interconversion between these isomeric diketo acids with alkali[4] seems to favor this possibility. On heating IV with collidine, the starting ketone was substantially recovered and the *trans* isomer could not be detected. This excluded the foregoing possibility, indicating that the *cis*-bromide (XIII), unlike the *trans*-bromide (IX), on treatment with a base furnished a mixture of the double-bond isomers. The 2-bromo structure (XIII) for the *cis*-bromo-diketo acid can be assigned on the basis of its transformation to the Δ^1- compound (I) on dehydrobromination, since, in the 9-methyl-3-decalone systems, the 4-monobromo compound is unlikely to undergo rearrangement to the Δ^1-compound (I) on treatment with a base, especially when the bromine is tertiary.[17] From the relative stability to acid, the bromine in XIII may be assigned an equatorial conformation, though the shift in carbonyl absorption due to α-bromine is small (3 cm.$^{-1}$).[12]

It is interesting that, of the isomers of the bromodiketo acids, the *trans* fused one (IX) showed a much greater tendency to undergo rearrangement during dehydrobromination. A similar example is found in the results reported with the isomers of

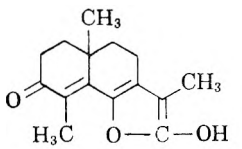
(14) A saturated methanolic solution of 1 part of 2,4-dinitrophenylhydrazine in 4 parts of concentrated sulfuric acid.

(15) M. Nishikawa, K. Morita, and H. Hagiwara, *J. Pharm. Soc. Japan*, 75, 1199 (1955).

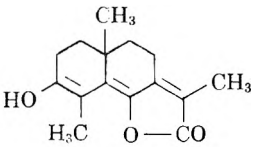
(16) M. Nishikawa, K. Morita, and H. Hasegawa, *J. Pharm. Soc. Japan*, 75, 1202 (1955).

(17) M. Yanagita and R. Futaki, *J. Org. Chem.*, 21, 949 (1956).

2,4-dibromo-9-methyl-3-decalone, of which the *trans* isomer on collidine treatment is rearranged into the $\Delta^{4,5}$-dienone, whereas the *cis* isomer forms the normal $\Delta^{1,4}$-dienone.[18] It is also noted that the Δ^4-diketo acid (XI) readily forms the enol lactone ring on heating, while the *cis*-Δ^4-diketo acid (I) remains unaffected. The facile dehydration in the former may be due to an electronic factor which favors elimination by the formation of a linear-conjugated dienone system. The two structures XIV and XV for the enol lactone (XII) were proposed by Nishikawa *et al.*[16] on the basis of ultraviolet and infrared absorption spectra. These formulations find further support in our observation that 3,5-diketo-β-sant-Δ^4-enic acid, a C_{11}-methyl epimer of XI, was converted to the same enol lactone by a similar procedure.[19] The unsuccessful recovery of the crystalline enol lactone from the usual solvent on heating may be attributed to the possible formation of a tautomeric equilibrium between the keto (XII) and the enol forms (XIV or XV or both) in the solution. The mutarotation[15] of the enol lactone in alcohol supports this assumption.



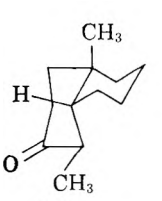
XIV



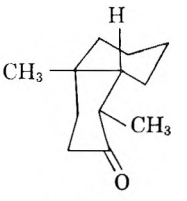
XV

It is recorded that bromine preferentially attacks the 4- position in *cis*-4,9-dimethyl-3-dedalone[17] and in the 3-ketosteroids of the natural series.[20] On the other hand, *cis*-tetrahydro-α-santonin is reported to be brominated at the 2- position,[5] like the *cis*-diketo acid (V) described above.

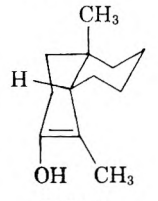
Dreiding[21] proposed an interesting rationalization for the position of bromination in the juncture isomers of 3-decalones and 3-ketosteroids in connection with the direction of enolization, which is governed by the steric (skew interaction) and the electronic factors (hyperconjugation effect). It was postulated by this author that, in 3-ketosteroids of the natural series, an enolization toward the 4- position is more favored by one less skew interaction than that toward the 2- position, agreeing with the bromination result of these ketones. The 4- bromination of *cis*-4,9-dimethyl-3-decalone can be connected with preference of Δ^3-enolization (XVIII and XIX, respectively) in the two conformations (XVI and XVII), which are more stabilized by the above factors than the Δ^2-enolization.



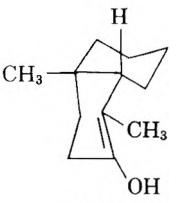
XVI



XVII

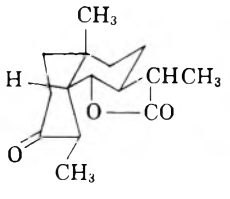


XVIII

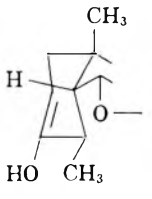


XIX

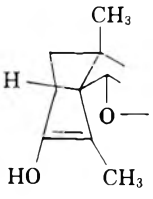
The bromination of *cis*-tetrahydro-α-santonin at the 2- position seems to be inconsistent with the stability of an enol structure which is governed by the above factors. In this case, however, a new non-bonded interaction must be considered to appear between the hydroxyl group of the lactone ring and the methyl group at the 4- position. This interaction, the strength of which is equivalent to that of the *meta*-diaxial effect in the cyclohexane ring, may be expected to play an important part in determining the direction of enolization in this molecule. Examination of molecular models showed that the strength of this interaction remains almost unchanged in the Δ^2-enol structure (XXI). On the other hand, the enolization toward the 4- position (XXII) causes a closer proximity of the two referred substituents, by which the interaction should be increased to exert a severe steric hindrance to uniplanar arrangement of the double bond. Thus, in XX, the steric factor outweighs the electronic effect, favoring the Δ^2-enolization (XXI) which is in agreement with the result of bromination in this ketone.



XX



XXI



XXII

In two possible conformations[1] of the *cis*-diketo acid (IV), an analogous steric interference is assumed to exist between the methyl group at the 4- position and the keto group at the 5- position. The 2- bromination of IV is similarly explained on the basis of preference of the Δ^2-enolization which is conceivable for the same reasons as stated for XX.

In the *trans*-fused 3-decalone rings, the relative stability of two enol structures may be predicted

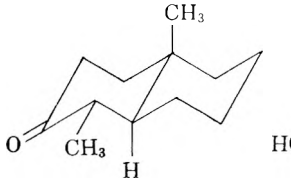
(18) M. Yanagita and A. Tahara, *J. Org. Chem.*, 18, 792 (1953); *cf.* M. Yanagita, K. Yamakawa, A. Tahara, and H. Ogura, *J. Org. Chem.*, 20, 1767 (1955).

(19) Unpublished work.

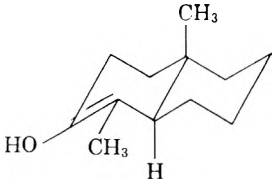
(20) C. W. Shoppee and E. Shoppee in E. H. Rodd's *Chemistry of Carbon Compounds*, Elsevier Publishing Company, New York, 1953, Vol. II B, p. 833.

(21) A. S. Dreiding, *Chem. & Ind. (London)*, 1419 (1954).

only by the hyperconjugation effect, when the other factors operating between the ring substituents are equal.[21,22] Thus, in the 3-keto-steroids of allo series (rings A/B; *trans*), this effect favors the Δ^2-enol structure, being in harmony with the 2- bromination of these ketones.[20] The 4-bromination in *trans*-4,9-dimethyl-3-decalone (XXIII) can be similarly rationalized by the Δ^3-enolization (XXIV) due to the electronic factor.

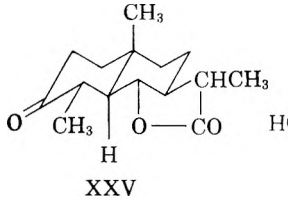


XXIII

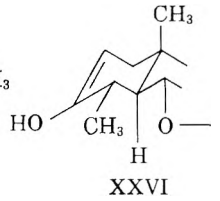


XXIV

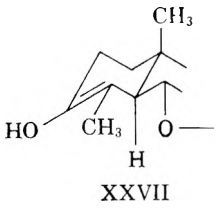
On the other hand, the 2- bromination of *trans*-tetrahydro-α-santonin (VII, R=H), which is described by XXV, is assumed to be attributable to the nonbonded interaction between the two substituents at the 4- and 5- positions which prefers the Δ^2-structure (XXVI) rather than the Δ^3-structure (XXVII) as in the case of the *cis* isomer (XX). The same steric interpretation can be adapted for the 2- bromination of the *trans*-diketo acid (V).



XXV



XXVI



XXVII

EXPERIMENTAL[23]

All temperatures are uncorrected. Rotations were determined in a 0.5-dm. semimicro tube; infrared absorption spectra were measured with a Perkin-Elmer model 21 double-beam spectrophotometer.

Attempted isomerization of cis-3,5-diketo-α-sant-Δ¹-enic acid (I). This reaction was carried out by the procedure employed previously for the isomerization of the *cis*-diketo acid (IV) into the *trans* isomer (V).[4] To a solution of 0.15 g. of the Δ^1-*cis*-diketo acid (I)[1] in 2 cc. of methanol was added 6 cc. of 3% aqueous potassium hydroxide, and the mixture was warmed on a water bath for 15 min. After cooling, the mixture was acidified with dilute sulfuric acid, saturated with sodium chloride, and extracted with ether. Evaporation of the dried ether solution left a colorless oil (0.15 g.) which, on treatment with ether-petroleum ether, gave 0.07 g. (47%) of the starting material (I), m.p. 175° (mixed m.p.) (after recrystallization from benzene-petroleum ether). The mother liquor of the crystals furnished a colorless oil (0.08 g.), which was chromatographed on silica gel (80-mesh, 1 × 20 cm.). Elution with benzene-ethanol (1:1) afforded an oil (0.07 g.), which was treated with diazomethane in ether. The methylation product was again chromatographed on alumina (1.2 × 20 cm.) and eluted with benzene-petroleum ether (1:1). The more readily eluted fraction gave a methyl ester (0.02 g.) of the starting ketone as prisms, m.p. (mixed m.p.) 100°; reported m.p. 99°.[1] From the less readily eluted fraction was obtained an oil (0.03 g.), which formed a *2,4-dinitrophenylhydrazone* (0.03 g.) as a yellow crystalline powder. Recrystallization from methanol gave yellow needles, m.p. 191–192°. It caused no depression of the melting point on admixture with the same derivative, m.p. 191–192° (after recrystallization from methanol), prepared from the methyl ester of the starting acid (I) with Brady's reagent. It had $\lambda_{max}^{CHCl_3}$ 259 mμ (log ε 4.06) and 373 mμ (log ε 4.42).

Anal. Calcd. for $C_{22}H_{26}O_7N_4$: C, 57.64; H, 5.72. Found: C, 58.07; H, 5.46.

Reaction of 2-bromo-trans-tetrahydro-α-santonin (VII, R = Br) *with lithium chloride and dimethylformamide.* A solution of 0.20 g. of the bromide (VII, R = Br) and 0.078 g. of lithium chloride in 4 cc. of dimethylformamide was heated at 95–100° for 2 hr. in a stream of nitrogen. The reaction mixture was diluted with ether and was washed successively with water, dilute sulfuric acid, bicarbonate solution, and water. Evaporation of the ether extract left 0.12 g. (70%) of the 2-chlorotetrahydrosantonin (R = Cl), m.p. 201° (dec.). Recrystallization from ethanol gave colorless platelets, m.p. 208° (dec.); $[\alpha]_D^{11}$ +14.3° (*c*, 0.28; EtOH) and +16.2° (c, 0.87; $CHCl_3$). It melted at 210° on admixture with a sample described in the following paragraph. Cocker and McMurry[9] gave m.p. 178–179° (variable); $[\alpha]_D^{23}$ +19.3° (*c*, 0.4; $CHCl_3$), for the chloro compound prepared in a similar way.

Anal. Calcd. for $C_{15}H_{21}ClO_3$: C, 63.26; H, 7.43. Found: C, 63.26; H, 7.09.

2-Chloro-trans-tetrahydro-α-santonin (VII, R = Cl). This was prepared by the modification of a previous method which was described only briefly.[8] Into a solution of 0.05 g. of *trans*-tetrahydro-α-santonin[5] (VII, R = H) in 3 cc. of chloroform was introduced chlorine gas (1.2 equivalents), generated from 10 mg. of potassium permanganate, at room temperature. The reaction mixture was washed with water, dried, and evaporated to leave 0.04 g. (70%) of the chloro compound (VII, R = Cl) as colorless platelets, m.p. 205° (dec.). Recrystallization from ethanol raised the m.p. to 213° (dec.); reported, m.p. 214° (dec.).[8]

The chloro compound (10 mg.) was refluxed with 30 mg. of zinc dust (activated with copper salt) in 5 cc. of ethanol for 15 hr. on a water bath. After removal of zinc, the reaction solution was evaporated, and the residue was dissolved in benzene. Washing, drying, and evaporation of the benzene solution gave 5 mg. of tetrahydrosantonin (VII, R = H)[5] as colorless leaflets, m.p. 150°. Recrystallization from ethanol raised the m.p. to 151° (mixed m.p.).

The chloro compound (VII, R = Cl, 40 mg.) was heated with γ-collidine at 275–180° for 20 min. in a stream of nitrogen. Working up of the mixture as usual afforded crystals (28 mg.) m.p. 130°, which were recrystallized from ethanol to give the starting material (13 mg.) as plates, m.p. 205° (mixed m.p. 107°). The mother liquor of recrystallization afforded a further amount of the starting material, m.p. 200° (after chromatography on alumina).

Attempted conversion of Δ¹-trans-dihydro-α-santonin (VI) *to the Δ¹-diketo acid* (III). The Δ^1-dihydro compound (VI) was subjected to hydrolysis of the lactone ring and subsequent oxidation, principally according to the procedure de-

(22) D. A. H. Taylor, *Chem. & Ind. (London)*, 250 (1954).

(23) Microanalyses were carried out by Miss Ch. Shibuya and the ultraviolet measurements by Miss M. Suzuki.

scribed previously for the preparation of the *trans*-diketo acid (V) from *trans*-tetrahydrosantonin[4] (VII, R = H).

Compared with the tetrahydro compound[24] (VII, R = H), the dihydro compound (VI, 0.12 g.) more readily dissolved in 6% potassium hydroxide (2 cc.) on warming on a water bath. The alkali solution was washed with ether and slowly acidified with 10% sulfuric acid under cooling with a mixture of sodium chloride and ice, and was at once extracted with ether-chloroform (10:1). After addition of 3 drops of pyridine, the extract was dried over sodium sulfate and the solvent was distilled off under reduced pressure. The residue was mixed with a mixture of 0.10 g. of chromium trioxide and 3 cc. of pyridine and was stored in an ice box for 36 hr. Treatment as described previously[4] furnished an acidic fraction (nonlactonic fraction) as a colorless oil (0.07 g.), which was chromatographed on silica gel (80 mesh, 0.8 × 13 cm.). Elution with petroleum ether-benzene (1:1) gave a minute amount of crystals, m.p. 134° (after recrystallization from petroleum ether-benzene). This material, which formed no precipitates with Brady's reagent and exhibited no ultraviolet absorption bands corresponding to the α,β-unsaturated ketone, was not further investigated.

Similar treatment of *cis*-Δ^1-dihydrosantonin gave only a minute amount of crystals, m.p. 156° (after recrystallization from petroleum ether-benzene). This material showed no characteristics of the α,β-unsaturated ketone, obviously being different from the Δ^1-*cis*-diketo acid (I), m.p. 190–191°.[1]

2-Bromo-trans-3,5-diketo-α-santanic acid (IX, R = H). To a solution of 0.30 g. of the above described *trans*-diketo acid (V, R = H),[4] m.p. 148° ($\nu_{C=O}^{CHCl_3}$ 1706 cm.$^{-1}$), in 5 cc. of chloroform was added, dropwise, a solution of 0.19 g. of bromine in 2 cc. of the same solvent under cooling. Bromine absorption proceeded rapidly. The reaction mixture was washed with water, dried over sodium sulfate, and evaporated to a small bulk. Addition of a small amount of petroleum ether precipitated 0.35 g. (90%) of almost white needles, m.p. 143° (dec.). Recrystallization from ethyl acetate–petroleum ether gave white needles, m.p. 152° (dec.); $[\alpha]_D^{11}$ −73.8° (*c*, 0.43; EtOH), $\nu_{C=O}^{CHCl_3}$ 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{21}BrO_4$: C, 52.18; H, 6.13. Found: C, 52.00; H, 6.19.

Methyl 2-bromo-trans-3,5-diketo-α-santonate (IX, R = CH_3). (*a*) The above bromide (IX, R = H) was treated with an ether solution of diazomethane under ice cooling. The methyl ester was obtained as colorless leaflets (0.02 g., 96%), m.p. 132°. Recrystallization from benzene–petroleum ether raised the melting point to 137°, undepressed on admixture with a sample described just below.

(*b*) Methyl ester (V, R = CH_3), prepared from the *trans*-diketo acid (V, R = H) with diazomethane,[25] was brominated with bromine as described above for the acid (V, R = H). The product was a colorless oil, which partly crystallized from ether on addition of petroleum ether as colorless leaflets (44%), m.p. 132°. Further recrystallization from benzene–petroleum ether raised the melting point to 137–138°; $[\alpha]_D^{14}$ −92.3° (c, 0.87; EtOH).

Anal. Calcd. for $C_{16}H_{23}BrO_4$: C, 53.49; H, 6.45. Found: C, 53.93; H, 6.34.

2-Methoxy-trans-3,5-diketo-α-santanic acid 2,4-dinitrophenylhydrazone (X). (*a*) The above bromo acid (IX, R = H, 0.05 g.) was dissolved in Brady's Reagent (a solution of 0.04 g. of 2,4-dinitrophenylhydrazine and 0.05 cc. of concentrated sulfuric acid in 3 cc. of methanol). On standing at room temperature, the hydrazone (X) soon deposited as a yellow crystalline powder (0.06 g., 93%), m.p. 196°. Three crystallizations from methanol afforded fine yellow needles, m.p. 201°, undepressed on admixture with a sample described below (*c*).

Anal. Calcd. for $C_{22}H_{28}N_4O_8$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.51; H, 5.95; N, 11.98.

(*b*) 2-Methoxy-*trans*-tetrahydro-α-santonin (VII, R = OCH_3),[6] m.p. 135°, was subjected to hydrolysis-oxidation, essentially according to the procedure described earlier for the preparation of V (R = H) from VII (R = H).[4] A hydroxy acid, prepared from the methoxy lactone (VII, R = OCH_3, 0.10 g.), was treated with a mixture of chromium trioxide (0.06 g.) and pyridine (1 cc.) under cooling. After standing at 5–10° for 12 hr., the mixture was worked up as usual. The starting material (0.05 g.) was recovered as crystals, m.p. 130–132°, from the neutral fraction. The acidic fraction, a colorless oil (0.01 g.), formed a small amount of 2,4-dinitrophenylhydrazone (X), m.p. 196° (after recrystallization from methanol).

(*c*) Oxidation of the above hydroxy acid with chromium trioxide in acetic acid at higher temperature somewhat improved the result. To a stirred solution of chromium trioxide (0.18 g.) in acetic acid (5 cc.) containing a drop of water was added, dropwise, the alkaline solution of the hydroxy acid, prepared from the methoxy lactone (VII, R = OCH_3, 0.01 g.), at 20–25°. The addition was completed in about 30 min. and the stirring was continued further for 30 min. To decompose the excess of chromium trioxide, aqueous solution of sodium bisulfate was added, the mixture was diluted with water, and extracted with ether. The ether extract was washed three times with sodium chloride-saturated water and then with bicarbonate solution. Evaporation of the ether solution left the starting lactone (0.01 g.), m.p. 133° (mixed m.p.).

The bicarbonate solution was acidified and extracted with ether. Evaporation of the dried ether solution gave a colorless oil (0.02 g.), which formed the 2,4-dinitrophenylhydrazone (X, 0.01 g.), m.p. 191°. Two recrystallizations from methanol afforded fine yellow needles, m.p. 200°.

Dehydrobromination of 2-bromo-trans-3,5-diketo-α-santanic acid (IX, R = H). (*a*) *With γ-collidine.* The above bromo acid (IX, R = H, 0.10 g.) was heated with purified collidine (b.p. 169–170°) at 175–180° for 20 min. in a stream of nitrogen. After cooling, the mixture was diluted with ether and the separated collidine salt (0.06 g. 1.02 moles) was filtered off. The filtrate was washed successively with dilute sulfuric acid, water, and sodium bicarbonate. Evaporation of the dried ether solution gave a brown sirup (0.02 g.), which formed a 2,4-dinitrophenylhydrazone (0.02 g.). Recrystallization from ethyl acetate gave beautiful orange leaflets, m.p. 241° (dec.). It showed no depression of the melting point on admixture with the same derivative of the enol lactone (XII) of the Δ^4-diketo acid, described below.

The above bicarbonate wash, showing a green fluorescence, was acidified and extracted with ether. Evaporation of the dried ether solution left a red sirup (0.01 g.), which was methylated with diazomethane. The ester (0.01 g.) was chromatographed on alumina (0.8 × 12 cm.) and the elution with petroleum ether–benzene (1:1) furnished a minute amount of white needles, m.p. 166°, which is described below (*b*).

(*b*) *With lithium chloride and dimethylformamide.* A solution of 0.25 g. of the bromo acid (IX, R = H) and 0.10 g. of lithium chloride in 2 cc. of dimethylformamide was heated at 150–155° (oil bath temperature) for 30 min. in a stream of nitrogen. The reaction mixture was worked up as described above for the bromotetrahydro compound (VII, R = H). There was obtained, as a neutral product, a light brown sirup (0.08 g.) which (0.06 g.) formed the *2,4-dinitrophenylhydrazone* (0.07 g.) of the enol lactone (XII) as beautiful light orange leaflets, m.p. 240–241° (dec., mixed m.p.) (after recrystallization from ethyl acetate).

Anal. Calcd. for $C_{21}H_{22}N_4O_6$: C, 59.15; H, 5.20. Found: C, 58.95; H, 5.49.

Methylation of the above bicarbonate-soluble fraction gave the same methyl ester (0.01 g.), m.p. 167° (mixed m.p.

(24) H. Matsumura, I. Iwai, and E. Ohki, *J. Pharm. Soc. Japan*, **74**, 1206 (1954).

(25) H. Matsumura, I. Iwai, and E. Ohki, *J. Pharm. Soc. Japan*, **75**, 1043 (1955).

166°) (after recrystallization from petroleum ether), as obtained in (*a*). It had λ_{max}^{MeOH} 253.5 mμ (log ε 3.83), which is obviously different from the absorption band (λ_{max}^{MeOH} 225 mμ) of the *cis*-Δ¹-diketo acid (I).[1] Also the nonidentity of this ester with methyl ester of the Δ¹-3,5-diketo acid (XI), m.p. 61°, described below, is shown by a large discrepancy of the melting point, though the ultraviolet absorption maxima of the two esters are practically identical in position.

3,5-Diketo-α-santa-Δ¹,⁴-dienic acid (5-dehydro-α-santoninic acid) (II). This compound, m.p. 138°, was prepared from α-santoninic acid as reported previously.[1] It had $\nu_{C=O}^{CHCl}$ 1704 cm.⁻¹ and 1661 cm.⁻¹ (cross-conjugated dienone). With Brady's reagent, it formed a *2,4-dinitrophenylhydrazone* as a crystalline powder in 70% yield. Recrystallization from glacial acetic acid gave fine needles, m.p. 248°; $\lambda_{max}^{CHCl_3}$ 263 mμ (log ε 4.27), 310 mμ (log ε 3.81), and 395 mμ (log ε 4.62).

Anal. Calcd. for $C_{21}H_{22}N_4O_7$: C, 57.01; H, 5.01. Found: C, 56.99; H, 5.13.

Enol lactone of 3,5-diketo-α-santa-Δ¹,⁴-dienic acid. With a slight modification of the method reported previously,[15] this compound was prepared from the above acid (II) (0.30 g.) by heating at 170–180° and 1-mm. pressure for 15 min. The molten mass, partly crystallized, was dissolved in chloroform. The chloroform solution was washed with sodium bicarbonate solution, dried over magnesium sulfate, and evaporated to give yellow crystals (0.20 g.). Recrystallization from ether-chloroform furnished yellow plates, m.p. 147°; $[\alpha]_D^{17}$ +182.5° (*c*, 1.07; $CHCl_3$); reported, yellow solid, m.p. 135°,[26] and beautiful yellow needles, m.p. 166°; $[\alpha]_D^{18}$ +187°.[15] The discrepancy of the melting points of the latter and our sample may be due to dimorphism, since the values of the optical rotation of these substances are almost the same.

The acetate was prepared from the enol lactone by refluxing with acetic anhydride as reported previously.[15] It was obtained as yellow plates, m.p. 114–116°, after recrystallization from ether–petroleum ether. The acetate was also obtained in 50% yield directly from the Δ¹,⁴-diketo acid (II, 0.05 g.) by gentle refluxing with acetic anhydride (0.5 cc.) for 30 min.

3,5-Diketo-α-sant-Δ⁴-enic acid (XI). The above Δ¹,⁴-diketo acid (II, 2.00 g.), m.p. 138°, was dissolved in 50 cc. of purified acetone and was shaken in hydrogen over 0.4 g. of 0.6% palladium-charcoal. After 181 cc. (1.06 equivalents) of hydrogen was absorbed in about 2 hr., the gas uptake almost ceased. Removal of the catalyst and evaporation of the solvent afforded 2.0 g. of a colorless oil, which crystallized from ethyl acetate by addition of petroleum ether, as colorless plates (1.07 g., 54%), m.p. 129°. Further recrystallization from dilute ethanol raised the melting point to 138°, which was obviously depressed on admixture with the *trans*-diketo acid (V), m.p. 147–148°.[4] It had λ_{max}^{MeOH} 255 mμ (log ε 4.08); $\nu_{C=O}^{CHCl_3}$ 1689 cm.⁻¹ (α,β-unsaturated ketone), and $[\alpha]_D^{25}$ +100.0° (*c*, 0.5; EtOH).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.72; H, 7.78.

The mother liquor of the crude crystals (XI) gave an additional 0.25 g. (total 66%) of XI, m.p. 105°, identified as 2,4-dinitrophenylhydrazone described just above.

The Δ⁴-diketo acid (XI) with Brady's reagent formed, in 71% yield, a *2,4-dinitrophenylhydrazone*, which was recrystallized from ethyl acetate to afford orange needles, m.p. 224° (dec.); $\lambda_{max}^{CHCl_3}$ 265 mμ (log ε 4.27), 360 mμ (log ε 4.04) (shoulder), and 386 mμ (log ε 4.67).

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.40; H, 5.64.

A *semicarbazone* was obtained in 83% yield as colorless needles, m.p. 135° (dec.) from ethanol solution in the usual manner. Recrystallization from ethanol did not change the m.p.; $[\alpha]_D^{14}$ +240.0° (*c*, 1.33; EtOH).

Anal. Calcd. for $C_{16}H_{23}N_3O_4$: C, 59.79; H, 7.21. Found: C, 59.34; H, 7.38.

Methyl ester was prepared by treatment of the acid (XI, 0.03 g.) in ether with an ether solution of diazomethane. The ester (0.02 g.), m.p. 56°, was purified by passing the solution in petroleum ether–benzene (1:1) through alumina (0.8 × 13 cm.) and then recrystallized from petroleum ether. There were obtained colorless prisms, m.p. 61°; λ_{max}^{EtOH} 255 mμ (log ε 4.03) and $[\alpha]_D^{14}$ +93.5° (*c*, 0.51; EtOH). Drying in vacuum over P_2O_5 for 10 days caused no change in the melting point.

Anal. Calcd. for $C_{16}H_{22}O_4.H_2O$: C, 64.84; H, 8.16. Found: C, 64.90; H, 8.03.

The methyl ester formed, in 76% yield, a *2,4-dinitrophenylhydrazone*, which on recrystallization from ethyl acetate afforded orange needles, m.p. 226°.

Anal. Calcd. for $C_{22}H_{26}N_4O_7$: C, 57.63; H, 5.72. Found: C, 58.04; H, 5.47.

Zinc-ethanol reduction of 3,5-diketo-α-sant-Δ⁴-enic acid (IX). A solution of 0.10 g. of the above Δ⁴-diketo acid (XI) in 20 cc. of 99% ethanol was refluxed with 0.4 g. of zinc (activated with copper sulfate) on a water bath for 8 hr. Filtration of zinc and evaporation of the ethanol gave 0.10 g. of a colorless oil which was dissolved in ether. The ether solution was shaken with sodium bicarbonate, and the bicarbonate solution was acidified and extracted with ether. Evaporation of the dried ether extract left 0.05 g. (50%) of *cis*-3,5-diketo acid (IV) as colorless plates, m.p. 180°. Recrystallization from dilute ethanol raised the melting point to 185° (mixed m.p.); $\nu_{C=O}^{CHCl_3}$ 1709 cm.⁻¹ (unconjugated ketone).

With Brady's reagent, it gave a *2,4-dinitrophenylhydrazone*, as yellowish plates, m.p. 216° (dec.), after recrystallization from ethanol.

Anal. Calcd. for $C_{21}H_{26}N_4O_7$: C, 56.49; H, 5.87. Found: C, 56.76; H, 5.54.

To a solution of 0.03 g. of the *cis*-diketo acid (IV) in 5 cc. of methanol was added 0.1 cc. of concentrated sulfuric acid, and it was refluxed for 5 hr. on a water bath. Evaporation of methanol under reduced pressure left an oil, which was dissolved in ether. The ether solution was washed with aqueous sodium bicarbonate, dried, and evaporated. There was obtained *methyl ester* of IV (0.03 g., 95%), m.p. 116°, which was recrystallized from ether–petroleum ether to colorless prisms, m.p. 124°; $[\alpha]_D^{21}$ −150.0° (*c*, 0.4; $CHCl_3$).

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.98; H, 8.30.

trans-3,5-Diketo-α-santanic acid (V) *from the Δ¹,⁴-diketo-acid* (II). To a previously reduced mixture of 3 g. of Raney nickel and 1 g. of potassium carbonate in 30 cc. of methanol and 5 cc. of water was added a solution of 1.0 g. of the above Δ¹,⁴-diketo acid (II) in 10 cc. of methanol, and the resultant mixture was shaken in atmosphere of hydrogen. After 165 cc. (2.06 equivalents) of hydrogen was absorbed in 15 min., gas uptake ceased. The catalyst was filtered off, and the filtrate was acidified, diluted with aqueous sodium chloride–saturated solution, and extracted with ether. Evaporation of the dried ether extract gave the *trans*-diketo acid (0.8 g., 79%) as needles, m.p. 96°. Crystallization from dilute ethanol caused no changes in the melting point. The dehydrated material had the m.p. 149° (mixed m.p.); $\nu_{C=O}^{CHCl_3}$ 1706 cm.⁻¹ (unconjugated ketone). It showed no depression of the melting point on admixture with the same compound reported previously.[4]

With Brady's reagent, it formed, in 60% yield, a *2,4-dinitrophenylhydrazone*, as a yellow crystalline powder, which recrystallized from ethanol to needles, m.p. 185–186°.

Anal. Calcd. for $C_{21}H_{26}N_4O_7$: C, 56.49; H, 5.87. Found: C, 56.82; H, 5.50.

The esterification was smoothly effected by refluxing the acid (V, 0.05 g.) with a mixture of methanol (5 cc.) and concentrated sulfuric acid (0.1 cc.) for 3 hr., similarly as de-

(26) S. S. Medvedev, *Chem. Abstr.*, 21, 2476 (1927); 22, 1978 (1928).

scribed above for the methyl ester of the *cis* acid (IV). There was obtained the *methyl ester* (0.04 g., 76%) as colorless leaflets, m.p. 83.5° (after recrystallization from ether–petroleum ether). Reported,[13] m.p. 80–81°.

trans-5-Keto-3-hydroxy-α-santanic acid (VIII). A solution of 0.50 g. of the $\Delta^{1,4}$-diketo acid (II), m.p. 138°, in 15 cc. of glacial acetic acid was shaken in atmosphere of hydrogen in the presence of platinum black (prepared from 0.02 g. of platinic oxide). After 127 cc. (3.0 equivalents) of hydrogen was absorbed in 1.5 hr., the gas uptake almost ended. The catalyst was filtered off and the filtrate was evaporated to a small bulk under reduced pressure, and a small amount of water was added. On standing at room temperature, the solution deposited 0.40 g. (78%) of the hydroxy acid (VIII) as prisms, m.p. 174°. Recrystallization from ethyl acetate raised the m.p. to 181°; $[\alpha]_D^{18}$ +9.6° (c, 1.87; EtOH). It showed an obvious depression (*ca.* 20°) of the m.p. on an admixture with *cis*-5-keto-3-hydroxy-α-santanic acid, m.p. 182–183°, obtained previously by catalytic hydrogenation of the *cis*-diketo acid (IV, R = H).[4]

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.50; H, 9.28.

Oxidation of this hydroxy acid (VIII, 0.01 g.) with chromium trioxide-pyridine in the usual manner gave the *trans*-diketo acid (V, 5 mg.) m.p. 95° (after crystallization from dilute ethanol). The dehydrated sample had the m.p. 149° (mixed m.p.).

Enol lactone (XII) *of 3,5-diketo-α-sant-Δ⁴-enic acid* (XI). (*a*) *Pyrolysis of 3,5-diketo-α-sant-Δ⁴-enic acid* (XI). This reaction was conducted at a somewhat lower temperature than that reported previously. The above Δ^4-3,5-diketo acid (XI, 0.05 g.), m.p. 138°, was heated at 160–170° (oil bath temperature) and 1 mm. pressure for 30 min. Evolution of gas began at about 140°. The molten mass, partly crystallized, was rapidly recrystallized from ethanol to yellow plates (0.03 g., 64%), m.p. 181–182°. Reported, 184–187°[15] and 192–196°.[16] On recrystallization of this material, care must be taken, since on brief heating its solution in usual solvents did not give the parent crystals, but only a yellow sirup which could not be induced to crystallize even after chromatography on silica gel (eluted with petroleum ether–benzene).

With Brady's reagent, it formed a *2,4-dinitrophenylhydrazone*, which was recrystallized from ethyl acetate to orange leaflets, m.p. 240–241° (dec.).

Anal. Calcd. for $C_{21}H_{22}N_4O_6$: C, 59.15; H, 5.20. Found: C, 58.95; H, 5.49.

(*b*) *Reaction of the Δ⁴-diketo acid* (XI) *with lithium chloride–dimethylformamide.* This reaction was carried out similarly as described above for dehydrobromination of IX (R = H). Thus, the acid (XI, 0.05 g.) was heated with lithium chloride (0.02 g.) and dimethylformamide (0.5 cc.) at 160–165° (oil bath temperature) for 20 min. The starting acid (0.01 g.), m.p. 135° (mixed m.p. 137°) was recovered from the bicarbonate-soluble fraction. The neutral fraction, a yellow oil (0.03 g.), formed a 2,4-dinitrophenylhydrazone (0.03 g.) of the enol lactone (XII), which was recrystallized from ethyl acetate to orange leaflets, m.p. 242° (dec.) (mixed m.p. 241.5° with the above sample).

(*c*) *Hydrogenation of the enol lactone of 3,5-diketo-α-santa-Δ¹,⁴-dienic acid* (II). By the procedure described above for the preparation of the Δ^4-3,5-diketo acid (XI) from II, the enol lactone of the $\Delta^{1,4}$-diketo acid (II) was hydrogenated over 1.2% palladium-charcoal (0.1 g.) in purified acetone (10 cc.). Filtration of the catalyst and evaporation of the solvent gave XII (0.04 g., 57%), m.p. 178° (mixed m.p. 179–180° with the above sample).

2-Bromo-cis-3,5-diketo-α-santanic acid (XIII). Bromination of the *cis*-3,5-diketo acid (IV) was performed under more severe conditions than that of the *trans* isomer (V, R = H).

To a solution of 0.25 g. of IV in 5 cc. of chloroform 0.16 g. of bromine was added and allowed to stand at room temperature (20°) for 1.5 hr. The light yellow solution was worked up as described above for the *trans*-bromo acid (IX, R = H). The crude product crystallized as white needles (0.25 g., 77%), m.p. 153° (dec.), from ethyl acetate by addition of petroleum ether. Further recrystallization by the same procedure raised the m.p. to 163° (dec.); $[\alpha]_D^{17}$ −153.3° (*c*, 0.6; EtOH).

Anal. Calcd. for $C_{15}H_{21}BrO_4$: C, 52.18; H, 6.13. Found: C, 51.95; H, 6.60.

Dehydrobromination of 2-bromo-cis-3,5-diketo-α-santanic acid (XIII). (*a*) *With γ-collidine.* The above 2-bromo-*cis*-diketo acid (XIII, 0.13 g.) was heated with γ-collidine (1 cc.) at 175–180° (oil bath temperature) for 20 min. in a stream of nitrogen and worked up as described above for the *trans*-bromo acid (IX, R = H). The collidine salt amounted to 0.07 g. (0.92 mole). The bicarbonate-soluble fraction, a brown sirup (0.05 g.), partly crystallized (0.01 g.) from dilute ethanol. Further recrystallization from the same solvent furnished white plates, m.p. 176°. It showed no depression of the melting point on admixture with the Δ^1-*cis*-3,5-diketo acid (I), m.p. 178°.[1]

The mother liquor of the crude *cis*-acid was treated with Brady's reagent and gave a *2,4-dinitrophenylhydrazone*, an orange crystalline powder (0.01 g.), which was recrystallized from ethyl acetate to orange needles, m.p. 196° (dec.). It melted at 198° (dec.) on admixture with an authentic sample m.p. 201° (dec.), prepared from I with Brady's reagent and crystallized from ethyl acetate.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 57.04; H, 5.27.

The above neutral fraction, a brown sirup (0.03 g.), was converted to a 2,4-dinitrophenylhydrazone (0.015 g.) as orange crystalline powder. Recrystallization from ethyl acetate afforded orange leaflets, m.p. 242° (dec.), undepressed on admixture with the same derivative of enol lactone (XII) of the Δ^4-diketo acid, described above.

(*b*) *With lithium chloride and dimethylformamide.* The bromo acid (XIII, 0.03 g.) was treated with lithium chloride (0.015 g.) and dimethylformamide (0.3 cc.) as described for the *trans*-bromo acid (IX, R = H). The acidic fraction, a colorless sirup (0.01 g.), gave the *cis*-Δ^1-diketo acid (I, 0.005 g.), m.p. 165°, from ether by addition of petroleum ether. Recrystallization from ethyl acetate by addition of petroleum benzine raised the m.p. to 176° (mixed m.p. 177°). The neutral fraction, a yellow sirup (0.01 g.), formed 2,4-dinitrophenylhydrazone (0.01 g.) of the enol lactone (XII) of the Δ^4-compound, which on recrystallization from ethyl acetate had the m.p. 241° (dec.) (mixed m.p.).

Collidine treatment of cis-3,5-diketo-α-santanic acid (IV). The *cis*-diketo acid (IV, 0.05 g.) was heated with γ-collidine (0.7 cc.) under the same conditions as described above for the dehydrobromination of the *cis*-bromo acid (XIII). The bicarbonate-soluble fraction, a light brown sirup (0.05 g.), soon solidified on standing. Washing with dilute ethanol gave the starting material (0.04 g., 80%) as a colorless needles, m.p. 185° (mixed m.p.) (after recrystallization from dilute ethanol). As the neutral fraction, only a trace of a brown sirup was obtained.

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Santonin and Related Compounds. XIV.[1] Bromination and Dehydrobromination of *cis*- and *trans*-2,9-Dimethyl-3-Decalones

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Received August 2, 1957

The *trans*-ketone (Ib) mentioned in the title was prepared by formylation-hydrogenation of *trans*-9-methyl-3-decalone. Monobromination of the isomeric ketones (Ia and Ib) afforded the corresponding 2-bromo compounds (IIa and IIb), which were converted to the *cis*- and *trans*-Δ^1-ketones (IIIa and IIIb), respectively. The dibromo compounds (IVa and IVb) of these ketones were dehydrobrominated to the same dienone (V), which underwent rearrangement to the phenol (VII). The latter was unequivocally established by synthesis. A possible mechanism for explaining differences in behavior toward dehydrobromination between the 2-bromo derivatives of 9-methyl- and 2,9-dimethyl-3-decalones is proposed.

In previous communications[2-4] from our laboratory, striking differences between 9-methyl- and 4,9-dimethyl-3-decalones in their behavior on bromination-dehydrobromination were disclosed. The former ketones, both *cis* and *trans*, gave the corresponding 2-bromo derivatives, which underwent rearrangement to the same Δ^4-ketone on collidine treatment. On the contrary, the isomers of 4,9-dimethyl-3-decalone were brominated at the 4-position and a normal dehydrobromination took place to yield the Δ^4-ketone. The 2,4-dibromo derivatives of these ketones were reacted with bases to give the expected cross-conjugated dienones, except that of *trans*-9-methyl ketone which was dehydrobrominated to the rearranged linear-conjugated dienone.

In the present work, these reactions were extended to *cis*- and *trans*-2,9-dimethyl-3-decalones (Ia and Ib). In view of the above results, it may be safely predicted that these two ketones with bromine would afford the corresponding 2-bromo and 2,4-dibromo compounds. It seemed of interest, however, to examine whether dehydrobromination of these bromo compounds is attended with rearrangement, as reported for some of the bromo compounds.

The *cis*-ketone (Ia)[4] with one equivalent of bromine gave a monobromo compound (IIa) which was treated with a variety of bases. There was always obtained the same unsaturated ketone (IIIa), which was characterized as its 2,4-dinitrophenylhydrazone. The Mattox-Kendall procedure[5] furnished the same hydrazone derivative. The location of the double bond at the 1- and 2-positions in IIIa rests mainly on the ultraviolet absorption spectrum, λ_{max}^{EtOH} 238 mμ (log ϵ 4.08), characteristic of an α,β-unsaturated ketone with two substituents.[6] Catalytic hydrogenation of the Δ^1-3-ketone gave only the starting *cis*-ketone (Ia) of steric homogeneity, probably supporting the structure (IIIa). Since reaction of the *cis*-monobromo ketone (IIa) with bases led invariably to the Δ^1-compound (IIIa), it is obvious that no rearrangements took place during dehydrobromination reactions of II. Therefore, this bromo ketone, as anticipated, can be assigned the 2-bromo structure (IIa).

Treatment of the *cis*-ketone (Ia) with two equivalents of bromine readily yielded a 2,4-dibromo compound (IVa), which was dehydrobrominated to the dienone (V), characterized as its 2,4-dinitrophenylhydrazone. The dienone had λ_{max}^{EtOH} 244 mμ (log ϵ 3.94), in agreement with the value expected for an $\alpha,\beta,\alpha',\beta'$-unsaturated ketone.[6]

The *trans*-2,9-dimethyl ketone (Ib) was prepared by formylation and hydrogenation of *trans*-9-methyl-3-decalone[7] as reported for the *cis*-isomer (Ia).[4] The hydroxymethylene compound (VI), obtained in 70% yield as a solid, readily absorbed two equivalents of hydrogen over palladium-charcoal to furnish Ib in almost quantitative yield. The location of the newly introduced methyl group at the 2-position was evidenced by the non-identity with *trans*-4,9-dimethyl-3-decalone which was previously reported.[4]

Catalytic hydrogenation of 9-methyl-Δ^4-3-octalone (XXII) presents a convenient method for preparing *cis*-9-methyl-3-decalone on a laboratory scale.[8,9] From the hydrogenation mixture, the predominant *cis*-9-methylketone was isolated as crystals of low melting point, usually in 40–50% yield. Further separation of the mother oil, which has not

(1) Paper XIII, M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 443 (1958).

(2) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **22**, 291 (1957).

(3) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **21**, 500 (1956).

(4) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956).

(5) V. R. Mattox and E. C. Kendall, *J. Am. Chem. Soc.*, **70**, 882 (1948).

(6) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 190.

(7) M. Yanagita, K. Yamakawa, A. Tahara, and H. Ogura, *J. Org. Chem.*, **20**, 1767 (1955).

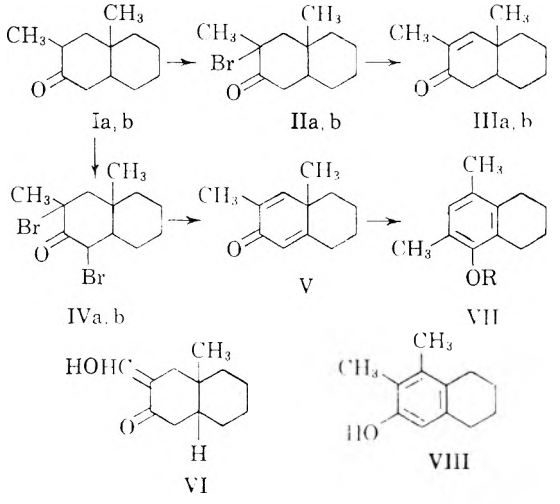
(8) E. C. du Feu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

(9) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4226 (1952).

been recorded, was effected by conversion to the hydroxymethylene derivatives, and the above *trans*-derivative (VI) was isolated in 10% yield.

Monobromination of the *trans*-ketone (Ib) with bromine proceeded less readily than that of the *cis*-isomer (Ia). It has been reported from our laboratory[2] that in isomeric pairs of 9-methyl-3-decalone systems bearing no substituents at the 2-position, the *trans*-locked isomer is always more readily attacked by electrophilic reagents at the position α to the keto group than the *cis*-isomer. It is noteworthy that the relative reactivity of the isomers of 2,9-dimethyl-3-decalone toward bromine is opposite to this generalization. The *trans*-monobromide (IIb) was always dehydrobrominated to the *trans*-Δ^1-ketone (IIIb), the structure of which was proved on the same grounds as described for IIIa. This indicated that monobromination in the *trans*-ketone (Ib) also occurred at the 2-position. The 2-bromination of both isomers of 2,9-dimethyldecalone can be rationalized by the assumption that in conformations of these ketones (Ia and Ib), the Δ^2-enol structures are more favored than the Δ^3-enol structure by the electronic factor (hyperconjugation effect), as discussed earlier with the simple 3-decalone rings.[1,10]

A 2,4-dibromo derivative (IVb) of the *trans*-ketone was normally eliminated with γ-collidine or 2,4-dinitrophenylhydrazine to give the dienone (V) or its hydrazone. The use of anhydrous sodium acetate in place of these bases gave a mixture of the dienone (V) and the monoenone (IIIb), which were separated only with difficulty as the 2,4-dinitrophenylhydrazone. Elevation of the reaction temperature seems to favor the formation of the dienone.



Catalytic hydrogenation of the dienone (V) over palladium-charcoal resulted in a possible mixture of the isomeric ketones, from which only the predominant *cis*-ketone (Ia), as its 2,4-dinitrophenylhydrazone, was isolated after persistent recrystallization. It had been shown[4] that 4,9-dimethyl-Δ^4-3-decalone was catalytically hydrogenated to the *trans*-locked decalone as the chief product. The difference in behavior between these two types of Δ^4-3-octalones systems on hydrogenation is in accord with the previous argument[4] that the steric course in such hydrogenation is governed by the catalyst hindrance due to the combined effect of the substituents at the 4- and 9-positions in the 3-octalone ring.

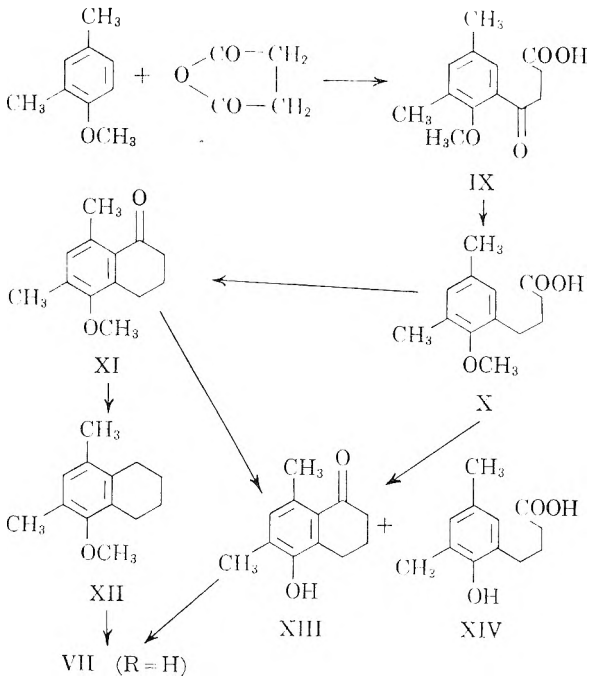
The dienone-phenol rearrangement of V was readily carried out with acetic anhydride and concentrated sulfuric acid in the usual manner. Of the two possible structures (VII and VIII) for the rearranged product, the former seems preferable since the product has a different melting point from the compound (VIII) reported previously.[11] The structure of the phenol (VII) was unequivocally proved by the independent synthesis, as follows.

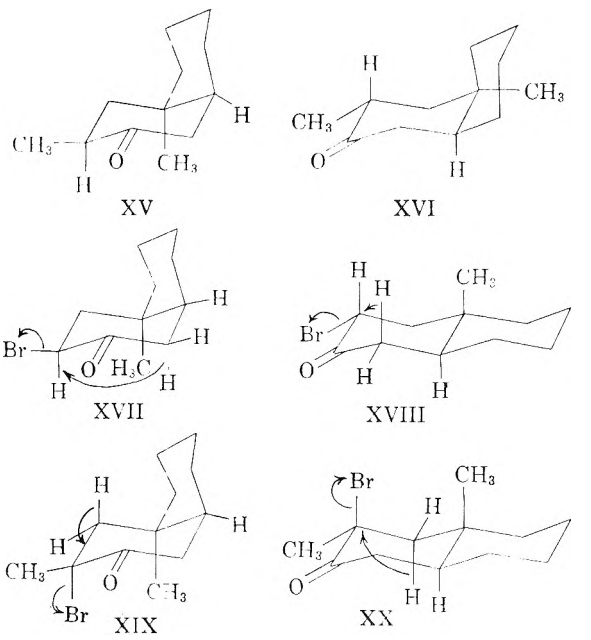
A route to the tetralol methyl ether (XII) from 2,4-xylenol methyl ether through IX, X, and XI was announced by Cocker and Lipman.[12] The yield in each step of this sequence was reported to be relatively low or unspecified. On repeating this reaction, it was found that their results are in some respects incompatible with the present observation. Correction of the melting point of certain intermediates as well as improvement in all steps were made, details of which will be described in the Experimental section. It is worthwhile, however, to mention here that, when an intermediate, the methoxybutyric acid (X), of high purity was heated with 48% hydrobromic acid in acetic acid, demethylation of the methoxyl group was accompanied by ring closure to form a tetralone (XIII) in 70% yield. No sizable amount of acidic product could be isolated from the reaction mixture. A similar result was obtained by substitution of hydrobromic acid with hydriodic acid. It was reported[12] that on reaction with hydriodic acid alone, the methoxybutyric acid (X) was converted to the normal hydroxy acid (XIV).[12] Since this reaction process was described only briefly, it could not be repeated exactly by the reported procedure, but the use of 57% hydriodic acid alone gave only the tetralone (XIII) in 90% yield. When the methoxybutyric acid of relatively low purity was employed in this reaction, the above hydroxy acid (XIV) was obtained together with XIII. Also it was found that the hydroxy acid (XIV) was converted, though in a low yield, to the tetralone (XIII) on similar treatment with hydrobromic acid. This tetralone, which was also obtained from XI by hydrobromic acid, was readily reduced by the Clemmensen procedure to the end product (VII, R=H), which was identified with the rearranged phenol from the dienone (V).

(10) A. S. Dreiding, *Chemistry & Industry*, 1419 (1954).

(11) W. Cocker, *J. Chem. Soc.*, 36 (1946).

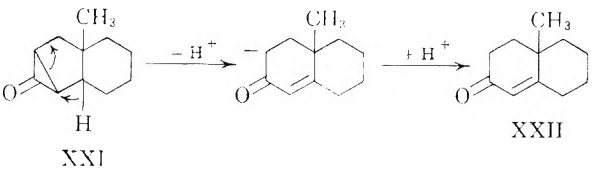
(12) W. Cocker and C. Lipman, *J. Chem. Soc.*, 533 (1947).





The methyl group at the 2-position in *cis*- and *trans*-2,9-dimethyl-3-decalones (Ia and Ib) is most likely to possess the equatorial orientation. The *cis*-ketone (Ia) can be represented by two conformations (XV and XVI), in which the former is assumed to be more favored by steric effects.[10] It was demonstrated[13] that in α-bromocyclohexanone rings with gem-dimethyl (or methylene) groups at the 4-position, the bromine preferably assumes an equatorial position. When the methyl group is present at the brominated 2-position, these cyclic ketones are shown to possess the methyl group equatorial and bromine axial, in a stable form.[14] Following these conclusions, the 2-bromo compounds of *cis*-[2] and *trans*-9-methyl-3-decalones[3] may possibly be assigned, respectively, the stereoformulas XVII[15] and XVIII, both carrying the bromine in an equatorial position. On the other hand, the 2-bromo derivatives (IIa and IIb) of *cis*- and *trans*-2,9-dimethyl-3-decalones are assumed to possess preferably an axial bromine, as shown in XIX and XX, respectively.

For explanation of the rearrangement during dehydrobromination of cyclic α-bromo ketones, a possible mechanism was offered involving an intermediate formation of cyclopropane ring.[16] A similar mechanism may possibly be applied to the conversion of the 2-bromo compounds of *cis*- and *trans*-9-methyl-3-decalones into the identical Δ^4-3-ketone (XXII).[2,3] It may be assumed that in XVII and XVIII, extraction of axial hydrogen at the 4-position by a base and simultaneous separation of equatorial bromine would result in the formation of a 2,4-cyclopropane ring (XXI), involving a *trans*-steric course. Such transannular γ-elimination finds analogy in a plausible mechanism suggested by Shoppee and Summers[17] for explanation of 3,5-cyclosteroid rearrangements.[18] Ready elimination of hydrogen bromide from the 2-bromo compound (IIa and IIb) of 2,9-dimethyl-3-decalones to form the corresponding Δ^1-ketones is in accord with the stereoformulas (XIX and XX, respectively), both of which possess the most favorable geometry for ionic β-elimination.



EXPERIMENTAL[19]

All temperatures are uncorrected. Infrared absorption spectra were determined with a Perkin-Elmer Model 21 double-beam spectrophotometer.

Separation of cis- and trans-9-methyl-3-decalones from hydrogenation mixture of 9-methyl-Δ^4-3-octalone (XXII). The octalone (XXII, 5.7 g.) was catalytically hydrogenated over palladium-charcoal as reported previously.[2] The oily product was distilled with steam and the crystalline *cis*-isomer (2.61 g., 47%), m.p. 47°, was isolated. The remaining oil was distilled to give a colorless oil (3.00 g.), b.p. 95–97°

(13) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953).

(14) S. Inayama, *Pharm. Bull. Japan*, **4**, 198 (1956).

(15) Of two possible conformations, only XVII, considered more stable, is used here.

(16) M. Yanagita and S. Inayama, *J. Org. Chem.*, **19**, 1724 (1954); M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **20**, 1473 (1955); *cf.* M. Gates and G. M. K. Hughes, *Chemistry & Industry*, 1506 (1956).

(17) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952).

(18) During the preparation of this manuscript, a similar mechanism for explanation of the Favorskii rearrangement of 3-ketosteroids was proposed by D. E. Evans, A. C. de Paulet, C. W. Shoppee, and F. Winternitz [*J. Chem. Soc.*, 1451 (1957)].

(19) Microanalyses were by Miss Ch. Shibuya; ultraviolet measurement by Miss M. Suzuki, both of this school.

at 3 mm., which formed a mixture of 2,4-dinitrophenylhydrazones, melting in the range 90–97°. Repeated recrystallization from ethanol separated only the hydrazone of the *cis*-isomer, m.p. 173–175°,[2] probably indicating that the oil consists mainly of the *cis*-ketone. This fraction was formylated by the procedure reported previously for *trans*-3-keto-9-methyl-$\Delta^{1,6}$-hexahydronaphthalene.[9]

Reaction of this fraction (2.68 g.) with ethyl formate (5.8 g.) in the presence of dried sodium methoxide (from 0.95 g. of sodium) in benzene (11 cc.) gave 2.95 g. of an alkali-soluble oil, which was kept in a refrigerator for 2 days. The 2-hydroxymethylene derivative (VI) of the *trans*-ketone (0.85 g., 10% from XXII) was obtained as yellow crystals, m.p. 68–70°. Recrystallization from petroleum ether raised the melting point to 75–75.5°, undepressed on admixture with an authentic sample described below.

A brown-red oil (1.84 g.), separated from the crystals, was heated in 20 cc. of 10% sodium hydroxide on a boiling water bath for 5 hr. The separated oil was taken up in ether, the ether solution was dried, and evaporated. The residual oil (1.30 g.) was distilled with steam, and the distillate was kept in a refrigerator, an additional 0.42 g. (6%) of the *cis*-ketone, m.p. 47–48° separating.

Attempt was made to effect separation of the above hydrogenation mixture with ethyl oxalate as described earlier for the separation of isomeric mixture of 4,9-dimethyl-3-decalones,[4] but it failed.

cis-2,9-Dimethyl-3-decalone (Ia) was prepared from *cis*-9-methyl-3-decalone by formylation and subsequent hydrogenation as reported previously.[4] The crude hydroxymethylene derivative was obtained in 93% yield. Distillation afforded a pure sample as a light yellow oil, b.p. 85–87° at 0.012 mm.; n_D^{20} 1.5300. Hydrogenation of the crude hydroxymethylene compound afforded a 88% yield of the 2,9-dimethyl ketone (Ia), which was distilled to give a colorless oil, b.p. 95–98° at 3 mm.; n_D^{19} 1.4893. This ketone formed the *2,4-dinitrophenylhydrazone* in four modifications, of which the one of yellowish brown crystals, m.p. 164–165°, was reported previously.[4] Two crystallizations from ethanol-chloroform (10:1) gave yellowish brown plates, m.p. 175–177°.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.98; H, 6.97; N, 15.71.

Recrystallization from ethanol furnished a mixture of two forms, yellow needles, m.p. 183–184°, and orange-red prisms, m.p. 178°, which were separated mechanically.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found (sample of m.p. 183–184°): N, 15.87. Found (sample of m.p. 178°): C, 60.11; H, 6.78; N, 15.59.

This ketone gave, in quantitative yield, a semicarbazone, melting in the range 180–187°, which was recrystallized from ethanol to give cubes, m.p. 203–205° (sublim.).

Anal. Calcd. for $C_{13}H_{23}N_3O$: C, 65.78; H, 9.77; N, 17.71. Found: C, 65.42; H, 9.43; N, 17.89.

With acid, it generated the parent ketone (Ia), b.p. 85–90° at 3 mm.; n_D^{20} 1.4870; λ_{max}^{EtOH} 235 mμ (log ε 1.51) and 284 mμ (log ε 1.28); $\nu_{C=O}$ 1709 cm.$^{-1}$ (liquid film).

trans-2-Hydroxymethylene-9-methyl-3-decalone (VI). *trans*-9-Methyl-3-decalone (4.24 g.), prepared from the above octalone (XXII) with lithium and liquid ammonia as reported previously,[7,20] was treated with ethyl formate (9.1 g.) in the presence of sodium methoxide (from 1.47 g. of sodium) by the procedure described above. The alkali-soluble fraction, which mostly solidified, was washed with a small amount of cold ethanol to give 3.45 g. (70%) of light yellow crystals, m.p. 70–72°. Two crystallizations from petroleum ether afforded white prisms, m.p. 75–75.5°. It gave violet color with alcoholic ferric chloride.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.88; H, 9.53.

The crystals slowly decomposed at room temperature.

trans-2,9-Dimethyl-3-decalone (Ib). The above 2-hydroxymethylene compound (VI, 3.45 g.), m.p. 70–72°, was hydrogenated over palladium-charcoal (prepared from 8 cc. of 1% palladium chloride solution and 0.4 g. of charcoal). About 2 moles (825 cc., 104%) of hydrogen was absorbed in 1.5 hr. Removal of the catalyst and evaporation of the solvent left a pale yellow oil, which was fractionated to a colorless oil (2.90 g., 91%) b.p. 92–94° at 2 mm.; n_D^{20} 1.4888. This oil showed a negative test with alcoholic ferric chloride. It formed quantitatively a *2,4-dinitrophenylhydrazone*, m.p. 142–144°, which was twice recrystallized from ethanol to brownish yellow needles, m.p. 149–150°.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.90; H, 6.38; N, 15.97.

This ketone formed almost quantitatively a *semicarbazone*, melting in the range of 155–165°, which was recrystallized from dilute ethanol to colorless prisms, m.p. 187–190° (sublim.).

Anal. Calcd. for $C_{13}H_{23}N_3O$: C, 65.78; H, 9.77; N, 17.71. Found: C, 65.81; H, 9.43; N, 17.90.

This derivative with acid regenerated the parent ketone, b.p. 85–90° at 3 mm.; n_D^{20} 1.4888; λ_{max}^{EtOH} 240 mμ (log ε 1.29) and 284 mμ (log ε 1.37); $\nu_{C=O}$ 1710 cm.$^{-1}$ (liquid film).

Monobromination and dehydrobromination of cis-2,9-dimethyl-3-decalone (Ia). This reaction sequence was carried out essentially as described previously for 4,9-dimethyl-3-decalone[4] and others.[2] The *cis*-ketone (Ia, 0.30 g.) was treated with 1 equivalent of bromine in chloroform. Bromine uptake took place smoothly to give the crude monobromide (IIa, 0.44 g.) in quantitative yield.

Dehydrobromination of the monobromide (IIa, 0.44 g.) with hot collidine (1.5 cc.) in a stream of nitrogen yielded 0.24 g. (63% as 1 equivalent) of the collidine salt. The monoenone (IIIa) was obtained as a pale yellow oil (0.15 g., 50%), b.p. 87–90° at 3 mm.; λ_{max}^{EtOH} 239 mμ (log ε 3.78). It formed in 90% yield a *2,4-dinitrophenylhydrazone* as red crystals, m.p. 120–124°, which was recrystallized from ethanol to red plates, m.p. 139°.

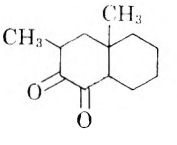
Anal. Calcd. for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 59.92; H, 5.81; N, 15.46.

The monoenone (0.12 g.) was dissolved in a solution of semicarbazide hydrochloride (0.08 g.) and sodium acetate crystals (0.09 g.) in dilute methanol, and a little water was added until the appearance of turbidity. The separated oil began to solidify in a few days. After standing for three weeks, a solid (0.08 g.) was obtained. Recrystallization from dilute ethanol gave a *semicarbazone*, as prisms, m.p. 188–193°.

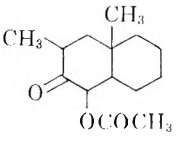
Anal. Calcd. for $C_{13}H_{21}N_3O$: C, 66.35; H, 9.00; N, 17.86. Found: C, 66.37; H, 8.59; N, 17.47.

Catalytic hydrogenation of the *cis*-monoenone over palladium-charcoal in methanol gave back the parent ketone (Ia), identified as its 2,4-dinitrophenylhydrazone, yellow-brown plates, m.p. 173–175° (mixed m.p.), after recrystallization from ethanol.

The monobromide (IIa, 0.44 g.) was treated with sodium acetate (0.30 g.) in glacial acetic acid (3 cc.). As the alkali-soluble product there was obtained a minute amount of a brown viscous oil, showing dark violet color with alcoholic ferric chloride. Presumably it indicated that this oil contained the α-diketone (XXIII), and hence, the neutral fraction was contaminated with the ketol acetate (XXIV).



XXIII



XXIV

After treatment with alkali to remove XXIV, the neutral oil was fractionated to 0.11 g. (37%) of a colorless oil, b.p. 93–98° at 4 mm., consisting mainly of the monoenone (IIIa). It formed in about 80% yield a red-brown 2,4-di-

(20) *Cf.* ref. (4), footnote (22).

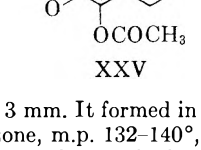
nitrophenylhydrazone, melting in the range of 150–230°. Two recrystallizations from ethanol gave the hydrazone of IIIa as red plates, m.p. 137–138° (mixed m.p.). The mother liquor of the first recrystallization of the above hydrazone furnished a small amount of red-brown plates, m.p. 280–281°, which was not further investigated.

Reaction of the monobromide (IIa, 0.15 g.) with 2,4-dinitrophenylhydrazone (0.15 g.) in hot glacial acetic acid (3 cc.) for 5 min. gave a red sirup (0.15 g.), which was chromatographed on neutral alumina. Elution with carbon tetrachloride furnished the hydrazone of the *cis*-monoenone (IIIa) as red plates (0.08 g.), m.p. 139° (mixed m.p.), after recrystallization from ethanol.

Dibromination and dehydrobromination of cis-2,9-dimethyl-3-decalone (Ia). This reaction sequence was carried out essentially as described previously for 4,9-dimethyl-3-decalone.[4] The yield of the crude dibromide (IVa) was quantitative. The dibromide (0.95 g.) was gently refluxed with γ-collidine (5 cc.) for 30 min., yielding the collidine salt (1.1 g., 95% as 2 equivalents). The product, a dark red viscous oil (0.41 g.), was fractionated to give 0.18 g. (36%) of the dienone (V) as a pale yellow oil, b.p. 105–106° at 6 mm., which on refractionation had b.p. 105–106° at 6 mm.; λ_{max}^{EtOH} 244 mμ (log ε 3.98).

It formed in 82% yield a 2,4-dinitrophenylhydrazone, m.p. 157–162°, which was recrystallized from ethanol to deep red plates, m.p. 170°. It showed no depression of the melting point on admixture with a sample obtained from the *trans*-dibromide (IVb), which will be described below.

Treatment of IVa (0.95 g.) with sodium acetate (1.5 g.) in glacial acetic acid (5 cc.) gave a brown oil (0.52 g.) as the neutral product and a dark brown oil (20 mg.) as the alkali-soluble fraction. The latter showed dark green color with alcoholic ferric chloride, probably indicating the presence of the above α-diketone (XXIII) in it. It seems that the neutral fraction was contaminated with the enol acetate (XXV) of the α-diketone. On treatment with alkali to remove XXV, a pale yellow oil (0.17 g.) was obtained which was fractionated to 0.08 g. of the dienone (V), a colorless



XXV

oil, b.p. 95–97° at 3 mm. It formed in 70% yield the 2,4-dinitrophenylhydrazone, m.p. 132–140°, which was recrystallized from ethanol to deep red plates, m.p. 170° (mixed m.p.).

Monobromination and dehydrobromination of trans-2,9-dimethyl-3-decalone (Ib). Employing the conditions described above for the *cis*-ketone (Ia), the *trans*-ketone (Ib) was brominated with bromine and then treated with bases. The monobromination started smoothly, but when about one third of bromine had been added, the bromine uptake became slow. After completion of the addition, the stirring was further continued for 1 hr. A yellow-brown solution gave in a quantitative yield the crude monobromide (IIb) as a brown oil. Treatment of IIb (0.30 g.) with γ-collidine gave, with the collidine salt (60% as 1 equivalent), the *trans*-monoenone (IIIb, 0.18 g., 60%), a pale yellow oil, b.p. 93–95° at 4 mm.; λ_{max}^{EtOH} 239 mμ (log ε 4.0). It formed in 90% yield a *2,4-dinitrophenylhydrazone*, melting in the range of 132–144°, which was recrystallized from ethanol to red plates, m.p. 160–161°.

Anal. Calcd. for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.33; H, 5.89; N, 15.45.

On standing with the semicarbazide in dilute acetic acid overnight, the monoenone (0.16 g.) much more readily formed a *semicarbazone* (0.15 g., 71%) than the *cis*-isomer (IIIb). It was recrystallized from dilute ethanol to white cubes (0.11 g., 50%), m.p. 215–217°.

Anal. Calcd. for $C_{13}H_{21}N_3O_4$: C, 66.35; H, 9.00; N, 17.86. Found: C, 66.56; H, 8.59; N, 17.68.

The semicarbazone with acid regenerated the parent ketone (IIIb), b.p. 130° at 4 mm. (bath temperature); λ_{max}^{EtOH} 238 mμ (log ε 4.08).

Hydrogenation of the monoenone (IIIb) over palladium-charcoal gave only the *trans*-ketone (Ib), which was identified as the 2,4-dinitrophenylhydrazone, m.p. 148–150° (mixed m.p.), after two crystallizations from ethanol.

On reaction with sodium acetate and subsequent treatment with alkali, the monobromide (IIb, 0.30 g.) gave the *trans*-monoenone (IIIb, 0.03 g.), forming in about 80% yield the 2,4-dinitrophenylhydrazone, melting in the range of 68–102°. Five recrystallizations from ethanol gave red plates, m.p. 160–161° (mixed m.p.).

Dibromination and dehydrobromination of trans-2,9-dimethyl-3-decalone (Ib) was carried out essentially by the procedure described above for the *cis*-ketone (Ia). Dibromination of Ib (0.5 g.) was effected by slow addition of bromine for 70 min. The crude dibromide (IVb, 0.91 g., 95%) was obtained as a light brown oil which was used without delay for dehydrobromination with bases.

Collidine treatment of IVb afforded the dienone as a pale yellow oil, b.p. 100–107° at 4 mm.; λ_{max}^{EtOH} 243 mμ (log ε 3.9). On standing with Brady's reagent overnight, it formed quantitatively a *2,4-dinitrophenylhydrazone* as red plates m.p. 162–167°. Three recrystallizations from ethanol raised the m.p. to 171°. It showed an obvious depression (about 15°) of the melting point on admixture with the same derivative of the *trans*-monoenone (IIIb), m.p. 160–161°.

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.40; H, 5.90; N, 15.91.

When the reflux time with collidine was shortened to 20 min., the reaction was incomplete.

An oily product from acetolysis of the dibromide (IVb) formed a mixture of 2,4-dinitrophenylhydrazones, from which a minute amount of derivatives of the *trans*-monoenone (IIIb) and the dienone (V) was separated only after tedious procedure. Therefore, the elimination reaction was conducted under more drastic conditions.

The *trans*-dibromide (IVa, 1.00 g.), prepared from 0.52 g. of the ketone (Ib), was heated to reflux with 1.50 g. of anhydrous sodium acetate in 5 cc. of glacial acetic acid for 3 hr. The dark red mixture was worked up as described above for the *cis*-dibromide (IVa). There was obtained, with the acidic product (0.015 g., positive ferric chloride test), a neutral dark oil (0.29 g.), which was fractionated to a yellow oil (0.16 g.), b.p. 100–115° at 3 mm. Alkali treatment of this distillate afforded a neutral brown oil, which was refractionated to a pale yellow oil (0.07 g., 14%), b.p. 95–102° at 3 mm.

It formed the 2,4-dinitrophenylhydrazone, m.p. 161–164°, of the dienone (V). Two recrystallizations from ethanol afforded red plates, m.p. 169–170° (mixed m.p.).

The mother liquor of the crystallization of the above hydrazone furnished a red solid (0.04 g.), from which a minute amount of the hydrazone of the *trans*-monoenone (IIIb) was isolated after chromatography on alumina (elution with carbon tetrachloride).

Hydrogenation of 3-keto-2,9-dimethyl-$\Delta^{1,4}$-hexahydronaphthalene (V). The dienone (V, 0.09 g.) was hydrogenated over palladium-charcoal (prepared from 1 cc. of 1% palladium chloride solution and 0.05 g. of charcoal) in 3 cc. of methanol. Hydrogen absorption (20.8 cc., 84% as 2 moles) almost ceased in about 10 min. After removal of the catalyst, the solution was distilled to a small bulk and Brady's reagent was added. On standing overnight, the 2,4-dinitrophenylhydrazone (0.15 g., 83%) was obtained as a brown crystalline powder, melting in the range of 98–107°. Persistent fractional recrystallization from ethanol-chloroform (5:1) afforded the hydrazone (0.075 g., 42% from V), m.p. 170–173°, of the *cis*-ketone (Ia). Further recrystallization from the same solvent mixture raised the m.p. to 175–177° (mixed m.p.).

From the mother liquor of the above hydrazone, the de-

rivative of the *trans*-ketone (Ib) could not be isolated in a pure state.

Dienone-phenol rearrangement of 3-keto-2,9-dimethyl-$\Delta^{1,4}$-hexahydronaphthalene (V). To a solution of 0.05 g. of the dienone (V) in 3 cc. of acetic anhydride was added 1 cc. of a mixture of 10 cc. of acetic anhydride and 0.18 cc. of concentrated sulfuric acid, and the mixture was allowed to stand for 2 days. The reaction solution was mixed with water and colorless elongated needles soon separated. After standing in a refrigerator overnight, the crystals (0.05 g., 83%), m.p. 62–63°, were collected. Recrystallization from dilute methanol did not raise the melting point. It showed no depression of the melting point on admixture with the acetate (VII, R = $COCH_3$) of 1,3-dimethyl-*ar*-4-tetralol described below.

The acetate (0.03 g.) was heated with concentrated hydrochloric acid in ethanol as usual.[4] Evaporation of the solvent at reduced pressure left yellowish needles, which were dissolved in 20% sodium hydroxide and washed with ether. Acidification of the alkali solution deposited the tetralol (VII, R = H) as white elongated needles (0.02 g.), m.p. 76–77°. Recrystallization from dilute methanol raised the m.p. to 77–78°, undepressed on admixture with 1,3-dimethyl-*ar*-4-tetralol described below.

Methyl 2,4-xylenol ether. 2,4-Xylenol (5 g.) was methylated with dimethyl sulfate (10 g.) in 15% sodium hydroxide and the methyl ether was obtained as a colorless liquid (4.9 g., 88%), b.p. 73–75° at 13 mm. (reported, b.p. 188–191°[12]).

β-(3,5-Dimethyl-6-methoxybenzoyl) propionic acid (IX) was prepared by an effective variation of the method reported by Cocker and Lipman.[12] To a stirred solution of 8.8 g. of the above xylenol methyl ether and 7.0 g. of succinic anhydride in 50 cc. of nitrobenzene was added, in small portions, 22 g. of powdered aluminum chloride, and the temperature of the mixture was controlled within the range 35–40° by external cooling. After the addition was completed, the stirring was maintained for an additional 2 hr. at this temperature. The dark red mixture was poured into dilute hydrochloric acid and shaken with ether. The ether extract was washed with water and the solvent was removed by distillation with steam. The residual brown crystals were dissolved in 10% sodium carbonate and filtered. Acidification of the filtrate deposited crystals which were collected after standing in a refrigerator overnight. There was obtained 11.9 g. (65%) of the keto acid (IX), m.p. 121–124°, which was of sufficient purity to be used for the following step. A pure sample was prepared by recrystallization from dilute acetic acid as elongated white needles, m.p. 129–130° (reported m.p. 129–130°[15]).

γ-(3,5-Dimethyl-6-methoxyphenyl)butyric acid (X) was prepared by an effective variation of the method reported by Cocker and Lipman.[12] The above crude keto acid (IX, 3.0 g.), m.p. 121–124°, in 3 cc. of toluene was heated to reflux with 9 g. of zinc amalgam (prepared from 9 g. of granular zinc and a solution of 0.5 g. of mercuric chloride in 10 cc. of water containing 0.5 cc. of hydrochloric acid), 3 cc. of water, and 7 cc. of concentrated hydrochloric acid. After heating for 6 hr., a further 1 cc. of concentrated hydrochloric acid was added and the refluxing was continued for an additional 12 hr. On cooling, white crystals separated, which, after addition of the same volume of water, were taken up in ether. The separated organic layer was shaken with 10% sodium carbonate and the carbonate solution was filtered. Acidification of the filtrate deposited 2.5 g. (89%) of the butyric acid (X), m.p. 114–119°. Recrystallization from benzene-petroleum ether gave white plates, m.p. 120–121°. Cocker and Lipman[12] reported m.p. 92–93°. Their sample may be impure since no pure compounds of such low melting point were encountered in the present work.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.95; H, 7.65.

Cocker and Lipman[12] reported the isolation of the hydroxy acid (XIV), m.p. 116–117°, as a by-product during the Clemmensen reduction of the keto acid (IX) with relatively concentrated hydrochloric acid in the absence of toluene. This hydroxy acid, the preparation of which is described below, was not isolated in the present experiment.

1-Keto-6,8-dimethyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (XI). The above crude methoxy acid (X, 1.5 g.), m.p. 114–119°, was treated with concentrated sulfuric acid (9 cc.) as described earlier for the preparation of 1-keto-5,8-dimethyl-7-methoxy-1,2,3,4-tetrahydronaphthalene.[4] There was obtained the tetralone (XI), (1.02 g., 74%) as brown needles, m.p. 36–39°. Fractionation gave an oil (1.02 g., 74%), b.p. 145–147° at 6 mm., which immediately solidified, m.p. 38–40°. Recrystallization from petroleum ether furnished white prisms, m.p. 41°. Cocker and Lipman[12] reported m.p. 61.5–62° for the tetralone (XI) prepared from the above "methoxy acid (X)," m.p. 92–93°.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 75.84; H, 7.85.

5,7-Dimethyl-8-methoxy-1,2,3,4-tetrahydronaphthalene (methyl 1,3-dimethyl-ar-4-tetralol ether) (XII). The above methoxy ketone (XI, 0.9 g.), m.p. 38–40°, was reduced by the Clemmensen procedure as described above for the butyric acid (X). The product (0.85 g.), a yellowish brown liquid, was distilled to give a pale yellow oil (0.57 g., 68%), b.p. 114–116° at 4 mm. Refractionation afforded a colorless oil, b.p. 108–110° at 3 mm.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.29; H, 9.65.

Cocker and Lipman[12] claimed that the Clemmensen reduction of the "tetralone (XI)," m.p. 61.5–62°, yielded this tetralol methyl ether, b.p. 128° at 3 mm., which solidified to colorless needles (the melting point was not given).

1,2-Dimethyl-ar-4-tetralol (VII, R = H). This was prepared from the above tetralol methyl ether (XII, 0.20 g.) by refluxing with a mixture of glacial acetic acid (1 cc.) and 48% hydrobromic acid (2 cc.) for 3 hr. On standing overnight, the dark red solution deposited the tetralol (VII, R = H) as elongated needles, m.p. 75–76°. Additional crystals (total 0.14 g., 97%) were obtained from the mother liquor on addition of water. Recrystallization from dilute methanol and then from petroleum ether gave colorless needles, m.p. 78°.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.72; H, 9.33.

The tetralol (0.1 g.) was added to a mixture of 1 cc. of acetic anhydride and a drop of concentrated sulfuric acid, and warmed at 40–50° for 10 min. Water was added to the reaction and soon the *acetate* (VII, R = $COCH_3$) separated as brown needles (0.12 g., 99%), m.p. 60–63°. Recrystallization from dilute methanol gave colorless needles, m.p. 64–65°.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 67.18; H, 7.25. Found: C, 67.39; H, 7.27.

Reaction of γ-(3,5-dimethyl-6-methoxyphenyl)butyric acid (X) with hydrobromic acid. The pure methoxybutyric acid (X, 0.20 g.), m.p. 120–121°, was treated with hydrobromic acid exactly as described for XII. The dark red solution was poured into water, extracted with ether, and the ether layer was washed with bicarbonate solution and then with water. Evaporation of the dried ether solution left 0.13 g. (76%) of 1-keto-6,8-dimethyl-5-hydroxy-1,2,3,4-tetrahydronaphthalene (XIII) as yellowish crystals, m.p. 58–60°. Recrystallization from dilute ethanol afforded white needles, m.p. 60–61°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.78; H, 7.50.

Similar treatment of the methoxytetralone (XI, 0.20 g.) with hydrobromic acid gave the same hydroxy tetralone (XIII) (0.18 g., 97%), m.p. 58–60°, which was recrystallized from dilute methanol to needles, m.p. 61°. (mixed m.p.). It formed a *2,4-dinitrophenylhydrazone*, which was recrystallized from ethanol to red silk-like needles, m.p. 273°.

Anal. Calcd. for $C_{18}H_{18}N_4O_5$: N, 15.13. Found: N, 15.40.

Clemmensen reduction of the hydroxytetralone (XIII, 0.20 g.) led to a quantitative yield of the tetralol (VII, R = H) as brown crystals, m.p. 71–75°. Recrystallization from dilute methanol afforded colorless needles, m.p. 78° (mixed m.p.).

When the relatively impure specimen of the methoxy acid (X) was used in the above reaction, a different result was obtained. X (0.70 g.), m.p. 114–115°, was treated with 48% hydrobromic acid (7 cc.) in glacial acetic acid (3.5 cc.), as described above. Along with the tetralone (XIII, 0.11 g., 20%), an acid (XIV, 0.13 g., 19%) was obtained as brown needles, m.p. 110–113°. Recrystallization from water gave colorless elongated needles, m.p. 116–117°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.27; H, 7.80.

Shortening (1 hour) of the reflux time in this reaction increased the yield of the two products, XIII (23%) and XIV (50%).

Based on the identity of the melting points, this hydroxy acid (XIV) is assumed to be identical with the sample of Cocker and Lipman,[12] which was obtained either by Clemmensen reduction of the keto acid (IX) or by reaction of "the methoxy acid (X)," m.p. 92–93°, with hydriodic acid.

Reaction of γ-(3,5-dimethyl-6-methoxyphenyl)butyric acid (X) with hydriodic acid. By the procedure described in the preceding paragraph, the pure methoxy acid (X, 0.2 g.) was treated with 57% hydriodic acid-glacial acetic acid, except that the refluxing time was shortened to 2 hours. The tetralone (XIII, 0.11 g.) m.p. 56–58° (mixed m.p.) was obtained in 64% yield. Also, the use of hydriodic acid alone raised the yield of the tetralone (XIII) to 91%.

Reaction of γ-(3,5-dimethyl-6-hydroxyphenyl)butyric acid (XIV) with hydrobromic acid. The hydroxy acid (XIV, 0.2 g.) was treated with 48% hydrobromic acid-glacial acetic acid, exactly as described above for the methoxy acid (X). From the alkali-soluble fraction, the starting acid (0.12 g., 60%) was recovered. The neutral fraction gave the hydroxy-tetralone (XIII, 0.04 g., 23%), m.p. 59–60° (mixed m.p.), after recrystallization from dilute ethanol.

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Reaction of 2,4-Dibromomenthone with Zinc and Ethanol. Investigation of the Thujone of Guha and Nath

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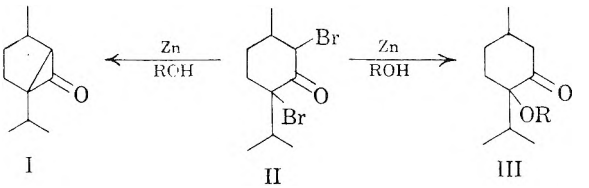
It was reported by Guha and Nath that a cyclopropanone, thujone, was formed in the reaction of 2,4-dibromomenthone with zinc and ethanol. It has been found that the product actually is an ethoxymenthone, most likely the 4-substituted derivative.

The formation of a transient cyclopropanone in the reaction of an α-haloketone with base has been postulated by Loftfield[1] on the basis of results obtained in his study of the Favorski rearrangement. Although such an intermediate could well be expected to show the reactions postulated,[2] little is known about such small ring ketones. The preparation of cyclopropanones has been claimed many times but in most cases the proof of structure was not definitive.[3–8] One case of special interest is that of a thujone (I)[5] in view of its similarity to the postulated intermediate of Loftfield. Guha and Nath[5] reported that when 2,4-dibromomenthone (II) was allowed to react with zinc and ethanol, the



I II III

thujone (I) was obtained. The proof of structure was based upon elementary analysis, carbonyl derivatives, reduction to thujane with zinc and hydrochloric acid, and reduction to menthol with sodium and ethanol. If, indeed, the material was a cyclopropanone, it possessed a chemical reactivity entirely different from that expected on the basis of the work of Loftfield. In order to establish the structure of the compound of Guha and Nath, the reaction of 2,4-dibromomenthone has been reexamined.

When 2,4-dibromomenthone was allowed to react with zinc and ethanol, a 50% yield of a material possessing the physical properties reported by Guha and Nath[5] was obtained. Care had to be taken in the distillation of the material since it was found that upon prolonged distillation through an efficient column, the elements of ethanol were lost and an unsaturated product slowly formed. The elemental analysis of the product, however, differed from that expected for a thujone (I). A Zeisel ether determination established the presence of one

(1) R. B. Loftfield, *J. Am. Chem. Soc.*, **72**, 632 (1950); R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951); R. B. Loftfield and L. Schaad, *J. Am. Chem. Soc.*, 76, 35 (1954).

(2) For an alternate explanation of the results, see J. G. Burr, Jr., and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954).

(3) C. K. Ingold, *J. Chem. Soc.*, 119, 305 (1921); C. K. Ingold, S. Sako, and J. F. Thorpe, *J. Chem. Soc.*, 121, 1177 (1922).

(4) P. Lipp, J. Buchkremer, and H. Seeles, *Ann.*, **499**, 1 (1932).

(5) P. C. Guha and B. Nath, *Ber.*, **70**, 931 (1937).

(6) N. Ya. Demyanov and V. V. Feofilaktov, *J. Gen. Chem.*, (U.S.S.R.), **9**, 340 (1939).

(7) J. F. Cogdell and O. R. Quayle, 118th Meeting of the American Chemical Society, Chicago, 1950, p-6N.

(8) M. Mousseron, R. Jacquier, and R. Fraisse, *Compt. rend.*, **243**, 1880 (1956).

ethoxyl grouping and all data fit a formula best represented as an ethoxymenthone (III). The ultraviolet spectrum showed the presence of a normal isolated carbonyl grouping (λ_{max} 302 mμ, log ϵ 1.5) and the infrared spectrum showed absorption at 5.83μ which also is characteristic of the same grouping. In addition, bands at 8.91 and 8.98μ, characteristic of ethereal linkages, were present. The compound did not react with Tollen's reagent, sodium nitroprusside or bromine but did form a semicarbazone which melts in the range reported by Guha and Nath.[5] The analytical data for this derivative also fit a structure related to an ethoxymenthone. In order to establish the generality of the reaction of the dibromide, methanol also was employed as the solvent and in this case a methoxymenthone was obtained. On the basis of the present work, it must be concluded that the material obtained by Guha and Nath[5] was not the cyclopropanone derivative postulated.

In an attempt to locate the alkoxyl grouping, the material was allowed to react with *p*-nitrobenzaldehyde and a mono-*p*-nitrobenzal derivative of the ethoxymenthone was obtained. This result suggested the presence of a methylene grouping adjacent to the carbonyl function and eliminated C_2 as a possible location for the ethoxyl grouping.

When ethoxymenthone was treated with hydrochloric acid, Δ^4-menthenone was obtained. This product was characterized as the 2,6-dibenzal derivative and possessed an ultraviolet spectrum identical with authentic material. The isolation of this degradation product indicated that the alkoxyl group was present either on C_4 or C_5 of the ring or on C_8 of the isopropyl sidechain, *i.e.*, α or β to the carbonyl grouping.

The reaction of ethoxymenthone with 2,4-dinitrophenylhydrazine in hot alcoholic hydrochloric acid indicated that the ethoxyl group was located on the ring. It was found that the 2,4-dinitrophenylhydrazone formed had lost the elements of ethanol and possessed a λ_{max} at 379 mμ (ϵ 26,000). When this derivative (m.p. 141.0–143.3°), was admixed with the 2,4-dinitrophenylhydrazone of Δ^4-menthenone (m.p. 143.9–144.2°), no depression in melting point was observed. That the derivative of menthenone was the original product formed and not a rearrangement product of pulegone was shown by the preparation of the 2,4-dinitrophenylhydrazone of the latter compound (m.p. 147.5–148.5°) under the same acidic conditions. The pulegone derivative depressed the melting point (to 130–132°) of the derivative obtained from ethoxymenthone or Δ^4-menthenone upon mixing.

To differentiate between the C_4 and C_5 positions on the ring, the stability of the ethoxymenthone toward base was studied since an alkoxyl group at C_6 being β to the ketone should be lost with great facility. As it is known that such a reaction is reversible,[9] the stability of Δ^4-menthenone and pulegone towards alcoholic potassium hydroxide was studied. It was found that neither compound showed any tendency to add the elements of ethanol during the course of 7 days. When ethoxymenthone was subjected to similar reaction conditions, no band characteristic of either unsaturated ketone developed. These experiments support an assignment of the ethoxyl grouping at C_4 on the ring.

EXPERIMENTAL[10]

Ethoxymenthone. A mixture of 110 g. (0.35 mole) of 2,4-dibromomenthone (m.p. 76–77°)[11] and 71.5 g. of zinc (1.1 moles) in 275 ml. of absolute ethanol was stirred at room temperature for 24 hr. and then refluxed on a steam bath for 24 hr. The reaction mixture was filtered and acidified with aqueous 5% sulfuric acid. The insoluble layer was removed, diluted with ether, and the ethereal solution dried. After removal of the solvent, the product was distilled from a Claisen flask, b.p. 95–102° (10 mm.), $[\alpha]_D^{21}$ + 26.7° ($CHCl_3$), n_D^{20} 1.4526, yield 33.2 g. (51%) [lit.[5] b.p. 110–112° (14 mm.), $[\alpha]_D^{26}$ + 25.1° n 1.4505.] The ultraviolet spectrum showed a maximum at 302 mμ (ϵ 30), characteristic of an isolated ketone, and a maximum at 236 mμ (ϵ 160), indicating 1–2% of a conjugated unsaturated ketone (Δ^4-menthenone).

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; OEt, 22.72. Found: C, 72.60; H, 11.29; OEt, 22.32.

The semicarbazone was prepared using semicarbazide hydrochloride and sodium acetate in ethanol and allowing the reaction mixture to reflux for 5 hr. The crude product was recrystallized from aqueous ethanol, m.p. 182.5–184.5°.

Anal. Calcd. for $C_{13}H_{25}O_2N_3$: C, 61.14; H, 9.87; N, 15.46. Found, C, 61.58; H, 9.89; N, 16.10.

The 2,4-dinitrophenylhydrazone was prepared by heating the ethoxymenthone with an ethanolic hydrochloric acid solution of 2,4-dinitrophenylhydrazine. The crude product was recrystallized twice from ethanol, m.p. 141.0–143.2°, λ_{max} 379 mμ (ϵ 26,000).

Anal. Calcd. for $C_{16}H_{20}O_4N_4$: C, 57.82; H, 6.07. Found: C, 57.62; H, 6.01.

The *p*-nitrobenzal derivative was prepared by allowing the ether to react with *p*-nitrobenzaldehyde and sodium ethoxide in absolute ethanol solution. The product was recrystallized from benzene-ethanol, m.p. 135.0–136.0°.

Anal. Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.08; H, 7.65; N, 4.17.

Methoxymenthone. This material was prepared as described above except that absolute methanol was used as the solvent. Starting with 62 g. (0.2 mole) of the dibromide there was obtained 14 g. (41%) of product, b.p. 85–88° (10 mm.), n_D^{20} 1.4452.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94; OMe, 16.84. Found: C, 71.94; H, 11.04; OMe, 16.52.

Cleavage of ethoxymenthone with hydrochloric acid. A mixture of 10 g. (0.055 mole) of ethoxymenthone and 130 ml. of 6*N* hydrochloric acid was refluxed for 6 hr. During the course of this period, 6 ml. of concentrated hydrochloric acid was added each hour. At the end of this time, the mixture was steam distilled, the distillate saturated with sodium chloride, and extracted with ether. The ethereal solution was dried, the solvent removed and the product distilled, b.p. 106–109° (20 mm.), n_D^{23} 1.4730, λ_{max} 236 mμ (log ϵ 3.96),

(9) D. K. Fukashima and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951).

(10) Analyses were performed by the Microanalytical Laboratory of the Department of Chemistry, University of California, Berkeley.

(11) O. Wallach, *Ann.*, **414**, 296, 333 (1918).

yield 5.3 g. (65%). Authentic Δ^4-menthenone prepared from Δ^3-menthene nitrosochloride[12] has the following properties: n_D^{23} 1.4710, λ_{max} 236 mμ (log ϵ 3.97).

The dibenzal derivative was prepared by allowing the cleavage product to react with benzaldehyde in absolute ethanol in the presence of sodium ethoxide. The product was recrystallized from ethanol and sublimed, m.p. 138–139°, λ_{max} 275 mμ (log ϵ 4.35) [lit.[13] 140–141°].

Anal. Calcd. for $C_{24}H_{24}O$: C, 87.76; H, 7.36. Found: C, 87.86; H, 7.31.

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(12) J. Reid and G. J. Robertson, *J. Chem. Soc.*, 2209 (1926).

(13) O. Wallach, *Ann.*, **397**, 214 (1913).

[CONTRIBUTION NO. 1464 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Contribution to the Study of Marine Products. XLVI. 24- and 25-Dehydrocholesterol

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24- and 25-dehydrocholesterol have been prepared from 25-ketonorcholesterol. The identity of desmosterol and 24-dehydrocholesterol has been substantiated.

Desmosterol is one of the two new sterols which Stokes, Fish, and Hickey[1] have recently isolated from chick embryos. It shows some superficial resemblance to 25-dehydrocholesterol[2,3] (IIa) but the absence in its infrared spectrum of a strong band at 11.3μ indicated a lack of terminal unsaturation and consequently a difference in the two compounds. On the basis of other chemical evidence, and on good biogenetic grounds, the authors drew the significant conclusion that desmosterol is 24-dehydrocholesterol (IVa), a compound assumed to be one of the final steps in the biosynthesis of cholesterol.

Since it is to be expected that desmosterol will be encountered in many other natural sterol mixtures, its preparation and that of its 25-dehydro-isomer have been included in the program of synthesis of natural sterol now in progress in this laboratory.[4] The 25-dehydrocholesterol (IIa) may readily be prepared from 25-ketonorcholesterol by means of the Wittig reaction. This very useful method was first applied to sterols by Barton, Campos-Neves, and Cookson[5] in their preparation of 3-methylsterols, and more extensively also by Sondheimer and Mechoulian.[6] More recently the method has been used in the synthesis of 24-methylenecholesterol by the present authors[7] and Idler and Fagerlund.[8] The latter authors largely anticipated our own observations on the Wittig-type synthesis of 25-dehydrocholesterol (IIa). In the present approach 25-ketonorcholesterol (Ia) was first converted by a transpyranylation reaction into the ether (Ic) which afforded the corresponding 25-dehydrocholesterol derivative (IIc) when treated with the required Wittig reagent. To prove its structure, the sterol (IIa) was converted to cholestanol and to 25-ketonorcholesterol (Ia). In the latter conversion the double bond of the sidechain was first selectively hydroxylated with osmium tetroxide, and the resulting glycol cleaved with periodic acid according to procedures previously described.[7] The properties of 25-dehydrocholesterol are in close agreement with those reported by Idler and Fagerlund.[8]

Compounds assigned the structure of 25-dehydrocholesterol had first been prepared by the direct or indirect dehydration of 25-hydroxycholesterol (IIIa).[2,3] The presence in these preparations of terminal unsaturation was well substantiated through spectrographic evidence by the original authors and subsequently by Stokes.[1] Idler and Fagerlund,[8] however, did not observe the characteristic infrared band at 11.3 μ, and concluded that such preparations contained little if any of 25-dehydrocholesterol (IIa), and consisted essentially of the 24-dehydroisomer (IVa). We have reinvestigated the dehydration of the tertiary alcohol (III) in the hope of finding a method leading mainly if not exclusively to the 24-isomer, *i.e.*, desmosterol (IVa). An analogous elimination has recently been used in the synthesis of lanosterol.[9] When the monoacetate of the tertiary al-

(1) W. M. Stokes, W. A. Fish, and F. C. Hickey, *J. Biol. Chem.*, 220, 415 (1956).

(2) A. I. Ryer, W. H. Gebert, and N. M. Murrill, *J. Am. Chem. Soc.*, 72, 4247 (1950).

(3) W. G. Dauben and H. Leon Bradlow, *J. Am. Chem. Soc.*, 72, 4248 (1950).

(4) The authors are greatly indebted to Dr. W. M. Stokes for his cooperation.

(5) D. H. R. Barton, A. S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

(6) F. Sondheimer and R. Mechoulian, Abstracts 131st Meeting American Chemical Society, Miami, Fla., 35–O (1957).

(7) W. Bergmann and J. P. Dusza, *Ann.*, **603**, 36 (1957).

(8) D. R. Idler and U. H. M. Fagerlund, *J. Am. Chem. Soc.*, 79, 1988 (1957).

(9) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).

cohol (IIIb) is treated with phosphorus oxychloride in pyridine, or refluxed with glacial acetic acid, there is obtained a mixture of compounds among which the 25-dehydrocholesterol (IIa) represents at least twenty-five per cent. Hydrolysis of this mixture, and recrystallization of the resulting sterols results in products in which the 25-dehydro-isomer has been enriched. Ozonolysis of such mixtures affords both formaldehyde and acetone, indicating the presence of both the 25- and 24-isomer.

If the dehydration of IIIb is carried out in dioxane containing sulfuric acid a product is obtained which no longer shows absorption at 11.3 μ, and which is therefore devoid of significant amounts of the 25-dehydroisomer (IIa). The recrystallized product was shown to be 24-dehydrocholesterol (IVa) by its hydrogenation to cholestanol and its ozonolysis, which afforded acetone, identified as its 2, 4-dinitrophenylhydrazone. A direct comparison of the melting points and infrared spectra of synthetic 24-dehydrocholesterol and desmosterol from chick embryos proved the identity of the two compounds.

EXPERIMENTAL

All melting points were taken in open capillary tubes with Anschutz thermometers. Optical rotations were determined in a 1-dm. tube with a Rudolph photoelectric polarimeter. The samples were dissolved in 2.0 ml. of chloroform. The infrared spectra were determined in potassium bromide pellets with a Perkin-Elmer Model 21 spectrophotometer. The values were corrected against the spectrum of the atmosphere.

25-Norcholestene-3β-ol-25-one (Ia) (*25-ketonorcholesterol*). A generous sample of this material was obtained through the courtesy of the Schering Corp. Recrystallization afforded large plates, m.p. 115–116° with clearing at 127°; $[\alpha]_D^{25}$ −44.4° (c = 0.81); λ_{max} 2.96, 5.83, 6.00μ; lit., m.p. 126–127° with sintering at 110°;[10] 117–127° and 127–129°.[11]

The *acetate* (Ib) m.p. 140.5–142°; $[\alpha]_D^{27}$ −43.6° (c = 2.09); λ_{max} 5.77, 5.84, 6.00, 7.98μ (lit. m.p. 141.5–142°,[9] m.p. 137.5–138.5°[10]).

25-Norcholesten-25-one-3β-(2'-tetrahydropyranyl)-ether (Ic). A mixture of 25-ketonorcholesterol (Ia) (2.0 g.), 2-methoxytetrahydropyran[12] (20 ml.), and Dowex-50 (H-form, dried at 70° for 24 hr.) (2.0 g.) was kept in a flask protected with a calcium chloride tube. The resin was collected by filtration and washed with ether. The combined solvents were evaporated to dryness, and the residue dissolved in a small amount of hexane and chromatographed on neutral alumina (activity VI). The hexane eluate was evaporated to dryness and the residue recrystallized from methanol; 1.91 g., m.p. 104–106°; $[\alpha]_D^{23}$ −29.7° (c = 1.18); λ_{max} 5.83, 6.00μ (lit. m.p. 104.9–106.2°; $[\alpha]_D^{28}$ −28.6°[13]). Additional material was obtained from the mother liquors.

$\Delta^{5,25}$-*Cholestadiene-3β-(2'-tetrahydropyranyl)-ether* (IIc). The following operations were carried out in an atmosphere of purified nitrogen and under exclusion of moisture. In a pressure flask was placed triphenylmethylphosphonium bromide (1.31 g.) and anhydrous ether (25 ml.). To this suspension was added 3.9 ml. of a 0.95N butyllithium solution in ether, and the mixture was stirred magnetically until a clear, yellow-orange solution had been obtained. Under suitable precautions,[7] this solution was mixed with a solution of Ic (1.72 g.) in anhydrous ether (50 ml.) which resulted in the immediate formation of a voluminous precipitate. An additional quantity of ether (25 ml.) was added, the mixture stirred for 1 hr., and finally heated under pressure in an oil bath at 65° for 10 hr.

The flask was cooled and the excess reagent destroyed by addition of ordinary ether (U.S.P.), and the suspension filtered through a pad of Celite. The ether was evaporated and the residue dissolved in hexane and chromatographed on a silicic acid–Celite 535 (2:1) column. The pyranyl ether was eluted by benzene-hexane (1:1). Evaporation of the solvent gave the crystalline pyranyl ether (IIc) (1.67 g.); m.p. 124–125°. After several recrystallizations from ethanol it afforded large plates, m.p. 126–127°; $[\alpha]_D^{27}$ −21.4° (c = 1.38); λ_{max} 3.27, 11.30μ.

Anal. Calcd. for $C_{32}H_{52}O_2$: C, 81.99; H, 11.18. Found: C, 81.75; H, 10.95.

5,25-Dehydrocholesterol (*25-dehydrocholesterol*). The pyranyl ether (IIc)(1.67 g.) was dissolved in hexane (75 ml.), and to this solution was added methanol (75 ml.) containing six drops of concentrated hydrochloric acid. The mixture was kept at room temperature with occasional stirring for one hour and then evaporated to dryness *in vacuo*. The crystalline residue was recrystallized from methanol; long needles (1.0 g.), m.p. 132–133.5°; $[\alpha]_D^{24}$ −42.9° (c = 1.42); λ_{max} 2.96, 3.26, 5.65, 6.09, 11.30 μ. Idler and Fagerlund[8] have reported m.p. 132.5°; $[\alpha]_D^{22}$ −40.7°. The acetate was prepared by treatment of the sterol with acetic anhydride in pyridine; m.p. 110.5–112°; $[\alpha]_D^{25}$ −44.5° (c = 2.08); λ_{max} 3.27, 5.75, 6.07, 8.05, 11.27 μ. Idler and Fagerlund[8] have reported m.p. 112°; $[\alpha]_D^{22}$ −44.4°.

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.38; H, 10.73.

Oxidation of 25-dehydrocholesterol. To a solution of 25-dehydrocholesteryl acetate (0.335 g.) in benzene (5 ml.) and a few drops of pyridine was added osmium tetroxide (0.2 g.) in benzene (20 ml.). The black solution was stirred for 5 hr. and then mixed with a solution of sodium sulfite (2 g.) in ethanol (90 ml.) and water (12 ml.). The stirring was continued overnight, the black precipitate was collected on a Celite pad and washed with ethanol. The clear solution was reduced in volume *in vacuo*, poured into water, and the precipitate was extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The white amorphous residue was dissolved in ethanol (20 ml.) and pyridine (4 ml.) and treated with a solution of periodic acid (0.275 g.) in water (1 ml.). After 10 hr. the solution was poured into water, the resulting precipitate extracted with chloroform, and the extract was washed with sodium bicarbonate solution, water, and finally dried over anhydrous sodium sulfate. The extract was evaporated and the residue dissolved in hexane and chromatographed on neutral alumina (activity I). The fraction eluted with benzene-ether (9:1) was recrystallized from methanol, 0.175 g., m.p. 140–142° which did not change upon further recrystallization; $[\alpha]_D^{25}$ −42.0° (c = 1.14). The material proved to be identical in all respects with the 25-ketonorcholesteryl acetate (Ib) described above. The sterol obtained by hydrolysis of the acetate, m.p. 114–116°, clearing at 127°; $[\alpha]_D^{27}$ −42.4° (c = 1.49) proved to be identical with 25-ketonorcholesterol (Ia).

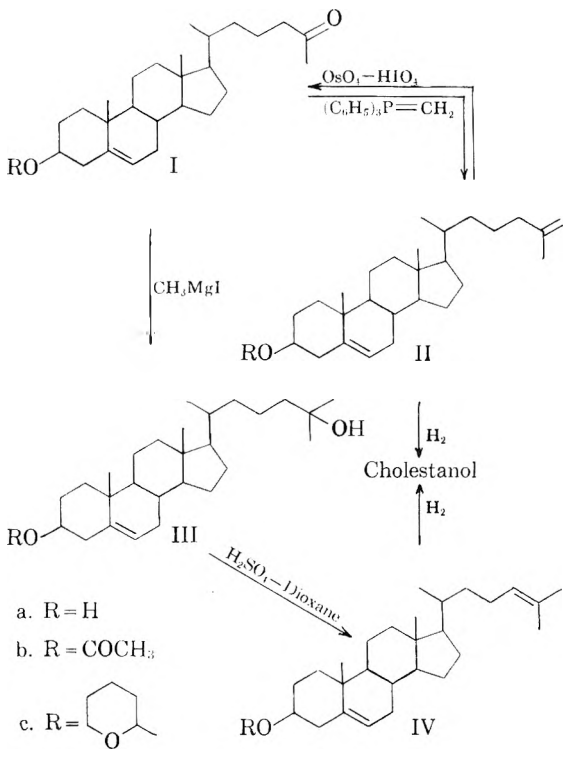
Hydrogenation of 25-dehydrocholesterol. Catalytic hydrogenation of 25-dehydrocholesterol with a 5% palladium on carbon catalyst in absolute ethanol gave cholestanol, m.p. 141–142°; $[\alpha]_D^{24}$ +20.6° (c = 1.36); acetate, m.p. 109–110°; $[\alpha]_D^{24}$ +11.8 (c = 0.64).

(10) L. Ruzicka and W. H. Fischer, *Helv. Chim. Acta*, 20, 1291 (1937).

(11) J. Hattori, *J. Pharm. Soc. Japan*, 58, 548 (1938).

(12) G. F. Woods and D. N. Kramer, *J. Am. Chem. Soc.*, 69, 2246 (1947). It was found most convenient to prepare 2-methoxytetrahydropyran by adding Dowex-50 as the acid catalyst to an equimolar mixture of methanol and dihydropyran.

(13) W. G. Dauben and H. L. Bradlow, *J. Am. Chem. Soc.*, 74, 559 (1952).



Δ^5-*Cholestene-3β,25-diol* (*25-hydroxycholesterol*) (IIIa). This sterol was prepared by the action of methylmagnesium iodide on either 25-ketonorcholesterol (Ia) or its acetate (Ib) as previously described;[2,3] m.p. 179–180° (lit. m.p. 181.8–182.5°[2]); acetate, m.p. 139.5–140.5°, clearing at 143°; $[\alpha]_D^{25}$ −39.7° (*c* = 1.20); λ_{max} 3.00, 5.76, 8.03, 12.47μ; (lit. m.p. 142–142.8°[2]; $[\alpha]_D^{20}$ −40.4°).

$\Delta^{5,24}$-*Cholestadiene-3β-ol* (*24-dehydrocholesterol, desmosterol*) (IVa). A solution of 25-hydroxycholesteryl acetate (IIIb) (1.00 g.) in 10% sulfuric acid–dioxane (wt./wt.) (225 ml.) was allowed to stand overnight at room temperature. The solution was then poured into water, the acid neutralized by addition of solid sodium bicarbonate, and the precipitate extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The crude residue was reacetylated with acetic anhydride (10 ml.) and pyridine (10 ml.) at 100° for one hour, and the crude acetate dissolved in hexane and chromatographed on neutral alumina (activity II). The fraction eluted by hexane-benzene (9:1) was recrystallized several times from methanol; 0.35 g. of large plates, m.p. 92.5–93°;[14] $[\alpha]_D^{25}$ −40.6° (*c* = 0.9); λ_{max} 5.76, 7.32, 8.02, 12.45μ.

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.51; H, 10.95.

The acetate was hydrolyzed by aqueous alcoholic potassium hydroxide to afford 24-dehydrocholesterol (desmosterol), m.p. 120.5–121°; $[\alpha]_D^{25}$ −39.2 (*c* = 1.71); λ_{max} 2.96, 7.28, 12.51μ. Desmosterol,[1] m.p. 120.8–121.2°, $[\alpha]_D^{27}$ −40.2°.

Anal. Calcd. for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.12; H, 11.56.

The compound proved identical with the desmosterol isolated from chick embryos.[1]

Hydrogenation of 24-dehydrocholesterol acetate. Hydrogenation of IVb with a platinum oxide catalyst in glacial acetic acid gave cholestanyl acetate, m.p. 108–109°, which afforded cholestanol upon hydrolysis, m.p. 139–140°. The compounds gave no depression of melting points with authentic samples and showed identical infrared spectra.

Ozonolysis of 24-dehydrocholesteryl acetate. A stream of ozone (6%) was passed for 15 min. through a solution of the acetate (0.15 g.) in highly purified glacial acetic acid (20 ml.). The gases leaving the solution were passed through a scrubber containing water (50 ml.). At the end of the reaction the water and acetic acid solution were combined, diluted with more water (50 ml.), and subjected to steam distillation. The distillate (50 ml.) was added to a solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid. After standing overnight the precipitate (38 mg.) was collected, dissolved in benzene, and the solution passed through an alumina column. Evaporation of the solvent and recrystallization of the residue from ethanol gave acetone 2,4-dinitrophenylhydrazone, m.p. 124–125°, which did not depress the melting point of authentic material and gave the same infrared spectrum as the reference compound.

Other dehydrations of 25-hydroxycholesteryl acetate. A solution of 25-hydroxycholesteryl acetate (0.51 g.) in pyridine (15 ml.) was refluxed with freshly distilled phosphorus oxychloride for 0.5 hr., the solution cooled, poured on ice, and extracted with ether. The extract was washed with dilute hydrochloric acid, water, dried, and evaporated to dryness. The residue was dissolved in hexane, the solution passed through a neutral alumina column (activity VI) and the hexane eluate recrystallized from methanol; 0.345 g. of plates, m.p. 91–93° $[\alpha]_D^{25}$ −42.6° (*c* = 1.05). The infrared spectrum of this material indicated the presence of at least 25% of 25-dehydrocholesteryl acetate (IIb). Hydrolysis of the acetate gave a sterol mixture, m.p. 121.5–122°; $[\alpha]_D^{25}$ −40.9° (*c* = 1.08) in which the 25-isomer had been enriched to more than 50%. A similar mixture was obtained when 25-hydroxycholesteryl acetate was refluxed for 12 hr. with glacial acetic acid.

The mixed acetates were ozonized by the same procedure described above. The 2,4-dinitrophenylhydrazones were extracted with ether, the extract washed thoroughly with water, dried, and evaporated. The residue was dissolved in chloroform and chromatographed on a bentonite-Celite 535 (3:1) column.[15] The first zone eluted by chloroform-ethanol (20:1) was formaldehyde 2,4-dinitrophenylhydrazone. After two recrystallizations from methanol it afforded nice needles, m.p. 165°. The second zone eluted with chloroform-ethanol (10:1) proved to be acetone 2,4-dinitrophenylhydrazone, m.p. 125°. Both compounds did not depress the melting points of authentic samples and gave the same infrared spectra as the reference compounds.

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(14) It has been pointed out to us by W. M. Stokes in a private communication that on a Kofler block the melting point of this acetate is 98°.

(15) J. W. White, *Anal. Chem.*, 20, 725 (1948); J. A. Elvidge and M. Whalley, *Chem. and Ind. (London)*, 1955, 589.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEPAUL UNIVERSITY]

Degradation of DL-2-Hydroxymethyl-2,3-dihydro-4*H*-pyran, a Model Carbohydrate, to Racemic Mixtures Related to D-Glyceraldehyde[1]

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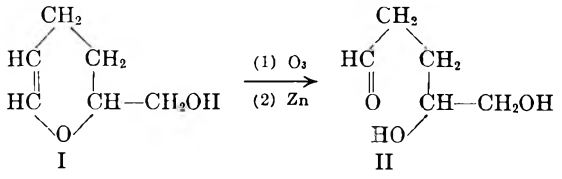
DL-2-Hydroxymethyl-2,3-dihydro-4*H*-pyran (I), racemic 3,4-dideoxyglucal, has been degraded to racemic mixtures of which enantiomorphs can be configurationally related to D-glyceraldehyde. The procedures would preserve the configuration of the asymmetric carbon in the pyran ring.

The ready conversion of 2,3-dihydro-4*H*-pyran to polydeoxyaldopentoses[3] and of *dl*-2-hydroxymethyl-2,3-dihydro-4*H*-pyran (I) to polydeoxyaldohexoses[4] has demonstrated that these compounds are model carbohydrates. An optically active form of I would be the precursor for novel types of synthetic carbohydrates.

This paper describes the development of a model route for the degradation of the racemic 3,4-dideoxyglucal (I) to racemic mixtures of which enantiomorphs are known to be configurationally related to D-lactic acid and thus to D-glyceraldehyde and D-glucose. The procedures employed would preserve the configuration of the asymmetric carbon of I and allow the designation of an enantiomorphic form, not yet obtained, as D or L. Of the four degradation routes tested, two were successful, one was partially completed, and another failed because of isolation difficulties.

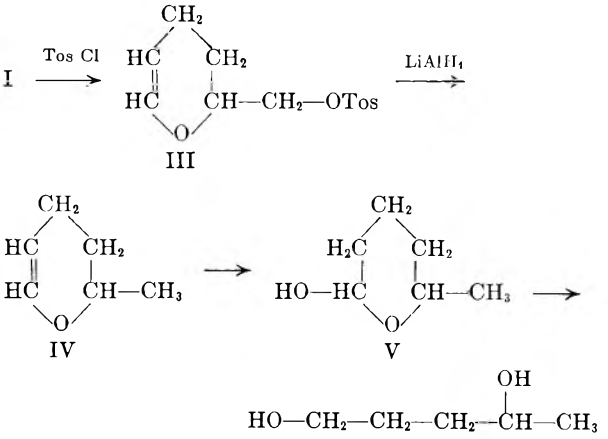
The shortest route appeared to be the ozonolysis of I to DL-dideoxyribose (II) and its conversion to



the dibenzylmercaptal since both L-2,3-dideoxyribose and its dibenzylmercaptal have been reported in the literature.[5] Unfortunately, our attempts to apply this scheme failed and neither II nor its mercaptal could be isolated.

Levene and Haller[6] have demonstrated that L-(+)-4-hydroxypentanoic acid has the configuration of L-(+)-lactic acid[7] and that the lactone of its enantiomorph is reduced by sodium and acetic acid to D-(−)-1,4-pentanediol.[8] Therefore, the degradation of I to racemic 1,4-pentanediol was the goal of the second scheme.

This approach required the preparation of 2-methyl-2,3-dihydro-4*H*-pyran (IV) by lithium aluminum hydride reduction of the toluenesulfonate (III) of I. Hydration of IV to 6-methyltetrahydropyran-2-ol (V) and subsequent oxidation would yield 5-hydroxyhexanoic acid which might then be degraded to 1,4-pentanediol by the classical sequence developed by Levene and Haller.[6] However, although the pyran intermediates III, IV,



and V were obtained, the poor yields in the steps leading to V, together with length of the subsequent degradation scheme, legislated against this course.

The third route proceeded with the dihydroxylation of 2-methyl-2,3-dihydro-4*H*-pyran (IV) to 6-methyltetrahydropyran-2,3-diol (VI), which was not isolated, according to the procedure used by Hurd[3] for the analogous hydroxylation of 2,3-di-

(1) Abstracted from the master's thesis of Herman J. Eichel, DePaul University, 1956.

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(3) (a) L. E. Schniepp and H. H. Geller, *J. Am. Chem. Soc.*, **68**, 1646 (1946); (b) C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.*, **70**, 1484 (1948); (c) C. D. Hurd and O. E. Edwards, *J. Org. Chem.*, **14**, 680 (1949); (d) C. D. Hurd, J. Moffat, and L. Rosnati, *J. Am. Chem. Soc.*, **77**, 2793 (1955).

(4) R. Zelinski, A. Verbiscar, and H. Eichel, *J. Org. Chem.*, **23**, 184 (1958).

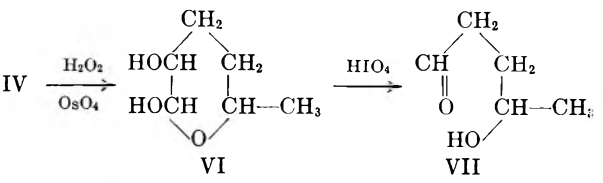
(5) R. Allerton, W. G. Overend, and M. Stacey, *J. Chem. Soc.*, 255 (1952).

(6) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **69**, 165 (1926).

(7) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **65**, 49 (1925); **67**, 329 (1926).

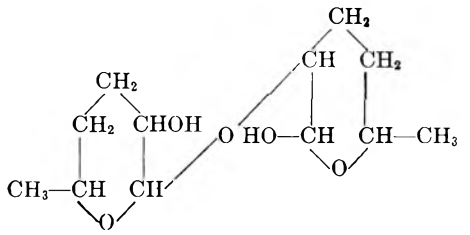
(8) P. A. Levene, H. L. Haller, and A. Walti, *J. Biol. Chem.*, **72**, 591 (1927).

hydro-4*H*-pyran. The diol VI was degraded by periodate oxidation to 4-hydroxypentanal (VII)



which was then reduced to 1,4-pentanediol by means of sodium borohydride.

The diol VI is a mixture of 3,4,6-trideoxyhexopyranoses probably in tautomeric equilibrium[9] with a small amount of 2,5-dihydroxyhexanal. It readily formed a 2,4-dinitrophenylosazone and showed the browning reaction reported for tetrahydropyran-2,3-diol.[3b] And in similar manner, an attempt to distill VI gave a reducing compound which had an elemental analysis in close agreement with that of a reducing disaccharide such as 2-(3,4,6-trideoxyhexopyranosyl)-3,4,6-trideoxyhexopyranose (VIII). This compound gave a positive



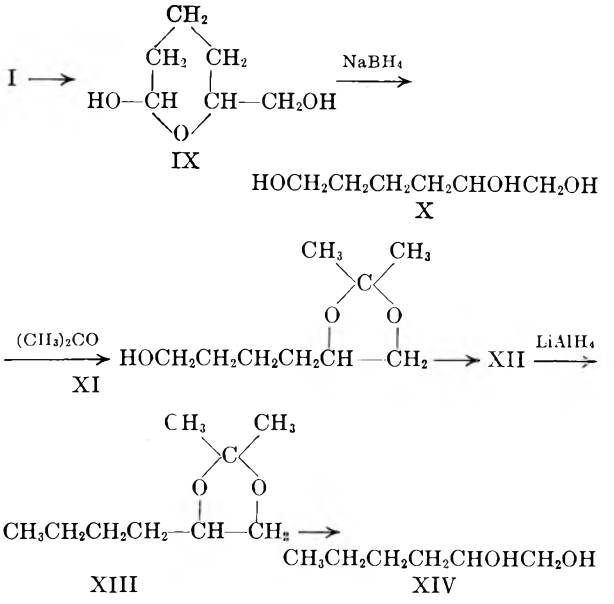
VIII

Fehling test and showed the browning reaction. Infrared analysis confirmed the presence of a carbonyl group. However, in acidic solution it formed the same 2,4-dinitrophenylhydrazone as the undistilled parent compound VI. Although it is possible that VIII was an impure form of 2,5-dihydroxyhexanal (VI), it is also possible that during derivative preparation a disaccharide such as VIII would be hydrolyzed. In fact, under the conditions used,[10] lactose did hydrolyze and form a product with 2,4-dinitrophenylhydrazine which was identical to that obtained from glucose.

Periodic acid oxidation of racemic 3,4,6-trideoxyaldohexoses VI went in low yield, but 4-hydroxypentanal (VII) was isolated. Infrared analysis showed the presence of the carbonyl group. In view of Hurd and Saunders' work[9] on the amounts of cyclic hemiacetals in equilibrium with hydroxy aldehydes, VII is probably a tautomeric mixture consisting largely of 5-methyltetrahydrofuran-2-ol. In demonstration of the greater stability of the six-membered ring, infrared analysis of 6-methyltetrahydropyran-2-ol (V) did not show the presence of a carbonyl group although the compound readily reduced Fehling's solution. The amount of 5-hydroxyhexanal present in tautomeric equilibrium must, therefore, be small.

The fourth and last degradation route was also successful and required converting 2-hydroxymethyl-2,3-dihydro-4*H*-pyran (I) to 1,2-hexanediol (XIV). Enantiomorphs of the latter have been configurationally related to L-(+)-lactic acid by Levene and coworkers.[11]

In this scheme, compound I was converted to racemic 1,2,6-hexanetriol (X) by sodium borohydride reduction of the unisolated 6-hydroxymethyltetrahydropyran-2-ol (IX), a racemic 2,3,4-trideoxyaldohexose, obtained by hydrating I. The hexanetriol was then readily converted to 2,2-dimethyl-4-(4-hydroxybutyl)dioxolane (XI), a racemic 1,2-isopropylidene-3,4,5-trideoxyhexitol, and thence to the toluenesulfonate (XII). This was then reduced by lithium aluminum hydride to 4-butyl-2,2-dimethyldioxolane (XIII) which was subsequently hydrolyzed to 1,2-hexanediol (XIV). This scheme appears to be a satisfactory means of relating the configuration of optically active 2-hydroxymethyl-2,3-dihydro-4*H*-pyran (I) to D-glyceraldehyde.



EXPERIMENTAL[12]

2-Hydroxymethyl-2,3-dihydro-4H-pyran (I). This compound was conveniently prepared by reduction of 2,3-dihydro-4*H*-pyran-2-carboxaldehyde[13] (acrolein dimer) with sodium borohydride.[4]

2,3-Dihydro-4H-2-pyranylmethyl p-toluenesulfonate (III). A solution of 17 g. (0.15 mole) of the hydroxymethylpyran (I) and 38 g. (0.20 mole) of *p*-toluenesulfonyl chloride was prepared at −15° in 35 ml. of anhydrous ether and 25 ml. of pyridine was added slowly. After 4 days at 5° the resultant

(9) C. D. Hurd and W. H. Saunders, *J. Am. Chem. Soc.*, **74**, 5324 (1952).

(10) R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, Third Edition, John Wiley and Sons, Inc., New York, 1948, p. 171.

(11) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **79**, 475 (1928).

(12) Analyses by Micro Tech Laboratories, Skokie, Ill.

(13) A sample was generously supplied by the Shell Development Company, Emeryville, Calif.

slurry was diluted with 2 volumes of ice water and chilled to 0–5° during acidification with 10% hydrochloric acid. The organic layer was separated and combined with two subsequent ether extracts of the water phase. The ether solution was washed with water and 10% sodium carbonate solution, dried, and evaporated to two thirds its volume. Storage at 5° for several days gave crystals which were washed with ether to give 13 g. (32%) of the *p*-toluenesulfonic ester (III), m.p. 44–45.5°. Recrystallization from ether shortened the range to 45–45.5°.

Anal. Calcd. for $C_{13}H_{16}SO_4$: C, 58.2; H, 6.01. Found: C, 58.0, 58.5; H, 6.3, 6.1.

2-Methyl-2,3-dihydro-4H-pyran (IV). A solution of 74 g. (0.28 mole) of the *p*-toluenesulfonate (III) in 350 ml. of anhydrous ether was added during 2 hr. with stirring to 11.4 g. (0.30 mole) of lithium hydride in 100 ml. of ether under a nitrogen blanket. The mixture was gently boiled for 4 hr., 50 ml. of water was slowly added, and the organic phase was separated by filtration. It was combined with two 50-ml. ether extracts of the aqueous phase, dried, and distilled through a 1 × 22 cm. column packed with clay saddles to give 8.5 g. (31%) of 2-methyl-2,3-dihydro-4*H*-pyran (IV), b.p. 76–80°/737 mm., n_D^{25} 1.4314. The infrared spectrum conformed with the expected structure.

Anal. Calcd. for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 74.35; H, 10.92.

6-Methyltetrahydropyran-2-ol (V). A mixture of 1.5 g. (0.015 mole) of 2-methyl-2,3-dihydro-4*H*-pyran (IV) and 7 ml. of 0.2*N* hydrochloric acid was refluxed for 2.5 hr., allowed to stand overnight, and adjusted to *p*H 7–8 with 0.5*N* sodium hydroxide. Three 2-ml. ether extracts were combined, washed with water, dried, and distilled to give 0.5 g. (30%) of 6-methyltetrahydropyran-2-ol (V), b.p. 61–62/6 mm., n_D^{25} 1.4482 (lit.[14] b.p. 71–78/11 mm., n_D^{18} 1.4452). The infrared spectrum did not show the presence of carbonyl absorption.

A high boiling viscous oil left from the distillation of IV was hydrolyzed in like manner to give a substance, b.p. 61–65/5 mm., n_D^{25} 1.4439 which had an infrared spectrum identical to that of V.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.02; H, 10.42. Found: C, 62.21; H, 10.49.

6-Methyltetrahydropyran-2,3-diol (VI). To 4.2 g. (0.043 mole) of 2-methyl-2,3-dihydro-4*H*-pyran (IV), cooled in an ice bath, there was added 1.2 ml. of a 0.5% solution of osmium tetraoxide in *t*-butyl alcohol. Then 33 ml. of a solution of hydrogen peroxide in *t*-butyl alcohol[15] was added with shaking. After storage overnight at 5° the solution was stripped of solvent at 20° and 5 mm. pressure to leave a viscous oil. Continuous extraction for 9 hr. with cyclohexane and distillation of that solvent left 2.3 (41%) of crude 6-methyltetrahydropyran-2,3-diol (VI). It was characterized by conversion[10] to the racemic 2,4-dinitrophenylosazone, m.p. 243–245° (sintered at 226°).

Anal. Calcd. for $C_{18}H_{18}O_9N_8$: N, 22.85. Found: N, 22.11.

An attempt to distill VI gave a fraction, n_D^{25} 1.4461, boiling above 56° at 5 mm. It reduced Fehling solution, gave the browning reaction[3b] with glycine in 1 min. at 100°, and formed[10] the same osazone as VI. The infrared spectrum showed the presence of carbonyl and hydroxyl absorption, but no carbon to carbon unsaturation. These data and the elementary analysis are in conformity with a disaccharide structure such as 2-(3,4,6-trideoxyhexopyranosyl) 3,4,6-trideoxyhexopyranose (VIII).

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.60; H, 9.17. Calcd. for $C_{12}H_{22}O_5$: C, 58.50; H, 9.00. Found: C, 58.16; H, 8.79.

When glucose and lactose were similarly treated with the acidic 2,4-dinitrophenylhydrazine reagent,[10] each gave the same product, m.p. 126–127°, with no mixed melting point depression.

4-Hydroxypentanal (VII). A 2.0 g. (0.015 mole) sample of 6-methyltetrahydropyran-2,3-diol (VI) was allowed to stand overnight with 12.4 g. of periodic acid in 120 ml. of water. This was then made neutral to phenolphthalein with strontium hydroxide and filtered. About 0.8 g. of strontium carbonate was added to the filtrate which was concentrated to about 100 ml. volume at 70° and 25 mm. This mixture was extracted with three 60-ml. portions of ether which were combined and dried. Removal of the ether left 0.5 g. (32%) of 4-hydroxypentanal (VII) which was distilled to make a final 26% yield of product, b.p. 37–41°/5 mm., n_D^{25} 1.4352 (lit.[16] b.p. 63–65°/10 mm., n_D^{17} 1.4359). Infrared scanning showed the presence of both carbonyl and hydroxyl absorption.

Further identification of VII was made by reduction with sodium borohydride to 1,4-pentanediol, b.p. 220°/735 mm., n_D^{25} 1.4461, which had a satisfactory elemental analysis. Literature[17,18] values are b.p. 219–220°/713 mm., n_D^{25} 1.4452. A sample made[19] from γ-valerolactone had a refractive index of n_D^{25} 1.4461.

1,2,6-Hexanetriol (X). Ten grams (0.088 mole) of 2-hydroxymethyl-2,3-dihydro-4*H*-pyran (I) was boiled for an hour with 50 ml. of 0.2*N* hydrochloric acid. The resultant solution of 2-hydroxymethyltetrahydropyran-2-ol (IX) was made slightly alkaline with potassium carbonate, stirred with 3.8 g. (0.10 mole) of sodium borohydride and allowed to stand overnight. It was brought to *p*H 7 by hydrochloric acid, concentrated to 10 ml. by vacuum distillation and cooled and filtered. Distillation of the filtrate gave 3.0 g. (25%) of 1,2,6-hexanetriol (X), b.p. 172°/3 mm., n_D^{25} 1.4754 (lit.[20] b.p. 170°/3 mm.).

Anal. Calcd. for $C_6H_{14}O_3$: C, 53.70; H, 10.50. Found: C, 53.91; H, 10.50.

The infrared spectrum was identical with that of a commercial sample, n_D^{25} 1.4763.

2,2-Dimethyl-4-(4-hydroxybutyl)dioxolane (XI). This racemic 1,2-isopropylidene-3,4,5-trideoxyhexitol was prepared by shaking overnight a mixture of 2.0 g. (0.015 mole) of 1,2,6-hexanetriol, 1.2 g. of sodium sulfate and 15 ml. of a 1% solution of hydrogen chloride in anhydrous acetone. The decanted solution was neutralized with lead carbonate, filtered, and distilled to give 1.8 g. (67%) of XI, b.p. 118°/5 mm., n_D^{25} 1.4432.

Anal. Calcd. for $C_9H_{18}O_3$: C, 61.99; H, 10.42. Found: C, 61.81; H, 10.43.

Thirty grams of a commercial sample of the triol treated the same way gave 24.5 g. of XI, b.p. 119–120°/5 mm., n_D^{25} 1.4455, with an identical infrared spectrum.

4-Butyl-2,2-dimethyldioxolane (XIII). Fifteen grams (0.086 mole) of XI and 18 g. (0.095 mole) of *p*-toluenesulfonyl chloride was stirred in 30 ml. of pyridine at less than 40°. After the initial exothermic reaction, the slurry was stirred for 6 hr. at room temperature. Water was added and the oily layer was extracted into ether which was then dried. However, since attempts to distill or to crystallize the 2.7 g. of the *p*-toluenesulfonate (XII) were unsuccessful, the crude product was used in the next step.

The crude XII in 10 ml. of anhydrous ether was added in 10 min. to a solution of 1.0 g. (0.026 mole) of lithium aluminum hydride in 25 ml. of ether. This was boiled under reflux for 5 hr. and cautiously treated with 3 ml. of water. The ether layer was dried and distilled to give 0.5 g. of 4-butyl-2,2-dimethyldioxolane (XIII), b.p. 47–48°/5 mm., n_D^{25} 1.4349.

(14) B. Helferich and T. Malkemes, *Ber.*, 55, 702 (1922).

(15) N. A. Milas and S. Sussman, *J. Am. Chem. Soc.*, 58, 1302 (1936).

(16) B. Helferich, *Ber.*, 52, 1128, 1802 (1919).

(17) A. Lipp, *Ber.* 22, 2567 (1889).

(18) L. E. Schniepp, H. H. Geller, and R. W. Von Korff, *J. Am. Chem. Soc.*, 69, 672 (1947).

(19) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, 70, 3738 (1948).

(20) H. Schulz and H. Wagner, *Angewandte Chem.*, 62, 105 (1950).

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.33; H, 11.47. Found: C, 68.48; H, 11.37.

In confirmation, XIII was prepared from 1,2-hexanediol (prepared from 1-hexene) by shaking 2.0 g. (0.017 mole) of the diol with 2 g. of sodium sulfate and 20 ml. of 1% hydrogen chloride in acetone for 6 hr. followed by standing overnight. Distillation gave 1.2 g. (45%) of XIII, b.p. 62°/15 mm., n_D^{25} 1.4351.

1,2-Hexanediol (XIV). A mixture of 300 mg. (0.0019 mole) of XIII and 10 ml. of 2% sulfuric acid was refluxed for 2 hr., neutralized with barium hydroxide and centrifuged. Evaporation of the supernatant and distillation gave 150 mg. (67%) of 1,2-hexanediol, b.p. 140°/760 mm., n_D^{25} 1.4400 (lit.[11] b.p. 110–113°/6 mm.).

Anal. Calcd. for $C_6H_{14}O_2$: C, 60.96; H, 11.94. Found: C, 60.75; H, 11.79.

A sample prepared from 1-hexene by conditions described[21] for the hydroxylation of 1-octene gave a 29% yield of XIV, b.p. 107–108°/4 mm., n_D^{25} 1.4414.

Infrared results. A Perkin-Elmer Model 21 Spectrophotometer was used with rock salt, variable thickness absorption cells for liquid compounds. Solids were examined by the pressed plate technique using potassium chloride as the carrier. The results are summarized in Table I.

TABLE I

INFRARED ABSORPTION CHARACTERISTICS (Cm^{-1})

Compound	C=O	C=C	OH
2,3-Dihydro-4*H*-pyran-2-carboxaldehyde	1742	1653	Absent
2-Hydroxymethyl-2,3-dihydro-4*H*-pyran (I)	Absent	1653	3367
2-Methyl-2,3-dihydro-4*H*-pyran (IV)	Absent	1647	Absent
6-Methyltetrahydropyran-2-ol (V)	Absent	Absent	3367
4-Hydroxypentanal (VII)	1776	Absent	3401
Reducing "disaccharide" (VIII)	1718	Absent	3378
1,2,6-Hexanetriol (X)	Absent	Absent	3311
2,2-Dimethyl-4-(4-hydroxybutyl)dioxolane (XI)	Absent	Absent	3378
p-Toluenesulfonate (XII) of XI	Absent	Absent	Absent
4-Butyl-2,2-dimethyldioxolane (XIII)	Absent	Absent	Absent

Acknowledgment. We wish to thank Dr. H. V. Knorr of the Charles F. Kettering Foundation, Yellow Springs, Ohio, for the infrared analyses.

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(21) D. Swern, G. N. Billen, and J. T. Scanlan, *J. Am. Chem. Soc.*, 68, 1504 (1946).

[CONTRIBUTION FROM RESEARCH AND DEVELOPMENT DEPARTMENT, U. S. NAVAL POWDER FACTORY]

Effect of Aqueous Sulfuric Acid on Reducing Sugars. V. Infrared Studies on the Humins Formed by the Action of Aqueous Sulfuric Acid on the Aldopentoses and on the Aldehydes Derived from Them[1]

F. A. H. RICE

Received May 16, 1957

Studies on the infrared absorption spectra of the polymeric materials, formed by the treatment of aldopentoses with sulfuric acid, indicated that the chemical structure of the polymer did not depend on the conditions of acid concentration or temperature under which it was formed. The ethanol-soluble and -insoluble fractions into which the polymeric material could be separated were found, so far as could be determined from the infrared spectra, and by carbon and hydrogen analysis, to be identical.

A comparison between the infrared spectrum of the polymeric material obtained by the treatment of L-arabinose with sulfuric acid and the infrared spectra of the polymeric materials prepared by the sulfuric acid treatment of either furfural alone, or furfural admixed with crotonaldehyde, or mixtures of furfural, crotonaldehyde, acetaldehyde, and formaldehyde strongly suggested that furfural alone was not responsible for the insoluble material obtained when a pentose is treated with sulfuric acid. The polymeric material obtained by the treatment of mixtures of furfural, crotonaldehyde, acetaldehyde, and formaldehyde with sulfuric acid were almost identical with the polymers prepared by treating L-arabinose with sulfuric acid.

This finding can explain the fact that the ultraviolet absorbance of an aldopentose in sulfuric acid reaches a steady state after an interval of time that depends on the concentrations of aldopentose and acid and the temperature.

In previous communications on the effect of sulfuric acid on the aldosugars[2,2a] it was shown that the ultraviolet spectrum which develops when an aldopentose or aldohexose is treated with sulfuric acid, depends on the formation of certain specific compounds, and that these compounds can be extracted from aqueous acid into ether solution. It was found possible to isolate and identify the compounds in the ether solution by forming and chromatographing the mixture of their 2,4-dinitrophenylhydrazones. The separated hydrazones gave crystalline products which were identified. Furfuraldehyde, crotonaldehyde, acetaldehyde, and formaldehyde were found to be formed from the action of acid on the pentose series of reducing sugars.[2]

Examination of the ultraviolet spectra as they developed in acid solution of reducing sugars

(1) Published with permission of the Bureau of Ordnance, Navy Department. The opinions and conclusions are those of the author.

(2) F. A. H. Rice and L. Fishbein, *J. Am. Chem. Soc.*, 78, 1005 (1956).

(2a) F. A. H. Rice and L. Fishbein, *J. Am. Chem. Soc.*, 78, 3731 (1956).

showed that after a period of time a steady state was reached. The time required and the optical density of the solution at the steady state depended on the concentration of the sugar, the concentration of the acid, and the temperature. The steady state, when it was reached under the same conditions, was characteristic of the sugar. When the aqueous acid solution of the sugar was continuously extracted with ether, the concentration in the ether phase of those compounds which are primarily responsible for the ultraviolet absorption spectrum of the sugar, steadily increased. A steady state, however, was not reached over a period of time several times greater than that required by the sugar when the ether-soluble products were not continuously removed by extraction. Undoubtedly the continuous increase in the optical density at 290 mμ of the ether extract, is due to the continuous shifting of the equilibrium in the aqueous phase by the extraction of the aldehydes.

It was suggested,[2] that at the steady state, the rate of formation of ether-soluble products from the sugar was the same as that at which these same compounds polymerized to form insoluble humin materials. The humins do not show any absorption maxima in the ultraviolet[3] and hence would not contribute to the ultraviolet absorption spectrum.

It has been suggested that the formation of humins from a hexose under the influence of acid, is due to the formation and polymerization of either 5-hydroxymethyl-2-furaldehyde or acid degradation products of 5-hydroxymethyl-2-furaldehyde.[4] The yield of polymeric material from the hexose under the influence of either hydrochloric or sulfuric acid is relatively high[5] (37 to 39 per cent) and depends on both the configuration of the sugar[6] and the concentration of the acid.[7]

Although it has been claimed that the polymers formed by the action of strong mineral acid on carbohydrate material are definite chemical entities[8] the analyses that have been reported for carbon and hydrogen[6,8,9] on various preparations show considerable disagreement.

Marcussen[10] treated furan with hydrochloric acid and obtained a polymeric product. Since the analyses of the product were lower than would be expected (C, 65.5; H, 2.5) from a polyfuran (C, 70.6; H, 5.9), Marcussen suggested that the furan ring had opened and the resulting unsaturated dialdehyde had polymerized.

In our studies on the effect of sulfuric acid on reducing sugars, three compounds, in addition to furfural, were isolated from the reaction of a pentose with acid.[2] Since the formation of a steady state, as measured by ultraviolet absorption, requires the continuous removal of at least two of these compounds (furfural and crotonaldehyde which make the greatest contribution to the ultraviolet spectrum), it was suggested[2] that these two compounds polymerized as they were formed at a rate which depended on the concentration of the acid and the temperature. If such were the case, the polymer formed through the action of acid on a pentose should be different from that formed from furfural alone but identical with the one formed from a mixture of the compounds responsible for the ultraviolet absorption spectrum. If compounds other than those which show ultraviolet absorption and are extractable from aqueous acid into ether, entered into the constitution of the polymer formed from the pentose, the polymer obtained from the pentose should have distinct characteristics of its own.

It was thought that a comparison of the infrared spectra of the polymers formed by the action of acid on a pentose with the infrared spectra of polymers formed by the action of acid on mixtures of the compounds responsible for the ultraviolet absorption spectrum of the pentose might establish the identity or dissimilarity of the two polymeric materials.

Accordingly, humin material was prepared from L-arabinose by treating the sugar with various concentrations of sulfuric acid at the temperature of the boiling water bath and at room temperature. The polymers which formed were isolated by filtration on a fritted glass filter, washed with water, ethanol, and ether and dried at 80° in a high vacuum, over anhydrous calcium chloride.

Furfural, and mixtures of furfural and the other aldehydes isolated from the reaction of a pentose with sulfuric acid,[2] were treated in the same manner as were the pentoses. The polymeric material which formed was isolated, washed in the same way as the polymers obtained from the pentose, and dried in a high vacuum over anhydrous calcium chloride.

The infrared spectrum of each polymer pressed at the same concentration into a potassium bromide disc,[11] was recorded and the spectra were compared (Fig. 1 and 2).

The infrared spectra of the insoluble humins obtained from L-arabinose at various concentrations of acid, from $5N$ to $20N$, were found to be identical. A small fraction of the humin which was soluble in

(3) V. B. Evstigneer and V. N. Nikiforova, *Biokhimiya*, **15**, 86 (1950); *Chem. Abstr.*, **44**, 5212 (1950).

(4) V. E. Bookly, *J. Agr. Sci.*, **11**, 69 (1921); J. J. Blanksma and G. Egmond, *Rec. trav. chim.*, **65**, 309 (1946); J. Marcussen, *Z. Angew. Chem.*, **34**, 437 (1921); J. Marcussen *Mitt. Materialprüfungsamt.*, **40**, 591 (1923).

(5) Jeiso Takahashi, *J. Agr. Chem. Soc., Japan*, 20, 553 (1944).

(6) W. B. Bottomley, *Biochem. J.*, 9, 260 (1915).

(7) T. Ploetz, *Naturwissenschaften*, 29, 707 (1941).

(8) A. Schweizer, *Rec. trav. chim.*, **57**, 345, 956 (1938).

(9) W. Eller, *Ann.*, **431**, 133 (1923).

(10) J. Marcussen, *Ber.*, **54**, 542 (1921).

(11) M. M. Stimson and M. J. O'Donnel, *J. Am. Chem. Soc.*, **74**, 1805 (1952); V. Schiedt and H. Reinwein, *Z. Naturforsch.*, **7b**, 270 (1952).

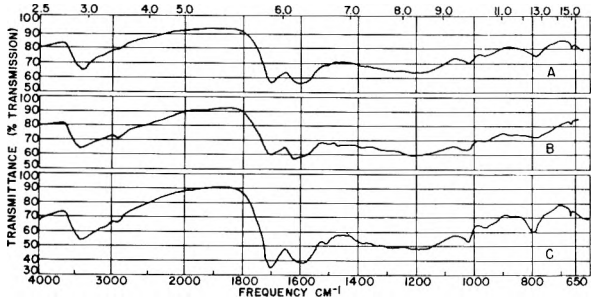

Fig. 1. Infrared spectra of humins obtained from L-arabinose under the influence of hot aqueous sulfuric acid. *A*, from reaction with 10*N* acid, ethanol-insoluble; *B*, from reaction with 5*N* acid, ethanol-soluble; *C*, from reaction with 5*N* acid, ethanol-insoluble. Concentrations were 2.0 per cent in KBr

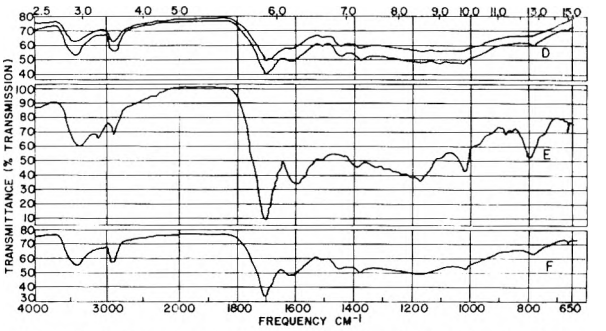

Fig. 2. Infrared spectra on the products obtained by: *D*, action of 10*N* sulfuric acid on a mixture of furfural, crotonaldehyde, acetaldehyde, and formaldehyde. Upper curve, ethanol-insoluble fraction; lower curve, ethanol-soluble fraction. *E*, action of 10*N* sulfuric acid on furfural, ethanol-insoluble. *F*, action of 10*N* sulfuric acid on a mixture of furfural and crotonaldehyde, ethanol-insoluble. Concentrations were 2.0 per cent in KBr

ethanol also showed the same infrared spectrum as the ethanol insoluble material. Fig. 1 shows the infrared spectra obtained on polymeric material prepared from L-arabinose by treatment with 10*N* (*A*) and 5*N* (*C*) sulfuric acid. The ethanol-soluble fraction (*B*) of the polymer obtained from L-arabinose by treatment with 5*N* acid is included for comparison. No essential differences will be observed. It is possible that the difference between the ethanol-insoluble and -soluble material is one of molecular weight. In agreement with the results of the infrared analyses, the analytical values for carbon and hydrogen on *A*, *B*, and *C* are essentially the same.

Fig. 2 shows the infrared spectra of polymers prepared from mixtures of furfural, crotonaldehyde, acetaldehyde, and formaldehyde (*D*). The upper curve in *D* is the spectrum of the ethanol-insoluble fraction, while the lower curve in *D* is the spectrum of that portion of the material which is soluble in ethanol. *E* is the spectrum of the polymer prepared from furfural alone and *F* is the spectrum of the polymeric material prepared from mixtures of furfural and crotonaldehyde. Although 10*N* sulfuric acid was used in the preparation of the materials whose infrared spectra are shown, other concentrations of acid gave polymeric material with identical spectra.

A comparison of the two curves in *D* shows that as far as can be determined by the infrared spectra, both the ethanol-soluble and ethanol-insoluble fractions are identical. The differences in solubility could be due to differences in molecular weight rather than differences in the chemical structure of the repeating units. Comparisons between the ethanol-soluble and -insoluble fractions of each of the other polymeric materials indicated the same identity between the ethanol-soluble and the -insoluble product.

If the spectra *D*, *E*, and *F* are compared, although certain features are common to the three spectra, *E*, the product from furfural alone seems to be quite different from the other two. The intensity of the absorption in the 1400 to 1800 cm.$^{-1}$ region compared to the 2500 to 3000 cm.$^{-1}$ region is much increased over that found in either *D* or *F*, and when it is remembered that all the spectra were run under as near as possible the same conditions and we also find that under these conditions spectra *A*, *B*, and *C* are essentially superimposable, considerable importance can be attached to this finding. In addition there are additional absorption bands in the 800 to 1200 cm.$^{-1}$ region. The analytical values for carbon and hydrogen obtained on the polymeric material from furfural are also lower than the values obtained on the other two polymers, the spectra of which are given in *D* and *E*.

No unequivocal conclusions can be drawn from a comparison of the infrared spectrum of the humin obtained from L-arabinose and the infrared spectra of the polymeric material obtained from the various mixtures of saturated and unsaturated aldehydes. In general, however, particularly if the importance of the relative intensities of the absorption bands is stressed, the infrared absorption spectrum of the humin from L-arabinose is almost identical with the spectrum of the product formed by the action of acid on the two unsaturated aldehydes (*F*) which indeed is essentially the same as the spectra of the product formed when the four aldehydes were subjected to the action of sulfuric acid (*D*). The chief difference in the infrared spectra of humin from L-arabinose and the polymeric material formed by the action of acid on the four aldehydes is in the intensity of absorption at 2900 cm.$^{-1}$ On the basis of this absorption at 2900 cm.$^{-1}$ it is possible that additional compounds, which are not extractable from aqueous acid by means of ether, enter into the formation of the humin materials formed from the reducing pentoses under acid conditions.

It is of interest to note that the infrared spectra indicate[12] that hydroxyl (3440 cm.$^{-1}$), carbonyl

(12) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y.

(1705 cm.$^{-1}$) and possibly carbon-carbon double bonds (1620 cm.$^{-1}$) are present in each one of the polymeric materials investigated.

EXPERIMENTAL

Infrared spectra. The infrared spectra were recorded on a Perkin-Elmer, model 21, double beam infrared spectrophotometer. The sample for analysis (200 mg.) was ground in a mortar with anhydrous potassium bromide (1 g.) and the mixture (300 mg.) was pressed into a disk in a high vacuum under 18,000 p.s.i.

Preparation of humins from L-arabinose. Four 10-g. samples of L-arabinose ($[\alpha]_D^{21}$ + 104°) were respectively dissolved in 200 ml. of 5*N*, 10*N*, 15*N*, and 20*N* sulfuric acid contained in 1-liter flasks. The solutions were heated on the steam bath for a period of 12 hr. During this period a heavy brownish black precipitate formed. An equal volume of ice cold distilled water was then added to the contents of each flask and the precipitate removed by filtration on a fritted glass funnel. The precipitate was washed on the funnel with several liters of distilled water and then extracted with 1 liter of boiling ethanol, followed by 200 ml. of ether. The insoluble material was then dried at 80° in a high vacuum over anhydrous calcium chloride.

The ethanol extract was concentrated to dryness on the steam bath and then washed with ether and dried in a high vacuum over anhydrous calcium chloride. No differences were found in the carbon and hydrogen content of the polymers formed under the influence of the several concentrations of acid.

Anal. Found: C, 64.2 to 67.8; H, 4.2 to 4.9.

No analytical differences could be found between the ethanol-soluble and -insoluble material.

Anal. (ethanol-soluble). Found: C, 65.8 to 67.5; H, 4.1 to 4.9.

Preparation of humin from furfural. An amount of 0.96 g. of furfural was dissolved in 200 ml. of 10*N* sulfuric acid. The solution was heated on the steam bath in a flask equipped with a reflux condenser. The resulting polymeric material was then isolated in the same way as was the humin from L-arabinose (above).

Anal. (ethanol-soluble). C, 68.6; H, 4.6; (ethanol-insoluble), C, 68.4; H, 4.5.

Preparation of humin from furfural and crotonaldehyde. An amount of 0.95 g. of furfural together with 0.7 g. of crotonaldehyde was dissolved in 200 ml. of 10*N* sulfuric acid. The rest of the procedure was identical with the above.

Anal. (ethanol-soluble) C, 69.8; H, 6.6; (ethanol-insoluble), C, 70.4; H, 6.4.

Preparation of humin from a mixture of furfural, crotonaldehyde, acetaldehyde, and formaldehyde. A mixture consisting of 0.96 g. furfural, 0.7 g. of crotonaldehyde, 0.44 g. of acetaldehyde, and 0.30 g. of formaldehyde was dissolved in 200 ml. of 10*N* sulfuric acid.

Further treatment was the same as for furfural (above).

Anal. (ethanol-soluble). C, 63.0; H, 4.3; (ethanol-insoluble), C, 63.4; H, 4.7.

Acknowledgments. I should like to thank Mrs. P. P. Wheeler for the microanalyses, Mrs. N. F. Lyons for running the infrared spectra, and Mr. A. H. Johnstone for technical assistance in preparing the polymeric materials.

INDIAN HEAD, MD.

[CONTRIBUTION NO. 473 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

Synthetic Tuberculostats. XII. Structure of the Reaction Product of Isoniazid and Formaldehyde

H. HERBERT FOX

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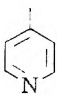
The compound prepared by the interaction of isoniazid with formaldehyde contains a triazane ring and is probably the monohydrate of hexahydro-1,3,5-triisonicotinamido-*s*-triazine.

During the course of an investigation into the tuberculostatic activity of isoniazid and its derivatives, an effort was made to synthesize 1-isonicotinyl-2-methylidenehydrazine according to the following scheme:

$$PyCONHNH_2 + CH_2O \longrightarrow PyCONHN{=}CH_2$$

where Py = 

The reaction was carried out by refluxing a mixture of isoniazid, aqueous formaldehyde (35%), and isopropyl alcohol. As the reaction proceeded, a fine white crystalline precipitate appeared which proved to be practically insoluble in all of the common solvents with the exception of dilute hydrochloric acid and dilute sodium hydroxide. Since the anticipated methylidene derivative was expected to have solubility characteristics quite similar to those of the parent isoniazid, the marked insolubility of the product (hereinafter called Ro 2-4969) strongly suggested that it was not the desired compound at all. This was subsequently confirmed by elementary analysis.

In view of its marked tuberculostatic activity, it was decided to investigate the structure of the compound in some detail.

One obvious line of approach was to determine the molecular weight of the compound. Every attempt in this direction failed—principally because of its insolubility, although instability and possibly the presence of water of hydration were also contributory factors. Most of these attempts involved modifications of the Rast procedure with a variety

of solvents but an attempt was also made using the isothermal distillation method of Signer.[1]

Failing a molecular weight determination, it seemed desirable to determine the ratio between methylene and hydrazide moieties in the molecule. Accordingly, Ro 2–4969 was oxidized with 30% H_2O_2 to isonicotinic and formic acids which were then quantitatively determined by titration (see Experimental for details).

In a series of experiments, the data listed in Table I were obtained. If a 1:1 ratio of methylene to isoniazid is assumed in a generalized structure such as $[(PyCONHIN)(CH_2)]_X$ then 2.86 grams and 1.43 grams of the compound should produce 0.38 mole and .019 mole of total acid respectively. This is in reasonable agreement with the experimental data (Table I).

TABLE I

Grams of Ro 2-4969 Used	Total Acid Formed, Moles
2.86	0.036
2.86	.0363
1.43	.0182
1.43	.0188
1.43	.0183

For further evidence, it was decided to determine whether half of the total acid formed by the peroxide oxidation was indeed formic acid. In order to distinguish between the formic acid and the isonicotinic acid formed in the oxidation mixture, advantage was taken of the fact that formic acid quantitatively reduces mercuric chloride to the insoluble mercurous chloride in accordance with the equation:

$$2HgCl_2 + HCOOH \longrightarrow 2HgCl + CO_2 + 2HCl$$

The titration mixture obtained after the peroxide oxidation and back-titration with standard hydrochloric acid was therefore treated with a large excess of mercuric chloride and was heated on a steam bath under a reflux condenser overnight (see Experimental for details). The precipitated mercurous chloride was washed, isolated, and dried. The data obtained in these experiments are listed in Table II.

TABLE II

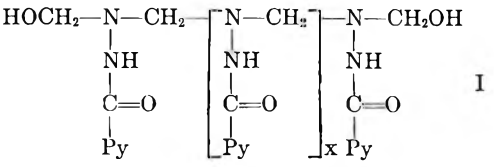
Wt. of Ro 2-4969 Oxidized, Gm.	Total Acid (Fd.), Moles	HCOOH (Calcd.), Moles	HCOOH (Fd.), Moles
1.43[a]	—	—	0.00874
1.43	0.0182	0.0091	0.00877
1.43	0.0188	0.0094	0.00885

[a] Total acid was not determined in this experiment.

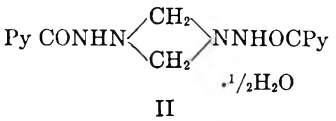
(1) R. Signer, *Ann.*, 478, 246 (1930).

From these data it is apparent that each mole of Ro 2–4969 on peroxide oxidation yield 2 moles, or a multiple of 2 moles of acid, of which one half is formic acid and one half is isonicotinic acid. The ratio of methylene to isoniazid must be 1:1.

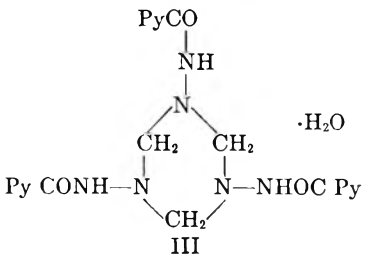
At this point in the study, sufficient data had been accumulated to permit the tentative selection and testing of several possible structures for Ro 2–4969, each of which constituted a reasonable surmise from the reactivity and the conditions of the reaction as well as from the known physical and chemical properties. These included a linear polymeric structure (I) and two cyclic structures—a dimeric hemihydrate (II) and a trimeric monohydrate or triazane structure (III).



I



II



III

Microchemical analyses of two different batches of Ro 2–4969 gave:

1. C, 54.4; H, 5.0
2. C, 54.6; H, 4.7

The linear structure corresponds quite satisfactorily to these findings in the interval between X = 2 and X = 5.

Calcd. where X = 2 mol.wgt. = 644 C = 54.0 H = 5.0
Calcd. where X = 5 mol. wgt. = 1091 C = 55.0 H = 4.9

A similarly satisfactory correspondence is obtained with the dimeric structure (II) which gives:

Calcd. for $C_{14}H_{16}N_6O_2.{}^1/_2H_2O$
mol. wt. = 307 C = 54.7 H = 4.9

and with the trimeric or triazine structure (III) which gives:

Calcd. for $C_{21}H_{21}N_9O_3.1H_2O$
mol. wt. = 465 C = 54.2 H = 4.9

When the structures were tested against the data obtained by the peroxide oxidation of Ro 2–4969 and the subsequent oxidation of the formic acid with mercuric chloride, it was found that the results calculated on the basis of the cyclic dimer

TABLE III

Structure	Mol. Wt.	Wt. of Sample-Gms.	Moles of Sample (a)	Calcd. Moles of Acid per Mole of Sample (b)	Total Acid		HCOOH	
					Calcd., moles (a) × (b)	Found, moles (Av.)	Calcd., moles	Found, moles (av.)
Linear	644	2.86	0.00444	9	0.0400	0.0362		
X = 2		1.43	.00222	9	.0200	.0184	0.0111	0.00879
X = 5	1091	2.86	.000262	15	.0392	.0362		
		1.43	.000131	15	.0197	.0184	.0105	.00879
Dimer (III)	307	2.86	.00932	4	.0373	.0326		
		1.43	.00466	4	.0186	.0184	.0093	.00879
Trimer (IV)	465	2.86	.00615	6	.0369	.0362		
		1.43	.00308	6	.0185	.0184	.0093	.00879

(II) and the trimer (III) structures were in close agreement with the experimental findings whereas those based on the "linear" (I) structure were widely divergent. This is illustrated in Table III.

There are other reasons for questioning the applicability of the linear structure. We have seen that to conform to the analytical findings, X must fall somewhere in the range between 2 and 5. Since all degrees of polymerization can be expected, X must perforce be an average figure and the average molecular weight must be somewhere between 644 and 1091. However, individual molecules could be expected to vary from 346 (where X = 0) to 1389 (where X = 7)—or even more. It is difficult to reconcile this picture with the fact that different batches of Ro 2–4969 made by different methods are indistinguishable and have reasonably sharp melting points in the vicinity of 172°.

The apparent homogeneity of Ro 2–4969 suggested the possibility of testing the validity of the linear polymeric structure by means of differential solubility determinations. If we assume the linear structure for Ro 2–4969 we can expect, with reasonable assurance, that any given sample of the substance would be made up of different sized molecules with varying solubilities in water. Such a sample should exhibit a marked decrease in solubility as the smaller, more soluble molecules are dissolved out and the larger, more insoluble ones are left behind.

Two procedures were used in establishing the solubility behavior of Ro 2–4969. In one of these, a series of samples of equal weight were suspended in varying volumes of water, shaken for equal lengths of time, and then filtered, dried, and weighed. The weights of the dissolved material were determined by difference. The data from these experiments are listed in Table IV.

In the other procedure, a weighed sample of the material was shaken with 100 cc. of water, filtered, dried, and weighed and the quantity in solution determined by difference. The dried precipitate was resuspended in 100 cc. of water and the procedure was repeated several times. The data obtained in these experiments are listed in Table V.

TABLE IV

SOLUBILITY OF RO 2-4969 IN MILLIGRAMS PER 100 CC. WHEN SHAKEN WITH VARYING VOLUMES OF WATER

Vol. of H_2O, Cc.	Amount Dissolved (Mg.) in		Solubility, Mg./100 Cc.	
	5 hours	14 hours	5 hours	14 hours
100	22.2	25.1	22.2	25.1
500	—	100.4	—	20.
500	—	99.6	—	19.9
1000	190.1	189.8	19.	19.
1000	—	177.9	—	17.8
1000	—	187.1	—	18.7
2000	389	361.4	19.4	18.

It will be observed from Table IV that whereas the solubility is substantially constant, there is a small apparent decrease in solubility with increasing volume. A similar effect is noticeable in Table V where the solubility apparently decreases with repeated extraction of the same material. This is an artifact produced by the differences in particle (not molecular) size which exist within the sample. It is well known that the degree as well as the rate of solution is an inverse function of particle size. Proof of the fact that the observed phenomenon is due to particle rather than molecular size, is presented in Table V. In Experiment A, Table V, the solubility is seen to fall off approximately 1 mg. for each extraction. At the end of the 4th extraction, the material was very lightly ground in a mortar for a short time to increase the number of small particles, whereupon the solubility promptly increased in the 5th extraction and then proceeded to fall off again in the 6th extraction. Similarly, in Experiment B, the solubility increased when the material was ground after the 4th extraction.

Though the two remaining cyclic structures are equally satisfactory extrapolations of the data obtained so far, the trimer or triazine structure has several points in its favor. (1) The six membered ring of the trimer is inherently more stable than the four membered dimer ring. (2) The great insolubility of Ro 2-4969 bespeaks a larger molecule than the dimer. (3) The triazane ring of the trimer has

TABLE V

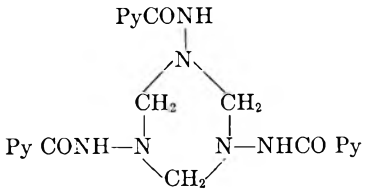
SOLUBILITY OF RO 2-4969 IN SUCCESSIVE 100-CC. VOLUMES OF WATER

	Ro 2-4969, %	Time of Shaking	Solubility in Mg./100 Cc. 1st 100 cc.	2nd 100 cc.	3rd 100 cc.	4th 100 cc.	5th 100 cc.	6th 100 cc.
Expt. A	500 mg.	2 hrs.	19.7	18.8	17.6	16.4	20.2[a]	18.8
Expt. B[b]	500 mg.	4 hrs.	24.1	24.5	20.2	18.4	20.0[a]	18.7

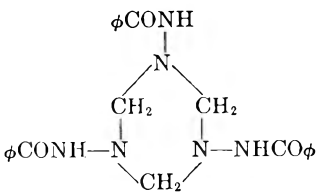
[a] Substance ground a little at this point. [b] Substance ground at beginning of experiment.

been reported in the literature as the product of the reaction between formaldehyde and various substituted amines.

Since none of these points is sufficiently convincing to permit a choice to be made between the two structures, it was decided to study the infrared absorption curves of some pertinent compounds in the hope of obtaining conclusive evidence in favor of one of the structures. The compounds studied and some of their more significant absorption bands are listed in Table IV. From these data it can be seen that the only ones with absorption peaks in the regions 10.2–10.3 μ and 10.7–10.8 μ are Ro 2-4969, its benzene analog and the three compounds with known triazane structures. The only apparent common denominator is the probable presence of the triazane ring in Ro 2-4969 and its benzene analog IV.

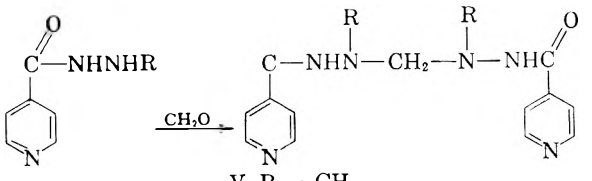


Ro 2-4969



IV

To further test this concept, it was decided to react 1-isonicotinyl-2-methylhydrazine with formaldehyde in the hope of obtaining a methylene bis derivative of the type V.



V, R = CH_3
VI, R = $(CH_3)_2CH$—

Whether the product obtained actually has the hoped for structure is open to question, but that is of minor consideration.

The important fact is that the reaction could *not* produce a triazane ring and the product should therefore *not* absorb in the 10.2 and 10.7 regions. No such absorption was obtained. The analogous compound VI prepared from iproniazid and formaldehyde also failed to show absorption peaks at 10.2 and 10.7 μ.

Both of these compounds were obtained in the form of thermoplastic glasses or resins which could not be crystallized or purified. They are very soluble in water and in polar organic solvents and in this regard are very different from Ro 2-4969. These differences tend to support the infrared findings.

Since the triazane structure for Ro 2-4969 calls for a molecule of water of hydration in order to make it conform to the elementary analysis, a moisture determination was done by the Karl Fischer method.[2] The results of two determinations are as follows: (1) in methanol—found 3.8% moisture. (2) in methanol-pyridine—found 3.9% moisture. Calcd. for $C_{21}H_{21}N_9O_3.1H_2O$—3.9% moisture.

It is therefore established that Ro 2-4969 is hexahydro-1,3,5-triisonicotinamido-*s*-triazine monohydrate. By analogy the reaction product of benzoylhydrazine and formaldehyde is probably hexahydro-1,3,5-tribenzamido-*s*-triazine monohydrate.

EXPERIMENTAL

Peroxide oxidation of Ro 2-4969. To exactly 1.43 g. of Ro 2-4969 in a 400-cc. beaker fitted with a watch glass cover and a magnetic stirrer was added 6 g. (*ca.* 6 cc.) of 30% H_2O_2, exactly 25 cc. of 1*N* NaOH and 50 cc. of H_2O. The mixture, which vigorously evolved gas, was stirred and kept covered so that the entrained vapor condensed on the watch glass and dropped back into the beaker. When gas evolution had markedly diminished, the reaction mixture was brought to a boil and then allowed to cool spontaneously, with stirring. When gas evolution had ceased, the watch glass cover was carefully rinsed into the beaker with a little water and the mixture was then titrated with 1*N* HCl using a Beckmann *p*H meter. Neutralization required 6.85 cc. of 1*N* HCl.

25 cc. − vol. 1*N* HCl required = vol. of NaOH used

$\frac{\text{(vol. of NaOH required)}}{1{,}000}$ = equivalents of acid formed

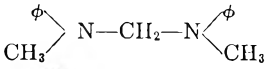
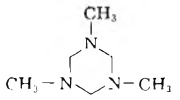
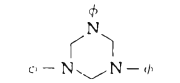
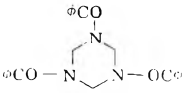
25 cc. − 6.85 cc. HCl = 18.15 cc. NaOH used

$\frac{18.15}{1{,}000}$ = .01815 equivalents of acid formed

(2) K. Fischer, *Angew. Chem.*, **48**, 394 (1935).

TABLE VI

ABSORPTION PEAKS IN INFRARED REGION

Compound	Ref.	Wave Length in Microns						
		7.70	8.25–8.35	8.55–8.65	10.2–10.3	10.7–10.8	10.9–11.0	11.65–11.8
R—$NHNH_2$	3	−	−	−	−	−	−	−
Ro 2-4969	E	+	+	+	+	+	+	+
$RNHNHCH_3$	4	+	+	+	−	−	+	+
$RN(CH_3)NH_2$	5	+	−	−	−	−	−	−
$RNHN(CH_3)_2$	6	+	+	+	−	−	+	+
$[RNHN{=}CH]_2$	5	+	+	+	−	−	+	−
Benzene analog of Ro 2-4969	E	+	+	+	+	+	+	+
R—N(—$CH_2\phi$)—$N(CH_3)_2$	5	−	−	−	−	−	+	+
$\phi CONHNH_2$	3	−	−	−	−	−	+	−
$(CH_3)_2N—CH_2—N(CH_3)_2$	7	−	+	+	−	−	−	−
	8	−	+	+	−	−	−	−
	7	+	+	+	+	−	+	+
	9	−	+	+	+	+	+	−
	10	+	+	+	+	+	+	−

R = PyCO—. E—See Experimental. − equals no peak. + equals peak.

Formic acid determination. To a titrated mixture from the peroxide oxidation transferred to a round bottom flask fitted with a condenser was added 15 g. of mercuric chloride. The clear mixture was heated on a steam bath overnight to give a lustrous precipitate of mercurous chloride. The mixture was filtered hot and the precipitate was washed successively with water, methanol, and ether and finally dried. The precipitated mercurous chloride weighed 4.132 g.

4.132 g. HgCl ≡ .403 g. HCOOH

.403 g. HCOOH ≡ .00877 moles HCOOH

Syntheses. Ro 2-4969 (Hexahydro-1,3,5-triisonicotinamido-s-triazine monohydrate). A mixture of 30 g. of isonicotinylhydrazine, 30 cc. of 35% aqueous formaldehyde, and 200 cc. of 2-propanol is heated under reflux. A fine white crystalline precipitate begins to appear almost before the isonicotinylhydrazine is completely dissolved. After refluxing for about 0.5 hr., most of the solvent is removed to yield 25 g. of product; m.p. 171.5–173.5° corr.

Anal. Calcd. for $C_{21}H_{21}N_9O_3.1H_2O$: C, 54.2; H, 4.9. Found: C, 54.4; H, 5.0.

The same product can be obtained by substituting paraformaldehyde for aqueous formaldehyde, or water for 2-propanol as a solvent.

Benzene analog of Ro 2-4969 (hexahydro-1,3,5-tribenzamido-s-triazine monohydrate). Add 15 cc. of 38% aqueous formaldehyde to a solution of 20 g. of benzoylhydrazine in 400 cc. of hot 2-propanol. The mixture is warmed on a steam bath for about 0.5 hr. and the pure product which precipitates is collected. The product is obtained in the form of small white needles which melt with decomposition and prior softening at 160–163° corr. and which are insoluble in all common solvents including dilute hydrochloric acid and dilute sodium hydroxide solution.

Anal. Calcd. for $C_{24}H_{24}N_6O_3.H_2O$: C, 62.3; H, 5.6. Found: C, 62.6; H, 6.1.

Acknowledgment. Thanks are due Mr. B. Pecherer for valuable suggestions and to Mr. D. Wagner for technical assistance during the course of the infrared studies. The author also acknowledges his indebtedness to Dr. A. Steyermark and his staff for the microanalysis.

NUTLEY 10, N. J.

(3) H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **17**, 1653 (1952).
(4) H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **18**, 994 (1953).
(5) H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **21**, 356 (1956).
(6) H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **20**, 60 (1955).
(7) L. Henry, *Bull. Acad. roy. de Belgique* [3] **26**, 200 (1893).
(8) J. v. Braun, *Ber.*, **41**, 2147 (1908).
(9) G. Pulvermacher and W. Loeb, *Ber.*, **25**, 2765 (1892).
(10) P. Duden and M. Scharff, *Ann.*, **288**, 251 (1895).

[CONTRIBUTION FROM THE INSTITUTE OF INDUSTRIAL MEDICINE, NEW YORK UNIVERSITY-BELLEVUE MEDICAL CENTER]

Isolation and Identification of Some Components of Cigarette Smoke Condensate[1]

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Alkali extraction of a fraction from cigarette smoke condensate gave a mixture of long chain acids and phenols. Chromatographic separation of the methyl esters and ethers gave a mixture of the esters of normal long chain monocarboxylic acids. Mass spectral and vapor phase chromatographic analysis showed that the mixture consists mainly of the C_{13}–C_{18} acids, with palmitic acid predominating. In addition trace amounts of the higher acids up to C_{27} are present. Oleic acid and linolenic acids were isolated and identified by comparison with authentic samples. Other products from the acid fraction were more highly unsaturated fatty acids and their oxidation products and phenols. The neutral fraction contained long chain hydrocarbons and saturated and unsaturated long chain ketones.

In an earlier report from this laboratory[3] the preparation and fractionation of cigarette smoke condensate was described. Long term tests for carcinogenicity on mice[4] focused attention on the two most active fractions designated[3] K and M. In the present report some findings of a chemical investigation of fraction K are described. This fraction contains a large number and variety of compounds and can best be described as cigarette smoke condensate from which volatiles, bases, acetone-insolubles, and some of the aliphatic hydrocarbons have been removed. Fraction K constitutes 4.9% of the whole tar.

Preliminary experiments on fraction K showed that a satisfactory separation of the components could not be obtained by either high vacuum distillation or by chromatography. The material could be readily separated into a petroleum ether soluble and a petroleum ether insoluble fraction by repeated extraction with petroleum ether (b. p. 30–60°) at room temperature.

Both these fractions showed in their infrared absorption spectra pronounced bands in the C—H stretching, carbonyl, and carbon-carbon double bond regions. The petroleum ether soluble fraction was treated with aqueous alkali and separated into acidic, basic, and neutral components by extraction under appropriate conditions.

The ether soluble part of the crude mixture of acids and phenols obtained in the alkali treatment was chromatographed on acid-washed alumina. The ether eluate on evaporation left a light yellow wax which from its infrared absorption spectrum consisted of a mixture of *normal* long chain saturated and unsaturated monocarboxylic acids in the range C_{14} to C_{18}. No further separation could be affected by chromatography. The yellow wax was treated with diazomethane and after rechromatography on acid-washed alumina gave a number of distinct fractions:

(*a*) a colorless methyl ester m.p. 33–34°, the infrared spectrum of which is superimposible on that of methyl palmitate. The analysis of the ester agreed with that of methyl palmitate and hydrolysis gave an acid m.p. 53–55°. This material was subjected to mass spectrographic analysis,[5] Table I. Acids with both even and odd numbers of carbon atoms were present and 94% of the mixture consisted of acids in the C_{13}–C_{18} range. Corroborative evidence for the mass spectral results was obtained from a vapor phase chromatographic analysis[6] conducted on the same sample.

TABLE I

MASS SPECTRAL ANALYSIS OF ACID MIXTURE AS METHYL ESTERS

Number of Carbon Atoms in Acid	Percent Composition
12	1
13	5
14	5
15	3
16	66
17	4
18	11
19	1
20	1

Shiroskaya[7] and Shmuk[8] have reported the presence of palmitic acid in tobacco leaf. It is probable that the material which they had in hand was a mixture similar to that obtained in the present investigation. Recently[9] the nature of the steam

(1) This research was supported by a grant from the American Cancer Society.

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(3) A. I. Kosak, J. S. Swinehart, and D. Taber, *J. Nat. Cancer Inst.*, 17, 375 (1956).

(4) W. E. Smith, N. Nelson, L. Orris, and A. I. Kosak, unpublished.

(5) By Drs. A. H. Boultbee and G. P. Hinds of Shell Oil Co., Houston, Tex.

(6) By Dr. K. E. Wilkens and staff of Wilkens Instrument and Research, Inc., Berkeley, Calif.

(7) V. N. Shiroskaya, *Sborn. Rabot Khim. Tabak Bull.*, 125, 151 (1935).

(8) A. Shmuk, *Vsesoyuz Inst. Tabach i Makhoroch, Prom.*, 133, 3 (1937).

(9) D. E. Buyske, P. Walder, and M. E. Hobbs, *Anal. Chem.*, 29, 105 (1957).

volatile fatty acids up to C_{12} in cigarette smoke condensate was described.

(*b*) a liquid methyl ester, n_D^{45} 1.4560. The infrared absorption spectra of the methyl ester and the free oily acid were identical with those of authentic samples of methyl oleate and oleic acid, respectively. The acid gave a crystalline *p*-phenylphenacyl ester, m.p. 54–55° which gave no depression on admixture with an authentic sample of *p*-phenylphenacyl oleate. The refractive index for oleic acid is 1.4522 at 45°.[10] The higher value found may be due to the presence of traces of more highly unsaturated acids of higher refractive indices. The acid could be hydrogenated with platinum as catalyst. One mole of hydrogen was absorbed and stearic acid, m.p. 68°, undepressed on admixture with an authentic sample, obtained.

(*c*) a yellow oil, n_D^{45} 1.4730, which was hydrolyzed and brominated to yield 9,10,12,13,15,16-hexabromostearic acid, m.p. 180–181°. The melting point was not depressed on admixture with an authentic sample and the infrared absorption spectra were identical thus identifying the unsaturated acid as linolenic acid.

Since in the fractionation of whole tar by which fraction K is obtained basic components are removed by acid extraction,[3] the bases obtained in the alkali treatment of fraction K must have arisen by hydrolysis of structures such as amides which are hydrolyzed by alkali. The mixture of acids obtained from the alkali treatment (22.9% of fraction K) could have been present in K as such or as derivatives such as esters, amides, and anhydrides. Exhaustive extraction of fraction K with sodium bicarbonate gave a 14% yield of acids, *i.e.*, more than two-thirds of the acids and phenols in fraction K are present as free carboxylic acids. No indications were obtained from infrared absorption spectra for the presence of anhydrides so that the balance of the acids are probably present as esters and amides. The nature of the phenols in fraction K was not studied.

(*d*) a yellow oil, n_D^{45} 1.5112 which differed in its infrared absorption spectrum from the methyl esters described above in that it showed, in addition to aliphatic C—H and acid C=O, the presence of hydroxyl group (3.0μ), and carbon-carbon double bond absorption (6.2μ). This suggests the presence of more highly unsaturated long chain fatty acids and their auto-oxidation products. The infrared absorption spectra of such acids and their autoxidation products have been studied[11–13] and show a close similarity to the materials obtained in this study.

In addition to the materials listed above a number of other products were obtained as mixtures of various compound types. A mixture of phenols was obtained but not separated further. A mixture of long chain ketones, m.p. 65–75° gave an infrared absorption spectrum virtually identical with that of palmitone. This product gave a negative iodoform test for a methyl ketone. The available evidence suggests that this mixture consisted of long chain saturated ketones (symmetrical or with the carbonyl group near the center of the chain), with chain lengths approximating that of palmitone, $C_{31}H_{62}O$. Schürch and Winterstein[14] reported the isolation of a material which they tentatively identified as dipalmityl ketone. In addition a product which from its infrared spectrum appears to be a mixture of unsaturated long chain ketones was obtained. This material showed in the infrared absorption spectrum bands at 5.95 μ (conjugated carbonyl) and at 6.20 μ (C=C). A saturated, long chain aliphatic hydrocarbon was obtained from fraction K. This material was identical in infrared absorption spectrum and melting point with the product previously isolated in this laboratory[3] from a similar fraction of cigarette smoke condensate. This hydrocarbon was identified as a mixture of hentriacontane and tritriacontane[3] and is present in much lower concentration in the fraction described in this study.

EXPERIMENTAL[15]

Preparation of fraction K. The preparation and fractionation of cigarette smoke condensate from five popular brands of American cigarettes has been described in an earlier paper.[3] Fraction K represents a mixture of water-insoluble acidic and neutral components of high boiling points.

The acids and phenols from fraction K. Fraction K, a viscous dark brown liquid, 34.5 g., was stirred with petroleum ether (b.p. 30–60°) and the extract decanted off. This process was repeated until only minute amounts of material could be extracted at a time. The solvent was removed from the extract at 25°/20 mm. and gave 23.2 g. of a dark brown viscous liquid. The petroleum ether insoluble residue, 11.2 g., was a viscous brown resin. The petroleum ether soluble fraction was dissolved in 100 ml. ether and stirred with 30 ml. of 10% aqueous sodium hydroxide for one hour under nitrogen. The alkali extract was removed and the alkali extraction repeated three times by which time only negligible quantities of material were extracted by the alkali. The combined aqueous alkaline extracts were acidified with dilute aqueous hydrochloric acid (1:1) and extracted with ether (10 × 100 ml.). The ether extract was washed with water and evaporated to dryness under nitrogen. The product was finally dried at 1.0 mm. over phosphorus pentoxide; a dark brown resin, 7.34, g., was obtained. The ether solution left after removal of the acids was extracted with aqueous hydrochloric acid (1:1; 6 × 50 ml.). Removal of the ether gave 12.1 g. of a neutral fraction. The acidic aqueous solution was made alkaline with aqueous sodium hydroxide, extracted with ether and the solvent distilled off to give 0.30 g. of a

(10) A. W. Ralston, *Fatty Acids and Their Derivatives*, J. Wiley and Sons, Inc., New York, 1948.

(11) O. S. Privett, W. O. Lundberg, N. A. Khan, W. E. Tolberg, and D. H. Wheeler, *J. Am. Oil Chem. Soc.*, **30**, 61 (1953).

(12) L. R. Dugan, B. W. Beadle, and A. S. Henick, *J. Am. Oil Chem. Soc.*, **26**, 681 (1949).

(13) C. S. Privett, C. Nickell, and W. O. Lundberg, *J. Am. Oil Chem. Soc.*, **32**, 505 (1955).

(14) O. Schürch and A. Winterstein, *Z. Krebsforsch.*, **42**, 76 (1935).

(15) All melting points are corrected.

brown oil with a strong amine odor. The amine gave a positive isocyanide test for a primary amine.

Chromatography of the acids and phenols. The crude mixture described in the previous experiment was separated into a petroleum ether soluble and a petroleum ether insoluble fraction. The petroleum ether soluble fraction, 6.6 g., was chromatographed on 200 g. of acid-washed alumina. No material could be eluted with eluents less polar than ether; the latter gave 4.5 g. of a yellow wax, m.p. 35–40°. The rest of the material was eluted with ethanol to give 0.6 g. of an orange colored resin. The wax from the ether eluate was soluble in aqueous alkali, ether, petroleum ether, chloroform, and ethanol, and insoluble in water. This product gave a *p*-phenylphenacyl ester, m.p. 87–88°. The infrared absorption spectrum of this was very similar in all respects to that of long chain *normal* monocarboxylic acids in the range C_{14}–C_{18}.

Chromatography of the methyl esters. The wax from the ether eluate described in the previous experiment was dissolved in ether and converted to methyl esters and ethers by treatment with an excess of diazomethane in ether at 0°. After standing overnight and removal of solvent, the residue was chromatographed on acid-washed alumina. Elution with a petroleum ether (b.p. 30–60°)–ether mixture (9.5:0.5) gave 1.8 g. of a colorless liquid, n_D^{24} 1.4521, neut. equiv. 285. Elution with ether gave 0.80 g. of a yellow oil and elution with ethanol gave 0.10 g. of a brown resin.

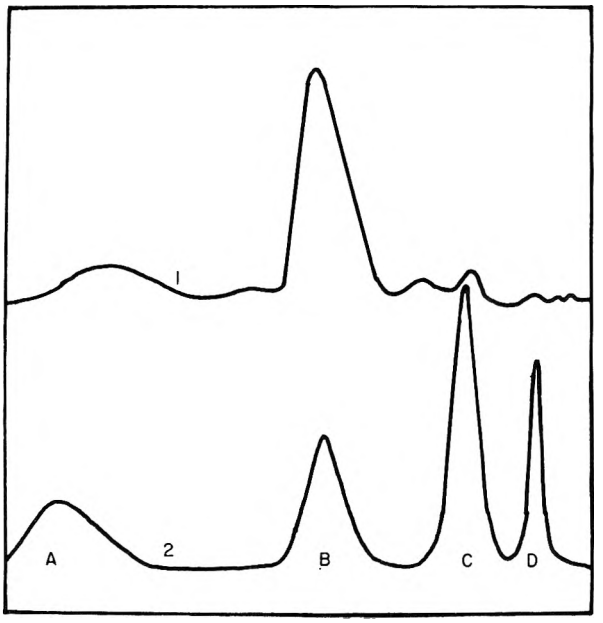

Fig. 1. Vapor phase chromatographic separation of long chain saturated acids (as methyl esters): 1. unknown mixture; 2. mixture of methyl esters of (a) stearic, (b) palmitic, (c) myristic, and (d) lauric acids. Silicone column five feet long, 225°, flow rate 100 ml./min.; chart speed 16 in./hr.

Rechromatography of the oil from the petroleum ether–ether eluate on alumina gave the following components:

(*a*) *Long chain monocarboxylic acids.* The petroleum ether eluate gave a colorless solid which was distilled in vacuum, n_D^{45} 1.4300 (reported:[10] methyl myristate, n_D^{45} 1.4281; methyl palmitate n_D^{46} 1.4317; methyl stearate n_D^{55} 1.4346), m.p. 33–34°.

Anal. Calcd. for $C_{17}H_{34}O_2$: C, 75.6: H, 12.6. Found C, 75.2; H, 12.5.

The results of the mass spectral analysis of this material is given in Table I. The various peaks obtained in a vapor phase chromatographic analysis corroborates the findings of the mass spectral analysis and are shown in Fig. 1. Hydrolysis of the mixture of methyl esters gave an acid, m.p. 53–55° (reported: myristic acid, 53–54°; palmitic acid, 62°; stearic acid, 69–70°).

(*b*) *Oleic acid.* A second fraction with the same eluent gave 0.20 g. of a colorless oil, n_D^{45} 1.4560. Hydrolysis of this ester gave a liquid acid which with *p*-phenylphenacyl bromide gave a crystalline ester, m.p. 50–53°. The product was purified by chromatography on acid-washed alumina with petroleum ether (b.p. 30–60°) as eluent followed by recrystallization from ethanol; m.p. 54–55°, undepressed on admixture with an authentic sample of *p*-phenylphenacyl oleate, m.p. 55–57°. The infrared absorption spectra of the free acid and the methyl ester were identical in every respect with that of oleic acid and methyl oleate, respectively. On hydrogenation of the free acid in ethanol with Adams catalyst one mole of hydrogen was absorbed. The product was recrystallized from ethanol-water to give a white solid, m.p. 67–68°, undepressed on admixture with an authentic sample of stearic acid, m.p. 69–70°.

(*c*) *Linolenic acid.* With petroleum ether (b.p. 30–60°)–ether (1:1) as eluent there was obtained 0.56 g. of a yellow oil, n_D^{45} 1.4730. The ester was hydrolyzed and the free acid isolated. The yellow oily acid was dissolved in 5 ml. of ether, cooled to 0°, and bromine added dropwise to the stirred solution until the yellow color persisted. On standing in ice yellow crystals separated. After standing at 0° for 8 hr. the mother liquor was decanted, the crystals washed with ether and recrystallized from dioxane; m.p. 180–181°. The melting point was undepressed on admixture with authentic 9,10,12,13,15,16-hexabromostearic acid and their infrared absorption spectra were identical. No other crystalline bromo acids could be obtained from the oily residue from the mother liquor. Chromatography on acid-washed alumina gave traces of the same hexabromostearic acid but no other crystalline compounds.

Infrared absorption spectra. All spectra were obtained in chloroform solutions with a Baird instrument equipped with sodium chloride optics.

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Notes

A department for short papers of immediate interest.

Decarbethoxylation of Perfluoroacid Esters

ELLIOT BERGMAN[1]

Received May 1, 1957

The cleavage of negatively substituted esters with alkoxide is a well known reaction. Diethyl nitromalonate is cleaved by sodium ethoxide in ethanol to ethyl carbonate and ethyl nitroacetate.[2] Ethyl trichloroacetate reacts smoothly with ethoxide at room temperature to yield diethylcarbonate.[3] We wish to report an extension of this reaction to the esters of perfluoroacids.

Nes and Burger[4] reported the ethoxide-catalyzed condensation of ethyl trifluoroacetate with benzyl cyanide in refluxing ethanol to yield α-cyanobenzyl trifluoromethyl ketone in 87% yield. Our attempts to extend this reaction using ethyl heptafluoro-*n*-butyrate proved less successful; the best yield obtained was 24% of the corresponding α-cyanoketone. In addition, 1,1,2,2,3,3,3-heptafluoropropane was formed. The cleavage of the ethyl esters of perfluoroacetic, perfluoropropionic, perfluoro-*n*-butyric, and perfluoro-*n*-octanoic acids with sodium ethoxide was, therefore, investigated in order to design procedures for the utilization of higher perfluoroacid esters in condensation reactions. The esters were refluxed with approximately 2 molar sodium ethoxide in absolute ethanol and the rates of evolution of the gaseous monohydrogen compounds were observed (except for 1-*H*-perfluoroheptane, which is a liquid at room temperature). At the same concentration the perfluorobutyrate and perfluoropropionate esters reacted at about 16 times the rate of ethyl perfluoroacetate. By this procedure the monohydrogen perfluoroalkanes could be produced in high yield under relatively mild conditions. This method thus affords a convenient way of decarboxylating perfluoroacids which ordinarily require much more drastic decarboxylating conditions.[5,6]

The general reaction is illustrated in Equations 1–3. Only in the case of the decarbethoxylation of ethyl trifluoroacetate was decomposition to fluoride noted with the consequent decrease in the yield of monohydrogen compound.

$$R_FCO_2C_2H_5 + C_2H_5ONa \rightleftharpoons R_F-\underset{\displaystyle OC_2H_5}{\overset{\displaystyle ONa}{\overset{|}{\underset{|}{C}}}}-OC_2H_5 \quad (1)$$

$$R_F-\underset{\displaystyle OC_2H_5}{\overset{\displaystyle ONa}{\overset{|}{\underset{|}{C}}}}-OC_2H_5 \longrightarrow R_F^- + C_2H_5O\overset{\displaystyle O}{\overset{\|}{C}}OC_2H_5 + Na^+ \quad (2)$$

$$R_F^- + C_2H_5OH \longrightarrow R_FH + C_2H_5O^- \quad (3)$$

Decomposition of ethyl trifluoroacetate to give fluoride probably proceeds *via* a difluorocarbene intermediate. The tendency of trifluoromethyl anion to decompose into difluorocarbene and fluoride ion is implied by the fact that McBee *et al.*[7] produced perfluoro-*n*-propyllithium by an exchange reaction between methyllithium and perfluoro-*n*-propyl iodide but obtained only tetrafluoroethylene in the same exchange when trifluoromethyl iodide was employed.

$$CF_3^- \longrightarrow CF_2 + F^- \quad (4)$$

$$2CF_2 \longrightarrow CF_2{=}CF_2 \quad (5)$$

Experiments are now being conducted, using the technique of Doering and Hoffman,[8] to determine whether or not difluorocarbene is an intermediate in the degradation of trifluoromethyl derivatives to fluoride ion.

EXPERIMENTAL

Ethyl trifluoroacetate, ethyl pentafluoropropionate, and ethyl heptafluoro-n-butyrate were prepared as follows: A flask containing 434 g. (3.80 moles) of trifluoroacetic acid was cooled in an ice bath while 212 g. (4.60 moles) of ethyl alcohol was added. After heat ceased evolving 445 ml. (8.0 moles) of concentrated sulfuric acid was added with cooling. The product was refluxed for 0.5 hr. and then distilled from the concentrated sulfuric acid through a long Vigreux column. Fractions boiling 62–64° at 755 mm. were collected. A total of 509 g., 94%, having $n_D^{20.5}$ of 1.3069 to 1.3072 was obtained.

Similarly, ethyl pentafluoropropionate, b.p. 75.0–75.5° at 750 mm., n_D^{25} 1.2988, was prepared in 93% yield. Likewise, ethyl heptafluoro-*n*-butyrate, b.p. 94.5–96.0°, n_D^{25} 1.3001–1.3003 was prepared in 90% yield.

Preparation of ethyl perfluoro-n-octanoate. To a solution of 166 g. (2.30 moles) of silver perfluoro-*n*-octanoate in 200 ml. of reagent acetone was added with swirling, 78 g. (0.50 mole) of pure ethyl iodide in 100 ml. of acetone such that the mixture refluxed gently. After standing overnight 74 g. (98%) of silver iodide was filtered from the acetone solution

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(2) C. Ulpiani, *Atti. accad. Lincei*, [5] 13, II, 346 (1904).

(3) M. L. Bender, *J. Am. Chem. Soc*, 75, 5986 (1953).

(4) W. R. Nes and A. Burger, *J. Am. Chem. Soc.*, 72, 5409 (1950).

(5) I. Auerbach, F. H. Verhoek, and A. L. Henne, *J. Am. Chem. Soc.*, 72, 299 (1950).

(6) L. J. Hals, T. S. Reid, and G. H. Smith, Jr., *J. Am. Chem Soc.*, 73, 4054 (1951).

(7) E. T. McBee, O. R. Pierce, and G. F. Judd, *J. Am. Chem. Soc.*, 76, 474 (1954).

(8) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, 76, 6162 (1954).

and the latter distilled to yield 2 fractions, the first, 69 g. (49%) of ethyl perfluoro-*n*-octanoate, b.p. 74–76° at 18 mm., n_D^{20} 1.3119 and the second, 37% of perfluoro-*n*-octanoic acid.

Anal. Calcd. for $C_{10}H_3F_{15}O_2$: C, 27.17; H, 1.14. Found: C, 26.59; H, 1.49.

Reaction of ethyl trifluoroacetate with sodium ethoxide. A cold solution of freshly prepared sodium ethoxide [6.9 g. (0.30 g.-atom) of sodium in 100 ml. of absolute ethanol] was mixed with a solution of 43 g. (0.30 mole) of ethyl trifluoroacetate in 15 ml. of ethanol. The cool reaction mixture was attached to a reflux condenser in series with a sulfuric acid bubbler, a Dry Ice trap, and a liquid nitrogen trap. The whole system was blanketed under dry nitrogen and the mixture was warmed to reflux whence gas began evolving at a measurable rate. After approximately 4 hr. the gas evolution ceased. A total of 9.0 g. (43%) of fluoroform identified by its infrared spectrum and its molecular weight (found 70.5, 70.5; calcd. 70.0) collected in the liquid nitrogen trap. The reaction mixture gave a strong test for fluoride. No diethyl carbonate was obtained on distillation of the reaction mixture. Presumably, this compound was decomposed by long exposure to ethoxide.

Reaction of ethyl pentafluoropropionate with sodium ethoxide. When ethyl pentafluoropropionate was subjected to the above reaction conditions, a 72% yield of pentafluoroethane, was evolved during a 20-min. period. Distillation of the fluoride free reaction mixture yielded 1 g. of diethyl carbonate, b.p. 126°, n_D^{25} 1.3821.

Reaction of ethyl heptafluoro-n-butyrate with sodium ethoxide. When a solution of 0.10 mole of ethyl heptafluoro-*n*-butyrate in 50 ml. absolute ethanol was added all at once to a solution of 2*N* sodium ethoxide in ethanol and the resulting solution was refluxed, a 71% yield of heptafluoropropane, free of perfluoropropene, evolved over a 15-min. period. Distillation of the fluoride free reaction mixture yielded 30% of diethyl carbonate, b.p. 126°, n_D^{25} 1.3827.

Reaction of ethyl perfluoro-n-octanoate with sodium ethoxide. A solution of 0.14 g.-atom of sodium in 40 ml. of absolute ethanol was mixed with a solution of 55 g. (0.124) mole of ethyl perfluoro-*n*-octanoate in 20 ml. of ethanol and refluxed for one hour. Distillation of the fluoride free reaction mixture yielded 44.5 g., b.p. 69–70°, of an ethanol azeotrope with 1-*H*-pentadecafluoroheptane. In addition, 10.5 g., b.p. 124–125°, n_D^{18} 1.3845–1.3855 was obtained, corresponding to a 72% yield of diethyl carbonate. The azeotrope was washed with saturated calcium chloride and redistilled from phosphorous pentoxide to give 33.5 g. (73%) yield of pentadecafluoroheptane, b.p. 94.0° at 762 mm.

Anal. Calcd. for C_7HF_{15}: C, 22.71; H, 0.27. Found: C, 22.53; H, 0.93.

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A New Synthesis for Triphenylene[1]

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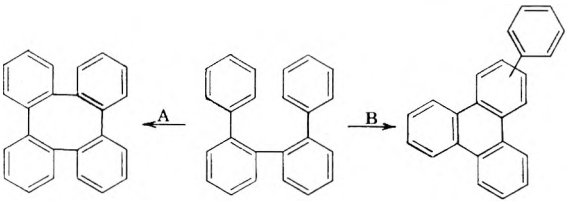
Although several different methods for the synthesis of triphenylene and its derivatives have been devised,[3–9] none offers a convenient route with good yield.

We have discovered that triphenylene can be made in approximately 10% yield in the one step dehydrocyclization of 1,2-diphenylbenzene. 1,2-Diphenylbenzene is a commercial product. The material used in this work is called Santowax and was supplied by the Monsanto Chemical Company. We have found that the dehydrogenation of the crude Santowax gives as good yields as the dehydrogenation of pure 1,2-diphenylbenzene.

This synthesis of triphenylene was suggested by the results we obtained in an attempted synthesis of 1,2,3,4,5,6,7,8-tetrabenzocyclooctatetraene. The dehydrocyclization of 2,2′-diphenylbiphenyl did not give the cyclooactatetraene as was hoped, but instead the reaction seems to have gone by path B to give either 1-, or 2-phenyltriphenylene.



The compound we obtained from the above dehydrogenation did not form a picrate and melted at 183–184°. Rapson[10] reports a melting point of 233° for the tetrabenzocylcooctatetraene. Although 1-phenyltriphenylene is what would be expected to form it is very likely that this would rearrange to the 2-isomer which would be more stable because of less steric strain. It has been shown, for example, that 1-phenylnaphthalene rearranges at 350° over silica gel to 2-phenylnaphthalene.[11]

EXPERIMENTAL[12]

Phenyltriphenylene. 2,2′-Diphenylbiphenyl (8 g. in liquid form) was processed over 10 ml. of 8% chromia on alumina catalyst[13] at 615° during a period of 27 min. The 5.8 g. of condensate obtained was chromatographed over 180 g. of alumina. First the alumina column was eluted with six 100-ml. portions of petroleum ether. Evaporation of the solvent from these fractions gave 0.2 g. of starting material. Then the column was eluted with eleven 100-ml. portions of 10% benzene-10% petroleum ether. Evaporation of the solvents

(1) This research was supported by the Office of Naval Research under contract N9onr 676(00).

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(3) H. Schmidt and G. Schultz, *Ann.*, **203**, 135 (1880).

(4) W. E. Bachmann and H. T. Clarke, *J. Am. Chem. Soc.*, **49**, 2093 (1927).

(5) C. Mannich, *Ber.*, **40**, 159 (1907).

(6) O. Diels and A. Karstens, *Ber.*, **60**, 2324 (1927).

(7) H. Adkins, L. M. Richards, and J. W. Davis, *J. Am. Chem. Soc.*, **63**, 1320 (1941).

(8) C. D. Nenitzecu and D. Curcaneau, *Ber.*, **70**, 346 (1937).

(9) W. S. Rapson, *J. Chem. Soc.*, 15 (1941).

(10) W. S. Rapson, R. G. Shuttleworth, and J. N. van Niekerk, *J. Chem Soc.*, 326 (1943).

(11) F. Mayer and R. Schiffner, *Ber.*, **67**, (1934).

(12) Melting points are corrected.

(13) C. Hansch and W. A. Blondon, *J. Am. Chem. Soc.*, **70**, 1561 (1948)

gave 4 g. of crude starting material. Next the column was eluted with nine 100-ml. portions of 50% benzene-50% petroleum ether. Evaporation of these fractions gave 1.6 g. of white crystals which after recrystallization from ether melted at 183–184° (0.48 g.).

Anal. Calcd. for $C_{24}H_{16}$: C, 94.70; H, 5.30; mol. wt., 304. Found: C, 95.08; H, 5.63; mol. wt., 298.

Triphenylene. Santowax (crude 1,2-diphenylbenzene), 23 g., was dissolved in 78 g. of thiophene-free benzene and this solution was then passed over 10 ml. of chromia on alumina catalyst at 625° during the course of 215 min. The catalyst activity as indicated by the rate of hydrogen evolution was almost constant during the course of the run. The benzene was evaporated from the condensate and the white solid remaining was crystallized from 320 ml. of ethanol. Crude triphenylene (2.6 g.) m. p. 182–193° was obtained. This material was again crystallized from ethanol to give 2 g. of pure triphenylene m.p. 197–198°. No melting point depression was observed when a mixed melting point was made with triphenylene as prepared above and an authentic sample.

A number of variations of the above procedure were tried in attempts to improve the yield. Temperatures of 500 to 650° at various space velocities were investigated without success, however.

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Chlorosulfonation of Ethyl Chloride

Cheves Walling and W. F. Pease

Received July 29, 1957

The photochemical reaction of hydrocarbons with sulfur dioxide and chlorine to yield alkanesulfonyl chlorides (the Reed reaction)[1] has received much technical investigation as a step in the preparation of synthetic detergents and in the modification of polyethylene. It is considered[2,3] to be a radical chain process involving the propagating steps

$$Cl\cdot + RH \longrightarrow HCl + R\cdot \quad (1)$$

$$R\cdot + SO_2 \longrightarrow RSO_2\cdot \quad (2)$$

$$RSO_2\cdot + Cl_2 \longrightarrow RSO_2Cl + Cl\cdot \quad (3)$$

in which (2) competes with chlorination,

$$R\cdot + Cl_2 \longrightarrow RCl + Cl\cdot \quad (4)$$

and, in fact, alkyl chlorides are often obtained as by-products.

The sulfochlorination of small molecules has received relatively little study, although Asinger and co-workers have studied the reaction of propane,[4] butane,[5] and isobutane,[6] and Helberger, Manecke and Fischer[7] have investigated the reaction of propyl and higher chlorides.

The reaction attracted our attention as a possible route to derivatives of 2-substituted ethanesulfonic acids, and we find in fact that 2-chloroethanesulfonyl chloride can be prepared in reasonable yield by this route.

Trials of various experimental conditions indicated that the best yields are obtained under strong illumination by the slow introduction of chlorine into a mixture of sulfur dioxide and ethyl chloride, allowed to reflux under a Dry Ice-condenser. Typical results appear in Table I, and it is evident that various additives had a deleterious effect on the process, as did attempts to generate chlorine and sulfur dioxide *in situ* from SO_2Cl_2 and pyridine.[2,8]

TABLE I

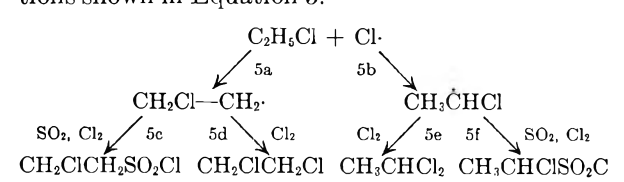
Sulfochlorination of Ethyl Chloride

Reactants (Moles)			Time of Cl_2 Addn.	Yield (% [a])	
EtCl	SO_2	Cl_2	(hr.)	$C_2H_4SO_2Cl_2$	$C_2H_4Cl_2$
1.0	2.34	1.31	3.5	26.6	18.2
4.0	9.37	4.0	11	31.8	28.3
6.0	14.0	6.0	8	35.0	25.5
7.5	14.0	6.0	4	12.0	—
2.12[b]	4.7[b]	2.0[b]	1.5	13	17
2.5[c]	4.7[c]	2.0[c]	1.5	Trace	56
7.5[d]	13.0[d]	6.0[d]	4	2	7.7
1.0[e]	0.5 (SO_2Cl_2)[e]		—	5.2	35.9

[a] Based on Cl_2 added. [b] 10 cc. water added. [c] 0.5 cc. C_2H_5SH added. [d] 1 cc. pyridine added. [e] 0.5 cc. pyridine added.

The sulfonyl chloride obtained was identified as the 2-chloro isomer by its physical constants, and by conversion to known derivatives by reaction with aniline and with thiourea, and none of the lower-boiling 1-chloro isomer was detected on fractional distillation. The best yield was 35%, based on Cl_2, or 58% based on organic products isolated. The difference probably represents SO_2Cl_2 formed by reaction between SO_2 and chlorine, and considerable quantities were actually detected during product work-up. The dichloroethane produced was chiefly 1,1-dichloroethane, containing a small amount (<7%) of 1,2-dichloroethane.

Aside from any possible synthetic utility, the sulfochlorination of ethyl chloride has some interesting features, since the products arise from a rather complicated set of competitive radical reactions shown in Equation 5.



(1) C. F. Reed, U. S. Pat. 2,174,492 (September 26, 1939).

(2) M. S. Kharasch, T. H. Chao, and H. C. Brown, *J. Am. Chem. Soc.*, **62**, 2393 (1940).

(3) J. Stauff, *Z. Elektrochem.*, **49**, 550 (1942).

(4) F. Asinger, W. Schmidt, and F. Ebeneder, *Ber.*, **75**, 34 (1942).

(5) F. Asinger, F. Ebeneder, and E. Böck, *Ber.*, **75**, 42 (1942).

(6) F. Asinger and F. Ebeneder, *Ber.*, **75**, 344 (1942).

(7) J. H. Helberger, G. Manecke, and H. M. Fischer, *Ann.*, **562**, 23 (1949).

(8) M. S. Kharasch and A. T. Read, *J. Am. Chem. Soc.*, **61**, 3089 (1939).

Evidently, under our conditions (5a–5c) and (5b–5e) are the only important paths, the 2-chloroethyl radical picking up SO_2, while the 1-chloroethyl radical reacts preferentially with chlorine. This rather striking difference in selectivity has some parallel in the behavior of SO_2—olefin copolymerization reactions. Hydrocarbonradical attack on SO_2 is a highly reversible process, the reversibility increasing (as evidenced by lower ceiling temperatures) with increasing substitution,[9] and the reaction is also repressed by electron-withdrawing groups on the hydrocarbon radical.[10] Thus, vinyl chloride, which grows through a 1-chloroalkyl radical analogous to the product of (5b) is one of the few olefins giving a copolymer containing several monomer units per SO_2 residue.[11]

If we attempt to reconcile our yields with chlorination data, the results are more puzzling. The photochlorination of ethyl chloride gives approximately 80% 1,1-dichloroethane,[12] indicating that step (5b) occurs 4 times as rapidly as (5a), and since we are dealing with a chain process, this should set an upper limit of 20% on the possible yield of 2-chlorosubstituted products. In contrast, our data indicate yields of at least 35–60% of 2-chloroethanesulfonyl chloride.

At present we can offer no unequivocal resolution of this discrepancy, but it may be due to the high SO_2 media in which our reactions have been carried out. Recently Russell and Brown have noted significant differences in selectivity for different C—H bonds in chlorinations employing Cl_2 and SO_2Cl_2, and has suggested that the latter involve the $\cdot SO_2Cl$ radical.[13] In our system it is certainly possible that the equilibrium

$$SO_2 + Cl \rightleftarrows \cdot SO_2Cl \qquad (6)$$

lies well to the right so that $\cdot SO_2$ Cl is the actual attacking species in (5a) and (5b). Alternatively, SO_2 may act as a "complexing" solvent for chlorine atoms analogous to aromatic solvents[14,15] and alter their reactivity without forming an actual covalently bonded radical. Admittedly these two alternatives would be extremely difficult to differentiate by experiment, and the latter could be an explanation of Russell and Brown's SO_2Cl_2 results.[13]

EXPERIMENTAL

Materials were ordinary commercial reagents. The ethyl chloride had a slight mercaptan odor, so in some experiments it was treated with cold, concentrated sulfuric acid before use, but without significant change in results.

Sulfochlorinations were carried out in all-glass equipment, using a round-bottomed flask fitted with a gas inlet tube and a Dry Ice-cooled condenser. During reaction the system was illuminated by one or two Westinghouse RS 275-watt sunlamps at a distance of about 6 in.

Product isolation and identification. Reaction mixtures were first separated by atmospheric pressure distillation from a water bath. The amount of dichloroethanes in the low-boiling fraction was determined by adding a 20-g. aliquot to 125 g. of 20% NaOH solution frozen at −70° and warming slowly to 0°. This procedure removed HCl, SO_2, and SO_2Cl_2. The solution was next neutralized with HCl and the dichloroethanes separated by steam distillation into a calibrated trap.

1,1-Dichloroethane boils at 57°, and 1,2-dichloroethane boils at 83°. Fractional distillation of the dichlorides from one run showed that most of the material boiled below 65°. Analysis of the higher-boiling fractions by index of refraction indicated a total of 6–7% 1,2-dichloroethane.

2-Chloroethanesulfonyl chloride was obtained from the residue of the first separation by vacuum distillation as a water-white lachrymatory liquid, b.p. 84°/12 mm., d_4^{20} 1.560, n_D^{20} 1.4934, lit.,[16] d_4^{20} 1.550, n_D^{20} 1.4920, and containing 44.95% Cl. The 1-chloro isomer is reported[17] to boil at 70–1°/13 mm., but no significant lower boiling fraction was detected. On reaction with excess aniline in ether, the sulfonyl chloride gives a chlorine-free product, m.p. 69.6–70.2° on recrystallization from CCl_4, apparently identical with that reported by Kohler[18] who gives m.p. 69–70°. Kohler considered this product to have a cyclic structure, but its infrared spectrum is consistent with the expected ethylenesulfonanilide, $CH_2{=}CHSO_2NHC_6H_5$, reported m.p. 69°.[19] Although isolation of the ethylenesulfonanilide was not quantitative due to losses during recrystallization, during the reaction in ether aniline hydrochloride, 1.82 moles, precipitated out and was separated by filtration and identified by neutralization equivalent (129.8, calc., 129.6). The analogous reaction of 1-chloroethanesulfonyl chloride has not been described, but it is reported to react with ammonia to give 1-chloroethanesulfonamide[17] and should accordingly liberate only one mole of aniline hydrochloride. A better proof of structure was obtained by hydrolyzing the sulfonyl chloride by boiling with water, neutralizing with bicarbonate and converting to 2-*S*-thiuronium ethanesulfonate. The product, obtained in 42.6% yield, had an x-ray powder diagram identical with authentic material,[20] and also the proper iodine titration on hydrolysis to 2-mercaptoethanesulfonate ion.

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(9) R. D. Snow and F. E. Frey, *Ind. Eng. Chem.*, **30**, 176 (1938).

(10) For a more detailed discussion see C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 223–8.

(11) C. S. Marvel and L. H. Dunlap, *J. Am. Chem. Soc.*, **61**, 2709 (1939).

(12) Gas phase chlorination at about 200° gives 80% 1,1-dichloroethane, W. E. Vaughan and F. F. Rust, *J. Org. Chem.*, **6**, 479 (1941), and J. D'Ans and J. Kautzach, *J. Prakt. Chem.*, **2**, 305 (1909) report at least 70% in the liquid phase at the boiling point. A recent measurement by M. F. Mayahi at Columbia indicates 81.5% 1,1- and 18.5% 1,2-dichloroethane at 0° in CCl_4.

(13) G. A. Russell and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 4031 (1955).

(14) G. A. Russell, *J. Am. Chem. Soc.*, **79**, 2977 (1957).

(15) C. Walling and B. Miller, *J. Am. Chem. Soc.*, **79**, 4181 (1957).

(16) E. F. Landau, *J. Am. Chem. Soc.*, **69**, 1219 (1947).

(17) E. Müller and H. Raudenbusch, *Ber.*, **64B**, 94 (1931).

(18) E. P. Kohler, *Am. Chem. J.*, **19**, 744 (1897).

(19) P. W. Clutterbuck and J. B. Cohen, *J. Chem. Soc.*, 121 (1922).

(20) C. H. Schramm, H. Lemaire, and R. H. Karlson, *J. Am. Chem. Soc.*, **77**, 6231 (1955).

Aromatic Organosilicon Compounds

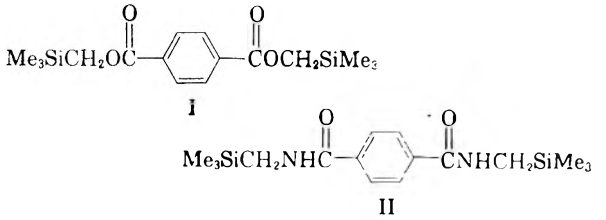
GERALD BAUM

Received July 30, 1957

The use of silicone resins as high temperature insulating materials has led to the study of new types of polymerizable organosilane monomers. Four such compounds containing aromatic nuclei are reported herewith.

Compound I, bis(trimethylsilylmethyl) terephthalate and Compound II, *N,N'*-bis(trimethylsilylmethyl) terephthalamide were both prepared by interchange reactions starting with dimethyl terephthalate. According to the method of Speier,[1] chloromethyltrimethylsilane was converted *via* its acetate to hydroxymethyltrimethylsilane, and the reaction of this alcohol with dimethyl terephthalate using *p*-toluenesulfonic acid as a catalyst gave an 85% yield of Compound I. For the preparation of Compound II, an amide-ester interchange reaction was employed, starting with aminomethyltrimethylsilane[2] and dimethyl terephthalate. Removal of methanol from the reaction mixture yielded the diamide II.

Compound IVa, 4,4'-bis(chlorodimethylsilyl)-biphenyl, and Compound IVb, 4,4'-bis(chlorodimethylsilyl)biphenyl ether, were both prepared by halogen-metal interconversion reactions. The appropriate aryl bromides IIIa and IIIb were treated with *n*-butyllithium according to the procedure of Gilman[3] to yield diaryllithium derivatives which were then coupled with excess dimethyldichlorosilane. Distillation of the reaction mixtures then gave good yields of the chlorosilanes IVa and IVb.



a, R = C_6H_4—C_6H_4—
b, R = C_6H_4—O—C_6H_4—

An attempt was made to react the aryl bromides IIIa and IIIb directly with both magnesium and lithium. 4,4'-Dibromobiphenyl could not be made to react with either metal, and the reaction of 4,4'-dibromobiphenyl ether with lithium apparently yielded only a monolithio derivative which was carbonated to yield an acidic gum.

EXPERIMENTAL[4]

Bis(trimethylsilylmethyl) terephthalate (I). A mixture of 40.5 g. (0.39 mole) of hydroxymethyltrimethylsilane, 29.2 g. (0.15 mole) of dimethyl terephthalate (DMT), and 0.5 g. of *p*-toluenesulfonic acid was placed in a 500-cc. flask connected to a short stripping column. The flask was heated and with nitrogen sparging 10.2 ml. of methanol was collected (theory = 12.1 ml.) followed by 8 ml. of excess alcohol. Then one gram of unreacted DMT sublimed out of the reaction mixture. The flask containing the residue was connected to a small Claisen head and distilled. There was obtained 45 g. (89% crude yield) of the diester I, a pale yellow solid b.p. 155–160°/1. mm., m.p. 85–95°. The solid was recrystallized from a 4:1 methanol-benzene mixture to yield 40 g. of white flat shiny plates, m.p. 105–106°.

Anal. Calcd. for $C_{16}H_{26}O_4Si_2$: Si, 16.55; sapon. equiv. 169. Found: Si, 16.4; sapon. equiv. 166.

N,N'-bis(trimethylsilylmethyl) terephthalamide (II). In a 500-cc. round bottom flask was placed 38.8 g. (0.2 mole) of DMT and 62 g. 0.6 mole) of aminomethyltrimethylsilane. The flask was stoppered, shaken vigorously for nine days and then heated to 80° for 8 hr. The flask was then charged to a short stripping column and (with nitrogen sparging) 27 ml. of a mixture of methanol and excess amine was collected. The semisolid residue was placed in a small Claisen flask, distilled, and 20 g. of yellow solid was obtained, b.p. 130–5°/1. mm., m.p. 64–70°. This material is probably the monosubstituted silyl amide–ester and was not investigated further.

The residue from the Claisen distillation consisted of yellow-brown crystals, m.p. 190–210°, weight 22 g. (a 33% crude yield). One recrystallization from an ethanol-water solution yielded 16.3 g. of short colorless plates, m.p. 228–229°.

Anal. Calcd. for $C_{16}H_{28}N_2O_2Si_2$: Si, 16.65. Found: Si, 16.5.

4,4'-Bis(chlorodimethylsilyl)biphenyl (IVa). In a 1-l. three-necked flask fitted with a condenser, stirrer, and dropping funnel was placed 30.2 g. (0.1 mole) of 4,4'-dibromobiphenyl dissolved in a mixture of 150 cc. of toluene and 50 cc. of benzene. The flask was flushed with nitrogen and 200 cc. of a 1.6*N* solution of *n*-butyllithium[3] in diethyl ether was added with stirring. The mixture warmed slightly and a heavy white precipitate formed. Ether was distilled out through the condenser until the flask temperature had reached 78°. The mixture was then stirred and refluxed at this temperature for 0.5 hr. After cooling, the above mixture of 4,4-dilithiobiphenyl and excess *n*-butyllithium was added fairly rapidly with stirring to 64.5 g. (0.5 mole) of dimethyldichlorosilane. After two hours reflux, Color Test I[5] was negative.

The solution was cooled, filtered, and the precipitate was washed several times with hot benzene. The combined filtrates were stripped of mixed solvents and excess dimethyldichlorosilane. The residue was then Claisen distilled, and a fraction was collected having b.p. 195–205°/1.8 mm., solidifying in the receiver to a white crystalline solid m.p. 65–70°, weight 24 g. (71% yield). A redistilled sample of this material had b.p. 200–208°/1.8 mm., m.p. 68–70°.

Anal. Calcd. for $C_{16}H_{20}Cl_2Si_2$: Cl, 20.8; Si, 16.5. Found: Cl, 21.2; Si, 16.6.

4,4'-Bis(chlorodimethylsilyl)biphenyl ether (IVb). Following the general procedure given above, 320 cc. of a 1.5*N*

(1) J. L. Speier, B. F. Daubert, and R. R. McGregor, *J. Am. Chem. Soc.*, **70**, 1117 (1948).

(2) L. Sommer and J. Rockett, *J. Am. Chem. Soc.*, **73**, 5130 (1951).

(3) H. Gilman, W. Langham, and F. W. Moore, *J. Am. Chem. Soc.*, **62**, 2337 (1940).

(4) The melting points were determined on a Fisher-Johns melting point block and are uncorrected.

(5) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

n-butyllithium solution was added to 59 g. (0.15 mole) of 4,4′-dibromobiphenyl ether dissolved in 400 cc. of benzene. The solution was refluxed for 30 min., cooled, and added to 129 g. (one mole) of dimethyldichlorosilane. After refluxing for an additional 3 hr., the mixture was filtered, the excess chlorosilane and solvents were stripped from the filtrate, and Claisen distillation of the residue yielded a pale yellow oil, b.p. 200–205°/mm., weight 38 g. (71% yield). The oil crystallized on standing to a white waxy solid, m.p. 27–28°.

Anal. Calcd. for $C_{16}H_{20}Cl_2OSi_2$: Cl, 20.2; Si, 15.7. Found: Cl, 20.0; Si, 15.7.

Reaction of 4,4′-dibromobiphenyl ether with lithium. An organolithium reagent was prepared in the usual manner from 7 g. (one mole) of lithium wire, 75 g. (0.23 mole) of 4,4′-dibromobiphenyl ether, and 300 cc. of ether. An aliquot of this solution was taken for titration, and the solution was found to contain 0.25 mole of organolithium reagent. After cooling and filtering from excess lithium, the solution was poured rapidly onto a Dry Ice–ether slurry. The ether layer was washed and extracted with dilute potassium carbonate solution. Acidification of the aqueous solution gave a sticky yellow precipitate, weight 20 g. This material dried to a brittle resin, m.p. 150–170°.

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A New Synthesis of Menthofuran

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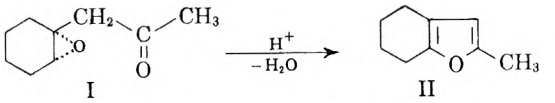
Received July 31, 1957

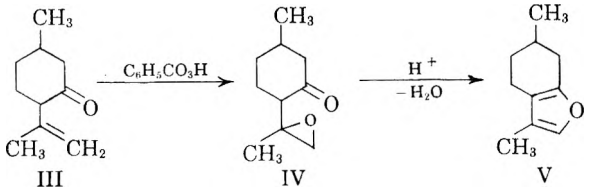
In a recent paper[1] it was shown that keto epoxides such as I could be cyclodehydrated readily to furans when heated with a catalytic amount of acid:



I II

A similar synthesis has been performed on epoxyacetals resulting from a Darzens reaction on ketoacetals.[2]

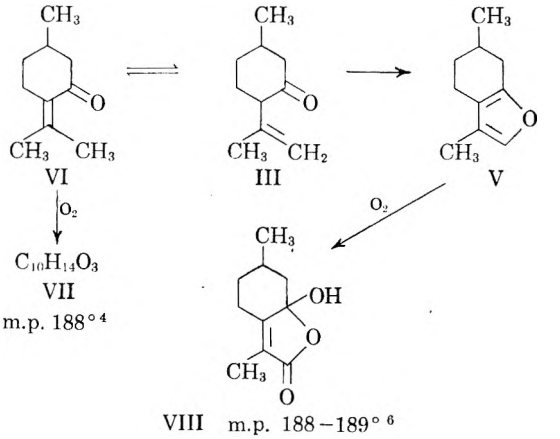
This reaction has been extended now to the keto epoxide (IV), prepared by the action of perbenzoic acid on isopulegone (III). Menthofuran (V) was obtained in poor yield and shown to be identical with an authentic sample, prepared from pulegone according to the method of Treibs.[3] Cyclodehydration of IV occurs under very mild conditions, which are not essentially different from biological ones.



III IV V

Autoxidation of pulegone[4] (VI) or pennyroyal oil[5] gives, among other compounds, a substance (VII), the melting point of which agrees with that of the lactone (VIII), isolated from the products of autoxidation of menthofuran[6]. The structure of VIII has been elucidated recently, but the identity of VII and VIII has not been verified completely.[6]

The results described in this note strengthen the hypothesis of biosynthesis of menthofuran *via* isopulegone:



EXPERIMENTAL

(*A*) To a solution of perbenzoic acid (0.04 mole) in chloroform, was added 4.32 g. of isopulegone.[7] The solution was kept at 0° and the course of the reaction was followed by titration of the unreacted peracid in aliquots. After completion of the reaction (14 hr.) the solution was washed with 10% sodium carbonate, saturated sodium chloride, dried and concentrated under reduced pressure. The residual oil was refluxed for 10 min. with a mixture of 20 ml. of water, 20 ml. of methanol, and 1 ml. of concentrated sulfuric acid, neutralized and steam distilled; the distillate was extracted with ether and worked up as usual. The yield of pure product was 0.55 g. (13%), b.p. 97–98°/22 mm., n_D^{22} 1.4805.[6,8,9]

The infrared spectrum was identical with that of authentic menthofuran. Menthofuran gives a wine-like characteristic color when treated with chloranil.

Maleic anhydride adduct: m.p. 134°, undepressed when mixed with an authentic sample.[8]

(*B*) When cyclodehydration of the keto epoxide was carried out at room temperature (14 hr.), the yield of menthofuran was lower (5%).

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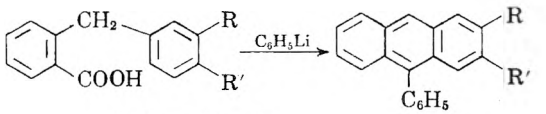
(1) H. Fritel and P. Baranger, *Compt. rend.*, **241**, 674 (1955); H. Fritel, thesis (Paris 1956).
(2) D. M Burness, *J. Org. Chem.*, **21**, 102 (1956).
(3) W. Treibs, *Ber.*, **70**, 85 (1937).
(4) E. Sernagiotto, *Gazz. chim. ital.*, **47** (I), 150 (1917).
(5) Y. R. Naves, *Perfumery Essent. Oil Record*, 121 (1945).
(6) R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **72**, 399 (1950).
(7) C. Harries and G. Roeder, *Ber.*, **32**, 3368 (1899); our sample b.p. 98–101°/13 mm., n_D^{19} 1.4700, was purified through its semicarbazone m.p. 174–175°.
(8) P. Z. Bedoukian, *J. Am. Chem. Soc.*, **70**, 621 (1948).
(9) P. Carles, *Parfumerie mod.*, **22**, 615 (1929).

Further Extension of the Base-Catalyzed Cyclization

C. K. Bradsher and Sidney T. Webster[1]

Received August 12, 1957

In an earlier communication[2] it was shown that *o*-benzylbenzoic acid (I) will react with an excess of phenyllithium to afford a 70% yield of 9-phenylanthracene (II). In the interest of learning more about the limits of this novel cyclization, the



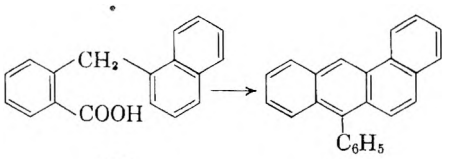
I, R = R′ = H — II
III, R = H, R′ = CH_3 — IV
V, R = R′ = CH_3 — VI

action of phenyllithium on some substituted benzylbenzoic acids has been investigated.

With *o*-(4-methylbenzyl)benzoic acid (III) a 42% yield of the known[3–5] 2-methyl-9-phenylanthracene (IV) was obtained. In one experiment in which an excess of a lithium metal was present, none of the 2-methyl-9-phenylanthracene (IV) was isolated as such, and the principal product was a new, well-defined molecular compound, containing 2-methyl-9-phenyl-9,10-dihydroanthracene in combination with the fully aromatic analog (IV).[6]

The reaction of *o*-(3,4-dimethylbenzyl)benzoic acid (V) with an excess of phenyllithium gave a 41% yield of what is believed to be 2,3-dimethyl-9-phenylanthracene (VI).[7]

With *o*-(1-naphthylmethyl)benzoic acid (VII) cyclization takes place into the 2-position producing the known[8] 10-phenyl-1,2-benzanthracene (VIII) in 58% yield. These observations eliminate the somewhat remote possibility that the entering



VII VIII

phenyl group is introduced at the methylene bridge, and is further confirmation for the reaction mechanism proposed earlier.[2]

EXPERIMENTAL

Spectroscopic data. All ultraviolet absorption spectra were obtained in 95% ethanol solution using a Warren Spectracord spectrophotometer and 1-cm. quartz cells. All infrared spectra were determined in carbon tetrachloride solution a Perkin-Elmer Model 21 double beam spectrophotometer with 1.0-mm. sodium chloride cells.

Phenyllithium. Except as noted phenyllithium was prepared by the action of 31.4 g. of bromobenzene on 2.78 g. lithium in 350 ml. of dry ether, the procedure being carried out under a nitrogen atmosphere. An additional 3–4 ml. of bromobenzene was added to react with any remaining lithium and stirring continued for one hour.

2-Methyl-9-phenylanthracene (IV). To an ether solution of phenyllithium a solution containing 5 g. of *o*-(4-methylbenzyl)benzoic acid[9] in 150 ml. of dry ether was added gradually with stirring over a period of 30 min. The dark reaction mixture was stirred for 15 hr. at room temperature and then about 200 ml. of ice water was added dropwise with cooling and stirring. The ether layer was separated, washed with water until neutral and finally dried over sodium sulfate. The ether was removed on the steam bath and the residue dissolved in 50 ml. of dry benzene and chromatographed by passing it through a 2.5 × 35 cm. column carefully packed with 125 g. of alumina (Merck and Co.). Benzene was used for elution of the hydrocarbon fraction. Since no crystalline product was obtained, the chromatographic process was repeated, the benzene solution was concentrated and the fluorescent residue crystallized from ethanol. The granular light yellow crystals were collected, 2.48 g. (42%), m.p. 120°[10] (lit.[3,4] 119°). A mixed melting point with an authentic sample[11] of 2-methyl-9-phenylanthracene gave no depression. Ultraviolet absorption maxima were observed at 227, 257, (316), 333, 348, and 366 mμ. These maxima correspond closely to those reported for a 9-phenylanthracene system.[12]

Products obtained with excess lithium metal. When the above reaction was carried out as described but using 4.1 g. instead of 2.78 g. of lithium metal, and only a total of 31.4 g. of bromobenzene, the hydrocarbon fraction amounted to 2.13 g. (48%) of white crystals of what is believed to be a molecular compound between 2-methyl-9-phenyl-9,10-dihydroanthracene and 2-methyl-9-phenylanthracene (IV). The analytical sample, crystallized from ethanol, melted at 87–88°; ultraviolet absorption maxima occurred at 257, (271), 316, 333, 348, and 366 mμ.

Anal. Calcd. for $C_{21}H_{16}$·$C_{21}H_{18}$:[13] C, 93.64; H, 6.36. Found: C, 93.92; H, 6.01.

(1) Monsanto Chemical Co. Fellow, 1956–1957.

(2) C. K. Bradsher and S. T. Webster, *J. Am. Chem. Soc.*, **79**, 393 (1957).

(3) R. Scholl, H. Dehnert, and L. Wanka, *Ann.*, **493**, 56, 82 (1932).

(4) H. Hemilian, *Ber.*, **16**, 2360 (1883).

(5) F. A. Vingiello and J. G. Van Oot, *J. Am. Chem. Soc.*, **73**, 5070 (1951).

(6) It is well known that the alkali metals reduce the anthracene nucleus at the 9,10 positions, *e.g.*, W. Schlenk, J. Appentodt, A. Michael, and A. Thal, *Ber.*, **47**, 473 (1914); W. Schlenk and E. Bergmann, *Ann.*, **463**, 158, 276 (1928).

The formation of a well-defined molecular compound containing one mole of 9-phenylanthracene to one mole of 9-phenyl-9,10-dihydroanthracene has been observed earlier, E. Haack, *Ber.*, **62**, 1771 (1929).

(7) The possibility that cyclization has occurred *ortho* rather than *para* to a methyl group has not been excluded, but it has already been shown that in the aromatic cyclodehydration of 2-(3′-methylbenzyl)benzophenone only the *para* cyclization product is isolated (76% yield; ref. 5).

(8) F. A. Vingiello, A. Borkovec, and J. Shulman, *J. Am. Chem. Soc.*, **77**, 2320 (1955).

(9) L. Gresley, *Ann.*, **234**, 234 (1886).

(10) All melting points were determined on the Fisher-Johns block and are corrected.

(11) We are indebted to Dr. Frank A. Vingiello of the Virginia Polytechnic Institute for this sample.

(12) E. de B. Barnett, J. W. Cook, and T. E. Ellison, *J. Chem. Soc.*, 855 (1928).

(13) This calculation is based upon the assumption that the molecular compound is a 1:1 combination of the two hydrocarbons. The carbon and hydrogen analysis seems to indicate a possibility that there is a larger proportion of the fully aromatic compound (IV).

A sample of the molecular compound was dehydrogenated in the presence of 10% palladium-charcoal catalyst at a temperature of 220–310°, affording a 70% yield of 2-methyl-9-phenylanthracene (IV), m.p. 120.5–122°. This material gave no depression of melting point when mixed with an authentic sample.[5]

Oxidation of the molecular compound: 3-methyl-10-phenyl-10-hydroxyanthrone.[14] One gram of the molecular compound was dissolved in 3.5 ml. of acetic acid and oxidized by dropwise addition of a water solution containing 1.87 g. of chromic anhydride. After the mixture had been heated on the steam bath for 1.5 hr., it was poured into water and the product which separated was crystallized from ethanol, yield 0.85 g. (75%) of granular crystals, m.p. 192–199°. The analytical sample was obtained as colorless granular crystals, m.p. 197.5–199.5° (lit.[15] 198°).

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 83.70; H, 5.35.

The infrared absorption spectrum showed the characteristic absorptions for hydroxyl and carboxyl at 2.79 and 5.98 μ, respectively.[16]

2-Methyl-9-phenyl-9,10-dihydroanthracene. From the mother liquor from which the molecular compound had separated, 0.12 g. of long white needles were obtained, m.p. 87–88°. Once recrystallized from ethanol the fine white needles melted at 89.5–90.5°.

Anal. Calcd. for $C_{21}H_{18}$: C, 93.29; H, 6.71. Found: C, 93.45; H, 6.72.

Ultraviolet absorption maxima were observed at 250, (262), 267, 271, and 276 mμ.

2,3-Dimethyl-9-phenylanthracene (VI). A solution containing 5 g. of *o*-(3,4-dimethylbenzyl)benzoic acid[17] (V) in dry ether was treated with phenyllithium and worked up as in the preparation of 2-methyl-9-phenylanthracene (IV). Recrystallization of the crude product from ethanol afforded 2.42 g. (41%), m.p. 164–166°. The analytical sample crystallized from ethanol as shiny yellow crystals, m.p. 171.5–172.5°.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.57; H, 6.43. Found: C, 93.36; H, 6.51.

The ultraviolet absorption spectrum had maxima at 228, 259, (316), 332, 348, and 366 mμ.

10-Phenyl-1,2-benzanthracene (VIII). Starting with 5 g. of *o*-(1-naphthylmethyl)benzoic acid (VII),[18] and following the procedure used in the case of the preparation of the analogs (IV and VI), the benzene solution containing the hydrocarbon fraction from the chromatographic separation was concentrated and the product crystallized by addition of ethanol as light yellow plates, m.p. 182–185°, yield 4.06 g. (58%). A sample recrystallized from benzene-ethanol melted at 184–186° (lit.[8] 183–184°) and did not depress the melting point of an authentic sample.[19]

The ultraviolet absorption spectrum showed maxima at 222, 259, 271, 281, 291, (300), 320, 335, 351, and 366 mμ. This is in good agreement with the reported values.[8]

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(14) L. F. Fieser, *Experiments in Organic Chemistry*, Second Edition, D. C. Heath and Co., New York, N. Y., 1941, p. 233.

(15) A. Guyot and C. Staehling, *Bull. soc. chim. France*, [3] **33**, 1104 (1905).

(16) It was shown that 10-phenyl-10-hydroxyanthrone [E. de B. Barnett and J. W. Cook, *J. Chem. Soc.*, **123**, 2638 (1923)] gave absorptions at 2.79 and 5.98 μ.

(17) E. de B. Barnett and F. C. Marrison, *Ber.*, **64**, 535 (1931).

(18) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **59**, 1028 (1937).

(19) We are indebted to Frances Montgomery for preparing this sample, using the method of Vingiello, Borkovec, and Shulman (ref. 8).

A Quantitative Study of the Decomposition of *N*-Bromoacetamide in Chloroform and Ethyl Alcohol

ROBERT E. BUCKLES, BOOKER T. SIMPSON, AND WALTER F. EDGELL[1]

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Reports[2–4] on the synthesis of *N*-bromoacetamide (NBA) mention its decomposition to form bromine. Also bisacetamide hydrobromide has been reported as a decomposition product[5] or as a by-product from slow addition reactions of NBA.[6] The present investigation involves quantitative iodometric analysis and quantitative measurements of hydrogen bromide formation during the decomposition of NBA in chloroform–ethyl alcohol mixtures.

Both the NBA and any bromine formed during decomposition would be expected to react with excess potassium iodide to give triiodide ion. In aqueous acetic acid one mole of NBA has been reported to react with iodide ion to give two equivalents of iodine.[7] This reaction has now been investigated in water with and without acid present as shown in Table I. With acid present these analytical results show that two equivalents of iodine were formed per mole of NBA while in the absence of acid one equivalent of iodine was formed per mole of NBA. The interaction of the acid with the NBA before the potassium iodide was added caused some loss of oxidizing capacity so that the results were low and relatively unreliable as shown in the second entry of Table I. The best analyses in an acid medium were obtained when the acid was added with the potassium iodide or after the potassium iodide. The average value for the determinations with delayed acid addition was 1.996 ± 0.011 where the precision sets the 95% confidence limits of the average.

These analytical results on NBA are consistent with Equation 1 for the reaction in the absence of acid. When acid was added after this reaction took place further iodine was released according to Equation 2 (see the last two entries of Table I). When acid was added with the potassium iodide the reaction given in Equation 3, which is the sum of Equations 1 and 2, took place. No other equations are consistent with the analytical results in the presence of excess iodide ion. No reaction producing hydrogen ion and iodate ion in the absence of added acid can be considered because the reaction

(1) Present Address: Department of Chemistry, Purdue University, Lafayette, Ind.

(2) A. W. Hofmann, *Ber.*, **15**, 407 (1882).

(3) C. Mauguin, *Ann. chim.*, [8], **22**, 302 (1911).

(4) A. Wohl, *Ber.*, **52**, 51 (1919).

(5) A. Hantzsch and F. E. Dollfus, *Ber.*, **35**, 249 (1902).

(6) R. E. Buckles, *J. Am. Chem. Soc.*, **71**, 1157 (1949).

(7) T. Seliwanow, *Ber.*, **26**, 423 (1893).

TABLE I

IODOMETRIC DETERMINATION OF *N*-BROMOACETAMIDE (NBA) IN AQUEOUS SOLUTIONS OF VARYING ACIDITY

H_2SO_4 Concn., *N*	Equiv. Thiosulfate per Mole NBA
0	0.997 ± 0.003[a,b]
0.1–7.0[d]	1.939 ± 0.058[a,c]
0.5[e]	1.999
0.5[e]	1.987
0.05[f]	2.005
0.05[f]	1.986
0[g]	1.005
0.05[g]	0.996

[a] The precision represents the 95% confidence limits of the average. [b] This average represents 9 determinations. [c] This average represents 15 determinations. [d] The acid was allowed to react with the NBA before the potassium iodide was added. [e] The acid was added with the potassium iodide solution. [f] The acid was added after the reaction between potassium iodide and *N*-bromoacetamide had taken place. [g] The acid was added after the first end point was reached with sodium thiosulfate and the mixture was titrated to a second end point.

of Equation 2 would take place and the net result would be Equation 1. Any reaction producing hydroxide ion would lead to the formation of hypoiodite ion which would react to give iodate ion by Equation 4 and the sum of the equations would again be Equation 1.

$$6AcNHBr + 10I^- + 3H_2O \longrightarrow 6AcNH_2 + 3I_3^- + 6Br^- + IO_3^- \quad (1)$$

$$IO_3^- + 8I^- + 6H^+ \longrightarrow 3I_3^- + 3H_2O \quad (2)$$

$$AcNHBr + 3I^- + H^+ \longrightarrow AcNH_2 + I_3^- + Br^- \quad (3)$$

$$3IO^- \longrightarrow IO_3^- + 2I^- \quad (4)$$

Chloroform solutions of NBA containing varying amounts of ethyl alcohol were analyzed iodometrically as decomposition progressed. No acid was added during the analyses so that each mole of NBA required one equivalent of thiosulfate while each mole of molecular bromine required two. Each mole of bromine must have been formed from two moles of *N*-bromoacetamide, however, so that the titration was a measure of the fraction of the original NBA still unchanged or decomposed to molecular bromine on the basis of one equivalent per mole. The same sample could then be used to determine hydrogen ion concentration as a measure of hydrogen bromide formed as a product of decomposition. This was most conveniently done by the addition of potassium iodate followed by titration with thiosulfate solution. Since NBA reacted so fast with hydrogen bromide to form bromine[6] it was assumed that no acid would be detected when *N*-bromoacetamide was still present. Representative results of these experiments are given in Table II.

For each mole of NBA the number of equivalents of sodium thiosulfate used plus the number of equivalents of hydrogen ion present should total

TABLE II

ANALYSIS OF THE DECOMPOSITION PRODUCTS OF *N*-BROMOACETAMIDE IN CHLOROFORM–ETHYL ALCOHOL SOLUTIONS

EtOH Volume Fraction	AcNHBr M × 10^3	Reaction Time, Min.	Products, Equiv./Mole NBA: Reducible Br	Acid	Total
0.00[a]	—	—	1.36	0.10	1.46
.00[b]	—	73	0.88	.00.	0.88
.00[b]	—	105	.60	.00	.60
.00[b]	—	140	.38	.00	.38
.01	1.72	10	1.04	.00	1.04
.05	1.68	10	0.97	.03	1.00
.05	—	20	.73	.10	0.83
.05	—	45	.46	.28	0.74
.16	1.09	10	.75	.28	1.03
.16	1.57	10	.67	.33	1.00
.25	2.11	10	.78	.18	0.96
.35	1.95	10	.64	.32	.96
.50	2.21	10	.53	.41	.94
.75	0.69	10	.43	.49	.92
1.00	1.80	10	.53	.37	.90

[a] This run was carried out until bromine color was deepest. There was a fairly large air space above the reaction mixture. [b] An effort was made to keep the air space at a minimum in the reaction tubes.

one if the decomposition involved oxidation only. Bromine substitution on the other hand would lead to a total lower than one with a minimum value of zero. When pure chloroform was used as a solvent a slow decomposition to bromine took place and the total of equivalents of reducible bromine and acid was often greater than one. This result was assumed to be caused by air oxidation of the chloroform to phosgene and hydrogen chloride. When the amount of available air was carefully limited no acid was detected and the total of equivalents was considerably less than one as expected for substitution. With ethyl alcohol present the total was never more than one within experimental error. In fact, except when the reaction mixture stood for long enough to allow considerable bromine substitution to take place, the total was very close to one. This fact that nearly all of the bromine from the NBA could be accounted for as either molecular bromine or hydrogen bromide is consistent with the view that the main reaction (Equation 5) was the oxidation of ethyl alcohol to acetaldehyde, which was detected as a product. The oxidations of secondary alcohols[8] and of aromatic alcohols[9] by NBA have been reported so that such a reaction with ethyl alcohol is not surprising.

$$CH_3CH_2OH + AcNHBr \longrightarrow CH_3CHO + AcNH_2 + HBr \quad (5)$$

The hydrogen bromide formed would be expected[6] to react rapidly with NBA as shown in Equation 6. From the type of data given in Table

(8) L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, 71, 3935 (1949).

(9) J. Le Comte and C. Dufour, *Compt. rend.*, 234, 1887 (1952).

$$AcNHBr + HBr \longrightarrow AcNH_2 + Br_2 \qquad (6)$$

II it was possible to estimate the relative rates of the reactions of Equations 5 and 6. On the assumption that each reaction was first order with respect to each reagent and that any subsequent reactions of bromine would be considerably slower, Equation 7 was derived and was integrated to give Equation 8. The rate constants for Equations 5 and 6 are

$$\frac{dx}{dy} = \frac{Ak_5}{xk_6} - 1 \qquad (7)$$

$$x + y = (k_5/k_6)A \ln\left(\frac{A}{A - (k_6/k_5)x}\right) \qquad (8)$$

represented by k_5 and k_6, respectively, while x, y, and A are the concentrations of hydrogen bromide, bromine, and ethyl alcohol (assumed to be constant), respectively. Over the entire range of alcohol concentrations, which were used, the reaction of Equation 6 was found to be $(1.3 \pm 0.3)10^4$ times as fast as that of Equation 5 at room temperature (26°).

EXPERIMENTAL

Pure anhydrous N-bromoacetamide. Crude NBA[6] was dissolved in a minimum amount of warm water (60°), and the solution was cooled in an ice bath. The crystals were dried thoroughly in an anhydrous atmosphere and then dissolved in cold absolute ether. This solution was chilled and evaporated. The crystals which formed were thoroughly dried at room temperature and then at 45°. A yield of about 50% of NBA, m.p. 108°, was obtained from the purification. The melting point checks well with that of Hofmann[2] and is considerably higher than those observed (usually around 103°) for products obtained by crystallization from chloroform.[6,10]

Anal. Calcd. for C_2H_4NOBr: C, 17.41; H, 2.92; N, 10.15; Br, 57.93. Found for product of m.p. 108°: C, 17.39; H, 2.89; N (Dumas), 10.21; Br, 57.80. Found for product of m.p. 102–103°: C, 16.80; H, 3.11; N, 10.93; Br, 57.30.

Iodometric determination of N-bromoacetamide. A carefully weighed sample of 0.2–0.8 g. of NBA was dissolved in about 25 ml. of water and enough 6*N* sulfuric acid was added to give a final solution of the desired normality. Potassium iodide (about 3 g.) was then added in enough water to make a total volume of 100 ml. The iodine formed was titrated with standard sodium thiosulfate. The results are tabulated in Table I.

Decomposition of N-bromoacetamide in chloroform and ethyl alcohol. Commercial chloroform was washed free of alcohol by several extractions with concentrated sulfuric acid. The chloroform was washed with water, dried over anhydrous sodium sulfate, and distilled as needed. Samples of 0.1–1.0 g. of NBA were dissolved in 100 ml. of the chloroform, chloroform–ethyl alcohol mixtures, or absolute ethyl alcohol. The solutions were sealed into Pyrex tubes with a minimum of air space and illuminated by a fused silica mercury arc. The tip of each tube was then broken beneath the surface of water. The water solution was first treated with an excess of potassium iodide and titrated with standard sodium thiosulfate solution to determine the amount of reducible bromine present. The solution was then boiled for two minutes, treated with an excess of potassium iodate, and again titrated with standard thiosulfate solution to determine the amount of acid present. The acid was also determined in many experiments by titration with standard sodium hydroxide solution following the iodometric titration of bromine. The two methods gave comparable results. Representative data are tabulated in Table II.

Qualitative experiments on the decomposition of N-bromoacetamide. A bromine color rapidly developed when a chloroform solution of NBA with or without ethyl alcohol present was illuminated with ultraviolet radiation. The color reached a maximum intensity, as it was followed by a spectrophotometer, and then the color slowly faded as crystals of bisacetamide hydrobromide precipitated. The melting point varied from 127° to 139° and the material may have been contaminated by monoacetamide hydrobromide or by acetamide. Dry hydrogen bromide reacted with acetamide in chloroform to yield bisacetamide hydrobromide of m.p. 140–141° while the value 139.5° has been reported.[11] In other experiments a chloroform-insoluble liquid with the color of bromine was observed partway through the decomposition reaction. Eventually this liquid deposited crystals of bisacetamide hydrobromide and gradually disappeared. It is probable that this liquid was a mixture composed mostly of *N*-bromoacetamide and acetamide with bromine dissolved in it. In some experiments evaporation of the chloroform solution led to the isolation of small amounts of acetamide. Diacetylhydrazine, m.p., 140°, might be expected as a product, but methods of isolation, which were successful with an authentic sample,[12] did not yield this material from the decomposition solutions.

Detection of acetaldehyde. A solution of 1.4 g. (0.010 mole) of NBA in 20 g. of chloroform and 5 g. of absolute ethanol was stirred rapidly with 2.5 g. of calcium carbonate in diffuse light. Only a very light bromine color was observed. After thirty minutes the solution was filtered and then shaken with water in the presence of a little copper wire. Addition of excess 2,4-dinitrophenylhydrazine solution to the aqueous layer yielded 0.40 g. (18%) of acetaldehyde 2,4-dinitrophenylhydrazone, m.p. 155–159°, which after two crystallizations melted at 165–167° and did not depress the melting point of an authentic sample.

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(10) E. P. Oliveto and C. Gerold, *Org. Syntheses*, **31**, 17 (1951).

(11) J. Topin, *Ann. chim.*, [7], **5**, 109 (1895).

(12) G. Pellizzari, *Gazz. chim. ital.*, **39I**, 536 (1909).

Diels-Alder Reactions on 1,2-Cyclohexenedicarboxylic Anhydride

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1,2-Cyclohexenedicarboxylic anhydride (Δ^1-tetrahydrophthalic anhydride) has been reported to undergo the Diels-Alder reaction with butadiene[1,2] to form the octalin derivative, 1,4,4a,5,6,7,8,8a-octahydro-4a,8a-naphthalenedicarboxylic acid. In the present investigation some new octalin derivatives have been prepared by using other dienes with this anhydride. Six dienes were allowed to react with the dienophile in a sealed reaction tube, and adducts were obtained with isoprene and di-

(1) K. Alder and K. H. Backendorf, *Ber.*, **71B**, 2199 (1938).

(2) P. Brigl and R. Herrmann, *Ber.*, **71B**, 2280 (1938).

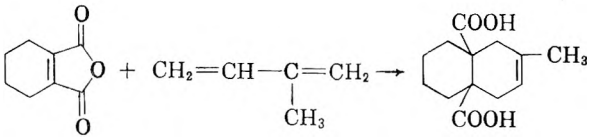
TABLE I

DIENE ADDUCTS OF 1,2-CYCLOHEXENEDICARBOXYLIC ANHYDRIDE

Deriv. of Diene adduct	M.P., °C.[a]	Yield,[b] %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
			Isoprene				
Acid	200–203[c]	60	$C_{12}H_{18}O_4$	65.5	65.7	7.61	7.66
Anhydride[d]			$C_{13}H_{16}O_3$	70.9	70.6	7.32	7.19
Imide[e]	137		$C_{13}H_{17}O_2N$	71.2	71.1	7.82	7.82
			2,3-Dimethyl Butadiene				
Acid	194[c]	57	$C_{14}H_{20}O_4$	66.6	66.5	7.99	7.99
Anhydride[f]	54–55		$C_{14}H_{18}O_3$	71.8	71.7	7.74	7.75
Imide[g]	145		$C_{14}H_{19}O_2N$	72.1	71.8	8.21	8.13

[a] All melting points are corrected. They were taken in capillaries unless otherwise indicated. [b] Yields were determined after one recrystallization. [c] This value was determined on the hot stage of a low power microscope. [d] n_D^{25}, 1.5052; b.p. 143° (3 mm.). [e] N, *anal.*: 6.38 (calcd.), 6.08 (found). [f] n_D^{27}, 1.5060; b.p. 154° (4 mm.). [g] N, *anal.*: 6.00 (calcd.), 6.14 (found).

methylbutadiene as summarized in Table I. Butadiene gave results comparable with those reported.[1,2] Only starting material and polymers were obtained with furan, chloroprene, and cyclopentadiene. The adducts were isolated as the octalindicarboxylic acids. The imide derivatives were prepared by way of the anhydrides by treatment of the acids with acetyl chloride followed by concentrated aqueous ammonia solution.



The 2,3-cyclohexenedicarboxylic anhydride also has the double bond conjugated with one of the carboxyl functions and it would be expected to undergo the Diels-Alder reaction. Only starting material and polymers were isolated from reactions of this compound with isoprene, however. This Δ^2 isomer has been reported[3] to undergo thermal isomerization to the Δ^1 isomer, but none of the latter compound nor any of its octalin addition product could be isolated from the reaction mixture.

EXPERIMENTAL

1,2-Cyclohexenedicarboxylic anhydride. The isomer was prepared by heating 4,5-cyclohexenedicarboxylic anhydride (Δ^4) with 1% phosphorus pentoxide at 200° for 48 hr.[4]

2,3-Cyclohexenedicarboxylic anhydride. The Δ^4 isomer was partially isomerized with phosphorus pentoxide to yield a mixture of the Δ^3, Δ^2, and Δ^1 isomers.[4] This mixture was converted to the Δ^2 isomer by heating with sodium hydroxide solution.[5-7]

Other reagents. The dienes were commercially available. The Δ^4-tetrahydrophthalic anhydride was kindly supplied by the National Aniline Division of the Allied Chemical and Dye Corp.

Diels-Alder reactions. The general procedure which was originally reported[1] was followed. In a typical run, a mixture of 6 ml. of benzene, 1 g. of hydroquinone, 7.0 ml. (4.8 g., 0.071 mole) of isoprene, and 2.0 g. (0.012 mole) of the anhydride was heated for 12 hr. at 175° in a 90-ml. Monel metal Carius tube supplied by High Pressure Equipment Co. The dimerized olefin was distilled at reduced pressure from the yellow solution, and the residue was heated for 30 min. with excess 10% potassium hydroxide. The solution was treated with charcoal, filtered, and extracted several times with ether. The basic solution was acidified and the product was collected by filtration. The 2-methyl-1,4,4a,-5,6,7,8,8a-octahydro-4a,8a-naphthalenedicarboxylic acid was recrystallized from boiling acetonitrile. The product could also be recrystallized from an ethyl alcohol–water mixture. The adducts from butadiene and 2,3-dimethylbutadiene were prepared in a similar fashion. All of the acids were white crystalline solids.

Anhydrides. The acids were heated with excess acetyl chloride. The isoprene adduct and the 2,3-dimethylbutadiene adduct were distilled as colorless oils. The butadiene adduct was a white crystalline solid obtained from petroleum ether.

Imides. Excess 28% aqueous ammonia was added to the anhydride and the water was boiled off. The residue was heated in an oven at 100° for 15 min. The resulting product was recrystallized from an ethyl alcohol–water mixture to yield a white crystalline imide in each case.

Gas chromatography. The anhydrides from isoprene and 2,3-dimethylbutadiene were analyzed on a Perkin-Elmer Vapor Fractometer. At 215° with helium as a carrier gas at 25 lb./in.^{2} gage and 0.68 ml./sec. and with a 2 m. column (4 mm. i.d.) filled with silicone oil on Celite the isoprene adduct gave a well defined peak at 15.0 min. and the 2,3-dimethylbutadiene adduct gave one at 19.0 min. In neither case was any contaminant detected. The Δ^1-tetrahydrophthalic anhydride gave a peak at 21.0 min. under the same conditions at 148°.

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(3) A. Baeyer, *Ann.*, 258, 145, 198 (1890).
(4) M. E. Bailey and E. D. Amstutz, *J. Am. Chem. Soc.*, 78, 3828 (1956).
(5) R. E. Buckles, *Chem. Revs.*, 57, 641 (1957).
(6) A. Baeyer, *Ann.*, 258, 188 (1890).
(7) H. J. Pistor and H. Plieninger, *Ann.*, 562, 239 (1949).

Preparation and Properties of *S*-Acetyl-*N*-benzoylcysteamine[1]

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The acetylation of aromatic amines in a physiological system is known to proceed through the intermediate acetyl coenzyme A,[2] a molecule in which the acetyl group is attached to coenzyme A through a thioester linkage.[3] The known susceptibility of thioesters to nucleophilic agents in general,[4] and particularly to aminolysis, has led Tarbell *et al.* to study the kinetics of the acetylation of the aliphatic amine, *n*-butylamine, by model thioesters related to acetyl coenzyme A.[5,6] However, the *enzymatic* acetylation of aromatic amines in a system in which the acetyl group is transferred to the acceptor amine from a model acetyl thioester instead of from acetyl coenzyme A has not been studied. We became interested in this problem in the course of experiments concerned with the effect of structure of the aromatic amine on the rate of *in vitro* acetylation. It was hoped that a simple, stable acetyl thioester could be synthesized which might replace the rather complex and relatively unstable acetyl coenzyme A as the acetylating agent. *S*-Acetyl-*N*-benzoylcysteamine was selected because it was thought that this compound, unlike most of the model thioesters employed by Tarbell *et al.*[5,6] would be a solid. This expectation was fully realized and the compound proved to be a stable solid melting at 91.5–92°.

Ethyleneimine was benzoylated and the intermediate, benzoylethyleneimide,[7] prepared *in situ*, was converted to the thioester by reaction with thioacetic acid. *S*-Acetyl-*N*-benzoylcysteamine was found to exhibit only feeble acetylating activity in the standard enzymatic test.[2] As these rate studies are no longer being pursued, we wish to report the preparation and properties of this new thioester.

EXPERIMENTAL

A solution of 42.2 g. (0.30 mole) of benzoyl chloride in 35 ml. of benzene was added dropwise to an ice cold, stirred mixture of 12.9 g. (0.30 mole) of ethyleneimine, prepared by the modifications[8,9] of the procedure of Wenker,[10] and 30.4 g. (0.30 mole) of triethylamine in 250 ml. of anhydrous benzene. After stirring for 1 hr., the precipitate of triethylamine hydrochloride was removed by filtration. The benzene filtrate was then added rapidly to a cooled (ice bath), stirred solution of 22.8 g. (0.30 mole) of thioacetic acid in 100 ml. of benzene. After 1 hr., the benzene was removed by distillation *in vacuo* at room temperature to incipient precipitation of the product. The product was collected after stirring the mixture with 500 ml. of ligroin, and the crude material was dissolved in approximately 750 ml. of a mixture of benzene and ethyl acetate (4:1). The solution was washed three times with 50 ml. portions of distilled water and dried over anhydrous sodium sulfate. The solution was then concentrated *in vacuo* to 400 ml., warmed slightly, and diluted to 800 ml. with ligroin. On standing at room temperature, the product precipitated as fine, flocculent clusters (needles). There was obtained 52.1 g. of material melting at 90–91° (corr.); 78% yield. An analytical sample was recrystallized from ethyl acetate:ligroin, m.p. 91.5–92.0° (corr.).

Anal. Calcd. for $C_{11}H_{13}O_2NS$: C, 59.2; H, 5.87; S, 14.4. Found: C, 59.4; H, 5.89; S, 14.2.

The ultraviolet absorption spectrum of the compound in ethanol showed an absorption maximum at 230 mμ (ϵ = 15,100). The infrared spectrum showed the characteristic thioester band at 5.90 μ.[11] Hydrolysis of the thioester was accomplished with 0.5*N* sodium hydroxide. The hydrolysis was followed spectrophotometrically by the decrease in absorption at 230 mμ and was essentially complete in 30 min., but was allowed to proceed for 4 hr. Calculation of the molar extinction coefficient of the thioester bond based on the difference spectrum gave a value of 4.54×10^3. This is in excellent agreement with the values for ethyl thioacetate and β-acetaminoethyl thioacetate (4.57×10^3 and 4.51×10^3 respectively) reported by Hawkins and Tarbell.[5]

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(1) This work was supported by Grant C-2571, National Cancer Institute, U. S. Public Health Service.

(2) N. O. Kaplan and F. Lipmann, *J. Biol. Chem.*, **174**, 37 (1948).

(3) F. Lynen, *Federation Proc.*, **12**, 683 (1953).

(4) D. S. Tarbell and D. P. Harnish, *Chem. Revs.*, **49**, 1 (1951).

(5) P. J. Hawkins and D. S. Tarbell, *J. Am. Chem. Soc.*, **75**, 2982 (1953).

(6) D. S. Tarbell and D. P. Cameron, *J. Am. Chem. Soc.*, **78**, 2731 (1956).

(7) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).

(8) P. A. Leighton, W. A. Perkins, and M. L. Renquist, *J. Am. Chem. Soc.*, **69**, 1540 (1947).

(9) W. A. Reeves, G. L. Drake, Jr., and C. L. Hoffpauir, *J. Am. Chem. Soc.*, **73**, 3522 (1951).

(10) H. Wenker, *J. Am. Chem. Soc.*, **57**, 2328 (1935).

(11) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York 1954, p. 160.

p,p'-Nitro and Amino Derivatives of 1,3-Diphenylpropane

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Nitration of 1,3-diphenylpropane by fuming nitric acid has been reported to yield a dinitro derivative of m.p. 139°.[1] Investigation of a variety of nitrating conditions has shown that the *p,p'*-dinitro derivative, m.p. 140–141°, may be obtained in 22% yield by use of acetic anhydride, nitric, and sulfuric acids. The proof of structure lies in the oxidation to *p*-nitrobenzoic acid in substantially greater than 50% yield. Reduction of the

(1) A. Michaelis and A. Flemming, *Ber.*, **34**, 1293 (1901).

dinitro compound by hydrazine, catalyzed by Raney nickel, afforded the *p,p'*-diamino compound. From the partial reduction of the dinitro compound by sodium polysulfide, the *p*-amino-*p'*-nitro compound was obtained in 38% yield. Although the aminonitro compound is bright yellow in the solid state in contrast to the dinitro and the diamino compounds both of which are colorless, the ultraviolet absorption spectrum of the aminonitro compound in 95% ethanol is virtually identical with a calculated spectrum derived from the dinitro and the diamino compounds, indicative of a lack of intramolecular complexing in the former compound in solution.[2]

The potentiometric titration curve for the diamine was markedly similar to that for *p*-toluidine. The lack of two breaks is suggestive of only a small difference in the first and second ionization constants, in accord with the results of Schwarzenbach on a series of straight chain aliphatic diamines.[3] The lack of appreciable interaction of the aryl amino group with the aryl ammonium group is also suggested by the close resemblance of the ultraviolet absorption spectrum of a 50% ethanol-water solution of the diamino compound 0.1*N* in sulfuric acid with that of 1,3-diphenylpropane. The correspondence in ultraviolet spectra of protonated aryl amines with the spectra of the parent hydrocarbons has been observed in other cases.[4]

EXPERIMENTAL[5]

p,p'-Dinitro-1,3-diphenylpropane. A nitration medium was prepared by the slow addition of 4 ml. of concentrated sulfuric acid and 12 ml. of concentrated nitric acid to 20 ml. of acetic anhydride, keeping the temperature below 0°. To the medium was added a solution of 15 ml. of 1,3-diphenylpropane (b.p. 78–80° at 0.1 mm.; n_D^{25} 1.5570) in 20 ml. of acetic anhydride over a 30-min. period. After the mixture was stirred at 0° for 30 min., 100 ml. of water was added and the mixture was stirred at room temperature for an additional 30 min. The crude product was collected by filtration and washed with water, 19 g., m.p. 85–100°. Four recrystallizations from ethanol afforded 4.5 g. (yield 22%) of colorless needles, m.p. 140–141° (reported for *x,x*-dinitro-1,3-diphenylpropane, white needles, m.p. 139°).[1] The ultraviolet absorption spectrum in 95% ethanol has a maximum at 216 mμ (ε 15,400) and 278 mμ (ε 21,000) and a minimum at 233 mμ (ε 4,250).

Oxidation of a 0.28-g. sample of the dinitro compound essentially by the procedure of Shriner, Fuson, and Curtin[6] afforded 0.24 g. (yield 74%) of *p*-nitrobenzoic acid after recrystallization from ethanol, m.p. 234–236°, mixed m.p. with an authentic sample, 238–240°.

p,p'-Diamino-1,3-diphenylpropane was prepared by a modification of the general procedure of Balcom and Furst.[7] To a warmed solution of 0.55 g. of the dinitro compound and 0.5 ml. of 95% hydrazine hydrate in 10 ml. of dioxane was added 0.5 g. of Raney nickel catalyst. After 1 hr. at 60°, during which time additional small amounts of catalyst were added, the solution was filtered, treated with Norite, filtered, and 30 ml. of water was added. White platelets separated on cooling, m.p. 99–101°. Recrystallization from 20 ml. of hexane afforded 0.2 g. (yield 50%) of lustrous white needles, m.p. 103–104°.

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.54; H, 8.14; N, 12.29.

The ultraviolet absorption spectrum of the diamine in 95% ethanol has maxima at 238 mμ (ε 21,200) and 290 mμ (ε 2,960) and minima at 216 mμ (ε 7,810) and at 266 mμ (ε 1,280).

p-Amino-p'-nitro-1,3-diphenylpropane. To a solution of 2 g. of *p,p'*-dinitro-1,3-diphenylpropane in 150 ml. of ethanol was added 3.2 g. of sodium sulfide nonahydrate and 0.8 g. of sulfur in 12 ml. of water. The mixture was heated at reflux for 4 hr., cooled, diluted with 500 ml. of water, and extracted with 4–100 ml. portions of ether. The combined ether layers were extracted with 4–80 ml. portions of 5% hydrochloric acid. From the ether layer, 0.23 g. of impure starting material was recovered. The acidic aqueous phase was made basic and extracted with ether. Removal of ether after drying over magnesium sulfate yielded 1.34 g. of a red oil. The oil was dissolved in benzene and chromatographed on a 50-g. column of alumina in benzene. Elution with benzene afforded 776 mg. (yield 38%) of crystalline material. Two recrystallizations from cyclohexane afforded bright yellow needles m.p. 92–93°.

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.31; N, 10.93. Found: C, 70.34; H, 6.45; N, 10.61.

The ultraviolet absorption spectrum in 95% ethanol has maxima at 238 mμ (ε 4,080) and 278 mμ (ε 11,100) and minima at 225 mμ (ε 9,680) and at 256 mμ (ε 8,150).

Further elution of the column with benzene-ether yielded 180 mg. of impure diamine, established as such by m.p. and mixed m.p. of 103–104° for a recrystallized sample. Elution with ether and ether-methanol yielded two oily fractions which were not investigated further.

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(2) For a discussion of the color changes produced by the mixing of aniline and nitrobenzene, see R. E. Gibson and O. H. Loeffler, *J. Am. Chem. Soc.*, **62**, 1324 (1940), and L. J. Andrews, *Chem. Revs.*, **54**, 713 (1954).

(3) G. Schwarzenbach, *Helv. Chim. Acta*, **16**, 522 (1933).

(4) A. O. Tischler and J. N. Howard, National Advisory Committee Aeronautics, A. R. R. No. E5H27a. L. A. Flexler, L. P. Hammett, and A. Dingwall, *J. Am. Chem. Soc.*, **57**, 2107, Fig. 3 (1935).

(5) Melting points are corrected. We are indebted to Dr. S. M. Nagy and his associates for analyses and spectra.

(6) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds.* Fourth Edition, John Wiley and Sons, Inc., New York, 1956, p. 250.

(7) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953).

Hydrogen Bromide–Acetic Acid Cleavage of Several Methoxyindanones and Methoxytetralones

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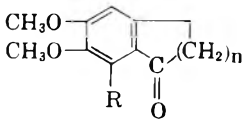
The cleavage of methoxyl groups *ortho* to the

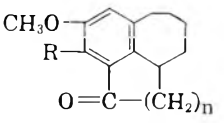
(1) A portion of the Doctoral Dissertation of Bryant W. Rossiter.

carbonyl group in a benzosuberone III[2a] and in acetophenones[2b] by means of *ca.* 6% hydrogen bromide-acetic acid has been shown to proceed in good yield at room temperature provided that a second methoxyl group is present *ortho to the group cleaved.*[2c]

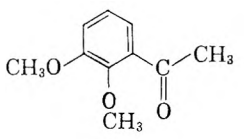
The cleavage of VI with hydrogen bromide-acetic acid was attempted since the necessary acetophenone-like structure was present. The compound did not react. Similarly the indanone I failed to cleave. These cases constitute the only exceptions found thus far to the generalization made above. The five-membered ring is implicated in this failure to react as shown by the expected cleavage of the six-membered ring ketones II and VII.



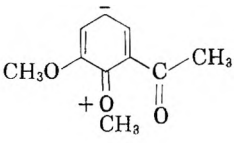
I, n, 1; R, OCH_3
II. n, 2; R, OCH_3
III, n, 3; R, OCH_3
IV, n, 2; R, OH
V, n, 3; R, H



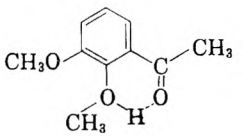
VI, n, 1; R, OCH_3
VII, n, 2; R, OCH_3
VIII, n, 1; R, OH
IX, n, 2; R, OH



X



XI

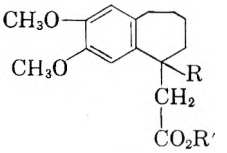


XII

In a careful study of the rate of cleavage of X[2c] it was concluded that the role of the 3-methoxyl group is steric in that it distorts the 2-methoxyl group out of the plane of the benzenoid ring thereby decreasing the contribution of the resonance form XI. The effect of this suppression of XI is to increase the basicity of the oxygen atom at the site of cleavage. This proposal assumes that protonation of this oxygen atom is an essential prerequisite to cleavage.

The role of the indispensable carbonyl group in this cleavage reaction is not completely understood. It seems likely that it too decreases the contribution of XI by forcing the 2-methoxyl group out of the benzenoid plane. The failure of I and VI to cleave might then be ascribed to the expected decrease in interference between the methoxyl and carbonyl groups in indanones as contrasted to tetralones or benzosuberones. An alternate explanation postulates as an essential requirement for cleavage a hydrogen-bonded structure[3] XII which is less stable in indanones due to the increase in ether oxygen-carbonyl oxygen distance.

The benzosuberone V with methyl bromoacetate in a Reformatsky reaction gave XIII in 88% yield. Catalytic reduction of this ester and saponification gave XIV which was also obtained by dehydration



XIII, R, OH; R′, CH_3
XIV, R, H; R′, H

of XIII followed by catalytic reduction of the unsaturated ester and saponification. Polyphosphoric acid (PPA) brought about cyclization of XIV to the ketone VI in 87% yield. Although hydrogen bromide-acetic acid on VI produced no isolateable phenol, aluminum chloride in ether gave (36%) crystalline VIII.

In a similar manner the propionic acid obtained from XIV in the Arndt Eistert reaction gave VII (22%) when PPA was used. Hydrogen bromide-acetic acid produced the phenol IX in 67% yield. The known indanone I was recovered unchanged (89%) after hydrogen bromide-acetic acid treatment whereas the tetralone II under the same conditions gave IV in 62% yield.

EXPERIMENTAL[4]

2,3-Dimethoxybenzosuberone (V). Glutaric acid-glutaric anhydride (188.5 g.) from Carbide and Carbon Chemicals Company was converted to the anhydride (185 g.) by refluxing for 2 hr. with 320 ml. of acetyl chloride. The anhydride, refluxed for 2 hr. with 95 ml. of absolute ethanol, gave 193 g. (74.3%) of ethyl hydrogen glutarate, b.p. 140–148° (12 mm.). Reported b.p. 159–165° (17 mm.).[5]

A mixture of 67.5 g. of veratrole, 78.0 g. of ethyl hydrogen glutarate and 660 g. of polyphosphoric acid (PPA) was thoroughly stirred without heating. The temperature rose to 40°. The mixture was then heated in a bath at 53–58° for 2.5 hr. with occasional stirring. When thorough prior mixing or good temperature control was neglected, an intense red ether insoluble material was formed which made isolation of the product very difficult. The PPA complex was decomposed with 1500 g. of crushed ice and water and the alkali washed benzene extract yielded after crystallization from ethanol 96.8 g. (70.5%) of ethyl γ-(3,4-dimethoxybenzoyl)-

(2) (a) P. D. Gardner and W. J. Horton, *J. Org. Chem.*, **19**, 213 (1954). (b) W. J. Horton and J. T. Spence, *J. Am. Chem. Soc.*, **77**, 2894 (1955). P. D. Gardner, W. J. Horton and R. E. Pincock, *J. Am. Chem. Soc.*, **78**, 2541 (1956). (c) It has been found that 3-methyl-2-methoxyacetophenone cleaved faster than X indicating that groups other than methoxyl can be effective. W. J. Horton and J. T. Spence, unpublished work.

(3) Such a hydrogen-bonded structure was proposed to account for the selectivity in the cleavage of methoxyacetophenones by G. K. Hughes, *et al.*, *Australian J. Sci. Res., Ser. A*, **5**, 207 (1952). Objections have been put forward by L. A. Wiles, *Chem. Revs.*, **56**, 353 (1956).

(4) Melting points of materials for analysis are corrected. Petroleum ether refers to the fraction b.p. 60–120°.

(5) W. E. Bachman, S. Kushner, and A. C. Stevenson, *J. Am. Chem. Soc.*, **64**, 974 (1942).

butyrate as colorless needles m.p. 58.5–60.5° (lit.[6] 63°). Saponification of the ester gave the acid m.p. 144–146° (lit.[7] 145–146°). The latter was reduced catalytically[6] (97.6%) or by the Clemmensen reduction[7] (70.5%) to δ-(3,4-dimethoxyphenyl)valeric acid which was cyclized to V by PPA. The product (93.7%) melted at 61.5–64° and at 64–65° after crystallization from ether (lit.[7] 63–64°).

Methyl 2,3-dimethoxy-5-hydroxy-5-benzosuberylacetate (XIII). A solution of 13.3 g. of the above suberone in 800 ml. of 1:1 anhydrous ether-benzene was combined with 20 g. of cleaned zinc and a crystal of iodine and 2 g. of methyl bromoacetate. After 3 hr. stirring and refluxing, additional zinc, iodine, and methyl bromoacetate were added so that after 10 hr. 27.5 g. of bromoacetate and 45 g. of zinc had been used. The product, isolated in the usual manner and crystallized from ethyl acetate–petroleum ether, weighed 15.5 g. (88%) m.p. 106–106.5°.

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.28; H, 7.54. Found: C, 65.24; H, 7.43.

2,3-Dimethoxy-$\Delta^{5,\alpha}$ *(or* $\Delta^{5,6}$*)-5-benzosuberenylacetic Acid.* (*a*) The hydroxy ester XIII (10.0 g.) after 15 min. at 165° (0.20 mm.) gave crystals on trituration with petroleum ether. After recrystallization from methanol, 6.3 g. (67%) of colorless crystals of methyl ester were obtained m.p. 102–104° raised to 105–105.5° by further purification from methanol.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 70.28; H, 7.58.

Saponification of the ester gave the corresponding acid which was recrystallized from aqueous ethanol m.p. 152.5–153.0° (gas evol.). The ultraviolet spectrum was identical to that of the acid obtained in (*b*).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.56; H, 6.82.

(*b*) A solution of 1.45 g. of the hydroxy ester XIII in 2 ml. of anhydrous benzene and 0.6 ml. of pyridine was treated with 1.2 ml. of thionyl chloride for 30 min. at room temperature. The solvent was distilled at the aspirator at 30° and the residue, dissolved in 15 ml. of benzene, was decanted from pyridinium chloride and saponified by refluxing with aqueous methanolic potassium hydroxide. On acidification, 1.15 g. (89%) of buff colored crystals m.p. 133–139° was obtained. The material for analysis, recrystallized from dilute ethanol, melted at 147–148° (gas evol.); $\lambda_{max}^{ethanol}$ 255 mμ (log ε 4.04) and 292 mμ (log ε 3.69).

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.24; H, 7.02.

A mixture of the acids from (*a*) and (*b*) melted at 151.8–152.4° (gas evol.).

2,3-Dimethoxy-5-benzosuberylacetic acid (XIV). (*a*) The ester XIII (24.1 g.) in 200 ml. of acetic acid was shaken with 1.2 g. of 5% palladium-carbon at 90° under 30 lb. pressure of hydrogen. After 5 hr. the resultant oil was saponified to yield the acid XIV which crystallized from benzene-petroleum ether. The colorless crystals weighed 20.8 g. (97.4%) and melted at 100–102°. (*b*) Reduction of 5.5 g. of the olefinic acid obtained by dehydration of XIII, in 100 ml. of acetic acid with hydrogen and 0.1 g. of platinum oxide at room temperature gave 5.41 g. (98.6%) of colorless crystals m.p. 100–102° identical by mixed melting point to the material in (*a*). Purification by crystallization from ethyl acetate-petroleum ether gave material m.p. 100.4–102.0°.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.36; H, 7.47.

8,9-Dimethoxy-1-keto-1,2,2a,3,4,5,6-heptahydrobenz[cd]-azulene (VI). A solution of 4.20 g. of the acid XIV in 96 g. of PPA was held at 90° for 25 min. The reaction mixture was poured onto 200 g. of ice and the aqueous suspension was extracted four times with benzene. After washing the extract with 10% sodium hydroxide and water, the solution was concentrated, warm petroleum ether added, and the material was cooled. The light yellow crystals (3.43 g. 87.6%) melted at 120–122° and recrystallization gave a melting point of 120.5–121.5°.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.18; H, 7.54.

The *oxime* from ethanol melted at 187.0–190.5°.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 69.28; H, 7 58.

9-Hydroxy-8-methoxy-1-keto-1,2,2a,3,4,5,6-heptahydrobenz-[cd] azulene (VIII). To 1.60 g. of anhydrous aluminum chloride and 10 ml. of ether was added 1.23 g. of VI and the mixture was refluxed for 10.5 hr. The complex was decomposed with hydrochloric acid and the ether solution on addition of benzene and petroleum ether (b.p. 60–72°) gave 0.55 g. (36.5%) of yellow crystals, m.p. 118–123.0°. Several crystallizations from petroleum ether (b.p. 60–72°) gave material m.p. 124.8–126.0°. The compound gave a deep green ferric chloride test and melted with decomposition when mixed with VI.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.95. Found: C, 72.02; H, 6.97.

Attempted ether cleavage with hydrogen bromide-acetic acid[2b] gave less than 10% phenolic material with an 80% recovery of crystalline starting compound.

4,5-Dimethoxy-3-keto-1,2,3,7,8,9,10,10a-octahydrocyclohepta[de] naphthalene (VII). The acid XIV (5.25 g.) in the Arndt-Eistert reaction[8] gave 3.87 g. of β-(2,3-dimethoxy-5-benzosuberyl) propionic acid as a light orange oil. This was combined with 55 g. of PPA and heated at 95° for 20 min. On addition of ice and water 0.80 g. (22%) of crystalline VII was obtained which melted at 72.0–73.5° after several crystallizations from benzene-petroleum ether.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.68; H, 7.61.

4-Hydroxy-5-methoxy-3-keto-1,2,3,7,8,9,10,10a-octahydrocyclohepta[de]naphthalene (IX). Hydrogen bromide-acetic acid splitting[2b] of 0.600 g. of VII gave 0.44 g. (67%) of yellow solid sodium salt of IX when the product in benzene was washed with 40% sodium hydroxide. The sodium salt was treated with 2*N* hydrochloric acid, the oil obtained was collected in benzene and concentrated. Addition of petroleum ether precipitated an oil which crystallized after several days at −5°, m.p. 55.5–58.5°. Additional crystallizations from petroleum ether (60–72°) containing a small amount of acetone gave yellow cubelets m.p. 66.5–67.0°.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.48; H, 7.36.

Attempted cleavage of 5,6,7-trimethoxyindanone (I). The indanone was obtained in 82% yield (m.p. 94–98°) by cyclization of β-(3,4,5-trimethoxyphenyl)propionic acid in PPA.[9] It melted after further purification using ethyl acetate-petroleum ether (carbon) at 107–111° (lit.[9] 111.5–113.5°). When 1.0 g. of the indanone was allowed to stand with hydrogen bromide-acetic acid,[2b] 89% of the crystalline trimethoxyindanone I was recovered. The crude reaction product failed to give a color with alcoholic ferric chloride.

6,7-Dimethoxy-8-hydroxy-1-keto-1,2,3,4-tetrahydronaphthalene (IV). β-(3,4,5-Trimethoxyphenyl)propionic acid was converted by the Arndt-Eistert reaction[8] to the butyric acid in 41.7% yield. The acid melted at 80–84° (lit.[10] 83–84°). PPA cyclization gave II m.p. 123–126° in 68% yield (lit.[10] 125°).

From 0.60 g. of II, hydrogen bromide-acetic acid[2b] gave 0.35 g. (62%) of IV m.p. 110–112°. Repeated recrystal-

(6) E. C. Horning and J. Koo, *J. Am. Chem. Soc.*, **73**, 5830 (1951).

(7) J. A. Barltrop, A. J. Johnson, and G. D. Meakins, *J. Chem. Soc.*, 181 (1951).

(8) W. E. Bachman, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

(9) J. Koo, *J. Am. Chem. Soc.*, **75**, 1891 (1953).

(10) R. D. Haworth, B. P. Moore, and P. L. Pauson, *J. Chem. Soc.*, 3271 (1949).

lizations from ethanol gave crystals m.p. 112.0–113°. With ferric chloride a deep wine-red color was obtained.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.74; H, 6.32.

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Synthesis of Analogs of Thymidine[1]

JAMES E. GEARIEN AND STEPHEN B. BINKLEY

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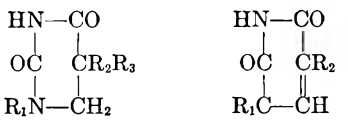
The concept of antimetabolites has been in vogue for several years and the application of this concept to cancer chemotherapy has lead to the preparation of several active compounds, *e.g.* azaguanine, 6-mercaptopurine, 2,6-diaminopurine, 6-azathymine, 5-hydroxy and 5-aminouridine, A-methopterin, etc. It has been shown that these effect thymine metabolism.[2,3] Since DNA is concerned with cell division and differs from RNA in that it contains thymine instead of uracil, it appeared that a logical approach to the problem of reducing cell division would be to prepare an antimetabolite which will block the introduction of thymine into DNA. The fact that mammalian cells incorporate the corresponding nucleosides indicates that an effective antimetabolite might be a pyrimidine substituted in the one position. Since it has been shown that 5-bromouracil inhibits the growth of several bacteria, it appeared that the 5-halogenated-1-substituted pyrimidines should also be prepared for testing.[4] We have prepared, therefore, and tested a number of 1-substituted uracils, 1-substituted-5-bromouracils, 1-substituted dihydrouracils, and 1-substituted-5-bromodihydrouracils in which the substituent was either methyl, isopropyl, or benzyl.



R_1 = benzyl, isopropyl, or methyl
R_2 = hydrogen or bromine
RR_3 = hydrogen or bromine

R_1 = benzyl, isopropyl, or methyl
R_2 = hydrogen or bromine

While several of the uracils and 5-bromouracils have previously been prepared, the following method was developed as it offered an unequivocal synthesis of the uracils and produced as intermediates the desired dihydro and 5-bromodihydrouracils.

N-Substituted-β-alanine esters, prepared by the addition of the proper primary amine to ethyl acrylate, were converted to dihydrouracils when treated with potassium cyanate and hydrochloric acid. This is an adaptation of a method employed by Johnson and Livak for the conversion of β-substituted-β-alanines to 6-substituted dihydrouracils.[5] The resulting *N*-substituted dihydrouracils were brominated to give 1-substituted-5-bromodihydrouracils, which upon dehydrohalogenation gave the corresponding substituted uracils. Since the uracils with the exception of *N*-isopropyl uracil were known, this served as a further confirmation of the structures of the previous unreported 1-substituted dihydro-and 1-substituted-5-bromodihydrouracils.

Previous bromination of substituted dihydrouracils had been carried out in sealed tubes.[6] 1-Benzyldihydrouracil and 1-methyldihydrouracil, however, gave satisfactory yields of the corresponding 5-bromo compounds when one molecular equivalent of bromine was added to a boiling acetic acid solution of the dihydrouracil. 1-Isopropyldihydrouracil, however, failed to give a pure monobrominated derivative but when treated with two molecular equivalents of bromine yielded 1-isopropyl-5,5-dibromodihydrouracil. 1-Benzyl dihydrouracil was also brominated to yield 1-benzyl-5,5-dibromodihydrouracil.

When added to boiling dimethylformamide the 1-substituted-5-bromodihydrouracils were dehydrohalogenated to give good yields of 1-substituted uracils and the 1-substituted-5,5-dihydrobromouracil gave good yields of 1-substituted-5-bromouracils (Table I).

1-Methyl-5-bromouracil was prepared by the direct bromination of 1-methyl uracil.[7]

EXPERIMENTAL[10]

The ethyl esters of *N*-methyl-β-alanine and *N*-benzyl-β-alanine were prepared by the procedure described by Adamson.[11] When 30.0 g. (0.30 mole) of ethyl acrylate was added dropwise to a cooled solution of 35.4 g. (0.60 mole of isopropylamine in 100 ml. of absolute alcohol and the product distilled, 40.5 g. (85%) of *N*-isopropyl-β-alanine ethyl ester was obtained. It boiled at 91–92° (20 mm.).

(1) Presented in part before the Medicinal Division of the American Chemical Society, Miami, Fla., April, 1957.
(2) R. Maxwell and V. Nickel, *Science*, **120**, 270 (1954).
(3) M. Balis and J. Daniels, *Cancer Research*, **15**, 603 (1955).
(4) W. Prusoff, *Proc. Soc. Exptl. Biol. Med.*, **85**, 564 (1954).
(5) T. Johnson and J. Livak, *J. Am. Chem. Soc.*, **58**, 299 (1936).
(6) J. Evans and T. Johnson, *J. Am. Chem. Soc.*, **52**, 4993 (1930).
(7) T. Johnson and I. Matuso, *J. Am. Chem. Soc.*, **41**, 786 (1919).
(8) T. Johnson and A. Joyce, *J. Am. Chem. Soc.*, **38**, 1385 (1916).
(9) T. Johnson and Derby, *Am. Chem. J.*, **40**, 453 (1901).
(10) All melting points are uncorrected.
(11) D. Adamson, *J. Chem. Soc.*, Suppl. Issue No. 1, S144 (1949).

TABLE I

DEHYDROHALOGENATION OF 5-BROMO AND 5,5-DIBROMODIHYDROURACILS

Dihydrouracil	Uracil	Yield	M.P.	Reported M.P.
1-Methyl-5-bromo	1-Methyl	96%	232–233°	232°[7]
1-Benzyl-5-bromo	1-Benzyl	78%	171–172°	173–174°[8]
1-Isopropyl-5,5-dibromo	1-Isopropyl-5-bromo	64%	202–204°	—
1-Benzyl-5,5-dibromo	1-Benzyl-5-bromo	78%	203–205°	204°[9]

Anal. Calcd. for $C_8H_{12}O_2N$: N, 8.80. Found: N, 8.65.

1-Methyldihydrouracil. A solution of 30.0 g. (0.23 mole) of the ethyl ester of *N*-methyl-β-alanine in 30 ml. of water and 23.5 ml. of hydrochloric acid was added dropwise to a cooled solution of 24.3 g. (0.30 mole) of potassium cyanate in 30 ml. of water. This reaction mixture was allowed to stand overnight, the water removed by distillation under vacuum, and the semisolid residue heated at 100–110° (25 mm.) for 1 hr. The solid residue was extracted with boiling absolute alcohol. Upon evaporation of the alcohol a white crystalline solid was obtained. Recrystallization from ethanol yielded 13.0 g. (50%) of 1-methyldihydrouracil, which melted at 173–174°. (Lit. 174–175°).[12]

1-Isopropyldihydrouracil. When 31.8 g. (0.20 mole) of the ethyl ester of *N*-isopropyl-β-alanine was allowed to react with 21.0 g. (0.26 mole) of potassium cyanate and 20.0 ml. of hydrochloric acid according to the procedure described for the preparation of 1-methyldihydrouracil, 20.0 g. (61%) of 1-isopropyldihydrouracil was obtained. The compound after recrystallization from water melted at 140–141°.

Anal. Calcd. for $C_7H_{12}O_2N_2$: N, 17.93. Found: N, 17.68.

1-Benzyldihydrouracil. When 22.0 g. (0.11 mole) of the ethyl ester of *N*-benzyl-β-alanine was allowed to react with 9.7 g. (0.12 mole) potassium cyanate and 10.7 ml. of hydrochloric acid according to the procedure described for the preparation of 1-methyldihydrouracil a water insoluble oil formed. After shaking the mixture overnight, the oil was separated and heated at 110° for 2 hr. Upon cooling the oil solidified and was recrystallized from isopropyl alcohol to yield 15.0 g. (67%) of a white crystalline solid melting at 125–127°.

Anal. Calcd. for $C_{11}H_{12}O_2N_2$: N, 13.72. Found: N, 13.56.

Bromination of 1-substituted dihydrouracils. A well-stirred solution of the 1-substituted dihydrouracil in ten times its weight in acetic acid was heated to boiling. To this boiling solution one or two molecular equivalents of bromine in 3 times its volume of acetic acid was added dropwise. When the bromine color was discharged, most of the acetic acid was removed by distillation, the residue diluted with 20 ml. of water and neutralized with 10% sodium hydroxide solution. A solid precipitated from the neutral solution and was purified by recrystallization.

1-Methyl-5-bromodihydrouracil. When 1-methyldihydrouracil was treated with one molecular equivalent of bromine a 59% yield of 1-methyl-5-bromodihydrouracil was obtained. After recrystallization from ethanol it melted at 132–135°.

Anal. Calcd. for $C_5H_7O_2N_2Br$: N, 13.53; Br, 38.60. Found: N, 13.58; Br, 38.42.

1-Benzyl-5-bromodihydrouracil. 1-1-Benzyldihydrouracil when treated with one molecular equivalent of bromine gave 1-benzyl-5-bromodihydrouracil in 51% yield. After several recrystallizations from ethanol it melted at 150-152°.

Anal. Calcd. for $C_{11}H_{11}O_2N_2Br_2$: N, 9.90; Br, 28.22. Found: N, 9.76, Br, 28.36.

1-Isopropyl-5,5-dibromodihydrouracil 1-Isopropyldihydrouracil when treated with one equivalent of bromine yielded a mixture of brominated compounds which could not be separated. When treated with two molecular equivalents of bromine, a 52% yield of 1-isopropyl-5,5-dibromodihydrouracil was obtained. After several recrystallizations from ethanol it melted at 129–132°.

Anal. Calcd. for $C_7H_{10}O_2N_2Br_2$: N, 8.92; Br, 50.89. Found: N, 8.88; Br, 50.46.

1-Benzyl-5,5-dibromodihydrouracil. 1-Benzyldihydrouracil when treated with two molecular equivalents of bromine gave 1-benzyl-5,5-dibromouracil in 51% yield. After recrystallization from alcohol it melted at 157–159°.

Anal. Calcd. for $C_{11}H_{10}O_2N_2Br_2$: N, 7.74; Br, 44.14. Found: N, 7.52; Br, 43.79.

Dehydrohalogenation of 5-bromo and 5,5-dibromodihydrouracils. The brominated uracil was added in small portions to ten times its weight of boiling dimethylformamide, and the resulting solution refluxed for one hour. The dimethylformamide was removed by distillation under reduced pressure, and the residue treated with a small quantity of water. The resulting solid was filtered and recrystallized from alcohol (see Table I).

When 4.4 g. (0.014 mole) of 1-isopropyl-5,5-dibromodihydrouracil was dehydrogenated according to the above procedure, 2.3 g. (70%) of 1-isopropyl-5-bromouracil was obtained. It melted at 202–204°.

Anal. Calcd. for $C_7H_9O_2N_2Br$: N, 12.02; Br, 34.28. Found: N, 12.10; Br, 33.99.

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(12) G. Hilbert, *J. Am. Chem. Soc.*, 54, 2076 (1932).

Reduction of Trimethylacetonitrile with Grignard Reagents. II. The Reaction of Trimethylacetonitrile with *t*-Butylmagnesium Chloride at Elevated Temperatures[1]

ERWIN J. BLANZ, JR., AND HARRY S. MOSHER

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It has been shown that *t*-butylmagnesium chloride reacts readily with trimethylacetonitrile at high temperature (150°) and pressure to yield the reduction products, trimethylacetaldehyde, 2,2-dimethylpropylidene-2′,2′-dimethylpropylamine (I), and higher boiling material of unknown structure. These findings have been interpreted in terms of the six-membered ring transition state mechanism for the "abnormal" Grignard reaction.

In the reaction of Grignard reagents with trimethylacetonitrile it was found[2] that as the

(1) Abstracted from the thesis submitted by Erwin J. Blanz, Jr., to Stanford University in partial fulfillment of the requirements for the M.S. degree, April 1957.

(2) H. S. Mosher and W. T. Mooney, *J. Am. Chem. Soc.*, 73, 3948 (1951).

branching on the carbon atom *alpha* to the magnesium increased, the yield of reduction product, trimethylacetaldehyde, increased at the expense of normal addition. This reaction with *t*-butylmagnesium chloride and trimethylacetonitrile was so hindered, however, that under usual conditions (ether solution and room temperature) sixty per cent of the trimethylacetonitrile was recovered unchanged. Since the use of a solvent such as diisoamyl ether introduced certain problems, we decided to study this reaction in a stainless steel rocking autoclave at elevated temperatures.

When the reaction was carried out at 150° for approximately twelve hours with the ratio of *t*-butylmagnesium chloride and trimethylacetonitrile 1.3:1 there was isolated after hydrolysis a 10% yield of trimethylacetaldehyde, a 31% yield of the aldimine 2,2-dimethylpropylidene-2′,2′-dimethylpropylamine (I) and a high boiling material of unknown structure; 7% of the unreacted nitrile

$$(CH_3)_3CCH{=}NCH_2C(CH_3)_3$$
I

was recovered. No addition product 2,2,4,4-tetramethyl-3-pentanone was isolated. When the ratio of the Grignard reagent to the nitrile was increased to 2.6:1, there was isolated a 17% yield of trimethylacetaldehyde, a 26% yield of the aldimine (I), and material of unknown structure; neither neopentylamine, 2,2,4,4-tetramethyl-3-pentanone, nor unreacted nitrile were isolated.

Although ketimines have been isolated from the reaction of Grignard reagents with nitriles we have found no report of the isolation of an aldimine by this reaction. A possible way of formation of the aldimine is set forth in the following series of equations:

(*a*) $(CH_3)_3CC{\equiv}N + (CH_3)_3CMgCl \longrightarrow (CH_3)_3CCH{=}NMgCl + CH_2{=}C(CH_3)_2$
II

(*b*) $II + (CH_3)_3CMgCl \longrightarrow (CH_3)_3CCH_2N(MgCl)_2 + CH_2{=}C(CH_3)_2$
III

(*c*) $II + III \rightleftharpoons (CH_3)_3CCHN(MgCl)_2$
$NMgCl$
$CH_2C(CH_3)_3$

(*d*) $\xrightarrow{3H_2O}$ $(CH_3)_3CCHNH_2 + 3Mg(OH)Cl$
NH
$CH_2C(CH_3)_3$

$+ NH_3 \longleftarrow$ $C(CH_3)_3$
CH
$\|$
N
CH_2
$C(CH_3)_3$
I

Equations (*a*) and (*b*) represent the reduction of the trimethylacetonitrile to the aldimine and amine stage respectively. Equation (*c*) represents the condensation of the substituted aldimine II and the substituted amine III. Since aldimines are generally prepared from aldehydes and amines,[3] there is a possibility that the aldimine was formed after the hydrolysis of the Grignard reaction. If this is so, the equations for the formation of the aldimine (I) may be represented as follows:

(*e*) $II + 2H_2O \longrightarrow (CH_3)_3CCHO + Mg(OH)Cl + NH_3$
IV

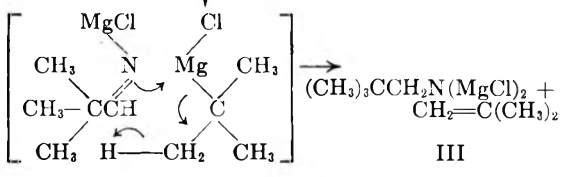
(*f*) $III + 2H_2O \longrightarrow (CH_3)_3CCH_2NH_2 + Mg(OH)Cl$
V

(*g*) $IV + V \rightleftharpoons (CH_3)_3CCH{=}NCH_2C(CH_3)_3 + H_2O$

No experimental evidence is available to decide between these two possibilities. The fact that no neopentylamine was found is explained on the reasonable assumption that reactions (*e*) or (*g*) are essentially complete as written.

The six-membered ring theory for "abnormal" Grignard reactions[4] has been used to explain the formation of trimethylacetaldehyde.[2] This theory also can be readily applied to the formation of neopentylamine derivatives. The following equations represent this postulated mechanism:

(*h*) $(CH_3)_3CCH{=}NMgCl + (CH_3)_3CMgCl$
II



$\longrightarrow (CH_3)_3CCH_2N(MgCl)_2 + CH_2{=}C(CH_3)_2$
III

Hydrolysis of the magnesium salt III would give neopentylamine or this salt (III) could react further as indicated by Equation (*e*). Isobutylene was identified by its infrared spectrum as a product of this reaction as required by this mechanism.

The proof of structure of 2,2-dimethylpropylidene-2′,2′-dimethylpropylamine (I) has been reviewed in a previous publication.[5]

The high-boiling material from this reaction was shown by gas-partition chromatography on both Carbowax and silicon oil columns to be a complex mixture. In addition it was found that the material was not stable on standing; crystals of trimethylacetamide separated from the high-boiling material after a period of a month. Before the complexity of this material was appreciated the following evidence had been obtained: (*a*) Hydrolysis of the material gave trimethylacetaldehyde and am-

(3) M. R. Tiollais, *Bull. soc. chim. France*, 14, 708 (1947).

(4) Whitmore and George, "The Common Basis of the Reaction of Grignard Reagents with Carbonyl Compounds; Addition, Reduction, Enolization and Condensation." Paper presented at the 102nd Meeting of the American Chemical Society, September 9, 1941. For further details see the Ph.D. thesis of R. S. George, The Pennsylvania State College, July 1943; available from University Microfilms, Ann Arbor, Mich.

(5) H. S. Mosher and E. J. Blanz, Jr., *J. Org. Chem.*, 22, 445 (1957).

monium chloride; (*b*) hydrogenation of this material gave dineopentylamine; (*c*) the infrared spectrum of the material showed a very narrow, pronounced absorption at 6.01 μ characteristic of the C=N group and a wider, less pronounced absorption at 3.00 μ indicating the presence of NH.

EXPERIMENTAL[6,7]

t-Butylmagnesium chloride and trimethylacetonitrile. To a titrated ether solution of 0.172 mole of *t*-butylmagnesium chloride in a stainless steel autoclave was added 11.6 g. (0.135 mole) of trimethylacetonitrile (b.p. 104–105°). The autoclave was quickly sealed under a blanket of nitrogen and heated for 12 hr. at 150°. After the autoclave was cooled, the contents were hydrolyzed in an aqueous solution of ammonium chloride at 0°, and the ether layer and ether extracts of the aqueous layer were dried over anhydrous sodium sulfate. The ether was removed by fractionation through a sixteen-plate column and the residue was fractionated further from a column of small holdup to give the following cuts: 1–3 ether; cuts 4–5, b.p. 68–71°, n_D^{21} 1.3803–1.3829, 1.10 g., impure trimethylacetaldehyde; cut 6, b.p. 71–92°, n_D^{21} 1.3900, 0.45 g.; cuts 7–8, b.p. 92–118°, n_D^{21} 1.3860–1.3898, 0.81 g., impure trimethylacetonitrile and hexamethylethane; cut 9, b.p. 118–141°, n_D^{21} 1.4029, 0.36 g.; cuts 10–15, b.p. 141–145°, n_D^{21} 1.4080–1.4099, 3.42 g., 2,2-dimethylpropylidene-2′,2′-dimethylpropylamine; cuts 16–19, b.p. 110–115° (15 mm.), n_D^{21} 1.4334–1.4376, 3.58 g., high boiling mixture of unknown structure; residue 0.59 g. The material from cuts 4–5 gave a 2,4-dinitrophenylhydrazone, m.p. 205–206°; melting point when mixed with an authentic sample of 2,4-dinitrophenylhydrazone of trimethylacetaldehyde 206–207°.

Cuts 10–15 were further purified by means of gas-liquid partition chromatography. The infrared spectrum of the aldimine (I) was identical to the aldimine prepared from trimethylacetaldehyde and neopentylamine.[5] Infrared spectrum included bands at 3.40(s), 3.56(s), 5.98(s), 6.77(s), 6.95(m), 7.18(m), 7.33(s), 8.00(w), 8.26(m), 9.38(m), 9.89(w), 10.52(w), 11.13(m), and 13.42(w) μ.

Infrared analysis of the gas collected when the autoclave was vented showed that it consisted of a mixture of isobutylene and ether.

A second experiment in which 2.6 molar equivalents of Grignard reagent were used was carried out as indicated above starting with 10 g. (0.120 mole) of trimethylacetonitrile and 0.316 mole of *t*-butylmagnesium chloride. After fractionation there was obtained trimethylacetaldehyde 1.72 g. (17%), 2,2-dimethylpropylidene-2′,2′-dimethylpropylamine 2.39 g. (26%) and 4.42 g. b.p. 86–90° (9 mm.) of the high-boiling material of unknown structure.

Hydrogenation of the high-boiling material. The material from cuts 16–19, 548 mg., methanol, 15 ml., and Raney nickel catalyst, approximately 150 mg., were stirred under one atmosphere of hydrogen in a microhydrogenation apparatus for 34 hr. A total uptake of 100.9 ml. of hydrogen at 18° was recorded. This corresponds to an equivalent weight of 128 ± 5. The basic product from this reduction was separated by extraction with acid and was regenerated with base. The phenylthiourethane melted at 138–140°; melting point when mixed with a known sample of the phenylthiourethane of dineopentylamine,[5] 138–140°.

Hydrolysis of the high-boiling material. To 20 ml. of 6*N* hydrochloric acid was added 500 mg. of high boiling material. The reaction mixture was heated for 30 min. at 100° because the material appeared to be quite unreactive in the acid solution. The ether extract gave a 2,4-dinitrophenylhydrazone, m.p. 205–206°; melting point when mixed with an authentic sample of the 2,4-dinitrophenylhydrazone of trimethylacetaldehyde, 205–206°. Ammonium chloride was isolated from the aqueous acid layer by evaporation. After standing one month white crystals had separated in the vial containing the high boiling material. These crystals were separated, washed with petroleum ether and sublimed; m.p. 153.5–154.5°; melting point when mixed with an authentic sample of trimethylacetamide 154–155°.

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(6) All melting points and boiling points are uncorrected; microanalysis was done by Microchemical Specialties Company, Berkeley, Calif.

(7) Infrared spectra were taken with a Perkin-Elmer Model 21 Recording Infrared Spectrophotometer.

Nitration of Nitroolefins with Nitric Acid

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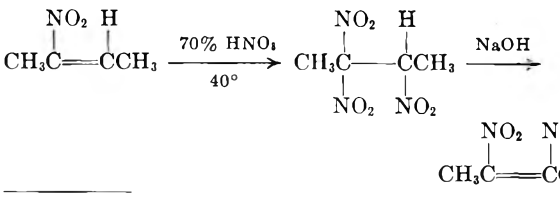
The addition of dinitrogen tetroxide to simple olefins has been studied extensively by Levy and Scaife[1] who isolated and characterized three types of reaction products—dinitroalkanes, nitroalcohols, and nitroalkylnitrates. This reaction has also been applied to nitroolefins. The addition of dinitrogen tetroxide to 2-nitro-2-butene and 2,3-dinitro-2-butene has given 2,2,3-trinitrobutane[2] and 2,2,3,3-tetranitrobutane,[3] respectively. The nitration of olefins with nitric acid has been studied by various workers,[4] but to our knowledge the reaction of nitroolefins and nitric acid has not been reported.

We have studied the reaction of 2-nitro-1-propene, 2-nitro-1-butene, and 2-nitro-2-butene with 70% nitric acid under various conditions. Mixtures were obtained from these reactions and only in the case of 2-nitro-2-butene, where a solid product was obtained, was it possible to purify and identify the major product. When the nitric acid was warmed to 40° and 2-nitro-2-butene was added dropwise at this temperature, there was isolated a 25.3% yield of a white solid, m.p. 46–48°. The analysis of this product corresponded to an empirical formula of $C_4H_7N_3O_6$, a trinitrobutane. The structure of the trinitrobutane was established as 2,2,3-trinitrobutane by degradation with base to the known 2,3-dinitro-2-butene:



(1) N. Levy and C. W. Scaife, *J. Chem. Soc.*, 1093, 1096, 1100 (1946).

(2) **OSRD Rept. 2016**, Nov. 15, 1943.

(3) C. E. Gabriel, D. E. Bisgrove, and L. B. Clapp, *J. Am. Chem. Soc.*, **77**, 1293 (1955).

(4) H. Wieland and E. Sakellarios, *Ber.*, **53**, 201 (1920); A. D. Petrov and M. A. Bulygina, *Doklady Akad. Nauk, S.S.S.R.*, **77**, 1031 (1951).

EXPERIMENTAL[5,6]

Nitration of 2-nitro-2-butene. Nitric acid, 150 ml. of 70%, was warmed to 40° and 25 g. (0.25 mole) of 2-nitro-2-butene[7] was added dropwise in 90 min. The temperature was maintained at 39 to 41° by intermittent cooling during the addition and for 1 hr. after the addition was completed.[8] At the end of this time, the temperature began to drop, indicating that the reaction was completed. The mixture was cooled to 5°, causing a white solid to separate, and poured onto ice. The white solid was collected, washed thoroughly with water, and dried *in vacuo* over potassium hydroxide. The yield of 2,2,3-trinitrobutane was 12.1 g. (25.3%), m.p. 42–45°. Recrystallization from isopropyl ether raised the melting point to 46–48°. A Liebermann test for the nit ite group was negative.

Anal. Calcd. for $C_4H_7N_3O_6$: C, 24.88; H, 3.65; N, 21.76; mol. wt., 193. Found: C, 24.85; H, 3.75; N, 22.00; mol. wt., 211.

Proof of structure of 2,2,3-trinitrobutane. A solution of 19.3 g. (0.10 mole) of 2,2,3-trinitrobutane in 150 ml. of ether was cooled to 18–20° and a solution of 4.0 g. (0.10 mole) of sodium hydroxide in 50 ml. of water was added dropwise with stirring. The yellow ether layer was separated and the orange aqueous layer was extracted with ether. The combined ether extracts were dried and concentrated leaving 13.3 g. (91.2%) of yellow liquid. A sample was distilled from a Claisen flask, b.p. 102–103° (2.5 mm.), n_D^{25} 1.4830, m.p. 26°.[9]

Anal. Calcd. for $C_4H_6N_2O_4$: C, 32.86; H, 4.12; N, 19.17. Found: C, 32.69; H, 4.19; N, 18.79.

When treated with ammonia it produced 2-amino-3-nitro-2-butene, m.p. 159–160°, identical to the product previously obtained from the reaction of 2,3-dinitro-2-butene with ammonia.[10]

Acknowledgment. We are indebted to the Office of Naval Research for the financial support of this work.

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(5) All melting points are uncorrected.

(6) Microanalyses by Elek Microanalytical Laboratories, Los Angeles, Calif.

(7) H. B. Hass, *J. Org. Chem.*, **15**, 8–14 (1950).

(8) When 2-nitro-2-butene and 70% nitric acid were mixed at 5–10° and then allowed to warm up, a fume off occurred.

(9) E. M. Nygaard and T. T. Noland, U. S. Patent 2,396,282, March 12, 1946, reported 2,3-dinitro-2-butene to have a boiling point of 97–100° (1–2 mm.) and a melting point of 25.9°.

(10) L. B. Clapp, J. F. Brown, Jr., and L. Zeftel, *J. Org. Chem.*, **15**, 1043 (1950).

Amount of β-Isomer Formed in the Bromination of Naphthalene[1]

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In connection with a recent study of the kinetics of bromination of naphthalene in 50% aqueous acetic acid,[2] it seemed important to determine the amount of β-bromonaphthalene formed under these conditions. The extent of β-bromination has not previously been determined in solution, but its presence could be inferred from other data. Wibaut and co-workers have determined the amount of α- and β-bromonaphthalene in uncatalyzed *liquid phase* bromination in the temperature range 85–215°, and in the gas phase.[3] In the gas phase above 300° the reaction follows a free-radical course, but in the liquid phase a polar reaction occurs, and the amount of β-isomer varies with temperature from 3% to 6.8%. Small amounts of β-isomer are formed in nitration,[4] and apparently also in chlorination[5] and iodination.[6] More significant amounts are obtained in the Friedel-Crafts acylation[7] and alkylation,[8] and in sulfonation,[9] although, at least in the last two cases, the proportions of isomers are determined by their equilibrium concentrations, rather than their rates of formation.[10]

The amount of β-bromination of naphthalene at 25° in 50% aqueous acetic acid was determined by the isotopic dilution method, using molecular bromine containing the isotope Br^{82} as the substituting agent and adding an excess of inactive β-bromonaphthalene to the completed reaction mixture. From the amount and the activity of the recovered pure β-bromonaphthalene, the extent of β-bromination could be calculated. The percentages of β-isomer in three different runs, each $0.01M$ in naphthalene, $0.1M$ in potassium bromide, and approximately $0.005M$ in bromine, were 1.07 ± 0.056, 0.981 ± 0.024, and 0.992 ± 0.032. The weighted average[11] is 1.00 ± 0.02, and this represents the percent. β-bromonaphthalene in the total bromination products.

(1) Taken from the senior honors thesis of F. J. Ochs, 1957.

(2) E. Berliner and M. C. Beckett, *J. Am. Chem. Soc.*, **79**, 1425 (1957).

(3) (a) J. F. Suyver and J. P. Wibaut, *Rec. trav. chim.*, **64**, 65 (1945); (b) G. M. Badger, *The Structure and Reactions of the Aromatic Compounds*, Cambridge University Press, Cambridge, 1954, pp. 259–262.

(4) See M. J. S. Dewar and T. Mole, *J. Chem. Soc.*, 1441 (1956) for the most recent determination and for previous references.

(5) Quoted by R. W. Beattie and F. C. Whitmore, *J. Chem. Soc.*, 50 (1934); for iodine-catalyzed vapor phase chlorination, see J. P. Wibaut and G. P. Bloem, *Rec. trav. chim.*, **69**, 586 (1950).

(6) A. Edinger and P. Goldberg, *Ber.*, **33**, 2875 (1900).

(7) Ref. 3b, Chapter 7. L. F. Fieser and M. Fieser, *Organic Chemistry*, Third Edition, D. C. Heath and Co., Boston, Mass., 1956, Chapter 31. G. Baddeley, *J. Chem. Soc.*, S99 (1949).

(8) C. C. Price in *Org. Reactions*, Vol. III, pp. 1–82 (1946).

(9) C. M. Suter and A. W. Weston in *Org. Reactions*, Vol. III, pp. 141–197 (1946).

(10) For the view that acylation of naphthalene is also a reversible reaction see P. H. Gore, *Chem. Revs.*, **55**, 229 (1955).

(11) A. G. Worthing and J. Geffner, *Treatment of Experimental Data*, John Wiley and Sons, Inc., New York, N. Y., Sixth Printing, 1950, Chapter VIII.

The above result is reasonable in view of a figure of 1.46% calculated by extrapolation from the data for bromination in the *liquid phase* at 85-215°.[3] It is also consistent with the values of 5–10% of β-isomer reported in nitration,[4] because nitration is known to be a less selective reaction than bromination by molecular bromine.[12]

EXPERIMENTAL

Materials. The 50% aqueous acetic acid was prepared from purified acetic acid as described before.[2] The recrystallized naphthalene sample melted at 80.0–80.4°,[13] and β-bromonaphthalene was prepared by the method of Newman and Wise.[14] It was recrystallized repeatedly from slightly aqueous ethanol, and the final sample melted sharply at 55.7–55.9°.

Bromination of naphthalene and isolation of β-isomer. In one of the three runs, about 3 mc of Br^{82} as bromide ion, and as obtained from the Oak Ridge National Laboratory, was dissolved in about 400 ml. of a 0.01*M* potassium bromide solution. Ten ml. of this solution was evaporated to dryness, and the residue was dissolved in 50 ml. of a stock solution of 50% aqueous acetic acid, 0.1*M* in potassium bromide and about 0.1*M* in bromine. A 25-ml. sample of this solution was added to 475 ml. of a solution which contained the other reagents in such concentrations as to give a final reaction mixture, 0.01*M* in naphthalene and 0.1*M* in potassium bromide. The initial bromine concentration, determined by titration of two 10-ml. samples of the active bromine solution was exactly 0.005*M*. One 5-ml. sample was withdrawn from the reaction mixture for counting of the total activity and was diluted to 500 ml. with 95% aqueous ethanol (sample A). After 17 hours at 25.00 ± 0.02°, ten ml. of the reaction mixture was titrated for completion of reaction (98.72%). A small amount of sodium bisulfite was added to destroy unreacted bromine in the reaction mixture. To this was added 4.3000 g. of pure inactive β-bromonaphthalene dissolved in acetone, and more acetone was added to keep the solution homogeneous. About 1 l. of cold water was then added and the reaction mixture was extracted with one 300-ml. and four 200-ml. portions of petroleum ether. The organic layer was washed with 5% sodium bicarbonate solution, using a total of 500 ml., and then with water. The solvent was dried and evaporated, and the remainder was crystallized five times from slightly aqueous ethanol. The final sample (sample B, 1.3519 g.) melted at 55.6–55.8°, with very slight softening at 55.1°.

Counting and calculations. The Br^{82} activity was measured with an Atomic Instrument Co. Model 810A well-type scintillation counter and a Model 1090 scaler with a pulse-height discriminator. Only γ-activity was counted and the discriminator was set to accept only the higher energy γ-particles. Samples of β-bromonaphthalene in a solution of exactly 5-ml. volume were counted in a calibrated Pyrex test tube. The total sample was immersed in the well. Because only high energy γ particles were counted, the counting rate was independent of the solvent and other possible solute species. In all cases, times for 10,000 counts were recorded in order to keep the uncertainty constant.

The above sample of recovered β-bromonaphthalene (sample B), dissolved in acetone to exactly 5 ml., had an activity of 5.85 counts per second, corrected for the background count. Five ml. of the diluted reaction mixture (sample A) had a count of 4.29 counts per second, corrected for background and for radioactive decay during the time interval between counting samples A and B. On account of the dilution, the activity of the total reaction mixture is therefore 4.29×10^4 counts per second. Because of the immediate establishment of the tribromide equilibrium, the Br^{82} is randomly distributed between bromide and bromine, and the fraction of activity in the bromine molecule is $\frac{0.005 \times 2}{0.11} = 0.09091$, and hence the activity in the total amount of bromine that has reacted is $4.29 \times 10^4 \times 0.9872 \times 0.09091$ or 3.850×10^3 counts per second. One half of that amount, or 1.925×10^3 counts per second, has entered the naphthalene molecules. Corrected for 15 ml. of solution withdrawn for counting and titration, the total counts for α- plus β-bromonaphthalene are 1867 counts per second. The amount of β-bromonaphthalene recovered was 31.44%, and hence the activity for the total β-isomer is 5.85/0.3144, or 18.61 counts per second, neglecting the weight of the very small amount of β-isomer formed during substitution. The fraction of β-isomer is therefore 18.61/1867 or 0.997%. After counting, the β-isomer was once more recrystallized, when 0.8426 g. of material melting sharply at 55.8–56.0° was obtained. Counting of this sample afforded a value of 0.987% of β-isomer, or an average of 0.992%.

In order to obtain some information about the depression of the melting point of pure β-bromonaphthalene on admixture with possible contaminants, artificial mixtures were prepared and their melting points determined by the usual capillary method. Mixtures of pure β-bromonaphthalene with 5% and 2% by weight of naphthalene, which under the experimental conditions is the most likely contaminant, melted at 53.2–54.0° and at 54.4–55.4°, respectively, with some softening below these temperatures. A mixture of 95% of β- and 5% of α-bromonaphthalene melted at 44.2–52.2°. All of the purified samples of the β-isomer used for counting purposes contained therefore considerably less than these amounts of impurities, because no sample started to melt below 55°.

In the calculation of the weighted average, a statistical error of 1% was applied to each counting, and reasonable errors were estimated for titration and dilution.

Acknowledgment. We wish to express our thanks to the Committee on the Coordination of the Sciences of Bryn Mawr College for the purchase of the counting equipment and the isotopes.

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

(13) All melting points are corrected.

(14) M. S. Newman and P. H. Wise, *J. Am. Chem. Soc.*, 63, 2847 (1941).

Reaction of Methylenedinitramine and Formaldehyde with Various Diaminoalkanes[1]

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The condensation of methylenedinitramine (I), formaldehyde, and several primary aliphatic amines

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has been reported by Chapman[2] and Wright;[3] the products were the 1-alkyl-3,5-dinitro-1,3,5-triazacyclohexanes,[2] 1,3-dialkyl-5-nitro-1,3,5-triazacyclohexanes,[2] and 1,3-dialkyl-5,7-dinitro-1,3,5,7-tetraazacyclooctanes.[3] Similarly, ethylenedinitramine, methylamine, and formaldehyde yielded 1-methyl-3,6-dinitro-1,3,6-triazacycloheptane.[4] However, the condensation of I with formaldehyde and aliphatic diamines has not been reported.

The diamines $H_2N(CH_2)_nNH_2$ (where **n** = 2,3,4,5,6,7, and 8) were found to interact with methylenedinitramine (I) in formalin solutions at 0° to yield crystalline derivatives as shown in Table I. In most of the reactions addition of the amine to the formalin solution of I caused the precipitation of the cyclic derivatives; but in a few runs where no deposition occurred the product was removed by extraction with methylene chloride. With the 1,3-diaminopropane and 1,4-diaminobutane higher yields were obtained by the slow addition of potassium carbonate to a solution of I and the amine hydrochloride in formalin.

In the case of the ethylenediamine there was produced the 3-nitro-1,3,5-triazabicyclo[3.2.1]octane (IIa) which apparently resulted from the degradation of the nitramine I to the dimethylolnitramide, $HOCH_2N(NO_2)CH_2OH$; the latter subsequently underwent a Mannich reaction with the formaldehyde and the amine to yield IIa which was slowly precipitated. Wright and co-workers[5] reported that a mixture of nitramide,[6] formalin, and ethylenediamine also produced IIa. Lamberton[7] has shown that methylenedinitramine is unstable in solutions of *p*H 3–8. The *p*H of the reaction mixtures were found to be within this range and a slow evolution of gas was noted when the temperature of the formalin solutions exceeded 10°. Lamberton[7] suggested that the production of 3,7-dinitro-1,3,5,7-tetraazabicyclo[3.3.1]nonane from an aqueous solution of the monoammonium salt of I and formaldehyde involved the formation of nitramide, or its methylol derivative. Chapman[2] also postulated the formation of dimethylolnitramide from I to explain the isolation of the 1,3-dialkyl-5-nitro-1,3,5-triazacyclohexanes from formalin solutions of I and alkylamines. With 1,3-diaminopropane, the 3-nitro-1,3,5-triazabicyclo[3.3.1]nonane (IIb) was easily obtained; 1,3-diamino-butane gave a corresponding derivative, *i.e.*, the 3-nitro-8-methyl-1,3,5-triazabicyclo[3.3.1]nonane (IIc). However, 1,4-diamino-

TABLE I

PROPERTIES OF THE CONDENSATION PRODUCTS OF METHYLENEDINITRAMINE, ALKANEDIAMINES, AND FORMALDEHYDE

	M.P., °C.	Yield, %	Formula	Analysis						Cryoscopic Mol. Wt.[a]	
				Calcd.			Found			Calcd.	Found
				C	H	N	C	H	N		
II, $O_2N-N<^{CH_2-N-(CH_2)_n}_{CH_2-N-CH}$ R											
IIa, n = 1, R = H	165° dec.	74[b]									
IIb, n = 2, R = H	135° dec.	56	$C_6H_{12}N_4O_2$	41.85	7.03	32.54	41.99	7.19	32.70	172	178
IIc, n = 2, R = CH_3	125° dec.	51	$C_7H_{14}N_4O_2$	45.15	7.58	30.09	45.24	7.80	29.70	186	181
IId, n = 5, R = H	170° dec.	5	$C_9H_{18}N_4O_2$	50.45	8.47	26.15	50.61	8.60	26.22	214	208
IIe, n = 6, R = H	78–80°	20	$C_{10}H_{20}N_4O_2$	52.61	8.83	24.54	52.33	8.99	24.70	228	230
IIf, n = 7, R = H	94–95°	28	$C_{11}H_{22}N_4O_2$	54.52	9.15	23.12	54.88	9.48	23.33	242	235
III, $\left[CH_2<^{N(NO_2)CH_2}_{N(NO_2)CH_2}N-(CH_2)_n\right]_2$											
IIIa, n = 4	128° dec.	60	$C_{10}H_{20}N_{10}O_8$	29.41	4.94	34.30	29.39	5.04	33.95	408	398
IIIb, n = 5	125° dec.	40	$C_{11}H_{22}N_{10}O_8$	31.28	5.25	33.17	31.36	5.37	32.99	422	431

[a] Nitrobenzene was employed as the solvent. [b] A compound previously prepared from nitramide, ethylenediamine, and formalin, ref. 5.

(2) F. Chapman, P. G. Owston, and D. Woodcock, *J. Chem. Soc.*, 1638 (1949).

(3) E. Aristoff, J. A. Graham, R. H. Meen, G. S. Myers, and G. F Wright, *Can. J. Res.*, B27, 520 (1949).

(4) G. S. Myers and G. F Wright, *Can. J. Res.*, B27, 489 (1949).

(5) W. J. Chute, D. C. Downing, A. F. McKay, G. S. Myers, and G. F Wright, *Can. J. Res.*, B27, 218 (1949).

(6) Nitramide in excess formalin is believed to exist largely as dimethylolnitramide, ref. 5.

(7) A. H. Lamberton, C. Lindley, and J. C. Speakman, *J. Chem. Soc.*, 1650 (1949).

butane yielded the 1,4-bis(3,5-dinitro-1,3,5-triazacyclohexyl)butane (IIIa); the 1,5-diaminopentane produced an analogous derivative, *i.e.*, 1,5-bis(3,5-dinitro-1,3,5-triazacyclohexyl)pentane (IIIb). The 1,6-diaminohexane, 1,7-diaminoheptane, and 1,8-diaminooctane yielded 3-nitro-1,3,5-triazabicyclo[6.3.1]dodecane (IId), 3-nitro-1,3,5-triazabicyclo[7.3.1]tridecane (IIe), and 3-nitro-1,3,5-triazabicyclo[8.3.1]tetradecane (IIf), respectively, although in low yields; the major reaction was the formation of a rubbery insoluble polymer of the amine and formaldehyde which contained only a few nitramino groups. The 1,9-diaminononane produced solely polymer. The latter derivatives IId, IIe, and IIf, represent ring enlargements of the bicyclic system obtained with ethylenediamine, 1,3-diaminopropane, or 1,3-diaminobutane.

The formation of the derivatives II and III is analogous to the production of the 1,3-dialkyl-5-nitro-1,3,5-triazacyclohexanes[2] and 1-alkyl-3,5-dinitro-1,3,5-triazacyclohexanes,[2] respectively, from primary amines. In no case was there any evidence for the formation of more than one condensation product even when a two-fold excess of amine or I was employed. The cyclic derivatives were slowly soluble in dilute mineral acid with the formation of the dihydrochloride of the amine, and in the case of the two derivatives of III, methylenedinitramine. Warm alkali rapidly degraded the derivatives II or III with the formation of the diamine and formaldehyde; in addition III yielded disodium methylenedinitramine. All of the condensation products slowly decomposed on storage at room temperature; the odor of formaldehyde and the diamine became noticeable after 2–4 weeks.

EXPERIMENTAL[8]

The formation of 3-nitro-1,3,5-triazabicyclo[3.2.1]octane (IIa) is representative of a condensation using the free amine, formalin, and I. To a solution of 4.08 g. (0.0300 mole) of methylenedinitramine[9] (I) (m.p. 100–101°) in 72 ml. (0.86 mole) of 36% formalin maintained at 0°, was added (dropwise) 1.80 g. (0.0300 mole) of ethylenediamine. The mixture was allowed to stand 4 hr. at 0°. The fine needles which had deposited were filtered to yield 5.14 g. (74%) of IIa, m.p. 160° dec.; m.p. 165°, dec., depending on rate of heating (reported 130° by Wright[6]) after recrystallization from acetone. No methylenedinitramine was isolated in several alkaline degradations of IIa; only ethylenediamine (isolated as the diacetyl derivative, m.p. 174–175°, reported 172° by Hofmann[10]) and formaldehyde were recovered. Similar results were obtained with the other derivatives of II. All derivatives of II were soluble in 3*N* hydrochloric acid; no methylenedinitramine could be isolated from the solutions.

The formation of 1,4-bis(3,5-dinitro-1,3,5-triazacyclohexyl)-butane (IIIa) is typical of a run employing an amine hydrochloride and potassium carbonate. To a solution of 4.08 g. of I in 72 ml. of 36% formalin was added 10 ml. of a solution containing 2.64 g. (0.0300 mole) of 1,4-diaminobutane which had been neutralized by 6*N* hydrochloric acid. To the resulting solution which was maintained at 0°, was added finely powdered potassium carbonate until the reaction mixture was alkaline to nitrazine test paper. The reaction mixture, which contained precipitated IIIa, was allowed to stand 1 hr. at 0° and then filtered to yield 7.30 g. (60%) of crude IIIa, m.p. 120° dec.; m.p. 135° dec. after recrystallization from acetone. Alkaline decomposition of the two derivatives of III produced 1,4-diaminobutane from IIIa (isolated as the diacetyl derivative, m.p. 136°, reported 137° by Haga[11]) and 1,5-diaminopentane from IIIb (isolated as the dibenzoyl derivative, m.p. 134–135°, reported as 132° by Braun[12]) as well as formaldehyde. The alkaline solution was acidified and extracted with ether; evaporation of the ether left methylenedinitramine in 85% yield. Dilute hydrochloric acid, 3*N*, dissolved III with the formation of formaldehyde, the corresponding diamine dihydrochloride, and methylenedinitramine (I).

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(8) All melting points are corrected. The combustion analyses were performed by Mr. Everett Bens of this laboratory.

(9) R. C. Brian and A. H. Lamberton, *J. Chem. Soc.*, 1633 (1949).

(10) A. W. Hofmann, *Ber.*, 21, 2332 (1888).

(11) T. Haga and R. Majima, *Ber.*, **36**, 338 (1903).

(12) J. Braun and S. W. Pirkernelle, *Ber.*, **67**, 1056 (1934).

An Ivanov Reaction with the Use of α-Phenylpropionic Acid

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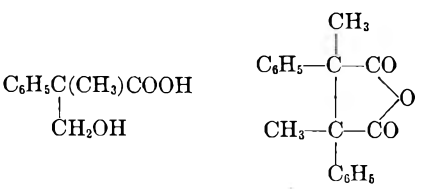
The renewed interest in the Ivanov reaction lately exhibited in several laboratories[1–3] prompts us to report the results of an Ivanov reaction of α-phenylpropionic acid with formaldehyde. When a procedure, adapted from that reported by Blicke, Raffelson, and Barna[4] for the preparation of tropic acid in 80% yield from phenylacetic acid and formaldehyde, was applied to α-phenylpropionic acid, α-methyltropic acid (I) was obtained in only trace amounts. Also isolated in poor yield was a somewhat larger quantity of *sym.* dimethyldiphenylsuccinic anhydride (II), m.p. 157–159°,



I II

(1) F. F. Blicke and H. Zinnes, *J. Am. Chem. Soc.*, **77**, 5399, 6051, 6247 (1955) and previous papers.

(2) H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, **79**, 1920 (1957).

(3) A. W. Weston and R. W. DeNet, *J. Am. Chem. Soc.*, **73**, 4221 (1951).

(4) F. F. Blicke, H. Raffelson, and B. Barna, *J. Am. Chem. Soc.*, **74**, 253 (1952).

formed by oxidative coupling of two molecules of the Ivanov reagent.[5] McKenzie and Ritchie[6] prepared the succinic acid corresponding to II by treatment of α-chloro-α-phenylpropionic acid with either metallic copper or ethylmagnesium bromide. They assigned the racemic configuration to this acid, which split off water at the melting point to give the anhydride II, m.p. 159–160°. In the present work, the low yields of characterized products do not preclude the possibility that some of the meso-form of *sym.* dimethyldiphenylsuccinic acid, which does not form the corresponding anhydride at its melting point,[6] was formed also. However, it is felt that if an appreciable amount had been present, it would have interfered considerably with the purification of the minute amount of α-methyltropic acid formed in the reaction. If one can assume that the racemic form of the succinic acid is indeed formed to the near exclusion of the meso-form, a transition state involving minimum phenylphenyl interaction similar to the one proposed by Zimmerman and Traxler[2] for the Ivanov reaction of phenylacetic acid with benzaldehyde may also be involved in the oxidative coupling reaction. However, any extension of these stereochemical mechanisms to the coupling reactions of the α-chloro derivatives studied by McKenzie and Ritchie[6] must account for their observation that the use of metallic silver led to the meso-form of *sym.* dimethyldiphenylsuccinic acid in contrast to the production of the racemic form when metallic copper was used.

It should be noted that the purpose of this work was to prepare α-methyltropic acid by a reasonably unequivocal method. Foster and Ing[7] reported the preparation of this acid by the action of nitrous acid on ethyl β-amino-α-methyl-α-phenylpropionate followed by hydrolysis of the hydroxy ester, but later found[8] that their hydroxy acid was actually the isomeric rearranged product, α-benzyllactic acid, m.p. 98°. The α-methyltropic acid obtained in the present work melted at 86–87°.

EXPERIMENTAL

To a stirred solution of isopropylmagnesium bromide in ether (prepared from 87 g. of isopropyl bromide and 16 g. of magnesium) was added, with cooling, a solution of α-phenylpropionic acid (35 g., 0.23 mole) in 500 ml. of dry toluene. The mixture was then stirred and refluxed overnight. After removal of the ether by distillation, gaseous formaldehyde (generated from 23 g. of trioxane) was introduced into the stirred refluxing mixture over a 4-hr. period by means of a stream of dry nitrogen. The mixture was then stirred overnight at room temperature, cooled in an ice bath and treated with excess aqueous ammonium chloride followed by dilute sulfuric acid. The layers were separated and the toluene layer was extracted with excess 10% sodium carbonate solution. Acidification of the carbonate extract gave an oil which was taken up in ether and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation followed by vacuum (0.5 mm.) distillation of the residue gave three fractions, b.p. 90–135° (7.9 g., n_D^{25} 1.5268), b.p. 135–150° (4.5 g., n_D^{25} 1.5510), and b.p. 150–215° (5.8 g., n_D^{25} 1.5569). The first fraction was largely unreacted α-phenylpropionic acid. The other two fractions were treated separately with saturated sodium bicarbonate solution. Insoluble neutral material (a larger amount from the third fraction) crystallized from the second and third fractions and was filtered. Recrystallization from a benzene-cyclohexane mixture gave colorless *sym.* dimethyldiphenylsuccinic anhydride, m.p. 157–159° (lit.,[6] m.p. 159–160°).

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75; O, 17.12. Found: C, 77.08; H, 5.98; O, 16.97.

The infrared spectrum of this product indicated the presence of a phenyl, a C-methyl, a five-membered anhydride ring, and the absence of hydroxyl.

The filtered bicarbonate extract of the middle fraction was acidified with dilute hydrochloric acid. The precipitated oil was taken up in ether and dried over anhydrous magnesium sulfate. Filtration, removal of the ether by distillation and trituration of the residue with pentane gave a small amount of a solid acid. Recrystallization from an ethylene dichloride–pentane mixture gave α-methyltropic acid, m.p. 86–87°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71; O, 26.65. Found: C, 66.37; H, 6.89; O, 26.82.

The infrared spectrum was entirely consistent with the assigned structure.

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

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(5) D. Ivanov and A. Spassov, *Bull. soc. chim. France* [5] 2, 76 (1935), reported the formation of *sym.* diphenylsuccinic acid by oxidation of the Ivanov reagent of phenylacetic acid with either oxygen (8% yield) or bromine (22% yield).

(6) A. McKenzie and A. Ritchie, *Ber.*, 71, 643 (1938).

(7) R. Foster and H. R. Ing, *J. Chem. Soc.*, 938 (1956).

(8) R. Foster and H. R. Ing, *J. Chem. Soc.*, 925 (1957).

Monochloro-*p*-dioxane and Trichloro-*p*-dioxanes

R. K. SUMMERBELL AND HANS E. LUNK

Received September 23, 1957

Among the characterized chlorination products of *p*-dioxane, the dichloro and tetrachloro derivatives predominate.[1] In the chlorination of *p*-dioxane at 90°, the second chlorine atom is introduced more readily than the first as indicated by the failures to isolate a monosubstituted product.[2] However, it appears that the ease of introduction decreases for the third chlorine atom as evidenced by the very high yields of 2,3-dichloro-*p*-dioxane.

(1) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, 1957, Volume 6, p. 11.

(2) Ref. (1), p. 10.

Continued chlorination over extended periods of time or under more severe conditions gives rise to tetrachloro-*p*-dioxanes.[3]

In the chlorination at low temperature in carbon tetrachloride solution the reaction proceeds slowly enough to permit the isolation of intermediate products. If the chlorination of *p*-dioxane is interrupted at a proper time, substantial quantities of monochloro-*p*-dioxane can be isolated by distillation,[4] but the instability of the compound makes a quantitative determination in this way impossible. We have therefore treated the chlorination mixture with an excess of phenylmagnesium bromide. From the amount of monophenyl-*p*-dioxane[5] isolated it was calculated that monochloro-*p*-dioxane had been formed to an extent of at least 34% at the time the chlorination was stopped. We have also determined by infrared spectroscopy that the dichloro-*p*-dioxane fraction in the low temperature chlorination consists of 2,5-dichloro-*p*-dioxane and both *cis*- and *trans*-2,3-dichloro-*p*-dioxane.

The introduction of chlorine at low temperatures into the two different 2,3-dichloro-*p*-dioxanes leads to the formation of two of the four possible 2,3,5-trichloro-*p*-dioxanes. Chlorination of *trans*-2,3-dichloro-*p*-dioxane in carbon tetrachloride solution at −5° produces a trichloro-*p*-dioxane, m.p. 41°, whereas chlorination of *cis*-2,3-dichloro-*p*-dioxane[6] under similar conditions yields a trichloro-*p*-dioxane, m.p. 70°. A third trichloro-*p*-dioxane with the chlorine atoms in positions 2,2,3 was prepared by addition of chlorine to 2-chloro-*p*-dioxene.

EXPERIMENTAL

Monochloro-p-dioxane in the low temperature chlorination of p-dioxane. A solution of 100 ml. (1.14 moles) of *p*-dioxane in 100 ml. of carbon tetrachloride was cooled to −10° and chlorinated until crystals first appeared, about eight hours. After most of the solvent had been evaporated under reduced pressure, the major part of the reaction product (⅔) was subjected to a fractional distillation. There was obtained a fraction of 13.6 g., b.p. 30–50°/35 mm., consisting of mainly monochloro-*p*-dioxane and some dioxane. The remaining part of the reaction product (⅓) was added to a Grignard solution prepared from 24.3 g. (1 mole) of magnesium and 157 g. (1 mole) of bromobenzene. The mixture was poured on 1 kg. of ice and 50 ml. of sulfuric acid, and the ether layer was shaken with sodium bicarbonate solution and dried with calcium chloride. After evaporation of ether, the residue was distilled *in vacuo*, yielding 33 g. of a colorless product b.p. 76–85°/1–1.5 mm. This product was identified by means of its infrared spectrum as a mixture of monophenyl-*p*-dioxane and diphenyl. Infrared analysis on the basis of the absorption peaks at 11.2 microns (monophenyl-*p*-dioxane) and 6.7 microns (diphenyl) showed that the mixture contained 63% monophenyl-*p*-dioxane. Based on starting material, *p*-dioxane, this would mean a 34% yield of monochloro-*p*-dioxane at the point of interruption of the chlorination. The Grignard reaction is assumed to proceed with 100% yield, and the 34% yield must therefore be considered as a minimum figure.

In another experiment the chlorination was continued to give mainly dichloro-*p*-dioxanes. An investigation of the infrared spectrum of the crude reaction product showed that it contained considerable amounts of *cis*-2,3-dichloro-*p*-dioxane.

Preparation of 2,3,5-trichloro-p-dioxane, m.p. 41°. A solution of 100 g. of *trans*-2,3-dichloro-*p*-dioxane in 100 ml. of carbon tetrachloride was chlorinated for 6.5 hr. under irradiation with ultraviolet light, while the temperature was kept between −5° and 0°. The mixture was fractionally distilled *in vacuo*, and the fractions with refractive indices higher than 1.50 were placed in the cold room. After several days, the highest boiling fraction (60–62°/0.5 mm., n_D^{20} 1.5173) had separated 11.4 g. (9.3%) of crystals, which were filtered and dried on clay. M.p. 41° after recrystallization from pentane.

Anal. Calcd. for $C_4H_5O_2Cl_3$: C, 25.09%; H, 2.62%. Found: C, 25.16%; H, 2.51%.

In another run, the distillation gave fractions with higher refractive indices. On standing in the cold room, a mixture of trichloro-*p*-dioxane, m.p. 41°, and *sym.* tetrachloro-*p*-dioxane, m.p. 101°, crystallized. They can be separated by fractional crystallization from carbon tetrachloride.

When the new trichloro-*p*-dioxane was hydrolyzed by refluxing it with distilled water, and *p*-nitrophenylhydrazine hydrochloride was added, there was obtained 1.88 equivalents of the *p*-nitrophenylosazone of glyoxal. This proves the chlorine atoms to be in positions 2,3,5, giving rise on hydrolysis to one mole of glyoxal and 1 mole of glycolaldehyde.

Preparation of 2,3,5-trichloro-p-dioxane, m.p. 70°. A solution of 12 g. (0.077 mole) of *cis*-2,3-dichloro-*p*-dioxane[6] in 75 ml. of carbon tetrachloride was chlorinated for 1 hr. at −10°. Strong irradiation with ultraviolet light had to be used to initiate the reaction. The liquid chlorination product did not solidify on cooling, but upon addition of 20 ml. of pentane and cooling to −20° there was obtained 1 g. (6.9%) of a colorless substance, m.p. 69–70°, after recrystallization from pentane.

Anal. Calcd. for $C_4H_5O_2Cl_3$: C, 25.09%; H, 2.62%. Found: C, 25.13%; H, 2.56%.

Assuming that the two chlorine atoms in the starting material have not changed their positions during the reaction, the compound must be assigned the structure of a 2,3,5-trichloro-*p*-dioxane since the only other possible structure, 2,2,3-trichloro-*p*-dioxane, is associated with a different compound.

Preparation of 2,2,3-trichloro-p-dioxane. To a solution of 40 g. (0.33 mole) of 2-chloro-*p*-dioxene[6] in 50 ml. of carbon tetrachloride was added chlorine at −10°. The yellow color of the solution indicated the completion of the reaction. Distillation *in vacuo* yielded 48 g. (76%) of material, b.p. 60–61°/1 mm. A fraction of it was recrystallized several times from pentane at −50° and melted at 20–21°.

Anal. Calcd. for $C_4H_5O_2Cl_3$: C, 25.09%; H, 2.62%. Found: C, 25.20%; H, 2.61%.

Acknowledgment. We wish to thank the Hercules Powder Company for a fellowship held by H. E. L.

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(3) C. L. Butler and L. H. Cretcher, *J. Am. Chem. Soc.*, 54, 2987 (1932).

(4) Monochloro-*p*-dioxane was isolated from the low temperature chlorination of *p*-dioxane for the first time by W. M. Smedley and G. H. Kalb in this laboratory. Determination of the yield was not attempted.

(5) R. K. Summerbell and L. N. Bauer, *J. Am. Chem. Soc.*, 57, 2364 (1935).

(6) R. K. Summerbell and H. E. Lunk, *J. Am. Chem. Soc.*, 79, 4802 (1957).

Addition of Triphenylsilane, Diphenylsilane, and Phenylsilane to Benzophenone

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Received October 2, 1957

It has been reported that triphenylsilylpotassium[1] and triphenylsilyllithium[2] add to the carbonyl group of benzophenone. Upon hydrolysis, however, the "abnormal" addition product benzohydryloxytriphenylsilane (II) was obtained, in which the silicon atom is bonded to the oxygen. It has been shown recently,[3] that the "normal" addition product (I) might have been formed as an intermediate, since I rearranges in the presence of a catalytic amount of base to form II.

$$(C_6H_5)_3SiLi + (C_6H_5)_2CO \longrightarrow [(C_6H_5)_3SiC(C_6H_5)_2] \longrightarrow (C_6H_5)_3SiOCH(C_6H_5)_2$$

(I: $(C_6H_5)_3SiC(C_6H_5)_2$, OH; II: $(C_6H_5)_3SiOCH(C_6H_5)_2$)

We wish to report some results on the addition of triphenylsilane, diphenylsilane and phenylsilane to benzophenone at high temperatures, in the absence of any added catalyst or an activating agent, as a new approach to similar compounds containing an Si—O—C group. Among the analogous carbon compounds triphenylmethane, diphenylmethane, and toluene, the two latter were reported[4] to add to benzophenone after prolonged radiation in sunlight to form the "normal" addition products 1,1,2,2-tetraphenylethanol and 1,1,2-triphenylethanol. In the reaction of silicon hydrides with benzophenone, however, only "abnormal" addition products were obtained, and there is no evidence for the formation of any Si—C—OH type by-products. However, a rearrangement of the carbinol by catalytic influences is not excluded.

When an equimolecular mixture of triphenylsilane and benzophenone was heated for 3 hr. at 250–270°, II was obtained in a 62% yield. Diphenylsilane on heating for 2 hr. at 220–230° with benzophenone gave benzohydryloxydiphenylsilane (III) in a 68.5% yield.

$(C_6H_5)_2SiHOCH(C_6H_5)_2$
III

On heating phenylsilane with benzophenone (1:1 ratio) in a sealed tube for 5 hr. at 200°, starting material was recovered. However, when the same reaction was carried out at 250°, distillation of the reaction mixture gave benzohydryloxyphenylsilane (IV) in a 20% yield and *bis*(benzohydryloxy)phenylsilane (V) in a 64.5% yield.

$$C_6H_5SiH_3 + (C_6H_5)_2CO \longrightarrow C_6H_5SiH_2OCH(C_6H_5)_2 + C_6H_5SiH[OCH(C_6H_5)_2]_2$$

(IV: $C_6H_5SiH_2OCH(C_6H_5)_2$; V: $C_6H_5SiH[OCH(C_6H_5)_2]_2$)

In other reactions, attempts to isolate the addition products of two molecules of benzophenone to one of diphenylsilane or three molecules of benzophenone to one of phenylsilane have not yet been successful. Using higher reaction temperatures or longer reaction periods gave mixtures from which only decomposition products such as benzohydrol, benzohydryl ether, and 1,1,2,2-tetraphenylethane were isolated. Benzalacetophenone did not react with triphenylsilane at 150°. At higher temperatures only decomposition products (stilbene,[5] benzylacetophenone, triphenylsilanol, and hexaphenyldisiloxane) were obtained.

In a publication,[6] which just appeared, the reaction of trichlorosilane and triphenylsilane with aliphatic ketones in the presence of ultraviolet radiation was investigated and similar compounds containing an Si—O—C group were obtained. Under their conditions, however, acetophenone and benzophenone failed to react.

EXPERIMENTAL[7]

Materials. Triphenylsilane was prepared as reported previously.[8] Diphenylsilane and phenylsilane were prepared by reduction of the corresponding chlorosilanes with lithium aluminum hydride by a variation of the method of R. A. Benkeser,[9] using tetrahydrofuran as a solvent instead of ether. Eastman White Label benzophenone was used in all reactions.

Triphenylsilane and benzophenone. Thirteen grams (0.05 mole) of triphenylsilane and 9.1 g. (0.05 mole) of benzophenone were heated in a distillation flask for 3 hr. at 250–270°. After removal of 4.7 g. (21%) of starting material by distillation, boiling over the range 135–175°/3 mm., the residue was dissolved in petroleum ether (b.p. 60–70°) and allowed to stand overnight in the refrigerator. There was obtained 13.7 g. (62%) of benzohydryloxytriphenylsilane (II), m.p. 82.5–84°. Recrystallization of a sample from petroleum ether (b.p. 60–70°) raised the melting point to 83–84°. A mixed melting point with an authentic sample obtained from the reaction of triphenylsilyllithium and benzophenone[2] was not depressed. Also the infrared spectra were identical.

(1) H. Gilman and T. C. Wu, *J. Am. Chem. Soc.*, **75**, 2935 (1953).

(2) H. Gilman and G. D. Lichtenwalter, *J. Am. Chem. Soc.*, **80**, 607 (1958).

(3) A. G. Brook, private communication.

(4) E. Paterno and G. Chieffi, *Gazz. chim. ital.*, **39**, II, 415 (1909); G. Ciamician and P. Silber, *Ber. deut. chem. Ges.*, **43**, 1536 (1910).

(5) Stilbene is one of the reported pyrolysis products of benzalacetophenone; H. Stobbe and K. Bremer, *J. prakt. Chem.*, [2] **123**, 36 (1929).

(6) R. Calas and N. Duffaut, *Compt. rend.*, **245**, 906 (1957).

(7) Melting points and boiling points are uncorrected.

(8) H. Gilman and H. W. Melvin, Jr., *J. Am. Chem. Soc.*, **71**, 4050 (1949). See also H. H. Reynolds, L. A. Bigelow, and C. A. Kraus, *J. Am. Chem. Soc.*, **51**, 3070 (1929).

(9) R. A. Benkeser, H. Landesman, and D. J. Foster, *J. Am. Chem. Soc.*, **74**, 648 (1952).

Diphenylsilane and benzophenone. Nine and two-tenths grams (0.05 mole) of diphenylsilane and 9.1 g. (0.05 mole) of benzophenone were heated in a distillation flask for 2 hr. at 220–230°. Distillation gave 0.3 g. (3%) of crude diphenylsilane, b.p. 113–125°/3 mm., and 1.05 g. (11%) of crude benzophenone, b.p. 130–135°/3 mm. The colorless, solid distillation residue was recrystallized from petroleum ether (b.p. 60–70°) to give 12.5 g. (68.5%) of benzohydryloxydiphenylsilane (III), m.p. 79–81°. Recrystallization of a sample from ethanol raised the melting point to 81.5–82.5°.

Anal. Calcd. for $C_{25}H_{22}OSi$: Si, 7.65. Found: Si, 7.59, 7.59.

Supporting evidence for the structure was obtained by the infrared spectrum, which was almost identical with the spectrum of compound II except for a band at 4.7 μ attributable to the Si—H group.

Additional evidence conforming the structure of this compound was obtained by acid hydrolysis, which yielded an oil, from which some benzohydryl ether, m.p. 108–109° was isolated. This benzohydryl ether was shown to be identical with an authentic sample by mixed melting point and infrared spectra.

Phenylsilane and benzophenone. Five and four-tenths grams (0.05 mole) of phenylsilane and 9.1 g. (0.05 mole) of benzophenone were placed under nitrogen in a Schlenk tube. The sealed tube was immersed in an oil bath, which was heated slowly up to 250° and maintained at this temperature for 4 hr.[10] The run was worked up by distillation. There were recovered 0.35 g. (6.5%) of phenylsilane, b.p. 115–120°/750 mm., and 0.55 g. (6%) of crude benzophenone, boiling over the range 130–145°/3 mm. In addition, 2.9 g. (20%) of benzohydryloxyphenylsilane (IV), b.p. 145–148°/0.07 mm., n_D^{20} 1.5863, d_{20}^{20} 1.076, and 7.6 g. (64.6%) of bis(benzohydryloxy)phenylsilane (V), b.p. 238–243°/0.07 mm., n_D^{20} 1.6032, were obtained. After standing for 5 days in the refrigerator, V crystallized, melting over the range 53–60°. Recrystallization from methanol raised the melting point to 63–63.5°.

Anal. Calcd. for $C_{19}H_{18}OSi$ (IV): Si, 9.66; MR, 90.44. Found: Si, 9.49, 9.56; MR, 90.62. Calcd. for $C_{32}H_{28}O_2Si$ (V): Si, 5.94. Found: Si, 5.98, 6.07.

Supporting evidence for the structure of both compounds IV and V was obtained by the infrared spectra, which were almost identical with that of compound III except some difference in the absorption intensity at 4.6–4.7 μ where the Si—H band is located.

Triphenylsilane and benzalacetophenone. Thirteen grams (0.05 mole) of triphenylsilane and 10.4 g. (0.05 mole) of benzalacetophenone were heated in a distillation flask for 16 hr. at 150°. Distillation under reduced pressure thereafter gave back 85% of the starting materials. No crystalline material was isolated from the dark brown distillation residue.

In a second run 13 g. (0.05 mole) of triphenylsilane and 10.4 g. (0.05 mole) of benzalacetophenone were heated for 2 hr. at 250°. The dark brown reaction mixture was worked up by distillation. Fraction 1, 1.7 g., boiling at 145–160°/3 mm., gave after crystallization from petroleum ether (b.p. 60–70°) 0.70 g. (15.5%) of stilbene, m.p. 120–122°. Fraction 2, 3.1 g., boiling at 175–200°/3 mm., gave after crystallization from petroleum ether (b.p. 60–70°) 0.80 g. (5.8%) of triphenylsilanol. The dark brown distillation residue was dissolved in petroleum ether and chromatographed on alumina. Besides yellow oils, which could not be crystallized or further purified, there were obtained 0.60 g. (5.5%) of benzylacetophenone, m.p. 71–72°, and 1.25 g. (9.4%) of hexaphenyldisiloxane, m.p. 223–226°.

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(10) As a precautionary measure, this sealed tube reaction was carried out behind appropriate shields.

Preparation of 3,4-Dichlorotetrahydrothiophene-1,1-dioxide-Cl[36]

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Received October 3, 1957

After the discovery of the nematocidal activity of 3,4-dichlorotetrahydrothiophene-1,1-dioxide,[1] it became necessary to prepare this compound in a radioactive form for tracer studies. The incorporation of carbon-14, sulfur-35, and chlorine-36 in the compound was considered. Chlorine-36 was selected because it involved the minimum handling of radioactive material and would provide desired information on the fate of the chlorine in the molecule.

Although the steps in the synthesis are not new, modification was necessary for the use of radioactive chlorine. The need for preparing the compound with an adequate specific activity made it necessary to avoid an excessive dilution of the chlorine-36 with stable chlorine, and to perform the reaction at elevated temperatures to ensure the maximum yield of product. (The reaction of chlorine with 2,5-dihydrothiophene-1,1-dioxide does not proceed readily at room temperatures.) The availability of chlorine-36 labeled hydrochloric acid[2] fixed the starting point, and the known chloride-chlorine exchange reaction[3] was selected to provide the labeled chlorine gas. The reaction between equivalent quantities of the labeled chlorine and 2,5-dihydrothiophene-1,1-dioxide at 60–70°C for four hours gave an 80% yield (crude) of the 3,4-dichlorotetrahydrothiophene-1,1-dioxide -Cl[36], consisting predominantly of the *trans* isomer.

EXPERIMENTAL

The radiochlorination method of Craig, Tryon, and Brown[4] was used with some modifications. A gas train was arranged in the following sequence: a cylinder of chlorine gas, a concentrated sulfuric acid bubbler, a bleed-off valve, a fritted

(1) Diamond Alkali Company, trade name, "PRD."
(2) Oak Ridge National Laboratory, Oak Ridge, Tenn.
(3) R. S. Halford, *J. Am. Chem. Soc.*, **62**, 3233 (1940).
(4) J. T. Craig, P. F. Tryon, and W. G. Brown, *Anal. Chem.*, **25**, 1661 (1953).

glass tube immersed in 3 ml. of radioactive hydrochloric acid solution (containing 10 microcuries of chlorine-36), a concentrated sulfuric acid bubbler, a fritted glass tube immersed in 6 ml. of chloroform in a heavy walled glass tube containing 1.6 g. (0.014*M*) of 2,5-dihydrothiophene-1,1-dioxide (m.p. 64–66°) chilled to −58 ± 3°C, and a calcium chloride drying tube.

Chlorine gas from the cylinder was slowly bubbled through the gas train. An immediate exchange occurred between the chlorine gas and the radioactive hydrochloric acid solution.[3,5] One gram (0.014*M*) of radioactive chlorine gas was collected and the glass tube was then sealed.

The sealed tube was heated to 60–70° for about 4 hr. The tube was chilled, opened, and the contents poured into an evaporating dish. After evaporating to dryness, the yield of crude 3,4-dichlorotetrahydrothiophene-1,1-dioxide was 2.4 g., or about 80%.

The dry crystals were dissolved in 20 ml. of hot water and filtered hot. The filtrate was then chilled in ice water for 3 hr. and the crystals filtered on a Büchner funnel. The recrystallization was repeated; the final purified material weighed 1.6 g., representing 65% of the theoretical yield.

Infrared analysis[6] showed that the final product contained 58% of the *trans* 3,4-dichlorotetrahydrothiophene-1,1-dioxide, 37% of the *cis* isomer, and 5% of 3-chloro-2,3-dihydrothiophene-1,1-dioxide. These values were obtained by comparing the infrared curves of the product with standards made from solutions of the pure *cis* and *trans* isomers in acetonitrile and a solution of pure 3-chloro-2,3-dihydrothiophene-1,1-dioxide in nitromethane. The *trans* isomer shows an absorption peak at 8.25 μ, the *cis* isomer at 8.33 μ, and 3-chloro-2,3-dihydrothiophene-1,1-dioxide at 13.03 μ.

The purified product was dissolved in acetone and aliquots were pipetted into stainless steel cup planchets. The acetone was evaporated and the radioactivity of the product was determined.

The measured activity in a windowless counter was 6.4 counts per minute per microgram.

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(5) F. A. Long and A. R. Olson, *J. Am. Chem. Soc.*, 58, 2214 (1936).

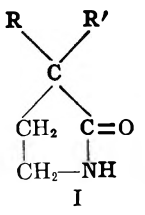
(6) I. E. Smiley and J. J. Mannion, unpublished results.

Some 3,3-Disubstituted-2-Pyrrolidinones

FREDERICK J. MARSHALL

Received October 11, 1957

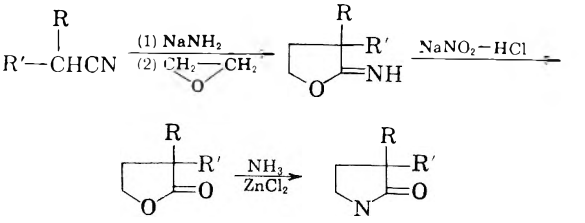
Certain barbituric acid derivatives have long been standard as hypnotics and for use as anticonvulsants. They offer a natural starting point for studies seeking other compounds possessing similar activities. 3,3-Disubstituted-2-pyrrolidinones (I)



I

maintain part of the configuration of the barbiturates and seemed to offer a promising field for investigation.

Because of its relationship to phenobarbital (5-ethyl-5-phenylbarbituric acid), 3-ethyl-3-phenyl-2-pyrrolidinone was the first compound prepared. The synthetic scheme for this and related pyrrolidinones was as follows:



R = aryl, R′ = alkyl

The method of preparation of the lactones was a modification of the procedure used by Anker and Cook[1] for some related compounds.

Variations of the aryl-alkyl derivatives include 3-*n*-butyl-3-phenyl-, 3-ethyl-3-*p*-chlorophenyl-, and 3,3-diphenyl-2-pyrrolidinone. An *N*-methyl derivative was prepared by alkylation of 3-ethyl-3-phenyl-2-pyrrolidinone employing sodium hydride.

Attempts at preparation of dialkyl derivatives by the same methods failed when the aliphatic nitriles could not be alkylated in the presence of sodamide. No further investigation of other methods was made. Related compounds of this type, with *N*-alkyl substitution, have been prepared by Clarke, Mooradian, Lucas, and Slauson[2] using a different approach.

When tested orally in rats the best compound was 3-ethyl-3-phenyl-2-pyrrolidinone. The average protective dose against both electro- and metrazol shock was shown to be about 60 mg./kg. This was considerably below the average hypnotic dose of about 188 mg./kg. A limited clinical trial has shown that the anticonvulsant activity carries over to human use.

EXPERIMENTAL[3]

α-Ethyl-α-phenyl-γ-butyrolactone. To the sodamide prepared from 4.2 g. (0.187 g.-atom) of sodium in 200 ml. of liquid ammonia was added, at a dropwise rate, 27.38 g. (0.187 mole) of α-phenylbutyronitrile.[4] Stirring was continued for one hour and then there was added 8.25 g. (0.187 mole) of ethylene oxide in 50 ml. of dry ether. After stirring for 44 hr., 15 g. of ammonium chloride was added and then, cautiously, 5 ml. of water. The solids were separated by filtration, were washed with ether, and the ether was re-

(1) R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 806 (1948).

(2) R. L. Clarke, A. Mooradian, P. Lucas, and T. J. Slauson, *J. Am. Chem. Soc.*, 71, 2821 (1949).

(3) The Skelly B referred to throughout the Experimental is petroleum ether (b.p. 60–71°).

(4) F. Bodroux and F. Taboury, *Bull. soc. chim. France*, [4] 7, 666 (1910).

moved by distillation. To the residual oil was added 200 ml. of 1*N* hydrochloric acid and the stirred mixture was cooled to 0° before dropwise addition of 12 g. (0.17 mole) of sodium nitrite dissolved in a small amount of water. The mixture was stirred for one hour and then, after removal of the ice salt bath, was allowed to stand overnight. The product was isolated by ether extraction, drying over magnesium sulfate, and removal of the ether by distillation. Fractionation gave 17.5 g. (49%) boiling at 123–125° (0.4 mm.), n_D^{25} 1.5254.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.75; H, 7.42. Found: C, 75.72; H, 7.49.

3-Ethyl-3-phenyl-2-pyrrolidinone.[5] A mixture of 100 g. (0.53 mole) of α-ethyl-α-phenyl-γ-butyrolactone and 2 g. of anhydrous zinc chloride in 200 ml. of liquid ammonia was heated in a bomb at 225° for 21 hr. After cooling and opening the bomb the ammonia was allowed to evaporate and the residue was removed by dissolving it in absolute ethanol. Most of the ethanol was removed under reduced pressure and the addition of Skelly B and chilling produced a crystalline mass. Subsequent to filtration, the solids were treated twice with boiling Skelly B. This separated the product, which crystallized from the solution, from an insoluble oil. The product from two runs was combined and recrystallized twice from Skelly B to give 157 g. (79%) of product melting at 88–90°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.23; H, 7.99. Found: C, 76.11; H, 7.76.

α-(p-Chlorophenyl)-α-ethyl-γ-butyrolactone. The procedure previously described was employed to convert 33.6 g. (0.187 mole) of α-(*p*-chlorophenyl)butyronitrile[6] to the lactone in a yield of 12 g. (29%) boiling at 136–145° (0.5 mm.), n_D^{25} 1.5402. In a subsequent run the yield was 41%.

Anal. Calcd. for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83. Found: C, 64.22; H, 5.78.

3-(p-Chlorophenyl)-3-ethyl-2-pyrrolidinone. Twelve grams (0.053 mole) of the lactone was converted to the pyrrolidinone which, after one recrystallization from Skelly B, weighed 6.5 g. and melted at 67–70°. Two additional recrystallizations gave 3.7 g. (31%) melting at 69–70°.

Anal. Calcd. for $C_{12}H_{14}ClNO$: C, 64.49; H, 6.32. Found: C, 64.73; H, 6.18.

3-Ethyl-1-methyl-3-phenyl-2-pyrrolidinone. To 0.7 g. (0.029 mole) of sodium hydride in 10 ml. of dimethylformamide (purified by azeotropic distillation from benzene to a boiling point of 150–151°) was added, dropwise with the temperature at 15–20°, a solution of 5.5 g. (0.029 mole) of 3-ethyl-3-phenyl-2-pyrrolidinone in 15 ml. of purified dimethylformamide and 10 ml. of dry benzene. The mixture was stirred for 35 min. and there was then added 5 g. (0.035 mole) of methyl iodide. Sodium iodide began to appear immediately and the solution was neutral after stirring overnight. Five milliliters of water was added and the benzene layer was separated, washed with water and with sodium bisulfite solution, and dried over magnesium sulfate. Distillation gave 2.3 g. (39%) of product boiling at 130–132° (0.75 mm.), n_D^{25} 1.5430.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.84; H, 8.43; N, 6.89. Found: C, 76.84; H, 8.43; N, 6.75.

3-Ethyl-1,3-diphenyl-2-pyrrolidinone. Based on a procedure of Pernot and Willemart,[7] a mixture of 4.2 g. (0.022 mole) of α-ethyl-α-phenyl-γ-butyrolactone, 8.8 g. (0.095 mole) of aniline, and 4.75 g. (0.037 mole) of aniline hydrochloride was heated at 180° for 4 hr. It was poured into 80 ml. of 2*N* hydrochloric acid and the oil which separated was extracted with chloroform. The extracts were washed with water and were dried over magnesium sulfate. Removal of the solvent and two distillations gave 1.8 g. (31%) of product which boiled at 150–160° (0.25 mm.), n_D^{25} 1.5789.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.48; H, 7.23; N, 5.28. Found: C, 80.96; H, 7.75; N, 5.43.

3,3-Diphenyl-2-pyrrolidinone. α,α-Diphenyl-γ-butyrolactone[8] (40 g., 0.167 mole) was treated with ammonia as described. The product was recrystallized twice from 95% ethanol to give 20 g. (52%) melting at 208–210°. An analytical sample melted at 209–211°.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37. Found: C, 80.84; H, 6.45.

α-(n-Butyl)-α-phenyl-γ-butyrolactone. The lactone was prepared from α-phenylhexanonitrile[9] (50 g., 0.29 mole). After completion of the initial reaction ammonium chloride and ether were added. The mixture was filtered and from the ether was obtained 39 g. of oil. The solids, after dissolving in water and extraction with ether, yielded an additional 16 g. of dark oil. The combined oils in 330 ml. of 1*N* hydrochloric acid were treated with 20.7 g. (0.3 mole) of sodium nitrite. Work-up gave 30.5 g. (48%) boiling at 144–147° (1 mm.), n_D^{25} 1.5146.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.21; H, 8.38.

3-(n-Butyl)-3-phenylpyrrolidinone. This pyrrolidinone was prepared from 21.8 g. (0.1 mole) of the lactone. Purification from Skelly B gave 13 g. (60%) of product melting at 87.5–89.5°. An analytical sample melted at 88.5–90.5°.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.38; H, 8.62; N, 6.51.

α-(2-Hydroxyethyl)-α-(p-chlorophenyl)-γ-butyrolactone. The procedure of Anker and Cook[1] for the synthesis of α-(2-hydroxyethyl)-α-phenyl-γ-butyrolactone was employed in the preparation of the corresponding *p*-chlorophenyl derivative from 57.9 g. (0.375 mole) of *p*-chlorophenylacetonitrile. At the iminolactone stage, 25 g. of ether soluble oil and 36 g. of solid, insoluble in both ether and water, were both used in the conversion to the lactone which distilled at 193–203° (1.5 mm.). The product solidified when stirred with Skelly B and a crystallization from a 1:3 mixture of chloroform and benzene gave 29.5 g. (33%) of colorless crystals melting at 85–88°. An analytical sample melted at 89–91°.

Anal. Calcd. for $C_{11}H_{13}ClO_3$: C, 59.85; H, 5.43. Found: C, 59.46; H, 5.30.

α-(2-Bromoethyl)-α-(p-chlorophenyl)-γ-butyrolactone. Twenty grams (0.083 mole) of the 2-hydroxyethyl derivative was converted to the 2-bromo compound by means of 48% hydrobromic acid and concentrated sulfuric acid according to the procedure of Anker and Cook[1] for the corresponding phenyl derivative. The crystals which separated from the ether extracts weighed 17 g. (68%) and melted at 90–93°. Removal of the ether gave 7 g. of usable but less pure material melting at 85–89°. An analytical sample was prepared from the higher melting product by recrystallization from benzene–Skelly B and melted at 92–94°.

Anal. Calcd. for $C_{12}H_{12}BrClO_2$: C, 47.50; H, 3.97. Found: C, 47.73; H, 3.98.

α-(2-Diethylaminoethyl)-α-p-chlorophenyl-γ-butyrolactone. To a warm solution of 17 g. (0.056 mole) of the 2-bromoethyl compound in 100 ml. of dry benzene was added 8 g. (0.112 mole) of diethylamine in 5 ml. of dry benzene. The mixture was stirred and refluxed for 24 hr. and was filtered to remove the diethylamine hydrochloride. The product was isolated from the benzene by extraction with 10% hydrochloric acid, followed by addition, with cooling, of ammonium hydroxide. Following ether extraction the extracts were dried over magnesium sulfate. Distillation gave 11.7 g. (71%) boiling at 169–171°, n_D^{25} 1.5311.

(5) The method of preparation of the pyrrolidinones was based on a procedure of E. Späth and J. Lintner, *Ber.*, **69**, 2727 (1936).

(6) M. A. Spielman, A. O. Geiszler, and W. J. Close, *J. Am. Chem. Soc.*, **70**, 4189 (1948).

(7) A. Pernot and A. Willemart, *Bull. soc. chim., France*, 324 (1953).

(8) J. Attenburrow, J. Elks, B. A. Hems, and K. N. Speyer, *J. Chem. Soc.*, 510 (1949).

(9) L. H. Baldinger and J. A. Nieuwland, *J. Am. Chem. Soc.*, 55, 2851 (1933).

Anal. Calcd. for $C_{16}H_{22}ClNO_2$: Cl, 11.99; N, 4.74. Found: Cl, 12.29; N, 4.94.

3-p-Chlorophenyl-3-(β-diethylaminoethyl)-2-pyrrolidinone. Conversion of 4 g. (0.016 mole) of the lactone gave 2.2 g. (48%) of the pyrrolidinone which boiled at 175–180° (0.2 mm.).

Anal. Calcd. for $C_{16}H_{23}ClN_2O$: C, 65.23; H, 7.87; N, 9.50. Found: C, 64.95; H, 7.67; N, 9.11.

Acknowledgment. The author is grateful to Dr. H. L. Breunig for supplying some of the starting materials and to J. J. Traverso and W. B. Scanlon for carrying out the pressure reactions leading to the pyrrolidinones. Thanks also are due to W. L. Brown, H. L. Hunter, G. M. Maciak, and Miss Gloria Beckmann for the microanalyses.

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Derivatives of Ferrocene. V. The Preparation of Some *N*-Substituted Ferrocenecarboxamides[1]

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Many years ago Leuckart reported that the reaction of benzene with phenyl isocyanate in the presence of aluminum chloride produced good yields of benzanilide.[2] Leuckart extended the reaction to other benzene derivatives as well as to thiophene.[2,3] Since the original references, however, this convenient preparation of anilides has seldom been reported in the chemical literature.[4]

It was of interest to us to determine if this reaction of phenyl isocyanate with aluminum chloride could be applied to the aromatic-type compound ferrocene, and further, to determine if other alkyl and aryl isocyanates could be reacted in a similar manner. As is indicated in Table I, the reaction of ferrocene with various alkyl and aryl isocyanates in the presence of aluminum chloride appears to be a general method for the preparation of *N*-alkyl- and *N*-arylferrocenecarboxamides. The yields are very satisfactory when compared to other methods of synthesis (see below), especially the yields based on the readily recovered, unreacted ferrocene.

The reaction of ferrocenoyl chloride with aniline produced *N*-phenylferrocenecarboxamide in 19% yield. During the preparation of the acid chloride from carboxyferrocene and phosphorus pentachloride, however, appreciable decomposition occurred. This fact may be responsible for the low yield of the anilide. *N*-Phenylferrocenecarboxamide was also isolated in 9.7% yield from the reaction of lithioferrocene with phenyl isocyanate, followed by chromotography on alumina.

The stability of the *N*-substituted ferrocene carboxamides was determined under both basic and acidic conditions. Of the two possible methods for determining the stability, *i.e.* the determination of the amine produced or the determination of the amount of carboxamide remaining, the latter procedure was employed for convenience. The extensive decomposition of the carboxylic acid in the hydrolytic media precluded its use in a quantitative determination.

As can be seen from Table II, the *N*-aryl and the *N*-octadecyl compounds are quite stable under vigorous hydrolysis conditions, whereas the *N*-ethyl derivative was partially degraded in alkali, and no starting material was recovered from the acid treatment. The stability of these amides may be due in part to their insolubility in the hydrolytic medium; however, it was noted that all of the amides exhibited some solubility in the aqueous ethanol, and the *N*-ethyl derivative was nearly completely soluble at room temperature.

EXPERIMENTAL[5]

Starting materials. The phenyl, 4-bromophenyl, 4-biphenylyl, 1-naphthyl and ethyl isocyanates used were Eastman reagents. The *n*-octadecyl isocyanate was a gift from Mr. Milton Kosmin, Monsanto Chemical Company, Dayton, Ohio, and was distilled before use, b.p 145–147°/0.045 mm. Ferrocene was generously supplied by Dr. R. L. Pruett, Linde Air Products Company, Tonawanda, N. Y. Carboxy- and 1,1′-dicarboxyferrocene were prepared by a modification[6] of the procedure originally reported by Benkeser *et. al.*[7]

Preparation of N-substituted ferrocenecarboxamides from ferrocene, aluminum chloride, and isocyanates. All compounds listed in Table I were prepared by essentially the same procedure, using a slight excess of both aluminum chloride and isocyanate to ferrocene. The preparation of *N*-4-bromophenylferrocenecarboxamide is given as a typical example.

A solution of 21.8 g. (0.11 mole) of 4-bromophenyl isocyanate and 14.7 g. (0.11 mole) of anhyd. aluminum chloride in 400 ml. of methylene chloride (dried over calcium hydride) was added with stirring under a nitrogen atmosphere and over a period of 30 min. to a solution of 18.6 g. (0.10 mole) of ferrocene in 200 ml. of the same solvent. The reaction mixture was stirred at room temperature for 20 hrs., hydrolyzed with 200 ml. of 10% hydrochloric acid and filtered, leaving 10.0 g. of a yellow-brown crystalline solid. The filtrate was separated into phases, the organic phase

(1) Presented in part before the Division of Organic Chemistry at the 131st Meeting of the American Chemical Society, Miami, Fla., April 10, 1957.

(2) R. Leuckart, *Ber.*, 18, 873 (1885).

(3) R. Leuckart and M. Schmidt, *Ber.*, 18, 2338 (1885).

(4) There has just appeared an article in which *N*-phenylferrocenecarboxamide (m.p. 205–207°) was prepared by this procedure, in order to prove that the Beckmann rearrangement product of the *p*-toluenesulfonate of benzoylferrocene oxime was this same anilide: N. Weliky and E. S. Gould, *J. Am. Chem. Soc.*, 79, 2742 (1957).

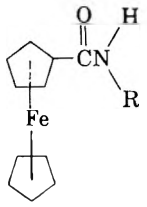
(5) All analyses were performed by the Schwarzkopf Microanalytic Laboratory, Woodside 77, N. Y.

(6) D. W. Mayo, P. D. Shaw, and M. D. Rausch, *Chem. & Ind. (London)*, 1388 (1957).

(7) R. A. Benkeser, D. Goggin, and G. Schroll, *J. Am. Chem. Soc.*, **76**, 4025 (1954).

TABLE I

N-SUBSTITUTED FERROCENECARBOXAMIDES[a]



R	Physical Appearance	M.P.,[c] °C.	Conversion, %	Yield,[h] %	Analyses Calcd. C	H	Fe	N	Found C	H	Fe	N
Phenyl	Orange needles[b]	215–216[f]	57	67	66.91	4.96	18.30	4.59	67.14	5.23	18.31	4.43
									67.03	5.20	18.35	4.59
4-Bromophenyl	Orange crystals[b]	239–240[f]	47	66	53.16	3.67	14.54	3.65	53.12	3.79	14.36	3.49[i]
									53.23	3.83	14.37	3.70
4-Biphenylyl	Orange-red crystals[b]	242.5–243.5[f]	23	68	72.46	5.02	14.65	3.67	73.11	5.02	14.25	3.79
									72.94	5.20	14.18	3.83
1-Naphthyl	Golden-brown powder[c]	>280[g]	39	51	71.01	4.82	15.72	3.94	70.93	4.95	15.63	3.99
									70.82	5.02	15.67	3.71
Ethyl	Yellow-orange needles[b]	164.4–164.8	30	37	60.73	5.88	21.72	5.45	60.89	5.99	22.00	5.69
			54[j]	61[j]					60.72	5.85	22.00	5.47
n-Octadecyl	Light-yellow powder[d]	113.8–117.0	58	63	72.33	9.84	11.60	2.91	72.45	9.96	11.37	3.00
									72.42	9.91	11.35	3.18

[a] Carbonyl absorption occurred in all cases at 1635 cm.$^{-1}$ except for the 1-naphthyl (1630) and *n*-octadecyl (1625). [b] From 95% ethanol. [c] From methyl isobutyl ketone. [d] From ligroin, b.p. 66–75°. [e] All melting points are corrected. [f] Melts with decomposition. [g] Slowly chars on heating over 280°. [h] Yield based on recovered ferrocene. [i] Br, calcd. 20.81; found, 20.69, 20.89. [j] Using a 2.5 molar excess of both ethyl isocyanate and aluminum chloride.

TABLE II

STABILITY OF *N*-SUBSTITUTED FERROCENECARBOXAMIDES

Compound	Acidic Hydrolysis[a] Amide Recovered, %	Basic Hydrolysis[b] Amide Recovered, %
N-Phenylferrocenecarboxamide	64	93
N-4-Bromophenylferrocenecarboxamide	91	91
N-4-Biphenylylferrocenecarboxamide	98	100
N-1-Naphthylferrocenecarboxamide	88	96
N-Ethylferrocenecarboxamide	0	81
N-*n*-Octadecylferrocenecarboxamide	98	99

[a] In 30 ml. of 6*N* aqueous-ethanolic hydrochloric acid (2:1). [b] In 30 ml. of 39% aqueous-ethanolic potassium hydroxide (2:1).

was washed several times with water, and the solvent was evaporated. The resulting residue was combined with the filtered material, and this mixture was extracted four times with 10-ml. portions of hot ligroin, b.p. 66–75°, to remove the unreacted ferrocene[8]; after recrystallization, 3.40 g. of ferrocene was recovered. The crude product remaining after ligroin extraction was recrystallized once from acetone and once from 95% ethanol to produce 14.6 g. of *N*-4-bromophenylferrocenecarboxamide, described in Table I. From the blue acidic phase and washings, after reduction with zinc dust, was obtained an additional 1.85 g. of ferrocene, for a total ferrocene recovery of 5.25 g.

(8) In the preparation of *N*-ethyl- and *N*-*n*-octadecylferrocenecarboxamide this step was omitted, due to the solubility of these products in hot ligroin.

During one preparation of *N*-phenylferrocenecarboxamide, the reaction mixture was stirred at reflux overnight instead of at room temperature. The yield of product did not appear to increase, and the product obtained was less pure than that obtained from the room temperature reaction.

Several reactions of ferrocene with a 2.5 molar excess of both phenyl isocyanate and aluminum chloride failed to produce the expected *N*,*N*′-diphenylferrocenedicarboxamide. Similar experiments using ethyl isocyanate were also not successful. It should be pointed out that Leuckart was likewise not successful in introducing more than one carboxanilide group into biphenyl.[2]

Preparation of N-phenylferrocenecarboxamide from carboxyferrocene and aniline. Ferrocene monocarboxylic acid (1.5 g.) was suspended in 10 ml. of benzene followed by the addition of 1.5 g. of phosphorus pentachloride. An immediate exothermic reaction took place with the evolution of gas and within a few minutes the solid mixture had completely dissolved. The clear dark red solution was shaken for 3 hr. and then the solvent removed under reduced pressure. The black tarry residue was treated with a solution of 2 g. of aniline dissolved in 10 ml. of benzene. The mixture was warmed on the steam bath for 3 min. and then diluted with 300 ml. of benzene, followed by 30 ml. of water. The phases were separated and the organic layer washed, first with dilute hydrochloric acid (15 ml.), then with dilute sodium hydroxide (15 ml.), and finally with distilled water (20 ml.). The benzene solution was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure yielding a dark amorphous solid. One crystallization from benzene gave *N*-phenylferrocenecarboxamide (370 mg., 19% yield) as orange needles, m.p. 212–213°.

Reaction of lithio- and dilithioferrocene with phenyl isocyanate. A solution of 8.18 g. (0.044 mole) of ferrocene in 250 ml. of freshly distilled tetrahydrofuran was added, with stirring and under a nitrogen atmosphere, to 330 ml. of 1.06 molar *n*-butyllithium in ethyl ether at −40°. The reaction mixture was slowly warmed to room temperature (about 2.5 hr.) and stirred at room temperature for an

additional 1.5 hr. The resulting solution of mono- and dilithioferrocene was transferred to an addition funnel and rapidly added (15 min.) to a solution of 47.8 g. (0.40 mole) of phenyl isocyanate in 200 ml. of ethyl ether. Vigorous refluxing occurred during the addition. The orange reaction mixture was stirred at room temperature for 20 hr. and then hydrolyzed with 250 ml. of 10% hydrochloric acid. The phases were separated, the aqueous phase was extracted with ether, and the combined ether portion was dried over anhyd. sodium sulfate. After the solvent was evaporated, the residue was extracted five times with 100-ml. portions of hot ligroin, b.p. 66–75°. The yellow powder which remained weighed 30.0 g.

One-half (15.0 g.) of the above mixture was washed with 50 ml. of chloroform and filtered from 1.8 g. of an insoluble white solid, identified as *sym*-diphenylurea, m.p. 238–239°. The chloroform solution was placed on a 4 × 75 cm. column packed with activated alumina, and the mixture chromatographed using benzene and benzene-chloroform mixtures. Two bands developed, a broad yellow band followed by a bright orange band.

From the first band, after recrystallization of the product from 95% ethanol, 0.65 g. of *N*-phenylferrocenecarboxamide, m.p. 214–215°, was obtained. On this basis, the yield of *N*-phenylferrocenecarboxamide was 9.7%. Mixed melting points with samples of this anilide obtained from the other procedures were undepressed, and the infrared spectra (cesium bromide pellets) of all three anilides were identical.

From the second band was obtained a very small amount of material, which after recrystallization from chloroform produced about 0.03 g. of an orange crystalline solid. This material has not as yet been characterized.

Attempted alkaline hydrolysis of N-substituted ferrocenecarboxamides. Each of the *N*-substituted ferrocenecarboxamides (1.00 g.) listed in Table I was suspended in 30 ml. of a 2:1, water:95% ethanol solution containing 11.7 g. of potassium hydroxide. The mixtures were refluxed for 24 hr., cooled to room temperature and filtered to remove unreacted starting material. The residues were washed with water and the washings combined with the filtrates. These solutions were cooled in an ice bath and acidified with concentrated hydrochloric acid to give only a trace of a red-brown precipitate. The unreacted starting material was dried and weighed.

Attempted acid hydrolysis of N-substituted ferrocenecarboxamides. Each of the *N*-substituted ferrocenecarboxamides (1.00 g.) listed in Table I was suspended in 30 ml. of a 2:1, water:95% ethanol solution, 6*N* in hydrochloric acid and the mixtures refluxed for 16 hr. They were then cooled to room temperature and filtered. The filtrates were discarded, and the residues were suspended in 20 ml. of a 5% aqueous solution of sodium carbonate. The mixtures were allowed to stand at room temperature with occasional stirring for 3 hr. and then filtered. The colorless filtrates were discarded, and the residues were dried and weighed.

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Communications TO THE EDITOR

1-Hydroxylation of 9α-Fluorohydrocortisone

Sir:

Two reports of 1-hydroxylation of steroids induced by microorganisms have appeared recently. The first[1] relates to the production of 1α-hydroxy-4-androstene-3,17-dione and 1α-hydroxydehydroepiandrosterone with species of *Penicillium* and the second[2] to the 1ξ-hydroxylation of 4-pregnene-17α,21-diol-3,20-dione (Reichstein's Substance S) by *Rhizoctonia ferrugena*. In the latter communication reference was made to unidentified products arising from similar incubations with cortisone and hydrocortisone as substrates. We wish now to report on the formation of 1ξ-hydroxy-9α-fluorohydrocortisone upon the incubation of 9α-fluorohydrocortisone 21-acetate (I) with a species of *Streptomyces* (Merck collection number MA 320). The substrate I (80.0 g) was incubated for 72 hours with *Streptomyces sp.* in 400 l. of broth which had been pregrown for 48 hours in an Edamin-cerelose-cornsteep medium. The culture filtrate was extracted with ethyl acetate and the extract concentrated *in vacuo* at 45° to a viscous oil. The residue was triturated with petroleum ether (30–60°) to remove excess oils, dissolved in benzene:ethyl acetate (9:1) and charged to a column of Super-Cel saturated with water:methanol (1:1). Development of the column with benzene:ethyl acetate (9:1) brought the steroidal substrate off in the first fractions, the 1ξ-hydroxylated product in the middle fractions and 20-dihydro-9α-fluorohydrocortisone in the final fractions. Subsequent development with benzene:ethyl acetate (8:2) eluted a more polar product, 6β-hydroxy-9α-fluorohydrocortisone.

Combination of the middle fractions yielded 5.9 g. of crude 1ξ-hydroxy-9α-fluorohydrocortisone (II). Recrystallization first from acetone and then from methanol yielded 1.9 g. of white crystalline material in the first crop, m.p. 247–252°, λ_{max}^{MeOH} 237 mμ, $\epsilon^{\%}$ 425, λ_{max}^{Nujol} 2.9 μ (OH), 5.89 μ (20 carbonyl), 6.02 μ (α,β-unsaturated ketone). Calcd. for $C_{21}H_{29}O_6F$: C, 63.56; H, 7.31. Found: C, 63.94; H, 7.60. Homogeneity was also indicated by paper strip chromatography.

The isolated alcohol was treated with acetic anhydride in pyridine at room temperature for 16 hours to yield a diacetate, III, m.p. 218–221°C., λ_{max}^{MeOH} 238 mμ, $\epsilon^{\%}$ 343. Calcd. for $C_{25}H_{33}O_8F$: C, 62.50; H, 6.88. Found: C, 62.63; H, 7.14.

The identity of III was established by converting the diacetate to 1-dehydro-9α-fluorohydrocortisone 21-acetate IV. This was effected by refluxing a portion of the diacetate in glacial acetic acid for 1 hour. Paper strip chromatographic examination of the reaction mixture showed it to contain principally IV contaminated with traces of starting material. The solution was evaporated to dryness *in vacuo*, the residue chromatographed over acid-washed alumina and the eluted III, freed of starting material, was crystallized twice from acetone-Skellysolve B, m.p. 225–236°, λ_{max}^{MeOH} 238 mμ, $\epsilon^{\%}$ 358. Calcd. for $C_{23}H_{29}O_6F$: C, 65.64; H, 6.90. Found: C, 65.92; H, 6.97. Mixed melting point with an authentic sample gave no depression and the infrared spectra were identical. The original alcohol can be similarly converted to 1-dehydro-9α-fluorohydrocortisone. From this evidence it is clear that the fermentation product is 1ξ-hydroxy-9α-fluorohydrocortisone. The configuration of the 1-hydroxy group has not yet been established.

Other species of *Streptomyces* have been found to 1-hydroxylate 9α-fluorohydrocortisone. It is our impression that this is an ubiquitous transformation with *Streptomyce* cultures.

Surprisingly enough we found that I is virtually inactive in the liver glycogen and systemic granuloma assays. In the sodium metabolism test I appears to be less strongly active, in retaining Na^+, than the parent 1-desoxy compound.

Other substrates (hydrocortisone, cortisone, Reichstein's Substance S and progesterone) were incubated with the organisms and although transformation products were formed there was no evidence of 1-hydroxylation with these steroids.

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(1) R. M. Dodson, A. H. Goldkamp, and R. D. Muir, *J. Am. Chem. Soc.*, 79, 3921 (1957).

(2) G. Greenspan, C. P. Schaffner, W. Charney, H. L. Herzog, and E. B. Hershberg, *J. Am. Chem. Soc.*, 79, 3922 (1957).