Notes

A department for short papers of immediate interest.

Reduction of Conjugated 1,4-Diketones with Tin Amalgam

JOHN P. SCHAEFER

Received March 28, 1960

A kinetic study of the oxidation of 1,4-diketones in which we are currently engaged has necessitated the synthesis of a series of these compounds. Since the unsaturated 1,4-diketones are readily available, reduction of the olefinic linkage offers a convenient route to these substances.

The usual reducing agent for effecting this conversion is zinc in acetic acid; however, this reduction is often accompanied by serious side reactions which make it useless as a synthetic tool. In studies on the reduction of 1,4-diphenyl-2-butene-1,4-dione (I) Lutz[1,2] has reported the isolation of five different bimolecular reduction products along with the desired saturated diketone. In an effort to develop a reliable system for converting 1,4-enediones to 1,4-diones a more specific reducing agent was sought.

We have found that amalgamated tin and acid will rapidly reduce unsaturated 1,4-diketones to the saturated derivative in high yield without any detectable side reactions in the cases studied. Reduction of I with tin amalgam and hydrochloric acid in ethanol gave 1,4-diphenylbutane-1,4-dione (II) in 90% yield. 1,4-*p*-Chlorophenyl-2-butene-1,4-dione (III) reacted in an analogous manner to give similar results.

Utilizing the same procedure β-norcholest-4-ene-3,6-dione (IV) was quantitatively reduced to β-norcoprostane-3,6-dione[3] and quinone (V) to hydroquinone. Substitution of acetic acid for hydrochloric acid was attempted in the cases I and V and also worked well, although reaction times were considerably longer and the reaction mixtures were usually lightly colored. Typical experimental procedures are illustrated below.

EXPERIMENTAL

Tin amalgam. To a flask containing 15 g. of mercuric chloride and 100 ml. of water was added 100 g. of 30-mesh tin metal. The flask was stoppered and shaken for a few minutes until all of the tin appeared to have a shiny coating of mercury on the surface. The tin amalgam was then washed repeatedly with water until the washings were clear, and stored under distilled water.

Reduction of 1,4-diphenyl-2-butene-1,4-dione. To 5.0 g. of 1,4-diphenyl-2-butene-1,4-dione and 10 g. of tin amalgam was added 150 ml. of ethanol. The solution was heated to reflux and 20 ml. of concd. hydrochloric acid was added cautiously. After 5 min. the solution was colorless. The solution was filtered and cooled to give 4.5 g. (90%) of crystalline product, m.p. 142–143°.

Reduction of quinone. To 5.7 g. of quinone was added 10 g. of tin amalgam and 50 ml. of glacial acetic acid. The mixture was heated on a steam bath and after 3 min. lustrous green crystals separated (quinhydrone). The crystals soon dissolved to give a light yellow solution. After 0.5 hr. the solution was filtered and the solvent removed *in vacuo*. Recrystallization of the hydroquinone from benzene-acetone gave 5.0 g. (88%) of product, m.p. 169–170°.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
BERKELEY 4, CALIF.

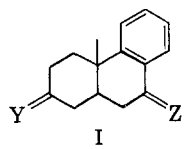
(1) R. E. Lutz, *J. Am. Chem. Soc.*, **51**, 3008 (1929).
(2) R. E. Lutz and F. S. Palmer, *J. Am. Chem. Soc.*, **57**, 1947 (1935).
(3) W. G. Dauben and W. Templeton, private communication.

The Stereochemistry of Some Hydrophenanthrones[1]

ERNEST WENKERT AND JAMES W. CHAMBERLIN

Received March 7, 1960

The recent synthesis of hydrophenanthrones Ia by three new routes[2] has made available compounds which can serve as the backbone for tricarbocyclic diterpenes. A partial use of Ia for the synthesis of the latter has been illustrated already,[3] while further work in this connection is continuing. Since any rational synthesis of the natural products was dependent, among other things, on the stereochemistry of the two isomers of Ia every effort had to be made to determine their configuration. Thus, a correlation of *cis*- and *trans*-Ia with substances of known constitution was sought, even though a large body of stereochemical evidence had been accumulated already.[2,3]



I

a, Y = O, Z = H_2
b, Y = Z = H_2
c, Y = H_2, Z = O

(1) This work was aided by research grant NSF-G6226. The authors are grateful to the National Science Foundation for this support.
(2) (a) and (b) E. Wenkert and T. E. Stevens, *J. Am. Chem. Soc.*, **78**, 2318, 5627 (1956); (c) E. Wenkert and R. D. Youssefyeh, unpublished data, *cf.* Ph.D. dissertation of R. D. Youssefyeh, Iowa State University, June 1959.
(3) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, 81, 5601 (1959).

A few years ago the stereoisomeric hydrocarbons Ib were converted *via* their ketones Ic to dibasic acids of known configuration.[4] As a consequence the saturated ketones Ia were transformed into their aromatic counterparts Ic by Wolff-Kishner reduction followed by chromic acid oxidation and the 2,4-dinitrophenylhydrazones of the latter compared with authentic samples.[5] These experiments were in full accord with the previous stereochemical assignment[2,3] of the isomers of Ia.

EXPERIMENTAL

Hydrocarbons Ib. A mixture of 350 mg. of *cis*-Ia and 0.7 ml. of hydrazine hydrate in 12 ml. of diethylene glycol was heated at 190° for 1 hr. After cooling to 70°, a solution of 700 mg. of sodium in 10 ml. of diethylene glycol was added and the mixture heated at 215–220° for 6 hr. Thereupon the mixture was cooled, poured into 100 ml. of saturated brine solution, and extracted with benzene. The extract was washed with water, dried, and its solvent removed, leaving 265 mg. of an oil. Chromatography of the latter on 25 g. of alumina and elution with petroleum ether (b.p. 30–60°) gave 204 mg. of colorless oil, which was used directly in the chromic acid oxidation.

A similar operation on 150 mg. of *trans*-Ia yielded 105 mg. of crude product which on chromatography on 9 g. of alumina led to 88 mg. of colorless hydrocarbon. The latter also was used for oxidation without further purification.

Ketones Ic. A solution of 50 mg. of chromic oxide in 0.1 ml. of water and 0.4 ml. of glacial acetic acid was added dropwise with stirring to a solution of 52 mg. of *cis*-Ib in 0.5 ml. of glacial acetic acid. The mixture was allowed to stand at room temperature for 6.5 hr. and then was diluted with 15 ml. of saturated brine solution and extracted with chloroform. The extract was washed three times with 10% sodium hydroxide solution and once with saturated brine solution, dried over anhydrous sodium sulfate, and evaporated. The resulting 30 mg. of residual neutral oil was chromatographed on 5 g. of alumina, yielding 9 mg. of colorless liquid ketone, infrared spectrum (chloroform): C=O 5.88(s)μ, C=C 6.26 (m)μ, by 9:1 petroleum ether–ether elution.

A similar operation on 126 mg. of *trans*-Ib, however for 11 hr. reaction time,[6] led to 105 mg. of neutral oil which on chromatography on 10 g. of alumina and 9:1 petroleum ether–ether elution gave 31 mg. of colorless liquid ketone, infrared spectrum (chloroform): C=O 5.88(s)μ, C=C 6.26(m)μ.

2,4-Dinitrophenylhydrazones. The derivative of *cis*-Ic melted at 182–183°, m.m.p. 179–183° with authentic sample[4] (m.p. 182.5–184°), identical infrared spectrum with that of an authentic sample.

The derivative of *trans*-Ic melted at 208–210.5°, m.m.p. 207°–210° with an authentic specimen[4] (m.p. 209.5–210.5°), identical infrared spectrum with that of an authentic specimen.

Department of Chemistry
Iowa State University
Ames, Iowa

(4) R. A. Barnes and M. T. Beacham, *J. Am. Chem. Soc.*, **77**, 5388 (1955) and preceding papers.

(5) The authors wish to express their gratitude to Professor Barnes for his gift of comparison samples.

(6) The *trans* hydrocarbon is over-oxidized more slowly than its *cis* isomer [*cf.* E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **80**, 211 (1958)].

A Reinvestigation of the Action of Formaldehyde on 1,2- and 1,3-Hydroxyamines in the Pyrrolidine and Piperidine Series

Richard K. Hill and Larry J. Loeffler

Received March 21, 1960

In 1913, Hess reported[1] a remarkable synthesis of the coca alkaloid hygrine (V) by heating the amino alcohol I with formaldehyde in acidic solution. Although direct comparison of his product with the natural base was not made at the time, the empirical formula and the close correspondence of the physical and chemical properties of the base and its derivatives[2] all supported his conclusion that a disproportionation reaction had occurred which resulted in simultaneous methylation of the nitrogen and oxidation of the secondary hydroxyl. Continued investigation showed that the reaction was apparently a general one for 1,2- and 1,3-hydroxyamines, and over a dozen examples were reported.[4,5]

It must be noted that except in two cases (those which gave hygrine and the isomeric ketone VI, both of which were reported to yield oximes) no experimental evidence was offered for the presence of either the *N*-methyl or the carbonyl group in the products. The structures were proposed solely on the empirical formulas of their picrates and the analogy to the initial reaction which had afforded hygrine. The only chemical behavior reported was first, that many of the reaction products gave a positive silver mirror test, and second, that with the exception of the two cases already mentioned, every effort to prepare carbonyl derivatives yielded only the corresponding derivative of formaldehyde plus the original hydroxyamine.

It is not surprising, in the face of this tenuous evidence, that it soon became apparent that some of Hess' products were incorrectly formulated. It was pointed out by both Kohn[6] and Rolfes[7] that the products from the reactions of aldehydes with diacetone alcohol amine were more likely tetrahydro 1,3-oxazines. In two other cases,[8,9]

(1) K. Hess, *Ber.*, **46**, 4104 (1913).

(2) The picrate of the synthetic base was first reported to melt at 174°, although hygrine picrate melts at 149–150°; Hess regarded this discrepancy as due to differences in purity of the two samples. Some years later,[3] he reported that the original sample of the synthetic picrate now melted at 149–150°, and did not depress the melting point of authentic hygrine picrate.

(3) K. Hess and H. Fink, *Ber.*, **53**, 781 (1920).

(4) K. Hess, F. Merck, and C. Uibrig, *Ber.*, **48**, 1886 (1915).

(5) K. Hess and C. Uibrig, *Ber.*, **48**, 1974 (1915).

(6) M. Kohn, *Ber.*, **49**, 250 (1916).

(7) H. Rolfes, *Ber.*, **53**, 2203 (1920).

(8) K. Hess and A. Eichel, *Ber.*, **50**, 1407 (1917).

(9) K. Hess and W. Corleis, *Ber.*, **54**, 3010 (1921).

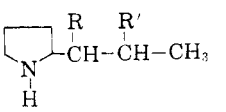
including the closely related piperidine alcohol III, Hess found that the supposed aminoketones were different from genuine samples prepared by other routes, and was forced to assign tetrahydrooxazine and oxazolidine structures to them, too.

While it is surprising that the reaction should take different courses with compounds of such similar structure, there seemed to be no doubt about the constitution of the ketones from I and II, as both reportedly formed oximes of the expected composition. Hess' work is still widely cited in texts as the first synthesis of hygrine. It appeared worthwhile to reinvestigate these reactions to confirm their authenticity and with a view to studying the mechanism.

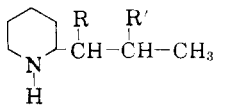
The reaction of the pyrrolidine alcohols I and II with formaldehyde in aqueous acid was carried out in sealed tubes exactly as described by Hess. Basic products were isolated whose empirical formulas and physical properties agreed with those reported. The infrared spectra quickly revealed, however, the complete absence of absorption in the carbonyl region. As the spectra were also devoid of N—H and O—H absorption, the only plausible structures for the products are the tetrahydrooxazine VII and the oxazolidine IX, respectively. A closer examination of the spectra showed the presence of the triplet in the 1080–1200 cm.$^{-1}$ region characteristic of cyclic compounds containing the —N—C—O— grouping.[10] Also consistent with this formulation was the liberation of formaldehyde, identified as its dimedone derivative, on mild hydrolysis with dilute hydrochloric acid. Even when the initial reaction mixture was made alkaline and extracted with ether, no trace of carbonyl absorption could be found in the infrared spectra of the total extracts, and consequently it must be concluded that *N*-methyl aminoketones are not formed in detectable amounts in these reactions.[11] We are unable to account for the reported formation of oximes from these two bases, since in our hands, the reaction of VII with hydroxylamine following Hess' procedure gave no solid product.

We have also carried out the reaction with compounds III and IV, the corresponding alcohols of the piperidine series. The mixture of diastereoisomers of formula III was first reported[4] to yield an *N*-methyl aminoketone, but later[8] the structure was changed to a tetrahydrooxazine and the isolation of a second product containing an additional carbon was claimed. We were able to isolate only the base VIII, with an analysis corresponding to $C_9H_{17}NO$; the tetrahydrooxazine structure is again supported by the infrared spectrum[12] and the hydrolysis to formaldehyde. In this case, the starting amino alcohol was also isolated from the hydrolysis.

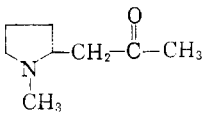
Finally, in the case of *d,l*-conhydrine (IV), the starting material was available as a single isomer of known configuration.[13] Once again, the product from formaldehyde treatment was shown to be the oxazolidine (X) by its infrared spectrum and hydrolysis to formaldehyde.



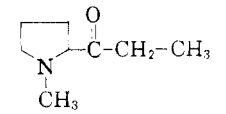
I. R = H, R′ = OH
II. R = OH, R′ = H



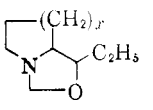
III. R = H, R′ = OH
IV. R = OH, R′ = H



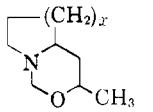
V



VI



IX. $x = 1$
X. $x = 2$



VII. $x = 1$
VIII. $x = 2$

EXPERIMENTAL

Preparation of starting amino alcohols. 1-α-Pyrrolidyl-2-propanol (I), prepared by the method of Hess,[14] distilled at 115–125° (16 mm.), lit. b.p. 115–120° (15 mm.).

1-α-Pyrrolidyl-1-propanol (II). 1-α-Pyrryl-1-propanone was prepared by a modification of Oddo's method[15]; steam distillation of the acidified Grignard reaction mixture gave directly the pure ketone, m.p. 52–53°, lit. m.p. 52.5°, in 12–14% yields. Reduction with sodium and ethanol, according to Hess,[14] followed by vacuum sublimation, gave hygroscopic needles of II, m.p. 45–52°, lit. m.p. 50°. The picrate, after three recrystallizations from ethanol, melted at 125–127°.

Anal. Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.57; H, 5.06; N, 15.64: Found: C, 43.41; H, 5.17; N, 15.78.

1-α-Piperidyl-2-propanol (III) was prepared by hydrogenation of 1-α-pyridyl-2-propanol[16] in 85–90% yields. The mixture of stereoisomers obtained melted at 52–59°; reported[17] melting points are 75° and 70–71° for the two pure isomers, 45–55° for the mixture obtained by hydrogenation.

1-α-Piperidyl-1-propanol (*d,l-conhydrine*) (IV), m.p. 99.5–100°, was synthesized as described previously.[13]

(10) E. D. Bergmann, *Chem. Rev.*, **53**, 309 (1953).

(11) After this work had been completed, the same conclusion was announced by Lukeš and co-workers; R. Lukeš, J. Kloubek, J. Kovář, and K. Bláha, *Coll. Czech. Chem. Comm.*, **24**, 2433 (1959).

(12) The crude basic product showed weak but reproducible absorption at 5.82 and 5.95 μ, but the grouping responsible for this absorption could not be identified. No pure material containing either band could be isolated, a 2,4-dinitrophenylhydrazone could not be formed from the crude product, and the picrate of the crude base showed no absorption in this region.

(13) R. K. Hill, *J. Am. Chem. Soc.*, **80**, 1609 (1958).

(14) K. Hess, *Ber.*, **46**, 3113 (1913).

(15) B. Oddo, *Ber.*, **43**, 1012 (1910).

(16) L. A. Walter, *Org. Syntheses*, Coll. Vol. II, 757.

(17) H. C. Beyerman, J. Eenshuistra, W. Eveleens, and A. Zweistra, *Rec. trav. chim.*, **78**, 43 (1959).

Reaction of I *with formaldehyde.* A solution of 2.0 g. of 1-α-pyrrolidyl-2-propanol in 5 ml. of water was acidified with concd. hydrochloric acid and treated with 6 ml. of 40% formalin solution. The resulting mixture was heated in a sealed pyrex tube at 117° (refluxing 1-butanol) for 4 hr. The dark brown contents of the tubes were cooled, made alkaline with 50% potassium hydroxide solution, and the base extracted with ether and dried over magnesium sulfate. Vacuum distillation gave 1.5 g. of a colorless liquid, b.p. 83–84° (21 mm.), lit.[1] b.p. 89–92° (22 mm.). The picrate melted at 174–175°, lit.[2] m.p. 174°.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.15. Found: C, 45.33; H, 4.93; N, 15.44.

In an attempt to prepare the reported oxime, 1.4 g. of VII, 0.7 g. of hydroxylamine hydrochloride and 0.6 g. of potassium hydroxide were warmed on the steam bath in 20 ml. of water for 2 hr. Working up the mixture in the manner described by Hess[1] gave no solid products.

Hydrolysis of VII. A solution of 0.25 g. of VII in 5 ml. of ethanol, 5 ml. of 1*N* hydrochloric acid, and 5 ml. of a 10% alcoholic solution of dimedone was refluxed for 2 hr., neutralized with potassium hydroxide and concentrated on the steam bath. Chilling gave a crude solid, which was recrystallized from ethanol to yield 50 mg. of the dimedone derivative of formaldehyde, m.p. and mixed m.p. 188–191.5°.

Reaction of II *with formaldehyde.* The base (1.66 g.) isolated by vacuum distillation of the product from reaction of 2.0 g. of II with formaldehyde, as described above, gave a picrate, needles from ethanol, melting at 101–103°, lit.[1] m.p. 103°.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.15. Found: C, 45.35; H, 5.03; N, 15.38.

Hydrolysis of the base in the presence of dimedone, as described above, gave the crystalline derivative of formaldehyde.

Reaction of III *with formaldehyde.* A solution of 10 g. of III in 17.5 ml. of water was acidified with 8.2 ml. of concd. hydrochloric acid, treated with 10.5 ml. of 40% formalin solution, and heated at 117° for 4 hr. The mixture was worked up as described above, affording 9.1 g. of colorless liquid, b.p. 110–113° (14 mm.), 70–72° (6 mm.), lit.[3] b.p. 108–111° (28 mm.).

Anal. Calcd. for $C_9H_{17}NO$: C, 69.70; H, 11.04; N, 9.03. Found: C, 69.31; H, 11.06; N, 9.08.

The picrate, twice recrystallized from ethanol, melted at 140.5–144°, lit. m.p. 162–163°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.87; H, 5.24; N, 14.58. Found: C, 46.89; H, 5.31; N, 14.71.

Hydrolysis of the base in the presence of dimedone again afforded the dimedone derivative of formaldehyde. The starting amino alcohol (III) was also recovered by crystallization and identified by its infrared spectrum.

Reaction of IV *with formaldehyde.* The reaction of 1.70 g. of IV with formaldehyde was carried out as described above, and yielded 1.50 g. of colorless product. The picrate was recrystallized twice from ethanol, and melted at 142–144°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: 46.87: H, 5.24; N, 14.58. Found: C, 47.06; H, 5.11; N, 14.85.

Formaldehyde was isolated as the dimedone derivative when the base was hydrolyzed as described above.

FRICK CHEMICAL LABORATORY
PRINCETON UNIVERSITY
PRINCETON, N. J.

The Dinitration of *m*-Toluic Acid

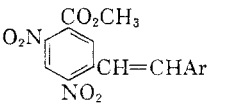
A. H. BLATT

Received February 29, 1960

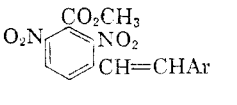
The first report of the dinitration of *m*-toluic acid is that of van Scherpenzeel[1a] who nitrated the acid in one- to two-gram quantities with 100% nitric acid and obtained in an unspecified, low yield a dinitro acid (m.p. 173°) which he formulated as 2,6-dinitro-*m*-toluic acid.[1b] From methyl *m*-toluate by the same procedure he obtained, again in an unspecified, low yield, a methyl ester (m.p. 104°) which he considered to be methyl 2,6-dinitro-*m*-toluate because it could be hydrolyzed with hydrochloric acid to the dinitro-*m*-toluic acid he had already prepared. No direct comparison was made of the two samples of the dinitro acid and no comment was made about the ready hydrolysis of a di-*ortho* substituted benzoic ester.

In the second report of the dinitration of *m*-toluic acid, Hargreaves and McGookin[2] described the use of mixed acid to furnish in 60% yield a dinitro-*m*-toluic acid which they considered to be identical with the acid obtained by van Scherpenzeel. They converted the acid to the acid chloride with thionyl chloride. From the crude acid chloride with methanol they obtained a methyl ester, m.p. 104°, which confirms the identity of their acid and van Scherpenzeel's, and a second unidentified product, m.p. 67°, which casts doubt on the homogeneity of their acid.

Since the nitration of *m*-toluic acid with 100% nitric acid was so unpromising and inconvenient, we used mixed acid and obtained consistent yields of 85% of a crude product which is a mixture containing 2,6-dinitro- and 4,6-dinitro-*m*-toluic acid in approximately equal amounts. The two acids can be separated and structures may be assigned to them from the behavior of the crude product on heating with methanol containing sulfuric acid: 4,6-dinitro-*m*-toluic acid is converted to the methyl ester (m.p. 104°) while 2,6-dinitro-*m*-toluic acid is unaffected. The two reactions, nitration and treatment with methanol and sulfuric acid, show that the earlier workers actually had in hand an impure 4,6-dinitro-*m*-toluic acid rather than the 2,6-dinitro acid as they believed. It also follows from these two experiments that 2,6-dinitro-*m*-toluic acid and its esters have not hitherto been prepared, that the description of these compounds in the literature are erroneous, and that the substituted stilbenes prepared by Hargreaves and McGookin[2] from aromatic aldehydes and the 104° methyl ester have structure I rather than the structure II that was assigned to them.



I



II

(1a) L. van Scherpenzeel, *Rec. trav. chim.*, **20**, 149–182 (1901).

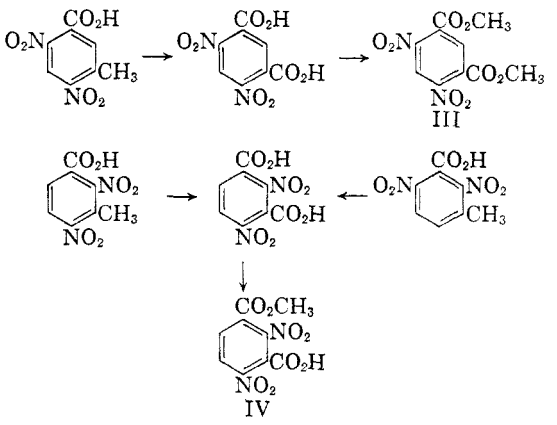
(1b) In *m*-toluic acid and its substitution products the carboxyl group and the methyl group are assigned positions 1 and 3, respectively.

(2) K. R. Hargreaves and A. McGookin, *J. Soc. Chem. Ind. (London)*, **69**, 190 (1950).

We next nitrated methyl *m*-toluate by the same procedure we had used to nitrate the acid. This furnished in quantitative yield a product that is obviously identical with the unidentified esterification product described earlier by Hargreaves and McGookin. We first thought that this product, most samples of which melt fairly sharply in the neighborhood of 65°, might be methyl 2,6-dinitro-*m*-toluate. Actually it is a mixture that contains methyl 2,6-dinitro-*m*-toluate and methyl 4,6-dinitro-*m*-toluate in about a 5 to 4 ratio. On heating with concentrated hydrochloric acid, the crude ester mixture furnishes 4,6-dinitro-*m*-toluic acid and unattacked methyl 2,6-dinitro-*m*-toluate. Nitration of methyl *m*-toluate followed by heating with hydrochloric acid is therefore a route to the 4,6-dinitro acid and the methyl ester of the 2,6-dinitro acid, which complements the nitration and esterification described in the previous paragraph both as a preparative procedure and as a basis for assigning structure.

The structure of 2,6-dinitro-*m*-toluic acid and its methyl ester are adequately established by their resistance to esterification and hydrolysis, respectively. We have considered the isomeric dinitro acid to be the 4,6- rather than the 2,4-dinitro derivative because of the identity in melting point (104°) of the methyl ester prepared by (a) esterification of the acid in question, (b) dinitration of methyl *m*-toluate, and (c) esterification of the acid obtained by the partial oxidation of 4,6-dinitro-1,3-dimethylbenzene.[3] Direct comparison of the methyl ester prepared by routes (a) and (b) has been made, but no direct comparison has been made between these samples and the ester made by route (c). Instead of preparing the ester by route (c) and comparing it with our samples, we chose to confirm its structure by the following method which is independent of the orientation of 4,6-dinitro-1,3-dimethylbenzene.

Oxidation of 4,6-dinitro-*m*-toluic acid would yield 4,6-dinitroisophthalic acid, which should esterify to the neutral dimethyl ester III. Oxidation of 2,4-dinitro-*m*-toluic acid would yield 2,4-dinitroisophthalic acid, which should esterify to the acid monomethyl ester IV. On oxidation, our presumed 4,6-dinitro-*m*-toluic acid furnished a dinitroisophthalic acid which esterified to a dimethyl ester, thus establishing the correctness of the structure of the dinitro-*m*-toluic acid as the 4,6-isomer and confirming the orientation of 4,6-



dinitro-*m*-xylene and 4,6-dinitroisophthalic acid.[4] For completeness we also oxidized 2,6-dinitro-*n*-toluic acid and found, as we expected, that the resulting hitherto unknown 2,4-dinitroisophthalic acid esterifies only to the acid methyl ester IV.

The material in the preceding paragraphs provides new and somewhat different examples of the high *ortho-para* ratio in the nitration products of aromatic compounds containing a *meta*-directing group. The phenomenon and possible explanations for it have been discussed earlier[4a] so that it is necessary here only to mention by way of illustration that the nitration of benzonitrile furnishes, in addition to the principal product *m*-nitrobenzonitrile, the *ortho* and *para* nitrobenzonitriles in a ratio greater than 3:1. On statistical grounds a 2:1 ratio would be expected and steric effects should lower this ratio. *m*-Toluic acid and its methyl ester differ from the monosubstituted benzenes hitherto studied in that the 2-, 4-, and 6-positions would be activated. Statistically one would expect equal amounts of the 2,4-, 4,6-, and 2,6-dinitro derivatives, while steric factors would favor the 4,6-isomer at the expense of both the 2,4- and 2,6-isomers. One finds that all of the dinitration products are substituted in the 6-position, and that the ratio of 2-substitution to 4-substitution is about 1:1 with the acid and about 5:4 with the methyl ester. Since these ratios are based on products isolated (64% of the material was accounted for in the nitration of the acid and 80% in the nitration of the ester) we cannot say that none of the 2,4-dinitration product was formed. It is clear, however, that activation *ortho* to the nitro group is occurring and that it is sufficient to offset the considerable hindrance to substitution in the 2-position. Although our results constitute additional evidence of *ortho* activation, they do not enable us to add to or distinguish between the explanations already advanced.

Two other items should be mentioned. The first is the extraordinary solubility in water of 2,6-dinitro-*m*-toluic acid: 1 g. of the acid will dissolve

(3) R. D. Haworth and P. R. Jeffries, *J. Chem. Soc.*, 2069 (1951).

(4) T. Nozoe, Y. Kitahara, K. Yamane, and K. Yamaki, *Proc. Japan Acad.*, **26**, No. 8, 14–18 (1950) [*Chem. Abstr.*, **45**, 7097 (1951)] reported that nitration of hinokitiol followed by oxidation furnished 4,6-dinitroisophthalic acid, m.p. 240–241°. The acid, which was crystallized from boiling water, gave a dimethyl ester, m.p. 141°. The properties of this acid and its dimethyl ester do not agree with those of 4,6-dinitroisophthalic acid and dimethyl 4,6-dinitroisophthalate. See the Experimental section.

(4a) Pertinent references are to be found in an article by George S. Hammond and Katharine J. Douglas, *J. Am. Chem. Soc.*, **81**, 1184 (1959).

in less than 5 ml. of hot water. Presumably, the crowding and resulting nonplanarity of the four adjacent substituents prevents close packing in the crystals and favors solvation at the carboxyl group. Similar striking solubility relations are observed with the dinitroisophthalic acids. The second is that the dinitro acids and their derivatives described in this paper show the yellow color that is characteristic of dinitro aromatic compounds in acetone solution in the presence of iodide ion.[5]

EXPERIMENTAL

We are indebted to the Hercules Powder Co. for the *m*-toluic acid and methyl *m*-toluate used in these experiments.

Melting points are uncorrected.

Nitration of m-toluic acid. Isolation of 2,6-dinitro-m-toluic acid and methyl 4,6-dinitro-m-toluate. Nitrating acid was prepared from 89 ml. of chilled fuming nitric acid (*d.* 1.5) and an equal volume of chilled fuming sulfuric acid (30% sulfur trioxide) in a 500-ml., three-necked, round-bottomed flask that was fitted with a mechanical stirrer and thermometer and was surrounded by an ice-water bath. The temperature of the nitrating acid was kept between 25 and 30° during its preparation and during the subsequent nitration.

Stirring and cooling were continued while 27.2 g. (0.2 mole) of *m*-toluic acid was added in portions. As soon as the addition was complete—about 50 min. was required—the cooling bath was removed. Stirring was continued for 90 min., then the reaction mixture, which usually contained a considerable amount of precipitate, was drowned on 400 g. of ice. The solid was filtered, washed with 75 ml. of water, stirred for a few minutes with 100 ml. of water, filtered, and dried. The yield of crude product, an almost white solid that turns superficially yellow on prolonged exposure to light, averaged 38.5 g. (85%). On heating, the product begins to soften at about 155° and melts from 162 to 170°. If larger amounts of ice are used to decompose the reaction mixture or more water is used to wash the product, the yield decreases.

In order to separate the reaction products, 22.6 g. (0.1 mole) of the crude dinitro-*m*-toluic acids was dissolved in 226 ml. of cold absolute methanol and 22.6 ml. of cold concd. sulfuric acid was added. The solution, protected from moisture, was heated under reflux for 16 hr. and then chilled. The precipitate of methyl 4,6-dinitro-*m*-toluate was filtered, and the filtrate was diluted with 400 ml. of ether and shaken with one 300-ml. and two 150-ml. portions of water. The ether was then extracted with 1% aqueous sodium carbonate and dried over sodium sulfate. Evaporation of the ether left methyl 4,6-dinitro-*m*-toluate.

The sodium carbonate extract was freed of ether by a current of air, filtered if necessary, acidified with hydrochloric acid, and extracted with an equal volume of ether divided in two portions. The combined ether extracts were washed with water, dried over sodium sulfate, and evaporated to leave a residue of 2,6-dinitro-*m*-toluic acid as an off-white solid.

The average recovery in a series of these separations was 7.7 g. of crude ester (32%) m.p. 94–98°, and 7.5 g. of acid (33%) m.p. 174–178°. After it had been established that the two isomeric dinitro-*m*-toluic acids were present in approximately equal amounts in the crude dinitration product, a single separation was carried out with half the amounts of methanol and sulfuric acid called for above. This gave a 75%, instead of a 65%, recovery with a small but not significant increase in the relative amount of the 2,6- acid.

It should be possible to separate the mixture of dinitro-*m*-toluic acids without going through the esterification just described, for the 2,6-dinitro acid is far more soluble in hot water than is the 4,6-dinitro acid. (See below.) We have not attempted to work out a procedure for such a separation.

Nitration of methyl m-toluate. Isolation of 4,6-dinitro-m-toluic acid and methyl 2,6-dinitro-m-toluate. The nitrating mixture was prepared from 110 ml. of fuming nitric acid and 110 ml. of fuming sulfuric acid as described for the preceding nitration. To the stirred mixed acid, whose temperature was held between 20° and 30° by an ice-water bath, was added dropwise 30 g. (0.20 mole) of methyl *m*-toluate during 20 min. The ice bath was removed and the clear yellow solution was stirred for an hour, then poured onto 450 g. of ice. The precipitate was filtered, washed with water, and dried to yield 48 g. (quant.) of a pale yellow solid. The crude product usually melts over less than a 2° range, *e.g.*, 63–65°, with some preliminary softening.

In order to separate the nitration products, 24 g. (0.1 mole) of the crude ester mixture was suspended in 400 ml. of concd. hydrochloric acid and heated under reflux for 24 hr. during which time a slow stream of nitrogen was bubbled through the reaction mixture to reduce oxidative discoloration and to remove methanol and methyl chloride. The reaction mixture was cooled and ether was added to dissolve the dark yellow oil and admixed crystals. Water was added, the aqueous acid layer was discarded, and the ether was washed three times with water. The ether was then extracted with 1% aqueous sodium carbonate, washed with water, and dried over sodium sulfate. On evaporation, the ether left methyl 2,6-dinitro-*m*-toluate, m.p. 80–83°. The sodium carbonate extract was freed of dissolved ether by an air stream, filtered if necessary, and acidified with hydrochloric acid which precipitated 4,6-dinitro-*m*-toluic acid as an off-white solid, m.p. 166–170°.

The average recovery in a number of these separations was 12 g. of methyl 2,6-dinitro-*m*-toluate (50%) and 7 g. of 4,6-dinitro-*m*-toluic acid (30%). By extracting with ether the acidified sodium carbonate extract from which the 4,6-dinitro acid had precipitated, it was possible to increase the recovery of that acid to about 40%, but the additional material obtained in this way was of such poor quality that the extra operation was not worthwhile.

By crystallizing the crude dinitro ester mixture from methanol one can obtain reasonable amounts of methyl 4,6-dinitro-*m*-toluate, the less soluble of the two esters, and by a laborious and inefficient fractional crystallization from the same solvent one can isolate identifiable amounts of methyl 2,6-dinitro-*m*-toluate. We have not, however, been able to work out a satisfactory procedure for separating the ester mixture into its components by crystallization.

4,6-Dinitro-*m*-toluic acid is an almost colorless solid with a faint yellow cast. On exposure to direct sunlight the material turns superficially bright yellow. The acid is exceedingly soluble in the common organic solvents except ligroin or benzene. It can be crystallized from benzene (*ca.* 40 ml./g.) or water (*ca.* 50 ml./g.) with a 75% recovery. The pure acid, obtained in this way as very fine transparent crystals, melts at 178–179°.

The acid is esterified only slowly with methanol or ethanol and sulfuric acid. When 1 g. of the acid is heated under reflux with 10 ml. of methanol or ethanol and 1 ml. of concd. sulfuric acid, 16 hr. is required for complete esterification. *Methyl 4,6-dinitro-m-toluate*, obtained by esterification of the acid or by nitration of methyl-*m*-toluate, is very soluble in hot benzene, methanol, acetone, dioxane, tetrahydrofuran, dimethylformamide, or pyridine and is only very sparingly soluble in the same solvents cold. It is very slightly soluble in ether. The ester can be purified conveniently by crystallization from methanol (*ca.* 10 ml./g.; recovery, 85%). The pure ester is obtained as small pale yellow crystals that melt at 103–104°. The ester is hydrolyzed slowly by aqueous hydrochloric acid: 1.2 g. of ester heated under reflux with 20 ml. of concd. hydrochloric acid requires 16 hr. for complete hydrolysis.

(5) A. H. Blatt and Norma Gross, *J. Org. Chem.*, **22**, 1046 (1957).

Ethyl 4,6-dinitro-m-toluate can be prepared by esterifying the acid with ethanol as described above for the methyl ester. It can also be prepared by heating the acid, suspended in benzene, with excess thionyl chloride until the solid goes into solution (*ca.* 4 hr.), adding excess absolute ethanol, heating for a short time, and then evaporating the solvents. Both procedures give better than 90% yields. The ester is purified by dissolving it in ethanol at 35° and cooling the solution slowly. The pure ester, pale yellow crystals, melts at 47–48°.

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: C, 47.24; H, 3.93. Found: C, 47.17; H, 4.11.

This ester has previously been prepared by esterification of the acid obtained by the partial oxidation of 4,6-dinitro-1,3-dimethylbenzene. It was described[6] as brown prisms, m.p. 61–62°. We have no explanation for the difference in color and melting point between the earlier sample and ours.

Oxidation of 4,6-dinitro-m-toluic acid to 4,6-dinitroisophthalic acid. The procedure was taken from that of Ruggli and Schmid for the oxidation of 4,6-dinitro-1,3-dimethylbenzene.[7] A solution of 4.6 g. of 4,6-dinitro-*m*-toluic acid in 60 ml. of concd. sulfuric acid was stirred and chilled in an ice-salt bath to −7°, then a solution of 4.6 g. of chromium trioxide in 6.5 ml. of water was added dropwise slowly enough to permit the temperature of the reaction mixture to be held below 20°. Stirring was continued until the temperature dropped to 5°, when the reaction mixture was poured onto 300 g. of ice. The precipitate of unoxidized acid, 1.2 g., identified by melting point and mixed melting point, was removed by filtration and the filtrate was extracted with 120 ml. and then 60 ml. of ether. The ether, after washing, drying, and evaporating, left 3 g. of crude dinitroisophthalic acid, which melted at 241–243° after it had been digested with hot benzene. The pure acid, crystallized by solution in nitrobenzene at 160°, was obtained as sandy transparent crystals, m.p. 246–247° dec.

Since our material melted higher than the material prepared by Ruggli and Schmid by the oxidation of 4,6-dinitro-1,3-dimethylbenzene (246° *vs.* 234°), we esterified our product not only with methanol but also with ethanol so as to be able to compare the melting point of the diethyl ester with that reported by Ruggli and Schmid.

A solution of 1.28 g. of 4,6-dinitroisophthalic acid in 22.6 ml. of absolute methanol and 2.26 ml. of concd. sulfuric acid was heated under reflux for 16 hr. during which time a large precipitate of glistening white crystals formed in the hot solution. The precipitate was filtered, the filtrate was diluted with ether, washed with water, and extracted with 10 ml. of 1% aqueous sodium carbonate. On evaporation the ether left 0.3 g. of product which, with the original precipitate, made a total yield of 1.25 g. or 88%. The strongly alkaline carbonate extract on acidification furnished a small precipitate which was rejected since the ester already obtained accounted for 88% of the starting material.

The dimethyl ester was purified for analysis by crystallization from methanol and by solution in acetone followed by addition of methanol and heating to expel most of the acetone. The pure ester, obtained as colorless glistening crystals which are moderately soluble in hot acetone and very sparingly soluble in hot methanol, melts at 162–163°.

Anal. Calcd. for $C_{10}H_8N_2O_8$: C, 42.25; H, 2.8; OCH_3, 21.8. Found: C, 42.71; H, 2.83; OCH_3, 21.35.

The diethyl ester, prepared in 86% yield in the same way as its lower homolog, melted at 126°, in satisfactory agreement with the melting point of 124° given by Ruggli and Schmid for a sample prepared from the silver salt of the acid and ethyl iodide.[7]

Anal. Calcd. for $C_{12}H_{12}N_2O_8$: C_2H_5O, 28.84. Found C_2H_5O, 28.45, 29.48.

2,6-Dinitro-m-toluic acid is an almost colorless solid with a faint yellow cast. It is very soluble in the common organic solvents except ligroin or benzene and is remarkadly soluble in hot water: 1.0 g. requires less than 5 ml. of water for solution on the steam bath and about 0.75 g. crystallizes on cooling the solution. Benzene is the most satisfactory solvent for purification: 1.0 g. of the acid dissolves in about 50 ml. of benzene and 0.75 g. can be recovered on cooling. The pure acid, obtained in large transparent chunky crystals from benzene and in very small crystals from water, melts at 182–183° with considerable sublimation.

Anal. Calcd. for $C_8H_6N_2O_6$: C, 42.48; H, 2.67. Found: C, 42.74; H, 2.81.

The hindrance to esterification of the 2,6-dinitro acid is pronounced. When 1.0 g. of the acid in 10 ml. of absolute methanol and 1 ml. of concd. sulfuric acid was heated under reflux for 16 hr.—conditions under which the isomeric 4,6-dinitro acid is quantitatively esterified—only enough of the methyl ester was formed to permit identification by melting point and mixed melting point.

Methyl 2,6-dinitro-m-toluate can be prepared by the nitration of methyl *m*-toluate (see above) and in quantitative yield from the acid by conversion to the acid chloride with thionyl chloride followed by reaction of the crude acid chloride with methanol. The ester crystallizes as large chunky pale yellow lozenges that melt at 83–84°. Its solubility is similar to but greater than that of the isomeric 4,6-dinitro ester. It is conveniently purified by crystallization from methanol (*ca.* 5 ml./g.) with an 80–85% recovery.

Anal. Calcd. for $C_9H_8N_2O_6$: C, 45.0; H, 3.33. Found: C, 45.67; H, 3.40.

The ester is resistant to hydrolysis. A suspension of 1.2 g. of the ester in 20 ml. of concd. hydrochloric acid was heated under reflux for 24 hr. in a nitrogen stream. The material solidified on cooling. It was dissolved in ether and the ether shaken out with 1% aqueous sodium carbonate. The carbonate extract on acidification gave no precipitate and an ether extract of the acidified carbonate solution yielded only about 0.06 g. of the 2,6-dinitro acid, which corresponds to about 5% hydrolysis. (The isomeric 4,6-dinitro ester is completely hydrolyzed in 16 hr. under the same conditions.) The original ether solution that had been shaken out with sodium carbonate left unhydrolyzed ester on evaporation.

Ethyl 2,6-dinitro-m-toluate was prepared by converting the acid to the acid chloride with thionyl chloride in the presence of benzene as a solvent and heating the crude acid chloride with absolute ethanol. The yield of crude ester left on evaporation of the solvents at room temperature was quantitative. The ester was purified by dissolving it in ethanol at 35°, filtering, and cooling the filtrate slowly. A second crystallization from a larger volume of ethanol diluted with a little water after filtering did not change the melting point, 58–59°. The pure ester is colorless.

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: C, 47.24; H, 3.93. Found: C, 47.33; H, 3.99.

2,6-Dinitro-*m*-toluic acid was oxidized to 2,4-dinitroisophthalic acid by the procedure described above for the oxidation of 4,6-dinitro-*m*-toluic acid. The amount of unoxidized 2,6-dinitro-*m*-toluic acid that precipitated on pouring the reaction mixture into water was small: 2,6-dinitro-*m*-toluic acid is quite soluble in water. Evaporation of the ether extract gave 2.1–2.3 g. of crude product which was purified for analysis by crystallization from nitrobenzene and then from ether–petroleum ether (b.p. 60–90°). The pure acid melts at 246–247°, as does the isomeric 4,6-dinitroisophthalic acid. Mixtures of the two acids melt from 215 to 225°.

Anal. Calcd. for $C_8H_4N_2O_8$: C, 38.28; H, 1.56. Found: C, 38.22; H, 1.86.

2,4-Dinitroisophthalic acid was esterified with methanol and sulfuric acid following the procedure described above

(6) G. Errera and R. Maltese, *Gazz. chim. ital.*, **33**, II, 277 (1903).

(7) P. Ruggli and O. Schmid, *Helv. Chim. Acta*, **18**, 247 (1935).

for the preparation of dimethyl 4,6-dinitroisophthalate. No precipitate formed on cooling the reaction mixture so the solution was diluted with ether and shaken out three times with water to remove sulfuric acid and most of the methanol. The ether was then shaken out with 1% aqueous sodium carbonate; 20 ml. was required. The carbonate extract freed of ether was acidified and furnished the crude acid methyl ester IV in 43% yield. The poor yield is probably a result of the high solubility of the acid ester. No attempt was made to obtain more of the acid ester from the water washings or the acidified carbonate extract. The ether solution that had been extracted with sodium carbonate left no residue on evaporation showing that no neutral ester had been formed. The acid methyl ester is too soluble in aqueous methanol to permit crystallization from that solvent. For analysis, the material was crystallized from ether–petroleum ether (b.p. 60–90°). The pure methyl acid ester IV melts at 184–185°.

Anal. Calcd. for $C_9H_6N_2O_8$: CH_3O, 11.1. Found: CH_3O, 11.44.

DEPARTMENT OF CHEMISTRY
QUEENS COLLEGE
FLUSHING, N. Y.

Reaction of Hydrogen Bromide with Conjugated Dienols[1]

R. L. LOHMAR, C. R. SMITH, JR., AND T. L. WILSON

Received March 7, 1960

Dimorphecolic acid, the major fatty acid of *Dimorphotheca aurantiaca* seed oil, rapidly consumes essentially one molar equivalent of hydrogen bromide in the Durbetaki titration for oxirane oxygen.[2] Formulation of this acid as 9-hydroxy-*trans*,*trans*-10,12-octadecadienoic acid indicated no grouping known to consume hydrogen bromide in this manner. We report here a comparison of the behavior of dimorphecolic acid with that of two model compounds, 2,4-hexadiene-1-ol (sorbyl alcohol) and 4,6-octadiene-3-ol, when treated with hydrogen bromide in nonaqueous media.

Although several aliphatic compounds with a secondary hydroxyl group in α-position to a conjugated diene are known, their behavior toward hydrogen bromide has not been examined. Kuhn and Grundmann[3] showed that 4,6-octadiene-3-ol is readily dehydrated by *p*-toluenesulfonic acid to 2,4,6-octatriene. Heilbron and co-workers,[4] as well as Braude and co-workers,[5] examined the effect of acid catalysts on related unsaturated alcohols. They found that compounds containing the system —CH=CH—CHOH—CH=CH— showed a pronounced tendency to rearrange to secondary conjugated dienols (—CHOH—CH=CH—CH=CH—) which were readily dehydrated to trienes. Heilbron examined the action of hydrochloric acid on the closely related hex-4-ene-1-yne-3-ol and similar compounds. Rearrangement similar to that of the dienols was observed, accompanied by replacement of hydroxyl by chlorine. However, the action of hydrobromic acid led to "unstable heterogeneous products."

2,4-Hexadiene-1-ol does not consume hydrogen bromide under the conditions of the Durbetaki[6,7] titration, but 4,6-octadiene-3-ol behaves in a manner analogous to that of dimorphecolic acid. It rapidly consumes a like amount of hydrogen bromide. Ultraviolet absorption studies indicate that essentially all the dienoid absorption is preserved immediately after titration, but triene is then formed at a slower rate. Appearance of triene is accompanied by disappearance of diene, suggesting that an initially formed bromodiene is dehydrobrominated. Similar results are obtained when a chloroform solution of hydrogen bromide is used rather than an acetic acid solution. Hydrogen chloride in acetic acid is not consumed rapidly.[8] Treatment of the octadienol with two thirds the titrimetric amount of hydrogen bromide results in eventual turning of the indicator. This observation supports the interpretation of replacement followed by elimination. The presence of free acid in mixtures that had stood some time after Durbetaki titration was confirmed by the rapid neutralization of sodium carbonate dissolved in acetic acid.

Although consumption of hydrogen bromide appears to be stoichiometric or nearly so, formation of triene is not. Diene and triene are in equilibrium (Fig. 1). The molar sum of conjugated diene and triene is 75–80% of that expected. The fate of the remainder is not known, but a possibility exists that in the equilibrium reaction some of the hydrogen bromide is added to yield a nonconjugated bromodiene that would not be estimated by the spectral method used. Conversion of diene to triene is reminiscent of the results Bergström and Hansson[9] obtained by treating linoleate with *N*-bromosuccinimide. The initially formed conjugated dienoid bromide lost hydrogen bromide to form a conjugated triene. They also observed that about 30% of the bromide was not eliminated, even after prolonged refluxing.

The mechanism sequence may resemble that proposed by DeWolfe and Young[10] for the reaction of

(1) This is a contribution from the laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

(2) C. R. Smith, Jr., T. L. Wilson, E. H. Melvin, and I. A. Wolff, *J. Am. Chem. Soc.*, **82**, 1417 (1960).

(3) R. Kuhn and C. Grundmann, *Ber.*, **71**, 442 (1938).

(4) I. M. Heilbron, J. T. McCombie, and B. C. L. Weedon, *J. Chem. Soc.*, **1945**, 84, and preceding papers.

(5) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, **1951**, 2085, and preceding papers.

(6) A. Durbetaki, *Anal. Chem.*, **28**, 2000 (1956).

(7) American Oil Chemists' Society, "Official and Tentative Methods," 2nd ed. (1958 revision), Method Cd 9-57.

(8) Miss Glenda Geisinger carried out this experiment.

(9) S. Bergström and G. Hansson, *Acta Chem. Scand.*, **4**, 435 (1950).

(10) R. H. DeWolfe and W. G. Young, *Chem. Revs.*, **56**, 753 (1956).

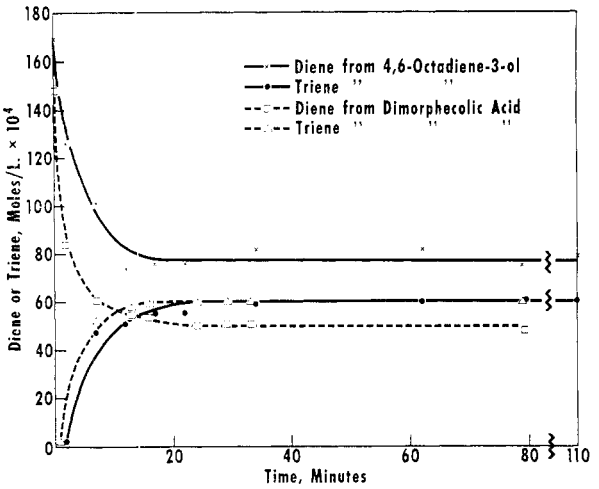


Fig. 1. Effect of hydrogen bromide on 4,6-octadiene-3-ol and on dimorphecolic acid

monoethenoid allylic alcohols with hydrogen bromide, followed by elimination to form triene. Interpretation of the initial substitution as an S_N2 mechanism is favored by the similar uptake of hydrogen bromide in either acetic acid or chloroform solution, by the slower uptake of the more weakly nucleophilic hydrogen chloride, and by the appearance of triene only after the uptake of hydrogen bromide, rather than concurrently as would occur from a carbonium ion intermediate in an S_N1 scheme. However, an S_N1 route is strongly supported by the lack of uptake of hydrogen bromide by the primary alcohol, 2,4-hexadiene-1-ol, which should have a lesser tendency toward carbonium ion formation than the secondary dienols.[11]

EXPERIMENTAL

Dimorphecolic acid. An analytically pure sample was prepared by chromatographing acid isolated by solvent partitioning of mixed acids from *Dimorphotheca aurantiaca* seed oil.[12] A benzene solution of acid (0.5 g.) was added to a silica gel column (5 g.) pretreated with 80% aqueous methanol:hexane (1:1). The pure acid (0.22 g.) was eluted by benzene under nitrogen. It was a semisolid at room temperature. $\lambda_{max}^{C_2H_5OH}$ 231, ϵ 28,800.

Anal. Calcd. for $C_{18}H_{32}O_3$: C, 73.0; H, 10.8. Found: C, 73.3; H, 10.9.

Trans,trans-2,4-hexadiene-1-ol. Ethyl sorbate was reduced by lithium aluminum hydride by a slight modification of the method of Nystrom and Brown.[13] The alcohol was obtained as a colorless mobile liquid. Its 3,5-dinitrobenzoate, prepared according to Reichstein and co-workers,[14] melted at 82–84° (Fisher-Johns[15] block) (lit. m.p., 85°).

Trans,trans-4,6-octadiene-3-ol. Technical grade hexadienal[16] was purified by distillation at 65.5–66°/18 mm., $\lambda_{max}^{C_2H_5OH}$ 271, ϵ 28,700. Hausser, *et al.*[17] reported ϵ 26,500. The distilled hexadienal was condensed with ethylmagnesium bromide according to Kuhn and Grundmann[3] to give the octadienol (78%) $\lambda_{max}^{C_2H_5OH}$ 229, ϵ 24,200. Distillation at 77–79°/20 mm. gave a product having $\lambda_{max}^{C_2H_5OH}$ 229, ϵ 28,400, n_D^{18} 1.4895 (lit., 1.4892).

Hydrogen bromide consumption. Uptake of hydrogen bromide by the unsaturated alcohols was determined by Durbetaki titration[6,7] in benzene–acetic acid solution. For spectral studies, acetic acid only was used as solvent. This solvent change reduced the molar hydrogen bromide uptake to 0.77 (from 0.9 or higher).

Hydrogen bromide reactions. The unsaturated alcohols (0.15–0.2 mmole) were dissolved in 5–10 ml. of glacial acetic acid and were treated with a volume of 0.03–0.05*N* hydrogen bromide in acetic acid found, by prior titration, to be rapidly consumed. At intervals, 0.1-ml. aliquots were removed and diluted to 100 ml. with absolute ethanol. Conjugated diene was determined in 1-cm. cells in a Beckman Model DU spectrophotometer, using the experimentally determined extinction coefficients given above. A molecular extinction of 59,200 at 264 mμ[18] was used for conjugated triene. Data in Fig. 1 are from one of several similar experiments.

NORTHERN REGIONAL RESEARCH LABORATORY
PEORIA, ILL.

(11) E. R. Alexander, *Principles of Ionic Organic Reactions*, John Wiley & Sons, New York, 1950, p. 41.

(12) C. R. Smith, Jr., M. C. Burnett, T. L. Wilson, R. L. Lohmar, and I. A. Wolff, *J. Am. Oil Chemists' Soc.*, **37**, 320 (1960).

(13) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 1197, 2548 (1947); *J. Am. Chem. Soc.*, **70**, 3738 (1948).

(14) T. Reichstein, C. Ammann, and G. Trivelli, *Helv. Chim. Acta*, **15**, 261 (1932).

(15) Mention of firm names or trade products does not imply that they are endorsed or recommended by the U. S. Department of Agriculture over other firms or similar products not mentioned.

(16) Generously supplied by Union Carbide Chemicals Co.

(17) K. W. Hausser, R. Kuhn, A. Smakula, and M. Hoffer, *Z. physik. Chem.*, **B29**, 371 (1935).

(18) American Oil Chemists' Society, "Official and Tentative Methods," 2nd ed. (1958 revision), Method Cd 7-58.

Specificity of the Phenolic Component for Sakaguchi Reaction[1]

KSHIROD R. BHATTACHARYA, JYOTIRINDRA DATTA, AND DURLAV K. ROY

Received March 14, 1960

In 1925, Sakaguchi observed that an intense red color was produced when arginine was treated in alkaline solution with 1-naphthol and hypohalite[2]; it was found later that the reaction was specific for a class of monosubstituted guanidines.[2,3] The specificity of the phenolic component for this reaction has not, however, been studied adequately

(1) (a) This constitutes Paper V in a series *Studies on Sakaguchi Reaction;* for Paper IV, see K. R. Bhattacharya, *Ann. Biochem. Exptl. Med.*, **20**, 57 (1960). (b) Presented in part by K. R. Bhattacharya and J. Datta before the 46th session of the Indian Science Congress Association, Delhi, January 21–28, 1959.

(2) S. Sakaguchi, *J. Biochem. (Tokyo)*, **5**, 25 (1925). See for review R. J. Block and D. Bolling, *The Amino Acid Composition of Proteins and Foods*, 2nd Ed., Charles C. Thomas, Springfield, Ill., 1951, p. 47.

(3) (a) C. J. Weber, *J. Biol. Chem.*, **86**, 217 (1930). (b) J. D. Mold, J. M. Ladino, and E. J. Schantz, *J. Am. Chem Soc.*, **75**, 6321 (1953).

so far, although a few aromatic hydroxy compounds other than 1-naphthol have been employed from time to time in analytical work as useful substitutes for the latter.[4] Color response of various substituted phenols to this reaction was therefore studied in detail. It was hoped that apart from throwing useful light on the mechanism of the reaction, this might also indicate the point of coupling between the guanidine and the phenolic residues in the colored reaction product.[9]

In Table I are listed a few of the results obtained with arginine. That all the indicated positive tests were in response to specific Sakaguchi reactions

TABLE I

COLOR PRODUCTION BY VARIOUS PHENOLIC COMPOUNDS BY SAKAGUCHI REACTION WITH ARGININE

Compound	Color Produced[a]	Relative Intensity of Color[b]
Phenol	LY	++
p-Phenylphenol	—	...
o-Cresol	Y	+++
m-Cresol	GY	++++
p-Cresol	—	...
Thymol	GY	++++
Salicylic acid	Y	++
p-Hydroxybenzoic acid	—	...
o-Aminophenol	LY	±
p-Aminophenol	—	...
Resorcinol	Y	±
Hydroquinone	—	...
o-Chlorophenol	LY	++
p-Chlorophenol	LY	++
2,4-Dichlorophenol	LY	±
2,4,6-Trichlorophenol	—	...
1-Naphthol-8-sulfonic acid	R	++++
1-Naphthol-4-sulfonic acid	—	...
1,4-Naphthoquinone	—	...
5-Quinolinol	RS	++++
2-Methyl-4-quinolinol	—	...
2-Naphthol	B	++
2-Naphthol-6-sulfonic acid	B	+
1-Nitroso-2-naphthol	—	...

[a] Y = Yellow; LY = lemon yellow; GY = golden yellow; R = red; B = brown; RS = reddish saffron;— = none. These refer to the color in alkaline soln. In acid,[10] the color varied from very faint (in the case of a benzene ring) to fairly strong (naphthalene or quinoline ring) yellow. [b] The intensities are based on visual comparison. The larger the number of plus signs, the higher is the color intensity. The sign ± indicates very feeble coloration.

was shown by the fact that no other amino acid nor creatine could replace arginine in these color reactions, but glycocyamine[2,3a] reacted positively like arginine. It is clear from these results that the Sakaguchi reaction is actually a general reaction of phenolic compounds but that a free *para* position in the phenol is specifically required for participation in it. The positive response of a few (though not all) *p*-halophenols (also observed earlier[4]) is admittedly at variance with the latter requirement, but such occasional exceptional behavior of some *p*-halophenols is not without precedent. Thus although the Gibbs indophenol reaction[11a] is in general specific for *para*-unsubstituted phenols, *p*-chlorophenol is able to give the same reaction.[11b] Similarly, in the indophenol reaction between *p*-aminodimethylaniline and phenols in presence of hypohalite, *p*-cresol gives no reaction but *p*-chlorophenol does (although trichlorophenol, as in the present work, does not).[12] This behavior thus appears to be a property inherent in a phenolic *p*-halogen substituent itself which, under the conditions of these reactions, is apparently sufficiently activated to be eliminated or migrated to another position.

The overall nature of the Sakaguchi reaction would thus place it in the general class of the coupling-type reactions of phenols, the point of coupling being limited here to the carbon atom at position *para* with respect to the phenolic hydroxyl.[13] More specifically, however, the great similarity in the circumstances of reaction and in the nature and specificity of the reactants involved (including the singular reactivity of some *p*-halophenols) suggest in particular that there is probably a good deal of similarity between the mechanism of Sakaguchi reaction and those of the two indophenol reactions noted above (and probably other indophenol and indamine reactions as well). This view is further strengthened by our recent finding[9b] that the colored product of this reaction also, like the indophenols, behaves as a typical redox system. Another very similar indophenol reaction is that between ammonia and phenol mediated by hy-

(4) The following compounds have been used: 8-quinolinol,[5] 7-chloro-8-quinolinol, and 5,7-dichloro-8-quinolinol,[5b] 1-naphthol-8-sulfonic acid,[6] 2,4-dichloro-1-naphthol,[7] and 2-naphthol.[8]

(5) (a) S. Sakaguchi, *J. Biochem.* (*Tokyo*), **37**, 231 (1950). (b) J. W. Janus, *Nature*, **177**, 529 (1956).

(6) H. Kraut, E. von Schrader-Beielstein, and M. Weber, *Z. physiol. Chem.*, **286**, 248 (1950). Cited in *Chem. Abstr.*, **47**, 5977-a (1953).

(7) J. McLeish and H. S. A. Sherratt, *Exptl. Cell Research*, **14**, 625 (1958).

(8) P. M. Strocchi and P. Drago, *Ann. chim.* (*Rome*), **44**, 836 (1954). Cited in *Chem. Abstr.*, **49**, 6035-d (1955).

(9) See discussion in (a) K. R. Bhattacharya, J. Datta, and D. K. Roy, *Arch. Biochem. Biophys.*, **77**, 297 (1958); (b) K. R. Bhattacharya, *Nature*, **184**, 53 (1959).

(10) See K. R. Bhattacharya, J. Datta, and D. K. Roy, *Arch. Biochem. Biophys.*, **84**, 377 (1959), for the effect of *p*H on color in the case of 1-naphthol.

(11) (a) H. D. Gibbs, *J. Biol. Chem.*, **72**, 649 (1927). See for review F. D. Snell and C. T. Snell, *Colorimetric Methods of Analysis*, Vol. III, 3rd Ed., D. Van Nostrand Company, Inc., New York, N. Y., 1953, pp. 106, 118. (b) M. B. Ettinger and C. C. Ruchhoft, *Anal. Chem.*, **20**, 1191 (1948).

(12) G. U. Houghton and R. G. Pelly, *Analyst*, **62**, 117 (1937).

(13) As neither *para*-substituted phenols nor a simple derivative of 4-quinolinol could participate in the reaction, any linkage through the aromatic hydroxyl group itself[2] or through positions *ortho* or *meta* to it can be safely ruled out. Similarly, the nonparticipation of hydroquinone or 1,4-naphthoquinone would show that the linkage is also not through the 2-position of a preformed *p*-quinone. With 2-naphthol, the linkage is apparently at position 1.

pohalite.[14] The only apparent difference between these two types of reaction is that, whereas in one the phenol is condensed with a simple amine (or ammonia) under the influence of hypohalite,[15] it is condensed with a guanido group in the other. It may thus be speculated that perhaps their products also parallel each other in structure, although it must be remembered that the indophenols and indamines as a class (blue, green or purple) differ appreciably from the products of Sakaguchi reaction (yellow to red) in being more intensely colored.

Incidentally, thymol, 5-quinolinol and 5-chloro-7-iodo-8-quinolinol (the latter in ethyl acetate solution), besides 8-quinolinol, gave sufficiently intense color to be of possible use as substitutes for 1-naphthol in the estimation of arginine by Sakaguchi reaction; 1-naphthol is known to have several disadvantages in this respect.[5b,6,10] With thymol, moreover, blank coloration was practically absent.

EXPERIMENTAL

Arginine and glycocyamine[2,3a] were employed as the guanidine compounds. Because of the advantage of a clear contrast between the color of the spot and that of the surrounding areas, the reactions were carried out on filter paper[9a] rather than in solution. Briefly, spots of arginine (or glycocyamine) were treated first with 2.5% potassium hydroxide in ethanol, then with a 0.1–0.2% solution of the phenol[16] in a suitable solvent, and finally with aqueous hypobromite solution (0.1–2 g. % bromine in 1*N* potassium hydroxide).

Note added in proof: After this note went to the press, a copy of the paper of Kraut *et al.*[6] has been procured. It has been noted that these workers, while selecting a suitable naphtholsulfonic acid for the method, found 1-naphthol-4-sulfonic acid to be ineffective in producing color by this reaction and so concluded that a free 4-position in 1-naphthol was apparently essential for Sakaguchi reaction.

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(14) A. P. Orr, *Biochem. J.*, **18**, 806 (1924); J. A. Russell, *J. Biol. Chem.*, **156**, 457 (1944).

(15) It is noteworthy that the 2,6-dibromoquinonechlorimine of Gibbs is itself prepared by the action of hypochlorite on 2,6-dibromo-*p*-aminophenol.[11a]

(16) We wish to express our appreciation to Prof. B. D. Tilak of the Department of Chemical Technology, University of Bombay, for generous gifts of 1-naphthol-4-sulfonic acid and 2-naphthol-6-sulfonic acid.

Isolation and Characterization of a Phenol Half-Salt

A. T. SHULGIN AND H. O. KERLINGER

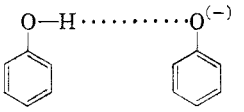
Received April 1, 1960

Many observations have been made of anomalous behavior at or near the half neutralization point in the nonaqueous titration of weak acids. In conductometric titration[1] conductivity maxima have frequently been recorded, whereas in potentiometric titration[2] there have been observed corresponding inflections or distortions in the titration curve.

These anomalies have been explained[2a] by the generation, during titration, of an association species in which the generated anion (of either a

R—O—H . . . . . O⁻—R

carboxylic acid or a phenol) protects an equivalent amount of acid, the association being stoichiometric at the half-titration point. This new species is then the acidic participant for the remainder of the titration. The evidence for such a material has been entirely physical and predominately spectroscopic. Pool[3] and Kaufman[4] have presented cryoscopic evidence for the formation of a solid compound composed of one molecule of a base and two molecules of a carboxylic acid, the latter preparing several half-salts between fatty acids and tertiary amines. Analysis of the infrared spectra of dilute solutions of carboxylic acids and tertiary amines[5] has yielded support for this same 2:1 relationship. Recently the alkali half-salts of several carboxylic peptide precursors have been described.[6] In the case of phenols, the evidence for this relationship with bases has been heretofore titrimetric The structural requirements of an unhindered —OH group,[1b,2a,b] and for the exclusion of appreciable amounts of polar solvents (as hydrogen bonding competitors)[1b] imply that the acid-anion structure is a dimer as shown:



We have found that the inclusion of a sterically hindered formamido group *para* to the phenolic —OH group greatly increases the stability of these half-salts, permitting their isolation and manipulation as discrete chemical substances.

When a solution of 4-formamido-3,5-xylenol in methyl isobutyl ketone is titrated with tetrabutylammonium hydroxide in solution in a mixture of methanol and isopropanol, there is obtained a titration curve typical of those described earlier.[2a] In addition, however, there is the generation of a

(1) (a) A. A. Maryott, *Journ. of Res. Nat. Bureau. Standards*, **38**, 527 (1947). (b) D. B. Bruss and G. A. Harlow, *Anal. Chem.*, **30**, 1836 (1958).

(2) (a) G. A. Harlow, and D. B. Bruss, *Anal. Chem.*, **30**, 1833 (1958). (b) H. B. van der Heijde, *Anal. Chem. Acta*, **16**, 392 (1957).

(3) W. O. Pool, H. J. Harwood, and A. W. Ralston, *J. Am. Chem. Soc.*, **67**, 775 (1945).

(4) S. Kaufman, and C. R. Singleterry, *J. Phys. Chem.*, **56**, 604 (1952).

(5) G. M. Barrow, *et al.*, *J. Am. Chem. Soc.*, **76**, 5211 (1954). *J. Am. Chem. Soc.* **77**, 4475 (1955). *J. Am. Chem. Soc.*, **78**, 5802 (1956).

(6) M. Goodman, and K. C. Stueben, *J. Org. Chem.*, **24**, 112 (1959).

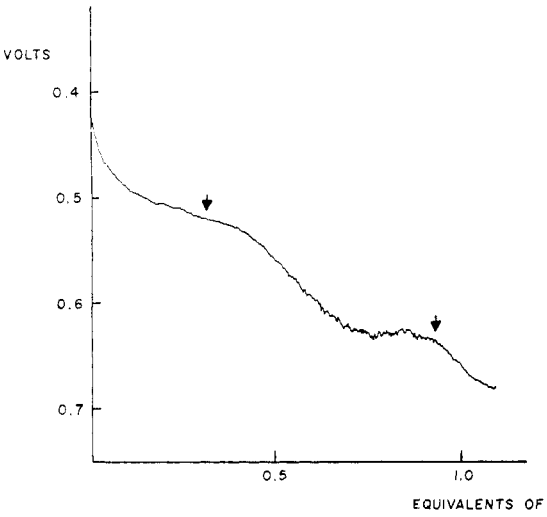


Fig. 1. Titration curve of 4-formamido-3,5-xylenol with tetrabutylammonium hydroxide. The arrows indicate the point of first appearance and of final disappearance of the crystalline half-salt

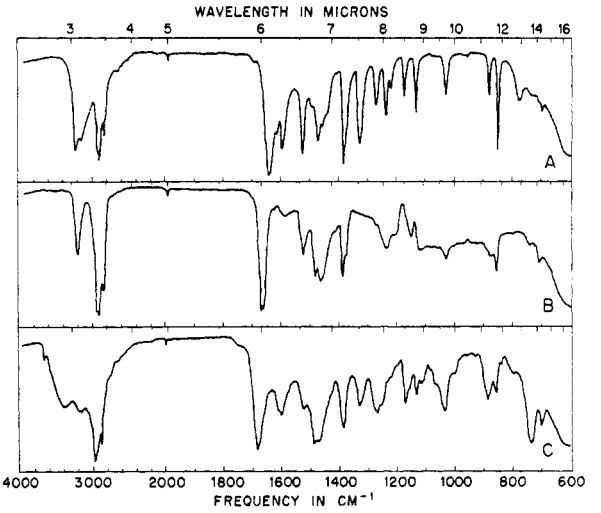


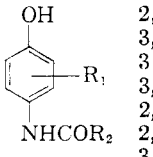
Fig. 2. Spectra of: a) 4-Formamido xylenol (mineral oil mull). b) 4-formamido xylenol·tetrabutylammonium 4-formamido xylenate (mineral oil mull). c) Tetrabutylammonium 4-formamido xylenate (smear). All from a Beckman prism-grating IR-7 spectrophotometer

crystalline product prior to the half-neutralization point, which redissolves prior to the final endpoint (see Fig. 1).

This material may be filtered free of the solvent and recrystallized as required. If the titration is continued to the full 1:1 endpoint, the normal salt is formed (in solution) from which the half-salt may be regenerated by the introduction of an additional mole of phenol. The normal salt cannot be isolated from this ketone medium, however.

As to the structural requirements permitting formation of an isolatable half-salt under these conditions, it appears that both a hindered formamido group and an unhindered —OH group are necessary. The acetamido homolog yielded no such precipitate.

The following table summarizes the structural requirements permitting the formation of a stable, insoluble half-salt with tetrabutylammonium hydroxide under the experimental conditions mentioned below.



R_1	R_2	Formulation of Half-Salt
H	H	−
2,6-CH_3	H	−
3,5 CH_3	H	+
3 CH_3,5 C_2H_5	H	+
3,5-C_2H_5	H	+
2,3,5-CH_3	H	+
2,3,5,6-CH_3	H	−
3,5-CH_3	CH_3	−

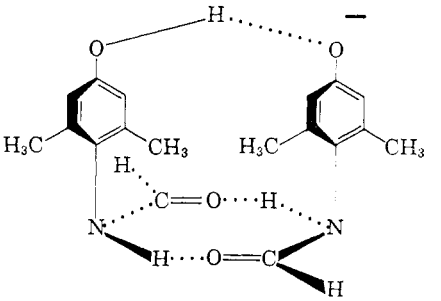
The solvent employed in the titration is not critical. Various diethers of ethylene glycol and diethylene glycol all yielded an insoluble half-salt and a redissolved normal salt. However, dioxane yielded a dark solution at the endpoint and lower ketones (acetone) were unsatisfactory.

When the tetrabutyl ammonium hydroxide was in water solution, apparently any solvent may be used in which both the phenol and water are soluble. Dimethyl formamide and diethylene glycol dimethyl ether were satisfactory.

The only other base employed was trimethylbenzylammonium hydroxide in methanol (with the phenol in methyl isobutyl ketone). The half-salt was a gummy solid, and was not further pursued.

Structure of the half-salt. Infrared spectra of the free phenol, the half-salt, and the normal salt of 4-formamido-3,5-xylenol and tetrabutylammonium hydroxide are shown in Fig. 2.

The unexpected stability of this half-salt, demonstrated by its formation in water and its insolubility, suggests a more strongly bonded dimer than one associated by the phenolic —OH alone. In the structure below these arguments are



achieved. Infrared spectra of dilute solutions (saturated in methylene chloride solution, 1 cm. cells) show no unbonded —OH in the half-salt, whereas the free phenol contains such an —OH (at 3595 cm.$^{-1}$).[7] Any attempt to provide a quinone-like structure for the anionic portion of the half-

salt must allow for the complete absence of color in all the half-salts observed so far.

EXPERIMENTAL

Acylamido phenols. All formulations and acetylations were performed as described by Smith, *et al.*[8] for the formation of 4-formamido-2,3,5-trimethylphenol from the aminophenol. It was desirable, however, to employ boiling water or a water–formic acid mixture as a recrystallization solvent, after prior treatment of the crude reaction product with charcoal.

4-Formamido phenol melted at 137.5–139° (from water).

4-Formamido-2,6-xylenol melted at 159–160° (from water).

4-Formamido-3,5-xylenol melted at 233° (from water).

5-Ethyl-4-formamido-m-cresol melted at 185–186° (from formic acid-water).

3,5-Diethyl-4-formamido phenol melted at 208–209° (from formic acid–water).

4-Formamido-2,3,5-trimethylphenol melted at 215° (from water).

4-Formamido-2,3,5,6-tetramethylphenol melted at 298° dec. (from formic acid–water).

4-Acetamido-3,5-xylenol was obtained as the monohydrate from water; m.p., 179–180.5°, with sintering at 90°. The anhydrous form may be obtained by dehydration with boiling benzene and recrystallization from ether-pentane.

4-Formamido-3,5-xylenol tetrabutylammonium 4-formamido-3,5-xylenate. Preparation in nonaqueous medium. A solution of 1.0 g. of 4-formamido-3,5-xylenol in a minimum amount of methyl isobutyl ketone was titrated to its normal endpoint with a full equivalent of 0.2*M* tetrabutylammonium hydroxide[2a] in isopropyl alcohol methanol (5:1 V/V). To this solution of the normal salt was then added an additional 1.0 g. of the parent phenol in a minimum amount of solvent. The mixture was stirred for 2 hr. during which time the half-salt was deposited as a white, crystalline solid. It was removed by filtration and washed sparingly with methyl isobutyl ketone. Recrystallization from acetonitrile yielded 2.5 g. (72%) of a fine, white microcrystalline product; m.p. 189° dec.

Anal. Calcd. for $C_{34}H_{57}N_3O_4$: C, 71.41%; H, 10.05%; N, 7.35%; neut. equiv. ($HClO_4$) 571. Found: C, 71.08%; H, 9.96%; N, 7.28%; neut. equiv. 560.

Preparation in aqueous medium. To a solution of 4-formamido-3,5-xylenol in three times its weight of dimethylformamide there was added exactly 0.5 equivalent to a 1*M* solution of tetrabutylammonium hydroxide in water (Southwestern Analytical Chemical Co.). Crystallization of the half-salt started immediately and was essentially complete in 10 min. Filtration and recrystallization yielded a product identical with that formed in preparation in nonaqueous medium, above.

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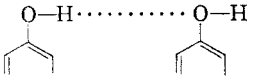
(7) This does not exclude a dimeric form for the free phenol, as a normal —OH group would still be expected for the unbonded form, and the bonded —OH may well lie outside of the narrow, transparent region available in methylene chloride.



Unfortunately, neither the free phenol nor the half-salt was sufficiently soluble in carbon tetrachloride or carbon disulfide to permit their use as solvents.

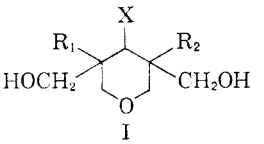
(8) L. I. Smith, H. H. Hoehn, and A. G. Whitney, *J. Am. Chem. Soc.*, **62**, 1867 (1940).

The Preparation of Tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)pyran

THOMAS J. PROSSER

Received April 29, 1960

Limited evidence found in the literature indicates that the base catalyzed, exhaustive hydroxymethylation of ketones in which the carbonyl group is flanked by methylene groups gives rise to substituted tetrahydropyran-4-ols. Thus, the reaction of acetone and formaldehyde gives anhydroenneaheptitol (Ia),[1] whereas methyl ethyl ketone and diethyl ketone are reported to give tetra-

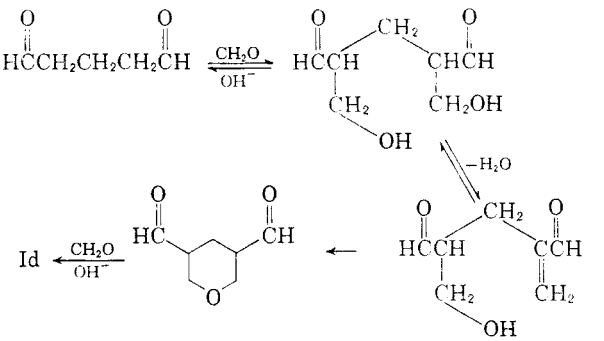


I

a) $R_1 = R_2 = CH_2OH$; X = OH
b) $R_1 = CH_2OH$; $R_2 = CH_3$; X = OH
c) $R_1 = R_2 = CH_3$; X = OH
d) $R_1 = R_2 = CH_2OH$; X = H

hydro-3,3,5-tris(hydroxymethyl)-5-methylpyran-4-ol (Ib) and tetrahydro-3,5-bis(hydroxymethyl)-3,5-dimethylpyran-4-ol (Ic), respectively.[2]

It has now been found that a similar reaction takes place in a 1,3-bis(methylene) system activated by terminal aldehyde groups rather than by a central ketone function. The exhaustive hydroxymethylation of glutaraldehyde gives the previously unreported tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)pyran (Id). A general reaction mechanism would seem to apply to all of the above cases. The following scheme is proposed for the glutaraldehyde-formaldehyde reaction and is analogous to that suggested for the formation of dipentaerythritol in the preparation of pentaerythritol from acetaldehyde and formaldehyde.[3]



The tetraacetate, dibenzylidene acetal, and diisopropylidene ketal derivatives of Id were prepared.

(1) M. Apel and B. Tollens, *Ber.*, **27**, 1089 (1894), *Ann.*, **289**, 46 (1896); C. Mannich and W. Brose, *Ber.*, **55**, 3155 (1922).

(2) I. R. Roach, H. Wittcoff, and S. E. Miller, *J. Am. Chem. Soc.*, **69**, 2651 (1947).

(3) S. Wawzonek and D. A. Rees, *J. Am. Chem. Soc.*, **70**, 2433 (1948).

EXPERIMENTAL[4]

Tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)pyran (Id). To 236 g. (3.30 moles) of 42% aqueous formaldehyde solution adjusted to *p*H 11.0 by addition of 50% sodium hydroxide solution was added 200 g. (0.50 mole) of 25% aqueous glutaraldehyde (Union Carbide Chemicals Co.) at 40–45° over a 1-hr. period. Thereafter, the temperature of the mixture was held at 50, 60, and 70° for 4, 3, and 2 hr., respectively. A *p*H of 11.0 was maintained throughout by intermittent addition of base. Theoretical base consumption was observed following the complete heating period. Deionization of the total crude reaction solution by passage through columns of Dowex 50 and Dowex 1 exchange resin, in that order, gave 60.6 g. of crystalline to semicrystalline product in the initial portions of effluent. Further rinsing gave an additional 10.3 g. of oily by-product considered to represent lower condensation products. The major portion of the latter material was absorbed by the exchange resin and not recovered. The main product contained 55.5% Id (32.6% yield) as determined by quantitative isolation of its dibenzylidene derivative. Preparation of an analytical sample of Id by water recrystallization gave a white crystalline solid; m.p. 176.5°.

Anal. Calcd. for $C_9H_{18}O_5$: C, 52.41; H, 8.80; OH, 32.99; mol. wt., 206.23. Found: C, 52.64, 52.51; H, 8.80, 8.96; OH (acetylation), 32.3, 31.9; mol. wt. (cryoscopic in ethanol), 206, 206.

Derivatives of tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)-pyran (Id). (1) *Tetraacetate.* A mixture of 10 g. (0.049 mole) of Id, 40 g. (0.39 mole) of acetic anhydride, and 4 ml. of glacial acetic acid was heated under reflux for 1 hr., allowed to stand overnight, and then poured into 100 ml. of water. The crystalline, white solid which separated amounted to 7.8 g. (43% yield), m.p. 91–95°, recrystallized from *n*-hexane, 94°.

Anal. Calcd. for $C_{17}H_{26}O_9$: C, 54.54; H, 7.00; mol. wt., 374.38; Sapon. No., 599.48. Found: C, 54.81, 55.00; H, 7.09, 7.17; mol. wt. (Rast), 386, 381; Sapon. No., 604.

(2) *Dibenzylidene acetal.* A mixture of 5.0 g. (0.024 mole) of impure Id, 25 ml. of water, 25 ml. of methanol, and 5 ml. of concd. hydrochloric acid was reacted with 10 ml. of benzaldehyde for 45 min. at steam bath temperature. There was obtained 8.14 g. (89% yield) of crude, white solid which upon recrystallization from butyl acetate melted at 232–234°.

Anal. Calcd. for $C_{23}H_{26}O_5$: C, 72.22; H, 6.85; mol. wt., 382.43. Found: C, 72.37, 72.47; H, 7.01, 7.02; mol. wt. (Rast), 388, 403.

Tests with pure Id showed the dibenzylidene reaction to be quantitative and applicable to the determination of Id in mixtures, or compounds hydrolyzed under the reaction conditions.

(3) *Diisopropylidene ketal.* A mixture of 10 g. (0.048 mole) of Id, 150 ml. of acetone, 5 drops of concd. sulfuric acid, and 15 g. of 2,2-dimethoxypropane (Dow Chemical Co.) was heated under reflux overnight. Concentration of the reaction mixture gave 11.6 g. (91.4% yield) of white crystals. Recrystallization from acetone gave a melting point of 201–205°.

Anal. Calcd. for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 63.27, 63.25; H, 9.39, 9.29.

The Id content of the recrystallized product was determined by conversion to its dibenzylidene derivative: calcd., 72.02; found, 71.2. Various samples of Id diisopropylidene ketal melted over a range of 153–206°, suggesting the presence of allotropic crystalline forms.

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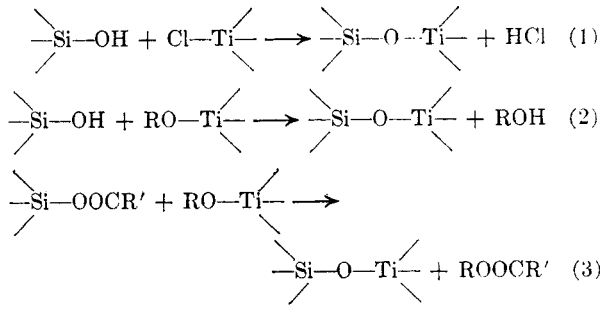
(4) All melting points are uncorrected.

Reaction of Trimethylacetoxysilane with Tetraisopropoxytitanium[1]

J. B. RUST, H. H. TAKIMOTO, AND G. C. DENAULT[2]

Received April 25, 1960

The preparations of organotitanium derivatives containing the silicon-oxygen-titanium linkage have been reported by several investigators.[3–9] These compounds have been prepared by any one of the following methods:



Although these three methods have been utilized in the synthesis of the tetrasubstituted triorganosiloxy titanium derivatives, only Danforth[8] has reported the preparation of monomeric, partially substituted trimethylsiloxy titanium esters. He studied the reaction of trimethylsilanol with tetraisopropoxytitanium. The reaction was reported to proceed as follows:

$$n(CH_3)_3SiOH + Ti(OC_3H_7)_4 \longrightarrow [(CH_3)_3SiO]_nTi(OC_3H_7)_{4-n} + nC_3H_7OH \quad (4)$$

where n is 1, 2, or 4. The extent of the substitution may be controlled by the stoichiometry of the reactants used.

The condensation reaction of trimethylacetoxysilane with tetrabutoxytitanium as reported by Andrianov and Ganina[10] results not in the desired tetrakis(trimethylsiloxy)titanium but rather in

(1) This work was supported in part by the Office of Naval Research under Contract No. Nonr 2540(00).

(2) Hughes Research Laboratories, A Division of Hughes Aircraft Company, Malibu, Calif.

(3) W. D. English and L. H. Sommer, *J. Am. Chem. Soc.*, **77**, 170 (1955).

(4) V. A. Zeitler and C. A. Brown, *J. Am. Chem. Soc.*, **79**, 4616 (1957).

(5) D. N. Dolgov and N. F. Orlov, *Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim Nauk*, 1395 (1957). *Doklady Akad. Nauk S.S.S.R.*, **117**, 617 (1957).

(6) K. A. Andrianov, A. A. Zhdanov, N. A. Kurasheva, and V. G. Dulova, *Doklady Akad. Nauk. S.S.S.R.*, **112**, 1050 (1957).

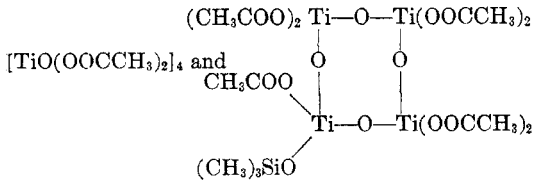
(7) D. C. Bradley and I. M. Thomas, *Chem. and Ind.*, **17** (1958).

(8) J. D. Danforth, *J. Am. Chem. Soc.*, **80**, 2585 (1958).

(9) H. H. Takimoto and G. C. Denault, *Reactions of Acetoxysilanes with Tetraisopropyl Titanate*, Pacific Southwest Regional Meeting of the American Chemical Society, Redlands, Calif., October 1958.

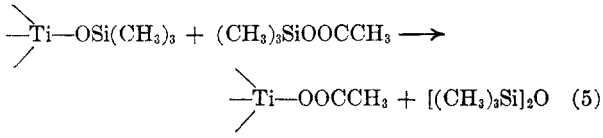
(10) K. A. Andrianov and T. N. Ganina, *Z. Obschei Khimii S.S.S.R.*, **29**, 605 (1959).

solid infusible substances. Among the products characterized and reported were



These authors concluded that the basic reaction between trimethylacetoxysilane and tetrabutoxytitanium resulted in the substitution of the butoxy group by acetoxy groups with the formation of cyclic structures.

Bradley and Thomas,[11] on the other hand, obtained a 95% yield of the tetrakis(trimethylsiloxy)titanium by the reaction of trimethylacetoxysilane with tetraisopropoxytitanium; furthermore, they also found that the treatment of tetrakis(trimethylsiloxy)titanium with trimethylacetoxy silane resulted in a solid product containing acetoxy groups. Thus, the following reaction appears to take place readily:

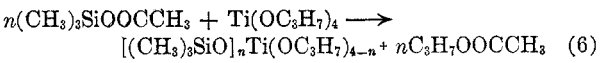


It is apparent from this work that the use of an excess of the acetoxysilane would result in the destruction of the trimethylsiloxy titanium derivative formed initially in the condensation reaction.

The apparent anomaly of the ester-interchange reaction reported by Andrianov and Ganina becomes clear upon the re-examination of their experimental procedures. These workers used a six to one molar ratio of trimethylacetoxysilane to tetrabutoxytitanium, whereas stoichiometry would require a ratio of four to one. In addition, the titanium orthoester was added to the acyloxysilane, and consequently the latter compound was in considerable excess at all times. Under these reaction conditions, then, it is expected that the formation of Ti—$OOCCH_3$ compounds would be favored to the point of exclusion of tetrakis(trimethylsiloxy)titanium.

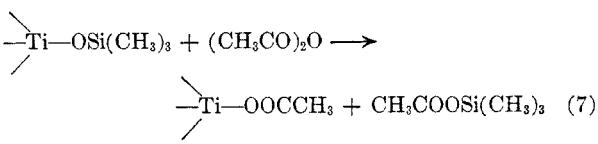
In the present study the findings of Bradley and Thomas have been confirmed. Under proper reaction conditions, the condensation of trimethylacetoxysilane with tetraisopropoxytitanium proceeds smoothly to yield trimethylsiloxy titanium derivatives. By the control of the stoichiometry of the reaction as well as of the order of addition, the mono-, di-, tri-, and tetrasubstituted trimethylsiloxy titanium esters have been produced in good yields.

(11) D. C. Bradley and I. M. Thomas, *J. Chem. Soc.*, 3404 (1959).



To obtain a high yield of the desired product, the purity of the starting materials is very important. Strict care must be taken to exclude moisture from the reaction mixture, as both the acyloxysilane and the titanium esters are readily hydrolyzed. In our later work on the synthesis of tetrakis(trimethylsiloxy)titanium, we found that cooling of the reaction mixture during the slow addition of the trimethylacetoxysilane and minimizing the subsequent period of heating resulted in an improved yield. The use of this modified procedure would probably give higher yields of the partially substituted trimethylsiloxy titanium esters than that reported here.

In analogy to the reaction of tetrakis(trimethylsiloxy)titanium with trimethylacetoxy silane as reported by Bradley and Thomas, the treatment of the former compound with acetic anhydride was investigated. The use of acetic anhydride was of interest in our work on metalloxane polymers. Trimethylacetoxysilane was liberated with the formation of a white, solid product containing acetoxy groups. The reaction may be written as



and is analogous to the acetylation of $(CH_3)_3SiO$—Ti with trimethylacetoxysilane.

EXPERIMENTAL

Materials. Trimethylacetoxysilane was prepared by the method of Schuyten[12] using freshly distilled trimethylchlorosilane. A commercially available tetraisopropoxytitanium was distilled and the product, boiling at 89–91°/3–4 mm., n_D^{25} 1.4608, was used.

Trimethylsiloxytriisopropoxytitanium. Trimethylacetoxysilane (13.2 g., 0.10 mole) was slowly added to 28.4 g. (0.10 mole) of tetraisopropoxytitanium (n_D^{25} 1.4630) in a flask equipped with a stirrer and an addition funnel. Drying tubes were used to protect the mixture from moisture. The addition of acetoxysilane caused the temperature of the mixture to rise. The contents of the flask were stirred for 1.5 hr. and the condensation by-product, isopropyl acetate, was then removed.

Fractionation of the residual material was carried out at reduced pressure to give 26.10 g. (93.1% yield) of product boiling at 91°/5 mm., n_D^{25} 1.4509.

Anal. Calcd. for $C_{12}H_{30}O_4SiTi$: C, 45.85; H, 9.62. Found: C, 45.80, H, 9.56.

Bis(trimethylsiloxy)diisopropoxytitanium. Trimethylacetoxysilane (132.0 g., 1.00 mole) was slowly added to 142.0 g. (0.50 mole) of tetraisopropoxytitanium. A considerable amount of heat was evolved upon addition of the acetoxysilane. The reaction mixture was stirred for 2 hr. and the isopropyl acetate was removed. The product (131.6 g., 76% yield) distilling at 103°/9 mm., n_D^{25} 1.4378 was collected.

Anal. Calcd. for $C_{12}H_{32}O_4Si_2Ti$: C, 41.85; H, 9.37. Found: C, 41.66; H, 9.22.

(12) H. A. Schuyten, J. W. Weaver, and J. D. Reid, *J. Chem. Soc.*, **69**, 2110 (1947).

Tris(trimethylsiloxy)isopropoxytitanium. Trimethylacetoxysilane (26.4 g., 0.20 mole) was treated with 19.0 g. (0.067 mole) of tetraisopropoxytitanium as described previously. Isopropyl acetate was removed. Fractionation of the residual material yielded 16.3 g. (65.3% yield) of product boiling at 107°/8 mm., n_D^{25} 1.4321.

Anal. Calcd. for $C_{12}H_{34}O_4Si_3Ti$: C, 38.49; H, 9.15. Found: C, 38.48; H, 9.08.

Tetrakis(trimethylsiloxy)titanium. This compound was prepared by the addition of 26.4 g. (0.20 mole) of trimethylacetoxysilane to 14.3 g. (0.05 mole) of tetraisopropoxytitanium. After isopropyl acetate was removed, fractionation of the reaction mixture gave 16.6 g. 82.5% yield of product distilling at 125°/8 mm., n_D^{25} 1.4283.

Anal. Calcd. for $C_{12}H_{36}O_4Si_4Ti$: C, 35.62; H, 8.98. Found: C, 35.42, H, 8.73.

Reaction of tetrakis(trimethylsiloxy)titanium with acetic anhydride. Acetic anhydride (5.1 g., 0.05 mole) was added over a period of 10 min. to 10.1 g., (0.025 mole) of tetrakis(trimethylsiloxy)titanium. The temperature of the reaction mixture rose from 28° to 51° during the addition, and a low boiling material was observed refluxing on the wall of the flask. The contents of the flask became increasingly cloudy and a viscous, opaque gel appeared after 15 min. After 30 min. the gel turned into a white solid. The reaction mixture was heated for 30 min. At this time the mixture consisted of two phases, a clear fluid and a white solid. Distillation of the volatile material yielded 9.4 g. of the product boiling at 102°, n_D^{25} 1.3810. The infrared spectrum taken on the volatile product was similar to that of trimethylacetoxysilane. The white solid pot residue weighed 4.5 g. (Si, 10.7%; Ti, 13.8%).

HUGHES RESEARCH LABORATORIES
HUGHES AIRCRAFT CO.
CULVER CITY, CALIF.

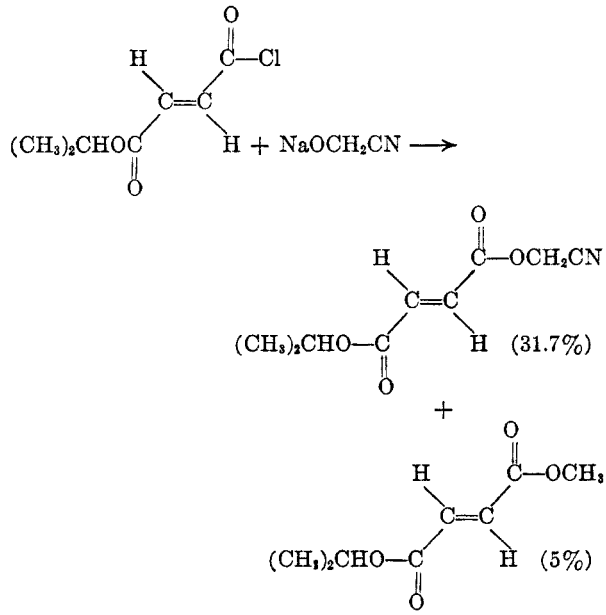
The Preparation of *i*-Propyl Cyanomethyl Fumarate

PAUL G. CAMPBELL AND CHARLES H. SCHRAMM

Received May 2, 1960

In the course of the preparation of new vinyl monomers, a convenient synthesis for alkyl fumaryl chlorides was developed. These acid chlorides served as intermediates for the preparation of various thiolfumarate esters and alkyl aryl fumarates *via* the Schotten-Baumann reaction.[1] As there are numerous examples of the synthesis and polymerization of cyanomethyl esters of α,β-unsaturated acids reported in the literature,[2] it was thought that alkyl cyanomethyl fumarates might also have useful properties.

Generally, the cyanomethyl esters of α,β-unsaturated acids have been prepared by alcoholysis of methyl or ethyl acrylates,[2d] the esterification reaction between an acyl halide and glycolonitrile,[2a,b,c,f] dehydrochlorination of the appropriate ester with quinoline,[2c] and the reaction of an acyl halide, formaldehyde, and an alkali metal cyanide.[2a,c] While Mowry was able to prepare a series of cyanomethyl esters by essentially a Schotten-Baumann reaction involving sodium cyanide and an appropriate acyl halide, these derivatives of dibasic acid halides, including fumaryl chloride, were formed in insignificant yield by this method. Instead biscyanomethyl fumarate was prepared from fumaryl chloride and glycolonitrile in the presence of a tertiary amine. However, as previously mentioned, the Schotten-Baumann reaction had been used successfully with various alkyl fumaryl chlorides, and the reaction between *i*-propyl fumaryl chloride, formaldehyde, and sodium cyanide was undertaken. The yield of



i-propyl cyanomethyl fumarate obtained was 31.7%. However, material of the empirical formula $C_8H_{12}O_4$ was also formed. This was shown to be methyl *i*-propyl fumarate by comparison with an authentic sample prepared from *i*-propyl fumaryl chloride and methanol in the presence of pyridine. The probable explanation for the presence of this by-product is the formation of methanol by the Cannizzaro reaction involving formaldehyde in the alkaline sodium cyanide solution. The methanol could then compete for the available acyl halide.

EXPERIMENTAL

Boiling points are uncorrected. Unless otherwise indicated, distillations were carried out through an 80-cm. Podbielniak-type column.

i-Propyl fumaryl chloride. A sample of crude *i*-propyl hydrogen maleate was prepared by warming a mixture of 0.5 mole each of maleic anhydride and *i*-propyl alcohol on the steam bath until a sirupy liquid resulted. To this

(1) P. G. Campbell, G. Sumrell, and C. H. Schramm, to be published.

(2a) D. T. Mowry, *J. Am. Chem. Soc.*, **66**, 371 (1944); (b) J. Harmon and C. J. Mighton, U. S. Patent **2,379,297** [*Chem. Abstr.*, **39**, 5128 (1945)]; (c) D. T. Mowry, U. S. Patents **2,380,061** and **2,380,062** [*Chem. Abstr.*, **40**, 91 (1946)]; (d) C. E. Rehberg, M. B. Dixon, and W. A. Faucette, *J. Am. Chem. Soc.*, **72**, 5199 (1950); (e) G. F. D'Alelio, U. S. Patent **2,583,062** [*Chem. Abstr.*, **48**, 11806 (1954)]; (f) C. S. Marvel, *et al.*, *Ind. Eng. Chem.*, **47**, 344 (1955).

mixture was added dropwise and with stirring, 0.6 mole of thionyl chloride. After the addition was complete, the mixture was gradually heated to 100°, in *ca.* 2 hr., and maintained at this temperature for an additional 4 hr. The amber colored mixture was fractionally distilled, yielding 41.2 g. (46.8%) of product at 87–89° (12 mm.), n_D^{25} 1.4539.

Anal. Calcd. for $C_7H_9ClO_3$: C, 47.60; H, 5.14; Cl, 20.08. Found: C, 47.69; H, 5.30; Cl, 20.23.

i-Propyl cyanomethyl fumarate. This compound was prepared by essentially the method of Mowry.[2a] A mixture of 13.9 g. (0.17 mole as a 37% aqueous solution) of formaldehyde, 8.4 g. (0.17 mole) of sodium cyanide, and 100 ml. of water was cooled to 5–10°. *i*-Propyl fumaryl chloride, 26.5 g. (0.15 mole) was added dropwise and the mixture was allowed to stir overnight. The solution was extracted with ether and the combined ether extracts were washed with dilute sodium carbonate, dilute hydrochloric acid, and finally with water. After drying over Drierite, the material was distilled through a 15-cm. Vigreux column. The bulk of the distillate, 9.4 g., b.p. 112–113° (1.1 mm.), n_D^{25} 1.4534, represented a 31.7% yield of the desired product.

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.80; H, 5.75; N, 6.82.

However, in the forerun, there was obtained 1.3 g. of material of b.p. 40° (0.2 mm.), n_D^{25} 1.4364.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.65; H, 7.15; N, 0.26.

Methyl i-propyl fumarate. A mixture of 6 g. (0.18 mole) of methanol and 50 ml. of pyridine was cooled to 0°, 12.4 g. (0.07 mole) of *i*-propyl fumaryl chloride was added dropwise and the mixture was allowed to stir overnight. The solution was poured into ice water with stirring. The aqueous solution was extracted with ether and the combined ether extracts were washed with dilute hydrochloric acid and water. The material was fractionally distilled and 7.0 g. (63.4%) of product at 98° (10 mm.), n_D^{25} 1.4354 was obtained.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.91; H, 7.12.

The infrared spectra of this material and the above-mentioned forerun were identical.

Acknowledgment. The authors wish to thank Alfred Foulds for the microanalyses, N. Kerschner for the infrared spectra, and C. F. Hartman for technical assistance in this work.

J. T. Baker Chemical Co.
Phillipsburg, N. J.

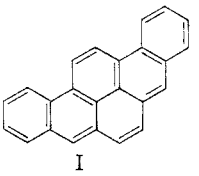
New Synthesis of Dibenzo[a,i]pyrene[1]

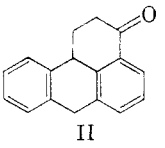
Guido H. Daub and Margaret A. Smith

Received May 5, 1960

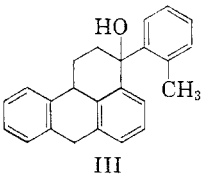
Recently Buu-Hoï and Lavit reported a five-step synthesis of dibenzo[a,i]pyrene (I) from benzo[a]pyrene in approximately 1% over-all yield.[2] Previously, the synthesis of I has been reported by several workers by the reduction of dibenzo[a,i]pyrene-5,8-quinone.[3–5]

A new synthesis of I has been accomplished in 7% over-all yield in this laboratory *via* 3-keto-1,2,3,11b-tetrahydro-7H-*meso*-benzanthracene (II), an intermediate readily available from previously reported research.[6,7] The ketone II was treated with *o*-tolylmagnesium bromide and the resulting carbinol, III, was dehydrated with Lucas reagent and chromatographed on alumina. The red, oily 3-(*o*-tolyl)-1,11b-dihydro-7H-*meso*-benzanthracene (IV) (or isomers thereof) thus obtained was cyclodehydrogenated with palladium on charcoal to dibenzo[a,i]pyrene (I).

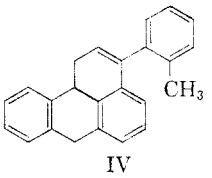

I



II



III



IV

EXPERIMENTAL

3-Hydroxy-3-(o-tolyl)-1,2,3,11b-tetrahydro-7H-meso-benzanthracene (III). A solution of 4.68 g. (0.02 mole) of 3-keto-1,2,3,11b-tetrahydro-7H-*meso*-benzanthracene (II) in 75 ml. of dry benzene was added dropwise over a period of 30 min. to a stirred ether solution of *o*-tolylmagnesium bromide prepared from 4.28 g. (0.025 mole) of *o*-bromotoluene. After refluxing for 1 hr. the reaction mixture was hydrolyzed with 50 ml. of 10% hydrochloric acid. The organic layer was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent left 3-hydroxy-3-(*o*-tolyl)-1,2,3,11b-tetrahydro-7H-*meso*-benzanthracene (III) as a viscous brown oil which failed to crystallize.

3-(o-Tolyl)-1,11b-dihydro-7H-meso-benzanthracene (IV). The crude carbinol, III, was dissolved in anhydrous benzene and refluxed for 90 min. with 30 ml. of Lucas reagent. The organic layer was washed with water and saturated sodium carbonate solution, dried over anhydrous sodium sulfate, and chromatographed on alumina. Removal of the solvent yielded 5.2 g. of the hydrocarbon IV as a light red oil.

Dibenzo[a,i]pyrene (I). The hydrocarbon IV was cyclodehydrogenated by heating with 0.78 g. of 10% palladium on charcoal at 320–400° for 30 min. The crude hydrocarbon was sublimed from the reaction mixture at 275° and 0.05 mm. A toluene solution of the sublimate was chromatographed on alumina and concentration of the eluants yielded 0.42 g. (7% over-all yield from II) of dibenzo[a,i]pyrene (I) as small yellow plates, m.p. 281.5–282.5° uncorr.

Department of Chemistry
University of New Mexico
Albuquerque, N. M.

(1) This investigation was supported in part by a research grant (C-1595) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) N. P. Buu-Hoï and D. Lavit, *Tetrahedron*, **8**, 1 (1960).

(3) R. Scholl and H. Neumann, *Ber.*, **55**, 118 (1922).

(4) E. Clar, *Ber.*, **72**, 1645 (1939).

(5) N. P. Buu-Hoï and D. Lavit, *Rec. Trav. Chim.*, **75**, 1194 (1956).

(6) G. H. Daub and W. C. Doyle, *J. Am. Chem. Soc.*, **74**, 4449 (1952).

(7) J. L. Adelfang and G. H. Daub, *J. Am. Chem. Soc.*, **77**, 3297 (1955).

A Convenient Synthesis of Crystalline L-Threonolactone

JAMES M. PEREL AND PETER G. DAYTON

Received March 28, 1960

Many attempts to obtain L-threonolactone have resulted in poor yields of crude, syrupy material which had to be characterized by derivatives.[1,2] Reichstein, Grüssner, and Bosshard[2] isolated L-threonolactone as the brucine and quinine salts, using acetone L-ascorbic acid as a starting material. Gätzi and Reichstein[3] synthesized for the first time crystalline L-threonolactone directly from L-ascorbic acid in 32% yield. Subsequently, Gätzi and Reichstein,[4] in degradation studies of 3,5:4,6-di-*O*-ethylidene-L-glucitol, obtained very small yields of crystalline L-threonolactone. Later, Lucas and Baumgarten,[5] upon reduction of L-threuronic acid, were unable to obtain crystalline L-threonolactone by the Gätzi and Reichstein[3] isolation procedure and had to characterize it as the brucine salt. Also, Micheel and Peschke,[6] starting from L-threaric acid, obtained a poor yield of a syrup which, upon several months of standing, crystallized and was characterized as L-threonolactone. Hardegger *et al.*[7] obtained crystalline L-threonolactone by direct oxygenation of L-ascorbic acid; in this and one other publication,[8] no yields were given.

The original method of Reichstein, *et al.*[2] has now been simplified, and crystalline material of purity higher than reported[3,7] has been consistently obtained in better yield. L-Threonolactone was needed, in order to continue studies of the metabolism of L-ascorbic acid.[9]

EXPERIMENTAL

5,6-O-Isopropylidene-L-ascorbic acid was prepared from L-ascorbic acid and dry acetone in the presence of anhydrous cupric sulfate, m.p. 218–220°; yields of 95% can be obtained.[10]

Potassium 3,4-O-isopropylidene-L-threonate was prepared by a twenty-fold enlargement of the method of Reichstein, *et al.*[2] The 5,6-*O*-isopropylidene-L-ascorbic acid (86 g., 0.37 mole) was dissolved in 2000 ml. of carbon dioxide-saturated water and was cooled to 0°, causing part of the sugar compound to precipitate. To the resulting suspension, a solution of potassium permanganate (84 g., 0.53 mole) and potassium carbonate (70 g., 0.51 mole) in 2400 ml. of water was added dropwise during 2–3 hr., with constant mixing, the reaction mixture being kept at 0–5°. After reaction was complete (as noticed by lack of decolorization of the permanganate solution), the mixture was heated to 50° to coagulate manganese dioxide, which was filtered off. Two milliliters of ethanol were added and the solution was again filtered. The filtrate was evaporated to dryness with a rotary evaporator at 40°. The residue was extracted three to four times with 100-ml. portions of hot absolute ethanol, and solutions were pooled and evaporated *in vacuo* to about 25 ml. Crystallization was induced by the addition of 3 ml. of cold acetone and, upon evaporation of the solvents, 62 g. (0.29 mole, 78% yield) of a pale yellow solid was obtained. For this synthesis, it was not necessary to recrystallize the crude compound, which melted at 148–150° (m.p. recrystallized material 158°).

L-Threonolactone. A solution of 62 g. (0.29 mole) of the above potassium salt in 175 ml. of distilled water was passed through a 250 g. column of Amberlite IR-120(H), resin, analytical grade. The effluent and 300 ml. water wash were pooled, and the solution (*p*H 3–4) was evaporated to dryness *in vacuo* at 50°. The residue was dissolved in 200 ml. of hot absolute ethanol, and treated twice with 2.5 g. of activated carbon. Upon evaporation to dryness, 35 g. of a pale yellow syrup was obtained which was distilled as described by Gätzi and Reichstein.[3] The first fraction, 8 g. of yellow, nonviscous syrup, distilled at 100–130° (0.8 mm.); it had a sweet odor, and $[\alpha]_D^{21}$ + 10.3° (methanol, *c* 1.90). The main fraction distilled at 145–150° (0.25 mm.) (some decomposition towards the end), and consisted of 18 g. (0.15 mole, 52% yield) of a pale yellow syrup which rapidly solidified into a white crystalline material. The low boiling fraction, suspected to be the acetone derivative of L-threonic acid, when dissolved in 50 ml. of water, refluxed for 1 hr., and treated as above, gave about 4 g. of additional crystalline L-threonolactone. This increased the yield to 65%. Upon recrystallizing from dry ethyl acetate and washing with anhydrous ether,[3] 16 g. of L-threonolactone melting at 66–71° was obtained[11]; phenylhydrazide, m.p. 160–161°, $[\alpha]_D^{21}$ + 52.5° (methanol, *c* 0.73); brucine salt, m.p. 209–210° dec., $[\alpha]_D^{21}$ −19.7° (H_2O *c* 1.92).

A small portion of the lactone, recrystallized three more times, melted at 74–75°, $[\alpha]_D^{19}$ + 51.2 (methanol, *c* 1.54). Infrared (potassium bromide): 1775 cm.$^{-1}$ (γ-lactone), 3380 cm.$^{-1}$ (OH).

Anal. Calcd. for $C_4H_6O_3$: C, 40.63; H, 5.16. Found: C, 40.74; H, 5.37.

The compound gave a quantitative hydroxamic acid as-

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say for a glyconic acid lactone.[12] The best physical constants previously reported are: L-threonolactone, m.p. 74–76°,[8] $[\alpha]_D^{20}$ + 47.0° (methanol)[3]; phenylhydrazide, m.p. 161–161.5°, $[\alpha]_D^{21}$ + 48.6° (methanol)[3]; brucine salt, m.p. 209–210° dec., $[\alpha]_D^{22}$ −19.3° (H_2O).[3] Despite the high melting point given by Hardegger, *et al.*,[7] these authors report $[\alpha]_D$ −27.0° (H_2O) for the brucine salt, indicating the presence of optically active impurities; this suggests that the lower melting (65–68°) material obtained by Gätzi and Reichstein[3] was purer.

Acknowledgment. The authors wish to thank Dr. J. J. Burns for his helpful suggestions and Mr. Julian Kanfer for the analyses.

THE RESEARCH SERVICE
THIRD (NEW YORK UNIVERSITY) MEDICAL DIVISION
GOLDWATER MEMORIAL HOSPITAL
NEW YORK 17, N.Y.

THE LABORATORY OF CHEMICAL PHARMACOLOGY
NATIONAL HEART INSTITUTE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD.

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Strong Analgesics. Some Ethyl 1-Alkyl-4-phenylpiperidine-4-carboxylates

BILL ELPERN,[1] PHILIP M. CARABATEAS, ALBERT E. SORIA, AND LEONARD GRUMBACH

Received May 5, 1960

Some time ago, it was shown,[2] that when the *N*-methyl substituent of meperidine, ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride, was replaced by lower alkyl groups the analgesic potency remained relatively constant although the toxicity gradually increased.

Recently it was reported[3] that replacement of the *N*-methyl substituent of meperidine by aralkyl groups other than benzyl gave compounds having significantly higher analgesic potency. It seemed of interest to us to see if relatively long alkyl groups would effect the same enhancement of analgesic potency.

Accordingly, analogs were prepared wherein the *N*-methyl substituent was replaced by various relatively long chain alkyl groups, both straight and branched.

The alkylation of ethyl 4-phenylpiperidine-4-carboxylate was accomplished using either alkyl halides or toluenesulfonates.

The pharmacological evaluation of these compounds for analgesic potency by the Bass, Vander Brook modification[4] of the D'Amour, Smith rat thermal stimulus method[5] will be reported more fully elsewhere, but a brief summary can be given here. It is apparent that the substituent on the nitrogen of meperidine can be extended to at least nine carbons without loss of any analgesic potency; in fact, the compounds having straight chains and one of the branched chain compounds are more potent than meperidine itself.

EXPERIMENTAL

Ethyl 1-heptyl-4-phenylpiperidine-4-carboxylate hydrochloride. A mixture of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride (13.5 g., 0.05 mole), *n*-heptyl bromide (8.95 g., 0.05 mole), sodium carbonate (20 g.), and *n*-butyl alcohol (100 ml.) was refluxed with stirring for 24 hr. The solids were removed by filtration and a small piece of Dry Ice added to the filtrate to precipitate any secondary amine still present. The filtrate was then concentrated *in vacuo* on a steam bath and the residual oil taken up in ether. A small amount of precipitate was removed by filtration and ethereal hydrogen chloride was added to the filtrate. The product was collected and crystallized from ethyl acetate (150 ml.), then recrystallized from a mixture of benzene (65 ml.) and cyclohexane (65 ml.). There was obtained 14.3 g. (78.0%) of product, m.p. 146.4–149°.

2-Hexyl-p-toluenesulfonate. 2-Hexanol (255 g., 2.5 moles) and pyridine (595 g., 7.5 moles) were stirred in an open beaker and cooled to 0°. *p*-Toluenesulfonyl chloride (858 g., 4.5 moles) was added portionwise over 3 hr. at such a rate as to keep the temperature at about 15°. When the addition was completed, the reaction mixture was allowed to reach room temperature. The unchanged *p*-toluenesulfonyl chloride was hydrolyzed by addition of 150 ml. of water and 200 ml. of pyridine. After hydrolysis was completed, concd. hydrochloric acid was added, the aqueous layer was separated, and the organic layer was washed with water, dilute sodium bicarbonate solution, and water again. Traces of water were removed from the organic layer by heating at 50–60° at reduced pressure, first with a water pump and then with a mechanical pump. There was obtained 533 g. (82%) of yellow oil which was used without further purification.

Ethyl 1-(2-hexyl)-4-phenylpiperidine-4-carboxylate. Methane sulfonate. Ethyl 4-phenylpiperidine-4-carboxylate hydrochloride (1700 g., 6.3 moles) was dissolved in 2.5 l. of water. The solution was made basic with 35% aqueous sodium hydroxide, extracted with ether, the extract dried over anhydrous sodium sulfate, and concentrated to an oil. 2-Hexyl-*p*-toluenesulfonate (768 g., 3.0 moles) was added all at once. The reaction mixture turned into a thick magma after stirring for 3 hr. at room temperature. Heating on the steam bath caused the mixture to liquify, then resolidify after 1 hr. Heating was continued for 1 hr. more and the mixture allowed to stand overnight. Three liters of water was added to the solid reaction mixture, which was heated on the steam bath until solution was complete. The cooled solution was extracted with ether several times. A 750-ml. portion of water was added to the ether extracts and 252 ml. of concd. hydrochloric acid added with cooling. In 15 min. the product precipitated. After drying there was obtained 848 g. (80%) of ethyl 1-(2-hexyl)-4-phenylpiperidine-4-carboxylate hydrochloride, m.p. 162–164. A 1098-g. sample (3.1 moles) of the above hydrochloride was dissolved in 3 l. of water, made basic with 35% sodium hydroxide, and extracted with benzene. The extract was concentrated *in vacuo* and the oily residue dissolved in 250 ml. of isopropyl alcohol and 4 l. of ether. Methanesulfonic acid (328 g., 3.41 moles) was added with cooling and stirring. The product

(1) Present address: Cutter Laboratories, Berkeley, Calif.

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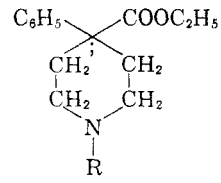
TABLE I

ETHYL 1-ALKYL-4-PHENYLPIPERIDINE-4-CARBOXYLATES



R—	Formula	Yield, %	M.P.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Activity[d]
$CH_3(CH_2)_5$—	$C_{20}H_{32}ClNO_2 \cdot HCl$	48.6	160.0–161.4	67.87	67.81	9.12	9.10	10.02	10.02	6.7
$CH_3(CH_2)_6$—	$C_{21}H_{34}ClNO_2 \cdot HCl$	78.0	146.4–149.0	68.54	68.40	9.31	9.26	9.64	9.49	3.3
$CH_3(CH_2)_7$—	$C_{22}H_{36}ClNO_2 \cdot HCl$	68.4	137.0–138.0	69.16	69.44	9.50	9.09	9.28	8.99	4.0
$CH_3(CH_2)_8$—	$C_{23}H_{38}ClNO_2 \cdot HCl$	43.0	132.4–134.2	69.76	69.58	9.67	9.47	8.95	8.77	2.5
$CH_3(CH_2)_9$—	$C_{24}H_{40}ClNO_2 \cdot HCl$	28.7	135.4–136.2	70.30	70.61	9.83	10.48	8.65	8.60	0
$CH_3(CH_2)_{11}$—	$C_{26}H_{44}ClNO_2 \cdot HCl$	16.4	131.6–132.6	71.27	71.35	10.13	10.01	8.09	8.16	0
CH_3 \ $CHCH_2CH_2$— / C_2H_5	$C_{20}H_{32}ClNO_2 \cdot HCl$	59.9	163.4–165.4	67.87	67.97	9.12	9.59	10.02	9.99	3.0
CH_3 \ CH— / C_4H_9	$C_{20}H_{31}NO_2$[c]	68.8	120–122	60.97	61.01	8.53	8.56	7.75[a]	7.78	5.8
C_2H_5 \ CH— / C_4H_9	$C_{21}H_{34}ClNO_2 \cdot HCl$	17.6	145.0–147.4	8.69[b]		8.70		9.63	9.54	1.7
C_2H_5 \ CH— / C_3H_7	$C_{20}H_{32}ClNO_2 \cdot HCl$	35.6	179.6–182.6	9.04[b]		8.95		10.02	9.99	0.23
Meperidine										1

[a] Analyzed for sulfur. [b] Analyzed for oxygen. [c] B. CH_3SO_3H salt. [d] Relative to meperidine.

precipitated after a few minutes of stirring. The product was collected, washed with ether and dried; yield 1089 g. (86%), m.p. 120–122°.

Anal. Calcd. for $C_{20}H_{31}NO_2 \cdot CH_3SO_3H$: C, 60.97; H, 8.53; S, 7.75. Found: C, 61.01; H, 8.56; S, 7.78.

Acknowledgment. We are greatly indebted to Messrs. M. E. Auerbach, K. D. Fleischer, and staff for the chemical analysis and to Miss L. Oona, Mrs. H. Lawyer, and Mrs. A. Pierson for technical assistance in the pharmacological evaluations.

STERLING-WINTHROP RESEARCH INSTITUTE,
RENSSELAER, N. Y.

N-Substituted *N'*-Phenylureas

CHARLES G. SKINNER AND WILLIAM SHIVE

Received April 11, 1960

A factor which stimulated growth in mature carrot phloem cells has been identified as 1,3-diphenylurea.[1] The possibility that other phenylurea derivatives might possess physiological activity is suggested by the fact that various structural modifications of another plant growth factor, Kinetin[2] [6-(2-furfurylamino)purine], have been found to be effective in stimulating biological responses in a number of assay systems. For example, the furfuryl group of Kinetin can be replaced, with retention of biological activity, by phenyl-,[3] ω-phenylalkyl-,[4] ω-cyclohexylalkyl-,[5] and heterocyclicaminopurines.[6] Accordingly, a number of substituted amines were condensed with phenylisocyanate to produce the corresponding *N*-substituted *N'*-phenylureas. These compounds were subsequently examined in several biological assay systems.

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TABLE I

N-SUBSTITUTED *N'*-PHENYLUREAS[a]

$$C_6H_5—NH—\overset{\overset{O}{\|}}{C}—NH—R$$

R	M.P.[b]	Empirical Formula	Calcd. C,%	Calcd. H,%	Calcd. N,%	Found C,%	Found H,%	Found N,%
3-Phenylpropyl-	87- 90	$C_{16}H_{18}N_2O$	75.56	7.13		75.30	7.03	
4-Phenylbutyl-	107–110	$C_{17}H_{20}N_2O$			10.44			10.44
5-Phenylpentyl-	98–100	$C_{18}H_{22}N_2O$	76.56	7.85	9.92	76.11	7.87	10.00
7-Phenylheptyl-	95- 96	$C_{20}H_{26}N_2O$			9.02			8.89
(2-Methyl-2-phenyl)ethyl-	136–137	$C_{16}H_{18}N_2O$	75.56	7.13		75.19	6.75	
2-α-Naphthylethyl-	154–156	$C_{19}H_{18}N_2O$	78.62	6.25		78.20	6.35	
3-Cyclohexylpropyl-	112–113	$C_{16}H_{24}N_2O$	73.80	9.29		73.66	8.90	
6-Cyclohexylhexyl-	117–120	$C_{19}H_{30}N_2O$	75.45	10.00	9.26	74.35	9.83	9.34
2-Pyridylmethyl-	128–130	$C_{13}H_{13}N_3O$	68.70	5.77	18.55	68.55	5.55	18.46
3-Pyridylmethyl-	103–105	$C_{13}H_{13}N_3O$	68.70	5.77		68.55	5.80	
4-Pyridylmethyl-	134–136	$C_{13}H_{13}N_3O$			18.50			18.88
2-Thenyl-	165–168	$C_{12}H_{12}N_2OS$	62.04	5.21	12.06	62.01	5.24	12.11
2-Furfuryl-	118–120	$C_{12}N_{12}N_2O_2$	66.65	5.59	12.96	66.77	5.79	13.04
3-Methoxypropyl-	248–249	$C_{11}H_{16}N_2O_2$			13.45			13.23

[a] The authors are indebted to Mr. B. S. Gorton for technical assistance with some of these syntheses. [b] M.p. are uncorrected.

The various *N*-substituted *N'*-phenylureas were prepared through the usual procedure by condensing the appropriate amine with phenylisocyanate under anhydrous conditions as indicated in the accompanying equation, and were obtained in essentially quantitative yields. Some physical

$$RNH_2 + C_6H_5—N=C=O \longrightarrow C_6H_5NHCONHR$$

properties and analytical data for the previously unreported derivatives which were prepared are summarized in Table I.

Because of the limited solubility of many of these *N*-substituted *N'*-phenylureas in water, most of the biological assays were carried out using a saturated aqueous solution of the compound as the highest concentration tested. The biological systems studied included an attempt to (a) augment the rate of lettuce seed germination,[7] (b) inhibit hydra tentacle regeneration,[8] (c) inhibit the growth of *Escherichia coli*, and (d) augment the growth inhibition of 2,4-diamino-6,7-diphenylpteridine in *Lactobacillus arabinosus*.[9] Under the testing conditions cited in the references, representative members of each of the homologous series of 6-substituted purine derivatives possessed a significant biological response; however, none of the *N*-substituted *N'*-phenylurea analogs were found to be appreciably active in any of these assay systems. Recently, these compounds were also tested for their ability to stimulate growth in carrot tissue, and no significant growth-promoting effects were observed; in contrast, several of the corresponding 6-substituted aminopurines were active in this test system.[10]

CLAYTON FOUNDATION BIOCHEMICAL INSTITUTE
AND THE DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF TEXAS
AUSTIN 12, TEX.

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(10) The authors are indebted to Dr. E. M. Shantz, Cornell University, for a preliminary report of these data.

The Mechanism of the *N,N*-Dichloro-*sec*-alkylamine Rearrangement

G. H. ALT AND W. S. KNOWLES

Received April 7, 1960

In recent papers[1,2] on the rearrangement of *N,N*-dichloro-*sec*-alkylamines to α-amino ketones Baumgarten and coworkers visualize a mechanism similar to that proposed by Cram and Hatch[3,4] for the Neber rearrangement of oxime tosylates. A key intermediate in this reaction sequence is the dehydrohalogenation of the *N,N*-dichloroamine to

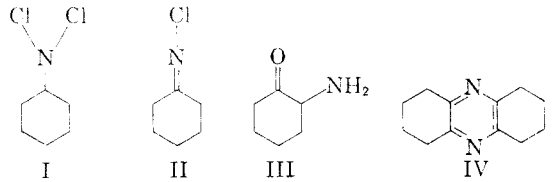
(1) H. E. Baumgarten and F. A. Bower, *J. Am. Chem. Soc.*, **76**, 4561 (1954).

(2) H. E. Baumgarten and J. H. Petersen, *J. Am. Chem. Soc.*, **82**, 459 (1960).

(3) D. J. Cram and M. S. Hatch, *J. Am. Chem. Soc.*, **75**, 33 (1953).

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

the *N*-chloroimine. The *N*-chloroimine being isoelectronic with the oxime tosylate can then undergo closure to an azirine intermediate, evidence for which has already been presented.[2] Positive evidence that the *N*-chloroimine is an intermediate is now submitted.



I II III IV

Treatment of *N,N*-dichlorocyclohexylamine, I, with potassium acetate in ethanol at the reflux temperature gave *N*-chlorocyclohexylimine, II,[5,6] as a colorless liquid. The compound was characterized by its infrared spectrum, elemental analysis and by its conversion to cyclohexanone on hydrolysis with aqueous acid. Treatment of II with one mole of sodium methoxide in absolute methanol gave an excellent yield of 2-aminocyclohexanone, III, isolated and characterized by its conversion to 1,2,3,4,6,7,8,9-octahydrophenazine, IV.[7]

The conversion of II to III with one mole of base proceeds at least as well as the conversion of I to III with two moles of base, so that the *N*-chloroimine II appears to be an intermediate in the *N,N*-dichloro-*sec*-alkylamine rearrangement.

EXPERIMENTAL

N-Chlorocyclohexylimine. To a solution of 25 g. (0.25 mole) of potassium acetate in 130 ml. of absolute ethanol at the reflux temperature was added dropwise over a period of 30 min. 16.8 g. (0.1 mole) of *N,N*-dichlorocyclohexylamine.[1] The reaction mixture was heated for a further 3 hr., cooled to room temperature and 200 ml. of ether and 100 ml. of benzene added. The ethereal solution was washed with 3 × 100 ml. of water, then with 3 × 50 ml. of 2*N* hydrochloric acid and again with water. The solvent layer was dried with calcium sulfate and the solvent removed at room temperature under vacuum. The residue consisted of 13 g. of an oil which was submitted to vacuum distillation through a column at 3 mm. of mercury. After a small forerun, the product distilled at 53–54°. The product was redistilled to give 7.5 g. (57%) of *N*-chlorocyclohexylimine, b.p. 36°/1.5 mm., n_D^{25} 1.5056. The infrared spectrum showed absorption due to C=N at 1612 cm.$^{-1}$, probably displaced from its normal position because of the chlorine.

Anal. Calcd. for $C_6H_{10}ClN$: C, 54.75; H, 7.66; Cl, 26.94; N, 10.65. Found: C, 54.92; H, 7.82; Cl, 26.68; N, 10.53.

Acid hydrolysis of N-chlorocyclohexylimine. A solution of 0.2 g. of *N*-chlorocyclohexylimine in aqueous ethanol was heated on the steam bath with 1 ml. of concd. hydrochloric acid for 30 min. The reaction mixture was treated with 2,4-dinitrophenylhydrazine reagent and on cooling cyclohexanone 2,4-dinitrophenylhydrazone, m.p. and mixture m.p. 160–162° crystallized.

Rearrangement of N-chlorocyclohexylimine. A solution of 1.0 g. (0.0075 mole) of *N*-chlorocyclohexylimine in 20 ml. of methanol was treated with 8 ml. of a 1.0*N* solution of sodium methoxide in methanol at the reflux for 1 hr. The solution was cooled and 30 ml. of dry ether added. The sodium chloride produced was filtered and amounted to 410 mg. (92%). The ethereal solution was extracted with 3 × 70 ml. of 10% hydrochloric acid and with water. The combined aqueous extracts were heated on the steam bath for 15 min., 30 ml. of 50% sodium hydroxide solution and 5 ml. of 30% hydrogen peroxide were then added, and the heating was continued for a further 15 min. The reaction mixture was cooled in ice and the precipitate filtered. The solid was recrystallized from acetone giving 530 mg. (74%) of 1,2,3,4,6,7,8,9-octahydrophenazine, m.p. 108–109°; mixture melting point with an authentic sample[7] was not depressed.

Acknowledgment. The authors are indebted to Dr. B. Katlafsky for the interpretation of the infrared spectra.

ORGANIC CHEMICALS DIVISION
ST. LOUIS RESEARCH DEPARTMENT
MONSANTO CHEMICAL CO.
ST. LOUIS, MO.

(5) S. Reid and D. Sharpe of Central Research Laboratories, Monsanto Chemical Company, Dayton, Ohio (private communication) have also prepared this compound by a different method.

(6) U. S. Patent 2,894,028 claims the preparation of this compound as a crystalline solid, m.p. 20°, by the action of chloramine on cyclohexanone; however, no analysis is given and in our hands the compound failed to crystallize.

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Three 2-Fluoroalkyl-5-nitrofurans

WILLIAM R. SHERMAN, MORRIS FREIFELDER, AND GEORGE R. STONE

Received May 5, 1960

In an excellent series of papers[1] sulfur tetrafluoride has recently been introduced as a unique fluorinating agent. By means of this reagent aldehydes and ketones are readily converted to *gem*-difluoro compounds and carboxylic acids to trifluoromethyl derivatives. Using sulfur tetrafluoride we have been able to obtain three 2-fluoroalkyl-5-nitrofurans. This type of nitrofuran has not previously been reported. Thus sulfur tetrafluoride reacted with 5-nitro-2-furaldehyde to form 2-difluoromethyl-5-nitrofuran, with 2-acetyl-5-nitrofuran to give 2-(α,α-difluoroethyl)-5-nitrofuran, and with 5-nitro-2-furoic acid to produce 2-trifluoromethyl-5-nitrofuran.

All of the fluoroalkylnitrofurans had antibacterial activity. The most active member of the group was 2-difluoromethyl-5-nitrofuran. In a two-fold agar dilution test[2] this compound completely inhibited the growth of *Escherichia coli* and *Salmonella typhimurium* at a concentration of 6 mcg. per ml., *Staphylococcus aureus* at 12 mcg. per ml. and *Proteus vulgaris* at 25 mcg. per ml.

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(2) Carried out by R. J. Otto and staff of Abbott Laboratories.

EXPERIMENTAL[3]

2-Trifluoromethyl-5-nitrofuran. 5-Nitro-2-furoic acid (15.7 g., 0.1 mole) was placed in a 183 ml. stainless steel bomb, which was sealed and cooled in an acetone–Dry Ice bath. After evacuation to about 0.3 mm. pressure, the vessel was charged with sulfur tetrafluoride[4] (43 g., 0.4 mole). After allowing the mixture to warm to room temperature, the reactor was heated to 120° for 7 hr. under autogenous pressure. Following the reaction the cooled bomb was vented and the oily residue taken up in chloroform. The chloroform extract was washed with sodium carbonate solution followed by water, then dried and the solvent removed. The residual oil was fractionally distilled to give 5.47 g. of a light yellow liquid with a camphor-like odor, b.p. 108° (102 mm), n_D^{25} 1.4368. When the sodium carbonate extract was neutralized with acetic acid and cooled, 3.5 g. of the sodium salt of 5-nitro-2-furoic acid (explodes at 247°) was obtained. Based on recovered starting material the yield of pure trifluoromethyl compound was 37%.

Anal. Calcd. for $C_5H_2F_3NO_3$: C, 33.16; H, 1.11; N, 7.74. Found: C, 33.39; H, 1.39; N, 7.60.

2-Difluoromethyl-5-nitrofuran. Sulfur tetrafluoride (42 g., 0.39 mole) was added to 5-nitro-2-furaldehyde (26.4 g., 0.187 mole) in the manner described above. After heating for 8 hr. at 65°, the bomb was cooled and vented. The residue was worked up as before and distilled to provide 6.7 g. of the difluoromethyl compound, b.p. 96–98° (13 mm), $n_D^{21.3}$ 1.4910–1.4922 and 6.2 g. of starting nitrofuraldehyde. Based on recovered starting material the yield was 28%.

Anal. Calcd. for $C_5H_3F_2NO_3$: C, 36.82; H, 1.85; N, 8.59. Found: C, 36.88; H, 1.99; N, 8.56.

2-(α,α-Difluoroethyl)-5-nitrofuran. A mixture of 2-acetyl-5-nitrofuran (31 g., 0.2 mole) and water (1 ml.) was charged with sulfur tetrafluoride (63.0 g., 0.575 mole) as described above. The addition of water was necessary in order to generate hydrofluoric acid to catalyze the reaction. After heating at 75° for 10 hr., the reaction was worked up in the usual way to give 8.9 g. (25%) of the difluoroethyl derivative b.p. 58–60° (0.5 mm.), n_D^{25} 1.4717. When the reaction was carried out at 55–60° for 10 hr., the yield was increased to 34%.

Anal. Calcd. for $C_6H_5F_2NO_3$: C, 40.68; H, 2.84; N, 7.91. Found: C, 40.81; H, 3.09; N, 7.98.

In an attempt to prepare the difluoroethyl compound by carrying out the reaction with catalyst at 40° for 10 hr. only starting ketone was recovered, in 70% yield. When the reaction was run at 75° for 10 hr. in the absence of catalyst, starting material was again recovered, this time in 50% yield. At 110° only tars were formed.

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RESEARCH DIVISION, ABBOTT LABORATORIES
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(3) Boiling and melting points are uncorrected. Analyses were carried out by E. F. Shelberg and staff of Abbott Laboratories.

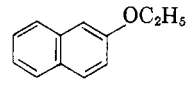
(4) Purchased from E. I. du Pont de Nemours and Company.

Novel Synthesis of Heterocyclic Ketones

WILLIAM C. ANTHONY

Received March 3, 1960

The introduction of an aldehyde function into aromatic (I)[1] and heterocyclic (II)[2] compounds

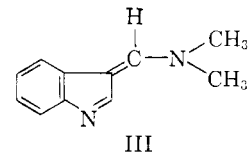


I

II

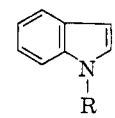
by use of phosphorus oxychloride and methyl formanilide or dimethylformamide has been described in the literature. In this paper we report the introduction of a ketone function into certain indoles and pyrroles by means of phosphorus oxychloride and the appropriate amide. The compounds which were prepared by this method are listed in Table I. All attempts to acylate β-ethoxynaphthalene, thiophene, dimethylaniline, and fluorene by this method failed.

It has been stated[1] that only *one* replaceable hydrogen on the aromatic system is necessary for the reaction with formamides to proceed. Smith[3] has applied this procedure to the preparation of indole-3-carboxaldehyde. He isolated and characterized the intermediate III and proposed a reaction mechanism which would require two replaceable hydrogens on the nucleophile.



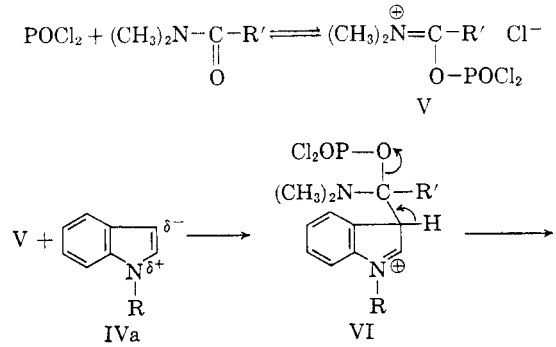
III

In the course of our investigation of indole and pyrrole ketone formations, we have found that an indole compound (IV) with only one replaceable hydrogen, is also convertible into a ketone. With such a starting material, an intermediate similar to III is not possible.



IV R = ethyl

The following reaction scheme may apply to acylations of indoles and pyrroles which contain either one or two replaceable hydrogens:



V

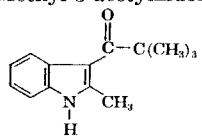
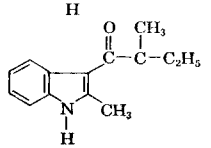
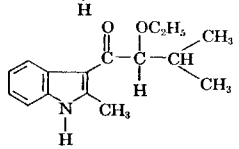
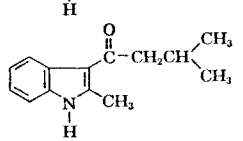
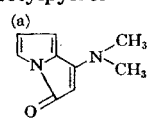
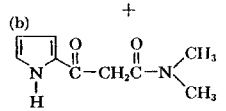
IVa VI

(2) E. Campaigne and W. L. Archer, *J. Am. Chem. Soc.*, **75**, 989 (1953).

(3) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(1) *Org. Syntheses*, Coll. Vol. III, 98 (1955).

TABLE I

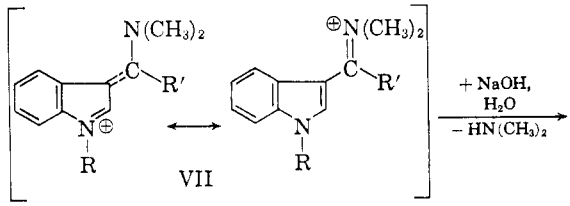
	Nucleophile	Electrophile	Product	M.P.	Yield, %	C,% Calcd.	C,% Found	H,% Calcd.	H,% Found	Z,% Calcd.	Z,% Found	Recrystallization Solvent
1.	5-Benzyl oxy-indole	*N,N*-Dimethylacetamide	5-Benzyloxy-3-acetylindole	189–190[a]	71							95% Ethanol
2.	Indole	*N,N*-Dimethylpropionamide	3-Propionylindole	171–173[a]	85.5							Benzene-petroleum ether, b.p. 60–71°
3.	Indole	*N,N*-Dimethylchloracetamide	3-Chloroacetylindole	233–234[b]	36.6							95% Ethanol
4.	Indole	*N,N*-Dimethylbenzamide	3-Benzoylindole	241–243.5[c]	51	81.42	81.35	5.01	5.03	6.33	6.39	95% Ethanol
5.	Indole	*N*-Methylacetamide	3-Acetylindole	191–193[d]	22.4							95% Ethanol
6.	2-Methylindole	*N,N*-Dimethylacetamide	2-Methyl-3-acetylindole	195–196[e]	98.0							95% Ethanol
7.	2-Methylindole	*N,N,α,α,α*-Pentamethylacetamide		134–135	49.0	78.11	78.20	7.94	8.53	6.50	6.32	Benzene-petroleum ether, b.p. 60–71°
8.	2-Methylindole	*N,N,α*-Trimethylbutyramide		101–103	18.0	78.11	78.01	7.94	8.28	6.50	6.28	Petroleum ether, b.p. 60–71°, 95% ethanol
9.	2-Methylindole	*α*-Ethyl-*N,N,β*-trimethylbutyramide		106–109	24.0	78.92	78.97	8.65	9.11	5.75	5.74	95% Ethanol
10.	2-Methylindole	*N,N*-Dimethylisovaleramide		139–141	62	78.09	78.21	7.56	7.85	6.50	6.35	95% Ethanol
11.	1-Ethylindole	*N,N*-Dimethylacetamide	1-Ethyl-3-acetylindole	87–89[f]	76							95% Ethanol
12.	Pyrrole	*N,N*-Dimethylacetamide	2-Acetylpyrrol	91–92[g]	49							Pet.ether, b.p. 60–71°
13.	Pyrrole	*N,N,N',N'*-Tetramethylmalonamide	(a)  + (b) 	143–144 B.p. 154°/ 1 mm.	6 Undetermined	66.58 59.42	66.99 60.28	6.21 6.71	6.03 6.24	17.27 15.54	17.20 15.73	Benzene

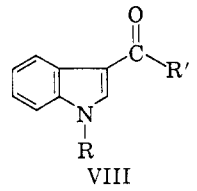
[a] Identical with a sample prepared according to the method described by J. Szmuszkovicz in *J. Am. Chem. Soc.*, 82, 1180 (1960). [b] D. E. Ames, R. E. Bowman, D. D. Evans, and W. A. Jones, *J. Chem. Soc.* (1956) 1958. [c] Bernardo Oddo and Fuigi Sessa, *Gazz. Chim. Italia*, 41, I, 243 (1911). [d] Carlo Zatti, *Ber.*, 22, 662 (1889). [e] O. R. Jackson, *Ber*, 14, 880 (1881). [f] Yu A. Baskakov and N. N. Meljnikov Solbrnik, *Sbornik Statei Obshchei Khim., Akad. Nauk, U.S.S.R.*, 1, 712–713 (1953). [g] Robert Schiff, *Ber.*, 10, 1501 (1877).

TABLE II

ABSORPTION SPECTRA OF NEW COMPOUNDS PREPARED

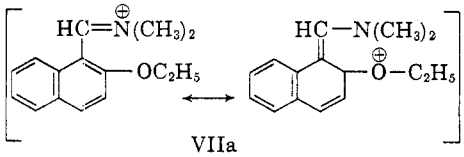
Compd. No.	Infrared, cm.$^{-1}$	Ultraviolet, mμ (ϵ) 95% ethanol
4	NH (3085); C=O (1595); amide vinylog (1565); C=C (1515, 1490); aromatic (747, 713, 697)	313 (12,000); 266 (10,550); 247 (15,075); 303 (14,325); 260 (10,975); 243 (15,400); 206 (47,935)
7	NH (3140); C=O (1592); C=C (1574, 1560, 1527, 1483); C—N (1270, 1205, 1128, 1058, 990); aromatic (795, 752, 740, 720)	302 (10,300); 270 (9,525); 244 (10,675); 216 (29,300)
8	NH (3150, 3080sh); C=O (1592); C=C (1573, 1523, 1485); C—N (1173, 1147, 973); aromatic (785, 751, 747, 735)	301 (10,725); 269 (9,900); 244 (11,675); 216 (29,600)
9	NH (3280); C=O [(plus C=C) 1613]; C=C (1585, 1573, 1485); vinylog (1520); C—N (1267, 1172, 1110); aromatic (757, 738, 728, 700)	303 (11,800); 269.5 (10,375); 245 (11,975); 216 (31,000)
10	NH (3230); C=O (1625, 1610); C=C (1580 sh., 1532, 1492); C—N (1260, 1178, 1052); aromatic (757, 743, 728)	301 (11,450); 268 (10,600); 243 (12,850); 215 (29,400)
13	(a) NH/OH (absent); C=O (1687); C=C (1615, 1357); aromatic (13070); (748, 740sh, 713, 677); other bonds (1430, 1408, 1310, 1250, 1240, 1160, 1073)	431 (2,113); 308 (12,650); (16,375); 274 (15,010); 212 (13,547)
	(b) NH/OH (3200); 6μ region (1680sh, 1655sh, 1625, 1610sh, 1545sh); other bonds (1131, 1107, 1050, 920, 750)	433 (357); 292 (16,269)





R = H or alkyl
R' = alkyl or aryl

A comparison between the behavior of pyrrole and other systems such as β-ethoxynaphthalene in this type of acylation reaction is informative. Although the latter form only aldehydes, the former give both aldehydes and ketones. Furthermore, intermediates such as III have been isolated in the synthesis of compounds containing a pyrrole nucleus but not with other systems. Even in the acetylation of indoles and pyrroles with *N,N*-dimethylcarboxamides, a water soluble compound is formed when water is added to the reaction mixture. This fact lends support to the intervention of intermediates such as VII in the reaction sequence. The counterpart of this intermediate in reactions such as the formylation of β-ethoxynaphthalene would be VIIa. Unlike VII, which probably is sufficiently stabilized by resonance to permit its detection, VIIa may be expected to hydrolyze much more rapidly. The failure of β-ethoxynaphthalene to acetylate with *N,N*-dimethylacetamide is attributable to the relatively low nucleophilicity and higher steric requirements in the former compound.



When this work was essentially complete the existence of German Patent **614,326** was brought to our attention. This patent claims the preparation of 1-methyl-3-*p*-chlorobenzoylindole using *p*-chlorobenzanilide and 1-methylindole. We applied the German procedure to the preparation of 3-acetylindole and found that the procedure reported in this paper is superior to the patented method as the yields were much better and the isolation and purification of the product was simpler. In addition, considerably less time is required to obtain the product.

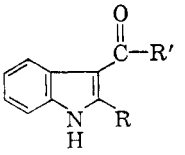
In the course of these experiments some interesting chemical and physical properties of the indolic ketones were observed. It was found that when a carbonyl group is attached to the indole nucleus in the 3-position, the 1-position can be readily alkylated with an alkyl halide and potassium carbonate.[4] When the side chain of the indole ketone was branched, *N*-alkylation could not be achieved under these mild conditions, but could be achieved using much stronger basic conditions.[5]

In the ultraviolet region an alcoholic solution of a 1-unsubstituted 3-acyl indole exhibits a new maximum at 332 mμ in the presence of alkali which is an indication of the degree of enolization. When the 2-position is substituted, branching in the side chain lowers the intensity at this wave length until

(4) W. B. Whalley, *J. Chem. Soc.*, 1651 (1954).
(5) Hans Plieninger, *Ber.*, **87**, 127 (1954).

TABLE III

ULTRAVIOLET ABSORPTIVITY OF[a]

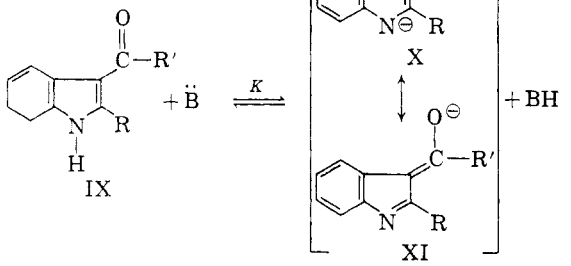


Compd. No.	R	R′	a_M Neutral	a_M KOH	a_M KOH/a_M neutral
5	H	$-CH_3$	483	4750	13.95
2	H	$-CH_2CH_3$	216	2435	11.25
6	$-CH_3$	$-CH_3$	515	1275	2.48
10	$-CH_3$	$-CH_2CH(CH_3)_2$	781	1334	1.71
7	$-CH_3$	$-C(CH_3)_3$	1225	1700	1.38
11[b]	H	$-CH_3$	1071	1047	0.98

[a] (Table I) at 332 mμ (ε) in 95% ethanol and in 0.01*N* 95% ethanolic potassium hydroxide. [b] The compound has a 1-ethyl substituent.

it approaches the value observed in neutral solution as shown in Table III.

The difference in ease of alkylation of the ketones in Table III can be explained on the basis of differences in the degree of steric inhibition of resonance for the various compounds and their respective anions.



The value of K depends on the size of R and R′. If R and R′ are large, then XI is destabilized relative to IX since all the groups cannot become coplanar. Thus the acyl indole becomes a weaker acid, and the value of K is diminished. As a result, a stronger base is needed to effect alkylation. The ultraviolet absorption data of Table III supports this contention.

EXPERIMENTAL[6,7]

The necessary amides which were utilized in this investigation were obtained commercially or were prepared according to literature procedures and used in their crude state. The ketones were prepared essentially as described in the following examples.

5-Benzyloxy-3-acetylindole (I). An 18-ml. sample of *N,N*-dimethylacetamide was cooled to 5° and 7.0 ml. (0.072 mole) of phosphorus oxychloride was slowly added keeping the temperature below 20°. After the addition was complete, a solution of 12.5 g. (0.056 mole) of 5-benzyloxyindole and 9 ml. of *N,N*-dimethylacetamide was slowly added keeping the temperature below 40°. The mixture was heated to 87° for 2 hr. and allowed to cool. The red mass was dissolved in water and extracted with ether. The water solution was made basic with sodium hydroxide and filtered. The solid was washed well with water, refluxed in alcohol containing Darco "60" and filtered. Upon cooling the solution deposited 10.5 g. (71%) of product, m.p. 189–190°. This solid caused no depression in melting point when mixed with an authentic sample (see Table I, footnote *a*).

3-Benzoylindole (4). A mixture of 14 ml. (0.15 mole) of phosphorus oxychloride, 36 g. (0.24 mole) of *N,N*-dimethylbenzamide and 13.0 g. (0.122 mole) of indole was heated to 84° for 2 hr., cooled, and dilute sodium hydroxide was added. The mixture was stirred until a fine suspension was obtained and then filtered. The solid was thoroughly extracted with alcohol to yield 13.5 g. (51%) of product, m.p. 241–243.5°.

Reaction of pyrrole and N,N,N′,N′-tetramethylmalonamide (13). A 93-g. (0.57 mole) sample of phosphorus oxychloride was slowly added to 47.4 g. (0.3 mole) of *N,N,N′,N′*-tetramethylmalonamide at 10–20°. The mixture was cooled to 10° and 20.1 g. (0.3 mole) of pyrrole was slowly added keeping the temperature below 45°. After the addition was complete the mixture was heated over 45 min. to 55–60°. The mixture was maintained at this temperature for 30 min., then cooled and poured into ice water. The solution was made basic with sodium hydroxide and filtered. The solid (7.9 g.) was washed well with water and dried. The solid was shaken twice with 300 ml. of ether and filtered. The ether solution was concentrated yielding 3.5 g. of residue. After three recrystallizations from benzene compound no. 13a was obtained, m.p. 143–144°.

The original basic solution was extracted with ether for 24 hr. and concentrated yielding 16.2 g. of an oil. The oil was dissolved in ether, with a trace of ethyl acetate, and treated with anhydrous hydrogen chloride. The precipitate was washed with ether until free of acid and then treated with potassium hydroxide solution. The mixture was extracted with ethyl acetate. Concentration of the organic layer

(6) All melting points were taken by capillary and are uncorrected.

(7) The author wishes to express his appreciation to Drs. Jacob Szmuszkovicz and R. V. Heinzelman of our Department of Chemistry for their helpful discussions and advice in this work and to Professor D. J. Cram of the University of California, Los Angeles, for his criticisms of and assistance in preparing this paper. The author is also indebted to Dr. J. L. Johnson and associates for spectral data and Mr. W. A. Struck and staff for analytical determinations.

yielded an orange colored oil. A sample of the oil was distilled at 154°/1 mm. to yield compound no. 13b.

Supporting evidence for structure 13a. A 0.003-mole sample of 13a was dissolved in one equivalent of 0.1 *N* hydrochloric acid. After 30 min. bubbles appeared and the solution began to decolorize. After 2 hr. the colorless solution deposited 2-acetylpyrrol, m.p. 91–92°, in quantitative yield.

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KALAMAZOO, MICH.

Halogenated Aminobenzaldehydes and Aminostyrylquinolines[1]

CARL TABB BAHNER, WILLIAM CHAPMAN, CLARENCE COOK, OAKLEY CRAWFORD, CHARLES HANNAN, NORVELL HUNT, LYDIA M. RIVES, WARREN YEE, AND WILLIAM EASLEY

Received April 11, 1960

4-(4′-Dimethylaminostyryl)quinolines bearing a halogen atom on the benzene ring of the quinoline portion of the molecule have been prepared from halogen substituted anilines.[2] Additional halogenated styrylquinolines listed in Table I have been prepared, for testing against animal tumors at the Chester Beatty Research Institute. The presence of a bromine atom usually seems to make the compounds less toxic and less active against tumors. Chloride atoms have similar but smaller effect and fluorine atoms have even less effect, but even a fluorine atom in the 2′ position reduces biological activity sharply. The ratio of maximum tolerated dose to minimum effective dose is not necessarily greatest in the most potent compounds and the position of the halogen atom makes a great deal of difference.

EXPERIMENTAL

The 2-chloro-, 2-fluoro-, 3-fluoro-, and 2,5-difluorobenzaldehydes were prepared from the corresponding halodimethylanilines by the method of Campaigne and Archer.[3] 3-Bromo- and 3-chloro-4-dimethylaminobenzaldehyde were prepared by halogenation of 4-dimethylaminobenzaldehyde.[4] Attempts to prepare 3,5-dibromo- and 3-chloro-5-bromodimethylaminobenzaldehyde by treatment of the monohalo compounds with bromine in glacial acetic acid produced crystalline products which seemed to be perbromide hydrobromides of the monohalo compounds. Heating these crystals 3 hr. at 110–130° formed crystalline substances whose composition corresponded to 3,5-dibromo-4-aminobenzaldehyde and 3-chloro-5-bromo-4-aminobenzaldehyde. The loss of the alkyl groups from the dialkylamino group was less surprising in view of Fries[5] report that 2,4,6-tribromo-*N*,*N*-dimethylaniline perbromide hydrobromide on treatment with water in glacial acetic acid formed 2,4,6-tribromo-*N*-monomethylaniline. Molecular models indicate that the crowding of large groups at the amino end of the molecule would produce severe strain, and that even a single bromine or chlorine atom adjacent to the dimethylamino group would cause some strain. It is interesting to note that, although a halogen atom on the benzene ring in the quinoline portion of the styrylquinolines tends to raise the melting point, 4-(4-dimethylamino-3-bromostyryl)quinoline, 4-(4-dimethylamino-3-chlorostyryl)quinoline, and 4-(4-dimethylamino-3-fluorostyryl)quinoline melt approximately 25°, 40°, and 50° lower, respectively, then the unhalogenated parent compound.

3-Bromo- and 3-chlorolepidine, obtained in poor yield by the method of Ellinger,[6] formed styryl derivatives without undue difficulty. In a modification of the Leese method, the picrate was used instead of the hydrochloride, keeping in mind the possible explosive character of the picrate. Numerous efforts to condense 2-chlorolepidine with 4-dimethylaminobenzaldehyde failed, but this base did condense with 4-nitrobenzaldehyde and the resulting nitrocompound was reduced by stannous chloride to 4-(4-aminostyryl)-2-chloroquinoline. 6-Fluorolepidine, b.p. 135° (23 mm.), was prepared from 4-fluoroaniline by William K. Easley, L. Free, and Frank Howell at East Tennessee State College using the method of Campbell and Schaffner.[7] 6-Fluoroquinaldine, m.p. 49.5–51° was provided by Dr. W. F. Little and Mr. Clarence Cook, of the University of North Carolina.

3-Bromo-4-dimethylaminobenzaldehyde perbromide hydrobromide was prepared by adding 171 g. (1.07 moles) of bromine in 100 ml. of glacial acetic acid dropwise, with stirring, during 15 min., to 75 g. of 4-dimethylaminobenzaldehyde in 240 ml. of glacial acetic acid, then continuing to stir 45 min. while cooling with an ice bath. The orange crystals were washed well with benzene and dried overnight over sodium hydroxide; yield 216 g., m.p. 128.5–129.3°.

Anal. Calcd. for $C_9H_{10}NOBr.HBr.Br_2$: Oxidizing bromine 34.1%; total bromine 68.18%. Found: Oxidizing bromine 34.19, 34.01; total bromine 68.1, 68.3.[8]

3,5-Dibromo-4-aminobenzaldehyde was prepared by heating 67 g. of the above perbromide 3 hr. at 110–130°. The remaining porous mass was recrystallized from ethanol, from isohexane, and again from ethanol; yield 9.0 g., m.p. 149.5–150.8°; after sublimation m.p. 151.7–152.7°.[10]

Anal. Calcd. for $C_7H_5Br_2NO$: C, 30.14; H, 1.81. Found: C, 30.83; H, 2.10, 1.81.[8]

3-Chloro-4-dimethylaminobenzaldehyde perbromide hydrobromide was prepared similarly from 50 g. of 3-chloro-4-dimethylaminobenzaldehyde; yield 66.4 g., m.p. 125.4–127.1°.

Anal. Calcd. for $C_9H_{10}NOCl.HBr.Br_2$: Oxidizing bromine, 37.61; total halogen 64.84. Found: Oxidizing bromine, 36.68, 36.55; total halogen, 63.7, 63.8.[8]

3-Chloro-5-bromo-4-dimethylaminobenzaldehyde was prepared by heating 51.8 g. of the perbromide 8 hr. at 115°,

(1) The research was supported in part by grants from the American Cancer Society and the National Cancer Institute. Some of the compounds described were prepared in the laboratories of the Chester Beatty Research Institute. A portion of this paper was presented at the Southeastern Regional Meeting, ACS, at Raleigh, N. C., in November 1957.

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TABLE I

HALOGEN SUBSTITUTED STYRYLQUINOLINES

Compound	M.P.	Reaction Method	Reaction Temp.	Reaction Time	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
4-(4-Dimethylaminostyryl)quinolines												
2′-Chloro[f]	159.4–160.6	Leese[g]	150–170	10 min.		$C_{19}H_{17}N_2Cl$	73.90	5.55		73.55	5.50	9.4[b]
										73.62	5.47	9.5
2′-Fluoro	126.3–127.5	Leese	150–160	1 hr.	22.8	$C_{19}H_{17}N_2F$	78.04	5.86		73.29	5.71[a]	
										78.29	5.81	
3′-Bromo	117.4–119.1	Fain[2]	119–120	20 hr.	34	$C_{19}H_{17}N_2Br$	64.56	4.83		64.72	4.83[a]	
										64.80	4.79	
3′-Chloro	103.5–104.6	Fain	115–120	23 hr.	13	$C_{19}H_{17}N_2Cl$	73.90	5.55		73.94	5.61[a]	
										73.73	5.65	
3′-Fluoro	92.1–93.1	Leese	150–160	1 hr.	14	$C_{19}H_{17}N_2F$	78.04	5.86		77.78	6.02[a]	
										78.06	5.82	
2′,5′-Difluoro	107.8–108.5	Leese	150–160	1 hr.	23.5	$C_{19}H_{16}N_2F_2$	73.53	5.20		73.50	5.09[a]	
										73.65	5.12	
3-Bromo	193–194.5	Picrate	95–100	2 hr.		$C_{19}H_{17}BrN_2$	64.56	4.83	7.91	64.59	4.85	7.93[c]
3-Chloro	165.9–167.2	Leese	150	25 min.	23	$C_{19}H_{17}ClN_2$	73.90	5.55	9.07	73.95	5.52	9.10[c]
6-Fluoro	159–160.5	Leese	150–154	1 hr.	9.45	$C_{19}H_{17}N_2F$	78.03	5.86		77.81	5.76[a]	
										77.73	5.77	
2-(4-Dimethylaminostyryl)quinolines												
6-Fluoro	195–196	Leese	155–160	1 hr.	25.2	$C_{19}H_{17}N_2F$	78.04	5.86		77.73	5.68[a]	
										77.85	5.90	
4-(4-Nitrostyryl)quinoline												
2-Chloro	240–241	Leese	130	3 hr.	38.3	$C_{17}H_{11}N_2ClO_2$	65.70	3.57		65.53	3.61[a]	
										65.80	3.77	
4-(4-Aminostyryl)quinoline												
3′,5′-Dibromo	222.5–224.0	Leese	145–150	2 hr.		$C_{17}H_{12}N_2Br_2$	50.52	2.99		50.50	2.98[d]	
										50.39	2.84	
2-Chloro	203–204	$SnCl_2$[e]			9.4	$C_{17}H_{13}N_2Cl$	72.71	4.67		72.43	4.60[a]	
										72.47	4.75	

[a] Analysis by Galbraith. [b] Analysis by Weiler and Strauss. [c] Analysis by Burroughs Wellcome. [d] Calcd. Br 39.6. Found: Br 39.6, 39.2 (analysis by Weiler & Strauss). [e] Reacted in concd. hydrochloric acid at room temperature, then heated at 80–90°, 1 hr. [f] Numbers having a prime refer to positions on the styryl portion of the molecule.

TABLE II

FLUOROALDEHYDES

Name	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
4-Dimethylamino-2-fluorobenzaldehyde	62.9–64.5°	74.3	$C_9H_{10}FNO$	64.66	6.03	64.31	5.83[a]
						64.46	5.83
4-Dimethylamino-2,5-difluorobenzaldehyde	60.8–62.0°	17.3	$C_9H_9F_2NO$	58.37	4.90	58.43	5.00[a]
						58.45	5.20

[a] Analysis by Weiler and Strauss.

recrystallizing the residue repeatedly from ethanol, and subliming in vacuum, m.p. 145.7–147.0°.

Anal. Calcd. for $C_7H_5BrClNO$: C, 35.85; H, 2.15. Found: C, 35.63, 35.48; H, 2.23, 2.33.[8]

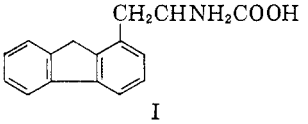
CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN.

Synthesis of *dl*-β-(1-Fluorenyl)alanine

D. C. MORRISON

Received January 26, 1960

In continuation of work begun with the synthesis of *dl*-β-(2-fluorenyl)alanine[1] the corresponding 1-fluorenyl isomer has been prepared. The substance I may be of interest in cancer chemotherapy and as an aromatic amino acid.



I

It was obtained from fluorene-1-carboxylic acid[2] II as starting material by a route similar to that used for the 2-isomer. Reduction of the 1-methyl ester by lithium aluminum hydride gave the 1-carbinol[3] III, which was converted to the corresponding bromide[3] with phosphorus tribromide. The bromide was employed to alkylate the sodium derivative of diethyl acetamidomalonate, and the intermediate ester was hydrolyzed by hydrochloric acid to the amino acid hydrochloride. This salt, when dissolved in dilute alkali and acidified with acetic acid gave the free amino acid. The hydrochloride serves to characterize the compound.

The amino acid was a very sparingly soluble crystalline powder, similar in most physical properties to the 2-isomer. The melting point and that of the hydrochloride were not very sharp as is usually observed with this type of compound.

The infrared spectrum of the free amino acid in a potassium bromide disk showed a wide multicomponent band between 3100–2900 cm.$^{-1}$, probably due to C—H stretching and NH_3^+ stretching. A series of peaks at 1640 (sh), 1613, 1584, 1486, and 1410 cm.$^{-1}$ may be ascribed to C=C stretching, NH_3^+ deformation, and carboxylate ion vibrations but single assignments would be difficult. A very strong band at 759 cm.$^{-1}$ is attributable to C—H out of plane bending.

(1) D. C. Morrison, *J. Org. Chem.*, **24**, 463 (1959).
(2) D. C. Morrison, *J. Org. Chem.*, **23**, 1772 (1958).
(3) L. A. Pinck and G. E. Hilbert, *J. Am. Chem. Soc.*, **68**, 752 (1946).

EXPERIMENTAL

Melting points are uncorrected and were taken on a Fisher-Johns block.

1-Hydroxymethylfluorene. Methyl fluorene-1-carboxylate was prepared by conventional esterification with methanol and sulfuric acid. It was distilled from a small still at 1 mm. pressure and recrystallized from acetone-water. The greater solubility of the ester in organic solvents was an advantage over use of the free acid in reductions. The methyl ester (8.4 g. or 0.038 mole) was treated with lithium aluminum hydride as described for the 2-isomer[1] and gave a nearly theoretical yield (7.4 g.) of crude fluorenyl-carbinol. This melted at 137–146°, and after several recrystallizations from ether–petroleum ether (b.p. 30–60°) had a melting point of 146.5–147.5°. Pinck and Hilbert[3] give 148° corr. The carbinol could also be distilled at 1 mm. to aid in its purification.

1-Bromomethylfluorene. This was prepared by a process similar to that used for the 2-isomer[1] and was obtained in nearly theoretical yield. If insufficient phosphorus tribromide is used, some starting material may be recovered unchanged. The crude product melted at 97–102° and when recrystallized from ether and petroleum ether, this was raised to 100–101.5° with previous sintering; lit.[3] m.p. 104° corr.

Diethyl (1-fluorenylmethyl)acetamidomalonate. A solution of 0.92 g. (0.04 mole) of sodium in absolute ethyl alcohol was treated with 8.7 g. (0.04 mole) of diethyl acetamidomalonate and warmed for solution. Now 10.4 g. (0.04 mole) of the bromide (m.p. 97–102°) was added and the mixture refluxed 16 hr. If variations from the theoretical amounts are used, the product cannot be purified easily. Most of the ethanol was distilled and 3 ml. of acetic acid and an excess of water were added. After leaving overnight on ice, the solid product was filtered, washed with water, and dried. It weighed 15 g. or 94.9%. The ester could be recrystallized from aqueous acetone with difficulty. Slow crystallizations from clear solutions, taking center fractions, were carried out twelve times to obtain a pure product. This was a cream-white powder, m.p. 120–121°.

Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.87; H, 6.33. Found: C, 69.91; H, 6.19.

DL-β-*(1-Fluorenyl)alanine hydrochloride.* A solution of 14.8 g. (0.0375 mole) of the crude ester in 150 ml. of glacial acetic acid was heated to boiling under reflux. While boiling, a mixture of 60 ml. of concd. hydrochloric acid and 10 ml. of water was added and reflux continued for 48 hr. Most of the solvent was now distilled and the residue extracted repeatedly with boiling 2*N* hydrochloric acid until nothing further was removed. The extracts were filtered at 90° or higher and the filtrates cooled to obtain the product. This was filtered and the filtrates concentrated to a small volume for a second crop. The combined weight of hydrochloride was 9.3 g. or 85.8%. The hydrochloride could be

recrystallized from hot dilute hydrochloric acid but it was best to cause slow deposition of the salt from the dilute acid at room temperature on standing. After several recrystallizations in this way, it was further recrystallized from ethanol-toluene and then formed a nearly white crystalline powder. The best material, on heating, began to turn orange at 210–215° with melting at 228–234° to an orange-brown melt.

Anal. Calcd. for $C_{16}H_{16}NO_2Cl$: C, 66.32; H, 5.53. Found: C, 66.69; H, 5.80.

DL-*β*-(*1-Fluorenyl*)*alanine.* The hydrochloride could be converted to the free amino acid by extraction with ammonium hydroxide and acidification with acetic acid. This tended to form a pink product, especially if heated. It was found preferable to acidify a very dilute solution of the hydrochloride in dilute potassium hydroxide with acetic acid so that the amino acid slowly deposited at room temperature. In this way, a nearly white crystalline product was formed. On heating, the best sample began to turn orange at 210–212° and melted 221–230° to an orange-brown melt.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.93. Found: C, 76.04; H, 5.96.

Reaction with ninhydrin. The amino acid was suspended in dilute acetic acid and treated with an excess of ninhydrin and heated. A greenish-gray solution was formed at first which became dark blue-gray on further heating. On boiling a few minutes, a purple solution was produced with dark blue-gray particles (from undissolved amino acid) in suspension.

DEPT. OF PHYSIOLOGICAL CHEMISTRY
UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE
BERKELEY, CALIF.

Preparation of *N*-Substituted Glycines. II. *N*-(3,5-Dinitro-2-thienyl)glycine[1,2a]

JACK M. TIEN AND I. MOYER HUNSBERGER[2b]

Received March 13, 1960

Our interest in *N*-heteroaryl derivatives of the sydnone ring system[3] led us to attempt the preparation of an *N*-thienylsydnone. As no *N*-thienylglycines have been reported in the literature, we first attempted to prepare *N*-2-thienylglycine by condensation of 2-chlorothiophene with glycine ethyl ester hydrochloride (I); however, only unchanged chlorothiophene was isolated. The more reactive 2-bromo-5-nitrothiophene (II) also failed to condense with I. Finally, the hitherto unreported 2-bromo-3,5-dinitrothiophene (III) was prepared in high yield by nitration of 2-bromo-5-nitrothiophene with mixed acid at low temperature. After considerable difficulty the condensation of III with I was effected by heating in absolute ethanol containing a rather carefully regulated amount of zinc oxide. In this way the ethyl ester (IV) of *N*-(3,5-dinitro-2-thienyl)glycine, m.p. 125–126°, was obtained in good yield. Acid hydrolysis of IV then afforded the desired *N*-(3,5-dinitro-2-thienyl)glycine (V). Esterification of V regenerated IV.

All attempts to nitrosate both the glycine (V) and its ethyl ester (IV) were unsuccessful; methods specifically designed for nitrosating weakly basic amines gave only unchanged starting material. As 3,5-dinitro-2-thienol[4] is a much stronger acid than 2,4-dinitrophenol, it seems likely that IV and V also are weaker bases than the corresponding benzene derivatives. Apparently, two nitro groups on the thiophene ring exert effects comparable to three nitro groups on the benzene ring. In this connection it is noteworthy that V separated as the free base from aqueous hydrochloric acid and that IV did not form a hydrochloride salt in absolute ethanol saturated with dry hydrogen chloride.

Further work in this series was abandoned because of the extremely potent vesicant action of both II and III (see Experimental).

EXPERIMENTAL[5]

2-Bromo-3,5-dinitrothiophene (III).[6] Concentrated sulfuric acid (45 ml.) and 60 ml. of yellow fuming nitric acid (sp. gr. 1.49–1.50)[7] were mixed at −5°. The mixed acid was kept at −5° (ice-salt bath) while 14.6 g. (0.070 mole) of II[8] was added portionwise (stirring) during 25 min. After about 10 min. a pasty mass had formed. The ice-salt bath was replaced by a water bath, and stirring was continued for another 25 min. The yellow slurry was poured onto chipped ice to yield 17 g. (96%) of III as a pale yellow crystalline powder, m.p. 135–136°. Recrystallization from hot ethanol afforded colorless plates of unchanged m.p.

Anal. Calcd. for $C_4HN_2O_4BrS$: Br, 31.59; S, 12.67. Found: Br, 31.51; S, 12.53.

This compound was very soluble in acetone, chloroform, dioxane, and petroleum ether; it was soluble in ether but insoluble in benzene, water, and concentrated or dilute hydrochloric acid.

Ethyl ester (IV) *of N-(3,5-dinitro-2-thienyl)glycine.* A hot solution of 6.3 g. (0.045 mole) of I in 450 ml. of absolute ethanol was treated with 11.0 g. (0.0435 mole) of III and 1.40 g. (0.0172 mole) of zinc oxide. The reagents were added alternately and in about six equal portions, a given portion not being added until the preceding one had dissolved. The yellow solution was refluxed in a hot water bath for 2 hr. On cooling, the solution deposited 9.80 g. (82%) of crude IV as yellow to brown needles. Recrystallization from hot

(1) Paper I: J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.* **77**, 6696 (1955).

(2) (a) Supported, in part, by a research grant (CY-2962) from the National Cancer Institute of the Public Health Service and by the U. S. Air Force under Contract No. AF 18(603)-127, monitored by the Air Force Office of Scientific Research of the Air Research and Development Command. Reproduction in whole or in part is permitted for any purpose of the United States government. (b) To whom all inquiries should be sent: Department of Chemistry, University of Massachusetts, Amherst, Mass.

(3) J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.*, **77**, 6604 (1955).

(4) C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, **74**, 2965 (1952).

(5) All combustion analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(6) This procedure is similar to that used[4] for nitrating 2-chloro-5-nitrothiophene.

(7) Red fuming nitric acid produced virtually identical results.

(8) V. S. Babasinian, *J. Am. Chem. Soc.* **57**, 1764 (1935).

ethanol saturated with hydrogen chloride[9] afforded the analytical sample as thin lemon-yellow needles, m.p. 125–126°, which contained no halogen.

Anal. Calcd. for $C_8H_9N_3O_6S$: C, 34.91; H, 3.27; N, 15.27; S, 11.64. Found: C, 35.18; H, 3.27; N, 15.00; S, 11.57.

Both the nature of the solvent and the proportion of zinc oxide used in this preparation are critical. Thus, the above-stated proportion of zinc oxide in 95% ethanol produced only a red gum. Larger proportions of zinc oxide in absolute ethanol gave about 70% yields of IV, but the product had a dark purplish-brown color. Use of absolute ethanol containing no zinc oxide produced a small amount of unidentified white flakes, m.p. 120–121°. With pyridine as solvent, an intractable black product formed immediately. The effect of the varying reflux periods used in these experiments is believed to be slight.

Using pyridine as a solvent, we were unable to effect condensation of I with either 2-chlorothiophene or II. II and I also did not react in absolute ethanol containing zinc oxide.

N-(3,5-Dinitro-2-thienyl)glycine (V). A solution of 0.275 g. (1.00 mmole) of the ethyl ester IV in 12 ml. of concd. hydrochloric acid and 12 ml. of water was boiled, diluted with 20 ml. of water, and then refrigerated to yield 0.235 g. (95%) of V as tiny yellow needles, m.p. 215–217°, with some prior decomposition and sublimation.

Anal. Calcd. for $C_6H_5N_3O_6S$: C, 29.15; H, 2.02. Found: C, 29.64; H, 2.53.

The glycine V was reconverted to IV by saturating its solution in absolute ethanol with dry hydrogen chloride. Concentration and cooling afforded IV as lemon-yellow needles, m.p. 125–126°; no depression when mixed with a sample prepared as described above.

Vesicant properties. Both II and III produced a very persistent skin rash and painful blisters. More than 6 months was required for the irritation to disappear completely, even after treatment with certain cortisone ointments. The person most seriously affected had worked with a large variety of thiophene compounds of other types for several years without any ill effects. In addition to its vesicant properties, III exhibited a potent corrosive action similar to that of the phenols. An acetone solution of III removed the skin in a short time.

Acknowledgment. The authors are indebted to Mr. Jean-Pierre Anselme for repeating and checking the preparations described in this paper.

DEPARTMENT OF CHEMISTRY
FORDHAM UNIVERSITY
NEW YORK 58, N. Y.

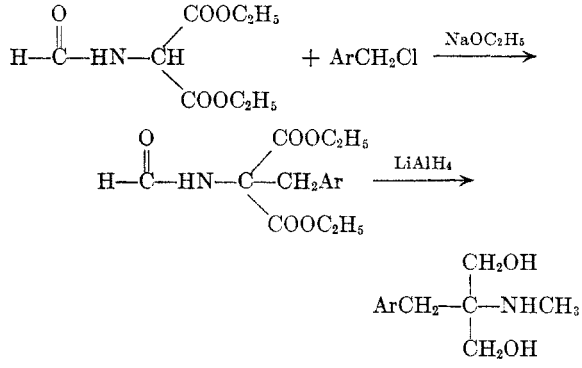
(9) The hydrogen chloride is necessary to remove the color from crude IV.

Syntheses of Some 1-Alkylamino-1,1-di(hydroxymethyl)-2-phenylethanes

B. VITHAL SHETTY AND ALLAN R. DAY[1]

Received March 23, 1960

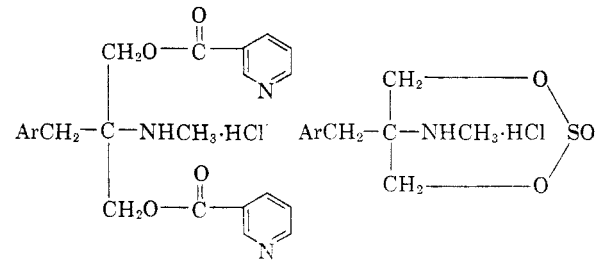
Many derivatives of β-phenylethylamine have been synthesized by earlier investigators with the hope of obtaining physiologically active compounds. In the present study a number of derivatives of β-phenylethylamine, having a trisubstituted carbon atom attached to the amino group, have been synthesized. In all cases the trisubstituted carbon is attached to two hydroxymethyl groups, to a benzyl or a substituted benzyl group and to an alkylamino group. The synthetic steps may be illustrated by the following example:



Ar = C_6H_5, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-HOC_6H_4.

In one case the ethylamino group was introduced in place of the methylamino group. Diethyl acetamidomalonate was the starting material for the preparation of the ethylamino compound.

The dinicotinates and the sulfites of most of these compounds were also prepared.



EXPERIMENTAL

Ethyl isonitrosomalonate, I. This compound was prepared by the procedure of Cerchez.[2] The yield was 81%.

Ethyl formamidomalonate, II. Compound I was reduced with zinc dust and formic acid by the method of Conrad and Schulze.[3] The crude yield was 71%. The product was sufficiently pure for the subsequent steps.

Ethyl α-formamido-α-carbethoxy-β-phenylpropionate, III. Compound III was prepared from II by treatment with sodium ethoxide and benzyl chloride.[4] The yield was 96%, m.p. 105–107°.

N-Methyl-1,1-di(hydroxymethyl)-2-phenylethylamine hydrochloride, IV. Lithium aluminum hydride (19.9 g., 0.52 mole) was added to 470 ml. of dry ether and the mixture stirred for 20 min. at room temperature and then for 20 min. while cooling in an ice bath under an atmosphere of dry nitrogen. Then 50 g. (0.17 mole) of compound III, suspended in 250 ml. of dry ether, was added in small amounts during a period of 45 min. while maintaining the temperature below 30°. After the addition was complete, the stirring was continued for 6 hr. The cooled reaction mixture was carefully

(1) The authors are indebted to the Wyeth Institute for Medical Research for their assistance during this investigation.

(2) V. Cerchez, *Bull. soc. chim. France,* **47**, 1279 (1930).

(3) M. Conrad and A. Schulze, *Ber.*, **42**, 733 (1909).

(4) A. Cohen, E. G. Hughes, and J. A. Silk, British Patent **621,706** (1949).

TABLE I

$ArCH_2-C(CH_2OH)_2-NHR\cdot HCl$

	Formula	Ar	R	Yield, %	M.P.	C, %		H, %		N, %		Cl, %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
IV	$C_{11}H_{16}ClNO_2$	C_6H_5	CH_3	41	153–155	57.02	56.95	7.77	7.54	6.04	6.22	15.31	15.51
V	$C_{18}H_{22}ClNO$	C_6H_5		13	218–220	67.60	67.70	6.88	6.99	4.38	4.28	11.11	11.14
VI	$C_{12}H_{20}ClNO_3$	o-$CH_3C_6H_4$	CH_3	35	163–165	58.67	58.75	8.14	8.24	5.70	5.87	14.42	14.40
VII	$C_{12}H_{20}ClNO_3$	m-$CH_3C_6H_4$	CH_3	30	117–119	58.67	58.40	8.14	8.40	5.70	5.90	14.42	14.21
VIII	$C_{12}H_{20}ClNO_3$	p-$CH_3C_6H_4$	CH_3	56	157–158	58.67	58.87	8.14	8.22	5.70	5.70	14.42	14.20
IX	$C_{12}H_{20}ClNO_3$	C_6H_5	C_2H_5	15	141–143	58.67	58.52	8.14	8.27	5.70	5.91	14.42	14.27
X	$C_{12}H_{20}ClNO_4$	p-$CH_3OC_6H_4$	CH_3	40	168–170	55.08	55.00	7.65	7.80	5.35	5.65	13.54	13.49
XI	$C_{11}H_{18}ClNO_3$	p-HOC_6H_4	CH_3	33	174–176	53.33	53.19	7.27	7.54	5.65	5.87	14.34	14.53

treated with water to decompose the lithium aluminum compounds and the ether layer then separated. The aqueous layer was extracted with ether and the combined ether extracts were then dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the residue was dissolved in 300 ml. of dry ether. The ether solution was treated with dry hydrogen chloride and the gummy precipitate so obtained was extracted with dry ether until it solidified. The solid was dissolved in 75 ml. of dry methanol and the solution decolorized with charcoal. Fifty milliliters of dry acetone was then added followed by 300 ml. of dry ether. After standing overnight at −10°, 18 g. of the hydrochloride was obtained.

The dinicotinate of compound IV was prepared by refluxing a solution of 2 g. of nicotinic anhydride[5] and 1 g. of IV in 200 ml. of dry benzene for 28 hr. The mixture was filtered while hot and the residue washed with hot benzene. The benzene filtrate and washings were combined and the benzene removed *in vacuo*. The residue was dissolved in 50 ml. of dry ethanol, decolorized with charcoal, 300 ml. of dry ether added, and the solution then allowed to stand overnight at −10°. The colorless crystals so obtained were dried *in vacuo*, yield 51%, m.p. 189–190°.

Anal. Calcd. for $C_{23}H_{24}ClN_3O_4$: C, 62.51; H, 5.43; Cl, 8.04; N, 9.41. Found: C, 62.29; H, 5.33; Cl, 8.0; N, 9.44.

The hydrochloride of the sulfite of compound IV was also prepared. Eight grams of *N*-methyl-1,1-di(hydroxymethyl)-2-phenylethylamine hydrochloride was thoroughly mixed with 83 ml. of freshly distilled thionyl chloride. The mixture was allowed to stand for the 30 min. The solid was then removed by filtration and washed with petroleum ether (b.p. 30–60°). It was recrystallized from 60 ml. of methanol with the aid of decolorizing carbon. The yield was 62%, m.p. 157–158°.

Anal. Calcd. for $C_{11}H_{16}ClNO_3S$: C, 47.56; H, 5.76; Cl, 12.79; N, 5.04; S, 11.52. Found: C, 47.53; H, 5.80; Cl, 12.60; N, 5.02; S, 11.30.

N-[1,1-Di(hydroxymethyl)-2-phenylethyl]-1,3-dihydroisoindole, V. Ethyl phthalimidomalonate was prepared by the method of Sheehan and Bolhofer.[6] This compound was converted to sodium ethyl phthalimidomalonate by the procedure of Barger and Weichselbaum.[7]

Ethyl benzyl phthalimidomalonate was made by the method reported by Sorensen.[8] The yield was 90%, m.p. 105–106°.

Lithium aluminum hydride (3.5 g., 0.092 mole) was stirred with 200 ml. of dry ether at room temperature for 20 min. and then for 20 min. at 0°, in an atmosphere of nitrogen. Then 10 g. (0.025 mole) of ethyl benzyl phthalimidomalonate dissolved in 150 ml. of dry ether, was added over a period of 30 min. The mixture was stirred and refluxed for 3 hr. It was then cooled and treated carefully with water. The ether layer was separated and the aqueous layer extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and the ether removed by distillation. The residue was warmed with 50 ml. of 20% hydrochloric acid and the solution filtered. On cooling, the product (V) separated.

N-Methyl-1,1-di(hydroxymethyl)-2-(2-methylphenyl)ethylamine hydrochloride, VI. Sodium (2.07 g., 0.09 g.-atom) was dissolved in 175 ml. of dry ethanol. To this solution was added 15.0 g. (0.09 mole) of ethyl formamidomalonate with stirring. Then 19.5 g. (0.13 mole) of *o*-methylbenzyl chloride[9] was added over a period of 10 min. with stirring. Stirring

(5) W. A. Schrecker and B. P. Maury, *J. Am. Chem. Soc.*, **76**, 5803 (1954).

(6) J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2786 (1950).

(7) G. Barger and T. E. Weichselbaum, *Org. Syntheses*, **Coll. Vol. II**, 384 (1943).

(8) S. P. L. Sorensen, *Centrl.*, **II**, 33 (1943).

(9) K. Kindler and E. Yehlhaar, *Archiv. Pharm.*, **274**, 385 (1936).

and refluxing were continued for 1 hr. The mixture was filtered while hot and the residue was washed with hot alcohol. The alcohol was removed under reduced pressure and the product, ethyl α-formamido-α-carbethoxy-β-2-methylphenylpropionate, was recrystallized from acetone-water, yield 68%, m.p. 92–94°.

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.60; H, 7.03; N, 4.67.

This product was reduced to compound VI with lithium aluminum hydride by the procedure used for making compound IV.

The corresponding sulfite was prepared as described for compound IV. The yield was 65%, m.p. 164–165°.

Anal. Calcd. for $C_{12}H_{18}ClNO_3S$: C, 49.39; H, 6.17; Cl, 12.17; N, 4.80; S, 10.97. Found: C, 49.30; H, 6.15; Cl, 12.40; N, 4.79; S, 10.89.

The corresponding dinicotinate, prepared by the method described for compound IV, melted at 193–194°, yield 38%.

Anal. Calcd. for $C_{24}H_{26}ClN_3O_4$: C, 63.22; H, 5.71; Cl, 7.79; N, 9.22. Found: C, 63.01; H, 6.05; Cl, 7.6; N, 8.92.

N-Methyl-1,1-di(hydroxymethyl)-2-(3-methylphenyl)ethylamine hydrochloride, VII. Ethyl α-formamido-α-carbethoxy-β-3-methylphenylpropionate was prepared by the procedure used for making α-formamido-α-carbethoxy-β-phenylpropionate except that *m*-methylbenzyl chloride was used in place of benzyl chloride. The yield was 84%, m.p. 94–96°.

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.50; H, 6.81; N, 4.76.

Ethyl α-formamido-α-carbethoxy-β-3-methylphenylpropionate was reduced with lithium aluminum hydride to compound VII.

The dinicotinate of VII was prepared in 38% yield, m.p. 185–186°.

Anal. Calcd. for $C_{24}H_{26}ClN_3O_4$: C, 63.22; H, 5.71; Cl, 7.79; N, 9.22. Found: C, 63.20; H, 5.88; Cl, 7.72; N, 9.37.

The sulfite of VII was prepared in 65% yield, m.p. 148–149°.

Anal. Calcd. for $C_{12}H_{18}ClNO_3S$: C, 49.39; H, 6.17; Cl, 12.17; N, 4.80; S, 10.97. Found: C, 49.26; H, 6.42; Cl, 12.20; N, 5.13; S, 10.75.

N-Methyl-1,1-di(hydroxymethyl)-2-(4-methylphenyl)ethylamine hydrochloride, VIII. Ethyl α-formamido-α-carbethoxy-β-4-methylphenylpropionate was prepared by the method used for making ethyl α-formamido-α-carbethoxy-β-phenylpropionate except that *p*-methylbenzyl chloride was used in place of benzyl chloride. The yield was 93%, m.p. 135–136°.

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.63; H, 7.26; N, 4.79.

Ethyl α-formamido-α-carbethoxy-β-4-methylphenylpropionate was reduced with lithium aluminum hydride to compound VIII.

The sulfite of VIII was prepared in 65% yield, m.p. 156–157°.

Anal. Calcd. for $C_{12}H_{18}ClNO_3S$: C, 49.39; H, 6.17; Cl, 12.17; N, 4.80; S, 10.97. Found: C, 49.68; H, 6.45; Cl, 12.15; N, 4.96; S, 10.81.

N-Ethyl-1,1-di(hydroxymethyl)-2-phenylethylamine hydrochloride, IX. Ethyl acetamidomalonate was the starting material for this preparation. Otherwise the procedure was similar to that used for making compound IV.

N-Methyl-1,1-di(hydroxymethyl)-2-(4-methoxyphenyl)ethylamine hydrochloride, X. Ethyl α-formamido-α-carbethoxy-β-4-methoxyphenylpropionate[4] was reduced with lithium aluminum hydride to compound X.

The dinicotinate of X melted at 172–173°, yield 33%.

Anal. Calcd. for $C_{24}H_{26}ClN_3O_5$: C, 61.08; H, 5.51; Cl, 7.52; N, 8.90. Found: C, 61.13; H, 5.56; Cl, 7.6; N, 8.95.

The corresponding sulfite melted at 167–168°, yield 73%.

Anal. Calcd. for $C_{12}H_{18}ClNO_4S$: C, 46.82; H, 5.85; Cl, 11.54; N, 4.55; S, 10.40. Found: C, 46.93; H, 5.82; Cl, 11.45; N, 4.68; S, 10.55.

N-Methyl-1,1-di(hydroxymethyl)-2-(4-hydroxyphenyl)ethylamine hydrochloride, XI. One gram of compound X was refluxed in 2 ml. of 48% hydrobromic acid and 5 ml. of acetic acid for 20 min. On diluting with 20 ml. of water a dark gummy material separated. The gum was washed with dilute sodium hydroxide solution and then with water. The residue was dissolved in ether, the solution dried and treated with dry hydrogen chloride. The hydrochloride, which was quite hygroscopic, was recrystallized from propanol and dry ether.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA 4, PA.

Synthesis of *N*-(2-Hydroxyethyl)-*N'*-(4-pentenyl)ethylenediamine

E. F. CLUFF AND H. F. MCSHANE, JR.

Received March 24, 1960

As an intermediate for the preparation of a certain polyurethane elastomer[1] the substituted ethylenediamine (I) was required in a state of high purity. Diamine syntheses involving alkylation reactions usually give mixtures which contain difficultly separable tertiary amine isomers. The latter materials act as chain terminating agents in polycondensation reactions and prevent the attainment of high molecular weight. Consequently the synthetic route shown in the flowsheet was chosen to provide a diamine of unequivocal structure.

Aminolysis of dimethyl oxalate (II) with *N*-(2-hydroxyethyl)ethylenediamine (III) provided crystalline *N*-(2-hydroxyethyl)piperazine-2,3-dione (IV) in 20–35% yield. This reaction has been shown to be general for many *N*-substituted ethylenediamines.[2] The present reaction most likely proceeds through the formation and subsequent breakdown of a linear polyamide. As the temperature was slowly raised to about 180°, an essentially quantitative yield of alcohol was obtained, and the reaction mass became increasingly more viscous. At this point, the product was insoluble in alcohol and no piperazinedione (IV) could be isolated. Increasing the temperature above 180° to about 220° produced a marked viscosity reduction in the reaction mass which was then alcohol soluble and deposited crystals of IV.

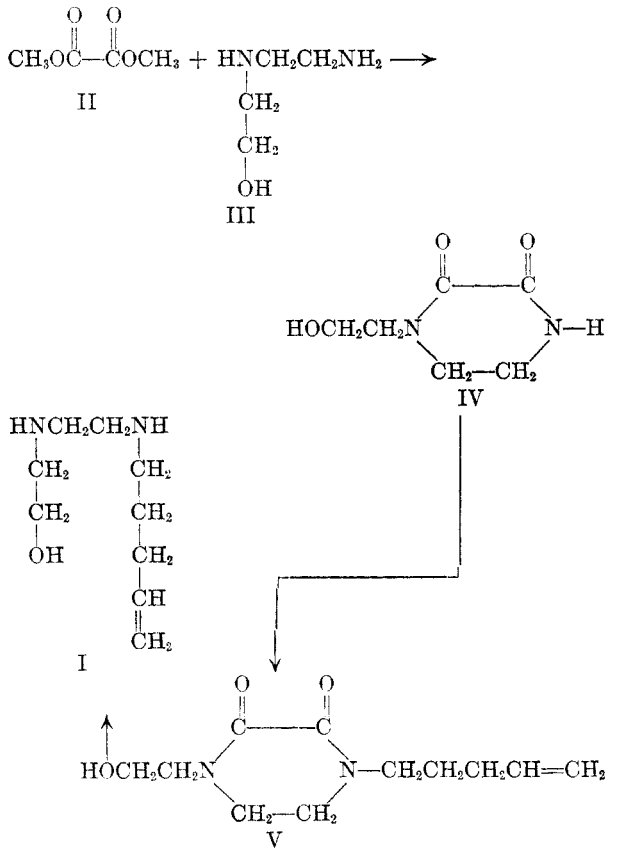
Conversion of IV to the monopotassium salt proceeded smoothly in refluxing *t*-butyl alcohol. The salt was not isolated but was alkylated directly with 1-bromo-4-pentene to provide the crystalline disubstituted piperazinedione (V) in 70% yield. Hydrolysis of V with aqueous-alcoholic potassium hydroxide provided an excellent yield of *N*-(2-hydroxyethyl) - *N'* - (4 - pentenyl)ethylenediamine (I). That alkylation of the piperazinedione (IV) had occurred on nitrogen and not on hydroxyl

(1) E. F. Cluff and E. K. Gladding, Proceedings International Rubber Conf., Washington, D. C., 1959, p. 543.

(2) J. L. Riebsomer, *J. Org. Chem.*, **15**, 68 (1950).

was established by analysis of the diamine (I) for primary amino nitrogen which was absent. The purity of the diamine (I) was ultimately established by its polymerization with polytetramethylene-ether glycol bischloroformate to form a high molecular weight polyurethane.[1]

This sequence of reactions should provide a general route for the preparation of unsymmetrically *N,N'*-disubstituted ethylenediamines of high purity.



EXPERIMENTAL

N-(2-Hydroxyethyl)piperazine-2,3-dione (IV). A mixture of 343 g. (3.30 moles) of aminoethylethanolamine (III) and 5 ml. of concd. hydrochloric acid was added to 389 g. (3.30 moles) of dimethyl oxalate (II) over a period of 15 min. with good agitation. The temperature was raised gradually to 218° in about 1 hr., during which time 206 g. (6.44 moles, 97.6%) of methanol distilled from the reaction mixture. The reactants gradually formed a viscous polymer which broke down above 180° to form the piperazinedione (IV) and a red noncrystalline material which was not further investigated. The mixture was cooled to room temperature, taken up in 400 ml. of ethanol, cooled, and filtered. The crude product (199 g., 38%) was recrystallized from alcohol until pure, m.p. 163–164°.

Anal. Calcd. for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37; N, 17.72. Found: C, 45.2, 45.5; H, 5.9, 6.1; N, 17.4, 17.6.

N-(2-Hydroxyethyl)-N'-(4-pentenyl)piperazine-2,3-dione (V). A 3-l., four-necked flask equipped with a stirrer, thermometer, and reflux condenser fitted with a calcium sulfate drying tube was flamed out and cooled while being flushed with dry nitrogen. Distilled *t*-butyl alcohol (1600 ml.) was added followed by 61.4 g. (1.57 moles) of potassium. The mixture was refluxed and agitated until the metal had completely reacted. *N*-(2-Hydroxyethyl)piperazine-2,3-dione (248 g., 1.57 moles) was added, and the agitated suspension was refluxed overnight. The temperature was lowered to 70°, 234 g. (1.57 moles) of 1-bromo-4-pentene[3] was added, and the mixture was again refluxed overnight. After cooling, the solid potassium bromide was filtered (160 g., 86%), and the *t*-butyl alcohol was distilled. The last traces of solvent were removed under reduced pressure. The viscous residue was extracted with benzene (one 500-ml. and three 250-ml. portions) and then with tetrahydrofuran (three 500-ml., eight 250-ml., and six 100-ml. portions). The tetrahydrofuran was distilled, and the residue placed in a 0° coldbox overnight to crystallize. The solid was recrystallized from tetrahydrofuran (wt. 127 g.). The filtrate was diluted with 2 l. of tetrahydrofuran and the supernatant liquid was decanted from the precipitated oil. The tetrahydrofuran solution was again concentrated, seeded, and cooled to yield another 56 g. of solid. Further concentration of the filtrate yielded an additional 8.5 g. of product, bringing the total yield to 191.5 g. (54%). The residue from the benzene extract, combined with the end tetrahydrofuran filtrate from the recrystallizations, was chromatographed on 200-mesh activated alumina with tetrahydrofuran and ethanol. This resulted in the recovery of an additional 56.5 g. (16%) of material. Recrystallization of the combined solids from tetrahydrofuran afforded pure *N*-(2-hydroxyethyl)-*N'*-(4-pentenyl)piperazine-2,3-dione, m.p. 75–76.5°.

Anal. Calcd. for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.5, 58.5; H, 7.8, 7.9; N, 12.5, 12.7.

N-(2-Hydroxyethyl)-N'-(4-pentenyl)ethylenediamine (I). To a solution of 50 g. (0.770 mole) of 85% potassium hydroxide in 500 ml. of ethanol was added 0.1 g. of 2,6-di-*t*-butyl-*p*-cresol, a solution of 0.1 g. of sodium sulfite in 25 ml. of distilled water, and 83 g. (0.376 mole) of *N*-(2-hydroxyethyl)-*N'*-(4-pentenyl)piperazine-2,3-dione (V). The clear solution was refluxed overnight under an atmosphere of nitrogen. A precipitate began forming after about 15 min. The mixture was cooled, the solid potassium oxalate monohydrate was filtered (65.5 g., 96.8%), and the solvent was distilled from the filtrate. Vacuum distillation of the residue yielded hydroxyethylpentenylethylenediamine (57.6 g., 91.5% yield, b.p. 97.5° (0.15 mm.), n_D^{25} 1.4772).

Anal. Calcd. for $C_9H_{20}N_2O$: C, 62.75; H, 11.70; N, 16.27; primary amino N, absent. Found: C, 62.5, 62.8; H, 11.4, 11.5; N, 16.1, 16.1; primary amino N, absent.

A drop of amine added to aqueous oxalic acid yielded the bisoxalate, m.p. 236–237°.

Anal. Calcd. for $C_{13}H_{24}N_2O_9$: C, 44.31; H, 6.87; N, 7.95. Found: C, 44.0, 44.2; H, 6.8, 6.9; N, 7.8, 7.8.

The amine forms a solid hemihydrate, m.p. 41.5–42°, on admixture with 0.5 mole equivalent of water.

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(3) Prepared according to the method of P. Gaubert, R. P. Linstead, and H. N. Rydon, *J. Chem. Soc.*, 1971 (1937) and E. M. Van Heyningen, *J. Chem. Soc.*, **76**, 2241 (1954), b.p. 124° (760 mm.), n_D^{25} 1.4615 (reported b.p. 124.5–128°, n_D^{25} 1.4642).

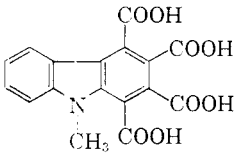
Decarboxylation of *N*-Methylaminoaromatic *ortho*-Carboxylic Acids

WAYLAND E. NOLAND AND GEORGE J. MEISTERS[1]

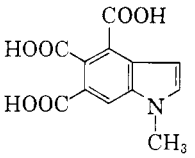
Received April 7, 1960

Dry distillation with soda-lime has been shown previously to produce *N*-demethylation (and con-

comitant decarboxylation to carbazole) of the salt of 9-methylcarbazole-1,2,3,4-tetracarboxylic acid (I).[2] No *N*-demethylation occurred under similar conditions, however, with 9-methylcarbazole[2] or with the salt of a triacid believed to be 1-methylindole-4,5,6-tricarboxylic acid (II).[3] The possibility that



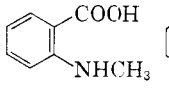
I



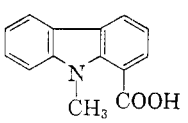
II

N-demethylation of I is occurring by neighboring group participation of the *ortho* carboxylate anion led us to test the generality of *N*-demethylation accompanying decarboxylation by use of selected *N*-methylaminoaromatic *ortho* carboxylic acids.

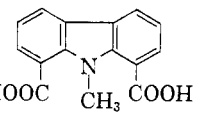
N-Methylanthranilic acid (III),[4] upon decarboxylation with soda-lime,[2] gave a liquid amine, which was isolated in 34% yield as the acetyl derivative, shown to be identical by mixed melting point and infrared comparison in Nujol with an authentic sample of *N*-methylacetanilide. 9-Methylcarbazole-1-carboxylic acid (IV)[5] and 9-methylcarbazole-1,8-dicarboxylic acid (V)[5] were similarly decarboxylated to 9-methylcarbazole in yields of 58% and 50%, respectively.



III

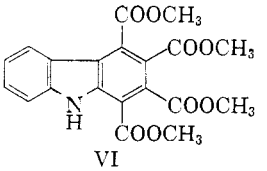


IV



V

These results show that *N*-demethylation accompanying decarboxylation of *N*-methylaminoaromatic *ortho* carboxylic acid salts is not a general phenomenon; that the presence of one or two *ortho* carboxylate groups is, in itself, insufficient cause for *N*-demethylation. It is concluded that, in the case in which it occurs (I), *N*-demethylation is favored by unusual stabilization of the resulting anion, attributable to the combined resonance and inductive effects of the four carboxylate substituent groups. In this connection, it is perhaps of interest to note that our efforts to *N*-methylate the sodium salt of the ester (VI)[2] of the corresponding unsubstituted



VI

compound have been unsuccessful. The results cited in this paper provide no evidence either for or against neighboring group participation by the *ortho* carboxylate group in *N*-demethylation in the case in which it occurs.[2]

Because of its importance to the conclusions drawn in this work, it appeared desirable to establish rigorously the position of the carboxyl group in 9-methylcarbazole-1-carboxylic acid (IV), prepared by action of *n*-butyllithium on 9-methylcarbazole, followed by reaction with carbon dioxide.[5] The structure had been logically assigned previously by analogy with numerous examples of *ortho* lithiation of aromatic amines[5] and with the fact that 9-ethylcarbazole-1-carboxylic acid, prepared similarly, had been shown to be identical with a sample prepared by ethylation of carbazole-1-carboxylic acid.[6]

Carbazole-1-carboxylic acid, most readily prepared from carbazole by reaction of its potassium salt[7] with carbon dioxide at 270°,[8] has been prepared unambiguously by two different methods,[9,10] and the product in the first case has been shown to be identical with a sample prepared from carbazole. After unsuccessful methylation attempts with dimethyl sulfate or methyl iodide in the presence of alkali,[11] we obtained 9-methylcarbazole-1-carboxylic acid (IV) in 11% yield from carbazole-1-carboxylic acid[8] by the action of sodamide and methyl iodide in liquid ammonia.[12] The sample was shown to be identical by mixed melting point (188.5–190°) and infrared comparison in Nujol with a sample[5] prepared from 9-methylcarbazole, thus constituting a proof of structure for 9-methylcarbazole-1-carboxylic acid (IV).

EXPERIMENTAL

Melting points were determined on a calibrated Kofler micro hot stage.

Decarboxylation of N-methylanthranilic acid (III). *N*-Methylanthranilic acid[4] (3.00 g., 0.0198 mole) was mixed thoroughly with powdered soda-lime (9 g.) and the mixture pyrolyzed under a stream of nitrogen with the aid of a Meker burner, in the manner previously described.[2] The liquid distillate was refluxed with acetic anhydride[13] for 30

(1) Graduate School research assistant, summer 1959. It is a pleasure to acknowledge the support of this work through a grant from the General Research Fund of the Graduate School of the University of Minnesota.

(2) W. E. Noland, W. C. Kuryla, and R. F. Lange, *J. Am. Chem. Soc.*, **81**, 6010 (1959).

(3) O. Diels, K. Alder, and H. Winckler, *Ann.*, **490**, 267 (1931).

(4) J. Houben and W. Brassert, *Ber.*, **39**, 3233 (1906). We are indebted to James A. Elberling[1] for this preparation.

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(8) G. L. Ciamician and P. Silber, *Gazz. chim. ital.*, **12**, 272 (1882); *J. Chem. Soc. Abstracts*, **42**, 1103 (1882).

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(11) T. S. Stevens and S. H. Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

(12) K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2641 (1954).

(13) S. M. McElvain, *The Characterization of Organic Compounds*, rev. ed., The Macmillan Co., New York, N. Y., 1953, p. 210.

min., yielding a colorless precipitate (1.01 g., 0.0068 mole, 34%), m.p. 97–98.5°. After recrystallization from ether the sample melted at 99.5–100.5°, mixed m.p. 100.5–101.5° with a sample of *N*-methylacetanilide prepared[13] from Eastman Kodak Co. White Label *N*-methylaniline. The infrared spectra of the two samples in Nujol were identical. ν_{NH} none; $\nu_{C=O}$ 1672 cm.$^{-1}$ in Nujol.

Decarboxylation of 9-methylcarbazole-1-carboxylic acid (IV), 9-Methylcarbazole-1-carboxylic acid[5] (0.50 g., 0.00221 mole) was mixed thoroughly with powdered soda-lime (2.5 g.) and the mixture decarboxylated as described previously. The white sublimate (0.23 g., 0.00127 mole, 58%), m.p. 87.5–89.0°, did not depress the melting point of authentic 9-methylcarbazole,[5] and the infrared spectra in Nujol were identical. ν_{NH} none.

Decarboxylation of 9-methylcarbazole-1,8-dicarboxylic acid (V). 9-Methylcarbazole-1,8-dicarboxylic acid[5] (0.50 g., 0.00186 mole) was decarboxylated as described previously. The white sublimate (0.17 g., 0.00094 mole, 50%), m.p. 84–86°, did not depress the melting point of authentic 9-methylcarbazole[5] (it is interesting to note, however, that the mixed melting point of equal quantities of carbazole and 9-methylcarbazole is 83–87°) and the infrared spectra in Nujol were essentially identical, except for the presence of a medium weak NH or OH band at 3500 cm.$^{-1}$, suggesting contamination by a small amount of carbazole, the *N*-demethylation product.

SCHOOL OF CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS 14, MINN.

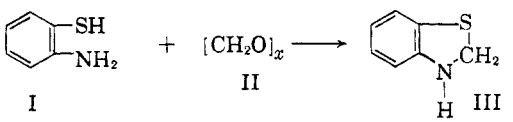
A New Synthesis of Benzothiazoline

GLENN L. JENKINS, ADELBERT M. KNEVEL, AND CHARLES S. DAVIS

Received April 25, 1960

Although a number of syntheses for benzothiazoline have been reported in the literature,[1–4] none offers the convenience of the method which we report here.

We found that benzothiazoline (III) was formed in good yields by refluxing 2-aminobenzenethiol (I) with paraformaldehyde (II) followed by distillation under reduced pressure.



I II III

EXPERIMENTAL

To 12.5 g. (0.1 mole) of 2-aminobenzenethiol (American Cyanamid, tech. grade) dissolved in 20 ml. of anhydrous methyl alcohol was added a mixture of 4 g. of paraformaldehyde (Eastman Kodak, pract. grade) suspended in 10 ml. of anhydrous methyl alcohol. The mixture was refluxed until the original yellow color disappeared (about 12 hr.).

Upon cooling to room temperature, two distinct layers formed. The bottom layer was withdrawn and distilled. The fraction collected at 146–149°/18 mm. was identified as benzothiazoline. The yield was 75–80% based on 2-aminobenzenethiol.

Identification of the product was accomplished as follows: (a) The infrared spectrum showed an intense nitrogen-hydrogen stretching band at 3.0 μ. (b) The boiling point was identical with that reported,[1,5] in the literature (b.p. 270°). (c) The phenylisocyanate derivative melted at 161–162°. The literature[5] value was 162°.

Acknowledgment. The authors are grateful to the American Cyanamid Co. for graciously supplying 2-aminobenzenethiol.

RESEARCH LABORATORIES
SCHOOL OF PHARMACY
PURDUE UNIVERSITY
LAFAYETTE, IND.

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Schiff Bases from 4-(4-Aminostyryl)quinoline and Aldose Sugars[1]

CARL TABB BAHNER, NORVELL HUNT, AND LYDIA M. RIVES

Received May 2, 1960

4-(4-Aminostyryl)quinoline (I) reacted readily with 4-dimethylaminobenzaldehyde to form a Schiff base that was less toxic than I.[2] It seemed that aldose sugars might produce similar products and that the sugar moiety might cause the compounds to be water soluble. The use of a small amount of dimethylformamide made it possible to bring the reactants into a homogeneous liquid reaction mixture at the desired temperature, 120–130°. Glyceraldehyde, ribose, galactose(II), glucose(III), lactose, and maltose all seemed to react smoothly under these conditions, but only II formed crystals that were purified readily by recrystallization. The other products tended to precipitate as gels or amorphous solids.

EXPERIMENTAL

Galactose Schiff base of 4-(4-aminostyryl)quinoline. A mixture of 30.0 g. of I and 15.0 ml. of dimethylformamide was heated to 130° to produce a clear solution. This solution was cooled to 110°, 21.6 g. of II was added slowly with stirring, and the mixture was heated 10 min. at 120–130°. The resulting solid mass was washed with benzene and with water to remove excess starting materials. One gram of solid was dissolved in 30 ml. of dimethylformamide, 20 ml. of the solvent was removed by distillation at 60° at 2.5 mm. The bright yellow crystals which formed were recrystallized

(1) This research was supported by a grant from the National Cancer Institute.
(2) Carl T. Bahner, Clarence Cook, John Dale, John Fain, Fred Hannan, Patricia Smith, and Joan Wilson, *J. Org. Chem.*, **23**, 1060 (1958).

four times in this way, darkening at 209°, melting with decomposition at 216–217°; yield 60%.

Anal. Calcd. for $C_{23}H_{23}N_2O_5$: C, 67.71; H 5.92. Found: C, 67.48–67.75; H, 5.85, 6.06.[3]

Dextrose Schiff base of 4-(4-aminostyryl)quinoline. To a solution formed by heating 9.8 g. of I and 5 ml. of dimethylformamide to 130°, 13.8 g. of III was added slowly, with stirring, at 110°. The mixture was then heated to 120–130° for 30 min., until it solidified. The product was washed with benzene and with water and recrystallized four times from isopropyl alcohol, using a Soxhlet extractor, and three times from methanol; m.p. 189.7–191.7° (dec.).

Anal. Calcd. for $C_{23}H_{23}N_2O_5$: C 67.71; H, 5.92. Found: C, 67.48, 67.75; H, 5.85, 6.06.[3]

These compounds were not readily soluble in water but dissolved readily in hot propyleneglycol and in dimethylformamide.

CHEMISTRY DEPARTMENT
CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN.

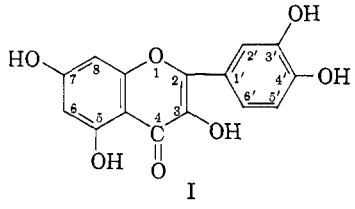
(3) Analyses by Galbraith Microanalytical Laboratories.

Methyl Ethers of Quercetin in Tobacco Flowers[1]

C. H. YANG, H. D. BRAYMER, E. L. MURPHY, W. CHORNEY, N. SCULLY, AND S. H. WENDER

Received February 26, 1960

Monomethyl and dimethyl ethers of quercetin (3,3′,4′,5,7-pentahydroxyflavone, I) having no methoxyl group at the 3-position, such as rhamnetin (quercetin-7-methyl ether), isorhamnetin (quercetin-3′-methyl ether), quercetin-4′-methyl ether, and rhamnazin (quercetin-3′,7-dimethyl ether) have been found previously in natural products, usually as glycosides. A 3,7,4′-trimethyl ether of quercetin, ayanin, has been isolated from the heartwood of the tree *Distemonanthus Benthamianus* by King, *et al.*[2] However, monomethyl and dimethyl ethers of quercetin that contain a methoxyl group at the 3-position have been obtained only by laboratory synthesis.[3–5] This note describes the isolation and identification of quercetin-3,3′-dimethyl ether from tobacco flowers. We have also found other related flavonol ethers in these flowers. One of these other compounds has been tentatively identified as quercetin-3-methyl ether.



I

EXPERIMENTAL

Separation of quercetin ethers. Samples each containing 100 g. of powdered, oven-dried flowers from tobacco plants, *Nicotiana tabacum*, one-sucker variety, grown in the greenhouse at Argonne National Laboratory during 1958, were extracted with 500 ml. of the following solvents in the order named: *n*-pentane, benzene, chloroform, ethyl acetate (anhydrous), and acetone. Each 500-ml. extract was concentrated *in vacuo* to 5 ml. and studied by paper chromatography. The flavonol ethers were mostly in the chloroform fraction, although at least two such compounds were present in small amounts in the ethyl acetate extract.

Each 5-ml. chloroform concentrate was streaked onto eight sheets of Whatman No. 3 MM chromatography paper (approx. 7″ × 22½″), and the chromatograms were developed by descending chromatography in 15% acetic acid–water for about 24 hr. The upper part of each chromatogram, containing the methylated flavonol compounds which moved only a relatively short distance in this solvent, was cut out and sewn onto a new sheet of S & S chromatography paper, No. 589, Red Ribbon. Each sheet was next developed in *n*-butyl alcohol–acetic acid–water (6:1:2 v./v.). After drying, the papers were viewed under long wave-length ultraviolet light (3660 Å). A dark brown zone was seen near the solvent front; it was poorly separated from some blue-fluorescing material. The broad, dark brown zone containing the mixture of methylated flavonols was cut from each chromatogram, eluted with methanol, and then subjected to further extended chromatography, first in 15% acetic acid for 36–48 hours, then on fresh sheets in 60% acetic acid–water. The latter effected separation of the quercetin dimethyl ether from a trace amount of another brown fluorescing substance which had the same mobility as authentic quercetin-3-methyl ether on chromatograms. The yield of this latter compound from the 1958 tobacco flowers was insufficient to confirm its identity. After elution of the brown fluorescing zone containing the quercetin dimethyl ether, the methanol eluates were subjected to further chromatography on S & S No. 589 paper, using four different solvent systems in the order: 15% acetic acid–water: ethyl acetate–formic acid–water (10:2:3 v./v., upper layer); *n*-butyl alcohol–acetic acid–water (6:1:2 v./v.); and finally 60% acetic acid–water. The quercetin dimethyl ether zone of each final chromatogram was then pure enough for identification studies.

Identification of quercetin-3,3′-dimethyl ether. On paper chromatograms, the quercetin dimethyl ether exhibited a dark brown fluorescence under ultraviolet light, but after the compound had been sprayed with a 1% solution of aluminum chloride in ethanol, it gave a yellow fluorescence. Flavone aglycones such as apigenin (4′,5,7-trihydroxyflavone); flavonol glycosides such as isoquercitrin (quercetin-3-glucoside); and certain 3-methyl ethers of flavonols, such as quercetin-3-methyl ether and quercetin-3,7-dimethyl ether exhibit this fluorescent behavior.

After the isolated tobacco quercetin dimethyl ether was refluxed with hydriodic acid, sp. gr. 1.7, for 4 hr., a product was obtained which proved to be quercetin. Identity was established by comparison of color tests, fluorescence, ultraviolet absorption spectra, and co-chromatography with authentic quercetin.

After the tobacco quercetin dimethyl ether was refluxed with dimethyl sulfate and sodium carbonate in acetone for 6 hr., the product showed a blue fluorescence under ultraviolet light and was identified as quercetin-3,3′,4′,5,7-pentamethyl ether by paper chromatographic comparison with an authentic sample. Thus, the unknown was definitely a methyl ether

(1) This work was performed in part under the auspices of the U. S. Atomic Energy Commission.

(2) F. E. King, T. J. King, and K. Sellars, *J. Chem. Soc.*, **155**, 92 (1952).

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of quercetin with at least one methoxy group at the 3-position.

An attempt was made to hydrolyze the quercetin dimethyl ether isolated from tobacco flowers by heating it in 7% sulfuric acid solution for 12 hr. on a steam bath. No sugar was found on paper chromatograms of the reaction mixture, nor was there any significant change observed in the unknown compound, although a trace of some nonflavonol material could be located on the chromatogram by observing the chromatogram under ultraviolet light. These tests indicated that the unknown compound was not a flavone nor a glycoside of quercetin.

When an ethanol solution of the tobacco quercetin dimethyl ether was shaken with sodium amalgam, and then acidified with hydrochloric acid, a salmon pink color was obtained. Thus, substitution of the 3-position of the quercetin was again indicated.[6]

Mixtures of quercetin-3-methyl ether and quercetin-3,7-dimethyl ether, which were synthesized and purified in our laboratory as described in later paragraphs, could be readily separated by paper chromatography, using the solvent system nitromethane-benzene-water (2:3:5 v./v., upper layer), with R_f values of 0.13 and 0.85, respectively. The naturally occurring compound had a R_f value of 0.83 in this solvent system, thus indicating the likelihood of its being a dimethyl, and not a monomethyl quercetin 3-methyl ether.

The fluorescence was quenched by the addition of acetic anhydride to the solid compound,[3] indicating a free 5-hydroxy group on the quercetin. The reaction of the isolated compound with alcoholic ferric chloride solution, and its behavior during methylation, likewise indicated a free phenolic group at the 5-position.

Addition of anhydrous sodium acetate to the solution of the tobacco quercetin dimethyl ether, by the method of Jurd and Horowitz,[7] caused a shift in the short wave-length band of its ultraviolet absorption spectrum from 254 to 275 mμ. This indicates that the 7-hydroxy position of the tobacco quercetin dimethyl ether is open.

The long wave-length band of the ultraviolet absorption spectrum of the tobacco unknown did not shift in absolute ethanol saturated with boric acid and anhydrous sodium acetate, by the spectral method of Jurd.[8] Thus, at least one hydroxyl of the *o*-dihydroxy group (3′,4′) of quercetin was blocked in the tobacco unknown in question.

Degradation of the isolated tobacco quercetin dimethyl ether was carried out by dissolving 1 mg. of the unknown in 30 ml. of a 2*N* solution of sodium hydroxide in a mixture of 50% ethanol and 50% water, and evaporating the solution to dryness in an oven at 120°. The residue was dissolved in water, acidified with hydrochloric acid to a *p*H of 2, and extracted four times with 20-ml. portions of ether. The ether solution was concentrated to 1 ml. and studied by paper chromatography. The acid obtained after degradation proved to be vanillic acid (4-hydroxy-3-methoxybenzoic acid) by the identification procedure of Hergert and Goldschmid.[9] Thus, the 4′-position of the tobacco quercetin dimethyl ether has a free phenolic group, whereas the 3′-position has a methoxy group on it. The structure of the isolated tobacco compound is, therefore, quercetin-3,3′-dimethyl ether.

Studies on both tobacco leaves and flowers obtained from a 1955 field-grown crop at Argonne indicated the presence in each of a quercetin dimethyl ether (which may have been quercetin-3,3′-dimethyl ether instead of the reported quercetin-3,7-dimethyl ether), plus a compound giving color tests similar to and co-chromatographing with authentic quercetin-3-methyl ether.[10] A third compound appeared to be kaempferol-3-methyl ether by preliminary tests. Kaempferol is 3,4′,5,7-tetrahydroxyflavone. The spectral tests of Jurd and Horowitz[7] and of Jurd[8] were not run on these 1955 samples, and their identifications were only tentative. On the 1958 greenhouse-grown tobacco flowers, the quercetin-3,3′-dimethyl ether was present in relatively larger amount, but the compounds which might have been flavonol monomethyl ethers were not present in sufficient amount to undertake the studies needed for unequivocal confirmation of their structures.

Preparation of pure quercetin-3-methyl ether and quercetin-3,7-dimethyl ether. Both of these compounds were synthesized by the method reported by Jain and co-workers[4] for quercetin-3,7-dimethyl ether. On paper chromatographic examination, the resulting methylated quercetin precipitate appeared to be a complicated mixture containing five or more different derivatives of quercetin. Using methanol as the suspending medium, the precipitate was adsorbed onto Magnesol (Food Machinery and Chemical Corp., New York). The column was developed with a solvent system containing two parts of water-saturated ethyl acetate and one part nitromethane. Brown-fluorescing material, with some traces of blue-fluorescing impurities, moved rapidly off the column, leaving the major portion of the blue-fluorescing substances on the column. The eluates containing the brown-fluorescing mixture were then further purified by extended paper chromatography, using in order the solvent systems 60% acetic acid–water, 15% acetic acid–water, and nitromethane–benzene–water (2:3:5 v./v. upper layer) for purification of the quercetin-3-methyl ether. For obtaining pure quercetin-3,7-dimethyl ether, the 60% acetic acid–water, nitromethane-benzene–water, and finally 60% acetic acid–water systems were used. R_f values in the 15% acetic acid and 60% acetic acid systems were respectively: quercetin-3-methyl ether, 0.17 and 0.63 and quercetin-3,7-dimethyl ether, 0.19 and 0.72. Each of these compounds was eluted from its final chromatogram with 50% methanol–water. The purified quercetin-3-methyl ether checked in every respect (fluorescence, R_f values, color tests, and spectral studies) with authentic quercetin-3-methyl ether kindly furnished by Dr. R. M. Horowitz, USDA Fruit and Vegetable Laboratory, Pasadena, Calif. The identity of the purified, synthetic quercetin-3,7-dimethyl quercetin was checked by procedures similar to those described above for the determination of the structure of the tobacco quercetin-3,3′-dimethyl ether isolated from tobacco.

CHEMISTRY DEPARTMENT
UNIVERSITY OF OKLAHOMA
NORMAN, OKLA.
AND
DIVISION OF BIOLOGICAL AND MEDICAL RESEARCH
ARGONNE NATIONAL LABORATORY
ARGONNE, ILL.

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Fluoro Analogs of Prostigmine

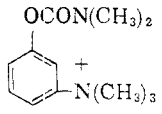
SEYMOUR L. SHAPIRO, THEODORE BAZGA, AND LOUIS FREEDMAN

Received March 17, 1960

The useful physiological properties of prostigmine,[1] I, and its analogs suggested exploration of

(1) A. Stempel and J. A. Aeschlimann, *Medicinal Chemistry*, Vol. III, John Wiley & Sons, New York, N. Y., 1956. p. 239 (see pp. 270–274).

trifluoromethylphenyl carbamates, and related compounds, II.



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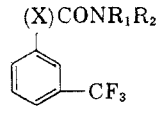


II

X = O, NH
R_1R_2 = H, alkyl, aryl

In particular, employment of a strongly *meta* orienting trifluoromethyl group[2] evaluated replacement of the electronically similar trimethylammonium group[3,4] of I. The steric effects of the trifluoromethyl group[5] and its incorporation into biologically active agents[6] have been recently described. The *meta* relationship of the oxy function in II was indicated on pharmacological[7] and chemical[2,8–12] bases.

The compounds were conveniently prepared by reaction of the appropriate isocyanate ester with *m*-trifluoromethylphenol or *m*-trifluoromethylaniline and are described in Table I.

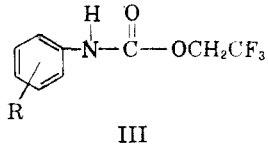
TABLE I

m-TRIFLUOROMETHYLPHENYL CARBAMATES AND UREAS, II

No.	R_1[a]	M.P.[b,c]	Formula	Nitrogen,[d] % Calcd.	Found
		X = —O—			
1	CH_3—[e]	[f]	$C_{10}H_{10}F_3NO_2$	[g]	
2	C_2H_5—	52–53	$C_{10}H_{10}F_3NO_2$	6.0	6.1
3	*n*-C_4H_9—	43–44	$C_{12}H_{14}F_3NO_2$	5.4	5.0
4[h]	C_6H_5—	142[c1]	$C_{14}H_{10}F_3NO_2$	5.0	5.0
5	*p*-$C_2H_5OC_6H_4$—	137–138	$C_{16}H_{14}F_3NO_3$	4.3	4.7
		X = —NH—			
6	C_2H_5—	119–120[c2]	$C_{10}H_{11}F_3N_2O$	12.1	12.0
7	C_4H_9—	[i]	$C_{12}H_{15}F_3N_2O$	10.8	10.5
8	$C_2H_5OOCH_2$—	112–114	$C_{12}H_{13}F_3N_2O_3$	9.7	9.8

[a] R_2 is hydrogen unless otherwise indicated. [b] Melting points are not corrected (capillary). [c] Recrystallizing solvent is hexane unless otherwise shown; [c1]ethanol;[c2]acetonitrile. [d] Analyses by Weiler and Strauss, Oxford, England. [e] R_2 is methyl. [f] B.p. 84–86° (0.2 mm.). [g] *Anal.* Calcd. C, 51.5; H, 4.3. Found: C, 51.7; H, 4.2. [h] Reported by M. T. Leffler and E. J. Matson, *J. Am. Chem. Soc.*, **70**, 3439 (1948), m.p. 138–140°. [i] B.p. 184–192° (2 mm.).

On testing[13] compound 1, the trifluoromethyl analog of I, gave complete ganglionic block at 5 mg./kg., although it was without anticholinesterase activity.[1] Other noted effects were tranquilizing activity with compound 2, anti-tremorine effects with compound 3, and anti-inflammatory activity with compounds 6–8. Compound 6 showed anesthetic activity somewhat better than procaine. The noted tranquilizing activity of compound 2 suggested examination of β,β,β-trifluoroethylcarbanilate analogs, III,[14] which proved to be inactive.



III

R = *p*-CH_3O— (m.p. 81–83°)
R = *p*-Cl— (m.p. 70–71°)

EXPERIMENTAL[15]

N,N-Dimethyl-(m-trifluoromethyl)phenyl carbamate (Compound 1). To a stirred refluxing solution of 8.1 g. (0.05 mole) of *m*-trifluoromethylphenol in 30 ml. of benzene and 10 ml. of triethylamine there was added dropwise 6.0 g. (0.056 mole) of dimethylcarbamyl chloride over 75 min. Stirring and refluxing was continued for 3 hr. When cool, the formed triethylamine hydrochloride was separated and washed with benzene. The filtrate and the benzene washings were combined, the benzene was removed, and the residue distilled to give 8.36 g. (72%) of product, b.p. 84–86° (0.2 mm.).

N-Ethyl-(m-trifluoromethyl)phenyl carbamate (Compound 2). A mixture of 3.24 g. (0.02 mole) of *m*-trifluoromethylphenol, 1.36 g. (0.02 mole) of ethyl isocyanate, and 1 drop of pyridine was warmed under reflux in an oil bath maintained at 100° for 1 hr. When cool, the reaction mixture crystallized and upon trituration with cold hexane gave 2 g. (43%) of product.

Compounds 3–5 were similarly prepared.

N-Ethyl,N'-(m-trifluoromethyl)phenylurea (Compound 6). A mixture of 3.2 g. (0.02 mole) of *m*-aminobenzotrifluoride and 1.36 g. (0.02 mole) of ethyl isocyanate reacted at 20° and solidified. Upon trituration with hexane 2.8 g. (61%) of product was obtained.

Compounds 7 and 8 were similarly prepared.

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(12) R. H. Groth, *J. Org. Chem.*, **25**, 102 (1960).
(13) For ganglionic block, anti-tremorine and anesthetic activity testing procedure see S. L. Shapiro, H. Soloway, E. Chodos, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 203 (1959); for tranquilizing test see S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc. Sci. Ed.*, **46**, 333 (1957); for anti-inflammatory method see E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exptl. Biol. Med.*, **95**, 729 (1957).
(14) Reported by V. T. Oliverio and E. Sawicki, *J. Org. Chem.*, **20**, 1733 (1955); III, R = *p*-CHO—, m.p. 84–85°; III, R = *p*-Cl—, m.p. 72–73°.
(15) Data shown in Table I are not reproduced. Representative examples are shown for the general procedures used.

Acknowledgment. The authors wish to thank Dr. G. Ungar and his staff for the pharmacological screening of the compounds, and Dr. I. Rose for the preparation of compound 1.

ORGANIC RESEARCH DIVISION
U. S. VITAMIN & PHARMACEUTICAL CORP.
YONKERS 1, N. Y.

Mescaline Analogs. X. 3,4-Dimethyl-, 3,4-Dichloro-, and 3,5-Dimethoxy-4-methyl-β-phenethylamines[1]

F. BENINGTON,[2] R. D. MORIN,[2] AND LELAND C. CLARK, JR.[3]

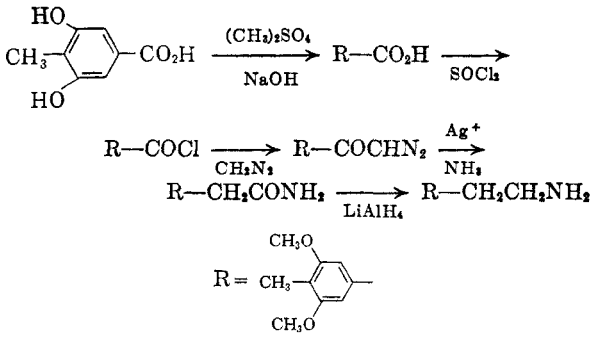
Received March 22, 1960

In a continuation of a long-range study of the influence of ring substituents on β-phenethylamines on psychopharmacological activity,[4] three new β-phenethylamines substituted in the 3-, 4-, or 5-positions of the ring were synthesized, and the effect of these compounds on normal cat behavior was examined. The sham rage response[5] induced by 3,4,5-trimethyl-, 4-methyl-, 4-chloro-, and 3,5-dimethyl-4-methoxy-β-phenethylamines[4] prompted investigation of other β-phenethylamines with these ring substituents.

The three new β-phenethylamines described in this communication, 3,4-dimethyl-, 3,4-dichloro-, and 3,5-dimethoxy-4-methyl-, all induced a strong rage response in cats. These findings confirmed previous observations that the substitution of methyl or chloro groups in the 3- and 4-positions of the β-phenethylamine molecule results in compounds which produce a rage syndrome in cats. Replacement of just the 4-methoxy group in mescaline (3,4,5-trimethoxy-β-phenethylamine) with methyl is sufficient to impart rage-producing properties to the compound, whereas mescaline itself does not induce rage.

3,4-Dimethyl-β-phenethylamine was synthesized from 3,4-dimethylbenzyl chloride by conversion to 3,4-dimethylphenylacetonitrile and reduction with lithium aluminum hydride. 3,4-Dichloro-β-phenethylamine was obtained in a similar manner.

3,5-Dimethoxy-4-methyl-β-phenethylamine was synthesized from 3,5-dihydroxy-*p*-toluic acid[6] by the following steps:



Details of the pyschopharmacological properties of these compounds will be published elsewhere.

EXPERIMENTAL[7]

3,4-Dimethylbenzyl chloride. A rapid stream of dry hydrogen chloride gas was passed into a stirred mixture of 106 g. of *o*-xylene, 84 g. of 35% aqueous formaldehyde solution, and 450 ml. of concd. hydrochloric acid kept at 65 ± 5° for 6 hr. The organic layer was separated, the aqueous layer extracted with ether, and the combined organic layer was washed thoroughly with water and aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and distilled through a 12-in. Vigreux column. After removal of unchanged *o*-xylene and a small intermediate fraction, 3,4-dimethylbenzyl chloride was collected as the fraction boiling at 113–116°/22 mm.; yield, 98.4 g. (64%). The structure of this chloromethyl compound has been demonstrated.[8]

3,4-Dimethylphenylacetonitrile. To a stirred solution of 26 g. of sodium cyanide in 30 ml. of water was added a solution of 62 g. of 3,4-dimethylbenzyl chloride in 100 ml. of alcohol, and the resulting mixture was stirred and refluxed for 4 hr. The dark reaction mixture was filtered from inorganic salts, and most of the alcohol was removed from the filtrate by evaporation under reduced pressure. The residue was treated with water, and the crude oily product extracted with ether. The ether solution was washed three times with 50-ml. portions of 1:1 hydrochloric acid to remove foul-smelling isonitrile, then several times with water, and finally dried over anhydrous magnesium sulfate. After removal of ether, the residue was distilled under reduced pressure through a 12 in.-Vigreux column; b.p. 147–150°/22 mm.; yield, 44.6 g. (77%).

Anal. Calcd. for $C_{10}H_{11}N$: C, 82.7; H, 7.6. Found: C, 82.4; H, 7.5.

3,4-Dimethyl-β-phenylethylamine. To a stirred solution of 11.7 g. of lithium aluminum hydride in 250 ml. of dry absolute ether was added slowly a solution of 29 g. of 3,4-dimethylphenylacetonitrile at a rate which caused the ether to reflux. The mixture was then stirred and heated under reflux for 0.5 hr., cooled in an ice bath, and hydrolyzed by slow and cautious addition of water until decomposition of the reaction complex was complete. Inorganic matter was removed by filtration, the filtrate was dried (anhydrous magnesium sulfate), filtered again, and treated with alcoholic hydrogen chloride to precipitate the 3,4-dimethyl-β-phenethylamine as its hydrochloride salt; yield, 21 g. (57%); recrystallization from hot alcohol afforded colorless plates, m.p. 222–223°.

Anal. Calcd. for $C_{10}H_{16}ClN$: Cl, 19.1; N, 7.55. Found: Cl, 19.0; N, 7.47.

3,4-Dichlorophenylacetonitrile. A mixture of 100 g. of α,3,4-trichlorotoluene,[9] 130 ml. of ethanol, 33.4 g. of sodium cyanide, and 40 ml. of water was stirred and heated under

(1) This research was supported by Battelle Memorial Institute funds and by Public Health Service Grant M-1588.
(2) Battelle Memorial Institute.
(3) The University of Alabama Medical School.
(4) F. Benington, R. D. Morin, L. C. Clark, Jr., and R. P. Fox, *J. Org. Chem.*, **23**, 1979 (1958).
(5) S. Norton and E. J. deBeer, *Ann. N. Y. Acad. Sci.*, **65**, 249 (1956).
(6) Obtained from Aldrich Chemical Co., Milwaukee, Wis.
(7) Melting points are uncorrected.
(8) G. Vavon, J. Bolle, and J. Calin, *Bull. soc. Chim.*, [5] **6**, 1025 (1939).
(9) From Eastman Organic Chemicals.

reflux for 3.5 hr. Most of the ethanol was distilled under reduced pressure, and the dark residue was added to 500 ml. of water. The crude nitrile was extracted with ether, washed with 1:1 hydrochloric acid and water, dried (anhydrous magnesium sulfate), ether removed, and distilled under reduced pressure; b.p. 115–130°/0.5 mm. (reported,[10] b.p. 170°/12 mm.); yield, 71.5 g. (76%). The distillate gradually solidified, and melted at 45–46° after recrystallization from petroleum ether.

Anal. Calcd. for $C_8H_5Cl_2N$: Cl, 38.2; N, 7.53. Found: Cl, 37.8; N, 7.34.

3,4-Dichloro-β-phenethylamine. To a stirred solution of 16.9 g. of lithium aluminum hydride in 300 ml. of dry absolute ether was added gradually a solution of 37.2 g. of 3,4-dichlorophenylacetonitrile in 100 ml. of dry ether. The reaction mixture was then refluxed for an additional hour, cooled, hydrolyzed cautiously with water, and filtered from inorganic matter. The dried ether solution was treated with dry hydrogen chloride to precipitate 3,4-dichloro-β-phenethylamine hydrochloride, which was recrystallized from methanol-ether; yield, 7.5 g. (17%); m.p. 178–179°.

Anal. Calcd. for $C_8H_{10}Cl_3N$: Cl, 47.0; N, 6.18. Found: Cl, 46.9; N, 6.14.

3,5-Dimethoxy-4-methylbenzoic acid. To a stirred solution of 40 g. of 3,5-dihydroxy-p-toluic acid in 57 g. of sodium hydroxide and 250 ml. of water were added three 33-ml. portions of methyl sulfate at such a rate that the temperature remained below 30° during addition of the first portion, at 30 to 35° during the second, and at 40 to 45° during the third.[11] The mixture was then boiled under reflux for 2 hr., treated with a solution of 20 g. of sodium hydroxide in 30 ml. of water, and boiled for an additional 2 hr. Acidification with dilute hydrochloric acid precipitated the crude product, which was purified by recrystallization from acetone; yield, 30.5 g. (65%); m.p. 216–217°; (reported[12] m.p., 213–214°).

ω-Diazo-3,5-dimethoxy-4-methylacetophenone. A mixture of 30 g. of 3,5-dimethoxy-4-methylbenzoic acid, 30 ml. of dry benzene, and 22 ml. of thionyl chloride was refluxed for 2 hr. After removal of benzene and excess thionyl chloride, the residue was distilled under reduced pressure to yield 21 g. (64%) of 3,5-dimethoxy-4-methylbenzoyl chloride, b.p. 107–110°/0.5 mm. A solution of this acid chloride was added to a cooled (ice bath) and stirred solution of 0.316 mole of diazomethane (generated from *N*-nitroso-*N*-methylurea and 45% potassium hydroxide and assayed against benzoic acid) in 680 ml. of dry ether. After stirring for 20 hr. at room temperature, the diazoketone had separated as a yellow solid. Collection of this solid and concentration of the filtrate by evaporation yielded a total of 19.6 g. (90%) of the pure diazoketone; m.p. 138–139° dec.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5. Found: C, 59.7; H, 5.7.

3,5-Dimethoxy-4-methylphenylacetamide. To a mixture of 19 g. of ω-diazo-3,5-dimethoxy-4-methylacetophenone and 100 ml. of dioxane was added 200 ml. of concd. ammonium hydroxide and 20 ml. of 10% aqueous silver nitrate. The mixture was heated on a steam bath under a reflux condenser for 16 hr. when evolution of nitrogen, brisk at first, was complete. The hot reaction mixture was treated with Norite, filtered, and concentrated by evaporation whereupon the crude solid amide crystallized on cooling. Recrystallization of the crude product from alcohol-water yielded 10.5 g. (58%) of pure 3,5-dimethoxy-4-methylphenylacetamide, m.p. 166–167°.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.2; H, 7.2. Found: C, 63.2; H, 7.4.

3,5-Dimethoxy-4-methyl-β-phenethylamine. To a stirred solution of 6.8 g. of lithium aluminum hydride in 200 ml. of dry absolute ether was added a slurry of 10 g. of 3,5-dimethoxy-4-methylphenylacetamide in 125 ml. of hot dry reagent benzene, using part of the benzene to rinse in the last of the amide. The resulting mixture was stirred and refluxed for 1 hr., cooled in an ice bath, and hydrolyzed by slow and cautious addition of water. The ether solution of the amine obtained after filtration from inorganic matter and drying (anhydrous magnesium sulfate) was treated with dry hydrogen chloride to precipitate the product as its hydrochloride salt; yield, 8.9 g. (80%); m.p. 233–235°. Recrystallization from ethanol–ethyl acetate raised the melting point to 244–245°.

Anal. Calcd. for $C_{11}H_{16}ClNO_2$: C, 57.0; H, 7.8; Cl, 15.3. Found: C, 56.2; H, 8.0; Cl, 15.2.

BATTELLE MEMORIAL INSTITUTE
COLUMBUS 1, OHIO

THE UNIVERSITY OF ALABAMA MEDICAL SCHOOL
BIRMINGHAM 3, ALA.

(10) C. E. Kwartler and P. Lucas, *J. Am. Chem. Soc.*, **68**, 2395 (1946) reported this compound as an oil rather than the crystalline solid which we obtained.

(11) See F. Mauthner, *Org. Syntheses*, Coll. Vol. I, 537 (1943) for methylation of gallic acid.

(12) K. Yamaguchi, *J. Chem. Pharm. Soc. (Japan)*, **62**, 491 (1952).

Nobiletin from the Peel of the Valencia Orange (*Citrus sinensis* L.)[1]

LYLE JAMES SWIFT

Received March 28, 1960

During an investigation of the constituents of orange peel, a substance was isolated which was identified as nobiletin by physical and chemical properties, elemental analysis, and degradation products.

Nobiletin was first isolated by Tseng[2] from the Chinese drug chen-pi which, in turn, was made from the peel of a variety of mandarin (*Citrus nobilis*, Lour.). In the original work the isolation was made by a rather tedious process from a cold methanolic extract of the drug but in the present study the juice of fresh orange peel was utilized.

The structural formula for nobiletin was partly elucidated by Tseng[2] and Robinson and Tseng,[3] who isolated veratric acid and acetoveratrone (as the oxime) from the alkaline hydrolysis mixture. On the basis of this and other evidence, Robinson and Tseng came to the conclusion that nobiletin was 3′, 4′, 5, 6, 7, 8-hexamethoxyflavone. This view was supported later by syntheses carried out by Horii,[4] Sreerama Murti and Seshadri,[5]

(1) Presented before the Symposium on Chemistry of the Citrus Fruit Industry at the Miami meeting of the American Chemical Society, April, 1957.

(2) K. Tseng, *J. Chem. Soc.*, 1003 (1938).

(3) R. Robinson and K. Tseng, *J. Chem. Soc.*, 1004 (1938).

(4) Z. Horii, *J. Pharm. Soc. Japan*, **60**, 614, Abstracts 246 (1940); *Chem. Abstr.* **35**, 7964 (1941).

(5) V. V. Sreerama Murti and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **27-A**, 217 (1948).

and by Oliverio and Casinovi.[6] Thus there is no doubt about the proposed structural formula.

EXPERIMENTAL

Isolation of nobiletin. Orange peel juice was obtained from the peel oil centrifugals which were operated in connection with a frozen concentrate plant. Peel from the orange juice extractors passed directly through grooved rolls which expressed an emulsion of peel oil and the aqueous peel juice. After screening to remove peel fragments, the emulsion was fed directly to the centrifugals which separated part of the oil.

Juice so obtained was filtered in the laboratory with a diatomaceous filter aid on precoated Büchner funnels. The filtrate was extracted once with petroleum ether (b.p. 60–68°) to remove any remaining peel oil and adjusted to *p*H 8.0 with sodium hydroxide pellets. The alkaline mixture was then extracted batchwise with carbon tetrachloride, using two 50-ml. portions to each 1.5-l. portion of juice. The combined extracts were then concentrated *in vacuo* nearly to dryness and the residue was dissolved in hot methanol. After treatment with a small quantity of decolorizing carbon, the hot solution was filtered and allowed to crystallize. The precipitate was repeatedly recrystallized from methanol to a constant melting point of 137–138° cor. The yield was quite small, 4.7 g. nobiletin being obtained from about 250 l. of peel juice.

The ultraviolet spectrum was determined in 95% ethanol solution. The locations of the maxima and corresponding log ϵ values were as follows: 210 mμ (4.627), 248 mμ (4.341), 271 mμ (4.283), 333 mμ (4.449).

Anal. Calcd. for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51; —OCH_3, 46.28. Found: C, 62.95, 63.05; H, 5.67, 5.72; —OCH_3, 46.34, 46.29. Nobiletin is tasteless in the crystalline form, probably because of its slight solubility. Alcoholic solutions diluted with water are quite bitter.

Hydrolysis of nobiletin. A 2.0-g. portion of nobiletin was refluxed with a mixture of 100 ml. of ethanol and 100 ml. of 20% aqueous potassium hydroxide for 6 hr. The mixture was concentrated at atmospheric pressure to half its volume and 100 ml. of water were added. Carbon dioxide was bubbled into the mixture until it was saturated. An ether extraction of the neutral products of hydrolysis was then made and reserved for the isolation of acetoveratrone. The aqueous residue was also retained for the isolation of the acidic hydrolysis products.

Isolation of acetoveratrone oxime. The ethereal extract of the neutral hydrolysis products was evaporated nearly to dryness. To this was added a mixture containing 0.5 g. of hydroxylamine hydrochloride and 4 ml. of 5% sodium hydroxide and enough ethanol to give a clear solution. After heating for 10 min. in a hot water bath, the mixture was cooled and placed in a cold room at 4°. A yield of 0.23 g. of crystals melting at 141° cor. was obtained which agrees with that reported by Robinson and Tseng[3] for acetoveratrone oxime.

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 61.55; H, 6.66; —OCH_3, 31.80; N, 7.18. Found: C, 61.98, 61.74; H, 6.65, 6.72; —OCH_3, 31.24, 31.09; N, 6.76, 6.80.

Acidic hydrolysis products. Veratric acid. The aqueous residue remaining after the extraction of the neutral hydrolysis products was acidified with dilute sulfuric acid and extracted again with ether. The ether was removed by evaporation and the residue weighing 1.4 g. was twice crystallized from about 70 ml. water. After drying, the melting point was found to be 182° cor. A mixture with anisic acid gave a melting-point depression of 30°, thus excluding this as a possibility. Analysis and a neutral equivalent determination were in agreement with those of veratric acid. The yield was 0.4 g. The amide melted at 164–166°, which is in agreement with the values given in the literature for veratric acid.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53; —OCH_3, 34.07; Neut. equiv., 182.2. Found: C, 59.56, 59.67; H, 5.70, 5.68; —OCH_3, 34.26, 34.34; Neut. equiv., 185.1.

(6) A. Oliverio and C. Casinovi, *Gazz. Ital.*, **80**, 798 (1950); *Chem. Abstr.* **46**, 977 (1952).

Acknowledgment. The author is indebted to L. E. Brown of the Southern Regional Research Branch, ARS, for the elemental analyses.

FRUIT AND VEGETABLE PRODUCTS LABORATORY
SOUTHERN UTILIZATION RESEARCH AND DEVELOPMENT DIVISION
AGRICULTURAL RESEARCH SERVICE
U. S. DEPARTMENT OF AGRICULTURE
WINTER HAVEN, FLA.

Reaction of Cyclic Sulfites of 1,3-Glycols with Sodium Iodide

STANLEY WAWZONEK AND J. T. LOFT[1]

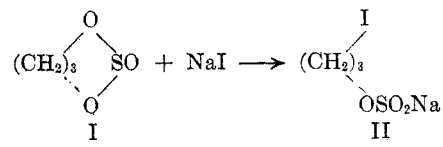
Received February 22, 1960

Alkyl sulfites have not been studied extensively as alkylating agents because of the ease of preparation and reactivity of the corresponding sulfates and sulfonates.

Cyclic sulfites of 1,3-glycols which are much more readily available than the cyclic sulfates have not been studied in this respect. Their behavior as alkylating agents would offer a convenient route to 3-monosubstituted derivatives of 1-propanol.

In this work the reaction of sodium iodide with the sulfites of trimethylene glycol, 3,3-bishydroxymethyloxetane, pentaerythritol, 3,3-dimethyl-1,3-propanediol, and 3-methyl-3-hydroxymethyl-1,3-propanediol has been studied and found to proceed normally with the first three compounds; 3-iodo-1-propanol, 3-hydroxymethyl-3-iodomethyloxetane, and 2,2-bisiodomethyl-1,3-propanediol were obtained, respectively.

The reaction was carried out in methyl ethyl ketone and found to proceed in a similar fashion to that found by others[2] for the reaction of sodium



I II

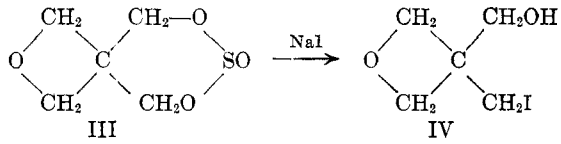
iodide with alkyl sulfites in acetone. Simultaneous condensation of methyl ethyl ketone apparently occurs with the liberation of water and subsequent hydrolysis of the intermediate sulfite. The methyl ethyl ketone bisulfite addition compound in contrast to the findings of Foster, *et al.*[2] coprecipitated

(1) Abstracted in part from the Ph.D. thesis of J. T. Loft, August 1959.

(2) A. B. Foster, E. B. Hancock, W. G. Overend, and J. C. Robb, *J. Chem. Soc.*, 2589 (1956).

with sodium iodide during the reaction. The alkylation in the presence of water was found to cause the precipitation of sodium bisulfite instead and to increase the yield of 3-iodo-1-propanol in the reaction of trimethylene sulfite (I) with sodium iodide. A similar addition of water to a solution of pentaerythrityl disulfite and sodium iodide in methyl ethyl ketone was deleterious, as the alkylation reaction was slower and hydrolysis of the sulfite to pentaerythritol occurred.

The structure of 3-hydroxymethyl-3-iodomethyloxetane (IV) obtained from 2,4,8,3-trioxathiaspiro[5,3]nonane-3-oxide (III)[3] was indicated by its elemental analysis and its infrared spectra.



III IV

The sulfite of 2-methyl-2-hydroxymethyl-1,3-propane-diol[3] required methyl isopropyl ketone as a solvent to effect a reaction. The reaction proceeded normally but the product, 2-methyl-2-hydroxymethyl-3-iodo-1-propanol was isolated as a 1:1 complex with 2-methyl-2-hydroxymethyl-1,3-propanediol. Dissociation of the complex occurs in acetone since after five crystallizations from this solvent 2-methyl-2-hydroxymethyl-1,3-propanediol could be obtained in pure condition.

The sulfite of 2,2-dimethyl-1,3-propanediol was resistant to alkylation and after refluxing with sodium iodide in methyl isopropyl ketone for forty-eight hours gave very little product. The stability of this cyclic sulfite is no doubt brought on by the *gem* methyl groups.

EXPERIMENTAL[4]

3-Iodo-1-propanol. A solution of 1,3,2-dioxanthiane-2-oxide[5] (24.4 g.), sodium iodide (30 g.), and water (3.6 g.) in methyl ethyl ketone (300 ml.) was refluxed for 24 hr. and formed a light yellow precipitate. The entire mixture was dried with anhydrous sodium sulfate and filtered. Fractional distillation under nitrogen gave 24.5 g. of 3-iodo-1-propanol boiling at 112° (31 mm.); n_D^{20} 1.5515; d_4^{25} 2.014. The literature[6] reports a boiling point of 115° (38 mm.) and a refractive index of n_D^{20} 1.5585.

Anal. Calcd. for C_3H_7OI: C, 19.38; H, 3.79. Found: C, 19.42; H, 3.58.

3-Hydroxymethyl-3-iodomethyloxetane (IV). 2,4,8,3-Trioxathiaspiro[5,3]nonane-3-oxide[3] (III) (10 g.) and sodium iodide (14.2 g.) were refluxed in methyl ethyl ketone for 20 hr. The solution was filtered, then acidified with dilute hydrochloric acid and separated from the water layer. Removal of the methyl ethyl ketone gave an oil which distilled at 128° (2 mm.); yield, 2.6 g.; n_D^{24} 1.5603.

Anal. Calcd. for $C_5H_9O_2I$: C, 26.31, H, 3.95. Found: C, 25.8; H, 3.80.

The infrared spectra of 3-hydroxymethyl-3-iodomethyloxetane had the characteristic oxetane absorption peak at 970 cm.$^{-1}$,[7] and hydroxyl peaks at 2850 and 3400 cm.$^{-1}$

2,2-Bisiodomethyl-1,3-propanediol. A mixture of sodium iodide (30 g.) and 2,4,8,10-tetraoxa-3,9-dithia[5,5]undecane-3,9-oxide[8] (22.8 g.) in dry methyl ethyl ketone (300 ml.) was refluxed for 36 hr. with constant stirring. Removal of the solvent gave a heavy oil which was extracted twice with methylene chloride (150 ml.). The solid which remained proved to be the starting material (2.7 g.).

The combined methylene chloride extracts were dried with calcium sulfate and upon removal of the solvent gave an oil (17 g.). Trituration with ethanol gave additional starting material (1 g.). Removal of the ethanol gave an oil which was crystallized from water and gave 2,2-bisiodomethyl-1,3-propanediol (11 g.) melting at 129–130°. The literature[9] reports a similar melting point.

Anal. Calcd. for $C_5H_{10}O_2I_2$: C, 16.86; H, 2.81. Found: C, 16.65; H, 3.02.

Reaction of sodium iodide with 5-methyl-5-hydroxymethyl-1,3,2-dioxathiane-2-oxide. A solution of sodium iodide (60 g.) and 5-methyl-5-hydroxymethyl-1,3,2-dioxathiane-2-oxide[3] (64 g.) in methyl isopropyl ketone (500 ml.) protected from light was refluxed with stirring for 48 hr. Removal of the solvent gave an oil which was separated by distillation into two fractions. The first fraction boiling at 110–140° (7 mm.) proved to be mainly starting materials (35 g.). The second fraction, which distilled at 160° (7 mm.), gave an oil which upon crystallization from chloroform gave 13.4 g. of a white solid melting at 70–71°. Analysis and a molecular weight determination in camphor indicated that this solid was a molecular complex of 2-methyl-2-hydroxymethyl-1,3-propanediol and 2-methyl-2-hydroxymethyl-3-iodo-1-propanol.

Anal. Calcd. for $C_{10}H_{22}O_5I$: C, 32.35; H, 6.76; I, 37.33. Found: C, 32.67; H, 6.58; I, 37.24. Mol. wt. 349.9. Found: 354.4, 350.8 (Rast) (Acetone, b.p. el.) 184, 145.

Five fractional crystallizations of the complex (3 g.) from acetone at −70° gave 0.05 g. of 2-methyl-2-hydroxymethyl-1,3-propanediol melting at 199–200°.

Reaction of 5,5-dimethyl-1,3,2-dioxathiane-2-oxide with sodium iodide. 5,5-Dimethyl-1,3,2-dioxathiane-2-oxide[10] (30 g.) and sodium iodide (30 g.) were refluxed in methyl isopropyl ketone (600 ml.) with stirring and protected against light for 48 hr. Removal of the solvent gave a dark residue which was fractionally distilled. Starting material (17.6 g.) was obtained together with 2.0 g. of a liquid which boiled at 106–110° (35 mm.). Two further distillations gave a sample which had an approximate analysis for 2,2-dimethyl-3-iodo-1-propanol.

DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA

(3) S. Wawzonek and J. T. Loft, *J. Org. Chem.*, **24**, 641 (1959).

(4) Melting points and boiling points are not corrected.

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(9) H. Bincer and K. Hess, *Ber.*, **61B**, 537 (1928).

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Preparation of 2,2,2-Trinitroethanol[1]

HENRY FEUER AND THOMAS J. KUCERA

Received April 4, 1960

The synthesis of trinitroethanol (I) has been reported from the reaction of trinitromethane with

(1) From the Ph.D. Thesis of Thomas J. Kucera, Purdue University, August 1953.

an excess of paraformaldehyde.[2] The experimental procedure involved distillation of I and the authors reported that explosions were encountered during this operation. In addition, compound I made by this method was very low melting (30°) and unstable.

An investigation of this reaction in this laboratory by G. Leston[3] showed that compound I could be obtained with a much higher melting point (65–66°), but that it was still hygroscopic and decomposed in the presence of moisture.

We now wish to report a more efficient preparation of I which eliminates the explosion hazard and affords in 80% yield pure I, m.p. 72°, directly from the reaction solution.

Pure I was found to be nonhygroscopic and stable. The presence of small amounts of water and formaldehyde was found to decrease the melting point and to cause I to react with the absorbed atmospheric moisture. The ready dissociation of I to trinitromethane and formaldehyde in water has recently been studied.[4]

EXPERIMENTAL

2,2,2-Trinitroethanol. In a three-necked flask which was provided with a stirrer, reflux condenser, and thermometer were placed 100 ml. of carbon tetrachloride, 2.12 g. (1.4 mmoles) of trinitromethane and 0.45 g. of paraformaldehyde (14.3 mmoles of formaldehyde assuming 95% formaldehyde). The turbid solution was heated with stirring for 3 hr. at 60–65° and then at reflux for 30 min. Concentrating the solution to 30 ml. and cooling in the refrigerator gave trinitroethanol in the form of long needles. Further concentration of the filtrate gave additional crops of crystals, m.p. 72°. The overall yield was 80%.

Anal. Calcd. for $C_2H_3O_7N_3$: C, 13.26; H, 1.66; N, 23.20. Found: C, 13.22; H, 1.62; N, 23.02.

Acknowledgment. We are indebted to the Office of Naval Research for the financial support of this work.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, IND.

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(3) Unpublished results from the M.S. dissertation of G. Leston, Purdue, 1949.

(4) J. Reinhart, J. G. Meitner, and R. W. Van Dolah, *J. Am. Chem. Soc.*, **77**, 496 (1955).

Polymerizable Esters of Trinitroethanol[1]

HENRY FEUER, HENRY B. HASS, AND R. D. LOWREY

Received April 11, 1960

The preparation of polymerizable mononitroalcohol esters of acrylic acid was described by D'Alelio.[2] Marans and Zelinski[3] showed that trinitroethanol (I) reacts readily with acetyl chloride and propionyl chloride to give the expected esters of I in high yields. We now wish to report the preparation of esters of I with unsaturated acids which are enumerated in Table I. In all cases the acid chlorides were employed and with the monobasic acids the highest yields were obtained in the absence of a solvent. This was also the case with fumaryl chloride, but the reaction temperature had to be raised to 130°. In the preparation of ditrinitroethyl itaconate the reaction was performed in petroleum ether. On heating, trinitroethyl acrylate and trinitroethyl methacrylate (II) were converted to high melting translucent solids of high softening range. Ester II was also copolymerized with ditrinitroethyl fumarate.

Attempts to prepare a monomer from isopropenyl isocyanate and compound I were unsuccessful. Reactions which were carried out in the presence of a polymerization inhibitor such as trinitrobenzene led to a viscous oil which turned to a solid during distillation at low pressure. It had the correct analysis for a polymer of trinitroethyl *N*-isopropenylcarbamate.

EXPERIMENTAL

Trinitroethyl methacrylate (II). Three grams (0.019 mole) of trinitroethanol and 10 ml. of methacrylyl chloride were agitated with a stream of dry nitrogen while the temperature was raised to 80° and kept there for 3 hr. The excess acid chloride was removed *in vacuo*, the residue dissolved in ether, washed successively with water, 1.5*N* potassium carbonate, and again with water, and the ether solution was dried with calcium sulfate. Distillation at 95° and 5 mm. caused the ester to crystallize in the condenser. Recrystallization from petroleum ether (b.p. 60–70°) at −60° gave *trinitroethyl methacrylate*, m.p. 26°.

Trinitroethyl acrylate. The procedure was the same as described above, except that the reaction was carried out at 28° for 2 hr.

Ditrinitroethyl fumarate. The reaction was conducted at 100° for 4 hr. and then at 130° for 3 more hr. After work-up as described above, a solid, m.p. 119°, remained. It was recrystallized from dibutyl ether to give *ditrinitroethyl fumarate*, m.p. 150°.

Ditrinitroethyl itaconate. The procedure was the same as described for the preparation of ester II except that petroleum ether (b.p. 60–70°) was employed as a solvent and the reaction mixture was refluxed for 16 hr. Removal of the solvent gave an oil which solidified on adding ethanol. Recrystallization from ethanol gave *ditrinitroethyl itaconate*, m.p. 97°.

Polymerization experiments. Heating ester II at 70° in an airtight flask for 6 days gave a yellow translucent solid which softened at 250–280°.

Similar treatment of trinitroethyl acrylate gave a solid of softening range 170–210°.

Heating an equimolar mixture consisting of ester II and ditrinitroethyl fumarate in a sealed flask at 70° for 6 days gave a translucent solid softening at 150–190°.

(1) From the Ph.D. Thesis of Robert D. Lowrey, Purdue University, February 1950.

(2) G. F. D'Alelio, U. S. Patent 2,499,804 (Sept. 21, 1948).

(3) N. S. Marans and R. P. Zelinski, *J. Am. Chem. Soc.*, **72**, 5329 (1950).

TABLE I

UNSATURATED ESTERS OF TRINITROETHANOL

Compound	B.P.	M.P.	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Trinitroethyl acrylate	80/2 mm.	...	41	$C_5H_5N_3O_8$	25.53	2.21	17.87	25.25	2.18	17.90
Trinitroethyl methacrylate	95/5 mm.	26	54	$C_6H_7N_3O_8$	28.92	2.83	16.87	28.60	2.76	16.78
Trinitroethyl crotonate	97/5 mm.	...	60	$C_6H_7N_3O_8$	28.92	2.83	16.85	29.90	2.88	16.32
Ditrinitroethyl fumarate	...	150	18	$C_8H_6N_6O_{16}$	21.71	1.35	19.00	22.05	...	18.45
Ditrinitroethyl itaconate	...	97	9	$C_9H_8N_6O_{16}$	23.68	1.75	18.42	...	...	18.00

Polytrinitroethyl N-isopropenylcarbamate. Three grams (0.019 mole) of trinitroethanol, 0.85 g. (0.01 mole) of isopropenyl isocyanate[4] and 0.005 g. of trinitrobenzene were allowed to stand 1 week at 24°, and the mixture was then diluted with ether. A small amount of material which did not dissolve was discarded. Washing the solution with water until the water layer was colorless, drying with anhydrous calcium sulfate, and distilling *in vacuo*, left a dark semisolid which did not distill at 100° and 2 mm. It was purified by washing with hot petroleum ether (b.p. 60–70°).

Anal. Calcd. for $C_6H_8N_4O_8$: C, 27.28; H, 3.05, N, 21.21. Found: C, 27.35; H, 3.38; N, 21.18.

Acknowledgment. We are indebted to the Office of Naval Research for the financial support of this work.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, IND.

(4) D. D. Coffmann, U. S. Patent **2,334,476** (Nov. 16, 1943).

Polymerization of Perfluorobutyne-2[1]

HENRY C. BROWN AND HERMAN L. GEWANTER

Received March 18, 1960

High molecular weight polymers of perfluorobutyne-2 have not been previously reported although recent publications[2–4] have described the thermal and catalytic preparation of trimers and tetramers of this bis(perfluoroalkyl)acetylene.

It has now been found that perfluorobutyne-2 forms a new, thermally stable, high molecular weight polymer under the influence of γ-radiation. Exposure of perfluorobutyne-2 to a Co^{60} source for sixty-seven hours at a rate of 3.6×10^5 r./hr. produced, in quantitative yield, a white, inert, solid polymer that is not attacked or wetted by boiling concentrated sulfuric acid, concentrated nitric acid or 50% sodium hydroxide solution. The polymer is insoluble in ether, carbon tetrachloride, methyl alcohol, benzene, and all other common laboratory solvents.

Preliminary data indicate that the thermal behavior of this polymer, polyperfluorobutyne, is quite different from that of polytetrafluoroethylene. The decomposition curve obtained from a thermogravimetric analysis in nitrogen showed an initiation point at 425°, approximately the same temperature as was found for polytetrafluoroethylene; at the 50% decomposition point, however, the curve for polyperfluorobutyne was about 75° above that of polytetrafluoroethylene.

Pyrolysis of polyperfluorobutyne and polytetrafluoroethylene in an evacuated system showed a more marked difference in behavior. Production of gaseous products from polytetrafluoroethylene began at 430°; the temperature was raised to 550°, and after six hours, one-half of the polytetrafluoroethylene had formed gaseous products; three hours at 630° completed the decomposition of this polymer sample. In contrast, with the same heating schedule, polyperfluorobutyne did not form gaseous products until a temperature of 550° had been reached, and after four hours at 630° only about 40% of the weight of the sample was converted to gaseous products. This pyrolysis does not necessarily indicate greater thermal stability in polyperfluorobutyne but does show a type of decomposition different from that of polytetrafluoroethylene.

The infrared spectrum of polyperfluorobutyne resembled that of polytetrafluoroethylene in the position of its major absorption peaks; there was a shift, however, to somewhat higher frequencies than those found for polytetrafluoroethylene.

Elemental analysis confirmed the assumption that this new product is a polymer of perfluorobutyne and that neither carbon nor fluorine was lost by fragmentation in the irradiation process. An empirical formula of C_4F_6 was obtained from the analysis.

Assumptions of the structure of this new polymer are at the present only speculative. As perfluorobutadiene is known to polymerize rather easily,[5] the possibility that perfluorobutyne-2

(1) This work was supported in part by the Office of Naval Research, Chemistry Branch, under Contract N-onr 580(03); NR 356-333 with the University of Florida. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) H. C. Brown, H. L. Gewanter, D. M. White, and W. G. Woods, *J. Org. Chem.*, **25**, 634 (1960).

(3) J. F. Harris, Jr., R. J. Harder, and G. N. Sausen, *J. Org. Chem.*, **25**, 633 (1960).

(4) J. F. Harris, Jr., U. S. Patent **2,923,746**, February 2, 1960.

(5) C. Slesser and S. R. Schram, *The Preparation, Properties, and Technology of Fluorine and Organic Fluorine Compounds*, McGraw-Hill Book Company, New York, New York, 1951, pp. 624–626.

might isomerize to perfluorobutadiene and subsequently polymerize was considered. A 1,4-linear polymerization of perfluorobutadiene would leave one carbon-carbon double bond in each monomer unit and this should be detectable in the infrared spectrum. The spectra of the new polymer showed no absorption in this region. The known homopolymers of perfluorobutadiene decompose at approximately 300° and thus do not resemble the polymer obtained in the present work.

There was no apparent phase change when polyperfluorobutyne was heated in a melting point tube to 500°. This fact and the lack of unsaturation seem to indicate a highly branched and highly cross-linked structure.

Small yields of polyperfluorobutyne (*ca.* 7%) have been obtained also in the thermal preparation of hexa(trifluoromethyl)benzene from perfluorobutyne-2.[2]

EXPERIMENTAL

Polyperfluorobutyne. Hexafluorobutyne-2 (2.25 g., 0.0139 mole) was condensed in a previously evacuated heavy-wall Pyrex tube 40 cm. × 1.3 cm. (*ca.* 50 ml. capacity). The reaction tube was then sealed and placed in the Co^{60} irradiation tank for 67 hr. to receive γ-radiation at a rate of 3.6×10^5 r./hr. (total dosage 2.4×10^7 r.).

The polymerization tube was then opened and 0.24 g. of unchanged perfluorobutyne-2 recovered. Remaining in the tube was 2.0 g. of a white, solid polymer. This polymer was refluxed with concd. sulfuric acid, with concd. nitric acid and with 50% sodium hydroxide solution with no apparent degradation. It was insoluble in ethyl ether, carbon tetrachloride, methyl alcohol, benzene, and a variety of other common laboratory solvents.

The infrared spectra of solid polyperfluorobutyne shows strong absorption peaks at 8.05, 8.36, and 8.50 μ; a weak absorption peak was found at 8.80 μ. These peaks are in the same region as the major peaks for polytetrafluoroethylene but at slightly higher frequencies.

Anal. Calcd. for C_4F_6: C, 29.63; F, 70.37. Found: C, 29.14; F, 70.27.

Comparative pyrolysis of polyperfluorobutyne and polytetrafluoroethylene. Polyperfluorobutyne, 2.0 g. and polytetrafluoroethylene, 2.0 g. were placed in individual heavy-wall Pyrex tubes and each tube was connected by Tygon pressure tubing to its own liquid-air cooled trap for condensation of gaseous pyrolysis products. The pyrolysis tubes were then bound together, placed in a vertical tube furnace, and the system evacuated.

The temperature of the furnace was raised to 100° and held at this temperature for 1 hr. while the system was pumped to remove residual moisture or air from the polymer samples. The furnace temperature was then raised to 524°, to 550°, and to 630° in steps as shown in Table I. Moles of gaseous products were determined in following the course of the reaction.

TABLE I

PYROLYSIS OF POLYPERFLUOROBUTYNE AND POLYTETRAFLUOROETHYLENE

Temp.	Time, Hr.	Moles, gaseous product, × 10^3: Polytetrafluoroethylene	Moles, gaseous product, × 10^3: Polyperfluorobutyne
524–550	3.5	10.1	0.0
550	5.5	14.9	0.0
550	11.5	17.4	0.0
550–630	13.3	—	3.1[a]
630	14.5	20.0	—
630	16.3	(Completely pyrolyzed)	6.9[b]

[a] Av. mol. wt., 116. [b] Av. mol. wt., 123.

Pyrolysis of polytetrafluoroethylene resulted in an almost quantitative decomposition to tetrafluoroethylene. The infrared spectra of the polyperfluorobutyne gaseous decomposition products indicated that it was largely hexafluoroethane, though other compounds, at least one of which showed C—C unsaturation, were also present.

In addition to the volatile products, the pyrolysis of polyperfluorobutyne produced 0.95 g. of a tan powder, collected from the upper part of the pyrolysis tube and the connecting tubing that evidently contained unsaturation as it decolorized an acetone solution of potassium permanganate. Further investigation of this pyrolysis product will be reported in a subsequent publication.

Acknowledgment. The authors wish to thank the Materials Laboratory, Wright Air Development Division, U. S. Air Force, for the thermogravimetric analysis data.

DEPARTMENT OF CHEMISTRY
DEPARTMENT OF CHEMICAL ENGINEERING
UNIVERSITY OF FLORIDA
GAINESVILLE, FLA.