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Santonin and Related Compounds. XXI.[1] 3-Keto-5-hydroxy-α-santanic Acid-*a*[2]

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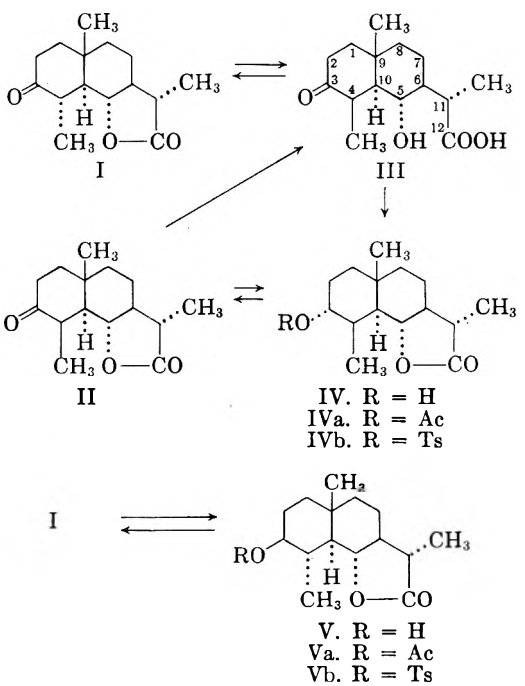
It was conclusively elucidated that both the ketohydroxy acid (III) and the ketodiol (VIII) derived from tetrahydro-α-santonin-*b* (I) (*trans*-decalin type) possessed the same configuration of the methyl group at the 4- position as in tetrahydro-α-santonin-*a* (II) (*trans*-decalin type). The 3-desoxydiol-*a* (X), newly obtained from the ketodiol (VIII), formed mono- and bis-*p*-nitro- and -3,5-dinitrobenzoates (Xa, b, c, d) under controlled reaction conditions, but the diol-*b* (XII) formed only mono-*p*-nitro- and -3,5-dinitrobenzoates (XIIa,b) even under drastic conditions. From these results, it appears that the methyl group at the 4- position is axial in the ketohydroxy acid-*a* (III), ketodiol-*a* (VIII), and 3-desoxydiol-*a* (X). 3-Desoxyhydroxy acid-*a* (XIV) produced *via* 3-desoxylactone-*a* (XI) (*trans*-decalin type) from the 3-desoxydiol-*a* (X) was readily oxidized to keto acid-*a* (XV), which isomerized into the *cis*-fused one (XIX) under alkaline conditions.

In a previous paper of this series,[3] it was reported that the *trans*-fused tetrahydro compound from β-santonin, the more stable isomer-*b* was converted to the less stable isomer-*a* by means of opening and careful closure of the lactone ring with cold concentrated sulfuric acid (corresponding to the sequence I → III → II in the α-santonin series). This course involving migration of the methyl group at the 4-position from equatorial to axial position was explained on the basis of conformational analysis. It seemed desirable, however, to establish these steric relationships by chemical means. Because of scarcity of β-santonin at hand, structural examination was made with *trans*-fused tetrahydroketone-*a* and -*b* (II and I)[2] of α-santonin, which are the respective epimers at the 11- position of the isomer-*a* and -*b* of β-santonin series. In order to convert the more stable tetrahydro-ketone-*b* (I) into the less stable isomer-*a* (III), 3-keto-5-hydroxy-α-santanic acid-*a* (III)[4] from I was treated with cold concentrated sulfuric acid by the same procedure employed for the corresponding reaction in the β-santonin series cited above. Unexpectedly, there resulted a substantial recovery of the starting ketone (I) and no



(1) Part XX, M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **24**, 903 (1959).

(2) For definition of the nomenclature and the numbering used in this paper, see Part XVIII of this series (ref. 3) (*cf.* Part XIII).

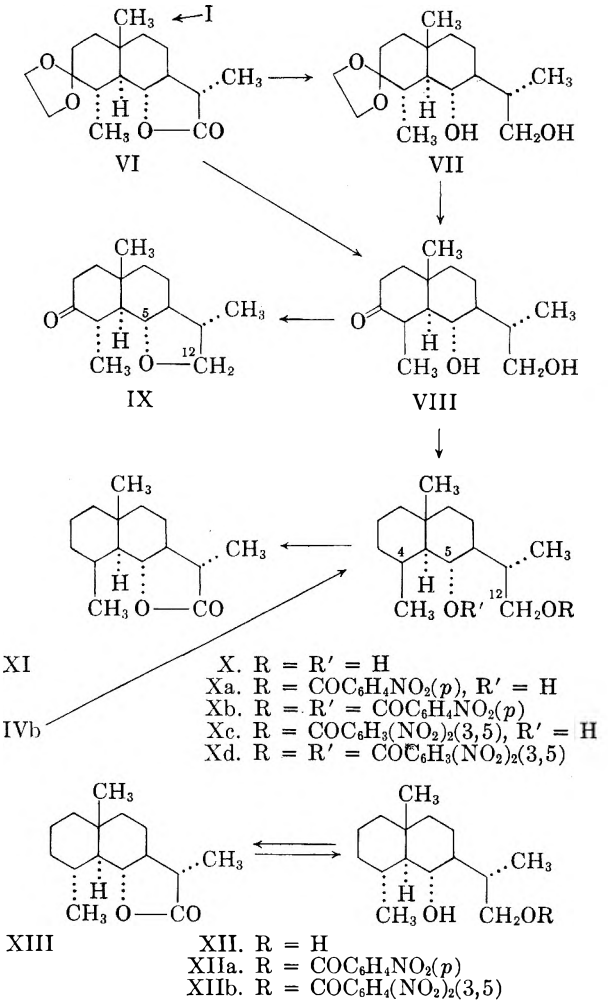
(3) M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 1268 (1958).

(4) Wienhaus and Öttingen, and Tahara obtained the keto-hydroxy acids (m.p. 85–115° and 95–97°) with no description about the configuration. The present specimen showed the melting point of 140° (*cf.* Experimental).

evidence for the formation of II could be obtained from this reaction. As shown below, the lactone ring opening of the tetrahydro-ketone-*b* (I) was accompanied by inversion of the methyl group at the 4- position resulting in formation of the keto-hydroxy acid (III), which was also formed from tetrahydro-ketone-*a* (II) by the same procedure. It is clear that in spite of careful treatment of this hydroxy-ketone with sulfuric acid, the 4-methyl group was again inverted to the original position on lactonization. This indicates that the spatial arrangement of the methyl group at the 21- position could have a considerable influence on the relative stability of the methyl group at the 4- position.

It has already been shown that catalytic hydrogenation of tetrahydro-ketone-*α* (II) with platinum oxide in acetic acid gave one isomer (IV) of the hexahydrosantonin,[5] which was also prepared directly from *α*-santonin by similar hydrogenation.[6] The alcohol (IV), whose newly formed hydroxyl group was assigned the axial orientation (*trans* to the angular methyl group),[5,6] was now found to be almost quantitatively prepared from II by sodium borohydride in methanol. By the same procedure, the hydroxy acid (III) gave the same alcohol (IV) in a good yield, indicating that the methyl group at the 4- position in III possesses the same configuration as that in the ketone-*a* (II). It is notable that hydrogenation of the carbonyl group in II with these reagents proceeded in a highly stereoselective manner. On the other hand, the ketone-*b* (I) was catalytically hydrogenated with platinum oxide mainly to the corresponding alcohol (V) with smaller amount of an epimer.[5,6] The alcohol (V), in which the hydroxyl group was assigned the equatorial position (*cis* to the angular methyl group),[5,6] was also obtained almost quantitatively by reduction with sodium borohydride and converted to the original ketone (I) in a moderate yield by oxidation with chromium oxide–acetic acid. It is obvious that the C—O bond of the lactone ring in the ketone-*b* (I) must be much more sterically hindered by the methyl group at the 4- position than that in the ketone-*a* (II). The difference of such steric interference naturally increases by opening of the lactone ring in these ketones, as indicated by formation of the same hydrolysis product from both ketones. For establishment of the configuration of the methyl group at the 4- position in these ketones, it seemed of interest to examine the relative reactivity of the hydroxyl group in suitably constructed epimers at the 4- position.

Before describing transformations of the ketones (I and II), it is necessary to mention the result concerning the derivatives of I reported by Matsumura, Iwai, and Ohki.[7] These workers found that



the diol ketal (VII), prepared from the ketal (VI) of I with lithium aluminum hydride, gave only mono-*p*-nitrobenzoate in which the hydroxyl group at the 5- position remains unaffected, whereas the keto-diol (VIII) from VII formed a mono- or a bis-*p*-nitrobenzoate depending on the amount of *p*-nitrobenzoyl chloride used. Furthermore, these workers[8] stated that the diol (XII), prepared from 3-desoxytetrahydro-*α*-santonin-*b* (XIII) by reduction with lithium aluminum hydride, formed only a mono-*p*-nitrobenzoate, as the diol ketal (VII). From these results it seems probable to suggest that the methyl groups at the 4- position in the diol ketal (VII) and in the diol (XII) are both equatorial, whereas the keto-diol (VIII) possesses the axial 4-methyl group. However, three derivatives in question differ from each other in the substituents at the 3- position. In view of the fact that a small variation of the molecular structure frequently causes a significant change in the reaction rate, this comparison about the configuration of a methyl group at the 4- position in the above diols cannot be made. Consequently, preparation of the epimeric diol-*a* (X) was attempted.

(5) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4549 (1956).

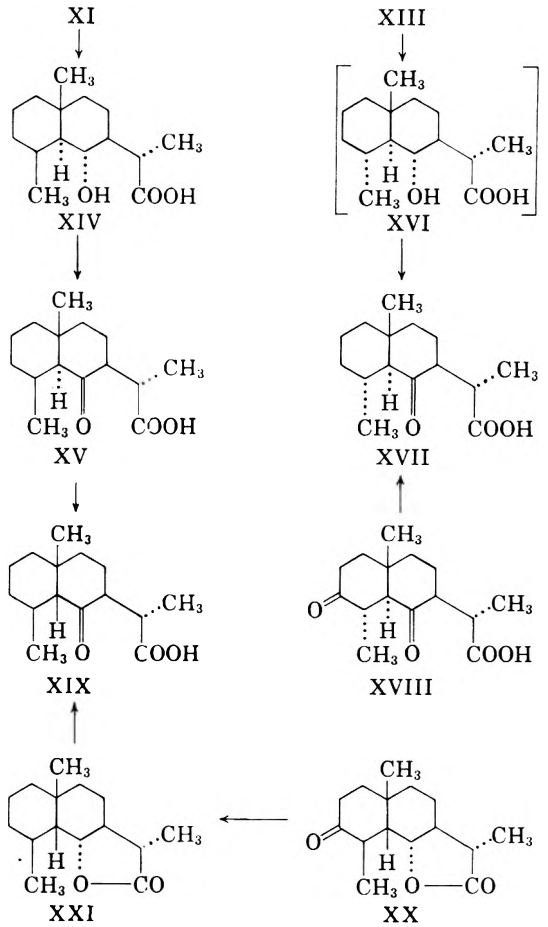
(6) B. Riniker, Thesis, E. T. H. Zürich, 1955.

(7) H. Matsumura, I. Iwai, and E. Ohki, *J. Pharm. Soc. Japan*, **75**, 687 (1955).

(8) H. Matsumura, I. Iwai, E. Ohki, and K. Kanzaki, *J. Pharm. Soc. Japan*, **75**, 689 (1955).

As the first route to X, reduction of the tosylate of hexahydrosantonin-*a* (IV) with lithium aluminum hydride[9] came into consideration. In preliminary experiments, this reaction gave an oil which was resistant to crystallization. The second line of approach to X involved reductive removal of the carbonyl group in the keto-diol (VIII) mentioned above. This keto-diol-*a* (VIII), prepared in a good yield directly from VI by hydride reduction, was subjected to the Martin-Clemmensen reduction in the usual manner. Surprisingly, the carbonyl group in VIII showed considerable resistance to this hydrogenation. The only product, obtained in a practically quantitative yield, was a dehydrated compound, in which the carbonyl group remained untouched, as shown by the formation of a 2,4-dinitrophenylhydrazone and the infrared spectrum, $\gamma_{C=O}$ 1712 cm.$^{-1}$ (cyclohexanone). It may be assumed that the product possesses the tetrahydrofuran structure (IX). The structure of IX was further supported by the infrared spectrum, γ_{C-O} 1125 cm.$^{-1}$, probably corresponding to the cyclic ether,[10] and the absence of a hydroxy band which was proved by inability to form a benzoate and resistance to the Clemmensen reduction. The keto-diol (VIII) was readily cyclized to IX with hydrochloric acid or *p*-toluenesulfonyl chloride, paralleling the smooth conversion of the 3-desoxy-diol-*b* (XII) into the corresponding tetrahydrofuran compound.[11] A few examples[12] involving such an unusual resistance of a ketone to the Clemmensen reduction have been recorded in the literature, and the reason for these abnormal results including the present case is entirely obscure. Removal of the keto group in VIII was readily effected by the Huang-Minlon modification of the Wolff-Kishner reduction, leading to a satisfactory yield of the desired product (X). The latter is differentiated from the above diol-*b* (XII) by comparison of melting point and infrared spectrum. In view of easy sublimation of X, the oily reduction product from the tosylate (IVb) mentioned above, was heated with sea-sand *in vacuo* and the diol-*a* (X) was obtained in a fair yield. This indicates that the methyl group at the 4- position has the same conformation in the tetrahydro-ketone-*a* (II), the hydroxy acid (III), and the keto-diol (VIII).

The diol-*a* (X) was subjected to acylation with *p*-nitro- or 3,5-dinitrobenzoyl chloride in pyridine by the Deninger-Einhorn method. By controlling the amount of the reagent (1.1 molar equivalents) and the reaction temperature to 0°, the mono-*p*-nitro-(Xa) or the mono-3,5-dinitrobenzoate (Xc) was formed. On the other hand, excess of the reagent (2.4 molar equivalents) and reaction at room temperature for 48 hr. resulted in the formation of the bis-*p*-nitro- (Xb) or the bis-3,5-dinitro benzoate (Xd) in a reasonable yield. From a steric viewpoint, it is obvious that the monobenzoates (Xa and Xc) possess the benzoyl group at the C-12 position. These results are in contrast to the above-cited fact regarding XII[8] and clearly indicate that the hydroxyl group at the 5- position in X is less hindered than that in XII, supporting these structures of the diols.



This steric explanation found further support in the following observation. The lactone (XI), prepared from the diol (X) by chromium trioxide oxidation, was hydrolyzed to a relatively stable hydroxy acid (XIV), whereas the epimeric acid (XVI) from the lactone (XIII) was so unstable that it could not be isolated in a pure state. It has been previously reported[13a] that oxidation of the hydroxy

(9) M. E. Wall and S. Serota, *J. Am. Chem. Soc.*, **78**, 1747 (1956).

(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley & Sons, Inc., New York, 1958, p. 114.

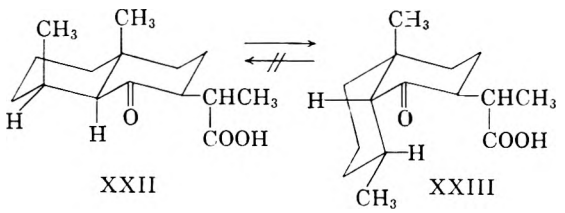
(11) O. Kovacs, V. Herout, M. Herak, and F. Sorm, *Collection Czechoslov. Chem. Communs.*, **21**, 225 (1956).

(12) For example see, W. T. Smith, Jr., *J. Am. Chem. Soc.*, **73**, 1883 (1951).

(13) (a) H. Matsumura, I. Iwai, and E. Ohki, *J. Pharm. Soc. Japan*, **74**, 1206 (1954). (b) Keto-acid-*a* (XV) was purified by chromatography on alumina, but the purity was not examined in so unstable a liquid (see Experimental). Nevertheless, the acid (XV) formed a *s*-(*p*-nitrobenzyl)thiuronium salt (m.p. 168–169°) in 69% yield, which was obviously different from the *cis*-fused (XIX; m.p. 141–142°) and *trans*-fused salts (XVII; m.p. 175°) in both melting point and infrared spectrum.

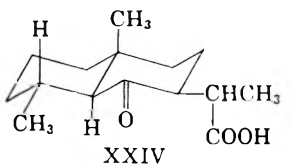
acid (XVI) with chromium trioxide in pyridine gave the keto-acid-α (XVII) in a very low yield (12%), with a larger amount (70%) of the recovered lactone (XIII). This experiment was repeated but attempts to raise the yield of XVII with other oxidizing agents were unsuccessful. Compared with XVI, the epimer (XIV) was more readily oxidized with chromium trioxide under similar conditions, and the keto-acid-*a* (XV)[13b] was obtained in a better yield (63%) with a smaller amount of XI. This indicated that the methyl group at the 4- position in XVI had a stronger effect on the oxidation process than that in XIV. The *trans*-fused diketo-acid (XVIII)[14,15] was converted to XVII in a good yield by the Martin-Clemmensen reduction in the usual manner, as the reductive removal of only carbonyl group at the 3-position in XVIII was expected from the steric view point mentioned above. Furthermore, this result supported the equatorial configuration of the methyl group at the 4-position in XVIII.

The newly formed keto-acid-*a* (XV) was relatively less stable since it underwent conversion to the more stable crystalline isomer (XIX) merely upon distillation. Riniker[6] stated that the crystalline keto-acid obtained from XI by a similar oxidation of the ester of XIV, including alkaline hydrolysis of the product, possessed the same conformation as the stable isomer (XIX) on the basis of conformational analysis. It is obvious in view of steric considerations, that the keto-acid-*a* (XV) corresponding to the conformation of XXII should be much more hindered than its inverted isomer (XIX) corresponding to that of XXIII. It seems desirable, however, to give a decisive proof of it. The *cis*-fused 3-deoxy compound-*d* (XXI), prepared from tetrahydro-α-santonin-*d* (XX),[2,5,11,15,16] converted to the corresponding keto-acid-*d* (XIX) which was



XXII

XXIII



XXIV

completely identical with the more stable keto-acid (XIX) mentioned above, but in a poorer yield (16%), with reasonable recovery of the starting lactone-*d* (XXI). This keto-acid-*d* (XIX) was prepared in a good yield (67%) from the same lactone-*d* (XXI), *via* the methyl ester of the *cis*-fused hydroxy acid corresponding to the *trans*-isomer (XVI). Therefore, the less stable isomer (XV) has to belong to the *trans*-fused tetrahydro compound series, and the more stable isomer (XIX) to the *cis*-fused series. This ring inversion could be effected by 3% potassium hydroxide solution under the same condition employed for the equilibration reaction between the *trans*-fused 3,5-diketo-α-santanic acid (XVIII) and the corresponding *cis*-isomer, the 3-keto derivatives of XIX (*trans*/*cis* = $^5/_3$).[14] The *trans*-fused isomer (XV) was thus quantitatively inverted to the *cis*-fused one (XIX), whereas no reverse reaction could proceed at all. It is of interest that the *cis*-fused keto-acid (XIX) could not be inverted to another isomer (XVII) possessing an all *trans*-conformation (XXIV), compared with the result of observation about the corresponding 3-keto derivatives. An effort is now being made in this laboratory to establish the steric aspects in the interconversions of the keto-acids compared with the diketo-acids.

EXPERIMENTAL[17]

All melting points were uncorrected. Rotations were determined in a 0.5-dm. microtube, unless otherwise noted.

Catalytic hydrogenation of α-santonin. (a) *In benzene.* α-Santonin (3.00 g.) was hydrogenated over platinum oxide (0.20 g.) in dry benzene (100 cc.), and absorption of 2.1 molar-equivalents (580 cc.) of hydrogen required 0.5 hr. After removal of the catalyst, the solution was evaporated to a small volume giving 1.20 g. (39%) of tetrahydro-α-santonin-*a* (II), colorless leaflets, m.p. 140°. Recrystallization from ethyl acetate gave colorless leaflets, m.p. and mixed m.p. 147°.[16]

The mother liquor from crystallization of II was evaporated to a colorless sirup, which was dissolved in ethanol (5 cc.) containing 3% hydrochloric acid (3 cc.). The solution was warmed for 0.5 hr. on a water bath. On cooling, the solution deposited 1.00 g. (33%) of tetrahydro-α-santonin-*b* (I) m.p. and mixed m.p. 152–154°.[15,16]

With Brady's reagent, it formed a 2,4-dinitrophenylhydrazone, m.p. 253°. Reported m.p. 248–249°.[6]

(b) *In dry acetone.* α-Santonin (3.00 g.) was hydrogenated over 0.02 g. of 5% palladium charcoal in dry acetone (30 cc.). Hydrogen (560 cc., 2 molar equivalents) was absorbed within 0.5 hr. Worked up as above, the residual sirup furnished 1.73 g. (58%) of tetrahydro-α-santonin-*a* (II), colorless leaflets, m.p. 126–135°, from a small amount of ethyl acetate. Recrystallization from ethanol afforded 1.23 g. (40%) of colorless leaflets, m.p. and mixed m.p. 141–143°.

(c) *Pressure hydrogenation over platinum oxide.* By an effective modification of the method reported by Kovacs *et al.*,[11] α-santonin (3.00 g.) was hydrogenated in methanol (30 cc.) over platinum oxide (0.15 g.) at room temperature and 100 atm. pressure. The catalyst was filtered off and the filtrate evaporated to a small volume, and a little water was added. There was obtained 2.10 g. of white needles, melting in the range 97–110°. Recrystallization from dilute methanol furnished 1.70 g. (55%) of white fine needles, m.p. 120–121°. Reported m.p. 135°.[11]

(14) A. Tahara, *J. Org. Chem.*, 21, 442 (1956).

(15) M. Yanagita and H. Ogura, *J. Org. Chem.*, 22, 1092 (1957).

(16) M. Yanagita and A. Tahara, *J. Org. Chem.*, 20, 959 (1955).

(17) Microanalyses were carried out by Mrs. C. Inayama of this school.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found, C, 71.55; H, 9.46.

The hydrogenated product (0.64 g.) treated with acetic anhydride–pyridine as below, gave an acetate (IVa, 0.35 g., 47%), colorless needles, m.p. and mixed m.p. 199–200° (see below). This acetate (IVa) was hydrolyzed in 5% sodium hydroxide solution to the 3α-hydroxy tetrahydro-α-santonin-*a* (IV), m.p. and mixed m.p. 106–107° (see below).

The mother liquor of crystallization of the acetate (IVa) was evaporated to a white powder (0.15 g., m.p. 114°). Recrystallization from ethanol furnished colorless leaflets (0.05 g., m.p. 129°), which was chromatographed on alumina. Elution with benzene afforded 0.02 g. (0.7%) of another acetate (Va) as colorless plates, m.p. and mixed m.p. 138° (see below).

3-Keto-5-hydroxy-α-santanic acid-a (III). (a) *From tetrahydro-α-santonin-b* (I). Tetrahydro-α-santonin-*b* (I, 0.30 g.) was added to 5 cc. of 5% aqueous sodium hydroxide, and the mixture was warmed on a water bath for 10 hr. After cooling, the clear solution was washed with ether, acidified with 10% acetic acid under ice cooling, and extracted with chloroform. The dried chloroform solution was evaporated under reduced pressure, and the residual semisolid (0.30 g.) was washed with a small amount of benzene. Careful recrystallization from ethyl acetate gave 0.20 g. (63%) of the monohydrate of the keto-acid (III), colorless plates, m.p. 110°.

Anal. Calcd. for $C_{15}H_{24}O_4 \cdot H_2O$: C, 62.91; H, 9.15. Found: C, 62.88; H, 9.47.

The hydrate was dried *in vacuo* on phosphorus pentoxide (at room temperature, for 12 hr.), gave a white anhydrous acid (III) m.p. 140°; $\nu_{C=O}^{CHCl_3}$ 1709 cm.$^{-1}$ (Reported m.p. 95–97°,[14] and 85–115°.[18])

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.22; H, 9.39.

It showed obvious depression of the melting point on admixture with I and II, respectively.

(b) *From tetrahydro-α-santonin-a* (II). Tetrahydro-α-santonin-*a* (II, 0.40 g.) was treated as described above, giving 0.30 g. (70%) of the hydroxy-acid (III), m.p. 96°. Recrystallization from ethyl acetate afforded colorless plates, m.p. 112°, undepressed on admixture with the monohydrate of III.

Lactonization of the acid (III). (a) *By concentrated sulfuric acid.* When the hydroxy acid (III, 0.10 g.) was treated as previously reported,[3] it gave white leaflets (0.09 g., the melting range showed 139–146°), and showed 145–152° on admixture with tetrahydro-α-santonin-*b* (I). Recrystallization from ethyl acetate raised the melting point to 154–155° (mixed m.p. with I).

(b) *In glacial acetic acid containing trace of concentrated sulfuric acid.* The hydroxy-acid (III, 0.01 g.) was dissolved in glacial acetic acid (0.5 cc.). After adding trace of concentrated sulfuric acid, the reaction mixture was allowed to stand at room temperature for 8 hr. Worked up as usual, it gave white leaflets (0.005 g.), m.p. 148–150°, undepressed on admixture with I. But it showed obvious depression of the melting point on admixture with the isomer-*a* (II).

(c) *By 2,4-dinitrophenylhydrazine in glacial acetic acid.* To a solution of the hydroxy acid (III, 0.01 g.) in acetic acid (0.4 cc.) was added 2,4-dinitrophenylhydrazine (0.01 g.). After standing for 8 hr., the reaction mixture was evaporated *in vacuo* at room temperature, and then fine yellow needles (0.01 g.) were deposited as a 2,4-dinitrophenylhydrazone of I, m.p. 253° (mixed m.p.).

3β[19]*-Hydroxy-tetrahydro-α-santonin-b* (V, R = H). To a solution of tetrahydro-α-santonin-*b* (I, 0.50 g.) in methanol (30 cc.) was added dropwise, 0.10 g. of sodium borohydride in 0.5 cc. of water. After standing at room temperature for 2 hr., the mixture was acidified with 10% hydrochloric acid and the solvent was evaporated under reduced pressure, and the residue was mixed with water and extracted with benzene, washed with water, dried, and evaporated. There was obtained 0.47 g. (93%) of the 3β-hydroxy-tetrahydro-α-santonin-*b* (V), m.p. 167°. Recrystallization from benzene-petroleum ether afforded colorless plates, m.p. 168–169°; $\lambda_{max}^{CHCl_3}$ 3472, 1770, 1460, 1385, 1143, 1119, 1047, 1013, 983, 935 cm.$^{-1}$ Reported,[5] m.p. 171–172°.

To a solution of the hexahydro compound (V, 0.05 g.) in glacial acetic acid (1 cc.), was added dropwise, 0.01 g. of chromium trioxide in the same solvent (1 cc., containing 0.02 cc. water) under stirring. After stirring was continued for 0.5 hr. at room temperature, the solution was poured into water, and taken up in chloroform. The chloroform solution was washed with aqueous sodium bicarbonate and then with water. Evaporation of the dried chloroform solution left 0.04 g. (81%) of the pure ketone (I) as colorless plates, m.p. and mixed m.p. 152–153°.

An *acetate* (Va, R = Ac) obtained in 85% yield from the hexahydro compound (V) by the usual procedure, was recrystallized from ethanol affording colorless plates, m.p. 139°; $[\alpha]_D^{14}$ +64.2° (*c* 0.37; $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 1773, 1733, 1458, 1379, 1250, 1134, 1047, 1026 (sh.), 1010, 983, 939 cm.$^{-1}$ Reported[5] m.p. 143°; $[\alpha]_D$ +63.1°.

A *tosylate* (Vb, R = Ts.). To an ice cold solution of V (0.05 g.) in pyridine (0.5 cc.) was added *p*-toluenesulfonyl chloride (0.05 g.). After standing at room temperature for 7 days, the reaction mixture was poured into ice water, and the separated white needles was filtered, washed with water, and dried, giving 0.06 g. (74%) of the tosylate (Vb), m.p. 135–140°. Recrystallization from methanol gave colorless needles, m.p. 155°; $[\alpha]_D^{15}$ +55.8° (*c* 0.57; $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 1779, 1610, 1460, 1362, 1176, 1135, 1098, 1015, 993, 935, 862, 835 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{30}O_5S$: C, 64.99; H, 7.44. Found: C, 65.27; H, 7.78.

3α[19]*-Hydroxy-tetrahydro-α-santonin-a* (IV, R = H). (a) *From tetrahydro-α-santonin-a* (II) *by sodium borohydride.* Tetrahydro-α-santonin-*a* (II, 0.80 g.) was dissolved in methanol (15 cc.), and sodium borohydride (0.08 g.) in water (0.4 cc.) was added. The reaction mixture was carried out as described above for IV, giving 0.75 g. (93%) of the 3α-hydroxytetrahydro-α-santonin-*a* (IV) as colorless needles, m.p. 103–104°. Recrystallization from aqueous ethanol afforded colorless needles, m.p. 107–108°; $[\alpha]_D^{18}$ +36.2° (*c* 1.43; $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 3448, 1776, 1460, 1385, 1149, 1126, 1047, 1028, 1015, 990, 910 cm.$^{-1}$ Reported,[5] m.p. 108–110°; $[\alpha]_D^{20}$ +36.0° (*c* 0.95).

(b) *From tetrahydro-α-santonin-a* (II) *by catalytic hydrogenation.* Tetrahydro-α-santonin-*a* (II, 1.00 g.) was hydrogenated over platinum oxide (0.03 g.) in glacial acetic acid. About 1 molar equivalent (88 cc.) of hydrogen was absorbed within 1 hr. The catalyst was filtered off and the filtrate was evaporated under reduced pressure, gave 1.00 g. (99%) of IV, as white needles, m.p. 89–92°. Recrystallization from ethanol and then from acetone–petroleum ether raised the melting point to 107°, undepressed on admixture with an authentic specimen. From the hexahydro compound (IV), the acetate (IVa) was formed by the usual method (see below).

(c) *From 3-keto-5-hydroxy-α-santanic acid-a* (III). To the solution of hydroxy acid (III, 0.05 g.) in methanol (5 cc.), dropwise, an aqueous solution of sodium borohydride (0.02 g. in 0.1 cc. water) was added. After standing at room temperature for 1 hr., the reaction mixture was saturated with sodium chloride and then extracted with ether. The organic layer was washed with aqueous sodium bicarbonate, water, dried, and evaporated. There was obtained 0.04 g. (85%) of a hexahydro-α-santonin-*a* (IV) as colorless needles, m.p. 100–102°. Recrystallization from benzene-petroleum ether raised the melting point to 107–108° (mixed m.p.). From the hexahydro compound (IV), the acetate (IVa) was formed by the usual method (see below).

(18) Wienhaus and Ottingen, *Ann.*, 397, 219 (1913).

(19) Relative configurations were expressed as α or β for the groups except to be designated according to the definition[3] of the nomenclature in this series.

An *acetate* (IVa, R = Ac), obtained in 80–90% yield from the hexahydro compound (IV) by the usual method, was recrystallized from ethanol, giving colorless prisms, m.p. 200–201°; $[\alpha]_D^{14}$ +19.4° (*c* 1.13; $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 1776, 1733, 1456, 1372, 1250, 1149, 1127, 1042, 1029, 1018, 995, 935 cm.$^{-1}$ [reported,[5] m.p. 199–200°; $[\alpha]_D^{20}$ +15.4° (*c* 0.72)].

The acetate (IVa) was hydrolyzed with 3% methanolic sodium hydroxide. Acidification of the reaction mixture gave the original hexahydro compound (IV) as colorless needles, m.p. and mixed m.p. 108–109°.

A *tosylate* (IVb, R = Ts) was obtained in 93% yield from the hexahydro compound (IV) by the same procedure as in Vb. Recrystallization from ethanol furnished colorless plates, m.p. 168–169° (dec. 170°); $[\alpha]_D^{15}$ +20.0° (*c* 1.70; $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 1776, 1608, 1456, 1357, 1174, 1126, 1098, 1017, 996, 946, 849 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{30}O_5S$: C, 64.99; H, 7.44. Found: C, 65.33; H, 7.19.

Tetrahydro-α-santonin-b-3-ketal (VI). By a slight modification of the procedure previously reported,[7] the ketal (VI) was obtained in 70% yield from tetrahydro-α-santonin-*b* (I), as colorless plates, m.p. 168°; $[\alpha]_D^{14}$ +26.1° (*c* 5.4; $CHCl_3$). Reported,[7] m.p. 167–168.5°; $[\alpha]_D^{8}$ +23.4°.

α-Santan-5,12-diol-b-3-ketal (VII). By an effective modification of the method,[7] the ketal (VI, 0.40 g.) was reduced in absolute ether-benzene solution with lithium aluminum hydride, gave 0.35 g. (86%) of VII, as colorless needles, m.p. 145°. Recrystallization from acetone raised the melting point to 149°; $[\alpha]_D^{16}$ −10.7° (*c* 6.7; $CHCl_3$). Reported,[7] m.p. 149–151°; $[\alpha]_D^{8}$ −14.0°.

3-Keto-α-santan-5,12-diol-a (VIII). (a) By an effective modification of the method,[7] the diol ketal (VII, 0.17 g.) was treated with sulfuric acid in acetone, giving 0.11 g. (76%) of VIII, as colorless needles, m.p. 119–120°; $\nu_{max}^{CHCl_3}$ 3413 (OH), 1706 cm.$^{-1}$ (C=O) (reported[7] m.p. 117–118°).

(b) The above keto-diol (VIII) was also prepared directly from the ketal (VI) as follows: To an ethereal solution (60 cc.) of lithium aluminum hydride (0.6 g.), the ketal (VI, 2.00 g.) in absolute ether benzene (6:1, 60 cc.) was added dropwise, with stirring (1 hr.). After heating under reflux with stirring for 3 hr., the reaction mixture was cooled with water, and cold dilute sulfuric acid (7%, 30 cc.) was added into the reaction mixture with careful stirring. After the mixture was heated under reflux for 1 hr., the organic layer was separated and washed with water. Evaporation of the dried solution left 1.20 g. (70%) of VIII, as colorless needles m.p. 117–118° (mixed m.p.).

3-Keto-α-santan-5,12-oxide (IX). (a) *Clemmensen method.* By an effective modification of the procedure previously reported,[3] the ketodiol (VIII, 0.80 g.) in toluene (2 cc.) was heated to reflux for 24 hr. with amalgamated zinc (prepared from 2.0 g. of zinc and 0.08 g. of mercuric chloride) in 3 cc. of concentrated hydrochloric acid and 2 cc. of water. One cc. each of concentrated hydrochloric acid was added to the refluxed reaction 3 times during a period of 5 hr. After cooling, benzene was added to the reaction mixture, and the organic layer was separated, washed with water, dried, and evaporated. There was obtained 0.73 g. (98%) of an oxide (IX) as colorless plates, m.p. 70–75°. Recrystallization from petroleum ether raised the melting point to 84–85°; $[\alpha]_D^{28}$ +11.8° (c 3.4; $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 1712 (C=O), 1125 cm.$^{-1}$ (tetrahydrofuran).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.47; H, 9.99.

It showed obvious depression of the melting point (71–77°) on admixture with the starting material (VIII, m.p. 118–119°).

With Brady's reagent, IX gave in 70% yield a *2,4-dinitrophenylhydrazone*, which was recrystallized from ethyl acetate to golden yellow plates, m.p. 188–189°.

Anal. Calcd. for $C_{21}H_{28}O_5N_4$: C, 60.56; H, 6.78; N, 13.45. Found: C, 60.55; H, 6.66; N, 13.61.

(b) *With hydrochloric acid.* The keto-diol (VIII, 0.05 g.) in toluene (1 cc.) was mixed with concentrated hydrochloric acid (0.3 cc.) and water (0.1 cc.), and then the mixture was heated to reflux for 16 hr. On working up as described for (a), the oxide (IX, 0.04 g., 86%) was obtained as colorless plates, m.p. and mixed m.p. 83–84°.

(c) *With p-toluenesulfonic acid.* The keto-diol (VIII, 0.03 g.) was dissolved in benzene (2 cc.), which was heated under reflux with *p*-toluenesulfonic acid (monohydrate, 0.01 g.) for 0.5 hr. After cooling, the benzene solution was washed with aqueous sodium bicarbonate. Evaporation of the dried solution left a pale yellow sirup (IX, 0.02 g., 72%), which furnished in 57% yield the 2,4-dinitrophenylhydrazone, m.p. 188–189° (mixed m.p.).

(d) *Deninger-Einhorn method.* To a cold solution of the keto-diol (VIII, 0.16 g.) in pyridine (1.5 cc.) was added *p*-toluenesulfonyl chloride (0.16 g.). After standing at room temperature for 5 days, the reaction mixture was poured into ice water, and taken up in ether. The ether solution was washed, successively, with water, 5% hydrochloric acid, aqueous sodium bicarbonate, and then water. Evaporation of the dried ethereal solution left a colorless sirup (IX, 0.12 g., 80%), which gave in 60% yield of the 2,4-dinitrophenylhydrazone, m.p. 188–189° (mixed m.p.).

The oxide (IX, 0.05 g.) was treated with Clemmensen reduction the same condition as mentioned in (a), giving quantitative recovery of the starting material as colorless plates, m.p. and mixed m.p. 83–84°.

α-Santan-5,12-diol-a (X, R = H). (a) *From 3-keto-α-santan-5,12-diol-a* (VIII). To a solution of metallic sodium (0.31 g.) in diethylene glycol (9 cc.) was added the keto-diol (VIII, 1.30 g.) and hydrazine hydrate (80%, 0.65 cc.). After refluxing for 2 hr. at 180–190° (bath temperature) the condenser was removed. The reaction continued until the bath temperature had reached 200–210°, when reflux continued for 5 hr. After cooling, the reaction mixture was poured into an equal amount of water and extracted with ether. The ethereal solution was washed with water, dried, and evaporated, giving 1.07 g. (87%) of the diol (X) as white needles, m.p. 100–103°. Recrystallization from ethanol or sublimation *in vacuo* (2 mm., 85–90°) gave colorless prisms, m.p. 107–108°; $[\alpha]_D^{28}$ −28.2° (*c* 2.2; $CHCl_3$) and $[\alpha]_D^{30}$ −21.5° (*c* 2.6; EtOH); λ_{max}^{Nujol} 3226, 1107, 1025 cm.$^{-1}$ (OH).

Anal. Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.93; H, 11.94.

(b) *From 3α-hydroxy-tetrahydro-α-santonin-a* (IV). A solution of the tosylate (IVb, 0.20 g.) in absolute benzene-ether (6:1, 7 cc.) was added dropwise, with stirring to the solution of lithium aluminum hydride (0.06 g.) in absolute ether (6 cc.). After reflux with stirring for 10 hr., excess reagent in the cooled reaction mixture was decomposed with water and then 5% hydrochloric acid. The separated organic layer was washed with water, dried, and evaporated, giving a pale yellow sirup (0.11 g.), which was chromatographed on alumina (10 g.). Elution with benzene-ethanol (1:1) afforded a pale yellow sirup (0.10 g.), which was sublimated at 3 mm. (85–90°, bath temperature), gave 0.06 g. (51%) of the diol (X) as colorless needles, m.p. and mixed m.p. 107–108°.

Deninger-Einhorn reactions of α-santan-5,12-diol-a (X). (a) *With p-nitrobenzoyl chloride at lower temperature.* To a cold solution of the diol (X, 0.10 g.) in pyridine (6 cc.) was added 1.1 molar equivalents of *p*-nitrobenzoyl chloride (0.08 g.). After standing in refrigerator at 0° for 48 hr., the reaction mixture was poured into ice water, and the separated solid was taken up in ether. The ethereal solution was washed, successively, with 10% hydrochloric acid, water, aqueous sodium bicarbonate and water, giving 0.12 g. (75%) of the mono-*p*-nitrobenzoate (Xa), as white needles, m.p. 150°. Recrystallization from benzene raised the melting point to 165–166°; $\lambda_{max}^{CHCl_3}$ 1727, 1531, 1350, 1277, 1166, 1103, 1053, 1038, 1016, 974 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.77; H, 8.06; N, 3.50.

(b) *With p-nitrobenzoyl chloride at room temperature.* To a cold solution of the diol (X, 0.15 g.) in pyridine (10 cc.) was added 2.4 molar equivalents of *p*-nitrobenzoyl chloride (0.30 g.). After standing at room temperature for 48 hr., the reaction mixture was treated as above. The bis-*p*-nitrobenzoate (Xb, 0.25 g., 74%) m.p. 160–164° deposited as white needles, which was recrystallized from ethanol (contained small amount of ethyl acetate) to white needles, m.p. 169–170°; $\lambda_{max}^{CHCl_3}$ 1727, 1534, 1348, 1274, 1172, 1117, 1104, 1017 cm.$^{-1}$

Anal. Calcd. for $C_{29}H_{34}N_2O_8$: C, 64.67; H, 6.36; N, 5.20. Found: C, 64.44; H, 6.40; N, 5.14.

It showed obvious depression (139–142°) of the melting point on admixture with the mono-*p*-nitrobenzoate (Xa).

To a cold solution of the mono-*p*-nitrobenzoate (Xa, 0.05 g.) in pyridine (3 cc.) was added the same reagent (0.05 g.). After standing at room temperature for 48 hr., the reaction mixture was treated as above, giving 0.06 g. (87%) of the bis-*p*-nitrobenzoate (Xb) as white needles, m.p. and mixed m.p. 168–169°.

(c) *With 3,5-dinitrobenzoyl chloride at lower temperature.* The diol (X, 0.15 g.) was treated at lower temperature as described above, with 1.1 molar equivalents of 3,5-dinitrobenzoyl chloride (0.16 g.), giving crude product as a white powder (0.21 g., the melting range of 120–134°). The material was triturated with ethanol (0.5 cc.) at room temperature. After removal of an insoluble substance (0.005 g.), solvent was evaporated with addition of a small amount of benzene, and then deposited the mono-3,5-dinitrobenzoate (Xc, 0.12 g., 45%) as white needles, m.p. 135–138°. Recrystallization from benzene raised the melting point to 141–142°, $\lambda_{max}^{CHCl_3}$ 1736, 1553, 1348, 1280, 1167, 1081, 1036, 1003, 987, 920 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{30}N_2O_7$: C, 60.81; H, 6.96; N, 6.45. Found: C, 60.88; H, 6.93; N, 6.43.

The mother liquor from crystallization of Xc gave a white powder (0.08 g.), which was chromatographed on alumina (6 g.). Elution with benzene afforded an additional 0.03 g. (total 0.15 g., 54%) of the monobenzoate (Xc) as white needles, m.p. and mixed m.p. 141–142°. The following fractions, eluted with ethyl acetate, afforded 0.05 g. (33%) of the starting diol (X) as colorless needles, m.p. and mixed m.p. 103–104° (sublimation at 3 mm.).

An ethanol insoluble substance was recrystallized from ethyl acetate–ethanol (2:1), giving the bis-3,5-dinitrobenzoate (Xd, described below) as white needles, m.p. 181–182° (mixed m.p.).

(d) *With 3,5-dinitrobenzoyl chloride at room temperature.* The diol (X, 0.15 g.) was treated at room temperature as described above for (b), with 2.2 molar equivalents of the reagent (0.32 g.), giving 0.34 g. (87%) of the bis-3,5-dinitrobenzoate (Xd) as white needles, m.p. 162°. Recrystallization from ethyl acetate–ethanol (2:1) raised the melting point to 181–182°; $\lambda_{max}^{CHCl_3}$ 1736, 1553, 1347, 1277, 1167, 1075, 1034, 1005, 980, 953, 921 cm.$^{-1}$

Anal. Calcd. for $C_{29}H_{32}N_4O_{12}$: C, 55.41; H, 5.13; N, 8.91. Found: C, 55.42; H, 5.05; N, 8.77.

The mono-3,5-dinitrobenzoate (Xc, 0.02 g.) was treated with the same reagent (0.02 g.) in pyridine, as described above for (b), giving 0.02 g. (70%) of the bis-3,5-dinitrobenzoate (Xd), m.p. and mixed m.p. 181–182°.

Deninger-Einhorn reactions of α-santan-5,12-diol-b (XII, R = H). (a) *With p-nitrobenzoyl chloride.* The diol-*b* (XII, 0.05 g.) was treated at room temperature as described above for Xb, with 2.4-molar equivalents of the reagent (0.10 g.), giving a mono-*p*-nitrobenzoate (XIIa, 0.07 g., 86%) as white needles, m.p. 120°. Recrystallization from ethanol containing small amount of ethyl acetate, raised the melting point to 135–136°; $\lambda_{max}^{CHCl_3}$ 1730, 1613, 1534, 1351, 1279, 1117, 1104, 1017, 975 cm.$^{-1}$ (reported,[8] m.p. 134–135.5°).

The mono-*p*-nitrobenzoate (XIIa, 0.05 g.) was warmed with the same reagent (0.05 g.) in pyridine at 60° for 5 hr. The starting material (0.05 g.) was recovered, m.p. and mixed m.p. 135°.

(b) *With 3,5-dinitrobenzoyl chloride.* The diol-*b* (XII, 0.05 g.) was treated at room temperature as described above, with 2.0 molar equivalents of the reagent (0.11 g.), giving 0.10 g. of semicrystalline product. Recrystallization from ethanol gave 0.07 g. (54%) of mono-3,5-dinitrobenzoate (XIIb) as white needles, m.p. 140°; $\lambda_{max}^{CHCl_3}$ 1736, 1635, 1552, 1347, 1279, 1166, 1075, 1025, 978, 911 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{30}N_2O_7$: C, 60.81; H, 6.96; N, 6.45. Found: C, 60.73; H, 6.73; N, 6.85.

3-Desoxytetrahydro-α-santonin-a (XI). (a) *With chromium trioxide in acetic acid.* To a solution of chromium trioxide (0.14 g., 1.2 molar equivalents) in glacial acetic acid (5 cc.) and water (0.2 cc.), added dropwise the diol-*a* (X, 0.20 g.) in glacial acetic acid (2 cc.) at 15–20° with stirring. After stirring was continued for 1 hr. at 20°, the solution was poured into twice volume of water to decompose the excess chromium trioxide with aqueous sodium bisulfite. The deposited colorless leaflets were filtered and washed with water, showing m.p. 142° (0.13 g.). The crude product was taken up in ether and washed with aqueous sodium bicarbonate, water, and dried, giving the 3-desoxytetrahydro-α-santonin-*a* (XI, 0.12 g., 67%) as colorless plates, m.p. 149°. Recrystallization from ethanol raised the melting point to 151–152°; $[\alpha]_D^{27}$ +57.6° (*c* 2.64; $CHCl_3$); λ_{max}^{Nujol} 1776 (γ-lactone), 1460, 1388, 1332, 1189, 1155, 1133, 1117, 1030, 1014 cm.$^{-1}$ (reported,[6] m.p. 153–155°, $[\alpha]_D$ +46.7°; and m.p. 155–157°, $[\alpha]_D$ +47.5°).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.49; H, 10.11.

A residual semisolid, obtained from the mother liquor of XI was worked up as above. The residual semicrystalline mixture was triturated with petroleum ether. Recrystallization from ethanol furnished an additional 0.02 g. (total 0.14 g., 71%) of XI, m.p. 145–148° (mixed m.p.).

(b) *With chromium trioxide in pyridine.* To a solution of the desoxy diol-*a* (X, 0.50 g.) in pyridine (6 cc.) was added a complex of chromium trioxide (0.81 g.) in pyridine (12 cc.). After standing at room temperature for 24 hr. the precipitate on addition of ether, was filtered off and then the ethereal solution was washed, successively, with aqueous sodium bicarbonate, water, 10% hydrochloric acid, and water. Evaporation of the dried ethereal solution afforded 0.12 g. (49%) of XI as colorless plates, m.p. 148–149°. Recrystallization from ethanol raised the melting point to 150–151° (mixed m.p.). It showed obvious depression (*ca.* 30°) of the melting point on admixture with XIII described below.

3-Desoxy-tetrahydro-α-santonin-b (XIII), was prepared in 68% yield, from α-santan-5,12-diol-*b* (XII, m.p. 154–155°)[11] by oxidation with chromium trioxide in pyridine, as described for XI, m.p. and mixed m.p. 152°.[3,6,11]

5α-Hydroxy-α-santanic acid-a (XIV). After the 3-desoxytetrahydro-α-santonin-*a* (XI, 0.25 g.) was dissolved in methanol (3 cc.) and 5% sodium hydroxide (10 cc.), the solution was heated on a water bath under reflux for 5 hr. The methanol was removed under reduced pressure, the aqueous alkaline solution was washed with ether, and acidified with cold 10% hydrochloric acid. The acidic solution was extracted with ether, which was washed with water. Evaporation of the dried ethereal solution under reduced pressure, furnished 0.20 g. (74%) of the hydroxy acid (XIV) as white needles, m.p. 130°. Recrystallization from ether–petroleum ether raised the melting point to 148–149°; $[\alpha]_D^{28}$ +64.1° (*c* 0.97; $CHCl_3$); λ_{max}^{Nujol} 3236, 2604, 1773, 1681 cm.$^{-1}$

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.77; H, 10.26.

It showed obvious depression (*ca.* 20°) of the melting point on admixture with the starting lactone (XI).

A *s-(p-nitrobenzyl)thiuronium salt*[20] *of* XIV was prepared

(20) R. L. Shriner, R. C. Fuson, and D. Y. Curtin "The Systematic Identification of Organic Compounds," 4th ed., John Wiley & Sons, Inc., New York, 1956, p. 202.

from the hydroxy acid (XIV, 0.03 g.) and *p*-nitrobenzyl thiuronium chloride (0.05 g.) in ethanol (1.5 cc.). The solution was concentrated under reduced pressure to deposit white needles (0.05 g., 91%), m.p. 148–150° (turned to brown). Recrystallization from minimum amount of ethanol, raised the melting point to 153–154° (turned to brown).

Anal. Calcd. for $C_{23}H_{35}N_3O_5S$: C, 59.33; H, 7.58. Found: C, 59.16; H, 7.70.

The hydroxy acid (XIV, 0.05 g.) was heated under reflux on a water bath in methanol (2 cc.) and 5% hydrochloric acid (1 cc.) for 1 hr. The solution was condensed under reduced pressure, and the residue was extracted with ether, washed with water, dried, and evaporated. Recrystallization of the residue from ethanol, afforded 0.04 g. (86%) of the starting lactone (XI) as colorless plates, m.p. and mixed m.p. 150–151°.

5-Keto-α-santanic acid-a (XV). The hydroxy acid (XIV, 0.10 g.) was added to a solution of chromium trioxide (0.10 g.) in pyridine (2 cc.). After standing at room temperature for 72 hr., the precipitate formed on addition of ether, was filtered off and then the ethereal solution was extracted with aqueous sodium bicarbonate. The alkaline solution was acidified with hydrochloric acid and warmed on a water bath for 0.5 hr. After cooling, the separated oil was extracted with ether. The ethereal solution was again extracted with aqueous sodium bicarbonate, which was acidified with 10% hydrochloric acid and taken up in ether. Evaporation of the dried ethereal solution left 0.05 g. (63%) of the keto-acid (XV) as colorless oil, the attempt of crystallization of which was unfruitful after it was chromatographed on alumina. Furthermore, it could not form the 2,4-dinitrophenylhydrazone by the usual method.

A *s-(p-nitrobenzyl)thiuronium salt of* XV was obtained in 69% yield, by the same procedure as described for XIV, as white fine needles (m.p. 162–163°). Recrystallization from ethanol, afforded white leaflets, m.p. 168–169° (turned to orange), λ_{max}^{Nujol} 1706, 1527, 1408, 1130, 1105 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{33}N_3O_5S$: C, 59.58; H, 7.18; N, 9.06. Found: C, 59.42; H, 7.03; N, 8.88.

Inversion of 5-keto-α-santanic acid-a (XV) *to 5-keto-α-santanic acid-d* (XIX). (a) *By only heating.* The keto-acid (XV, 0.22 g.) was heated *in vacuo* (2 mm.) at 180–190°. A distilled colorless sirup was readily crystallized to colorless needles (0.12 g., 55%), m.p. 152–154°. The residue from the above distillation was crystallized from petroleum ether to the same crystal (0.07 g., total 86%), m.p. and mixed m.p. 156–157°. Recrystallization from petroleum ether furnished colorless needles, m.p. 159–160.5°. It showed no depression of the melting point on admixture with an authentic specimen of 5-keto-α-santanic acid-*d* (XIX), obtained from *cis*-fused tetrahydro-α-santonin-*d* (XXI) described below.

(b) *By 3% potassium hydroxide solution.* The keto-acid (XV, 0.07 g.) was heated on a water bath in dioxan (0.5 cc.) and 3% potassium hydroxide (1.4 cc.) as reported previously.[14] The acidified solution was extracted in ether. Evaporation of the dried ethereal solution left 0.06 g. (86%) of XIX as white needles, m.p. 153–155°. Recrystallization from petroleum ether raised the melting point to 159–160.5° (mixed m.p.).

5-Keto-α-santanic acid-b (XVII). (a) *From 3-desoxytetrahydro-α-santonin-b* (XIII). The 3-desoxy compound (XIII, 1.00 g.) was dissolved in an aqueous potassium hydroxide (3%, 40 cc.) and a minimum amount of ethanol (3 cc.). After distillation of organic solvent, the ice cold reaction mixture was acidified with dilute acetic acid and extracted with ether. To the ethereal solution of the acid (XVI) was added a few drops of pyridine to prevent relactonization, as reported previously.[14] After distillation of the ether under reduced pressure, the residual crude acid (XVI) was mixed with a mixture of 2 g. of chromium trioxide and 17 cc. of pyridine. The mixture was allowed to stand at room temperature over night. Ether was added to the reaction mixture, the precipitate was filtered off, and the ethereal solution was washed successively with 10% hydrochloric acid, water, and saturated sodium bicarbonate. The alkaline solution was acidified with 10% hydrochloric acid and heated on a water bath for 0.5 hr., and the separated oil was taken up in ether. The ethereal solution was extracted with aqueous sodium bicarbonate. The combined ethereal solution was dried and evaporated to give 0.70 g. (70%) of recovered XIII (m.p. and mixed m.p. 150–151°). The alkaline solution was acidified with 10% hydrochloric acid, and extracted with ether. Evaporation of the dried ethereal solution left 0.17 g. (16%) of the keto-acid-*b* (XVII) as colorless prisms, m.p. 80°. Recrystallization from petroleum ether melting point raised to 95–96° (reported, m.p. 98–99°).

A *s-(p-nitrobenzyl)thiuronium salt of* XVII was prepared in 96% yield by the method as described for XV, as white fine needles, m.p. 175° (turned to orange) (from ethanol), λ_{max}^{Nujol} 1709, 1524, 1404, 1117, 1092 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{33}N_3O_5S$: C, 59.58; H, 7.18; N, 9.06. Found: C, 59.69; H, 7.42; N, 8.82.

An attempt of purification of XVI was unfruitful: The 3-desoxy lactone (XIII, 1.00 g.) was dissolved as above to aqueous alkaline solution, and acidified with 3% hydrochloric acid under ice cooling, and extracted with ether. The dried ethereal solution was evaporated *in vacuo*. There was obtained the starting lactone XIII (0.95 g.) as colorless leaflets, m.p. and mixed m.p. 150–151°.

On the other hand, when 3-desoxytetrahydro-α-santonin-*b* (XIII) was oxidized with *N*-bromoacetamide by the method reported previously,[14] or aqueous alkaline permanganate solution, the starting material was recovered in 90% and 67% yield, respectively.

The keto-acid (XVII) was quantitatively recovered in the attempt of equilibration under the same alkaline condition as described for XV. With Brady's reagent, it could not form the 2,4-dinitrophenylhydrazone.

(b) *From 3,5-diketo-α-santanic acid-b* (XVIII). The keto-acid-*b* (XVII) was furnished in 77% yield from 3,5-diketo-α-santanic acid-*b* (XVIII)[14,15] by the Clemmensen reduction as described for IX (m.p. and mixed m.p. 97–98°).

3-Desoxytetrahydro-α-santonin-d (XXI). The Clemmensen reduction of *cis*-fused tetrahydro-α-santonin-*d* (XX, 2.00 g.)[16] was carried out as the same procedure as for IX. 3-Desoxy compound (XXI) was afforded in 96% yield as crude crystals (m.p. 76°), which was recrystallized from petroleum ether to colorless prisms, m.p. 85°; $[\alpha]_D^{31}$ −16.8° (*c* 1.67; EtOH); $\nu_{C=O}^{Nujol}$ 1772 cm.$^{-1}$ (γ-lactone) [reported,[11] m.p. 86–87° and $[\alpha]_D^{20}$ −27.9° ($CHCl_3$)].

5-Keto-α-santanic acid-d (XIX). (a) 3-Desoxytetrahydro-α-santonin-*d* (XXI, 0.40 g.) was dissolved in an aqueous potassium hydroxide (1.2%, 40 cc.), and was carried out the same procedure as described for *trans*-fused isomer (XVII). The crude hydroxy acid was oxidized in pyridine (6 cc.) with chromium trioxide (0.60 g.) as described for XI. There was obtained 0.07 g. (16%) of crude keto-acid-*d* (XIX) as white needles, m.p. 157°, and 0.22 g. (55%) of the starting lactone (XXI). Recrystallization from petroleum ether raised the melting point to 159–160.5°; $[\alpha]_D^{12}$ −88.5° (*c* 1.33; $CHCl_3$); $\nu_{C=O}^{CHCl_3}$ 1709 cm.$^{-1}$ (reported,[6] m.p. 159–160°, $[\alpha]_D$ −84.2°).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.64.

A *s-(p-nitrobenzyl)thiouronium salt of* XIX was prepared from the keto-acid (XIX, 0.05 g.) in the usual manner. There was obtained 0.08 g. (87%) of the salt as white leaflets, m.p. 138–139°. After recrystallization from ethanol the melting point raised to 141–142° (turned to brown); λ_{max}^{Nujol} 1700, 1521, 1393, 1135, 1115 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{33}N_3O_5S$: C, 59.58; H, 7.18; N, 9.06. Found: C, 59.67; H, 7.05; N, 9.04.

The keto-acid (XIX) was quantitatively recovered in the attempt of equilibration under the same alkaline condition as described for XV, and it could not form the 2,4-dinitrophenylhydrazone of XIX in the usual manner.

(b) The 3-desoxy compound (XXI, 0.50 g.) was dissolved in an aqueous potassium hydroxide (1.2%, 50 cc.). The ice cooled reaction mixture was acidified with dilute hydrochloric acid, and extracted with ether. The ethereal solution was esterified with diazomethane in the usual manner. To the residue, which was obtained on evaporation of the ethereal solution, was added a mixture of chromium trioxide (1 g.) in pyridine (10 cc.). After standing at room temperature for 72 hr., the reaction mixture was treated as usual, giving a colorless sirup (0.47 g.). It was hydrolyzed with an aqueous potassium hydroxide in methanol, and acidified with dilute hydrochloric acid. On cooling, 0.36 g. (67%) of XIX deposited as white needles, m.p. 150°, which was raised by recrystallization from petroleum ether to 160–161° (mixed m.p.).

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[CONTRIBUTION NO. 1055 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Reaction of Dicobalt Octacarbonyl with Some Acetylenic Compounds[1]

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The relative rates of reaction of acetylenic acids, alcohols, esters, ethers, halides, and hydrocarbons with dicobalt octacarbonyl have been determined. The differences in the relative reactivities are not great; however, carboxy-, carbomethoxy- and methylol- groups appear to enhance the reactivity when attached to the triple bonded carbon. The observed relative reactivities are not correlated with possible electronic effects. A decrease in relative reactivity can be traced to steric factors. An anomalous behavior of certain propargyl-type halides was found and has been attributed to a possible coupling reaction of these halides in the presence of dicobalt octacarbonyl.

In a recent investigation,[5] it was reported that dicobalt octacarbonyl reacts with acetylenic compounds producing acetylenic dicobalt hexacarbonyls and evolving carbon monoxide according to the reaction

$$R{-}C{\equiv}C{-}R' + Co_2(CO)_8 \longrightarrow RC_2R'Co_2(CO)_6 + 2CO. \quad (1)$$

A kinetic study of this reaction with hexyne-1 and with hexyne-2 has been made.[6] This investigation gave kinetic evidence that in solution a small amount of a reactive form of dicobalt octacarbonyl is present. Kinetic evidence was also found for an acetylenic dicobalt heptacarbonyl intermediate.[6]

The purpose of the present study was to determine the effect of various groups (R- and R'-) upon the rate of reaction. The relative reactivities of various acetylenic acids, alcohols, esters, ethers, halides, and hydrocarbons were determined from the half-lives of their reactions. These half-lives were obtained from a plot of volume of evolved carbon monoxide *versus* time. The half-life of the reaction with hexyne-1 was assigned a value of 100 on the relative reactivity scale and the relative reactivity of each acetylenic compound was calculated from

$$\text{Relative reactivity} = \frac{t_{1/2}\,(\text{hexyne-1})}{t_{1/2}\,(\text{acetylenic compound})} \times 100 \quad (2)$$

The average half-life ($t_{1/2}$) for hexyne-1 calculated from twenty-one individual experiments was found to be 320 seconds.

EXPERIMENTAL

Procedure. The rates of reaction of various acetylenic compounds were determined by measuring the rates of evolution of carbon monoxide. The apparatus and procedure that were used have been described in a previous paper.[6] Liquid acetylenes were introduced into the reaction flask with a hypodermic syringe. Standard solutions of acetylenic solids were prepared in toluene and aliquots of these solutions were injected into the reaction flask. The total volume of solution in the reaction flask was 50 ml.

The initial concentrations of both the dicobalt octacarbonyl and the acetylenic compound were 0.200 moles $l.^{-1}$ In all cases the reaction was carried out in toluene solution and at a temperature of 25°.

Materials. Toluene was obtained from the Neville Chemical Co., Pittsburgh, Pa. and was redistilled; b.p. 108–109°. Dicobalt octacarbonyl was obtained through the courtesy of the Bureau of Mines, Bruceton, Pa. The dicobalt octacarbonyl reagent was prepared in toluene solution as described in a previous paper.[6]

The acetylenic compounds were prepared with the purpose of obtaining pure materials; hence, no attempt was made to determine yields of the new compounds. These materials (as listed in Tables I, II and III) were obtained by the general syntheses or specific procedures as indicated below:

A. Alkylation (one- or two-step) of sodium acetylide in liquid ammonia.

(1) Abstracted from a portion of the Ph.D. Thesis of M. R. Tirpak, University of Pittsburgh (1958).

(2) Air Reduction Chemical Company Fellow, 1955–56.

(3) Present address, Standard Oil Co. (Ind.), Whiting, Ind.

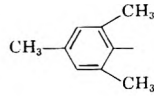
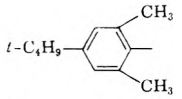
(4) Diamond Chemical Company, Painesville, Ohio.

(5) H. Greenfield, H. W. Sternberg, R. A. Friedel, J. H. Wotiz, R. Markby, and I. Wender, *J. Am. Chem. Soc.*, **78**, 120 (1956).

(6) M. R. Tirpak, J. H. Wotiz, and C. A. Hollingsworth, *J. Am. Chem. Soc.*, **80**, 4265 (1958).

TABLE I

ACETYLENIC HYDROCARBONS

R—C≡C—R′		Preparation,	Physical Properties			Relative
R—	—R′	Method (Ref.)	B.P., ° (mm.)	n_D (°C.)	d_4 (°C.)	Reactivity[a]
n-C_4H_9—	—H	A (7)	70.5 (atm.)	1.3970 (24)	0.7137 (26)	100
n-C_4H_9—	—D	B (8)	70–74 (atm.)	1.3970 (23)	0.722 (22)	105
n-C_3H_7—	—CH_3	A (9)	82–83 (atm.)	1.4127 (24)	0.7401 (20)	60
C_2H_5—	—C_2H_5	A (9)	79–80 (atm.)	1.4101 (23)	0.7231 (20)	98
t-C_4H_9—	—H	E (10)	35–36 (atm.)	1.3743 (21)	0.6683 (20)	88
CH_3—	—CH_3	C . . .	29 (atm.)	1.3880 (27)	0.6913 (20)	56
CH_2=C(CH_3)—	—H	C . . .	32.5 (atm.)	1.4148 (21)	0.695 (25)	119
H—C≡C—$(CH_2)_4$—	—H	A (9)	32.5–33.5 (55)	1.4454 (21)	0.8195 (24)	81
C_6H_5—	—H	D-1 (9)	44–45 (22)	1.5488 (22)	0.9283 (22)	114
o-$CH_3C_6H_4$—	—H	F (11)	42–44 (6)	1.5460 (21)	0.9224 (24)	78
m-$CH_3C_6H_4$—	—H	F (12a)	62–64 (18)	1.5427 (21)	0.9073 (26)	110
p-$CH_3C_6H_4$—	—H	D-1 (9)	61–62 (20)	1.5455 (24)	0.9159 (20)	112
2,4-$(CH_3)_2$—C_6H_3—	—H	D-2 (9)	69–71 (9)	1.5451 (25)	0.930 (23)	88
2,5-$(CH_3)_2$—C_6H_3—	—H	D-1 (12b)	49 (2)	1.5412 (24)	0.9180 (21)	88
3,4-$(CH_3)_2$—C_6H_3—	—H	D-1 (12c)	59–62 (3)	1.5494 (25)	0.9246 (24)	115
	—H	D-1 (9)	62–63 (2.5)	1.5440 (25)	0.9185 (25)	20
	—H	D-1 (12d)	88–90 (2)	1.5313 (23)	0.9018 (22)	23
C_6H_5—	—C_6H_5	G (9)	150 (8) (M.p. 58–60)	. . .	. . .	60

[a] Relative to a value of 100 assigned to hexyne-1.

B. Deuterolysis of 1-hexynylsodium with deuterium oxide (99.5%).

C. Courtesy of the Air Reduction Chemical Co., Murray Hill, N. J.

D. Reaction of the acetophenone-type compound with phosphorus pentachloride followed by dehydrochlorination with (1) sodium amide in liquid ammonia or (2) alcoholic potassium hydroxide.

E. Chlorination of pinacolone with phosphorus pentachloride and then dehydrochlorination with a mixture of potassium hydroxide in mineral oil (equal parts by weight). Redistillation of the low boiling fraction (up to 70°) from this mixture gave a pure product.

F. Reaction of a methylphenylmagnesium bromide with gaseous acetaldehyde followed by hydrolysis, dehydration to the styrene-type compound, addition of bromine and dehydrobromination with sodium amide in liquid ammonia.

G. Addition of methylmagnesium bromide to benzophenone followed by hydrolysis, dehydration to 1,1-diphenylethylene, addition of bromine, and dehydrobromination accompanied with rearrangement using sodium amide in liquid ammonia.

H. Alkylation of sodium acetylide in liquid ammonia with a chlorobromide and conversion of the resultant ω-chloroacetylene to the corresponding iodo-compound by refluxing with sodium iodide in acetone solution.

I. Courtesy of the General Aniline and Film Corp., Easton, Pa.

J. Chlorination of the analogous propargyl-type alcohol with (1) phosphorus trichloride or (2) thionyl chloride and pyridine in dry ether.

K. Bromination of the corresponding alcohol or diol with phosphorus tribromide in dry ether.

L. Decarboxylation of the copper(II) salt of the chlorophenyl propiolic acid.

M. Reaction of the alkynylmagnesium bromide in dry ether with gaseous (1) formaldehyde or (2) acetaldehyde followed by hydrolysis.

N. Reaction of sodium amide with dibutylchloroacetal in liquid ammonia.

O. Action of dimethyl sulfate on the sodium salt of propargyl alcohol.

P. Courtesy of C. C. Price and J. Frank Gillespie of the University of Pennsylvania.

Q. Suspension of hexynylsodium in ether poured on a large excess of Dry Ice followed by hydrolysis with aqueous ammonium chloride.

R. Preparation of 1-iodo-4-heptyne, as described in Method H, followed by conversion to 1-cyano-4-heptyne with aqueous potassium cyanide in acetone solution and then hydrolysis.

S. Dehydrobromination of ethyl-α,β-dibromo-β-phenylpropionate in alcoholic potassium hydroxide followed by acidification.

T. Esterification of the analogous alkynoic acid with methanol.

U. Reaction of dihydropyran with propargyl alcohol.

DISCUSSION

The relative reactivities of the various acetylenic compounds are given in Tables I, II, and III. The method of synthesis and the physical properties of these materials are also listed.

All the compounds indicated in Tables I and II, except *n*-butoxyacetylene, reacted normally. The

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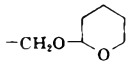
(8) R. E. Dessy, J. H. Wotiz, and C. A. Hollingsworth, *J. Am. Chem. Soc.*, **79**, 358 (1957).

(9) T. L. Jacobs, *Org. Reactions*, John Wiley & Sons, Inc., New York, 1949, Vol. V, pp. 1–78.

(10) P. D. Bartlett and L. J. Rosen, *J. Am. Chem. Soc.*, **64**, 543 (1942).

TABLE II

ACETYLENIC ACIDS, ALCOHOLS, ESTERS, ETHERS, AND HALIDES

R—C≡C—R′		Preparation, Method (Ref.)	Physical Properties			Relative Reactivity[a]
R—	—R′		B.P., ° (mm.)	n_D (°C.)	d_4 (°C.)	
n-C_4H_9—	—CO_2H	Q (13)	116 (7)	1.4607 (23)	0.9775 (23)	160
C_2H_5—	—$(CH_2)_3CO_2H$	R (14)	126–127 (8)	1.4543 (28)	0.9762 (28)	60
C_6H_5—	—CO_2H	S (15)	(M.p. 135–137)	—	—	226
H—	—CH_2OH	I —	111–112 (atm.)	1.4312 (22)	0.9338 (24)	194
H—	—$C(OH)(CH_3)_2$	C —	103 (atm.)	1.4202 (24)	0.8518 (28)	177
n-C_4H_9—	—CH_2OH	M-1 (14)	77–78 (4)	1.4520 (30)	0.8810 (28)	120
n-C_4H_9—	—$CH(OH)CH_3$	M-2 (16)	67–69 (8)	1.4468 (23)	0.8747 (24)	123
t-C_4H_9—	—CH_2OH	M-1 (10)	68–69 (17)	1.4421 (24)	0.8600 (23)	89
n-C_5H_{11}—	—CO_2CH_3	T (14)	96 (12)	1.4460 (23)	0.9260 (22)	152
C_2H_5—	—$(CH_2)_3CO_2CH_3$	T (14)	85–86 (9)	1.4447 (21)	0.9365 (21)	68
CH_3—	—$(CH_2)_4CO_2CH_3$	T (14)	94 (13)	1.4470 (22)	0.9552 (23)	55
H—	—$(CH_2)_5CO_2CH_3$	T (14)	85–86 (10)	1.4403 (23)	0.9428 (24)	92
H—	—OC_4H_9—n	N (17)	40–41 (65)	1.4000 (29)	0.8161 (29)	<1[b]
H—	—CH_2OCH_3	O (18)	60.0–60.5 (atm.)	1.3948 (23)	0.8410 (23)	177
H—	—$CH_2OC(C_6H_5)_3$	P —	(M.p. 110.5–111.0)	—	—	186
H—		U (19)	57.5–58.0 (7)	1.4573 (21)	1.0148 (21)	201
H—	—$(CH_2)_5Br$	A (14)	76.5–77.0 (18)	1.4773 (22)	1.2342 (22)	87
H—	—$(CH_2)_4I$	H (14)	62–63 (8)	1.5260 (28)	1.5822 (26)	86
H—	—C_6H_4—F—p	D-2 (12e)	(M.p. 25–27)	—	—	92
H—	—C_6H_4—Cl-p	D-2 (9)	(M.p. 43.0–44.5)	—	—	90
H—	—C_6H_4—Cl-m	L (20)	58–60 (9)	1.5630 (23)	1.116 (25)	102
H—	—C_6H_4—Cl-o	L (20)	65–66 (12)	1.5694 (25)	1.1249 (25)	102
H—	—C_6H_4—Br-p	D-2 (9)	(M.p. 64.5–66.0)	—	—	100

[a] Relative to a value of 100 assigned to hexyne-1. [b] Very little, if any, carbon monoxide was evolved.

TABLE III

PROPARGYL-TYPE HALIDES

R—C≡C—R′		Preparation, Method (Ref.)	Physical Properties			Relative Reactivity[a]	Total CO Evolved[b] (Vol. %)	
R—	—R′		B.P., ° (mm.)	n_D (°C.)	d_4 (°C.)			
H—	—CH_2Cl	J-1 (21)	55.5 (atm.)	1.4335 (22)	1.0385 (23)	172	95	101
H—	—CH_2Br	I ...	82 (atm.)	1.4928 (22)	1.5775 (22)	385	127	128
H—	—$C(Cl)(CH_3)_2$	C ...	74 (atm.)	1.4160 (25)	0.9085 (25)	178	95	118
n-C_4H_9—	—CH_2Cl	J-2 (14)	56–57 (10)	1.4585 (25)	0.9470 (25)	91	92	98
n-C_4H_9—	—CH_2Br	K (14)	64–65 (8)	1.4910 (22)	1.2427 (22)	315	125	...
n-C_4H_9—	—CH_2I	H (23)	78–79 (7)	1.5387 (25)	1.4914 (23)	476	120	120
$BrCH_2$—	—CH_2Br	K (22)	81–82 (7)	1.5844 (30)	2.0237 (29)	325	175	...

[a] Relative to a value of 100 assigned to hexyne-1. [b] The percentage of carbon monoxide evolved was calculated from the amount expected according to reaction 1. The first number is the total percentage of carbon monoxide evolved in the reaction with the acetylenic compound. The second number includes additional carbon monoxide that was evolved when some hexyne-1 was added to the reaction solution to determine the amount of uncharged dicobalt octacarbonyl.

(11) V. Prey and H. Berbalk, *Monatsh.*, **82**, 990 (1951).

(12) New compounds: (a) *Anal.* Calcd. for C_9H_8: C, 93.1; H, 6.9. Found: C, 92.9; H, 7.1. (b) *Anal.* Calcd. for $C_{10}H_{10}$: C, 92.3: H, 7.7. Found: C, 92.6; H, 7.6. (c) *Anal.* Calcd. for $C_{10}H_{10}$: C, 92.3; H, 7.7. Found: C, 92.6; H, 7.5. (d) *Anal.* Calcd. for $C_{14}H_{18}$: C, 90.3; H, 9.7. Found: C, 89.8; H, 9.7. (e) *Anal.* Calcd. for C_8H_5F: C, 79.2; H, 4.2. Found: C, 78.7; H, 4.9.

(13) A. D. Zoss and G. F. Hennion, *J. Am. Chem. Soc.*, **63**, 1151 (1941).

(14) M. S. Newman and J. H. Wotiz, *J. Am. Chem. Soc.*, **71**, 1292 (1949).

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(21) L. Henry, *Ber.*, **8**, 398 (1875).

(22) John H. Wotiz, Ph.D. Thesis, *Isomeric Normal Octynoic Acids*, (under the direction of M. S. Newman), Ohio State University (1948).

(23) A. W. Johnson, *J. Chem. Soc.* (London), **1946**, 1009.

reactions of these compounds were followed until at least 90% of the carbon monoxide (as calculated from reaction 1) had been evolved. Excess hexyne-1 was then added to determine the amount of unchanged dicobalt octacarbonyl. In all cases the total amount of carbon monoxide evolved was within 5% of the theoretical amount. The anomalous behavior of *n*-butoxyacetylene might be caused by the polymerization of this compound in the presence of dicobalt octacarbonyl.

The differences in relative reactivity in most cases are not very great. From the results of twenty-one experiments with hexyne-1 (average half-life 320 sec.) the mean square deviation for the half-life of hexyne-1 was found to be ± 17 seconds. It was estimated that a difference in relative reactivities less than 12% could not be considered significant.[24]

In most cases the observed relative reactivities cannot be correlated with possible electronic (inductive and mesomeric) or steric effects in the groups attached to the triple bonded carbon. Groups such as carboxy, carbomethoxy, and methylol appear to enhance the reactivity when attached to the acetylenic carbon. The low relative reactivity for mesitylacetylene and 2,6-dimethyl-4-tertiarybutylphenylacetylene is probably caused by steric requirements.[25]

All the propargyl-type compounds in Table III, except propargyl chloride and 1-chloro-2-heptyne, reacted anomalously as indicated by the total volume of carbon monoxide that was obtained. The additional carbon monoxide evolved in these reactions might result from the coupling of these propargyl-type halides in the presence of dicobalt octacarbonyl. Such a coupling reaction of allylic chlorides with nickel carbonyl in methanol solution at 25° has been investigated.[26] Thus, the evolution of excess carbon monoxide might be caused by the following reactions taking place simultaneously with reaction 1:

$$4\ R{-}C{\equiv}C{-}CH_2{-}X + Co_2(CO)_8 \longrightarrow 2\ R{-}C{\equiv}C{-}CH_2CH_2{-}C{\equiv}C{-}R + Co_2(CO)_4X_4 + 4\ CO \quad (3)$$

$$R{-}C{\equiv}C{-}CH_2CH_2{-}C{\equiv}C{-}R + 2\ Co_2(CO)_8 \longrightarrow (RC_2CH_2)_2Co_4(CO)_{12} + 4\ CO \quad (4)$$

and perhaps,

$$Co_2(CO)_4X_4 \longrightarrow 2\ CoX_2 + 4\ CO. \quad (5)$$

Qualitatively, one would expect the extent of coupling to be dependent on the number and the type of halogen in the propargyl-type halide. This might explain the greater amount of carbon monoxide produced by 1,4-dibromo-2-butyne. Since primary chlorides should have the least tendency to couple, it is not surprising that propargyl chloride and 1-chloro-2-heptyne do not show an anomalous behavior.

In the reaction with 3-chloro-3-methyl-1-butyne an increase in the evolution of carbon monoxide was observed upon the addition of some hexyne-1 to the apparently completed reaction. It appears that at least 20% of the initial concentration of dicobalt octacarbonyl was available at the completion of the reaction. This fact might indicate that the acetylenic compound may have (1) had a purity of 80%, (2) polymerized during the reaction, or (3) coupled to produce a sterically hindered diacetylene that could not react with dicobalt octacarbonyl.

In summary, it must be pointed out that no significant correlation of these data can be made in terms of the present classical organic reaction mechanisms. These results are consistent with the various reactions that involve compounds of transition metals and unsaturated organic substrates. This investigation may provide information that will aid in the elucidation of the nature and the mechanisms involved in reactions of such compounds.

Acknowledgment. The authors wish to thank Drs. H. W. Sternberg and I. Wender, Bureau of Mines, Bruceton, Pa., for helpful discussions during this investigation. They also wish to thank Sol Metlin, Bureau of Mines, Bruceton, Pa., for preparing the dicobalt octacarbonyl that was used in this study.

PITTSBURGH 13, PA.

(24) For further information concerning the precision of the experiments see Michael R. Tirpak, Doctoral Thesis, University of Pittsburgh, 1958.

(25) W. G. Sly, *J. Am. Chem. Soc.*, **81**, 18 (1959).

(26) I. D. Webb and G. T. Borcherdt, *J. Am. Chem. Soc.*, **73**, 2654 (1951).

[CONTRIBUTION NO. 569 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & COMPANY]

Pyrolysis of Silver *o*-Halobenzoates

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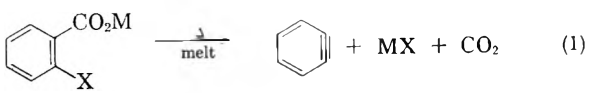
The pyrolysis of several metal salts of *o*-halobenzoic acids was studied. Silver *o*-chlorobenzoate pyrolyzed smoothly above its melting point to give phenyl *o*-chlorobenzoate, silver chloride, and carbon dioxide. Evidence is presented suggesting that benzyne, C_6H_4, may be an intermediate in the formation of the phenyl ester.

Dry pyrolyses of metal salts of carboxylic acids are generally complicated reactions which may result in the decarboxylative formation of ketones[1] and olefins.[2] Metal salts of simple aromatic acids frequently undergo extensive degradation when heated above their melting points.

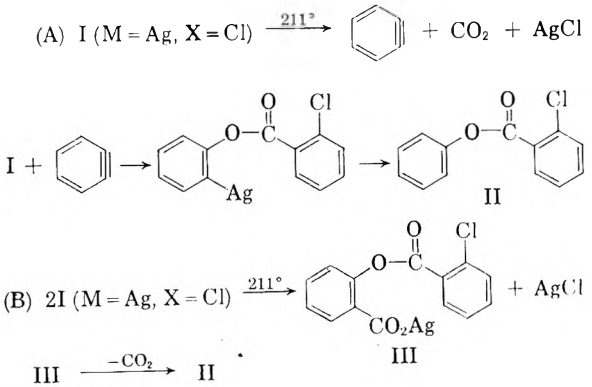
In the course of some studies in this laboratory aimed at new syntheses of benzyne,[3] the bulk pyrolysis of metal *o*-halobenzoates (I) was investigated briefly in an attempt to demonstrate Reaction 1.[4]



I

Of the several salts that were examined, only the combination M = Ag and X = Cl gave results that suggested Reaction 1 could be realized.

Silver *o*-chlorobenzoate (I, M = Ag, X = Cl) melted at 211° *in vacuo* and underwent an exothermic reaction accompanied by the evolution of carbon dioxide and the formation of silver chloride. Phenyl *o*-chlorobenzoate (II) was isolated in 50.5% yield as the sole organic product. Two mechanisms for the formation of II are readily suggested:



In mechanism A, benzyne is presumably formed *via* a cyclic transition state with the near simultaneous loss of carbon dioxide and silver chloride. Phenyl *o*-chlorobenzoate results from a rapid reaction[5] of benzyne with undecomposed salt in the melt followed by hydrogen abstraction[6] to give II. In mechanism B, a metathetical coupling of two molecules of salt produces the ester III, which is decarboxylated in the melt to II.[6]

In order to test the latter hypothesis the ester–silver salt III was synthesized from *o*-chlorobenzoyl chloride and salicylic acid in pyridine followed by treatment of the ammonium salt of the resulting acid with silver nitrate. When a sample of authentic III was pyrolyzed under conditions identical with those used in the case of silver *o*-chlorobenzoate, a reaction occurred at approximately 200°. No liquid fraction was observed, and the product was a hard, black, insoluble mass. Extraction of this residue with ether afforded a trace of chlorobenzene as the only organic product. When the pyrolysis was carried out in the presence of a small amount of added silver chloride, similar results were obtained.

These results strongly suggest that III is not an intermediate in the pyrolysis of silver *o*-chlorobenzoate and that mechanism B is untenable. Although these observations in no sense prove the intermediacy of benzyne in the pyrolysis of I (M = Ag, X = Cl), some support is lent to mechanism A. Other paths to the observed product can be constructed but are difficult to rationalize. Since one of the benzene nuclei in the product, phenyl *o*-chlorobenzoate, is no longer bonded to either of its original substituents (carboxyl and chlorine) and since the pyrolysis occurs cleanly and in reasonable yield, the multistep paths to II which can be

(1) R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, John Wiley & Sons, New York, N. Y., 1953, pp. 331–332.

(2) Unpublished observations in these laboratories. Also see O. Neunhoeffer and P. Paschke, *Ber.*, **72B**, 919 (1939).

(3) J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith, and C. W. Vaughan, *J. Am. Chem. Soc.*, **75**, 3290 (1953).

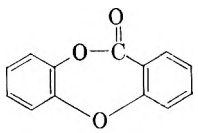
(4) The author is indebted to Prof. G. Wittig and Dr. G. Köbrich (Chemisches Institut der Universität, Heidelberg) for informing him of their work in this area prior to Dr. Köbrch's forthcoming publication.

(5) The nucleophilic addition of anions to benzyne at high temperatures is well known; see O. Kym, *J. prakt. Chem.*, **51**, 325 (1895); C. Haeussermann, *Ber.*, **32**, 1912 (1899); **33**, 939 (1900); **34**, 38 (1901). For a discussion of the mechanism of nucleophilic additions to benzyne, see J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).

(6) The source of hydrogen is not clear but could be due to small amounts of water (see Experimental) in the salt or to degradative hydrogen abstraction from reactant or products.

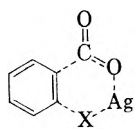
written involving free radical intermediates offer initially many conceptual difficulties.

When silver *o*-fluorobenzoate was pyrolyzed at its melting point (231°), a low yield of fluorobenzene was isolated. Silver *o*-bromobenzoate at 182° gave tars, while silver *o*-iodobenzoate underwent a vigorous reaction at 147°. From the latter experiment there was isolated a low yield of a colorless crystalline solid whose analysis, spectra, and properties are in accord with the previously unreported lactone of *o*-carboxy-*o'*-hydroxydiphenyl ether (IV).



IV

Possibly the difference in products observed in the pyrolyses of I (M = Ag, X = F, Cl, Br, I) is due to different timing in the collapse of a cyclic transition state, such as V.



V

The carbon-halogen bond energies decrease in the order C-F>C-Cl>C-Br>C-I. When X = F, transition states like V are most difficult to attain, and other reactions (*e.g.* decarboxylation) occur in preference to loss of silver fluoride. Experimentally carbon-fluorine bond rupture was not observed, and fluorobenzene was the only organic product isolated. When X = Cl, delocalization stabilization of transition state V is predominant, and collapse must occur with essentially simultaneous loss of carbon dioxide and silver chloride. When X = Br, I, silver bromide or iodide is probably expelled very easily before the benefit of the delocalized cyclic state V is manifested.[7]

Attempts were made to trap benzyne by pyrolyzing silver *o*-chlorobenzoate in the presence of addends. When pure furan and the anhydrous salt were heated alone in a bomb at 250°, high yields of benzoic acid were isolated and no other organic products were detected. At 175°, the same reactants gave only *o*-chlorobenzoic acid. Apparently under the strenuous reaction conditions, hydrogen abstraction from furan interferes with the normal course of reaction, for neither the expected Diels-Alder adduct[8] nor II was detected in the products. When the reaction with furan was run in benzene as solvent at 190°, only *o*-chlorobenzoic acid was isolated. Hydrogen abstraction also occurred in the presence of N-methylpyrrole, which gave fair yields of benzoic acid even at 190°. When an intimate mixture of silver *o*-chlorobenzoate and anthracene was pyrolyzed, no triptycene was detected among the products, which consisted mostly of phenyl *o*-chlorobenzoate.

A few other metal *o*-halobenzoates were pyrolyzed with unpromising results (Table I).

TABLE I

METAL *o*-HALOBENZOATES

I			
M	X	M.P.,° dec.	Remarks
Ag	F	231–232	See Experimental
Ag	Cl	211–212	See Experimental
Ag	Br	182–183	Isolated only tar on pyrolysis
Ag	I	147–148	See Experimental
Li	Cl	227	Stable at 300°
Cu/2	Cl	270–271	Isolated I (M = H, X = Cl) on pyrolysis
Hg/2	Cl	178–180	Stable at 300°

EXPERIMENTAL[9]

Preparation of metal o-halobenzoates. All of the silver salts employed in this work were prepared by suspending the pure carboxylic acid in distilled water and adding one equivalent of coned. ammonium hydroxide. The solution of the ammonium salt was filtered, and a solution of one equivalent of silver nitrate in distilled water was added slowly with vigorous stirring. The mixture was stirred for 30 min. and allowed to stand in the dark for 30 min. The silver salt was collected by suction filtration and was washed well with distilled water.

Lithium *o*-chlorobenzoate was prepared from the acid and lithium hydroxide in good yield.

Cupric and mercuric *o*-chlorobenzoate were prepared from the ammonium salt of the acid and cupric sulfate and mercuric chloride, respectively.

All of the salts were dried at 100° in a vacuum oven at reduced pressure. The silver salts of the *o*-halobenzoic acids gave satisfactory analyses, but the infrared spectra indicated traces of residual water which was difficult to remove.[6]

Pyrolysis of I (M = Ag, X = Cl). The dried salt I (47.2 g., 0.18 mole) was placed in a large sublimation tube with a solid carbon dioxide cold finger. The apparatus was evacuated to 0.05 mm. pressure and was heated externally in an oil bath. The salt began to melt at approximately 200°, and a vigorous reaction occurred with the evolution of carbon dioxide (in one run at 1 mm. the carbon dioxide was collected in a liquid nitrogen trap and was identified). A viscous liquid collected on the cold finger and the sides of the apparatus. The reaction subsided in a few minutes, and the tube was allowed to cool. The cold finger and the dark solid residue were extracted with ether, and the extracts were combined and washed successively with cold 1% hydrochloric acid and with water. The solvent was removed and the residue was distilled through a semimicro spinning-band column[10] to give 10.6 g. (50.5%) of pure phenyl *o*-chloro-

(7) The occurrence of the aromatic ether linkage in IV is difficult to explain, and the low yields of this product make speculation unwarranted. Possibly IV arises from decarbonylation in the presence of silver salts of the cyclic bislactone of salicylic acid, a product not unexpected from the above considerations.

(8) G. Wittig and L. Pohmer, *Angew. Chem.*, **67**, 348 (1955).

(9) All melting points are corrected and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 21 double-beam infrared spectrometer equipped with sodium chloride optics (2–15 μ). Spectra were obtained on pure liquids or in potassium bromide wafers.

(10) R. G. Nester, *Anal. Chem.*, **28**, 278 (1956).

benzoate (II), b.p. 142–143° (1 mm.), n_D^{25} 1.5846. The distillation residue was negligible.

Anal. Calcd. for $C_{13}H_9ClO_2$: C, 67.11; H, 3.90; Cl, 15.24; mol. wt., 234. Found: C, 66.96; H, 4.27; Cl, 15.39; mol. wt., 245 (b.p. in benzene). The infrared spectrum showed ester carbonyl absorption at 5.73 μ. Basic hydrolysis of a small sample of the product gave *o*-chlorobenzoic acid (isolated) and phenol (identified as tribromophenol).

A sample of the dark solid obtained in the pyrolysis was shown by x-ray diffraction to contain large amounts of silver chloride.

An authentic sample of II was prepared in 67% yield from *o*-chlorobenzoyl chloride and phenol in dry pyridine. The pure ester had boiled at 125–127° (0.5 mm.), n_D^{25} 1.5843, and had a satisfactory analysis. The infrared spectrum of the authentic sample was identical with that of the pyrolysis product as isolated above.

Preparation of III. *o*-Chlorobenzoic acid (20.0 g., 0.13 mole) was converted to the acid chloride with 40 ml. of thionyl chloride. The acid chloride was added dropwise to a cooled (0°) and stirred solution of salicylic acid (17.7 g., 0.13 mole) in dry pyridine (60 ml.). The mixture was allowed to stand at 3° overnight and was then poured into a large excess of cold water. The solid was collected, washed with water, and sucked dry. Pure *o*-carboxyphenyl *o*-chlorobenzoate was obtained as colorless needles after one recrystallization from benzene, m.p. 169–170°. The yield was 12.4 g. (35%).

Anal. Calcd. for $C_{14}H_9ClO_4$: C, 60.77; H, 3.28. Found: C, 61.22; H, 3.51.

The recrystallized acid (12.4 g., 0.045 mole) was finely ground and suspended in 100 ml. of water. The mixture was stirred and cooled to 5° and was then slowly neutralized by the dropwise addition of one equivalent of concd. ammonium hydroxide. The cold solution was filtered into a beaker surrounded by an ice bath, and a cold solution of silver nitrate (7.6 g., 0.045 mole) in water (30 ml.) was added slowly with vigorous stirring. The thick, white salt that precipitated was stirred for an additional hour at 0° and was then collected by suction filtration. The salt was washed well with cold water and was dried. There was obtained 12.0 g. (69%) of pure III, m.p. 177–178° dec.

Anal. Calcd. for $C_{14}H_8AgClO_4$: Ag, 28.13. Found: Ag, 27.92.

Pyrolysis of III. Salt III (10.0 g., 0.03 mole) was pyrolyzed under conditions identical with those under which silver *o*-chlorobenzoate gave phenyl *o*-chlorobenzoate. Exothermic decomposition occurred at approximately 180°, and the temperature was raised to 225° over 3 hr. No volatile product appeared on the cold finger, and on cooling there was obtained approximately 8 g. of a black, hard, insoluble mass. The apparatus was washed out with ether, and the solid was pulverized and extracted with boiling ether. The combined ether solutions gave on concentration 0.3 g. of an oil which afforded a trace of chlorobenzene on distillation. No other volatile products could be distilled even at bath temperatures over 200° at 0.05 mm. The experiment was repeated with an intimate mixture of 10 g. of III and 0.5 g. of silver chloride. The results were substantially unchanged. In neither run could any II be detected.

Pyrolysis of I (M = Ag, X = F). The dried salt I (36.5 g., 0.15 mole) was pyrolyzed in bulk in the apparatus described for I (M = Ag, X = Cl). A vigorous reaction occurred slightly above the melting point of the salt, and the products were worked up as described above. Distillation of the liquid product afforded 4.0 g. of fluorobenzene, b.p. 85°, n_D^{25} 1.4657. A residue of less than 0.5 g. could not be distilled.

Pyrolysis of I (M = Ag, X = I). The dried salt I (34.1 g., 0.10 mole) was pyrolyzed in bulk in the apparatus described for I (M = Ag, X = Cl). A vigorous reaction occurred at approximately 150° and appeared to be complete in a few seconds. The solid products were worked up in the usual manner to give 3.2 g. (31%) of the lactone of *o*-carboxy-*o'*-hydroxydiphenyl ether, m.p. 180–181°, from benzene/pentane.

Anal. Calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.80. Found: C, 73.29; H, 3.76. The infrared spectrum showed a sharply split carbonyl absorption at 5.65, 5.70, and 5.75 μ. Scale molecular models predict a complex carbonyl spectrum on the basis of conformation considerations. The spectrum was free from hydroxyl absorption and showed no other characteristic functionality. Strong absorption at 13.70 μ suggested *o*-disubstituted phenyl.

Attempts to prepare an authentic sample of IV by the Baeyer-Villiger oxidation of xanthone with peracetic acid using sulfuric acid and *p*-toluenesulfonic acid catalysts failed, and in both cases xanthone was recovered unchanged after treatments of 1 week.

WILMINGTON 98, DEL.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Reaction of Propylene Oxide, Styrene Oxide, and Cyclohexene Oxide with an Ivanov Reagent

F. F. BLICKE AND P. E. WRIGHT[1,2]

Received November 30, 1959

Propylene oxide reacted with the Ivanov reagent, the α-chloromagnesium derivative of the chloromagnesium salt of phenylacetic acid, to form α-phenyl-β-hydroxyvaleric acid and two stereoisomeric α-phenyl-β-methylbutyrolactones. From styrene oxide and the Ivanov reagent, two stereoisomeric α,γ-diphenyl-β-hydroxybutyric acids were obtained. Cyclohexene oxide and the Ivanov reagent reacted to form α-phenyl-α-(2-hydroxycyclohexyl)acetic acid.

Ethylene oxide has been found[3] to react with the α-chloromagnesium derivative of the sodium salt of phenylacetic acid (an Ivanov reagent) to produce α-phenyl-γ-hydroxybutyric acid.

This paper described the reactions of propylene oxide, styrene oxide, and cyclohexene oxide, re-

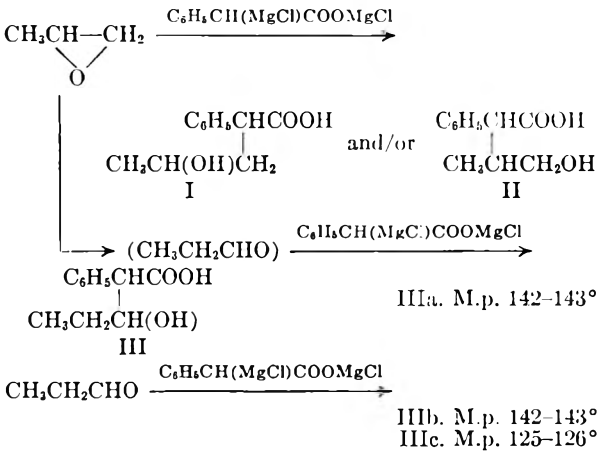
(1) This paper represents part of a dissertation submitted by P. E. Wright for the Ph. D. degree in the University of Michigan.

(2) The Wm. S. Merrell Fellow.

(3) F. F. Blicke and H. Raffelson, *J. Am. Chem. Soc.*, **74**, 1730 (1952).

spectively, with the chloromagnesium derivative of the chloromagnesium salt of phenylacetic acid (an Ivanov reagent).

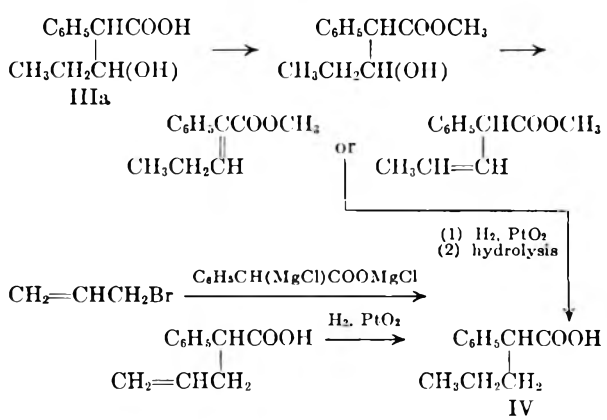
Propylene oxide can react with a Grignard reagent either in the epoxide form or as propionaldehyde.[4,5] The epoxide and the Ivanov reagent could interact to form I and/or II; from the aldehyde, III would be formed. After reaction of propylene oxide and the Ivanov reagent, α-phenyl-β-hydroxy-



valeric acid (IIIa)(m.p. 142–143°) was obtained. In addition, there were isolated a solid lactone of α-phenyl-β-methyl-γ-hydroxybutyric acid (II) and a liquid product, presumably a stereoisomer.

Proof that propylene oxide had reacted, to some extent, in the aldehyde form to yield III was obtained by a separate experiment in which propionaldehyde was allowed to react with the Ivanov reagent. An acid (IIIb) which melted at 142–143°[6] was obtained from the reaction mixture; in addition, an isomeric α-phenyl-β-hydroxyvaleric acid (IIIc) was isolated which melted at 125–126°. Both stereoisomeric acids were converted into their methyl and β-diethylaminoethyl esters.

In conformity with the assigned structure, IIIa, after successive esterification dehydration, hydrogenation, and hydrolysis, was converted into α-phenylvaleric acid (IV). This same acid (IV) would have been formed if compound I had been sub-



(4) F. H. Norton and H. B. Hass, *J. Am. Chem. Soc.*, 58, 2147 (1936).

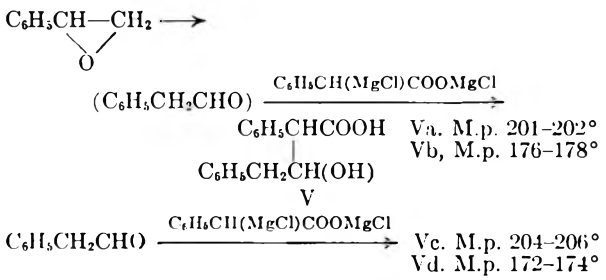
mitted to this series of reactions; however, compound II would have been converted into α-phenylisovaleric acid.

In order to obtain a sample of IV for a mixed melting point determination, it was synthesized by hydrogenation of α-phenyl-α-allylacetic acid.[7]

Oxidation of the solid lactone, isolated from the reaction mixture, with the use of bromine, sodium hydroxide and magnesium sulfate,[8] yielded α-phenyl-α′-methylsuccinic acid, a substance which could have been produced only from the lactone of II. The same succinic acid was obtained by oxidation of the liquid lactone.

Both the solid and the liquid lactone were converted by ammonia into α-phenyl-β-methyl-γ-hydroxybutyramide. Lithium aluminum hydride reduced the amide to β-phenyl-γ-methyl-δ-hydroxybutylamine.

Styrene oxide reacted in the form of phenylacetaldehyde with the Ivanov reagent to form two stereoisomeric α,γ-diphenyl-β-hydroxybutyric acids (Va, Vb). The two acids Vc and Vd were obtained from the interaction of phenylacetaldehyde and the Ivanov reagent. A mixture of Va and Vc and also a mixture of Vb and Vd showed no melting point depression.



Methyl esters were prepared from acids Va and Vb and from acids Vc and Vd. The esters of Va and Vc proved to be identical; identity was also established for the esters of Vb and Vd. Methyl esters of Va and Vb, when heated with phosphorus pentoxide in benzene solution, were dehydrated. It was not established whether the dehydration product was a methyl ester of 2,4-diphenyl-2-butenoic or of 2,4-diphenyl-3-butenoic acid.

A lactone was obtained from acid Va when it was refluxed with acetic anhydride, and a lactone was produced from Vb when it was heated in methanol solution with a small amount of concentrated sulfuric acid.

(5) P. G. Stevens and J. A. McCoubrey, *J. Am. Chem. Soc.*, 63, 2847 (1941).

(6) This acid has been obtained previously from propionaldehyde and the Ivanov reagent (ref. 3. R. H. Cox, Dissertation, University of Michigan, 1954.

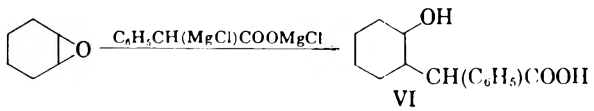
(7) G. R. Ackermann, Dissertation, University of Michigan, 1956.

(8) Lactones have been oxidized in this manner by R. R. Russell and C. A. VanderWerf (*J. Am. Chem. Soc.*, 69, 11 (1947)) and by J. A. McRae, E. H. Charlesworth, and D. S. Alexander (*Canadian J. Res.*, 21, Sect. B, 1 (1943)).

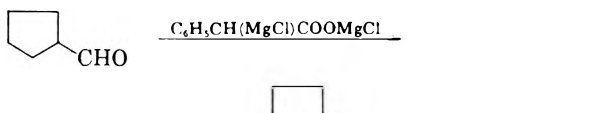
2,4-Diphenyl-1,3-butanediols were prepared from Va and Vb by the use of lithium aluminum hydride.

Incidentally, it was found that when Va was heated in acetic acid with phosphorus and iodine, in the expectation that α,γ-diphenylbutyric acid would be formed, α,γ-diphenyl-β-acetoxybutyric acid was produced.

It is believed that cyclohexene oxide reacted in the epoxide form with the Ivanov reagent to produce α-phenyl-α-(2-hydroxycyclohexyl)acetic acid (VI); the product isolated melted at 153–154°.



VI



VII

After the preparation of the methyl ester of VI, dehydration of the ester with phosphorus pentoxide in benzene solution yielded an unsaturated ester which may have been either methyl α-phenyl-α-(1-cyclohexenyl)acetate or methyl α-phenyl-α-(2-cyclohexenyl)acetate.

A lactone was obtained when VI was heated in methanol with a small amount of concentrated sulfuric acid.

In the event that cyclohexene oxide reacted in the form of cyclopentanecarboxaldehyde,[9] α-phenyl - β - cyclopentyl - β - hydroxypropionic acid (VII) would have been formed. Compound VII had already been synthesized[10] from the aldehyde and the Ivanov reagent and it was stated that VII melted at 145–148°. As the melting point (153–154°) of the product obtained from cyclohexene oxide and the melting point reported for VII are rather close, VII was synthesized from cyclopentanecarboxaldehyde and the Ivanov reagent in order to make a mixed melting point determination. The product obtained, after one recrystallization, melted at the reported melting point (145–148°). However, by the use of different solvents, it was possible to separate the product into two components; one melted at 130–131°, the other at 161–162°. The analytical data for each component corresponded to that calculated for VII.

EXPERIMENTAL

Reaction of propylene oxide with the Ivanov reagent. Formation of α-phenyl-β-hydroxyvaleric acid (IIIa) and α-phenyl-β-methylbutyrolactones. Phenylacetic acid (272.2 g., 2.0 moles), dissolved in 1500 ml. of benzene, was added, dropwise, to a stirred solution of isopropylmagnesium chloride prepared from 112 g. (4.6 g.-atom) of magnesium, 361 g. (4.6 moles) of isopropyl chloride and 1000 ml. of ether; the reaction was initiated with 5 ml. of ethyl bromide. The mixture was refluxed for 4 hr.

Propylene oxide (133.6 g., 2.0 moles), dissolved in 500 ml. of benzene, was added, dropwise, to the stirred mixture. It was stirred for 20 hr., the ether was removed by distillation, and a mixture of 400 ml. of conc. hydrochloric acid and 1500 ml. of ice water was added to the stirred material. The layers were separated and the aqueous layer was extracted with benzene. The combined benzene layers were concentrated to a volume of 400 ml. and the solution was placed in a refrigerator for 24 hr. The precipitate (IIIa) was filtered, then the filtrate was concentrated to 300 ml., cooled for 24 hr., and filtered (filtrate A) to yield more product. The combined material was washed with hot petroleum ether (60–75°); it weighed 83.0 g. (21.4% yield); m.p. 142–143° after recrystallization from toluene.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27; neut. equiv., 194.2. Found: C, 68.17; H, 7.18; neut. equiv., 194.1.

The benzene filtrate (A) was stirred with 84 g. of sodium bicarbonate, dissolved in 1000 ml. of water, and the aqueous layer was separated and extracted with benzene. The benzene solutions were combined, the solvent was removed, and the residue was distilled. The fraction (123 g.) which boiled at 109° (0.3 mm.) partially solidified after 48 hr. in a refrigerator. After filtration through a sintered glass funnel, the crystals, α-phenyl-β-methylbutyrolactone, weighed 35.3 g., (10% yield); m.p. 93–94° after recrystallization from petroleum ether (60–75°).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.90; H, 6.66.

The liquid filtrate which, based on analytical data, was another α-phenyl-β-methylbutyrolactone, weighed 83.8 g. (23% yield).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.76; H, 6.61.

This liquid filtrate was refluxed with an aqueous sodium hydroxide solution until it dissolved. Upon acidification at 0°, an oil precipitated. The oil was separated and cooled whereupon it partially solidified. The solid material melted at 93–94° after recrystallization from petroleum ether (60–75°). The liquid portion was distilled; b.p. 109° (0.3 mm.). The distillate was refluxed with aqueous sodium hydroxide until it dissolved and the process mentioned above was repeated. Again a solid, m.p. 93–94°, and a liquid, b.p. 109° (0.3 mm.), were obtained.

Preparation of α-phenyl-β-hydroxyvaleric acids (IIIb, IIIc) from propionaldehyde and the Ivanov reagent. Propionaldehyde (116.2 g.), dissolved in 500 ml. of benzene, was added, dropwise, to a stirred suspension of the Ivanov reagent prepared in the manner described above from 272.2 g. of phenylacetic acid. The mixture was refluxed for 6 hr. and hydrolyzed with a mixture of 333 ml. of conc. hydrochloric acid and 1500 ml. of ice water. The layers were separated and the aqueous layer was extracted with ether and benzene. After concentration of the combined extracts, 167.5 g. (43%) of crystals precipitated; they were removed by filtration (filtrate A) and after recrystallizaton from toluene they melted at 142–143°.[6] This product (IIIb) proved to be identical with IIIa; mixed m.p. 142–143°.

After concentration and cooling of filtrate A, 65.3 g. (16%) of material (IIIc) was obtained; m.p. 125–127° after recrystallization from toluene. This product, based on an analysis and a neutralization equivalent, seems to be another stereoisomeric α-phenyl-β-hydroxyvaleric acid.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27; neut. equiv., 194.2. Found: C, 68.05; H, 7.25; neut. equiv., 196.1.

Methyl and β-diethylaminoethyl esters of α-phenyl-β-hydroxyvaleric acids (IIIa, IIIc). The methyl ester of IIIa was prepared from 3.8 g. (0.02 mole) of the acid, dissolved

(9) Reaction of cyclohexene oxide in this form has often been reported. See M. S. Kharasch and O. Reinmuth, Grignard Reactions of Nonmetallic Substances, Prentice-Hall, Inc., New York, N. Y.

(10) F. F. Blicke and H. Zinnes, *J. Am. Chem. Soc.*, **77**, 6247 (1955).

in 500 ml. of the dimethyl ether of ethylene glycol, by the addition of excess diazomethane dissolved in ether. The mixture was allowed to remain at 0° for 2 hr., then the solvent and excess diazomethane were removed in a stream of air; yield 3.3 g. (79%); m.p. 57–58°[11] after recrystallization from petroleum ether (60–75°).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.00; H, 7.90.

The methyl ester of IIIc was obtained in 64% yield by the method described above; b.p. 90° (0.3 mm.).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.17; H, 7.74.

The β-diethylaminoethyl ester of IIIa was prepared by dissolving 2.3 g. of sodium in 250 ml. of isopropyl alcohol, adding 19.4 g. of the acid and 17.5 g. of β-diethylaminoethyl chloride hydrochloride and refluxing the mixture for 16 hr. After filtration and removal of the solvent from the filtrate, the residue was made basic with sodium carbonate solution, extracted with ether, and the ether solution was dried with anhydrous magnesium sulfate. After removal of the ether, the residue was recrystallized from petroleum ether (60–75°); yield 15.8 g. (53%); m.p. 78–80°.

Anal. Calcd. for $C_{17}H_{27}O_3N$: C, 69.59; H, 9.28. Found: C, 69.80; H, 9.36.

The dihydrogen citrate was prepared in ether; m.p. 96–98° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{23}H_{35}O_{10}N$: C, 56.89; H, 7.27. Found: C, 56.92; H, 7.28.

The β-diethylaminoethyl ester of IIIc was prepared in the manner described above; yield 51%; b.p. 111° (0.5 mm.).

The dihydrogen citrate was prepared in ether; m.p. 93–94° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{23}H_{35}O_{10}N$: C, 56.89; H, 7.27. Found: C, 56.76; H, 7.25.

Conversion of methyl α-phenyl-β-hydroxyvalerate into α-phenylvaleric acid (IV). The methyl ester (10.4 g.) of IIIa was dissolved in 250 ml. of benzene and added, dropwise, to a stirred, refluxing mixture of 20 g. of Celite, 15 g. of phosphorus pentoxide, and 750 ml. of benzene. The mixture was stirred and heated for 4 hr., cooled and filtered. The filtrate was washed with bicarbonate solution, dried with magnesium sulfate, and evaporated to dryness. The oily dehydration product (9.2 g., 96%) boiled at 155° (20 mm.).

A portion (3.8 g.) of this oil, dissolved in absolute methanol, was hydrogenated under an initial pressure of 50 lbs., in the presence of 0.1 g. of platinum dioxide, until the calculated amount of hydrogen had been absorbed (2 hr.). The solvent was removed from the filtered mixture whereupon an oil was obtained. This liquid was allowed to remain in the presence of 2.2 g. of potassium hydroxide, dissolved in 25 ml. of 90% ethanol, for 5 days. The solution was diluted with 150 ml. of water and extracted with ether. Upon acidification of the cold, alkaline solution, 2.5 g. (70%) of IV precipitated; m.p. 51–53°[12] after recrystallization from petroleum ether (90–100°).

Preparation of α-phenylvaleric acid (IV) from 2-phenyl-4-pentenoic acid. 2-Phenyl-4-pentenoic acid[7] (3.5 g.) was dissolved in 100 ml. of absolute methanol and hydrogenated under an initial pressure of 50 pounds in the presence of 0.1 g. of platinum dioxide. After filtration, the solvent was removed from the filtrate and the residue was recrystallized from petroleum ether (90–100°); m.p. and mixed m.p. 51–53°.

Oxidation of α-phenyl-β-methylbutyrolactones. The liquid lactone (17.6 g.) was added to 15 g. of sodium hydroxide, dissolved in 75 ml. of water, and the mixture was heated until a solution was obtained. The solution was stirred and kept hot while a hot solution of 43.5 g. of hydrated magnesium sulfate in 33 ml. of water was added slowly. The mixture was cooled to 10° and 5.5 ml. of bromine was added, dropwise, over a period of 2 hr. The cold mixture was stirred for several hours and acidified with 33 ml. of 32% sulfuric acid. The precipitate was filtered and washed with toluene. The product, α-phenyl-α′-methylsuccinic acid, melted at 169–172°[13] after recrystallization from water; yield 6.2 g. (29%).

The solid lactone (17.6 g.) was treated in the manner described above. This reaction yielded 4.1 g. (19%) of the same product; m.p. 169–172°.

α-Phenyl-β-methyl-γ-hydroxybutyramide. The liquid lactone (8.8 g.) was shaken with 15 ml. of conc. ammonia water for 18 hr. The precipitated amide was filtered and the excess ammonia was removed from the filtrate by a stream of air whereby an additional amount of amide was obtained; total yield 9.4 g. (97%); m.p. 145–146° after recrystallization from methyl ethyl ketone.

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.35; H, 7.60; N, 7.25.

The solid lactone (4.4 g.) was dissolved in 200 ml. of absolute ethanol and ammonia was bubbled slowly into the solution for 6 hr. After evaporation of the solvent and recrystallization of the residue from methyl ethyl ketone, the amide melted at 145–146°.

β-Phenyl-γ-methyl-δ-hydroxybutylamine. α-Phenyl-β-methyl-γ-hydroxybutyramide (11.4 g.), dissolved in 100 ml. of anhydrous tetrahydrofuran, was added slowly to a stirred solution of 5.3 g. of lithium aluminum hydride in 250 ml. of the same solvent. The mixture was stirred for 4 hr., and 10 ml. of water was added, dropwise, to the stirred mixture. After filtration, the solvent was removed from the filtrate and the residue was distilled; b.p. 132° (0.7 mm.); yield 5.1 g. (48%). After some time, the pure hydroxy amine became very viscous.

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56. Found: C, 73.59; H, 9.50.

Reaction of styrene oxide with the Ivanov reagent. The formation of α,γ-diphenyl-β-hydroxybutyric acids (Va, Vb). Styrene oxide[14] (48.0 g., 0.4 mole), dissolved in 250 ml. of benzene, was added, dropwise, to a stirred suspension of the Ivanov reagent which had been prepared from 54.4 g. (0.4 mole) of phenylacetic acid. The material was refluxed for 72 hr., then hydrolyzed with a mixture of 67 ml. of conc. hydrochloric acid and 1000 ml. of ice water. The precipitate (Va), which formed between the two layers, was filtered. Partial evaporation of the organic layer in the filtrate yielded more Va; the total yield of Va, after recrystallization from ethanol, was 41.2 g. (40%); m.p. 201–202°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; neut. equiv., 256.3. Found: C, 75.07; H, 6.30; neut. equiv., 258.5.

Further concentration of the organic layer gave material (Vb) which, after recrystallization from toluene, weighed 17.2 g. (16%); m.p. 176–178°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; neut. equiv., 256.3. Found: C, 74.84; H, 6.40; neut. equiv., 256.4.

Methyl and β-diethylaminoethyl esters of α,γ-diphenyl-β-hydroxybutyric acids. A mixture of 128 g. of Va, 1500 ml. of methanol, and 5 ml. of conc. sulfuric acid was refluxed for 20 hr. The solution was concentrated whereupon the ester precipitated. After recrystallization from petroleum ether (60–75°), the yield was 107 g. (79%); m.p. 98–99°.[15]

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.49; H, 6.68.

In order to prepare the methyl ester of Vb, about twice the calculated amount of diazomethane, dissolved in 100 ml. of ether, was added to a solution of 17.0 g. of the acid in 500 ml. of dioxane which had been cooled to 0°. After 2 hr.

(11) In a separate experiment, IIIb was treated with diazomethane. The methyl ester produced melted at 57–58°; mixed m.p. 57–58°.

(12) H. Veldstra and C. van de Westeringh, *Rec. trav. chim.*, **70**, 1113 (1951); m.p. 51–52°.

(13) C. A. Miller, H. I. Scholl, and L. M. Long, *J. Am. Chem. Soc.*, **73**, 5608 (1951); m.p. 169–172°.

(14) Purchased from the Dow Chemical Company.

(15) A small amount of ester, prepared by the use of diazomethane, melted at 98–99°.

at this temperature, the solvent was removed; the yield, after recrystallization from petroleum ether (60–75°), was 17.0 g. (95%); m.p. 49–50°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.48; H, 6.55.

The β-diethylaminoethyl ester of Va was prepared by the addition of 2.3 g. of sodium to 250 ml. of isopropyl alcohol and heating the mixture until the sodium had disappeared. After the addition of 25.6 g. of Va and 17.5 g. of β-diethylaminoethyl chloride hydrochloride, the mixture was refluxed for 16 hr. After filtration, most of the solvent was removed from the filtrate. The precipitated ester hydrochloride (5.0 g.) was removed by filtration (filtrate A) and recrystallized from isopropyl alcohol; m.p. 100–101°.

Anal. Calcd. for $C_{22}H_{30}O_3NCl$: C, 67.41; H, 7.72; Cl, 9.05. Found: C, 67.45; H, 7.62; Cl, 9.19.

Filtrate A was made basic with sodium carbonate solution, extracted with ether and the extract was dried over magnesium sulfate. Removal of the ether and distillation of the residue yielded the ester base of Va; b.p. 106° (0.7 mm.); yield 13.5 g.

The methobromide, prepared in ether, melted at 158–159° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{23}H_{32}O_3NBr$: C, 61.33; H, 7.16. Found: C, 61.35; H, 7.24.

The β-diethylaminoethyl ester of Vb was prepared in the manner described above. The precipitated ester hydrochloride was filtered; yield 8.6 g.; m.p. 100–101° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{22}H_{30}O_3NCl$: C, 67.41; H, 7.72; Cl, 9.05. Found: C, 67.41; H, 7.79; Cl, 9.20.

Although the basic ester hydrochlorides of Va and of Vb melted at the same temperature, the mixed melting point was 85–95°.

The methobromide was prepared in ether by the use of the crude ester base obtained from the filtrate in the manner described above; m.p. 129–130° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{23}H_{32}O_3NBr$: C, 61.33; H, 7.16. Found: C, 61.38; H, 7.12.

Dehydration of the methyl esters of Va and Vb. The methyl ester prepared from Va, dissolved in 250 ml. of benzene, was added, dropwise, to a stirred, refluxing mixture of 50 g. of Celite, 140 g. of phosphorus pentoxide, and 1000 ml. of benzene. The stirred mixture was refluxed for 4 hr. After filtration and evaporation of the solvent from the filtrate, the oily residue was distilled; b.p. 151° (0.5 mm.); yield 78 g. (77%). The product rapidly decolorized an aqueous solution of potassium permanganate and bromine dissolved in carbon tetrachloride. The analytical data corresponded to that calculated for the methyl ester of 2,4-diphenyl-2-butenoic or of 2,4-diphenyl-3-butenoic acid.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.78; H, 6.51.

When the isomeric methyl ester, prepared from Vb, was subjected to dehydration in the manner described above, a product was isolated which boiled at 150° (0.7 mm.); yield 12.5 g. (78%). The material decolorized solutions of potassium permanganate and bromine. The analytical data corresponded to that calculated for the methyl ester of 2,4-diphenyl-2-butenoic or of 2,4-diphenyl-3-butenoic acid.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.92; H, 6.30.

Preparation of α,γ-diphenyl-β-hydroxybutyric acids (Vc, Vd). Phenylacetaldehyde (18.0 g.) dissolved in 75 ml. of benzene, was added, dropwise, to a stirred suspension of the Ivanov reagent prepared from 20.4 g. of phenylacetic acid. The material was refluxed for 12 hr. and then hydrolyzed with a mixture of 25 ml. of conc. hydrochloric acid and 250 ml. of water. The precipitate (Vc), which separated between the two layers, was filtered and the filtrate (filtrate A) was retained. The product, after recrystallization from ethanol, weighed 33.0 g. (85%) and melted at 204–206°. It proved to be identical with Va; mixed melting point 201–202°.

The ether-benzene layer of filtrate A was separated, concentrated, and cooled whereupon 2.5 g. (6%) of Vd precipitated; m.p. 172–174° after recrystallization from toluene. This substance was identical with Vb; mixed melting point 172–174°.

Methyl esters of Vc and Vd. In order to obtain the methyl ester of Vc, 5.1 g. of the acid was dissolved in 750 ml. of the dimethyl ether of ethylene glycol and the solution was cooled to 0°. Excess diazomethane, dissolved in 100 ml. of ether, was added and the mixture was allowed to remain at 0° for 2 hr. After removal of the solvent the residue, after recrystallization from petroleum ether (60–75°), weighed 4.6 g. (85%) and melted at 98–99°. A mixture of the methyl esters of Va and Vc melted at 98–99°.

The methyl ester of Vd was prepared in the manner described above except that only 500 ml. of the dimethyl ether of ethylene glycol was employed. The product, after recrystallization from petroleum ether (60–75°), weighed 2.8 g. (51%) and melted at 54–55°. Although this melting point is somewhat higher than the melting point (49–50°) of the methyl ester of Vb, the mixed melting point of the two esters was 49–50°.

Lactones of α,γ-diphenyl-β-hydroxybutyric acids Va and Vb. A mixture of 25.6 g. of Va and 50 ml. of acetic anhydride was refluxed for 8 hr. After removal of the acetic anhydride, the residue was distilled; b.p. 170° (0.4 mm.); yield 6.5 g. The distillate solidified after some time, and the lactone was then recrystallized from ether; m.p. 125–126°; yield 5.9 g.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.66; H, 6.02.

A mixture of 12.8 g. of Vb, 250 ml. of methanol and 1 ml. of conc. sulfuric acid was refluxed for 20 hr. After removal of the solvent, the residue was treated with hot ether. The solvent was removed from the cold, filtered ether solution and the lactone was recrystallized from ether; m.p. 82–84°; yield 9.2 g. (77%).

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.63; H, 5.90.

2,4-Diphenyl-1,3-butanediols. Lithium aluminum hydride (1.5 g.) was suspended in 250 ml. of ether and 10.2 g. of Va, suspended in 500 ml. of ether, was added. After the mixture had been stirred for 24 hr., 3 ml. of water was added, dropwise, to the stirred mixture. The precipitated salts were filtered, the solvent was removed from the filtrate, and the residue was recrystallized from diisopropyl ether; yield 2.8 g. (28%); m.p. 96–98°.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.33; H, 7.72.

An isomeric 2,4-diphenyl-1,3-butanediol was obtained in 35% yield, in the manner described above, from Vb; m.p. 154–155° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 78.99; H, 7.33.

α,γ-Diphenyl-β-acetoxybutyric acid. A mixture of 12.8 g. of Va, 3.1 g. of red phosphorus, 1.2 g. of iodine, and 350 ml. of acetic acid was refluxed for 8 hr. After filtration, the acetic acid was removed from the filtrate and the residue was recrystallized from toluene; yield 8.1 g.; m.p. 124–126°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08; neut. equiv., 298.3. Found: C, 72.43; H, 6.18; neut. equiv., 298.8.

Reaction of cyclohexene oxide with the Ivanov reagent. Formation of α-phenyl-α-(2-hydroxycyclohexyl)acetic acid (VI). Cyclohexene oxide[16] (196.0 g.), prepared from *trans*-2-chlorocyclohexanol,[17] was dissolved in 500 ml. of benzene and added, dropwise, to the stirred suspension of the Ivanov reagent prepared from 272.2 g. of phenylacetic acid. The stirring was continued for 48 hr. and the mixture was then hydrolyzed with a cold mixture of 333 ml. of conc. hydro-

(16) *Org. Syntheses*, Coll. Vol. I, 185 (1941).

(17) Purchased from the Aldrich Chemical Company.

chloric acid and 1500 ml. of water. After removal of the solvents from the organic layer, the residue was recrystallized from toluene; yield 187.0 g. (40%); m.p. 153–154°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; neut. equiv., 234.3. Found: C, 71.78; H, 7.51; neut. equiv., 235.1.

Dehydration of methyl α-phenyl-α-(2-hydroxycyclohexyl)-acetate. The methyl ester was prepared from 8.2 g. of VI, dissolved in 300 ml. of ether, by the addition of excess diazomethane, dissolved in ether, at 0°. After 2 hr. at this temperature, the solvent was removed; yield 7.9 g. (90%) after recrystallization from petroleum ether (60–75°); m.p. 94–95°.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.27; H, 8.02.

The ester (12.4 g.), dissolved in 250 ml. of benzene, was added dropwise to a stirred, refluxing mixture of 20 g. of Celite, 15 g. of phosphorus pentoxide, and 750 ml. of benzene. The mixture was stirred and refluxed for 4 hr., cooled, and filtered, and the filtrate was shaken with an aqueous sodium bicarbonate solution. The solvent was removed from the dried benzene layer and the residue was distilled; yield 7.8 g. (67%); b.p. 166–170° (20 mm.). The product, which instantly decolorized solutions of potassium permanganate and bromine, may have been methyl α-phenyl-α-(1-cyclohexenyl)acetate or methyl α-phenyl-α-(2-cyclohexenyl)acetate.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.82; H, 7.75.

Lactone of VI. A mixture of 9.3 g. of VI, 150 ml. of methanol, and 1 ml. of conc. sulfuric acid was refluxed for 4 hr. The solvent was removed, the residue was dissolved in ether, and the solution was extracted with aqueous sodium bicarbonate solution. The solvent was removed from the ether layer and the residue was recrystallized from petroleum ether (60–75°); m.p. 75–77°; yield 8.4 g. (97%).

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.75; H, 7.45.

The same lactone was isolated in at least 90% yield when attempts were made to prepare the β-diethylaminoethyl ester of VI by the following procedures: (a) a mixture of the silver salt of VI, β-diethylaminoethyl chloride, and acetone was stirred for 24 hr.; (b) attempted transesterification with the use of the methyl ester of the acid, β-diethylaminoethanol, sodium methoxide, and petroleum ether (60–75°).

The lactone was converted into VI in the following manner. A mixture of 8.4 g. of the lactone, 1.6 g. of potassium hydroxide, and 150 ml. of water was refluxed for 3 hr. The solution was extracted with ether. The cold aqueous layer was acidified and the precipitate (VI) was recrystallized from toluene; yield 8.8 g. (94%); m.p. and mixed m.p. 153–155°.

α-Phenyl-β-cyclopentyl-β-hydroxypropionic acids (VII). Cyclopentanecarboxaldehyde[18] (31.0 g.), dissolved in 100 ml. of benzene, was added dropwise to the stirred suspension of the Ivanov reagent prepared from 43.0 g. of phenylacetic acid. The material was stirred and refluxed for 4 hr. and poured into a mixture of 53 ml. of conc. hydrochloric acid and 500 ml. of ice water. After removal of the solvent from the organic layer and recrystallization of the residue from toluene, 53.5 g. (72%) of product was obtained; m.p. 145–148° (lit.[10] m.p. 145–148°). When 50 g. of this material was heated with petroleum ether (60–75°), some of the product remained undissolved. The soluble portion, obtained after removal of the solvent, was recrystallized from petroleum ether (60–75°); yield 35.5 g. (51%); m.p. 130–131°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.66; H, 7.51.

The petroleum ether-insoluble portion was recrystallized from toluene; yield 5.6 g. (8%); m.p. 161–162°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.77; H, 7.52.

ANN ARBOR, MICH.

(18) J. English, Jr., J. D. Gregory, and J. R. Trowbridge, II, *J. Am. Chem. Soc.*, **73**, 615 (1951).

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

Solvolysis of Dimethylcyclopentyl Halides

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The rates of solvolysis of 1,2-dimethylcyclopentyl halides are only slightly faster than those of 1-methylcyclopentyl halides. This observation implies that some reservation is necessary in considering the I-strain explanation of the relative reactivities of cyclopentyl halides.

In connection with another study,[3] the rates of solvolysis of mixtures of *cis*- and *trans*-1,2-dimethylcyclopentyl bromides and chlorides were measured. As a matter of collateral interest the rates of solvolysis of 1-methylcyclopentyl bromide and chloride were determined under comparable conditions.

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RESULTS

The first-order rate constants for solvolysis of various cyclopentyl halides are summarized in Table I and Table II. All rates were measured at 25.00 ± 0.02° in ethanol solutions containing 0.100*N* lithium perchlorate.

Scrutiny of the data shows that the rates measured for various samples of dimethylcyclopentyl halides were not as consistent as might be desired. This was shown to be not readily resolvable into two rates because of different reactivities of *cis* and *trans* isomers. Samples prepared from dimethylcyclopentene known to be relatively rich in the *cis* isomer[3] (*ca.* 30%) were solvolyzed and the data

TABLE I

RATES OF SOLVOLYSIS OF CYCLOPENTYL BROMIDES IN ABSOLUTE ETHANOL
(25.0°, 0.1*N* $LiClO_4$)

Bromide	Source[a]	% Solvolysis Followed	$k_1 \times 10^4$ sec.$^{-1}$
1,2-Dimethylcyclopentyl	1,2-Dimethylcyclopentene	99	11.3
1,2-Dimethylcyclopentyl	1,2-Dimethylcyclopentene	85	11.2
1,2-Dimethylcyclopentyl	1,2-Dimethylcyclopentene	86	9.2
1,2-Dimethylcyclopentyl	1,2-Dimethylcyclopentene	93	9.0
1,2-Dimethylcyclopentyl	1,2-Dimethylcyclopentene	93	7.3
1,2-Dimethylcyclopentyl	1,2-Dimethylcyclopentene	97	7.5
1,2-Dimethylcyclopentyl	*cis*-1,2-Dimethylcyclopentene	98	9.7
1,2-Dimethylcyclopentyl	*cis*-1,2-Dimethylcyclopentanol	92	11.2
1,2-Dimethylcyclopentyl	*trans*-1,2-Dimethylcyclopentanol	90	12.0
1,2-Dimethylcyclopentyl	*trans*-1,2-Dimethylcyclopentanol	89	8.3
1-Methylcyclopentyl	1-Methylcyclopentene	99	5.8
1-Methylcyclopentyl	1-Methylcyclopentene	97	5.2
1-Methylcyclopentyl	1-Methylcyclopentene	94	5.0
1-Methylcyclopentyl	1-Methylcyclopentene	76	4.2

[a] Compound from which bromide was prepared by reaction with hydrogen bromide.

TABLE II

RATES OF SOLVOLYSIS OF CYCLOPENTYL CHLORIDES IN ABSOLUTE ETHANOL
(25.0°, 0.1*N* $LiClO_4$)

Chloride	Source[a]	% Solvolysis Followed	$k_1 \times 10^6$ sec.$^{-1}$
1,2-Dimethylcyclopentyl	1,2-Dimethylcyclopentene	92	15.3
1,2-Dimethylcyclopentyl	1,2-Dimethylcyclopentene	80	13.5
1,2-Dimethylcyclopentyl	*cis*-1,2-Dimethylcyclopentanol	91	19.5
1,2-Dimethylcyclopentyl	*cis*-1,2-Dimethylcyclopentanol	95	16.0
1,2-Dimethylcyclopentyl	*trans*-1,2-Dimethylcyclopentanol	91	16.5
1-Methylcyclopentyl	1-Methylcyclopentene	69	8.7
1-Methylcyclopentyl	1-Methylcyclopentene	79	8.3

[a] Material from which chloride was prepared by reaction with hydrogen chloride.

TABLE III

SOLVOLYSIS RATES OF CYCLOALKYL HALIDES

Compounds	k^{25} 80% C_2H_5OH sec.$^{-1}$	k^{25} 98% C_2H_5OH sec.$^{-1}$	k^{25} C_2H_5OH sec.$^{-1}$
1-Chloro-1-methylcyclohexane	3.22×10^{-6} [a]		2.93×10^{-8} [b]
1-Bromo-1-methylcyclohexane		6.85×10^{-6} [c]	3.30×10^{-6} [d]
1-Chloro-1,2-dimethylcyclohexane	4.00×10^{-6} [a]		3.72×10^{-8} [b]
1-Bromo-1,2-dimethylcyclohexane		7.50×10^{-6} [c]	3.61×10^{-6} [d]
1-Chloro-1-methylcyclopentane	3.83×10^{-4} [a]		3.55×10^{-6} [b]
1-Chloro-1-methylcyclopentane			8.50×10^{-6} [e]
1-Bromo-1-methylcyclopentane			5.00×10^{-4} [e]
1-Chloro-1,2-dimethylcyclopentane			1.56×10^{-5} [e]
1-Bromo-1,2-dimethylcyclopentane			9.33×10^{-4} [e]

[a] From Brown *et al.*[7] [b] Calculated using $m = 1$. [c] From Nevitt and Hammond.[8] [d] Calculated using $m = 0.9$. [e] This paper.

were treated by the differential kinetic method.[4] The rates could not be resolved into two components by this procedure. However, it is still possible that some of the differences are due to variations in the reactivities of the two isomers which are too small to be resolved by the mathematical analysis or to interconversion of the isomers under solvolysis conditions. If this is the case, it must be assumed that the *cis* isomer reacts more slowly than the *trans* compound by less than a factor of two.

Table III shows comparisons among the rates of solvolysis of various tertiary cycloalkyl halides. Data collected under different reaction conditions are extrapolated to absolute ethanol by means of the Grunwald-Winstein equation:[5]

(4) J. S. Fritz and G. S. Hammond, *Quantitative Organic Analysis*, John Wiley and Sons, New York (1957), p. 158.

(5) E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, **70**, 846 (1948).

$$\log \frac{k}{k_0} = mY$$

The Y values used were those recently reported by Fainberg and Winstein[6] and m values were estimated by comparison with structurally similar tertiary halides.[5]

The data show that, for cyclohexyl compounds, bromides are faster than chlorides by a factor of 100 and that in the cyclopentyl series the bromides are faster by a factor of 60. As an average, cyclopentyl compounds react about 250 times as fast as the corresponding cyclohexyl compounds.

Brown[7] has attributed the difference in reactivity between cyclopentyl and cyclohexyl compounds to I-strain. Steric strain is believed to be increased in the conversion of an sp^3 cyclohexyl carbon atom to an sp^2 transition state. In contrast, strain due to interactions between eclipsed *cis* groups in cyclopentanes should be relieved by passing to a transition state in which a ring member is assuming a planar configuration.

The data now available are not easily understood in terms of the most straightforward application of the theory of I-strain. If 1-methylcyclopentyl halides are seriously strained because of the nearly eclipsed relationship between the methyl group, halogen atoms and the hydrogens on adjacent carbon atoms, this strain should be increased by replacement of one of the adjacent hydrogens by another methyl group. If this were the case, one should expect that ionization of 1,2-dimethylcyclopentyl halides should relieve more strain than is the case with 1-methylcyclopentyl compounds. The data show that introduction of the second methyl group increases solvolysis rates by a factor of two or less.

There is no very good way of estimating the magnitude of the effects to be expected. The fully eclipsed form of *cis*-1,2-dimethylcyclopentyl halides contains one methyl-methyl interaction similar to that in the fully eclipsed form of *n*-butane.[9] Comparison of the *n*-butane barriers with that in ethane indicates that methyl-methyl eclipsing should increase strain by 0.5–0.8 kcal. per mole in comparison with hydrogen-methyl eclipsing. One would ordinarily expect less than faithful reflection of such a small energy difference in the rates of solvolysis. However, if the I-strain theory is right, a considerable amount of the eclipsing strain in cyclopentyl halides is released in the transition stages for solvolysis. We have been unable to find data satisfactory for estimation of the added strain in *trans*-1,2-dimethylcyclopentyl halides. However, as solvolysis of samples known to be mixtures of *cis* and *trans* halides does not give kinetically resolvable rates, the reactivity of the two isomers must be very similar. Data for the mixtures may therefore be taken as representative of the *cis* compounds. One would certainly expect that the *trans* bromide would also be strained, although the case is not as clear with the *trans* chloride, as study of the barriers in compounds such as 1,2-dichloroethane[10] indicates that there is attraction between eclipsed hydrogen and chlorine atoms.

Several possibilities come to mind for the explanation of the absence of increased reactivity predicted by simple I-strain theory. It is conceivable that the internal steric effect of a 2-methyl group is compensated by an increase in steric hindrance to solvation. This line of reasoning is made unattractive by the fact that the solvolysis rates of 1-methylcyclohexyl and 1,2-dimethylcyclohexyl halides are also very close together. While cyclopentyl and cyclohexyl systems are not exactly analogous, the effects of 2-methyl substituents on solvation energies should be rather similar in the two systems.

There is an interesting possibility for elaboration of the I-strain theory to accommodate the results. Perhaps the puckering motion of the cyclopentane ring[11] no longer oscillates about the ring in functional derivatives. The substituted ring member in cyclopentyl halides may be permanently displaced from the average plane of the ring. If this is the case, additional substituents in the 1- and 2-positions would enter in more or less staggered conformations. This might account for the small magnitude of the influence of a 2-methyl group. An interesting corollary of this view would be the prediction that substituents in the 3-position would cause further steric acceleration.

Finally, it is, of course, possible that I-strain is less responsible than has been supposed for the difference in reactivity between cyclopentyl and cyclohexyl compounds. The usual conglomerate of effects, such as special electronic considerations, and both internal and external steric effects, should perhaps be reconsidered.

EXPERIMENTAL

Materials. The preparation of *cis*- and *trans*-1,2-dimethylcyclopentanol and 1,2-dimethylcyclopentene is described elsewhere.[3] 1-Methylcyclopentanol was prepared by the *addition of cyclopentanone to freshly prepared methylmagnesium chloride*, b.p., 45–46° at 15 mm., m.p., 35°. The compound has previously been prepared in unspecified yield[12] by the reaction of cyclopentanone with methyl magnesium iodide. It was our experience that all reactions using methylmagnesium iodide or methyllithium and the addition of

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(8) T. D. Nevitt and G. S. Hammond, *J. Am. Chem. Soc.*, **76**, 4124 (1954).

(9) K. S. Pitzer, *J. Chem. Phys.*, **8**, 711 (1940).

(10) J. C. M. Li and K. S. Pitzer, *J. Am. Chem. Soc.*, **78**, 1077 (1956).

(11) J. E. Kilpatrick, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2483 (1947).

(12) N. Zelinsky and S. Namjetkin, *Ber.*, **35**, 2683 (1902); G. Chavanne and L. DeVogel, *Bull. soc. chim. Belg.*, **37**, 141 (1928).

methylmagnesium chloride to cyclopentanone gave very low yields of the alcohol (20% or less). The principal product in these reactions was 2-cyclopentylidenecyclopentanone, b.p. 103–118° at 13 mm., oxime[13,14] m.p., 122°, and 2,5-dicyclopentylidenecyclopentanone,[13] m.p. 66–68°. Addition of the ketone to methylmagnesium chloride gave the alcohol in 62% average yield.

Halides were prepared by reactions of anhydrous hydrogen halides with the alcohols and 1,2-dimethylcyclopentene as described elsewhere.[3] Excess hydrogen halide was removed from the reaction mixtures by extraction with cold water and the pentane solution was dried briefly over anhydrous calcium sulfate. No solution was stored for more than an hour before use.

Procedure. The pentane solutions of halides (approximately 0.02 mole in 20–25 cc. of pentane) were diluted to exactly 25 ml. with pentane. Ten-milliliter aliquots were added to 75 ml. absolute alcohol containing 0.1*N* lithium perchlorate. Solvolysis rates were measured using the rapid intermittent titration method.[15] The titrant was a standard 1*N* solution of triethylamine in absolute ethanol. Bromophenol blue was employed as the visual indicator. Solvolysis of the bromides was followed for about 100 min. and the reactions of the chlorides were followed for about 5000 min. As neither initial concentrations nor infinity titers were known with high precision, the rate constants were determined by the method of Guggenheim.[16] Plots of milliequivalents of base added versus time were used to obtain pairs of concentration values at fixed time intervals (25 min. for the bromides and 1000 min. for the chlorides). The values of log (C_2-C_1) were plotted against t and the rate constants were calculated by multiplication of the slopes of the resulting straight lines by 2.303. While rates sometimes decreased slightly toward the end of a run, the data could never be resolved to give two clearly distinct rates. The values reported in Tables I and II represent maximum rates, as earlier points were used in runs in which the decrease in rate was noticeable.

Acknowledgment. This work was supported by a grant from the Office of Basic Ordnance Research of the United States Army.

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

Conformational Analysis. IX. The *Gem*-Dimethyl Effect[1,2]

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The *gem*-dimethyl effect is quantitatively interpreted for a group of ring closure reactions which lead to substituted cyclohexane systems. The pronounced effect of alkyl substituents in shifting the equilibrium toward the cyclic compound is due in part to an enthalpy effect and in part to an entropy effect. The effect of alkyl groups on the enthalpy of ring closure is interpreted in terms of the change in the number of *gauche* interactions in going from the reactant to the product. The entropy effect, after allowing for the different symmetries of the compounds, is interpreted as being due mainly to the increased height of the barriers to internal rotations in the acyclic compounds upon chain branching.

While the fact that alkyl substitution tends to promote the rate of formation of a cyclic system from its noncyclic analog as well as to increase the concentration of the cyclic material at equilibrium has been recognized for nearly half a century,[3] no convincing explanation of the effect has been forthcoming.[4] Various attempts to explain the phenomenon have been made, and some of these such as the "Thorpe-Ingold effect"[5] and steric hindrance to rotation[4] are probably of importance in certain cases. It is the purpose of this paper to show that certain aspects of the phenomenon have a straightforward thermodynamic basis and are completely general. This general effect, which for historical[4] reasons has been simply called the *gem*-dimethyl effect in this paper, must always be taken into account before the importance of any "special" effects such as the Thorpe-Ingold effect can be ascertained.

The present paper will be limited in scope as far as quantitative aspects are concerned to equilibria, and the treatment will be applied quantitatively to six-membered ring systems since these are particularly amenable to study and the necessary data are available.[6] The same considerations will apply, in principle, to compounds of other classes equally well.

Consider the reaction of *n*-hexane to give cyclohexane and hydrogen in the gas phase at 25°. This reaction can be taken as the reference point,

(1) This work was supported by a grant from the Sloan Foundation.

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TABLE I

THERMODYNAMIC QUANTITIES FOR THE CYCLIZATION REACTIONS OF SUBSTITUTED HEXANES (H) TO CYCLOHEXANES (C)

Hexane	σ_H	σ_C	Optical Isomers H	Optical Isomers C	—ΔH Calcd.	—ΔH Found	ΔS Calcd.	ΔS Found	—ΔF Calcd.	—ΔF Found
n	2	6	1	1	0.0	0.0	0.0	0.0	0.0	0.0
2-CH_3	1	1	1	1	0.8	0.9	3.4	3.3	1.8	1.9
3-CH_3	1	1	2	1	1.6	1.6	2.0	2.2	2.2	2.2
2,2-$(CH_3)_2$	3	1	1	1	0.0	0.1	6.8	5.7	2.0	1.8
2,3-$(CH_3)_2$[a]	1	2	2	2	1.6	2.4	3.2	4.1	2.6	3.6
2,3-$(CH_3)_2$[b]	1	1	2	2	0.0	0.6	4.6	5.0	1.4	2.0
2,4-$(CH_3)_2$[a]	1	1	2	2	0.8	0.3	4.6	5.0	2.2	1.8
2,4-$(CH_3)_2$[b]	1	1	2	1	2.4	2.3	3.2	3.6	3.4	3.3
2,5-$(CH_3)_2$[a]	2	2	1	1	1.6	1.4	4.6	3.8	3.0	2.6
2,5-$(CH_3)_2$[b]	2	1	1	1	0.0	−0.5	3.2	5.2	1.0	1.1
3,3-$(CH_3)_2$	1	1	1	1	1.6	1.2	4.6	4.1	3.0	2.4
3,4-$(CH_3)_2$[a,c]	2	2	2	2	3.2	2.6	4.6[c]	3.0	4.2	3.6
3,4-$(CH_3)_2$[b,c]	1	1	1	2	0.8	0.8	6.0[c]	3.9	2.2	2.0
2-C_2H_5	1	1	2	2	0.8	0.8	3.4	2.7	1.8	1.6
3-C_2H_5	1	1	1	2	1.6	1.2	4.8	3.5	3.0	2.2

[a] For ring closure to *trans* form. [b] For ring closure to *cis* form. [c] The *dl* closes to give *trans*, and the *meso* to give *cis*. It has been assumed that the open chain material is a 1:1 mixture of the two diastereomers.

and for the reaction we can define $\Delta F = \Delta H = \Delta S = 0$. If now various alkyl groups are substituted on the hexane chain so that various alkylcyclohexanes are obtained upon cyclization, these latter reactions will, relative to the unsubstituted case, generally show negative values for ΔF. The task at hand is to calculate these values of ΔF from elementary principles. It is necessary to calculate ΔH and ΔS separately, and then to find ΔF.

One simplifying assumption is made to facilitate the calculations, which is to consider for each isomer only the form or forms of lowest enthalpy instead of using partition functions. The errors introduced by this approximation are expected to cancel to a large extent when only comparisons between fairly similar compounds are used. The ultimate justification for this approximation is the agreement between the calculated and experimental results.

The calculation of ΔH for the ring closure will be considered first. The experimental values listed in Table I are taken directly from the API tables.[6] The calculated values are arrived at as follows. A given chain structure is considered in the form of minimum enthalpy and the number of *gauche* interactions are counted and substracted from the number of *gauche* interactions in the most stable form of the cyclic reaction product. The result is the increase in *gauche* interactions upon ring closure. The closure of *n*-hexane to cyclohexane requires 6 additional *gauche* interactions. The increase in *gauche* interactions in the substituted case, less this number 6, gives the increase in *gauche* interactions relative to the unsubstituted case. When this increase is multiplied by 0.8 kcal. per *gauche* interaction,[7] the change in enthalpy of ring closure relative to the unsubstituted case is found. These values are listed as the calculated enthalpies in Table I.

Hammond[8] has suggested that the entropy loss upon cyclization is less in the substituted compound than with the corresponding methylene compound since the substituents would restrict the rotation in the acyclic system thereby lowering its entropy.

The entropies of the branched chain hydrocarbons dealt with in the present work have previously been calculated by the statistical method.[9,10] Similar calculations have also been carried out for the methylated cyclohexanes.[11] A simplified approximate expression for calculating the entropy of a branched chain paraffin has also been presented by Pitzer and Scott[12] and is given by Eq. 1 where

$$S = S_n + R\ln 2 + R\ln(I/\sigma_e\sigma_i) - 3.5B \qquad (1)$$

S and S_n are the entropies of the branched and normal isomers, I is the number of optical or other isomers considered, σ_e and σ_i are the symmetry numbers for external and internal rotation respectively, and B is the number of chain branchings. The constant 3.5 is to take care of the branching effects not evaluated in detail and is empirical. Clearly a similar equation can be written for the cyclic compounds. If the ΔS for the ring closure of a substituted hexane (H) to a substituted cyclohexane (C) relative to the parent case of *n*-hexane to cyclohexane is considered, then Eq. 2 may

(7) K. S. Pitzer, *Chem. Revs.*, **27**, 39 (1940).

(8) G. S. Hammond, Chapter of *Steric Effects in Organic Chemistry*, edited by M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 468.

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(10) K. S. Pitzer and J. E. Kilpatrick, *Chem. Rev.*, **39**, 435 (1946).

(11) C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2488 (1947).

(12) K. S. Pitzer and D. W. Scott, *J. Am. Chem. Soc.*, **63**, 2419 (1941).

$$\Delta S = R\ln 6 - R\ln 2 + R\ln [I_C/(\sigma_e\sigma_i)_C] - R\ln [I_H/(\sigma_e\sigma_i)_H] + aB \quad (2)$$

be written to describe the entropy of the reaction. The first two terms account for the symmetry present in cyclohexane and *n*-hexane respectively. The constant a is to be evaluated empirically. The constant used by Pitzer and Scott (3.5 e.u./branch) contains a contribution from the increased barrier to internal rotation upon branching. The higher rotational barrier leads to a smaller entropy for the branched open-chain structure than for the unbranched one. The cyclic compounds have lost all of their internal rotational entropy (except for the side chains), and consequently the entropy loss upon cyclization is less for the branched structure. Therefore the constant a is expected to have a value of less than 3.5. It is found empirically that the best value is 1.2. If Eq. 2 is then rewritten as Eq. 3, the predicted entropies of cyclization for the various compounds can be easily found:

$$S = 2.18 + 1.2B + 1.98 \ln [I_C(\sigma_e\sigma_i)_H/I_H(\sigma_e\sigma_i)_C] \quad (3)$$

The symmetry numbers have the usual meaning, where σ_i applies only to rotation of part of the carbon skeleton, not to the rotation of a methyl. The isomers to be considered in the open-chain compounds are only the actually physically separable ones, not the conformers. For the rings on the other hand, a compound like *cis*-1,2-dimethylcyclohexane is taken to be DL, since it so exists at any instant.[13] The presence of less stable forms, such as axial-methylcyclohexane and boat forms, is ignored as they have a negligible (for present purposes) effect on the free energy.

The total entropy changes calculated are included in Table I, and from these values and the calculated enthalpies the calculated free energies are obtained. The corresponding experimental values for all the cyclohexanes for which data are available are also listed for comparison, and the agreement is satisfactory. The calculated and experimental values are found to differ by 1 kcal./mole at most. This is not much more than the maximum deviation expected from the combined probable errors in the heats of combustion (about 0.2 kcal./mole for each compound). It seems likely that the agreement between theory and experiment would be somewhat improved if the statistical entropies were used, if the corresponding enthalpies were calculated from the partition functions, and if correlation energies[14] were taken into account. The authors feel however that agreement between theory and experiment has been shown, and more refined calculations hardly justify the labor involved. A pronounced shift of equilibrium toward the cyclic compound upon substitution is noted in every case, the free energy changes brought about by substitution varying from 1.6 to 4.2 kcal./mole. The entropy and enthalpy effects are of comparable importance and neither can be neglected if a proper interpretation of the effect is to be made. In more general cases where the product is not the highly symmetrical cyclohexane in the unsubstituted ring closure, the entropy effect will be of lesser importance.

The agreement between the calculated and observed free energies summarized in Table I appears to support the suggestion that a fundamental basis for the *gem*-dimethyl effect as it pertains to equilibria is to be found in the considerations outlined above. These considerations apply in principle to other compounds containing heteroatoms and more complicated substituents although additional factors may also become important in such cases.

The rates at which ring closure reactions occur are also known to be accelerated by the presence of alkyl substituents. If an open-chain compound forms a cycle in the rate determining step of a reaction, the arguments presented here for ΔF, ΔH, and ΔS will carry over directly to $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ and consequently to $\Delta F^{\ddagger}$ and to the rate of ring closure. This is because in a reaction in which the ring closure is the rate determining step, the absolute rate theory shows that $\Delta F^{\ddagger}$ can be considered as determined by an equilibrium between the starting state (open chain) and transition state. The latter has the geometry of the cyclic system except that one bond is somewhat stretched. The *gauche* interactions in the transition state and cycle are very similar and consequently, as far as the *gem*-dimethyl effect is concerned, going from the open chain to the transition state is essentially the same as going from the open chain to the cycle.

Ring closure reactions in which the cyclization does not occur in the rate-determining step need individual consideration, but can be handled in a straightforward way utilizing the ideas developed previously in conjunction with standard methods of kinetics.

A ring-opening reaction is on the contrary quite a different situation. In this case ordinarily either the rate determining step will be the ring opening, or it will precede the ring opening. In either situation the number of *gauche* interactions is the same in the starting and transition states, and the entropy changes are expected to be relatively independent of the presence of alkyl groups unless there is a direct interaction between the alkyl group and the incoming reagent or the solvation shell. The only way the *gem*-dimethyl effect could apply directly in a ring opening would appear to be in a case where the rate-determining step followed an equi-

(13) The treatment of "optical isomerism" used in the cyclic systems is the more correct one. The open chains are treated in a simplified manner because of the large number of conformers which would need to be considered. Justification for this approximation has been made.[10,12]

(14) K. S. Pitzer and E. Catalano, *J. Am. Chem. Soc.*, 78, 4844 (1956).

librium step between cyclic and noncyclic structures.

It seems reasonable that these ideas should apply to other than six-membered rings, and an examination of the equilibrium data for five-membered rings shows a qualitative parallelism.[6] In this case because of the indefinite ring conformation[15] the concept of *gauche* interactions cannot be applied in as straightforward a manner. For larger and smaller rings again the same qualitative results are expected, but quantitative calculations are difficult and detailed experimental data are unavailable. Qualitatively the existence of a *gem*-dimethyl effect on ring closures in small rings is well known, and it has also been observed in the eight-membered ring.[16]

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(16) Unpublished work of S. Greenberg and S. Hu.

[CONTRIBUTION NO. 114 FROM THE INSTITUTO DE QUIMICA DE LA UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO]

Intensities of Carbonyl Bands in the Infrared Spectra of Substituted Cycloalkanones

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The molecular extinction coefficient and the integrated absorption areas (A) of the carbonyl group of some alicyclic and aliphatic ketones were measured, and the results, discussed in terms of polar and steric effects, show that the nature of the substituent and the steric environment of the ketone affect the intensity of the carbonyl absorption band.

The stretching vibation of the carbonyl group that occurs in the 1600–1900 cm.$^{-1}$ region has been thoroughly studied.[1] Recently, quantitative studies of the infrared bands have been a subject of attention, and several attempts have been made to correlate the integrated absorption area (A), with molecular structure.[2,3] The work of Jones *et al.* in the steroid field is especially noteworthy.[2] They found that the intensity of the carbonyl band in a five membered ring such as the C-17 position of the steroid molecule (2.69 units) is greater than that of a six membered ring ketone (2.2–2.5 units). The A of an aliphatic ketone, such as a 20-keto steroid, is smaller (1.79 units) while the introduction of a bromine atom in the α-position of the carbonyl lowers the value considerably, *i.e.* 2.55 units for a 3-keto steroid and 1.89 units for a 2-bromo-3-keto steroid. These correlations, and finding that the integrated absorption area is an additive quantity, are very useful for characterizing the type and number of carbonyl groups present in the molecule.

Richards[3] showed that the intensity of the absorption band is related to the nature of the carbonyl group and its value increases in the following order: aldehyde, ketone, acid, chloride, ester, acid, amide.

Brown,[4] studying the intensity of the nitrile band of benzonitriles in various solvents found that the intensity of the band is solvent dependent, and that A increases when the electron release ability of the substituent is increased, *i.e.* in carbon tetrachloride, *p*-methylbenzonitrile has an A of 0.28 units and *p*-chlorobenzonitrile, only 0.20 units.

EXPERIMENTAL

The spectra were recorded on a Perkin Elmer 21 model spectrophotometer equipped with a sodium chloride prism. In order to make 1 μ cover 40 cm. two number 45 gears were installed in the A and C positions.[5]

The solutions were approximately 0.02–0.03 molar (in 10 ml. carbon tetrachloride) depending on the band intensity. A cell 0.049 cm. thick was used. This was measured by the interference fringe method and with a microscope, focusing the upper and lower windows in the inner part and measuring the difference. By using a cell of this width the error in nonuniformity and changes in the width is believed to be less than 1%.

All the measurements were made under the same experimental conditions in order to get the minimum possible error.

The absorption curves were measured over a frequency range of 100 cm.$^{-1}$ on each side of the maximum with a slit opening of 49 μ. The enlargement of the scale allows one to measure $\Delta\nu$ 1/2 in a very accurate way.

The integrated absorption areas were calculated by the direct integration method by means of the equation[6]:

$$A = \frac{K}{cl} \log_{10} \frac{I_0}{I} \Delta\nu \, 1/2 \qquad (1)$$

(1) For leading references see R. N. Jones and C. Sandorfy, Chapter IV in *Chemical Applications of Spectroscopy*, Technique of Organic Chemistry, Vol. IX. Interscience Publishers, Inc., New York, 1956.

(2) R. N. Jones, D. A. Ramsay, D. S. Keir, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 80 (1952).

(3) R. E. Richards and W. R. Burton, *Trans. Faraday Soc.*, **45**, 874 (1949).

(4) T. L. Brown, *J. Am. Chem. Soc.*, **80**, 794 (1958).

(5) For a more complete description see the Perkin Elmer manual.

(6) D. A. Ramsay, *J. Am. Chem. Soc.*, **74**, 72 (1952).

TABLE I

INTEGRATED ABSORPTION INTENSITY[a]

Cholestan-3-one	Conc. × 10^2 mole $l.^{-1}$	Io	I	ϵ	$\Delta\nu$ 1/2	A
a	1.7546	96.7	39.9	447.1	16.79	2.72
b	1.7546	97.0	40.0	447.4	16.79	2.72
c	2.115	91.05	32.3	434.3	17.32	2.72
d	2.115	91.95	32.8	432	17.60	2.75
See lit.[b]	...	...	...	440	17.4	2.63
Δ^5-Cholesten-3-one						
a	2.0989	90.5	29.6	472	16.61	2.83
b	2.0989	91.0	32.3	437.4	17.74	2.81
See lit.[b]	...	...	...	490	16.1	2.80

[a] Calculated by the method of direct integration using carbon tetrachloride as a solvent. [b] See ref. 2.

A base line was drawn between the end of the wings and from it a perpendicular to the maximum. The molecular extinction coefficient was calculated by the expression

$$\epsilon = \frac{1}{cl} \log_{10} \frac{I_0}{I} \qquad (2)$$

and the $\Delta\nu$ 1/2 was measured directly with a ruler where ϵ has half of its value. These values, applied directly to formula 1 gave the A value.[7]

The discussion about the accuracy and reproducibility of the results can be found elsewhere[2,6] and we will not cover this point further.

A typical experiment is illustrated in the calculation of cholestan-3-one and Δ^5-cholesten-3-one (Table I). The results agree in a satisfactory way with those previously reported by Jones for these two steroidal compounds, thus demonstrating the validity of our technique.

RESULTS AND DISCUSSION

The results obtained are listed in Table II. The values of the integrated absorption areas[8] show that the value of cyclopentanone is lowered when a methyl group occupies the α or the β position. In the cyclohexanones, a methyl group lowers the value of A: in 2,2-dimethylcyclohexanone the value is lower than for the 2-methyl compound, and in the 3-methylcyclohexanone the value of A is higher than in cyclohexanone. Wherever a substituent is located in the α-position of the carbonyl group the same result is observed, *i.e.* a lowering in the intensity of the absorption band. These results suggest two factors operating at the same time that can affect the intensity of the band. The first is the inductive effect of the alkyl group that increases the value of A while the second and more important is steric in nature and lowers the value of A.

It is known that there are many factors that affect the shape and intensity of the infrared bands, mainly connected with the interactions of electric and magnetic moments present in the molecule and occurring during the vibration. We have found that the values obtained can be explained in an empirical form as a function of the inductive and steric factors.

Aliphatic ketones. An interesting example where the two effects can be clearly seen is the aliphatic ketones, acetone, methyl ethyl ketone, methyl isopropyl ketone, and methyl *tert*-butyl ketone. The A values for these are 1.71, 1.85, 2.20, and 1.40 units, respectively.[9] In the first three ketones the increase is due to the inductive effect that increases in the same order, but in pinacolone, the value of A is only 1.40 units and this is probably due to the steric effect of the *tert*-butyl group which hinders the carbonyl group.

Cyclopentanones. Cyclopentanone has an A value of 2.66 units and the 3-methyl derivative only 2.50 units. This small difference is possibly due to the inductive effect of the methyl group. In the 2,4,4-trimethylcyclopentanone the intensity decreases to 1.97 units due to the bulk of the substituents, especially in the position *alpha* to the carbonyl. Cyclopentanones usually have two maxima for the carbonyl stretching vibration due to an intramolecular vibration.[10] Under our working conditions (low resolution) only one band is present, which is used for the calculations. The value of α-bromocyclopentanone follows the same trend observed in other α-haloketones.

Camphor has an A value of 2.75 units, and in comparison with its λ max. and A value this compound behaves more like a cyclopentanone than a cyclohexanone, although this A value would be high for a substituted cyclopentanone.

Cyclohexanones. The values of A for cyclohexanone, 2-methylcyclohexanone and 2,2-dimethylcyclohexanone are 2.49, 2.14, and 1.62 units, showing clearly the importance of the steric effect. The effect that can be ascribed to the dipole-dipole interaction is not important because it is believed that

(7) One intensity unit = 1×10^4 $mole^{-1}$ liter $cm.^{-2}$ Ref. 6.

(8) The value of the molecular extinction coefficient is not accurate enough to make correlations because it is subject to factors like the width and height of the band. The A values take $\Delta\nu$ 1/2 in consideration and are more useful for this kind of correlations.

(9) In these acyclic ketones the same order is obtained in the values of $\Delta\nu$ 1/2 (15.5, 16.4, 20.1, and 8.5) but this is not a general trend in the other ketones. It is mentioned only for further observations.

(10) R. N. Jones, private communication.

TABLE II

INTENSITY MEASUREMENTS OF THE CARBONYL BAND[a]

	Compound[b]	ε	A	Δν 1/2
I				
	Acetone	305	1.71	15.5
	Methyl ethyl ketone	312	1.85	16.4
	Methyl isopropyl ketone	303	2.20	20.1
	Methyl *tert*-butyl ketone	457	1.40	8.5
II				
	Cyclopentanone	391	2.66	18.66
	3-Methylcyclopentanone	425	2.50	16.37
	2,4,4-Trimethylcyclopentanone	300	1.97	18.17
	α-Bromocyclopentanone	348	2.21	17.61
	Camphor	543	2.75	13.54
III				
	Cyclohexanone	361	2.49	19.11
	2-Methylcyclohexanone	387	2.14	15.32
	2,2-Dimethylcyclohexanone	276	1.62	16.24
	3-Methylcyclohexanone	381	2.76	20.02
	4-Methylcyclohexanone	428	1.91	12.50
	4-*Tert*-butylcyclohexanone	492	2.06	11.57
	Cycloheptanone	329	2.35	19.77
IV				
	α-Bromocyclohexanone, bromine axial	402	2.09	14.30
	α-Bromocyclohexanone, bromine equatorial	183	1.34	20.26
	Cis-2-bromo-4-*tert*-butylcyclohexanone	275	1.54	15.51
	Trans-2-bromo-4-*tert*-butylcyclohexanone	283	1.89	18.40
V				
	3-Methoxyestrone	594	2.80	13.03
	Lanosten-3-one	433	2.52	16.1
	Cholestan-3-one	438	2.72	17.14
	Δ⁴-Cholesten-3-one	587	3.32	15.62
	Δ⁴-Cholesten-3-one	454	2.82	17.17

[a] Average values of three experiments at different concentrations. [b] All the samples were purified specimens; since all of them are known, only their physical constants are reported:

Acetone, $n_D^{20} = 1.3590$; methyl ethyl ketone, $n_D^{20} = 1.3790$; methyl isopropyl ketone, $n_D^{20} = 1.3882$; methyl *tert*-butyl ketone, $n_D^{18} = 1.3995$, b.p. 106°; cyclopentanone, $n_D^{20} = 1.4368$; 2-methylcyclopentanone, $n_D^{20} = 1.4364$; 3-methylcyclopentanone, $n_D^{25} = 1.4320$; 2,4,4-trimethyl cyclopentanone, $n_D^{14} = 1.4365$, $n_D^{27} = 1.4360$; α-bromocyclopentanone, b.p.$_2$ 58–59°; cyclohexanone, $n_D^{19} = 1.4495$; 2-methylcyclohexanone, $n_D^{26} = 1.4442$; 2,2-dimethylcyclohexanone, $n_D^{24} = 1.4459$; 3-methylcyclohexanone, b.p. 169°; 4-methylcyclohexanone, b.p. 171°; 4-*tert*-butylcyclohexanone = m.p. 49°; α-bromocyclohexanone b.p.$_2$ = 59–60° $n_D^{23} = 1.5143$; *cis*-2-bromo-4-*tert*-butylcyclohexanone, m.p. 66.5°; *trans*-2-bromo-4-*tert*-butylcyclohexanone, $n_D^{22} = 1.4984$; camphor, m.p. 179.5°; cycloheptanone, $n_D^{15} = 1.4365$; 3-methoxyestrone, m.p. 168–169°, lanostenone, m.p. 115–116°; cholestan-3-one, m.p. 130–131°; Δ⁴-cholesten-3-one, m.p. 78–79°; Δ⁵-cholesten-3-one, m.p. 124–126°.

the methyl group does not affect substantially the dipole of the ketone.

It is possible that repulsive forces of nonbonded atoms between a methyl and a hydrogen spread the carbon—carbon—carbon bond angle and change the force constant of the carbon—oxygen bond.[11]

It is known that when the carbon—carbon—carbon angle in alicyclic ketones is less than 120°, due to the repulsions of the alkyl groups in the neighborhood of the ketone, it is not possible to have a complete sp^2 hybridization, and therefore the force constant and the stretching frequency of the carbon—oxygen bond is altered.

It may be that a factor of this kind is responsible for the values of A. The 3-methylcyclohexanone showed a higher value than cyclohexanone. Since in this case there is no steric effect operating in the β-position of the carbonyl, this increase can be ascribed to the small inductive effect of the methyl group.[4,12] The values for the 4-methyl and 4-*tert*-butylcyclohexanone (1.91 and 2.06 units) cannot be due to steric effects which are absent in this position nor to the inductive effect of the alkyl group which is separated by two methylene groups. The low A values in these two ketones must be produced by some other cause.

Cycloheptanone has a lower value (2.35 units) than cyclopentanone or cyclohexanone and it is in reasonable agreement with the value of 2.21 recently reported by Gunthard.[13]

α-Bromocyclohexanones. The introduction of a bromine atom in the α-position of a carbonyl affects considerably the frequency of the absorption band. A bromine atom in cyclohexanone shifts the frequency of the band *ca.* 16 cm.$^{-1}$ when it is in the equatorial position and 2–4 cm.$^{-1}$ when it is axial.[14]

The intensity of the carbonyl band is reduced by halogen in a similar way and we get a value of 1.34 units (46% reduction) for the α-bromo cyclohexanone when the halogen atom is in the equatorial position, and a value of 2.09 units (17% reduction) when it is axial. This observation together with the shift on the frequency of the absorption band can be useful for characterizing the configuration of the halogen in α-halo ketones.

Comparing the value of cyclopentanone (2.66) with the value of α-bromocyclopentanone (2.21 units) we get the same 17% reduction in intensity of the band. The axial position of the cyclohexane and the position of the substituents in the cyclopentane ring can be considered to some extent similar since in both cases they are almost perpendicular to the so-called horizontal plane of the ring. It is interesting to note that in these two cases where the halogen have a similar geometry with respect to the carbonyl group and the plane of the molecule, the intensity is lowered in the same proportion.

In the 4-*tert*-butylcyclohexanone A is 2.06 units and this value diminishes to 1.89 (8.5%) when a

(11) P. D. Bartlett and M. Stiles, *J. Am. Chem. Soc.*, **77**, 2806 (1955).

(12) R. N. Jones, ref. 2, found that a halogen in the α-position of a carbonyl lowers the intensity of the absorption band; if an electronegative group lowers the value of A, a group like an alkyl should show the opposite effect.

(13) T. Bürer and H. H. Gunthard, *Helv. Chim. Acta* **39**, 356 (1956), found a pronounced dependence of half width and absorption intensity on the medium size ring of cycloalkanones.

(14) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301, 3297 (1953).

bromine atom is introduced in the axial position. The reduction is still greater when the bromine is in the equatorial position (1.54 units, 25%).

In both cases the lower intensity is observed when halogen is in the equatorial position.

Steroid ketones. A few steroidal ketones were studied to compare our values with those reported by other workers and the results are given in Table I. There are some facts that should be mentioned: Lanostenone (2.52 units), which can be considered to be an α,α-dimethyl derivative of a 3-keto steroid, has a lower value than cholestan-3-one (2.72 units). Estrone methyl ether, a five-membered ring ketone has a higher value (2.80 units) than a six-membered ring ketone such as cholestan-3-one.

The intensity of an α,β-unsaturated ketone such as Δ^4-cholesten-3-one (3.32 units) is much higher than cholestan-3-one. The intensity of a β,γ-unsaturated ketone such as Δ^5-cholesten-3-one (2.82 units) is between the values of the saturated and the α,β-unsaturated ketones, showing that the effect of the double bond in this position (homoallylic resonance[15]) can also be noted by infrared spectroscopy.

Other evidence in the steroid field is the fact that a 3-keto group in the molecule shows a value of 2.55 units[2] and other ketones that are known to be more highly hindered show lower values, *i.e.* the 7-ketone, 2.16 units, the 11-ketone, 2.21 units, and the 12-ketone, 2.27 units. The ketones in the five-membered ring D of the steroid nucleus, show the same effect, *i.e.* the ketone in the 16-position has a value of 2.74 units and the 17-ketone which is adjacent to the C ring and to a methyl group has a 2.69 units value.

In all ketones that are subjected to steric effect we observe a lower intensity value so the assumption made before agrees reasonably well.

Analysis of overlapped areas. One of the possible applications of the study of integrated absorption areas, is the quantitative determination of some isomers that absorb in almost the same position. The use of this method of calculation to evaluate the proportion of isomers is restricted to mixtures that show a well defined inflection point in the infrared, and the results will be more accurate with better resolution of the peaks.

In the monobromination of 4-*tert*-butylketone the *cis* and *trans* isomers are obtained. These were recently separated and their infrared spectra were studied by Allinger,[16] who found that the *cis* isomer absorbs at 1737 cm.$^{-1}$, and the *trans* isomer (bromine axial) at 1724 cm.$^{-1}$ with slight shifts according to the composition of the mixture. By chromatography and fractional crystallization, 66% of the equatorial and 28% of the axial isomers are obtained.[17] These percentages, normalized to 100% are 70% equatorial and 30% axial.

By examination of the curve obtained from this mixture, an inflection point can be seen, which shows much better by enlarging the scale. If in the asymmetric curve a symmetric one is drawn on the principal maxima and the log. Io/I is calculated we can determine the percentage of the isomer in the mixture by the following procedure: Since we know the values of A for the pure axial isomer, it is possible to get c from Equation 1.

$$c' = \frac{K}{A1} \log. \frac{I_0}{I} \Delta\nu 1/2$$

The ratio of the obtained concentration (c') and the weighed concentration will be the ratio of isomers in the mixture.

$$\frac{c'}{c} \times 100 = \% \text{ axial isomer}$$

The value obtained is 80.3% which agrees, with an error of 2%, with the reported data of Allinger for the equilibrium position for these bromoketones.

Another empirical way to obtain the ratio of isomers in the mixture, is to take the ratio of half

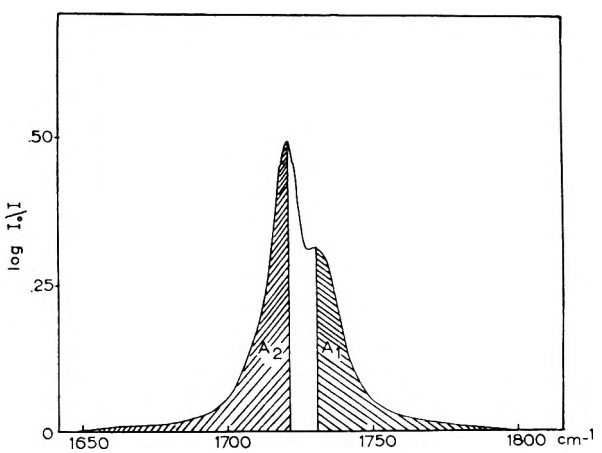

Fig. 1. A_2/A_1 = proportion of isomers in the mixture. A_2 is the area for the axial isomer and A_1 the area for the equatorial isomer. Although this kind of analysis is not exact, it gives values close to those that can be obtained by the use of more elaborate and difficult methods

(15) S. Winstein and R. Adams, *J. Am. Chem. Soc.*, **70**, 838 (1948).

(16) N. L. Allinger and J. Allinger, *J. Am. Chem. Soc.*, **80**, 5476 (1958).

(17) In ref. 16. See Experimental part. In the separation of the isomers the equatorial was obtained from crystallization in pentane. From 1.8 g. of fractionally distilled compound 1.2 g. of white needles m.p. 54–64° are obtained that are purified by repeated crystallizations. From the same distilled compound by chromatography in silica gel 0.85 g. are obtained from 3 g. of starting material. This material is subjected to another chromatography and is obtained in a purity of at least 95%. From these amounts the percentage of isomers obtained in the reaction can be calculated to be 66% equatorial and 28% axial. These isomers can be equilibrated with anhydrous hydrobromic acid in carbon tetrachloride solution and 78% of the axial isomer is obtained the equilibria being equatorial $\rightleftharpoons$ axial = 3.5.

of the areas in the part where there is not overlapping. Fig. 1. A_2/A_1 would give the ratio in which both isomers are present.

This kind of analysis was made in α-bromocyclohexanone; the curve was carefully measured at each cm.$^{-1}$ and its area calculated using Simpson's rule. The ratios A_2/A_1 obtained in two experiments were 1.372 and 1.278; that is a proportion of 57.85% and 56.10% for the axial isomer in the mixture. Further experiments on quantitative analysis of overlapped areas will be reported later.

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Mexico 20, D. F.

[Contribution from the Deparıment of Chemistry, University of Washington, and the Nobel Institute of Chemistry]

Isolation and Proof of Structure of 1,1,4,4-Tetramethyl-6-*t*-butyl-1,2,3,4-tetrahydronaphthalene[1]

PHILIP C. MYHRE[2] AND W. M. SCHUBERT

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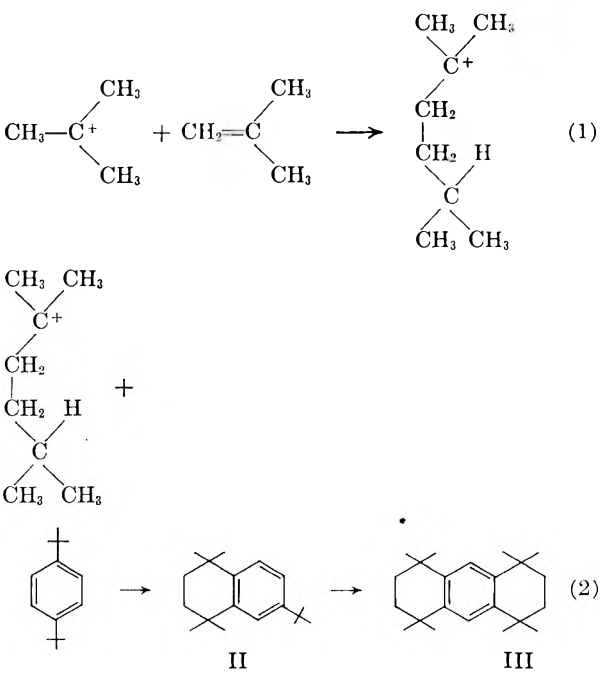
A new hydrocarbon has been isolated as a by-product of the preparation of 1,3,5-tri-*t*-butylbenzene by the reaction of 1,4-di-*t*-butylbenzene and *t*-butyl chloride in the presence of aluminum chloride. This hydrocarbon has been identified as 1,1,4,4-tetramethyl-6-*t*-butyl-1,2,3,4-tetrahydronaphthalene (II). Its properties indicate that it is not Senkowski's hydrocarbon, as previously proposed.

The Friedel-Crafts alkylation of 1,4-di-*t*-butylbenzene with *t*-butyl chloride gives a complex mixture.[3,4] The products previously identified are 1,3-di-*t*-butylbenzene,[3] 1,3,5-tri-*t*-butylbenzene (I)[3] and 1,1,4,4,5,5,8,8-octamethyl-1,2,3,4,5,6,7,8-octahydroanthracene (III).[4] It has been suggested that formation of compound III proceeds *via* the alkylation of 1,4-di-*t*-butylbenzene by the 2,5-dimethyl-2-hexyl cation with the attendant or prior loss of *t*-butyl cations from the aromatic nucleus, and that the unknown compound II is an intermediate (equations 2, 3, and 4).[5,6] The 2,5-dimethyl-2-hexyl cation is thought to arise by dimerization of isobutylene followed by several rearrangement steps (equation 1).[6] Evidence for the suggested mode of formation of III are the observations that (1) *t*-butyl chloride yielded about 1% of 2,5-dichloro-2,5-dimethylhexane when contacted briefly with aluminum chloride near 0°;[6] and (2) Friedel-Crafts alkylations of 1,4-di-*t*-butylbenzene and of benzene with 2-chloro-2,5-dimethylhexane produced III.[5]



In these laboratories, application of the procedure of Bartlett, Roha, and Stiles[3] to the preparation of large quantities of 1,3,5-tri-*t*-butylbenzene led to the isolation of a small yield of a new colorless crystalline compound, m.p. 63–64°, which has been found to have the structure of the proposed intermediate II. This compound was obtained from a complex mixture of high boiling products by fractional distillation and recrystallization. Evidence for the structural assignment is presented below.

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(1) Taken in part from the Ph.D. thesis of Philip C. Myhre, University of Washington, 1958.

(2) National Science Foundation postdoctoral fellow at the Nobel Institute, 1958–59.

(3) P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Am. Chem. Soc.*, **76**, 2349 (1954).

(4) L. R. C. Barclay and E. E. Betts, *J. Am. Chem. Soc.*, **77**, 5735 (1955).

(5) L. R. C. Barclay and J. W. Hilchie, *J. Org. Chem.*, **22**, 633 (1957).

(6) F. E. Condon, *J. Org. Chem.*, **21**, 761 (1956).

The molecular formula of the compound as determined by carbon-hydrogen analysis and molecular weight measurements was found to be $C_{18}H_{28}$. The compound was inert to treatment with basic permanganate. Dehydrogenation of a sample of the hydrocarbon yielded a material which had an ultraviolet spectrum characteristics of a naphthalene, indicating that the compound is bicyclic. The ultraviolet spectrum of the hydrocarbon had the characteristic 260 mμ absorption band of a benzene derivative. There were no indications in the ultraviolet spectrum that strongly conjugating groups are attached to the benzene ring. The infrared spectrum indicated that the compound is an unsymmetrically trisubstituted benzene. This is, in the 900 to 675 cm.$^{-1}$ region assigned to out of plane bending vibrations of aromatic hydrogens, strong absorption bands were found at 892 cm.$^{-1}$ and 825 cm.$^{-1}$. The 825 cm.$^{-1}$ absorption is in the region (820 cm.$^{-1}$) assigned to out of plane bending vibrations of two adjacent hydrogens.[7] The band at 892 cm.$^{-1}$ although higher than the normally observed frequency (860 cm.$^{-1}$) might be considered to be an out of plane bending vibration of an isolated aromatic hydrogen.

Two independent syntheses of the hydrocarbon were achieved. The first synthesis involved the alkylation of *t*-butylbenzene with 2,5-dichloro-2,5-dimethylhexane (see Fig. 1). A product identical in all respects with the unknown hydrocarbon was isolated in 14% yield. In addition, the hydrocarbon identified by Barclay, III, was isolated in 20% yield. Moreover, a large amount of 1,4-di-*t*-butylbenzene also was obtained presumably through disproportionation of *t*-butylbenzene. Its occurrence makes the reaction of doubtful value as an unambiguous proof of structure. Consequently an alternative synthesis of the hydrocarbon was undertaken, starting with the previously reported 1,1,-4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene, IV.[8] The 6-methyl group of IV was converted to a 6-*t*-butyl group by standard methods as shown in Fig. 1. None of these steps appears to be of a type which would lead to a rearrangement of the carbon skeleton. All conversions in this sequence were effected in yields of 80% or better with the exception of the last coupling step. The final product had a melting point identical with that of the hydrocarbon obtained in the alkylation of 1,4-di-*t*-butylbenzene with *t*-butyl chloride and the mixed melting point was not depressed. The infrared and ultraviolet spectra of the two materials were identical.

The structure of the acid V, obtained by oxidation of the known compound IV, also was related to the structure of the known phenol X. The acid V was converted to an aromatic primary amine by

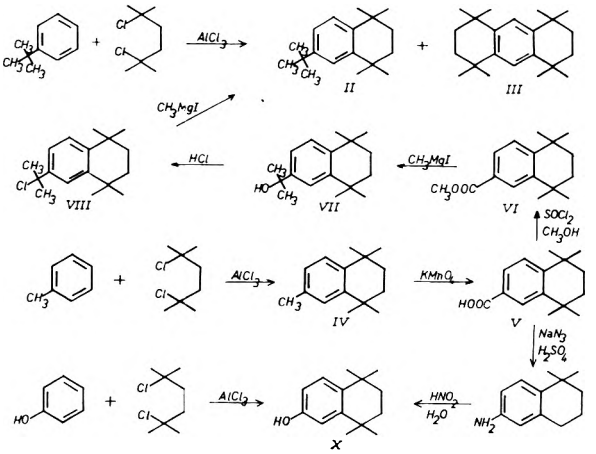

Figure 1

use of the Schmidt reaction and the resulting amine was converted *via* the diazonium salt to a phenol identical with compound X. The structure of X had previously been established by degradation as well as by its synthesis through the alkylation of phenol with 2,5-dichloro-2,5-dimethylhexane.[8]

Barring unexpected rearrangements in the independent syntheses of the hydrocarbon, it appears definitely to have the structure II, *i.e.*, 1,1,4,4-tetramethyl-6-*t*-butyl-1,2,3,4-tetrahydronaphthalene.

The fact that compound II is obtained along with compound III in both the Friedel-Crafts alkylation of 1,4-di-*t*-butylbenzene with *t*-butyl chloride and the alkylation of *t*-butylbenzene with 2,5-dichloro-2,5-dimethylhexane lends support to Barclay's suggestion that compound II is an intermediate in the formation of III.[5] Barclay also has proposed that compound II is identical with hydrocarbon obtained by Senkowski in 1890.[9] Senkowski had obtained a "flaky white solid" (m.p. 128°, b.p. 291–292°/736.6 mm.) along with *t*-butylbenzene and 1,4-di-*t*-butylbenzene from the reaction of benzene, isobutyl chloride, and aluminum chloride and had erroneously thought it to be a tri-*t*-butylbenzene.[5] However, Senkowski's hydrocarbon is probably not compound II either, in view of the wide discrepancy in melting points.[10]

EXPERIMENTAL

Alkylation of p-di-t-butylbenzene with t-butyl chloride.[3] Cold *t*-butyl chloride (445 g., 4.8 moles) was added over a period of 2 hr. to a mixture of 785 g. (4.1 moles) of 1,4-di-*t*-butylbenzene, 661 g. (4.9 moles) of aluminum chloride, and 2 l. of ethylene dichloride which was cooled to below 5°. The reaction mixture was stirred vigorously for 4 hr. at a

(7) N. B. Colthup, *J. Optical Soc. Am.*, **40**, 397 (1950).

(8) H. A. Bruson and J. W. Kroeger, *J. Am. Chem. Soc.*, **62**, 36 (1940).

(9) M. Senkowski, *Ber.*, **23**, 2412 (1890).

(10) The infrared spectrum of II differs considerably from that of a compound (m.p. 129°) isolated from the residues of a commercial preparation of 1,4-di-*t*-butylbenzene and believed to be Senkowski's hydrocarbon (ref. 3). We are indebted to Professor P. D. Bartlett for kindly furnishing us an infrared spectrum of the latter compound.

temperature between −5° and 5° and then was hydrolyzed by cautiously pouring onto ice and water. The organic layer was separated and washed several times with water and then was dried over sodium carbonate. The solvent was removed by distillation and the remaining oil was distilled through a modified Claisen distilling head under reduced pressure. The following fractions were obtained:

Fraction	B.P.	Pressure, Mm.	Wt., G.
1	105–110	12	115
2	113–118	12	116
3	119–124	12	282
4	>125	12–5	51
Residue	...	...	125

(a) *1,3,5-Tri-t-butylbenzene.* Fraction 3, which was partially solid, was suction filtered. The solid, which was washed with two 50-ml. portions of cold ethanol and air dried, weighed 107 g., m.p. 66–69°. Two recrystallizations from ethanol yielded 78 g., 8% yield, of 1,3,5-tri-*t*-butylbenzene, m.p. 70.5–72°.[11,12]

Further recrystallization and sublimation gave a sample melting at 72.2–72.8°, reported[3] m.p. 72.5–73.0°.

Anal. Calcd. for $C_{18}H_{30}$: C, 87.74; H, 12.26. Found: C, 87.66; H, 12.21.

(b) *1,1,4,4,5,5,8,8-Octamethyl-1,2,3,4,5,6,7,8-octahydroanthracene* (III). The solid collected by suction filtration from the partially crystallized fraction 4 was combined with the crystalline product obtained from the residue by crystallization from *n*-heptane. The combined solids after several recrystallizations from *n*-heptane and chloroform-methanol weighed 35 g. and melted at 205–210°, reported[3] m.p. 209–210°. The infrared and ultraviolet spectra of this material were identical with those reported by Barclay for compound III.[12]

(c) *Compound* II. *1,1,4,4-Tetramethyl-6-t-butyl-1,2,3,4-tetrahydronaphthalene.* The filtrate from fraction 4 was distilled through a 20-in. spinning band column under reduced pressure. The first fraction collected was mainly 1,3,5-tri-*t*-butylbenzene. The second fraction (10 g. of viscous oil, b.p. 130–131°/5 mm., n_D^{25} 1.5066) crystallized after standing for several days. The solid was collected on a suction funnel, washed with cold ethanol (about 20 ml.) and recrystallized twice from absolute ethanol yielding 2.5 g. of colorless, square platelets (m.p. 62.5–64°). Repeated crystallization and sublimation yielded a sample which melted at 63–64°. The infrared spectrum in the aromatic C—H bending region[7] had strong bands at 825 and 892 cm.$^{-1}$. The ultraviolet spectrum in ethanol had the following λ_{max} and ϵ_{max} values: 266 mμ (515); 274 mμ (418); shoulder at 260 mμ (375).

Anal. Calcd. for $C_{18}H_{28}$: C, 88.45; H, 11.55. Found: C, 88.66; H, 11.33. Calcd. mol. wt.: 244. Found: 242 (Rast method).

(d) *Other products.* 1,3-Di-*t*-butylbenzene and 1,4-di-*t*-butylbenzene were the principal constituents of fractions 1 and 2. These compounds were not isolated in a pure state. There were also considerable amounts of high boiling materials and residue which were not identified. Solutions of these materials were fluorescent in normal artificial light indicating the presence of polycyclic aromatic hydrocarbons.

Dehydrogenation of compound II. Compound II (0.10 g.) was dehydrogenated over 5% palladium on charcoal (2 g.) in an evacuated sealed tube heated to 450° for 12 hr. After releasing the internal pressure, the contents of the tube were placed in a gravity filter and washed thoroughly with purified pentane. The filtrate was evaporated to dryness and the residue was dissolved in ethanol. The ultraviolet spectrum of the ethanol solution possessed the characteristic absorption bands of a naphthalene in the 300–320 mμ and 280–290 mμ region. Absorption bands at 266 and 276 mμ characteristic of the starting hydrocarbon also were present, indicating that the dehydrogenation had not gone to completion.

Alkylation of t-butyl benzene with 2,5-dichloro-2,5-dimethylhexane. Alternative preparation of compound II. Anhydrous aluminum chloride (0.18 g.) was added to a solution of *t*-butylbenzene (10.6 g., 0.79 mole) and 2,5-dichloro-2,5-dimethylhexane[4] (3.3 g., 0.18 mole) in a flask fitted with a magnetic stirrer. The reaction mixture was stirred vigorously at room temperature for 40 min. and then was hydrolyzed with ice and dilute hydrochloric acid. Pentane was added, and the organic phase was separated, washed with water, and dried over anhydrous sodium sulfate. The pentane and *t*-butylbenzene were removed by distillation, and the semisolid residue was distilled through a spinning band column under reduced pressure. 1,4-Di-*t*-butylbenzene (1.9 g., b.p. 120°/12 mm.) was isolated from the distillate. This compound was characterized by its melting point, infrared spectrum, and elementary analysis. The residue remaining in the distillation flask was dissolved in chloroform-methanol and allowed to crystallize. The crystalline material collected (0.55 g., m.p. 195–211°) was shown to be III by comparison of the infrared spectra. The filtrate was concentrated and the residue was collected. Fractional crystallization from ethanol and sublimation yielded 0.65 g. of colorless square platelets, m.p. 62.5–64°, no depression in melting point when mixed with the hydrocarbon, m.p. 62.5–64°, obtained in the alkylation of 1,4-di-*t*-butylbenzene with *t*-butyl chloride (described above).

1,1,4,4,6-Pentamethyl-1,2,3,4-tetrahydronaphthalene (IV).[8] Two grams of aluminum chloride was added cautiously to a stirred solution of 2,5-dichloro-2,5-dimethylhexane (47 g.) and toluene (100 ml.) and cooled to 0°. The mixture was warmed slowly to room temperature (24–26°) and was stirred overnight. The mixture was hydrolyzed with dilute hydrochloric acid and washed with water until neutral. The organic phase gave a negative test when treated with methanolic silver nitrate. After the solution was dried over magnesium sulfate, the excess toluene was removed by distillation under 20 mm. pressure, leaving 50.5 g. (88%) of a colorless solid, m.p. 32–34°. Recrystallization from methanol-acetone yielded platlets, m.p. 34°.

Anal. Calcd. for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.06; H, 10.92.

1,1,4,4-Tetramethyl-6-carboxy-1,2,3,4-tetrahydronaphthalene (V). The procedure used was essentially that of Schlatter[13] as adapted by Wepster *et al.*[14] A 500-ml. flask equipped with a stirrer and reflux condenser was charged with 35 g. of IV, 10 g. of sodium hydroxide, 120 ml. of pyridine, and 60 ml. of water. The flask was heated in an oil bath maintained at 95° and 67 g. of potassium permanganate was added in portions over a period of 3 hr. The reaction mixture was heated and stirred for an additional 2 hr. Then 10 ml. of ethanol was added slowly to reduce any remaining permanganate. After being cooled, the reaction mixture was suction filtered (Hyflo), and the collected manganese dioxide was washed with 350 ml. of 2*N* sodium hydroxide. The combined filtrate was concentrated to about 250 ml. and acidified with 10% sulfuric acid. The flocculent precipitate was collected by suction filtration, redissolved in ether, and extracted with 10% sodium hydroxide. The basic solution was acidified and the precipitate collected by suction filtration. Recrystallization from glacial acetic acid gave 32 g. (80%) of fine white crystals, m.p. 197–199°. Repeated recrystallization from benzene–petroleum ether (80–90°) gave a sample, melting at 198–199.5°.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.61; H, 8.68. Found: C, 77.67; H, 8.92. Neut. equiv.: Calcd. 232.3. Found: 232.

(11) Undoubtedly the best method of preparation of this compound is described by Barclay and Betts.[12]

(12) L. R. C. Barclay and E. F. Betts, *Can. J. Chem.*, **33**, 672 (1955).

(13) M. J. Schlatter, U. S. Patent 2,635,114; *Chem. Abstr.*, **48**, 7059 (1954).

(14) W. van Hartinsveldt, P. E. Verkade, and B. M. Wepster, *Rec. trav. chim.*, **75**, 349 (1956).

1,1,4,4-Tetramethyl-6-carbomethoxy-1,2,3,4-tetrahydronaphthalene (VI). A mixture of 13.0 g. of the acid V and 15.0 ml. of thionyl chloride was heated gently to reflux for 1 hr. and allowed to stand for 3 hr. Excess thionyl chloride was removed by distillation under reduced pressure. Fifteen milliliters of absolute methanol was added to the residual acid chloride and the mixture was heated at reflux temperature overnight. The reaction mixture was dissolved in 30 ml. of ether and washed successively with water, 5% sodium bicarbonate, and water. After being dried over anhydrous magnesium sulfate the ether was removed by distillation under reduced pressure, leaving a viscous straw-colored liquid which was distilled to yield 12.9 g. (93%), b.p. 161–164°/7–8 mm., n_D^{25} 1.5258.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.25; H, 9.47.

1,1,4,4-Tetramethyl-6-(α-hydroxy-α,α-dimethyl)methyl-1,2,3,4-tetrahydronaphthalene (VII). A solution of methyl magnesium iodide was prepared in the usual manner starting with 12.7 g. of methyl iodide, 2.16 g. of magnesium turnings and 35 ml. of absolute ether. A solution of 10.0 g. of the ester VI and 25 ml. of absolute ether was added dropwise to the Grignard reagent (20 min.). The resulting mixture was heated at reflux for 1 hr. and allowed to stand overnight. After hydrolysis with 2*N* hydrochloric acid, the ether layer was washed with water, 5% sodium bicarbonate, 5% sodium thiosulfate, and water. After being dried over magnesium sulfate, the ether was removed by distillation, and the residue was recrystallized from petroleum ether (80–90°) to yield 12.5 g. (98%) of flocculent white crystals, m.p. 91–93°. Repeated crystallization from petroleum ether and sublimation afforded a sample melting at 95.5–96.3°.

Anal. Calcd. for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 83.02; H, 10.75.

1,1,4,4-Tetramethyl-6-(α-Chloro-α,α-dimethyl)methyl-1,2,3,4,4-tetrahydronaphthalene (VIII). An ether solution (30 ml.) of the alcohol VII (7.0 g.) was cooled to 0°. Anhydrous hydrogen chloride was passed through the solution for 2 hr. During this time square platelets deposited from the ether solution. Ice and water were added and the ether layer was washed rapidly with water, 5% sodium bicarbonate, and water. The ether layer was dried over magnesium sulfate and the ether removed by distillation to leave 7.1 g. (93%) of the white crystalline chloride which was used without purification in the next step.

1,1,4,4-Tetramethyl-6-t-butyl-1,2,3,4-tetrahydronaphthalene (II). A solution of the crude chloride VIII (7.0 g.) in ether (30 ml.) was added dropwise to a Grignard solution prepared from 7.0 g. of methyl iodide, 1.0 g. of magnesium turnings, and 20 ml. of absolute ether. The reaction mixture was stirred and heated at reflux temperature for 3 days. The mixture was hydrolyzed with 20 ml. of 3*N* hydrochloric acid and washed in the usual manner, followed by drying of the ether solution over magnesium sulfate. A viscous, colorless oil (5.5 g.) was obtained upon evaporation of the ether. When the oil was dissolved in 30 ml. of absolute ethanol, 0.60 g. of white crystalline material precipitated upon cooling. After recrystallization from petroleum ether (90–100°), the material melted at 213–216°. This is possibly a diphenylethylene derivative arising from the coupling of two molecules of VIII.

The filtrate was distilled to remove the ethanol and the residual oil was sublimed (80°/6–7 mm.) to yield 2.5 g. (39%) of crystalline product, m.p. 52–58°. After repeated crystallization from methanol-acetone (3 to 1), 1.2 g. of flaky colorless crystals (m.p. 62.5–64°) were obtained. The infrared spectrum of this material was identical with that of compound II. A mixed melting point showed no depression.

1,1,4,4-Tetramethyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene (X).[8] Three grams of phenol and 5 g. of 2,5-dichloro-2,5-dimethylhexane were suspended in 6 ml. of petroleum ether (90–100°). Aluminum chloride (0.3 g.) was added and the mixture was stirred at room temperature for 24 hr. The reaction mixture was hydrolyzed with dilute hydrochloric acid, and the partially crystallized organic layer was dissolved in warm benzene, washed with water until neutral, and dried over magnesium sulfate. Concentration of the solvent to about 10 ml. and cooling give 3.2 g. of crystalline product, m.p. 140°. Two recrystallizations from petroleum ether (90–100°) raised the melting point to 145°, reported[8] m.p. 145°.

1,1,4,4-Tetramethyl-6-amino-1,2,3,4-tetrahydronaphthalene (IX). Sodium azide (1.70 g.) was added in small portions to a well stirred mixture of V (5.0 g.), chloroform (20 ml.), and 96% sulfuric acid (6.0 ml.) over a 30-min. period. The temperature was maintained at 45° with an oil bath during the addition and for 1 hr. following. The mixture was then heated at 65° for 3 hr. Evolution of nitrogen was rapid during the first hour. The product was isolated by the addition of water, neutralization with sodium hydroxide, and extraction with ether. Evaporation of the solvent left 3.5 g. (80%) of brownish crystals, m.p. 73°.

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.69; H, 10.41; N, 6.89. Found: C, 82.89; H, 10.21; N, 7.05.

X *from* IX. A solution of sodium nitrite (0.33 g. in 6 ml. of water) was added dropwise to an iced suspension of the amine hydrochloride IX (1.0 g.) in 20 ml. of 0.1*N* hydrochloric acid. After the addition of sodium nitrite, 50 ml. of cold water was added and the resulting suspension was stirred vigorously for 4 hr. The fine yellow precipitate which formed during this period was collected and dried (0.51 g.). Recrystallization from petroleum ether (Norit) yielded 0.4 g. colorless needles, m.p. 145°. A mixed melting point with X prepared from phenol and 2,5-dichloro-2,5-dimethylhexane showed no depression.

Acknowledgment. The authors would like to express their appreciation to Mr. Donald Wilson for preparation of many of the intermediates.

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[CONTRIBUTION FROM THE WARNER-LAMBERT RESEARCH INSTITUTE]

2,2-Disubstituted 1,3-Dioxolanes and 2,2-Disubstituted 1,3-Dioxanes

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In a search for central nervous system depressants there were prepared a number of 1,3-dioxolanes and 1,3-dioxanes substituted by a tertiary alcohol. The most active compound was 2-methyl-2-(3-hydroxy-3-ethylpentyl)-1,3-dioxolane (XIV).

It has been found possible to produce paralysis of the skeletal muscles by means of chemical agents which act either at the myoneural junction or which act on the central nervous system. In these laboratories we have been interested in agents of both types. Among the agents of the latter type, we have investigated a series of 1,3-dioxolanes and 1,3-dioxanes which are herewith reported.

Berger has reported[2] on a series of 1,3-dioxolanes synthesized by Boekelheide *et al.*[3] The compounds tested indicated that effective drugs were to be found in the series, but that the activity was of short duration and was accompanied by some undesirable side effects. The work was primarily concerned with 4-hydroxymethyl-1,3-dioxolane derivatives. There was, however, reported one compound which had a hydroxyl group on a substituent which was other than on the 4-position of the dioxolane ring. This compound, 2-methyl-2-(1-hydroxymethyl-*n*-amyl)-1,3-dioxolane, had a high order of activity.

The presently reported series of compounds was suggested by the following two considerations. As recognized by Berger,[2] the metabolism of the dioxolanes may, as in the case of mephenesin, proceed through an oxidation of the primary alcohol with resulting deactivation of the molecule. By introduction of the hydroxyl group in the form of a tertiary alcohol, such ready oxidation would be inhibited. Furthermore, tertiary alcohols may, in and of themselves, be expected to have central nervous system depressant activity. Boekelheide and his group had investigated a large number of 4-(hydroxyalkyl)-1,3-dioxolanes but had not followed the lead of the 2-(hydroxyalkyl)-1,3-dioxolane which they reported. We, therefore, prepared a series of 2-(hydroxyalkyl)-1,3-dioxolanes and 2-(hydroxyalkyl)-1,3-dioxanes in which the alcohols were tertiary.

Condensation of ethyl acetoacetate with ethylene glycol gave 2-methyl-2-carbethoxymethyl-1,3-dioxolane (I). By treatment of this ester with two moles of ethylmagnesium bromide there was obtained 2-methyl-2-(2-hydroxy-2-ethylbutyl)-1,3-dioxolane (II). This material showed an order of activity which was of interest. Reaction of the ester was therefore carried out with both methyl and propylmagnesium halides. The resulting tertiary alcohols (III and IV) both showed a lower activity than did the first prepared alcohol (II).

We prepared 2,2-diisopropyl-4-hydroxymethyl-1,3-dioxolane (V) (Promoxolane) for comparison and found that it, too, had an activity of shorter duration than that of compound II in our mouse test, although it possibly did show a better therapeutic index.

Because there was some thought that hydrolysis of II in the body to give ethylene glycol might not be desirable, condensation was carried out between ethyl acetoacetate and propylene glycol to give 2,4-dimethyl-2-carbethoxymethyl-1,3-dioxolane (VI). Treatment of this ester with ethylmagnesium bromide gave 2,4-dimethyl-2-(2-hydroxy-2-ethylpropyl)-1,3-dioxolane (VII), which proved to be less active than the previously prepared II. For the reason given for the preparation of VII we carried out the condensation between trimethylene glycol and ethyl acetoacetate to give 2-methyl-2-carbethoxymethyl-1,3-dioxane (VIII), which was converted by ethylmagnesium bromide to 2-methyl-2-(2-hydroxy-2-ethylbutyl)-1,3-dioxane (IX), which also was not as active as II.

We next considered that we might be able to increase the activity of the 1,3-dioxane compounds if we employed as a glycol 2,2-diethylpropane-1,3-diol, which itself is a central nervous system depressant. By carrying out the appropriate condensation to give ester X and treatment of this ester with ethylmagnesium bromide, the corresponding tertiary alcohol XI was obtained. This proved to be less active pharmacologically than was II.

At this point we thought it would be interesting to prepare a 1,3-dioxane which had its hydroxyalkyl group at a position other than at the 2-position. To this end we attempted to condense diisopropyl ketone with trishydroxymethylmethane in the way in which we had carried out our other similar condensations. In this we were unsuccessful. We were also unsuccessful when we changed to dioxane as a solvent in order to get a homogeneous reaction mixture and when we changed to dimethoxyethane or to diethoxyethane to get higher reaction temperatures. Anhydrous zinc chloride

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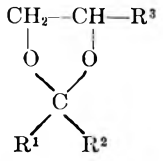
(2) F. M. Berger, *Arch. intern. pharmacodynamie*, **85**, 474 (1951).

(3) V. Boekelheide, L. Liberman, J. Figueras, C. Krespan, F. C. Pennington, and D. S. Tarbell, *J. Am. Chem. Soc.*, **71**, 3303 (1949).

TABLE I

SUBSTITUTED 1,3-DIOXOLANES



Cmpd.	R^1	R^2	R^3	B.P. °C	B.P. Mm.	n_D at	°C	Yield, %	Empirical Formula	Analysis, % Calcd. C	Calcd. H	Found C	Found H
I	CH_3	$CH_2CO_2C_2H_5$	H	112–114	33[a]	1.4304	24	70					
II	CH_3	$CH_2C(C_2H_5)_2OH$	H	122–123	20	1.4489	24.5	30	$C_{10}H_{20}O_3$	63.79	10.71	63.81	10.94
III	CH_3	$CH_2C(CH_3)_2OH$	H	99	24	1.4401	25	34	$C_8H_{16}O_3$	59.97	10.07	59.85[b]	10.20
IV	CH_3	$CH_2C(n\text{-}C_3H_9)_2OH$	H	133	15[b]	1.4484	25	15	$C_{12}H_{24}O_3$	66.63	11.18	66.80	11.27
V	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	CH_2OH	98–100	4[c]	1.4532	21	30					
VI	CH_3	$CH_2CO_2C_2H_5$	CH_3	75–76	4[d]	1.4275	25	37					
VII	CH_3	$CH_2C(C_2H_5)_2OH$	CH_3	104–108	9	1.4437	25	58	$C_{11}H_{22}O_3$	65.31	10.96	65.21	10.89
XIII	CH_3	$CH_2CH_2CO_2C_2H_5$	H	106–107	13[e]	1.4326	25	65					
XIV	CH_3	$CH_2CH_2C(C_2H_5)_2OH$	H	118–119	4	1.4575	25	75	$C_{11}H_{22}O_3$	65.31	10.96	65.27	11.14
XV	CH_3	$CH_2CH_2C(CH_3)_2OH$	H	110	10.5	1.4475	25	15	$C_8H_{18}O_3$	62.04	10.41	61.94	10.66
XVI	CH_3	$CH_2CH_2CH(OH)CH(CH_3)_2$	H	112.5–113	10.5	1.4412	25	7	$C_{10}H_{20}O_3$	63.79	10.71	63.91	10.80
XVII	CH_3	$CH_2CH_2CH_2CO_2C_2H_5$	H	128–129	15	1.4460	25	65	$C_{10}H_{18}O_4$	59.38	8.97	59.51	9.12
XVIII	CH_3	$CH_2CH_2CH_2C(C_2H_5)_2OH$	H	116–118	1.9	1.4572	24	70	$C_{12}H_{24}O_3$	66.83	11.42	66.63	11.18

[a] Kahn[4] reported b.p. 100° (17–18 mm.), n_D^{20} 1.4326. Salmi[5] reported b.p. 99.5–101° (17–18 mm.), n_D^{20} 1.43262. [b] 90° (1 mm.). [c] Boekelheide *et al.*[3] reported b.p. 115° (9 mm.), n_D^{21} 1.4502. [d] Salmi[5] reported b.p. 84.6–86° (6 mm.), n_D^{20} 1.4288. [e] Kahn[4] reported b.p. 110–112 (15 mm.).

(4) M. Kahn, *J. prakt. Chem.* (2) **156**, 103 (1940).
(5) E. J. Salmi, *Ber.*, **71**, 1803 (1938).

TABLE II

SUBSTITUTED 1,3-DIOXANES

Cmpd.	R^1	R^2	R^3	B.P. °C	B.P. Mm.	n_D^{25}	% Yield	Empirical Formula	Analysis, % Calcd. C	Calcd. H	Found C	Found H
VIII	H	H	$CH_2CO_2C_2H_5$	106–108	11	1.4432[a,b]	40					
IX	H	H	$CH_2C(C_2H_5)_2OH$	126	11.5	1.4560	10	$C_{11}H_{22}O_3$	65.31	10.96	65.46	11.11
X	C_2H_5	C_2H_5	$CH_2CO_2C_2H_5$	94–96	0.4	1.4482	37	$C_{13}H_{24}O_4$	63.90	9.90	63.81	9.98
XI	C_2H_5	C_2H_5	$CH_2C(C_2H_5)_2OH$	121	1	1.4613	13	$C_{15}H_{30}O_3$	69.72	11.70	69.80	11.88
XII	CH_2OH	CH_3	n-C_6H_{11}	123	2	1.4560[c]	25.5	$C_{12}H_{24}O_3$	66.68	11.18	66.50	11.30

[a] At 20°. [b] Salmi[5] reported b.p. 95° (4 mm.), n_D^{20} 1.44425. [c] At 25.5°.

was used instead of toluenesulfonic acid as condensing catalyst with no more success. The obvious difficulty was steric, coupled with the difficult formation of 1,3-dioxanes, as compared with the ready formation of 1,3-dioxolanes. To test this hypothesis, we tried a condensation between diisopropyl ketone and trimethylene glycol, using the same conditions under which water was readily eliminated in the condensation of the ketone with glycerine to give the 1,3-dioxolane (V). Water was eliminated only very slowly. This bears out what Boekelheide *et al.*[3] and Dworzak and Herrmann[6] had already indicated, namely that 1,3-dioxolanes are evidently more easily formed than are 1,3-dioxanes. Unlike Boekelheide *et al.*,[3] however, we found that methyl amyl ketone did condense with trimethylene glycol and so we tried the condensation between this less hindered ketone and trishydroxymethylmethane. The resulting compound, 2,5-dimethyl-2-amyl-5-hydroxymethyl-1,3-dioxane (XII), was no improvement pharmacologically over compound II.

We next carried out the condensation between ethyl levulinate and ethylene glycol. The resulting ester (XIII) was allowed to react with ethylmagnesium bromide to give 2-methyl-2-(3-hydroxy-3-ethylpentyl)-1,3-dioxolane (XIV). This compound showed an interesting order of activity which was of prolonged duration. The ester, XIII, was therefore allowed to react with methylmagnesium iodide and isopropylmagnesium bromide. The former reaction gave the expected tertiary alcohol XV, whereas the reaction with isopropylmagnesium bromide resulted in the product obtained by addition of one mole of Grignard to the ester, followed by reduction of the resulting ketone with a second mole of Grignard, to give 2-methyl-2-(3-hydroxy-4-methylpentyl)-1,3-dioxolane (XVI). Neither of these new alcohols was as interesting pharmacologically as was XIV, which in turn was longer acting than either II or V. In mice, XIV had the most advantageous ratio of effective dose to lethal dose of any of the compounds tested.

In view of the increase in activity obtained by introducing an additional methylene group between the tertiary alcohol and the dioxolane ring (XIV compared to II), it was of interest to ascertain the effect of another methylene group. By the procedure of Albertson,[7] ethyl 5-oxocaproate was prepared. Condensation with ethylene glycol gave XVII, which by reaction with ethyl Grignard reagent gave the desired 2-methyl-2-(4-hydroxy-4-ethylhexyl)-1,3-dioxolane (XVIII). This compound was not as active as was XIV.

We prepared one compound which had no hydroxyl group in it. This compound, 2,2-diisobutyl-4-chloromethyl-1,3-dioxolane was prepared to ascertain the effect on central nervous system depres-

(6) R. Dworzak and K. Herrmann, *Monatsh.*, **52**, 83 (1929).

(7) N. F. Albertson, *J. Am. Chem. Soc.*, **72**, 2594 (1950).

sion of replacing a hydroxyl group by a chlorine atom. Central nervous system depression was observed but the toxicity was high.

The pharmacological comparisons of the compounds were carried out by Miss Mary Lewis[8] of our Pharmacology Department.

EXPERIMENTAL[9,10]

As an example of the procedure used for the condensation of ketones with alcohols to give the cyclic acetals, I, V, VI, VIII, X, XII, XIII, and XVII, the following is an illustration.

2,5-Dimethyl-2-pentyl-5-hydroxymethyl-1,3-dioxane. A mixture of 60 g. (0.5 mole) of trishydroxymethylmethane, 250 ml. of toluene, and 0.5 g. of *p*-toluenesulfonic acid was allowed to reflux with a Dean-Stark trap until no water distilled. Methyl *n*-pentyl ketone, 57 g. (0.5 mole), was added, and refluxing was continued until no water distilled. The reaction mixture was cooled, and filtered if necessary from starting trishydroxymethylmethane. The filtrate was washed with 30 ml. of 10% sodium carbonate and then with water. After drying, the organic layer was distilled.

As an example of the procedure used for the reaction of the cyclic ketones with the Grignard reagents to give the products II, III, IV, VII, IX, XI, XIV, XV, XVI, and XVIII the following is illustrative.

2-Methyl-2-(3-hydroxy-3-ethylpentyl)-1,3-dioxolane. To methylmagnesium bromide prepared from 71 g. (0.65 mole) of ethyl bromide in 200 ml. of ether was added with cooling 47 g. (0.25 mole) of 2-methyl-2-(2-carbethoxyethyl)-1,3-dioxolane in 250 ml. of ether over a period of about 1 hr. When spontaneous refluxing ceased, the reaction mixture was refluxed for 1.5 hr. and then was decomposed with saturated aquecus ammonium chloride. The ether layer was dried over magnesium sulfate, filtered, and concentrated. The residue was allowed to reflux for 20 hr. with an equal volume of 20% aqueous sodium hydroxide, diluted with sufficient methanol to give a homogeneous solution, and then a volume equal to the added methanol was removed by distillation. The reaction mixture was extracted thoroughly with Skellysolve B and the extract was dried and distilled. The product, distilling at 147–149° (23–25 mm.), was carefully fractionated to give a pure product distilling at 118–119° (4 mm.), n_D^{24} 1.4575.

Ethyl 5-ketohexanoate. Condensation of ethyl acetoacetate and acrylonitrile was carried out according to the procedure of Albertson.[7] Our constants were in excellent agreement with those reported. Decarboxylation to 5-oxocapronitrile, however, found us in less satisfactory agreement. Our product, obtained in 79% yield, distilled at 98–99° (5.5 mm.), n_D^{25} 1.4287. Reported b.p. 86.5° (5.2 mm.), n_D^{25} 1.4790.

Anal. Calcd. for C_6H_9NO: C, 64.84; H, 8.16; N, 12.81. Found: C, 64.67; H, 8.32; N, 12.61.

On treatment of the nitrile with absolute alcoholic hydrogen chloride, followed by water in the usual way, a 62% yield of product b.p. 107° (15 mm.), n_D^{25} 1.4254 was obtained. Reported[11] b.p. 110–15° (12 mm.).

2,2-Diisobutyl-4-chloromethyl-1,3-dioxolane. Into a flask containing 100 ml. of carbon tetrachloride were added simultaneously from one dropping funnel 162 g. of freshly distilled diisobutyl ketone mixed with 95 g. of epichlorohydrin in 150 ml. of carbon tetrachloride and from another dropping funnel 13 g. of stannic chloride in 50 ml. of carbon tetrachloride at such rates as to finish both additions at once. By means of an ice bath the temperature of the reaction mixture was kept at 25–38°. After the addition was completed, the reaction was allowed to stand overnight and was then treated in an ice bath with 80 ml. of 20% sodium hydroxide dropwise with stirring. Layers were separated, and the aqueous layer was extracted with ether. The ether and carbon tetrachloride solutions were dried over magnesium sulfate and distilled. The product, b.p. 127–129° (20 mm.), n_D^{24} 1.4465 weighed 162 g. (67%).

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(8) Present address: Pharmacological Research, Plympton, Mass.

(9) Temperatures are uncorrected.

(10) Analyses were carried out by Miss Linda Einstein.

(11) L. Ruzicka, *Helv. Chim. Acta.*, **2**, 144 (1919).

[CONTRIBUTION FROM THE CELLULOSE RESEARCH INSTITUTE AND THE EMPIRE STATE PULP AND PAPER RESEARCH INSTITUTE, STATE UNIVERSITY COLLEGE OF FORESTRY AT SYRACUSE UNIVERSITY]

Reactions of *p*-Hydroxybenzyl Alcohol Derivatives and Their Methyl Ethers with Molecular Chlorine[1]

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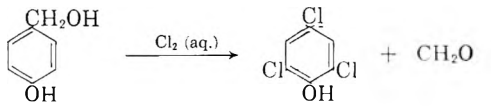
Molecular chlorine displaces the carbinol group in a number of *p*-hydroxybenzyl alcohol derivatives and their methyl ethers forming an aldehyde and a chlorinated aromatic ring. The rate of displacement of a primary carbinol group is close to the same order of magnitude of comparable chlorine substitution and probably higher than the displacement rates of an aldehyde group.

In aqueous and partially aqueous media, molecular chlorine acts as a catalyst to hydrolyze aromatic methoxyl groups to phenolic hydroxyl groups and methanol under conditions where no proton-catalyzed hydrolysis is observed. The mechanisms involved in the displacement and hydrolysis reactions are discussed.

In common usage, the expression "aromatic substitution" mainly is used in cases where hydrogen attached to an aromatic nucleus is replaced by some other group, such as halogen. For this reason, reactions involving the replacement of a group other than hydrogen by an electrophilic reactant generally are not called substitution reactions, but rather "electrophilic aromatic displacements," the common aromatic substitution forming a subgroup of the latter reactions.[2] Examples of this sort in-

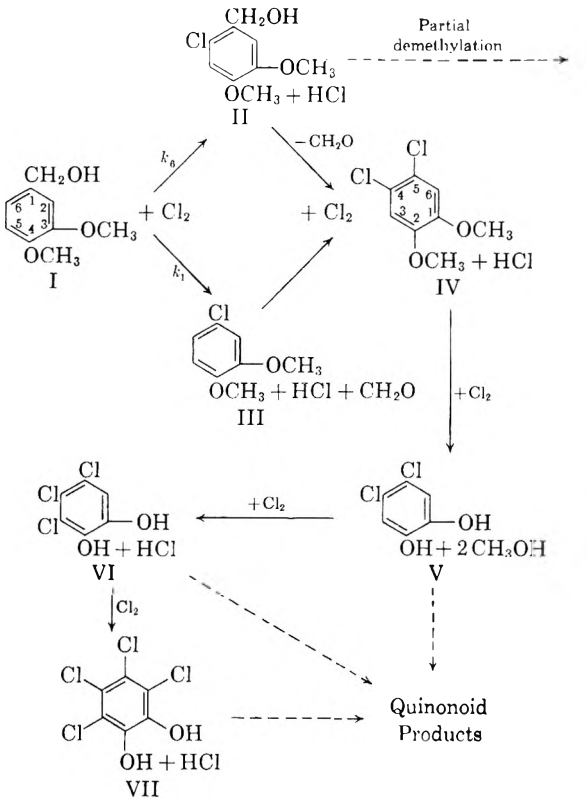
clude decarboxylations,[3] replacements of alkyl,[4] SO_3H,[5] $B(OH)_2$[6] or $SiMe_3$[7] groups by bromine, exchange of an *alpha* carbinol[8] or ether for a nitro group,[9] and others.

In the present study it has been possible to demonstrate that an *alpha* carbinol or alkyl ether group, in a position *para* to an activating phenolic hydroxyl or methoxyl group, is replaced by chlorine with remarkable ease. In the simplest case, *p*-hydroxybenzyl alcohol treated with chlorine water at room temperature, is instantly converted to 2,4,6-trichlorophenol and formaldehyde:



Similarly, 3,4-dimethoxybenzyl alcohol (veratryl alcohol) was found to form 4,5-dichloroveratrole in 78% yield when chlorinated in glacial acetic acid. The yield from the corresponding benzyl methyl ether was substantially smaller, under comparable conditions. When 3-methoxy-4-hydroxybenzyl alcohol (vanillyl alcohol) was exhaustively chlorinated in glacial acetic acid, tetrachloroguaiacol was isolated from among the reaction products indicating the replacement of the carbinol group. 3,4,5-Trimethoxybenzyl alcohol was chlorinated in 80% yield to 1,2,3-trimethoxy-4,5,6-trichlorobenzene in acetic acid–water mixtures.[10] Pinoresinol dimethyl ether, a dimer containing two alkyl ether groups in position *alpha* to the aromatic nuclei similarly was converted to 4,5-dichloroveratrole. However, the maximum yield obtainable always remained below 5% in this case. The above examples serve to illustrate the generality of the displacement reaction.

The chlorination of 3,4-dimethoxybenzyl alcohol in 0.1*N* hydrochloric acid in acetic acid–water mixtures offered an especially interesting case of electrophilic displacement by chlorine and was therefore studied in detail. The results obtained indicate the following sequence of reactions for the process:



Evidence for this sequence of reactions was obtained by chlorinating veratryl alcohol (I) and some of the reaction intermediates with varying amounts of chlorine. All the reactions of the sequence are relatively rapid and go to completion in a period of half an hour. As will be shown later, the electrophilic displacement of the carbinol group competes initially with the substitution at the 6-position, resulting in a mixture of products II and III. Both compounds are then converted to 4,5-dichloroveratrole (IV) by further chlorination, as demonstrated by the fact that the neutral portion of the product mixture, after treatment with two moles of chlorine, consisted of almost pure 4,5-dichloroveratrole. This finding also points out that substitution in the 5-position is negligible before the demethylation stage (IV → V). The ready conversion of synthetic 6-chloro-3,4-dimethoxybenzyl alcohol to 4,5-dichloroveratrole by chlorine was established by a separate experiment.

Apparently, demethylation of the two methoxyl groups in 4,5-dichloroveratrole occurs in a rapid sequence, since the methoxyl content of the alkali-soluble portion of the chlorination products was found to be negligible (less than 1%). That a partial demethylation of the intermediate II also takes place, was demonstrated in the following way: When the alkali-soluble portion of the chlorinated

(1) Taken in part from a thesis submitted by C. W. Dence in partial fulfillment of the requirements of the degree of Doctor of Philosophy, State University College of Forestry at Syracuse University. A part of the subject matter was presented at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 1958. The financial support from the Empire State Pulp and Paper Research Associates is gratefully acknowledged.

(2) P. B. D. de la Mare, in Klyne and de la Mare, *Progress in Stereochemistry*, Vol. 2, p. 65. Academic Press, New York, 1958.

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(8) C. Gustafsson and L. Andersen, *Paperi ja Puu*, **37**, 1 (1955).

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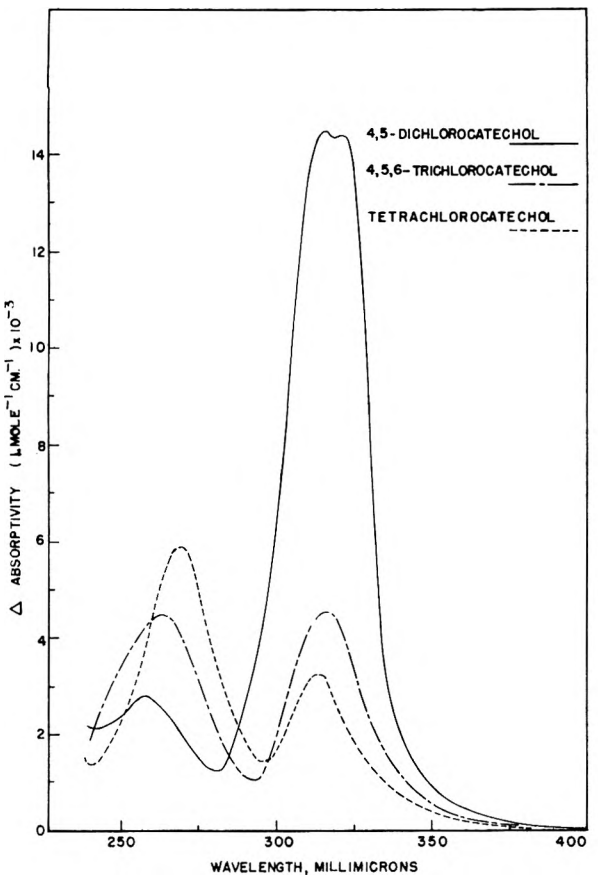


Fig. 1. Ionization difference spectra of 4,5-dichloro-, 4,5,6-trichloro-, and tetrachlorocatechols

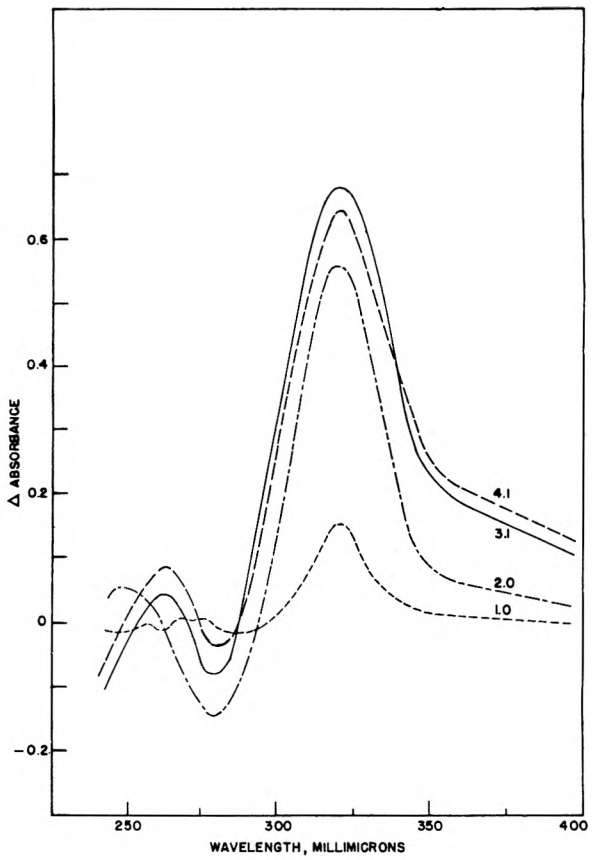


Fig. 2. Ionization difference spectra of the chlorinated products of veratryl alcohol at various chlorine/substrate ratios

products was methylated with dimethyl sulfate and alkali, the chlorocatechols V, VI, and VII suffered degradation rather than undergoing methylation. The only isolated product was crystalline 6-chloro-3,4-dimethoxybenzyl alcohol (II), apparently formed by the methylation of the corresponding catechol or catechol monomethyl ether.

The demethylation reaction has certain peculiar characteristics. First, the reaction appears to be rapid only in aqueous or partially aqueous media. As mentioned earlier, in veratrole derivatives the demethylation is much more rapid than chlorine substitution in position *ortho* to the methoxyl groups. However, if veratrole or guaiacol is treated with gaseous chlorine in glacial acetic acid or some other organic solvent, tetrachlorination can be accomplished without any apparent sign of demethylation.[11]

Secondly, no oxidative mechanism is involved in the demethylation reaction, since recent experiments[10] demonstrate the formation of methanol during the reaction. The possibility of acid-catalyzed hydrolysis of the phenolic ether bond was obviated by the fact that mineral acids have no effect on 4,5-dichloroveratrole at room temperature. Neither can demethylation be accomplished by a hypochlorous acid solution at *p*H 5.4. Consequently, the demethylation must be caused by the presence of elemental chlorine and, moreover, since both oxidative and substitution effects are absent, this action appears to be of catalytic nature.

The chlorocatechols V, VI, and VII (see Experimental) possess characteristic ionization difference spectra (Fig. 1). The position of the high wavelength maximum at 320 mμ region readily distinguished these spectra from those of 3-methoxy-4-hydroxybenzyl alcohol[12] and its chlorine-substituted derivatives (maximum at 300 mμ region) as well as from guaiacol derivatives containing a carbonyl in position *para* to the phenolic hydroxyl group (maximum at 350 mμ region).[13] 3,4-Dimethoxybenzyl alcohol, after chlorination with two to three moles of chlorine, exhibits ionization difference spectra closely similar to that of dichlorocatechol (Fig. 2). Further chlorination changes the form of the spectrum toward those of tri- and tetrachlorocatechols, in full accordance with the proposed mechanism.

The presence of chlorocatechols was proven beyond doubt by chlorinating 4,5-dichloroveratrole and methylating the alkali-soluble part of the prod-

(11) R. Fort, J. Sleziona, and L. Deniville, *Bull. soc. chim. France*, 810 (1955).

(12) G. Aulin-Erdtman, *Svensk Papperstidn.*, **56**, 91 (1953).

(13) O. Goldschmid, *J. Am. Chem. Soc.*, **75**, 3780 (1953).

uct with diazomethane. Crystalline tetrachloroveratrole was isolated from the resulting mixture.

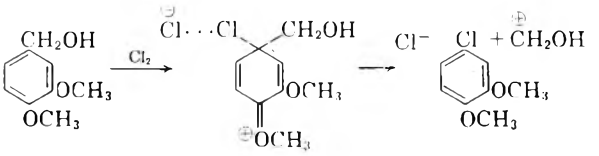
Two aspects of the electrophilic displacement reaction can be studied on the basis of the reaction sequence for the chlorination of 3,4-dimethoxybenzyl alcohol. First, it is possible to estimate, with reasonable precision, the ratio of the rate constant for the electrophilic displacement at position 1 (k_1) to that of substitution at the 6-position (k_6). This can be done by determining the molar ratio of formaldehyde formed to the total chlorine consumption at low levels of chlorine consumption (0.05 to 0.3 mole). By carrying out an extrapolation to zero chlorine consumption, a value equal to $k_1/(k_1 + k_6)$ is obtained. The ratio k_1/k_6, estimated in this way, was found to be 0.10. It may be observed, however, that whereas both 1- and 6-positions are activated by a *p*-methoxyl group, the latter receives additional activation from the carbinol group in the *o*-position. Consequently, under strictly comparable conditions, the ratio of displacement of a primary carbinol group to aromatic substitution could be reasonably expected to be somewhat higher than the presently found experimental value.

Secondly, the electrophilic displacement of groups other than primary carbinol can be studied by replacing this group in 3,4-dimethoxybenzyl alcohol by other substituents. A displacement rate close to that of the carbinol group would result in the formation of 4,5-dichloroveratrole. Failure to isolate dichloroveratrole or to demonstrate the presence of its conversion products, the chlorocatechols, in the chlorination of 4-*n*-propylveratrole, 3-methoxy-4-hydroxytoluene-ω-sulfonic acid and 6-chloro-3,4-dimethoxybenzaldehyde, demonstrates that electrophilic displacement in these compounds either does not occur at all, or is substantially retarded.

In compounds containing a phenolic hydroxyl in the position *para* to the group to be replaced, aldehyde and carboxyl groups appear to be subject to electrophilic displacement. Both *p*-hydroxybenzaldehyde and *p*-hydroxybenzoic acid were converted to 2,4,6-trichlorophenol by treatment with chlorine water at room temperature.

The presence of quinonoid compounds in chlorination products was indicated by the light absorption in the near visible ultraviolet region which showed maximum growth after the consumption of two moles of chlorine. Because of their instability and complex nature, the quinonoid compounds were not studied in detail. The assumption of their formation from the chlorocatechols gained support from the observation that chlorination of tetrachlorocatechol produced the characteristic spectral pattern of tetrachloro-*o*-quinone.

The mechanisms of electrophilic displacement and demethylation reactions. By analogy with aromatic substitution reactions,[14] the electrophilic displacement reaction probably proceeds *via* a transitory *sigma* complex, according to the following scheme:



XI

The nature of the products formed, the observed rate of the reaction as well as the absence of photochemical effects are all in accordance with the proposed mechanism. Furthermore, the displacement reaction resembles the aromatic substitution by chlorine in that it was found to occur also in relatively nonpolar media, such as ethyl ether and carbon tetrachloride.

A polarized chlorine molecule, rather than a chloronium ion (Cl^+ or $ClOH_2^+$), has been pictured as the participant of the transition complex, in line with the evidence gained from aromatic substitution studies.[15] The formaldehyde formed apparently is released from the aromatic nucleus in the form of its protonated, positively charged ion.

A number of reported displacement reactions by a nitronium ion and by bromine (Table I) probably follow a reaction mechanism similar to the chlorine displacement. This is suggested by the nature of substituents replaced and the products from them, as well as by the relatively high rates of these reactions. The fact that the displacement of aldehyde and carboxyl groups has only been observed in instances where these groups are activated by a *para*-hydroxyl group, whereas carbinol and carbinol ether groups in position *para* to a methoxyl group are displaced is in accordance with the results of the present study.

TABLE I

ELECTROPHILIC DISPLACEMENT REACTIONS BY NITRONIUM ION AND BY BROMINE

Reactant	Substrate	Substituent Displaced	Displacement Product from Substituent
NO_2^+	Dibromopinoresinol dimethyl ether[9]	Sec. carbinol ether	Aldehyde
NO_2^+	Vanillyl alcohol[8]	Prim. carbinol	Not determined
NO_2^+	Vanillin[8]	Aldehyde	Not determined
NO_2^+	Vanillic acid[8]	Carboxyl	Not determined
Br_2	*p*-Hydroxybenzaldehyde[16]	Aldehyde	CO
	p-Hydroxybenzoic acid[16]	Carboxyl	CO_2

(14) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1257 (1937).

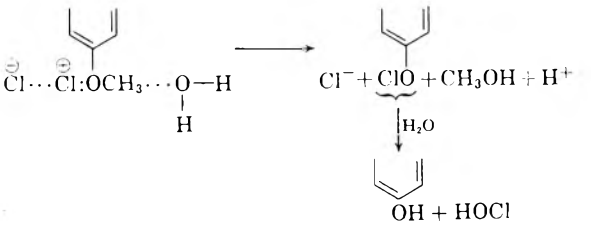
(15) P. B. D. de la Mare, E. D. Hughes, and C. A. Vernon, *Research (London)*, **3**, 192 (1950).

(16) A. W. Francis and A. J. Hill, *J. Am. Chem. Soc.*, **46**, 2498 (1924).

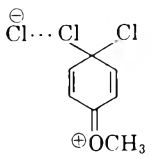
In general, the ease of electrophilic displacement appears to be highly dependent on the nature of the substituent to be replaced, suggesting the release of the substituent to be the rate-determining step in the process rather than the formation of the transition complex. Resonance stabilization of the departing positive ion would conceivably facilitate such a release. Consequently, the observed high rate of displacement of primary carbinol group tentatively can be assigned to this factor. In contrast, the rate-determining step in aromatic substitution by bromine appears to be the formation of the *sigma* complex.[17]

In visualizing the mechanism of the demethylation reaction, it is necessary to account for the fact that chlorine acts as a catalytic agent rather than as an oxidant, as was assumed earlier for similar processes.[18]

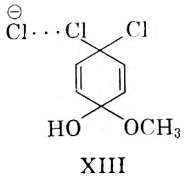
Two alternative mechanisms may be considered for the chlorine-catalyzed demethylation. First, molecular chlorine, by virtue of its strongly electrophilic character, may play a role similar to a proton in an acid-catalyzed hydrolysis:



The second mechanism consists of an attack of the chlorine molecule in the position *para* to the methoxyl group resulting, in aqueous solution, in the formation of the intermediate XII or XIII.



XII



XIII

Either of these species may be converted to the free phenol with the simultaneous generation of methanol and regeneration of the chlorine molecule.

The occurrence of demethylation reactions has been observed earlier in the nitration of aromatic methyl ethers, both in aqueous[19] and acetic acid[20] media. Results by Ingold and co-workers[20] point out that these reactions have the nature of a nitronium ion-catalyzed solvolytic cleavage and, as such, appear to be closely related to chlorine-catalyzed demethylations. The former reactions do differ, however, from demethylations by chlorine in that they proceed readily in acetic acid solution, liberating methyl acetate from the original methoxyl group.

Results from a separate study[21] indicate that both the electrophilic displacement and demethylation reactions take place in the chlorination in wood lignin and in commercial wood pulps. They appear to contribute significantly to the lignin solubilization process both by degrading the macromolecules to smaller fragments and by increasing their hydrophilic nature.

EXPERIMENTAL

Chlorination of p-hydroxybenzoic acid, p-hydroxybenzyl alcohol, and p-hydroxybenzaldehyde. One gram (0.0072 mole) of *p*-hydroxybenzoic acid was dissolved in 200 ml. of water and chlorine water (0.025 mole in 100 ml. of 0.1*N* hydrochloric acid) added. A flocculent precipitate slowly formed which was filtered, dried, and sublimed in vacuum. The melting point of the sublimate (67–68°) was undepressed in admixture with authentic 2,4,6-trichlorophenol. 2,4,6-Trichlorophenol was isolated from chlorinated *p*-hydroxybenzaldehyde and *p*-hydroxybenzyl alcohol in the same manner. Formaldehyde was identified among the reaction products, in the latter case, by distilling the filtrate and precipitating the dimedone derivative, m.p. 189–190°, from the distillate.

In order to establish the approximate yields of 2,4,6-trichlorophenol and formaldehyde, the following experiments were carried out: *p*-Hydroxybenzyl alcohol (0.500 g.) was chlorinated in aqueous solution with 3.2 moles of chlorine per mole of substrate. After total consumption of chlorine, the solution was thoroughly extracted with ether. After drying and removal of the solvent, the residue consisted of impure crystals of 2,4,6-trichlorophenol (crude yield: 81%).

To determine the quantitative amount of formaldehyde liberated in the reaction, 8.3 mg. of *p*-hydroxybenzyl alcohol was chlorinated in aqueous solution with 3.2 moles of chlorine. After exhaustion of the chlorine, the sample was diluted to 100 ml. with distilled water and a 10 ml. aliquot removed for formaldehyde analysis by the chromatropic acid method.[22] The yield determined in this way was 80%.

4,5-Dichloroveratrole. Isolation from the chlorination products of 3,4-dimethoxybenzyl alcohol, 3,4-dimethoxybenzyl methyl ether, and pinoresinol dimethyl ether. 3,4-Dimethoxybenzyl alcohol (0.5 g.) was dissolved in 50 ml. of aqueous acetic acid (1:1 by volume) and 130 ml. of chlorine water (3.56 g./l. in 0.1*N* hydrochloric acid) was added, corresponding to a chlorine to alcohol ratio of 2.2. A white, crystalline precipitate formed rapidly and was filtered. An additional amount of the same material crystallized from the distillate obtained by concentrating the filtrate at atmospheric pressure. Combined yield after recrystallization from aqueous ethanol: 0.18 g. (30%), m.p., 83°. A mixed melting-point determination with authentic 4,5-dichloroveratrole[23] gave no depression.

Anal. Calcd. for $C_8H_8O_2Cl_2$: C, 46.39; H, 3.89; OCH_3, 29.96; Cl, 34.27. Found: C, 46.54; H, 3.99; OCH_3, 29.99; Cl, 34.28.

Formaldehyde was identified in the distillate as its dimedone derivative, m.p. 189°. The quantitative formaldehyde determination was carried out in a manner similar to the

(17) P. B. D. de la Mare, T. M. Dunn, and J. T. Harvey, *J. Chem. Soc.*, 923 (1957).

(18) E. V. White, J. N. Swartz, Q. P. Peniston, H. Schwartz, J. L. McCarthy, and A. Hibbert, *Tech. Assoc. Papers*, **24**, No. 1, 179 (1941).

(19) R. M. Schramm and F. H. Westheimer, *J. Am. Chem. Soc.*, **70**, 1782 (1948).

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(21) C. W. Dence and K. V. Sarkanen, *TAPPI*, **43**, 87 (1960).

(22) C. E. Bricker and H. R. Johnson, *Ind. Eng. Chem., Anal. Ed.*, **17**, 400 (1945).

(23) A. Peratoner and G. Ortoleva, *Gazz. chim. ital.*, **28**, (I) 229 (1898).

case of *p*-hydroxybenzyl alcohol, with the following exceptions: The chlorine to substrate ratio was 2.5 and the formaldehyde was determined in the aqueous distillate of the neutralized chlorination mixture. Yield: 96%.

A higher yield of 4,5-dichloroveratrole (78%) was obtained when the chlorination of 3,4-dimethoxybenzyl alcohol was carried out in glacial acetic acid solution. 6-Chloro-3,4-dimethoxybenzyl alcohol, chlorinated with 1.3 moles of chlorine in acetic acid–water mixture, gave a 33% yield of 4,5-dichloroveratrole. The same compound was isolated in 7% yield when 3,4-dimethoxybenzyl methyl ether was chlorinated with 2.5 moles of chlorine in acetic acid–water mixture. When pinoresinol dimethyl ether[24] (0.2 g.) was chlorinated (Cl_2/mole of substrate = 4.1) in an acetic acid–water mixture, no precipitation of dichloroveratrole took place. After dilution with water and neutralization to *p*H 7.2, the solution was extracted with ether and the extract sublimed in vacuum. The sublimate was subsequently recrystallized from a small amount of ether and from aqueous ethanol giving 4.5 mg. of crystals melting at 78–82°, identified as 4,5-dichloroveratrole by mixed melting point determination.

Tetrachloroguaiacol. Isolation from the chlorination products of 4-hydroxy-3-methoxybenzyl alcohol (vanillyl alcohol). One gram of vanillyl alcohol was dissolved in 25 ml. of glacial acetic acid and chlorine gas bubbled through the solution for 60 min. while maintaining the temperature slightly above the melting point of the medium. The excess chlorine and the solvent were removed under reduced pressure. The orange residue was recrystallized several times from aqueous ethanol to which a small amount of sodium hydrosulfite had been added, and finally from solvent naphtha. The resulting white compound, melting at 119–121°, did not depress the melting point of authentic tetrachloroguaiacol, prepared according to Fort *et al.*[11] Tetrachloroguaiacol also was isolated by chlorinating 6-chlorovanillyl alcohol in glacial acetic acid.

6-Chloro-3,4-dimethoxybenzyl alcohol. Preparation and isolation from the methylated chlorination products of 3,4-dimethoxybenzyl alcohol. Five grams of 6-chloro-3,4-dimethoxybenzaldehyde (m.p. 146°), obtained by dimethyl sulfate methylation of 6-chlorovanillin,[25] was reduced in refluxing methanol solution (100 ml.) with 1 g. of sodium borohydride, until the carbonyl test with 2,4-dinitrophenylhydrazine was negative. The solution was concentrated in vacuum, diluted with water, and adjusted to *p*H 7. On cooling, the alcohol precipitated in the form of crystals which were filtered, washed with water, and dried. The crystals (73% yield) melted at 82–83° after recrystallization from chloroform-solvent naphtha mixture.

Anal. Calcd. for $C_9H_{11}O_3Cl$: C, 53.34; H, 5.43; OCH_3, 30.62; Cl, 17.51. Found: C, 53.26; H, 5.60; OCH_3, 30.60; Cl, 17.45.

3,4-Dimethoxybenzyl alcohol (20 g.) was dissolved in 2 l. of 0.1*N* hydrochloric acid, cooled to 20°, and allowed to react with gaseous chlorine until the increase in weight corresponded to 2.4 chlorine to substrate ratio. The precipitated dichloroveratrole was removed by filtration and the filtrate made alkaline. After a thorough ether extraction to remove any neutral constituents (including 6-chloro-3,4-dimethoxybenzyl alcohol), the solution was concentrated in vacuum and methylated at 60° with dimethyl sulfate and alkali. At the completion of the reaction, the alkaline solution was extracted with ether. The extract contained a crystalline constituent which, after recrystallization from aqueous ethanol, melted at 80–81° and did not depress the melting point of synthetic 6-chloro-3,4-dimethoxybenzyl alcohol.

Anal. Calcd. for $C_8H_8O_2Cl(OCH_3)$: OCH_3, 30.62. Found: OCH_3, 30.62.

Tetrachlorocatechol dimethyl ether. Isolation from the methylated chlorination products of 4,5-dichloroveratrole. 4,5-Dichloroveratrole (5 g.) was dissolved in 30 ml. of glacial acetic acid and water added in an amount slightly less than that required to reprecipitate the material. Chlorine, dissolved in glacial acetic acid, was added in an amount corresponding to a chlorine to substrate ratio of 1.5. After 15 min. reaction time at room temperature, excess chlorine was destroyed with sodium thiosulfate solution and most of the acetic acid present neutralized with sodium carbonate. The solution was extracted several times with ether and the combined ether extracts in turn, with 2*N* sodium hydroxide solution. Acidification and ether extraction of the alkaline solution gave a practically methoxyl-free product (OCH_3, 0.45%) which showed a dark-green ferric chloride reaction. After methylation with excess diazomethane in ether solution, crystals separated from the product which, after recrystallization from aqueous ethanol, melted at 88–89° and did not depress the melting point of authentic tetrachloroveratrole.[26]

Anal. Calcd. for $C_6H_6O_2Cl$: C, 34.80; H, 2.18; OCH_3, 22.48; Cl, 51.42. Found: C, 34.95; H, 2.33; OCH_3, 22.32; Cl, 51.51.

Determination of ionization difference spectra. The procedure was essentially the same as those used by earlier workers.[12,13] A Cary recording spectrophotometer, model 11, was utilized for direct recording of the difference in spectra between equimolar solutions of the substrate at *p*H 1 and in 2*N* sodium hydroxide solution. The selection of the low *p*H value for the blank solution was based on the relatively high acidity of chlorinated catechols as well as on the absence of carboxylic acid groups.

Absence of the demethylation reaction in acidic hydrolysis and on treatment with hypochlorous acid. A solution of 0.08 g. of 4,5-dichloroveratrole in a mixture of 50 ml. of glacial acetic acid and 150 ml. of 0.1*N* hydrochloric acid was prepared and allowed to stand for a period of 2 days. During this time the ionization difference spectra were determined on aliquots withdrawn at various time intervals. Failure to obtain ionization spectra demonstrated the absence of acidic hydrolysis of methoxyl groups under the prevailing reaction conditions. A hypochlorous acid solution (2.5 g./l. Cl_2) at *p*H 5.4 was prepared by neutralizing chlorine water with calcium carbonate and subsequent filtration. A 25-ml. aliquot of this solution, mixed with 10 ml. of a saturated aqueous solution of 4,5-dichloroveratrole, caused no observable hydrolysis of the methoxyl groups.

Relative rates of electrophilic displacement and aromatic substitution. A stock solution of 2.007 g. of 3,4-dimethoxybenzyl alcohol in 250 ml. of distilled water was prepared. Twenty-five-milliliter aliquots of this solution were placed in each of five 100-ml. volumetric flasks and chlorine, dissolved in 0.1*N* HCl, applied in such amounts as to give the desired chlorine to substrate ratios. After 15 min. reaction time, the *p*H was adjusted to 7 ± 0.2 and the flasks diluted to volume with distilled water. Eighty milliliters of each sample was distilled into an ice-cooled 100-ml. measuring cyclinder containing a small amount of water, with the delivery tube extending below the surface of the water. After dilution to 100 ml., the formaldehyde was determined on a 10 ml. aliquot using the chromotropic acid method.[22] The blank consisted of a sample prepared from the 3,4-dimethoxybenzyl alcohol solution in exactly the same manner without treating it with chlorine. The chlorine to 3,4-dimethoxybenzyl alcohol molar ratios were 0.05, 0.10, 0.20, and 0.30 and the observed ratios of formaldehyde formed to total chlorine consumption 0.088, 0.102, 0.090, and 0.098, respectively.

SYRACUSE 10, N. Y.

(24) This compound was obtained as a gift from Professor H. Erdtman, Royal Institute of Technology, Stockholm, Sweden. The donation is hereby gratefully acknowledged.

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

Hydrogen Bromide–Acetic Acid Demethylation of 2,3-Dimethoxy-6-bromobenzoic Acid. An Example of Concomitant Bromine Migration[1,2]

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Demethylation of 2,3-dimethoxy-6-bromobenzoic acid in hydrogen bromide–acetic acid solution was shown to yield 2,3-dihydroxy-5-bromobenzoic acid. Under similar conditions, 3,4-dimethoxy-6-bromonitrobenzene was found to yield substantial amounts of the unrearranged product of demethylation, 3,4-dihydroxy-6-bromonitrobenzene, accompanied by 3,4-dihydroxynitrobenzene. The structural and environmental features which appear to influence halogen migration in the bromohydroxybenzoic series are summarized.

Although rearrangement reactions involving migration of a bromine atom are encountered infrequently, a number of well documented examples are now known.[3] An early instance of this type of reaction involved rearrangement of 2,6-dibromo-*N*-nitroaniline to 2-nitro-4,6-dibromoaniline in hydrochloric acid solution.[3a] Several years later, Sen[3b] described the conversion of 2-bromo-5-hydroxytoluene to 2,4-dinitro-5-hydroxy-6-bromotoluene with nitric acid, while treatment of *p*-bromoaniline with 48% hydrobromic acid at 150° was found to afford aniline and 2,4-dibromoaniline.[3c] Both hydrochloric and hydrobromic acids were found capable of transforming 5-bromo-6-methoxy-8-aminoquinoline to 6-methoxy-7-bromo-8-aminoquinoline.[3d] Recently, Tomita and Kugo[3h] reported the results of demethylation studies with 3,4-dimethoxy-6-bromobenzoic acid, (Ia) and its diethoxy (Ib) derivative. When the reaction was carried out with hydrogen bromide in glacial acetic acid at 120–125°, the product in each case was shown to be 3,4-dihydroxy-5-bromobenzoic acid (II). In a subsequent series of experiments, Tomita and collaborators[3i-k] obtained the same product (II) employing 2-bromo-3,4-dimethoxybenzoic acid (III). Further, 3-methoxy-6-bromobenzoic acid was found to yield 3-hydroxy-4-bromobenzoic acid. Analogous results were realized employing 48% hydrobromic acid as solvent. However, the use of hydriodic acid, hydrochloric acid, hydrogen chloride in glacial acetic acid, or anhydrous aluminum chloride led to either partial or complete demethylation without effecting a rearrangement. Substitution of chlorine for the bromine substituent, or an aldehyde, acetyl, or methyl group for the carboxylic acid moiety of Ia also prevented halogen migration. Rearrangement of the bromine substituent was again not observed when either 2-bromo-4-methoxy- or 3-bromo-4-methoxybenzoic acid was subjected to demethylation in hydrogen bromide–acetic acid solution.

The interesting work of Tomita and coworkers[3h-k] suggested that the following minimum requirements must be met before halogen migration can be expected to occur in the bromohydroxybenzoic acid series: (1) a bromine atom must be suitably situated *ortho* to a carboxylic acid group and either *ortho* or *para* to a potential hydroxy substituent, (2) the bromine atom must occupy a position in the original molecule that would not be favored by simple bromination of the corresponding phenol derivative, and (3) a source of bromide ion must be available.

As part of a study concerned with the synthesis of certain catechol derivatives, it was of interest to test the reliability of these criteria as a basis for predicting related bromine rearrangements. Hydrogen bromide–acetic acid demethylation of 2,3-dimethoxy-6-bromobenzoic acid (IV) was first selected as a model experiment, since all requirements for concurrent bromine migration seemed to be satisfied.

A synthesis of the required bromobenzoic acid (IV) from 2,3-dimethoxybenzaldehyde *via* the 6-nitrobenzoic acid derivative (V) was reported by

(1) Abstracted in part from the Master of Science thesis submitted by D. M. Piatak to the Graduate School, University of Maine, August 1959.

(2) This study was supported in part by the Upjohn Company, Kalamazoo, Mich., and aided by a grant from the American Cancer Society.

(3) For example, consult (a) K. J. P. Orton and C. Pearson, *J. Chem. Soc.*, 725 (1908); (b) A. B. Sen, *Proc. Natl. Acad. Sci. India*, **9**, 89 (1939) (*Chem. Abstr.*, **35**, 1038 (1941)); (c) R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.*, **63**, 1757 (1941); (d) W. M. Lauer, C. T. Claus, R. W. von Korff, and S. A. Sundet, *J. Am. Chem. Soc.*, **74**, 2080 (1952); (e) M. Kohn, *J. Org. Chem.*, **18**, 530 (1953); (f) B. G. Gavrilov and N. A. Mal'tseva, *Uchenye Zapiski Leningrad Gosudarst Univ. im. A. A. Zhdanova No. 169, Ser. Khim. Nauk*, No. **13**, 203 (1953) (*Chem. Abstr.*, **49**, 14658 (1955)); (g) E. Fujita, T. Kitamura, and R. Hirano, *Ychugaku Zasshi*, **77**, 747 (1957) (*Chem. Abstr.*, **51**, 17916 (1957)); (h) M. Tomita and T. Kugo, *Yahugaku Zasshi*, **75**, 1354 (1955) (*Chem. Abstr.*, **50**, 10052 (1956)); (i) M. Tomita, Y. Kondo, and S. Tanaka, *Yahugaku Zasshi*, **76**, 1119 (1956) (*Chem. Abstr.*, **51**, 3505 (1957)); (j) M. Tomita, Kura, and S. Tanaka, *Yahugaku Zasshi*, **76**, 1122 (1956) (*Chem. Abstr.*, **51**, 3505 (1957)); (k) M. Tomita and K. Fujitani, *Yahugaku Zasshi*, **76**, 1126 (1956) (*Chem. Abstr.*, **51**, 3506 (1957)); (l) M. Martin-Smith and M. Gates, *J. Am. Chem. Soc.*, **78**, 5351 (1956); and (m) H. L. Goering and L. L. Sims, *J. Am. Chem. Soc.*, **79**, 6270 (1957).

Sugasawa[4] in 1933 although the acid (IV) was found to be an oil and only its crystalline anilide derivative was characterized. In our hands, this reaction sequence again gave an oily product which resisted crystallization. However, saponification followed by methylation of the product (VI) derived from the bromination of methyl-2-acetoxy-3-methoxybenzoate (VII)[5] led to a crystalline acid melting at 87–89°. The anilide derivative (m.p. 140.5–141.5°) was found to be identical with the specimen prepared by way of intermediate V, thus establishing the fact that bromination of the ester (VII) affords a 6-bromo derivative.[6] The latter route was most convenient for preparative purposes and subsequent experimental work was carried out with crystalline 2,3-dimethoxy-6-bromobenzoic acid (IV) prepared by this procedure.

The reaction between hydrogen bromide and the acid (IV) in glacial acetic acid at *ca.* 140° was found to yield a bromophenol melting at 222–223°. However, the expected product of demethylation and bromine migration, 2,3-dihydroxy-5-bromobenzoic acid, was reported to melt at 215°.[7] The product (m.p. 222–223°) was easily distinguishable from an authentic sample of the 6-bromo (IX, m.p. 182–185°) isomer prepared by aluminum chloride demethylation of 2-hydroxy-3-methoxy-6-bromobenzoic acid (VI). Since rigorous structural evidence had never been provided to support the 5-bromo (VIIIa)[7] formulation, it could not be temporarily excluded in favor of the unknown 4-bromo isomer. For this reason, a sample assumed to be the 5-bromophenol (VIIIa) was prepared as described by von Hemmelmayr.[7] The product (VIIIa), m.p. 222–224° was identical with the bromophenol (m.p. 222–223°) isolated from the demethylation of 2,3-dimethoxy-6-bromobenzoic acid (IV). In order either to eliminate or establish the 5-bromo (VIIIa) representation for the demethylation product, von Hemmelmayr's isomer[7] (VIIIa) was remethylated with dimethyl sulfate and the product was compared with an authentic specimen of 2,3-dimethoxy-5-bromobenzoic acid (VIIIb) obtained by silver oxide oxidation of the corresponding aldehyde X.[8] The two substances were found to be identical. Consequently, hydrogen bromide–acetic acid demethylation of 2,3-dimethoxy-6-bromobenzoic acid (IV) yields 2,3-dihydroxy-5-bromobenzoic acid (VIIIa), the predicted product of concomitant bromine migration.

The apparent dependence of bromine migration upon the presence of an *ortho* carboxylic acid group prompted an experiment directed at further defining the role of the acid substituent. Treatment of 3,4-dimethoxy-6-bromonitrobenzene (XI) with hot hydrogen bromide–acetic acid was chosen for this purpose. Nitration[9] of 4-bromoveratrole[10] (XII) provided a practical route to the nitro compound XI.

The reaction between 3,4-dimethoxy-6-bromonitrobenzene (XI) and hydrogen bromide–acetic acid at approximately 140° afforded 3,4-dihydroxy-6-bromonitrobenzene (XIIIa) in 30–35% yields accompanied by a small quantity of 3,4-dihydroxynitrobenzene (XIVa). The bromophenol XIIIa could be isolated from the initial reaction products; however, the dehalogenated phenol XIVa was only detected after partial chromatographic separation of the acetylated (acetic anhydride–pyridine) reaction mixture. A cursory examination of the remaining complex mixture of acetates did not reveal the presence of the predictable product of bromine migration, 3-bromo-4,5-dihydroxynitrobenzene,[11] prepared by bromination of 4-nitrocatechol (XIVa).[12]

Bromination of catechol acetonide (XV) with *N*-bromosuccinimide followed by nitration of the resulting 4-bromo derivative XVI gave 3,4-(dimethylmethylenedioxy) - 6 - bromonitrobenzene (XVII). Acid hydrolysis of the acetonide (XVII) provided an authentic specimen of the bromophenol XIIIa[13] arising from simple demethylation of 3,4-dimethoxy-6-bromonitrobenzene (XI). In both cases the bromophenol XIIIa was characterized as the diacetate XIIIb.

The present study augments the possibility of employing the guides suggested above as a basis for determining the predisposition of certain bromohydroxybenzoic acids toward halogen migration. Additional work will be necessary before a reasonable delineation of the mechanism can be presented.

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(4) S. Sugasawa, *J. Chem. Soc.*, 1621 (1933).

(5) C. Weizmann and L. Haskelberg, *J. Org. Chem.*, **9**, 121 (1944).

(6) The structure of 2,3-dimethoxy-6-nitrobenzoic acid (V) rests with the ready conversion of 2,3-dimethoxy-6-nitrobenzaldehyde to an indigotin: W. H. Perkins, Jr., R. Robinson, and F. W. Stoyle, *J. Chem. Soc.*, 2355 (1924).

(7) F. von Hemmelmayr, *Montash.*, **33**, 971 (1913), prepared the 5-bromo (VIIIa) isomer by bromination of 2,3-dihydroxybenzoic acid.

(8) The bromodimethoxy acid VIIIb has been related to 2,3-dimethoxy-5-nitrobenzoic acid by L. Rubenstein, *J. Chem. Soc.*, 618 (1926), and structural evidence for the latter substance has been provided beyond doubt since decarboxylation yields 3,4-dimethoxynitrobenzene: J. C. Cain and J. L. Simonsen, *J. Chem. Soc.*, 156 (1914).

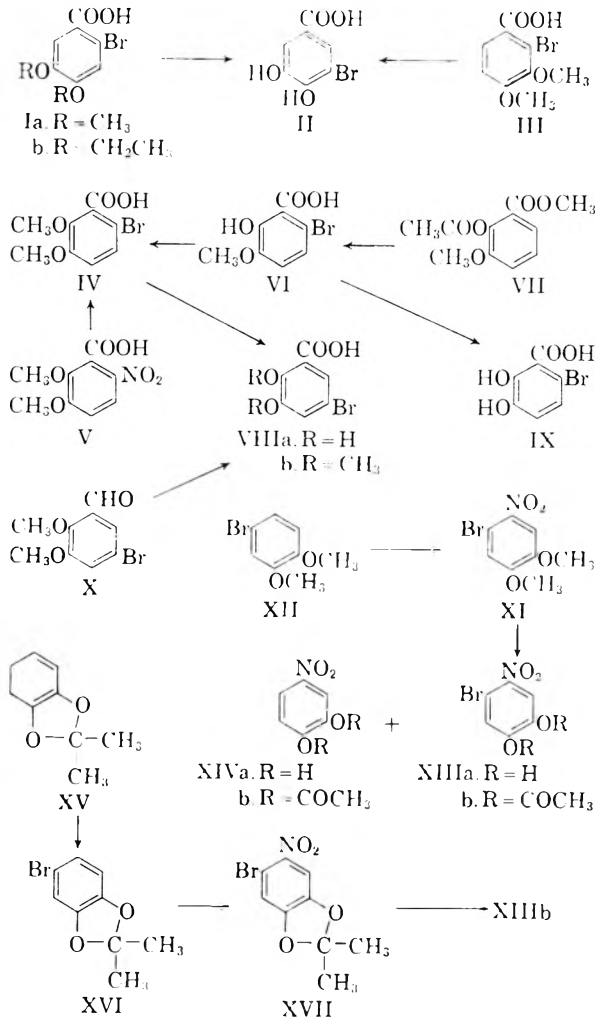
(9) A. Gaspari, *Accad. die Lincei Rend.*, **5**, I, 396 (1896) (*Chem. Zentr.*, **67**, (2) 154 (1896)).

(10) R. A. B. Bannard and G. Latremouille, *Can. J. Chem.*, **31**, 469 (1953).

(11) H. Cousin, *Ann. Chim. Phys.*, (7) **13**, 480 (1898).

(12) D. H. Rosenblatt, J. Epstein, and M. Levitch, *J. Am. Chem. Soc.*, **75**, 3277 (1953). After the present investigation was concluded K. Quelet and A. A. Ezz, *Bull. soc. chim. France*, 349 (1959), reported the hydrobromic acid demethylation of 3,4-dimethoxy-6-chloronitrobenzene. Only the product of demethylation, 3,4-dihydroxy-6-chloronitrobenzene, was isolated.

(13) R. G. Slooff, *Rec. trav. Chim.*, **54**, 995 (1935).



EXPERIMENTAL[14]

2,3-Dimethoxy-6-bromobenzoic acid (IV). *Procedure A.* Hydrogenation (3 atm.) of 2,3-dimethoxy-6-nitrobenzoic acid[6] (V, 1.5 g.) was carried out in ethanol (20 ml.) solution containing 3 drops of 48% hydrobromic acid with 75 mg. of 10% palladium-charcoal catalyst over a 1.75-hr. period. The mixture was filtered through Celite and treated with ethereal hydrogen bromide before removing the solvent *in vacuo*. A solution of the residue in 30 ml. of water was cooled to 5° and then allowed to react with sodium nitrite (0.55 g.) in 2 ml. of water. After allowing the diazotization mixture to remain at 5° an additional 45 min., a mixture containing copper (I) bromide, prepared from copper (II) sulfate (1.0 g.), 0.65 g. of copper powder, sodium bromide (2.6 g.), and 1 g. of sulfuric acid, was added. The resulting reaction mixture was stored at room temperature overnight before extraction with ether. The residue obtained by removing the solvent *in vacuo* was dissolved in chloroform and chromatographed on silica gel.[15] Seven fractions were eluted with the same solvent (160 ml. total). In each case, evaporation of solvent gave a dark colored oil which resisted crystallization; total yield 0.766 g. (44.7%). The chromatographic procedure was repeated and eight fractions were eluted with chloroform (85 ml. total). Evaporation of solvent from each fraction again gave oily residues; total weight 0.669 (38.8%). The latter three fractions (6–8, 0.204 g.) were combined and converted to the corresponding anilide derivative (thionyl chloride followed by aniline) which melted at 139–141°[16] (lit.,[4] m.p. 135–137°) after recrystallization from ethyl acetate–petroleum ether (b.p. 60–90°).

Procedure B. To 0.5 g. (0.002 mole) of 2-hydroxy-3-methoxy-6-bromobenzoic acid[5] and sodium hydroxide (0.2 g., 0.005 mole) dissolved in 50 ml. of water was added 0.5 ml (0.0054 mole) of dimethyl sulfate. At the conclusion of a 2-hr. period at reflux, the *p*H was adjusted to 11 with sodium hydroxide. Heating at reflux was continued an additional 2 hr. After cooling, the solution was acidified with hydrochloric acid and extracted with ether. Removal of solvent from the dry (magnesium sulfate) ethereal extract gave 0.5 g. (97.6%) of oily product which was partially purified by chromatography on silica gel.[16] Elution with chloroform (80 ml.) yielded 0.45 g. (85.1%) of colorless oil which crystallized after drying (*in vacuo*). Repeated recrystallization from benzene–petroleum ether (b.p. 30–60°) gave pure material melting at 87–89°,[16] ν_{max}^{KBr} 1708 cm.$^{-1}$

Anal. Calcd. for $C_9H_9BrO_4$: C, 41.40; H, 3.47; Br, 30.61. Found: C, 41.11; H, 3.42; Br, 31.12.

The anilide derivative, prepared as described in procedure A, was found to melt at 140.5–141.5°[16] after recrystallization from ethyl acetate–petroleum ether (b.p. 60–90°). Mixture melting point and infrared comparison (chloroform solution) of the anilide derivative with an authentic sample of 2,3-dimethoxy-6-bromobenzanilide (Procedure A) substantiated the assignment of structure IV to the crystalline acid (m.p. 87–89°).

Hydrogen-bromide–acetic acid demethylation of 2,3-dimethoxy-6-bromobenzoic acid (IV). A Pyrex glass tube containing 2,3-dimethoxy-6-bromobenzoic acid (0.93 g.) and 5 ml. of 41% hydrogen bromide–glacial acetic acid (sealed after adding the reactants at ice-salt temperature), was heated to 130° during 1.6 hr. and at 130–142° an additional 65 min. The tube was then cooled (45 min.), opened and the red-colored solution concentrated to dryness (*in vacuo*). The residue, m.p. 180–222° dec., recrystallized from methanol-chloroform as tan colored crystals; weight, 0.08 g. (9.6%), m.p. 190–210° (fraction A). Removal of solvent from the mother liquors and extraction of the residue with warm chloroform left a second fraction (B), 0.15 g. (18.1%), m.p. 219–222°. Evaporation of the chloroform extracts gave a third fraction (C); yield, 0.57 g. (68.7%), m.p. 194–203°. Recrystallization of fraction B from methanol-water afforded colorless crystals melting at 222–223° dec.,[16] ν_{max}^{KBr} 1665 cm.$^{-1}$

Anal. Calcd. for $C_7H_5BrO_4$: C, 36.07; H, 2.16; Br, 34.30. Found: C, 36.46; H, 2.23; Br, 33.86.

An infrared spectral study of the three crude fractions (A–C) indicated that only a small quantity of impurity existed. This observation was strengthened by further purification of fraction C, since recrystallization from water (Norit A) gave additional pure quantities of the product isolated from fraction B.

The product melting at 222–223° dec. was found to be identical with an authentic sample of *2,3-dihydroxy-5-bromobenzoic acid* (VIIIa)[7] by infrared comparison (tetrahydrofuran solution) and mixture melting-point determination.

Aluminum chloride demethylation of 2-hydroxy-3-methoxy-6-bromobenzoic acid (VI). A mixture of 2-hydroxy-3-methoxy-6-bromobenzoic acid (1.0 g.), anhydrous aluminum chloride (12.3 g.) and 80 ml. of dry benzene was heated at reflux during a 6-hr. period. An additional 7.5 g. of anhydrous aluminum chloride was added after 4 hr. at reflux and the reaction mixture cooled (ice bath) and cautiously treated with hydrochloric acid (50 ml.) and water (35 ml.). Extrac-

(14) Melting points are uncorrected and were observed employing a Fisher-Johns apparatus unless otherwise noted. The elemental analyses were provided by Dr. A. Bernhardt, Max-Planck-Institut, Mulheim, Germany. Infrared spectra were recorded by Messrs. E. Thomas and R. Young, Department of Chemistry, University of Maine.

(15) *Cf.* C. S. Marvel and R. D. Rands, Jr., *J. Am. Chem. Soc.*, **72**, 2642 (1950).

(16) Capillary tube melting point.

tion of the aqueous mixture with ether was preceded by separating and discarding the benzene solution. Removal of solvent from the dry ether extract afforded 0.85 g. (90.4%) of colorless crystals melting at 179–183° dec.[16] Repeated recrystallization from water gave an analytical sample,[17] m.p. 182–185° dec.,[16] ν_{max}^{KBr} 1642 cm.$^{-1}$

Anal. Calcd. for $C_7H_5BrO_4$: C, 36.08; H, 2.16; Br, 34.30. Found: C, 36.44; H, 2.27; Br, 34.19.

2,3-Dihydroxybenzoic acid. Anhydrous aluminum chloride (80 g.) was added to a solution of 2,3-dimethoxybenzoic acid[18] (18.7 g.) in 900 ml. of chlorobenzene and the mixture was heated at reflux. After 1 hr. an additional 30 g. of aluminum chloride was added and heating was continued for 2 hr. The residue, obtained by removing the solvent *in vacuo*, was cooled and cautiously treated with 800 ml. of hydrochloric acid. The brown colored product (11.2 g., m.p. 204–210°) was collected and reprecipitated from dilute sodium bicarbonate solution (Norit A). Recrystallization from water gave 8.3 g. (52.5%) of colorless crystals melting at 207–208°.[19]

2,3-Dihydroxy-5-bromobenzoic acid (VIIIa). A solution of 2,3-dihydroxybenzoic acid (3.0 g., 0.019 mole) in 100 ml. of glacial acetic acid was treated with 3.1 g. (0.019 mole) of bromine. Before removing the solvent *in vacuo*, the mixture was allowed to remain at room temperature for 24 hr. The colorless crystalline residue weighed 4.6 g. and melted at 215–222° after recrystallization from methanol-water; yield 3.2 g. (70.4%). A second recrystallization from the same solvent gave 2.5 g. melting at 222–224°.[16] Von Hemmelmayr[7] reported a melting point of 215° for the anhydrous compound and 187° for the hydrate.

Methylation of 2,3-dihydroxy-5-bromobenzoic acid (VIIIa). To 1.4 g. (0.006 mole) of 2,3-dihydroxy-5-bromobenzoic acid, obtained by bromination of 2,3-dihydroxybenzoic acid, and sodium hydroxide (1.4 g., 0.035 mole) in 30 ml. of water was added 2.2 g. (0.017 mole) of dimethyl sulfate. After 2 hr. at reflux, the mixture was adjusted to *p*H 11 with sodium hydroxide. Two additional hours at reflux followed by cooling and acidification with hydrochloric acid led to 1.1 g. (70.1%) of solid melting at 105–125°. Successive recrystallizations from water (Norit A) and benzene–petroleum ether (b.p. 60–90°) yielded colorless crystals, m.p. 118.5–120°.[16] The product was found to be identical (mixture melting point and infrared comparison) with an authentic sample of 2,3-dimethoxy-5-bromobenzoic acid (VIIIb) prepared as described below.

2,3-Dimethoxy-5-bromobenzoic acid (VIIIb). Sodium hydroxide (2.3 g., 0.057 mole) in 25 ml. of water was slowly added to a suspension of 2,3-dimethoxy-5-bromobenzaldehyde[20] (2.9 g., 0.012 mole) in a solution of silver nitrate (4.8 g., 0.028 mole) and water (50 ml.) heated at reflux. The mixture was filtered after 1 hr. at reflux and the filtrate acidified with concentrated hydrochloric acid. The colorless needles, 2.7 g. (87.4%) melting at 121–123°, were collected and recrystallized from water; yield 2.6 g. (84.1%), m.p. 122–124° (lit.,[21] m.p. 120°).

3,4-Dimethoxy-6-bromonitrobenzene (XI). A 10-g. sample of 4-bromoveratrole (XII),[10] b.p. 71–74° (0.07–0.10 mm.), was slowly added to a stirred solution of conc. nitric acid (70 ml.) and acetic acid (210 ml.) maintained at *ca.* 10°. After remaining at 15° for 1 hr., the mixture was diluted with water and the oily yellow product isolated by extraction with ether. Crystallization of the ethereal residue (11.1 g., 92.1%) from ethanol gave 9.9 g. (82%), m.p. 122–124° (lit.,[9] m.p. 124.5–125°).

Hydrogen bromide–acetic demethylation of 3,4-dimethoxy-6-bromonitrobenzene (XI). In a typical experiment, 3,4-dimethoxy-6-bromonitrobenzene (1.8 g.) was added to 7 ml. of 35% hydrogen bromide–glacial acetic acid solution contained in a cooled (ice-salt) Pyrex glass tube. The tube was sealed and heated at 141° during 1 hr. and then maintained at 140–142° for 50 min. before allowing the solution to cool (66 min.). Acetic anhydride–pyridine was added to the residue obtained by removing the solvent *in vacuo*, and the resulting solution was stored at room temperature overnight. Concentration to dryness *in vacuo* gave a pale yellow solid which led to colorless crystals, m.p. 116–120°, after recrystallization from benzene–petroleum ether (b.p. 60–90°); yield, 1.0 g. (45.8%). One additional recrystallization from the same solvent afforded 0.8 g. (36.7%) melting at 119–121°. A mixture melting-point determination and infrared spectral comparison (chloroform solution) with an authentic specimen of 3,4-diacetoxy-6-bromonitrobenzene (XIIIb, prepared as described below) was in complete accord with the assignment of formulation XIIIb to the product melting at 119–121°.

In several related experiments it was found that 3,4-dihydroxy-6-bromonitrobenzene (XIIIa) could be isolated directly in yields of 30–35% by crystallizing the crude reaction product from toluene (Norit A).

Evaporation of solvent from the mother liquors left an orange colored glass (1.2 g.) which resisted crystallization. Chromatography in 1:2 petroleum ether (b.p. 60–90°) benzene on 36 g. of Woelm neutral alumina, deactivated with 2.2 ml. of 10% acetic acid,[22] and elution with 75 ml. of the same solvent gave colorless crystals (0.21 g.) melting at 128–155°. Removal of solvent from a second fraction (50 ml.) yielded 0.56 g. of colorless crystals, m.p. 90–113°, while elution with two additional 50-ml. portions of the same solvent afforded 0.14 g., m.p. 68–75°, and 0.044 g. melting at 72–75°. Two recrystallizations of the latter residue from benzene–petroleum ether produced a pure sample of *3,4-diacetoxynitrobenzene* (XIVb), m.p. 80–81°. Identity was established by mixture melting-point determination and infrared comparison (chloroform solution) with an authentic sample (m.p. 80–81°, lit., [23,24] m.p. 78° and 84°). Initial attempts directed at further purification of the remaining mixture of acetates did not detect the presence of 3,4-diacetoxy-5-bromonitrobenzene, the predictable product of rearrangement, which had been prepared by acetylation (acetic anhydride–pyridine) of 3,4-dihydroxy-5-bromonitrobenzene.[11] After recrystallization from benzene–petroleum ether, an analytical sample of 3,4-diacetoxy-5-bromonitrobenzene melted at 110–111°, $\nu_{max}^{CHCl_3}$ 1786 cm.$^{-1}$

Anal. Calcd. for $C_{10}H_8BrNO_6$: C, 37.76; H, 2.54; Br, 25.12. Found: C, 37.80; H, 2.55; Br, 25.44.

3,4-(Dimethylmethylenedioxy) bromobenzene (XVI). A mixture of dimethylmethylenedioxybenzene[13] (XV, 3.0 g., 0.02 mole), *N*-bromosuccinimide (3.6 g., 0.02 mole) and 6 ml. of chloroform was heated at reflux during 6 hr. The mixture was diluted with ether and washed successively wth 2*N* sodium hydroxide and water. Removal of dry (sodium sulfate) solvent left an oily residue (3.9 g.). Distillation gave 3.4 g. (74.4%) of colorless oil, b.p. 97–102° (8 mm.). The main fraction (1.7 g.) boiled at 101–102° (lit.,[13] b.p. 122° at 20 mm.).

(17) The microanalysis of this sample was performed by Mr. Joseph F. Alicino, Metuchen, N. J.

(18) G. A. Edwards, W. H. Perkins, Jr., and F. W. Stoyle, *J. Chem. Soc.*, 195 (1925).

(19) W. H. Perkins, Jr., and V. M. Trikojus, *J. Chem. Soc.*, 2925 (1926).

(20) G. Stock and H. Conroy, *J. Am. Chem. Soc.*, **73**, 4743 (1951).

(21) W. Davies, *J. Chem. Soc.*, 1575 (1923).

(22) A subsequent experiment utilizing Merck acid-washed alumina gave comparable results. In both experiments, rapid chromatographic separation was essential, since extensive cleavage of the adsorbed acetates was found to occur when contact time was extended over a 2-hr. period.

(23) H. van Erp, *Ber.*, 64B, 2813 (1931).

(24) H. Burton and P. F. G. Praill, *J. Chem. Soc.*, 522 (1951).

3,4-Diacetoxy-6-bromonitrobenzene (XIIIb). A solution composed of 3,4-(dimethylmethylenedioxy)-6-bromonitrobenzene (XVII, 1.05 g.),[13] concd. hydrochloric acid (4 ml.) and dioxane was heated at steam bath temperature for 15 min. The solvent was removed (*in vacuo*) and replaced with acetic anhydride–pyridine. Heating (steam bath) was continued for 30 min. and the solid which separated upon cooling the acetylation mixture collected and discarded. Evaporation (*in vacuo*) of the filtrate to dryness and recrystallization of the residue, 0.91 g. (74.6%), from benzene (Norit A)–petroleum ether (b.p. 60–90°) gave a specimen of the acetate XIIIb, m.p. 120–122° (lit.,[13] m.p. 122°).

ORONO, ME.

[CONTRIBUTION FROM THE STAMFORD LABORATORIES, CENTRAL RESEARCH DIVISION, AMERICAN CYANAMID COMPANY]

Cyanoethylation. I. The Selective Cyanoethylation of 2-Aminoethanethiol Hydrochloride

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Over the *p*H range of 3.2 to 6.9 aqueous solutions of 2-aminoethanethiol hydrochloride react with acrylonitrile exclusively on the sulfhydryl group to give good yields of 3-(2-aminoethylthio)propionitrile hydrochloride. The selective sulfhydryl cyanoethylation is most rapid in the *p*H range of 6 to 6.9. In basic solutions a rapid and nonselective reaction is observed.

An obscure literature observation interpreted the fact that 2-aminoethanethiol (m.p. 99°[2]) melted nearly 30° higher than its hydrochloride (m.p. 70°[3]) as indicating that the free base existed as the Zwitterion Ib. This statement prompted us to utilize the cyanoethylation of 2-aminoethanethiol as a means of investigating this problem.

If the above rationalization is correct, then aqueous solutions of 2-aminoethanethiol, and similarly constituted mercaptoamines, should behave as shown. As the *p*H of the solution is increased the predominant species should pass from the ammonium salt (Ia) through the Zwitterion (Ib) to the free amine (Ic).

$$\underset{\text{Ia}}{HSCH_2CH_2NH_3^+} \rightleftharpoons \underset{\text{Ib}}{^-SCH_2CH_2NH_3^+} \rightleftharpoons \underset{\text{Ic}}{^-SCH_2CH_2NH_2}$$

From the accumulated data on the behavior of mercaptans and amines toward acrylonitrile, we would predict the following:

1. In strongly acid solution Ia would predominate and cyanoethylation either would not occur or would take place slowly and exclusively on sulfur.

2. As the *p*H is increased progressively more of Ib would be formed. The rate of the reaction should increase and reach a maximum at the *p*H corresponding to the isoelectric point. Addition should occur exclusively to the mercaptide anion.

3. In basic solution, where Ic would predominate, the reaction would, likewise, be rapid but completely nonselective.

To test these predictions, aqueous solutions of 2-aminoethanethiol covering the *p*H range 1.5–8.8 were allowed to react with excess acrylonitrile for at least one hour. The results are summarized in Table I.

At *p*H 1.5 no reaction was observed. At *p*H 3.6 a moderate reaction produced exclusively 3-(2-aminoethylthio)propionitrile hydrochloride as inferred from analytical data and failure of the product to give a color reaction with sodium nitroprusside.[4] The rate of the reaction increased, with retention of selectivity, up to *p*H 6.8 and, from our qualitative data, reached a maximum in the *p*H region 6–6.8.

In alkaline solution a fast, nonselective reaction produced an uncrystallizable sirup. To eliminate disulfide formation *via* air oxidation of 2-aminoethanethiol in alkaline solution, another reaction was run first at *p*H 6.4 then at *p*H 8.8. The same sirupy product was obtained.

The above evidence supports the postulate that aminoethanethiol exists as the internal salt both in the solid state and in solution and suggests that the cyanoethylation of similarly constituted aliphatic mercaptoamines[5] in slightly acid solutions should give good yields of the *S*-monocyanoethylated products.

EXPERIMENTAL

3-(2-Aminoethylthio)propionitrile hydrochloride. Acrylonitrile (63.6 g., 1.2 moles) was added at once to a stirred solution of 34 g. (0.3 mole) of 2-aminoethanethiol hydrochlo-

(1) Address correspondence to Department of Chemistry, John Carroll University, Cleveland 18, Ohio.

(2) S. Gabriel and J. Coleman, *Ber.*, **45**, 1643 (1912).

(3) E. J. Mills, Jr., and M. T. Bogert, *J. Am. Chem. Soc.*, **62**, 1173 (1940).

(4) M. D. Cheronis and J. B. Entriken, *Semimicro Qualitative Organic Analysis*, T. Y. Crowell Co., N. Y., 1947, p. 141.

(5) Mercapto-*t*-carbinamines might possibly be an exception since the cyanoethylation of *t*-carbinamines is acid catalyzed, *cf.*, L. S. Luskin, M. J. Culver, G. E. Gantert, W. E. Craig, and R. S. Cook, *J. Am. Chem. Soc.* **78**, 4042 (1956); E. Profft, *Ber.*, **90**, 1734 (1957).

TABLE I

CYANOETHYLATION PRODUCTS OF 2-AMINOETHANETHIOL

pH	Exotherm $^{\circ}_{max}$/min	Product	Yield, %	M.P.[a]
1.5	None	$HCl \cdot H_2NCH_2CH_2SH$[b]	—	69.5–70.3
3.6	36/30	$HCl \cdot H_2NCH_2CH_2SCH_2CH_2CN$	69	81.3–83.1
6.0	52/6	$HCl \cdot H_2NCH_2CH_2SCH_2CH_2CN$	81.4	81.5–83.5
6.8	52/<1	$HCl \cdot H_2NCH_2CH_2SCH_2CH_2CN$	77.8	77.5–78.8
8.8	52/<1	$NCCH_2CH_2SCH_2CH_2NHCH_2CH_2CN \cdot HCl$ $NCCH_2CH_2SCH_2CH_2N(CH_2CH_2CN)_2 \cdot HCl$	82.4[c]	Sirup

[a] All melting points are corrected. [b] Recrystallized from ethanol-ether. [c] Yield calculated as tricyanoethylation product.

ride[6] in 100 ml. of deionized water which had been adjusted to *p*H 6.8 with sodium hydroxide. A strongly exothermic reaction brought the temperature to 52° within 45 sec. After 60 min. the mixture was acidified with hydrochloric acid and vacuum concentrated (90°, 20 mm.) to a sirup. This was treated successively with several portions of ethanol-benzene, with removal of precipitated sodium chloride and further vacuum concentration, to give 50.6 g. (100%) of pale yellow sirup which crystallized on cooling. Recrystallization from ethanol-benzene afforded 38.9 g. (77.8%) of colorless crystals, m.p. 77.5–78.8°.

An analytical sample, m.p. 83.1–83.7°, was obtained after two recrystallizations from ethanol-benzene.

Anal. Calcd. for $C_5H_{11}N_2SCl$: C, 36.03; H, 6.65; N, 16.81. Found: C, 35.96; H, 6.62; N, 16.55.

3-(2-Aminoethylthio)propionic acid hydrochloride. A solution of 33.3 g. (0.2 mole) of 3-(2-aminoethylthio)propionitrile hydrochloride in 50 ml. of concd. hydrochloric acid was heated under reflux for 3 hr. The resulting solution was vacuum concentrated to a sirup which was dissolved in 100 ml. of boiling absolute ethanol. After removal of the precipitated ammonium chloride (9.4 g., 87.8%), the filtrate was again vacuum concentrated. Several successive treatments with ethanol-benzene and, finally, benzene alone gave 36 g. (97.1%) of crude acid, m.p. 116–120°. Recrystallization from ethanol-hexane afforded 27.4 g. (73.8%) of colorless crystals, m.p. 120.5–122.2°.

Analytical material, m.p. 124.7–125.3°, was obtained after two more recrystallizations from ethanol-hexane.

Anal. Calcd. for $C_5H_{12}ClNO_2S$: C, 32.34; H, 6.52; Cl, 19.10. N, 7.55; S, 17.27; Found: C, 32.55; H, 6.72; Cl, 18.83. N, 7.83; S, 17.33.

Hydrolysis of the product from reaction at pH 8.8. A solution of 42.5 g. of the uncrystallizable sirup in 100 ml. of concd. hydrochloric acid was heated under reflux for 4 hr. Upon chilling, 17.9 g. (74.6% of theory for tricyanoethylated product) of ammonium chloride was removed. Vacuum concentration of the filtrate gave 46.9 g. (94.7% of theory for tricarboxylic acid) of uncrystallizable yellow sirup.

Acknowledgment. The authors wish to thank Dr. Julius Kuck and the members of the Microanalytical Laboratory for their contributions.

STAMFORD, CONN.

(6) Obtained from Evans Chemetics, Inc., Waterloo, N. Y.

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Some Homologs of α,α-Dimethyl-β-phenethylamine

N. P. BUU-HOÏ AND L. PETIT

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A number of homologs of α,α-dimethyl-β-phenethylamine bearing substituents on the aromatic nucleus have been synthesized, starting from the corresponding benzyl chlorides, for investigation of their sympatho-mimetic activity. α,α-Dimethyl-β-(2-chlorophenyl)propionamide has been found to undergo Hofmann degradation to the corresponding symmetrical urea.

β-Arylethylamines containing a quaternary carbon atom *alpha* to the amine radical are interesting sympatho-mimetic substances with a wide range of secondary activities. The naphthyl derivatives, for instance, also possess local anesthetic properties greater than that of cocaine,[1] and *N*-methyl-α,α-dimethyl-β-phenethylamine is a valuable nasal shrinker causing no cerebral stimulation.[2]

It was deemed of interest to prepare a number of new β-arylethylamines for biological investigation, especially those bearing alkyl or halogen substituents on the aromatic nucleus. Recently, α,α-dimethyl-β-(3,4-dimethylphenethyl)amine was prepared in the course of a study of the Bischler-Napieralski reaction;[3] we now record the synthesis of two of its position isomers, starting from the chloromethylation-products of *m*- and *p*-xylene. These underwent Haller condensation[4] with isobutyrophenone in the presence of sodium amide to

(1) P. Cagniant, C. Mentzer, and N. P. Buu-Hoï, *Bull. Soc. Chim. France*, 10 [5], 145 (1943).

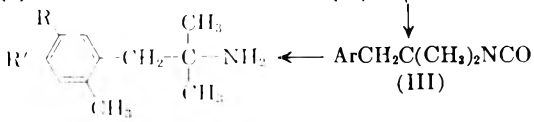
(2) *Cf.* A. Burger, *Medicinal Chemistry*, Interscience Publishers Inc., New York, 1951, p. 311.

(3) N. P. Buu-Hoï, C. T. Long, and N. D. Xuong, *J. Org. Chem.*, **23**, 12 (1958).

(4) A. Haller, *Bull. Soc. Chim. France*, **31**, [4], 1073 (1902).

the corresponding α,α-dimethyl-β-*m*- and α,α-dimethyl-β-*p*-xylylpropionylbenzene of general formula I; sodium amide cleavage of these tertiary ketones afforded α,α-dimethyl-β-*m*- and α,α-dimethyl-β-*p*-xylylpropionamide (general formula II), which in turn underwent Hofmann degradation[5] to yield α,α-dimethyl-β-*m*- and α,α-dimethyl-β-*p*-xylylethyl isocyanate (general formula III).

$$ArCH_2C(CH_3)_2COC_6H_5 \longrightarrow ArCH_2C(CH_3)_2CONH_2$$
(I) (II)

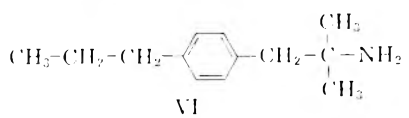


$$ArCH_2C(CH_3)_2NCO$$
(III)

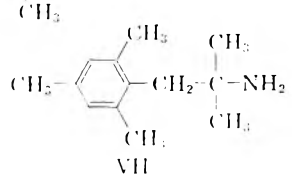
IV. R = H, R′ = CH_3
V. R = CH_3, R′ = H

These esters were readily hydrolyzed by hydrochloric acid to α,α-dimethyl-β-(2,4-dimethylphenethyl)amine (IV) and α,α-dimethyl-β-(2,5-dimethylphenethyl)amine (V).

Two higher homologs of these bases, namely α,α-dimethyl-β-*p*-propylphenethylamine (VI) and α,α-dimethyl-β-(2,4,6-trimethylphenethyl)amine (VII)



VI



VII

were prepared similarly, starting from the chloromethylation-products of propylbenzene and mesitylene. However, a similar synthesis with *o*-chlorobenzyl chloride as starting material was unsuccessful, as the Hofmann degradation of the corresponding propionamide led, not to the expected amine, but to the symmetrical urea (VIII). The formation of this compound is clearly due to a quick reaction between the isocyanate liberated and the amine resulting from its hydrolysis; an earlier example of such a reaction was recorded by Mentzer.[6]

$$[o\text{-}Cl\text{-}C_6H_4CH_2C(CH_3)_2NH]_2CO$$
VIII

The amines described herein are undergoing biological investigation, and results will be reported elsewhere.

EXPERIMENTAL

The experimental work was done with Miss O. Roussel.

Preparation of intermediates. *m*- and *p*-Xylene were chloromethylated according to the method of von Braun and Nelles,[7] as was propylbenzene (prepared by Kishner-Wolff reduction of propiophenone), which gave a 40% yield of *p-propylbenzyl chloride*, b.p. 205–207°, n_D^{24} 1.5534. Bert[8] reported the preparation of this compound without giving any data. The chloromethylation of mesitylene was performed according to Vavon and Bolle.[9]

Condensation of benzyl chlorides with isobutyrophenone. A solution of isobutyrophenone (0.1 mole) in 225 ml. of anhydrous toluene was refluxed with sodium amide (0.15 mole) for 10 hr.; after cooling, the substituted benzyl chloride (0.1 mole) was added, and refluxing was continued for 18 more hr. After cooling, the reaction mixture was treated with water and acidified with acetic acid, the toluene layer was decanted, washed with water, and dried over sodium sulfate, the solvent was removed, and the residue was vacuum-fractionated. Thus were obtained, in the form of pale yellow oils:

α,α-dimethyl-β-m-xylylpropionylbenzene (70% yield), b.p. 215–217°/25 mm., n_D^{25} 1.5629.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 85.7; H, 8.2.

α,α-dimethyl-β-p-xylylpropionylbenzene (60% yield), b.p. 197–200°/13 mm., $n_D^{18.5}$ 1.5699.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 85.9; H, 8.2.

α,α-dimethyl-β-(p-propylphenyl)propionylbenzene (40% yield), b.p. 210–212°/18 mm., n_D^{22} 1.5628.

Anal. Calcd. for $C_{20}H_{24}O$: C, 85.7; H, 8.6. Found: C, 85.4; H, 8.4.

α,α-dimethyl-β-(2,4,6-trimethylphenyl)propionylbenzene (52% yield), b.p. 226–228°/17 mm., n_D^{22} 1.5775.

Anal. Calcd. for $C_{20}H_{24}O$: C, 85.7; H, 8.6. Found: C, 85.3; H, 8.4.

α,α-dimethyl-β-o-chlorophenylpropionylbenzene (60% yield), b.p. 217°/17 mm., n_D^{23} 1.5902.

Anal. Calcd. for $C_{17}H_{17}OCl$: C, 74.9; H, 6.3. Found: C, 74.8; H, 6.2.

Haller cleavages of the propiophenones. A solution of ketone (0.1 mole) in 135 ml. of anhydrous toluene was refluxed with sodium amide (0.15 mole) for 24 hr., and the cooled reaction mixture was treated with water. The toluene solution was decanted, washed with water, and dried over sodium sulfate, the solvent was distilled off, and the residue was vacuum-fractionated. The following substances were obtained:

α,α-dimethyl-β-m-xylylpropionamide (60% yield), b.p. 205°/21 mm., needles (from petroleum ether), m.p. 56°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.1; H, 9.3; N, 6.8. Found: C, 76.2; H, 9.0; N, 7.0.

α,α-dimethyl-β-p-xylylpropionamide (85% yield), b.p. 196–198°/15 mm., leaflets (from petroleum ether), m.p. 60°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.1; H, 9.3; N, 6.8. Found: C, 75.9; H, 9.1; N, 6.9.

α,α-dimethyl-β-p-propylphenylpropionamide (45% yield), b.p. 206–208°/18 mm., n_D^{24} 1.5644, leaflets (petroleum ether), m.p. 43°.

Anal. Calcd. for $C_{14}H_{21}ON$: C, 76.7; H, 9.7; N, 6.4. Found: C, 76.5; H, 9.4; N, 6.3.

α,α-dimethyl-β-(2,4,6-trimethylphenyl)propionamide (60% yield), b.p. 207–208°/12 mm., n_D^{24} 1.5569.

Anal. Calcd. for $C_{14}H_{21}ON$: C, 76.7; H, 9.7; N, 6.4. Found: C, 76.8; H, 9.6; N, 6.7.

α,α-dimethyl-β-o-chlorophenylpropionamide (40% yield), b.p. 193–195°/14 mm., colorless prisms (cyclohexane), m.p. 76°.

Anal. Calcd. for $C_{11}H_{14}ONCl$: C, 62.4; H, 6.7. Found: C, 62.3; H, 6.6.

Hofmann degradation of the propionamides. An ice cold solution of potassium hypobromite (prepared from 25 g. of potassium hydroxide and 11 g. of bromine in 100 ml. of water) was shaken with the propionamide (0.05 mole) until two phases had formed (15 min.); the reaction product was

(5) *Cf.* M. Montagne and M. Casteran, *Compt. rend.*, 191, 139 (1930).

(6) C. Mentzer, *Compt. rend.*, 213, 581 (1941).

(7) J. von Braun, *Ber.*, 67, 1094 (1934).

(8) L. Bert, *Compt. rend.*, 186, 373 (1928).

(9) G. Vavon and C. Bolle, *Compt. rend.*, 204, 1826 (1937).

then taken up in ether, the ethereal solution washed with a few ml. of water and dried over sodium sulfate, the ether distilled, and the residue vacuum-fractionated. The following isocyanates were obtained, as colorless, pleasant-smelling oils:

α,α-dimethyl-β-m-xylylethyl isocyanate (46% yield), b.p. 151–152°/20 mm., n_D^{22} 1.5158.

Anal. Calcd. for $C_{13}H_{17}NO$: N, 6.9. Found: N, 6.5.

α,α-dimethyl-β-p-xylylethyl isocyanate (51% yield), b.p. 149–151°/20 mm., n_D^{22} 1.5172.

Anal. Calcd. for $C_{13}H_{17}NO$: N, 6.9. Found: N, 6.6.

α,α-dimethyl-β-(p-propylphenyl)ethyl isocyanate (47% yield), b.p. 145–147°/13 mm., n_D^{22} 1.5108.

Anal. Calcd. for $C_{14}H_{19}NO$: N, 6.5. Found: N, 6.2.

α,α-dimethyl-β-(2,4,6-trimethylphenyl)ethyl isocyanate (49% yield), b.p. 146–149°/13 mm.

Anal. Calcd. for $C_{14}H_{19}NO$: N, 6.5. Found: N, 6.2.

Hydrolysis of the isocyanates. The isocyanates (0.1 mole) were hydrolyzed by stirring on a water bath with a large excess of concd. hydrochloric acid (400 ml.), the reaction being manifest by a more or less rapid evolution of carbon dioxide. When this had terminated, the mixture was boiled until a totally limpid liquid was obtained; on cooling, water (250 ml.) was added, the liquid was made basic with 30% aqueous sodium hydroxide, and the reaction product was taken up immediately in ether. The ethereal solution was then washed with a minimum of water and dried over sodium sulfate, the solvent was removed, and the residue was vacuum-fractionated. The yields ranged from 30 to 88%. The following amines were obtained, as colorless oils, together with their hydrochlorides (prepared by saturating with hydrogen chloride a solution of the amine in ether, and crystallization of the precipitate from ethanol + benzene):

α,α-dimethyl-β-(2,4-dimethylphenethyl)amine (IV), b.p. 132–133°/22 mm., n_D^{20} 1.5231.

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.3; H, 10.8; N, 7.9. Found: C, 81.3; H, 10.6; N, 7.9.

Hydrochloride, colorless needles, m.p. 209° (sublimation above 170°).

Anal. Calcd. for $C_{12}H_{20}ClN$: Cl, 16.6; N, 6.6. Found: Cl, 16.8; 6.8.

α,α-dimethyl-β-(2,5-dimethylphenethyl)amine (V), b.p. 118°/15 mm., $n_D^{21.5}$ 1.5246.

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.3; H, 10.8; N, 7.9. Found: C, 81.3; H, 10.8; N, 7.9.

Hydrochloride, m.p. 230°.

Anal. Calcd. for $C_{12}H_{20}ClN$: Cl, 16.6; N, 6.6. Found: Cl, 16.5; N, 6.4.

α,α-dimethyl-β-p-propylphenethylamine (VI), b.p. 123–125°/14 mm., n_D^{22} 1.5182.

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.6; H, 11.1; N, 7.3. Found: C, 81.4; H, 10.9; N, 7.1.

Hydrochloride, m.p. 217° (sublimation above 166°).

Anal. Calcd. for $C_{13}H_{22}ClN$: Cl, 15.6; N, 6.2. Found: Cl, 15.5; N, 6.0.

α,α-dimethyl-β-(2,4,6-trimethylphenethyl)amine (VII), b.p. 130–131°/14 mm.

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.6; H, 11.1; N, 7.3. Found: C, 81.6; H, 10.9; N, 7.2.

Hydrochloride, m.p. 214° (sublimation above 175°).

Anal. Calcd. for $C_{13}H_{22}ClN$: Cl, 15.6; N, 6.2. Found: Cl, 15.8; N, 5.9.

N,N'(α,α-dimethyl-β-o-chlorophenethyl)urea (VIII). This compound was obtained as the sole product from the hydrolysis of the corresponding isocyanate, and crystallized from benzene in shiny colorless prisms, m.p. 224°.

Anal. Calcd. for $C_{21}H_{26}Cl_2N_2$: C, 64.1; H, 6.7; N, 7.1. Found: C, 64.1; H, 6.8; N, 7.0.

Acknowledgment. The authors thank the "Institut de Sérothérapie Hémopoïétique" and Dr. D. Sénac (Paris) for financial help.

PARIS (V^e), FRANCE

[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, ST. LOUIS RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

N-Substituted Glycinate and Alaninate Esters

A. J. SPEZIALE AND E. G. JAWORSKI

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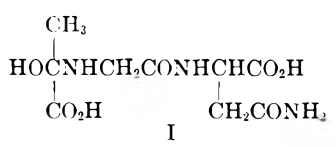
N-Substituted glycinate and α- and β-alaninate esters were prepared as possible antimetabolites for the control of *Fusarium* wilt diseases. Some qualitative results are presented on the relative ease of displacement of the α-halogen atom and aminolysis of the ester group in the reaction of haloacetate esters with primary aliphatic amines.

The pathogenicity of *Fusarium lycopersici* has been attributed to one of its metabolic products, lycomarasmin (I). Tomato wilt, an important economic plant disease, is caused by this organism. The toxic effects of I are also reproduced by the synthetic peptide serylglycylasparatic acid and reversed by serylglycylglutamic acid.[1]



I

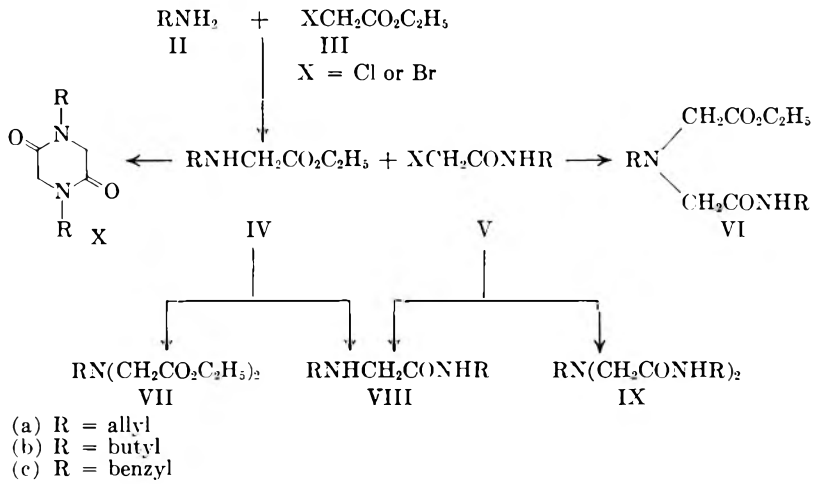
Since lycomarasmin is a tripeptide composed of asparagine, glycine, and α-hydroxyalanine units, it was felt that antimetabolites for the control of wilt diseases[2] might be found in *N*-substituted glycinates and alaninates. These amino acid derivatives might prevent the formation of the toxic agent, lycomarasmin. Growth inhibition of the fungus would also result if the biosynthesis of the tripeptide were essential to the *Fusarium* organism.

N-Substituted glycinates have been prepared by the alkylation of amines with haloacetates,[3] by reductive alkylation of aldehydes and ketones with

(1) J. W. Foster, *Chemical Activities of Fungi*, Academic Press Inc., New York, N. Y., 1949, p. 494.

(2) *Plant Diseases, The Year Book of Agriculture*, U. S. Dept. of Agriculture, Washington, D. C., 1953.

glycine,[4] by a modified Strecker synthesis,[5] and by alkylation of glycine with dialkyl sulfates.[6] Since our interest was mainly the preparation of *N*-monosubstituted glycinates (IV), a study of only the first of these methods was undertaken. Because of the numerous side reactions resulting from competitive reactions involving the displacement of the α-halogen atom and aminolysis of the ester group, yields of IV are about 50%. The yields or isolation of by-products such as VII–IX have not been reported by previous investigators.[3,7,8]



In the present study of the reaction of allyl-, butyl- and benzyl-amine with ethyl chloro- and bromoacetate, compounds of the type IV, VII–IX have been isolated. *N,N*-Disubstituted 2,5-diketopiperazines (X)[4a] were not isolated from among the reaction products but were formed in small amounts (*ca.* 5%) during storage of samples of IV for several months.

Allylamine and ethyl chloroacetate in ether at 0–5° gave only a 7% yield of ethyl *N*-allylglycinate (IVa) and a 72% yield of *N,N'*-diallylglycinamide (VIIIa). However, allylamine and ethyl bromoacetate, under the same conditions, gave a 75% yield of the alkylated product IVa. Butylamine and ethyl chloroacetate in refluxing benzene gave rise to three products: ethyl *N*-butylglycinate (IVb) in 12.5% yield, *N,N'*-dibutylglycinamide (VIIIb) in 50% yield and butylimino-bis-*N*-butylacetamide (IXb) in 26% yield. Ethyl bromoacetate and butylamine gave a 71% yield of IVb and a 16% yield of diethyl butyliminodiacetate (VIIb). Finally, benzylamine and ethyl chloracetate in refluxing benzene gave rise to a 61.5% yield of ethyl *N*-benzylglycinate (IVc) and only 10% yield of *N,N'*-dibenzyl glycinamide (VIIIc).

The course of reaction of allyl- and butylamine with ethyl chloro- and bromoacetate is clearly shown to be governed by the difference in lability of the halogen atoms. Aminolysis of the ester group and chloride displacement must have proceeded at about the same rate to account for the yields of products. If displacement proceeded much faster than aminolysis, at least a 50% yield of IVa or IVb should have been realized, based on the mole ratio of reactants used.

The effect of the nature of an electronegative α-substituent on the rate of aminolysis of aliphatic esters has been strikingly shown by Audrieth and Kleinberg.[9] Ethyl cyanoacetate afforded 96–100% yields of cyanoacetamide whereas ethyl acetate gave only 0–3% yields of amide under identical conditions.

It is interesting to compare the action of benzylamine with ethyl chloroacetate and butyl chloroacetate to give the respective glycine esters. The two reactions were performed similarly except that, in the former, the mixture was refluxed (79°) for one hour and, in the latter, it was held for four hours at 40–48°. The yield of glycinate ester was 61.5% for the ethyl ester and 31% for the butyl

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TABLE I

ETHYL *N*-SUBSTITUTED GLYCINATES

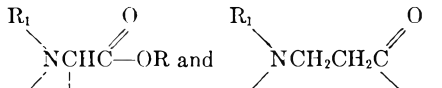
$R{\cdot}NHCH_2CO_2R'$

R	R′	Method	Yield, %	B.P.	Mm. Hg	n_D^{25}	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
i-C_3H_7	C_2H_5	B	39	46	4.0	1.4161	—	—	—	—	9.65	9.64
t-C_4H_9	C_2H_5	B	57	67	12.0	1.4206	—	—	—	—	8.80	8.74
n-$C_{12}H_{25}$	C_2H_5	A	46	160	2.7	1.4422	70.80	70.60	12.25	12.24	5.16	5.16
$CH_2{=}C(CH_3)CH_2$[a]	C_2H_5	A	65	76	10.0	1.4384	61.12	60.74	9.62	9.64	8.26	8.31
$(C_2H_5)_2NCH_2CH_2$	C_2H_5	B	45	78	1.1	1.4410	59.37	59.24	10.96	10.77	13.25	13.44
$CH_3O(CH_2)_3$	C_2H_5	A	70	63	0.6	1.4312	—	—	—	—	8.09	8.09
$C_2H_5O(CH_2)_3$	C_2H_5	B	57	75	0.5	1.4309	—	—	—	—	7.40	7.50
$C_6H_5CH(CH_3)$[b]	C_2H_5	A	59	85	0.25	1.5010	—	—	—	—	6.76	6.89
2,4-$Cl_2C_6H_3CH_2$[d]	C_2H_5	A	54	140	0.8	1.5342	—	—	—	—	27.05[c]	27.10
3,4-$Cl_2C_6H_3CH_2$[e]	C_2H_5	A	44	132	0.35	1.5327	—	—	—	—	27.05[c]	27.93
C_2H_5	$CH_2{=}CH{-}CH_2$	A	36	75	16.0	1.4357	58.72	58.18	9.15	9.11	9.78	9.49
$CH_2{=}CH{-}CH_2$	$CH_2{=}CH{-}CH_2$	A	50	89	13.0	1.4524	61.92	61.63	8.44	8.48	—	—
$C_6H_5CH_2$	$CH_2{=}CH{-}CH_2$	A	57	127	1.6	1.5142	70.22	70.08	7.37	7.29	6.83	6.77
$CH_2{=}CH{-}CH_2$[f]	C_4H_9	A	58	95	10.0	1.4383	63.12	63.22	10.01	9.97	8.18	8.24
$C_6H_5CH_2$[g]	C_4H_9	A	27	135	2.0	1.4962	70.56	70.49	8.65	8.74	6.33	6.52
$CH_2{=}CH{-}CH_2$[h]	$C_{12}H_{25}$	B	50	162	2.0	1.4508	—	—	—	—	4.94	4.79
$C_6H_5CH_2$	$C_{12}H_{25}$	B	88	—	—	1.4856	—	—	—	—	4.20	3.97

[a] *Picrate:* m.p. 77–78°. *Anal.* Calcd. for $C_{14}H_{18}N_4O_9$: C, 43.52; H, 4.70; N, 14.49. Found: C, 43.97; H, 5.01; N, 14.70. [b] *Hydrochloride:* m.p. 151–152°. *Anal.* Calcd. for $C_{12}H_{17}NO_2{\cdot}HCl$: Cl, 15.20. Found: Cl, 15.36. [c] Chlorine analysis. [d] *Hydrochloride:* m.p. 159–160°. *Anal.* Calcd. for $C_{11}H_{13}Cl_2NO_2{\cdot}HCl$: Cl, 35.63. Found: 35.64. [e] *Hydrochloride:* m.p. 206–207°. *Anal.* Calcd. for $C_{11}H_{13}Cl_2NO_2{\cdot}HCl$: Cl, 35.63. Found: Cl, 35.62. [f] *Picrate:* m.p. 94–95°. *Anal.* Calcd. for $C_{15}H_{20}N_4O_9$: C, 45.00; H, 5.04; N, 13.99. Found: C, 45.50; H, 5.17; N, 13.77. [g] *Hydrochloride:* m.p. 102–103°. *Anal.* Calcd. for $C_{13}H_{19}NO_2{\cdot}HCl$: N, 5.43; Cl, 13.75. Found: N, 5.45; Cl, 13.73. (N. L. Drake and S. Melamed, U. S. Patent 2,653,895.) [h] *Hydrochloride:* m.p. 97–98°. *Anal.* Calcd. for $C_{17}H_{33}NO_2{\cdot}HCl$: N, 4.38; Cl, 11.07. Found: N, 4.19; Cl, 11.26.

TABLE II

N-SUBSTITUTED ALANINATE ESTERS



XI XII

XI or XII	R	R_1	R_2	Yield, %	B.P.	Mm.	n_D^{25}	Nitrogen Analysis Calcd.	Nitrogen Analysis Found
XI	C_2H_5[a]	H	$CH_2{=}CH{-}CH_2$	41	68	11.0	1.4310	8.91	9.17
XI	C_2H_5		$-CH_2CH_2-$	—	32	1.0	1.4276	9.78	9.96
XII	C_2H_5		$-CH_2CH_2-$	88	75	13.0	1.4326	9.78	9.96
XII	C_4H_9		$-CH_2CH_2-$	88	85	4.5	1.4362	8.18	8.13
XII	$CH_3OCH_2CH_2$		$-CH_2CH_2-$	89	82	1.3	1.4432	8.09	8.19
XII	C_2H_5[b]	H	$CH_2{=}CHCH_2$	80	56	1.2	1.4390	8.52	8.91

[a] *Hydrochloride:* m.p. 95–96°. *Anal.* Calcd. for $C_8H_{15}NO_2{\cdot}HCl$: N, 7.23; Cl, 18.31. Found: N, 7.00; Cl, 18.36. [b] *Hydrochloride:* m.p. 82–83°. *Anal.* Calcd. for $C_8H_{15}NO_2{\cdot}HCl$: Cl, 18.32. Found Cl, 18.38.

ester. The butyl ester reaction gave a large high-boiling residue.

In contrast to the action of allylamine, diallylamine was ineffective in the aminolysis of ethyl chloroacetate. This reaction was performed in the presence of 8.4 mole percent of diallylamine hydrochloride in ethanol in the hope of catalyzing the aminolysis[10] of the ester group. The only product isolated was ethyl *N*,*N*-diallylglycinate.

In an attempt to repress side reactions in the preparation of glycinates of types IV, bases other than excess amine were studied. Triethylamine was used successfully in place of one mole excess of primary amine, but the yields in general were of the same order. The use of sodium carbonate and sodium acetate[11] lead to the isolation of over 50% yields of dialkylated products VII.

Tars were formed when either sodium hydroxide or a large excess of primary amine were used as the hydrogen halide scavengers.

(10) P. K. Glasoe and L. F. Audrieth, *J. Org. Chem.*, 4, 54 (1939); P. K. Glasoe, J. Kleinberg, and L. F. Audrieth, *J. Am. Chem. Soc.*, 61, 2387 (1939).

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The glycinates prepared during the course of this work and not reported previously are listed in Table I. α-(*N*-Substituted) alaninate esters were prepared from the α-bromoesters according to the procedure used for the glycinates. The β-alaninates were prepared by 1,4- addition of the amine to the appropriate acrylic ester. These new compounds are listed in Table II.

The fungicidal activities of the glycinates and alaninates are presented in Table III. Only the ethyl *N*-allyl- and *N*-benzylglycinates, their hydrochlorides, and the picrate of the benzyl derivative possessed activity. Modification of the ester grouping of *N*-allyl and *N*-benzyl glycinates resulted in a total loss in activity with the exception of allyl *N*-allylglycinate. Similarly, the ethyl α- or β-*N*-allylalaninates were without activity in these tests. From these results, it is apparent that the structural requirements for systemic fungicidal activity in the glycinate series are highly specific.

TABLE III

SYSTEMIC FUNGICIDAL ACTIVITY[a] OF *N*-SUBSTITUTED GLYCINATES AND ALANINATES

$RNHCH_2COOC_2H_5$		Activity Rating[b]
i-C_3H_7		N
CH_2=$CHCH_2$		E
CH_2=$CHCH_2$·HCl		E
t-C_4H_9		N
CH_2=$CH(CH_3)CH_2$		N
$(C_2H_5)_2NCH_2CH_2$—		N
$CH_3O(CH_2)_3$—		N
$C_2H_5O(CH_2)_3$—		N
C_6H_5—$CH(CH_3)$		N
$C_6H_5CH_2$—		E
$C_6H_5CH_2$—·HCl		E
$C_6H_5CH_2$—·picrate		E
2,4-$Cl_2C_6H_3CH_2$—		N
3,4-$Cl_2C_6H_3CH_2$—		N
$RNHCH_2COOR'$		
R	R′	
C_2H_5	CH_2=CH—CH_2—	N
CH_2=$CHCH_2$	CH_2=CH—CH_2—	P
$C_6H_5CH_2$—	CH_2=$CHCH_2$—	N
CH_2=$CHCH_2$	C_4H_9	N
$C_6H_5CH_2$—	C_4H_9	N
CH_2=$CHCH_2$	*n*-$C_{12}H_{25}$	N
$C_6H_5CH_2$—	*n*-$C_{12}H_{25}$	N
$RNHCH_2CH_2COOR'$		
R	R′	
CH_2=$CHCH_2$—	C_2H_5	N
CH_3		
RNH—CH—COOR′		
R	R′	
CH_2=$CHCH_2$—	C_2H_5	N

[a] The systemic test for the control of *Fusarium oxysporum* f-*lycopersici* in tomatoes is a modification of that by A. E. Dimond, *et al.*, *Connecticut Agr. Expt. Sta. Bull.*, 557 (1952). Chemicals were applied as foliage sprays at a concentration of 2500 p.p.m. rather than by the root soaking technique of Dimond. [b] N = no good; heavy vascular discoloration. P = promising; slight vascular discoloration. E = excellent; no vascular discoloration.

EXPERIMENTAL[12]

Glycinate esters. The method used for ethyl *N*-methallylglycinate is representative.

A solution of 21.3 g. (0.3 mole) of methallylamine, 30 g. (0.3 mole) of triethylamine and 200 ml. of ether or benzene was cooled to 0–5°. A solution of 47.5 g. (0.3 mole) of ethyl bromoacetate in 100 ml. of ether or benzene was added in 2.5 hr. at 0–5°. The mixture was allowed to warm to room temperature and stirred overnight. The triethylamine hydrobromide (92.5% recovery) was removed by filtration. After removal of the solvent, the product was distilled *in vacuo*. This procedure is designated as A in Table I; in procedure B, 2 equivalents of amine were used and triethylamine was omitted.

When anhydrous sodium carbonate was used in place of triethylamine as a hydrogen bromide scavenger only iminodiacetates were isolated. To a suspension of 53 g. (0.5 mole) of sodium carbonate and 29.6 g. (0.5 mole) of propylamine in 200 ml. of dry benzene, 83.5 g. (0.5 mole) of ethyl bromoacetate was added over about 2 hr. at 20–25°. The mixture was stirred overnight and the inorganic salts filtered. The solvent was removed and diethyl *N*-propyliminodiacetate was isolated in 77% yield; b.p. 127° (10 mm.), n_D^{25} 1.4346.

Anal. Calcd. for $C_{11}H_{21}NO_4$: N, 6.06. Found: N, 6.03.

The picrate was prepared in ethanol and recrystallized from hexane–ethyl acetate mixture: m.p. 83–84°.

Anal. Calcd. for $C_{17}H_{24}N_4O_{11}$: C, 44.23; H, 5.25; N, 12.14. Found: C, 44.24; H, 5.43; N, 12.10.

Diallyl N-ethyliminodiacetate was prepared similarly in 51.8% yield; b.p. 110° (0.9 mm.), n_D^{25} 1.4160.

Anal. Calcd. for $C_{12}H_{19}NO_4$: N, 6.07. Found: N, 6.05.

Diethyl N-ethylimidodiacetate was prepared in a similar manner in 45.5% yield. This compound was also formed in 54.8% yield when sodium acetate was used in place of carbonate; b.p. 113–115° (5.3 mm.), n_D^{25} 1.4247.

Anal. Calcd. for $C_{10}H_{19}NO_4$: N, 6.45. Found: N, 6.25.

Alaninate esters. The α-*N*-substituted alaninate esters were prepared according to Procedure A above. The β-*N*-substituted alaninate esters were prepared from the acrylate ester and amine as shown by this typical example for *butyl 1-aziridinepropionate.* Ethylenimine (12.9 g., 0.3 mole) was added to 38.4 g. (0.3 mole) of butyl acrylate at 20° during 0.5 hr. The reaction temperature was allowed to rise to 25–40° and held overnight. The aziridinepropionate was isolated by direct distillation. In some instances, absolute ethanol (100 ml./0.1 mole) was used as solvent.

Treatment of butyl 1-aziridinepropionate with anhydrous hydrogen chloride[13] in ether gave a 60% yield of *butyl β-(2-chloroethylamino)propionate hydrochloride*, m.p. 138–139°.

Anal. Calcd. for $C_9H_{18}ClNO_2$·HCl: ionic Cl, 14.52; total Cl, 29.34. Found: ionic Cl, 14.65; total Cl, 29.34.

Alkylation of amines. A. *Allylamine.* (1). *Ethyl chloroacetate.* A solution of 142 g. (2.5 moles) of allylamine and 122 g. (1.0 mole) of ethylchloroacetate in 300 ml. of ether was stirred at 0–5° for 5 hr., and allowed to stand at room temperature over the week-end. The ether layer was separated and the lower layer was extracted with ether and benzene. The solvents were combined, removed *in vacuo*, and the residue distilled. Two fractions were collected: Fraction I, b.p. 71–105° (8 mm.), n_D^{25} 1.4361; 10 g. (7% yield). Fraction II, b.p. 110–135° (2 mm.), n_D^{25} 1.4852 (15% yield).

Fraction I consisted chiefly of ethyl *N*-allylglycinate[3a] as shown by conversion to its hydrochloride; m.p. 115–116°.

Anal. Calcd. for $C_7H_{13}NO_2$·HCl: Cl, 19.74. Found: Cl, 19.84.

Fraction II was identified as *N,N′*-diallyl glycinamide by conversion to its hydrochloride; m.p. 128–129°.

Anal. Calcd. for $C_8H_{14}N_2O$·HCl: C, 50.39; H, 7.93; Cl, 18.59. Found: C, 50.25; H, 8.01; Cl, 18.70.

(12) We are indebted to A. Bybell, O. S. Kring, and J. L. O'Sullivan for the analyses.

(13) H. Bestian, *Ann.*, 566, 210 (1950).

The lower layer, after extraction with ether and benzene, was dissolved in chloroform and neutralized with sodium hydroxide. Separation and evaporation of the chloroform left 70 g. (57% yield) of *N,N'*-diallylglycinamide. The hydrochloride melted at 127–128°. A mixture melting point with the hydrochloride of Fraction II was not depressed.

(2). Ethyl bromoacetate. A solution of 114 g. (2.0 moles) of allylamine and 167 g. (1.0 mole) of ethyl bromoacetate in 500 ml. of ether was stirred at 5–10° during 3 hr. and then overnight at room temperature. Allylamine hydrobromide (97% recovery) was collected on a filter. The solvent was removed and the residue distilled to give 104 g. (73% yield) of ethyl *N*-allyl glycinate [b.p. 88–89° (30 mm.), n_D^{25} 1.4351]. The hydrochloride melted at 115–116° and was shown to be identical with that from Fraction I above by mixture melting point.

B. *Butylamine.* (1). *Ethyl chloroacetate.* A solution of 168 g. (2.3 moles) of butylamine in 1 l. of benzene was treated with 122 g. (1.0 mole) of ethyl chloroacetate at 25–30° during 1 hr. The solution was heated at reflux for 2 hr. Butylamine hydrochloride did not precipitate during the reaction period. The solution was made alkaline with sodium hydroxide and the organic layer was separated. The residue after removal of the solvent was distilled and yielded two fractions: Fraction I, b.p. 87–93° (15.5 mm.), n_D^{25} 1.4240, 15.5 g. (12.5% yield); Fraction II, b.p. 121–127° (0.55 mm.), n_D^{25} 1.4551, 75.5 g. (50% yield).

Fraction I consisted chiefly of ethyl *N*-butylglycinate as shown by conversion to its hydrochloride: m.p. 186–187°.

Anal. Calcd. for $C_8H_{17}NO_2$·HCl: C, 49.10; H, 9.27; Cl, 18.14; N, 7.15. Found: C, 49.16; H, 9.36; Cl, 18.38; N, 7.11.

Fraction II was shown to be *N,N'*-dibutyl glycinamide by conversion to its hydrochloride; m.p. 172–173°.

Anal. Calcd. for $C_{10}H_{22}N_2O$·HCl: C, 53.98; H, 10.35; Cl, 15.95; N, 12.60. Found: C, 53.84; H, 10.45; Cl, 16.02; N, 12.62.

The residue (46.5 g., 26% yield) which remained after distillation of Fraction I and II consisted of butyliminobis(*N*-butylacetamide) which was converted to its hydrochloride, m.p. 95–96°.

Anal. Calcd. for $C_{16}H_{33}N_3O_2$·HCl: C, 57.09; H, 10.20; Cl, 10.56; N, 12.52. Found: C, 56.60; H, 10.46; Cl, 10.62; N, 12.19.

Ethyl *N*-butylglycinate is reported[14] to have been prepared in 56.5% yield [b.p. 174–175° (20 mm.), n_D^{25} 1.4600] from ethyl chloroacetate and butylamine. The compound is undoubtedly *N,N'*-dibutylglycinamide.

(2). *Ethyl bromoacetate.* When butylamine was treated with ethyl bromoacetate according to the procedure as given for ethyl chloroacetate, a 94% recovery of butylamine hydrobromide was realized. There was obtained a 71% yield of ethyl *N*-butylglycinate [b.p. 52° (1.1 mm.), n_D^{25} 1.4236] and a 16% yield of diethylbutyliminodiacetate [b.p. 100–105° (1.1 mm.), n_D^{25} 1.4350], whose picrate melted at 94–95°. The hydrochloride formed as an oil.

Anal. Calcd. for $C_{18}H_{26}N_4O_{11}$: C, 45.59; H, 5.51; N, 11.81. Found: C, 45.82; H, 5.70; N, 11.60.

The above method of preparation is essentially that of Fugger, Tien, and Hunsberger[3b] but the iminodiacetate was not reported.

C. *Benzylamine.* Treatment of benzylamine with ethyl chloroacetate, as in the alkylation of butylamine, afforded a 61% yield of ethyl *N*-benzylglycinate[15]; b.p. 106° (0.9 mm.); n_D^{25} 1.5041 (picrate, m.p. 166–168°).

The residue from the distillation was dissolved in ethyl acetate, filtered, and saturated with hydrogen chloride. There was obtained about 10% yield of the *N,N'*-dibenzylglycinamide hydrochloride, m.p. 244–245°.

Anal. Calcd. for $C_{16}H_{18}N_2O$·HCl: C, 66.09; H, 6.59; Cl, 12.20; N, 9.65. Found: C, 66.58; H, 6.77; Cl, 12.34; N, 9.55.

D. *Diallylamine.* To 200 ml. of absolute ethanol containing 0.042 mole of hydrogen chloride, there was added 48.5 g. (0.5 mole) of diallylamine and 61 g. (0.5 mole) of ethyl chloroacetate. The mixture was held at 1–2° for 18 hr. and then at 24° for 24.5 hr. Samples were removed periodically and titrated for amine and chloride ion. The increase in chloride ion and decrease in amine concentrations were proportional at both temperatures and reached constant values of 0.25 mole each. Thus, aminolysis of the ester group was negligible. Alkylation was the predominant reaction. At the end of the reaction period, the mixture was poured into water and extracted with ether. There was obtained 0.19 mole (38% recovery) of ethyl chloroacetate, and 0.17 mole (68% yield on ester consumed) of ethyl *N,N*-diallylglycinate, b.p. 112–114° (0.35 mm.), n_D^{25} 1.4448, neut. equiv. 184 (theory neut. equiv. 183).

Saponification of the diallyl glycinate with 20% potassium hydroxide at reflux for 2 hr. afforded a 65% yield of *N,N*-diallylglycine, m.p. 109–110°. The melting point was not depressed on admixture with an authentic sample (m.p. 109–110°) prepared from diallylamine and chloroacetic acid.

Anal. Calcd. for $C_8H_{13}NO_2$: N, 9.02. Found: N, 9.19.

Acknowledgments. We are indebted to Dr. A. J. Suhovecky for valuable discussions and fungicidal testing of the compounds. The assistance of Dr. K. W. Ratts in the preparation of various compounds is gratefully acknowledged.

St. Louis 66, Mo.

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

Fluorinated Aromatic Amino Acids. I. *o*-, *m*-, and *p*-Trifluoromethylphenylalanines[1]

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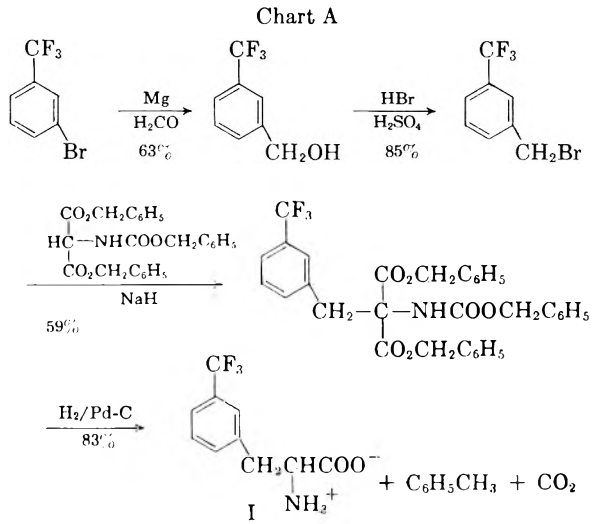
o-, *m*-, and *p*-Trifluoromethyl-*dl*-phenylalanines have been synthesized as part of a study of the effect of the trifluoromethyl group on the physical properties and physiological activity of aromatic amino acids. The *m*-amino acid was prepared in an over-all yield of 25% from *m*-bromobenzotrifluoride using the carbobenzyloxyaminomalonate method. This route failed for the preparation of the *o*-trifluoromethyl amino acid. All three amino acids were obtained *via* the corresponding unsaturated azlactones. The trifluoromethyl group exhibited remarkable hydrolytic stability under the strongly acidic conditions employed during these procedures.

Aromatic amino acids substituted with fluorine atoms in the aromatic nucleus have been prepared previously and have been shown to possess significant physiological activity. Thus, Schiemann and Winkelmuller[2] and later, English, Mead, and Niemann,[3] synthesized 3-fluoro-*dl*-tyrosine. May and Litzka[4] reported that this compound inhibited tumor growth in animals in which carcinoma had been experimentally induced. The three fluoro-*dl*-phenylalanines and 5-fluoro-*dl*-tryptophan, have also been prepared.[5-7]

We now wish to report the synthesis of the *o*-, *m*-, and *p*-trifluoromethyl-*dl*-phenylalanines as part of a study of the physical properties and physiological activity of trifluoromethyl aromatic amino acids.

m-Trifluoromethyl-*dl*-phenylalanine (I) was obtained in 25% overall yield *via* the method outlined in Chart A:

Chart A



I

m-Trifluoromethylbenzyl alcohol, prepared from the readily available *m*-bromobenzotrifluoride, was smoothly converted in 85% yield to the benzyl bromide by refluxing with 48% hydrobromic acid and concentrated sulfuric acid for six hours. There was no evidence of any hydrolysis of the trifluoromethyl group to carboxyl under these conditions. This is in contrast to several reports that the trifluoromethyl group is labile under strongly acid conditions.[8] It has been our experience that longer reflux periods are often required to effect this hydrolysis. The nature of other nuclear substituents also plays an important role.

m - Trifluoromethylbenzyl bromide was then treated with dibenzyl carbobenzyloxyaminomalonate[9] in refluxing toluene in the presence of sodium hydride to give a 59% yield of the condensation product. This material was readily converted to I in 83% yield by hydrogenolysis using palladium on charcoal. This debenzylation and decarboxylation step was similar to that described by Kissman and Witkop.[10]

o-Trifluoromethylbenzyl bromide was prepared from *o*-chlorobenzotrifluoride[11] *via* the benzyl al-

(1) This work was supported by a grant (CY-2879) from the National Cancer Institute, National Institutes of Health, USPHS. Presented in part at the 136th National Meeting of the American Chemical Society, Atlantic City, N. J., September 1959.

(2) G. Schiemann and W. Winkelmuller, *Ber.*, **66B**, 727 (1933).

(3) J. English, J. J. Mead, and C. Niemann, *J. Am. Chem. Soc.*, **62**, 350 (1940).

(4) N. May and G. Litzka, *Z. Krebsforsch.*, **48**, 376 (1939); *Chem. Abstr.*, **33**, 4662 (1939).

(5) G. Schiemann and M. Roselius, *Ber.*, **65**, 1439 (1932).

(6) H. K. Mitchell and C. Niemann, *J. Am. Chem. Soc.*, **69**, 1232 (1947).

(7) H. Rinderknecht and C. Niemann, *J. Am. Chem. Soc.*, **72**, 2296 (1950).

(8) (a) M. Hauptschein, E. A. Nodiff, and A. J. Saggiomo, *J. Am. Chem. Soc.*, **76**, 1051 (1954); (b) H. Gilman and D. Blume, *J. Am. Chem. Soc.*, **65**, 2467 (1943); (c) G. M. LeFave, *J. Am. Chem. Soc.*, **71**, 4148 (1949); (d) P. M. Maginnity and C. A. Gaulin, *J. Am. Chem. Soc.*, **73**, 3579 (1951).

(9) We wish to thank Dr. Marcel Harnik of Chemetron Corp., Newport, Tenn., for a sample of this material which was prepared from the diethyl ester by refluxing with excess benzyl alcohol in the presence of sodium hydride. Kissman and Witkop (ref. 10) prepared the dibenzyl ester by the reaction of dibenzylaminomalonate with benzyl chlorocarbonate.

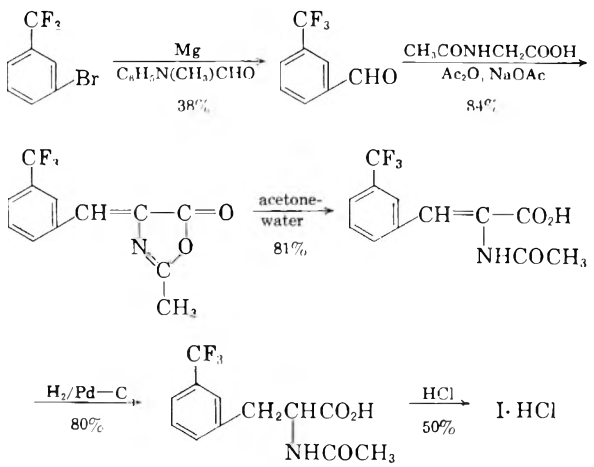
(10) H. M. Kissman and B. Witkop, *J. Am. Chem. Soc.*, **75**, 1967 (1953).

(11) *o*- and *p*-Chlorobenzotrifluoride were generously supplied by Hooker Electrochemical Co.

cohol. Attempted condensation of this bromide with dibenzyl carbobenzyloxyaminomalonate under several reaction conditions failed to yield an isolable product. It seems possible that the *o*-trifluoromethyl group may cause steric retardation of the condensation. No attempt was made to prepare *p*-trifluoromethyl-*dl*-phenylalanine by this procedure.

The successful synthesis of all three isomeric trifluoromethyl-*dl*-phenylalanines as their hydrochlorides was accomplished *via* the azlactone route which has been employed for *dl*-phenylalanine.[12] The free amino acids were then obtained by passing the hydrochloride salts through a column containing Dowex-3, a weakly basic ion-exchange resin. The method used is illustrated for the *m*-trifluoromethyl isomer (I) in Chart B.

Chart B



The preparation of *m*-trifluoromethylbenzaldehyde from the bromo Grignard reagent and *N*-methylformanilide has been described.[13] Our yield of 38% of pure aldehyde however, was considerably lower than the 52–59% previously reported.[13] It should be mentioned that autoxidation of this aldehyde to *m*-trifluoromethylbenzoic acid occurred within several hours at room temperature, so that the reaction with aceturic acid to form 2-methyl-4-(*m*-trifluoromethylbenzylidene)-5(4H)-oxazolone was carried out as soon as the aldehyde had been distilled. The azlactone ring was readily opened by refluxing with an acetone-water mixture to form α-acetamido-β(*m*-trifluoromethylphenyl) acrylic acid in 81% yield. Catalytic hydrogenation gave α-acetamido-β(*m*-trifluoromethylphenyl)propionic acid. The acetamido group was then hydrolyzed by refluxing with concentrated hydrochloric acid for ten hours to form the amino acid I as its hydrochloride. The trifluoromethyl group once again remained intact throughout the procedure.

When hippuric acid was substituted for aceturic acid in the azlactone synthesis and the subsequent steps carried out, it was found that the final hydrolysis of the benzamido group to give I could not be readily effected. Therefore, the *ortho*- and *para*-substituted amino acids were also obtained from the acetamido compounds.

The *ortho*-isomer was prepared by analogous reactions starting with *o*-chlorobenzotrifluoride.[11] The preparation of the Grignard reagent required the use of tetrahydrofuran in place of ether and the yield of aldehyde was only 20–25%.

An attempt to form this aldehyde from *o*-trifluoromethylphenyllithium was unsuccessful, although carbonation gave a good yield of *o*-trifluoromethylbenzoic acid, in agreement with Roberts and Curtin.[14] *p*-Trifluoromethylphenylmagnesium chloride was even more difficult to prepare although many sets of reaction conditions were tried. The difficulties may be due in large measure to the passivity of the surface of magnesium. Results were inconsistent, although we were successful in several small runs in isolating small amounts of *p*-trifluoromethylbenzoic acid after carbonation. These results are in agreement with those reported previously.[15] Attempts to form the organolithium compound using lithium dispersion or *n*-butyllithium, failed, however. The *para*-aldehyde was satisfactorily prepared from the Grignard reagent formed from *p*-bromobenzotrifluoride,[16] and the amino acid subsequently obtained *via* the azlactone.

The physical properties of these new "unnatural" amino acids are being examined and will be reported separately. The possibility that these compounds may exhibit physiological activity as amino acid antimetabolites is also being explored.

EXPERIMENTAL[17]

m-Trifluoromethylbenzyl alcohol. *m*-Bromobenzotrifluoride (112.5 g., 0.5 mole) in 100 cc. of dry ether was added dropwise to a mixture of 18 g. of magnesium in 200 cc. of dry ether. After the reaction subsided, stirring was continued for 1 hr. Paraformaldehyde (30 g.) was introduced into the system according to the procedure of Gilman[18] to produce 55 g. of product. The alcohol distilled at 86° (3 mm.) n_D^{21} 1.4597, yield 63% (lit.,[19] b.p. 100° (10 mm.), n_D^{25} 1.4574, yield 38%).

Anal. Calcd. for $C_8H_7OF_3$: C, 54.55; H, 4.01. Found: C, 54.63; H, 3.93.

m-Trifluoromethylbenzyl bromide. *m*-Trifluoromethylbenzyl alcohol (35.2 g.) was heated under reflux with 88 g. of 48%

(12) *Org. Synthesis*, Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y. (1943), p. 491.

(13) H. Gilman, L. Tolman, F. Yeoman, L. A. Woods, D. A. Shirley, and S. Avakian, *J. Am. Chem. Soc.*, 68, 426 (1946).

(14) J. D. Roberts and D. Y. Curtin, *J. Am. Chem. Soc.*, 68, 1658 (1946).

(15) H. E. Ramsden, A. E. Balint, W. R. Whitford, J. J. Walburn, and R. Cserr, *J. Org. Chem.*, 22, 1202 (1957).

(16) M. Markarian, *J. Am. Chem. Soc.*, 74, 1858 (1952).

(17) Melting points are uncorrected. Analyses by Micro-Tech Laboratories, Skokie, Ill.

(18) *Org. Synthesis*, Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y. (1941), p. 188.

(19) H. H. Szmant, J. F. Anzenberger, and R. Hartle, *J. Am. Chem. Soc.*, 72, 1419 (1950).

aqueous hydrobromic acid and 13 cc. of concd. sulfuric acid for 6 hr. Evidence of reaction could be observed since the alcohol layer was less dense and the organic bromide layer more dense than the aqueous layer. The bromide layer was separated, washed with concd. sulfuric acid to remove unchanged benzyl alcohol, washed twice with water, and dried. Distillation gave 41 g. (85%) of bromide, b.p. 69° (4 mm.) n_D^{25} 1.4895. This compound is a strong lachrymator.

Dibenzyl m-trifluoromethylbenzylcarbobenzyloxyaminomalonate. In a dry 250-cc. 3-necked flask, fitted with a stirrer and reflux condenser connected to a mercury-filled bubble counter, and swept with dry nitrogen, was placed 9.0 g. of *m*-trifluoromethylbenzyl bromide and 0.9 g. of sodium hydride to which was added a hot solution of 16.3 g. of dibenzyl carbobenzyloxyaminomalonate[10] in dry toluene. The mixture was heated under reflux for 45 min., the solution cooled and a few cc. of glacial acetic acid added, followed by 3 cc. of ethanol (to dissolve the unchanged sodium hydride). Fifty cc. of water and 50 cc. of ether were added, the mixture shaken, and the organic layer was separated, washed with water, and taken to dryness *in vacuo* to give 13.1 g. (59%) of a white solid, recrystallized from petroleum ether, m.p. 88–88.5°.

Anal. Calcd. for $C_{33}H_{28}NO_6F_3$: C, 67.00; H, 4.77. Found: C, 67.27; H, 4.96.

m-Trifluoromethylphenylalanine. The hydrogenolysis of the condensation product using palladium on charcoal in glacial acetic acid yielded the amino acid. Two recrystallizations from 95% ethanol gave a slightly impure product. The final purification was effected by sublimation at 160° and 1 mm. pressure. The amino acid, obtained in 83% yield, decomposed at 219–222°.

Anal. Calcd. for $C_{10}H_{10}HO_2F_3$: C, 51.50; H, 4.32; N, 6.01. Found: C, 51.40; H, 4.28; N, 6.25.

o-Trifluoromethylbenzyl alcohol. *o*-Chlorobenzotrifluoride[11] (91 g., 0.5 mole), 13 g. of dry magnesium turnings, 5 cc. of ethyl bromide (used as an "entrainer"), and 200 cc. of tetrahydrofuran were stirred vigorously. The exothermic reaction proceeded smoothly after an induction period. One hour after the tetrahydrofuran stopped refluxing, paraformaldehyde (30 g.) was introduced into the system to produce 30 g. (34%) of product, b.p. 82–83° (3.5 mm.), $n_D^{25.5}$ 1.4657; α-naphthyl urethan, m.p. 129.5–130.5°.

Anal. Calcd. for $C_{19}H_{14}NO_2F_3$: C, 66.08; H, 4.09. Found: C, 66.03; H, 4.18.

3,5-Dinitrobenzoate, m.p. 73–73.5°.

Anal. Calcd. for $C_{15}H_9N_2O_6F_3$: C, 48.66; H, 2.45. Found: C, 48.24; H, 2.55.

o-Trifluoromethylbenzyl bromide. *o*-Trifluoromethylbenzyl bromide, b.p. 72° (7.5 mm.), n_D^{25} 1.4961 was prepared in 80% yield in a manner similar to that used for *m*-trifluoromethylbenzyl bromide.

Anal. Calcd. for $C_8H_6F_3Br$: C, 40.19; H, 2.53. Found: C, 40.40, H, 2.56.

Attempted condensation of o-trifluoromethylbenzyl bromide with dibenzyl carbobenzyloxyaminomalonate. The procedure described above for the *meta-* analog gave a brown oil in this case. The oil failed to crystallize and similar procedures using dimethylformamide and tetrahydrofuran as solvents were also unsuccessful. An attempt to prepare the α-amino acid by hydrogenolysis of this oily material yielded an oil which gave a negative ninhydrin reaction.

m-Trifluoromethylbenzaldehyde. *m*-Trifluoromethylbenzaldehyde was prepared in 38% yield according to the procedure of Gilman and co-workers,[13] b.p. 80–82° (21 mm.), n_D^{20} 1.4659 (lit.,[13] b.p. 64–66° (10 mm.), n_D^{20} 1.4660, yield 52–59%).

o-Trifluoromethylbenzaldehyde. Method A. The Grignard reagent was formed as before from 0.5 mole of *o*-chlorobenzotrifluoride. One hour after the tetrahydrofuran had stopped refluxing, 68 g. of *N*-methylformanilide were added as rapidly as the rate of reflux would permit. The mixture was stirred for an additional hour. Aqueous sulfuric acid (10%) was carefully added in sufficient quantity to decompose the aldehyde complex and unchanged magnesium. The aqueous layer was separated from the tetrahydrofuran layer, extracted with ether and the extract added to the tetrahydrofuran. The organic layer was neutralized with 10% aqueous sodium bicarbonate, then washed twice with water, dried over anhydrous magnesium sulfate, filtered, and the filtrate concentrated on a steam bath. The liquid residue was distilled to give 18 g. (20%) of amber-colored aldehyde boiling at 61–67° (16 mm.), n_D^{25} 1.4640.

Method B. *o*-Trifluoromethylbenzyl bromide (*vide supra*) (24 g., 0.10 mole) was added to a solution formed from 100 cc. of absolute ethanol, 2.3 g. of sodium and 11.6 g. of 2-nitropropane according to the procedure of Hass and Bender[20] to yield 6 g. (35%) of aldehyde, b.p. 72° (20 mm.), n_D^{25} 1.4640.

p-Trifluoromethylbenzaldehyde. *p*-Bromobenzotrifluoride[16] (40 g.) in 50 cc. of dry ether was added dropwise to a mixture of 10 g. of magnesium in 100 cc. of dry ether after a 3-hr. induction period. After the reaction subsided, stirring was continued for 1 hr. *N*-Methylformanilide (24 g.) was added as quickly as the exothermic reaction would permit and after 1 hr. of stirring the product was isolated in a manner similar to that used for the corresponding *ortho-* aldehyde (Method A), to yield the *para-* aldehyde (40%), b.p. 64.5° (13 mm.), n_D^{20} 1.4630 (lit.[20] b.p. 66–67° (13 mm.), n_D^{20} 1.4630).

(a) *2-Phenyl-4-o-trifluoromethylbenzylidene-5-oxazolone;* (b) *2-phenyl-4-m-trifluoromethylbenzylidene-5-oxazolone.* Freshly distilled *o*-trifluoromethylbenzaldehyde (5 g.), 5.5 g. of hippuric acid, 8.5 g. of acetic anhydride, and 2.4 g. of sodium acetate were treated according to the usual procedure for preparation of unsaturated azlactones[21] to give a 33% yield of the azlactone, yellow crystals, m.p. 132.5–133.5°.

Anal. Calcd. for $C_{17}H_{10}NO_2F_3$: C, 64.35, H, 3.18. Found: C, 64.26, H, 3.24.

The *m*-trifluoromethyl azlactone was prepared similarly, in 79% yield, m.p. 138.5–139°.

Anal. Calcd. for $C_{17}H_{10}NO_2F_3$: C, 64.35; H, 3.18. Found: C, 64.76; H, 3.33.

(a) *α-Benzamido-β(o-trifluoromethylphenyl) acrylic acid;* (b) *α-benzamido-β(m-trifluoromethylphenyl) acrylic acid.* The two oxazolones were hydrolyzed with 10% sodium hydroxide, followed by acidification to give acid a in 79% yield, m.p. 184–185° and acid (b) (74%) m.p. 214–215°. Both compounds were recrystallized from acetone-water mixtures.

Anal. Calcd. for $C_{17}H_{13}NO_3F_3$: C, 60.90; H, 3.61. Found, compound (b): C, 60.81; H, 3.63.

(a) *2-Methyl-4-o-trifluoromethylbenzylidene-5-oxazolone;* (b) *2-methyl-4-m-trifluoromethylbenzylidene-5-oxazolone;* (c) *2-methyl-4-p-trifluoromethylbenzylidene-5-oxazolone.* Freshly prepared *m*-trifluoromethylbenzaldehyde[13] (41 g.), 18.6 g. of aceturic acid, 42 g. of acetic anhydride, and 9.6 g. of sodium acetate were mixed and heated according to a previously described procedure[22] to yield 2-methyl-4-*m*-trifluoromethylbenzylidene-5-oxazolone (b) in 84% yield, m.p. 130–131°. The *ortho-* substituted azlactone (*a*), prepared similarly in 30% yield, melted at 116–117°. The *p*-trifluoromethyl azlactone (*c*) m.p. 113.5–114.5°, was obtained in 80% yield.

Anal. Calcd. for $C_{12}H_8NO_2F_3$: C, 56.48; H, 3.16. Found: *ortho-* compound: C, 56.28; H, 3.14; *meta-* compound: C, 56.90; H, 3.31; *para-* compound: C, 56.39; H, 3.25.

(a) *α-Acetamido-β(o-trifluoromethylphenyl) acrylic acid;* (b) *α-acetamido-β(m-trifluoromethylphenyl) acrylic acid;* (c) *α-acetamido-β(p-trifluoromethylphenyl) acrylic acid.* The oxazolones described above (10 g.) were hydrolyzed in a solvent

(20) H. B. Hass and M. L. Bender, *J. Am. Chem. Soc.*, **71**, 1767 (1949).

(21) *Org. Syntheses*, **Coll. Vol. II**, John Wiley and Sons, Inc., New York, N. Y. (1943), p. 55.

(22) *Org. Syntheses*, **Coll. Vol. II**, John Wiley and Sons, Inc., New York, N. Y. (1943) p. 1.

consisting of 96 cc. of acetone and 38 cc. of water[22] to yield 53% of (*a*), m.p. 180–181°, 81% of (*b*), m.p. 225–226° and 59% of (c), m.p. 201.5–202.5°. The acids were recrystallized from acetone-water.

Anal. Calcd. for $C_{12}H_{10}NO_3F_3$: C, 52.75; H, 3.69. Found: *ortho-* compound: C, 53.24; H, 4.02; *meta-* compound: C, 52.51; H, 3.76; *para-* compound: C, 52.83; H, 3.56.

(a) *N-Acetyl-o-trifluoromethylphenylalanine;* (b) *N-acetyl-m-trifluoromethylphenylalanine;* (c) *N-acetyl-p-trifluoromethylphenylalanine;* (d) *N-benzoyl-o-trifluoromethylphenylalanine and* (e) *N-benzoyl-m-trifluoromethylphenylalanine.* In a typical reaction, 10 g. of the substituted acrylic acid was dissolved in 95% ethanol to which was added 1 g. of 5% palladium on charcoal. The mixture was shaken for 3 hr. in the presence of 40 lb. pressure of hydrogen. After filtering the mixture, the colorless filtrate was concentrated *in vacuo* and the solid residue recrystallized from acetone-water to yield 8 g. of product: (*a*) m.p. 179–180°, (*b*) m.p. 132–133°, (c) m.p. 178–178.5°, (*d*) m.p. 172–173°, and (*e*) m.p. 167–168°.

Anal. Calcd. for $C_{12}H_{12}NO_3F_3$: C, 52.36; H, 4.40. Found, compound (*b*): C, 52.49; H, 4.42.

Anal. Calcd. for $C_{17}H_{14}NO_3F_3$: C, 60.53; H, 4.18. Found, compound (*e*): C, 60.59; H, 4.05.

(a) *o-Trifluoromethylphenylalanine hydrochloride;* (b) *m-trifluoromethylphenylalanine hydrochloride;* (c) *p-trifluoromethylphenylalanine hydrochloride.* In a typical reaction, 5 g. of the *N*-acetylphenylalanine was hydrolyzed with 100 cc. of concd. hydrochloric acid under reflux for 10 hr. After concentrating the aqueous mixture, a white crystalline solid separated. The pure amino acid hydrochloride was dried *in vacuo*. A second crop of less pure product was obtained on further concentration. The total yield was 2.5 g. (51%). The *N*-benzoyl analogs were much more resistant to hydrolysis under a variety of conditions and no amino acids could be isolated. The decomposition points of the *o-*, *m-*, and *p*-trifluoromethyl amino acid hydrochlorides were 190–195°, 199–202°, and 196–203°, respectively.

Anal. Calcd. for $C_{10}H_{11}NO_2F_3Cl$: C, 44.54; H, 4.11; N, 5.19. Found: *o*-amino acid: C, 44.32; H, 4.15; N, 5.05; *m*-amino acid: C, 44.56; H, 4.23; N, 5.03; *p*-amino acid: C, 44.76; H, 3.92; N, 4.65.

(a) *o-Trifluoromethylphenylalanine;* (b) *m-trifluoromethylphenylalanine;* (c) *p-trifluoromethylphenylalanine.* In a typical conversion, 1 g. of the amino acid hydrochloride was dissolved in 50 cc. of hot water and the resulting solution passed through a column of Dowex-3 (a weakly basic ion-exchange resin). Hot water was then passed through the column until amino acid could no longer be detected in the eluate (ninhydrin test). The eluate gave a negative test for chloride ion. The solution was distilled *in vacuo* on a steam bath and the resulting solid collected and dried.

CHICAGO 16, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WEST VIRGINIA UNIVERSITY]

Condensation Reactions of a Nitro Group. II.[1] Preparation of Phenanthridine-5-oxides and Benzo(c)cinnoline-1-oxide[2]

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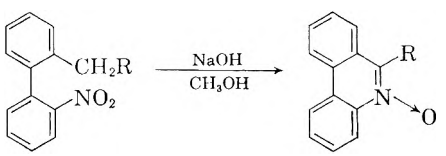
Additional examples in the biphenyl series of the condensation of a nitro group in the 2-position with an activated methylene group in the 2′-position in the presence of methanolic sodium hydroxide have been found. The additional activating groups are benzoyl and benzenesulfonyl; the phenyl group did not serve as an activator. Apparently, the benzoyl and benzenesulfonyl compounds underwent ring closure followed by nucleophilic displacement reactions by hydroxide ion to produce benzoate and benzenesulfinate ions, respectively. 2-Amino-2′-nitrobiphenyl reacted with both sodium hydroxide and sodium methoxide in methanol to yield benzo(c)cinnoline-1- oxide. The intramolecular reaction of a nitro group was not observed in appropriate test compounds outside the biphenyl series.

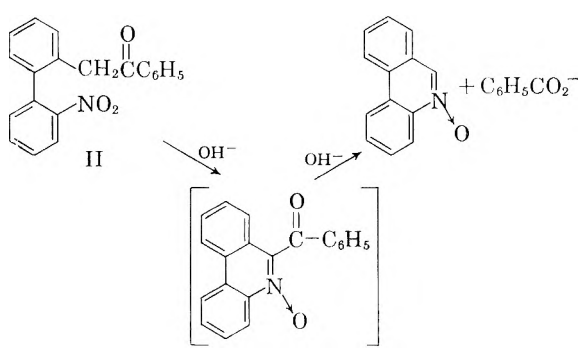
DISCUSSION

Recently it was reported[1] that certain biphenyls of the following type react with methanolic sodium hydroxide to form 6-substituted phenanthridine-5-oxides. The present paper deals with syntheses and testing of additional compounds to determine more about the generality of the foregoing ring closure reaction.



Type I R = CN, CO_2CH_3, $CONH_2$

Three more type I compounds have been treated with methanolic sodium hydroxide. First, with R as benzoyl in 2-(benzoyl)methyl-2′-nitrobiphenyl (II) ring closure occurred to produce phenanthridine-5-



(1) Paper I, C. W. Muth, J. C. Ellers, and O. F. Folmer, *J. Am. Chem. Soc.*, **79**, 6500 (1957).

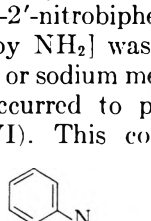
(2) Supported by the National Science Foundation Research Grant G-4236, whose help we wish to gratefully acknowledge. In part from the master's thesis of R. B. Wotring, 1958, and N. Abraham, 1960, both from West Virginia University.

oxide and sodium benzoate in nearly quantitative yields. Although it could not be isolated, apparently 6-benzoylphenanthridine-5-oxide formed as an intermediate and underwent a nucleophilic displacement reaction on the carbonyl carbon by the hydroxide ion. The foregoing cleavage reaction may be considered as analogous to those undergone by *beta*-keto esters and *beta*-diketones.[3] Efforts to oxidize 6-benzoylphenanthridine[4] with peracetic acid to 6-benzoylphenanthridine-5-oxide were unsuccessful.

Second, with R as benzenesulfonyl in 2-(2′-nitrophenyl)benzyl phenyl sulfone (III), a ring closure occurred and the products isolated were 6-hydroxyphenanthridine-5-oxide and/or its tautomer, *N*-hydroxyphenanthridone, and benzenesulfinic acid as 2,4-dinitrodiphenyl sulfone.[5] In this case 6-benzenesulfonylphenanthridine-5-oxide was probably an intermediate which underwent a nucleophilic displacement at the 6- position by the hydroxide ion to produce 6-hydroxyphenanthridine-5-oxide or its tautomer[6] and the benzenesulfinate ion. This postulate is different from the one made for the benzoyl compound where the attack was considered to occur on the carbonyl carbon.

Third, with R as phenyl in 2-benzyl-2′-nitrobiphenyl (IV) no ring closure occurred with sodium hydroxide or sodium methoxide in methanol. This was not surprising because the phenyl group is not as strong an electron-attracting group[7] as the carbonyl and sulfonyl groups. Only the stronger electron-attracting groups have been found to be activators for the ring closure.[1]

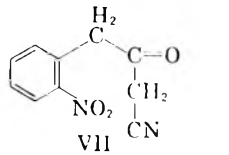
When 2-amino-2′-nitrobiphenyl (V) [CH_2R of type I replaced by NH_2] was treated with either sodium hydroxide or sodium methoxide in methanol a ring closure occurred to produce benzo(c)cinnoline-1-oxide (VI). This condensation reaction



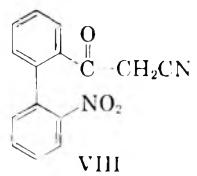
VI

between the nitro and amino groups required about two hours, which is much longer than the time required for the condensation reaction between the nitro and methylene groups. The foregoing was not unexpected because benzo(c)cinnoline-1-oxide (VI) has been prepared[8] by the chemical reduction of 2,2′-dinitrobiphenyl in the presence of sodium hydroxide.

The intramolecular reaction of a nitro group with a methylene group in the presence of methanolic sodium hydroxide *did not* occur with 4-(2′-nitrophenyl)-3-butanonitrile (VII) or [2-(2′-nitrophenyl)] benzoylacetonitrile (VIII). Likewise, in contrast to the behavior of 4-chloro-2-nitrophenylurea,[9] *o*-nitrophenylacetamide did not react intramolecularly with 30% sodium hydroxide.



VII



VIII

The new compounds prepared and characterized in this work are: 2-(benzoyl)methyl-2′-nitrobiphenyl (II); 2-(2′-nitrophenyl)benzyl phenyl sulfide (X); 2-(2′-nitrophenyl)benzyl phenyl sulfone (III); 2-nitro-2′-benzylbiphenyl (IV); ethyl 4-(2′-nitrophenyl)-3-keto-2-cyanobutanoate (IX); 4-(2′-nitrophenyl)-3-ketobutanonitrile (VII); ethyl [2-(2′-nitrophenyl)]benzoylcyanoacetate (XI); [2-(2′-nitrophenyl)]benzoylacetonitrile (VIII); 2-nitro-2′-acetylbiphenyl (XII); 2,4-dinitrophenylhydrazone and semicarbazone of XII.

EXPERIMENTAL[10]

2-(Benzoyl)methyl-2′-nitrobiphenyl (II). When 2-nitro-2′-biphenylacetyl chloride[11] prepared from 3.00 g. (0.0117 mole) of 2-nitro-2′-biphenylacetic acid and thionyl chloride was mixed with 18 ml. of carbon disulfide and 3.0 g. (0.0224 mole) of aluminum chloride a red oil separated. Five minutes later 8 ml. of benzene and 8 ml. of carbon disulfide were added. After 20 min. the mixture was boiled for 2 min. and then poured onto ice and conc. hydrochloric acid. The resulting mixture was extracted with ether. The ether extract was washed with cold 10% hydrochloric acid, 5% sodium bicarbonate, water, and saturated sodium chloride solution. After filtering through Drierite the solution was concentrated by distillation. The residue crystallized to a yellow solid (3 g.) after most of the benzene had been removed.

The bicarbonate solution was acidified to yield 0.20 g. of starting acid, m.p. 113–120°.

The yellow solid was dissolved in hot benzene and treated with decolorizing charcoal. To this filtrate was added 95% ethanol. After the mixture was cooled 1.24 g. (36%) of II as nearly white crystals, m.p. 98–100°, separated. After

(3) Jack Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp. 292–295.

(4) H. Gilman and J. Eisch, *J. Am. Chem. Soc.*, **79**, 4425 (1957).

(5) J. D. Loudon, *J. Chem. Soc.*, **537** (1935).

(6) This material (calcd. for $C_{19}H_{13}NO_2$: C, 73.92%; H, 4.30%; N, 6.63%. Found: C, 74.06%; H, 4.44%; N, 6.69%), was the same, as described by mixed melting point and infrared spectrum, as that obtained and characterized by Shih-Tsung Chiang, master's thesis, West Virginia University, 1959, in an independent study. This work will be reported later.

(7) G. E. K. Branch and M. Calvin, *The Theory of Organic Chemistry*, Prentice Hall, Inc., New York, N. Y., 1941, Chap. VI.

(8) F. E. King and T. J. King, *J. Chem. Soc.*, 824 (1945).

(9) F. J. Wolf, R. M. Wilson, Jr., K. Pfister III, and M. Tischler, *J. Am. Chem. Soc.*, **76**, 4611 (1954).

(10) All melting points are uncorrected unless otherwise stated. All microanalyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn. All infrared absorption values are in μ. We wish to thank Miss Patricia Estep for the infrared data taken in potassium bromide wafers.

(11) C. W. Muth, W. L. Sung, and Z. B. Papanastassiou, *J. Am. Chem. Soc.*, **77**, 3393 (1955).

three crystallizations from methanol pale yellow crystals were obtained, m.p. 98–100°, infrared absorption at 5.95 C=O, 6.65 and 7.45 μ NO_2 (chloroform).

Anal. Calcd. for $C_{20}H_{15}NO_3$; C, 75.68; H, 4.76; N, 4.41. Found: C, 75.68; H, 4.74; N, 4.45.

When the foregoing reaction was conducted at reflux temperature for 5 hr., none of II was isolated.

2-(Benzoyl)methyl-2′-nitrobiphenyl (II) *and Sodium Hydroxide.* As 0.27 g. (0.0068 mole) of sodium hydroxide in 6 ml. of methanol was added to a slurry of 2-(benzoyl)methyl-2′-nitrobiphenyl (II) in 6 ml. of methanol the solution color changed from yellow to orange-yellow. In 4 min. the temperature rose from 29 to 33°. The mixture was shaken intermittently. After 10 min. of reaction time the solid had dissolved; after 13 min. of reaction time the solution was cooled with ice water; and after 20 min. of reaction time 0.50 g. (25%) of light pink phenanthridine-5-oxide, m.p. 223–226° (lit.,[1] m.p. 226–228°), m.m.p. 223–226°, was filtered.

The filtrate was concentrated by warming under reduced pressure to yield a purple solid which became tan after washing with water. The tan phenanthridine-5-oxide weighed 0.115 g. (57%), m.p. 220–224°, m.m.p. 222–225°, and its infrared spectrum was the same as the spectrum of phenanthridine-5-oxide. The picrate of this product melted at 193–198° (lit.,[1] m.p., 198–200°).

The filtrate from the tan material was extracted with chloroform, acidified and extracted with ether. The ether solution was dried and concentrated by distillation to a residue which was sublimed to yield 0.80 g. (63%) of benzoic acid, m.p. 117–120°, m.m.p. with authentic benzoic acid showed no depression of the former. An additional 0.023 g. (17%) of slightly less pure benzoic acid was also obtained.

The chloroform extract yielded 0.03 g. of buff solid, m.p. 205–217°, m.m.p. with first crop 215–224°.

In a similar experiment with the initial temperature at 32° the yield of phenanthridine-5-oxide obtained by filtering the reaction mixture after 8 min. was 40%. The total yield of oxide after completing the isolation process was 96%.

From another experiment in which the reactants were refluxed for 1 hr., phenanthridine-5-oxide, m.p. 219–227° (88%) and benzoic acid, m.p. 115–120° (91%) were obtained.

2-(2′-Nitrophenyl)benzyl phenyl sulfide (X). In duplicate experiments adapted from the procedure of Bost *et al.*,[12] 4.00 g. (0.100 mole) of sodium hydroxide was added to 11.5 g. (0.104 mole) of benzenethiol in 300 ml. of absolute ethanol. This mixture was added to 14.6 g. (0.05 mole) of 2-(2′-nitrophenyl)phenylbromomethane dissolved in 50 ml. of absolute ethanol. Mild refluxing and stirring were used for 1 hr. Then the solution was filtered and concentrated to dryness under reduced pressure. The residue was leached with ether and the ether was washed with sodium hydroxide solution, water, and saturated sodium chloride solution and filtered through Drierite. Evaporation of the ether yielded 15.8 g. (99%) of X as a yellow, waxy solid, m.p. 48–55°.

The analytical sample, prepared by several crystallizations from 70% ethanol, consisted of yellow crystals, m.p. 54–55°, infrared absorption at 3.2, 6.4 NO_2 and 7.4 μ NO_2 (carbon tetrachloride).

Anal. Calcd. for $C_{19}H_{15}NO_2S$: C, 70.90; H, 4.70; N, 4.35; S, 9.97. Found: C, 70.66; H, 4.79; N, 4.47; S, 10.00.

2-(2′-Nitrophenyl)benzyl phenyl sulfone (III). The following procedure is modeled after a procedure of Truce and Knospe.[13] To 12.0 g. (0.038 mole) of X dissolved in 54 ml. of 1:1 glacial acetic acid-acetic anhydride was added 22 ml. (0.214 mole) of 30% hydrogen peroxide. The mixture stood at room temperature for 4 days and then was heated for 1.5 hr. on a steam bath. After cooling, manganese dioxide was added and the solvent was removed under reduced pressure to yield a brown oil. The oil was extracted with 400 ml. of absolute ether and the mixture was filtered to remove some brown solid. The filtrate was chromatographed on a 3 × 20 cm. column of Aluminum Oxide Merck using 200 ml. of absolute ether as the developer. The eluate was concentrated to yield 12.5 g. (93%) of greenish yellow oil. The oil partially decomposed when it was vacuum distilled. The analytical sample was chromatographed three times; infrared absorption at 6.6 and 7.4 NO_2, 7.5, 8.7, and 8.8 SO_2 and 9.3 μ (carbon tetrachloride).

Anal. Calcd. for $C_{19}H_{15}NO_4S$: C, 64.54; H, 4.27; N, 3.96; S, 9.07. Found: C, 64.38; H, 4.43; N, 4.07; S, 9.03.

2-(2′-Nitrophenyl)benzyl phenyl sulfone (III) *and Sodium Hydroxide.* After 2.01 g. (0.0063 mole) of III and 30 ml. of methanol containing 1.43 g. (0.036 mole) of sodium hydroxide had been heated for 1.5 hr. on a steam bath a white flocculent solid separated and the mixture was concentrated using reduced pressure to yield a solid residue which had pink, white, and yellow colors. The residue was made acidic by adding 3.2 ml. of conc. hydrochloric acid and the resulting mixture was extracted with ether, filtered, and washed with hot water to yield 1.07 g. (80%) of 6-hydroxyphenanthridine-5-oxide or its tautomer[6] as a buff-colored solid, m.p. 250–255°. The ether extracts were extracted three times with 5% sodium hydroxide with a total volume of 15 ml. A considerable amount of glistening white solid (A) was removed by filtration after the first sodium hydroxide extraction was made. The sodium hydroxide solution was concentrated to about 7 ml. volume, acidified with hydrochloric acid, and made slightly basic with sodium hydroxide. A gray solid (B) was removed by filtration.

The filtrate was heated for 1/2 hr. with 0.40 g. (0.0013 mole) of 2,4-dinitrochlorobenzene and about 10 ml. of 95% ethanol to yield after filtering and washing with 95% ethanol, 0.26 g. of pale yellow solid and filtrate A. The pale yellow solid was leached with 2 ml. of boiling acetic acid and the mixture was filtered to remove a white solid. On cooling, the filtrate yielded 0.11 g. of 2,4-dinitrodiphenyl sulfone, m.p. 154–156° (lit.,[5] m.p. 159–160°).

Filtrate A, solids A and B, and 0.2 g. (0.00065 mole) of 2,4-dinitrochlorobenzene were refluxed for 1/2 hr. to yield 0.50 g. of 2,4-dinitrodiphenyl sulfone (31% combined yields based on III) as nearly white crystals, m.p. 155–158°. The foregoing yielded 0.33 g. of nearly white crystals, m.p. 156–158°, after crystallization from acetic acid. In other experiments the yields of 6-hydroxyphenanthridine or its tautomer and 2,4-dinitrodiphenyl sulfone were as high as 90% and 38%, respectively.

2-Benzyl-2′-nitrobiphenyl (IV). As 6.1 g. (0.0021 mole) of 2-(2′-nitrophenyl)benzyl bromide was added with stirring to 125 ml. of benzene and 0.4 g. (0.003 mole) aluminum chloride an orange mixture resulted. The mixture was stirred for 1 day and allowed to stand 3 days before being poured into cold dilute hydrochloric acid. Benzene was added and the organic layer was separated, washed with dilute hydrochloric acid, 5% sodium carbonate, and water before being concentrated by distillation to yield a brown solid. The solid was recrystallized from ethanol to yield 4.79 g. (80%) of IV as nearly white crystals, m.p. 98–101°.

Anal. Calcd. for $C_{19}H_{15}NO_2$: C, 78.9; H, 5.23; N, 4.84. Found: C, 78.6; H, 4.95; N, 5.08.

2-Amino-2′-nitrobiphenyl (V). The methods of Purdie[14] and Badger and Sasse[15] involving the reduction of 2,2′-dinitrobiphenyl yielded orange and red oils, respectively. In both cases, for purification, the oil was dissolved in a minimum amount of ether and treated with a slight excess of 6*N* hydrochloric acid. After cooling, 2-nitro-2′-aminobiphenyl hydrochloride separated. Recrystallization from ethanol gave a light yellow product, m.p. 225–227° (lit.,[16]

(12) R. W. Bost, J. O. Turner, and R. D. Norton, *J. Am. Chem. Soc.*, **54**, 1985 (1932).

(13) W. E. Truce and R. H. Knospe, *J. Am. Chem. Soc.*, **77**, 5063 (1955).

(14) D. J. Purdie, *J. Am. Chem. Soc.*, **63**, 2276 (1941).

(15) G. M. Badger and W. F. H. Sasse, *J. Chem. Soc.*, 1 (1957).

(16) A. E. S. Fairful, D. A. Peak, W. F. Short, and T. I. Watkins, *J. Chem. Soc.*, 4709 (1952).

m.p. 228–229°). The yellow product was mixed with ammonium hydroxide and the mixture was extracted with ether which after evaporation yielded a red oil. After several conversions from the hydrochloride to the amine a solid product was obtained. After three crystallizations from ethanol and two from benzene-petroleum ether orange crystals, m.p. 62–64° (lit.,[15,16] 64–65°, lit.,[14] m.p. 94–94.5°), of 2-nitro-2′-aminobiphenyl were obtained.

2-Amino-2′-nitrobiphenyl (V) *and sodium hydroxide or sodium methoxide.* In a three necked flask equipped with a reflux condenser was placed 2.00 g. (0.0105 mole) of 2-nitro-2′-aminobiphenyl, m.p. 62–64°. One hundred milliliters of boiling 1*N* methanolic sodium hydroxide was added and as refluxing was continued 25-ml. portions of the deep orange solution were withdrawn after 15 min., 30 min., 1 hr. and 2 hr. Each of the 25 ml. portions was immediately put in an ice bath, diluted with 50 ml. of water, and allowed to stand for approximately 1 hr.

Each portion was treated as follows: The solid material and/or oil was removed by filtration or decantation and the filtrate (A) was saved. The solid and/or oil was leached with 70 ml. of 3*N* hydrochloric acid to remove starting material. The greenish yellow crystalline benzo(c)-cinnoline-1-oxide (VI) which remained was filtered, washed with water, and twice crystallized from aqueous ethanol. Filtrate (A) was concentrated by distillation and the residue was treated as in the foregoing.

The yields of (VI), m.p. 137–138° or 138–139° (lit.,[8] m.p. 138°) for reaction times of 15 min., 30 min., 1 hr., and 2 hr. were 17%, 33%, 61%, and 92%, respectively.

In one experiment similar to the foregoing except that sodium methoxide was used instead of sodium hydroxide the results were the same after 2 hr. reaction time, but the yields of VI were considerably lower at the other times.

o-Nitrophenylacetyl Chloride. In a system protected from moisture 96 g. (0.54 mole) of *o*-nitrophenylacetic acid (Eastman Kodak Co.) was mixed with 250 ml. of anhydrous ether and to this was added 213 g. of redistilled thionyl chloride. The mixture was refluxed for 5 min. and the resulting dark red solution was allowed to stand overnight. The solution was concentrated by distillation at atmospheric pressure at first and then under reduced pressure with a bath temperature which did not exceed 65°. (*In another attempt when this acid chloride was heated at 83°/1–3 mm. it decomposed violently.*) The yield of red oil was 105.5 g. The red oil was shaken with 35–37° petroleum ether and separated. It reacted with ammonium hydroxide to produce 2-nitrophenylacetamide, m.p. 160–161° (lit.,[17] 160–161°).

Ethyl 4-(2-nitrophenyl)-3-keto-2-cyanobutanoate (IX). The procedure was adapted from the method of Dornow and Fust.[18] In a three necked flask were placed 56.5 g. (0.50 mole) of ethyl cyanoacetate and 375 ml. of ether, and 10 g. (0.43 gram atom) of sodium shot was added. Vigorous stirring was used for 2.5 hr. during which time a white suspension developed. Then 50.4 g. (0.254 mole) of 2-nitrophenylacetyl chloride in 50 ml. of ether was added during 15 min. and the mixture was refluxed for 6 hr. Fifty milliliters of ether was added during the reflux period to thin the slurry which was present.

Fifty milliliters of ethanol was added and the reaction mixture was allowed to stand overnight after which time a red oil had separated. The mixture was extracted three times with a total volume of 800 ml. of ice cold 5% sodium hydroxide. Some unchanged sodium was destroyed during the first extraction. The combined red aqueous layers were extracted with ether and then acidified with cold dilute sulfuric acid. This mixture was extracted with benzene. About 1 g. of brown solid was insoluble in both layers. The red benzene solution was dried and concentrated by distillation to yield 46 g. of red oil which solidified after cooling. Two recrystallizations of the crude product from ethanol yielded 31.0 g. (45%) of IX as straw colored needles, m.p. 104.5–106.5°, infrared absorptions at 4.50 CN, 6.06 C=O, 6.55 and 7.45 μ NO_2 (potassium bromide wafer).

This compound did not react with 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14; neut. equiv., 276.2. Found: C, 56.30; H, 4 17; N, 9.92; neut. equiv., 276.8, 279.3, 277.7.

4-(2′-Nitrophenyl)-3-ketobutanonitrile (VII). Two grams of IX was refluxed with 60 ml. of 3*N* hydrochloric acid for 5 hr. As the mixture cooled white needle crystals separated as well as a small amount of brown solid, both of which were crystallized from ethanol. The yield of VII was 1.33 g. (90%), m.p. 139–140°, m.m.p. with 2-nitrophenylacetic acid (m.p. 140°) 115–120°, infrared absorptions at 4.41 (weak) CN, 5.80 C=O, 6.58 and 7.42 μ NO_2 (potassium bromide wafer).

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72; neut. equiv., 204.2. Found: C, 58.85; H, 3.82; N, 13.59; neut. equiv., 205, 206, 207.

This product reacted with 2,4-dinitrophenylhydrazine to form fine yellow crystals, m.p. 184–186°, after recrystallization from dimethylformamide.

(2-Nitrophenyl)acetone. After 2.0 g. of VII had been refluxed with 44 ml. of 6*N* hydrochloric acid for 3.5 hr. the mixture was made basic with potassium hydroxide and was extracted with ether. The ether extract was dried and concentrated to yield 1.22 g. (70%) of brown solid which gradually melted as the temperature rose to 29° (lit.,[19] m.p. 29°). The basic solution yielded 0.34 g. of VII, m.p. 135–140°, when it was acidified with hydrochloric acid. Semicarbazone, m.p. 212–214° (lit.,[19] m.p. 213–214°).

Ethyl [2-(2′-nitrophenyl)] benzoylcyanoacetate (XI). In a three necked flask equipped with an additional funnel, stirrer, and condenser with a soda lime tube were placed 2.54 g. (0.11 gram atom) of sodium and 100 ml. of absolute ether. To this was added 16.4 g. (0.145 mole) of ethyl cyanoacetate. After 2.5 hr. of refluxing and stirring all the sodium had been consumed and a white paste had formed. Then 2-(2′-nitrophenyl)benzoyl chloride[11] from 27.0 g. (0.11 mole) of 2-nitro-2′-carboxybiphenyl in 75 ml. of ether was added with stirring during 1/2 hr. The color of the solution changed to pale orange as refluxing and stirring were continued for 2 hr. After cooling, 30 ml. of ethanol was added and the mixture was refluxed for 30 min. before standing overnight. The mixture was extracted with one 150-ml. and three 100-ml. portions of 10% sodium carbonate. The basic extracts were acidified with dilute sulfuric acid to give a tan solid which was filtered, washed repeatedly with water and recrystallized from ethanol to yield 14.0 g. (40%) of XI as fine white crystals, m.p. 135–136°, infrared absorption at 4.4 CN, 5.98 C=O, 6.3, 6.58 and 7.40 NO_2, 7.8 μ (chloroform).

Anal. Calcd. for $C_{18}H_{14}N_2O_5$: C, 63.91; H, 4.17; N, 8.28. Found: C, 63.72; H, 4.23; N, 8.32.

[2-(2′-Nitrophenyl)]benzoylacetonitrile (VIII). With vigorous stirring 3.79 g. (0.011 mole) of XI was refluxed for 23 hr. with 100 ml. of 6*N* hydrochloric acid. Stirring without heat was continued for an additional 3 hr. and the mixture was allowed to stand for 2 days. Initially there was a white suspension and after 10 hr. a yellow-brown oil.

The aqueous layer was decanted from the oil and extracted with ether. When the oil was triturated with ether, 0.6 g. of white solid, m.p. 125–145°, separated. After two recrystallizations from ethanol the melting point was 142–145°.

The ether extract was extracted with 10% sodium hydroxide and then the sodium hydroxide solution was acidified with hydrochloric acid to yield 0.69 g. of white solid, m.p. 125–135°. After two recrystallizations from ethanol the melting point of VIII was 142–145°. The ether layer was dried and concentrated to yield 1.3 g. of 2-nitro-2′ acetylbiphenyl as a light brown solid.

(17) A. Reissert, *Ber.*, 41, 3814 (1908).

(18) A. Dornow and K. Fust, *Ber.*, 87, 985 (1954).

(19) F. Arndt, B. Eistert, and W. Partale, *Ber.*, 61, 1117 (1928).

In another experiment like the foregoing except that the acidic material was extracted with sodium bicarbonate, the acidic material (VIII) which was only soluble in sodium hydroxide was a tan solid, m.p. 135–143°, weight 0.455 g. (14%). The yield of 2-nitro-2′-acetylbiphenyl, m.p. 58–61°, was 1.47 g. (51%).

Repeated recrystallizations of VIII from ethanol yielded cream-colored crystals, m.p. 144–145.5°; infrared absorption 4.4 CN, 5.98 C=O, 6.3, 6.58 NO_2, 7.40 NO_2, 7.8 μ (chloroform).

Anal. Calcd. for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.72; H, 3.59; N, 10.68.

2-Acetyl-2′-nitrobiphenyl (XII). The light brown solid, m.p. 58–61°, obtained during the preparation of VIII was recrystallized three times from ethanol to yield nearly white crystals of XII, m.p. 60–61°.

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.60, 69.83; H, 4.57, 4.62; N, 5.83, 5.90.

The 2,4-dinitrophenylhydrazone of XII after two recrystallizations from ethanol–ethyl acetate consisted of orange crystals, m.p. 191–192.5°.

Anal. Calcd. for $C_{20}H_{15}N_5O_6$: N, 16.62. Found: N, 16.88, 16.78.

The semicarbazone of XII after three crystallizations from aqueous ethanol was a white powder, m.p. 214–216° dec.

Anal. Calcd. for $C_{15}H_{14}N_4O_3$: N, 18.78. Found: N, 18.78, 18.97.

MORGANTOWN, W. VA.

[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY OF THE DEPARTMENT OF SURGERY, UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE]

Derivatives of Fluorene. VII. New Mono and Dinitro Compounds and Some of Their Reactions[1]

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New mono and dinitro derivatives of substituted fluorenes are reported with some improved routes to known compounds. Usefulness of the trifluoroacetyl radical on the amino group is noted both with regard to its strong directing influence and the great ease with which it is removed. The first triamino- and tetraminofluorene are described.

In studying various series of fluorene compounds, especially ring-fluorinated *N*-2-fluorenylacetamides, we have found that hitherto unreported nitrations of some derivatives of 2-fluorenamine are extremely useful in giving substances with certain desired positions substituted or blocked. Reduction of this nitro group and further nitration, followed by a deamination at the first position of nitration, has given us high over-all yields of some disubstituted fluorenes by the best route available.

Like *N*-2-fluorenylperfluorobutyramide,[3] *N*-2-fluorenyltrifluoroacetamide can be nitrated in the 7- position. The yields approach 90%. *N*-2-Fluorenylacetamide on the other hand gives a mixture of the 3- and 7-nitro derivatives.[3-5] The 7-nitro derivative is obtained from the latter reaction in low yield following a time-consuming separation.[3,4] The trifluoroacetyl group is additionally useful because of ready cleavage. A few minutes in hot dilute alkali leads to almost quantitative recovery of high quality 7-nitro-2-fluorenamine. Anyone who has tried the customary dinitration of fluorene, separation of isomers, and monoreduction of 2,7-dinitrofluorene, will appreciate over-all yields of 75 to 80% from 2-fluorenamine in three easy steps, all conveniently carried out in a beaker or Erlenmeyer flask (one-mole level customarily). *N*-2-(7-nitrofluorenyl)trifluoroacetamide can be reduced with Raney nickel and hydrazine hydrate[6] (0.05 mole, 90%), and the resulting amine acetylated and hydrolyzed in hot alkali to give the known 2-acetamido-7-aminofluorene. The latter is also equally conveniently obtained from 2-amino-7-nitrofluorene by acetylation and reduction[6] (0.05 mole, 90%).

Nitration of *N*-2-(7-nitrofluorenyl)trifluoroacetamide, of *N*-2-(3-nitrofluorenyl)trifluoroacetamide and dinitration of *N*-2-(fluorenyl)trifluoroacetamide all gave 80 to 90% yields of *N*-2-(3,7-dinitrofluorenyl)trifluoroacetamide which was readily hydrolyzed to the known 2-amino-3,7-dinitrofluorene, identical with the hydrolysis product of *N*-2-(3,7-dinitrofluorenyl)acetamide.[7]

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(2) To whom communications regarding this manuscript should be addressed.

(3) E. Sawicki, B. Chastain, and H. Bryant, *J. Org. Chem.*, **21**, 754 (1958).

(4) *N*-2-(9-Oxofluorenyl)acetamide gives a 90% yield of the 3-nitro derivative [N. Ishikawa and M. Hayashi, *Yûki Gôsei Kagaku Kyôkai Shi*, **15**, 405 (1957)]. For certain 2,3- or 3-substituted fluorenones (*e.g.* 2,3-diamino- or 3-amino-) which can be reduced to fluorenes in high yield, nitration of *N*-2-(9-oxofluorenyl)acetamide is to be preferred as an approach.

(5) *N*-2-Fluorenyl-*p*-toluenesulfonamide gives high yields of the 3-nitro isomer but hydrolysis of the tosyl group is troublesome [N. Ishikawa and M. Hayashi, *Yûki Gôsei Kagaku Kyôkai Shi*, **15**, 202 (1957)].

(6) T. L. Fletcher and M. J. Namkung, *J. Org. Chem.*, **23**, 680 (1958). Footnote[d] in the table of this reference erroneously gives the melting point of the analytical sample of *N*-2-(7-nitrofluorenyl)trifluoroacetamide as 201–201.5°; this should read 248.5–249.5°.

Whereas it was reported[8] that *N*-2-(1,3,7-trinitrofluorenyl)-*p*-toluenesulfonamide was obtained by nitration of 2-*p*-tosylamidofluorene, the same procedure gave us 45 to 50% yields of *N*-2-(3,7-dinitrofluorenyl)-*p*-toluenesulfonamide. The latter was also obtained by nitration of *N*-2-(7-nitrofluorenyl)-*p*-toluenesulfonamide and of *N*-2-(3-nitrofluorenyl)-*p*-toluenesulfonamide.[5,8]

Reduction[6] of 2-acetamido-3,7-dinitrofluorene gave 2-acetamido-3,7-fluorenediamine and of 2-amino-3,7-dinitrofluorene gave us the first fluorenetriamine[9] to be reported.

Nitration[10] of 2,7-diacetamidofluorene gave the 3,6-dinitro derivative which we reduced[6] to the corresponding diamine. Hydrolysis of the diacetamidodinitro compound gave 2,7-diamino-3,6-dinitrofluorene which was reduced[6] to the first reported tetraminofluorene.

We repeated the interesting nitration of 2-*N*,*N*-dimethylaminofluorene[8] with sodium nitrite in cold acetic acid. These workers reported that their analytical sample melted at 100–103°. Before further work with this compound, we attempted to narrow the melting range by repeated crystallization from alcohol and raised this to 102.5–105.5° (corr.), but crops from the filtrates melted up to 120°. Samples melting at each range were analytically pure. We then found that recrystallization from ligroin, by the technique described below, gave us blocks and needles, melting at 107–108° and 125–126.5°, respectively, both of which were analytically identical. Reduction[6] of the lower melting isomer to the amine followed by dimethylation with trimethyl phosphate[11] gave 2,3-*N*,*N*,*N'*,*N'*-tetramethylfluorenediamine identical with the product of tetramethylation of authentic 2,3-diaminofluorene. The 3-*N*-acetyl and 3-*N*-benzylidene derivatives of the 3-amino compound were also prepared. The same reactions were carried out on the other isomer giving 2-*N*,*N*-dimethylamino-*x*-aminofluorene and the corresponding tetramethylated diamine.

Nitration of each nitrodimethylaminofluorene gave the same compound, 3,*x*-dinitro-2-(*N*-methyl-*N*-nitroso)fluorenamine, which was reported by Bell and Mulholland[8] as the 3,1-dinitro compound, from a more drastic nitration of 2-*N*,*N*-dimethylfluorenamine.

Since there appeared to be no direct confirmation that the higher melting isomer was the 1-nitro compound, we synthesized 1,2-fluorenediamine, a new compound. When the diamine was treated with an excess of trimethyl phosphate,[11] the 1,2-*N*,*N*,*N'*,*N'*-tetramethyldiamine was produced, identical with the tetramethyl compound above.

2-*N*-*N*-Dimethyl-9-oxofluorenamine was nitrated in a similar manner[8] to give deeply purple colored 2-*N*,*N*-dimethyl-3-nitro-9-oxofluorenamine. No isomer was detected, although there was one (possibly two) yellow by-product in small yield. The main product was identical with the compound resulting from oxidation of 2-*N*,*N*-dimethylamino-3-nitrofluorene, an oxidation effected by anil formation with *o*-nitrosotoluene, and hydrolysis.[12]

Reduction of 2-*N*,*N*-dimethyl-3-nitro-9-oxofluorenamine with sodium borohydride[13] led to the 9-ol, which was reduced[6] to 2-*N*,*N*-dimethyl, 3-(9-hydroxyfluorene)diamine.

EXPERIMENTAL[14]

N-2-(7-Nitrofluorenyl)trifluoroacetamide. To a suspension of 55.4 g. (0.2 mole) of *N*-2-fluorenyltrifluoroacetamide in 800 ml. of glacial acetic acid at 45°, 40 ml. of nitric acid (*d.*, 1.42) and 6 ml. of concd. sulfuric acid were added with stirring. When the mixture was heated to 55°, an exothermic reaction took place with a rise in temperature to 60° and formation of a mass of yellow needles. The stirring was continued for 10 min. and the reaction mixture was allowed to cool to room temperature. The precipitate was filtered, washed with 50 ml. of cold glacial acetic acid and with water, and dried, giving 53.5 g. (83.5%), m.p. 245–247°. One recrystallization from acetone (Darco) gave the pure product, m.p. 248.5–249.5°.[6]

N-2-(7-Acetamidofluorenyl)trifluoroacetamide. The preceding compound was reduced[6] and the amine acetylated in pyridine (30 min., steam bath). The product was stirred into water and the mixture acidified with hydrochloric acid. After filtration and drying a quantitative crude yield was obtained m.p. 315–318° (corr.) (capillary in an aluminum block). Two recrystallizations from alcohol gave an analytical sample, m.p. 323–324° (corr.), with slight discoloration at 322°.

Anal. Calcd. for $C_{17}H_{13}F_3N_2O_2$: C, 61.08; H, 3.92; N, 8.38. Found: C, 60.92; H, 3.80; N, 8.40.

Hydrolysis of N-2-(7-nitrofluorenyl)trifluoroacetamide. A suspension of 53.5 g. of the amide in 1 l. of alcohol was brought to a boil and 1 l. of boiling 1% aqueous sodium hydroxide was added. All the solids dissolved, but in a few minutes a dark red precipitate formed. After a few more minutes of boiling, the mixture was cooled and 2 l. of water was added. Upon filtration and drying, 37 g. (quantitative) was recovered, m.p. 228–232°. One recrystallization from acetone gave 25.7 g., m.p. 234–235° in the first crop. Another 9.2 g., m.p. 232–234° was obtained in further crops. The reported melting point of 2-nitro-7-fluorenamine is 232°.[15]

(7) N. Ishikawa and M. Hayashi, *Yûki Gôsei Kagaku Kyôkai Shi*, **14**, 80 (1956), reported 2-acetamido-3,7-dinitrofluorene, m.p. 270–272° dec.; our analytical sample melted at 280–281° dec. These workers reported that 2-amino-3,7-dinitrofluorene melted at 280–282° dec., whereas our analytically pure sample melted at 275–276° dec.

(8) F. Bell and D. B. Mulholland, *J. Chem. Soc.*, 2020 (1949).

(9) Reduction of 2,4,7-trinitrofluorenone [J. Schmidt and K. Bauer, *Ber.*, **38**, 3758 (1905)] gave 2,4,7-triaminotriaminofluoren-9-ol (as hydrochloride).

(10) A. Barker and C. C. Barker, *J. Chem. Soc.*, 870 (1954).

(11) T. L. Fletcher, M. E. Taylor, and A. W. Dahl, *J. Org. Chem.*, **20**, 1021 (1955).

(12) This is similar to the method using *p*-nitrosodimethylaniline [G. M. Bennett and E. V. Bell, *Org. Syntheses*, **Coll. Vol. II**, 223 (1943)].

(13) H. L. Pan and T. L. Fletcher, *J. Org. Chem.*, **23**, 799 (1958).

(14) Melting points were taken on a Fisher-Johns apparatus and are corrected to standards. Microanalyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(15) O. Diels, E. Schell, and S. Tolson, *Ber.*, **35**, 3284 (1902).

Hydrolysis of N-2-(7-acetamidofluorenyl)trifluoroacetamide. This compound was hydrolyzed in a similar manner to give the known *N*-monoacetyl-2,7-fluorenediamine.[6]

Trifluoroacetylation of 3-nitro-2-fluorenamine. To a solution of 1 g. of 3-nitro-2-fluorenamine in 100 ml. of benzene, 0.5 ml. of trifluoroacetic anhydride was added drop by drop. The mixture was heated on the steam bath for 1 hr., boiled down to small volume, and cooled. The yellow precipitate, filtered and dried, gave 1.2 g. (83.5%), m.p. 182–182.5°. Recrystallization from alcohol gave an analytical sample, m.p. 182–182.5°.

Anal. Calcd. for $C_{15}H_9F_3N_2O_3$: C, 55.91; H, 2.82; N, 8.69. Found: C, 56.06; H, 2.72; N, 8.59.

N-2-(3,7-Dinitrofluorenyl)trifluoroacetamide. (*a*) *Nitration of N-2-(7-nitrofluorenyl)trifluoroacetamide.* To a mixture of 30 ml. each of fuming nitric acid (*d.*, 1.5) and glacial acetic acid at 30°, 6.5 g. (0.02 mole) of the above was added in small portions with stirring. After warming to 60°, the mixture was removed from the heat. Stirring was continued and the temperature rose to a maximum of 70°. After cooling to room temperature, the pale yellow precipitate was filtered, washed with water, and dried, giving 6.6 g. (90%), m.p. 250–255°. Recrystallization from acetic acid (Darco) and from toluene gave a sample, m.p. 256–258° dec., slight discoloration at 255°.

(*b*) *Nitration of N-2-(3-nitrofluorenyl)trifluoroacetamide.* The 3-nitro isomer was nitrated in the same way to give a substance identical with the above melting point and mixture melting point.

(*c*) *Dinitration of N-2-(fluorenyl)trifluoroacetamide.* To a mixture of 40 ml. each of fuming nitric acid (*d.*, 1.5) and glacial acetic acid at 30°, 5.6 g. (0.02 mole) of *N*-2-fluorenyltrifluoroacetamide was added in small portions with stirring. The mixture was heated to 65° and removed from the heat. The temperature of the mixture rose to 70° and then gradually dropped to room temperature. The pale yellow product was filtered off, washed with water, and dried, giving 6.3 g. (86%), m.p. 250–255° dec. with discoloration at 215°. Recrystallization from acetic acid (Darco) and from toluene gave an analytical sample, m.p. 257–258° dec. and with discoloration at 255°. The mixture melting point with the two nitration products above were undepressed.

Anal. Calcd. for $C_{15}H_8F_3N_3O_5$: C, 49.05; H, 2.19; N, 11.44. Found: C, 49.24; H, 2.07; N, 11.40.

N-2-(3,7-Dinitrofluorenyl)acetamide. To a mixture of 200 ml. each of fuming nitric acid (*d.*, 1.5) and glacial acetic acid, 22.3 g. (0.1 mole) of *N*-2-fluorenylacetamide was added in small portions at room temperature. The mixture was heated to 55° and allowed to stand overnight. The precipitate was filtered, washed with water and then alcohol, and dried, giving 23.5 g. (75%), m.p. 275–280° dec. One recrystallization from toluene (Darco) gave an analytical sample, m.p. 280–281° dec.,[7] discoloration at 277°.

Anal. Calcd. for $C_{15}H_{11}N_3O_5$: C, 57.51; H, 3.54; N, 13.42. Found: C, 57.60; H, 3.49; N, 13.20.

3,7-Dinitro-2-fluorenamine. (*a*) *Hydrolysis of trifluoroacetyl derivative.* To a solution of 2 g. of *N*-2-(3,7-dinitrofluorenyl)trifluoroacetamide in 300 ml. of alcohol and 30 ml. of acetone, 25 ml. of 1% aqueous sodium hydroxide was added and the mixture was boiled down to 200 ml. The red precipitate was filtered, washed with acetone and dried, yielding 1.3 g. (88%), m.p. 270–274° dec. One crystallization from acetone raised the melting point to 275–276° dec.[7]

(*b*) *Hydrolysis of the acetyl derivative.* A mixture of 5 g. of *N*-2-(3,7-dinitrofluorenyl)acetamide, 500 ml. of acetone and 100 ml. of concd. hydrochloric acid was refluxed for 20 hr. as the solution turned dark and red needles formed. The solution was boiled down to 250 ml. and cooled. Filtration was followed by washing with dilute ammonium hydroxide. The dried material weighed 4.0 g. (93%), m.p. 272–276° dec. One recrystallization from acetone gave an analytical sample, m.p. 275–276° dec.[7] A mixture melting point with the preceding hydrolysis product showed no depression.

Anal. Calcd. for $C_{13}H_9N_3O_4$: C, 57.56; H, 3.34; N, 15.49. Found: C, 57.71; H, 3.34; N, 15.60.

N-2-(3,7-Dinitrofluorenyl)-p-toluenesulfonamide. (a) To a mixture of 20 ml. of fuming nitric acid (*d.*, 1.5) and 20 ml. of glacial acetic acid, 3.35 g. (0.01 mole) of *N*-2-fluorenyl-*p*-toluenesulfonamide was added gradually during 10 min. with stirring and cooling to 20°. The reaction mixture was then poured into water, and the precipitate filtered, washed with a little cold acetic acid followed by 50 ml. of alcohol, and dried, giving 4.2 g. of crude product. One recrystallization from acetone (Darco) gave 2.2 g. (52%) of the dinitro compound, m.p. 226–228°. Two further recrystallizations gave an analytical sample, m.p. 232.5–233.5°.

Anal. Calcd. for $C_{20}H_{13}N_3O_6S$: C, 56.46; H, 3.55; N, 9.88. Found: C, 56.54; H, 3.80; N, 9.65.

(b) To a nitrating mixture identical with the preceding, 3.81 g. (0.01 mole) of *N*-2-(7-nitrofluorenyl)-*p*-toluenesulfonamide was added gradually at 10–20°; the precipitate was worked up as before giving 2.2 g. (52%), m.p. 219–221°. One crystallization from acetone (Darco) gave 1.8 g., m.p. 232–232.5°.

(c) The same procedure with *N*-2-(3-nitrofluorenyl)-*p*-toluenesulfonamide gave 1.9 g. of product, m.p. 232–233°. Mixture melting points of this with each of the two preceding substances were undepressed.

N-2-(3,7-Diaminofluorenyl)acetamide. To a suspension of 1 g. of *N*-2-(3,7-dinitrofluorenyl)acetamide in a boiling mixture of 500 ml. of toluene and 200 ml. of alcohol, a small amount of Raney nickel and 2 ml. of 100% hydrazine hydrate were added.[6] The solid material dissolved gradually while the reaction mixture boiled down to 200 ml. at which point a white precipitate formed. Alcohol (200 ml.) was added to effect solution, and the boiling was continued (to 200 ml.) until no alkaline vapors were detected. The nickel was filtered off and the filtrate boiled down to 50 ml. and cooled. A white precipitate was filtered off and dried, giving 0.75 g. (82.5%), m.p. 262–265°. One recrystallization from methanol gave an analytical sample, m.p. 269–270°.

Anal. Calcd. for $C_{15}H_{16}N_3O$: C, 71.12; H, 5.97; N, 16.59. Found: C, 70.91; H, 6.09; N, 16.40.

2,3,7-Triaminofluorene. Reduction[6] in the usual manner of 1 g. of 3,7-dinitro-2-fluorenamine gave us 0.7 g. (90%) of the triamino compound, m.p. 224–227°. Two recrystallizations from alcohol gave an analytical sample, m.p. 230–232° (softening at 229°).

Anal. Calcd. for $C_{13}H_{13}N_3$: C, 73.90; H, 6.20; N, 19.89. Found: C, 73.99; H, 6.35; N, 20.05.

2,7-Diacetamido-3,6-fluorenediamine. To a suspension of 2 g. of 2,7-diacetamido-3,6-dinitrofluorene in 500 ml. of boiling alcohol, 4 ml. of 100% hydrazine hydrate, and a small amount of Raney nickel were added.[6] After 5 min., 4 ml. of 100% hydrazine hydrate and Raney nickel were again added and this was repeated three more times. A yield of 1.4 g. (84%) was obtained which decomposed slowly above 400° (capillary tube in aluminum block). One recrystallization from dimethylformamide gave an analytical sample which decomposed slowly above 400°.

Anal. Calcd. for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.91; H, 5.86; N, 18.07.

3,6-Dinitro-2,7-fluorenediamine. A solution of 2 g. of 2,7-diacetamido-3,6-dinitrofluorene in 8 ml. of concd. sulfuric acid and 2 ml. of water was heated on a steam bath for 40 min. The reaction mixture was cooled, poured into 100 ml. of water, and neutralized with aqueous sodium hydroxide. The dark purple precipitate was filtered, washed with water, and dried, giving 1.5 g. (96%). One recrystallization from nitrobenzene gave an analytical sample, m.p. 335° (vigorous decomposition), in a capillary in an aluminum block.

Anal. Calcd. for $C_{13}H_{10}N_4O_4$: N, 19.58. Found: N, 19.31.

2,3,6,7-Tetraminofluorene. The foregoing compound (0.7 g.) was reduced[6] to give 0.5 g. (90%), m.p. 259–262°. Two recrystallizations from alcohol raised the melting point to 265–267°, with some softening and discoloration ~260°.

Anal. Calcd. $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 68.92; H, 6.54; N, 24.44.

Nitration of 2-N,N-dimethylaminofluorene,[8] *and separation of isomers.* To a magnetically stirred solution of 104.5 g. (0.5 mole) of 2-*N*,*N*-dimethylaminofluorene in 1 l. of glacial acetic acid, a solution of 57 g. (0.83 mole) of sodium nitrite in 330 ml. of water was added gradually over a period of 15 min. (ice-water bath). The solution first turned green, then a brick-red color and a red precipitate formed. The temperature was kept at 14–16° and the reaction mixture stirred for 10 more min. after addition of the sodium nitrite. After 30 min. in the ice-water bath, the precipitate was filtered, washed with 50 ml. of cold acetic acid and then water, and dried, giving 116 g. (91%), m.p. 97–105°. Recrystallization from alcohol (1 l.) gave 106 g. in the first crop, m.p. 100–107°, and 4.4 g. in the second and third crops, m.p. 95–108°.

The mixture (106 g.) was boiled with 2.5 l. of ligroin (*d.*, 0.67–0.69) and the residue was separated by decantation. Upon cooling, two sets of crystals, blocks, and needles formed. The decantate was then warmed, the needle-like crystals dissolved, and separation was again effected by decantation. The two residues from ligroin were combined and recrystallized from 1.4 l. of ligroin (*d.*, 0.72–0.74), giving 60.8 g. (47.7%), m.p. 107–108°. The decanted solution was cooled to form both types of crystals. The mixture was heated again to dissolve the needles, decanted, and the residue recrystallized from ligroin three times (300 ml. each) to yield another 11.2 g., m.p. 106–108°. From the filtrates, 1.7 g. were recovered, m.p. 112–119°, which was combined with further like crops. The decanted solution was boiled down to 1.2 l. and cooled, and the process continued, aided by the easy mechanical separation of the large blocklike crystals. A further 8.5 g., m.p. 106–109°, was isolated in this way, and 21.0 g. of needles, m.p. 112–119°.

All of the crude higher-melting isomer (22.7 g.) was combined and recrystallized from methanol giving 17.8 g. (14.0%) in the first crop, m.p. 125–126.5°, and 2.8 g. (2.2%) in the second crop, m.p. 119–123°. Another recrystallization of the first crop from methanol gave an analytical sample, m.p. 125.5–126.5°.

Anal. Calcd. for $C_{15}H_{14}N_2O_4$: N, 11.02. Found: N, 10.98.

All of the 3-nitro- (lower-melting) isomer (81.2 g.) was combined and recrystallized from methanol, giving 71 g. (56.0%), m.p. 107.5–108.5°.

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.75; H, 5.66; N, 10.80.

Nitration of 2-N,N-dimethylamino-x(-1-)-nitro-fluorene (to 1,3-dinitro-2-(N-methyl-N-nitroso)fluorenamine). To a solution of 2.54 g. (0.01 mole) of 2-*N*,*N*-dimethylamino-1-nitrofluorene in 50 ml. of warm (50°) glacial acetic acid, 2 ml. of nitric acid (*d.*, 1.42) was added with stirring. The mixture was heated to 75° and allowed to cool. A yellow precipitate was filtered, washed with water, and dried, giving 2.5 g. (80%), m.p. 161–164°. Two recrystallizations from alcohol (the first with Darco) gave an analytical sample, m.p. 166–167°.[16]

Anal. Calcd. for $C_{14}H_{10}N_4O_5$: C, 53.51; H, 3.21; N, 17.83. Found: C, 53.59; H, 3.25; N, 17.98.

Nitration of 2-N,N-dimethylamino-3-nitrofluorene. This was performed in the same way as the preceding experiment. The recrystallized product (crude, 88%, m.p. 165–166°) melted at 165–166.5°. The mixture melting point with the above was undepressed.[16]

The 3- and the 1-mononitro compounds were each reduced in the usual way with Raney nickel and hydrazine hydrate[6] to give, respectively, *2-dimethylamino-3-aminofluorene* (85–90%), m.p. 155–156° (analysis reported previously[6]), and *2-dimethylamino-1-aminofluorene* (85–90%), m.p. 151.5–152°.

Anal. Calcd. for $C_{15}H_{16}N_2$: N, 12.49. Found: N, 12.69.

2,3-N,N,N',N'-Tetramethyldiaminofluorene. (a) In a 50-ml. pear-shaped flask, equipped with a reflux condenser and a mechanical stirrer through the condenser, 1.0 g. (0.0051 mole) of 2,3-fluorenediamine[6] and 2 g. (0.014 mole) of trimethylphosphate were combined and the mixture heated at 183° ± 2° in an oil bath for 1 hr. Sodium hydroxide (10 ml., 10% aqueous) was added and the mixture boiled for 5 min. and poured into 100 ml. of cold water. The precipitate was filtered and dried, giving 0.6 g. (47%), m.p. 99–102°. One recrystallization from alcohol gave a pure product, m.p. 101.5–102.5°.

(b) 2-Dimethylamino-3-aminofluorene (3.92 g., 0.0175 mole) and 5.6 g. (0.04 mole) of trimethyl phosphate were treated in a similar manner to yield 99% of a crude product, m.p. 90–97°. Crystallization from ethanol and then methanol gave material, m.p. 101–101.5°. The mixture melting point with the product from (a) was undepressed.

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.97; H, 8.02; N, 11.10.

N-3-(2-N',N'-Dimethylaminofluorenyl)acetamide. 2-Dimethylamino-3-aminofluorene was acetylated to give a product, m.p. 232–233°.

Anal. Calcd. for $C_{17}H_{18}N_2O$: N, 10.52. Found: N, 10.72.

3-N-Benzylidene-(2-N',N'-dimethylamino)fluorenamine. To a boiling solution of 1.12 g. (0.005 mole) of 2-dimethylamino-3-aminofluorene in 50 ml. of alcohol, 0.53 g. (0.005 mole) of benzaldehyde was added and the mixture was boiled down to 10 ml. (20 min.). After cooling to room temperature, the yellow precipitate was filtered off and dried, giving 1.45 g. (93%), m.p. 128.5–129.5°. One recrystallization from ligroin (*d.*, 0.67–0.69) gave an analytical sample, m.p. 128.5–129.5°.

Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.68; H, 6.40; N, 8.84.

2,1-N,N,N',N'-Tetramethyldiaminofluorene. (a) 2-Dimethylamino-1-aminofluorene (2.24 g.) was methylated by the procedure given above, giving 2 g. (80%), m.p. 62–64°. Three recrystallizations from methanol gave an analytical sample, m.p. 66.5–67°.

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 81.03; H, 8.12; N, 11.22.

(b) A mixture of 0.8 g. of 1,2-diaminofluorenone,[17] 0.6 g. of sodium hydroxide, 10 ml. of diethylene glycol, and 0.6 ml. of 85% hydrazine hydrate was refluxed for 3 hr., then the mixture was boiled without a condenser until the boiling point of the mixture rose to 205°, and refluxed for 2 more hr. The reaction mixture was cooled and poured into 50 ml. of water. The grayish white precipitate was filtered, washed with water, and dried, giving 0.6 g. (80%) m.p. 162–180°. This was extracted with ligroin (*d.*, 0.67–0.69) and the ligroin evaporated to dryness. The residue was recrystallized twice from benzene giving *1,2-diaminofluorene*, m.p. 182–183° which was tetramethylated in the same way as the 2,3-isomer giving a product (two recrystallizations from benzene) melting at 65–66°. A mixture melting point with the product from (a) was undepressed.

2-N,N-Dimethylamino-3-nitro-9-oxofluorene. (a) A solution of 32 g. (0.046 mole) of sodium nitrite in 80 ml. of water was added dropwise with stirring to 10 g. of 2-*N*,*N*-dimethylaminofluorenone in 600 ml. of glacial acetic acid at room temperature. The temperature rose slightly. Stirring was then continued for 30 min. The precipitate was filtered, washed with water, and dried, giving deep purple crystals, 6.8 g. (56.5%), m.p. 165.5–167°.

By dilution of the filtrate with water, a yellow precipitate was obtained (5 g.), m.p. 130–140°, which was recrystallized from carbon tetrachloride twice, to give 0.7 g., m.p. 174.5–176°, which has not been characterized further. The second crop from the first crystallization (3.1 g.) melted from 128–135° and has not been purified further.

(16) Bell and Mulholland[8] by further nitration of their crude reaction mixture isolated 1,3-dinitro-2-(*N*-methyl-*N*-nitroso)fluorenamine, m.p. 165° dec.

(17) J. W. Cook and J. S. Moffat, *J. Chem. Soc.*, 1160 (1950).

The main reaction product (6.8 g.) was crystallized from alcohol to give 6.0 g., m.p. 168.5–170°.

(b) *Condensation of 2-N,N-dimethylamino-3-nitrofluorene with o-nitrosotoluene*[12] *and hydrolysis of the azomethine.* In a procedure similar to Bergmann's,[18] using 2 drops of piperidine as catalyst, 2.24 g. (0.01 mole) of 2-dimethylamino-3-nitrofluorene and 1.21 g. (0.01 mole) of *o*-nitrosotoluene (Aldrich Chemical Co., m.p. 67–72°) were refluxed in 150 ml. of alcohol for 5 hr. and the alcohol boiled down to 60–70 ml. Upon standing, a tarry mass of crystals formed which appeared difficult to work with. After decanting the solution, fresh alcohol was added and 5 ml. of concd. hydrochloric acid. This mixture was refluxed for 30 min. and allowed to cool. The resulting crystalline precipitate was filtered and dried, 0.5 g., m.p. 160–167° (softening *ca.* 150°). Two recrystallizations from ethanol (Darco) and one from methanol gave a sample melting at 167–169°, with initial melting at 160° and immediate resolidification. Nitrogen analysis showed that one molecule of methanol was included. Drying at 125° for 3 hr. in a vacuum raised the melting point to 169–170° with melting or softening at a lower temperature.

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: N, 10.44. Found: N, 10.28.

A mixture melting point with the nitration product from (a) was undepressed.

An attempt to isolate the intermediate azomethine, *N-9-(2-dimethylamino-3-nitrofluorenylidene)-o-toluidine,* was more successful using sodium methylate (0.65 g.) as a catalyst with 0.01 mole of each of the reactants in boiling alcohol for 4 hr. The initial semicrystalline tar, after decantation and evaporation of residual solvent, amounted to 2.1 g. Upon extraction with hot methanol, filtration and cooling of the filtrate, 0.4 g. of a bright red substance was obtained melting at 125–133°. Two more recrystallizations from methanol raised the melting point to 129.5–131.5°.

Anal. Calcd. for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.74; H, 5.12; N, 11.65.

2-N,N-Dimethylamino-3-aminofluoren-9-ol. Reduction of *2-N,N-dimethylamino-3-nitrofluoren-9-ol*[19] with Raney nickel and hydrazine hydrate[6] gave a 95% yield of the 3-amino derivative, m.p. 129–133°. Two recrystallizations from ligroin (b.p. 30–60°) gave an analytical sample, m.p. 132–133°.

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.84; H, 6.77; N, 11.83.

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(18) E. D. Bergmann, *J. Chem. Soc.*, 1628 (1937).

(19) This was made by Mr. H. L. Pan, as an extension of our earlier study,[13] in high yield by sodium borohydride reduction in methanol, m.p. 126–127°.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.79; H, 5.50; N, 10.50.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, AEROJET-GENERAL CORPORATION]

Preparation of ω-Aminoalkyl Secondary Nitramines

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A method was developed for selectively converting secondary amines to the corresponding nitramines in the presence of primary amino groups. The method consists of three steps: (1) complete acetylation of the amino groups, (2) selective nitrolysis of the amido group by treatment of the acetylated amine with a nitric acid-trifluoroacetic anhydride mixture or with nitrogen pentoxide in a suitable solvent, and (3) hydrolysis of the diacetamido group. In this manner, *N*-methyl-1,3-propylenediamine, diethylenetriamine, and triethylenetetramine were converted to the hydrochloride salts of *N*-methyl-*N*-nitro-1,3-propylenediamine, 3-nitraza-1,5-pentanediamine, and 3,6-dinitraza-1,8-octanediamine.

3-Nitrazabutylamine was the first ω-aminoalkyl secondary nitramine to be prepared.[3] It was synthesized by a six-step process starting with 4-azapentanonitrile. It was of interest to find a general method for preparing ω-aminoalkyl secondary nitramines which was more direct and did not involve the preparation of the hazardous azide.

The most direct route would be the conversion of an ω-aminoalkyl imine to the corresponding nitramine:

$$\mathrm{RNCH_2CH_2NH_2} \longrightarrow \mathrm{RN(NO_2)CH_2CH_2NH_2}$$

However, direct nitration is not feasible, as both the primary and secondary amino groups would be attacked. To circumvent this, it would be necessary to block the primary amino group, nitrate the secondary amine without affecting the blocking group or groups, and finally regenerate the primary amino group.

In the first approach the Schiff bases of diethylenetriamine with benzaldehyde and salicylaldehyde were prepared. The Schiff base from benzaldehyde was unstable to nitric acid, but it was possible to prepare the nitric acid salt of the salicylaldehyde derivative. However, attempts to dehydrate this salt to the corresponding nitramine were unsuccessful, this approach was abandoned.

Another route to this problem was suggested by the facile nitrolysis of *N,N*-dialkyl acetamides in trifluoroacetic anhydride (TFAA):[4]

$$\mathrm{R_2NCOCH_3} \xrightarrow[\mathrm{TFAA}]{\mathrm{HNO_3}} \mathrm{R_2NNO_2}$$

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(3) M. B. Frankel and Karl Klager, *J. Am. Chem. Soc.* **78**, 5428 (1956).

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Inasmuch as *N,N*-dialkyl acetamides are stronger bases than *N*-alkyl diacetamides, it might be expected that the latter would be less susceptible to nitrolysis. In order to test this hypothesis, *N*-butyldiacetamide was prepared and an attempt to nitrolyze it to *N*-acetylbutylnitramine was made:

$$C_4H_9N(COCH_3)_2 \xrightarrow[TFAA]{HNO_3} C_4H_9\overset{NO_2}{\underset{|}{N}}COCH_3$$

As expected, this nitrolysis did not take place. On the basis of these results, it then seemed feasible to prepare ω-aminoalkyl secondary nitramines in three steps: (1) complete acetylation of an ω-aminoalkyl imine, (2) selective nitrolysis of the amide group, and (3) hydrolysis of the diacetamido groups:

$$RN(CH_2)_nNH_2 \xrightarrow{(CH_3CO)_2O} \underset{II}{RN(CH_2)_nN(COCH_3)_2} \xrightarrow[TFAA]{HNO_3}$$

Ia. R = CH_3, n = 3
Ib. R = $CH_2CH_2NH_2$, n = 2
Ic. R = $CH_2CH_2NHCH_2CH_2NH_2$, n = 2

$$\underset{III}{RN(CH_2)_nN(COCH_3)_2} \xrightarrow{HCl} \underset{IV}{RN(CH_2)_nNH_2.HCl}$$

The acetylation reactions were carried out by treating the amines with an excess of acetic anhydride at 10–15°. After the initial exothermic reaction was completed, the reaction mixture was refluxed under a fractionating column until the theoretical amount of acetic acid was collected. In this manner, *N*-methyl-*N,N',N'*-triacetyl-1,3-propylenediamine (IIa), *N,N,N',N',N''*-pentaacetyldiethylenetriamine (IIb), and *N,N,N',N',N'',N'''*-hexaacetyltriethylenetetramine (IIc) were prepared.

The nitrolysis of *N,N*-dialkyl acetamides, using absolute nitric acid and trifluoroacetic anhydride, was rapid, being complete in twenty minutes at −5°.[4] Robson and Reinhart[4] reported that the nitrolysis was retarded easily both by steric hindrance from the *N*-alkyl group and by electronegative substituents. This was proved in our work, where it was found that the nitrolysis of IIa, IIb, and IIc was very slow.

A series of experiments were carried out in which the nitrolysis mixture of IIb, nitric acid, and trifluoroacetic anhydride was allowed to stand at 0° and −21° for varying lengths of time. Optimum yields of *N,N,N',N'*-tetraacetyl-*N''*-nitrodiethylenetriamine (IIIb) were obtained after 65 hours at 0° (91.0%) and 168 hours at −21° (87.6%). Shorter reaction times gave mixtures of starting material and product, while higher temperatures gave low yields. It was of interest to investigate other methods for carrying out this nitrolysis reaction. Inasmuch as the principal product of reaction between nitric acid and trifluoroacetic anhydride is nitrogen pentoxide, the direct use of nitrogen pentoxide, prepared from nitric acid and phosphorus pentoxide, was investigated. Treatment of IIb with a solution of nitrogen pentoxide in methylene chloride at 0° for 65 hours gave a mixture of predominately starting material and some product. In order to determine whether this nitrolysis reaction would proceed more readily in a polar solvent, nitric acid, sulfuric acid, sulfur dioxide, dichloroacetic acid, and trifluoroacetic acid were tried as solvents. No product was obtained with either absolute nitric acid or concentrated sulfuric acid. Sulfur dioxide, dichloroacetic acid, and trifluoroacetic acid gave IIb in yields of 68.2%, 71.4%, and 80.8%, respectively. The use of nitric acid and trichloroacetic anhydride as a nitrolysis medium gave only a 11.6% yield of product. *N*-Methyl-*N*-nitro-*N,N'*-diacetyl-1,3-propylenediamine (IIIa) and *N,N,N',N'*-tetraacetyl-*N'',N'''*-dinitrotriethylenetriamine (IIIc) were prepared in 91.0% and 85.7% yields, respectively, using a nitrolysis mixture of nitric acid and trifluoroacetic anhydride.

Hydrolysis of IIIa, IIIb, and IIIc with concentrated hydrochloric acid took place readily with the formation of 4-nitraza-1-pentylamine hydrochloride (IVa), 3-nitraza-1,5-pentanediamine dihydrochloride (IVb), and 3,6-dinitraza-1,8-octanediamine dihydrochloride (IVc). The results are summarized in Table I.

EXPERIMENTAL[5,6]

N,N'-Disalicylidene-3-aza-1,5-pentanediamine. A mixture of 12.4 g. (0.12 mole) of diethylenetriamine, 22.4 g. (0.18 mole) of salicylaldehyde, and 70 ml. of dry benzene was refluxed under a Dean-Stark trap. After 4 hr. the theoretical amount of water was collected. The solution was concentrated *in vacuo* and the residual oil was poured into water. The organic layer was extracted with methylene chloride, dried, and concentrated to give 23.7 g. (82.9%) of viscous yellow oil, n_D^{29} 1.6134.

In a similar manner *N,N'*-dibenzylidene 3-aza-1,5-pentanediamine was prepared in quantitative yield after only 1 hr. of refluxing.

Nitric acid salt of N,N'-disalicylidene-3-aza-1,5-pentanediamine. A solution 3.1 g. (0.01 mole) of *N,N'*-disalicylidene 3-aza-1,5-pentanediamine in 25 ml. of methanol was cooled in an ice-bath and 0.63 g. (0.01 mole) of 99% nitric acid was added. A yellow solid precipitated; it was collected, washed with ether, and dried to give 3.4 g. (91.0%), m.p. 152–155°, of product. Recrystallization from methanol gave yellow needles, m.p. 153–155°.

Anal. Calcd. for $C_{18}H_{22}N_4O_5$: C, 57.74; H, 5.92; N, 14.97. Found: C, 57.75; H, 5.79; N, 15.38.

Attempted dehydration of the nitric acid salt of N,N'-disalicylidene-3-aza-1,5-pentanediamine. To 175 ml. of acetic anhydride was simultaneously added 112.2 g. (0.3 mole) of the nitric acid salt of *N,N'*-disalicylidene 3-aza-1,5-pentanediamine and 1.5 g. (0.015 mole) of 37% hydrochloric acid, at ambient temperature. After 2 hr. the solid had dissolved to give a brown solution. The mixture was hydrolyzed by the addition of 300 ml. of water which caused the formation of two layers. The aqueous layer was separated and ex-

(5) All melting points are uncorrected.

(6) Microanalyses by Dr. A. Elek, Elek Microanalytical Laboratory, 4763 W. Adams Blvd., Los Angeles, Calif.

TABLE I

NITROLYSIS AND HYDROLYSIS OF IIIa, IIIb, AND IIIc

Acetylated Amine	M.P.	Recryst. Solvent	Yield, %	Formula	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl
$CH_3N(COCH_3)CH_2CH_2CH_2N(COCH_3)_2$	[a]		90.7	$C_{10}H_{18}N_2O_3$	56.05	8.47	13.08		55.69	8.56	12.48	
$N(COCH_3)—[CH_2CH_2N(COCH_3)_2]_2$	109–110	Isopropanol	52.7	$C_{14}H_{23}N_3O_5$	53.66	7.40	13.41		53.37	7.20	12.99	
$[CH_2N(COCH_3)CH_2CH_2N(COCH_3)_2]_2$	150–151	Ethanol	72.0	$C_{18}H_{30}N_4O_6$	54.26	7.59	14.06		54.27	7.82	13.82	
Nitrolysis Product												
$CH_3N(NO_2)CH_2CH_2CH_2N(COCH_3)_2$	[b]		91.6[c]	$C_8H_{15}N_3O_4$								
$N(NO_2)—[CH_2CH_2N(COCH_3)_2]_2$	122–123	Ethanol	91.0[d] 87.6[e]	$C_{12}H_{20}N_4O_6$	45.56	6.37	17.71		46.12	6.47	17.58	
$[CH_2N(NO_2)CH_2CH_2N(COCH_3)_2]_2$	112–113	Methanol	85.7[f]	$C_{14}H_{24}N_6O_8$	41.58	5.98	20.79		41.53	5.90	20.56	
Nitrazamine Hydrochloride												
$CH_3N(NO_2)CH_2CH_2CH_2NH_2 \cdot HCl$	123–124	Ethanol	67.8	$C_4H_{12}ClN_3O_2$	28.34	7.14	24.79	20.92	28.68	7.50	24.24	21.21
$N(NO_2)—[CH_2CH_2NH_2 \cdot HCl]_2$	261–263	78% Ethanol	89.1	$C_4H_{14}Cl_2N_4O_2$	21.64	6.31	25.24	31.94	21.61	6.56	25.77	32.25
$[CH_2N(NO_2)CH_2CH_2NH_2 \cdot HCl]_2$	285–295	Water	90.0	$C_6H_{18}Cl_2N_8O_4$	23.31	5.87	27.19		23.77	5.99	26.89	

[a] B.p. 153°/0.5 mm., n_D^{25} 1.4862. [b] Could not be distilled without decomposition, n_D^{25} 1.5004. [c] Reaction time of 7 days at −20°. [d] Reaction time of 65 hr. at 0°. [e] Reaction time of 168 hr. at −20°. [f] Reaction time of 7 days at −20° and 3 days longer at 0°.

tracted with methylene chloride. The extracts were combined with the water insoluble layer, concentrated and fractionated through a Holzman column to give 36.1 g. of salicylaldehyde, b.p. 38–40°/0.55 mm., n_D^{25} 1.5701; and 16.8 g. of a yellow liquid, b.p. 88–90°/0.25 mm., n_D^{25} 1.5309, whose analyses corresponded to 2-acetoxybenzaldehyde.

Anal. Calcd. for $C_9H_8O_3$: C, 65.81; H, 4.91. Found: C, 65.91; H, 5.02.

The aqueous phase from the reaction mixture was made basic and extracted with methylene chloride for 12 hr. on a continuous extractor. Concentration of the methylene chloride solution left no residue.

N,N,N′,N′,N″-Pentaacetyldiethylenetriamine (IIb). To 4080 g. (40.0 moles) of acetic anhydride was added, dropwise, 515 g. (5.0 moles) of redistilled diethylenetriamine, keeping the temperature at 10–15° by external cooling. The solution was warmed to room temperature and then refluxed under a 20 plate Oldershaw column for 30 hr., during which time the theoretical amount of acetic acid was collected. The residue was concentrated *in vacuo*, leaving a viscous dark brown oil which solidified. The product was recrystallized from 3 l. of 2-propanol to give 823 g. (52.7%) of light yellow crystals, m.p. 106–108°. A second recrystallization gave a white solid; m.p. 109–110°.

The nitrolysis of N,N,N′,N′,N″-pentaacetyldiethylenetriamine. A. *With nitric acid and trifluoroacetic anhydride.* To 80 ml. (0.58 mole) of trifluoroacetic anhydride was added dropwise 16.8 ml. (0.4 mole) of 98–99% technical nitric acid, keeping the temperature at −10 to −20°. Then 31.3 g. (0.1 mole) of *N,N,N′,N′,N″*-pentaacetyldiethylenetriamine was added. The solid dissolved and the solution was allowed to stand in an ice-bath for 65 hr. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in methylene chloride, washed with saturated sodium carbonate solution, dried, and concentrated, leaving 28.8 g. (91.0%) of white solid, m.p. 120–122°. Recrystallization from ethanol raised the melting point to 122–123°.

B. *With nitrogen pentoxide in trifluoroacetic acid.* The Inorganic Synthesis preparation of nitrogen pentoxide[7] gives a yield of 50% and the procedure is only applicable for small-scale runs. This process was modified to give improved yields on a larger scale. In a 2-l. glass resin pot fitted with a sealed stainless steel horseshoe-shaped stirrer driven by an air motor, solid addition flask, and drying tube, was placed 336 ml. (8.0 moles) of 98–99% technical nitric acid. The acid was cooled to −20 to −10° and 426 g. (3.0 moles) of phosphorus pentoxide was added portionwise from the solid addition flask, keeping the temperature about −10° by external cooling. After the addition was complete, the reaction mixture was allowed to warm to room temperature. The addition flask was replaced with a distillation head and receiver which was connected through a drying tube to the water aspirator. The reaction mixture was then stirred under vacuum at ambient temperature for 4 hr. The nitrogen pentoxide which was collected in the receiver was light yellow to white needles, the yield was 333 g. (77%).

A mixture of 6.26 g. (0.02 mole) of *N,N,N′,N′,N″*-pentaacetyldiethylenetriamine, 12.0 g. (0.11 mole) of nitrogen pentoxide, and 10 ml. (0.16 mole) of trifluoroacetic acid was allowed to stand in an ice-bath for 43 hr., and then concentrated *in vacuo*. Working up in the same manner as described in A., above, there was obtained 5.1 g. (80.8%) yield of product, m.p. 121–122°.

C. *With nitrogen pentoxide in sulfur dioxide.* The procedure was the same as in B., above, except that a glass pressure bottle was used for the reaction vessel.

D. *With nitrogen pentoxide in dichloroacetic acid.* A mixture of 6.26 g. (0.02 mole) of *N,N,N′,N′,N″*-pentaacetyldiethylenetriamine, 10.8 g. (0.1 mole) of nitrogen pentoxide, and 38.7 g. (0.3 mole) of dichloroacetic acid was allowed to stand in an ice-bath for 24 hr. The reaction mixture was poured on ice and a saturated sodium carbonate solution was added until the resulting *p*H of the solution was 10. The product was collected and recrystallized from ethanol to give 4.52 g. (71.4%) of white crystals, m.p. 118–120°.

3-Nitraza-1,5-pentanediamine dihydrochloride (IId). A mixture of 31.6 g. (0.1 mole) of *N,N,N′,N′*-tetraacetyl-*N″*-nitrodiethylenetriamine and 50 ml. of 37% hydrochloric acid was refluxed for 4 hr. The reaction mixture was cooled and diluted with 50 ml. of methanol. The product was collected and dried to give 19.7 g. (89.1%) of white crystals, m.p. 259–263° dec. Recrystallization from 78% ethanol raised the melting point to 261–263° dec.

Acknowledgment. We are indebted to the Bureau of Ordnance for the financial support of this work and to Mr. E. R. Wilson for aid in the experimental work.

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[CONTRIBUTION FROM THE REGA INSTITUTE, UNIVERSITY OF LOUVAIN]

Phenoxazines. I. Ring-Substituted Derivatives

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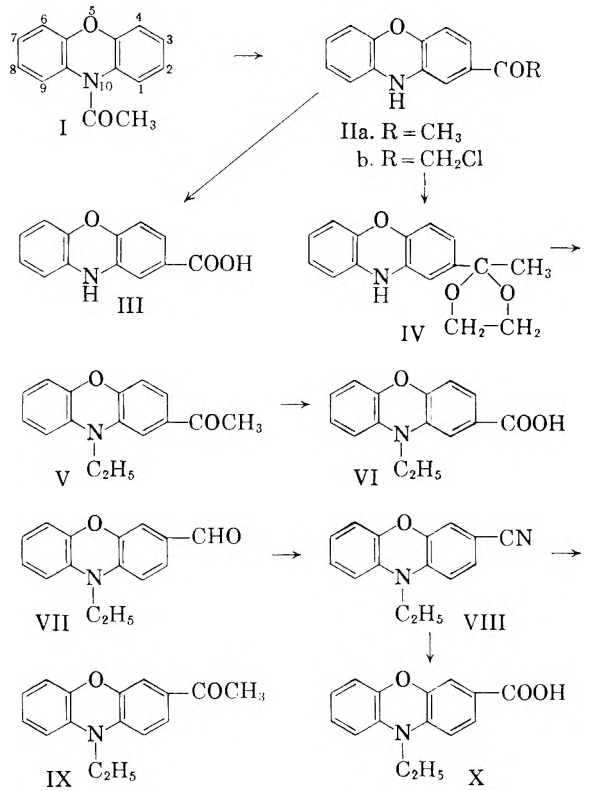
Several 2-acylphenoxazines have been prepared by a Friedel-Crafts reaction. The structure of these products is based on the examination of the infrared and ultraviolet spectra of 2- and 3-acetyl-10-ethylphenoxazine. Other 2-substituted phenoxazines also were synthesized.

Several C-monoacylphenoxazines were prepared by a Friedel-Crafts reaction with 10-acetylphenoxazine (I). Because no method is known for the transformation of phenoxazines into substances of known structure, the formulation of our reaction products is based on the infrared bands typical for substituted benzene derivatives and supported by a comparison of their ultraviolet spectra with those previously reported for phenothiazine.

Unsymmetrical trisubstituted benzene structures show a characteristic band in the 12.0–12.5 μ region, while vicinal trisubstituted derivatives have a band in the 12.5–13.15 μ region.[1,2,3] It has been shown that these bands are present in phenothi-

azines having a trifluoromethyl-[4,5,6,7] a fluoro-[5] or a methylmercapto- substituent.[8] These characteristic bands were also observed in the monomethylcarbazoles.[9]

The bands typical for 1,2,4-trisubstituted benzene derivatives were present in our acylphenoxazines. But, as both 2- or 3- substituted phenoxazines have this configuration, it was necessary to prepare compounds with these structures.



The direct ethylation of 2-acetylphenoxazine by heating with ethyl iodide, a method used for the preparation of 2-acetyl-10-ethylphenothiazine,[10] gave only starting material. It has already been observed that some phenoxazines are not acidic enough for ethylation under these conditions.[11]

It has been shown that alkylation of 2-acetylphenothiazine in the presence of sodamide gives poor yields, but that the same reaction could be effected after protection of the ketone group as a ketal.[12] The ethylenedioxy derivative of 2-acetylphenoxazine (IV) was prepared according to the method of Salmi[13] by azeotropic distillation of the ketone and ethyleneglycol in an inert solvent (benzene, toluene) in the presence of *p*-toluenesulfonic acid. The ketal was also prepared, in better yield, by acid catalysed exchange dioxolanation with 2-methyl-2-ethyl-1,3-dioxolane (butanone cycloethylene ketal).[14] From this ketal (IV), 2-acetyl-10-ethylphenoxazine (V) was prepared by ethylation in the presence of sodamide, followed by acid hydrolysis. 2-Acetyl-10-ethylphenoxazine was oxidized with sodium hypobromite to the corresponding acid (VI).

By analogy with observations in the carbazole[15] and phenothiazine series[16,17] the Vilsmeier-Haack reaction was expected to yield 3-formyl-10-ethylphenoxazine (VII). Its oxime was dehydrated to the nitrile (VIII). This product gave, by reaction with methylmagnesiumiodide, the corresponding acetyl derivative (IX). The nitrile was also hydrolysed to 3-carboxy-10-ethylphenoxazine (X), which had the melting point of the same product prepared by another method.[11b]

We had also hoped to prepare 3-acetyl-10-ethylphenoxazine by Friedel-Crafts acetylation of 10-ethylphenoxazine; but the product we obtained corresponded to analysis for a diacetyl derivative (formulated as 3,7-diacetyl-10-ethylphenoxazine). This structure is also supported by the infrared spectrum (Fig. 1, Curve D). The bands typical for a 1,2,4-trisubstituted benzene derivative (12.16 and 12.38 μ) are present, but the strong band in the 13.0–13.6 μ region, typical for an *o*-disubstituted benzene structure[3] is absent. The carbonyl band at 5.98 μ is also double. This result is in agreement with the work of Cauquil and Casadevall,[18] who proved that a Friedel-Crafts reaction with 10-methylphenothiazine gave 3,7-diacetyl-10-methylphenothiazine, and not 3-acetyl-10-methylphenothiazine, as has been stated.[19]

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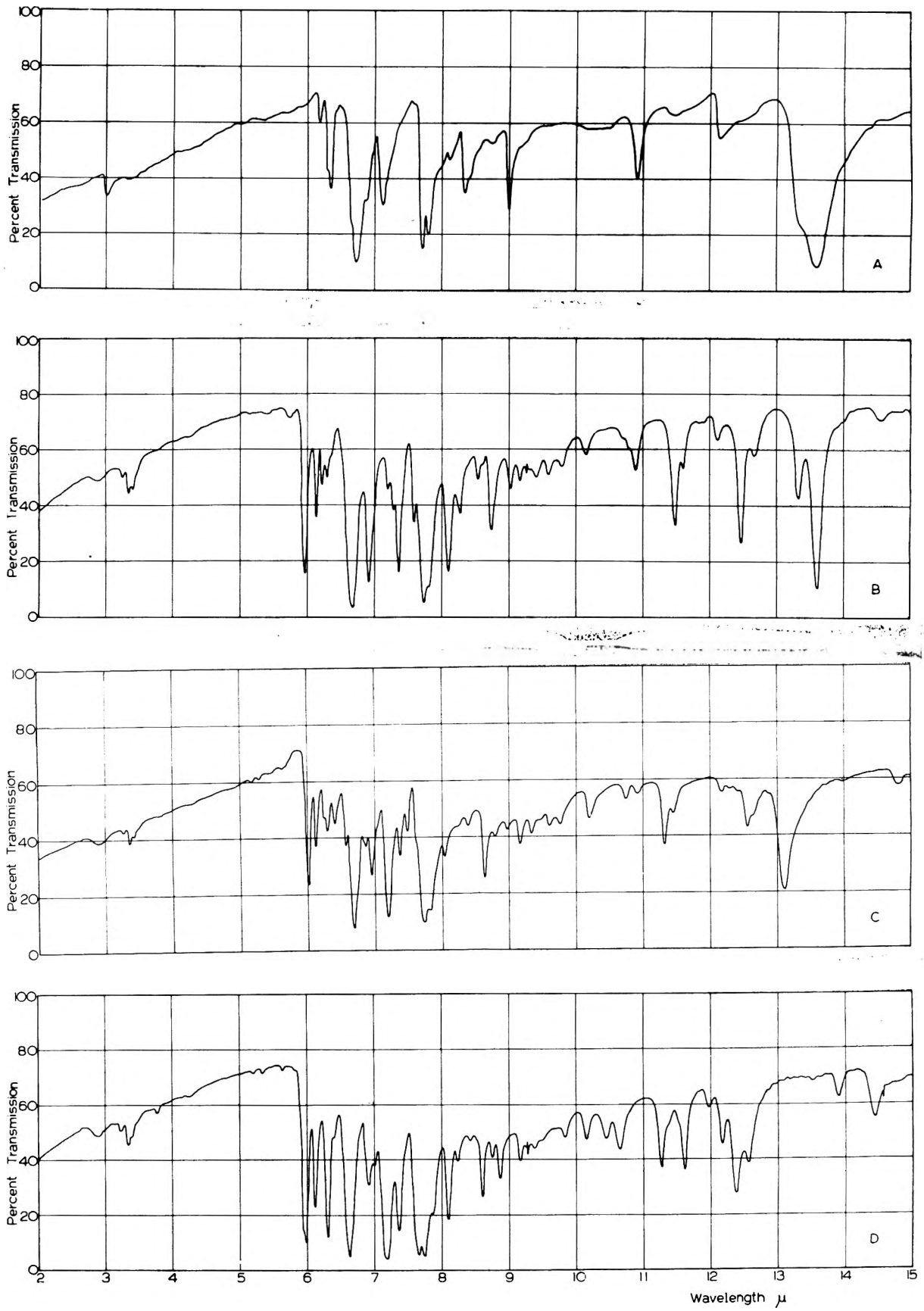


Fig. 1. Infrared spectra: curve A, phenoxazine; curve B, 2-acetyl-10-ethylphenoxazine (V); curve C, 3-acetyl-10-ethylphenoxazine (IX); curve D, 3,7-diacetyl-10-ethylphenoxazine. Concentration 0.5% in potassium bromide disks (approx. 0.5 mm. thick)

TABLE I

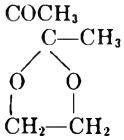
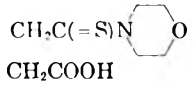
ULTRAVIOLET SPECTRA[a] OF ACETYLPHENOTHIAZINES AND -PHENOXAZINES

Phenothiazine	λmax. mμ (log ε)				
1 2-$COCH_3$	244.5 (4.42)		281.5 (4.44)		
2 2-$COCH_3$-10-C_2H_5	244.5 (4.35)		282.5 (4.33)		
3 3-$COCH_3$-10-CH_3	235 (4.24)	269 (4.33)	[285 (4.25)]		374 (3.74)
4 3,7-di($COCH_3$)-10-C_2H_5			289 (4.59)		400 (3.90)
Phenoxazine					
5 2-$COCH_3$	224 (4.32)		271 (4.49)	323 (3.84)	
6 2-$COCH_3$-10-C_2H_5	227 (4.30)	[260 (4.39)]	273 (4.48)	328 (3.95)	
7 3-$COCH_3$-10-C_2H_5		261 (4.38)	[274 (4.25)]		395 (4.11)
8 3,7-di($COCH_3$)-10-C_2H_5			273 (4.65)	334 (3.84)	418 (4.23)
9 2-$COCH_3$-10-$COCH_3$			244 (4.40)	279 (3.98)	

[a] Ultraviolet maxima were determined in ethanol solution. The figures between square brackets indicate a shoulder. The values for compounds 2-4 are taken from ref. 18.

TABLE II

SUBSTITUTED PHENOXAZINES

	Substituent Y	Substituent X	Method[a]	M.P.°	Yield, %	Formula	Nitrogen Calcd.	Nitrogen Found
IIa	$COCH_3$	H	A	211–213	89	$C_{14}H_{11}NO_2$	6.63	6.70
	$C(=NOH)CH_3$	H	A	217–220 dec.		$C_{14}H_{12}N_2O_2$	11.66	11.63
	$COCH_3$	$COCH_3$	A	106–108		$C_{16}H_{13}NO_3$	5.24	5.50
IV		H	E	127–129	39	$C_{16}H_{15}NO_3$	5.20	5.50
					60			
V	$COCH_3$	C_2H_5	E	77–79	56	$C_{16}H_{15}NO_2$	5.53	5.75
	$C(=NOH)CH_3$	C_2H_5	A	153–156		$C_{16}H_{16}N_2O_2$	10.44	10.16
	$COCH_2CH_3$	H	A	215–216	92[b]	$C_{15}H_{13}NO_2$	5.85	5.95
	$CO(CH_2)_2CH_3$	H	A	197–198	90[c]	$C_{16}H_{15}NO_2$	5.53	5.72
	COC_6H_5	H	A	197–201	38	$C_{19}H_{13}NO_2$	4.87	5.08
IIb	$COCH_2Cl$	H	A	218–219	96	$C_{14}H_{10}ClNO_2$	5.37	5.50
	$COCH_2Cl$	$COCH_3$	A	158–159	90[d]	$C_{16}H_{12}ClNO_3$	4.62	4.98
III	COOH	H	E	252–254	88	$C_{13}H_9NO_3$	6.17	6.21
VI	COOH	C_2H_5	E	218–220	28	$C_{15}H_{13}NO_3$	5.48	5.21
	$COOC_2H_5$	H	E	200–202	95	$C_{15}H_{13}NO_3$	5.48	5.58
	C_2H_5	H	E	110–112	83	$C_{14}H_{13}NO$	6.63	6.70
	C_2H_5	$COCH_3$	E	45–48		$C_{16}H_{15}NO_2$	5.53	5.70
	$CHOHCH_3$	H	E	132–134		$C_{14}H_{13}NO_2$	6.16	5.89
		H	E	187–189 dec.	54	$C_{18}H_{18}N_2O_2S$	8.58	8.41
	CH_2COOH	H	E	192–193 dec.	83	$C_{14}H_{11}NO_3$	5.81	5.92

[a] A: prepared by the method (a) described for 2-acetylphenoxazine. E: see Experimental. [b] When an equimolecular amount of propionyl chloride was used, the yield was 56%. It was also prepared from 10-propionylphenoxazine (m.p. 99–101°). [c] An equimolecular amount of butyrylchloride gave 75%. [d] Was also prepared by refluxing (2 hr.) 2-chloroacetylphenoxazine in acetic anhydride.

The infrared spectra of 2- and 3-acetyl-10-ethylphenoxazine (Fig. 1 Curves B and C) show the maxima of 1,2,4-trisubstituted (12.48 and 11.28, 12.56, and 11.32 μ) and of 1,2-disubstituted benzene derivatives (13.60 and 13.10 μ). The bands of asymmetrically substituted benzene structures are also present in the spectra of the acids VI and X but are weak (*cf.* ref. 11b).

The assignment of structure is also supported by the ultraviolet spectra (Table I). Cauquil and Casadevall[18] have found that 3-acetylphenothiazines absorb at a much higher wave length than the corresponding 2-acetyl derivatives. The same is true for the phenoxazines. *N*-alkylation has practically no influence on the maxima (compounds 1–2 and 5–6). Similarly, phenothiazine (254 and 318 mμ[20]) and 10-ethylphenothiazine (256 and 310 mμ[21]) have practically the same maxima. *N*-acetylation brings about a shift of the maxima to a shorter wave length (compounds 5–9). The same phenomenon was also observed with 10-acetylphenothiazine (229 and 260 mμ).[21]

Our results show that, when the amino group of phenoxazine is deactived by acylation, substitution during the Friedel-Crafts reaction occurs in one benzene ring at the carbon atom in the position *para*

(20) D. F. Houston, E. B. Kester, and F. De Eds, *J. Am. Chem. Soc.*, 71, 3816 (1949).

(21) R. Dahlbom and J. Ekstrand, *Acta Chem. Scand.*, 5, 102 (1951).

to the oxide bridge. Substitution occurs also in position 2 with *N*-acetylcarbazole,[22,23] -phenothiazine,[10,24-27] and -9,10-dihydroacridine.[28] 2,8-Diacetylphenothiazine could only be obtained by using a large excess of aluminum chloride and acetyl chloride.[29]

Friedel-Crafts reaction with *N*-alkyl carbazole,[30] -phenothiazine,[18] and also -phenoxazine gives a diacetyl derivative, with the substituents in the position *para* to the imino group.

Carbazole itself gives a 3,6-diacetyl derivative.[30] Phenothiazine yields 10-acetyl- and 2,10-diacetylphenothiazine.[24] Substitution of phenoxazine occurs at the same place as with phenothiazine. The properties of our 2-acetylphenoxazine are identical with those described for a product obtained recently by the same method,[31] but it has been formulated, without proof, as 3-acetylphenoxazine.

2-Ethylphenoxazine was obtained by Wolff-Kishner reduction, and 1-(2-phenoxazinyl)ethanol by sodiumborohydride reduction of 2-acetylphenoxazine. (IIa).

2-Phenoxazinyl acetic acid was prepared by hydrolysis of the thiomorpholide, obtained by Willgerodt reaction with 2-acetylphenoxazine. The decarboxylation of this acid to 2-methylphenoxazine did not proceed satisfactorily.

2-Phenoxazine carboxylic acid (III) was prepared by alkaline hydrolysis of the pyridine addition product of 2-chloroacetyl-10-acetylphenoxazine (*cf.* ref. 25, 27, 32).

EXPERIMENTAL[33]

2-Acetylphenoxazine (IIa). (a). A suspension of 22.5 g. (0.10 mole) of 10-acetylphenoxazine in 400 ml. of carbon disulfide was added slowly and with stirring to 40 g. (0.3 mole) of powdered aluminum chloride. After refluxing for 1 hr., 11.7 g. (0.15 mol) of acetyl chloride was added at a rate sufficient to maintain boiling. The mixture was refluxed with stirring for another 2 hr. and, after cooling, the solvent was decanted. The gummy residue was decomposed with crushed ice and conc. hydrochloric acid. The precipitate was filtered, washed, and suspended in 200 ml. of glacial acetic acid and 50 ml. of 20% hydrochloric acid and refluxed for 10 min. The precipitate was filtered, washed with water, and dried, 22 g., m.p. 209–212°. By continuous extraction with 250 ml. of benzene, 20.2 g. (89%) of greenish yellow crystals were obtained, m.p. 211–213°.

When aluminum chloride was added to a suspension of equimolecular amounts of acetyl chloride and 10-acetylphenoxazine in carbon disulfide, the yield was only 55%.

In one experiment, *2,10-diacetylphenoxazine* was isolated before hydrolysis. Recrystallization in ethanol gave a white product with a melting point of 106–108°.

The *oxime* of 2-acetylphenoxazine was prepared by refluxing with hydroxylamine hydrochloride in pyridine-ethanol solution: m.p. 217–220° dec.

(b) A suspension of 2.6 g. of 2-chloroacetylphenoxazine and 3.2 g. zinc powder in 20 ml. of glacial acetic acid was heated with stirring at 90–95° during 2.5 hours. After refluxing for a short time, zinc was removed by filtration and washed with 10 ml. of hot acetic acid. After cooling, 1.7 g. (75%) of greenish-yellow crystals, m.p. 213–215°, were obtained.

(c) Aluminum chloride was added to a solution of phenoxazine and acetyl chloride in carbon disulfide, as described by Müller.[31] The portion boiling at 215–230°/17 mm. was recrystallized from ethanol and gave 5.5 g. of 10-acetylphenoxazine, m.p. 142–145°. The portion boiling at 255–280°/17 mm. gave upon recrystallization in ethanol, 5.5 g. of yellow crystals, m.p. 100–130°. This material was refluxed in 25 ml. acetic acid and 6 ml. of 20% hydrochloric acid for 10 min., and gave, upon cooling, 4.20 g. of a product melting at 212–214°. Recrystallization in ethanol yielded greenish-yellow crystals, m.p. 214–216°, undepressed upon admixture of 2-acetylphenoxazine prepared by method a.

Phenoxazine-2-carboxylic acid (III). A 54-g. sample (0.18 mole) of 2-chloroacetyl-10-acetylphenoxazine was dissolved by heating in 200 ml. of pyridine. The solution was kept at 90° for 10 min., cooled, and poured into 500 ml. dry ether. The precipitate was filtered, washed with 150 ml. of ether, and dissolved in 150 ml. of hot ethanol. The solution was made basic by adding 500 ml. of 10% sodium hydroxide solution, refluxed for 10 min., distilled under reduced pressure to remove most of the alcohol, and acidified with 20% hydrochloric acid, to yield 38 g. (88%) of a tan-colored product, m.p. 242–244°. Recrystallization in ethanol-water raised the melting point to 252–254°.

The acid was transformed into the *ethyl ester* by refluxing for 12 hr. in hydrochloric acid-absolute ethanol. The melting point of the dark green product was 200–202°.

2-Ethylphenoxazine. A mixture of 64.5 g. of 2-acetylphenoxazine and 53 ml. 80% hydrazine hydrate in 270 ml. of ethylene glycol was refluxed for 30 min. A solution of 48 g. of potassium hydroxide in 110 ml. of ethylene glycol was added and refluxed for another hour. Water and ethylene glycol were distilled until a boiling point of 190–195° was reached; refluxing was continued for 3 hr. The solution was cooled, and after adding 600 ml. of ethanol and 1200 ml. of water, the precipitate was collected. A small amount of product that had sublimed during distillation and refluxing was washed with dilute acid and filtered. The wet products were dissolved in benzene, the water layer was removed, and the organic solution was dried. After evaporation of the solvent, the product was distilled, 50 g. (83%) b.p. 170°/0.7 mm. m.p. 108–110°. After sublimation at 140° (bath temperature)/0.5 mm. the melting point of the white product was 110–112°.

2-Ethyl-10-acetylphenoxazine. 2-Ethylphenoxazine was refluxed (3 hr.) with acetic anhydride. The solution was decomposed with water, and after standing for several weeks, the product crystallized. After three recrystallizations in ethanol-water, the melting point was 45–48°.

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(31) P. Müller, Ng. Ph. Buu-Hoï, and R. Rips, *J. Org. Chem.*, 24, 37 (1959).

(32) S. P. Massie, P. K. Kadaba, and C. Smith, *J. Org. Chem.*, 24, 251 (1959).

(33) All melting points are uncorrected. The microanalyses were performed by Dr. A. Bernhardt, Mülheim, Germany, and the infrared spectra were obtained by Dr. Z. Hainski, S.E.R.A.I. Laboratories, Brussels.

2,10-Diethylphenoxazine was a lightly colored oil, distilling at 160°/0.25 mm., that did not crystallize in the refrigerator. It was prepared by refluxing (3 hr.) equimolecular amounts of sodamide and 2-ethylphenoxazine in toluene with 1.6 moles of ethyl iodide. Ethylation in liquid ammonia gave a dark product, that decomposed upon distillation.

1-(2-Phenoxazinyl)ethanol. A 750-mg. sample of sodium borohydride dissolved in 20 ml. of isopropanol was added to a solution of 2.8 g. of 2-acetylphenoxazine in 80 ml. of dioxane. The mixture was stirred for 2 hr., then heated on the waterbath for an $^1/_2$ hr.; after cooling, the excess hydride was decomposed with acid. After concentrating *in vacuo* and adding water, 2.25 g. of a product melting at 90–100° was obtained. After recrystallization in benzene-petroleum ether, and cyclohexane-benzene, the melting point of the light rose colored product was 132–134°.

Reduction with lithium aluminum hydride in ether gave only a very dark product. There was no uptake of hydrogen when a dioxane solution of 2-acetylphenoxazine was shaken in the presence of platinum (Adams) catalyst.

2-Acetylphenoxazine cycloethylene ketal (IV). (a) A mixture of 20 g. 2-acetylphenoxazine, 160 ml. ethylene glycol, 500 ml. toluene (distilled over sodium) and 600 mg. *p*-toluenesulfonic acid monohydrate was distilled during 7 hr. During the operation, the upper phase of the distillate was returned to the flask.

The contents of the flask were cooled, neutralized with a sodium bicarbonate solution, washed with water, and dried over sodium sulfate. The filtered solution was evaporated to dryness, under reduced pressure, and the residue was taken up with 200 ml. of benzene. The unchanged acetylphenoxazine (2 g.) was filtered and the filtrate was poured into a column of silica gel (2 cm. diameter, 18 cm. height). The ketal was eluted with benzene (500 ml.). After evaporation of the solvent 9.4 g. (39%) of greenish crystals, m.p. 118–126°, was obtained. After recrystallization in ethanol, the melting point was 127–129°.

(b) A mixture of 10 g. of 2-acetylphenoxazine, 100 ml. of 2-methyl-2-ethyl-1,3-dioxolane, and 500 mg. *p*-toluene sulfonic acid monohydrate was heated, and the liberated butanone, admixed with the reactant dioxolane, was distilled slowly through a short Vigreux column for a period of 5 hr. (15 ml. distillate). The contents of the reaction flask were diluted with 100 ml. of benzene, neutralized with sodium bicarbonate, and further worked up as described under a. Yield: 7.30 g. (60%), m.p. 120–126°.

2-Acetyl-10-ethylphenoxazine (V). To a solution of 10.8 g. (40 mmoles) of 2-acetylphenoxazine cyclo ethylene ketal in 15 ml. toluene were added 1.60 g. (40 mmoles) of sodamide, and the mixture was refluxed with stirring for $^1/_4$ hr. A 10-g. sample (80 mmoles) of ethyl iodide was added and refluxing was continued for 2 hr. After washing with water and drying, the solvent was removed under reduced pressure and the residue was refluxed for 15 min. in 50 ml. ethanol and 10 ml. 3.5% hydrochloric acid solution. After diluting with water, the suspension was extracted with 500 ml. of benzene. The yellow insoluble product at the interphase was separated and identified as unchanged 2-acetylphenoxazine (0.64 g., m.p. 209–212°). The benzene solution, after washing and drying, was concentrated to a volume of 100 ml., and another 0.66 g. of 2-acetylphenoxazine, m.p. 208–216°, was filtered. The filtrate was poured onto a column of silica gel (diameter 2 cm., height 17 cm.), and the product was eluted with benzene. The solution was concentrated to a small volume and the product was precipitated by addition of petroleum ether, 5.7 g., m.p. 65–70°. After recrystallization in ethanol-water and in methanol, 4.0 g. of yellow crystals, m.p. 77–79°, was obtained.

An attempt to prepare 2-acetyl-10-ethylphenoxazine by heating 2-acetyl-phenoxazine with ethyl iodide in absolute ethanol at 120° gave only starting material.

10-Ethylphenoxazine-2-carboxylic acid (VI). A 2.37-g. sample (0.79 ml. = 15 mmoles) of bromine was dissolved in a cold (0°) solution of 1.60 g. (40 mmoles) of sodium hydroxide in 15 ml. water. A solution of 1.25 g. (5 mmoles) of 2-acetyl-10-ethylphenoxazine in 10 ml. dioxane was added, and the mixture was stirred at 0° for 30 min., and at room temperature for 60 min. The dioxane was distilled, under reduced pressure, at a bath temperature of maximum 50°, and the excess hypobromite was decomposed with a small amount of sulfite. The alkaline solution was extracted with ether; upon acidification of the aqueous solution, 400 mg. of a tan product, m.p. 215–217° dec., were obtained. Recrystallization in ethanol-water raised the melting point to 218–220°.

β-(2-Phenoxazinyl)thioacetomorpholide. A mixture of 11.2 g. (0.05 mole) of 2-acetylphenoxazine, 2.56 g. (0.08 mole) of sulfur, and 20 ml. freshly distilled morpholine was refluxed for 11 hr. After cooling overnight, 50 ml. of ethanol were added to the solid mass, which was filtered; 8.80 g. (54%) of a light tan product, m.p. 187–189° dec., were obtained. It was unchanged upon recrystallization in ethanol.

2-Phenoxazinyl acetic acid. A mixture of 8 g. β-(2-phenoxazinyl)thioacetomorpholide and 135 ml. of 10% alcoholic potassium hydroxide was refluxed for 14 hr. The solution was diluted with 270 ml. water and acidified with hydrochloric acid. The precipitate was filtered and crystallization from ethanol-water gave 5.2 g. (83%) of a tan product m.p. 185–189° dec. By recrystallization in ethanol the melting point was raised to 192–193°.

A 1-g. sample of the product was decarboxylated by heating at 195° in an oil bath. It was sublimed *in vacuo*, and the sublimate was taken up in benzene. The residue (140 mg.) obtained by evaporation of the solution, melted at 122–130°. It was resublimed *in vacuo*, and recrystallized, but the melting point remained undefinite (128–140°).

3-Formyl-10-ethylphenoxazine (VII). A mixture of 31 g. of 10-ethylphenoxazine, 21 g. of *N*-methylformanilide, 21 g. of phosphorus oxychloride, and 30 ml. *o*-dichlorobenzene was heated on the steambath for 4 hr. After addition of a solution of 90 g. of sodium acetate in 200 ml. water, the volatile products were removed by steam distillation. The residue was dissolved in a large volume of benzene. This solution, after drying, gave upon concentration, 11.3 g. of green crystals, m.p. 130–132°. A further crop was obtained by adding petroleum ether to the filtrate; 19 g., m.p. 110–115°. By recrystallization in an ethanol-benzene-petroleum ether mixture 6.0 g. of a product, m.p. 127–133°, were obtained. Total yield: 50%.

10-Ethylphenoxazine-3-aldoxime. A mixture of 12 g. (50 mmoles) of 3-formyl-10-ethylphenoxazine and 10.35 g. (150 mmoles) of hydroxylamine hydrochloride was warmed with 75 ml. of pyridine for 30 min. The mixture was poured into water and the green crystals were filtered, 12.5 g., m.p. 152–154°, unchanged upon recrystallization in ethanol-water.

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: N, 11.02. Found: N, 10.87.

3-Cyano-10-ethylphenoxazine (VIII). A 16.9-g. sample of 10-ethylphenoxazine-3-aldoxime was refluxed with 160 ml. acetic anhydride for 2 hr. The solution was poured into ice water and the product was extracted with ether. The solution was washed, dried, and evaporated, and the residue was distilled *in vacuo* (1.5 mm.) 10.5 g. (67%), m.p. 123–125°, unchanged upon recrystallization in ethanol-water.

Anal. Calcd. for $C_{15}H_{13}N_2O$: N, 11.81. Found: N, 11.95.

3-Carboxy-10-ethylphenoxazine (X). A solution of 1.78 g. of 3-cyano-10-ethylphenoxazine in 75 ml. of ethanol was refluxed with 18 ml. of 20% sodium hydroxide solution for 7 hr. The mixture was diluted with 18 ml. of water, the ethanol was distilled and the solution was acidified. The oily precipitate became solid after stirring with dilute hydrochloric acid. The product was filtered and gave upon crystallization in ethanol-water 1.30 g. (65%) of tan colored crystals, m.p. 200–202° dec. Further recrystallization in the same solvent mixture raised the melting point to 204–206°. Gilman and Moore[11b] give 207.5–210.5° for the same product prepared by a different method.

Anal. Calcd. for $C_{15}H_{13}NO_3$: N, 5.48. Found: N, 5.59.

The acid was transformed into the ethyl ester by refluxing for 20 hr. with hydrochloric acid-absolute ethanol. The melting point of the green crystals, after recrystallization in ethyl acetate–petroleum ether, was 86–89°.

Anal. Calcd. for $C_{17}H_{17}NO_3$: N, 4.94. Found: N, 5.09.

3-Acetyl-10-ethylphenoxazine (IX). A 0.72-g. sample (30 mmoles) of magnesium was treated in a nitrogen atmosphere, with 0.426 g. (20 mmoles) of methyl iodide in 15 ml. of anhydrous ether. A solution of 4.8 g. (20 mmoles) of 3-cyano-10-ethylphenoxazine in 50 ml. of benzene was added and refluxed with stirring for 2 hr. After cooling to 0°, 10 ml. of 6*N* hydrochloric acid was slowly added, and the mixture was refluxed, with stirring, for 6 hr. The benzene layer was removed, the brown precipitate was filtered and dissolved in ethanol. The solution was acidified with 10 ml. of 6*N* hydrochloric acid and refluxed for 6 hr. After diluting with water, the product was extracted with benzene. The combined benzene solutions were washed, dried, and evaporated. The residue was distilled *in vacuo* (250°/0.7 mm.). The product (2.43 g., m.p. 145–150°) was recrystallized from ethanol, and gave 1.8 g. (33%) of yellow crystals, m.p. 153–154°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: N, 5.53. Found: N, 5.48.

The melting point of the *oxime* is 175–178°.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: N, 10.44. Found: 10.66.

3,7-Diacetylphenoxazine. To a solution of 18 g. (0.085 mole) of 10-ethylphenoxazine and 6.89 g. (0.085 mole) of acetyl chloride in 300 ml. of carbon disulfide were added, slowly and with stirring, 34.5 g. (0.26 mole) of powdered aluminum chloride. After refluxing, with agitation, for 8 hr., the solvent was decanted and the residue was decomposed with crushed ice and conc. hydrochloric acid. The oily layer was extracted with ether; this solution gave, after evaporation and purification over a column of silica gel, 5 g. of unchanged 10-ethylphenoxazine. The ether insoluble residue (7.70 g., m.p. 160–165°) was extracted with benzene. The green insoluble product (2.2 g., m.p. 170–174°) gave upon recrystallization in ethanol 3,7-diacetyl-10-ethylphenoxazine, m.p. 178–180°. The benzene solution was filtered through a silica gel column and another 0.5 g. of unchanged 10-ethylphenoxazine was eluted with benzene. The 3,7-diacetyl-10-ethylphenoxazine was eluted with acetone. After evaporation and crystallization in ethanol, 2 g. of yellow green crystals, m.p. 178–180°, were obtained. The solutions of this product were strongly fluorescent.

Anal. Calcd. for $C_{18}H_{17}NO_3$: N, 4.76. Found: N, 5.26.

The *oxime* was prepared by reaction with hydroxylamine hydrochloride in pyridine-ethanol, and had melted at 236–237° dec.

Anal. Calcd. for $C_{18}H_{19}N_3O_3$: N, 12.96. Found: N, 12.28.

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LOUVAIN, BELGIUM

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

Preparation of Substituted 4,9-Naphth(2,3)imidazolediones

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A number of substituted 4,9-naphth(2,3)imidazolediones have been synthesized. Solubility in fatty oils has been increased by introducing substituents of high carbon and hydrogen content in the 2- position. Increased solubility in water was effected by introducing the hydroxyl or carboxyl group in the side chain in the 2- position and by introducing an amino group into the 5- position.

A number of 2-substituted-4,9-naphth(2,3)-imidazolediones have been prepared by Hoover and Day.[1] Certain of these compounds have a marked inhibiting effect on the growth of mutant microorganisms.[2]

In general, the 2-substituted-4,9-naphth(2,3)-imidazolediones are difficultly soluble and are not easy compounds to test. In this particular investigation it was decided to introduce substituents which would increase either solubility in fats or solubility in water. Long chain alkyl groups were introduced into the 2- position. 2-Dodecyl-, 2-hexadecyl-, and 2-chaulmoogryl-4,9-naphth(2,3)-imidazoledione were preparred by the general procedure described by Hoover and Day.[1] These compounds, compared with the 2-methyl derivative, are more soluble in fatty oils. 2-(2′-Phenylvinyl)-4,9-naphth-(2,3)imidazoledione, and 2-hydroxymethyl-4,9 naphth(2,3)imidazoledione were prepared by the same procedure. The last two were prepared as possible intermediates for making other compounds. It is interesting to note that the 2-hydroxymethyl compound is quite unreactive and it was impossible to make the corresponding chloromethyl or bromomethyl compound by the usual methods. The unreactivity of the 2-hydroxymethyl derivative in this series is similar to the unreactivity of 2-hydroxymethylnaphth(2,3)-imidazole noted by Brown.[3]

The preparation of these compounds may be outlined as follows:

2,3-dichloro-1,4-naphthoquinone $\xrightarrow[C_2H_5OH]{NH_3}$ 2-amino-3-chloro-1,4-naphthoquinone (I)

I + RCOCl $\longrightarrow$ 2-acylamino-3-chloro-1,4-naphthoquinone (II)

II in $C_6H_5NO_2$ + NH_3 $\longrightarrow$ 2-acylamino-3-amino-1,4-naphthoquinone (III)

III + NaOH $\longrightarrow$ 2-substituted-4,9-naphth(2,3)imidazoledione

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(2) A. R. Day, *Trans. New York Acad. Sci.*, **20**, 4 (1957).

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Two approaches were used to increase solubility in water: (1) introduction of a carboxyalkyl group in the two position; and (2) introduction of an amino group in the benzene ring of the 4,9-naphth(2,3)imidazoledione. 2-(4′)-Carboxylbutyl-4,9-naphth(2,3)imidazoledione was prepared by the usual method.[1] The sodium salt of this acid is quite soluble in water.

To introduce an amino group into the benzene ring, 4,9-naphth(2,3)imidazoledione was first nitrated with fuming nitric acid in concentrated sulfuric acid. In order to determine the position of the nitro group it was necessary to synthesize 5-nitro-4,9-naphth(2,3)imidazoledione from the known compound 5-nitro-2,3-dichloro-1,4-naphthoquinone.[4] The two nitro compounds have the same decomposition range and infrared spectra. The product of direct nitration therefore must be 5-nitro-4,9-naphth(2,3)imidazoledione. The corresponding 5-amino derivative was most conveniently prepared by reducing 5-nitro-2,3-dichloro-1,4-naphthoquinone with stannous chloride and reoxidizing the resulting amino hydroquinone with ferric chloride to 5-amino-2,3-dichloro-1,4-naphthoquinone. The latter was then converted to the corresponding imidazole by the usual procedure.[1]

These compounds are being examined for physiological activity at the University of Pennsylvania.

EXPERIMENTAL

The melting points reported are uncorrected values.

Preparations of 2-acylamino-3-chloro-1,4-naphthoquinones (Table I). *2-Dodecanoylamino-3-chloro-1,4-naphthoquinone,* (I), was prepared from 2-amino-3-chloro-1,4-naphthoquinone and lauroyl chloride in the presence of hydrogen chloride.[1] The mixture was heated at 160–170° for 2 hr. The resulting solid was broken up, washed with ether, recrystallized from ethanol and finally from benzene and benzene-petroleum ether. The product was obtained as yellow needles.

2-Hexadecanoylamino-3-chloro-1,4-naphthoquinone (II). Palmitoyl chloride was used in this case and the mixture was heated at 170–180° for 90 min. The crude product was purified by the procedure used for compound I and was obtained as yellow needles.

2-Chaulmoogrylamino-3-chloro-1,4-naphthoquinone (III). Chaulmoogryl chloride was prepared by a modification of the method of Burschkies.[5] The details of this modification are to be found in the dissertation of J. M. Wilbur, Jr.[6]

A mixture of 18 g. (0.06 mole) of chaulmoogryl chloride and 14.5 g. (0.07 mole) of 2-amino-3-chloro-1,4-naphthoquinone in 200 ml. of xylene was heated at 135–145° for 2 hr. The mixture was filtered while hot and the filtrate cooled. The resulting dark solid was dissolved in chloroform and the solution was filtered. The filtrate was chromatographed on Merck acid washed alumina using chloroform as the eluant. A yellow band moved down the column first followed by an orange band and the black tars remained on the column. The material from the yellow band was collected and the chloroform removed under reduced pressure. The crude product was recrystallized from ethanol and obtained as yellow crystals.

2-Cinnamoylamino-3-chloro-1,4-naphthoquinone (IV). A mixture of 4.15 g. (0.02 mole) of 2-amino-3-chloro-1,4-naphthoquinone and 10 g. (0.06 mole) of cinnamoyl chloride in 12 ml. of xylene was treated with dry hydrogen chloride for 5 min. and then heated at 145–150° for 3 hr. The product separated on cooling. It was washed with ether and recrystallized from benzene-petroleum ether and obtained as yellow needles. This product melted at 187–188° and was analytically pure. After standing for several weeks the melting point increased and after recrystallization from benzene-petroleum ether the compound melted at 194–195°. The analytical data for the two compounds were almost identical. It is believed that the higher melting product is the *trans* form.

2-Acetylglycolylamino-3-chloro-1,4-naphthoquinone (V). Acetylglycolyl chloride was prepared by a modification of the method of Auschutz and Bertram.[7] Acetylglycolic acid was treated with thionyl chloride in place of phosphorus trichloride.[8] The amide (V) was prepared by the procedure used for making compound IV. The product was recrystallized from ethanol and obtained as yellow needles.

Evaporation of the filtrate from V under reduced pressure gave an oil. When ether was added, crystals of the diamide separated. The product was recrystallized from ethanol and obtained as yellow plates. Analyses indicated the product to be 2-*N*,*N*-diglycolylamino-3-chloro-1,4-naphthoquinone (VI).

2-(4′-Carbomethoxypentanoyl)amino-3-chloro-1,4-naphthoquinone (VII). 5-Carbomethoxypentanoyl chloride was prepared by a previously described procedure.[8] Once the acyl chloride was obtained, the procedure that was used for making compound I was followed. The mixture was heated at 135–140° for 90 min. The product was purified by recrystallization from ethanol and was obtained as yellow crystals.

Preparations of 2-acylamino-3-amino-1,4-naphthoquinones (Table I). The following compounds were prepared by the action of ammonia on the corresponding 3-chloro compounds (I, II, III, IV and V) in nitrobenzene at 140–150°[1]: *2-dodecanoylamino-3-amino-1,4-naphthoquinone* (VIII), *2-hexadecanoylamino-3-amino-1,4-naphthoquinone* (IX), *2-chaulmoogrylamino-3-amino-1,4-naphthoquinone* (X), *2-cinnamoylamino-3-amino-1,4-naphthoquinone* (XI), *2-acetylglycolylamino-3-amino-1,4-naphthoquinone* (XII), *2-(4′-carbomethoxypentanoyl)amino-3-amino-1,4-naphthoquinone* (XIII).

Preparations of 2-substituted 4,9-naphth(2,3)imidazolediones. These preparations required modification of the original method[1] and for that reason a general method is included here.

2-Undecyl-4,9-naphth(2,3)imidazoledione (XIV). Fifty milliliters of 2*N* sodium hydroxide was added to a hot solution of 6 g. (0.016 mole) of 2-dodecanoylamino-3-amino-1,4-naphthoquinone in 200 ml. of 95% ethyl alcohol. The solution was refluxed for 30 min. The hot solution was treated with decolorizing carbon and filtered. About 100 ml. of the ethyl alcohol was removed under reduced pressure and the remainder was very carefully neutralized with 6*N* hydrochloric acid. After cooling, the product was removed, washed with water, and dried. It was purified by recrystallization from xylene and obtained as yellow crystals.

The other imidazoles which were prepared (Table II) included: *2-pentadecyl-4,9-naphth(2,3)imidazoledione* (XV), *2-[12′-(3-cyclopentenyl)dodecyl]-4,9-naphth(2,3)imidazoledione* (XVI), *2-(2′-phenylvinyl)-4,9-naphth(2,3)imidazoledione* (XVII), *2-hydroxymethyl-4,9-naphth(2,3)imidazoledione* (XVIII).

The phenylurethan of XVIII was prepared by heating it with phenylisocyanate in nitrobenzene solution. The ure-

(4) K. Fries, W. Pense, and O. Peeters, *Ber.*, 61, 1395 (1928).

(5) K. Burschkies, *Ber.*, 71, 233 (1938).

(6) J. M. Wilbur, Jr., Dissertation, University of Pennsylvania, 1959.

(7) R. Auschutz and W. Bertram, *Ber.*, 36, 467 (1903).

(8) A. J. Yu and A. R. Day, *J. Org. Chem.*, 23, 1004 (1958).

TABLE I

No.	Acyl Group	Yield, %	M.P.°	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Chlorine, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
				2-Acylamino-3-chloro-1,4-naphthoquinones								
I	Dodecanoyl	57	132–132.5	$C_{22}H_{28}O_3NCl$	67.77	67.81	7.24	7.36	3.59	3.50	9.09	8.93
II	Hexadecanoyl	53	130.5–131	$C_{26}H_{36}O_3NCl$	70.01	70.00	8.14	8.36	3.14	3.35	7.95	7.82
III	Chaulmoogryl	35	121–123	$C_{28}H_{35}O_3NCl$	71.54	71.77	7.72	7.51	2.98	3.11	7.54	7.52
IV	Cinnamoyl	46	187–188	$C_{19}H_{12}O_3NCl$	67.57	67.48	3.58	3.79	4.15	4.14	10.50	10.63
V	Acetylglycolyl	48	182–183	$C_{14}H_{10}O_5NCl$	54.64	54.70	3.28	3.23	4.55	4.50	11.52	11.44
VI	Di(glycolyl)	2	115–116	$C_{18}H_{14}O_8NCl$	53.02	53.23	3.46	3.62	3.43	3.56	8 69	8.72
VII	4-Carbomethoxypentanoyl	72	153–154	$C_{17}H_{16}O_5NCl$	58.37	58.49	4.61	4.53	4.00	4.11	10.14	10.09
				2-Acylamino-3-amino-1,4-naphthoquinones								
VIII[a]	Dodecanoyl	64	132.5–133.5	$C_{22}H_{30}O_3N_2$	71.33	71.53	8.16	8.01	7.56	7.68		
IX[b]	Hexadecanoyl	80	125–127	$C_{26}H_{38}O_3N_2$	73.20	73.47	8.98	8.76	6.57	6.50		
X[a]	Chaulmoogryl	58	118–120	$C_{28}H_{38}O_3N_2$	74.63	74.68	8.49	8.51	6.22	6.46		
XI[a]	Cinnamoyl	78	233–234	$C_{19}H_{14}O_3N_2$	71.68	71.50	4.43	4.40	8.80	8.76		
XII[b]	Acetylglycolyl	83	210.5–212	$C_{14}H_{12}O_5N_2$	58.33	58.45	4.20	4.03	9.72	9.80		
XIII[a]	4-Carbomethoxypentanoyl	86	156.5–157.5	$C_{17}H_{18}O_5N_2$	61.81	62.00	5.49	5.66	8.48	8.40		

[a] Recrystallized from ethanol. [b] Recrystallized from ethyl acetate and from ethanol.

TABLE II

No.	Substituents	Yield, %	M.P.°	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
				2-Substituted-4,9-naphth(2,3)imidazolediones						
XIV	Undecyl	71	127.5–129	$C_{22}H_{28}O_2N_2$	74.98	74.71	8.00	8.26	7.95	8.06
XV[a]	Pentadecyl	64	107–108	$C_{25}H_{36}O_2N_2$	76.42	76.47	8.88	9.02	6.86	6.83
XVI[b]	12-(3-Cyclopentenyl)dodecyl	57	110–111	$C_{28}H_{36}O_2N_2$	77.74	77.57	8.39	8.53	6.48	6.26
XVII[c]	2-Phenylvinyl	20	340–342 dec.	$C_{19}H_{12}O_2N_2$	75.99	75.82	4.03	4.15	9.33	9.12
XVIII[d]	Hydroxymethyl	66	276–278 dec.	$C_{12}H_8O_3N_2$	63.15	63.32	3.53	3.49	12.28	12.01
XIX[e]	4-Carboxybutyl	74	267–268 dec.	$C_{16}H_{14}O_4N_2$	64.42	64.66	4.73	4.88	9.39	9.43
XX[f]	4-Carboxamidobutyl	50	235–236 dec.	$C_{16}H_{15}O_3N_3$	64.64	64.87	5.07	4.95	14.13	13.95
				5-Substituted-4,9-naphth(2,3)imidazolediones						
XXI[e]	2-Methyl-5-amino	58	>410 dec.	$C_{12}H_9O_2N_3$	63.43	63.47	3.99	4.00	18.49	18.47
XXII[e]	5-Amino	89	>420 dec.	$C_{11}H_7O_2N_3$	61.94	61.72	3.31	3.35	19.70	19.52
XXIII[b,g]	5-Nitro	56	315–330 dec.	$C_{11}H_5O_4N_3$	54.33	54.19	2.07	2.27	17.27	17.20

[a] Recrystallized from benzene-petroleum ether. [b] Recrystallized from nitromethane. [c] Recrystallized from chloroform. [d] Recrystallized from nitrobenzene and finally from water. [e] Recrystallized from nitrobenzene. [f] Recrystallized from methanol. [g] From ring closure method.

than separated on cooling and was recrystallized from nitrobenzene.

Anal. Calcd. for $C_{19}H_{13}O_4N_3$: C, 65.70; H, 3.78; N, 12.10. Found: C, 65.55; H, 3.69; N, 11.95.

2-(4'-Carboxybutyl)-4,9-naphth(2,3)imidazoledione. (XIX). 2-(4'-Carbomethoxypentanoyl)amino-3-amino-1,4-naphthoquinone (23.5 g., 0.071 mole) was dissolved in 700 ml. of 95% ethyl alcohol. To the hot solution was added 105 ml. of 2*N* sodium hydroxide solution. The solution was refluxed for 1 hr. and most of the alcohol was then removed under reduced pressure. The residue was dissolved in 1 l. of hot water, treated with decolorizing carbon, and filtered. The filtrate was adjusted to *p*H 5 and cooled. The yellow product, so obtained, may be recrystallized from large volumes of water or from nitrobenzene.

The amide (XX) of compound XIX was prepared by converting the acid to the acid chloride by heating with thionyl chloride and then treating the acid chloride with cold conc. aqueous ammonia. The solution was treated with decolorizing carbon and filtered. The filtrate was carefully neutralized with 6*N* hydrochloric acid to precipitate the amide.

Preparation of 5-amino-2-methyl-4,9-naphth(2,3)imidazoledione (XXI). This preparation involved the initial preparation of 5-nitro-2,3-dichloro-1,4-naphthoquinone. This compound was reported in 1928.[4] As we were not able to reproduce the earlier results, we are including here a modification of their procedure. 2,3-Dichloro-1,4-naphthoquinone (246 g., 1.06 mole) was mixed with 320 ml. of conc. sulfuric acid. Then 640 ml. of red fuming nitric acid was added dropwise with stirring. After 150 ml. of nitric acid was added, a vigorous exothermic reaction occurred and cooling was necessary to keep the temperature below 100°. Above 120° decomposition occurs. The remaining nitric acid was slowly added while the temperature was maintained at 80–90°. The mixture was heated at this temperature for 7 hr. It was then poured onto cracked ice. The yellow product was removed, washed thoroughly with water and then stirred with 1*N* sodium carbonate solution for 8 hr. The product was removed, washed with water, and dried. It was purified by recrystallization from chloroform with the aid of decolorizing carbon. A 20% yield of pure compound was obtained, m.p. 174–175°.

Reduction of the nitro compound to the corresponding amino compound was accomplished with stannous chloride according to the procedure of Fries, Pense, and Peeters[4] with certain modifications.[6] The product was recrystallized from large amounts of 95% ethyl alcohol, yield 77%, m.p. 224–226°. 5-Amino-2,3-dichloro-1,4-naphthoquinone has been previously reported to melt at 220°.

The 5-amino-2,3-dichloro-1,4-naphthoquinone was converted to the corresponding 5-acetamido derivative by treatment with acetic anhydride and a few drops of conc. sulfuric acid. The acetyl derivative was recrystallized from ethanol and obtained as red crystals, yield 96%, m.p. 208–209°.

Anal. Calcd. for $C_{12}H_7O_3NCl_2$: C, 50.75; H, 2.48; N, 4.93; Cl, 24.96. Found: C, 50.66; H, 2.48; N, 4.89; Cl, 24.82.

5-Acetamido(2 or 3)-amino-(2 or 3)-chloro-1,4-naphthoquinone. 5-Acetamido-2,3-dichloro-1,4-naphthoquinone (26.7 g., 0.094 mole) was dissolved in 200 ml. of nitrobenzene. The solution was heated to 145–155° and ammonia was passed in for 1 hr. The hot solution was filtered to remove ammonium chloride and the filtrate cooled to crystallize the product. The latter was washed with ether, dried, washed with water, and again dried, yield 93%, m.p. 238–260° dec. This product was probably a mixture of isomers, but recrystallization from ethanol or benzene failed to give a single form. Attempts to separate isomers by chromatography also failed.

5-Acetamido-(2 or 3)-acetamido-(2 or 3)-chloro-1,4-naphthoquinone. A suspension of 23 g. (0.087 mole) of 5-acetamido-(2 or 3)-amino-(2 or 3)-chloro-1,4-naphthoquinone in 70 ml. of acetic anhydride was treated with 12 drops of conc. sulfuric acid. The mixture was warmed, with some stirring, until it formed a solid red mass. An additional 20 ml. of acetic anhydride and 5 drops of conc. sulfuric acid were added with stirring. After standing overnight the mixture was cooled and the solid removed by filtration. It was washed with ether, dried, and then washed with water and dried. The product was recrystallized from 95% ethyl alcohol and obtained as golden orange crystals, yield 76%, m.p. 244–245° dec.

Anal. Calcd. for $C_{14}H_{11}O_4N_2Cl$: C, 54.82; H, 3.62; N, 9.14; Cl, 11.56. Found: C, 54.93; H, 3.52; N, 9.12; Cl, 11.53.

The filtrate from the above product and the ether washings were combined. By evaporation and cooling another isomer was obtained. It was recrystallized from 95% ethyl alcohol and obtained as orange needles, yield 7% m.p. 208–210° dec.

Anal. Calcd. for $C_{14}H_{11}O_4N_2Cl$: C, 54.82; H, 3.62; N, 3.62; N, 9.14; Cl, 11.56. Found: C, 54.63; H, 3.80; N, 9.05; Cl, 11.39.

5-Acetamido-(2 or 3)-acetamido-(2 or 3)-amino-1,4-naphthoquinone. 5-Acetamido-(2 or 3)-acetamido-(2 or 3)-chloro-1,4-naphthoquinone (2.3 g., 0.0075 mole) was dissolved in 30 ml. of nitrobenzene. The solution was heated to 145–150° and ammonia passed into the solution for 1 hr. After standing overnight, the product was removed, washed with ether, dried, and then washed with water and dried. It was recrystallized from ethanol and obtained as brown needles, yield 73%, m.p. 270–272° dec.

Anal. Calcd. for $C_{14}H_{13}O_4N_3$: C, 58.54; H, 4.56; N, 14.63. Found: C, 58.56; H, 4.64; N, 14.71.

5-Amino-2-methyl-4,9-naphth(2,3)imidazoledione. Fifty milliliters of 2*N* sodium hydroxide solution was added to a hot solution of 5-acetamido-(2 or 3)-acetamido-(2 or 3)-amino-1,4-naphthoquinone (5 g., 0.0174 mole) in 200 ml. of 95% ethyl alcohol. The solution was refluxed for 1 hr. and then the alcohol was removed under reduced pressure. The residue was dissolved in boiling water. The solution was treated with decolorizing carbon and filtered. The hot filtrate was carefully neutralized with 6*N* hydrochloric acid and the product crystallized on cooling. The product may be purified by dissolving it in hot 20% sulfuric acid and carefully neutralizing the solution with 2*N* sodium hydroxide solution to reprecipitate the product and finally recrystallizing from nitrobenzene. It was obtained as red crystals.

Acetylation of this compound with acetic anhydride and a few drops of conc. sulfuric acid gave a monoacetyl derivative. It was recrystallized from nitrobenzene, yield 58%, m.p. > 410° dec. This product probably is 5-acetamido-2-methyl-4,9-naphth(2,3)imidazoledione.

Anal. Calcd. for $C_{14}H_{11}O_3N_3$: C, 62.44; H, 4.12; N, 15.60. Found: C, 62.30; H, 4.29; N, 15.71.

5-Amino-4,9-naphth(2,3)imidazoledione (XXII). Five grams of 5-acetamido- (2 or 3)-amino-1,4-naphthoquinone was dissolved in 250 ml. of boiling ethyl formate. Ten milliliters of conc. sulfuric acid was added dropwise over a period of 30 min. After each drop of acid was added, a vigorous reaction occurred. After standing overnight, the mixture was cooled and the solid removed by filtration and washed with ether. The product was purified by the same procedure which was used for purifying compound XXI and was obtained as red plates.

5-Nitro-4,9-naphth(2,3)imidazoledione (XXIII). This compound was prepared by two methods: (a) direct nitration of 4,9-naphth(2,3)imidazoledione,[1] and (b) ring closure of 5-nitro-(2 or 3)-acetamido-(2 or 3)-amino-1,4-naphthoquinone. The two products have identical infrared spectra and melting point ranges, 315–330° dec.

(a) A mixture of 2.1 g. (0.01 mole) of 4,9-naphth(2,3)-imidazoledione in 10 ml. of conc. sulfuric acid and 20 ml. of red fuming nitric acid was heated at 100° for 3 hr. After cooling, the mixture was poured onto cracked ice. The product was removed by filtration and washed with water. It was dissolved in hot 2*N* sodium hydroxide solution, treated with decolorizing carbon, filtered, and the filtrate carefully neutralized with 6*N* hydrochloric acid. The product sepa-

rated on cooling. It was removed, dried, recrystallized from nitrobenzene, and the yellow crystals were washed with toluene and petroleum ether. The yield was 75%.

(b) Concentrated sulfuric acid (5 ml.) was added dropwise to a refluxing solution of 2 g. of 5-nitro-(2 or 3)-acetamido-(2 or 3)-amino-1,4-naphthoquinone in 100 ml. of ethyl orthoformate. The acid was added over a period of 20 min. After cooling the product was collected and washed with ether. The product was purified by the procedure used in (a). The yield was 28%.

PHILADELPHIA 4, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Acridizinium Compounds by the Cyclization of Oximes

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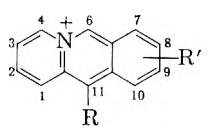
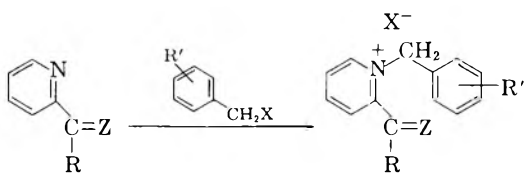
Picolinic aldoxime (III) is superior to the free aldehyde (II) with regard to the rate of reaction with benzyl halides and to the yield and purity of the resulting quaternary salts. The new 1-benzyl-2-aldoximinopyridinium salts cyclize in good yield to afford acridizinium salts (I). The overall yield is superior to that *via* the aldehyde. An improvement is observed when 2-acetylpyridine (IV) is replaced by its oxime (V) in the acridizinium synthesis.

In an earlier work it was shown[1,2] that derivatives of the acridizinium ion (I) can be synthesized



I, R = R′ = H

by cyclization of the quaternary salts (VI) formed when picolinic aldehyde (II) reacts with an appropriate benzyl halide.

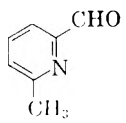


II. Z = O, R = H
III. Z = NOH, R = H
IV. Z = O, R = CH_3
V. Z = NOH, R = CH_3
VI. Z = O, R = R′ = H
VII. Z = NOH, R = R′ = H
VIII. Z = NOH, R = H, R′ = 4-CH_3
IX. Z = O, R = CH_3, R′ = H
X. Z = NOH, R = CH_3, R′ = H
XI. Z = NOH, R = CH_3, R′ = 4-CH_3
XII. Z = NOH, R = CH_3, R′ = 3-OCH_3

Despite the success met with in the use of this synthesis, there are some disadvantages which are inherent in the use of picolinic aldehyde. The aldehyde is itself unstable and deteriorates rapidly if not kept refrigerated. It is recommended that the aldehyde be stored under a nitrogen atmosphere. The quaternization of picolinic aldehyde at room temperature is quite slow, and although the rate is more rapid at higher temperatures, great care must be exercised to prevent deterioration of the aldehyde or of the quaternization product. Only a few of the quaternary salts (VI) derived from aldehydes have been obtained in a crystalline condition, and only three[3] of these in a state of analytical purity. When poor results are obtained in the over-all reaction, it is often difficult to judge at what stage the failure has occurred.

It was felt that derivative of picolinic aldehyde might offer some advantages, and the first studied has been the stable and commercially available oxime (III).

Perhaps because of the increased basicity of the ring nitrogen, picolinic aldoxime (III) quaternizes more readily than does the free aldehyde (II), and the quaternary salt (VII) is readily isolated and purified. The quaternary oximes (VII) can be cyclized by the action of hydrobromic acid under the same conditions used previously for the quater-



XIII

TABLE I

ACRIDIZINIUM SALTS BY THE OXIME METHOD

Acridizinium Salt	Yield, %			
			Overall via	
	Quatern.	Cycliz.	Oxime	Aldehyde
—	87.5	89	78	60[a]
9-CH_3	75	92.5[b]	69.5	55[a]
Benzo[h]	92	85	78	52[c]
11-CH_3	85	21	18	03[d]
9,11-$(CH_3)_2$	90	40	36	—
8-OH, 11-CH_3	90	99	90	—

[a] Reference 1a. [b] Sum of yields of bromide (28%) and picrate (64.5%). [c] Reference 1b. [d] Reference 8.

(1a) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).

(1b) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **78**, 2459 (1956).

(2) C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.*, **79**, 6033 (1957).

(3) C. K. Bradsher and T. W. G. Solomons, unpublished work.

TABLE II

1-ARYLMETHYL-2-(1-HYDROXIMINOALKYL)PYRIDINIUM BROMIDES

R	Ar	M.P.[a]	Formula	C		H		N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
H	C_6H_5	202	$C_{13}H_{13}BrN_2O$	53.25	53.00	4.46	4.41	9.55	9.64
H	4-$CH_3C_6H_4$	206	$C_{14}H_{15}BrN_2O$	54.73	54.60	4.92	4.62	—	—
H	1-$C_{10}H_7$	200–201	$C_{17}H_{15}BrN_2O$	59.48	59.47[b]	4.41	4.40	8.16	8.19
CH_3	C_6H_5	153[c,d]	$C_{14}H_{15}BrN_2O.1/4H_2O$	53.93	54.03	4.97	5.12	8.98	8.84
CH_3	4-$CH_3C_6H_4$	172[c,d]	$C_{15}H_{17}BrN_2O.1/4H_2O$	55.31	55.44	5.11	5.33	8.60	8.74
CH_3	3-$CH_3OC_6H_4$	122[c,d]	$C_{15}H_{17}BrN_2O_2.1/4H_2O$	52.70	52.78[e]	5.16	5.20	8.19	8.31

[a] Melting points taken in a sealed tube. [b] Reference 12. [c] With decomposition. [d] Crystallized from methanol-ethyl acetate. [e] Reference 13.

nary aldehydes (VI). From Table I, it will be noted that the overall yields obtained with the aldoxime (III) were superior to those starting with picolinic aldehyde (II).

Although 6-methyl-2-pyridinealdehyde (XIII) is available, it quaternizes too poorly[4] to provide a satisfactory synthetic route to 4-methylacridizinium salts.[5] The corresponding oxime[6] appeared to react, but as the oxime was recovered as the hydrobromide, oximino ether formation and hydrolysis may have occurred.[7]

In a recent publication[8] it was reported that 11-substituted acridizinium salts could be prepared by cyclization of the salts formed by quaternization of 2-benzoyl- or 2-acetylpyridine (IV) with benzyl halides. 2-Acetylpyridine gave very poor results (3% overall yield) with benzyl bromide, probably because of failure of the quaternization step. It has now been found that using the same halide, quaternization was much easier with the oxime (V) of 2-acetylpyridine (85% yield), and although the cyclization step went in only 21% yield, the overall yield (18%) represents a great improvement. A somewhat higher yield (36%) was obtained in the preparation of the new 9,11-dimethylacridizinium picrate.

The salt (XI) obtained from the reaction of *m*-methoxybenzyl bromide with the oxime (V) of 2-acetylpyridine cyclized (with ether cleavage) when heated in hydrobromic acid, affording 8-hydroxy-11-methylacridizinium bromide in 99% yield. Cyclization of XI in liquid hydrogen fluoride likewise yielded an 8-hydroxy-11-methylacridizinium salt (75%). The treatment of the other quaternized pyridyl oxime salts (VII, VIII, X) with hydrogen fluoride gave no isolable acridizinium salts. As hydrogen fluoride is known to produce the Beckmann rearrangement[9] of oximes, it may well be that with hydrogen fluoride, cyclization is observed only when cyclization can occur much more rapidly than rearrangement.

EXPERIMENTAL[10]

Quaternization Procedure. To a solution containing 0.01 mole of the oxime (III or V) in 5–6 ml. of dimethylformamide, 0.011 mole of the benzyl bromide was added and the mixture allowed to stand for 5 days to one week.[11] At the end

TABLE III

ACRIDIZINIUM (I) BROMIDES BY CYCLIZATION OF 1-ARYLMETHYL-2-(1-HYDROXIMINOALKYL)-PYRIDINIUM BROMIDES IN 48% HYDROBROMIC ACID

Acridizinium	Reflux Time, Hr.	Yield, %	M.P	
			Obsd.	Lit.
—	6	89	240–241	239–240[a]
9-CH_3	4	28[b]	192–194	191–193[a]
Benzo[h]	1.25	85	304–307	308–309[c]
11-CH_3	8	21	199–201	—[d]
9,11-$(CH_3)_2$	0.5	40[e]	208–209.5	—[f]
8-OH, 11-CH_3[g]	0.75	99	302–303	—[h]

[a] Ref. 1a. [b] From the filtrate an additional 64.5% was isolated as the picrate, m.p. 248–250°, Lit.,[1] m.p. 252–253°, total yield 92.5%. [c] Reference 1b. [d] *Anal.* Calcd. for $C_{14}H_{12}BrN\cdot1/3H_2O$: C, 60.01; H, 4.56; N, 5.00. Found[13]: C, 59.90; H, 4.89; N, 4.91. [e] The yield and melting point are for the picrate rather than the bromide. [f] *Anal.* Calcd. for $C_{21}H_{16}N_4O_7$: C, 57.79; H, 3.69; N, 12.84. Found[13]: C, 57.44; H, 3.88; N, 13.00. [g] Obtained from XII by combined cyclization and ether cleavage. [h] *Anal.* Calcd. for $C_{14}H_{12}BrNO\cdot H_2O$: C, 52.18; H, 4.38; N, 8.69. Found[12]: C, 51.97; H, 4.50; N, 8.81. The *picrate* was also prepared, as needles from acetonitrile, m.p. 201–203°. *Anal.* Calcd. for $C_{21}H_{16}N_4O_8$: C, 54.79; H, 3.22; N, 12.78. Found[13]: C, 54.74; H, 3.35; N, 12.77.

(4) The relative unreactivity of XIII as compared with picolinic aldehyde is in accord with the general observation that 2,6 disubstituted pyridines do not readily form quaternary salts, R. C. Elderfield, *Heterocyclic Compounds*, Vol. I, John Wiley & Sons, New York, N. Y. (1950), page 572.

(5) It is possible to obtain a 2.5% yield for the overall reaction by the picolinic aldehyde method.

(6) S. Ginsberg and I. B. Wilson, *J. Am. Chem. Soc.*, 79, 481 (1957).

(7) Ginsberg and Wilson (ref. 6) have shown that the reaction of methyl iodide with 6-methylpyridine-2-aldoxime yields the oximino ether.

(8) C. K. Bradsher and T. W. G. Solomons, *J. Am. Chem. Soc.*, 81, 2550 (1959).

(9) *Cf.*, F. Moller, O. Bayer, and H. Wilms, *Ger.* 924, 866; *Chem. Abstr.* 52, 14672 (1958). J. H. Simons, S. Archer, and D. I. Randall, *J. Am. Chem. Soc.*, 62, 485 (1940).

(10) Except as noted, all melting points were taken on a Fisher-Johns hot stage and are uncorrected. Unless otherwise indicated all analyses were by Drs. Weiler and Strauss, Oxford, England.

(11) With the oxime of 2-acetylpyridine 2 weeks were allowed.

(12) Analysis by Galbraith Laboratories, Knoxville, Tenn.

(13) Analysis by Dr. Ing. A. Schoeller, Kronach, West Germany.

of this period the crystalline product was triturated with ethyl acetate, and the product collected and washed with ether. Except as noted, the analytical samples formed colorless crystals from ethanol. The results of these experiments are summarized in Table II.

Cyclization of Oximes. One gram of the oxime was refluxed with 5–10 ml. of 48% hydrobromic acid, after which the hydrobromic acid was removed under reduced pressure (aspirator). About 10 ml. of ethanol was added, removed under vacuum, and the residue crystallized from ethanol. The results of these experiments are summarized in Table III.

4-Methylacridizinium Picrate. (a) *Attempted synthesis by the Oxime Method.* Quaternization of 6-methylpyridine-2-aldoxime (XIII oxime) with benzyl bromide was attempted by the usual method. The product, m.p. 208–209°, obtained by recrystallization was not the expected quaternary salt, and had the approximate composition for the hydrobromide of the original oxime.

(b) *By the Picolinic aldehyde method.*[14] Two grams of benzyl chloride and 2 g. of 6-methylpyridine-2-carboxaldehyde were refluxed for 14 hr. in 5 ml. of absolute methanol. The methanol was removed under vacuum and the residue washed with ether. The residue was dissolved in 25 ml. of conc. hydrochloric acid and refluxed for 8 hr. The residue (after removal of the hydrochloric acid *in vacuo*) was dissolved in ethanol and treated with ethanolic picric acid. The crude picrate was obtained as a dark yellow solid, m.p. 200–208° dec., yield 0.2 g. (2.5%). The analytical sample formed fine yellow needles from acetone, m.p. 230–233° dec.

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.87; H, 3.34; N, 13.27. Found[15]: C, 56.69; H, 3.89; N, 13.21.

Cyclization of 1-(3-methoxybenzyl)-2-(1-hydroximinoethyl)-pyridinium bromide (XII) *in hydrogen fluoride.* In a polyethylene bottle was placed 0.8 g. of the quaternary bromide (XII) to which 50 ml. of liquid hydrogen fluoride was added. The hydrogen fluoride was allowed to evaporate over a 2 day period. The gummy residue was dissolved in ethanol and treated with ethanolic picric acid. The picrate, crystallized from acetonitrile, was demonstrated to be *8-hydroxy-11-methylacridizinium picrate* by comparison of melting points and infrared spectra with those obtained from the sample prepared by the hydrobromic acid cyclization, yield 0.78 g. (75%).

DURHAM, N. C.

(14) This experiment was by J. H. Jones.

(15) Analysis by Micro Laboratories, Skokie, Illinois.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

1,2- and 3-Monoalkyl and 2-(β-D-Ribofuranosyl) Derivatives of 7-Dimethylamino-v-triazolo(d)pyrimidine and Related Compounds

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Three monoethyl derivatives have been isolated from the reaction of ethyl iodide and 7-dimethylamino-v-triazolo(d)-pyrimidine (VII). Each of these monoethyl derivatives has been assigned a definite structure by comparison of their ultraviolet absorption spectra with the spectra of 7-dimethylamino-3-ethyl-3H-v-triazolo(d)pyrimidine (V) and 7-dimethylamino-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine (XVIII), which have been synthesized by unequivocal methods. By the same methods the riboside obtained from the chloromercuri derivative of VII was shown to be 7-dimethylamino-2-(β-D-ribofuranosyl)-2H-v-triazolo(d)pyrimidine (IX). Similar results were obtained with 7-dimethylamino-5-methylmercapto-v-triazolo(d)pyrimidine (VI).

Analogs of 6-dimethylamino-9(3-amino-3-deoxy-β-D-ribofuranosyl)purine[1] (I) (the aminonucleoside derived from puromycin) are of interest because of the carcinostatic[2] and trypanocidal[3] properties of I. Previous reports have been concerned primarily with analogs of I containing variations either in the carbohydrate portion of the molecule[4] or in the substituents on the purine nucleus.[5] In this paper we wish to report on the results of some work carried out during an attempt to prepare the triazolo(d)pyrimidine analog 7-dimethylamino-3(3-amino-3-deoxy-β-D-ribofuranosyl)-3H-v-triazolo(d)pyrimidine (II).

When this work was begun the only reported v-triazolo(d)pyrimidines containing substituents on the triazole portion of the molecule were some 2-phenyl derivatives.[6] Therefore, in order to have available a model compound for ultraviolet absorption spectra studies, 7-dimethylamino-3-ethyl-3H-v-triazolo(d)pyrimidine (V) was synthesized by unequivocal methods. 5-Amino-6-dimethylamino-4-ethylamino-2-methylmercaptopyrimidine (III)[7] when treated with nitrous acid gave the expected 7-dimethylamino-3-ethyl-5-methylmercapto-3H-v-triazolo(d)pyrimidine (IV), which was then desulfurized with Raney nickel catalyst to give V.

(1) B. R. Baker, J. P. Joseph, and J. H. Williams, *J. Am. Chem. Soc.*, 77, 1 (1955).

(2) P. L. Bennett, S. L. Halliday, J. J. Oleson, and J. H. Williams, *Antibiotics Annual 1954–1955*, Medical Encyclopedia, Inc., New York, N. Y., 1954, pp. 766–769.

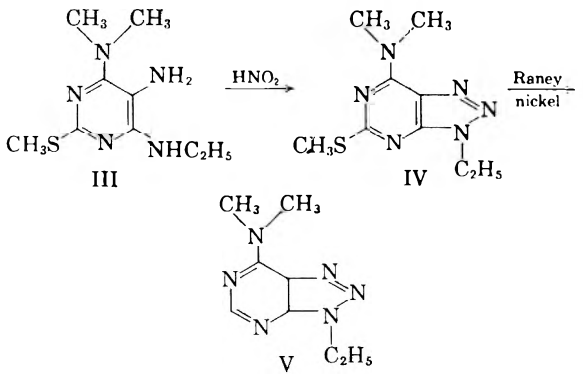
(3) R. I. Hewitt, A. R. Gamble, W. S. Wallace, and J. H. Williams, *Antibiotics and Chemotherapy*, 4, 1222 (1954).

(4) R. E. Schaub, M. J. Weiss, and B. R. Baker, *J. Am. Chem. Soc.*, 80, 4692 (1958); F. J. McEvoy, M. J. Weiss and B. R. Baker, *J. Am. Chem. Soc.*, 82, 209 (1960).

(5) L. Goldman, J. W. Marsico, and R. B. Angier, *J. Am. Chem. Soc.*, 78, 4173 (1956).

(6) F. R. Benson, L. W. Hartzel and W. L. Savell, *J. Am. Chem. Soc.*, 72, 1816 (1950).

(7) B. R. Baker, R. E. Schaub, and J. P. Joseph, *J. Org. Chem.*, 19, 638 (1954).



An attempt was then made to prepare a 3-ribosyl derivative of 7-dimethylamino-5-methylmercapto-v-triazolo(d)pyrimidine[8] (VI) (the more readily available ribose was used instead of 3-amino-ribose). Compound VI, treated with mercuric chloride gave a bis(triazolo(d)pyrimidyl) mercury derivative. The reaction between this derivative and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride by a slight variation of the method of Kissman *et al.*[9] gave a crude gum from which was isolated in small yield a crystalline riboside (VIII). A comparison of the ultraviolet absorption spectra of the riboside (VIII) with the spectra of IV quickly proved that VIII was not the 3-ribosyl derivative of VI but, as substitution may have occurred on either the 1- or 2- position, no positive assignment of structure could be made.

In conjunction with the above work a simple alkylation of VI was attempted. The reaction between VI and dimethyl sulfate in an aqueous alkaline solution gave a product which was separated by fractional crystallization into two isomeric monomethyl derivatives of VI. A study of their ultraviolet absorption spectra showed that the lower melting isomer (X, m.p. 186–188°) was 7-dimethylamino-3-methyl-5-methylmercapto-3H-v-triazolo-(d)pyrimidine while the other isomer (XI, m.p. 236–238°) had spectra very similar to the spectra of the riboside VIII).

As conversion of VI to the ribosyl derivative had not given the desired isomer, a similar reaction was run using 7-dimethylamino-v-triazolo(d)pyrimidine (VII). Compound VII was prepared by the action of nitrous acid on 4,5-diamino-6-dimethylaminopyrimidine, which was in turn prepared by a Raney nickel desulfurization of 4,5-diamino-6-dimethylamino-2-methylmercaptopyrimidine.[10] The chloromercuri derivative prepared from VII was treated with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in the usual manner to give a satisfactory yield of a single crystalline riboside (IX). Examination of the ultraviolet absorption spectra of IX demonstrated that it was not a 3-substituted derivative of VII.

Once again a simple alkylation reaction was performed. The treatment of VII with ethyl iodide in an aqueous alkaline solution gave a crude product which was separated by fractional crystallization into three isomeric monoethyl derivatives of VII. By direct comparison with an authentic sample the lowest melting isomer (V, m.p. 80–81°) was shown to be 7-dimethylamino-3-ethyl-3H-v-triazolo(d)pyrimidine (V). One of the other isomers (XIII, m.p. 117–119°) had ultraviolet absorption spectra very similar to the spectra of the riboside IX, prepared from VII, while the spectra of the third isomer (XIV, m.p. 205–206°) were very different. Thus, although a certain relationship had been established between the ribosides VIII and IX and the various alkyl derivatives, the only structures that were established were those of X (7-dimethylamino-3-methyl-5-methylmercapto-3H-v-triazolo(d)pyrimidine) and V (7-dimethylamino-3-ethyl-3H-v-triazolo(d)pyrimidine).

As this portion of the work was completed several papers appeared describing the preparation of v-triazolo(d)pyrimidines containing substituents on the triazole portion of the ring. Among these were descriptions[8,11,12] of the syntheses of a number of ribosides. In one case[8] a riboside of VI was prepared and then desulfurized with Raney nickel to give a riboside of 7-dimethylamino-v-triazolo(d)-pyrimidine (VII). No evidence of any kind was offered to prove the structure of this riboside. However, during the process of publication, the final compound was named, inadvertently but unequivocally, 7-dimethylamino-3-(β-D-ribofuranosyl)-v-triazolo(d)pyrimidine. The comparison of a sample of this product, kindly supplied by Dr. Andrews, with our compound (IX) showed them to be identical. Therefore, this product[8] could not have been a 3-ribosyl derivative.

Although several 3-alkyl derivatives of certain v-triazolo(d)pyrimidines[11,12,13] and two 1-glycosyl-5,7-dihydroxy-1H-v-triazolo(d)pyrimidines[12] have been described recently, these were not readily useful in determining the structures of our compounds. Likewise the 2-phenyl derivatives of VI and VII, which could easily be made, would be of little use as the increased conjugation due to the phenyl groups would result in ultraviolet absorption spectra entirely different from the spectra of a 2-alkyl derivative. However, our experience with the steric inhibition of resonance exhibited by 3′,5′-dichloromethotrexate[14] led us to believe that

(8) K. J. M. Andrews and W. E. Barber, *J. Chem. Soc.*, 2768 (1958).

(9) H. M. Kissman, C. Pidacks, and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955).

(10) B. R Baker, J. P. Joseph, and R. E. Schaub, *J. Org. Chem.*, **19**, 631 (1954).

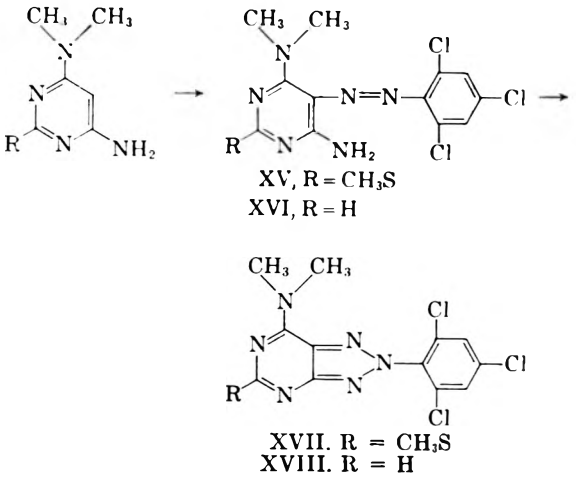
(11) J. Davoll, *J. Chem. Soc.*, 1593 (1958).

(12) J. Baddiley, J. G. Buchanan, and G. O. Osborne, *J. Chem. Soc.*, 1651 and 3606 (1958).

(13) K. L. Dille, M. L. Sutherland, and B. E. Christiansen, *J. Org. Chem.*, **20**, 171 (1955); F. L. Rose, *J. Chem. Soc.*, 4116 (1954).

(14) R. B. Angier and W. V. Curran, *J. Am. Chem. Soc.*, **81**, 2814 (1959).

2(2,4,6-trichlorophenyl) derivatives of VI and VII would have spectra very similar to the corresponding 2-alkyl or 2-ribosyl derivatives. Therefore, 4-amino - 6 - dimethylamino - 2 - methylmercapto - 5-(2,4,6-trichlorophenylazo)pyrimidine (XV) was prepared and converted to 7-dimethylamino-5-methylmercapto-2(2,4,6-trichlorophenyl)-2H-v-triazolo-(d)pyrimidine (XVII) by conventional methods. The ultraviolet absorption spectra of XVII were very similar to the spectra of the riboside VIII and also similar to one (XI, m.p. 236–238°) of the two methyl derivatives obtained by the methylation of VI.



An attempt to desulfurize XVII with Raney nickel was unsuccessful because of a simultaneous reductive dechlorination. Therefore, 4-amino-6-dimethylamino - 2 - methylmercaptopyrimidine was desulfurized to give 4-amino-6-dimethylaminopyrimidine which was then converted *via* the azo compound (XVI) to 7-dimethylamino-2-(2,4,6-trichlorophenyl) - 2H - v - triazolo(d)pyrimidine (XVIII). The ultraviolet absorption spectra of XVIII were very similar to the spectra of the riboside IX and also similar to the spectra of one (XIII, m.p. 117–119°) of the three *N*-ethyl derivatives obtained by the action of ethyl iodide on VII.

To tie the two series together further XI (7-dimethylamino-5-methylmercapto-2-methyl-2H-v-triazolo(d)pyrimidine) was desulfurized with Raney nickel to give a compound (XII) with spectra identical to the spectra of XIII (7-dimethylamino-2-ethyl-2H-v-triazolo(d)pyrimidine).

Ultraviolet absorption spectra and structure. An examination of the spectra (Table I and Fig. 1) of the 2-(2,4,6-trichlorophenyl) (XVII) and the postulated 2-methyl (XI) and 2-ribosyl (VIII) derivatives of 7-dimethylamino-5-methylmercapto-v-triazolo(d)pyrimidine (VI) shows that, although the curves are almost superposable, there is a bathochromic shift of some 5–10 mμ for most parts of the curve as one proceeds from XI to VIII to XVII. As only two of the likely three possible *N*-monomethyl derivatives of VI had been prepared. it could be argued that the unknown third methyl derivative might have spectra very similar to XI. However, when one examines the spectra (Table I and Figs. 2 +3)of the derivatives of VII (7-dimethylamino-

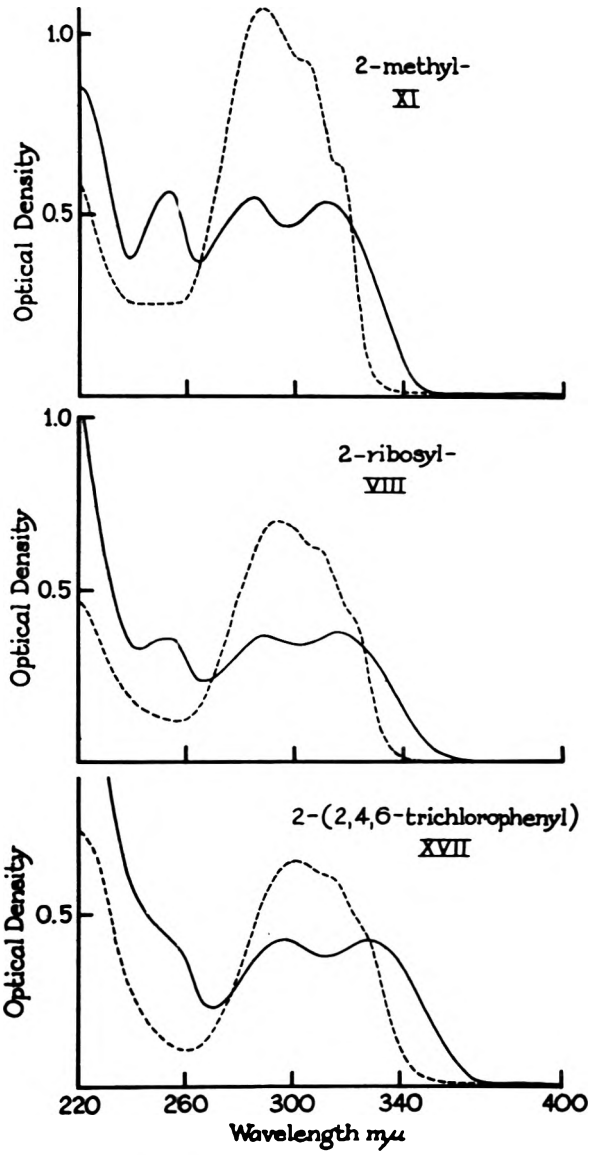


Fig. 1. Ultraviolet absorption spectra of derivatives of 7 - dimethylamino - 5 - methylmercapto - v - triazolo(d)-pyrimidine: ——, 0.1*N* sodium hydroxide or methanol (10γ/ml); – – – –, 0.1*N* hydrochloric acid (10γ/ml.)

v-triazolo(d)pyrimidine), any reasonable doubt of the structures is dispelled. The spectra of the 2-(2,4,6-trichlorophenyl) (XVIII) and the postulated 2-ethyl (XIII) and 2-ribosyl (IX) derivatives of VII again are essentially superposable when allowance is made for a small bathochromic shift from XIII to IX to XVIII. In this case all three of the likely *N*-monoethyl derivatives had been isolated and close inspection showed that only one of them (XIII) had spectra resembling the spectra of the known 2-(2,4,6-trichlorophenyl) - 7 - dimethylamino - 2H - v - triazolo(d)pyrimidine (XVIII). Although superficial examination may not quickly reveal this fact, it does become quite evident when one notes that the 2-(2,4,6-trichlorophenyl) derivative (XVIII) exhibits a bathochromic shift of its maximum when passing from the cation (0.1*N* HCl) to the neutral molecule. An examination of the other derivatives of VII then shows that the postulated 2-ethyl (XIII) and 2-ribosyl (IX) derivatives exhibit this same bathochromic shift while the

TABLE I

Substituent	Ultraviolet Absorption Spectra[a] λ_{max}, mμ (ϵ) 0.1N HCl	Methanol or 0.1N NaOH[b]
7-Dimethylamino-5-methylmercapto-v-triazolo(d)pyrimidine (VI)		
VI	250 (8,800)	248 (18,900)[b]
	286 (22,900)	296 (15,100)
2-Methyl (XI)	288 (24,000)	254 (13,000)
	302Sh (20,800)	284 (12,100)
	315Sh (14,400)	311 (12,400)
2-(β-D-Ribofuranosyl)[17] (VIII)	294 (23,600)	254 (12,100)
	309Sh (20,800)	290 (12,300)
	321Sh (14,400)	318 (12,700)
2-(2,4,6-Trichlorophenyl) (XVII)	300 (26,600)	254Sh (13,600)
	312Sh (25,000)	297 (13,300)
		328 (13,300)
3-Methyl (X)	253 (13,400)	255 (17,300)
	284 (19,700)	300 (13,700)
3-Ethyl (IV)	252 (14,500)	255 (19,700)
	283 (18,400)	300 (15,200)
2-Phenyl	303 (21,200)	250 (27,200)
	336 (26,600)	304 (15,400)
		347 (19,400)
7-Dimethylamino-v-triazolo(d)pyrimidine (VII)		
VII	286 (12,400)	292 (18,200)[b]
2-Methyl (XII)	303 (16,200)	309 (15,100)
2-Ethyl (XIII)	303 (16,500)	308 (15,300)
2-(β-D-Ribofuranosyl)[17] (IX)	310 (17,000)	314 (14,800)
2-(2,4,6-Trichlorophenyl) (XVIII)	314 (16,000)	323 (14,200)
1-Ethyl (XIV)	308 (17,800)	299 (14,800)
3-Ethyl (V)	275 (14,400)	296 (15,000)

[a] Sh = shoulder. [b] Except for VI and VII the spectra in methanol and 0.1N NaOH are essentially identical for any one compound. The spectra for VI and VII were run in 0.1N NaOH.

postulated 1-ethyl derivative[15] (XIV) shows a hypsochromic shift of its maximum in passing from the cation (0.1N HCl) to the neutral molecule.

Although ultraviolet absorption spectra comparisons alone may not be considered a rigorous proof of structure the authors feel that the evidence for the correctness of the assigned structures is very strong.

During the course of this work XVII was treated with refluxing 6N hydrochloric acid for seven hours and gave an easily separable mixture of 5,7-dihydroxy-2(2,4,6-trichlorophenyl)-2H-v-triazolo(d)-pyrimidine and 7-dimethylamino-5-hydroxy-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine.

EXPERIMENTAL[16]

4-Amino-6-dimethylaminopyrimidine. 4-Amino-6-dimethylamino-2-methylmercaptopyrimidine[10] (2.0 g., 11 mmoles), 75 ml. of 2-methoxyethanol and excess Raney nickel were mixed and heated on the steam bath for 2 hr. with stirring. Fresh Raney nickel was added and the mixture was heated another hour. The mixture was filtered and the catalyst was extracted with warm 2-methoxyethanol. The filtrates were combined and evaporated to 10 ml. *in vacuo*, diluted with water, and the product collected; yield: 0.3 g. of recovered starting material; melting point and mixed melting point with the starting material, 164-166°.

The filtrate was evaporated to dryness and the residue dissolved in a minimum amount of hot ethanol and cooled;

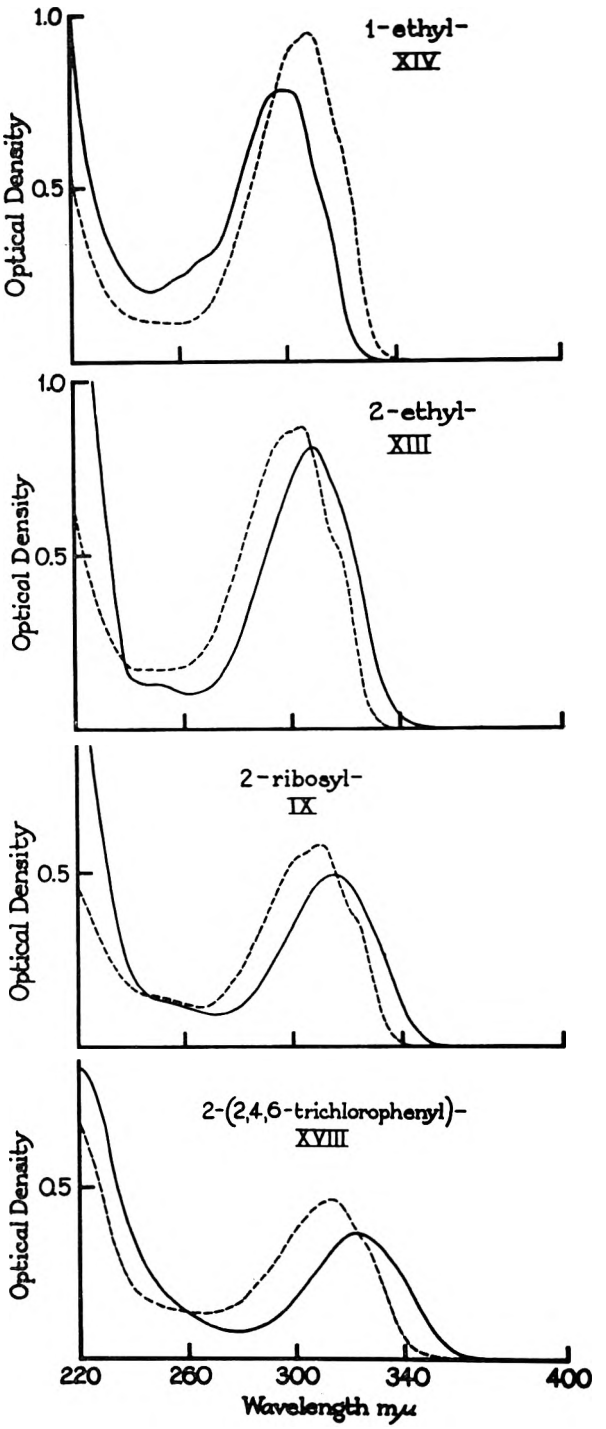
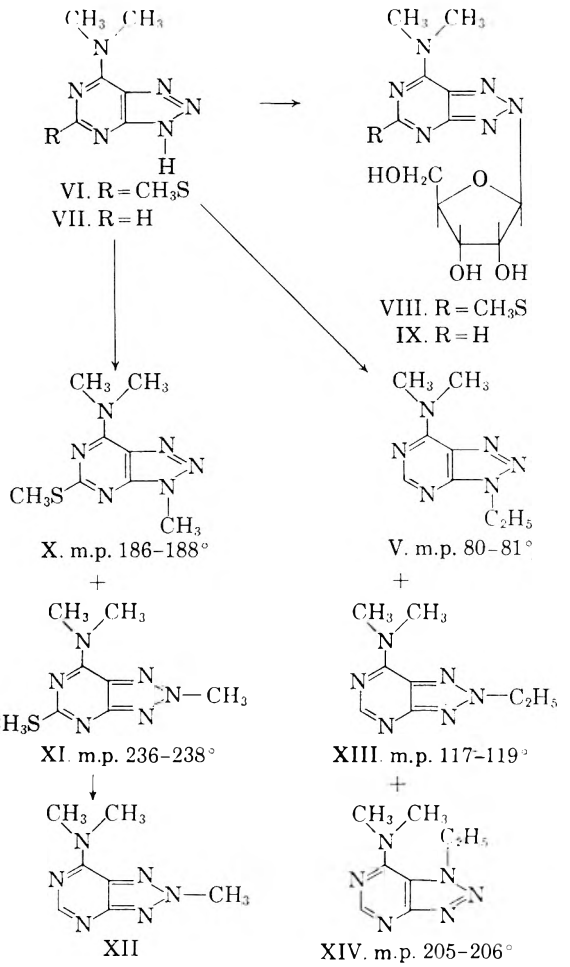


Fig. 2. Ultraviolet absorption spectra of derivatives of 7-dimethylamino-v-triazolo(d)pyrimidine: ——, 0.1N sodium hydroxide or methanol (10γ/ml); – – – –, 0.1N hydrochloric acid (10γ/ml.)

(15) It would have been desirable to have had an authentic sample of 7-dimethylamino-1-ethyl-1H-v-triazolo(d)-pyrimidine (XIV) available for direct comparison. However, several attempts to convert 4-amino-6-dimethylamino-6-ethylaminopyrimidine to XIV by the use of nitrous acid failed to give the desired product.

(16) The melting points were corrected for the exposed stem of the thermometer.



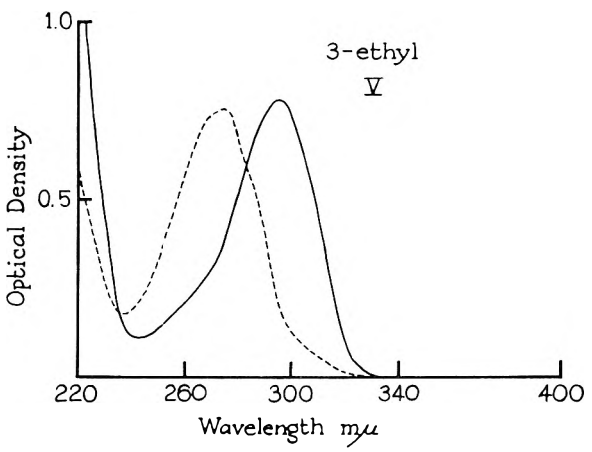


Fig. 3. Ultraviolet absorption spectra of 7-dimethylamino - 3 - ethyl - 3H - v - triazolo(d)pyrimidine (V): ——, 0.1*N* sodium hydroxide 10γ/ml.); – – – –, 0.1*N* hydrochloric acid (10γ/ml)

yield: 0.5 g. (39% based on recovered starting material); m.p. 206–208°. This was recrystallized from 5 ml. of ethanol; yield: 0.3 g., m.p. 207–209°.

Anal. Calcd. for $C_6H_{10}N_4$ (138): C, 52.2; H, 7.2; N, 40.6. Found: C, 52.1; H, 7.3; N, 40.8.

4,5-Diamino-6-dimethylaminopyrimidine. 4,5-Diamino-6-dimethylamino-2-methylmercaptopyrimidine[10] (20 g., 0.1 mole) was dissolved in 400 ml. of 2-methoxyethanol and slurried with 200 g. of Raney nickel catalyst. The mixture was heated on the steam bath with stirring for 1 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized from 350 ml. of benzene; yield varied from 6 to 10 g. (39—65%); m.p. 157–159°. This material was satisfactory for subsequent reactions. For analyses a small sample was sublimed; m.p. 158–160°.

Anal. Calcd. for $C_6H_{11}N_5$ (153): C, 47.0; H, 7.2; N, 45.7. Found: C, 47.5; H, 7.5; N, 45.5.

7-Dimethylamino-v-triazolo(d)pyrimidine (VII). 4,5-Diamino-6-dimethylaminopyrimidine (4.3 g., 28 mmoles) was was dissolved in a solution of 30 ml. of water and 5 ml. of acetic acid. After the addition of a solution of 2.0 g. (29 mmoles) of sodium nitrite in 5 ml. of water a solid appeared. The mixture was cooled and the product collected; yield: 4.4 g. (95%), m.p. 279–281°.

Anal. Calcd. for $C_5H_8N_6$ (164): C, 43.9; H, 4.9; N, 51.2. Found: C, 44.2; H, 5.2; N, 51.6.

7-Dimethylamino-3-ethyl-5-methylmercapto-3H-v-triazolo(d)pyrimidine (IV). A solution of 2.0 g. (8.3 mmoles) of 6-dimethylamino-4-ethylamino-2-methylmercapto-5-nitrosopyrimidine[7] in 40 ml. of warm acetone was added to a solution of 4.0 g. of sodium hydrosulfite in 20 ml. of water. This was shaken and warmed until the blue color disappeared. The mixture was diluted with 80 ml. of water and extracted with three 50-ml. portions of chloroform. The chloroform solution was dried with magnesium sulfate and filtered and the filtrate was evaporated to dryness. The residue (crude triamine III) was dissolved in a solution of 100 ml. of warm water and 10 ml. of acetic acid and mixed with a solution of 600 mg. of sodium nitrite in 10 ml. of water. A precipitate formed immediately. After 5 min. on the steam bath the mixture was cooled; yield: 1.4 g. (70%). This product was recrystallized from a solution of 25 ml. of acetic acid and 50 ml. of water; yield: 0.6 g. (30%), m.p. 114–115°.

Anal. Calcd. for $C_9H_{14}N_6S$ (238): C, 45.4; H, 5.9; N, 35.3; S, 13.4. Found: C, 45.7; H, 6.2; N, 35.3; S, 13.9.

7-Dimethylamino-3-ethyl-3H-v-triazolo(d)pyrimidine (V). A solution of 0.5 g. (2.1 mmoles) of IV in 40 ml. of warm 2-methoxyethanol was treated with several spoonfuls of Raney nickel catalyst and heated on the steam bath for 1 hr. The mixture was filtered and the filtrate was evaporated to dryness. The residue was recrystallized once from 7 ml. of water (yield 120 mg.) and a second time from 7 ml. of heptane; yield: 80 mg. (20%), m.p. 80–81°.

Anal. Calcd. for $C_8H_{12}N_6$ (192): C, 50.0; H, 6.3; N, 43.7. Found: C, 50.2; H, 6.1; N, 43.3.

Methylation of 7-dimethylamino-5-methylmercapto-v-triazolo(d)pyrimidine. A solution containing 4.1 g. (19.5 mmoles) of 7-dimethylamino-5-methylmercapto-v-triazolo(d)pyrimidine (VI),[8] 0.8 g. (20 mmoles) of sodium hydroxide, 80 ml. of water, 30 ml. of methanol, and 1.6 ml. (3.65 g., 25.6 mmoles) of methyl iodide was heated to reflux on a steam bath for 1 hr. The mixture was cooled and the product collected; yield 2.8 g. The solid was dissolved in a minimum amount (about 250 ml.) of hot acetone and allowed to cool slowly to room temperature. The solid was collected and recrystallized from 135 ml. of hot acetone; yield 0.45 g. (10%); m.p. 236–238°. As described in the discussion, this was shown to be 7-dimethylamino-5-methylmercapto-2-methyl-2H-v-triazolo(d)pyrimidine (XI).

Anal. Calcd. for $C_8H_{12}N_6S$ (224): C, 42.9; H, 5.4; N, 37.5; S, 14.3. Found: C, 43.1; H, 5.4; N, 37.0; S, 14.2.

The acetone filtrate remaining after removing the higher melting material was evaporated to about 65% of its original volume and cooled to 0°; yield 1.2 g. This was redissolved in 70 ml. of hot acetone, cooled just to room temperature, and filtered. The filtrate was cooled to 0° and the product collected; yield 0.85 g. (19%); m.p. 186–188°. This had ultraviolet absorption spectra essentially identical with those of IV and was therefore 7-dimethylamino-5-methylmercapto-3-methyl-3H-v-triazolo(d)pyrimidine (X).

Anal. Calcd. for $C_8H_{12}N_6S$ (224): C, 42.9; H, 5.4; N, 37.5; S, 14.3. Found: C, 43.1; H, 5.4; N, 37.4; S, 14.6.

7-Dimethylamino-2-methyl-2H-v-triazolo(d)pyrimidine (XII). 7-Dimethylamino-5-methylmercapto-2-methyl-2H-v-triazolo(d)pyrimidino (XI) (500 mg.; 2.22 mmoles) in 75 ml. of 2-methoxyethanol was desulfurized with Raney nickel in the usual manner. After removal of the catalyst the solution was evaporated to dryness. The residue was extracted with 12 ml. of boiling acetone which upon cooling gave 140 mg. (35% yield) of a crystalline product; m.p. 193–195°. Recrystallization from acetone did not change the melting point.

Anal. Calcd. for $C_7H_{10}N_6$ (178): C, 47.2; H, 5.6; N, 47.2. Found: C, 47.6; H, 5.9; N, 46.8.

Ethylation of 7-dimethylamino-v-triazolo(d)pyrimidine. A solution containing 2.0 g. (12.2 mmoles) of 7-dimethylamino-v-triazolo(d)pyrimidine (VII), 15 ml. of methanol, 6.5 ml. of 2*N* sodium hydroxide, and 1.06 ml. (2.05 g., 13 mmoles) of ethyl iodide was heated at reflux for 135 min. The clear yellow solution was evaporated to a gum *in vacuo*. The gum was dissolved in 15 ml. of a 10% sodium hydroxide solution and extracted with 40 ml. of chloroform followed by three 25-ml. portions of chloroform. The chloroform solution was dried over sodium sulfate and evaporated to a gum. The addition of heptane gave a solid which was collected; yield 414 mg. (fraction I). Upon standing the filtrate gave more solid; yield 545 mg. (fraction II); m.p. 65–105°. The filtrate from fraction II was evaporated to a gum and heptane added again to give 250 mg. of solid which was added to fraction II.

Fraction I (414 mg.) was recrystallized from 35 ml. of benzene; yield: 230 mg., m.p. 205–206°. As described in the discussion this was shown to be 7-dimethylamino-1-ethyl-1H-v-triazolo(d)pyrimidine (XIV).

Anal. Calcd. for $C_8H_{12}N_6$ (192): C, 50.0; H, 6.3; N, 43.7. Found: C, 50.2; H, 6.6; N, 43.7.

When fraction II was recrystallized from heptane and cooled in an ice bath, the product (fraction III) had essentially the same melting point as fraction II. However, the filtrate from fraction III was evaporated to dryness and the residue was recrystallized from heptane to give a product with m.p. 80–81°. This was shown by mixed melting point and ultraviolet absorption spectra to be identical with authentic 7-dimethylamino-3-ethyl-3H-v-triazolo(d)pyrimidine (V).

When fraction III was dissolved in hot heptane and cooled slowly to room temperature the product melted at 116–119°. Another recrystallization from heptane gave a product melting at 117–119°. This was shown to be 7-dimethylamino-2-ethyl-2H-v-triazolo(d)pyrimidine (XIII).

Anal. Calcd. for $C_8H_{12}N_6$: C, 50.0; H, 6.3; N, 43.8. Found: C, 50.5; H, 6.6; N, 43.7.

Bis(7-dimethylamino-5-methylmercapto-v-triazolo(d)pyrimidine) mercury. A solution of 0.33 g. (1.6 mmoles) of 7-dimethylamino-5-methylmercapto-v-triazolo(d)pyrimidine (VI)[8] in 40 ml. of warm 50% ethanol was treated with 0.8 ml. of 2*N* sodium hydroxide followed by 0.22 g. (0.85 mmole) of mercuric chloride dissolved in 3A ethanol. The salt precipitated immediately. The mixture was cooled and the product collected; yield: 0.45 g. (93%).

Anal. Calcd. for $C_{14}H_{18}N_{12}S_2Hg$ (619): C, 27.2; H, 2.9; N, 27.2. Found: C, 27.3; H, 3.3; N, 27.1.

7-Dimethylamino-5-methylmercapto-2-(β-D-ribofuranosyl)-2H-v-triazolo(d)pyrimidine (VIII).[17] 1-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose[9] (2.5 g., 5 mmoles) was dissolved in 10 ml. of acetyl chloride and the solution was poured into 50 ml. of anhydrous ether saturated with dry hydrogen chloride at ice-bath temperature. The solution remained at 3° for 3 days. It was then evaporated to a gum *in vacuo* on a steam bath and evaporated three times with 45-ml. portions of benzene. Meanwhile, 1.3 g. (2.1 mmoles) of bis(7-dimethylamino-5-methylmercapto-v-triazolo(d)pyrimidine) mercury was suspended in 100 ml. of dry xylene and 20 ml. distilled with stirring to dry the solid. The sugar derivative was dissolved in 20 ml. of dry xylene and added to the mercury derivative suspension. Another 25 ml. of xylene was distilled and the mixture was refluxed and stirred for 2.5 hr. The hot mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in 100 ml. of chloroform, filtered from traces of solid material, and washed with 15 ml. of 30% aqueous potassium iodide solution followed by 20 ml. of water. The chloroform solution was dried over sodium sulfate, filtered, and the filtrate concentrated to a yellow glass *in vacuo*. This was dissolved in 30 ml. of methanol containing 1.0 ml. of 1.0*N* methanolic sodium methoxide, refluxed for 45 min., and evaporated to a gum. Trituration with ether gave a white crystalline product which was recrystallized from water to give 250 mg. of crude product. This was recrystallized from 10 ml. of methanol; yield 87 mg. (5.5%); m.p. 171–172°.

Anal. Calcd. for $C_{12}H_{16}O_4N_6S \cdot CH_3OH$ (374): C, 41.7; H, 5.9; N, 22.5; S, 8.6; CH_3O, 8.3. Found: C, 42.1; H, 6.1; N, 22.6; S, 8.7; CH_3O, 7.6.

7-Dimethylamino-2-(β-D-ribofuranosyl)-2H-v-triazolo(d)-pyrimidine (IX).[17] 1-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose[9] (2.5 g., 5 mmoles) was converted to the corresponding ribosyl chloride just as described for compound VIII above. The reaction between this sugar derivative and 2.0 g. (5 mmoles) of chloromercuri-7-dimethylamino-v-triazolo(d)pyrimidine[18] was also carried out just as described for compound VIII. After washing with potassium iodide solution and drying, the solution was evaporated *in vacuo* to a gum. The gum was dissolved in 35 ml. of methanol containing 2 ml. of 1.0*N* methanolic sodium methoxide and refluxed for 45 min. The solution was neutralized with acetic acid and evaporated to a solid. Methanol (50 ml.) was added and heated to boiling, the solution was filtered, and the filtrate allowed to cool to room temperature; yield: 517 mg., m.p. 220–221°. Recrystallization from 50 ml. of methanol gave 435 mg. (29%) of product with same melting point.

Anal. Calcd. for $C_{11}H_{16}O_4N_6$ (296): C, 44.6; H, 5.4; N, 28.4. Found: C, 44.6; H, 5.5; N, 28.5.

4-Amino-6-dimethylamino-2-methylmercapto-5-(2,4,6-trichlorophenylazo) pyrimidine (XV). 2,4,6-Trichloroaniline (10.0 g., 51.0 mmoles) was suspended in a solution of 100 ml. of concd. hydrochloric acid and 50 ml. of water and warmed to convert to the hydrochloride. This was cooled in an ice bath with stirring and treated with a solution of 3.7 g. of sodium nitrite in 30 ml. of water. The solid dissolved. The excess nitrous acid was destroyed with urea and the solution was then poured into 1300 ml. of water and ice containing 115 g. of sodium bicarbonate.

A solution of 8.0 g. (37.0 mmoles) of 4-amino-6-dimethylamino-2-methylmercaptopyrimidine hydrochloride[10] in 350 ml. of warm water was added, with stirring, to the diazonium solution. An orange precipitate appeared during the addition. The product was collected and recrystallized from 600 ml. of 2-methoxyethanol; yield 11.4 g. (79%); orange-red crystals; m.p. 247–249°.

Anal. Calcd. for $C_{13}H_{13}N_6SCl_3$ (391.6); C, 39.9; H, 3.4; N, 21.4. Found: C, 40.1; H, 3.4; N, 21.6.

4-Amino-6-dimethylamino-5-(2,4,6-trichlorophenylazo)-pyrimidine (XVI). A solution of 0.41 g. (3 mmoles) of 4-amino-6-dimethylaminopyrimidine in 15 ml. of water was added to the diazonium chloride solution prepared from 0.8 g. (4 mmoles) of 2,4,6-trichloroaniline in the manner described above. The initial gelatinous product was converted to a solid by heating a short time on the steam bath. After cooling the product was collected; yield: 1.1 g. (88%),

(17) The *beta* configuration is assumed on the basis of analogy and theoretical grounds for which see B. R. Baker in *The Chemistry and Biology of Purines*, Ciba Foundation Symposium, Little, Brown and Co., Boston, Mass., 1957, p. 120; B. R. Baker *et al.*, *J. Org. Chem.*, 19, 1786 (1954).

(18) The chloromercuri derivative of VII was prepared just as described for the mercury derivative of VI except that one mole of mercuric chloride was used.

m.p. 225–227°. Recrystallization from 60 ml. of 2-methoxyethanol gave 0.9 g. (72%) of product; orange needles; m.p. 230–232°.

Anal. Calcd. for $C_{12}H_{11}N_6Cl_3$ (345.6): C, 41.8; H, 3.2; N, 24.4. Found: C, 41.5; H, 3.7; N, 24.8.

7-Dimethylamino-5-methylmercapto-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine (XVII). A mixture of 0.8 g. (2 mmoles) of 4-amino-6-dimethylamino-2-methylmercapto 5-(2,4,6-trichlorophenylazo)pyrimidine (XV), 2.5 g. of copper sulfate·pentahydrate, 7.0 ml. of water, and 14.0 ml. of pyridine was heated at reflux for 4 hr. The solution was then diluted with 50 ml. of water and cooled overnight; yield 0.75 g. (94%); m.p. 214–216°. This was recrystallized from 7 ml. of 2-methoxyethanol; yield: 0.58 g. (72%), m.p. 216–217°.

Anal. Calcd. for $C_{13}H_{11}N_6SCl_3$ (389.6): C, 40.1; H, 2.8; N, 21.6; S, 8.2; Cl, 27.4. Found: C, 39.9; H, 3.1; N, 21.8; S, 8.4; Cl, 27.3.

7-Dimethylamino-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine (XVIII). A mixture of 0.85 g. (2.5 mmoles) of 4-amino-6-dimethylamino-5-(2,4,6-trichlorophenylazo)-pyrimidine (XVI), 2.5 g. of copper sulfate pentahydrate, 7 ml. of water, and 14 ml. of pyridine were heated to reflux for 5 hr. The mixture was diluted with several volumes of water and cooled; yield 0.7 g. (83%); m.p. 262–267°. Recrystallization from 15 ml. of 2-methoxyethanol gave 0.55 g. (65% yield) of product; m.p. 266–268°.

Anal. Calcd. for $C_{12}H_9N_6Cl_3$ (343.6): C, 41.9; H, 2.7; N, 24.5; Cl, 31.0. Found: C, 41.9; H, 2.8; N, 24.8; Cl, 30.6.

Acid hydrolysis of 7-dimethylamino-5-methylmercapto-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine (XVII). A solution of 300 mg. (0.77 mmole) of XVII in 15 ml. of 6*N* hydrochloric acid was heated to reflux for 8 hr. during which time a crystalline solid separated. The solid was collected (yield 60 mg. (23%)), dissolved in 3 ml. of hot 2-methoxyethanol and 2 ml. of hot water added. Cooling gave 35 mg. of 5,7-dihydroxy-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine; m.p. >300°. Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, λ_{max} 317 mμ (ε 7,700); methanol, λ_{max} 280 mμ (ε 10,700); 0.1*N* hydrochloric acid, λ_{max} 281 mμ (ε 11,700).

Anal. Calcd. for $C_{10}H_4N_5O_2Cl_3$ (332.6): C, 36.1; H, 1.2; N, 21.0; Cl, 32.0. Found: C, 36.2; H, 1.5; N, 20.8; Cl, 32.0.

The 6*N* hydrochloric acid filtrate from the reaction was diluted to 70 ml. with water and brought to *p*H 4 with sodium acetate. A crystalline product separated; yield: 160 mg. (57%). This was recrystallized from 5 ml. of 2-methoxyethanol to give 80 mg. of 7-dimethylamino-5-hydroxy-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine; m.p. >300°. Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, λ_{max} 280 mμ (ε 6,800), 334 mμ (ε 9,500); methanol, λ_{max} 287 mμ (ε 16,500), 0.1*N* hydrochloric acid, λ_{max} 299 mμ (ε 12,900).

Anal. Calcd. for $C_{12}H_9N_6OCl_3$ (359.6): C, 40.1; H, 2.5; N, 23.4; Cl, 29.6. Found: C, 39.9; H, 2.8, N, 23.3; Cl, 29.7.

4-Amino-6-dimethylamino-2-methylmercapto-5-phenylazopyrimidine. Aniline (4.7 g., 50 mmoles) was diazotized as described by Benser *et al.*[6] and the diazonium solution was coupled with 9.2 g. (50 mmoles) of 4-amino-6 dimethylamino-2-methylmercaptopyrimidine dissolved in a solution of 300 ml. of water, 115 ml. of acetic acid, and 52 g. of sodium acetate; yield: 8.1 g. This was recrystallized from 100 ml. of 2-methoxyethanol; yield: 7.2 g. (50%) of an orange product, m.p. 197–198°.

A sample (0.45 g.) was recrystallized from 80 ml. of ethanol; yield: 0.25 g., m.p. 198–199°.

Anal. Calcd. for $C_{13}H_{16}N_6S$ (288): C, 54.2; H, 5.7; N, 29.2; S, 11.1. Found: C, 53.8; H, 5.6; N, 29.0; S, 11.0.

7-Dimethylamino-5-methylmercapto-2-phenyl-2H-v-triazolo(d)pyrimidine. A solution of 6.5 g. (22.6 mmoles) of 4-amino-6-dimethylamino-2-methylmercapto-5-phenylazopyrimidine, 16.7 g. of copper sulfate pentahydrate, 64 ml. of pyridine, and 34 ml. of water was heated at reflux for 2.5 hr. and cooled; yield of product 6.3 g. (98%); m.p. 193–194°; mixed melting point with starting material 165–180°.

A sample (0.5 g.) was recrystallized from 80 ml. of ethanol; yield of light yellow crystalline product 0.4 g.; m.p. 194–195°.

Anal. Calcd. for $C_{13}H_{14}N_6S$ (286): C, 54.6; H, 4.9; N, 29.4. Found: C, 54.4; H, 5.9; N, 29.7.

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PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ARIZONA STATE UNIVERSITY]

Potential Purine Antagonists. XXIII. Synthesis of Some 7-Substituted Amino-v-triazolo(d)pyrimidines[1]

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The preparation of certain 7-alkylamino-v-triazolo(d)pyrimidines from 7-methylthio-v-triazolo(d)pyrimidine (XIV) has been accomplished. Some 7-alkylthio-5-amino-v-triazolo(d)pyrimidines have been synthesized by ring closure of the corresponding 6-alkylthio-2,4,5-triaminopyrimidines with nitrous acid. 5-Amino-7-methoxy-v-triazolo(d)pyrimidine has been prepared.

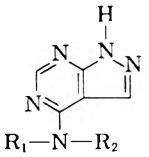
The antitumor activity of 5-amino-7-hydroxy-v-triazolo(d)pyrimidine[2] (8-azaguanine) and 6-amino-4-hydroxypyrazolo(3,4-d)pyrimidine[3] strongly suggested the possibility that antitumor activity similar to that exhibited by the 4-substituted-

(1) Supported by research grant CY-4008 from the National Cancer Institute of the National Institutes of Health, Public Health Service. Presented before the Division of Medicinal Chemistry at the 136th Meeting of the American Chemical Society, September 18, 1959, Atlantic City, N. J.

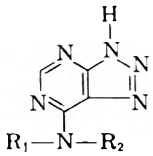
(2) G. W. Kidder, V. C. Dewey, R. E. Parks, and G. L. Woodside, *Cancer Research*, 11, 204 (1949).

(3) H. E. Skipper, R. K. Robins, J. R. Thomson, C. C. Cheng, R. W. Brockman, and F. M. Schabel, Jr., *Cancer Research*, 17, 583 (1957).

aminopyrazolo(3,4-d)pyrimidines (I)[3] might also be found with isomeric derivatives of 7-substituted-amino-v-triazolo(d)pyrimidine (II).



I



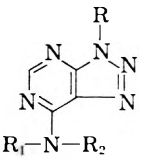
II

The synthesis of compounds of type II has now been accomplished in several steps from 4-amino-6-chloro-5-nitropyrimidine (III).[4]

Treatment of 4-amino-6-chloro-5-nitropyrimidine with a dialkylamine resulted in the preparation of the corresponding 4-amino-6-dialkylamino-5-nitropyrimidine (IV) which was reduced with hydrogen in the presence of Raney nickel to the corresponding 6-dialkylamino-4,5-diaminopyrimidine (V). Cyclization of V with nitrous acid gave the desired 7-dialkylamino-v-triazolo(d)pyrimidine (VI). The 7-dialkylamino-v-triazolo(d)pyrimidines (VI) prepared in this manner are listed as the first three compounds in Table I. The cyclization of 4,5-diamino-6-methylaminopyrimidine (VII)[5] with nitrous acid could theoretically give rise to either 7-methylamino-v-triazolo(d)pyrimidine (VIII) or 7-amino-3-methyl-v-triazolo(d)pyrimidine (IX).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SOME 7-ALKYLAMINO-V-TRIAZOLO(D)PYRIMIDINES

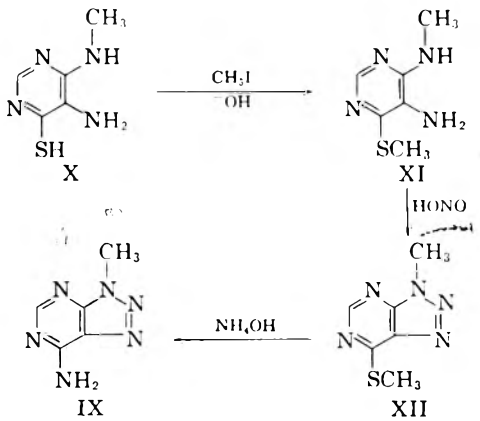


			pH 1		pH 11	
R	R_1	R_2	λ max, mμ	ε	λmax, mμ	ε
H	CH_3	CH_3	287	15,300	294	32,400
H	C_2H_5	C_2H_5	287	11,400	294	16,600
H	n-C_3H_7	n-C_3H_7	290	10,800	295	15,900
CH_3	H	H	263	12,900	277	12,400
CH_3	H	CH_3	270	12,800	288	12,700
CH_3	C_2H_5	C_2H_5	278	19,200	298	17,500
C_2H_5	H	C_2H_5	271	11,600	289	11,600

Ring closure of 4,5-diamino-6-methylaminopyrimidine (VII) with nitrous acid gave exclusively 7-amino-3-methyl-v-triazolo(d)pyrimidine (IX).

The structure of IX was established by independent synthesis from 3-methyl-7-methylthio-v-triazolo(d)pyrimidine (XII) and hot aqueous ammonia. The preparation of XII was accomplished in two steps from 5-amino-4-methylamino-6-pyrimidinethiol.[6]

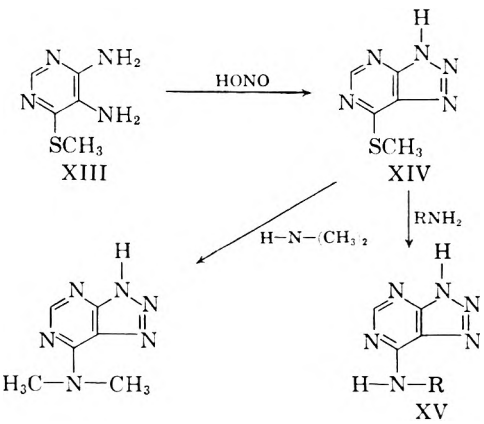
The ease of nucleophilic displacement of the methylthio group of 3-methyl-7-methylthio-v-triazolo(d)pyrimidine (XII) suggested that this might be a useful method of preparing a number of desired 7-alkylamino-v-triazolo(d)pyrimidines unsubstituted at position 3.



The synthesis of 7-methylthio-v-triazolo(d)pyrimidine (XIV) was accomplished in good yield from 4,5-diamino-6-methylthiopyrimidine (XIII)[7] and nitrous acid.

Treatment of XIV with various primary amines in refluxing aqueous solution gave the desired 7-alkylamino-v-triazolo(d)pyrimidines XV listed in Table II.

The replacement of the methylthio group has similarly been accomplished in the purine series to give 6-substituted-aminopurines.[8,9] Substitution of



the 2-methylthio group by amines has similarly been reported for 6-hydroxy-2-methylthiopurine.[10]

(4) S. M. Greenberg, L. O. Ross, and R. K. Robins, *J. Org. Chem.*, **24**, 1314 (1959).

(5) W. Daly and B. E. Christensen, *J. Org. Chem.*, **21**, 177 (1956).

(6) R. K. Robins and H. H. Lin, *J. Am. Chem. Soc.*, **79**, 490 (1957).

(7) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 3832 (1954).

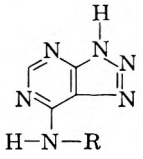
(8) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).

(9) J. A. Montgomery, L. B. Holum, and T. P. Johnston, *J. Am. Chem. Soc.*, **81**, 3963 (1959).

(10) G. B. Elion, W. H. Lange, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 217 (1956).

TABLE II

PREPARATION OF 7-ALKYLAMINO-v-TRIAZOLO(d)-PYRIMIDINES FROM 7-METHYLTHIO-v-TRIAZOLO(d)PYRIMIDINE



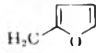
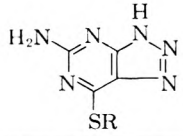
R	M.P.	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	Yield, %	Recrystallization Solvent	pH 1 λmax, mμ	pH 1 ε	pH 11 λmax, mμ	pH 11 ε
CH_3	>300	40.0	40.1	4.0	4.3	56.0	56.3	95.0	Water	270	22,300	285	15,200
C_2H_5	260–262	43.8	44.1	4.9	5.1	51.2	51.4	98.0	Water	270	16,600	285	18,700
t-C_4H_9	248–250	49.9	50.2	6.3	6.7	43.8	44.2	49.6	Ethanol	274	16,400	288	20,700
n-C_4H_9	223–225	50.0	50.5	6.3	6.0	43.8	44.2	61.0	Ethanol	273	14,700	297	17,500
	255–257	49.8	50.1	4.1	4.1	38.7	39.1	53.8	Ethyl acetate	278	17,300	284	12,700

TABLE III

SOME 7-ALKYLTHIO-5-AMINO-v-TRIAZOLO(d)PYRIMIDINES

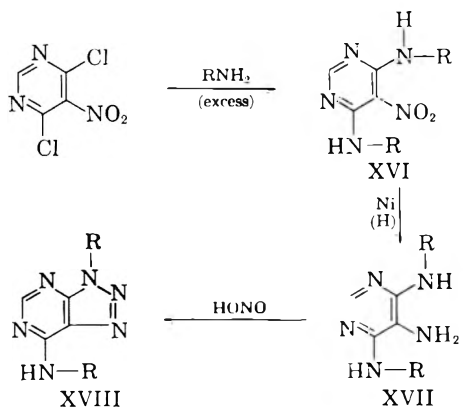


R	M.P.	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	Yield, %	Recrystallization Solvent	pH 1 λmax, mμ	pH 1 ε	pH 11 λmax, mμ	pH 11 ε
CH_3	282–284 dec.	33.0	33.4	3.3	3.5	46.2	46.5	78.7	Water-methanol	298	19,100	321	10,700
												265	10,000
C_2H_5	206–208	36.7	36.3	4.1	4.0	42.9	42.7	95.5	Water-ethanol	301	20,100	320	11,000
												265	9,600
n-C_3H_7	200–202	40.0	40.4	4.8	5.1	40.0	40.2	87.5	Ethyl acetate	304	20,400	324	11,400
												265	9,900
n-C_4H_9	195–197	42.8	43.3	5.4	5.6	37.5	37.8	71.5	Water-ethanol	303	32,800	324	15,200
												266	13,000
$CH_3CH_2{=}CH_2$	231–233	40.4	40.9	3.8	4.0	40.4	40.7	90.5	Ethyl acetate	304	18,300	323	11,400
												265	9,600
p-$ClCH_2C_6H_4$	242–244 dec.	45.2	45.7	3.1	2.8	28.7	29.0	33.8	Water-ethanol	307	12,400	323	23,500
												267	22,100

However, in each instance of replacement of the methylthio group by an amine reported in the purines, temperatures of 130° to 160° were employed. These conditions require sealed tubes or pressure reaction vessels. It is quite significant that the presence of an additional nitrogen atom at position 8 of the purine ring lowers the electron density in the pyrimidine ring to the extent that nucleophilic displacement of the methylthio group by amines can be effected without recourse to sealed tube procedures.

The preparation of 7-dimethylamino-v-triazolo-(d)pyrimidine was likewise accomplished from XIV and aqueous methylamine.

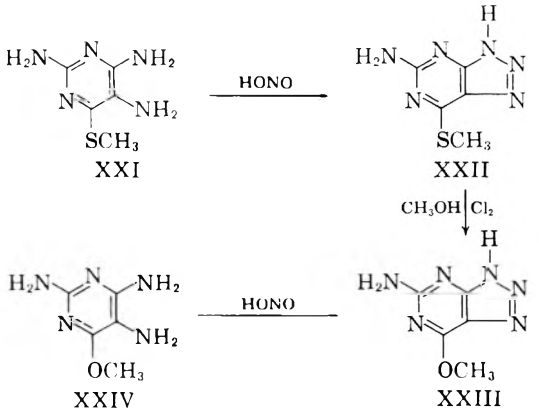
The preparation of 3-ethyl-7-ethylamino-v-triazolo(d)pyrimidine (XVIII R=C_2H_5) and 3-methyl-7-methylamino-v-triazolo(d)pyrimidine (XVIII R=CH_3) was accomplished according to reaction scheme I.



REACTION SCHEME I

Because of the antitumor activity of 6-benzylthiopurine,[11] 6-benzylthio-4,5-diaminopyrimidine (XIX)[12] was cyclized with nitrous acid to give 7-benzylthio-v-triazolo(d)pyrimidine(XX).

Interest in the antitumor activity of several 6-alkylthio-2-aminopurines[11,13] suggested the preparation of some related 7-alkylthio-5-amino-v-triazolo(d)pyrimidines. The simplest compound of this type, 5-amino-7-methylthio-v-triazolo(d)-pyrimidine (XXII) was prepared from 6-methylthio-2,4,5-triaminopyrimidine (XXI)[14] and nitrous acid. A number of additional 7-alkylthio-5-amino-v-triazolo(d)pyrimidines were prepared by ring closure of the corresponding 6-alkylthio-2-amino-4,5-diaminopyrimidines.[14] (See reaction scheme II.) These compounds are listed in Table III.



REACTION SCHEME II

Attempts to prepare 5-amino-7-chloro-v-triazolo-(d)pyrimidine from XXII with chlorine in methanol gave instead 5-amino-7-methoxy-v-triazolo-(d)pyrimidine XXIII. This reaction was unexpected, as 2-amino-6-methylthiopurine under similar conditions gives 2-amino-6-chloropurine.[14] That XXIII was indeed 5-amino-7-methoxy-v-triazolo-(d)pyrimidine was established by ring closure of 6-methoxy-2,4,5-triaminopyrimidine (XXIV)[15] with nitrous acid to yield XXIII identical to the product obtained from 5-amino-7-methylthio-v-triazolo(d)-pyrimidine (XXII).

EXPERIMENTAL[16]

Preparation of 4-amino-5-nitro-6-ni-n-propylaminopyrimidine (IV). To 85 ml. of *p*-dioxane, containing 6 g. of 4-amino-6-chloro-5-nitropyrimidine,[4] was added 6.7 g. of di-*n*-propylamine. The mixture was stirred for 30 min., cooled, and then poured onto 100 g. of ice water. The precipitate which formed was filtered and washed with water. The dried crude product was recrystallized from absolute ethanol to yield 7 g. of crystalline needles, m.p. 115–117°.

Anal. Calcd. for $C_{10}H_{17}N_5O_2$: C, 50.2; H, 7.1; N, 29.3. Found: C, 49.9; H, 7.4; N, 29.6.

4,5-Diamino-6-di-n-propylaminopyrimidine (V). Five grams of 4-amino-6-di-*n*-propylamino-5-nitropyrimidine was dissolved in 150 ml. of methanol, and the solution was shaken with Raney nickel catalyst at a hydrogen pressure of approximately 40 p.s.i. for 1 hr. The solution was boiled with charcoal and filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude product was recrystallized from ethyl acetate to yield 3.7 g. of light-green needles, m.p. 108–110°.

Anal. Calcd. for $C_{10}H_{19}N_5$: C, 57.4; H, 9.1; N, 33.5. Found: C, 57.1; H, 9.1; N, 33.2.

7-Di-n-propylamino-v-triazolo(d)pyrimidine (VI). One gram of 4,5-diamino-6-di-*n*-propylaminopyrimidine was dissolved in 30 ml. of water containing 10 ml. of glacial acetic acid. To this cold solution was added, with stirring, a solution of 0.6 g. of sodium nitrite in 10 ml. of water. A precipitate formed almost immediately. The product was filtered and washed with water to yield 0.7 g. of compound. A small portion was recrystallized from petroleum ether to give a melting point of 104–106°.

(11) H. E. Skipper, J. A. Montgomery, J. R. Thomson, and F. M. Schabel, Jr., *Cancer Research*, **19**, 425 (1959).

(12) G. B. Elion, W. H. Lange, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 2858 (1956).

(13) D. A. Clarke, G. B. Elion, G. H. Hitchings, and C. C. Stock, *Cancer Research*, **18**, 445 (1958).

(14) G. D. Daves, Jr., C. W. Noell, R. K. Robins, H. C. Koppel, and A. G. Beaman, "Potential Purine Antagonists. XXII . . . ," *J. Am. Chem. Soc.* (in press)

(15) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *J. Am. Chem. Soc.*, **73**, 2869 (1951).

(16) All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus, unless otherwise stated.

Anal. Calcd. for $C_{16}H_{16}N_6$: C, 54.6; H, 7.3; N, 38.2. Found: C, 54.8; H, 7.4; N, 38.6.

7-Diethylamino-v-triazolo(d)pyrimidine (VI). Preparation of this compound by the cyclization of 4,5-diamino-6-diethylaminopyrimidine[17] with nitrous acid was carried out in a manner identical to that employed for the preparation of 7-di-*n*-propylamino-v-triazolo(d)pyrimidine previously described. The product was recrystallized from water to give white crystals, m.p. 188–190°.

Anal. Calcd. for $C_8H_{12}N_6$: C, 50.0; H, 6.3; N, 43.7. Found: C, 50.0; H, 6.6; N, 43.4.

7-Methylthio-v-triazolo(d)pyrimidine (XIV). Two grams of 4,5-diamino-6-methylthiopyrimidine[7] was added to 110 ml. of water, containing 0.9 ml. of sulfuric acid. The mixture was filtered and cooled. To this solution was added, with stirring, 1 g. of sodium nitrite in 10 ml. of water. The product was filtered and washed with petroleum ether to give 1.5 g. of product which was recrystallized from water to give white needles, m.p. 203–205°.

Anal. Calcd. for $C_5H_5N_5S$: C, 35.9; H, 2.9; N, 41.8. Found: C, 35.7; H, 2.7; N, 41.5.

7-Benzylthio-v-triazolo(d)pyrimidine (XX). One gram of 6-benzylthio-4,5-diaminopyrimidine[12] was dissolved in 35 ml. of water, containing 7 ml. of hydrochloric acid. A solution containing 0.7 g. of sodium nitrite in 10 ml. of water was added slowly with stirring. The product was filtered and washed with petroleum ether to yield 1 g. Recrystallization from water yielded white crystals, m.p. 164–166°.

Anal. Calcd. for $C_{11}H_9N_5S$: C, 54.4; H, 3.7; N, 28.9. Found: C, 54.4; H, 3.7; N, 29.3.

Preparation of 7-alkylamino-v-triazolo(d)pyrimidines (see Table II). *Example A. 7-Furfurylamino-v-triazolo(d)pyrimidine.* Seven grams of 7-methylthio-v-triazolo(d)pyrimidine (XIV) was placed in a solution of 100 ml. of water to which had been previously added 8 g. of furfurylamine. This mixture was then refluxed for 4 hr. The solution was evaporated to dryness under reduced pressure using a steam bath as the source of heat. The crude product was collected and reprecipitated from dilute ammonium hydroxide with glacial acetic acid to give 4.9 g. of compound. Recrystallization from ethyl acetate yielded white crystals, m.p. 255–257°.

Anal. Calcd. for $C_9H_8N_6O$: C, 49.8; H, 4.1; N, 38.7. Found: C, 50.1; H, 4.1; N, 39.1.

Example B. 7-Dimethylamino-v-triazolo(d)pyrimidine (II). *Method (1).* 7-Methylthio-v-triazolo(d)pyrimidine (2.0 g.) was placed in a solution of 50 ml. of water containing 40 ml. of dimethylamine (40% in water). This was then refluxed for 3 hr. The solution was then evaporated to dryness under reduced pressure using a steam bath as a source of heat, and the product was recrystallized from ethyl acetate to give 1.7 g., m.p. 288–290°.

Method (2). One gram of 4,5-diamino-6-dimethylaminopyrimidine[15] was dissolved in 50 ml. of water containing 10 ml. of glacial acetic acid. To this cold solution was added, with stirring, a solution of 0.6 g. of sodium nitrite in 10 ml. of water. A precipitate formed almost immediately. The product was filtered and washed with water to yield 0.8 g. A small portion was recrystallized from ethyl acetate to yield white crystals, m.p. 288–290°. This product was identical with that prepared by method (1) as judged by mixed melting points and ultraviolet spectra at *p*H 1 and *p*H 11.

Anal. Calcd. for $C_6H_8N_6$: C, 43.8; H, 4.9; N, 51.2. Found: C, 43.9; H, 5.1; N, 51.5.

3-Methyl-7-methylamino-v-triazolo(d)pyrimidine (XVIII). Two grams of 5-amino-4,6-*bis*(methylamino)pyrimidine[6] was added to 50 ml. of water, and the solution was adjusted to *p*H 5 with acetic acid. To this cold solution was added 1 g. of sodium nitrite in 10 ml. of water. A precipitate formed almost immediately. The crude product was recrystallized from absolute ethanol to yield white crystals, m.p. 233–235°.

Anal. Calcd. for $C_6H_8N_6$: C, 43.9; H, 4.9; N, 51.2. Found: C, 44.1; H, 5.0; N, 50.8.

3-Ethyl-7-ethylamino-v-triazolo(d)pyrimidine (XVIII). Ten grams of 4,6-dichloro-5-nitropyrimidine[18] was dissolved in 200 ml. of ethyl alcohol. To this solution, which was constantly stirred, was added slowly 12 g. of ethylamine. The mixture was then boiled with charcoal and filtered, and the filtrate was evaporated to dryness under reduced pressure. A yellowish residue remained. The crude 4,6-bis(ethylamino)-pyrimidine was dissolved in 150 ml. of methanol, and the solution was shaken with Raney nickel catalyst at a hydrogen pressure of approximately 40 p.s.i. for 1 hr. The solution was boiled with charcoal and filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude 5-amino-4,6-bis(ethylamino)pyrimidine was added directly to 25 ml. of water containing 5 ml. of acetic acid. To this cold solution was added 3 g. of sodium nitrite in 10 ml. of water. A precipitate formed almost immediately. The crude product was recrystallized from ethanol to give a crystalline substance, m.p. 104–106°.

Anal. Calcd. for $C_8H_{12}N_6$:C, 50.0; H, 6.8; N, 43.7. Found: C, 50.1; H, 6.2; N, 44.0.

7-Diethylamino-3-methyl-v-triazolo(d)pyrimidine. Ten grams of 4-chloro-6-methylamino-5-nitropyrimidine[6] was dissolved in 120 ml. of 1,4-dioxane. To this solution was slowly added 8.3 g. of diethylamine, and then the solution was heated and refluxed for 1 hr. The solution was then evaporated to dryness under reduced pressure. A dark brown, oily residue remained. The crude material was dissolved in 150 ml. of methanol, and the solution was shaken with Raney nickel catalyst at a hydrogen pressure of approximately 40 p.s.i. for 1 hr. The solution was boiled with charcoal and filtered, and the filtrate was evaporated to dryness under reduced pressure. A dark brown residue remained. The crude material was dissolved in 50 ml. of water containing 7 ml. of acetic acid. To this cold solution was added, with stirring, 4 g. of sodium nitrite in 10 ml. of water. Stirring was continued for an additional hour. The product was filtered and washed with petroleum ether. A small portion of this compound was recrystallized from heptane to give a melting point of 87–89°.

Anal. Calcd. for $C_9N_6H_{13}$: C, 52.4; H, 6.8; N, 40.8. Found: C, 53.0; H, 6.7; N, 41.2.

3-Methyl-7-methylthio-v-triazolo(d)pyrimidine (XII). Five grams of 5-amino-4-methylamino-6-pyrimidinethiol[6] was dissolved in 50 ml. of 1*N* potassium hydroxide. The solution was stirred, and 2.5 ml. of methyl iodide was added. Stirring was continued for an additional 30 min. The product was filtered and washed with petroleum ether. The crude 5-amino-4-methylamino-6-methylthiopyrimidine was not purified but added directly to 150 ml. of water containing 5 ml. of sulfuric acid. The solution was cooled to 10°, and 4 g. of sodium nitrite in 10 ml. of water was added with stirring. After an additional 10 min. of stirring, the *p*H was adjusted to *p*H 8–9, cooled, and filtered to yield 2.8 g. of product. Recrystallization from water yielded white crystals, m.p. 122–124°.

Anal. Calcd. for $C_6H_7N_5S$: C, 39.7; H, 3.9; N, 38.7. Found: C, 40.1; H, 4.2; N, 38.7.

7-Amino-3-methyl-v-triazolo(d)pyrimidine (IX). *Method (1).* One gram of 4,5-diamino-6-methylaminopyrimidine sulfate was dissolved in 75 ml. of water and cooled to 10°. Sodium nitrite (0.5 g.) in 10 ml. of water was added dropwise with stirring. The mixture was then allowed to stir for an additional 30 min. at room temperature. At the end of this time the *p*H was adjusted to 8. The product was filtered and washed with a small amount of cold water to yield 0.5 g. A small portion was recrystallized from absolute ethanol to give a melting point of 313–315°.

Anal. Calcd. for $C_5H_6N_6$: C, 40.0; H, 4.0; N, 56.0. Found: C, 40.4; H, 4.4; N, 56.0.

(17) W. R. Boon and W. G. M. Jones, *J. Chem. Soc.*, 4104 (1958).

(18) W. R. Boon, W. C. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, 99 (1951).

Method (2). One gram of 3-methyl-7-methylthio-v-triazolo(d)pyrimidine was placed in 75 ml. of ammonium hydroxide, and the solution was refluxed for 2 hr. The mixture was then cooled to yield 0.8 g. of product which was found to be identical to that produced by method (1) as judged by mixed melting point behavior.

Preparation of 7-alkylthio-5-amino-v-triazolo(d)pyrimidines. (See Table III). Example A. *5-Amino-7-methylthio-v-triazolo(d)pyrimidine* (XXII). Ten grams of 6-methyl-2,4,5-triaminopyrimidine[14] was added to 30 ml. of acetic acid and 100 ml. of water. The solution was stirred, and 6 g. of sodium nitrite, in 24 ml. of water, was added dropwise over a period of approximately 20 min. The mixture was then allowed to stir an additional 30 min., and the precipitate was filtered and washed with water to give 3.4 g. of product. A small portion was recrystallized from a water-methanol solution to give a melting point of 282–284° dec.

Anal. Calcd. for $C_5H_6N_6S$: C, 33.0; H, 3.3; N, 46.2. Found: C, 33.3; H 3.5; N, 46.5.

Example B. 5-Amino-7-(p-chlorobenzylthio)-v-triazolo(d)-pyrimidine. Ten grams of 6-*p*-chlorobenzylthio-2,4,5-triaminopyrimidine[14] was added to 50 ml. of acetic acid and 150 ml. of water. Ten grams of sodium nitrite, in 40 ml. of water, was then added dropwise over a period of approximately 20 min. The mixture was then allowed to stir an additional hour. The crude product was collected and reprecipitated from dilute potassium hydroxide by glacial acetic acid to give 3.5 g. of product. A small portion was recrystallized from a water-ethanol solution for analysis, m.p. 242–244° dec.

Anal. Calcd. for $C_{11}H_9N_6S$: C, 45.2; H, 3.1; N, 28.7. Found: C, 45.7; H, 2.8; N, 29.0.

5-Amino-7-methoxy-v-triazolo(d)pyrimidine (XXIII). *Method (1).* Five grams of 5-amino-7-methylthio-v-triazolo-(d) pyrimidine was added to 50 ml. of methanol, and chlorine gas was allowed to bubble through the solution for approximately 20 min. with no external cooling. The product was filtered and washed with water. Recrystallization from water yielded a white crystalline substance, m.p. >300°.

Anal. Calcd. for $C_6H_6N_6O$: C, 36.2; H, 3.6; N, 50.6. Found: C, 36.5; H, 4.1; N, 50.2.

Method (2). To 1 g. of 6-methoxy-2,4,5-triaminopyrimidine sulfate,[15] in 40 ml. of water, was added, with stirring, 0.75 g. of sodium nitrite. The product was filtered and washed with a small amount of cold water to yield 0.7 g., m.p. >300°. An analytical sample was prepared by recrystallization from water. This product was identical with that prepared by method (1), as judged by identical ultraviolet and infrared absorption spectra. At *p*H 11, 5-amino-7-methoxy-v-triazolo(d)pyrimidine exhibits absorption maxima λ max. 291, mμ, ε 7,300; at *p*H 1, λ max. 283 mμ, ε 12,800, and λ max. 236 mμ, ε 8,800.

Anal. Calcd. for $C_6H_6N_6O$: C, 36.2; H, 3.6; N, 50.6. Found: C, 35.8; H, 3.5; N, 50.2.

TEMPE, ARIZ.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF LJUBLJANA]

Reaction of 4-Arylthiosemicarbazides with Some α-Keto Acids and Synthesis of Some Substituted 3-Thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines[1a]

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4-Arylthiosemicarbazides were treated with glyoxylic, pyruvic, and benzoylformic acids to form derivatives of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines *via* the corresponding intermediate thiosemicarbazones. The thione-thiol tautomerism of these substances is discussed.

It is well known that with thiosemicarbazones of α-keto acids ring closure can occur with the formation of derivatives of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (II) and these were reviewed recently.[1b] Besides the above-mentioned method of preparation they were prepared also from thiosemicarbazide and oximes of α-keto esters.[2,3] All these derivatives represent mainly 6-substituted derivatives. Known are also 2-substituted derivatives, formulated as 2-alkyl-3-mercapto-5-oxo-2,5-dihydro-1,2,4-triazines, which can be in turn prepared from 2-alkylthiosemicarbazides and α-keto acids.[4–7] Of 4-substituted derivatives only some alkyl derivatives are known[3,8,9] and the cyclization failed in the case of the benzyl derivative.[9] It was therefore desirable to study the cyclization of products, obtained from condensation of 4-substituted thiosemicarbazides with α-keto acids, and the tautomerism associated with these compounds.

The cyclization of thiosemicarbazones could be achieved by refluxing an ethanolic solution, except in the case of 4-arylthiosemicarbazones of glyoxylic acid. The use of an alkaline solution was therefore attempted as it is known that the cyclization of 2-alkylthiosemicarbazones of phenylpyruvic acid proceeds with great facility in dilute sodium hydroxide solution.[7] Such cyclization failed with 4-arylthiosemicarbazones of pyruvic acid and the compounds could be recovered unchanged, but in the case of some 4-arylthiosemicarbazones of glyoxylic acid the molecules were split into the corresponding *N*-arylthioureas (III).

(1a) Part VI of this series, *Arch. Pharm.*, **292/64**, 90 (1959).

(1b) J. G. Erickson, P. F. Wiley, and V. P. Wystrach, *The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines*, Interscience Publishers, New York, 1956, p. 78.

(2) A. Godfrin, *J. pharm. chim.*, **30**, 321 (1939).

(3) R. E. Hagenbach, E. Hodel, and H. Gysin, *Angew. Chem.*, **66**, 359 (1954).

(4) E. Cattelain, *Bull. soc. chim. France*, **11**, 249 (1944).

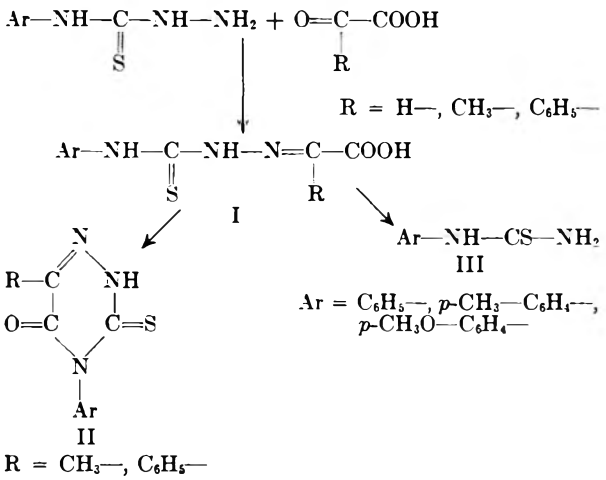
(5) E. Cattelain, *Bull. soc. chim. France*, **12**, 39 (1945).

(6) E. Cattelain, *Compt. rend.*, **208**, 1656 (1939).

(7) E. Cattelain, *Compt. rend.*, **210**, 301 (1940).

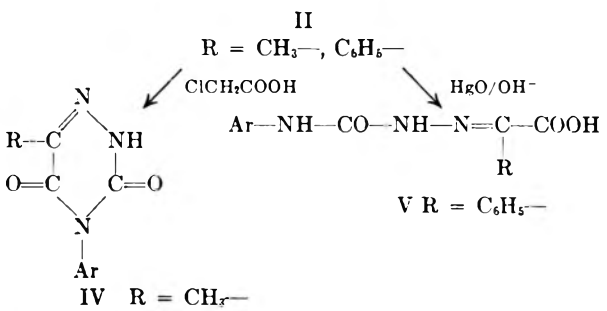
(8) E. Cattelain, *Bull. soc. chim. France*, **11**, 273 (1944).

(9) E. Cattelain, *Compt. rend.*, **210**, 763 (1940).



These findings are completely contrary to those of semicarbazones of α-keto acids where the cyclization in alkaline solution took place in the case of glyoxylic acid,[10] but failed with pyruvic acid.[11,12]

The replacement of the sulfur atom in the 3-thioxo compounds (II) with oxygen leads to substituted 6-azauracils. 6-Azauracil (IV. Ar = R = H; 3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine), the simplest member of the series, evoked particular interest after the discovery of its bacteriostatic[13-15] and antitumor[13,16,17] activity, particularly as ribofuranoside.[18] For the purpose of metabolic studies also labeled 6-azauracil was synthesized[19-22] and recently new 5-alkyl-6-azauracils were prepared.[23] The replacement of the sulfur atom was best accomplished with a boiling 20% aqueous solution of monochloroacetic acid, however only when one aromatic substituent was in the ring. In the case of the 4,6-diphenyl compound (II. Ar = R = C_6H_5—) and other similar compounds this reagent proved to be ineffective and an alkaline suspension of yellow mercuric oxide was used. Instead of the expected reaction the splitting of the molecule occurred and thus the 4,6-diphenyl compound (II. Ar = R = C_6H_5—) afforded the 4-phenylsemicarbazone of benzoylformic acid (V. Ar = R = C_6H_5—).



All known derivatives of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine, *e.g.*, the 2- and 6-substituted compounds are formulated as existing in the thiol form,[1,3,24] as 3-mercapto-5-oxo-2,5-dihydro-1,2,4-triazines. The presence of the thiol form was postulated on the basis of the observed acidity and the conversion of these compounds with aqueous iodine or cupric sulfate into the corresponding disulfides. It was not taken into account that the disulfides are also acidic and form colored complexes with cuprous and cupric ions.

The cyclization products we obtained did not react in an ethanolic solution with aqueous iodine solution and the infrared spectra showed no absorption bands in the 2600–2550 cm.$^{-1}$ region, characteristic for the mercapto group.[25] The spectra were determined as mulls in hexachlorobutadiene and Nujol and some as solutions in carbon disulfide. Moreover, further evidence could be obtained from the ultraviolet spectra as in the case of 2-mercaptobenzothiazoles[26-28] where the thione-thiol tautomerism was thus extensively studied. The only recorded ultraviolet spectrum was that of the 2-phenyl-4,6-dimethyl compound.[29] The comparison of the ultraviolet spectra of some of our compounds in ethanolic solution and in alkaline solution also clearly support the presence of the thione form in the solid state and neutral solutions, and excludes their formulation as VI which is to be favored in alkaline solution. In alcoholic solution the compounds show absorption maxima at 2740–2880 Å and the compounds with two aromatic substituents in the ring show, in ethanol an additional absorption band in the 3210–3340 Å region compared with those triazines bearing only one aromatic substituent. The absorption spectra of alcoholic solutions of II (Ar = R = C_6H_5—, λ_{max} 2840 and 3500 Å and Ar = p-CH_3-C_6H_4—, R = CH_3—, λ_{max} 2740 Å) differ markedly from those of alkaline solutions with only one maximum at 3200 Å (II.

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(18) R. Schindler and A. D. Welch, *Science*, **125**, 548 (1957).
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(23) P. K. Chang, *J. Org. Chem.*, **23**, 1951 (1958).
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(25) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, 1954, p. 288.
(26) H. P. Koch, *J. Chem. Soc.*, 401 (1949).
(27) R. A. Morton and A. L. Stubbs, *J. Chem. Soc.*, 1321 (1939).
(28) C. Hasan and R. F. Hunter, *J. Chem. Soc.*, 1672 (1936).
(29) J. A. Elvidge and F. S. Spring, *J. Chem. Soc.*, S 135 (1949).

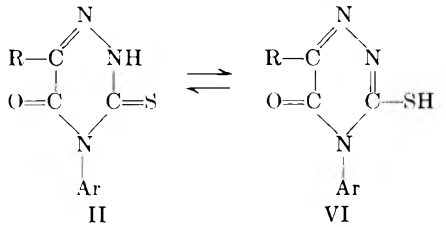
TABLE I

4-ARYLTHIOSEMICARBAZONES OF α-KETO ACIDS

Ar—NH—CS—NH—N=C(R)COOH

Compound No.	Ar	R	M.P., °C	Formula	Analyses Calcd. % C	% H	% N	Found % C	% H	% N	UV spectrum (C_2H_5OH) λ_{max}, Å	ϵ
1	Phenyl-	H	138	$C_9H_9O_2N_3S$	48.43	4.06	18.83	48.35	4.18	18.80	2940	29780
2	*p*-Tolyl-	H	147	$C_{10}H_{11}O_2N_3S$	50.63	4.67	17.72	50.75	4.85	17.68	2960	23240
3	*p*-Methoxyphenyl-	H	141	$C_{10}H_{11}O_3N_3S$	47.43	4.38	16.60	47.61	4.56	16.75	2940	24800
4	Phenyl-	Methyl-	186	$C_{10}H_{11}O_2N_3S$	50.63	4.67	17.72	50.60	4.72	17.59	2940	24000
											2980	23580
											3040	23580
5	*o*-Ethoxyphenyl-	Methyl-	174	$C_{12}H_{15}O_3N_3S$	51.24	5.38	14.94	51.22	5.38	15.15	3020	24220
6	*m*-Tolyl-	Methyl-	184	$C_{11}H_{13}O_2N_3S$	52.58	5.22	16.73	52.47	5.36	16.81		
7	*o*-Methoxyphenyl-	Methyl-	178	$C_{11}H_{13}O_3N_3S$	49.43	4.90	15.73	49.58	5.07	15.75		
8	*p*-Methoxyphenyl-	Methyl-	205	$C_{11}H_{13}O_3N_3S$	49.43	4.90	15.73	49.41	4.98	15.52		
9	*p*-Chlorophenyl-	Methyl-	195	$C_{10}H_{10}O_2N_3SCl$	44.20	3.71	15.47	44.26	3.93	15.58		

Ar = R = C_6H_5—) and 2800–2810 Å (II. Ar = *p*-CH_3-C_6H_4, R = CH_3—), respectively. On the basis of all above-mentioned indications these compounds are best represented as substituted 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines (II).



On the basis of the infrared spectra where typical carbonyl frequencies can be found (for example IV. Ar = C_6H_5—, R = CH_3—, at 1704 cm.$^{-1}$), the desulfurized compounds are represented most likely as derivatives of 3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine, while the dihydroxy form was not excluded by Bougalt[11,12] with similar compounds. Furthermore, the dioxo compounds show absorption maxima in the ultraviolet spectrum at about 2640–2660 Å and the spectra closely resemble those of 6-methyluracils.[30]

EXPERIMENTAL[31]

Condensation of 4-substituted thiosemicarbazides with α-keto acids. The condensation could be effected in acid or alkaline solution:

(a) To a solution of 4-arylthiosemicarbazide in hydrochloric acid (1:8) an equimolar quantity of an aqueous solution of α-keto acid (0.01 mole) was added and after a few minutes a precipitate of the thiosemicarbazone could be collected.

(b) To a cold alkaline solution of the α-keto acid (0.01 mole) was added an equimolar amount of solid 4-arylthiosemicarbazide. After standing for 15 min. the unchanged thiosemicarbazide was filtered off and after acidification of the filtrate the condensation product was obtained.

(30) R. N. Lacey and W. R. Ward, *J. Chem. Soc.*, 2134 (1958).

(31) All melting points were determined with Kofler's heating microscope.

For the preparation of compounds listed in Table I the following example is illustrative.

4-p-Tolylthiosemicarbazone of pyruvic acid. To a stirred solution of 4-*p*-tolylthiosemicarbazide (1.81 g.) in dilute hydrochloric acid (1:8, 40 ml.) was added an aqueous solution of pyruvic acid (0.88 g. in 20 ml. water). The precipitate was filtered, washed with dilute hydrochloric acid (1:8, 40 ml.), and finally with water until acid-free. After recrystallization from 20% ethanol the product melted at 192°. Yield: 90%.

Anal. Calcd. for $C_{11}H_{13}O_2N_3S$: C, 52.58; H, 5.22; N, 16.73. Found: C, 52.67; H, 5.01; N, 17.00.

In ethanol λ_{max} 2980 Å, ϵ 22,960.

Cyclization of 4-arylthiosemicarbazones of pyruvic and benzoylformic acid. The following example is illustrative for the preparation of triazines from 4-arylthiosemicarbazones of pyruvic acid.

4-p-Tolyl-6-methyl-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine. 4-*p*-Tolylthiosemicarbazone of pyruvic acid (2.0 g.) was refluxed in 20% ethanol (30 ml.) for 5 hr. Most of the ethanol and water were then distilled and the residue recrystallized from dilute ethanol (1:4) to give the pure triazine (yield: 51%), m.p. 208°.

Anal. Calcd. for $C_{11}H_{11}ON_3S$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.87; H, 4.80; N, 18.26.

In ethanol λ_{max} 2740 Å, ϵ 16,400; in 0.1*N* sodium hydroxide λ_{max} 2800–2810 Å, ϵ 11,840. Other compounds are listed in Table II. 4-Arylthiosemicarbazones of benzoylformic acid were not isolated and in this case the following procedure, used also for the preparation of other compounds listed in Table II, was applied.

4,6-Diphenyl-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine. 4-Phenylthiosemicarbazide (2.2 g.) was dissolved in boiling ethanol (30 ml.), benzoylformic acid (2.0 g.) added, and the mixture refluxed for 8 hr. The precipitate, collected after cooling, was recrystallized from ethanol and melted at 285–286°. Yield: 2.05 g. (55%).

Anal. Calcd. for $C_{15}H_{11}ON_3S$: C, 64.05; H, 3.94; N, 14.94. Found: C, 63.93; H, 4.02; N, 14.94. In ethanol λ_{max} 2840 Å, ϵ 23,800 and λ_{max} 3500 Å, ϵ 11,120; in 0.1*N* sodium hydroxide λ_{max} 3200 Å, ϵ 15,940.

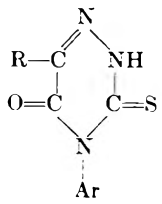
The diphenyl compound, when treated with an ethereal solution of diazomethane, afforded the *N*-methyl derivative which after two recrystallizations from ethanol melted at 211°.

Anal. Calcd. for $C_{16}H_{13}ON_3S$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.01; H, 4.56; N, 14.38. In ethanol λ_{max} 2840 Å, ϵ 26,260 and λ_{max} 3500 Å, ϵ 14,750.

Conversion of 4-arylthiosemicarbazones of glyoxylic acid into the corresponding N-arylthioureas. The attempted cyclization of 4-arylthiosemicarbazones of glyoxylic acid in ethano-

TABLE II

SUBSTITUTED 3-THIOXO-5-OXO-2,3,4,5-TETRAHYDRO-1,2,4-TRIAZINES



Compound No.	Ar	R	M.P.,°	Formula	Analyses						UV spectrum (C_2H_5OH)	
					Calcd.			Found			λ_{max}, Å	ϵ
					% C	% H	% N	% C	% H	% N		
1	Phenyl-	Methyl-	218.5	$C_{10}H_9ON_3S$	54.79	4.14	19.17	54.75	4.23	19.04	2740	16320
2	*m*-Tolyl-	Methyl-	230–231	$C_{11}H_{11}ON_3S$	56.65	4.75	18.02	56.72	4.83	18.27	2810	17810
3	*o*-Methoxyphenyl-	Methyl-	226	$C_{11}H_{11}O_2N_3S$	53.01	4.45	16.86	52.90	4.41	16.73	2750	16870
4	*p*-Methoxyphenyl-	Methyl-	184–185	$C_{11}H_{11}O_2N_3S$	53.01	4.45	16.86	53.08	4.55	16.64	2790	19630
5	*o*-Ethoxyphenyl-	Methyl-	150	$C_{12}H_{13}O_2N_3S$	54.75	4.98	15.96	54.62	4.92	15.82	2740	19850
6	*p*-Chlorophenyl-	Methyl-	224–225	$C_{10}H_8ON_3SCl$	47.34	3.18	16.56	47.36	3.25	16.57	2885	23540
7	*o*-Tolyl	Phenyl-	235–236	$C_{16}H_{13}ON_3S$	65.08	4.44	14.23	65.16	4.61	14.16	2850	19130
											3340	10240
8	*m*-Tolyl-	Phenyl-	263–264	$C_{16}H_{13}ON_3S$	65.08	4.44	14.23	64.99	4.43	14.07	2855	18980
											3280	13430
9	*p*-Tolyl-	Phenyl-	307–308	$C_{16}H_{13}ON_3S$	65.08	4.44	14.23	65.12	4.48	14.36	2855	18540
											3280	16090
10	*p*-Methoxyphenyl-	Phenyl-	290	$C_{16}H_{13}O_2N_3S$	61.73	4.21	13.50	61.76	4.38	13.55	2850	19390
											3285	15890
11	*m*-Chlorophenyl-	Phenyl-	250–251	$C_{16}H_{10}ON_3SCl$	57.05	3.19	13.31	56.92	3.08	13.48	2880	16040
											3230	17610
12	*p*-Chlorophenyl-	Phenyl-	318–320	$C_{15}H_{10}ON_3SCl$	57.05	3.19	13.31	57.01	3.27	13.35	2880	16660
											3210	17130

lic solution was not successful and therefore an alkaline medium was used. When the 4-phenylthiosemicarbazone of glyoxylic acid was refluxed with a 1M aqueous solution of potassium carbonate the compound at first dissolved, but after a few minutes a precipitate formed. The mixture was refluxed for 10 min. more, the solid filtered and crystallized from alcohol. The compound was identified as *N*-phenylthiourea, m.p. 154°, undepressed with an authentic specimen.

In the same way the formation of *N*-*p*-tolylthiourea (m.p. 188°) and *N*-*p*-methoxyphenylthiourea (m.p. 210°) was observed.

Desulfurization of derivatives of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine. 4-Phenyl-6-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine. The 3-thioxo compound (1.87 g.) was heated with aqueous monochloroacetic acid (9 ml. of 20%) and from the resulting solution a precipitate soon formed. After 5 hr. of refluxing the precipitate was collected, washed with water, and recrystallized from hot water, m.p. 242.5°. Yield: 0.7 g. (35%); in ethanol λ_{max} 2640 Å, ϵ 6360.

Anal. Calcd. for $C_{10}H_9O_2N_3$: C, 59.10; H, 4.46; N, 20.68. Found: C, 58.98; H, 4.60; N, 20.65.

4-p-Tolyl-6-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine was prepared by essentially the same procedure as above, starting from 1 g. of 3-thioxo compound. After recrystallization from water (0.62 g., 67% yield) the substance melted at 248°. In ethanol λ_{max} 2660 Å, ϵ 6270.

Anal. Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.82; H, 5.10; N, 19.35. Found: C, 60.85; H, 5.18; N, 19.18.

Attempted desulfurization of 4,6-diphenyl-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine. When the diphenyl compound (0.1 g.) was dissolved in 1*N* sodium hydroxide (10 ml.) with gentle heating and freshly precipitated mercuric oxide (1 g.) was added, this instantly turned black. After 5 min. of thorough mixing, the mixture was filtered and the clear filtrate acidified with dilute hydrochloric acid. The precipitate was collected and recrystallized from ethanol, m.p. 184°.

Anal. Calcd. for $C_{15}H_{13}O_3N_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.43; H, 4.96; N, 14.77.

This compound (V, Ar = R = C_6H_5—) was identical with the synthesized one, *e.g.*, from 4-phenylsemicarbazide and benzoylformic acid, which did not depress its melting point. The diphenyl compound could not be desulfurized with 20% monochloroacetic acid and after 5 hr. of reflux the compound was recovered unchanged. Other diaryl compounds failed to be desulfurized with aqueous monochloroacetic acid.

Acknowledgment. The authors are much indebted to Prof. D. Hadži for recording and interpreting the infrared spectra and to Prof. D. Stucin for some of the ultraviolet spectra.

LJUBLJANA, YUGOSLAVIA

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XXV.[2] Preparation of Some *cis*- and *trans*-2-(6-Substituted 9-Purinyl)cyclopentanols[2]

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Received December 4, 1959

cis- and *trans*-2-(6-Chloro-9-purinyl)cyclopentanols have been synthesized. Several 6-substituted analogs of these key intermediates have been prepared by nucleophilic displacement of the 6-chlorine atom on the purine moiety.

In the search for effective anticancer agents, numerous modifications of the purine nucleus have been made.[4] In a continuation of this search for effective anticancer agents, a variety of purine nucleosides has been prepared with the aim of inhibiting some stage of nucleotide metabolism in the cell. The modifications which have been made in the nucleosides, as compared to naturally occurring materials, have involved changes in the purine moiety,[5,6] in the sugar moiety,[7,8] or in both[9]; these alterations in structure have caused unpredictable changes in the anticancer activity of the nucleoside compared with the corresponding free purine. Consequently, the preparation of nucleoside analogs which would be sterically similar to, but more stable than, the corresponding nucleoside has been undertaken. In an earlier paper of this series,[10] the syntheses of some 9-(substituted-cyclohexyl)purines were described; the present paper gives details of the syntheses of derivatives of *cis*-and *trans*-2-(9-purinyl)cyclopentanols.

The key intermediates which were necessary for our program were *cis*-and *trans*-2-(6-chloro-9-purinyl)cyclopentanols, whose preparations were accomplished by procedures similar to the ones used in earlier papers of this series; the starting materials, *cis*- and *trans*-2-aminocyclopentanols, were prepared by modifications of previously described procedures.[11] Thus, cyclopentene was allowed to react with *N*-bromosuccinimide in aqueous solvent; the resulting bromohydrin upon reaction with ammonium hydroxide gave a good yield of *trans*-2-aminocyclopentanol.[11] The corresponding *N*-(*trans*-2-hydroxycyclopentyl)benzamide was converted in good yield into *cis*-2-aminocyclopentanol via an oxazolidine intermediate.[11]

Condensation of *cis*-2-aminocyclopentanol with 5-amino-4,6-dichloropyrimidine in the presence of triethylamine resulted in the formation of *cis*-2-(5-amino-6-chloro-4-pyrimidinylamino)cyclopentanol. Ring closure of this pyrimidine to *cis*-2-(6-chloro-9-purinyl)cyclopentanol was accomplished with diethoxymethyl acetate.[12]

Similarly, when *trans*-2-aminocyclopentanol was allowed to react with 5-amino-4,6-dichloropyrimidine, a good yield of *trans*-2-(5-amino-6-chloro-4-pyrimidinylamino)cyclopentanol was obtained. Attempted ring closure of this pyrimidine to *trans*-2-(6-chloro-9-purinyl)cyclopentanol with diethoxymethyl acetate resulted in considerable decomposition, and only low yields of the desired product could be isolated, especially when the reaction was carried out on a large scale. Subsequently, it was learned that *trans*-2-(6-chloro-9-purinyl)cyclopentanol could be prepared in good yield by allowing *trans*-2-(5-amino-6-chloro-5-pyrimidinylamino)-cyclopentanol to react with triethyl orthoformate at reflux temperature.[13] However, when an attempt was made to prepare *cis*-2-(6-chloro-9-purinyl)-cyclopentanol by ring closure of *cis*-2-(5-amino-6-chloro-4-pyrimidinylamino)cyclopentanol with triethyl orthoformate under identical conditions with those used for the *trans*-isomer, practically no reaction occurred, as evidenced by only a slight change in the ultraviolet absorption spectra of aliquots of the reaction mixture. The reason for the differences in reactivity of the two pyrimidines is probably steric in origin, but a detailed mechanistic interpretation with the limited experimental results at hand is not warranted.

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(1) Affiliated with Sloan-Kettering Institute. This work was supported by funds from the C. F. Kettering Foundation and the National Institutes of Health, Contract Number SA-43-ph-1740.

(2) For paper XXIV of this series, see Y. F. Shealy, *Experientia* (To be published.)

(3) Present address. Department of Medicinal Chemistry, University of Buffalo, Buffalo, New York.

(4) See, for example, D. A. Clarke, G. B. Elion, G. H. Hitchings, and C. C. Stock, *Cancer Research*, 18, 445 (1958) and the section on purine antagonists in J. A. Montgomery, *Cancer Research*, 19, 447 (1959).

(5) H. J. Schaeffer and H. J. Thomas, *J. Am. Chem. Soc.*, 80, 4896 (1958) and earlier papers in this series.

(6) J. Davoll, *J. Chem. Soc*, 1593 (1958).

(7) B. R. Baker and K. Hewson, *J. Org. Chem.*, 22, 959 (1957).

(8) E. J. Reist, R. R. Spencer, and B. R. Baker, *ibid.*, 23, 1958 (1958).

(9) H. M. Kissman and M. J. Weiss, *J. Am. Chem. Soc.*, 80, 5559 (1958).

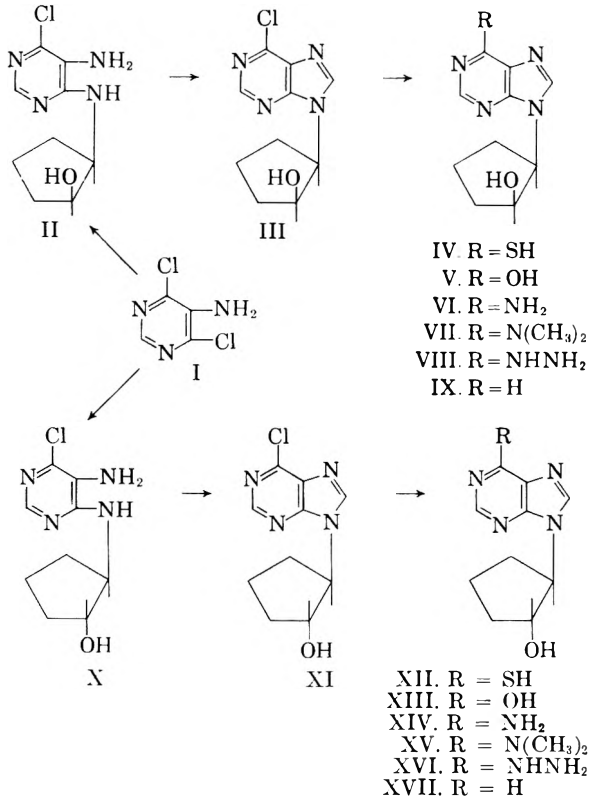
(10) H. J. Schaeffer and R. D. Weimar, Jr., *J. Am. Chem. Soc.*, 81, 197 (1959).

(11) G. E. McCasland and D. A. Smith, *J. Am. Chem. Soc.*, 72, 2190 (1950).

(12) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, 80, 409 (1958).

(13) J. A. Montgomery and C. Temple, in press.

CHART I



The purines (III and XI) were individually converted into analogs in which the 6- position was substituted with a hydrogen, mercapto, hydroxy, amino, dimethylamino, and hydrazino group. In Table I, the pertinent data for the purines prepared are summarized. Typical examples of the procedures employed for the preparation of these compounds are given in the Experimental.

EXPERIMENTAL[14]

cis-2-(5-Amino-6-chloro-4-pyrimidinylamino)cyclopentanol (II). A solution of 79.2 g. (0.487 mole) of 5-amino-4,6-dichloropyrimidine,[15] 51.6 g. (0.509 mole) of *cis*-2-aminocyclopentanol,[11] and 51.6 g. (0.509 mole) of triethylamine in 780 ml. of butyl alcohol was heated under reflux for 23 hr., and then the volatile materials were removed *in vacuo*. The residue on crystallization from water gave a white solid: yield, 101 g. (90.7%). For analysis, a small example was recrystallized from water; m.p. 171° λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 305 (13.0); *p*H 7, 265 (9.13), 290 (9.74); *p*H 13, 264 (8.79), 290 (9.06).

Anal. Calcd. for $C_9H_{13}ClN_4O$: C, 47.27; H, 5.73; N, 24.50. Found: C, 47.29; H, 5.74; N, 24.36.

trans-2-(5-Amino-6-chloro-4-pyrimidinylamino)cyclopentanol (X). A solution of 44.2 g. (0.273 mole) of 5-amino-4,6-dichloropyrimidine,[15] 29.8 g. (0.294 mole) of *trans*-2-aminocyclopentanol,[11] and 29.8 g. (0.294 mole) of triethylamine in 400 ml. of butyl alcohol was heated under reflux for 23 hr., and then the volatile materials were removed *in vacuo*. The residual oil after crystallization and recrystallization from water gave the pure product: yield, 45.9 g. (73.7%); m.p. 151°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 306 (13.6); *p*H 7, 265 (9.45), 292 (9.97); *p*H 13, 264 (9.57), 293 (10.1).

Anal. Calcd. for $C_9H_{13}ClN_4O$: C, 47.27; H, 5.73; N, 24.50. Found: C, 47.35; H, 5.50; N, 24.90.

cis-2-(6-Chloro-9-purinyl)cyclopentanol (III). A solution of 101 g. (0.442 mole) of *cis*-2-(5-amino-6-chloro-4-pyrimidinylamino)cyclopentanol in 510 ml. of diethoxymethyl acetate[12] was heated in an oil bath at 100° for 4 hr., and then the volatile materials were removed *in vacuo*. The residual oil was allowed to react overnight at 0° with 1 l. of a 21% solution of ammonia in methanol. The reaction mixture was evaporated *in vacuo*, and the residual glass was extracted with boiling water (6 × 300 ml.). Concentration of the combined extracts gave the product in four crops: yield, 52.8 g. (49.7%); m.p. 148°, resolidifies and remelts at 150°. For analysis, a small sample was recrystallized from water; m.p. 158°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 264 (9.00); *p*H 7, 265 (8.80); *p*H 13, 264 (9.00).

The analytical data are recorded in Table I.

trans-2-(6-Chloro-9-purinyl)cyclopentanol (XI).[16] A solution of 2.00 g. (8.76 mmoles) of *trans*-2-(5-amino-6-chloro-4-pyrimidinylamino)cyclopentanol in 20 ml. of triethyl orthoformate was heated under reflux for 63 hr. and then concentrated *in vacuo* to dryness. The residual glass was crystallized from water and gave the pure product in two crops in a 53% yield; m.p. 162–163°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 226 (9.72); *p*H 7, 266 (9.45); *p*H 13, 264 (9.18).

The analytical data are recorded in Table I.

A later, larger run gave material in 88% yield, melting at 162–163°. Its ultraviolet absorption spectrum was practically identical with that of the material described above.

cis-2-(6-Mercapto-9-purinyl)cyclopentanol (IV). A solution of 8.08 g. (33.8 mmoles) of *cis*-2-(6-chloro-9-purinyl)cyclopentanol and 2.59 g. (34.0 mmoles) of thiourea in 160 ml. of propyl alcohol was heated under reflux for 1 hr. and then cooled in an ice bath. The solid was collected by filtration, washed with cold propyl alcohol (5 ml.), and air-dried: yield, 5.76 g. (72.0%); m.p. 307–315° dec. One recrystallization from a mixture of methyl cellosolve and water gave the analytical sample: yield, 3.78 g. (47.3%); m.p. 308–316° dec. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 227 (9.32), 325 (21.2); *p*H 7, 321 (23.4); *p*H 13, 232 (13.5), 311 (22.6).

The analytical data are recorded in Table I.

cis-2-(6-Amino-9-purinyl)cyclopentanol (VI). A mixture of 1.25 g. (5.23 mmoles) of *cis*-2-(6-chloro-9-purinyl)cyclopentanol and 12 ml. of liquid ammonia was heated in a stainless steel bomb at 55° for 24 hr. The ammonia was allowed to evaporate, and the brown residual solid was extracted with boiling acetone (6 × 100 ml.). The combined acetone extracts after evaporation *in vacuo* gave *cis*-2-(6-amino-9-purinyl)cyclopentanol; yield, 0.95 g. (83%); m.p. 225°. The product was purified by sublimation *in vacuo* (190°/0.1 mm.); m.p. 225°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 259 (14.4); *p*H 7, 262 (14.6); *p*H 13, 261 (14.6). The analytical data are recorded in Table I.

cis-2-(6-Dimethylamino-9-purinyl)cyclopentanol (VII). A solution of 1.44 g. (6.02 mmoles) of *cis*-2-(6-chloro-9-purinyl)-cyclopentanol, 30 ml. of ethanol, and 30 ml. of a 25% aqueous solution of dimethylamine was heated under reflux for 1 hr. and then evaporated *in vacuo* to dryness. The residual white solid was recrystallized from 15 ml. of water and gave the pure *cis*-2-(6-dimethylamino-9-purinyl)cyclopentanol: yield, 1.12 g. (75.2%), m.p. 142°. λ_{max} in mμ ($\epsilon \times 10^{-3}$):

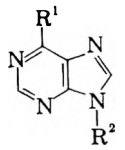
(14) The ultraviolet absorption spectra were determined in aqueous solution with a Beckman model DK-2 spectrophotometer, and the optical densities were determined with a Beckman D.U. spectrophotometer. Melting points below 260° were determined on a Kofler Heizbank and are corrected; melting points above 260° were determined in a capillary tube in an aluminum block and are uncorrected. All compounds were dried at 110°/0.1 mm. over phosphorus pentoxide before analysis.

(15) Krishell Laboratories, Inc., 1735 S. E. Powell Blvd., Portland 2, Oregon.

(16) This experiment was performed by Mr. C. A. Krauth.

TABLE I

cis- AND *trans*-2-(6-SUBSTITUTED 9-PURINYL)CYCLOPENTANOLS



Compound	Recrystn. solvent[a]	Yield, %	M.P., °	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
R^2 = *trans*-2-Hydroxycyclopentyl									
R^1									
Cl	A	53	162–163	50.32	50.60	4.65	4.99	23.47	23.15
SH	A + C	67	303–307 dec.	50.82	50.57	5.12	5.20	23.71	23.46
OH	E	49	282–285 dec.	54.54	54.56	5.49	5.89	25.44	25.44
NH_2	C	51	199	54.78	54.92	5.98	6.00	31.95	32.18
$N(CH_3)_2$	D	88	119–122	58.28	58.28	6.93	6.82	28.32	28.44
$NHNH_2$	E or F	49	182	51.27	51.11	6.02	5.94	35.88	36.19
H	G	87	132	58.81	58.66	5.92	5.90	27.44	27.41
R^2 = *cis*-2-Hydroxycyclopentyl									
R^1									
Cl	A	50	158	50.32	50.55	4.65	4.75	23.47	23.58
SH	A + C	47	308–316 dec.	50.82	50.58	5.12	5.18	23.71	23.76
OH	A	58[b]	276–278 dec.[c]	53.44[b]	53.59	5.61[b]	5.74	24.93[b]	24.81
NH_2	G	83	225	54.78	54.74	5.98	5.75	31.95	31.77
$N(CH_3)_2$	A	75	142	58.28	58.55	6.93	6.94	28.32	28.38
$NHNH_2$	G	58	203	51.27	51.42	6.02	6.21	35.88	35.66
H	G	95	140	58.81	58.53	5.92	5.84	27.44	27.40

[a] A, water; B, benzene and hexane; C, methyl cellosolve; D, extraction with *n*-hexane; E, ethanol; F, benzene; G, sublimation *in vacuo*. [b] Calcd. as $^1/_4$ hydrate. [c] This product melts at 254°, resolidifies and remelts at 276–278° dec.

*p*H 1, 269 (18.1); *p*H 7, 277 (18.5); *p*H 13, 276–277 (17.5). The analytical data are recorded in Table I.

9-(trans-2-Hydroxycyclopentyl)-6-purinol (XIII).[16] A mixture of 500 mg. (2.10 mmoles) of trans-2-(6-chloro-9-purinyl)-cyclopentanol and 10 ml. of 1*N* hydrochloric acid was heated under reflux for 2 hr., during which time solution occurred. To the cooled reaction solution was added 7.5 ml. of 1*N* sodium hydroxide, and the solution was evaporated *in vacuo* to dryness. The crude product was extracted from the residual sodium chloride with hot methyl cellosolve (25 ml.). The methyl cellosolve extract was evaporated *in vacuo* to dryness and the residue was recrystallized from ethanol; crude yield, 360 mg. (78%); m.p. 230–240°. One recrystallization of the crude product from butyl alcohol gave pure material in three crops which was dried at 140° *in vacuo* over phosphorus pentoxide; yield 227 mg. (49%); m.p. 285° dec. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 251 (10.7); *p*H 7, 250 (11.4); *p*H 13, 255 (12.6). The analytical data are recorded in Table I.

trans-2-(6-Hydrazino-9-purinyl)cyclopentanol (XVI). To 13 ml. of anhydrous hydrazine was added over a 3-min. period 1.95 g. (8.16 mmoles) of *trans*-2-(6-chloro-9-purinyl)-cyclopentanol. The reaction mixture was stirred for 4 hr. at room temperature under a nitrogen atmosphere and then evaporated *in vacuo* to dryness. Alternate recrystallizations of the crude product from ethanol and benzene gave the analytical sample; yield, 936 mg. (49%); m.p. 182°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 263 (16.9); *p*H 7, 265 (13.2); *p*H 13, unstable. The analytical data are recorded in Table I.

trans-2-(9-Purinyl)cyclopentanol (XVII). A mixture of 1.64 g. (6.86 mmoles) of *trans*-2-(6-chloro-9-purinyl)cyclopentanol, 0.553 g. (13.7 mmoles) of magnesium oxide, and 0.683 g. of 5% palladium-on-charcoal catalyst in 60 ml. of ethanol was hydrogenated at atmospheric pressure and room temperature until the theoretical amount of hydrogen was absorbed (45 min.). The catalyst was removed by filtration and the filtrate was added to 50 ml. of a 10% aqueous sodium carbonate solution. Evaporation of the solution and extraction of the residue with chloroform (2 × 200 ml.) gave a pure *trans*-2-(9-purinyl)cyclopentanol: yield, 1.22 g. (87.2%); m.p. 132°. If necessary, the product may be purified by sublimation *in vacuo;* m.p. 132°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 264 (6.03); *p*H 7, 264 (7.50); *p*H 13, 264 (7.76). The analytical data are recorded in Table I.

Acknowledgment. The authors are indebted to Dr. J. A. Montgomery for his advice and encouragement in this research, to Messrs. C. A. Krauth and C. A. O'Dell for technical assistance, to Messrs. J. P. Holmquist and J. W. Murphy for the microanalytical results reported and to Mr. W. A. Rose for the spectral determinations. Some of the analyses reported were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tennessee.

BIRMINGHAM, ALA.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XXXII. Analogs of Chlorambucil. II. Monofunctional Alkylating Agents Derived from 3-(*p*-Aminophenyl)propionic Acid

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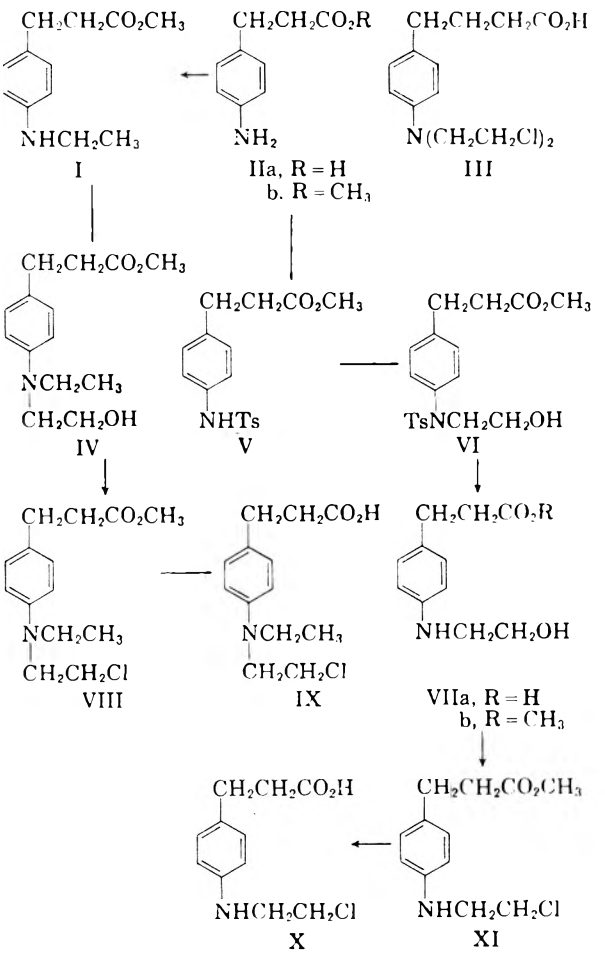
Four compounds containing monofunctional alkylating groups have been derived from 3-(*p*-aminophenyl)propionic acid, namely, 3-{*p*-[(2-chloroethyl)ethylamino]phenyl}propionic acid (IX), 3-[*p*-(2-chloroethylamino)phenyl]propionic acid (X), 3-(*p*-diazoniumphenyl)propionic acid bisulfate (XII), and methyl 3-[*p*-(*N*-nitrosoacetamido)phenyl]propionate (XIV)

It has been suggested[2] that anticancer agents consisting of an alkylating group on the proper carrier may function by selective irreversible inhibition of an enzyme system. If such a mechanism of irreversible inhibition is responsible for the activity of these agents, then one would suspect that a difunctional alkylating agent is not necessary for activity and that metabolites (carriers) containing a monofunctional alkylating group could also be effective.

Everett, *et al.*,[3] found that a series of *p*-[bis(2-chloroethyl)aminophenyl]carboxylic acids inhibited the growth of the transplanted Walker rat Sarcoma 256. The most active compound in the series was the butyric acid derivative, chlorambucil (III). The methyl and ethyl esters were also active. The activity of these compounds suggested testing the hypothesis of irreversible inhibition by the synthesis of chlorambucil analogs containing monofunctional alkylating groups. The choice of 3-phenylpropionic acid as a carrier moiety for an alkylating group in place of the somewhat more active 3-phenylbutyric acid carrier was based on the ready availability of the 3-phenylpropionic acid derivatives from the substituted cinnamic acids.

Recently,[4] a series of "one-armed" mustards derived from DL-phenylalanine were prepared and shown to be inactive against the Walker rat carcinoma 256. These results would indicate that phenylalanine mustards are not acting as selective irreversible inhibitors for Walker 256. This, however, does not rule out the possibility that the one-armed mustards derived from DL-phenylalanine might be more effective than the two-armed phenylalanine mustard on other tumors or that other one-armed mustards having a different carrier group could function as suggested.

3-{*p*-[(2-Chloroethyl)ethylamino]phenyl}propionic acid (IX) was synthesized in four steps from methyl 3-(*p*-aminophenyl)propionate (IIb). Reductive alkylation of IIb with acetaldehyde, hydrogen, and Raney nickel according to Emerson[5,6] yielded methyl 3-(*p*-ethylaminophenyl)pro-



(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center of the National Cancer Institute, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper of this series, *cf.* W. A. Skinner, H. F. Gram, M. O. Greene, J. Greenberg, and B. R. Baker, *J. Med. Pharm. Chem.*, in press.

(2) H. F. Gram, C. W. Mosher, and B. R. Baker, *J. Am. Chem. Soc.*, 81, 3103 (1959).

(3) J. L. Everett, J. J. Roberts, and W. C. J. Ross, *J. Chem. Soc.*, 2386 (1953).

(4) F. Bergel and J. A. Stock, *J. Chem. Soc.*, 90 (1959).

(5) W. S. Emerson, in *Org. Reactions*, R. Adams, ed., John Wiley and Sons, Inc., New York, N. Y., 1948, Vol. IV, p. 174.

(6) W. S. Emerson and P. M. Walters, *J. Am. Chem. Soc.*, 60, 2023 (1938).

pionate (I) in yields that varied from 46% to 61%. In order to obtain these higher yields, it was found necessary to keep the molar ratio of amine to acetaldehyde close to 1:1. Increasing the ratio of aldehyde to amine led to increased amounts of the diethylamino derivative being formed. Compound I was obtained as a solid, m.p. 35–36°, which traveled as a single spot (R_f 0.72) on acetylated paper[7] when detected by ultraviolet light or *t*-butyl hypochlorite spray[8] (violet color) for NH. The 3-[*p*(diethylamino)phenyl]propionate had an R_f of 0.58 in the same system and gave a negative *t*-butyl hypochlorite color test.

The preparation of methyl 3{-*p*-[ethyl(2-hydroxyethyl)amino]phenyl}propionate (IV) from I and ethylene oxide in acetic acid solution proceeded smoothly in 90% yield. The product was homogeneous on paper[7] (R_f 0.83).

The synthesis of methyl 3-{*p*-[(2-chloroethyl)-ethylamino]phenyl}propionate (VIII) from IV was accomplished in 61% yield, chlorination being effected by the use of thionyl chloride in chloroform. The product was purified by chromatography on a column of acid-washed alumina by elution with chloroform to yield the free base (VIII). This treatment removed colored by-products and allowed VIII to be obtained as an analytically pure, light yellow oil.

In larger-scale preparations of VIII, the reaction product could be purified more conveniently by stirring a chloroform solution of it with alumina to remove the pigmented by-products.

The desired final product, 3-{*p*-[(2-chloroethyl)-ethylamino]phenyl}propionic acid (IX) was obtained in 94% yield by hydrolysis of VIII with hot concentrated hydrochloric acid. An analytical sample, m.p. 85–86°, traveled as a single spot (R_f 0.72) on paper.[7] Chlorambucil had an R_f of 0.64 in the same system and could be detected in a concentration as low as one μg. Since no spot other than that with R_f 0.72 was detected when IX was run at 100 μg., the maximum amount of 3-[bis(2-chloroethyl)aminophenyl]propionic acid (a compound that would move more slowly (less polar) than IX) that could be present as an impurity in IX, would be 1%.

For the synthesis of the other "one-armed" mustard, 3-[*p*-(2-chloroethylamino)phenyl]propionic acid (X), the route II–V–VII–XI–X was successful. Tosylation of methyl 3-(*p*-aminophenyl)propionate yielded methyl 3-[*p*-(*p*-tolylsulfonamido)phenyl]propionate (V) in 84% yield, as a crystalline solid that traveled as a single spot (R_f 0.52) on paper.[7]

Attempts to hydroxyethylate V in the usual manner with ethylene oxide in aqueous acetic acid solution at room temperature failed to give any product, starting material being recovered. Heating V with ethylene oxide in benzene at 150° in a sealed tube gave a 93% yield of crude VI which could be purified by recrystallization from benzene–petroleum ether. This analytically pure VI moved as a single spot (R_f 0.61) on paper.[7]

Attempts to chlorinate VI using thionyl chloride in refluxing chloroform failed to yield any of the desired product, starting material and two other compounds, neither of which contained chlorine, being recovered. Therefore, VI was hydrolyzed to 3-[*p*-(2-hydroxyethylamino)phenyl]propionic acid (VIIa) using concentrated hydrochloric acid, followed by re-esterification with methanol. By this procedure, methyl 3-[*p*-(2-hydroxyethylamino)phenyl]propionate (VIIb) was obtained in 70% yield as a crystalline solid, m.p. 51–52°, that moved as a single spot (R_f 0.68) on paper.[7]

Several attempts to chlorinate VIIb using thionyl chloride in refluxing chloroform, followed by chromatography of the reduction products on acid-washed alumina, resulted only in intractable products containing variable amounts of chlorine. An analytical sample of methyl 3-[*p*-(2-chloroethylamino)phenyl]propionate (XI) was finally obtained in low yield by chlorination of VIIb as its hydrochloride with thionyl chloride in chloroform, followed by chromatography on acid-washed alumina and elution with chloroform. The product (XI) moved rapidly off the column and was shown to be homogeneous on paper[7] (R_f 0.60).

The low yields resulting from the action of thionyl chloride on the free base were primarily due to tar formation at the boiling point of chloroform. When the reaction was run at room temperature, it was too slow to be effective. However, when the chloride ion concentration was increased by addition of pyridine hydrochloride, the nucleophilic conversion of the intermediate chlorosulfite by the chloride ion to the chloroethyl derivative (XI) was greatly accelerated at room temperature compared with the rate of tar formation; XI was then isolated, after chromatography on acid-washed alumina, in 62% yield.

Hydrolysis of XI in concentrated hydrochloric acid by refluxing for one hour, followed by neutralization with sodium acetate, yielded 86% of 3-[*p*-(2-chloroethylamino)phenyl]propionic acid (X) as a colorless solid, m.p. 102–105°, that had R_f 0.66 on paper.[7]

Earlier attempts in these laboratories to prepare 3-[*p*-(2-hydroxyethylamino)phenyl]propionic acid (VIIa) *via* the method of Baxter and Cymerman-Craig,[9] *i.e.*, conversion of 3-(*p*-aminophenyl)propionic acid (IIa) or methyl 3-(*p*-aminophenyl)pro-

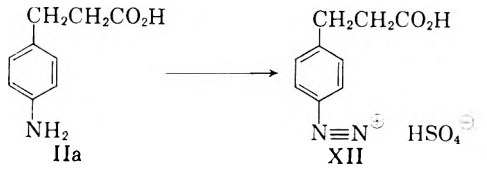
(7) Paper chromatograms were run by the descending technique on Schleicher and Schuell No. 2043B acetylated paper with benzene-methanol-water (6:2:1) as the solvent system. Compounds were detected by their ultraviolet absorption or by the use of *t*-butyl hypochlorite spray in the case of the monosubstituted amines.

(8) D. P. Schwartz and M. J. Pallansch, *Anal. Chem.*, **30**, 219 (1958).

(9) J. N. Baxter and J. Cymerman-Craig, *J. Chem. Soc.*, 1940 (1953).

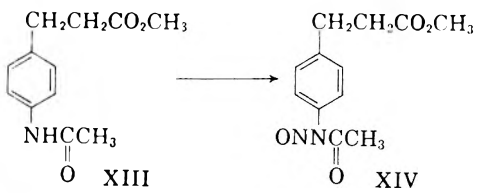
pionate (IIb) to the *N*-benzylidene derivative, quaternization with 2-bromoethanol, followed by acid hydrolysis of the quaternary salt to VIIa, failed.

3-(*p*-Diazoniumphenyl)propionic acid bisulfate (XII), another potential alkylating agent, was prepared in 64% yield by diazotization of 3-(*p*-aminophenyl)propionic acid using barium nitrite and sulfuric acid. Attempts to conduct the diazotization with sodium nitrite in hydrochloric acid



or 48% fluoboric acid[2] resulted in mixtures that could not be separated from the concomitantly formed inorganic salts. This difficulty was avoided in the barium nitrite–sulfuric acid diazotization by removing the insoluble barium sulfate by filtration prior to isolation of XII.

Methyl 3-[*p*-(*N*-nitrosoacetamido)phenyl]propionate (XIV) was prepared in 90% yield by the action of nitrosyl chloride on methyl 3-(*p*-acetamidophenyl)propionate (XIII) dissolved in glacial



acetic acid, in the presence of potassium acetate.[10] This compound (XIV) is stable in the solid state at 20° but decomposes at 0° in aqueous methanolic solutions.

Biological results.[11] Of the four alkylating agents, screening has been completed on all but X. Compounds IX, XII, and XIV showed no appreciable inhibiting effect at their maximum tolerated doses (9, 80, and 20 mg./kg., respectively) on Sarcoma 180, Adenocarcinoma 755, and Leukemia L-1210; chlorambucil is also noninhibitory on these three tumors. However, all three compounds produced a modest increase in survival time on mice bearing Ehrlich ascites, a tumor system that responds to chlorambucil. Compounds IX and XIV showed (+) activity, while compound XII had (±) activity.[12]

EXPERIMENTAL[13]

Methyl 3-(p-ethylaminophenyl)propionate (I). To a solution of 1.79 g. (0.01 mole) of methyl 3-(*p*-aminophenyl)-propionate (IIb)[14] in 50 ml. of ethanol was added, dropwise with shaking, 0.88 g. (0.02 mole) of freshly distilled acetaldehyde. Anhydrous sodium acetate (0.1 g.) and 11 g. of Raney nickel were added and the mixture shaken with hydrogen at 56 p.s.i.g. for 4 hr. The mixture was filtered and the catalyst washed well with ethanol. The colorless filtrate was concentrated *in vacuo* to a sirup which was partitioned between water and ether. Concentration of the ether solution *in vacuo* gave a sirup which crystallized on rubbing. Recrystallization of this material from methanol-water gave a 61% yield of solid, m.p. 30–33°. Two more recrystallizations of this solid (0.5 g.) from two 1.5-ml. portions of methanol by addition of a few drops of water, gave analytically pure material, m.p. 35–36°. $\lambda_{max\ (\mu)}^{film}$ 2.97 (NH), 5.77 (ester C=O), 6.20, 6.57 (aryl, NH), 8.30, 8.61 (ester C—O—C), 12.25 (*p*-disubstituted phenyl). The compound traveled as a single spot on paper[7] (R_f 0.72), as detected by ultraviolet light or by development with a *t*-butyl hypochlorite spray[8] (violet color). The starting material (IIb) has R_f 0.68 in this system and developed a blue color with *t*-butyl hypochlorite.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.5; H, 8.27; N, 6.76. Found: C, 69.2; H, 8.59; N, 6.73.

Methyl 3-{p-[ethyl(2-hydroxyethyl)amino]phenyl}propionate (IV). To a solution of 1.7 g. (8.3 mmoles) of methyl 3-*p*-ethylaminophenyl)propionate (I) dissolved in a solution of 10 ml. of glacial acetic acid and 10 ml. of water, was added 2 ml. of ethylene oxide with shaking. After 24 hr. at room temperature, the solution was poured into 40 ml. of water and neutralized with solid sodium hydrogen carbonate. The oil that separated was extracted with two 15-ml. portions of ethyl acetate. The combined extracts, dried over anhydrous magnesium sulfate, were filtered and concentrated *in vacuo* to a pale brown sirup; yield 1.87 g. (90%); $\lambda_{max\ (\mu)}^{film}$ 2.95 (OH), 5.73 (ester C=O), 8.35 (ester C—O—C), 9.55 (C—OH), 12.35 (*p*-disubstituted phenyl). The compound traveled as a single spot (R_f 0.83) on paper,[7] as detected by ultraviolet light. This sirup could not be crystallized, nor did it furnish a crystalline picrate.

Methyl 3-{p-[(2-chloroethyl)ethylamino]phenyl}propionate (VIII). To a solution of 1.4 g. (5.5 mmoles) of IV in 14 ml. of chloroform was added 0.60 ml. (8 mmoles) of thionyl chloride. After being refluxed for 15 min., the dark brown solution was poured onto ice; the chloroform layer was separated and dried over anhydrous magnesium sulfate. The filtered solution was concentrated *in vacuo* to about 5 ml., then chromatographed on a column of 20 g. of activated alumina (Merck acid-washed aluminum oxide). The product was eluted from the column with 30 ml. of chloroform, the pigmented impurities remaining adsorbed. Concentration of the pale yellow solution gave a light yellow sirup; yield 0.91 g. (61%); $\lambda_{max\ (\mu)}^{film}$ 5.72 (ester C=O), 8.30, 8.55, 9.65 (ester C—O—C), 12.33 (*p*-disubstituted phenyl), 13.60 (C—Cl), and no OH near 2.9. The sirup traveled as a single spot (R_f 0.79) on paper[7] as detected by ultraviolet light.

Anal. Calcd. for $C_{14}H_{20}ClNO_2$: C, 62.3; H, 7.43; Cl, 13.1; N, 5.19. Found: C, 62.6; H, 7.56; Cl, 13.3; N, 5.06.

3-[(2-Chloroethyl)ethylamino]phenyl propionic acid (IX).

(10) H. France, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 369 (1940).

(11) These tests were performed at this Institute by Dr. Joseph Greenberg and his staff under contract to the Cancer Chemotherapy National Service Center.

(12) H. J. Creech, T. S. Hauschka, F. F. Hankwitz, Jr., B. J. Littleton, and J. Andre, *Cancer Research*, Supplement No. 3, 47 (1955) have defined activity against Ehrlich ascites as (−) for 0–19%, a (±) for 20–50%, a (+) rating for 51–125%, a (++) rating for greater than 125% increase in survival time over untreated control animals.

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

(14) W. A. Skinner, H. F. Gram, C. W. Mosher, and B. R. Baker, *J. Am. Chem. Soc.*, 81, 4639 (1959).

A solution of 0.85 g. (3.1 mmoles) of VIII in 8.5 ml. of concd. hydrochloric acid was refluxed for 2 hr. The dark solution was chilled and neutralized with saturated sodium acetate solution. The product, which crystallized on rubbing, was collected on a filter and washed with water: yield 0.72 g. (94%), m.p. 82–85°; $\lambda_{max\ (\mu)}^{KBr}$ 5.85 (acid C=O), 6.58 (aryl), 12.25 (*p*-disubstituted phenyl) 13.50 (C—Cl). The compound traveled as a single spot (R_f 0.72) on paper.[7] An analytical sample was prepared by two recrystallizations from ethanol-water, m.p. 85–86°.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.1; H, 7.05; Cl, 13.9; N, 5.47. Found: C, 60.9; H, 7.16; Cl, 14.1; N, 5.45.

Methyl 3-[p-(p-tolylsulfonamido)phenyl propionate (V). To a solution of 1.79 g. (0.01 mole) of IIb[14] in 10 ml. of pyridine was added, with stirring in an ice bath, a solution of 2.86 g. (0.015 mole) of *p*-toluenesulfonyl chloride in 5 ml. of pyridine during a 10-min. period. The orange solution was stirred in ice for 3 hr., poured into 25 ml. of ice water, and extracted with three 10-ml. portions of ethyl acetate. The combined, dried solvent extracts were concentrated *in vacuo* to an orange sirup which was crystallized from methanol. The product was collected on a filter and washed with 50% aqueous methanol, yield 2.8 g. (84%), m.p. 83–87°; $\lambda_{max\ \mu}^{KBr}$ 3.10 (NH), 5.82 (ester C=O), 7.46 (—SO_2N—), 8.61 (ester C—O—C and —SO_2N—), 11.98, 12.24 (*p*-disubstituted phenyl). The compound traveled as a single spot (R_f 0.52) on paper.[7]

An analytical sample was prepared by three recrystallizations from methanol-water, m.p. 91–92°.

Anal. Calcd. for $C_{17}H_{19}NO_4S$: C, 61.2; H, 5.74; N, 4.20. Found: C, 61.5; H, 5.76; N, 4.08.

Methyl 3-{p-[N-(2-hydroxyethyl)-p-toluenesulfonamido]-phenyl}propionate (VI). To a solution of 1.0 g. (3 mmoles) of V in 10 ml. of benzene in a glass tube was added 5 ml. of ethylene oxide. The tube was sealed and heated in an oil bath at 150° for 5 hr. Concentration *in vacuo* gave a sirup that crystallized on standing. Recrystallization from benzene–petroleum ether gave 1.05 g. (93%), m.p. 94–96°.

An analytical sample was prepared by recrystallization from benzene–petroleum ether, m.p. 95–96°; $\lambda_{max\ (\mu)}^{Nujol}$ 2.88 (OH), 5.80 (ester C=O), 7.42 (—SO_2N—), 9.48 (C—OH), 12.25 (*p*-disubstituted phenyl). The compound moved as a single spot (R_f 0.61) on paper.[7]

Anal. Calcd. for $C_{19}H_{23}NO_5S$: C, 60.5; H, 6.14; N, 3.71. Found: C, 60.8; H, 6.22; N, 3.52.

A reaction time of 16 hr. gave a much lower yield.

Methyl 3-[p-(2-hydroxyethylamino)phenyl]propionate (VIIb). A suspension of 0.50 g. (1.3 mmoles) of VI in 5 ml. of concd. hydrochloric acid was heated under reflux for 1 hr. After 45 min., solution was almost complete; the mixture was decanted from a little oil and concentrated *in vacuo* to a pale brown sirup. This sirup (VIIa) was refluxed for 2 hr. in 20 ml. of methanol saturated with hydrogen chloride. The solution was concentrated *in vacuo* to a sirup, which was suspended in water and neutralized with 10% sodium hydrogen carbonate solution. The oil that separated was extracted with two 10-ml. portions of ethyl acetate and the combined extracts were dried over anhydrous magnesium sulfate. Concentration *in vacuo* of the extract freed from drying agent yielded 0.2 g. (70%) of a pale yellow sirup which crystallized on cooling. Recrystallization from benzene by addition of petroleum ether (b.p. 30–60°) yielded white platelets, m.p. 51–52°; $\lambda_{max\ (\mu)}^{Nujol}$ 3.00 (OH, NH), 5.78 (ester C=O), 6.20 (aryl), 6.55 (NH), 8.50, 8.65 (ester C—O—C), 9.50 (OH), 12.20 (*p*-disubstituted phenyl). The compound traveled as a single spot (R_f 0.68) on paper.[7]

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.5; H, 7.68. Found: C, 64.3; H, 7.67.

Methyl 3-[p-(2-chloroethylamino)phenyl]propionate (XI). A solution of 0.75 g. (3.3 mmoles) of VIIb in 8 ml. of chloroform was treated with hydrogen chloride. Then 1.1 g. (10 mmoles) of pyridine hydrochloride followed by 0.43 ml. (6 mmoles) of thionyl chloride, was added. The solution, protected from moisture, was allowed to stand for 16 hr. at room temperature and then refluxed for 10 min. The resultant solution was poured into ice water; the chloroform layer was separated, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to a light brown sirup (0.6 g.). This sirup was chromatographed on acid-washed alumina (20 g.) and eluted with chloroform, the yellow band being collected on elution. The eluate was a pale yellow sirup; yield, 0.5 g. (62%); $\lambda_{max\ (\mu)}^{film}$ 2.92 (NH), 5.72 (ester C=O), 8.30–8.60, 9.70 (ester C—O—C), 12.20 (*p*-disubstituted phenyl), 13.3–13.6 (C—Cl). The compound moved as a single spot (R_f 0.60) on paper.[7]

Anal. Calcd. for $C_{12}H_{16}ClNO_2$: C, 59.6; H, 6.67; Cl, 14.7; N, 5.79. Found: C, 59.9; H, 6.86; Cl, 14.3; N, 5.62.

3-[p-(2-Chloroethylamino)phenyl]propionic acid (X). A solution of 0.8 g. (3.3 mmoles) of XI in 8 ml. of concd. hydrochloric acid was refluxed for 1 hr., chilled, and neutralized with saturated sodium acetate solution. The precipitated solid was washed well with water and dried; yield 0.65 g. (86%), m.p. 102–105°. Three recrystallizations from 95% ethanol-water at room temperature yielded a sample with m.p. 103–105°; $\lambda_{max\ (\mu)}^{Nujol}$ 2.95 (NH), 5.81 (acid C=O), 7.65 (CO_2H), 12.18 (*p*-disubstituted phenyl), 13.80 (C—Cl). The compound moved as a single spot (R_f 0.66) on paper.[7]

Anal. Calcd. for $C_{11}H_{14}ClNO_2$: C, 58.0; H, 6.15; Cl, 15.6; N, 6.15. Found: C, 58.2; H, 6.17; Cl, 15.5; N, 6.20

3-(p-Diazoniumphenyl)propionic acid bisulfate (XII). A solution of 4.98 g. (0.03 mole) of 3-(*p*-aminophenyl)propionic acid (IIa)[14] in 9 ml. of concd. sulfuric acid was cooled in an ice bath to 3° and diluted with 12 ml. of water. A solution of 3.95 g. (0.019 mole) of barium nitrite in 7 ml. of water at 3° was added with vigorous stirring to the acid solution over a 25-min. period. The reaction mixture was allowed to stand for 2 hr. at 0–5° and filtered. The barium sulfate residue was washed with 5 ml. of ice water and the filtrate evaporated *in vacuo* to about one-half the original volume while being chilled in ice. Fifty milliliters of cold ethanol was added followed by 150 ml. of ether until the solution was turbid. The product, which crystallized when the mixture was rubbed and cooled in a Dry Ice–acetone bath, was collected on a filter and thoroughly washed with 200 ml. of cold ether; yield 5.3 g. (64%), m.p. 94° dec.; $\lambda_{max\ (\mu)}^{Nujol}$ 3.75 (acidic OH), 4.40 ($N^+{\equiv}N$), 5.94 (acid C=O), 8.57, 9.50 (HSO_4^-), 12.05 (*p*-disubstituted phenyl and HSO_4^-).

Anal. Calcd. for $C_9H_{10}N_2O_6S$: C, 39.4; H, 3.67; N, 10.2. Found: C, 39.5; H, 3.97; N, 10.0.

Methyl 3-(p-acetamidophenyl)propionate (XIV). A mixture of 1.0 g. (0.0056 mole) of methyl 3-(*p*-aminophenyl)-propionate and 3 ml. of acetic anhydride was warmed for 5 min. on a steam bath and then chilled. The precipitate was washed with water and collected on a filter; yield 1.05 g. (84%), m.p. 119–123°; $\lambda_{max\ (\mu)}^{KBr}$ 3.09 (NH), 5.80 (ester C=O), 6.05 (amide C=O), 6.45 (amide NH), 11.94 (*p*-disubstituted phenyl). A sample, recrystallized twice from methanol-water, had m.p. 125–126°.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.83; N, 6.33. Found: C, 65.3; H, 6.91; N, 6.08.

Methyl 3-[p-(N-nitrosoacetamido)phenyl]propionate (XIII). To a solution of 6.66 g. (0.03 mole) of methyl 3-(*p*-acetamidophenyl)propionate (XIV) in 250 ml. of glacial acetic acid, 90 ml. of acetic anhydride, and 24 g. of anhydrous potassium acetate, stirred and cooled to 0–5°, was added dropwise a solution of 60 ml. of acetic anhydride and 15 ml. (0.3 mole) of nitrosyl chloride.[10] The reaction mixture was stirred 2 hr. at 0–5°, poured onto 1 kg. of ice, and the mixture was diluted with 1 l. of water. A yellow precipitate formed which was collected on a filter and washed thoroughly with ice water (about 1 l.); yield 6.8 g. (90%), m.p. 62.5–63.0° dec. For analysis, a portion of the yellow solid (0.3 g.) was recrystallized by dissolving it in 10 ml. of cold methanol and then adding 10 ml. of ice water; m.p. 62.5–63.0° dec.; $\lambda_{max\ (\mu)}^{Nujol}$ 5.75 (ester and amide C=O), 6.62, 6.78 (N=O), 8.45 (ester C—O—C), 11.98 (*p*-disubstituted phenyl).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.6; H, 5.63; N, 11.2. Found: C, 57.4; H, 6.06; N, 11.4.

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MENLO PARK, CALIF.

[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF FLORIDA]

The Synthesis of 3-Deoxy-D-ribohexose-6-phosphate and 3-Deoxy-D-gluconic Acid-6-phosphate[1]

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3-Deoxy-D-ribohexose-6-phosphate and 3-deoxy-D-gluconic acid-6-phosphate have been prepared from 3-deoxy-D-ribohexose for testing as potential antimetabolites for cancer chemotherapy.

It is believed at the present time that glucose is metabolized in tumor tissue by two pathways, the Embden-Meyerhof glycolytic pathway, which is the main pathway quantitatively, and the pentose phosphate pathway, which apparently serves to supply reduced triphosphopyridine nucleotide (TPNH) for use in reductive syntheses.[4] There is evidence that the enzymes involved in the pentose phosphate pathway are present in greater amount in some tumor tissues than in normal tissues.[5]

Of the carbohydrate analogs which have been tested as glucose antagonists only those substituted in the 2-position have shown activity.[6] 2-Deoxy-D-glucose (2-deoxy-D-arabohexose) and 2-deoxy-D-galactose (2-deoxy-D-lyxohexose) are potent glycolytic inhibitors of human leucocytes, human leukemic cells, and a number of animal tumors.[7] Since the inhibition is competitive and is overcome by glucose-6-phosphate, it is apparently hexokinase, the enzyme which is necessary for the phosphorylation of glucose, which is affected.[7] This block occurs at a very early stage in the glycolytic pathway, before the pentose phosphate pathway begins to operate. It would be of interest, therefore, to prepare compounds having the potential ability to block the metabolic pathway at a later stage. This paper describes the preparation of two compounds which may have this potentiality, 3-deoxy-D-ribohexose-6-phosphate and 3-deoxy-D-gluconic acid-6-phosphate.

Using the procedure described by Reynolds and Evans[8] for the corresponding glucose derivative, 3-deoxy-D-ribohexose[9] was treated with triphenylmethyl chloride and then with acetic anhydride to obtain 1,2,4-tri-*O*-acetyl-6-*O*-triphenylmethyl-3-deoxy-β-D-ribohexose (I). Upon treatment with hydrobromic acid in acetic acid the triphenylmethyl group was removed, giving 1,2,4-tri-*O*-acetyl-3-deoxy-β-D-ribohexose (II). Analysis showed this compound to be a monohydrate and the infrared spectrum had an absorption band at 1655 $cm.^{-1}$, indicating the presence of water. Attempts to remove the water azeotropically were only partially successful. To prove it was actually the 1,2,4-triacetate it was converted back to 1,2,4-tri-*O*-acetyl-6-*O*-triphenylmethyl-3-deoxy-β-D-ribohexose (I).

The triacetate (II) was phosphorylated in the 6-position with diphenylphosphorochloridate using the procedure described by Lardy and Fischer[10] for the preparation of glucose-6-phosphate. The 1,2,4-tri-*O*-acetyl-3-deoxy-β-D-ribohexose-6-diphenylphosphate (III) was obtained as an oil. Low-pressure hydrogenation of (III) yielded 1,2,4-tri-*O*-acetyl-3-deoxy-β-D-ribohexose-6-phosphate (IV), also as an oil. Deacetylation in acid solution gave 3-deoxy-D-ribohexose-6-phosphate, which was isolated as the barium salt (V) and further purified as the brucine salt (VI).

Oxidation of the barium salt (V) was accomplished with barium hypoiodite by a modification of the procedure used by Levene and Raymond[11] for

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(10) H. A. Lardy and H. O. L. Fischer, *J. Biol. Chem.*, **164**, 513 (1946).

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the preparation of barium D-gluconic acid-6-phosphate. The barium 3-deoxy-D-gluconic acid-6-phosphate (VII) thus obtained was purified by conversion to the brucine salt (VIII). Just as in the case of the corresponding *D*-glucose derivatives,[11] 3-deoxy-D-ribohexose-6-phosphate forms a dibrucine salt and 3-deoxy-D-gluconic acid-6-phosphate a tribrucine salt.

Results of the biological testing of these two compounds will be reported elsewhere.

EXPERIMENTAL[12]

The 3-deoxy-D-ribohexose (3-deoxy-D-glucose) used in these experiments was an oil having $[\alpha]_D^{24}$ +23.6° (*c*, 0.8; water). Černý and Pacák give $[\alpha]_D^{18}$ +24.9° (*c*, 0.563; water).[9,13]

1,2,4-Tri-O-acetyl-6-O-triphenylmethyl-3-deoxy-β-D-ribohexose (I). A mixture of 3.4 g. (0.021 mole) of 3-deoxy-D-ribohexose, 17 ml. of pyridine, and 5.5 g. (0.024 mole) of triphenylmethyl chloride was warmed to 50°, shaken until homogeneous, and then kept at room temperature for 24 hr. Acetic anhydride (11 ml., 0.12 mole) was added and after standing overnight the mixture was stirred into 300 ml. of ice water containing 17 ml. of acetic acid. After allowing the precipitate to settle under refrigeration, the solid was removed by filtration and dried rapidly on filter paper before reaching room temperature. It was taken up in 12 ml. of ethanol, then heated until the oil which formed had dissolved and crystals began to form. Cooling and filtering gave 4.0 g. (36%) of crude 1,2,4-tri-*O*-acetyl-6-*O*-triphenylmethyl-3-deoxy-β-D-ribohexose. Recrystallization from a mixture of ethanol and acetone (3:1) gave 2.2 g. of white crystals, m.p. 196°. $[\alpha]_D^{25}$ +8.3° (*c*, 2.0; chloroform).

Anal. Calcd. for $C_{31}H_{32}O_8$: C, 69.9; H, 6.01. Found: C, 70.36, 70.27; H, 6.00, 6.02.

1,2,4-Tri-O-acetyl-3-deoxy-β-D-ribohexose (II). A mixture of 7 g. (0.013 mole) of 1,2,4-tri-*O*-acetyl-6-*O*-triphenylmethyl-3-deoxy-β-D-ribohexose and 50 ml. of acetic acid was heated on a steam bath to effect solution, then cooled in an ice bath to 5–10°. Hydrobromic acid (5 ml. of a 30–32% solution in acetic acid) was added at once and the mixture was shaken for 1 min. The precipitate of triphenylmethyl bromide which formed was removed by filtration and the filtrate was poured into 200 ml. of ice water. The precipitate which formed was removed by extraction of the aqueous mixture with chloroform, the chloroform extract was washed three times with ice water and then dried over anhydrous sodium sulfate. The chloroform was removed at reduced pressure, keeping the temperature below 40°. The partly crystalline residue was dissolved in warm chloroform and treated with hexane to turbidity. Upon cooling crystals were obtained. Repeated recrystallization from chloroform-hexane gave 2.8 g. (71.8%) of 1,2,4-tri-*O*-acetyl-3-deoxy-β-D-ribohexose, m.p. 95–96°. Analysis showed this compound to be a monohydrate. $[\alpha]_D^{25}$ −6.8° (*c*, 2; chloroform).

Anal. Calcd. for $C_{12}H_{18}O_3.H_2O$: C, 46.75; H, 6.49. Found: C, 46.78, 47.04; H, 6.45, 6.23.

Drying with organic solvents or *in vacuo* did not completely remove the water of hydration. To prove that this was the desired 1,2,4-triacetate, compound II (1 g.) was dissolved in 10 ml. of pyridine and 1 g. of triphenylmethyl chloride was added with ice cooling. After 12 hr. the mixture was poured into ice water, and extracted with chloroform. The chloroform extract was washed with dilute hydrochloric acid, then with water, and evaporated at reduced pressure. Recrystallization from ethanol gave a compound, m.p. 195°, which showed no depression in melting point when mixed with compound I.

1,2,4-Tri-O-acetyl-3-deoxy-β-D-ribohexose-6-diphenylphosphate (III). To an ice-cold solution of 1.5 g. (0.005 mole) of 1,2,4-tri-*O*-acetyl-3-deoxy-β-D-ribohexose (dried in a drying pistol at 65° for 5 hr.) in 7 ml. of pyridine was added dropwise 1.7 g. (0.006 mole) of diphenylphosphorochloridate.[14] After standing in the refrigerator overnight, during which time a precipitate of pyridine hydrochloride had formed, the reaction mixture was poured into ice water, extracted with chloroform, washed with dilute ice-cold hydrochloric acid until all the pyridine had been removed, then with ice water. After drying over sodium sulfate, the chloroform was removed by evaporation at reduced pressure, leaving 2.2 g. (84%) of 1,2,4-tri-*O*-acetyl-3-deoxy-β-D-ribohexose-6-diphenylphosphate as an oil.

1,2,4-Tri-O-acetyl-3-deoxy-β-D-ribohexose-6-phosphate (IV). A solution of 5.0 g. (0.01 mole) of III in 25 ml. of absolute ethanol containing 0.4 g. Adams' platinum oxide catalyst was hydrogenated at low pressure. Removal of the catalyst by filtration and evaporation of the solvent gave 3.1 g. (83.7%) of 1,2,4-tri-*O*-acetyl-3-deoxy-β-D-ribohexose-6-phosphate as an oil.

Barium salt of 3-deoxy-D-ribohexose-6-phosphate (V). 1,2,4-Tri-*O*-acetyl-3-deoxy-β-D-ribohexose-6-phosphate (3.0 g.; 0.008 mole) was added to a mixture of 3 ml. of conc. hydrobromic acid in 50 ml. of water (*ca.* 0.6*N* acid) and then the mixture was heated on the steam bath for 3 hr. with frequent shaking. After cooling and treating the solution with barium hydroxide to *p*H 8, the mixture was filtered, the residue was washed with cold water, and the clear filtrate was added to four times its volume of ethanol. The precipitate was collected by centrifugation, then suspended successively in 80% ethanol, absolute ethanol, ethanol-ether (3:1), ethanol:ether (1:3), and ether, each time being collected by centrifugation. The solid was again dissolved in 100 ml. of cold water, filtered to remove insoluble material, and then added to 400 ml. ethanol. The precipitate was again collected and washed as described above, giving 1.3 g. (43%) of the barium salt of 3-deoxy-D-ribohexose-6-phosphate. $[\alpha]_D^{28}$ +3.8° (*c*, 2; water).

Brucine salt of 3-deoxy-D-ribohexose-6-phosphate (VI). The barium salt of 3-deoxy-D-ribohexose-6-phosphate (0.4 g.) was dissolved in 4 ml. of water, passed through a column of Amberlite IR-120 ion exchange resin, the column was washed with water, and the eluate was treated with methanolic solution of brucine to *p*H 7.5. Evaporation of the solution left a white powder which was recrystallized several times from 2 ml. of acetone-water (2:1); after drying over phosphorus pentoxide at 3 mm. and 60°, $[\alpha]_D^{28}$ −24.2° (*c*, 0.784; water). Analysis corresponded to the dibrucine salt of 3-deoxy-D-ribohexose-6-phosphate.

Anal. Calcd. for $C_{52}H_{65}O_{16}N_4P$: N, 5.33; P, 3.0. Found: N, 5.33, 5.46; P, 2.73, 2.80.

Barium salt of 3-deoxy-D-gluconic acid-6-phosphate (VII). The barium salt of 3-deoxy-D-ribohexose-6-phosphate (V) (0.8 g.; 0.002 mole) was dissolved in 7.0 ml. of water, 0.5 g. of iodine and 1.0 g. of barium iodide were dissolved in 3 ml. of water, and the two solutions were mixed. With stirring, a solution of 0.5*N* barium hydroxide (16 ml.) was added dropwise at room temperature over a period of 20 min. After stirring for another 20 min. the iodine color had disappeared. Ethanol (50 ml.) was added and the barium salt was isolated by centrifugation, then washed by suspension in water, ethanol, and ether, giving 0.9 g. of a white powder.

Brucine salt of 3-deoxy-D-gluconic acid-6-phosphate (VIII). The barium salt of 3-deoxy-D-gluconic acid-6-phosphate

(12) Melting points are uncorrected. Microanalyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Rotations were determined with a Keston Polarimeter standardized against sucrose (National Bureau of Standards Standard Sample 17).

(13) For data on crystalline 3-deoxy-α-D-*ribo*hexose, see J. W. Pratt and N. K. Richtmyer, *J. Am. Chem. Soc.*, **79**, 2597 (1957).

(14) Prepared by the method of P. Brigl and H. Muller, *Ber.* **72**, 2121 (1939).

(0.8 g.) was dissolved in 5 ml. of water and passed through a column of Amberlite IR-120 ion exchange resin. The eluate was treated with a methanolic solution of brucine of *p*H 7.5–8. After evaporation at reduced pressure the residue was recrystallized several times from methanol, giving 0.5 g. of the brucine salt. $[\alpha]_D^{25}$ −20.2° (c, 0.97; water). The analysis showed the salt to be the tribrucine derivative of 3-deoxy-D-gluconic acid-6-phosphate.

Anal. Calcd. for $C_{75}H_{90}O_{21}N_6P$: N, 5.83; P, 2.15. Found: N, 5.74, 5.61; P, 1.92, 1.61.

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GAINESVILLE, FLA.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

The Chemistry of the Spiroaminoketal Side Chain of Solasodine and Tomatidine. I.[1] Improved Preparation of 3β-Acetoxy-5,16-pregnadien-20-one and 3β-Acetoxy-5α-pregn-16-en-20-one from Solasodine and Tomatidine.

YOSHIO SATO, NOBUO IKEKAWA,[2] AND ERICH MOSETTIG

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The steroidal alkaloids solasodine and tomatidine have been degraded in excellent over-all yields (65–68%) to 3β-acetoxy-5,16-pregnadien-20-one and 3β-acetoxy-5α-pregn-16-en-20-one by conversion of the *O,N*-diacetates of the alkaloids into the respective pseudoacetylamino derivatives, chromic anhydride oxidation of the latter and final hydrolysis with acetic acid.

The announcement from this laboratory[3] concerning the degradation of solasodine (IA) (via VA) to 3β-acetoxy-5,16-pregnadien-20-one (IVA) has spurred several laboratories[4,5,6] to effect an increase in the yields originally obtained by us (10–20%) in this process. We wish to describe in this paper a modified and greatly improved conversion of solasodine (IA), dihydrosolasodine (IC) and tomatidine (IB) to their respective pregnenolone derivatives IVA and IVB.

When a solution of *O,N*-diacetylsolasodine[7] (IIA) in glacial acetic acid (or propionic acid) was refluxed for 15 minutes, a crystalline 3β-acetoxy-26-acetylamino-5,20(22)-furostadiene (IIIA) was obtained in a yield of 95–98%. *O,N*-Diacetyltomatidine[8] (IIB) similarly gave a 95% yield of crystalline 3β-acetoxy-26-acetylamino-5α-furost-20(22)-ene (IIIB) by this procedure. IIIA and IIIB can also be readily obtained, but not as pure and in as good yields, by treating a solution of IIA and IIB respectively in acetic acid with mineral acids (perchloric or hydrochloric) at room temperature.[9] IIIA has previously been obtained by chromatography on alumina of the crude reaction mixture resulting from the treatment of solasodine with acetic anhydride.[10] The 3-hydroxy compound of IIIB has likewise been obtained by the alkaline hydrolysis of the so-called unsaturated triacetyltomatidine (VB).[11]

By chromic acid oxidation of the pseudo compounds IIIA and IIIB in aqueous acetic acid (80%) and subsequent hydrolysis of the acyloxy side chain with acetic acid according to the method of Cameron *et al.*[12] the respective pregnenolone acetates IVA and IVB were obtained in high yields. We have found that optimal results were obtained in the oxidation when two molar equivalents of chromium trioxide were used. Although these products are crystalline and can be readily purified by recrystallization, it has been found expedient to resort to chromatography at this stage. The yields of IVA and IVB (from IIA and IIB) ranged from about 75–80%. In a continuous operation, *i.e.* without the isolation and purification of IIA and IIIA, solasodine (IA) gave 65% of the pregnenolone derivative IVA. Similarly, tomatidine

(1) A preliminary account of this work was published in *J. Org. Chem.*, **24**, 893 (1959).

(2) Visiting Scientist, National Institutes of Health.

(3) Y. Sato, H. K. Miller, and E. Mosettig, *J. Am. Chem. Soc.*, **73**, 5009 (1951); Y. Sato, H. G. Latham, Jr., and E. Mosettig, *J. Org. Chem.*, **22**, 1496 (1957).

(4) P. Tuzson, Mitt. Ungar Akad. Wiss., *Sket für Chem.*, **5**, 77, (1956).

(5) K. Schreiber, "Über das Vorkommen von Solasodinglykosiden in Solanum nigrum L. und ihre industrielle Verwertung" Vortrag anlässlich der 6. Arbeitstagung der Deutschen Gesellschaft für Arzneipflanzenforschung vom 2–4, Oktober 1958 in Tübingen, Deutschland.

(6) N. N. Suvorov, *Med. Prom.*, **10**, 22 (1956); N. N. Suvorov, L. V. Sokolova, L. M. Morozovskaya, and V. S. Murasheva, *Khim. Nauka i Prom.*, **3**, 281 (1958).

(7) L. H. Briggs and T. O'Shea, *J. Chem. Soc.*, 1654 (1952).

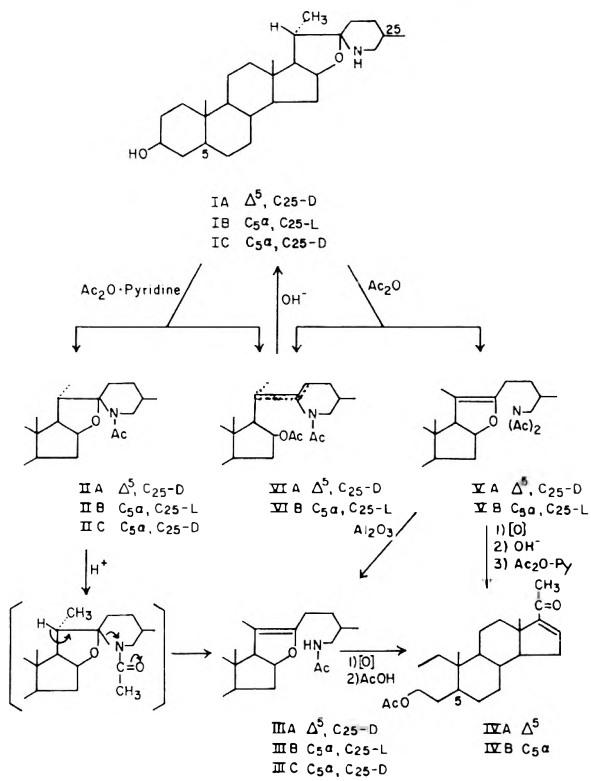
(8) T. D. Fontaine, J. S. Ard, and R. M. Ma, *J. Am. Chem. Soc.*, **73**, 878 (1951).

(9) The chemistry and structure proof of the byproduct obtained in this reaction will be discussed in a forthcoming publication of this series.

(10) Y. Sato, H. G. Latham, Jr., and E. Mosettig, *J. Org. Chem.*, **22**, 1496 (1957).

(11) Y. Sato, and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3150 (1956).

(12) A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, and A. G. Long, *J. Chem. Soc.*, 2807 (1955).



Compounds represented by partial formulas II, III, V, and VI possess a 3β-acetoxy function

(IB) yielded 68% of IVB. Dihydrosolasodine[13] (IC) also gave allopregnenolone acetate, IVB, in comparable yields via IIC and IIIC. As the degradation of these steroidal alkaloids starts from the corresponding *O,N*-diacetyl derivatives, it is of obvious importance to secure them in maximum yields. It is recognized[14] that considerable difference exists between these alkaloids in their behavior toward acetylation. Tomatidine(IB) can be readily acetylated in the conventional manner (acetic anhydride-pyridine, room temperature) to give in good yields the desired diacetate IIB, whereas solasodine (IA) under these conditions is not completely acetylated. Under more vigorous conditions normal diacetylation is accompanied by varying amounts of byproduct formation, VIA.[15] For example, if acetylation is conducted under the conditions of Briggs and O'Shea[7] (eight moles acetic anhydride-pyridine, two hours boiling) and the resulting product chromatographed, a mixture of VIA is obtained in about 20% yield in addition to the normal *O,N*-diacetyl derivative IIA. After attempting acetylation by various methods (acetic anhydride-pyridine-sodium acetate-reflux; acetic anhydride-pyridine-triethylamine-reflux; ketene), we found the use of 3.8 mole equivalents of acetic anhydride in pyridine (one hour boiling) to be the most satisfactory resulting in a minimum formation of VIA. 5,6-Dihydrosolasodine (IC) was found to behave in the same way towards acetylation as solasodine. It is of interest to note that VIA was formed almost to the extent of 50% when solasodine (IA) was refluxed with acetic anhydride for several hours.[10] The same treatment of tomatidine (IB)[16] yields VIB to a much lesser extent (20–25%). As oxidation[17] of VIA or VIB does not give the desired pregnenolones, the poor yield of the pregnadiene derivative IVA (in contrast to the fairly good yield of IVB) by the procedure formerly reported by us[10] is readily explained. As 5,6-dihydrosolasodine (IC) behaves more like solasodine than tomatidine, it is most probable that the difference in configuration of solasodine and tomatidine at C_{25}[18,19] is responsible for their behavior towards acetylation.

A salient feature of the byproducts VIA and VIB is that they can be readily reconverted into the corresponding original alkaloids IA and IB by treatment with alcoholic alkali.

The above series of conversions demonstrate that these steroidal alkaloids, and particularly solasodine, bear promise of serving as commercial starting material in the synthesis of steroidal hormones.

EXPERIMENTAL[20]

Acetic anhydride treatment of solasodine (IA) *to give 26-acetylamino-furosta-5,20(22)dien-3β-ol acetate* (IIIA) *and amorphous mixture* VIA. A solution of 824 mg. of solasodine in 15 ml. of acetic anhydride was refluxed for 3 hr. The acetic anhydride was removed *in vacuo* and the residue dissolved in benzene and placed on an alumina column to stand overnight. Elution with benzene-ether (1:1) the following morning gave 546 mg (51%) of an amorphous substance (VIA), m.p. 98–102°, $[\alpha]_D^{20}$ −3° ($CHCl_3$); $\lambda_{max}^{CHCl_3}$ 5.78 (acetoxy), 5.98, 6.07 μ; λ_{max}^{EtOH} 236 mμ (log ε 3.95).

Anal. Calcd. for $C_{33}H_{49}O_5N$: C, 73.43; H, 9.15; CH_3CO, 23.9. Found: C, 73.31; H, 9.07; CH_3CO, 24.3.

Elution with 0.5% methanol in ether yielded 398 mg. (40%) of the pseudo derivative, IIIA, which crystallized from acetone-hexane, m.p. 135–138°, identical in all respects with the substance obtained from the acetic acid catalyzed rearrangement of IIA. A small amount of a third component m.p. 175–178° (from acetone-hexane) was eluted with 2% methanol in ether; its structure will be discussed in a forthcoming paper. There was no substantial difference in the composition and yield when the reaction time of acetic anhy-

(13) L. H. Briggs, R. P. Newbold, and N. E. Stace, *J. Chem. Soc.*, 3 (1942).

(14) K. Schreiber, *Abhandl. Dtsch. Akad. Wiss. Berlin, Kl. für Chem., Geol. u. Biol.* 1956, 143 (1957).

(15) The chemistry and proof of structure of this mixture will be published in a forthcoming publication.

(16) Y. Sato, A. Katz, and E. Mosettig, *J. Am. Chem. Soc.*, **73**, 880 (1951), **74**, 538 (1952).

(17) To be described in a forthcoming publication.

(18) F. C. Uhle and J. A. Moore, *J. Am. Chem. Soc.*, **76**, 6412 (1954).

(19) Schreiber (14) also proposes a C_{22} isomerism for dihydrosolasodine and tomatidine but the evidence is meager and inconclusive.

(20) Melting points were taken on the Kofler block and are uncorrected. Microanalyses were performed by the Analytical Service Laboratory under the direction of Dr. William C. Alford. Woelm alumina, grade 1, was used in the chromatography.

dride with solasodine was prolonged to 9 hr. Solasodine was also refluxed with propionic anhydride but the yields of the product as indicated by chromatography were not as good.

Acetic anhydride treatment of tomatidine (IIB) *to give 26-aminodiacetyl-5α-furost-20(22)en-3β-ol acetate* (VB), *26-aminoacetyl-5α-furost-20(22)en-3β-ol acetate* (IIIB) *and amorphous mixture* VIB. Tomatidine (378 mg.) was refluxed with 10 ml. of acetic anhydride for 3 hr. After the reaction mixture was worked up in the manner previously reported[16] 195 mg. (40%) of crude VB was recovered. The mother liquor was evaporated to dryness and the residue subjected to alumina chromatography. Upon elution with benzene-ether (1:1) 115 mg. (23%) of an amorphous substance, m.p. 97–102°, VIB, $[\alpha]_D^{20}$ +92.5° ($CHCl_3$), λ_{max}^{EtOH} 236 mμ (log ε 3.92), $\lambda_{max}^{CHCl_3}$ 5.78 μ (acetoxy), 5.99, 6.08 μ was obtained.

Anal. Calcd. for $C_{33}H_{51}O_5N$: C, 73.16; H, 9.49; CH_3CO, 23.9. Found: C, 72.90; H, 9.31; CH_3CO, 25.5.

Elution with 0.5% methanol in ether yielded 145 mg. (32%) of IIIB, which after crystallization from acetone-hexane melted at 128–132°. This substance agreed in properties with IIIB obtained from the acetic acid catalyzed rearrangement of IIB.

Acetylation of solasodine to give IIA and VIA. (a) (8 mole equiv. of acetic anhydride). A solution of solasodine (520 mg.) 5 ml. of pyridine and 1 ml. of acetic anhydride was refluxed for 1 hr. and was poured on ice, followed by addition of aqueous ammonia and sodium chloride. After 1 hr. the product was collected and chromatographed on alumina (Grade 1). The diacetate (IIA) was eluted with benzene-ether (1:1), yield 410 mg. (65%), m.p. 164–166°.

Fractions eluted with ether-methanol (1%) gave 228 mg. of amorphous compound, which was rechromatographed on alumina (Grade II). Elution in this chromatography with benzene-ether (3:1) gave 136 mg. (20%) of VIA, identical in infrared spectrum with VIA obtained from the acetic anhydride treatment of solasodine. Further elution with ether-methanol (1%) gave 6% of an unresolved mixture.

(b) (3.8 mole equiv. of acetic anhydride) A mixture of 520 mg. of solasodine, 5 cc. of pyridine, and 0.46 ml. of acetic anhydride was refluxed for 1 hr. and the reaction mixture worked up as described above. Purification by chromatography on alumina or recrystallization from aqueous methanol gave 575 mg. (92%) of diacetate IIA. A second crop raised the yield to 95%.

(c) The yields after acetylation of solasodine under various conditions are tabulated below:

Acetic Anhydride-Pyridine	Time	Diacetate Yield (after chromatography)
2.2 mole equiv.	2 hr. (reflux)	55–60%
2.7 mole equiv.	2 hr. (reflux)	75%
3.5 mole equiv. plus sodium acetate (3 mole equiv.)	1.7 hr. (reflux)	85%
4 mole equiv. plus triethylamine (*ca.* 4 mole equiv.)	1 hr. (reflux)	85%
10 mole equiv.	15 hr. (room temp.)	30–40%
6 mole equiv.	15 hr. (5°)	mostly 3-acetate

With excess ketene an unpromising looking mass was obtained which was not investigated further.

Acetylation of Tomatidine to give IIB. A mixture of tomatidine (505 mg), 8 ml. of pyridine and 2 ml. (*ca.* 8 mole equiv.) of acetic anhydride was allowed to stand overnight and poured on ice and aqueous ammonia. The precipitated diacetate was recrystallized from petroleum ether-ether, fine needles, m.p. 184–188°, yield 585 mg. (96%). After recrystallization, the melting point rose to 190–192°.

Acetylation of Dihydrosolasodine to give IIC. A solution of dihydrosolasodine (100 mg.) and 0.1 cc. (*ca.* 4 mole equiv.) of acetic anhydride in 2 ml. of pyridine was refluxed for 1 hr. and poured into ice water. The product was collected, dried and chromatographed over alumina. The fraction eluted with ether gave 109 mg. (92%) of diacetate, m.p. 180–183°.[21]

A solution of dihydrosolasodine (100 mg.) and 0.75 cc. (*ca.* 30 mole) of acetic anhydride in 2 ml. of pyridine was allowed to stand for 15 hr. The product was chromatographed over alumina. The fraction eluted with ether gave 70 mg. (58%) of impure diacetate, (m.p. 155–170°) as revealed by its infrared spectrum.

26-Acetylamino-5,20(22)-furostadiene-3β-ol acetate (IIIA). (a) To boiling acetic acid (10 ml.), 500 mg. of solasodine diacetate (IIA) was added in small portions and refluxed further for 15 min. The solvent was evaporated *in vacuo* and the crystalline residue was recrystallized from acetone-hexane, m.p. 135–138°, $[\alpha]_D^{20}$ −23° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.90, 2.98 μ (N—H); 5.78 μ (3-acetoxy); 5.89 μ (vinyl ether, nujol); 5.98, 6.60 μ (N—H acetyl). The product may be chromatographed on an alumina column and eluted with 0.5% methanol in ether. The yields range from 95–98%.

Anal. Calcd. for $C_{31}H_{47}O_4N$: C, 74.81; H, 9.52. Found: C, 75.09; H, 9.36.

When propionic acid was used in place of acetic acid, the result was about the same.

(b) A solution of 235 mg. of IIA, 3 ml. of acetic acid, and 0.03 ml. of perchloric acid (60%) was allowed to stand at room temperature for 10 min., was poured on ice, and was partially neutralized with aqueous ammonia. The product was collected and dissolved in ether. After drying, the ether was evaporated and the residue was chromatographed on alumina.

From the fraction eluted with ether-methanol (0.5%) 171 mg. (73%) of pseudo compound (IIIA), m.p. 135–138° was obtained. A subsequent fraction eluted with ether-methanol (5%) gave 52 mg. (23%) of a crystalline hydroxyl derivative[9] which melted rather unsharply at 144–152°.

When hydrochloric acid (36%) was substituted for perchloric acid, the results were approximately the same.

26-Aminoacetyl-5α-25L-furost-20(22)-en-3β-ol acetate (IIIB). Tomatidine diacetate (IIB) (322 mg.) was converted into IIIB, m.p. 125–129°, 309 mg. (96%) in the same manner [method (a)] described above for IIIA. A sample recrystallized from acetone-hexane melted at 128–132°, $[\alpha]_D^{20}$ +1.5° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.89, 2.97 μ (N—H); 5.78 μ (3-acetoxy); 5.89 μ (vinyl ether, nujol); 5.99 6.59 μ (N—H-acetyl).

Anal. Calcd. for $C_{31}H_{49}O_4N$: C, 74.51; H, 9.88. Found: C, 74.66; H, 10.02.

26-Acetylamino-5α-25D-furost-20(22)-en-3β-ol acetate (IIIC).

IIIC was prepared in the manner [method (a)] of IIIA; IIC (120 mg.) yielded 111 mg. (93%) of IIIC, after alumina chromatography and elution with ether-methanol (0.5%), m.p. 78–80°, $[\alpha]_D^{20}$ +22° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.90, 2.98 μ (N—H), 5.79 μ (3-acetoxy), 5.99, 6.60 μ (N—H-acetyl).

Anal. Calcd. for $C_{31}H_{49}O_4N$: C, 74.51; H, 9.88. Found: C, 74.53; H, 10.09.

Oxidation of IIIA to 3β-acetoxypregna-5,16-dien-20-one (IVA). A solution of chromic anhydride (110 mg., 2 mole equiv. in 8 ml. of 80% aqueous acetic acid) was added dropwise over a period of 15 min. to a stirred solution of IIIA (280 mg.) in 10 ml. of acetic acid while cooling (15°). After the addition of the oxidant, the solution was stirred for 1 hr. at room temperature. Water (*ca.* 50 ml.) and a small amount of sodium sulfite were added. The mixture was saturated with sodium chloride and extracted with ether thoroughly. The combined ether extractions were dried over anhydrous sodium sulfate and the solvent (ether) was removed. The residue was dissolved in 25 ml. of acetic acid and refluxed for 2 hr. After removal of the acetic acid and

(21) Reported (7) m.p. 186–187°.

dilution with water, it was neutralized with sodium bicarbonate and extracted with ether. The ether layer was washed with sodium bicarbonate solution and water, and dried over anhydrous sodium sulfate. The residue (215 mg.) after removal of the solvent was recrystallized from methanol-water or chromatographed over alumina (ether eluate) and gave 152 mg. (76%) of IVA, m.p. 169–173°, analytical sample, m.p. 173–175.5°, $[\alpha]_D^{20}$ −35° ($CHCl_3$), λ_{max}^{EtOH} 239 mμ (log ε 4.0), identical in all respects with an authentic specimen.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.45; H, 9.11.

In a continuous operation from solasodine (IA) (1 g.) using 3.8 mole equiv. of acetic anhydride for the acetylation and without purification or isolation of the intermediates, an over-all yield of 65% of IVA, m.p. 169–173° was obtained.

A small amount of the lactone and a second component presumably the 3,5-diene were often detected by infrared spectra in these oxidations.

Oxidation of IIIB to 3β-acetoxy-5α-pregn-16-en-20-one (IVB). A solution of chromic anhydride (146 mg., 2 mole equiv.) in 10 ml. of 80% aqueous acetic acid was added over a period of 15 min. to a stirred solution of 365 mg. of IIIB in 16 ml. of acetic acid while cooling (10–20°). After stirring for 1 hr. at room temperature, the reaction mixture was worked up as described above for IVA and 285 mg. of oxidation product was obtained. Purification of the crude product by recrystallization from methanol-water or chromatography on alumina gave 206 mg. (79%) of IVB, m.p. 163–166°, analytical sample m.p. 165–167°, $[\alpha]_D^{20}$ +42° ($CHCl_3$), λ_{max}^{EtOH} 239 mμ (log ε 3.98). It agreed in all properties with an authentic sample.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.32; H, 9.58.

In a continuous operation from tomatidine (IB), analogous to solasodine, an over-all yield of 68% of IVB was obtained.

Oxidation of IIIC *to 3β-acetoxy-5α-pregn-16-en-20-one* (IVB). A solution of chromic anhydride (90 mg., 2 mole equiv.) in 7 ml. of 80% aqueous acetic acid was added over a period of 15 min. to a stirred solution of IIIC (230 mg.) in 8 ml. of acetic acid while cooling. After stirring for 1 hr. the reaction mixture was worked up in a manner similar to that described above for IVA. The crude product (188 mg.) was chromatographed over alumina; the fraction eluted with ether gave 123 mg. (75%) of IVB, m.p. 163–166°, identical in all respects with an authentic specimen.

Solasodine (IA) *from* VIA. A solution of 100 mg. of VIA in 20 cc. of 10% methanolic potassium hydroxide was refluxed for 12 hr. After partial concentration of the volume and addition of water, the product was collected and dried. Upon crystallization from aqueous methanol or chromatography over alumina (Grade II eluted with 2% methanol in ether), 61 mg. (80%) of IA, m.p. 199–202°, was obtained, identical in every respect with an authentic specimen of solasodine.

Tomatidine (*IB*) *from VIB.* Tomatidine was obtained from VIB in the same manner as described above for solasodine.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

The Chemistry of the Spiroaminoketal Side Chain of Solasodine and Tomatidine. II.[1] Chemistry of 3β,16β-Diacetoxy-20-(2′-Δ²′-*N*-acetyl-5′-methyltetrahydropyridyl)-5-pregnene

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The chemistry and the manifold interrelationship of the acetylated tetrahydropyridyl pregnenes and the diacetylaminofurostadiene derivative obtained in the treatment of solasodine with acetic anhydride are discussed.

The reaction of solasodine (I) with acetic anhydride[3] (three hours boiling) leads to the formation of a gummy resinous mass which is presumably a mixture of 26-aminodiacetyl-5,20(22)-furostadien-3β-ol acetate[4] (III), Δ²²(²³) tetrahydropyridylpregnene derivative IIA and the probable isomeric Δ²⁰(²²) piperidylpregnene derivative IIB. Upon chromatography[3] of this mixture on alumina, III is readily deacetylated and emerges from the column as 26-acetylamino-5,20(22)-furostadien-3β-ol acetate (VIa). It can be reconverted to the original hitherto unisolated crystalline aminodiacetyl derivative III by treatment with acetic anhydride and pyridine. The degradation of VIa to 3β-acetoxy-5,16-pregnadien-20-one has been described in the foregoing paper.[1] Compounds IIA and IIB, which are eluted from the column as an amorphous mixture, are assigned their structures from considerations of spectroscopic and chemical data. The mixture exhibits an ultraviolet absorption band at 236 mμ (log ε, 3.95) consistent with the assignment of an α,β-unsaturated acetylamino function.[5,6] The infrared spectrum reveals the

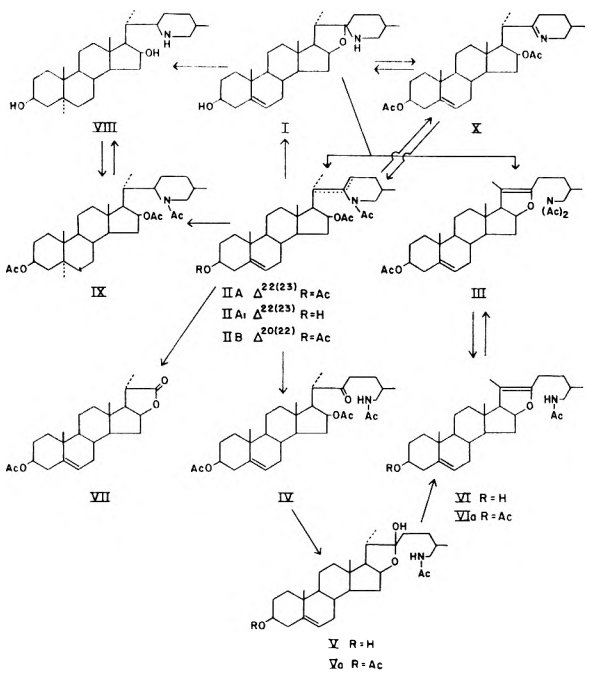
(1) Part I, Y. Sato, N. Ikekawa, and E. Mosettig, *J. Org. Chem.*, **25**, 783 (1960).

(2) Visiting Scientist, National Institutes of Health.

(3) Y. Sato, H. G. Latham, Jr., and E. Mosettig, *J. Org. Chem.*, **22**, 1496 (1957).

(4) *Cf.* Y. Sato, A. Katz, and E. Mosettig, *J. Am. Chem. Soc.*, **74**, 538 (1952). Compound III has never been directly isolated from the reaction mixture. It is assumed that the reaction proceeds in the same manner as with tomatidine where the corresponding 26-aminodiacetyl derivative can be directly crystallized from the reaction mixture. The chemistry of these related tomatidine derivatives will be discussed in a forthcoming publication.

(5) G. Rosenkrantz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956).



presence of an ester (5.78 μ) and a probable unsaturated tertiary amide (5.98, 6.07 μ) group.[6] Hydrolysis of this mixture with hydrochloric acid in acetic acid proceeds readily to yield the acetylamino ketone IV in good yields. The ease of hydrolysis of Δ^2-tetrahydropyridines is well known.[7] Another component in varying amounts (3–10%), along with the mixture of IIA and IIB and pure VIa, has been obtained from this chromatography.[1] It has been identified as IV and therefore considered as arising primarily from the mixture IIA and IIB as the result of hydrolysis taking place in the alumina column. A small amount of IV may have been present originally as a very rapid chromatography yields about 3% of IV. Compound IV displays the following absorption bands: $\lambda_{max}^{CHCl_3}$ 2.94 μ (N-H), 5.80 μ (OAc and CO), 6.0, 6.62 μ (HN-Ac), $\lambda_{max}^{CS_2}$ 5.75 μ (OAc), 5.83 μ (CO); $\lambda_{max}^{C_2H_5OH}$ 286 mμ (log ϵ, 1.85) and behaves chemically as expected. When IV is subjected to hydrolysis with methanolic alkali, hemiketal formation between the C-16 hydroxyl and C-22 carbonyl takes place and the compound, 26-acetylamino-3β,22-dihydroxy-5-furostene (V) is obtained. Hemiketalization of this type has been observed in the reduction of 5,6-dihydrokryptogenin diacetate[8] with Raney nickel. The 3-acetate of diol V (Va) has also been prepared by treating solasodine diacetate with hydrochloric acid in dioxane.[9] When V is refluxed briefly with acetic acid, it is converted into the pseudo derivative, 26-acetylamino-5,20-(22)-furostadien-3β-ol (VI), which is identical with the 3-alcohol of pseudodiacetylsolasodine (VIa) obtained from *O,N*-diacetylsolasodine.[1]

Further support for structures IIA and IIB has been derived from the synthesis of the crystalline compound IIA (m.p. 166–169°) through another route, *i.e.*, by allowing pesudosolasodine B[3] (X) to stand at room temperature with acetic anhydride in the presence of pyridine. The original mixture, when seeded with IIA thus obtained, yielded a fair amount of crystalline IIA. The samples from these two sources were identical in all respects and gave identical transformation products (I, IIA1, and IV). The $\Delta^{20(22)}$-isomer[10] has not been obtained as yet in crystalline form.

Although the above data do not preclude the alternate $\Delta^{20(22)}$ position for the site of unsaturation in IIA, the Δ^2-tetrahydropyridine structure is favored and is provisionally assigned to IIA on the basis of the recognized greater stability of the endocyclic double bond as compared with an exocyclic bond.[11] Chromic acid oxidation of IIA and IIB in aqueous 80% acetic acid did not permit a decision between IIA and IIB, as both pregnadienolone (3β-acetoxy-5,16-pregnadien-20-one) and the lactone, 3β-acetoxy-16β-hydroxy-5-bisnorcholenic 22→16-lactone (VII) were obtained from the amorphous mixture as well as from pure IIA. It is of interest to note that oxidation of IIA conducted under anhydrous conditions (sodium dichromate–benzene–acetic acid) yielded no identifiable product. Thus in aqueous media hydrolysis to the ketone precedes oxidation.

The catalytic reduction and subsequent alkaline hydrolysis of the amorphous mixture, IIA and IIB yields tetrahydrosolasodine identical with an authentic specimen prepared from the direct catalytic reduction of solasodine. Of some interest in this reduction is the resinous nature of the triacetyltetrahydrosolasodine[12] (IX) as compared with the

(6) R. Griot and T. Wagner-Jauregg, *Helv. chim. Acta*, 42, 121, 605 (1959).

(7) A. Lipp, *Ann.*, 289, 173 (1896); A. Lipp and E. Widnmann, *Ber.*, 38, 2471 (1905).

(8) H. Hirschmann and F. B. Hirschmann, *Tetrahedron*, 3, 243 (1958).

(9) Y. Sato and N. Ikekawa, *J. Org. Chem.*, Part III.

(10) The fact that the hydrolysis of the amorphous mixture yields IV in high yields and the good agreement of the elemental analysis[1] with formulas IIA and IIB point strongly to a mixture of isomers. The ultraviolet absorption band and extinction coefficient of the oil remaining after removal of IIA do not differ appreciably from the original mixture. Although the infrared spectra are practically identical some subtle differences, notably in the C—H stretching and deformation vibration regions are observed. Differences in the respective specific rotations are more pronounced (−3° to −36°). Attempts at obtaining homogeneous IIA by acid catalyzed isomerization of the amorphous mixture failed. IIA is also stable in boiling acetic anhydride. Thus IIA and IIB are not in equilibrium.

(11) R. B. Turner and R. H. Garner, *J. Am. Chem. Soc.*, 80, 1424 (1958).

(12) This is probably due to contamination by the C-22 epimer arising from the reduction of the mixture IIA and IIB. The reduction of solasodine to tetrahydrosolasodine (VIII) probably proceeds stereospecifically because of the rigid spatial configuration of the spiroaminoketal side chain.

crystalline triacetyl derivative[13] prepared from I via VIII.

Finally it is of interest to note that the treatment of IIA or the amorphous mixture with acetic acid or with hydrogen chloride gas in ether-benzene solution affords pseudosolasodine B (X).

EXPERIMENTAL[14]

3β,16β-Diacetoxy-20-(2'-Δ²'-N-acetyl-5'-methyltetrahydropyridyl)-5-pregnene (IIA) *and the 3-alcohol* (IIA1) *from* IIA *and the amorphous mixture.* The preparation and properties of the original amorphous substance are described in Part I of this series. The crystalline compound (IIA) was prepared in the following manner. A solution of 150 mg. of pseudosolasodine B[3] (X) in 5 ml. of pyridine and 2 ml. of acetic anhydride was allowed to stand for 20 hr. at room temperature. It was then poured on ice water and extracted with ether. The residue from the ethereal extract was chromatographed on alumina. Elution with ether yielded 127 mg. of the unsaturated triacetyl derivative, m.p. 166–169° (ether-hexane); $[\alpha]_D^{20}$ +97° ($CHCl_3$); $\lambda_{max}^{C_2H_5OH}$ 236 mμ (log ε, 3.93).

Anal. Calcd. for $C_{33}H_{49}O_5N$: C, 73.43; H, 9.15. Found: C, 73.10; H, 9.24.

When the amorphous mixture IIA and IIB (130 mg.) dissolved in ether-hexane was seeded with crystalline IIA thus obtained, it afforded 82 mg. of a crystalline substance (heavy columns, m.p. 120–150°) which when twice recrystallized from the same solvent melted at 165–168° (22 mg.). This agreed in every respect (melting point, mixture melting point, rotation and infrared spectrum) with IIA obtained from X.

The mother liquor yielded an amorphous matter, $[\alpha]_D^{20}$ −36° ($CHCl_3$), $\lambda_{max}^{C_2H_5OH}$ 236 mμ (log ε, 3.94) which exhibited infrared spectra bands similar to but not identical with IIA.

The *3-alcohol* IIA1, of amorphous IIA and IIB was prepared by hydrolysis with 2% methanolic potassium hydroxide (30 min. refluxing). The product was chromatographed over alumina and the substance was eluted with ether-methanol (0.5%) collected as the 3-hydroxy compound, m.p. 192–196° (acetone-hexane), $[\alpha]_D^{20}$ +107° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.77, 2.90 μ (hydroxyl); 5.78 μ (acetoxyl); 5.98, 6.08 μ (unsaturated tertiary amide).

Anal. Calcd. for $C_{31}H_{46}O_4N$: C, 74.95; H, 9.34. Found: C, 74.66; H, 9.31.

The mild alkaline hydrolysis of IIA in the above manner yielded IIA1 identical with IIA1 from amorphous IIA and IIB.

On the other hand the vigorous alkaline hydrolysis of IIA (10% potassium hydroxide in methanol for 12 hr.) produced the starting material solasodine (I) as in the case of amorphous mixture.[1]

3β,16β-Diacetoxy-26-acetylamino-5-cholesten-22-one (IV). A solution of 285 mg. of the amorphous mixture of IIA and IIB, 8 ml. of acetic acid, and 1.5 ml. of 4*N* hydrochloric acid was allowed to stand at room temperature for 45 min. After addition of excess water and partial neutralization with sodium bicarbonate solution, the precipitate was collected, dried, and crystallized from acetone-hexane. The compound (plates, 220 mg.) melted 168–171°. An analytical sample recrystallized from the same solvent pair melted 175–178°, $[\alpha]_D^{20}$ +9° ($CHCl_3$) and possessed the infrared and ultraviolet spectra bands as described in the text. An attempt to form the oxime with hydroxylamine hydrochloride in the presence of potassium acetate in methanol failed.

Anal. Calcd. for $C_{33}H_{51}O_6N$: C, 71.06; H, 9.22; N, 2.51. Found: C, 70.94; H, 8.96; N, 2.59.

IIA also yielded IV when hydrolyzed in the same manner with the above reagents. When IV thus obtained was compared with the sample, m.p. 175–178°, obtained from the chromatography (ether-2% methanol eluate) of the reaction mixture[1] of solasodine with acetic anhydride, it agreed in properties (melting point and infrared spectrum) with the latter.

26-Acetylamino-5-furostene-3β,22-diol (V). One hundred milligrams of the 22-oxo derivative IV was dissolved in 10 ml. of 2% methanolic potassium hydroxide and refluxed for 1.5 hr. After removal of the methanol *in vacuo*, water was added to the residue and the compound taken up in chloroform. The substance recovered from the chloroform phase was crystallized from acetone-hexane, m.p. 119–122°, $[\alpha]_D^{20}$ −55° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.78, 2.90 μ (OH, NH), 5.99, 6.58 μ (HNAc).

Anal. Calcd. for $C_{29}H_{47}O_4N$: C, 73.52; H, 10.00. Found: C, 73.78; H, 10.22.

The *acetate* Va of the above diol V prepared in the usual manner (acetic anhydride-pyridine-room temperature, 15 hr.) and chromatographed on alumina (elution with 3% methanol in ether) yielded plates (aqueous acetone) m.p. 152–155°; $\lambda_{max}^{CHCl_3}$ 2.81 μ (OH); 2.92 μ (N—H); 5.80 μ (OAc); 6.00, 6.63 μ (HNAc). Its spectrum agreed with that of the substance obtained from the treatment of diacetylsolasodine with 2*N* hydrochloric acid in dioxane.[9]

26-Acetylamino-5,20(22)-furostadien-3β-ol (VI). The diol V (40 mg.) was refluxed with 3 ml. of acetic acid for 30 min. The acid was removed *in vacuo* and the residue crystallized from acetone-hexane. It melted at 185–190°.

Anal. Calcd. for $C_{29}H_{45}O_3N$: C, 76.44; H, 9.95. Found: C, 76.29; H, 10.01.

VI *from 26-acetylamino-5,20(22)-furostadien-3β-ol acetate* (VIa). The diacetylpseudo derivative VIa[1] (50 mg.) was refluxed with 5 ml. of 2% methanolic potassium hydroxide for 1 hr. and the solvent was removed. After the addition of water, it was extracted with methylene chloride. The solvent was then removed and the residue crystallized from acetone-hexane. The compound, $[\alpha]_D^{20}$ −27.3° ($CHCl_3$), melted at 186–190°. It was identical in respect to melting point and infrared spectrum with VI obtained from the treatment of V with acetic acid.

26-Aminodiacetyl-5,20(22)-furostadien-3β-ol acetate (III) *from* VIa. *O,N*-Diacetylpseudosolasodine (VIa, 80 mg.) was dissolved in pyridine (1 ml.) and acetic anhydride (1 ml.) and refluxed for 3 hr. The reaction product was poured on ice water and collected. The compound, twice crystallized from aqueous methanol (plates), melted at 89–90°, $[\alpha]_D^{20}$ −23° ($CHCl_3$), $\lambda_{max}^{C_2H_5OH}$ 218 mμ (log ε, 4.09), $\lambda_{max}^{CS_2}$ 5.75, 8.06 μ (3-OAc); 5.86 μ (N—Ac_2), 5.97 μ (C=C—O—).

Anal. Calcd. for $C_{35}H_{49}O_6N$: C, 73.43; H, 9.15. Found: C, 73.23, H, 9.28.

3β-Acetoxy-16β-hydroxy-5-bisnorcholenic 22 → 16-lactone (VII). A solution of chromic acid (300 mg. chromium trioxide in 15 ml. 80% acetic acid) was added dropwise to a solution (15 ml. acetic acid) containing 350 mg. of amorphous IIA and IIB while stirring. After the addition of the oxidant, the stirring was continued for another 2 hr. Water and a small amount of sodium sulfite were then added and the mixture extracted with ether. The residue recovered from the ether extract was refluxed with ethanolic potassium hydroxide (3%) for 2 hr. and the solvent was removed. Water was added to the residue and the mixture was extracted with ether. The ether soluble fraction, after acetylation in the conventional manner, yielded 41 mg. of a neutral fraction which was subjected to chromatography on alumina.

(13) L. H. Briggs and T. O'Shea. *J. Chem. Soc.*, 1654 (1952).

(14) Melting points were taken on the Kofler block and are uncorrected. Micro analyses were performed by the Institute's Analytical Service Laboratory under the direction of Dr. W. C. Alford. The infrared spectra were taken on the Model 21 Perkin Elmer Infrared Spectrometer by Messrs. H. K. Miller and R. T. Brown. Neutral Woelm alumina, grade 1, was used in the chromatography, unless otherwise noted.

From the benzene eluate, 17 mg. of impure 3β-acetoxy-5,16-pregnadien-20-one were obtained, which yielded 6 mg. of the pure specimen. The aqueous layer from the ether extract was acidified with hydrochloric acid and reextracted with ether. This after acetylation yielded 143 mg. of crude lactonic material which was chromatographed on acidic alumina. From the ether eluate, 30 mg. of lactone VII, m.p. 212–215° (from acetone-hexane), was obtained, which was identical (melting point, mixture melting point, infrared spectrum) with an authentic specimen prepared from another source.[9]

Tetrahydrosolasodine (VIII) *from amorphous mixture.* The amorphous mixture (177 mg.) was dissolved in 6 ml. of acetic acid and reduced catalytically with 94 mg. of platinum oxide. In about 30 min. the consumption (2 moles) of hydrogen ceased. Although the tetrahydro derivative was chromatographed, it refused to crystallize,[12] $[\alpha]_D^{20}$ +24° ($CHCl_3$).

A part of the triacetate (64 mg.) was therefore hydrolyzed in methanolic potassium hydroxide (10%) for 3 hr. and the product crystallized from aqueous methanol. It formed prisms, m.p. 288–292°, $[\alpha]_D^{20}$ −8.7° ($CHCl_3$), identical in respect to melting point and infrared spectrum with an authentic specimen of tetrahydrosolasodine obtained from the direct reduction of solasodine.[15]

Conversion of IIA *and the amorphous mixture into pseudosolasodine B* (X). (a) The amorphous mixture (225 mg.) was refluxed with 15 ml. of acetic acid for 3 hr. The acetic acid was removed *in vacuo* and the residue chromatographed on alumina. The fraction eluted with ether (175 mg.) crystallized from methanol as plates, m.p. 184–191°, and agreed in properties (melting point and infrared spectrum) with an authentic specimen[3] prepared from the interaction of a solution of zinc chloride-acetic anhydride-acetic acid with solasodine.

Anal. Calcd. for $C_{31}H_{47}O_4N$: C, 74.81; H, 9.52. Found: C, 74.58; H, 9.43.

The treatment of IIA in the same manner also gave X in good yields.

(b) A solution of 130 mg. of amorphous IIA and IIB in 20 ml. of benzene-ether (1:1) containing hydrogen chloride gas (slow bubbling for *ca.* 5 min.) was allowed to stand overnight at 5°. The product was chromatographed on alumina. The ether eluate (45 mg.) proved to be X.

BETHESDA 14, MD.

(15) H. Rochelmeyer, *Arch. Pharm.*, **277**, 329 (1939).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

The Chemistry of the Spiroaminoketal Side Chain of Solasodine and Tomatidine. III.[1] The Reaction of *O,N*-Diacetylsolasodine in Acidic Media

YOSHIO SATO AND NOBUO IKEKAWA[2]

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The isomerization of *O,N*-diacetylsolasodine in nonpolar media forms the pseudo derivative, 26-acetylamino-5,20(22)-furostadien-3β-ol acetate in good yields. Aqueous or alcoholic acidic media promote the formation of C-22 substituted 26-acetylaminofurostene derivatives. The chemistry of the 22-hemiketal and alkoxyketals is discussed.

In the course of our investigations of the acid-catalyzed isomerization of the diacetates of the steroidal alkaloids, tomatidine, and solasodine[1] several interesting new compounds were obtained from the treatment of these diacetyl derivatives with mineral acid in polar solvents. In the presence of aqueous hydrochloric acid in dioxane[3] diacetylsolasodine (I) yields, along with the known pseudo compound II,[1] the 22-hydroxyl derivative III. This structure was deduced from the proposed course of the pseudomerization reaction (VIII→IX→X) and confirmed by spectroscopic and chemical data.

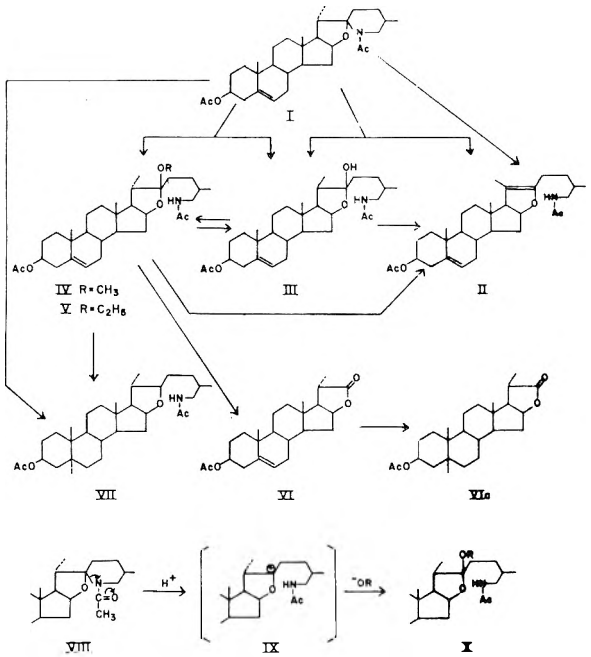
The infrared spectrum of III is characterized by the appearance of a hydroxyl absorption (2.78 μ) in addition to to the normal acetoxy (5.78 μ) and secondary amide function (2.90, 5.98, 6.60 μ). As would be expected III is readily converted into the pseudo derivative II by treatment with acetic acid. Structure III is further supported by the preponderant formation of the C-22 methoxy derivative IV when methanol is used as solvent in place of dioxane in its preparation from diacetylsolasodine. When ethanol is employed in place of methanol, the ethoxy derivative V is obtained, which can be converted to the methoxyl compound IV by allowing it to stand in a solution of methanol and acetic acid. The process is easily reversed (IV→V) by employing ethanol and acetic acid. By mild treatment with 80% acetic acid, these alkoxy derivatives IV and V are transformed into the hydroxyl compound III which, in turn, is readily reconverted into IV or V with acetic acid and the appropriate alcohol. More vigorous treatment with acetic acid converts compounds IV and V directly into II. This series of transformations parallels the sequence of reactions which Hirschman and Hirschman have found for the C-22 ketals obtained from kryptogenin.[4]

(1) For Part I and II see *J. Org. Chem.*, **25**, 783 (1960).

(2) Visiting Scientist, National Institutes of Health.

(3) Hydrochloric or perchloric acid (60%) in acetic acid also acts similarly.[1]

(4) H. Hirschman and F. B. Hirschman, *Tetrahedron*, **3** 243 (1958).



During the earlier phase of this work, before alkoxylation at C-22 was suspected, oxidative degradation of compounds IV and V were attempted. The principal substance isolated in these experiments was the lactone VI, accompanied by a small amount of 5,16-pregnadienolone acetate. The identity of VI was established by its reduction to the known tigogenin lactone (VIa).[5] It was also found that the C-22 alkoxy substituent can be reductively removed (platinum oxide–acetic acid) whereby 26-acetylamino-5α-furostan-3β-ol acetate (VII) is formed, which had been previously prepared from the catalytic reduction[6] of *O,N*-diacetylsolasodine.

As would be expected, in the absence of nucleophiles under anhydrous conditions the formation of these C-22 substituted by-products is avoided. For example *O,N*-diacetylsolasodine (I) is converted in good yields to the pseudo compound II (*ca.* 90%) in an anhydrous media (e.g., methylene chloride) with hydrogen chloride. Treatment of I with pyridine hydrochloride in dry pyridine also affords II in high yields (95%).

EXPERIMENTAL[7]

*26-Aminoacetyl-25*D*-furost-5-en-3β,22-diol 3-acetate* (III). A solution of solasodine diacetate (I) (105 mg.), 2*N* hydrochloric acid (0.5 ml.), and dioxane (6 ml.) was allowed to stand at room temperature for 30 min. Water and ammonium hydroxide were then added and the recovered product subjected to chromatography on alumina. The ether-methanol (0.2%) eluate yielded 66 mg. (63%) of pseudosolasodine diacetate (II), m.p. 128–134°, which upon recrystallization from acetone-hexane melted at 135–138°. It was identical (melting point, mixture melting point, infrared spectrum) with an authentic sample of II obtained previously.[1]

The fraction eluted with ether-methanol (5%) gave 27 mg. (26%) of the C-22 hydroxy derivative III, melting at 152–155° (plates from aqueous acetone) $[\alpha]_D^{20}$ −52° ($CHCl_3$). Its principal infrared absorption bands ($CHCl_3$) were located at 2.78 μ (OH), 2.90 μ (NH), 5.78 μ (OAc), and 5.98, 6.60 μ (HN—Ac).

Anal. Calcd. for $C_{31}H_{49}O_5N$: C, 72.19; H, 9.58. Found: C, 72.17; H, 9.58.

Solasodine diacetate (I) in acetic acid with hydrochloric or perchloric acid (60%) also affords II and III.[1]

*26-Aminoacetyl-22-methoxy-25*D*-furost-5-en-3β-ol acetate* (IV). To 300 mg. of *O,N*-diacetylsolasodine dissolved in 10 ml. of methanol was added 0.2 ml. of 6*N* hydrochloric acid and the solution allowed to stand for 15 min. at room temperature. Water and conc. ammonium hydroxide (0.5 ml.) were added and the precipitate chromatographed on alumina. The fraction eluted with ether-methanol (0.5%) yielded 270 mg. (85%) of the methoxy derivative, plates, (aqueous methanol) m.p. 141–144°; $[\alpha]_D^{20}$ −82° ($CHCl_3$).

Anal. Calcd. for $C_{32}H_{51}O_5N$: C, 72.55; H, 9.70; CH_3O—, 5.85. Found: C, 72.21; H, 9.81; CH_3O—, 5.65.

A fraction subsequently eluted with ether-methanol (3%) afforded 36 mg. (*ca.* 11%) of a mixture of the 3-alcohol and the C-22 hydroxy compound as judged from its infrared spectrum.

*26-Aminoacetyl-22-ethoxy-25*D*-furost-5-en-3β-ol acetate* (V). A solution consisting of solasodine diacetate (500 mg.), 6*N* hydrochloric acid (0.4 ml.), and ethanol (15 ml.) was allowed to stand for 1 hr. at room temperature and then for 1 hr. in the refrigerator (0°). The fine crystals which had precipitated amounted to 326 mg. (61%) and melted at 160–164°. This was recrystallized from acetone-hexane to form plates, m.p. 166–171°, $[\alpha]_D^{20}$ −75° ($CHCl_3$).

Anal. Calcd. for $C_{33}H_{53}O_5N$: C, 72.89; H, 9.82; EtO—, 8.28. Found: C, 72.88; H, 9.54; EtO—, 8.43.

To the mother liquor was added water and ammonia water and the precipitated product subjected to chromatography on alumina. The ether-methanol (0.5%) eluate yielded 70 mg. (14%) of starting material and 18 mg. (3%) more of the ethoxy derivative. A subsequent fraction (5% methanol in ether) gave 74 mg. (15%) of the C-22 hydroxy compound, m.p. 152–155°, identical in infrared spectrum with III obtained from the treatment of diacetylsolasodine with hydrochloric acid in dioxane.

Conversion of V *into* IV. Twenty milligrams of the ethoxy derivative V was dissolved in 2 ml. of methanol and 0.5 ml. of acetic acid and allowed to stand for 3 hr. at room temperature. The product which was crystallized twice from aqueous methanol melted at 140–143°. It was identical (melting point, infrared spectrum) with a sample of IV obtained directly from I.

Conversion of IV *into* V. The methoxy derivative IV (23 mg.) was allowed to stand for 5 hr. at room temperature in a mixture of ethanol (3 ml.) and acetic acid (0.6 ml.). The product, twice crystallized from acetone-hexane, melted at 164–169°. The substance agreed (melting point, infrared spectrum) with a sample of V prepared directly from I.

Conversion of IV *to* III. The methoxy compound IV (70 mg.) was dissolved in a solution consisting of 4 ml. of acetic acid and 0.8 ml. of water. After standing at room temperature for 2 hr. ether was added and the solution washed thoroughly with a dilute sodium bicarbonate solution. The residue, after removal of the ether, was either crystallized from aqueous acetone or chromatographed on alumina. The substance obtained from the ether-methanol (2%) eluate

(5) R. Tschesche and A. Hagedorn, *Ber.*, 68, 1412 (1935).

(6) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, 78, 3150 (1956).

(7) Melting points were taken on the Kofler block and are uncorrected. Microanalyses were performed by the Institute's Analytical Service Laboratory under the direction of Dr. W. C. Alford. The infrared spectra were taken on the Model 21 Perkin Elmer Infrared Spectrometer by Messrs. H. K. Miller and R. T. Brown of this laboratory. Woelm alumina grade 1 was used as adsorbent for chromatography unless otherwise stated.

crystallized as plates from aqueous acetone and melted at 152–155°. It proved to be identical (melting point, mixture melting point, infrared spectrum) with III.

Conversion of V *to* III. The ethoxy derivative V (95 mg.) was dissolved in 6 ml. of aqueous acetic acid (80%) and treated in the same manner as described above for conversion of IV to III. The properties of the compound (melting point, infrared spectrum) agreed with an authentic sample of III.

Conversion of III *into* IV. III (14 mg.) was dissolved in a mixture of 1.5 ml. of methanol and 0.3 ml. of acetic acid and allowed to stand for 10 min. It was taken up in ether and the ethereal solution washed thoroughly with water, 5% sodium bicarbonate solution, and again water. The residue from the ether extract crystallized from aqueous acetone to yield plates melting at 140–143°. It was identical (melting point, mixture melting point, infrared spectrum) with IV obtained directly from the treatment of *O,N*-diacetylsolasodine with hydrochloric acid in methanol.

Conversion of III *into* V. III (18 mg.) was dissolved in a mixture of 1.5 ml. of ethanol and 0.3 ml. of acetic acid and was allowed to stand for 10 min. The product was crystallized from acetone-hexane and melted at 165–170°. It agreed in properties (melting point, rotation, infrared spectrum) with an authentic specimen of V prepared from I with hydrochloric acid in ethanol.

Conversion of V, IV *and* III *to* II. Fifty milligrams of the ethoxy derivative V was refluxed with 4 ml. of glacial acetic acid for 0.5 hr. After removal of the solvent *in vacuo* the residue was crystallized from acetone-hexane, m.p. 134–136°. It was identical in respect to melting point and infrared spectrum with an authentic specimen of II.

In a similar manner IV and III respectively were converted to II.

Oxidation of IV *and* V *to 3β-acetoxy-16β-hydroxy-5-bisnorcholenic 22 → 16-lactone* (VI). To a solution of IV (250 mg.) in 12 ml. of acetic acid there was added dropwise with stirring a solution of chromium trioxide (250 mg.) in 3 ml. of acetic acid (90%). The stirring was continued for 1½ hr. and the solution poured into ice water and extracted with ether. After the ethereal extract had been washed with water, 5% sodium bicarbonate solution, and again with water, the solvent was removed. The residue was refluxed with 10 ml. of methanolic potassium hydroxide (2%) for 40 min. partially concentrated, water added, and extracted with ether. The ethereal extract yielded 28 mg. of a neutral substance which was acetylated in the usual manner with acetic anhydride and pyridine. When this was chromatographed on alumina, the ether eluate yielded 8 mg. of a compound which was identified as slightly impure 5,16-pregnadien-20-one-3β-acetate from its infrared spectrum. The residual aqueous layer was acidified with hydrochloric acid and re-extracted with methylene chloride. Upon removal of the solvent, 62 mg. of an acidic substance was obtained. After acetylation with acetic anhydride and pyridine, the crude acetate was chromatographed on acid alumina. The ether eluate yielded 16 mg. (9%) of lactone, VI, m.p. 212–215° (acetone-hexane) $[\alpha]_D^{20}$ −90° ($CHCl_3$), $\lambda_{max}^{CS_2}$ 5.62 (lactone), 5.76 μ (acetate).

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.73; H, 9.02.

Oxidation of V in the same manner yielded the same lactone VI.

Reduction of VI *to the acetate of tigogenin lactone* (VIa). The unsaturated lactone VI (21 mg.) was dissolved in 3 ml. of glacial acetic acid and reduced in the presence of 50 mg. of 10% palladium-charcoal. With the consumption of 1 mole equivalent of hydrogen, the uptake ceased. The compound crystallized from acetone-hexane and melted at 210–213°. Its melting point, rotation, and infrared spectrum agreed with an authentic specimen of 3-acetate of tigogenin lactone.[5]

Hydrogenation of the ethoxy derivative V *to N-acetyltetrahydrosolasodine acetate* (VII). The ethoxy compound V (100 mg.) was dissolved in 4 ml. of glacial acetic acid and hydrogenated in the presence of 49 mg. of Adams catalyst. The uptake of hydrogen (2 mole equivalents) was rapid and ended in 20 min. The product was chromatographed on alumina. The ether-methanol (1%) eluate yielded needles, m.p. 139–141°, $[\alpha]_D^{20}$ −3° ($CHCl_3$). The melting point, and infrared spectrum of this substance were in agreement with *N*-acetyltetrahydrosolasodine-3-acetate[6] obtained directly from the catalytic reduction of *O,N*-diacetylsolasodine.

Anal. Calcd. for $C_{31}H_{51}O_4N$: C, 74.21; H, 10.25. Found: C, 74.41; H, 10.02.

Isomerization of I *to* II. (a) To a 5 ml. solution of methylene chloride containing hydrogen chloride gas (prepared by bubbling gaseous hydrogen chloride slowly for 3 min. into methylene chloride) there was added 110 mg. of solasodine diacetate; the reaction was allowed to stand at room temperature for 20 min. The solution was washed with 5% sodium bicarbonate solution and water and dried over anhydrous sodium sulfate. The residue, after removal of the solvent, was chromatographed on alumina. The fraction eluted with 0.5% methanol in ether yielded 99 mg. of a product melting at 129–133°. The infrared spectrum of this substance was in agreement with an authentic specimen of II.

(b) A solution of 132 mg. of solasodine diacetate in 20 ml. of dry pyridine containing approximately 0.8% hydrogen chloride was refluxed for 1.5 hr. and poured on ice. The product upon chromatography yielded 125 mg. (95%) of II, m.p. 129–134°.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

Reduction of 7α-Bromosteroids with Tritium[1]

MARCEL GUT AND MILAN USKOKOVIĆ

Received August 12, 1959

7α-Bromocholesterol acetate was reduced catalytically with tritium with the incorporation of the bulk of tritium in the 7α- position of the resulting cholesterol-H³. Details of the isotope distribution are shown and a possible mechanism to account for this distribution is indicated.

A growing interest in tritium as a radioactive tracer, caused by its low cost and the high specific activities made possible, stimulated this study on the specific labeling of steroids. It was of particular interest to study the stability of the isotopic label and also to investigate the position(s) of the introduced isotope.

The introduction of tritium in specific positions of the steroid molecule is carried out the most readily either by the tritiation of a multiple bond or by the reduction of an appropriate halosteroid with tritium.[2] An excellent study of the first method, including the distribution of isotope and also of the mechanism as applied to the deuteration of the double bond of cholesterol acetate, has already been published.[3] The present paper provides a study of the second method, namely the catalytic reduction of 3β-acetoxy-7α-bromo-Δ⁵-steroids with tritium.[4] Labeling in the 7- position has the advantage that the label would "stick" in most biological experiments; *e.g.*, in contradistinction to 16-tritiated steroids, where oxidation to the 17-ketone would render the label labile by enolization of its α-ketone.

7α-Bromocholesterol acetate[5] was reduced catalytically[4] with a hydrogen-tritium mixture, containing one Curie (1 C) per mmole. The reduced product was saponified with methanolic sodium hydroxide solution and the cholesterol obtained had, after chromatographic purification, an activity of 0.75 C per mmole (calculated 0.5 C per mmole).

That the introduction of significantly more than one atom of tritium for one atom of bromine was accomplished without exception was substantiated by the palladium catalyzed reduction of a series of steroids, *e.g.*, 7α-bromo-3β-acetoxypregn-5-en-20-one, 7α-bromo-3β,17α-dihydroxypregn-5-en-20-one 3β-acetate and 7α-bromoandrostenolone acetate.[6]

The mechanism by which this catalytic hydrogenation took place with the usual stereospecificity might possibly have been brought about by coordination of the activated hydrogen atoms with palladium atoms in a d^2sp^3 fashion, whereby the attack of such "palladium hydride" would be sterically controlled. The attack of "palladium tritide" on the polarized C_7-Br_α bond might proceed through a cyclic intermediate formed from the less hindered α-side of the steroid molecule, which then in turn collapses by the heterolysis of the carbon-bromine bond, assisted by tritide ion transfer to C_7 and tritium cation transfer to the negatively charged bromine.[7]

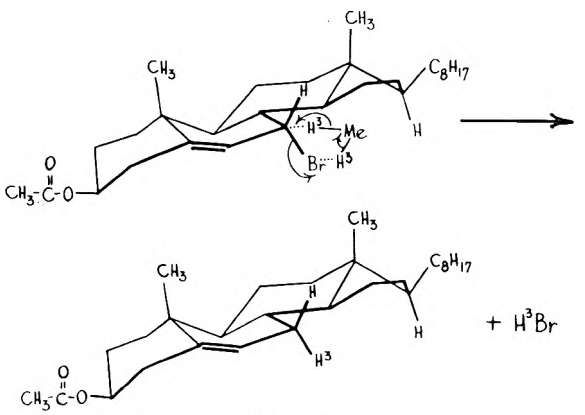

Figure 1

The axial orientation of the introduced isotope was established by reducing 7α-bromocholesterol acetate with pure deuterium.[4] Deuterium was chosen for this experiment because the use of tritium in a concentration sufficient for detection and interpretation of the conformation of the isotope by infrared analysis would have made the labeled product extremely unstable due to auto-

(1) Presented in part at the 135th Meeting of the American Chemical Society, Boston, Mass., April 1959. This investigation was supported in part by the AEC contract AT(30-1)-918.

(2) The reduction of ketones is omitted intentionally, since this would necessitate the rather lengthy and involved preparation of lithium aluminum tritide.

(3) D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **77**, 139 (1955).

(4) Compare D. K. Fukushima, S. Lieberman, and B. Praetz, *J. Am. Chem. Soc.*, **72**, 5205 (1950).

(5) K. Ziegler, A. Späth, W. Schumann, and E. Winkelmann, *Ann.*, **551**, 80 (1942). For the assignment of the α-orientation for the bromine atom see A. E. Bide, H. B. Henbest, E. R. H. Jones, and P. A. Wilkinson, *J. Chem. Soc.*, **1948**, 1788; L. F. Fieser, *Exp.*, **6**, 312 (1950).

(6) Marcel Gut and Milan Uskoković, *J. Org. Chem.*, **24**, 673 (1959).

(7) Compare F. J. McQuillin, *Chem. and Ind.*, **1951**, 251.

radiation, and because a determination of the orientation of deuterium substituents in steroids had already been accomplished.[8] The deuterated compound showed two weak bonds at 2155 and 2130 cm.$^{-1}$, characteristic of the axial orientation of the deuterium and in excellent agreement with the data in the literature,[8] while no absorption around 2170 cm.$^{-1}$ (equatorial orientation) could be observed.

This result is in agreement with the proposed mechanism, and a series of well known controlled oxidations was applied to the tritiated molecule to establish the relative concentration of the isotope in different positions.

Tritiated cholesterol (500 mC/mmole) was converted to cholesterol acetate (same specific activity) and the acetate was treated with *N*-bromosuccimimide[5] to give 7α-bromocholesterol acetate at a specific activity of 115 mC/mmole, the 7α-position therefore accounting for 77% of the total activity.

The conclusion that the total activity lost is derived from the 7α- position is based on spectral evidence (no equatorial isotope was detected). This suggests that the Wohl-Ziegler bromination proceeds in this case by preferential removal of the 7α-hydrogen by the succinimide radical followed by preferential formation of the 7α-bromo compound in the reaction of the allylic radical with *N*-bromosuccinimide.

Since only one hydrogen is removed in one step it seems proved that the original 7β-hydrogen is retained in the end product and thus the relation between the configuration of the bromine in the product and the configuration of the removed hydrogen established.

Oxidation of cholesterol (500 mC/mmole) with aluminum *tert*-butoxide[9] gave Δ^4-cholestenone containing 410 mC/mmole, indicating that the positions 2, 3, 4, and 6 contained at least 18% of the isotope. Finally, oxidation of cholesterol acetate (500 mC/mmole) with *tert*-butyl chromate[10] yielded 7-ketocholesterol acetate, which, after hydrolysis and thorough equilibration, yielded 7-ketocholesterol with an activity of 70 mC/mmole, demonstrating for the positions 8, 7, 6, and 4 an isotope content of 86%.

Although the incorporation of more than the calculated amount of isotope had been observed and discussed[3] before, it is noteworthy that milder conditions, such as palladium *vs.* platinum catalyst, neutral solution (ethyl acetate *vs.* acetic acid) and a much shortened reaction time bring about the same effect. Since the positions which have been analyzed for isotope content account for 104% (4, 6, 7, and 8 = 86% and 2, 3, 4, and 6 = 18%), there is little likelihood that there would be any isotope in ring C or D. Possible introduction of isotope into position 4 might be explained by the fact that the 7α-bromocholesterol acetate, which was not chromatographed prior to the reduction, might have contained minute amounts of 4β,7α-dibromocholesterol acetate.[11] The small amount of isotope (9%) found in positions 4, 6, 7β- and 8β- might result either from an isomerization of the bromide, which is easily brought about by polar solvents[12] or by the substitution of bromine for tritium in a S_N^2 fashion.

The two oxidation experiments lead to the conclusion that roughly 80% of the label is at the 7-position. The spectral evidence indicates that the bulk of the label must be at 7α.

EXPERIMENTAL

Radioactivity measurements were made on small aliquots by liquid scintillation in a Packard Tri-Carb spectrometer (Packard Instrument Co., La Grange, Ill.) with an error of ±10%. The infrared spectra were recorded on a Beckman model IR4 infrared spectrophotometer. Melting points were determined on a Fisher-Johns hot stage and are uncorrected. The chromatographic separations were made either on Davison Silica Gel Mesh 100-200 or on Woelm alumina, neutral, activity grade 1.

7α-Bromocholesterol acetate from cholesterol acetate. This reaction was carried out as described by Bide *et al.*[13] and the product melted at 107–109°.

Cholesterol-7α-H^3 from 7α-bromocholesterol acetate. This reaction was carried out as indicated by Fukushima *et al.*[4]

To a suspension of 3 g. of prereduced 5% palladium on calcium carbonate in 5 ml. of dry ethyl acetate was added 400 mg. of 7α-bromocholesterol acetate. Then the mixture was shaken for 35 min. together with a tritium-hydrogen mixture, containing 1 C per mmole. After removal of the residual gas the catalyst was filtered off, the solvent removed and the residue hydrolyzed by refluxing with 5% methanolic potassium hydroxide solution for 1 hr. After the usual workup and chromatography on alumina there was obtained 260 mg cholesterol-7α-H^3, which, after recrystallization from ethanol, gave 241 mg. pure cholesterol-7α-H^3, m.p. 148–149°. This material had an activity of 75 × 10^6 dps/mg. or 0.75 C/mmole. On subsequent equilibrations the specific activity remained the same.

7α-Bromocholesterol acetate from cholesterol-7α-H^3. Cholesterol-7α-H^3 (0.5 C/mmole) was acetylated with acetic anhydride-pyridine and the resulting crude acetate chromatographed on alumina. The pure material had the same specific activity as the free alcohol. The acetate was then treated with *N*-bromosuccinimide as indicated above and the bromo compound obtained was recrystallized twice from petroleum ether. The product melted 106–109° and had a specific activity of 115 mC/mmole.

Cholestenone-7α-H^3 from cholesterol-7α-H^3. Cholesterol-7α-H^3 (0.5 C/mmole) was oxidized with acetone and aluminum *tert*-butoxide.[10] The crude cholestenone was

(8) E. J. Corey, M. G. Howell, A. Boston, R. L. Young, and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 5036 (1956).

(9) R. V. Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).

(10) R. V. Oppenauer and H. Oberrauch, *Anal. assoc. quim. Argentina*, **37**, 246 (1949).

(11) Another reduction of very carefully purified 7α-bromocholesterol acetate (m.p. 110–111°) with tritium was shown to contain this time 9% of the radioactivity in position 3 + 4. Compare S. Lieberman and D. K. Fukushima, *J. Am. Chem. Soc.*, **72**, 5211 (1952).

(12) H. Schaltegger and F. X. Müllner, *Helv. Chim. Acta*, **34**, 1096 (1951).

(13) A. E. Bide, H. B. Henbest, E. R. H. Jones, R. W. Peevers, and P. A. Wilkinson, *J. Chem. Soc.*, **1948**, 1783.

equilibrated with alkali and then chromatographed on alumina and had a specific activity of 410 mC/mmole.

7-Ketocholesterol from cholesterol acetate-7α-H[3]. Cholesterol acetate-7α-H[3] was oxidized with *tert*-butyl chromate[10] and the crude 7-ketocholesterol acetate obtained was directly hydrolyzed by heating under reflux for 1 hr. in 1% methanolic potassium hydroxide solution. After the usual workup of the hydrolyzate, the product was chromatographed on silica gel and the pure material, obtained from the ethyl acetate-benzene eluates and recrystallized from methanol, had a specific activity of 70 mC/mmole.

Cholesterol-7α-D from 7α-bromocholesterol acetate. This reduction was carried out as described above, except that the palladium-on-calcium carbonate was prereduced with carrier free deuterium and that carrier free deuterium was used for the reduction proper. The deutero compound had two absorption bands in the C-D stretching region at 2155 and 2130 cm.$^{-1}$

3β-Hydroxypregn-5-en-20-one-7α-H[3] *from 3β-acetoxy-7α-bromopregn-5-en-20-one.* The 3β-acetoxy-7α-bromopregn-5-en-20-one was prepared as indicated by Antonucci *et al.*[14] and the bromo compound was then reduced with a tritium-hydrogen mixture containing 0.5 C/mmole as described for the 7α-bromocholesterol acetate. The crude reaction product was hydrolyzed, worked up in the usual manner and finally chromatographed on silica gel. The pure pregnenolone had a specific activity of 325 mC/mmole.

3β,17β-Dihydroxypregn-5-en-20-one-7α-H[3] *from 3β, 17α-dihydroxypregn-5-en-20-one 3β-acetate.* The bromination with *N*-bromosuccinimide followed by the reduction with tritium was carried out as described above. In this case the specific radioactivity amounted to 135% of the calculated amount.

3β-Hydroxyandrost-5-en-17-one-7α-H[3] *from 3β-acetoxy-7α-bromoandrost-5-en-17-one.* This preparation had already been described.[6]

SHREWSBURY, MASS.

(14) R. Antonucci, S. Bernstein, D. Giancola, and K. J. Sax, *J. Org. Chem.*, 16, 1126 (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY, AND THE LABORATORIES OF THE MEMPHIS CHEMICAL COMPANY, CAIRO]

Experiments with Furochromones. A Color Test for Hydroxyfurochromones and Related Substances with Uranyl Acetate

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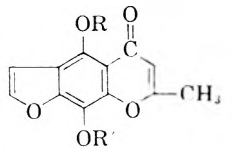
Syntheses for 8-(ω)-carboxymethoxy)-5-methoxy- (Ik) and 5-(ω-carboxymethoxy)-2-methylfuro-4′,5′,6,7-chromone (IId) are described. Whereas oxidation of IId with chromic acid effects the destruction of the furan ring with the formation of 5-(ω-carboxymethoxy)-6-formyl-7-hydroxy-2-methylchromone (IIIb), controlled oxidation with hydrogen peroxide in alkaline medium gives the corresponding furanosalicylic acid (Vc). The furanosalicylic acids Va–b and Vd are similarly obtained. Alkaline hydrolysis of Ik and IId results in the formation of the corresponding benzofuran derivatives (IVa–b) respectively. Hydroxyfurochromones and related substances (*cf.* Table I) give a color reaction with uranyl acetate solution. The importance of the free hydroxyl group in the *peri*- position to the carbonyl group is stressed (*cf.* Table II).

The recent publication of the preparation of a number of active water soluble derivatives of 2-methyl-5-hydroxy-8-methoxy-6,7-furochromone by the introduction of solubilizing groups, e.g., amino-,[1] or carboxyl group[2] prompts us to report some related work which we carried out some time ago.



Ia. R = R′ = CH_3
b. R = CH_2COOH; R′ = CH_3
c. R = H; R′ = CH_3
d. R = $CH_2COOC_2H_5$; R′ = CH_3
e. R = R′ = H
f. R = R′ = $CH_2COOC_2H_5$
g. R = R′ = CH_2COOH
h. R = H; R′ = CH_2COOH
i. R = H; R′ = $CH_2COOC_2H_5$
j. R = CH_3; R′ = $CH_2COOC_2H_5$
k. R = CH_3; R′ = CH_2COOH
l. R(R′) = $CH_2COOC_2H_5$; R′(R) = CH_2COOH.

The synthesis of 5-(ω-carboxymethoxy)-8-methoxy-2-methylfuro-4′,5′,6,7-chromone (Ib) by Mukerjee and Seshadri[3] now has been confirmed in our laboratories. The isomeric khellin derivative, namely, 8-(ω-carboxymethoxy)-5-methoxy-2-methylfuro-4′,5′,6,7-chromone (Ik) is now, similarly, prepared by allowing khellin-hydroquinone (Ie) to react with ethyl chloroacetate to yield Ii which, upon hydrolysis, produces Ik in an overall yield *ca.* 50% based on Ia used.

Refluxing 5,8-di(ω-carboxymethoxy)-2-methylfuro-4′,5′,6,7-chromone (Ig)[4] with 20% hydrochloric acid and/or 60% hydrobromic acid[5] does not accomplish the preparation of 8-(ω-carboxy-

(1) J. P. Fourneau, *Ann. Pharm. Franç.*, 11, 685 (1953).

(2) C. Musante and S. Fattuta, *Ann. Chim.* (Rome), 45, 918 (1955); L. Ritter and H. Kunsch, German Patent, 952,899, Nov. 22, 1956; *Chem. Abstr.*, 53, 2258 (1959).

(3) S. K. Mukerjee and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 35A, 323 (1952).

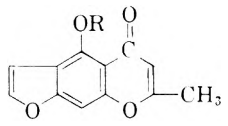
(4) A. Schönberg and A. Sina, *J. Am. Chem. Soc.*, 72, 3396 (1950).

(5) These are common reagents to effect selective demethylation of chromones in position 5, without causing an undesired rearrangement (*cf.* H. Abu-Shady and T. O. Soine, *J. Am. Pharm. Assoc.*, 41, 325 (1952); S. K. Mukerjee and T. R. Seshadri (ref. 3).

methoxy) - 5 - hydroxy - 2 - methyl - furo - 4′,5′,6,7-chromone (Ih). This may be attributed to the lower solubility of (Ig).

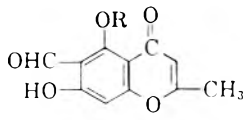
The stability of Ig toward these reagents is in contrast to the facile selective demethylation of Ia in position 5 by the same reagents, as well as by a number of other reagents.[6]

Similarly, 5-(ω-carboxymethoxy)-2-methylfuro-4′,5′,6,7-chromone (IId) has been prepared by allowing 5-norvisnagin (IIb), readily obtained by demethylation of the natural analog of Ia, namely, visnagin (IIa), to react with ethylchloroacetate, followed by hydrolysis of the intermediate ester (IIc).



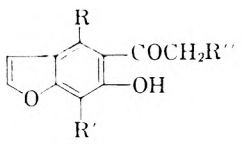
IIa. R = CH_3
b. R = H
c. R = $CH_2COOC_2H_5$
d. R = CH_2COOH

We now have found that when IId is treated with chromic acid, under the same experimental conditions described for the oxidation of IIa,[7] destruction of the furan ring and formation of 5-(ω-carboxymethoxy) - 6 - formyl - 7 - hydroxy - 2 - methylchromone (IIIb) takes place.

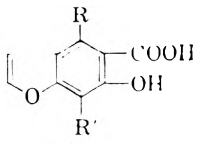


IIIa. R = CH_3
b. R = CH_2COOH

Recently, it has been shown that by controlled oxidation of Ia and IIa with hydrogen peroxide in alkaline medium[7] that 6-hydroxy-4,7-dimethoxybenzofuran-5-carboxylic acid (Ve) and 6-hydroxy-4-methoxybenzofuran-5-carboxylic acid (Vf) are obtained respectively. The furanosalicylic acid derivatives (Va-d) are now obtained, in a similar manner, by the controlled oxidation of Ig, Ik, IId, and Ib respectively.



IV

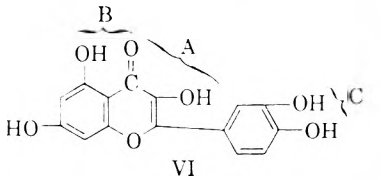


V

IVa. R = OCH_3; R′ = OCH_2COOH; R″ = H
b. R = OCH_2COOH; R′ = H; R″ = H
c. R = R′ = OCH_3; R″ = H
d. R = OCH_3; R′ = R″ = H
e. R = R′ = OCH_3; R″ = $COCH_3$
f. R = OCH_3; R′ = H; R″ = $COCH_3$
g. R = OCH_3; R′ = Br; R″ = H
Va. R = R′ = OCH_2COOH
b. R = OCH_3; R′ = OCH_2COOH
c. R = OCH_2COOH; R′ = H
d. R = OCH_2COOH; R′ = OCH_3
e. R = R′ = OCH_3
f. R = OCH_3; R′ = H

While the alkaline hydrolysis of Ia and IIa to khellinone (IVc) and visnaginone (IVd) respectively are already known,[8] the hydrolysis of the furochromones described in this paper has not been investigated. Thus, when Ik and IId are subjected to alkaline hydrolysis, the corresponding benzofuran derivatives (IVa-b) are obtained respectively.

Color Test. Color tests have been occasionally described for hydroxyflavones having a hydroxyl group in the *a-* or *peri*-position to the carbonyl group.[9,10] Their chelating ability has recently been studied by Hörhammer and Hänsel (*cf.* VI).[11,12]



VI

With a view to finding a color reaction for the naturally occurring hydroxyfurochromones[13] and hydroxychromones,[14] having a free hydroxyl group in the position *peri* to the carbonyl group,[15] we now have undertaken the study of the behavior of a number of these compounds toward uranyl acetate solution. Thus, when 2 ml. of a 0.05% ethyl alcohol solution (ethyl alcohol for spectroscopic measurement) of the chromone derivative was treated with 1 ml. of 0.1% aqueous uranyl acetate solution, a

(6) A. Schönberg and G. Aziz, *J. Am. Chem. Soc.*, **75**, 3265 (1953); W. Asker, A. F. A. M. Shalaby, and S. M. A. D. Zayed, *J. Org. Chem.*, **23**, 1781 (1958); N. A. Starkovsky, *Egyptian J. Chem.* **2**, 111 (1959).

(7) A. Schönberg, N. Badran, and N. A. Starkowsky, *J. Am. Chem. Soc.*, **75**, 4992 (1953).

(8) P. Fantl and S. I. Salem, *Biochem. Zeit*, **226**, 166 (1930); E. Späth and W. Gruber, *Ber.*, **74**, 1492 (1941).

(9) K. Tauböck, *Naturwissenschaften*, **30**, 439 (1942).

(10) C. W. Wilson, *J. Am. Chem. Soc.*, **61**, 2303 (1939).

(11) L. Hörhammer and R. Hänsel, *Arch. Pharm.*, **285**, 438 (1952); **286**, 425 (1953).

(12) L. Hörhammer, R. Hänsel, and W. Hieber, *Naturwissenschaften*, **41**, 529 (1954).

(13) Khellin (Ia) gives a intense red-violet color with potassium or sodium hydroxide pellets in the presence of little water (*cf.* Abd El-Rahman, masters' thesis, Fouad I University, Cairo (1943); I. Fahmy, N. Badran, and M. Messeid, *J. Pharm. Pharmacol.*, I, 529, 535 (1949). The application of this test for a colorimetric estimation of khellin (G. Anrep, M. Kenawy, G. Barsoum, and I. Fahmy, *Gazz. Fac. Med.*, Cairo, **14**, 1 (1947)) has been questioned (*cf.* A. Schönberg and A. Sina, *J. Chem. Soc.*, 3344 (1950)).

(14) The color test for 2-methylchromones with *m*-dinitrobenzene in the presence of dilute alkali has been reported to be inconclusive in the case of 2-methylchromones containing a free phenolic group [A. Schönberg and M. M. Sidky, *J. Org. Chem.*, **21**, 476 (1956)]. This may result because many of these chromones dissolve in alkali with a reddish-brown color [*Cf.* A. Schönberg and A. Sina, *J. Chem. Soc.*, 3344 (1950)].

(15) The possibility of chelation in furochromones, having a free hydroxyl group in position *peri* to the carbonyl group, *e.g.*, 5-norkhellin (VIIa), has recently been discussed (*cf.* A. Schönberg and G. Aziz, *J. Am. Chem. Soc.*, **75**, 3265 (1953)).

color developed, followed by the separation of an insoluble metal salt complex, upon dilution with water in some cases (cf. Table I). The limit for the detection of norvisviagin (IIb), taken as an example, with urnayl acetate solution is 5γ/ml., and the limit for the detection of uranium in uranyl acetate solution with IIb reagent is 5.6γ/ml. The color formed is readily destroyed on addition of mineral acids and even with an excess of dilute acetic acid solution, as well as with alkaline buffers (*p*H 9 and above) and with aqueous sodium hydroxide solution (4%), with the formation of the yellow sodium salt. Hydroxyfurochromones and hydroxychromones, listed in Table I, give no color with boric-citric or boric-oxalic acids reagents.[9,10]

TABLE I

COMPOUNDS GIVING A POSITIVE TEST[a]

Compound	Color
5-Norkhellin (VIIa)[d]	Red, green, violet-brown[b]
5-Norvisnagin (VIIb)[e]	Red, green, scarlet-red[b]
8-(Carbethoxymethoxy)-5-hydroxy-2-methylfuro-4',5',6,7-chromone (VIIc)	Red, green, orange-red[b]
5-Norkhellol (VIId)[f]	Red, green, deep-red
8-(*N*,*N*-Diethylaminoethoxy)-5-hydroxy-2-methylfuro-4',5',6,7-chromone (VIIe)[g]	Red, green
5,8-Dinorkhellin (VIIf)[h]	Violet-red, green changing immediately to red-brown, brown
5,6-Di-nor-isokhellin (VIII)[i]	Deep wine-red, green, violet-brown
6-Formyl-5-hydroxy-7-methoxy-2-methylchromone (IXc)	Bulky yellow precipitate, wine-red, yellow
6-Formyl-5,7-dihydroxy-2-methylchromone (IXe)[j]	Yellow precipitate, wine-red, yellow
Eugenitin (IXg)[j]	Red, deep violet-black, deep orange
7-Nor-eugenitin (IXh)[j]	Red, deep violet-black, buff-brown
5,6,7-Trihydroxy-2-methylchromone (IXa)[k]	Wine-red, brown, pale-brown
5,6,7-Trihydroxyflavone (IXb)[l]	Red-brown, brownish black, brown
6,7-Dihydroxy-5-methoxy-2-methylchromone (IXo)[m]	Brick-red, deep green, orange-brown
6,7-Dihydroxy-5-methoxyflavone (IXp)[n]	Red-brown, deep green, red
o-Hydroxyacetophenone	Yellow, violet
2-Hydroxy-4-methoxyacetophenone	Yellow, red-violet
ω-Acetokhellinone (IVe)	Yellow, red
ω-Acetovisnaginone (IVf)	Yellow, red
Khellinone (IVc)[o]	Orange, green
Visnaginone (IVd)[o]	Yellow, green
7-Bromovisnaginone (IVg)	Brownish-yellow, green

The importance of the free hydroxyl group in the position *peri* to the carbonyl group is stressed, as hydroxychromones with protected hydroxyl groups in the *peri* position give no color (*cf.* Table II). Morover, although the two isomeric chromones, 6-formyl-5-hydroxy-7-methoxy- (IXc) and 6-formyl-5-methoxy-7-hydroxy-2-methylchromone (IXd), give a wine-red color with ferric chloride, only IXc gives a bulky yellow precipitate with uranyl acetate solution.

TABLE II

COMPOUNDS GIVING A NEGATIVE TEST[c]

Compound	Color
6-Formyl-5-methoxy-7-hydroxy-2-methylchromone (IXd)[j]	Wine-red
6-Formyl-7-hydroxy-5-methoxy-8-nitro-2-methylchromone (IXi)[j]	Orange
6-Formyl-7-hydroxy-5-methoxy-2-hydroxymethylchromone (IXj)[m]	Wine-red
6-Formyl-7-hydroxy-5-(ω-carboxy-methoxy)-2-methylchromone (IXk)	Wine-red
6-Formyl-7-hydroxy-5-methoxyflavone (IXl)[n]	Red
6-Formyl-7-hydroxy-5-methoxy-8-bromo-2-methylchromone (IXm)[m]	Wine-red
6-Hydroxy-5,7-dimethoxy-2-methylchromone (IXn)[p]	Pale-brown developed gradually

[a] The colors given refer to the color developed with uranyl acetate, ferric chloride solution, and the color of the precipitate formed after dilution of the reaction mixture of uranyl acetate and the chromone derivative with water, respectively. [b] The precipitate is readily extractable with chloroform to give deep-red solution. [c] The given color refers to the color developed with aqueous ferric chloride solution. [d] See ref. 3, 5, 6. [e] A. Schönberg and N. Badran, *J. Am. Chem. Soc.*, **73**, 2960 (1951). [f] See ref. 6. [g] See ref. 1. [h] V. V. S. Murti and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **30A**, 107 (1949). [i] J. R. Clarke and A. Robertson, *J. Chem. Soc.*, 302 (1949). [j] See ref. 7. [k] S. K. Mukerjee and T. R. Seshadri, *J. Sci. Ind. Research (India)*, **13B**, 400 (1954); D. K. Charkravorty, S. K. Mukerjee, V. V. S. Murti, and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **35A**, 34 (1952). [l] See ref. 18. [m] A. Schönberg, N. Badran, and N. A. Starkowsky, *J. Am. Chem. Soc.*, **77**, 1019 (1955). [n] A. Schönberg, N. Badran, and N. A. Starkowsky, *J. Am. Chem. Soc.*, **77**, 5390 (1955). [o] See ref. 8. [p] See ref. 17.

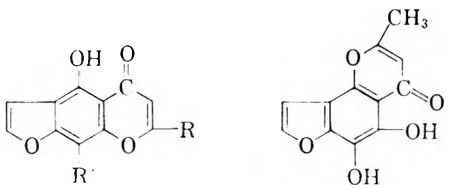
5,6,7-Trihydroxy-2-methylchromone (IXa) and 5,6,7-trihydroxyflavone (IXb), similar to IXe and IXf, have two chelate forming groups in the molecule and can form complexes with uranyl acetate. In contrast to the behavior of IXd and IXl, which give no color, red precipitates are formed in the case of IXo–p (without free hydroxyl groups in the *peri* position) with the same reagent, showing that the hydroxyl groups in positions 6 and 7 are capable of forming chelates,[16] as IXn gives no color.

o-Hydroxyacetophenone and IVc–g are ring-opened analogs of the 5-hydroxychromones and have the same chelating structure. Thus, a yellow

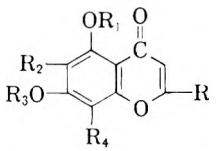
(16) *Cf.* The unability of polyhydroxyflavanols, *e.g.* VI, to form chelates by group C (ref. 12).

color developed when their cold solutions were treated with uranyl acetate solution (*cf.* Table I). Acetophenone gives no color with the same reagent.

The application of the color development for a colorometric estimation of hydroxyfurochromones (VIIa–c) and the spectrophotometrical study of the chloroform-soluble complex formation of these chromones with uranyl acetate is under investigation. This color test is of value for structural study.



VIIa. R = CH_3; R′ = OCH_3
b. R = CH_3; R′ = H
c. R = CH_3; R′ = $OCH_2COOC_2H_5$
d. R = CH_2OH; R′ = H
e. R = CH_3; R′ = $OCH_2CH_2N(C_2H_5)_2$
f. R = CH_3; R′ = OH



IXa. R = CH_3; R_1 = R_3 = R_4 = H; R_2 = OH
b. R = C_6H_5; R_1 = R_3 = R_4 = H; R_2 = OH
c. R = R_3 = CH_3; R = R_1 = H; R_2 = CHO
d. R = R_1 = CH_3; R_2 = CHO; R_3 = R_4 = H
e. R = CH_3; R_2 = CHO; R_1 = R_3 = R_4 = H
f. R = CH_3; R_2 = CHO; R_1 = R_3 = H; R_4 = NO_2
g. R = R_2 = R_3 = CH_3; R_1 = R_4 = H
h. R = R_2 = CH_3; R_1 = R_3 = R_4 = H
i. R = R_1 = CH_3; R_2 = CHO; R_3 = H; R_4 = NO_2
j. R = CH_2OH; R_1 = CH_3; R_2 = CHO; R_3 = R_4 = H
k. R = CH_3; R_1 = CH_2COOH; R_2 = CHO; R_3 = R_4 = H
l. R = C_6H_5; R_1 = CH_3; R_2 = CHO; R_3 = R_4 = H
m. R = R_1 = CH_3; R_2 = CHO; R_3 = H; R_4 = Br
n. R = R_1 = R_3 = CH_3; R_2 = OH; R_4 = H
o. R = R_1 = CH_3; R_2 = R_3 = OH; R_4 = H
p. R = C_6H_5; R_1 = CH_3; R_2 = R_3 = OH; R_4 = OH

EXPERIMENTAL[17]

5,8-Di-(ω-carbethoxymethoxy)-2-methylfuro-4′,5′,6,7-chromone (If). To a solution of 8 g. of 5,8-di-norkhellin (Ie)[4] in 100 ml. of dry acetone was added 8 g. of anhydrous potassium carbonate, 6.5 ml. of ethylchloroacetate, and 0.5 g. of sodium iodide. The reaction mixture was refluxed for 12 hr., then 4 g. of anhydrous potassium carbonate, 2.5 ml. of ethylchloroacetate and 40 ml. of acetone were added, and refluxing was extended for a further period of 28 hr. Acetone was then driven off and the residue was digested with cold water and the reaction mixture made acidic to methyl red by addition of dilute acetic acid. The colorless solid that separated on cooling was filtered off, washed with water, and extracted with cold sodium carbonate solution (5%). The insoluble part was crystallized from 50% ethanol m.p. 125–127°, and was identified as If (m.p. and mixed m.p.[4]); yield was *ca.* 6 g.

The sodium carbonate solution was treated with cold dilute hydrochloric acid, and the solid obtained gave upon crystallization from ethyl alcohol colorless crystals, m.p. 198–200°.

Anal. Calcd. for $C_{18}H_{16}O_9$: C, 57.44; H, 4.25. Found: C, 57.40; H, 4.23.

5(8)-(ω-Carbethoxymethoxy)-8(5)-(w-carboxymethoxy)-2-methylfuro-4′,5′,6,7-chromone (Il) is soluble in sodium carbonate solution (5%) and is almost insoluble in sodium bicarbonate solution (5%). It gives a crimson-red color when treated with sodium hydroxide pellets.[18]

The free dibasic acid (Ig) was readily obtained from either If or Il upon treatment with dilute sulfuric acid according to the procedure described by Schönberg and Sina.[4] Ig was unaffected when refluxed with 20% hydrochloric acid and/or with hydrobromic acid (60%) for 15 min.

8-(ω-Carbethoxymethoxy)-5-hydroxy-2-methylfuro-4′,5′,6,7-chromone (Ii) was obtained according to the procedure described above for the preparation of If. The reaction mixture was refluxed for 12 hr. only; acetone was driven off and the solution of the reaction residue in water was acidified with dilute acetic acid. The solid obtained was filtered off, washed with water, and crystallized from dilute ethyl alcohol as yellow plates, m.p. 129–130°. Yield is *ca.* 7 g.

Anal. Calcd. for $C_{16}H_{14}O_7$: C, 60.37; H, 4.40. Found: C, 60.30; H, 4.53.

8-(ω-Carboxymethoxy)-5-hydroxy-2-methylfuro-4′,5′,6,7-chromone (Ih). A solution of 1 g. of Ii in 25 ml. of glacial acetic acid was treated with a mixture of 20 ml. of water and 1 ml. of concentrated sulfuric acid. The reaction mixture was refluxed for 20 min. and cooled. The solid obtained was collected by filtration and was crystallized from ethyl alcohol as colorless crystals (0.7 g.), m.p. 220–222°.

Anal. Calcd. for $C_{14}H_{10}O_7$: C, 57.93; H, 3.44. Found: C, 57.88; H, 3.57.

8-(ω-Carbethoxymethoxy)-5-methoxy-2-methylfuro-4′,5′,6,7-chromone (Ij). A mixture of 1 g. of Ii, in 40 ml. of dry acetone, 3 g. of anhydrous potassium carbonate, and 2 ml. of methyl iodide, was refluxed for 20 hr. It was filtered and evaporated to dryness. The solid was crystallized from 20% ethyl alcohol as colorless crystals (*ca.* 1.0 g.), m.p. 110–112°. Ij gives a red color when treated with sodium hydroxide pellets.

Anal. Calcd. for $C_{17}H_{16}O_7$: C, 61.44; H, 4.81. Found: C, 61.52; H, 4.98.

8-(ω-Carboxymethoxy)-5-methoxy-2-methylfuro-4′,5′,6,7-chromone (Ik). Hydrolysis of 1 g. of Ij was carried out as described for Ih. The crude Ik, thus obtained, was crystallized from ethyl alcohol as colorless needles (*ca.* 0.75 g.), m.p. 278°.

Anal. Calcd. for $C_{15}H_{12}O_7$: C, 59.21; H, 3.94. Found: C, 59.44; H, 3.94. It is soluble in sodium carbonate solution with effervescence and gives a red color with sodium hydroxide pellets.

5-(ω-Carbethoxymethoxy)-2-methylfuro-4′,5′,6,7-chromone (IIc). 5-Norvisnagin (IIb)[17] (1 g.) was treated with ethylchloroacetate as described for If to give after crystallization from ethyl alcohol, 1 g. of colorless needles of IIc, m.p. 134–135°.

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.63. Found: C, 63.59; H, 4.72. It gives a red color with sodium hydroxide pellets.

5-(ω-Carboxymethoxy)-2-methylfuro-4′,5′,6,7-chromone (IId). One gram of IIc was treated with sulfuric acid as described above to give an almost quantitative yield of IId. It was crystallized from glacial acetic acid as colorless plates, m.p. 246–248°, and gives a violet color with sodium hydroxide pellets.

Anal. Calcd. for $C_{14}H_{10}O_6$: C, 61.31; H, 3.65. Found: C, 61.78; H, 3.86.

Oxidation of IId. (a) *Chromic acid.* Oxidation of 1 g. of IId with chromic acid according to the procedure described for IIa[7] gave colorless needles of 5-(ω-carboxymethoxy)-6-

(17) All melting points are uncorrected. Microanalysis was carried out by Dr. A. Bernhardt, Mülheim, and Drs. G. Weiler and F. Strauss, Oxford.

(18) A. Schönberg and A. Sina, *J. Chem. Soc.*, 3344 (1950).

formyl-7-hydroxy-2-methylchromone (IIIb) from ethyl alcohol, m.p. 202–204° (dec.). Yield was *ca.* 65%.

Anal. Calcd. for $C_{13}H_{10}O_7$: C, 56.11; H, 3.59. Found: C, 55.83; H, 3.76.

(b) *Hydrogen peroxide.* Oxidation of IId with hydrogen peroxide in alkaline medium according to the procedure described for the oxidation of IIa[7] led to the formation of yellowish needles of 4-(ω-carboxymethoxy)-6-hydroxybenzofuran-5-carboxylic acid (Vc), m.p. 229–230° (dec.). It gives a blue color when its alcoholic solution is treated with aqueous ferric chloride solution.

Anal. Calcd. for $C_{11}H_8O_7$: C, 52.38; H, 3.17. Found: C, 52.35; H, 3.58.

Oxidation with hydrogen peroxide in alkaline medium. (a) Ig. One gram of Ig gave upon oxidation with hydrogen peroxide in alkaline medium[7] 4,7-di-(ω-carboxymethoxy)-6-hydroxybenzofuran-5-carboxylic acid (Va) as colorless needles from water (*ca.* 0.5 g.), m.p. 222–223° (dec.). It gives a blue color with ferric chloride.

Anal. Calcd. for $C_{13}H_{10}O_{10}$, H_2O: C, 45.34; H, 3.48. Found: C, 45.42; H, 3.70.

(b) Ik. Similarly, oxidation of 1 g. of Ik with the same reagents under the same experimental conditions, led to the formation of colorless needles from ethyl alcohol (*ca.* 0.6 g.) of 7-(ω-carboxymethoxy)-6-hydroxy-4-methoxybenzofuran-5-carboxylic acid (Vb), m.p. 192–194° (dec.). It gives a blue color with ferric chloride.

Anal. Calcd. for $C_{12}H_{10}O_8$: C, 51.06; H, 3.54. Found: C, 51.28; H, 4.18.

(c) Ib. Oxidation of 1 g. of Ib[2] with hydrogen peroxide, as described for Ig, led to the formation of colorless needles from ethyl alcohol of 4-(ω-carboxymethoxy)-6-hydroxy-7-methoxybenzofuran-5-carboxylic acid (Vd) (*ca.* 0.5 g.), m.p. 202–203° (dec.). It gives a blue color with ferric chloride.

Anal. Calcd. for $C_{12}H_{10}O_8$: C, 51.06; H, 3.54. Found: C, 51.03; H, 4.18.

Alkaline hydrolysis. (a) Ik. Refluxing 1 g. of Ik with aqueous sodium hydroxide solution (40 ml.; 15%) for 2 hr., followed by cooling the reaction mixture and acidification with cold dilute hydrochloric acid, gave pale-yellow needles from dilute ethyl alcohol of 5-acetyl-7-(ω-carboxymethoxy)-6-hydroxy-4-methoxybenzofuran (IVa) (ca. 0.6 g.), m.p. 171–172°. It gives a green color with ferric chloride.

Anal. Calcd. for $C_{13}H_{12}O_7$: C, 55.71; H, 4.28. Found: C, 55.73; H, 4.61.

(b) IId. Similarly, treatment of 1 g. of IId with sodium hydroxide under the above mentioned conditions led to the formation of canary-yellow needles from ethyl alcohol (*ca.* 0.4 g.) of 5-acetyl-4-(ω-carboxymethoxy)-6-hydroxybenzofuran (IVb), m.p. 217–218° (dec.). It gives a blue color with ferric chloride.

Anal. Calcd. for $C_{12}H_{10}O_8$: C, 57.60; H, 4.00. Found: C, 57.51; H, 4.10.

Preparation of 6-Formyl-5-hydroxy-7-methoxy-2-methylchromone (IXc). One half gram of 6-formyl-5,7-dimethoxy-2-methylchromone[7] was refluxed for 1 hr. with a mixture of 10 ml. of concentrated hydrochloric acid and 10 ml. of water. The solid obtained upon cooling the reaction mixture was collected and crystallized from ethyl alcohol as colorless crystals (250 mg.), m.p. 250° (dec.).

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.53; H, 4.27. Found: C, 61.63; H, 4.14.

IXc is insoluble in aqueous sodium hydroxide solution (5%) and acquires a yellow color when treated with 50% sulfuric acid. It gives a violet-red color with ferric chloride.

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[FROM THE DEPARTMENT OF CHEMISTRY AND PHARMACEUTICAL CHEMISTRY, MEDICAL COLLEGE OF VIRGINIA]

Palladium Catalysts. X.[1,2] Substrate-Specific and Stereospecific Centers

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It is postulated that a hydrogenation catalyst prepared by depositing palladium on a suitable carrier consists of centers differing from each other not only in their reactivity toward specific substrates but toward specific stereoisomers of those substrates. Thus, centers effective for the hydrogenation of a given compound differ appreciably from those effective for another compound or even for a stereoisomer. Conditions are outlined for determining the validity of these postulates, and experimental results thus far obtained are in harmony therewith. For example, with identical catalysts the Schiff base formed with benzylamine and a racemic acyloin takes up hydrogen considerably faster than does the Schiff base formed with the D(−)acyloin. Other examples are also given.

Reactions depending on heterogenous catalysis are surface phenomena.[4] Studies of adsorption, reaction kinetics, poisoning, and promoter action lead to the conclusion that the catalytically active surface is nonuniform and that not all areas are equally active.[5]

In previous papers of this series it has been found that for palladium-on-carbon the catalytic properties are influenced by factors such as the presence of other metals,[6] by the ratio of metal to carrier,[7] and by the nature of the anion present when the pal-

(1) For number IX see R. W. Meschke and W. H. Hartung, *J. Org. Chem.* **25**, 137 (1960).

(2) This investigation was supported by Public Health Service Grant RG-5895, National Institutes of Health. For this assistance the authors express grateful appreciation.

(3) Present address: School of Pharmacy, University of South Carolina, Columbia, S. C.

(4) H. S. Taylor and R. M. Burns, *J. Am. Chem. Soc.* **43**, 1284 (1921).

(5) A. B. Kistiakowsky, E. W. Flosdorf, and H. S. Taylor, *J. Am. Chem. Soc.* **49**, 2200 (1927); H. S. Taylor and S. C. Liang, *J. Am. Chem. Soc.*, **69**, 1306, 2989 (1947); R. N. Pease and L. Stewart, *J. Am. Chem. Soc.*, **47**, 1235 (1925); E. B. Maxted *et al.*, *J. Chem. Soc.* **1933**, 502; **1935**, 393; 1938, 1228, 2071; W. W. Russell, *J. Chem. Ed.* **22**, 163 (1945).

(6) W. H. Hartung and Y. T. Chang, *J. Am. Chem. Soc.* **74**, 5927 (1952).

(7) J. G. Young and W. H. Hartung, *J. Org. Chem.* **18**, 1659 (1953).

ladium is deposited;[8] and the kinetics of the reaction may be further modified by the environment in which the reaction proceeds and the product formed.[1,8,9]

These observations coupled with the frequent comparison of heterogeneous catalysis with enzymic processes, especially in view of what is known about the stereochemical pathway of catalytic reactions,[10] raise the question to what extent *in vitro* catalytic processes may be compared with *in vivo* enzymic processes, many of which are known to be highly specific with respect to chemical function and stereo isomers. Thus, in catalysis may there not be a center which is active for one type of compound but quite inert for one of different structure or even configuration? For example, if one expands the "three-point" concept of Ogston[11] (the "multiplet" theory[12] though a bit more complex, may be equally satisfactorily adapted), then the hypothetically different sites in a catalyst may be represented as in Fig. 1.

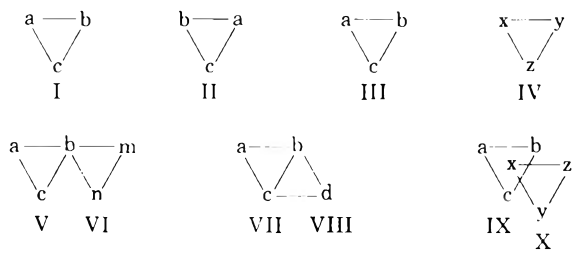

Fig. 1. Hypothetical active sites on a catalyst surface

I is the mirror image of II, randomly present in equal numbers and acting on a symmetrical substrate, e.g. α-oximino propiophenone,[13] jointly afford racemic norephedrine. With an unsymmetrical substate however, for example, the Schiff base resulting from the reaction of methylamine with D(−)acetylphenyl-carbinol, an intermediate which is reduced to natural ephedrine according to the procedure of Hildebrandt and Klavehn,[14] only one of the pair of sites will function. This results in the formation of an optically pure product, while the other enantiomorphous site will be inoperative. III will hypothetically be active for a substrate bearing the same functional groups as the I-specific substrate but with different molecular dimensions. IV is the active site for a different type of compound. V is identical with I, but with point *b* also shared by VI, will be inactive when VI is functioning; that is, V and VI, each active for its respective substrate, cannot function simultaneously. A similar condition exists for the VII-VIII Siamese twin pair and in the IX-X complex where one site is intertwined with another.

The validity of these postulates may be tested by properly designed experiments. It is expected that for a given substrate A only sites I, for example, are functional; all the others are nonfunctional. A properly designed catalyst for modifying optically active A must then have substantially only I sites operating fully throughout the experiment. In the same catalyst another substrate B will be affected by another center, for example IV; with only B present IV alone will be active and all IV-type sites will be working to full capacity. For each of these two cases it is possible to measure the rate at which hydrogen is taken up. If, now, both substrates A and B are present, then the I-site will reduce A at the rate already measured and the IV-site will reduce B; thus the uptake of hydrogen under ideal conditions will be additive. However, since there is no way of knowing what proportion of the V-VI, VII-VIII, and IX-X centers there may be, the rate probably will not be ideally additive, but it should be faster than the rate for either A or B alone.

One may also expect some sites to be highly specific and others less so. Perhaps here is an analogy of cholinesterase as compared to pseudocholinesterase; the former is specific for acetylcholine and the other is more general for the hydrolysis of esters.

Further, if these concepts are valid, then perhaps the chemist may aspire to the preparation of stereospecific catalysts, for example, a catalyst with I-type arrangement without the presence of the enantiomorphous II-type. This is not an idle hope, for already Akabori,[15] by depositing palladium on silk or acetylated silk fibroin, obtained a catalyst which reduces 4-benzyl-2-methyloxazol-5-one to phenylalanine with $[\alpha]_D$ 23.2°.

Few of the readily available compounds lend themselves for experimental examination of the validity of these proposals. However, the results thus far observed and reported here are in harmony with the postulates and sufficiently encouraging to warrant further studies; for these it will be necessary to synthesize substrate reagents that are not readily available.

Kinetic studies were made of available compounds which may be hydrogenated at comparable rates. These were measured according to the procedure described by Meschke.[1] The data are given graphically and are compared in Figs. 2-6.

Fig. 2 deals with the first twenty minutes of the reduction of five millimoles each of fumaric acid

(8) W. D. Cash, F. T. Semeniuk, and W. H. Hartung, *J. Org. Chem.* **21**, 999 (1956).

(9) Z. Csuros, *Muegyetemi Kozlemenyek* **1947**, 110; *Chem. Abstr.* **42**, 3726 (1948).

(10) R. L. Burwell, *Chem. Rev.* **57**, 895 (1957).

(11) A. G. Ogston, *Nature* **162**, 963 (1948).

(12) A. A. Balandin, *Advances in Catalysis*, Vol. X, Academic Press, New York and London, 96-129 (1958).

(13) Y. T. Chang and W. H. Hartung, *J. Am. Chem. Soc.* **75**, 89 (1953).

(14) G. Hildebrandt and W. Klavehn, U.S. Patent **1,956,950**, May 1, 1934; *Chem. Abstr.*, **28**, 4072 (1934).

(15) S. Akabori *et al.*, *Nature*, **178**, 323 (1956). *J. Chem. Soc. Japan* **77**, 1374 (1956); **78**, 886 (1957) *Biochemistry* (English translation from Russian) **22**, 147 (1957).

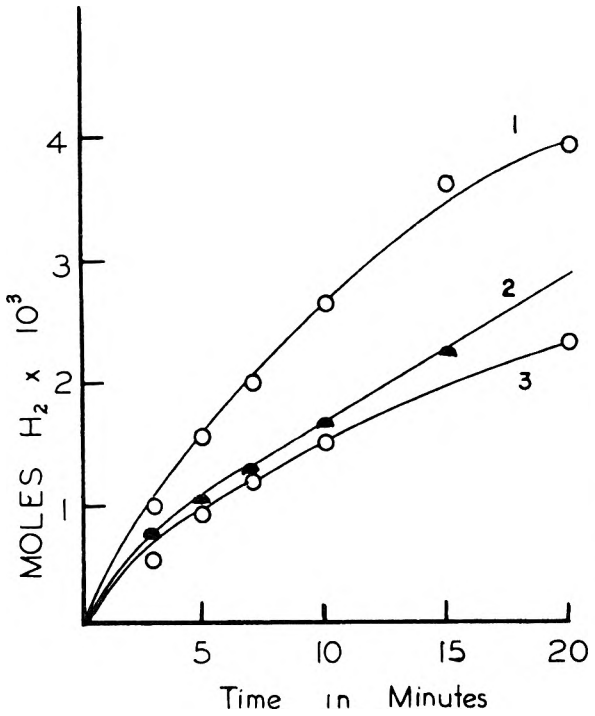

Fig. 2. Reduction of benzyl acetate and of fumaric acid, 5 millimoles in ethanol with 0.5 g. of A-12.5 catalyst. Curve 1, 2.5 millimoles benzyl acetate and 2.5 millimoles fumaric acid. Curve 2, 5 millimoles of fumaric acid. Curve 3, 5 millimoles of benzyl acetate

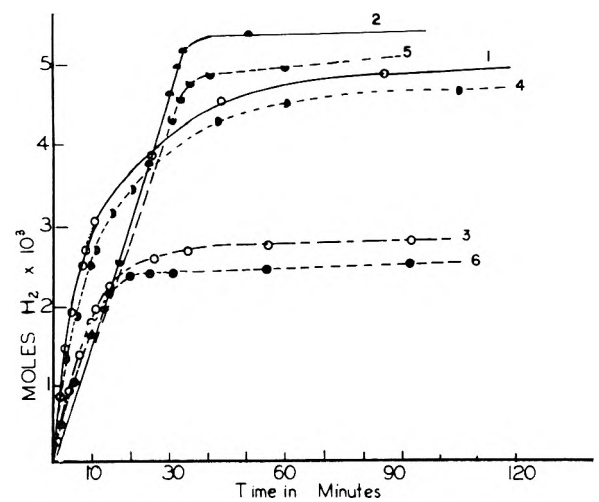

Fig. 3. Reduction of benzyl acetate and fumaric acid, 5 millimoles in ethanol with 0.5 g. of A-12.5 catalyst. Curves 1 and 4, 2.5 millimoles benzyl acetate and 2.5 millimoles fumaric acid. Curves 2 and 5, 5.0 millimoles of fumaric acid. Curves 3 and 6, 5.0 millimoles of benzyl acetate

and the hydrogenolysis of benzyl acetate. For this period of time, the two rates are quite comparable. Curve 1 shows the rate of hydrogen uptake with two and one half millimoles of fumaric acid and two and one half millimoles of benzyl acetate. It will be noted that this is significantly faster, although not additive, than the rates for the two substrates separately. In Fig. 3, curves 1, 2, and 3 are identical

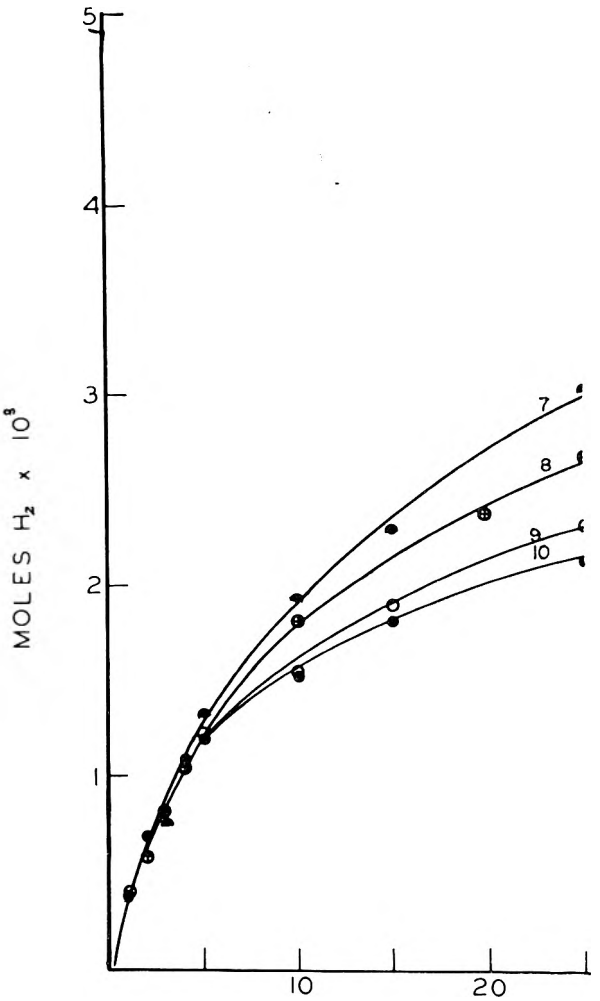

Fig. 4. Reduction of 4-methyl-2-pentene, 5 millimoles in ethanol with 0.5 g. of A-12.5 catalyst. Curve 10, 5 millimoles of *cis* isomer. Curve 9, 5 millimoles of *trans* isomer. Curve 7 and 8, 2.5 millimoles of *cis* isomer and 2.5 millimoles of *trans* isomer

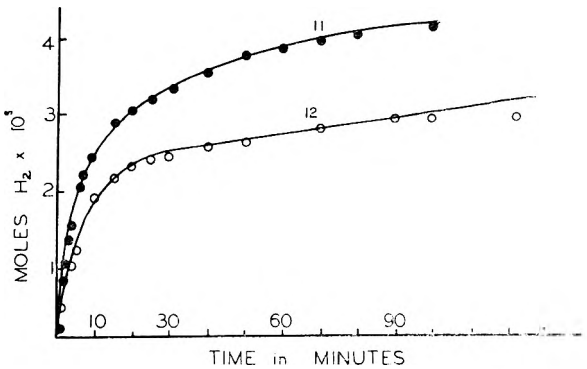

Fig. 5. Reduction of Schiff base from benzylamine and *m*-hydroxyphenylacetylcarbinol, 5 millimoles in ethanol with 0.5 g. of A-100 catalyst. Curve 11, schiff base from racemic acyloin. Curve 12, Schiff base from D-(−)-acyloin

with those of Fig. 2. Fig. 3 also gives curves for typical duplicates to show that the data are quite reproducible. These experiments have been repeated many times with the same results, thus giving them validity.

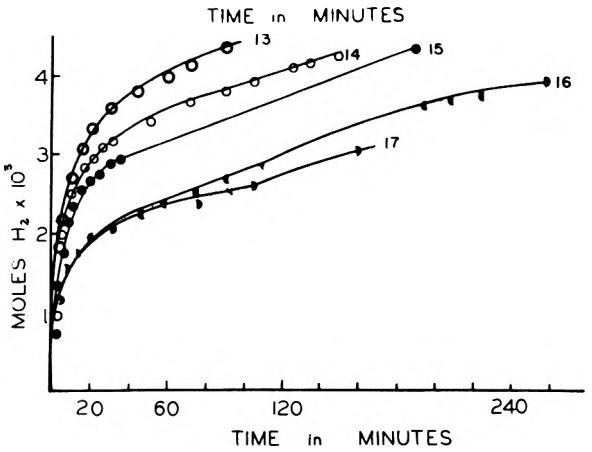

Fig. 6. Reduction of Schiff base from benzylamine and *m*-hydroxyphenylacetylcarbinol in ethanol. Curve 13, Schiff base from d(−)-acyloin with 1 g. of A-100 catalyst. Curves 14 and 15, Schiff base from racemic acyloin with 0.5 g. of A-100 catalyst. Curves 16 and 17, Schiff base from d(−)-acyloin with 0.5 g. A-100 catalyst

Fig. 4 summarizes the reduction of isomeric 4-methyl-2-pentenes during the first 25 minutes of the reaction. It is seen that both the *cis* and the *trans* isomers, curves 10 and 9, respectively, take up hydrogen at a slower rate than an equimolar mixture of the two, curves 7 and 8.

Hydrogenation of fumaric and maleic acids shows practically identical rates of reduction. A mixture of the two proceeds somewhat faster, but since a "minimal" catalyst was not employed, not much reliance can yet be placed on these differences.

The most interesting results are seen with the Schiff base formed from benzylamine and *m*-hydroxyphenylacetylcarbinol, Figs. 5 and 6. Reaction 12, using the substrate prepared from the D-(−)-acyloin is very much slower than reaction II with the racemic substrate. These experiments have been repeated and all results are in agreement with the observations recorded here. Fig. 6 shows more of these. Reaction 14, with racemic substrate, approaches the rate of 13.

DISCUSSION OF RESULTS

Rates of hydrogenation show that (a) the Schiff base of the racemic acyloin is reduced faster than the Schiff base of the D-(−)-acyloin under identical conditions; (b) the Schiff base of the D-(−)-acyloin requires almost twice the quantity of catalyst to be reduced at the same rate as does the racemate; (c) a mixture of equimolar amounts of benzyl acetate and fumaric acid, two chemically unrelated substrates, reduced at a significantly faster rate than either of the individual components by itself. These results are in harmony with the postulate that each substrate has an affinity for a particular site on the catalytic surface and that these sites may be different for specific compounds and specific isomers. The experimental data are not considered adequate to establish conclusively the presence of such stereospecific and substrate-specific centers in the catalyst. Missing are the data, for example in Figs. 5 and 6, for the reduction of the Schiff base of the unavailable L-(+)-acyloin, which would be expected to give curves identical to 12, 16, and 17. Nevertheless, the results thus far obtained are encouraging and further work is in progress, which it is hoped will confirm the hypotheses which prompted these studies.

EXPERIMENTAL

Materials and reagents. The isomeric 4-methyl-2-pentenes were purchased from Phillips Petroleum Company, Bartlesville, Okla. The *cis* isomer boils at 133.2° F. and the *trans* isomer boils at 137.1°F.

D-(−)-*m*-Hydroxyphenylacetylcarbinol was graciously supplied by Messrs. J. M. Sprague and E. L. Engelhardt of Merck Sharp and Dohme, West Point, Pa. After crystallization from ethyl acetate and hexane, it melted at 126–127°, $[\alpha]$, −341.7° in water; these values agree with those previously reported.[16] It was racemized according to the directions of Engelhardt, crystallized from ethyl acetate and hexane and melted at 98–101°. The infrared spectra of the racemic and of the D-(−)-acyloin are indistinguishable, thus confirming that only racemization occurred without concurrent isomerization to *m*-hydroxybenzoylmethylcarbinol.

Benzyl acetate was synthesized according to established procedures.[17]

Fumaric acid, prepared by students, was recrystallized from ethanol, m.p. 194–195° (uncorr.) Maleic acid, also a student preparation, after recrystallization from water, melted 131–132° (uncorr.).

The palladium was generously supplied as pure palladium chloride by Engelhard Industries, Inc., Newark, N. J.

The benzylamine used, Eastman (practical grade), was distilled through a column, the fraction boiling at 81–82°/25 mm. being collected.

Hydrogenation experiments. The preparation of the catalysts is described in earlier papers of this series. The apparatus for making kinetic studies was constructed as described by Meschke.[1]

The products formed by the hydrogenations described are well known except for those formed by the reduction of the Schiff base formed from the *m*-hydroxyphenylacetylcarbinol and benzylamine, *viz.*, *m*-$HOC_6H_4CHOHC(CH_3)NHCH_2C_6H_5$; the product from the D-(−)-acyloin was isolated as the hydrochloride, $C_{16}H_{19}NO_2HCl$, no definite melting point; Calcd. N, 4.78%; Found, 4.83%. The product from the racemic intermediate was hygroscopic and could not be properly purified for analysis.

RICHMOND, VA.

(16) E. L. Engelhardt, private communication.

(17) W. J. Hickenbottom, *The Reactions of Organic Compounds*, Longmans, Green, New York, 1948, p. 416.

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Catalytic Hydrogenation of α,β-Unsaturated Ketones. II. The Mechanism of Hydrogenation in Acidic Medium.[1,2]

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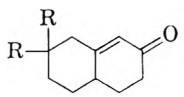
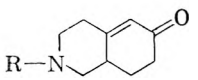
The catalytic hydrogenation of several α,β-unsaturated ketones under acidic conditions has been studied. The results of these experiments are discussed in the light of a mechanism postulated earlier.

In a previous communication,[3] the effect of acidic and basic media on the hydrogenation of $\Delta^{1,9}$-2-octalone (I. R = H) and *N*-benzoyl-$\Delta^{4,5}$-hexahydro-6-isoquinolone (II. R = C_6H_5CO) was noted. As hydrogenation in acidic medium gave primarily

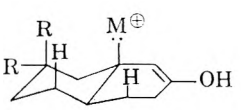


I

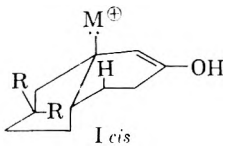


II

the *cis* isomer, a mechanism which involved a 1,4-addition of hydrogen was proposed. The intermediates for both the *cis* and *trans* cases can be represented as I-*cis* and I-*trans*, in which M is the catalyst surface on which the enolic portion of the molecules is also adsorbed. As there is less steric



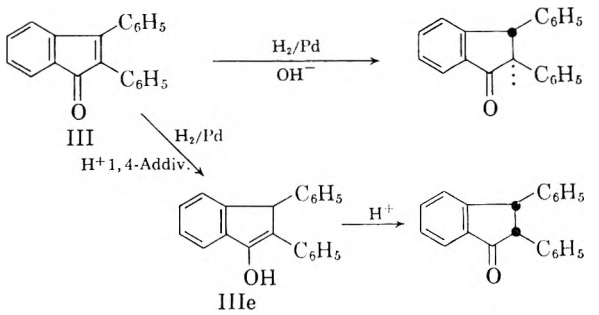
I *trans*



I *cis*

hindrance in the *cis* transition state, it follows that the *cis* isomer might predominate. Further evidence for this mechanism is found in that the *N*-methylisoquinolone (II. R = CH_3) was reported to give the *trans* isomer on hydrogenation in neutral medium[4] and the *cis* isomer in acid medium.[5]

This mechanism, however, is at variance with that of Weidlich, who proposed a 1,2-addition under acid conditions and a 1,4-addition under basic conditions.[6a] He made this proposal after finding that 2,3-diphenylindanone (III) gave the *cis* isomer on hydrogenation under acid conditions and the *trans* isomer under basic conditions.[6b] These results can be explained using the present mechanism as well. Under acidic conditions the hydrogenated product would be desorbed from the catalyst as the enol (IIIe) which would then ketonize. Zimmerman[7] has shown that rapid ketonization of enols takes place by attack of the acid from the least hindered side. Thus, ketoniza-



tion of IIIe would result in the formation of the *cis* isomer. As the *trans* isomer is the more stable of the two, it would be expected to predominate under basic conditions in which equilibration is possible.

It was thought, however, that further evidence was needed to support the idea that hydrogenation under acidic conditions did proceed *via* 1,4-addition. Introduction of more steric hindrance at a position 1–3 to the primary attachment of the catalyst surface would be one way of testing this hypothesis. Toward this end, 7,7-dimethyl-$\Delta^{1,9}$-2-octalone (I. R = CH_3) was synthesized by the reaction of 3,3-dimethyl-6-carbethoxycyclohexanone[8] with methyl vinyl ketone. It was predicted that hydrogenation of this unsaturated ketone in acidic medium should give almost entirely the *cis* isomer, as in the *trans* intermediate state (I *trans* R = CH_3) there is considerable steric hindrance. This prediction was borne out as the product contained over 95% of the *cis* isomer as shown by vapor phase chromatographic analysis.

It was then considered necessary to extend the study to nonoctalone type systems. Toward this end, 5,6,7,8-tetrahydroindanone-5 (IV),[9] 4,5,6,7-tetrahydroindanone-2 (V),[10] and 3,5-dimethyl-

(1) This work was supported by a grant from the University of Texas Research Institute.

(2) Presented in part at the 136th National American Chemical Society Meeting in Atlantic City, August, 1959.

(3) R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958).

(4) A. Marchant and A. R. Pindar, *J. Chem. Soc.*, 327 (1956).

(5) S. M. McElvain and P. H. Parker, Jr., *J. Am. Chem. Soc.*, **78**, 5312 (1956).

(6) (a) H. A. Weidlich, *Chemie*, **58**, 30 (1945). (b) H. A. Weidlich and M. Meyer-Delius, *Ber.*, **74**, 1195 (1941).

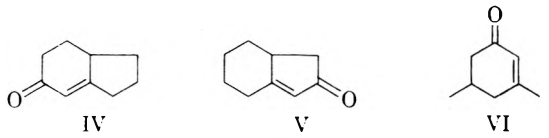
(7) H. E. Zimmerman, *J. Am. Chem. Soc.*, **78**, 1168 (1956).

(8) A. Brinner and H. Schinz, *Helv. Chem. Acta*, **35**, 1333 (1952).

(9) G. Stork and H. Landesman, *J. Am. Chem. Soc.*, **78**, 5128 (1956).

(10) A. M. Islam and R. A. Raphael, *J. Chem. Soc.*, 4086 (1952).

cyclohex-2-eneone (VI)[11] were synthesized and hydrogenated under neutral, acidic, and basic conditions. The ratio of products obtained was determined by vapor phase chromatographic analysis and the results are listed in Table I along with the results from the hydrogenation of I (R = CH_3). In each of these latter cases only one product was obtained regardless of the nature of the medium. However, because it is known that acid has an effect on the nature of the reaction, the same mechanism used to explain the results in the octalone series should also hold here.



IV V VI

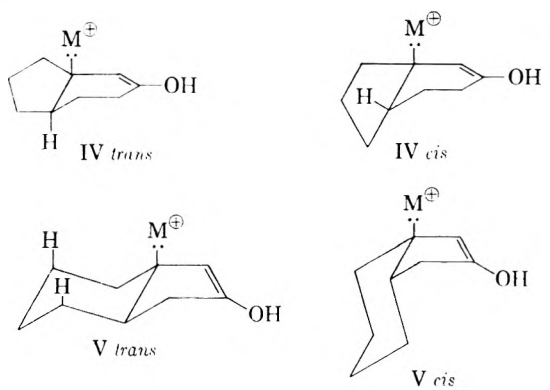
TABLE I

PERCENT *cis* ISOMER OBTAINED[a]

Compound	Medium		
	Neutral	Acid	Base
I(R = CH_3)	70	95	30
IV	100	100	100
V	100	100	100
VI	100	100	100

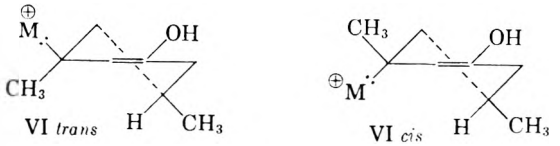
[a] As determined by vapor phase chromatography. In all cases an isomer of known configuration was chromatographed to note absorption time on the column, thus enabling the distinction of isomers, where necessary.

Thus in the acidic hydrogenation of each of the two indanones, two intermediates are possible, IV and V *trans* and IV and V *cis*. It is clear from an examination of these intermediates that the *cis* in each case has less steric hindrance than the *trans* and should, therefore, be favored.



IV *trans* IV *cis* V *trans* V *cis*

In the case of VI, inspection of models shows that when the ring is in the half-chair conformation the *cis* intermediate has less steric hindrance. The *trans* is favored, however, when the molecule is in the half-boat conformation; but, as the half-chair is more stable than the half-boat,[12] there is no need to consider the half-boat case here.



VI *trans* VI *cis*

Thus it seems quite probable that the mechanism for acidic hydrogenation is the one postulated. The effect of base, however, has not been defined. It has been proposed that in the hydrogenation of ring D unsaturated equilenin derivatives, the material hydrogenated in basic medium is not the unsaturated ketone, but instead the enol of the ketone.[13] If models of the enols of the various unsaturated ketones used in this work are examined they show that in all cases the isomer obtained is that which would be predicted on the basis of hydrogenation of these enols. Further clarification of this concept is, however, necessary before any general statement can be made.

EXPERIMENTAL[14]

7,7-Dimethyl $\Delta^{1,9}$*-octalone-2* (I. R = CH_3). To a solution of 1.6 g. of sodium in 100 ml. of absolute ethanol and 100 ml. of dry benzene was added slowly 13 g. of 3,3-dimethyl-6-carbethoxycyclohexanone.[8] The resulting solution was refluxed for 3 hr. and then cooled in an ice bath. To this cold solution was added dropwise a solution of 5.2 g. of methyl vinyl ketone in 50 ml. of dry benzene. The reaction mixture was stirred at room temperature overnight and refluxed for 1 hr. The mixture was cooled, poured into water, and extracted with benzene. The benzene was removed and the residue was refluxed overnight with a mixture of 40 ml. of 50% aqueous potassium hydroxide and 250 ml. of methanol under nitrogen. This reaction mixture was poured into water and the mixture extracted with ether. The ether solution was washed with dilute hydrochloric acid and water, dried over magnesium sulfate, filtered, and the ether removed. The residue was distilled, giving 4.6 g. of I (R = CH_3), b.p. 153°–154° (19 mm.). λ_{max} 240 mμ (ϵ = 13,000). The *2,4-dinitrophenylhydrazone* was recrystallized from ethyl acetate, m.p. 196°–197°.

Anal. Calcd. for $C_{18}H_{22}N_4O_4$; C, 60.33; H, 6.19. Found: C, 60.37; H, 6.22.

Hydrogenation reactions. (*a*) *Neutral Medium.* A mixture of 500 mg. of the unsaturated ketone, 10 ml. of ethanol, and 50 mg. of 10% palladium-on-charcoal was hydrogenated at room temperature under 1 atmosphere of hydrogen. After 1 mole of hydrogen was absorbed the reaction ceased. The catalyst was filtered and the solvent was removed under reduced pressure. The residue was subjected directly to vapor phase chromatography through a Perkin-Elmer Vapor-Fractometer, Model 154B, using a column composed of 1 m. of didecyl phthalate and 1 m. of 2-ethylhexyl sebacate. The temperature was maintained at 175° for all materials except those obtained by hydrogenation of I (R = CH_3) for which a temperature of 210° was used. Helium was used as the eluent gas at a 40 ml. per minute flow rate.

(*b*) *Acidic or Basic Medium.* A mixture of 500 mg. of the

(11) E. Knoevanagel, *Ann.*, 281, 104 (1894).

(12) C. W. Beckett, N. K. Freeman, and K. S. Pitzer, *J. Am. Chem. Soc.*, 70, 4227 (1948).

(13) A. L. Wilds, J. A. Johnson, Jr., and R. E. Sutton, *J. Am. Chem. Soc.*, 72, 5524 (1950).

(14) All melting points are uncorrected.

unsaturated ketone, 9 ml. of ethanol, 50 mg. of 10% palladium-on-charcoal, and 1 ml. of 3*N* hydrochloric acid or 1 ml. of 10% aqueous potassium hydroxide was subjected to hydrogenation at room temperature under 1 atmosphere of hydrogen. After 1 mole of hydrogen was taken up the reaction stopped. The catalyst was removed by filtration, the solvent evaporated under reduced pressure, and the residue taken up in ether. The ether solution was washed neutral with saturated sodium chloride solution, dried, and evaporated. The residue was subjected to vapor phase chromatography as described above.

trans-7,7-Dimethyl-2-decalone. One gram of I (R = CH_3) in 20 ml. of anhydrous ether was added to 150 ml. of liquid ammonia. To this milky solution was added 100 mg. of lithium metal giving a persistant blue solution. The solution was stirred for 2 hr. and the reaction mixture decomposed by the addition of 5 g. of ammonium chloride. The ammonia was evaporated and the residue taken up in water. The aqueous solution was extracted with ether and the extracts dried and evaporated. Yield, 0.7 g.

The *2,4-dinitrophenylhydrazone* was recrystallized from ethanol, m.p. 164°–165°.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71. Found: C, 59.98; H, 6.66.

cis-7,7-Dimethyl-2-decalone. A mixture of 1 g. of I (R = CH_3), 20 ml. of ethanol, 2 ml. of 3*N* hydrochloric acid, and 100 mg. of 10% palladium-on-charcoal was subjected to hydrogenation at room temperature under 1 atmosphere of hydrogen. After hydrogen uptake ceased the catalyst was removed by filtration and the solvent evaporated under reduced pressure. The residue was taken up in ether and washed with saturated sodium chloride solution. The ether solution was dried and evaporated giving 0.8 g. of product.

The *2,4-dinitrophenylhydrazone* was recrystallized from 95% ethanol, m.p. 129°–130°.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71. Found: C, 59.90; H, 6.79.

cis *2-Hydrindanone* was obtained from hydrogenation of IV[9] in acidic, basic, or neutral medium.

The semicarbazone was recrystallized from aqueous ethanol, m.p. 212°–213°. Reported m.p. 215°216°.[15]

cis *5-Hydrindanone* was obtained from hydrogenation of V[10] in acidic, basic, or neutral medium.

The *2,4-dinitrophenylhydrazone* was recrystallized from ethanol, m.p. 166°–167°. Reported m.p.'s 163°,[16] 163°–164°,[17] 168°–169°.[18]

The *semicarbazone* was recrystallized from aqueous ethanol, m.p. 195°–196°; reported melting points 203°,[16] 193°–195°,[17] 196°–197°,[18] 193°–195.5°.[19]

cis *3,5-Dimethylcyclohexanone* was obtained from hydrogenation of VI[11] in acidic, basic or neutral medium.

The *2,4-dinitrophenylhydrazone* was recrystallized from ethanol, m.p. 164°–165°; reported m.p. 166°–167°.[20]

The *semicarbazone* was recrystallized from aqueous ethanol, m.p. 200°–201°; reported melting points 206°–207°,[20] 200°,[21] 202°–203°.[22]

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(15) A. Kandiah, *J. Chem. Soc.*, 922 (1931).

(16) A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 946 (1934).

(17) V. Prelog and M. Zimmermann, *Helv. Chem. Acta*, **32**, 2360 (1949).

(18) J. Meinwald and M. Kohenkyla, *Chem. and Ind.*, 476 (1955).

(19) J. R. Nunn and W. S. Rapson, *J. Chem. Soc.*, 825 (1949).

(20) A. S. Bailey, N. Polgar, and R. Robinson, *J. Chem. Soc.*, 3031 (1953).

(21) R. Cornubert, R. Andri, and P. Hartmann, *Bull. Soc. Chim. France*, 863 (1948).

(22) J. von Braun and W. Haensel, *Ber.*, **59B**, 1999 (1926).

[CONTRIBUTION FROM THE FACULTY OF ENGINEERING, KYOTO UNIVERSITY]

Methioninemethylsulfonium Salts

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Methioninemethylsulfonium fluoborate was prepared. Its reaction with potassium salts of various acids afforded the corresponding sulfonium salts. Methioninemethylsulfonium perchlorate and fluosilicate were also prepared.

Only two existing methods are available for preparing DL-methioninesulfonium salts. One of the methods which affords sulfonium bromides and iodides as well as sulfates involves the interaction of alkyl halides[1-3] or sulfates[2,4,5] with methionine; while the other method which gives sulfonium chlorides[2] and acetates[2,4] employs anion exchange of sulfonium salts with the appropriate salts or acids.

Although the latter method has an advantage in that acetates and chlorides are obtainable which can never be prepared by the former method, an anion exchange method still has the limitations that intermediate sulfonium salts are prepared and purified with difficulty, and the desired sulfonium salts cannot easily be separated from the inorganic salts formed as a by-product.

During our investigation of sulfonium com-

(1) (a) G. Toennies, *J. Biol. Chem.*, **132**, 455 (1940); **133**, CII (1940). (b) G. Toennies and J. J. Kolbe, *J. Am. Chem. Soc.*, **67**, 849, 1141 (1945). (c) K. Pfister, 3rd, W. J. Leanza, J. P. Conbere, H. J. Becker, A. R. Matzuk, and E. F. Rogers, *J. Am. Chem. Soc.*, **77**, 697 (1955); α-methylmethioninemethylsulfonium iodide was prepared by the method of Toennies and Kolbe. (d) M. A. Bennett, *J. Biol. Chem.*, **141**, 573 (1941).

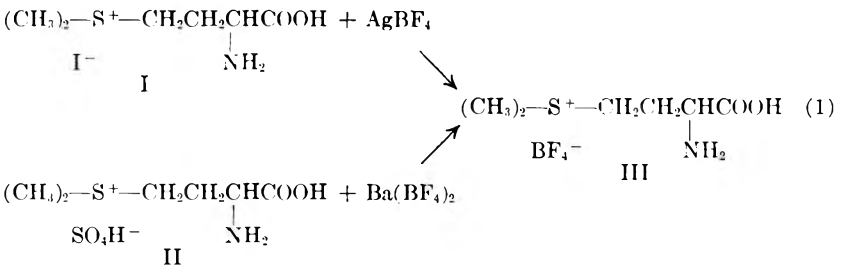
(2) R. O. Atkinson and F. Poppelsdorf, *J. Chem. Soc.*, 1378 (1951).

(3) K. Fukui and H. Kitano, Japanese Patent **231,753**, May 2, 1957; *Chem. Abstr.*, **52**, 2897 (1958).

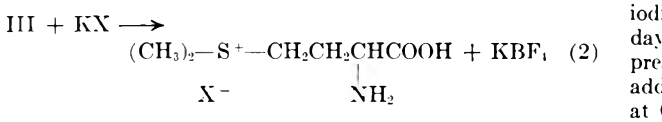
(4) S. Nakajima and G. Okuyama, *Chem. Abstr.*, **52**, 19972 (1958).

(5) T. F. Lavine and N. F. Floyd, *J. Biol. Chem.*, **207**, 97 (1954); T. F. Lavine, N. F. Floyd, and M. S. Cammaroti, *J. Biol. Chem.*, **207**, 107 (1954).

pounds,[6] it was found that sulfonium fluoborates were easily crystallized and relatively stable on storage. Methioninemethylsulfonium fluoborate (III) was prepared by the reaction of methioninemethylsulfonium iodide (I) with silver fluoborate, or by the reaction of methioninemethylsulfonium sulfate (II) with barium fluoborate.



Anion exchange Reaction 2 of III with potassium salts, KX, of various acids can be carried out smoothly in water or aqueous ethanol, and the sulfonium salts formed are separated effectively from the reaction mixture and recrystallized from suitable solvents to afford the corresponding sulfonium salts in good yields. Sulfonium salts thus



prepared are shown in Table I.

An attempt to prepare methioninemethylsulfonium permanganate was unsuccessful. The sulfonium bromate (VII) is highly explosive and heat or shock must be avoided. Methioninemethylsulfonium salts of complex anions containing metals do not melt but at increased temperature undergo slow decomposition as indicated by a change in color. The sulfonium chromate (XII) turns from yellowish brown to dark brown above 125°, sulfonium bichromate (XIII) from orange to brown above 105°, sulfonium ferrocyanide (XIV) turns from light yellow to cream color above 125°, and sulfonium ferricyanide (XV) from yellow to greenish yellow above 115°. The sulfonium fluosilicate (XVII) and perchlorate (IX) cannot be prepared from III and the corresponding potassium salts; however, these compounds can conveniently be prepared by the reaction of I and silver fluosilicate or perchlorate. The former (XVII) is somewhat difficult to purify because of its very hygroscopic property, while the latter (IX), though not so hygroscopic as XVII, is less stable to heating than III. Methyl bromide,[1,2] ethyl bromide,[2] benzyl and *p*-methylbenzyl chlorides,[10] as well as *bis*(2-chloroethyl)sulfide[11] react directly with methionine to yield the corresponding sulfonium salts, but methyl and ethyl chlorides do not give sulfonium salts of methionine even at 60° in an autoclave, and the methionine may be recovered.[6]

EXPERIMENTAL[12]

Methioninemethylsulfonium iodide (I). A.[13] A mixture of 149 g. (1 mole) of methionine, 900 ml. of 80% formic acid, 380 ml. of acetic acid, and 225 ml. (3.6 moles) of methyl iodide was kept in a dark place at room temperature for 2 days. The solution was concentrated under diminished pressure below 60°. To the resulting sirupy material was added 1.5 l. of methanol, and the mixture was maintained at 0° overnight. The precipitate was filtered, and washed with methanol and acetone. Recrystallization from water-methanol-acetone gave 262 g. (90%) of I, colorless plates, melting at 156–157° dec. (reported[1] 150°).

B.[3] A mixture of 29.8 g. (0.2 mole) of methionine, 500 ml. of acetic acid, 50 ml. of water, and 75 ml. (1.2 moles) of methyl iodide was gently refluxed on a water bath for 1.5 hr. The mixture was treated similarly as above to yield 54 g. (92%) of I, melting at 156–157° dec.

Methioninemethylsulfonium fluoborate. A. To a solution of 29.1 g. (0.1 mole) of I in 280 ml. of water was added 35 g. of 56% aqueous silver fluoborate solution at room temperature with stirring until the iodine ion just disappeared (by means of a spot test using bismuth nitrate and 8-hydroxyquinoline.[14]) The mixture was filtered, and the filtrate was concentrated under diminished pressure below 50°. The residual sirup was treated as in the case of I. After recrystallization from aqueous methanol, 24.9 g. (95%) of III, colorless crystals, m.p. 147–148° dec., was obtained.

B. A solution of 14.9 g. (0.1 mole) of methionine in 100 ml. of 18% sulfuric acid and 6 ml. (0.14 mole) of methanol was refluxed for 3 hr. The mixture was diluted with 250 ml. of water and partly neutralized with powdered barium hy-

(6) K. Fukui, K. Kanai, and H. Kitano, *Abstract Papers of 12th Meeting, the Chemical Society of Japan*, p. 159 (1959), Kyoto, Japan.

(7) M. Stahmann, J. S. Fruton, and M. Bergmann, *J. Org. Chem.*, 11, 704 (1946).

(8) W. Shive, Lecture delivered at University of Michigan. February 1952; W. Shive, *Intern. Rev. of Vitamin Research*, **23**, 329 (1952); R. A. McRorie, G. L. Sutherland, M. S. Lewis, A. D. Barton, M. R. Glazener, and W. Shive, *J. Am. Chem. Soc.*, **76**, 115 (1954).

(9) F. Challenger and Y. C. Lin, *Rec. trav. chim.*, **59**, 334 (1950).

(10) Benzyl and *p*-methylbenzyl chlorides reacted with methionine at 50–60° in 70% acetic acid.[8] Methioninebenzylsulfonium chloride had m.p. 123–124° dec. (Cl, calcd.: 12.9; found: 12.5), and methionine-*p*-methylbenzylsulfonium chloride, m.p. 131–132° (Cl, calcd.. 12.1; found: 11.8). Toennies and Kolbe reported[1b] that *N*-acetylmethionine reacted with cinnamyl chloride to yield corresponding sulfonium salt.

(11) W. H. Stein and S. Moore [*J. Org. Chem.*, 11, 681 (1946)] reported the formation of this sulfonium salt which was, however, not crystallizable.

(12) All melting points are uncorrected.

(13) Method A is a modification of Toennies and Kolbe (reported 75% yield; see Ref. 1).

(14) I. Tsubaki, *J. Chem. Soc. Japan, Pure Chem. Section*, **71**, 505 (1950).

TABLE I

DL-METHIONINEMETHYLSULFONIUM SALTS

$(CH_3)_2S^+(X^-)CH_2CH_2CH(NH_2)COOH$

Number	Formula of Anion (X)[a]	Method of Preparation[b]	Dec. Pt., °C.	Analyses, % Nitrogen Calcd.	Nitrogen Found	Anion (X) Calcd.	Anion (X) Found
I	I	A	156–157[c]	4.81	4.64	43.59	43.5
I	I	B	156–157	4.81	4.78	43.59	43.5
III	BF_4	C	147–148	5.58	5.51	34.58	34.5
III	BF_4	D	147–148	5.58	5.50	34.58	34.5
IV	Cl	B	137–138[d]	7.01	6.90	17.76	17.7
IV	Cl	E	137–138	7.01	6.90	17.76	17.4
IV	Cl	F	137–138	7.01	6.90	17.76	17.9
V	Br	B	140–141[e]	5.74	5.70	32.73	32.8
VI	ClO_3	B	129–130	—	—	39.69	40.1
VII	BrO_3	B	[f]	—	—	43.78	44.9
VIII	IO_3	B	110–111	—	—	51.58	51.7
IX	ClO_4	G	147–148	—	—	37.71	36.1
X	NO_2	B	128–129	13.32	13.00	21.88	21.8
XI	NO_3	B	147–148	12.38	12.08	27.40	27.4
XII	$^1/_2CrO_4$	B	[g]	6.30	6.11	26.10	26.0
XIII	$^1/_2Cr_2O_7$	B	[g]	5.15	5.18	39.67	39.6
XIV	$^1/_4Fe(CN)_6$	B	[g]	16.12	16.08	24.39	24.3
XV	$^1/_3Fe(CN)_6$	B	[g]	17.89	17.65	30.08	30.0
XVI	NH_2SO_3	B	124–125	10.76	10.72	—	—
XVII	$^1/_2SiF_6$	H	109–110	5.95	5.81	30.19	30.0
XVIII	CH_2FCOO[h]	B	121–122	5.81	5.86	—	—
XIX	CF_3COO	B	126–127	5.05	4.95	—	—
XX	$CHCl_2COO$	B	119–120	4.79	4.87	—	—
XXI	CCl_3COO	B	108–109	4.29	4.26	—	—
XXII	p-$NO_2C_6H_4COO$	B	147–148	7.65	7.90	—	—
XXIII	3,5-$(NO_2)_2C_6H_3COO$	B	141–142	11.19	11.28	—	—
XXIV	p-$CH_3C_6H_4SO_3$	B	143–144	4.18	4.08	—	—
XXV	β-$C_{10}H_7SO_3$	B	128–129	3.77	3.86	—	—
XXVI	p-$NH_2C_6H_4SO_3$	B	124–125	8.33	8.30	—	—
XXVII	4-$(CH_3)_2NC_6H_4N_2$-$C_6H_4SO_3$-4′	B	203–204	11.96	12.12	—	—

[a] All yields are from about 80 to 96%. [b] Method: A, Methionine with methyl iodide; B, III with potassium salt; C, I with silver fluoborate; D, Sulfonium sulfate (II) with barium fluoborate; E, I with silver chloride; F, IX with potassium chloride; G, I with silver perchlorate; H, I with silver fluoborate. [c] G. Toennies and J. J. Kolbe[1b] reported m.p. 150° dec.; M. Stahmann, J. S. Fruton, and M. Bergmann,[7] m.p. 168–169° dec.; F. Challenger and Y. C. Lin,[9] m.p. 157–158° dec.; R. O. Atkinson and F. Poppelsdorf,[2] m.p. 150° dec.; S. Nakajima and G. Okuyama,[4] m.p. 149° dec. [d] R. O. Atkinson and F. Poppelsdorf[2] reported m.p. 134° dec. [e] G. Toennies and J. J. Kolbe[1b] reported m.p. 140° dec.; W. Shive *et al.*,[8] m.p. 140° dec.; S. Nakajima and G. Okuyama,[4] m.p. 139° dec. [f] Several samples explosively decomposed in the range of 94–115° in spite of careful measurements of melting point. [g] This substance has no melting point. [h] This sulfonium salt is most likely a convulsant poison like other derivatives of fluoroacetic acid.

droxide to *p*H 2. The precipitated barium sulfate was filtered, and the filtrate was adjusted exactly to *p*H 5 with dilute barium hydroxide solution. The resulting mixture was filtered, and the filtrate[15] was treated with 15 g. of 30% aqueous barium fluoborate solution until no sulfate ion was detectable. Barium sulfate was again removed, and the clear filtrate was treated as above to yield 16.2 g. (67%) of III, melting at 147–148° dec.

Reaction of methioninemethylsulfonium fluoborate with potassium salts. To a solution of 0.05 mole of a potassium salt in 80 ml. of water was added with stirring a solution of 12.6 g. (0.05 mole) of III in 20 ml. of water. Ethanol (100 ml.) was then added to the above mixture. The potassium fluoborate formed was filtered, washed with 50% ethanol, and the filtrate was concentrated under diminished pressure below 50°. The residue was treated with 20 ml. of 70% ethanol, and the insoluble matter was removed by filtration. The filtrate was mixed with 200 ml. of methanol, and then acetone was added until the solution became turbid. The resulting mixture was maintained at 0° overnight to settle the precipitate. The precipitate was filtered, washed with methanol, and dried *in vacuo* to give a crude sulfonium salt. The crude product was recrystallized from water-methanol-acetone in suitable proportions to afford the pure sample listed in Table I.

Methioninemethylsulfonium perchlorate (IX). To a solution of 29 g. (0.1 mole) of I in 200 ml. of water was added a solution of 20.7 g. (0.1 mole) of silver perchlorate in 200 ml. of water. The mixture was treated as in the case of the preparation A of III to give 24.3 g. (92%) of IX which, after recrystallization from water-methanol, melted at 147–148° dec.

Methioninemethylsulfonium chloride (IV). A. IV was prepared in 91% yield through Reaction 2 of III and potassium chloride, and the product melted at 137–138° dec.

B. To a solution of 3.7 g. (0.05 mole) of potassium chloride in 60 ml. of water was added a solution of 12.6 g. (0.05 mole) of IX in 30 ml. of water. After cooling to 0°, the precipitated potassium perchlorate was filtered, and the filtrate was treated as described above to give 9.4 g. (94%) of IV, m.p. 137–138° dec.

C. To a suspension of 36 g. (0.25 mole) of freshly prepared

(15) The filtrate contains sulfonium sulfate (II) which cannot be isolated as pure crystalline material because it is extremely hygroscopic.

silver chloride in 150 ml. of water was added dropwise with vigorous stirring a solution of 29 g. (0.1 mole) of I in 60 ml. of water. The addition required about 30 min. The mixture was stirred for an additional 2 hr. until no iodide ion was detected by a spot test.[14] The resulting mixture was filtered, and the filtrate was concentrated under diminished pressure to about 45 ml. The residue was treated as above to yield 17.6 g. (88%) of IV, which melted at 137–138° dec.

Methioninemethylsulfonium fluosilicate (XVII). To a solution of 29.1 g. (0.1 mole) of I in 50 ml. of water was added 37 g. of freshly prepared 48% aqueous silver fluosilicate solution, and the mixture was treated as above to yield 21.4 g. (91%) of XVII as hygroscopic colorless needles, m.p. 109–110° dec. XVII was found to decompose slowly *in vacuo* at room temperature. XVII could be converted in good yield into IV by a procedure similar to that for XI.

KYOTO, JAPAN

[CONTRIBUTION FROM THE MATERIALS & PROCESSES STAFF, AERO-SPACE DIVISION, BOEING AIRPLANE COMPANY]

Synthesis of Monomeric Silanes

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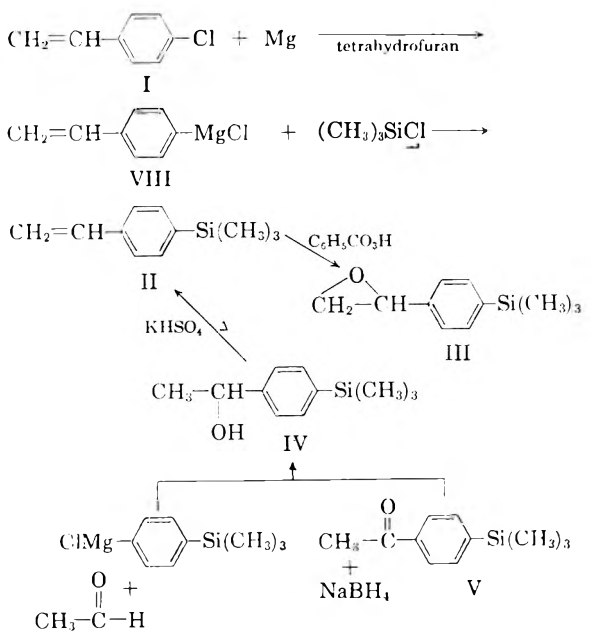
Received August 31, 1959

The preparations of 4-trimethylsilylstyrene and of 4-epoxyethylphenyltrimethylsilane are described, as well as attempts to extend these reactions to the preparation of the analogous difunctional monomers.

Two methods for the preparation of 4-trimethylsilylstyrene (II) have recently been described. Winslow[2] prepared it by the vapor phase dehydration of 1′-(4-trimethylsilylphenyl)ethanol (IV). Later Lewis[3] described the reaction of 4-styryltrichlorosilane with methylmagnesium bromide. In the present report, the synthesis of II from 4-styrylmagnesium chloride (VIII)[4] and trimethylchlorosilane is described. The conversion of the styrylsilane (II) to the corresponding epoxide (III) is also included. In addition, details are given for the preparation of Winslow's alcohol (IV) in crystalline form by the reduction of 4-trimethylsilylacetophenone[5,6] as well as from *p*-dichlorobenzene instead of the more expensive *p*-dibromo compound.



A number of attempts were made to prepare the analogous difunctional compounds, di(4-styryl)-dimethylsilane and di(4-epoxyethyl)dimethylsilane. Reaction of 4-styrylmagnesium chloride (VIII) with dimethyldichlorosilane appears to proceed normally, but attempts to isolate the product invariably led to polymer formation.

Reduction of di(4-acetylphenyl)dimethylsilane to the dialcohol, followed by dehydration, was next attempted. Although the reduction proceeded smoothly, attempts to dehydrate the dialcohol led to splitting of the silicon-phenyl bond.

In a previous paper from this laboratory, the use of 2-(4′-bromophenyl)-2-methyl-1,3-dioxolane as a reagent for the introduction of the 4-acetylphenyl group into silanes was described.[6] During the present work, we have discovered that the 1,3-dioxolane (ketal) structure is more stable than anticipated. Depending on the method of working up the Grignard product, it is possible to isolate pure ketals, pure ketones, or mixtures of these compounds. When water is used to decompose the Grignard product from trimethylchlorosilane, a ketal can be isolated. Treatment of this Grignard product with dilute hydrochloric acid in the cold yields a mixture of ketal and ketone. Use of hydrochloric acid plus gentle heat yields the ketone. Treatment of the difunctional Grignard product derived from dimethyldichlorosilane with water to yield the diketal proceeds smoothly. Acid treatment of this Grignard product, designed to split the ketal groups, yields a mixture of ketal, ketone, and decomposition products which is difficult to purify. After purifica-

(1) Present address: Propulsion Dept., Missile and Space Division, Lockheed Aircraft Corp., Palo Alto, Calif.

(2) F. H. Winslow. U. S. Patent 2,642,415, June 16, 1953.

(3) D. W. Lewis, *J. Org. Chem.*, 23, 1893 (1958).

(4) J. R. Leebrick and H. E. Ramsden, *J. Org. Chem.*, 23, 935 (1958).

(5) P. J. Campagna and H. W. Post, *J. Org. Chem.*, 19, 1753 (1954).

(6) R. G. Neville, *J. Org. Chem.*, 24, 111 (1959).

tion, however, the diketal can be hydrolyzed to the diketone readily. Compounds previously identified as ketones[6] have been shown to be largely ketals, containing enough ketonic impurities to account for the formation of the derivatives described. In the Experimental section, the physical properties of both ketals and ketones are given.

EXPERIMENTAL[7]

2-(4'-Trimethylsilylphenyl)-2-methyl-1,3-dioxolane. The reaction between the Grignard reagent of 2-(4'-bromophenyl)-2-methyl-1,3-dioxolane and trimethylchlorosilane has been previously described.[6] The reaction mixture was poured over cracked ice, the organic layer separated,[8] washed with water, dried over sodium sulfate, and distilled to give a liquid, b.p. 150–190°/2.5 mm. in 59% yield. It crystallized in the receiver and after recrystallization from isopropanol melted at 59–60°. The material previously described,[6] m.p. 41°, was apparently this compound with some ketone as an impurity.

Anal. Calcd. for $C_{13}H_{20}O_2Si$: C, 66.05; H, 8.53; Si, 11.88. Found: C, 66.00; H, 8.25; Si, 11.68.

The infrared spectrum showed a ketal doublet[9] at 1075 and 1030 cm.$^{-1}$, no absorption in the carbonyl region at 1680 cm.$^{-1}$, *p*-substitution band at 820 cm.$^{-1}$, and trimethylsilyl bands at 756, 836, and 1250 cm.$^{-1}$

4-Trimethylsilylacetophenone, (V).[5,6] Twenty-seven g. of the ketal was dissolved in 150 ml. of methanol and 30 ml. of concentrated hydrochloric acid. After 0.5 hr. 400 ml. of water was added and the product taken up in benzene. After washing and drying over sodium sulfate, distillation yielded 11.6 g. (53%) of liquid, b.p. 93–95°/1.5 mm., $n_D^{25°}$ = 1.5178, which solidified at 11°, showing a strong carbonyl band at 1680 cm.$^{-1}$; *p*-substitution at 818 cm.$^{-1}$; trimethylsilyl bands at 760, 842, and 1248 cm.$^{-1}$; Si-C_6H_5 at 1112 and 1382 cm.$^{-1}$

1'-(4-Trimethylsilylphenyl)ethanol, (IV). (*a*). *By reduction:* To 10 g. (0.052 mole) of 4-trimethylsilylacetophenone in 40 ml. of methanol was added a solution of 2.3 g. (0.060 mole) of sodium borohydride in 20 ml. of methanol, maintaining the temperature at 25–30°. After 20 hr. 300 ml. of 2% hydrochloric acid was added. The product was taken up in ether, washed with water, dried, and distilled to yield 7.2 g. (72%) of carbinol, b.p. 110–111°/4.5 mm. The product crystallized on cooling to give a solid. A sample redistilled for analysis melted at 46–47°.

Anal. Calcd. for $C_{11}H_{18}O$ Si: C, 67.98; H, 9.34; Si, 14.45. Found: C, 68.09; H, 9.32; Si, 14.59.

The infrared spectrum showed an associated O—H stretch, strong at 3333 cm.$^{-1}$; *p*-substitution at 823 cm.$^{-1}$; trimethylsilyl bands at 760, 846, 1250 cm.$^{-1}$; Si-C_6H_5 at 1111 and 1390 cm.$^{-1}$

(*b*) *By the Grignard synthesis:* 4-Chlorophenyltrimethylsilane,[10] synthesized from *p*-dichlorobenzene and trimethylchlorosilane by a Grignard reaction in tetrahydrofuran, was converted to the Grignard reagent in tetrahydrofuran, a 20% excess of acetaldehyde vapor was swept into the solution, and after refluxing 1 hr. and working up as usual, a liquid, b.p. 156–61°/25 mm. was isolated in 50% yield. The infrared spectrum of the liquid product was identical with that of the solid described above. Unless the 4-chlorophenyltrimethylsilane used was carefully fractionated, a solid, m.p. 92–93°, distilled as a forerun. This was shown to be *p*-di(trimethylsilyl)benzene by its infrared spectrum and melting point,[11] and was presumed to have arisen as a by-product in the preparation of 4-chlorophenyltrimethylsilane from *p*-dichlorobenzene.

4-Trimethylsilylstyrene, (II). (*a*) *By dehydration.* 1'-(4-Trimethylsilylphenyl)ethanol, (IV), was dehydrated by the potassium bisulfate method,[12] utilizing a pressure of 25 mm. and a bath temperature of 240°. Upon redistillation, after a forerun, b.p. 60–85°/25 mm., the product was obtained in 43% yield as a colorless liquid, b.p. 117–126°/25 mm., $n_D^{25°}$ = 1.5253.

Anal. Calcd. for $C_{11}H_{16}Si$: C, 74.92; H, 9.15. Found: C, 75.07; H, 9.18.

The infrared spectrum showed conjugated vinyl at 1636 cm.$^{-1}$=CH_2; deformation at 908 cm.$^{-1}$; *p*-substitution at 826 cm.$^{-1}$, trimethylsilyl bands at 756–763 (doublet), 846, and 1250 cm.$^{-1}$; Si-C_6H_5 at 1107 and 1392 cm.$^{-1}$

(*b*). *By the Grignard synthesis.* *p*-Chlorophenylmethylcarbinol[4] was dehydrated to *p*-chlorostyrene in 68% yield by dripping slowly through a 15-in. column packed with 8–14 mesh alumina at 300° and 60-mm. pressure. To the Grignard reagent[4] from 84.0 g. (0.60 mole) of the *p*-chlorostyrene was added a solution of 58.8 g. (0.54 mole) of trimethylchlorosilane in 225 ml. of tetrahydrofuran so that the solution refluxed. After 15 min. of additional reflux 1 g. of hydroquinone was added and the mixture stirred 1 hr. The mixture was poured over cracked ice, and the organic layer separated, washed with water, dried with sodium sulfate, and distilled to yield 58.5 g. (62%) of liquid, b.p. 120–136°/25 mm., $n_D^{25°}$ = 1.5218,[2] with an infrared spectrum identical with that of the above dehydration product.

4-Epoxyethylphenyltrimethylsilane, (III). At 0° 600 ml. (0.30 mole) of a 0.5*M* benzene solution of perbenzoic acid[13] was added to 49.2 g. (0.28 mole) of 4-trimethylsilylstyrene in 300 ml. of benzene. After the peroxide titer had fallen to a constant value (20 hr.), the solution was washed acid free with cold sodium carbonate solution, washed with water, dried with sodium sulfate, and distilled to yield 25.5 g. (50%) of a liquid, b.p. 105–108°/8 mm., $n_D^{25°}$ = 1.5150.

Anal. Calcd. for $C_{11}H_{16}OSi$: C, 68.69; H, 8.39; epoxide equivalent 192. Found: C, 68.85; H, 8.44; epoxide equivalent 215.[14]

Di-[4-(2'-methyl-1',3'-dioxolyl-2')-phenyl]dimethylsilane. This is the compound previously reported[6] to be the ketone. An analytical sample recrystallized from isopropanol melted at 132–133°.

Anal. Calcd. for $C_{22}H_{28}O_4Si$: C, 68.71; H, 7.34; Si 7.31. Found: C, 68.50; H, 7.09; Si, 7.44.

The infrared spectrum showed a ketal doublet at 1032 and 1075 cm.$^{-1}$; no absorption in the carbonyl region at 1680 cm.$^{-1}$; *p*-substitution at 826 cm.$^{-1}$; =$Si(CH_3)_2$ bands at 815 and 1252 cm.$^{-1}$; Si-C_6H_5 at 1116 and 1382 cm.$^{-1}$

Di(4-acetylphenyl)dimethylsilane. To 157 g. (0.361 mole) of recrystallized ketal dissolved in 4.8 l. of methanol was added 800 ml. of concentrated hydrochloric acid. After

(7) Melting points are uncorrected. Potassium bromide pellets were used in the determination of spectra of solids, and thin films in the case of liquids. Distillations were carried out in standard taper glassware without distilling columns.

(8) Following the suggestion of Dr. Thomas Waugh, Arapahoe Chemicals, Inc., we have found the addition of the disodium salt of ethylenediaminetetraacetic acid to be very helpful in breaking the persistent emulsions that frequently result from the use of tetrahydrofuran as a Grignard solvent.

(9) H. O. House and J. W. Blaker, *J. Org. Chem.*, **23**, 335 (1958).

(10) H. E. Ramsden and S. D. Rosenberg, British Patent **795,772**, May 28, 1958.

(11) H. A. Cook, British Patent **671,553**, May 7, 1952.

(12) E. C. Hornung, *Org. Syntheses*, **Coll. Vol. III**, 204 (1955).

(13) H. Gilman and A. H. Blatt, *Org. Syntheses*, **Coll. Vol. I**, 2nd ed., 431 (1951).

(14) By the pyridine hydrochloride method, method 7, page 136, from J. L. Jungnickel, *et al.* in *Organic Analysis*, **Vol. I**, Interscience, New York, 1953. This method gives slightly high results with styrene oxides due to acid-catalyzed rearrangement to acetyl compounds.

stirring 0.5 hr., the solution was poured into 15 l. of water, and the product extracted with three portions of benzene. Removal of the solvent left an oil which readily crystallized, yield 105 g. (87%). An analytical sample, recrystallized from isopropanol and methanol melted at 77.5–78.0°.

Anal. Calcd. for $C_{18}H_{20}O_2Si$: C, 72.93; H, 6.80; Si, 9.48. Found: C, 72.63; H, 6.67; Si, 9.28.

The infrared spectrum showed a strong carbonyl band at 1680 cm.$^{-1}$; *p*-substitution at 842 cm.$^{-1}$; $=Si(CH_3)_2$ bands at 818 and 1248 cm.$^{-1}$; $Si-C_6H_5$ at 1112 and 1382 cm.$^{-1}$

Di[4-(1'-hydroxyethyl)phenyl]dimethylsilane. The sodium borohydride reduction of the diketone to the dialcohol proceeded as described above. Removal of the solvent yielded 91% of an oil which readily crystallized. An analytical sample, recrystallized from isopropanol, melted at 97–98°.

Anal. Calcd. for $C_{18}H_{24}O_2Si$: C, 71.95; H, 8.05; Si, 9.35. Found: C, 71.47; H, 8.19; Si, 9.78.

The infrared spectrum showed an associated O—H stretch strong at 3280 cm.$^{-1}$; *p*-substitution at 843 cm.$^{-1}$; $=Si-(CH_3)_2$ at 816 and 1252 cm.$^{-1}$; $Si-C_6H_5$ at 1112 and 1390 cm.$^{-1}$

Attempted preparation of di(4-styryl)dimethylsilane. (a). By dehydration. Attempts to use the phosphorus pentoxide dehydration of Gilman *et al.*,[15] led to polymer formation. After passing the dialcohol over alumina at either 300° or 400° and 1 mm. pressure, only styrene, in the form of styrene dibromide, could be isolated from the products.

(*b*) *By Grignard synthesis.* A vigorous reaction took place on the addition of dimethyldichlorosilane to 4-styrylmagnesium chloride. Occasionally the reaction mixture polymerized to a rubbery mass at this stage. With carefully purified reagents, and addition of an antioxidant, the reaction mixture could be worked up as usual, so that solvent removal yielded a fluid liquid. Attempts to distill this material alone or with polymerization inhibitors led to immediate polymerization. The crude product consumed approximately 50% of the calculated amount of perbenzoic acid but no diepoxide could be isolated from the reaction. Addition of bromine produced a crystalline material, m.p. 134–135°, which had the following analysis: C, 41.12; H, 3.69; Br, 55.28%. In view of the apparent absence of silicon in this product, and the known case of cleavage of the phenylsilicon bond by bromine,[16] this was not investigated further.

Acknowledgment. We wish to thank Mr. Murray Taylor of this laboratory for the microanalyses reported, and Mr. Harry Goldberg and Mrs. Katharine Haldorsen for measurements of infrared spectra.

SEATTLE, WASH.

(15) H. Gilman, D. Aoki, and D. Wittenberg, *J. Am. Chem. Soc.*, **81**, 1107 (1954).

(16) R. Benkeser and A. Torkelson, *J. Am. Chem. Soc.*, **76**, 1252 (1954).

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

Trimethyl(iso)cyanogermane and Trimethyltin (Iso)cyanide[1]

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Trimethyl(iso)cyanogermane, on the basis of its infrared spectrum and its physical and chemical properties consists of an equilibrium mixture of the normal and the isocyano isomers. It reacts with sulfur, forming trimethylisothiocyanatogermane, and with boron trifluoride to give $(CH_3)_3GeCN\cdot BF_3$. Trimethyltin (iso)cyanide has properties consistent with its formulation as a highly polar cyanide. It reacts with sulfur, giving trimethyltin thiocyanate, and does not form an adduct with boron trifluoride. The preparation of trimethyl(iso)cyanogermane and trimethyltin (iso)cyanide is described.

Trimethyl(iso)cyanosilane could have the normal cyanide structure, I, or the isocyanide structure II.

$$(CH_3)_3Si-C\equiv N \text{ (I)} \quad (CH_3)_3Si-N=C \text{ (II)}$$

The question of the correct structure has been the subject of much discussion in recent years[2-7] and it is now assumed, on the basis of infrared[6] and chemical[3,6] studies, that "trimethyl(iso)cyanosilane" consists of an equilibrium mixture of trimethylcyanosilane and trimethylisocyanosilane, the former isomer predominating at room temperature. We report here the results of an investigation concerning the preparation and properties of the germanium and tin analogs of trimethyl(iso)-cyanosilane: trimethyl(iso)cyanogermane and trimethyltin (iso)cyanide.

Trimethyl(iso)cyanogermane. Tetra(iso)cyanogermane has been described,[6,8] as has (iso)cyanogermane.[9] No convincing proof was given for the postulated isocyanide structure of the latter. Two organogermanium (iso)cyanides, triethyl- and tri-*n*-

(1) The "(iso)cyano" and "(iso)cyanide" nomenclature used in this paper has no structural implications when the iso prefix is in parentheses and merely indicates the presence of the CN and/or the NC grouping.

(2) C. Eaborn, *J. Chem. Soc.*, 2757 (1949); 3077 (1950).

(3) J. J. McBride and H. C. Beachell, *J. Am. Chem. Soc.*, **74**, 5247 (1952); *J. Chem. Phys.*, **28**, 991 (1958).

(4) J. Goubeau and J. Reyling, *Z. anorg. u. allgem. Chem.*, **294**, 92 (1958).

(5) R. Linton and E. R. Nixon, *J. Chem. Phys.*, **28**, 990 (1958).

(6) T. A. Bither, W. H. Knoth, Jr., R. V. Lindsey, Jr., and W. H. Sharkey, *J. Am. Chem. Soc.*, **80**, 4151 (1958).

(7) (a) E. C. Evers, W. O. Freitag, J. N. Keith, W. A. Kriner, A. G. MacDiarmid, and S. Sujishi, Technical Report No. 3, Contract Nonr-551(21), October 1958 (AD-204,665); (b) Technical Report No. 4, October 1958 (AD-214,968); (c) Technical Report No. 5, October 1958 (AD-204,664).

(8) W. Menzer, *Angew. Chem.*, **70**, 656 (1958).

(9) S. Sujishi and J. N. Keith, Abstracts of Papers presented at the 134th A.C.S. Meeting, Chicago, September, 1958, p. 44-N.

propyl(iso)cyanogermane, have been reported,[10] but the question of their structure was not considered.

We used the method described[3] for the preparation of trimethyl(iso)cyanosilane in our synthesis of the germanium analog. Both chemical and physical properties of the germanium compound paralleled closely those reported for trimethyl(iso)cyanosilane.[3] Reaction with sulfur gave trimethylisothiocyanatogermane, $(CH_3)_3GeNCS$. This reaction, while being indicative of the presence of the (iso)cyanide structure, does not distinguish between the possibilities that the compound may be wholly the isocyanide, or that it may consist of an equilibrium mixture of both normal and isocyanide isomers. A comparison of the infrared spectrum of trimethyl(iso)cyanogermane with that of the analogous silicon compound (Fig. 1) showed that the germane also consists of a mixture of both isomers. The strong band at 2198 cm.$^{-1}$ in the spectrum of trimethyl(iso)cyanosilane has been assigned to the normal cyanide stretching frequency, while the weak band at 2105 cm.$^{-1}$ was assigned to the isocyanide bond.[6] The optical density of the C≡N band was about 4.5 times as great as that of the N=C band; these data were interpreted[6] as indicating that the normal cyano isomer predominates in a mixture of both isomers. The spectrum of trimethyl(iso)cyanogermane is quite similar, with a strong band at 2197 cm.$^{-1}$ and a much weaker absorption at 2100 cm.$^{-1}$, and the same interpretation, predominance of $(CH_3)_3Ge-C\equiv N$ in a mixture of both isomers, may be given in this case. However, on the basis of the available evidence, we do not consider the problem of the structures of trimethyl(iso)cyanosilane and trimethyl(iso)cyanogermane settled satisfactorily, and further experimental evidence seems desirable.

While sulfur appears to react only with the isocyanogermane in the mixture, continuously displacing the equilibrium $(CH_3)_3Ge-C\equiv N \rightleftharpoons (CH_3)_3Ge-N=C$ to the right, boron trifluoride apparently reacts with both isomers. When trimethyl(iso)cyanogermane and boron trifluoride diethyl etherate were mixed, stable, readily sublimable, white, crystalline $(CH_3)_3GeCN\cdot BF_3$ resulted. Its infrared spectrum showed two strong bands of about equal intensity at 2270 and 2230 cm.$^{-1}$ and a weak band at 2105 cm.$^{-1}$ The cause of the 2270–2230 cm.$^{-1}$ doublet is not known, but the presence of bands in the C≡N and N=C region suggests the tentative conclusion that both isomers act as donor molecules with boron trifluoride, and that formation of the N—B link results in an increase in the stretching frequency of the C≡N bond. It may be noted that organic nitriles, such as acetonitrile,[11] form 1:1 adducts with boron trifluoride.

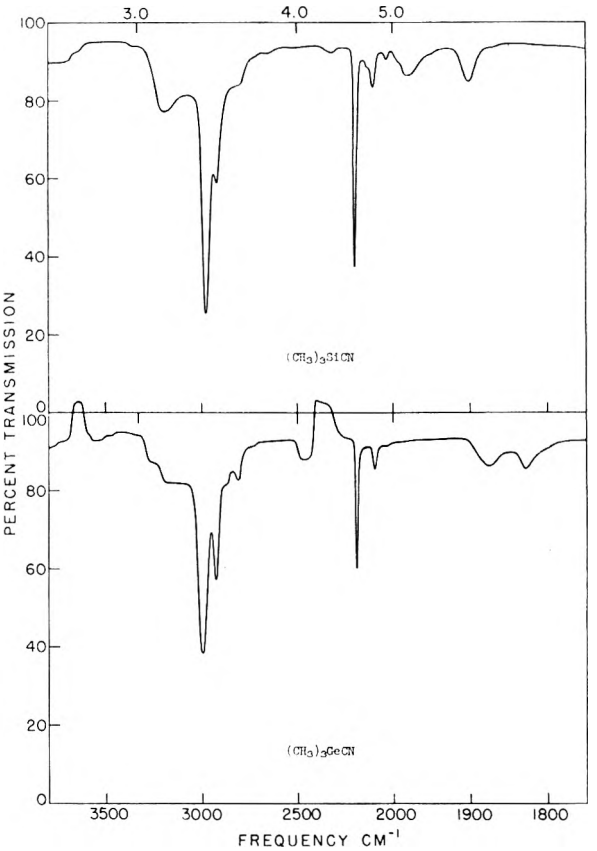

Fig. 1. Infrared spectra of trimethyl(iso)cyanosilane (liquid smear) and trimethyl(iso)cyanogermane (chloroform solution)

Their infrared spectra have been examined.[12] An increase in the C≡N stretching frequency similar to the one observed by us was noted when acetonitrile ($\nu_{C\equiv N}$ = 2248 cm.$^{-1}$) formed an adduct with boron trifluoride ($\nu_{C\equiv N}$ = 2359 cm.$^{-1}$). Also, a second band in the C≡N region was observed in the case of the acetonitrile adduct. On the other hand, we found that organic isonitriles, such as ethyl and *tert*-butyl isonitrile, react with boron trifluoride to form brown tars, probably polymerization products of the isonitrile. Even a catalytic quantity of boron trifluoride etherate seemed sufficient to cause polymerization of ethyl isonitrile. In contrast to trimethyl(iso)cyanogermane, trimethyl(iso)cyanosilane reacts with boron trifluoride to give trimethylfluorosilane and polymeric $(BF_2CN)_x$ as final products.[7b] These apparently result from the decomposition of the initially formed, unstable $(CH_3)_3SiCN\cdot BF_3$. (Iso)cyanosilane and (iso)cyanogermane show a similar difference in their behavior toward boron triufloride, (iso)cyanosilane giving monofluorosilane,[7b] and (iso)cyanogermane yielding the stable adduct $H_3GeCN\cdot BF_3$.[9]

Trimethyltin(iso)cyanide. The first organotin (iso)cyanide, triethyltin (iso)cyanide, was prepared

(10) H. H. Anderson, *J. Am. Chem. Soc.*, **73**, 5439 (1951).

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by Cahours[13] one hundred years ago by the reaction of silver cyanide with triethyltin bromide, and since then by other investigators[14,15] using different methods. We obtained trimethyltin (iso)-cyanide, a new compound, by two different procedures: by the silver cyanide method, using benzene as a solvent, and by the reaction of aqueous potassium cyanide with trimethyltin iodide in ether, a procedure reported by Luijten and van der Kerk.[15] The products obtained by both methods were shown to be identical. Trimethyltin (iso)-cyanide also reacts with sulfur, incorporating one atom of sulfur into the molecule. However, its physical properties indicate that it is much more polar than the silicon and germanium analogs, and therefore this reaction cannot be taken as conclusive evidence for the presence of the isocyanide structure, since it is known[16] that ionic cyanides react readily with sulfur at higher temperatures to form thiocyanates. Indeed, the trimethyltin-(iso)cyanide-sulfur product was identical with trimethyltin thiocyanate prepared from trimethyltin chloride and sodium thiocyanate in ethanol. Additional indirect evidence that in the case of trimethyltin(iso)cyanide we are dealing with a molecule of much less covalent character is given by its failure to form a molecular addition compound with boron trifluoride. The infrared spectrum of trimethyltin(iso)cyanide shows one band in the C≡N region at 2175 cm.$^{-1}$ and none in the isocyanide region. This does not permit us to distinguish between a covalent and a highly polar cyanide, nor does the absence of a second band in the N=C region allow us to rule out the possible presence in very low equilibrium concentration of an (iso)cyanide isomer. Indeed, the isolation in very low yield of $(CH_3)_3Sn—N=C—Fe(CO)_4$ from the reaction of trimethyltin (iso)cyanide with iron pentacarbonyl showed that at least at 100° some $(CH_3)_3Sn—N=C$ was present.[17a] However, the chemical and physical properties of trimethyltin (iso)cyanide are more in line with those of a highly polar compound, $(CH_3)_3Sn^{\delta+}\text{-}CN^{\delta-}$, rather than those of a mixture of covalent isomers as in the case of the analogous silicon and germanium compounds. Evidence obtained by others also points to a polar cyanide structure for organotin cyanides. Thus, the preparation of triethyltin (iso)cyanide using the action of aqueous potassium cyanide on triethyltin bromide[15] is not consistent with the hydrolytically sensitive covalent isocyanide structure. Also the report by Beermann and Hartmann[17b] that triphenyltin (iso)cyanide in liquid ammonia forms weak complexes with cyanide ion of the type $Na[(C_6H_5)_3Sn(CN)_2]$ speaks for an ionic or at least highly polar structure for organotin cyanides.

This difference between seemingly analogous compounds of silicon and germanium on one hand, and of tin on the other is not unusual. A few examples may serve to illustrate this point. Thus it has been found[18] that the carbonyl stretching frequency in the infrared spectrum of organosilicon acetates is at 1715 cm.$^{-1}$, only slightly lower than the analogous absorption in organic esters. On the other hand, the carbonyl frequency in organotin esters is found in the region characteristic for acetate salts (1580 cm.$^{-1}$). As other examples may be cited the great difference in physical and chemical properties of organosilicon[19] and organotin[20] fluorides, the differences in the reactivity of organosilicon and organotin hydrides,[21] and the hydrolytic behavior of dimethyldichlorosilane,[22] dimethyldichlorogermane,[23] and dimethyltin dichloride.[24]

EXPERIMENTAL[25]

Starting materials. Trimethyliodogermane. The method of Lesbre and Mazerolles[26] was used in this preparation. To 41 g. (0.309 mole) of tetramethylgermane in a three necked flask equipped with a stirrer, a Dry Ice condenser, and a thermometer, was added 78.3 g. (0.309 mole) of iodine and 1 g. of aluminum powder. An exothermic reaction commenced. The temperature was kept at 40° by external cooling, and the reaction mixture was stirred at this temperature for 5 hr. In this time the originally brown solution became nearly colorless. Filtration was followed by fractional distillation to give methyl iodide and 60.5 g. (80%) of trimethyliodogermane, b.p. 57–57.5° at 55 mm., n_D^{24} 1.5159.

Anal. Calcd. for C_3H_9IGe: C, 14.73; H, 3.71. Found: C, 14.56; H, 3.68.

The colorless iodide was very light sensitive, rapidly becoming yellow on standing in daylight.

Trimethyltin iodide was prepared by iodine cleavage of tetramethyltin in benzene solution, using a previously

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described[27] method. Distillation gave an 88.3% yield of $(CH_3)_3SnI$, b.p. 69–70° at 14 mm.

Preparation of the (iso)cyanides. Trimethyl(iso)cyanogermane. To a stirred solution of 58.5 g. (0.239 mole) of trimethyliodogermane in 220 cc. of dry benzene was added in portions during 0.5 hr. 50 g. (0.37 mole) of dry silver cyanide. A mildly exothermic reaction, accompanied by formation of yellow silver iodide, was observed. The mixture was heated at reflux for 2.5 hr., cooled, and filtered. The residue was washed well with benzene, and the washings added to the filtrate. After removal of the benzene, distillation of the remaining liquid resulted in a fraction boiling at 150° which crystallized immediately. The translucent white needles, m.p. 38–38.5°, thus obtained liquefied immediately when in contact with moist air. They were soluble in ether, chloroform, and acetone. Yield: 24.2 g. (70.5%).

Anal. Calcd. for C_4H_9NGe: C, 33.43; H, 6.31; N, 9.75. Found: C, 33.66; H, 6.39; N, 9.66.

Trimethyltin (iso)cyanide. In a similar manner 42.5 g. (0.32 mole) of silver cyanide was added to a solution of 78.5 g. (0.27 mole) of trimethyltin iodide in 400 cc. benzene. The mixture was refluxed for 3 hr. and stirred at room temperature overnight. Filtration was followed by washing of the residue with benzene. The combined filtrate and washings were evaporated, giving 4 g. of white solid. Extraction of the filtration residue in a Soxhlet extractor with chloroform gave very light yellow solid. Recrystallization from chloroform of both solid fractions resulted in 31.5 g. (61.5%) of trimethyltin (iso)cyanide, m.p. 184.5–186° (in a sealed tube filled with nitrogen).

Anal. Calcd. for C_4H_9NSn: C, 25.31; H, 4.78; N, 7.38; Sn, 62.54. Found: C, 25.11; H, 4.98; N, 7.59; Sn, 62.51. Trimethyltin (iso)cyanide is sparingly soluble in benzene and ether, soluble in chloroform and very soluble in acetone. The substance has a distinctly unpleasant odor, but less intense than that of its germanium analog.

The method of Luijten and van der Kerk[15] was also used to prepare this compound. Four grams (20%) of white needles of trimethyltin (iso)cyanide, which after recrystallization from a chloroform-ether mixture melted at 183–184.5°, were obtained from 0.1 mole trimethyltin iodide. Mixed melting point with trimethyltin (iso)cyanide prepared by the silver cyanide method: 183°.

Anal. Found: C, 24.90; H, 4.77; N, 7.26.

Infrared spectra of both samples, measured in chloroform solution, were superimposable.

Reactions with sulfur. Trimethyl(iso)cyanogermane. Nine grams (0.063 mole) of trimethyl(iso)cyanogermane was heated to 170° under nitrogen and 2.02 g. (0.063 mole) of sulfur was added, small portions at a time. After each addition the sulfur was allowed to dissolve completely before the next portion was added. During 5 hr. the temperature was increased to 185°. A clear, colorless liquid remained upon completion of the reaction. Distillation gave 10 g. (90.5%) of trimethylisothiocyanatogermane, b.p. 64–66° at 3 mm., 191.5–193° at atmospheric pressure, n_D^{22} 1.4960. A small amount of sulfur remained as a distillation residue.

Anal. Calcd. for C_4H_9NSGe: C, 27.96; H, 5.16; N, 7.97; S, 18.23. Found: C, 27.45; H, 5.36; N, 8.26; S, 18.06.

Since it has been shown conclusively that the product of the reaction between trimethyl(iso)cyanosilane and sulfur is trimethylisothiocyanatosilane,[28] it was assumed that our product was trimethylisothiocyanatogermane.

Trimethyltin (iso)cyanide. Sulfur (0.450 g., 0.014 mole) and trimethylin (iso)cyanide (2.5 g., 0.0133 mole) were heated under nitrogen for 1 hr. at 150–160°. The melt slowly darkened and a brown solid deposited. The cooled reaction mixture was extracted well with chloroform. Evaporation of the solvent and recrystallization of the residue from benzene gave 1.5 g. (51%) of white needles of trimethyltin thiocyanate, m.p. 105.5–106°. Sublimation raised the m.p. to 108.5°.

Anal. Calcd. for C_4H_9NSSn: C, 21.65; H, 4.09; N, 6.31; S, 14.44. Found: C, 21.82; H, 4.05; N, 6.26; S, 14.28.

Trimethyltin thiocyanate. A method previously described[29] was used to prepare trimethyltin thiocyanate in 86% yield from trimethyltin chloride. Recrystallization from benzene followed by sublimation at reduced pressure gave pure material, m.p. 108–108.5°.

Anal. Found: C, 21.83; H, 4.04; N, 6.45; S, 14.68.

The compound obtained from the trimethyltin (iso)cyanide-sulfur reaction was shown to be identical with the product from this reaction by mixed melting point 108°. The infrared spectra of both compounds, measured in chloroform solution, were identical in all respects. Trimethyltin thiocyanate is easily soluble in chloroform and acetone, difficultly soluble in ether.

Reactions with boron trifluoride. Trimethyl(iso)cyanogermane. A solution of 1.2 g. (8.35 millimoles) of trimethyl(iso)cyanogermane in 1.19 g. (8.35 millimoles) of redistilled boron trifluoride diethyl etherate was allowed to stand at room temperature for 2 hr. The ether then was removed *in vacuo* at 25°, leaving a residue of white crystalline $(CH_3)_3GeCN\cdot BF_3$. The compound, m.p. 85–87° (sealed tube, under nitrogen) sublimes readily *in vacuo* at 40°, is soluble in acetone and ether, less soluble in benzene, and immediately liquefies in moist air. Yield: 1.5 g. (85%).

Anal. Calcd. for $C_4H_9F_3NBGe$: C, 22.71; H, 4.29; N, 6.62. Found: C, 22.81; H, 4.47; N, 6.74.

The compound's infrared spectrum was measured in chloroform solution.

Trimethyltin (iso)cyanide. To 1 g. (5.3 millimoles) of trimethyltin (iso)cyanide was added 3 g. (21 millimoles) of boron trifluoride diethyl etherate. The tin compound dissolved completely. The solution was evaporated after 4 hr., leaving as residue only unchanged trimethyltin (iso)cyanide. The same experiment carried out at 70° during 12 hr. resulted in decomposition of the tin compound, giving a viscous brown oil.

Ethyl isonitrile. Seven-tenths grams of ethyl isonitrile (0.013 mole) was cooled with liquid nitrogen and then allowed to warm slowly. At its melting point, 1.2 g. of boron trifluoride diethyl etherate was added. An immediate, exothermic reaction resulted in a brown tar. A similar tar formation was observed when a drop of boron trifluoride diethyl etherate was added to a dilute solution of ethyl isonitrile in benzene. *tert*-Butyl isonitrile reacted in a similar fashion, but not as vigorously. These reactions were not investigated further.

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[CONTRIBUTION FROM THE POLYMER RESEARCH LABORATORY, THE DOW CHEMICAL CO.]

Thermally Stable Hydrocarbon Polymers: Polyterephthalylidenes

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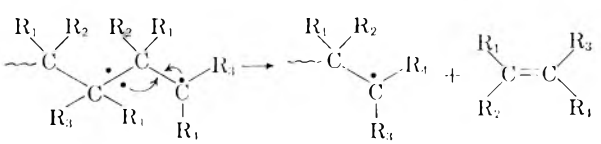
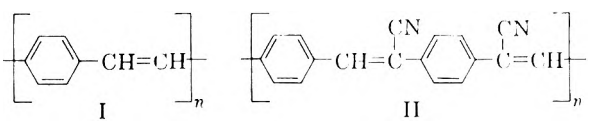
Polymers containing terephthalylidene repeating units were prepared by condensation polymerization employing the Knoevenagel reaction. Thermal stabilities of the polymers were interpreted on the basis of weight loss data and the change in the infrared spectra on pyrolysis. Thermal degradation at 550° resulted in a weight loss of less than 30% and the formation of a stable polymeric residue.

The current approach to the preparation of thermally stable plastics is to synthesize polymers with repeating units analogous in structure to compounds known or even thought to be thermally stable.[1] This approach necessitates the use of reactions which have not been sufficiently characterized to be satisfactorily applied to the formation of high molecular weight polymers. The main objective of this analogy approach, however, is to carry out the polymerization only to the point at which the polymeric products are nonvolatile and suitable for thermal degradation studies without attempting to achieve the degree of polymerization necessary for the realization of adequate stress-strain properties.

With the exception of polytetrafluoroethylene (Teflon), all linear polymers which have backbones consisting of only carbon-carbon bonds and which are prepared by addition polymerization of olefinic monomers are thermally unstable far below the present goal of 500°.[2] This instability is due to the thermodynamic reversibility of addition polymerization.[3] Kinetically, this instability is probably facilitated by the close energy couple characteristic of the elimination of a monomer unit from the radical end of a pyrolyzing polymer chain.[4] That is, the endothermic cleavage of the sigma bond in the chain is probably facilitated by the exothermic coupling of the two unpaired electrons remaining to form the pi bond in the monomer eliminated, as follows:



Condensation polymers cannot regenerate monomers on thermal degradation and, therefore, a close energy couple rarely exists. Accepting this characteristic and considering bond strengths, it should be possible to prepare by condensation polymerization a polymer with an all carbon-carbon backbone which would be kinetically stable above 500°. Several nonvinyl, hydrocarbon polymers have been studied from this point of view including polyphenylene,[5-7] poly-*p*-xylene,[8-11] phenol-formaldehyde polymers,[12] polybenzyl[13-15] and a polymeric Diels-Alder adduct.[16] These polymers were reported to be thermally stable up to temperatures ranging from a low of approximately 350° for polybenzyl to a high of 550° for polyphenylene. In the present study, condensation polymerizations employing the Knoevenagel reaction were applied to the preparation of polyterephthalylidene, I, and polycyanoterephthalylidene, II.



I II

These polymers were of interest because pure compounds of this basic structure prepared by unequivocal synthetic routes were reported to be stable above 350°.[17,18] Attempts were made to prepare

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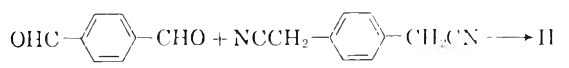
TABLE I

SOLUTION POLYMERIZATION OF TEREPHTHALALDEHYDE AND BENZENE-1,4-DIACETONITRILE

Polymerization	Catalyst	Reaction Temp.	Color of Polymer	Empirical Formula[a]	Aldehyde Content[b]	Decomposition Temp. In Air
A	Sodium methoxide	25–78	Orange	$C_{20}H_{12}N_2O_{2.4}$	5–10%[c]	440–480
B	Piperidine	25–78	Yellow	$C_{18}H_{11}N_2O_{1.1}$	[d]	—
C	Sodium ethoxide	5	Orange	$C_{18}H_{11}N_2O$	5–10%[e]	500–510
D[f]	—	—	Rust	$C_{20.6}H_{12}N_2O_{0.6}$[g]	—	480

[a] Theoretical formula for linear polymer: $C_{18}H_{10}N_2$. [b] By infrared analysis. [c] Ratio of C=C—CN to C—C—CN approximately 30 to 1 by infrared analysis; approximately 25% crystalline by x-ray diffraction. [d] No —OH or —C—C—CN by infrared analysis. [e] No —OH or —C—C—CN by infrared analysis; approximately 25% crystalline by x-ray diffraction. [f] Polymer from C after extraction with boiling quinoline. [g] Equivalent to an average degree of polymerization of four by assuming two aldehyde end groups per chain or a number-average molecular weight of approximately 1200.

polymer I by the self-condensation of *p*-tolualdehyde. Polymer II was prepared by the copolymerization of terephthalaldehyde and benzene-1,4-diacetonitrile:[19–21]



Results. The solution polymerization of terephthalaldehyde and benzene-1,4-diacetonitrile resulted in the formation of a brightly colored, insoluble, infusible product. Sodium ethoxide, sodium methoxide and piperidine proved to be effective catalysts and absolute ethanol was found to be the best solvent for the reaction. Equimolar mixtures of the monomers with these catalysts gave the polymeric products listed in Table I.

All polymeric products obtained were found to be infusible below the decomposition point and insoluble in a wide variety of solvents at the boiling point, including pyridine, nitrobenzene, dimethyl sulfoxide, *n*-butylaniline, 1-methyl naphthalene, *m*-cresol, *p*-chloroaniline, anthracene, dibenzofuran, quinoline, concentrated sulfuric acid, orthophosphoric acid, and concentrated aqueous zinc chloride. A fluorescence spectrum was obtained for polymer A of Table I. The fluorescence spectrum of this polymer contained only one band centered at about 5800 Å. A low molecular weight analog of polycyanoterephthalylidene, prepared from benzaldehyde and benzene-1,4-diacetonitrile, fluoresced with a pale blue color and a broad band centered at about 4800 Å. This compound, benzene 1,4-bis(α-benzoacetonitrile), was readily soluble in warm benzene and nitrobenzene.

Fusion polymerizations of terephthalaldehyde and benzene-1,4-diacetonitrile also gave infusible and insoluble products. These products ranged from light cream, to red, to black in color.

p-Tolualdehyde could not be polymerized in absolute ethanol solution or in mass using sodium ethoxide, pyridine, or piperidine as catalyst.

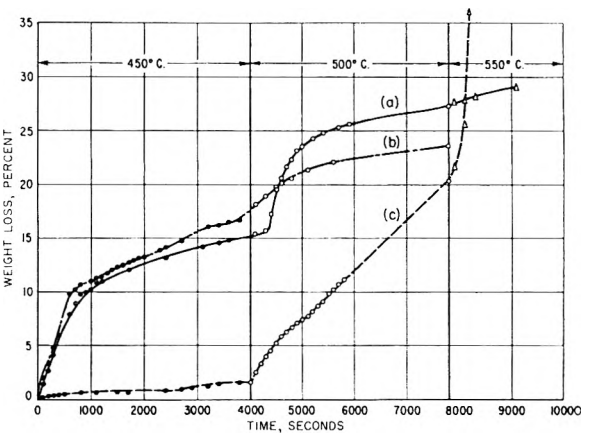


Fig. 1. Thermal gravimetric analyses of (a) polymer C of Table I, (b) polymer D of Table I, (c) polytetrafluoroethylene; weight loss *vs.* time under nitrogen

In both types of reactions, *p*-toluic acid was the principal product.

Thermal degradation studies were made on polycyanoterephthalylidene before and after extraction with boiling quinoline. Measurements were made on the rate of volatilization in a stream of nitrogen at consecutive temperatures of 450°, 500°, and 550° for polymers C and D and for Teflon for comparison, as Teflon is the most stable high polymer containing an all carbon backbone. The results obtained are plotted in Fig. 1. X-ray diffraction patterns and infrared spectra were obtained for polycyanoterephthalylidenes before and after pyrolysis. The infrared spectra of the original extracted polymer D and of this polymer after pyrolysis at 450°, 500°, and 550° consecutively, are shown in Fig. 2. The x-ray diffraction patterns showed that the crystallinity present in the original polymer disappeared completely on pyrolysis at 450°.

Discussion. Several of the polymeric products obtained from the polymerization of terephthalaldehyde and benzene-1,4-diacetonitrile, Table I, had empirical formulas very close to that of the desired repeating unit in polycyanoterephthalylidene, II. The oxygen present appeared to be mostly in the form of aldehyde end groups. Infrared

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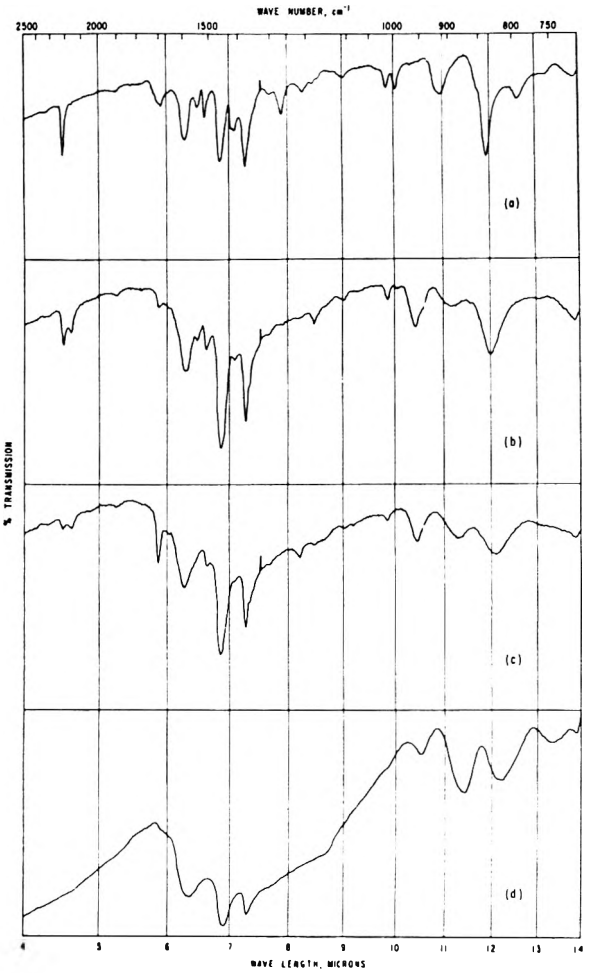


Fig. 2. Infrared spectra of polycyanoterephthalylidenes: (a) polymer C of Table I, (b) same pyrolyzed at 450°, (c) same pyrolyzed at 500°, (d) same pyrolyzed at 550°, (Nujol mulls)

spectroscopic analysis showed that only a very small fraction of the nitrile groups present were on saturated carbon atoms, indicating that the dehydration step went essentially to completion in these reactions and that only negligible amounts of hydroxyl groups were present in the polymers obtained.

The insolubility and infusibility of all of the polymeric materials prepared from both the solution and fusion polymerizations of these monomers suggests that extensive cross-linking occurred in these polymerizations, even though a fairly high order of crystallinity was observed for the polymers. It would not have been surprising, in fact, for the functional groups present in these monomers to have undergone several different types of side reactions. Under the conditions used, reactions which would have led to branching and cross-linking include the Michael addition of hydroxyl or benzylic groups to double bonds in the chain, the Thorpe reaction of these two groups with nitrile functions, and the cyclization of nitrile groups to form trifunctional triazine rings. Other side reactions may have resulted in the formation of thermally-labile linkages especially ester groups, from a Cannizzaro reaction, and carbon-carbon single bonds. Various catalysts, solvents, and reaction temperatures were studied to eliminate or minimize the branching reactions, but in no case was a soluble polymer obtained. The importance of the Cannizzaro reaction is readily apparent from the results of the polymerization studies on *p*-tolualdehyde. The only product isolated in both the solution and fusion runs was *p*-toluic acid even when a weak base, piperidine, was used as the catalyst.

Thermal stability. The thermal gravimetric analyses are presented in the plot of per cent loss in weight *vs.* time in Fig. 1. These curves indicate that polycyanoterephthalylidene was fairly resistant to thermal degradation. Teflon showed very little weight loss (1 to 2%) after one hour at 450°, but rapid decomposition occurred at 500° and complete volatilization ensued at 550°. Polycyanoterephthalylidene, on the other hand, showed a 15 to 20% loss after one hour at 450°, an additional 7 to 12% loss during one hour at 500°, but only an additional 2 to 3% loss after thirty minutes at 550°.

It would not have been possible for this polymer to "unzip" to monomer units or even to any conceivable, simple mixture of low molecular weight, organic products. Volatilization can, therefore, be attributed to one or more of the following effects: (1) low molecular weight polymers were volatilized leaving the high molecular weight fraction of the original polymer; or (2) weak links, built into the polymer chain or pendant to the chain by side reactions, were cleaved, forming volatile polymer fragments or other volatile species, leaving again high molecular weight fragments of the original polymer; or (3) the normal repeating units were being randomly degraded thermally, but the degradation products were largely recombining to form a more stable network structure before complete volatilization occurred.

The infrared spectrum of the original polymer was compared with the spectra after heating the polymer at 450°, 500°, and 550°. The infrared spectra of the material heated at 450° and 500° were essentially the same, but had changed considerably when compared to the spectrum of the original. The spectrum of the material heated to 550° indicated that extensive chemical change had occurred on pyrolysis. Considering both weight loss data and the infrared spectra of the polymer samples after successive heat treatments at 450°, 500°, and 550°, the following mechanisms for thermal degradation are offered.

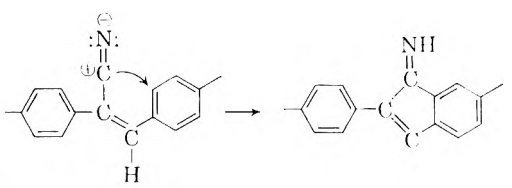
Comparison of the spectra of the original polymer and the polymer heated at 450° indicates that a considerable change in the composition of the polymer had taken place. The weight loss observed at this temperature, therefore, can not be

attributed only to the volatilization of low molecular weight polymer, but probably occurred as a result of a chemical or structural changes in the polymer. These changes could have been caused either by scission of weak links originally present in the skeletal structure of the polymer or by thermal decomposition of the normal repeating units through ionic or radical attack, or both. The original polymer, for example, showed no indication from infrared analysis of containing hydroxyl groups, but the polymers heated at 450° and 500° did contain small amounts of these groups.

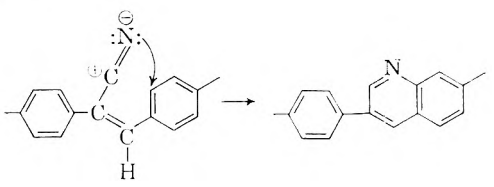
Comparison of the spectra of the samples heated at 450° and 500° indicates that basically little change in composition had occurred between these two temperatures even though a 7 to 12% weight loss was observed. This result indicates that most of the weight loss at 500° can be attributed to the volatilization of low molecular weight fragments which were formed by chemical reactions occurring at or below 450°.

The infrared spectrum of the polymer heated at 550° shows that at that temperature a drastic change had occurred in the molecular structure of the polymer. This material no longer contained measurable amounts of hydroxyl groups, nitrile groups, carbonyl groups, or olefinic double bonds. Closer inspection of all four spectra indicates that actually, the olefin and nitrile groups had been disappearing gradually when the polymers were heated to 450° and 500°. It is quite possible that these changes were caused by attack of the pendant nitrile group on the benzene ring with either, or both, of the following cyclizations occurring:

1. S_E reaction:



2. S_N reaction:



Either reaction would have resulted in the aromatization of the repeating units in the polymer, the first with the formation of iminoindene groups and the second with the formation of quinoline groups. The occurrence of these reactions is indicated, rather convincingly, by the significant increase in intensity of the infrared band at 11.4 microns associated with the presence of lone aromatic hydrogen atoms and the continuous, until complete, disappearance of the band at 11.9–12.2 microns for *p*-phenylene groups.

These reactions should have resulted in the formation of polymeric residues of considerably enhanced thermal stability. The curve in Fig. 1 for the extracted polymer indeed indicates that the residue obtained after heating the polymer at 550° had considerably improved thermal stability over the original polymer. This material showed a weight loss of only 2% after thirty minutes at 550°.

EXPERIMENTAL

Terephthalaldehyde. *p*-Xylene was photobrominated to the tetrabromo derivative and hydrolyzed with dilute sulfuric acid by the procedure of Snell and Weissberger.[22] An overall yield of recrystallized product of approximately 35% was obtained, m.p. 111–112.5°.

Anal. Calcd. for $C_8H_6O_2$: C, 71.5; H, 4.51. Found: C, 71.45; H, 4.46.

Benzene-1,4-diacetonitrile. Three-tenths mole (58 g.) of α,α'-dichloro-*p*-xylene (Eastman Kodak Co.) was dissolved in 350 cc. of 95% ethyl alcohol in a flask and heated to 50°. To this was added dropwise a solution of 0.77 mole (51 g.) of potassium cyanide in 110 cc. of water over a period of 30 min. The solution was then heated at reflux for 90 min. after which the ethyl alcohol was removed by distillation. The residue was combined with 600 cc. of ether and 1 l. of water in a separatory funnel, the ether layer was removed, and the water layer was extracted with three 100-cc. portions of ether. The ether layers were combined and the ether was removed by vacuum distillation on a steam bath. The residue was recrystallized from 95% ethyl alcohol: yield 16 g. (34.1%); m.p. 96–96.5°.

Anal. Calcd. for $C_{10}H_8N_2$: C, 76.9; H, 5.13; N, 17.9. Found: C, 76.79; H, 4.90; N, 17.87.

Polycyanoterephthalylidene. Sodium methoxide catalysis. To a solution of 1.56 g. (0.01 mole) of benzene-1,4-diacetonitrile and 1.34 g. (0.01 mole) of terephthalaldehyde in 200 ml. of ethanol was added dropwise with stirring a solution of 1.5 g. (0.0278 mole) of sodium methoxide (Fisher Scientific Co.) in 25 ml. of ethanol. The color of the reaction mixture changed from clear to bright orange during the addition, and after approximately 15 ml. of the catalyst solution had been added a solid precipitate commenced to form. After addition was complete, the solution was heated to boiling and solvent was distilled off at a slow, steady rate. Concurrently and at approximately the same rate, additional solvent was added dropwise until 250 ml. of solvent had been distilled over a period of approximately 6 hr. The precipitate was collected, washed with ethanol and ether, and dried in a vacuum oven.

Infrared analysis of a Nujol mull of the polymer indicated the presence of approximately 5–10% aldehyde, up to 5% hydroxyl, and a ratio of unsaturated —C=C—CN to saturated —C—C—CN of approximately 30 to 1.

Anal. Calcd. for the repeating unit $C_{18}H_{10}N_2$: C, 85.03; H, 3.94; N, 11.03. Found: C, 74.34; H, 3.98; N, 8.71.

Piperidine catalysis. The polymerization was performed as above but 0.09 g. (0.001 mole) of freshly distilled piperidine was used as the catalyst. A yield of 0.90 g. (35.4%) of a yellow solid was obtained. Infrared analysis of a Nujol mull of the polymer did not indicate any hydroxyl or saturated —C—C—CN present.

Anal. Found: C, 77.85; H, 4.38; N, 8.97.

Sodium ethoxide catalysis. The catalyst was prepared by the addition of 0.20 g. (0.0087 mole) of sodium to 50 ml. of ethanol. This solution was added dropwise to a solution of

(22) J. M. Snell and A. Weissberger, *Org. Syntheses*, Coll. Vol. III, 788 (1955).

2.00 g. (0.015 mole) of terephthalaldehyde and 2.33 g. (0.015 mole) of benzene-1,4-diacetonitrile in 250 ml. of ethanol held at 5° under an atmosphere of nitrogen. When approximately 10 ml. of the catalyst solution had been added the reaction mixture became yellow in color and an orange-yellow solid began to precipitate. Stirring was continued for approximately 16 hr. at 5° then the orange, solid product was filtered, washed with ethanol and ether, and dried in a vacuum oven. Infrared analysis of a Nujol mull indicated the absence of saturated —C—C—CN and hydroxyl groups and the presence of 5–10% aldehyde groups.

Anal. Found: C, 79.32; H, 4.02; N, 10.28.

Two fusion polymerizations were run on this monomer system using sodium methoxide as the catalyst and no solvent. In both experiments, the equimolar monomer mixture was first heated in a sealed glass ampoule under nitrogen. The ampoule was then opened and heating was continued at atmospheric pressure under a stream of nitrogen.

Polyterephthalylidene. The self-condensation of *p*-tolualdehyde was attempted by both solution and mass polymerizations as above. Sodium ethoxide, pyridine, and piperidine were used as catalysts and absolute ethanol as the solvent in the solution runs.

Thermal decomposition measurements. Thermal decomposition measurements were made on polymers C and D and on Teflon for comparison. A tubular electric furnace and a chainomatic balance were incorporated into an apparatus constructed for thermal gravimetric analysis. The polymers were pyrolyzed under a nitrogen atmosphere.

Acknowledgment. The authors wish to express their appreciation to R. A. Nyquist for assistance in obtaining and interpreting the infrared spectra of the polymers.

MIDLAND, MICH.

[COMMUNICATION NO. 2045 FROM THE RESEARCH LABORATORIES, EASTMAN KODAK CO.]

Bisesteramides of Terephthalic Acid

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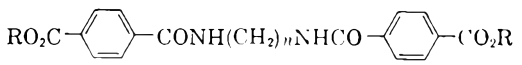
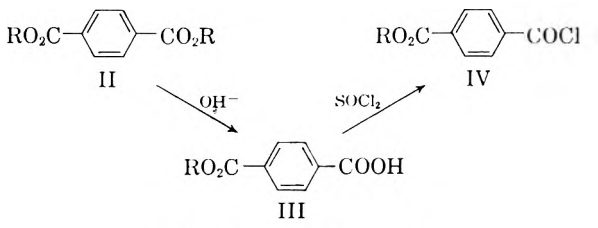
A general synthesis for a new class of bisesteramides I has been devised. Terephthalic esters were hydrolyzed to the ester acids and converted to the acid chlorides which, when treated with the diamine and base, yielded the bisesteramides. Alternate syntheses for specific esteramides are also discussed.

During the investigation of a new class of polyesters, it became necessary to prepare a series of esteramides of the type I.



I

The terephthalic esters (II) were hydrolyzed to the ester acid (III), which, in turn, was converted to the acid chloride (IV) with thionyl chloride.[1] Reaction of two moles of IV with one mole of an aliphatic diamine (V) in the presence of a base gave the required esteramide, I.



II IV III

$$2\text{IV} + \text{H}_2\text{N}(\text{CH}_2)_n\text{NH}_2 \longrightarrow \text{I}$$

V

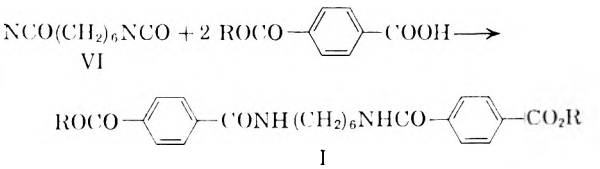
The physical constants and analytical data for the bis(4-carboalkoxybenzoyl)alkylenediamines which have been prepared by this method are collected in Table I. Three derivatives of secondary amines are appended at the end of the table.

(1) J. B. Cohen and H. S. DePennington, *J. Chem. Soc.*, 113, 57 (1918).

The required dialkyl terephthalates (II) were prepared by ester interchange from dimethyl terephthalate and the appropriate alcohol using titanium tetrabutoxide as a catalyst.

Formation of the esteramide, I, from IV and V was carried out, using either pyridine or aqueous sodium hydroxide as the acid-acceptor. The latter method was preferred since the use of pyridine led to the formation of colored by-products.

An alternate synthesis of the six carbon esteramides I (n = 6) was accomplished by the following isocyanate method:



VI

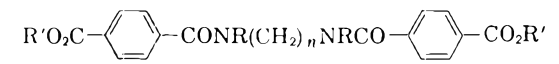
I

Where R, = C_2H_5, a yield of 71% was obtained.

During the preparation of *N,N'*-bis(*p*-carbomethoxybenzoyl)hexamethylenediamine, I (n = 6; R = CH_3), a high-melting impurity was isolated. Its formation was favored by long reaction times, high temperatures, and excess isocyanate. The high-melting by-product was more evident during a reaction time of fourteen minutes at 225° than at 175° for an hour and a half. Table II summarizes the reaction conditions and yields of various run in a number of solvents.

TABLE I

N,N'-BIS(4-CARBOALKOXYBENZOYL)ALKYLENEDIAMINES



I

n	R	R'	Compound	Yield, %	M.P., °C.	Empirical Formulas	Analyses Calcd. C	H	N	Found C	H	N
0	H	*i*-C_4H_9	*N,N'*-Bis(*p*-carboisobutoxybenzoyl)hydrazine	88.2	180–181	$C_{24}H_{28}N_2O_6$	65.5	6.4	6.4	65.1	6.4	6.4
2	H	CH_3	*N,N'*-Bis(*p*-carbomethoxybenzoyl)ethylenediamine	69	247–248	$C_{22}H_{24}N_2O_6$	64.2	5.8	6.8	64.5	6.1	7.3
2	H	C_2H_5	*N,N'*-Bis(*p*-carbethoxybenzoyl)-ethylenediamine	69	247–249	$C_{22}H_{24}N_2O_6$	64.2	5.8	6.8	64.2	6.1	7.3
2	H	*n*-C_4H_9	*N,N'*-Bis(*p*-carbobutoxybenzoyl)-ethylenediamine	92.6	211–212	$C_{26}H_{30}N_2O_6$	66.7	6.9	6.0	67.1	7.1	5.8
2	H	*i*-C_4H_9	*N,N'*-Bis(*p*-carboisobutoxybenzoyl)ethylenediamine	96.5	194–195	$C_{26}H_{30}N_2O_6$	66.7	6.9	6.0	67.1	6.8	5.8
3	H	*i*-C_4H_9	*N,N'*-Bis(*p*-carboisobutoxybenzoyl)trimethylenediamine	85.6	176–177	$C_{27}H_{34}N_2O_6$	67.2	7.0	7.8	67.4	7.2	7.9
4	H	CH_3	*N,N'*-Bis(*p*-carbomethoxybenzoyl)tetramethylenediamine	75.7	255–256	$C_{22}H_{26}N_2O_6$	64.3	5.8	6.8	64.1	6.1	7.2
5	H	*i*-C_4H_9	*N,N'*-Bis(*p*-carboisobutoxybenzoyl)pentamethylenediamine	86.5	140–141	$C_{29}H_{38}N_2O_6$	68.3	7.4	5.5	68.4	7.3	5.6
6	H	CH_3	*N,N'*-Bis(*p*-carbomethoxybenzoyl)hexamethylenediamine	63.0	232–233	$C_{24}H_{28}N_2O_6$	65.4	6.4	6.4	65.8	6.1	6.2
6	H	C_2H_5	*N,N'*-Bis(*p*-carbethoxybenzoyl)-hexamethylenediamine	88.8	207–208	$C_{26}H_{32}N_2O_6$	66.7	6.8	5.9	67.0	7.1	5.9
6	H	*n*-C_4H_9	*N,N'*-Bis(*p*-carbobutoxybenzoyl)-hexamethylenediamine	94	188–189	$C_{30}H_{40}N_2O_6$	68.7	7.6	5.4	68.8	7.8	5.3
6	H	*i*-C_4H_9	*N,N'*-Bis(*p*-carboisobutoxybenzoyl)hexamethylenediamine	80	165–166	$C_{30}H_{40}N_2O_6$	68.7	7.6	5.4	69.0	7.9	5.3
	CH_3	*i*-C_4H_9	*N,N'*-Dimethyl-*N,N'*-bis(*p*-carboisobutoxybenzoyl)ethylenediamine	51	138–139	$C_{28}H_{38}N_2O_6$	67.7	7.2	5.6	67.3	6.8	5.3
	CH_3	*i*-C_4H_9	*N,N'*-Dimethyl-*N,N'*-bis(*p*-carboisobutoxybenzoyl)hexamethylenediamine	71	81–82	$C_{32}H_{49}N_2O_6$	69.5	7.8	5.1	69.6	8.1	5.4
		CH_3	*N,N'*-Bis(*p*-carbomethoxybenzoyl)piperazine	56.1	230–231	$C_{22}H_{22}N_2O_6$	64.5	5.3	6.8	64.9	4.9	7.1

TABLE II

BISISOCYANATE PREPARATION OF *N,N'*-BIS(*p*-CARBOMETHOXYBENZOYL)HEXAMETHYLENEDIAMINE

Run	Temperature, °C.	Time, min.	Solvent	Yield, %
1	215	20	None	56
2	215	60	None	53
3	215	90	None	33
4	215	150	None	40
5	175	90	None	50
6	175	45	Dimethylformamide	12
7	175	60	Chlorobenzene	35
8	175	60	*m*-Dichlorobenzene	62–65
9	175	60	*n*-Octane	<2
10	175	60	Dow ethylbenzenes	65
11	175	135	Dioxane	3
12	175	60	Dimethylaniline	44

Although Dow diethylbenzene mixture was shown to be the preferred reaction medium, the reaction temperature remained critical. The diisocyanate method is more satisfactory for the preparation of *N,N'*-bis(*p*-carbethoxybenzoyl)-hexamethylenediamine [I (n = 6; R = C_2H_5)] and *N,N'*-bis(*p*-carbobutoxybenzoyl)hexamethylenediamine [I (n = 6; R = *n*-C_4H_9)] than for the higher-melting *N,N'*-bis(*p*-carbomethoxybenzoyl)-hexamethylenediamine [I (n = 6; R = CH_3)], since the latter must be prepared at temperatures in excess of 200°, a region where secondary reactions occur. Attempts to prepare *N,N'*-bis(*p*-carboisobutoxybenzoyl)hexamethylenediamine [I (n = 6; R = *i*-C_4H_9)] from the diisocyanate failed to produce the desired product.

Two other methods for making the amides [I (n = 6; R = *i*-C_4H_9 and n = 6; R = C_2H_5)] directly from the acid were investigated. The first method consisted in the reaction of phosphorus trichloride with a diamine form a reactive phosphazo derivative (VII) which readily condensed with acids to give amides. This reaction proceeded smoothly, and I (n = 6; R = *i*-C_4H_9) and I (n = 6; R = C_2H_5) have been prepared in yields of 80 to 85%.

$$H_2N(CH_2)_nNH_2 + PCl_3 \longrightarrow \overline{P{=}N(CH_2)_nN} + 2RCOOH \longrightarrow RCONH(CH_2)_nNHCOR$$

VII

The second method consisted in preparing the mixed anhydride (IX) from 4-carboisobutoxybenzoic acid and ethyl chlorocarbonate. This mixed anhydride, when treated with hexamethylenediamine, gave a 65 to 70% yield of I (n = 6; R = i-C_4H_9).

Preliminary synthetic experiments were carried out in the methyl and ethyl series, the intermediates of which were readily handled in small laboratory-sized runs. In order to take advantage of more favorable solubility characteristics and the resulting ease of handling of larger-scale preparations, the n-butyl and i-butyl systems were used in later preparations.

EXPERIMENTAL

p-Carbomethoxybenzoic acid [III (R = CH_3)]. To a solution of 100 g. (0.52 mole) of dimethyl terephthalate [II (R = CH_3)] in 150 ml. of refluxing methanol was added a solution of 32.6 g. (0.58 mole) of potassium hydroxide in 600 ml. of water. The saponification was completed in about 10 min. as evidenced by the fact that a sample of the reaction mixture was completely soluble in water. After the addition of an equal volume of water, the diluted reaction mixture was acidified with hydrochloric acid. The white precipitate was collected by filtration. The dried filter cake weighed 61.5 g. (65.5%). Pure III (R = CH_3), m.p. 228–230°, was obtained by crystallization from water.

The following acid esters were prepared in a similar fashion using the appropriate alcohol as the reaction medium: *p*-carbethoxybenzoic acid (III. R = C_2H_5), m.p. 169–171° from toluene, 74% yield; *p*-carboxoisobutoxybenzoic acid (III. R = i-C_4H_9), m.p. 153° from toluene, 69% yield; *p*-carbobutoxybenzoic acid (III, R = n-C_4H_9), m.p. 132.5–133.5° from toluene, 66% yield.

p-Carbomethoxybenzoyl chloride (IV. R = CH_3). A solution of 28.0 g. (0.16 mole) of III (R = CH_3) in 32.4 g. (0.3 mole) of thionyl chloride was heated under reflux for 18 hr. Distillation of the reaction mixture gave 27.6 g. (89%) of IV (R = CH_3), b.p. 135–138°/10 mm., m.p. 54–55°. *p*-Carbethoxybenzoyl chloride (IV. R = C_2H_5), m.p. 27°, b.p. 133–134°/6 mm.; *p*-carboisobutoxybenzoyl chloride (IV. R = i-C_4H_9), b.p. 155–157°/7 mm., m.p. 38.5° and *p*-carbobutoxybenzoyl chloride (IV. R = n-C_4H_9), b.p. 115–118°/0.5 mm., m.p. 13.5°, n_D^{25} 1.5260 were prepared in a similar fashion.

Diisobutyl terephthalate (II. R = i-C_4H_9). In a round bottomed, three-necked, 22-l. flask equipped with a 100-cm. long by 2.5-cm. wide helices-packed column and a partial-takeoff head there was placed 4 kg. (20.6 moles) of dimethyl terephthalate, 14 l. of isobutanol, and 25 ml. of titanium butoxide. By balancing the heat input to the mantle with the takeoff rate, the temperature of the distillate was maintained at 64–68°. After 1500 ml. of distillate was collected, the mantle heat was increased until the temperature reached 105°, at which time distillation was continued for 0.5 hr. The reaction mixture was cooled to 50°. The residual crude ester (II. R = i-C_4H_9) was used directly for the preparation of III (R = i-C_4H_9). Dibutyl terephthalate (II. R = C_4H_9) was prepared in a similar fashion. Diethyl terephthalate was prepared according to the method of Koelsch.[2]

N,N'-Bis(p-carbobutoxybenzoyl)ethylenediamine [I (n = 2, R = C_4H_9)]. a. *Alkali method.* In a 4-l. beaker equipped with an efficient stirrer was placed 19 g. (0.3 mole) of 95% ethylenediamine, 700 ml. of water, and 700 ml. of benzene. To the well stirred mixture was added, dropwise, one half of Solution A [144 g. (0.6 mole) of *p*-carbobutoxybenzoyl chloride in 150 ml. of benzene]. After 10 min., one half of Solution B [24 g. (0.6 mole) of sodium hydroxide in 150 ml. of water] was added dropwise, followed by one half of the remainder of Solution A and then one half of the remainder of Solution B. The sequence was continued until the addition of both solutions was completed. The viscous slurry was filtered and the solids washed by slurrying with 3-l. portions of hot water. The product, after it had been collected and dried, weighed 133 g. Crystallization from 1800 ml. of butyl alcohol yielded 130 g., 92.6% of I (n = 2, R = C_4H_9), m.p. 211°.

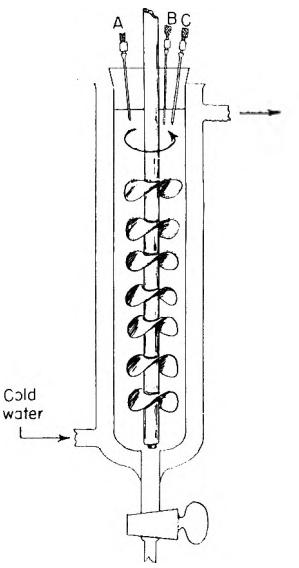


Fig. 1. Continuous Schotten-Baumann reactor

N,N'-Bis(p-carbethoxybenzoyl)hexamethylenediamine [I (n = 6, R = C_2H_5)]. b. *Pyridine method.* To a solution of 34.8 g. (0.3 mole) of hexamethylenediamine in 500 ml. of pyridine was added dropwise, with stirring, 127.5 g. (0.6 mole) of *p*-carbethoxybenzoyl chloride. After the addition was complete, the reaction mixture was stirred for 15 min. and poured into an ice-water slurry. The crude product which was collected by filtration was crystallized from 4 l. of ethanol to give 125 g. (88.8%) of I (n = 6, R = C_2H_5), m.p. 207–208°.

N,N'-Bis(p-carboisobutoxybenzoyl)hexamethylenediamine [I (n = 6, R = i-C_4H_9)]. c. *Using a continuous reactor.* In order to prepare larger quantities of this derivative, the glass water-jacketed reactor shown in Fig. 1 was used. The inner section of the reactor was 1.5 in. wide by 24 in. long, the upper end of which was closed with a rubber stopper. Nozzles A, B, and C, the stirrer shaft, and a thermometer were inserted through the stopper. The water jacket served to maintain the reaction temperature at the desired level. Agitation was provided for mixing by the motor-driven shaft bearing three-bladed propellers spaced 0.5 in. apart along its total length. A benzene solution of IV (R = i-C_4H_9) was injected through nozzle B while an aqueous solution of hexamethylenediamine and sodium hydroxide was admitted through nozzle C. Water was added through nozzle A at such a rate that the volume within the reactor remained constant. The reaction was immediate, and the solid product which settled slowly to the bottom of the vessel was withdrawn through the large-bore stopcock. Reaction solutions as follows were prepared: 4329 g. (18 moles) of IV (R = i-C_4H_9) was dissolved in benzene to a total volume of 4860 ml.; 1044 g. (9 moles) of hexamethylenediamine and 760 g. (18 moles) of sodium hydroxide in water to a total volume of 9720 ml. In a typical run, the reactants were added as follows: water, 15 l. per hr.; amine-alkali solution, 7.8 l. per hr.; acid chloride–benzene, 3.9 l. per hr. The agitator was rotated at 100 r.p.m. in such a manner that settling of the solids was

(2) C. F. Koelsch, *Org. Syntheses*, 26, 96 (1946).

retarded. By operation of the above procedure at 30° for 1.5 hr., there was obtained after recrystallization from isobutanol, 3850 g. (87%) of I (n = 6, R = i-C_4H_9), m.p. 165–166°.

d. *Mixed anhydride method.* p-Carboisobutoxybenzoic acid, 22.2 g. (0.1 mole), was dissolved in 100 ml. of dry chloroform and the solution cooled to 0°. Triethylamine, 10.1 g. (0.1 mole), was then added, followed by 10.8 g. (0.1 mole) of ethyl chlorocarbonate. The mixture was maintained at 0–5° for 2 hr., at which time a solution of 5.3 g. (0.05 mole) of hexamethylenediamine in 30 ml. of dry chloroform was added. The temperature of the mixture rose rapidly to 30° and carbon dioxide was evolved. The reaction mixture was allowed to stand at 5° for 18 hr. at which time the chloroform solution was washed with water and dilute sodium carbonate. The chloroform solution was dried over potassium carbonate and distilled to give a residue, which, after crystallization from ethanol, gave 20 g. of I (n = 6, R = i-C_4H_9), m.p. 165–166°.

N,N'-Bis(p-carbethoxybenzoyl)hexamethylenediamine [I (n = 6; R = C_2H_5)]. e. *Phosphorus trichloride method.* Phosphorus trichloride (3.25 ml.) was added slowly to 4.3 g. of hexamethylenediamine in 20 ml. of pyridine held at 10°. After the reaction mixture was stirred for 0.5 hr. at 20°, a solution of 9.3 g. of p-carbethoxybenzoic acid in 25 ml. of warm pyridine was added. The reaction mixture was heated on the steam bath for 3 hr. after which time excess pyridine was distilled at reduced pressure. The residue was stirred sequentially with water, dilute sodium carbonate, and methanol to give 9.4 g. (82%) of I (n = 6, R = C_2H_5), m.p. 228–229°.

ROCHESTER, N. Y.

[CONTRIBUTION FROM MELLON INSTITUTE]

Ozonolysis of Fluoranthene[1]

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During ozonolysis, a molecule of fluoranthene is attacked by two molecules of ozone. Using aqueous sodium bicarbonate to decompose the active-oxygen-containing products thus formed, fluorenone-1-aldehyde was obtained in high yield along with lesser amounts of fluorenone-1-carboxylic acid. Fluorenone-1-carboxylic acid was obtained in high yield by peracetic acid oxidation of fluorenone-1-aldehyde. A near quantitative yield of the dimethyl acetal of fluorenone-1-aldehyde was obtained by refluxing the aldehyde in methanol in the presence of a trace of peracetic acid. Alkaline cleavage of the dimethyl acetal of fluorenone-1-aldehyde produced the previously unreported isodiphenaldehydic acid in excellent yield. Good yields of isodiphenic acid were obtained by ozone oxidation of the aldehyde-acid. Baeyer-Villiger oxidation of fluorenone-1-carboxylic acid produced the previously unreported 1-carboxy-9-oxa-9,10-dihydrophenanthrene-10-one. The n-butyl ester of this lactone was also prepared and characterized.

Fluoranthene (I) reportedly has been ozonized to a mixture of fluorenone-1-aldehyde (II) and fluorenone-1-carboxylic acid (III),[2-4] but the yield was only about 30%. In recent years, there have been many new developments concerning the reaction of ozone with organic compounds.[5] It seemed advisable, therefore, to re-evaluate the action of ozone on fluoranthene in the light of new reactions and techniques. By analogy with the ozonolysis of naphthalene,[6] one might expect that one mole of fluoranthene would react readily with two moles of ozone to give the difficultly accessible 1-substituted fluorenones in high yield. This was indeed found to be so. It should be mentioned that a recent publication by Copeland and co-workers[7] (which appeared after the completion of our work) agrees with our conclusions although the experimental approach was different. Copeland reports an 84% yield of II and an 80% yield of III from the ozonolysis of fluoranthene in an unspecified solvent.

When a suspension of fluoranthene in anhydrous t-butyl alcohol was treated with two molecular equivalents of ozone at room temperature, an orange-yellow solution resulted. Titration of the active oxygen showed that 93% of the theoretical was present in the solution. Furthermore, the active oxygen was present as hydroperoxide since a positive test was obtained using lead tetraacetate.[8] It was not hydrogen peroxide, however, because a negative test was obtained with a titanium salt. The distinguishing test is based on the yellow-orange color which is developed by titanic acid in the presence of hydrogen peroxide but which is not developed with other hydroperoxides.[9] Decomposition of the active-oxygen-containing solution by steam distillation resulted in an orange-yellow solid, which was a mixture of fluorenone-1-aldehyde (about 60%) and fluorenone-1-carboxylic acid (about 40%). In addition, the aqueous phase was found to contain glyoxal, hydrogen peroxide, and

(1) Paper presented before the Division of Organic Chemistry, American Chemical Society, 136th Meeting, Atlantic City, N. J., Sept. 17, 1959.

(2) *The Ozonolysis of Aromatic Compounds: A Literature Survey*, Report No. 0181, The Coal Tar Research Association, April 12, 1957.

(3) H. Vollman, *Ann.*, **531**, 65 (1937).

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(5) Philip S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

(6) P. S. Bailey and F. J. Garcia-Sharp, *J. Org. Chem.*, **22**, 1008 (1957).

(7) P. G. Copeland, R. E. Dean, and D. McNeil, *Chem. & Ind. (London)*, p. 329 (March 7, 1959).

(8) R. Criegee, *Fortschr. chem. Forsch.*, **1**, 536 (1950).

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formic acid. Glyoxal was present only in a very small amount and was identified by the Ariyama color test,[10] which involves the formation of a deep blue color with arsenophosphotungstic acid solution. Formic acid was characterized by Duclaux values and estimated by titration. These facts are presumptive evidence for the reaction sequence as shown.

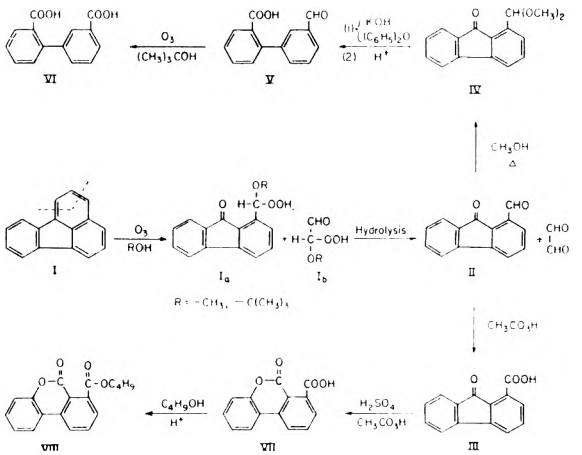
During the ozonolysis of fluoranthene in anhydrous *t*-butyl alcohol, the initial zwitterion intermediates react with the solvent to form fluorenone-1-*t*-butoxymethyl hydroperoxide (Ia) and *t*-butoxyformylmethyl hydroperoxide (Ib). Upon steam distilling, these two hydroperoxides are decomposed yielding fluorenone-1-aldehyde, glyoxal, hydrogen peroxide, and *t*-butyl alcohol. The hydrogen peroxide which is formed oxidizes most of the glyoxal to produce formic acid and part of the fluorenone-1-aldehyde to fluorenone-1-carboxylic acid. The hydrogen peroxide oxidation of glyoxal to formic acid has been reported in the literature.[11]

The highest yield of fluorenone-1-aldehyde was obtained by ozonolysis of fluoranthene in aqueous *t*-butyl alcohol. The intermediate was decomposed by the addition of aqueous sodium bicarbonate soution. The insoluble fluorenone-1-aldehyde precipitated and was removed by filtration. The yield was 77%. Distillation to remove the solvent, followed by acidification of the bicarbonate solution, produced fluorenone-1-carboxylic acid in 18% yield.

In methanol, ozonolysis takes the same course as in *t*-butyl alcohol but leads to some acetal formation. The acetal formation appears to be catalyzed by peroxides, and this will be more fully discussed later. The weakly basic sodium bicarbonate solution stabilizes the acetal, but acid hydrolysis results in the formation of the expected fluorenone-1-aldehyde. A typical run in methanol produced fluorenone-1-aldehyde in 36% yield, the dimethyl acetal of fluorenone-1-aldehyde in 25% yield, and fluorenone-1-carboxylic acid in 30% yield.

The reaction sequence which occurs when aqueous acetone is used as a solvent is not fully understood. It appears certain, however, that it is similar to the reaction in methanol or *t*-butyl alcohol since the same products are obtained. Aqueous acetone was actually the best solvent used since it dissolves fluoranthene more readily and thereby gives better ozone absorption. In a strictly commercial sense, it is also the cheapest of the solvents used. Using aqueous acetone, a 71% yield of fluorenone-1-aldehyde was obtained along with an 11% yield of fluorenone-1-carboxylic acid.

Since ozonolysis of fluoranthene affords the difficultly accessible 1-substituted fluorenones in good yield, some reactions of these materials were studied to determine their general utility in organic



synthesis. Fluorenone-1-aldehyde has apparently never been prepared, except by ozonolysis of fluoranthene; whereas, fluorenone-1-carboxylic acid can be obtained from the parent hydrocarbon using the usual oxidants. The yields of carboxylic acid, however, were only of the order of 50%.[12]

Fluorenone-1-aldehyde undergoes some reactions characteristic of aromatic aldehydes readily; others only with difficulty or not at all. For example, attempts to oxidize fluorenone-1-aldehyde to the carboxylic acid with ozone were unsuccessful, and the maximum yield obtained in any solvent was 26%. Liquid-phase air oxidation was also unsuccessful, but oxidation with peracetic acid gave an 80% yield. The dimethyl acetal of fluorenone-1-aldehyde was formed in almost quantitative yield by refluxing the aldehyde in methanol in the presence of a catalytic amount of peracetic acid. Attempts to reduce the aldehyde to an alcohol by means of the crossed Cannizzaro reaction and catalytic hydrogenation were unsuccessful, and Meerwein-Pondorf-Verely reduction gave 1-hydroxymethyl-9-fluorenol as the major product.

In his study on the opening of the ketonic ring in substituted fluorenones, Huntress[13] subjected fluorenone-4-carboxylic acid to the action of potassium hydroxide in diphenyl ether and obtained both diphenic and 2-phenyl isophthalic acid. The reaction was not complete, however, and 15 to 25% of the original keto-acid was recovered from the mixture of fusion products. When fluorenone-1-carboxylic acid was subjected to the action of alkali in diphenyl ether, a single product, isodiphenic acid, was obtained in 61% yield. Here, too, reaction was not complete, and 12% of the original keto-acid was recovered unchanged.

A novel way of causing the reaction to go to completion was discovered. The keto-aldehyde (fluorenone-1-aldehyde) was converted into the dimethyl acetal. Alkaline cleavage of the dimethyl acetal proceeded smoothly and resulted in a 94% yield of the heretofore unreported isodiphenaldehydic acid.

(10) N. Ariyama, *J. Biol. Chem.*, **77**, 359 (1928).

(11) J. H. Payne and G. F. Lemon, Jr., *J. Am. Chem. Soc.*, **63**, 226 (1941).

(12) L. Fieser, *J. Am. Chem. Soc.*, **57**, 2174 (1935).

(13) E. H. Huntress, *J. Am. Chem. Soc.*, **61**, 1358 (1939).

Ozone oxidation of this aldehyde-acid in *t*-butyl alcohol produced isodiphenic acid in 74% yield.

Baeyer-Villiger oxidation of fluorenone-1-carboxylic acid at room temperature with peracetic and sulfuric acids for two days produced a nearly quantitative yield of crude 1-carboxy-9-oxa-9,10-dihydrophenanthrene-10-one, which melted with decomposition above 200°. A portion of this material was recrystallized to a constant melting point of 244–247°. Proof of structure was accomplished by saponifying the product with sodium hydroxide and oxidizing with potassium permanganate. Depending on whether the lactone is the 1- or 8-carboxy isomer, hemimellitic or phthalic acid would be the expected product. Hemimellitic acid was the only product obtained; therefore, the lactone is the one-isomer. The *n*-butyl ester of the carboxy-lactone was obtained in 58% yield by refluxing the crude oxidation product with *n*-butyl alcohol and *p*-toluenesulfonic acid for five hours while removing water. The purified ester melts at 140–142°.

EXPERIMENTAL

The fluoranthene used in this work was commercial material, m.p. 110°, and was estimated to be 98 to 99.5% purity. The methanol, *t*-butyl alcohol, and acetone were reagent-grade materials. All melting points are uncorrected.

The ozonator used in this research was a Welsbach Corporation Model T-23 laboratory ozonator operated with 115 volt, 60 cycle current and using pure, clean, dry oxygen. The oxygen feed was obtained in commercial cylinders and dried to at least −60°F. dew point with a laboratory "Lectrodryer" sold by the Pittsburgh Lectrodryer Corporation. The reaction vessels were the usual gas-absorption type with the gas inlet at the bottom, a coarse-porosity sealed-in fritted disk just above the inlet to disperse the incoming gases, and the outlet at the top. The reaction vessel was equipped with a mechanical or magnetic stirring device and a reflux condenser to return solvent from the gas stream. Ozone concentrations were determined with a Welsbach Model C ozone meter or iodometrically as detailed in the *Welsbach Basic Manual of Applications and Laboratory Ozonization Techniques.*

I. Ozonizations. A. Ozonolysis of fluoranthene in anhydrous t-butyl alcohol to give fluorenone-1-aldehyde (II). A suspension of fluoranthene (10.0 g., 0.0495 mole) in 200 ml. of anhydrous *t*-butyl alcohol was treated with approximately 2.3 weight per cent ozone (in oxygen) at room temperature and a flow rate of 102 l. per hr. for 96 min. Using these conditions, 4.96 g. (0.103 mole) of ozone (2.08 molecular equivalents) was passed into the reaction mixture. The resulting yellow-orange solution was transferred into a 250-ml. volumetric flask and diluted to the mark with *t*-butyl alcohol. A 10-ml. aliquot was titrated for active oxygen. The total solution was found to contain 92.5 mmoles of active oxygen (theory = 99 mmoles). The solution gave a positive test for hydroperoxide with lead tetraacetate[8] and a negative test for hydrogen peroxide using titanous chloride solution.[9] The *t*-butyl alcohol was removed by steam distillation, and the residue which remained in the flask was removed by filtration yielding 9.9 g. of orange solids which melted at 152–162°. The aqueous filtrate gave the Ariyama[10] color test for glyoxal and a positive test for hydrogen peroxide.[9] The aqueous filtrate also contained formic acid, which was characterized by Duclaux values. The orange solids from above were allowed to reflux for 1 hr. with 200 ml. of 7% aqueous sodium bicarbonate solution. Filtration yielded 6.6 g. (64% yield) of crude fluorenone-1-aldehyde, which melted at 169–175°. Several recrystallizations from ethanol raised the melting point to 193–194°.[4] Upon acidification of the bicarbonate solution, precipitation occurred. Filtration yielded 3.3 g. (30% yield) of crude fluorenone-1-carboxylic acid, which melted at 175–183°. Several recrystallizations from glacial acetic acid raised the melting point to 196–197°.[4]

B. Ozonolysis of fluoranthene in aqueous t-butyl alcohol to give fluorenone-1-aldehyde (II). A suspension of fluoranthene (10.0 g., 0.0495 mole) in 200 ml. of 87.5% aqueous *t*-butyl alcohol was treated with approximately 2.0 weight per cent ozone (in oxygen) at room temperature (30°) and a flow rate of 102 l. per hr. for 2 hr. and 33 min. Under these conditions, 6.63 g. (0.138 mole) of ozone or 2.8 molecular equivalents were passed into the reaction mixture. The ozone absorption was poor and only about 2 molecular equivalents of ozone was actually absorbed. After flushing with oxygen, the light-yellow solution was transferred into an 800-ml. beaker containing 300 ml. of 5% aqueous sodium bicarbonate solution. Precipitation occurred, and the yellow solid was removed by filtration yielding 6.1 g. (59.2% yield) of fluorenone-1-aldehyde which melted at 188–191°. Recrystallization raised the melting point to 193–194°; lit.,[4] m.p. 194°. The filtrate was distilled to remove *t*-butyl alcohol. Filtration yielded an additional 1.9 g. (18.4% yield) of crude fluorenone-1-aldehyde, which melted at 145–158° (identified by infrared spectrum). Upon acidification of the remaining bicarbonate solution, precipitation occurred. Filtration yielded 2.0 g. (18% yield) of crude fluorenone-1-carboxylic acid as an orange solid which melted at 170–181°. Recrystallization from glacial acetic acid raised the melting point to 196–197°; lit.,[4] m.p. 197°.

C. Ozonolysis of fluoranthene in methanol. A solution of fluoranthene (10 g., 0.0495 mole) in 400 ml. of methanol was treated with approximately 4.3 weight per cent ozone (in oxygen) at a flow rate of 34 l. per hr. at room temperature (30°) for 2 hr. and 36 min. Under these conditions, 2.08 molecular equivalents (4.95 g., 0.103 mole) of ozone was passed into the reaction mixture. After flushing with oxygen, the light-yellow solution was transferred into a 1-l. flask, and a mixture of 200 ml. of 7% aqueous sodium bicarbonate solution and 200 ml. of water was added. The methanol was then removed by distillation to a head temperature of 95°. A brown viscous oil remained in the bicarbonate solution and was extracted using 100 ml. of chloroform. The chloroform was evaporated to dryness and the residue treated with aqueous acetone (100:50) and concd. hydrochloric acid (2 ml.). Upon refluxing, a precipitate formed yielding 3.7 g. (35.9% yield) of crude fluorenone-1-aldehyde which melted at 188–192°. A mixed melting point with an authentic sample showed no depression. Evaporation of the aqueous acetone yielded 3.3 g. (25% yield) of crude dimethyl acetal of fluorenone-1-aldehyde (identified by its infrared spectrum). Acidification of the bicarbonate solution yielded 3.3 g. (29.7% yield) of crude fluorenone-1-carboxylic acid which melted at 185–190° (no depression with an authentic sample).

D. Ozonolysis of fluoranthene in aqueous acetone. A suspension of fluoranthene (60 g., 0.297 mole) in a mixture of acetone (800 ml.) and water (400 ml.) was treated with approximately 3.8 weight per cent ozone (in oxygen) at a flow rate of 102 l. per hr. at room temperature (30°) for 5 hr. and 55 min. Under these conditions, 2.08 molecular equivalents (30.3 g., 0.62 mole) of ozone was passed into the reaction mixture. After flushing with oxygen, the light-yellow solution was transferred into a 4-l. beaker and 1200 ml. of 7% aqueous sodium bicarbonate solution added. Precipitation occurred, and the yellow solid was removed by filtration, washed with water, and dried yielding 44.2 g. (71.4% yield) of crude fluorenone-1-aldehyde which melted at 187–191°. Recrystallization from ethanol raised the melting point to 193–194°; lit.,[4] m.p. 194°. The filtrate was distilled to remove the acetone and then acidified with concd. hydrochloric acid. An orange solid precipitated and

was removed by filtration yielding 7.2 g. (10.8% yield) of crude fluorenone-1-carboxylic acid which melted at 177–185°. Recrystallization from glacial acetic acid raised the melting point to 196–197°; lit.,[4] m.p. 197°.

II. *Reactions involving the ozonolysis products of fluoranthene.* *A. Preparation of fluorenone-1-carboxylic acid* (III). A mixture of crude fluorenone-1-aldehyde (10.4 g., 0.05 mole), glacial acetic acid (100 ml.), and Becco 40% peracetic acid (10 ml., 0.06 mole) was placed in a 500 ml. three-neck flask equipped with a mechanical stirrer and reflux condenser. Heat was supplied using a heating mantle, and the mixture was allowed to reflux for 3 hr. The mixture was transferred into a 400-ml. beaker and an equal volume of water added. Precipitation occurred, and the product was removed by filtration, washed with water, and dried yielding 9.8 g. (87.5% yield) of fluorenone-1-carboxylic acid which melted at 181–189°. Recrystallization from glacial acetic acid raised the melting point to 197°.[4]

B. Preparation of the dimethyl acetal of fluorenone-1-aldehyde (IV). Recrystallized fluorenone-1-aldehyde (10 g., 0.048 mole), methanol (500 ml.), and Becco 40% peracetic acid (1 ml.) were placed in a 1-l. round-bottom flask. The flask was fitted with a reflux condenser and the mixture allowed to reflux for about 12 hr. (overnight). The fluorenone-1-aldehyde went into solution after about 10 min. After refluxing, a mixture of aqueous 7% sodium bicarbonate solution (50 ml.) and water (50 ml.) was added to the mixture and the methanol removed by distilling to a head temperature of 95°. Upon cooling, the yellow oil present in the aqueous residue solidified. Filtration yielded 12.0 g. (98.4% yield) of the dimethyl acetal of fluorenone-1-aldehyde, which melted at 81–82°. Recrystallization from *n*-heptane raised the melting point to 82–83°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.60; H, 5.52; methoxyl, 24.40. Found: C, 75.84; H, 5.76; methoxyl, 23.88.

C. Preparation of isodiphenaldehydic acid (V). A solution of the dimethyl acetal of fluorenone-1-aldehyde (5.0 g., 0.0197 mole) in diphenyl ether (120 ml.) was placed in a 500-ml. three-neck flask which had been fitted with a condenser, stirring device, and a thermometer. Solid potassium hydroxide (16.0 g., 0.286 mole) was added and the flask heated to 160° using a heating mantle. The mixture was stirred vigorously during the heating, and the potassium hydroxide gradually went into solution. The reaction was allowed to proceed for 2 hr. at a temperature of 160–175°. After completion of the cleavage reaction, the mixture was cooled and stirred with about one half its volume of water until both resultant salts and excess alkali were dissolved. The two layers were then separated and the diphenyl ether layer further extracted with water. The combined aqueous fractions were filtered. From the pale-yellow filtrate, insoluble acids were precipitated by acidification with concd. hydrochloric acid. The light-yellow product was removed by filtration, washed with water, and dried yielding 4.2 g. (94.3% yield) of crude isodiphenaldehydic acid melting at 104–106°. Recrystallization from an ethyl acetate–*n*-heptane mixture raised the melting point to 110–111.5°.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46; neut. equiv., 226. Found: C, 73.76; H, 4.51; neut. equiv., 218.

D. Preparation of isodiphenic acid (VI). A solution of the crude isodiphenaldehydic acid from the previous reaction (2.26 g., 0.01 mole) in anhydrous *t*-butyl alcohol (100 ml.) was treated with approximately 3 weight per cent ozone (in oxygen) at a flow rate of 34 l. per hr. at room temperature (30°) for 1 hr. Under these conditions, 1.4 molecular equivalents (0.67 g., 0.014 mole) of ozone was passed into the solution. After ozonization, the colorless solution was poured into a 500-ml. flask which contained 100 ml. of 7% aqueous sodium bicarbonate solution, and the *t*-butyl alcohol was removed by distillation to a head temperature of 95°. Upon acidification of the remaining bicarbonate solution with hydrochloric acid, precipitation occurred yielding 1.8 g. (74% yield) of isodiphenic acid which melted at 219–221°. The reported melting point for isodiphenic acid is 216°.[14]

Neut. equiv. Calcd.: 121.0. Found: 120.2.

E. Preparation of 1-carboxy-9-oxa-9,10-dihydrophenanthrene-10-one (VII). A mixture of recrystallized fluorenone-1-carboxylic acid (15.7 g., 0.07 mole), glacial acetic acid (100 ml.), and Becco 40% peracetic acid (17.5 ml., 0.11 mole) was placed in a 250-ml. Erlenmeyer flask and the mixture cooled in an ice bath to 0°. Concd. sulfuric acid (20 ml., 0.375 mole) was added slowly and the mixture stirred with a magnetic stirrer. The reaction was then allowed to proceed at room temperature for 72 hr. The glacial acetic acid was removed in a flash evaporator and the sulfuric acid carefully neutralized with a solution of sodium hydroxide (26 g.) in 260 ml. of water. Precipitation occurred, and the product was removed by filtration, washed with water, and dried yielding 16.2 g. (96.5% yield) of crude 1-carboxy-9-oxa-9,10-dihydrophenanthrene-10-one which melted at 214–231° dec. An analytical sample was prepared by repeated recrystallization (ethyl acetate), which raised the melting point to 244–247°. Proof of structure was accomplished by alkaline permanganate oxidation to yield hemimellitic acid, demonstrating that this compound was the 1- rather than the 8-carboxy isomer.

Anal. Calcd. for $C_{14}H_8O_4$: C, 70.0; H, 3.36; neut. equiv., 240. Found: C, 70.49; H, 3.65; neut. equiv., 247.

F. Preparation of the n-butyl ester of 1-carboxy-9-oxa-9,10-dihydrophenanthrene-10-one (VIII). A mixture of crude 1-carboxy-9-oxa-9,10-dihydrophenanthrene-10-one (9.3 g., 0.0388 mole), *n*-butyl alcohol (100 ml.), toluene (100 ml.), and *p*-toluenesulfonic acid hydrate (5 g.) was placed in a 500-ml. round bottom flask which was fitted with a reflux condenser and Dean Stark trap. The mixture was allowed to reflux until the theoretical amount of water had collected in the trap (5 hr.). After cooling, the solution was washed with 7% aqueous sodium bicarbonate (100 ml.) and twice with water (50 ml.). The solution was concentrated to a volume of about 50 ml. by evaporation, and the resulting precipitate was removed by filtration yielding 6.6 g. (57.8% yield) of crude *n*-butyl ester of 1-carboxy-9-oxa-9,10-dihydrophenanthrene-10-one which melted at 139–142°. Recrystallization of a portion from ethyl acetate raised the melting point to 140–142°. The purified product had a saponification equivalent of 149 (theoretical = 148).

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PITTSBURGH 13, PA.

(14) R. Fittig and F. Gebhard, *Ann.*, **193**, 155 (1878).

Notes

A department for short papers of immediate interest.

Lead Tetraacetate Oxidation of Some Glutaric Acids. Formation of γ-Lactones

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Received November 9, 1959

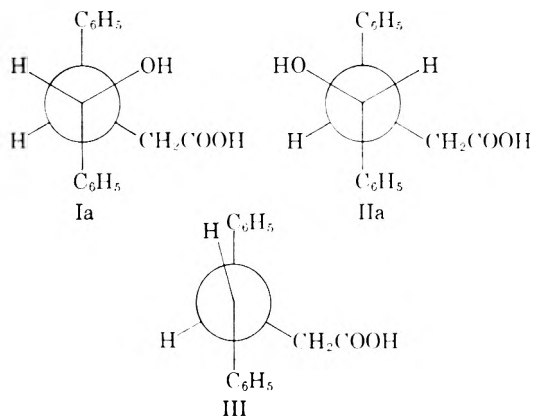
Recently, Grob, Ohta, Renk, and Weiss[1] reported an improved procedure for oxidative bis-decarboxylation of succinic acids to olefins.[2] Because of our interest in three-membered rings, we thought it would be interesting to apply this new method to glutaric acids with the hope that cyclopropanes would be formed. For a test system we prepared the two isomeric 2,3-diphenylglutaric acids, as both isomers can be obtained readily and the hoped for isomeric 1,2-diphenylcyclopropanes are both known.

Lead tetraacetate oxidation[1] of the high melting 2,3-diphenylglutaric acid occurred smoothly, but 1,2-diphenylcyclopropane was not obtained as a product. Instead, a compound (I), m.p. 110–111°, was obtained. The infrared spectrum of this material had a carbonyl band at 1787 cm.$^{-1}$, and the material dissolved slowly in hot, aqueous sodium hydroxide and was reprecipitated unchanged on acidification of the basic solution. This evidence suggests that monodecarboxylation has occurred with formation of a γ-lactone. The same product was obtained when the low melting 2,3-diphenylglutaric acid was oxidized in the same way.

Monodecarboxylation could occur at either of two different positions and the resulting lactones could each exist in two isomeric forms. Of the four possible isomeric lactones two were eliminated as possible structures for I by reducing I with hydriodic acid and red phosphorus to 3,4-diphenylbutyric acid. This showed that decarboxylation occurred at the benzylic position rather than the primary one.

3,4-Diphenylbutyrolactone, m.p. 112–113°, has been reported previously.[3] For comparison we prepared the lactone by reduction of desylacetic acid with either sodium borohydride or sodium amalgam in aqueous solution and then lactonization of the resulting hydroxy acid by warming with dilute aqueous acid or by heating above its melting point. The lactone (II) obtained melts at 109–110°. However, a mixed melting point of I and II was 75–85°. Apparently, the two lactones are stereoisomers.

A tentative assignment of configuration may be made by comparing the action of acidifying the sodium salts of the hydroxy acids corresponding to the two lactones. The salt from I gives the lactone spontaneously, while the salt from II gives the hydroxy acid. This suggests that lactone I is the more stable lactone; this isomer would have the two bulky phenyl groups *trans* on the lactone ring. Lactone II would be the less stable *cis* isomer. In the ring-opened hydroxy acids, the stability would be reversed if it is assumed that the bulky phenyl groups are the major control in determining the preferrred conformation, *i.e.*, Ia and IIa corresponding to the lactones with IIa more stable than



Ia. Additional evidence is presented by the decarboxylation reaction where both isomers of the diphenylglutaric acid give the same lactone. This means that decarboxylation and lactone formation are not concerted and it suggests that whatever intermediate is formed has sufficient life time to attain the most stable conformation III (radical or carbonium ion). This conformation, III, should lead to the *trans* lactone. Thus, the suggested assignment of configuration is lactone I *trans* and lactone II *cis*.

The infrared spectra of these two isomers is of some interest. That of the *cis* isomer shows two distinct carbonyl bands of about equal intensity at 1762 cm.$^{-1}$ and 1742 cm.$^{-1}$ and the *trans* isomer although showing a sharp band at 1787 cm.$^{-1}$ has a pronounced shoulder at 1753 cm.$^{-1}$ In both cases, there is a moderately strong band at about one-half the carbonyl frequency, *i.e.*, at 887 cm.$^{-1}$ (*cis*) and 885 cm.$^{-1}$ (*trans*). This possibly represents another example of Fermi

(1) (a) C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958); (b) C. A. Grob, M. Ohta, and A. Weiss, *Ang. Chem.*, 343 (1958).

(2) (a) W. von E. Doering, M. Farber, and A. Sayigh, *J. Am. Chem. Soc.*, **74**, 4370 (1952); (b) W. von E. Doering and M. Finkelstein, *J. Org. Chem.*, **23**, 141 (1958).

(3) F. R. Japp and G. D. Lander, *J. Chem. Soc.*, **71**, 154 (1897).

resonance similar to that described by Yates and Williams.[4]

Formation of a lactone in good yield in this decarboxylation reaction prompted us to try lead tetraacetate oxidation of two other five-carbon dibasic acids which happened to be available. One of these, glutaric acid, was inert under the conditions used and no butyrolactone was obtained. The other, camphoric acid, decarboxylated smoothly to give crude camphytolactone in 70% yield. This lactone was not purified as such, but was converted to the corresponding hydroxy acid which was readily purified and identified. It should be noted that decarboxylation occurred at the tertiary position in preference to the secondary.

These results are in accord with those reported by Mosher and Kehr[5] for the decomposition of lead IV salts of monocarboxylic acids in the presence of an excess of the acid. That work indicated that the ease of decomposition (decarboxylation) is in the order III>II>I. Although the product mixtures were complex, esters were formed, but usually in low yield. The high yields of lactones in the present work is quite possibly due to the proximity of the second carboxyl group in the same chain.

Although we have not explored the method appreciably, it appears to be a useful method for making some types of γ-lactones (those having tertiary or benzylic positions for the acid group to lactonize with), especially as many methods are available for preparing the requisite glutaric acids.

EXPERIMENTAL[6]

2,3-Diphenylglutaric acid. The high melting isomer was prepared essentially as described by Badger, Campbell and Cook,[7] m.p. 225–227° (lit.,[7] m.p. 230–231°). This isomer was converted to the anhydride,[7] m.p. 124–126° (lit.,[7] m.p. 125–126°), and subsequently to the low melting isomeric glutaric acid, m.p. 207–211° (lit.,[8] m.p. 208–210°), by the method of Avery and Maclay.[8]

Lead tetraacetate oxidation of 2,3-diphenylglutaric acid. The procedure is essentially the same as that given in an example by Grob, Ohta, Renk, and Weiss.[1a]

A. A mixture of high melting 2,3-diphenylglutaric acid (3.0 g., 0.01 mole), pyridine (1.6 ml., 0.02 mole), lead tetraacetate (4.7 g., 0.01 mole; contained a trace of acetic acid) and benzene (15 ml.) was stirred under nitrogen. On warming, a vigorous reaction with gas evolution began when the bath temperature reached about 50°. When the reaction subsided (2–3 min.), the bath temperature was raised and the mixture was maintained at gentle reflux for about 1.5 hr. During the course of the reaction a white precipitate, lead acetate, formed. The mixture was cooled, decanted from the lead acetate, and the lead acetate was washed with a small amount of benzene. The combined reaction solution and wash was washed with 10 ml. portions of water, 2*N* sodium carbonate, and 2*N* hydrochloric acid, and then dried over sodium sulfate. Removal of the benzene left a thick, yellowish material which crystallized readily. This was recrystallized from 50% aqueous ethanol and the resulting white crystals, 1.8 g. (72%), melted at 107–109°. An analytical sample recrystallized from cyclohexane and then sublimed melted at 110–111°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.47; H, 5.98.

The compound (I) dissolved slowly in hot, aqueous sodium hydroxide and was precipitated by acidification of the cooled basic solution. The infrared spectrum of I had a sharp band at 1787 cm.$^{-1}$ This evidence suggested that I is a lactone.

The carbon skeleton of I was established by reduction of I with hydriodic acid and red phosphorus. The procedure was the same as described for 2,4-diphenylbutyrolactone.[9] 3,4-Diphenylbutyric acid, m.p. 93–95° (recrystallized from cyclohexane and then sublimed) (lit.,[10] m.p. 95–96°), was obtained.

For comparison, 3,4-diphenylbutyrolactone was prepared from desylacetic acid in essentially quantitative yield by reduction with sodium borohydride or sodium amalgam in aqueous solution.[11] The immediate product appeared to be the hydroxy acid, but this was readily converted to the lactone by warming with dilute aqueous acid, or better, by heating slightly above the melting point (*ca.* 115°) for several minutes. The lactone (II) obtained and purified by recrystallization from cyclohexane melted at 109–110° (lit.,[3] m.p. 112–113°). A mixed melting point of I and II was 75–85°. The infrared spectrum of II has two bands of about equal intensity at 1762 cm.$^{-1}$ and 1742 cm.$^{-1}$, and in general, the infrared spectra of I and II are quite different.

B. Lead tetraacetate oxidation of the high melting 2,3-diphenylglutaric acid was repeated as in A but with acetonitrile as a solvent.[1a] In the workup, water and petroleum ether were added to the reaction mixture as described,[2a] but the product was insoluble in both phases. After separation of the product, it solidified and was then purified as in A to give 2.0 g. (80%) of the lactone, I. The infrared spectrum was identical with that for the lactone prepared in A.

C. Lead tetraacetate oxidation of the low melting 2,3-diphenylglutaric acid was carried out as in A. The product, 2.0 g. (80%) melted at 108–109° and its infrared spectrum was identical with that for the lactone prepared in A.

Lead tetraacetate oxidation of glutaric acid. Using the same procedure, A, described above did not result in the formation of any detectable amount of γ-butyrolactone from glutaric acid. Even while heating the reaction mixture at gentle reflux, gas evolution was negligible. During the workup with aqueous solutions a large amount of dark brown precipitate, probably lead dioxide, was formed. Apparently, oxidation did not occur.

Lead tetraacetate oxidation of camphoric acid. The same procedure, A, was applied to camphoric acid; the reaction went smoothly, gas evolution commencing with a bath temperature at about 55°. In one run, the gas evolved was measured; 80% of the theoretical amount of monodecar-

(4) P. Yates and L. L. Williams, *J. Am. Chem. Soc.*, **80**, 5896 (1959).

(5) W. A. Mosher and C. L. Kehr, *J. Am. Chem. Soc.*, **75**, 3172 (1953).

(6) Melting points are not corrected. Infrared spectra were obtained from a Perkin-Elmer Infracord and a Baird Recording Infrared Spectrophotometer; the compounds were prepared as mulls in Nujol. The analysis was done by Micro-Tech Laboratories.

(7) G. M. Badger, J. E. Campbell, and J. W. Cook, *J. Chem. Soc.*, 1084 (1949).

(8) S. Avery and W. D. Maclay, *J. Am. Chem. Soc.*, **51**, 2833 (1929).

(9) F. Bergmann, H. E. Eschinazi, and D. Shapiro, *J. Am. Chem. Soc.*, **64**, 557 (1942).

(10) S. Ruhemann, *J. Chem. Soc.*, **97**, 457 (1910).

(11) The reported preparation of this lactone[3] used desyleneacetic acid and sodium amalagam. A limited amount of sodium amalgam gave a mixture of desyleneacetic acid, desylacetic acid, and lactone, while an excess gave only the lactone. It seems reasonable, therefore, that desylacetic acid is an intermediate and can be used directly to prepare the lactone.

boxylation was obtained. The crude product, a lactone (infrared C = O: 1748 cm.$^{-1}$), was obtained in 70% yield as a liquid which very slowly partially crystallized. By gas phase chromatography this product mixture consisted of a major component (>95%) and two or possibly three trace components. The lactone could be sublimed, but no satisfactory melting point could be obtained.[12] Saponification of the lactone, however, gave the readily purified hydroxy acid, m.p. 118–119° (recrystallized from water) lit.,[12] m.p. 118.5°).

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(12) The melting point range was persistently 5–10° below that reported for camphytolactone. Bicyclic compounds of this sort are notorious for their large cryoscopic constants and difficulty of purification. From a published report [W. A. Noyes and R. S. Potter, *J. Am. Chem. Soc.*, **34**, 1067 (1912)] this lactone is no exception.

The Reaction of Certain Acid-Sensitive Steroid Ketones with Ethanedithiol–Borontrifluoride

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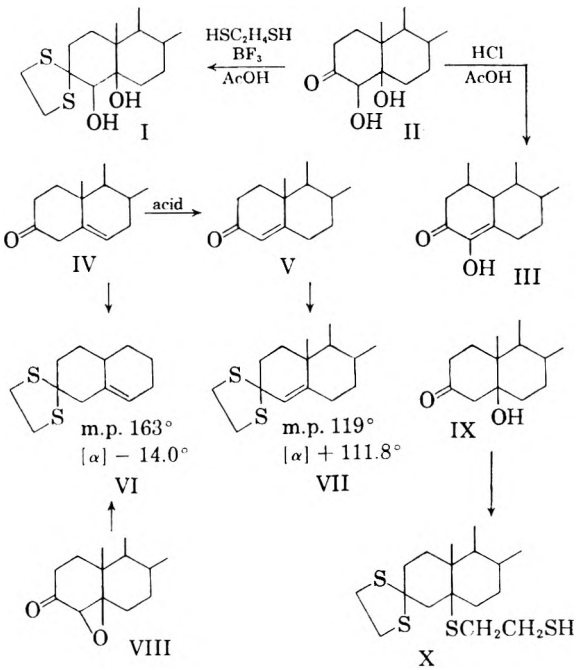
Recently we were successful in obtaining thioketal derivatives (I) from 4,5-dihydroxy-3-keto steroids (II) with ethanedithiol and boron trifluoride in acetic acid.[1] It was somewhat surprising that these strongly acid conditions, originated by Fieser,[2] gave derivative I in good yield, because the diolone II is easily dehydrated by acid to a diosphenol (III).[1] To check these conditions with another acid-sensitive functional arrangement, a thioketal derivative has been prepared from Δ^5-cholesten-3-one (IV), which is easily isomerized by acid to Δ^4-cholestenone (V). The derivative (VI) from the Δ^5-isomer (IV) is distinct from the derivative (VII) obtained[2] from the Δ^4-isomer (V). The negative specific rotation of VI is in accord with the structure assigned.[3]

Attempts to prepare thioketal derivatives of two other acid-sensitive functional arrangements under boron trifluoride catalysis have met with less success. 5-Hydroxycoprostan-3-one (IX) was treated with ethanedithiol and borontrifluoride in acetic acid, as a step in an attempted synthesis of the relatively rare monofunctional 5-hydroxy-steroids. Toward this end, 4,5β-oxidocoprostan-3-one (VIII) was treated with the acidic reagent. The yield of crystalline material from each compound was very slight. The small amount of crystalline product



from the epoxide (VIII) proved to be the derivative (VI) from Δ^5-cholesten-3-one. The product from the ol-one (IX) was not fully characterized but has an analysis in agreement with structure X. Although formation of compounds VI and X from VIII and IX respectively is intriguing, further discussion of their formation seems unwarranted until they are obtained in significant yield.

EXPERIMENTAL

Reaction of Δ^5-cholesten-3-one (IV) *with ethanedithiol.* A solution of 1.0 g. of Δ^5-cholesten-3-one in 20 ml. of acetic acid was treated with 1 ml. of ethanedithiol and 1 ml. of boron trifluoride etherate. The solution was stirred for a few minutes and allowed to stand for 3 hr. The crystalline material which precipitated was filtered, washed with water, and recrystallized from ethanol. No additional crystalline material could be isolated from the reaction mixture. After recrystallization the yield of the thioketal (VI) was 0.26 g., m.p. 162–163°, $[\alpha]_D^{25}$ −14.0° (c, in chloroform, 0.895).

Anal. Calcd. for $C_{29}H_{48}S_2$: C, 75.60; H, 10.50. Found: C, 75.48; H, 10.34.

Reaction of 4,5β-oxidocoprostan-3-one (VIII) *with ethanedithiol.* A solution of 1 g. of 4,5β-oxidocoprostan-3-one[4] in 10 ml. of acetic acid was treated with 1 ml. of ethanedithiol and 1 ml. of boron trifluoride etherate. Only a small amount of crystalline material precipitated from the reaction mixture. After recrystallization from ethanol, this material melted at 161–162° and showed no depression with Δ^5-cholesten-3-one ethylene thioketal (VI).

Reaction of 5-hydroxycoprostan-3-one (IX) *with ethanedithiol.* To a solution of 0.38 g. of 5β-hydroxycoprostan-3-one in 5 ml. of acetic acid were added 0.5 ml. of ethanedithiol and 0.5 ml. of boron trifluoride etherate. The solution was stirred and allowed to stand for several hours. The small amount of crystalline material which separated was collected and washed with water. The acetic acid was allowed to evaporate slowly to leave a dark oil which resisted all attempts at crystallization. After the crystalline material

(1) J. F. Eastham, G. B. Miles, and C. A. Krauth, *J. Am. Chem. Soc.*, **81**, 3114 (1959).

(2) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

(3) *Cf.* W. Klyne in E. A. Braude and F. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press Inc., New York, N. Y., 1955, p. 108 ff.

(4) P. A. Plattner, H. Heusser, and A. B. Kulkarni, *Helv. chim. Acta*, **31**, 1822 (1948).

was recrystallized from methanol, it melted at 166–168°, showed no absorption in the ultraviolet region, and had a weak, well-defined absorption at 2685 cm.$^{-1}$ characteristic of SH stretching.[5]

Anal. Calcd. for $C_{31}H_{54}S_4$: C, 67.11; H, 9.81; S, 23.07. Found: C, 67.02, 66.79; H, 9.56, 9.83; S, 23.20.

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(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, N. Y., 1958, p. 351.

5-Dibenzo[b,f]azepine

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Six-membered ring systems of the general type I have been shown to undergo dehydration on solvolysis with ring enlargement to seven-membered systems (II), *i.e.* 9,10-di(hydroxymethyl)-9,10-dihydroanthracene (I, X=CH(CH$_2$OH)),[1,2] 9-hydroxymethylxanthene (I, X=O)[3] and 9-hydroxymethylthioxanthene (I, X=S).[4]

In the present study, the transformation of 9-hydroxymethylacridane (I, X=NH) into 5-dibenzo[b,f]azepine (II, X = NH) is described.

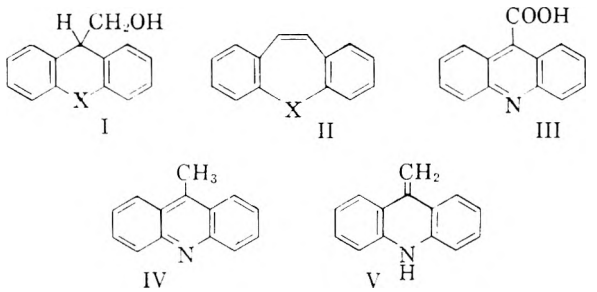
The primary alcohol (I, X=NH) was obtained by reduction of acridine-9-carboxylic acid (III) with lithium aluminum hydride. This reagent reduced not only the carboxyl group, but also the *ortho*-quinoid C=N system. Analogous observations have been made in other acridine derivatives.[5] Treatment of the alcohol with polyphosphoric acid at 160° caused the desired dehydration. Structure II, X = NH for the product, m.p. 189–191°, follows from the similarity of its spectrum with that of 2-amino-*cis*-stilbene:[6] II, X=NH: 262 mμ (4.60); 310 mμ (3.35; inflection); 360 mμ (2.90; inflection); 2-amino-*cis*-stilbene: 245 mμ (3.25; inflection); 2.80 mμ (3.05), and its nonidentity with 9-methylacridine (IV), m.p. 114°,[7] which would probably have formed spontaneously from 9-methylene-9,10-dihydroacridine (V).[8] The spectrum of II, X=NH is also very similar to that of II,X=O,[3] II, X=S[4] and II, X=CH$_2$.[2]

II,X=O: 230 mμ (4.35); 290 mμ (3.95)

II,X=S: 227 mμ (4.36); 262 mμ (4.47); 295 mμ (3.70)

II,X=CH$_2$: 288 mμ (4.19)

10,11 - Dihydro - 5 - dibenzo[b,f]azepine ("*o*-iminodibenzyl") has been described by Thiele and Holzinger,[9] but no derivatives of II, X=NH carrying a double bond in the 10,11- position appear to have been prepared.



EXPERIMENTAL

9-Hydroxymethyl-9,10-dihydroacridine (I, X = NH). In an atmosphere of nitrogen and at the temperature of an ice-salt mixture, 13 g. of lithium aluminum hydride was added in small portions to a suspension of 40 g. of acridine-9-carboxylic acid (III)[10] in ether. The mixture was gently refluxed for 3 hr. and decomposed by the successive addition of acetone and water. The ethereal solution was then decanted from the solid and the latter extracted several times with ether and benzene. When the solvents were evaporated (at a temperature not exceeding 40°), a colorless solid remained which was triturated with petroleum ether and recrystallized from benzene-petroleum ether or methanol. The compound formed white needles, m.p. 135–136°, and was very sensitive to oxygen, which caused quick discoloration to brown. The yield was 30 g. (80%). That the acridine system had been reduced, followed from the absence of the typical green fluorescence of the acridine derivatives in concentrated sulphuric acid solution.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.6; H, 6.2. Found: C, 79.6; H, 6.6.

5-Dibenzo[b,f]azepine (II, X = NH). A mixture of 2.5 g. of the foregoing substance and 150 ml. of polyphosphoric acid was heated at 160° for 3 hr. with vigorous agitation. Water was added and the product extracted with ether and benzene. The organic layer was washed with sodium bicarbonate solution, dried, and evaporated *in vacuo* and the ethereal solution of the residue chromatographed twice on activated alumina. The product contained in the yellow fraction (50-ml. fractions) was dissolved in petroleum ether and chromatographed again. The third fraction gave yellow leaflets which melted at 189–191°; the melting point did not change upon recrystallization from cyclohexane. The infrared spectrum (in potassium bromide pellet) showed 3333 cm.$^{-1}$ (strong, N—H stretching), 3030, 1587, 1481 (str.) (*ortho*-disubst. benzene), 1316 (C—N stretching), 1266, 1163, 1117, 939, 810, 746 (broad, strong) (*ortho*-disubst. benzene), 700 cm.$^{-1}$

(1) J. Rigaudy and P. Tardieu, *Compt. Rend.*, 248, 1538 (1959).

(2) E. D. Bergmann and M. Rabinovitz, *Bull. Res. Counc. Israel*, in press (1960).

(3) F. A. L. Anet and P. M. G. Bavin, *Can. J. Chem.*, 35, 1084 (1957).

(4) E. D. Bergmann and M. Rabinovitz, *J. Org. Chem.*, in press (1960).

(5) F. Bohlmann, *Ber.*, 85, 390 (1952); G. M. Badger, J. H. Seidler, and B. Thomson, *J. Chem. Soc.*, 3207 (1951).

(6) D. L. F. De Tar and L. A. Caprino, *J. Amer. Chem. Soc.*, 78, 475 (1956).

(7) H. Jensen and F. Rethwisch, *J. Amer. Chem. Soc.*, 50, 1144 (1928).

(8) This can be assumed from analogy to 9-methylene-9,10-dihydroanthracene.[2] However, Decker, *Ber.*, 38, 2493 (1905), has described some derivatives of V.

(9) J. Thiele and O. Holzinger, *Ann.*, 305, 100 (1899).

(10) K. Lehmstedt and F. Dostal, *Ber.*, 72, 804, 1071 (1939). G. I. Braz and T. V. Gortinskaya, *J. Gen. Chem. (U.S.S.R.)*, 10, 1751 (1940); *Chem. Abstr.*, 35, 4025 (1941).

Anal. Calcd. for $C_{14}H_{11}N$: C, 87.0; H, 5.7; N, 7.3. Found: C, 86.8; H, 6.1; N, 7.0.

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Dibenzo[bf]thiepin

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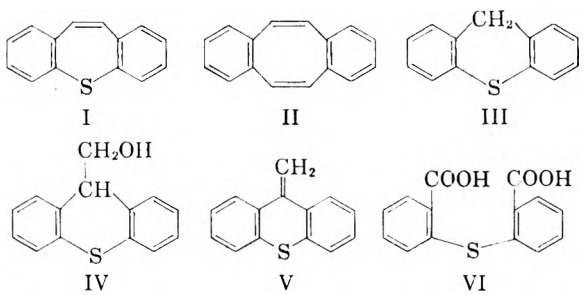
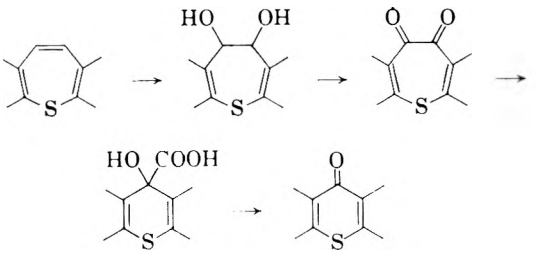
Studies on the correlation of structure with aromatic properties made it appear desirable to synthesize and study dibenzo[bf]thiepin (I), derivatives of which have been described recently by by Loudon, Sloan, and Summers.[1] This compound would be isoster with 1,2,5,6-dibenzo-1,3,5,7-cyclooctatetraene (II) which has olefinic character.[2-4] Compounds of the dibenz[bf]oxepin series have been described by Anet and Bavin.[5]

The synthesis of I followed the method developed by the Canadian authors. Thioxanthene (III) was metalated by means of butyl lithium[6] and condensed with formaldehyde to give 9-hydroxymethylthioxanthene (IV). The *p*-toluenesulfonate of this alcohol, on treatment with boiling 95% formic acid, lost toluenesulfonic acid and rearranged to I. That the product was not the theoretically possible 9-methylenethioxanthene (V) follows from its nonidentity with the compound described by Decker[7] and from its properties. The spectrum resembled that of *cis*-stilbene[8] and oxidation with permanganate in acetone gave diphenylsulfide-2,2′-dicarboxylic acid (VI). The ultraviolet spectrum of I shows bands at 227 mμ (4.36); 262 mμ (4.47); 295 mμ (3.70); *cis*-stilbene has bands at 274 mμ (4.04); 294 mμ (3.94).



Two reactions of I may be mentioned. When the oxidation was carried out in water, instead of acetone, thioxanthone was formed. A similar observation has been made by Manske and Ledingham[9] in the case of dibenz[bf]oxepin and can be explained as resulting from the benzilic rearrangement of the diketone formed by hydroxylation of the double bond in I and dehydrogenation of the di-secondary alcohol so formed:



Performic acid, on the other hand, did not attack the double bond in I, but transformed the compound into the corresponding sulfone, which has approximately the same *cis*-stilbene-type spectrum as I. Its infrared spectrum shows a number of bands in the 700–850 cm.$^{-1}$ region, in which the *cis*-disubstituted olefins absorb and two peaks at 1180 and 1307 cm.$^{-1}$ which represent the asymmetric and symmetric stretching vibrations of the sulfur-oxygen bond.[10]

It appears that the double bond in I is less "olefinic" than in II; this recalls the observation that 9-arylidenexanthenes and -thioxanthenes are more "heptafulvenic" in nature than the dibenzoheptafulvenes themselves.[11]

EXPERIMENTAL

Thioxanthene (III) was prepared from thioxanthone[12] essentially by the method of Graebe and Schultess[13]; the reduction was not carried out in a sealed tube, but under reflux during 20 hr. Care must be taken that the subliming thioxanthene does not block the reflux condenser.

9-Hydroxymethyl-thioxanthene (IV). In a 1 l. flask, mounted with stirrer and reflux condenser, 300 ml. of anhydrous ether and 4.3 g. of lithium metal was introduced and a current of dry nitrogen passed through the flask. By slow addition of a solution of 33.5 g of butyl bromide in 100 ml. of ether, butyl lithium was obtained. After 1 hr. the solution was cooled in an ice-salt bath and 35 g. of solid thioxanthene was added, which caused an orange-red color to appear. After 15 min. at 0° and 30 min. at reflux temperature, the reaction mixture was again cooled to 0° and 20 g. paraformaldehyde

(1) J. D. Loudon, A. D. B. Sloan, and L. A. Summers, *J. Chem. Soc.*, 3814 (1957).

(2) L. F. Fieser and M. M. Pechet, *J. Am. Chem. Soc.*, **68**, 2577 (1946).

(3) A. C. Cope and S. W. Fenton, *J. Am. Chem. Soc.*, **73**, 1668 (1950).

(4) G. Wittig, H. Tenhaeff, W. Schoch and G. Koenig, *Ann.*, **572**, 1 (1951).

(5) F. A. L. Anet and P. M. G. Bavin, *Can. J. Chem.*, **34**, 991 (1956); **35**, 1084 (1957).

(6) *Cf.* R. R. Burtner and J. W. Cusic, *J. Am. Chem. Soc.*, **65**, 1582 (1943).

(7) H. Decker, *Ber.*, **38**, 2493, 2511 (1905); see also Experimental.

(8) *Org. Syntheses*, **33**, 88 (1953).

(9) R. H. F. Manske and A. E. Ledingham, *J. Am. Chem. Soc.*, **72**, 4797 (1950).

(10) T. Momose and Y. Ohkura, *Chem. Abstr.*, **53**, 9159 (1959). *Cf.* M. Tamres and S. Searles, *J. Am. Chem. Soc.*, **81**, 2100 (1959).

(11) E. D. Bergmann *et al.*, *Bull. Soc. chim. France*, **19**, 262 (1952). *Cf.* H. C. Longuet-Higgins, *Trans. Faraday Soc.*, **45**, 173 (1949).

(12) E. G. Davis and S. Smiles, *J. Chem. Soc.*, **97**, 1290 (1910).

(13) C. Graebe and O. Schultess, *Ann.*, **263**, 1 (1891).

(dried over concentrated sulfuric acid for 24 hr.) added. At reflux temperature, the reaction was complete after 20 min.—as indicated by the discharge of the color—and a grayish precipitate had formed. The heating was continued for another 15 min. and the product decomposed with ice and 25% sulfuric acid. The aqueous layer was extracted with ether and chloroform, and the combined organic solutions were washed with sodium bicarbonate solution, dried and concentrated to a volume of 30 ml. Then 100 ml. of cyclohexane was added and the mixture heated to the boiling point and filtered. From the solution crystallized 30 g. of the product (75%); by concentration of the mother liquor a little more product could be obtained. Recrystallization from cyclohexane gave colorless needles, m.p. 110–111°.

Anal. Calcd. for $C_{14}H_{12}OS$: C, 73.7; H, 5.3. Found: C, 73.9; H, 5.6.

p-Toluenesulfonate. To a solution of 11 g. of the foregoing substance in 30 ml. of pyridine, 10 g. of *p*-toluenesulfochloride was added slowly at 0 to −5°. After 18 hr. at 0°, the product was poured into a mixture of ice and 30% hydrochloric acid. The oil which precipitated solidified upon standing or trituration with alcohol, and the product was recrystallized from methanol. It melted at 95°; yield, 15 g. (78%).

Anal. Calcd. for $C_{21}H_{18}O_3S_2$: C, 66.0; H, 4.7. Found: C, 65.8; H, 4.6.

Dibenzo[bf]thiepin (I). The following conditions have been found the most advantageous for the rearrangement: A solution of 9.5 g. of the *p*-toluenesulfonate in 75 ml. of 95% formic acid was refluxed for 30 min. and slowly poured into an excess of sodium carbonate solution, so that the reaction was alkaline all the time. The product was extracted three times with benzene and the benzene extract washed with dilute hydrochloric acid and 5% sodium bicarbonate solution, dried, and concentrated to a volume of 15 ml. After a first chromatography on alumina, 4 g. (77%) of a product was obtained which melted at 73–75° after recrystallization from cyclohexane. For the final purification, 2 g. of product in petroleum ether–benzene (5:1) was chromatographed on 35 g. of alumina. Of the 50-ml. fractions of eluate, the second fraction contained the pure compound, which was recrystallized from methanol and formed yellowish needles, m.p. 89–90°, yield, 1.2 g. (44%). The infrared spectrum showed the absence of a hydroxyl or ester group. The ultraviolet spectrum showed $\lambda_{max}^{ethanol}$ (log ϵ): 227 mμ (4.36); 262 mμ (4.47); 295 mμ (3.70).

Anal. Calcd. for $C_{14}H_{10}S$: C, 80.0; H, 4.8. Found: C, 80.2; H, 4.9.

Dibenzo[bf]thiepin-sulfone. A mixture of 1 g. of the foregoing compound in 18 ml. of 95% formic acid and 2.1 g. of 30% hydrogen peroxide, was heated at 40° for 30 min. with magnetic stirring, whereupon a clear solution resulted, and at 98° for 4 hr., and poured into water. The product crystallized from ethanol and melted at 171–172°. It was not affected by alkali or periodic acid and showed no hydroxyl absorption in the infrared. The ultraviolet spectrum showed $\lambda_{max}^{ethanol}$ (log ϵ): 229 mμ (4.54); 264 mμ (3.85); 300 mμ (4.08).

The infrared spectrum showed $\tilde{\nu}_{max}^{KBr}$: 1600, 1562, 1481, 1440, 1307 (s), 1260, 1180 (s), 1126, 1087, 1064, 818, 813 (s), 784, 763 (s), 725, 700 cm.$^{-1}$

Anal. Calcd. for $C_{14}H_{10}SO_2$: C, 69.4; H, 4.1. Found: C, 69.2; H, 4.1.

Diphenylsulfide-o,o'-dicarboxylic acid (VI). To a solution of 1 g. of the dibenzothiepin in 25 ml. of acetone (and a few drops of water), powdered potassium permanganate was added in small portions; after each addition, we waited until the color disappeared. When the permanganate color did not change for 3 hr., the solution was filtered and the solid phase washed with 2 ml. of acetone. The residue was then extracted twice with 10 ml. of boiling water and the combined extracts were acidified with dilute hydrochloric acid. The product was reprecipitated from dilute potassium hydroxide solution and finally recrystallized from aqueous alcohol. It melted at 230° (lit.,[14] m.p. 229°) and was identified by mixed melting point with a sample prepared according to Rosenmund and Harms.[14] The ultraviolet spectrum showed $\lambda_{max}^{ethanol}$ (log ϵ): 226 mμ (4.51); 255 mμ (3.98); 322 mμ (3.70).[15]

The infrared spectrum showed $\tilde{\nu}_{max}^{KBr}$: 2940, 1700 (s), 1600 (*o*-disubstituted benzene), 1568, 1475, 1418 (carboxyl), 1307 (s), 1283 (s) (carboxyl), 1266 (s), 1136, 1064, 1047, 939, 810 (s), 755 (s) (superposition of C—S—C and *o*-disubstituted benzene), 724, 714 cm.$^{-1}$

Anal. Calcd. for $C_{14}H_{10}O_4S$: C, 61.3; H, 3.7. Found: C, 60.9; H, 4.1.

Thioxanthone. To a well stirred mixture of 1.4 g. of dibenzothiepin and 60 ml. of boiling water, a mixture of 5 g. of potassium permanganate and 3 g. of sodium carbonate was added slowly. When the color was no longer discharged, the product was acidified with 25% sulfuric acid and decolorized by addition of sodium sulfite. The yellow precipitate was dissolved in benzene and chromatographed on alumina. Thus, 0.6 g. (43%) of thioxanthone was obtained which melted alone and upon admixture of authentic material at 209°.

Reaction of thioxanthone with methylmagnesium iodide. A repetition of the experiment of Decker[7] led to somewhat different results. The whole sequence of operations was carried out in a nitrogen atmosphere.

A solution of methylmagnesium iodide prepared from 6 g. of magnesium and 33 g. of methyl iodide in anhydrous ether, was added to a suspension of 16 g. of thioxanthone in warm benzene. During 4 hr. the ether was distilled off and the resulting product refluxed. It was decomposed with ice and ammonium chloride.[16] From the benzene layer, some thioxanthone crystallized which was removed by filtration. The benzene solution was then washed with water, dried, and evaporated *in vacuo* at a temperature not exceeding 40°. The remaining reddish oil was chromatographed on alumina and eluted with a mixture of benzene and petroleum ether (1:1). Thus, a yellow oil was obtained which crystallized upon trituration with cyclohexane. 9-Methylthioxanthydrol melted at 82–83°.

Anal. Calcd. for $C_{14}H_{12}OS$: C, 73.7; H, 5.3. Found: C, 74.0; H, 5.8.

On standing in a vacuum desiccator (or on heating with a mixture of acetic acid and acetic anhydride) the crystals liquefied through dehydration. 9-Methylenethioxanthene is a liquid which could not be obtained in pure form, as it quickly began to autoxidize and deposit thioxanthone, m.p. 205° and mixed m.p. 207°. The product described by Decker[7] as a semisolid of undefined melting point was, therefore, undoubtedly not 9-methylenethioxanthene.

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(14) K. W. Rosenmund and H. Harms, *Ber.*, **53**, 2226 (1920).

(15) For diphenylsulfide, 2 maxima (at 252 and 278 mμ) have been observed.

(16) Dehydration proceeds with great ease, if the decomposition is carried out with acid. Decker did not isolate the tertiary alcohol.

Dimer of 2-Pyridyl Isothiocyanate

JOHN C. HOWARD AND JULIAN G. MICHELS

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The synthesis of 2-pyridyl isothiocyanate, described as a brick-red solid, m.p. 110–111°, was

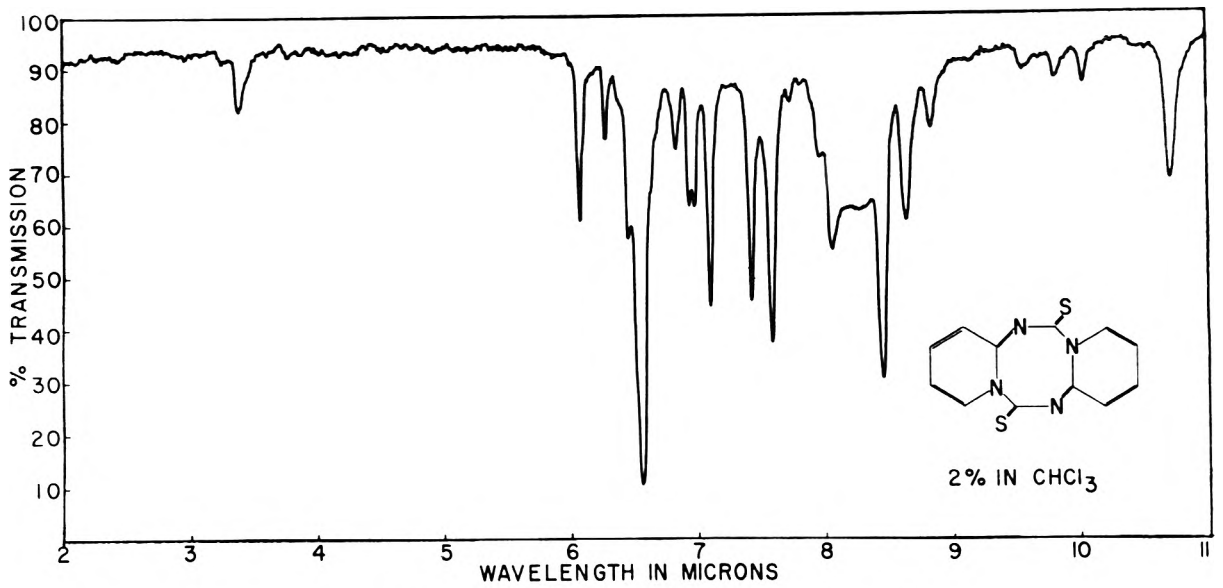


Fig. 1. Infrared spectrum of 2-pyridyl isothiocyanate dimer

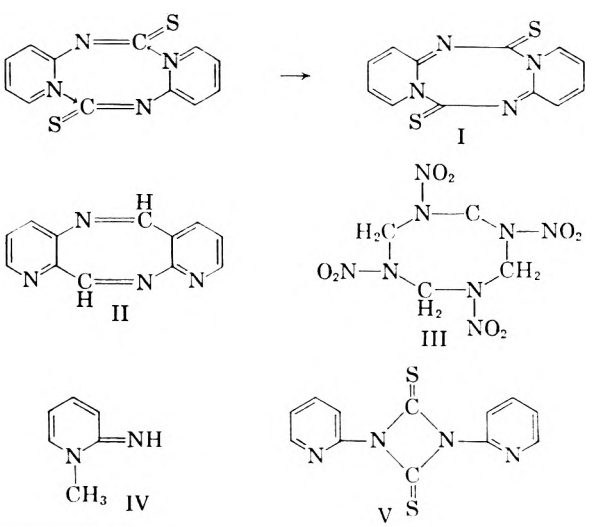
recently reported by Fairfull and Peak.[1] Structural assignment was made on the basis of a correct nitrogen analysis and conversion to the known *N*-phenyl-*N'*-2-pyridylthiourea by heating with aniline at 100°. It appeared to us that although the compound reacted at 100° as a typical isothiocyanate, its color and melting point were anomalous. Isothiocyanates are generally colorless liquids; in fact, 3-pyridyl isothiocyanate was so described by Fairfull and Peak.[1] We planned to use 2-pyridyl isothiocyanate as an intermediate and felt that the anomaly deserved closer examination. We have therefore repeated the synthesis following the published procedure and obtained a brick-red solid; our analytical sample melted at 119–120° after several reprecipitations from benzene-petroleum ether. A cyroscopic molecular weight determination corresponded to a *dimer* of 2-pyridyl isothiocyanate.

An infrared spectrum of a freshly prepared chloroform solution showed no characteristic isothiocyanate absorption at 5μ (Fig. 1). After thirty minutes refluxing, however, the solution became straw-colored and the infrared spectrum showed very intense absorption at 4.96μ (Figure 2). The ultraviolet spectrum also changed greatly after fifteen minutes heating; a fresh chloroform solution absorbed strongly at 295 mμ, 335 mμ, and 420 mμ. After heating, only one major peak, at 287 mμ, was observed.

This physical evidence proves that the brick red solid is not 2-pyridyl isothiocyanate and indicates that the substance is a dimer which dissociates to the monomer in solution. Several attempts were made to isolate the monomer by distillation. A solution of the dimer was refluxed until the red color disappeared, concentrated and distilled at reduced pressure. Upon removal of the solvent, the red solid reappeared. The substance distilled as a pale yellow liquid, then solidified to the red solid in the receiver. The boiling point was similar to that of 3-pyridyl isothiocyanate and the pale yellow liquid was doubtless 2-pyridyl isothiocyanate.

Having established that the red solid was a dimer, we turned our attention to the question of its structure. It occurred to us that an eight-membered ring, I, could be formed from two isothiocyanate molecules by the "head to tail" attack of one pyridyl-nitrogen on the thiocarbonyl of the other.

This tricyclic ring system[2] has not been described, although a similar type, II, was reported by Sucharda and Klisiecki.[3] The tetrazocine nucleus is



(1) A. E. S. Fairfull and D. A. Peak, *J. Chem. Soc.*, 796 (1955).

(2) We have named I "Dipyrido-[1,2-a,1',2'-e][1,3,5,7]-tetrazocine-6,13-dithione" in conformity with *Chemical Abstracts* usage.

(3) E. Sucharda and L. Klisiecki, *Roczniki Chem.*, **3**, 251 (1923). *Chem. Abstr.*, 19, 72 (1925).

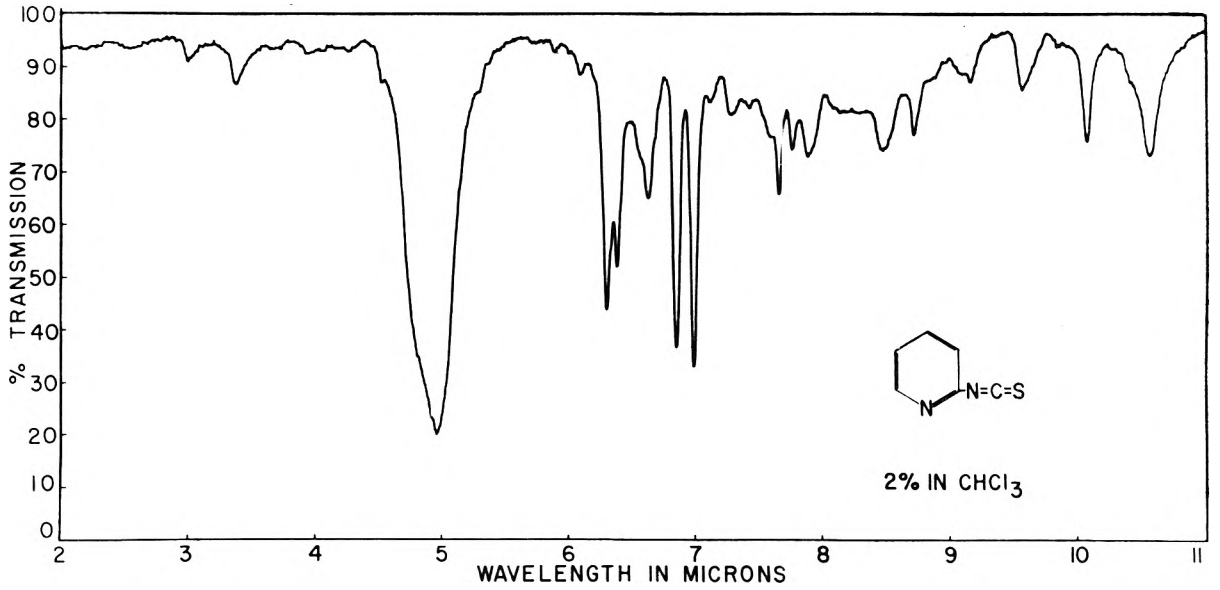


Fig. 2. Infrared spectrum of 2-pyridyl isothiocyanate

present in III, a derivative of hexamethylenetetramine.[4]

The infrared spectrum of the red solid is consistent with structure I. There is no absorption at 4.96μ (isothiocyanate); there is no typical pyridine ring absorption at 6.30 and 6.37μ (present in the monomer); and there is absorption at 6.07μ, a property shared with 1-methyl-2-pyridoneimine, IV.[5]

Because of the absence of model compounds containing the same chromophores, the ultraviolet spectrum of the dimer cannot be used with any confidence in the assignment of structure. However, IV absorbs at 350 mμ;[6] and extension of the chromophore by conjugation with a thiocarbonyl would be expected to have a bathochromic effect. This may account for the absorption above 400 mμ which gives the dimer its red color.

An alternative structure, V, analogous to the well-known aromatic isocyanate dimers,[7] was considered unlikely because it involved only the isothiocyanato group in its formation. Other isothiocyanate dimers have not been reported. The absence of pyridine ring absorption in the infrared spectrum of the dimer may also be evidence against V.

Dimers similar to I should be formed only by heterocyclic nitrogen compounds containing a 2-isothiocyanato group. A search for appropriate structures in the literature revealed mention of several polymeric 6-pyrimidinyl isothiocyanates which were not transformed to the monomer by distillation.[8] The synthesis and properties of similar compounds would be of interest.

EXPERIMENTAL[9]

2-Pyridyl isothiocyanate dimer (I). The preparation was carried out according to Fairfull and Peak[1] except that the product was purified by dissolving it in a minimum amount of benzene at room temperature and precipitating with twice its volume of ligroin, m.p. 119–120°.

Anal. Calcd. for $(C_6H_4N_2S)_2$: C, 52.92; H, 2.96; N, 20.57; m.w. 272.36. Found: C, 53.1; H, 3.09; N, 20.41; m.w. 284 ± 15.

Attempted isolation of 2-pyridyl isothiocyanate. A chloroform solution containing 9.5 g. of the dimer was refluxed for 1 hr. and the solvent was then distilled. The residual red oil was distilled at reduced pressure. At the beginning of the distillation the red oil solidified, then melted when the temperature reached 110°, and distilled as a pale yellow liquid which turned red on cooling. Six grams of red oil was collected; b.p. 110–120° (10 mm.). After several minutes it began to crystallize and after standing overnight melted at 112–114°. The infrared spectrum was identical with the dimer.

Effect of heat on the ultraviolet spectrum of I. The spectrum of a freshly prepared solution of the dimer in chloroform was determined. The ϵ_{max} at 420 mμ, 335 mμ, and 290 mμ was 4350, 25,600, and 25,600 respectively. After the solution was refluxed for 15 min. the ϵ_{max} at 287 mμ was 30,000 and the two longer wave length maxima disappeared.

(4) G. F. Wright, A. F. McKay, W. J. Chute, D. C. Downing, and G. S. Meyers, *Can. J. Res.*, **27**, 218 (1949).

(5) D. N. Shigarin, Ya. L. Danyushevskii, and Ya. L. Gol'dfarb, *Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk.*, 120 (1956). *Chem. Abstr.*, **50**, 8329 (1956).

(6) L. C. Anderson and N. V. Seeger, *J. Am. Chem. Soc.*, **71**, 343 (1949).

(7) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Rev.*, **57**, 54 (1957).

(8) T. B. Johnson and W. F. Storey, *Am. Chem. J.*, 40, 131 (1908); Yuoh-Fong Chi and Chi Ming Ma, *J. Am. Chem. Soc.*, 55, 4655 (1933).

(9) The melting points were determined on a calibrated Fisher-Johns block and the infrared spectra were determined on a Perkin-Elmer Model 21 equipped with sodium chloride optics; matched 0.1 mm. sodium chloride cells were used. The ultraviolet spectra were obtained on a Beckman DU quartz spectrophotometer. The elemental analyses and molecular weight determinations were performed by Mr. Gordon Ginther, Dr. Victor Ells, and associates of these laboratories and Schwarzkopf Analytical Laboratory, Woodside, New York.

Acknowledgment. We wish to thank Professor Jerrold Meinwald of Cornell University for his helpful suggestions and Mr. Frank Ebetino of this laboratory and a referee for nomenclature assistance.

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An O^{18} Tracer Study of the Acid-Catalyzed Formation of Enol Ethers

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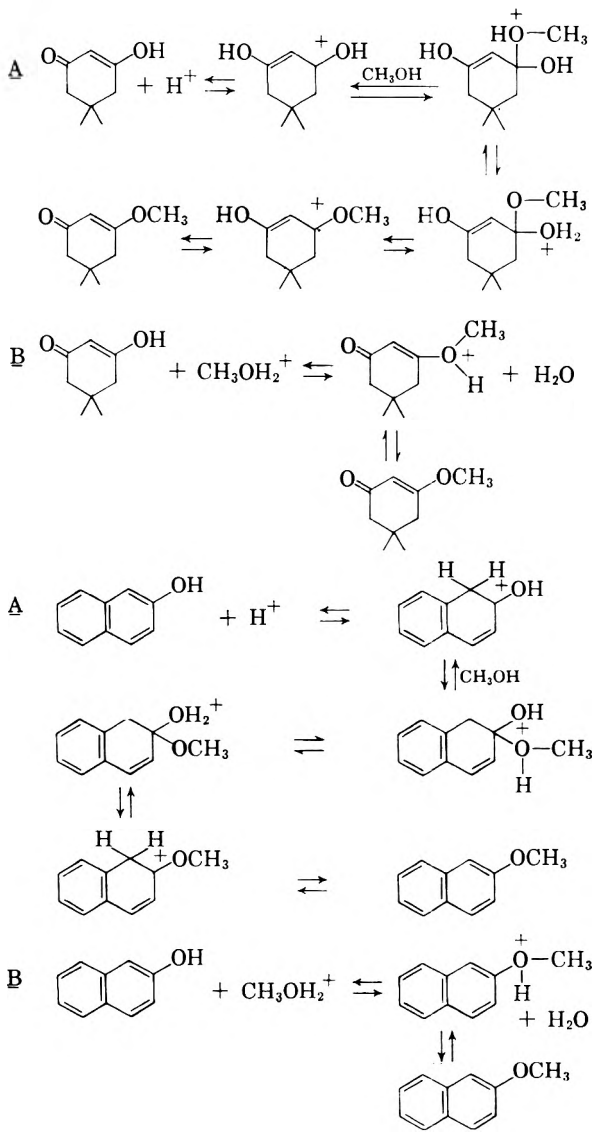
The conversion of enols, such as dimethyldihydroresorcinol,[1] and of some reactive phenols, such as β-naphthol[2] to the corresponding ethers may be effected by the acid-catalyzed reaction with the corresponding alcohol. In either case, there are two possible mechanisms:



The type A mechanism is, *a priori*, the more reasonable considering the facile formation of these ethers, and the small likelihood that the phenols are much more effective nucleophiles than is water. Further evidence for this mechanism may be found in the observation that resorcinol,[3] but not phenol, catechol, or hydroquinone, will form a monomethyl ether in this reaction, and that a dimethyl ether is not formed. Similarly, phloroglucinol reacts readily to form a dimethyl ether, but not a trimethyl ether.[4]

The two mechanisms are easily differentiated by using oxygen-18–labeled methanol, since mechanism A predicts incorporation of the label into the product ether, whereas mechanism B predicts that the ether will be devoid of isotope oxygen. The experiments were performed in the usual fashion and the results of the oxygen-18 analyses are given in Table I. It is readily apparent that nearly quantitative transfer of the label occurred, indicating the addition-elimination mechanism to be correct. The results also suggest that oxygen-18–labeling of these compounds should be easily effected by heating in acidified oxygen-18–enriched water, and that the ethers should be easily cleaved by acid-catalyzed hydrolysis.

TABLE I

OXYGEN-18 ANALYTICAL DATA

Compound	% O^{18} in CO_2	% excess O^{18}
Methanol	0.742	1.08
	0.749	1.09
2-Methoxynaphthalene	0.726	1.04
	0.726	1.04
5,5-Dimethyl-3-methoxy-cyclohexene-2-one	0.448	0.972
	0.448	0.972

EXPERIMENTAL

Reaction of dimethyldihydrolresorcinol. To 5 g. (36 mmoles) of dimethyldihydroresorcinol was added 50 ml. of benzene, 3.0 ml. of methanol-O^{18} (100% excess, containing 1.09 excess O^{18}), and 0.2 g. of *p*-toluenesulfonic acid. The solution was heated at reflux for 24 hr. in an apparatus in which the distilled solvent containing water was passed through potassium carbonate before being returned to the solution. Distillation gave 4.5 g. (81%) of the enol ether having b.p. 145–146° at 35 mm. Oxygen-18 analysis indicated the presence of 0.972 excess O^{18}.[5]

Reaction of β-naphthol. A solution of 1 g. of β-naphthol and 50 mg. of *p*-toluenesulfonic acid in 2.5 ml. of methanol was sealed in a tube and heated at 100° for 40 hr. The tube was opened and the contents were mixed with 10% potassium hydroxide solution and washed with same after filter-

(1) D. Vorländer and M. Kohlmann, *Ann.*, **322**, 253 (1902).
(2) L. Gattermann, *Ann.*, **244**, 72 (1888)
(3) V. Merz, *J. prakt. Chem.*, **61**, 109 (1900).
(4) H. Weidel and J. Pollak, *Monatsh*, **21**, 22 (1900).
(5) Oxygen-18 analyses were performed by the method of W. E. Doering and E. Dorfman, *J. Am. Chem. Soc.*, **75**, 5595 (1953).

ing. The product was allowed to dry after being washed with water several times. Recrystallization from ethanol-water gave 0.75 g. (70%), m.p. 70–71°.

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Benkeser Reduction of Norbornadiene and Norbornene[1]

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The question of occurrence and extent of conjugation effects in norbornadiene has been of interest in recent years. Although conjugation effects are not manifested in heat of hydrogenation experiments[2] and in free radical addition reactions,[3] the products obtained in ionic addition reactions are well accounted for in terms of a bridged-ion intermediate with homoconjugative character.[4] The exclusive formation in aqueous solution of a 1:1 norbornadiene–silver ion complex suggested conjugation effects (orbital overlap)[5] and the abnormal ultraviolet spectrum[6] of the diene is strong evidence for such conjugation effects in the excited state.

Recently Benkeser has shown that lithium in ethylamine is a powerful and selective reducing reagent toward aromatic rings.[7] The aromatic systems are rapidly reduced to monoolefins which are themselves far more slowly reduced.[7,8] Implicit in the tentative mechanism proposed[7] is the facile reduction of nonaromatic conjugated systems, specifically 1,3-dienes. It seemed of interest then to use the Benkeser reagent with norbornadiene to provide a different system for evaluating conjugation effects in that compound. Since isolated double bonds are reduced with difficulty,[7,8] it was expected that if the compound were reduced readily, nortricyclene would be formed by homoconjugative 1,5-addition.

When reduction of norbornadiene with lithium in ethylamine was tried, rapid color changes, similar to those described for the reduction of aromatic systems,[7] took place and nortricyclene was indeed present in the product mixture. It constituted a surprisingly small portion (13%) of that mixture however. The principal reduction product (64%) was that formed by simple 1,2- addition, norbornene. An appreciable amount of norbornane was also formed; with a 50% excess of lithium it became the major product (55%).

Since the equilibrium mixture of norbornene and nortricyclene contains 77% nortricyclene,[9] it seems very unlikely that the small amount of nortricyclene comes from a rearrangement of initially-formed norbornene precursor. Instead it is most probably a primary product itself, formed by some 1,5- addition to the homoconjugative system. Were isomerization a probable path, one might well expect that far more of the thermodynamically-favored isomer would be formed.[10,11] Homoconjugative addition of lithium to norbornadiene then seems possible but is a minor path in the over-all reaction.

The appearance of norbornane in the product mixture suggested that norbornene should be reduced by the Benkeser reagent also. When the experiment was tried, the color changes were again rapid, reduction proceeded, and norbornane was the only product isolated. In view of the slow reductions of other monoolefins,[7,8] the rapid reaction of norbornene is unexpected and is another example of unusual properties of these strained bridgehead compounds.

Although homoconjugative reduction of norbornadiene occurs only to a minor extent, two observations indicate that reduction (principally 1,2- addition) of the diene is nonetheless a faster process than reduction of norbornene (also 1,2-addition). Both norbornadiene and norbornene were reduced rapidly, but the color changes accompanying the reductions seemed to take place more rapidly with the diene. Secondly, with a small

(1) This research was supported in part by a grant from The Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

(2) R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Am. Chem. Soc.*, **79**, 4116 (1957).

(3) S. J. Cristol, G. D. Brindell, and J. A. Reeder, *J. Am. Chem. Soc.*, **80**, 635 (1958).

(4) S. Winstein and M. Shatavsky, *Chem. & Ind. (London)*, 56 (1956).

(5) J. G. Traynham and J. R. Olechowski, *J. Am. Chem. Soc.*, **81**, 571 (1959).

(6) K. Stich, G. Rotzler, and T. Reichstein, *Helv. Chim. Acta*, **42**, 1485 (1959).

(7) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 3230 (1955).

(8) R. A. Benkeser, G. Schroll, and D. M. Sauve, *J. Am. Chem. Soc.*, **77**, 3378 (1955).

(9) P. R. Schleyer, *J. Am. Chem. Soc.*, **80**, 1700 (1958).

(10) This assumes of course that the rate of isomerization is sufficiently rapid to allow equilibrium to be approached during the time of experiment. Some support for this assumption comes from the reaction between chilled norbornadiene and *p*-thiocresol;[3] within thirty minutes, a product mixture is formed which consists of 60% substituted nortricyclene and 40% substituted norbornene. The nortricyclene derivative was shown to be formed by rearrangement of the substituted norbornene precursor.

(11) One can envision a process whereby norbornene might be formed other than by simple 1,2- addition. Half-protonation of the nortricyclene 2,6-dianion would give an anion that could be pictured as a hybrid of nortricyclenyl-2 anion and norbornenyl-5 anion; final protonation to product could conceivably be rate-controlled so that norbornene was formed predominantly rather than nortricyclene, even through the initial reduction was actually a 1,5- addition. It is difficult to see, however, why the kinetic factor should so strongly favor formation of the thermodynamically-unfavored isomer from a hybrid anion whose canonical structures are essentially equivalent in geometry and steric requirements.

excess of lithium, norbornene was the principal product and was itself reduced to norbornane only to a small extent. Thus norbornadiene apparently reacts more rapidly than does norbornene which apparently reacts more rapidly than other olefins such as cyclohexene.[7] A similar order of reactivity for these olefins toward *p*-thiocresoxy radical[3] and toward aqueous silver ion[5] has been reported. The relative degrees of strain in the olefinic compounds probably account in large measure for this order.[3,5] However, the fact that isolable quantities of norborane were formed even though unchanged norbornadiene was recovered in the product mixture indicates that the differences in reactivities of norbornadiene and norbornene toward lithium in ethylamine are not great.

If the reduction involves the addition of lithium atoms (or of solvated electrons), then perhaps it should not be surprising that the course of the reaction with the diene should be more similar to free radical additions[3] than to cationic ones[4] insofar as the manifestation of conjugative properties are concerned.

EXPERIMENTAL

Norbornadiene and *norbornene* were supplied without charge by Shell Chemical Corp. and by Du Pont Polychemicals Dept., respectively; they were freshly distilled from sodium before use. *Norbornane* was prepared by the low pressure hydrogenation of norbornene with Raney nickel catalyst. Gas chromatography[12] and infrared spectroscopy[13] revealed no contaminants in the norbornene and norbornane samples and only traces of contaminants in the norbornadiene sample. A sample containing 81% *nortricyclene* and 19% norbornene graciously was supplied by Dr. Paul R. Schleyer, Princeton University, and was used without further purification as the source of authentic nortricyclene for spectral comparisons.

Reduction of norbornadiene. Lithium shot (8 mesh, 6.25 g., 0.90 g.-atom) was added to 250 ml. of anhydrous ethylamine in a flask equipped with stirrer, dropping funnel, Dry Ice condenser, and nitrogen atmosphere. The characteristic deep blue color developed quickly and after 30 min. stirring, norbornadiene (36.8 g., 0.40 mole) was added rapidly dropwise. After about half of the diene had been added, the blue color suddenly disappeared. The mixture appeared white with a lump of lithium floating in it. After 15 min., a muddy tan color developed and after 30 min. the lithium was no longer visible. The mixture was stirred for a total of 7 hr. Solid ammonium chloride (49 g., 0.90 mole) was added (attended by considerable heat evolution and probably some loss of volatile product material by entrainment) and the thick mixture was left standing overnight. Water was added and the mixture was extracted twice with ether. The ether solution was washed twice with water, twice with dilute hydrochloric acid, and again with water. After being dried with magnesium sulfate, it was distilled to give 22.2 g. of material, b.p. 95–103°, nearly all of which solidified in the receiver. Gas chromotography[12] resolved the distillate into three fractions (besides carbon tetrachloride solvent) which were shown by comparison of retention times and infrared spectra[13] with those of authentic samples to be norbornadiene (25%), norbornene (48%), and a mixture of norbornane and nortricyclene (27%). Although the last peak was symmetrical, the infrared spectrum of this fraction showed absorption for both norbornane and nortricyclene. Comparison with spectra of standard mixtures (absorbancies at 12.27 μ and 12.51 μ for norbornane and nortricyclene, respectively) indicated that this fraction of the product mixture consisted of 63% norbornane and 37% nortricyclene.

The products from the Benkeser reduction of norbornadiene then were 64% norbornene, 23% norbornane, and 13% nortricyclene.

In another experiment, with a 50% excess of lithium, no diene was recovered. The product, obtained in 74% yield, was found to be 24% norbornene, 55% norbornane, and 21% nortricyclene. Because of inadvertent loss of material by evaporation prior to analysis, these figures are less reliable than those above.

In both experiments small amounts of high boiling residue remained in the pot undistilled.

Reduction of norbornene. The same procedure was used twice with lithium, ethylamine, and norbornene. The deep blue color faded during addition of olefin and was essentially gone when addition was complete. The blue color continually redeveloped around the floating lump of lithium and the stirred mixture was aqua to lavender in color during the entire reaction period (7 hr.). Except for a very small amount of recovered norbornene in one experiment, norbornane was obtained in about 33% yield as the only product (gas chromatographic and infrared spectral analyses). A little high boiling residue remained in the pot undistilled.

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(12) Beckman GC-2 instrument; 6-ft. silicone column, 70–100°, 40–60 ml./min. flow rate of He. CCl_4 solutions.

(13) Beckman IR-5 instrument; CS_2 solutions.

Preparation of 3-Fluorophthalic Anhydride

ADAM HELLER

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For the synthesis of some polycyclic fluorine compounds, substantial quantities of 3-fluorophthalic anhydride were required. The ease with which the readily accessible 3-nitrophthalic anhydride can be converted by gaseous chlorine into the 3-chloro-compound,[1-3] led us to suspect that the chlorine atom in the latter might be reactive enough for a nucleophilic substitution reaction with potassium fluoride. Indeed, at 280–290° this reaction gave a 50% yield of the hitherto unknown 3-fluorophthalic anhydride.[4]

Similar exchange reactions with potassium fluoride have been observed for chlorine activated by nitro groups[5-7] or by a combination of a nitro-

(1) A. A. Ponomarenko, *Zhur. Obshcheĭ Khim.*, 20, 469 (1951); *Chem. Abstr.*, 44, 7810 (1950).

(2) M. S. Newman and P. G. Scheurer, *J. Am. Chem. Soc.*, 78, 5004 (1950).

(3) C. Shaw and Y. Thomas (to Imperial Chem. Ind.), British Patent 357,165; *Chem. Abstr.*, 26, 5768 (1932).

(4) The isomeric 4-fluorophthalic anhydride has been prepared before [F. F. Blicke and F. D. Smith, *J. Am. Chem. Soc.*, 51, 1865 (1929)].

(5) H. B. Gottlieb, *J. Am. Chem. Soc.*, 58, 532 (1936).

(6) H. G. Cook and B. C. Saunders, *Biochem. J.*, 41, 558 (1947).

group and a N=C double bond.[8] To the best of our knowledge, an analogous activation by a carbonyl group has not been observed before;[9] indeed, on the whole, experience has shown that in such cases fluorine is *the most easily replaceable substituent.*

3-Chlorophthalic anhydride did not react with potassium cyanide under the same operating conditions.

EXPERIMENTAL

3-Chlorophthalic anhydride was prepared according to Newman and Scheurer[2] from 3-nitrophthalic anhydride[10] and gaseous chlorine. The temperature of the bath was kept exactly at 250°, the liquid product poured into a mortar and, after it solidified, ground to a fine powder. It was not necessary to distill it; already in its crude stage it melted at 118–124° and after trituration with anhydrous ether at 125–127°. The yield was 76%.

3-Fluorophthalic anhydride. In a Claisen flask (for distillation of solid compounds) of 100-ml. capacity, 20 g. of anhydrous potassium fluoride[11] was covered with a layer of 20 g. of 3-chlorophthalic anhydride and the mixture heated at 280–290° for 45 min. Distillation at 220–225°, 80 mm. gave a clean fraction (11 g.), which solidified spontaneously and was recrystallized from 75 ml. of toluene, m.p. 160°; yield, 9 g. (50%).

Anal. Calcd. for $C_8H_3FO_3$: C, 57.8; H, 1.8; F, 11.4. Found: C, 58.1; H, 2.1; F, 11.0.

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(7) G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6034 (1956). See also J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 273 (1951).

(8) G. C. Finger and L. D. Starr, *J. Am. Chem. Soc.*, **81**, 2674 (1959).

(9) One may recall the easy replacement of sulfonic acid groups by molecular chlorine in the α-positions of the anthraquinone system. See, *e.g.*, V. V. Kozlov, *J. Gen. Chem.* (*U.S.S.R.*), **17**, 289 (1947); *Chem. Abstr.*, **42**, 550 (1948).

(10) *Org. Syntheses*, Coll. Vol. I, 408 (1941).

(11) Analytical grade (Messrs. Baker and Adamson, anhydrous, granulated) was used. It is necessary that the *p*H of an aqueous solution be about 8.0.

Unsymmetrical Quaternary Carbon Compounds. III. The Preparation and Resolution of Aliphatic Trialkylacetic Acids[1,2]

FRANKLIN S. PROUT, BOHDAN BURACHINSKY, WILLIAM T. BRANNEN, JR., AND HERBERT L. YOUNG

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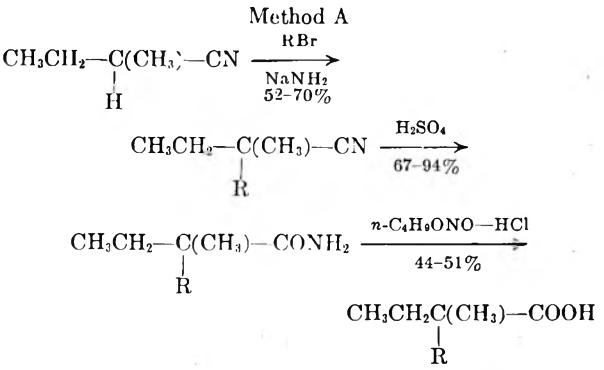
Trialkylacetic acids have been prepared by at least six different methods.[3-9] However, only the two procedures indicated by methods A and B seemed to afford convenient, general routes for the preparation of unsymmetrical, racemic trialkylacetic acids. Method A was derived from work of Sperber, Papa, and Schwenk[4,10] and method B was modified from the report of Hudson and Hauser.[5]

For method A, 2-methylbutanenitrile was prepared by the monoalkylation of propanenitrile with ethyl bromide in the presence of sodium amide,[3,4,10] a process which furnished only 30–36% of monoalkylation product and 12% of the dialkylation product, 2-ethyl-2-methylbutanenitrile. Better yields would have resulted from dehydration of the 2-methylbutanamide.[11]



R = *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, *n*-C_6H_{13}

The second alkylation with *n*-propyl, *n*-butyl, *n*-amyl, and *n*-hexyl bromides was more efficiently performed (52–70% yields). Hydrolysis of these nitriles in sulfuric acid[4] gave 67–94% yields of the amides. However, conversion of the amides to the corresponding acids with butyl nitrite and hydrochloric acid furnished poor yields (44–51%) of acids; for these acids contained the butyl ester, presumably because of water contamination in the reactants.

Method B essentially followed the procedure of Hudson and Hauser[5] substituting sodium hydride

(1) Paper II of this series was F. S. Prout, E. P.-Y. Huang, R. J. Hartman, and C. J. Korpics, *J. Am. Chem. Soc.*, **76**, 1911 (1954).

(2) Abstracted from the Masters Theses of Bohdan Burachinsky (1959) and Herbert L. Young (1953) and the Senior Thesis of William T. Brannen, Jr. (1958).

(3) K. Ziegler and H. Ohlinger, *Ann.*, **495**, 84 (1932).

(4) N. Sperber, D. Papa, and E. Schwenk, *J. Am. Chem. Soc.*, **70**, 3091 (1948).

(5) B. E. Hudson, Jr. and C. R. Hauser, *J. Am. Chem. Soc.*, **62**, 2457 (1940).

(6) C. L. Carter and S. N. Slater, *J. Chem. Soc.*, 130 (1946).

(7) W. v. E. Doering and K. B. Wiberg, *J. Am. Chem. Soc.*, **72**, 2608 (1950).

(8) S. Ställberg-Stenhagen, *Arkiv. Kemi*, **3**, 273 (1951).

(9) A. Haller and E. Bauer, *Compt. rend.*, **148**, 127 (1909); J. G. Aston, J. T. Clarke, K. A. Burgess, and R. B. Greenburg, *J. Am. Chem. Soc.*, **64**, 300 (1942); A. A. Sacks and J. G. Aston, *J. Am. Chem. Soc.*, **73**, 3902 (1951); C. T. Lester and J. R. Proffitt, Jr., *J. Am. Chem. Soc.*, **71**, 1877 (1949); C. Schuerch, Jr., and E. H. Huntress, *J. Am. Chem. Soc.*, **70**, 2824 (1948); J. Cason, *J. Org. Chem.*, **13**, 227 (1948); A review is given by A. C. Cope, H. L. Holmes, and H. O. House, *Organic Reactions*, IX, 107–331 (1957).

(10) *Cf.* also G. L. Goerner and A. A. Holzschuh, *J. Org. Chem.*, **23**, 1346 (1958).

(11) C. L. Stevens and T. H. Coffield, *J. Am. Chem. Soc.*, **73**, 103 (1951).

TABLE I

t-ALKYLCARBONITRILES, $R(C_2H_5)(CH_3)C—CN$

R	Yield, %	B.P. °C., (mm. Hg)	n_D^{25}	d^{25}	% Nitrogen Calcd.	% Nitrogen Found
C_2H_5	12[a]	153–154 (744)	1.4072	0.8034	12.60	12.36
n-C_3H_7	52[b]	172–173 (748)	1.4138	0.8062	11.19	10.93
n-C_4H_9	70[c]	94–95 (27)	1.4196	0.8095	10.06	9.78
n-C_5H_{11}	68[c]	120–121 (44–47)	1.4237	0.8123	9.14	9.01
n-C_6H_{13}	66[c]	114–115 (15–16)	1.4274	0.8147	8.37	8.21

[a] This product was a by-product from the monoalkylation of propanenitrile. [b] In this run 0.3 mole of 2-methylbutanenitrile, 0.375 mole of bromide, and 0.3 mole of sodium amide were used. [c] In these runs 0.5 mole of 2-methylbutanenitrile, 0.625 mole of alkyl bromide, and 0.5 mole of sodium amide were used.

for triphenylmethylsodium as the alkylating agent. The alkylation yields (41–47%) with normal iodides were lower than the 59% yield reported for the preparation of ethyl 2-ethyl-2-methylpentanoate.[5] However, the availability of sodium hydride and the ease of operation makes this the preferred procedure. Hydrolysis of the esters was essentially quantitative.

Method B

$$CH_3CH_2—\underset{\displaystyle H}{\underset{|}{C}}(CH_3)—COOC_2H_5 \xrightarrow[NaH\ 41\text{–}47\%]{RI} CH_3CH_2—\underset{\displaystyle R}{\underset{|}{C}}(CH_3)—COOC_2H_5 \xrightarrow[O(CH_2CH_2OH)_2\ 91\text{–}94\%]{KOH} C_2H_5—\underset{\displaystyle R}{\underset{|}{C}}(CH_3)—COOH$$

R = *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}.

The partial resolution of three of these acids was effected by extensive crystallization of their brucine salts. The specific rotations ($[\alpha]_D^{25}$) of these acids were low: +1.05°, +1.23° and +2.34° for 2-ethyl-2-methylpentanoic, 2-ethyl-2-methylhexanoic and 2-ethyl-2-methylheptanoic acids, respectively.[12] The homologous acids reported in the literature have recorded higher rotations: 2-ethyl-2-methyleicosanoic acid, $[\alpha]_D^{23}$ −4.28°[8] and 2-ethyl-2,4-dimethylpentanoic acid, $[\alpha]_D^{24}$ +21.55°.[7]

EXPERIMENTAL

The starting alkyl bromides and iodides, 2-methylalkanoic acids and propanenitrile were obtained commercially. Their boiling points agreed with literature values. Ethyl 2-methylbutanoate, ethyl 2-methylpentanoate, and ethyl 2-ethylhexanoate were prepared in 88%, 82.5%, and 89% yields from the acids by the benzene method of Pinkney.[13] Sodium and ammonia used for the preparation of sodium amide[14] were reagent grade. Fifty percent of sodium hydride emulsion in mineral oil supplied by Metal Hydrides, Inc., or by Callery Chemicals was usually used as alkylating agents; but crystalline sodium hydride (Metal Hydrides) was used in some instances. Dioxane was purified by the method of Fieser[15] or merely by distilling the dioxane from sodium.

All boiling points and melting points were uncorrected. Densities were taken in absolute units (g./cc.). Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois, and Drs. Weiler and Strauss, Oxford, England. Rotations were observed in a Rudolph Polarimeter with a Lippich double field polarizer. All final distillations were effected in a 60-cm., heated Vigreux column with no head (V-1), in a 40-cm., helix-packed column equipped with a total reflux, partial take-off head (V-2) or in a 25-cm., unheated helix-packed column with no head (V-3).

2-Methylbutanenitrile was prepared in 30–36% yields by the reaction of 2.0 moles of propanenitrile with 3.0 moles of ethyl bromide in boiling ether with a suspension of 2.0 moles of sodium amide.[14] (This method was essentially that described below for 2-ethyl-2-methylpentanenitrile.) The purified product had a boiling point of 124–126° (746 mm.), n_D^{25} 1.3875. The literature[11] reports b.p. 123–125°, n_D^{25} 1.3885. The yield was reduced by using an equivalent amount of bromide (14%), by using a lower temperature of 10–20° (25%), or by changing the solvent to benzene (12%).

Accompanying the desired product in 12% yield was the higher-boiling dialkylation product *2-ethyl-2-methylbutanenitrile* (see Table I).

A similar procedure using sodium hydride and butyl bromide has been reported.[10] However, this nitrile would have been prepared more efficiently by dehydration of the amide.[11]

2-Methylbutanamide prepared[4] from the nitrile melted at 109–111°. Newbold and Spring[16] reported a melting point 111–112°.

2-Ethyl-2-methylbutanamide was prepared[4] in 74% yield: m.p. 75.5–78.5° (reported,[17] m.p. 78–79°).

2-Ethyl-2-methylpentanenitrile. This alkylation was run under a nitrogen atmosphere in a three-necked flask equipped with a stirrer, condenser, and a dropping funnel also fitted with a stirrer. Sodium amide, prepared from 8 g. of sodium and about 200 ml. of anhydrous ammonia,[14] was suspended in 100 ml. of toluene and was placed in the dropping funnel. A solution of 25.5 g. of 2-methylbutanenitrile, 46.1 g. of *n*-propyl bromide, and 50 ml. of toluene was placed in the flask and the black amide suspension was added in 90 min. while the reaction mixture was heated gently under reflux. Reflux of the stirred mixture was continued for 2 hr. by which time the mixture had turned gray. (The time of reaction was established by measurement of the ammonia evolved during reaction.)

(12) 2-Ethyl-2-methyleicosanoic acid has a molecular rotation of −15.2° (ref. 8 gives $[\alpha]_D^{23}$ −4.23°). Thus, assuming that homologues have nearly the same molecular rotation, the estimated specific rotations for the three acids resolved in this work would be 10.5°, 9.6°, and 8.8°.

(13) P. S. Pinkney, *Org. Syntheses*, **Coll. Vol. II**, 265 (1943).

(14) M. T. Leffler, *Organic Reactions*, I, 99 (1942).

(15) L. F. Fieser, *Experiments in Organic Chemistry*, 3rd Ed., D. C. Heath and Co., New York, N. Y. (1957) p. 285.

(16) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 373 (1947).

(17) A. Haller and E. Bauer, *Compt. rend.*, **148**, 130 (1909).

The reaction mixture was filtered to remove the solids and the solution was distilled (V-2). After removal of the solvent and forerun (b.p. 93–170°) the product was obtained: b.p. 170–173°; 19.5 g. (52%); n_D^{25} 1.4138–1.4140.

When ether or benzene were solvents, the yields were reduced to 0% or 35%, respectively. Addition of the sodium amide in 30 min. reduced the yield to 44%.

Repetition of this procedure using *n*-butyl bromide, *n*-amyl bromide and *n*-hexyl bromide gave 70%, 68%, and 66% yields of trialkylacetonitriles. The properties of the purified products are summarized in Table I.

2-Ethyl-2-methylpentanamide. A mixture of 25.0 g. of 2-ethyl-2-methylpentanenitrile and 300 g. of 80% (by weight) sulfuric acid was heated and stirred at 85–95° for 12 hr.[4] The brownish reaction mixture was poured into ice and extracted three times with benzene. After washing the extracts with sodium carbonate solution and drying with magnesium sulfate, the solvent was removed and the product was distilled under reduced pressure: b.p. 91–116° (1 mm.); 19.2 g. (67%).

A somewhat lower yield (56%) resulted when 80% (by volume) sulfuric acid was used. The results of the other nitrile hydrolyses run essentially in the same way are assembled in Table II.

TABLE II

AMIDES, $R(C_2H_5)(CH_3)C—CONH_2$, FROM HYDROLYSIS OF *t*-ALKYLCARBONITRILES

R—	Boiling Point: Observed °C., (mm. Hg)	Boiling Point: Literature[a] °C., (mm. Hg)	Yield, %	% Nitrogen: Calcd.	% Nitrogen: Found
C_2H_5—	142–144 (19)[b]		74[c]		
n-C_3H_7—	105–112 (1)[d]	134–135 (12)	67		
n-C_4H_9—	122–132 (1)	124–144 (18)	84	8.91	8.62
n-C_5H_{11}—	127–128 (1)	147–153 (19)	90	8.18	7.96
n-C_6H_{13}—	143–148 (1)	152–162 (18)	94	7.56	7.18

[a] Results of Carter and Slater (ref. 6). [b] The melting point was 75.5–78.5° (lit.,[17] 78–79°). [c] This amide was extracted from the hydrolysis mixture with nine portions of chloroform. [d] Purified from the product described in the Experimental and having m.p. 40–41° (reference 5 gives m.p. 42–43°).

Ethyl 2-ethyl-2-methylpentanoate. A three-necked flask was fitted with a stirrer, a condenser and a thermometer and was arranged for a nitrogen atmosphere. After careful drying 45.5 g. of ethyl 2-methylbutanoate, 100 g., of *n*-propyl iodide, 25 g. of 50% sodium hydride emulsion (Callery Chemicals), and 100 ml. of purified dioxane[15] (or dioxane distilled only from sodium) were quickly added to the flask. This mixture was heated under gentle reflux for 8 hr. (Heating was adjusted so that about 1.25 l. of hydrogen per hour was evolved. Passing the evolved gases through a Dry Ice-acetone trap demonstrated that some *n*-propyl iodide was entrained.)

After the reflux had been completed 100 ml. of 95% ethanol was carefully added to destroy the excess sodium hydride. When hydrogen evolution had ceased 600 ml. of water was cautiously added. After the two clear phases were formed, the mixture was extracted with two portions of benzene. The organic extracts were washed with water and saturated sodium chloride solution, were dried by filtering through sodium sulfate, and were distilled (V-3). The fractions boiling from 120–260° were redistilled (V-2) to give 25.5–28 g. (42–47%) of product: b.p. 180–185°, n_D^{25} 1.4125.

When an approximately equal amount of iodide (0.39 mole) was used, the yields were 31–32.5%. The use of sodium hydride emulsion from Metal Hydrides reduced the yield (from 31% to 18% and from 44% to 33%). The use of toluene as solvent reduced yields 10–18% when propyl iodide was used. The substitution of *n*-propyl bromide for the iodide with toluene as solvent gave a 31% yield (*cf.* 26% using the iodide in toluene and 44% using iodide in dioxane). However, the use of a 200% excess of the *n*-propyl bromide in toluene gave a 41% yield. An old sample of crystalline sodium hydride gave poor yields (22–30%) of ester. Attempted alkylation with isopropyl iodide failed entirely.

This ester was also prepared in 53.5% yield by the action of ethyl iodide on ethyl 2-methylpentanoate. The reaction of *n*-butyl iodide and *n*-amyl iodide with ethyl 2-methylbutanoate produced *ethyl 2-ethyl-2-methylhexanoate* (41.2%) and *ethyl 2-ethyl-2-methylheptanoate* (45.0%), respectively. However, because of halide loss and low reaction temperature the alkylation of ethyl 2-ethylhexanoate with methyl iodide gave only an 8.2% yield of ethyl 2-ethyl-2-methylhexanoate. The results of all these runs are summarized in Table III.

Hydrolysis of amides. 2-Ethyl-2-methyloctanoic acid. As an example of amide hydrolysis,[4] a mixture of 48.7 g. of 2-ethyl-2-methyloctanamide in 300 ml. of dry dioxane was saturated with gaseous hydrochloric acid. Then 54 g. of *n*-butyl nitrite[18] was added to the well-stirred solution at room temperature over a 50-min. period. After heating the mixture for 2 hr. at 100°, it was diluted with three volumes of water and extracted with three portions of benzene. The benzene extracts were washed with water, four portions of 10% sodium carbonate, and water.

The aqueous phases were combined and acidified with hydrochloric acid. The acid was extracted with benzene; the extracts were dried over magnesium sulfate and were distilled: b.p. 155–163° (16–17 mm.); 28.0 g. (57%). Curiously, the acids still had high neutralization equivalents and a repetition of the basic extraction using ether for the extracting solvent and redistillation (V-2) gave the pure acids whose yields and properties are listed in Table IV.

The neutral benzene extracts were combined, dried over magnesium sulfate, and distilled to furnish 19.2 g. (30%) of *butyl 2-ethyl-2-methyloctanoate:* b.p. 100–115° (1 mm.); n_D^{25} 1.4314. Redistillation (V-1) of this ester gave the purified ester: b.p. 141–144° (15–16 mm.); n_D^{25} 1.4306.

Anal. Calcd. for $C_{15}H_{30}O_2$: C, 74.32; H, 12.47; Saponification equiv., 242.4. Found: C, 74.10; H, 12.56; Saponification equiv., 241, 240.

Ten grams of this ester was heated under reflux for 6 hr. with 10 g. of potassium hydroxide in ethylene glycol. After the usual work-up 7.0 g. (91%) of 2-ethyl-2-methyloctanoic acid was obtained; b.p. 148–156° (17 mm.), n_D^{21} 1.4380.

Refractionation (V-1) of the homologous esters gave the purified esters listed in Table IV.

Hydrolysis of ethyl esters. 2-Ethyl-2-methylpentanoic acid. Ethyl 2-ethyl-2-methylpentanoate (120 g.) was heated under reflux for 5 hr. with 241 g. of potassium hydroxide in 1360 ml. of diethylene glycol. The mixture was diluted and extracted with ether to remove neutral materials. The aqueous phases were acidified and extracted with benzene. After the usual work-up the acid was distilled to give 91.5 g. (91%) of a single fraction: b.p. 127–128° (20–21 mm.); n_D^{25} 1.4278; neut. equiv., 145 (calcd., 144.21).

Saponification with alcoholic potassium hydroxide gave only a 30–35% yield. In ethylene glycol the yield was 50–60%.

(18) W. A. Noyes, *Org. Syntheses*, Coll. Vol. II, 2nd. Ed., 108 (1943).

TABLE III

ALKYLATIONS TO PRODUCE ETHYL 2-ETHYL-2-METHYLALKANOATES

Starting Materials		Products, $R(C_2H_5)(CH_3)C—COOC_2H_5$						
$R_1R_2CHCOOC_2H_5$ R_1, R_2	RI R	R	B.P., (mm. Hg)	n_D^{25}	Sapon. Equiv. Calcd.	Sapon. Equiv. Found[a]	d^{25}	Yield, %
CH_3, C_2H_5	n-C_3H_7	n-C_3H_7	180–185 (752)[b]	1.4125	172.3	172	0.865	46.8
CH_3, n-C_3H_7	C_2H_5	n-C_3H_7	181–186 (754)[b]	1.4115	172.3	173	0.865	53.5
CH_3, C_2H_5	n-C_4H_9,	n-C_4H_9	94–95 (20)	1.4181	186.3	186[c]	0.863	41.2
C_2H_5, n-C_4H_9	CH_3	n-C_4H_9	94–97 (20)	1.4178	—	—	—	8.2
CH_3, C_2H_5	n-C_5H_{11}	n-C_5H_{11}	107–108 (20)	1.4238	200.3	199[d]	0.862	45.0

[a] Saponification equivalents were determined using potassium hydroxide in diethylene glycol. [b] Boiling point was also observed at 80–81° (20 mm.) The literature (ref. 5) reports, b.p. 180–185°. [c] *Anal.* Calcd. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 71.10; H, 12.20. [d] Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.07. Found: C, 71.54; H, 11.86.

TABLE IV

TRIALKYLACETIC ACIDS, $R—(C_2H_5)(CH_3)C—COOH$, AND BUTYL ESTERS BY HYDROLYSIS OF AMIDES

	Acid						Butyl Ester		
R—	B.P., (mm. Hg)	Yield[a]	n_D^{25}	d^{25}	Neut. Equiv. Calcd.	Neut. Equiv. Found	Yield[b]	B.P., (mm. Hg)	n_D^{25}
C_2H_5—	111–112 (16–17)[c]	50	1.4233	0.9273	130.2	131.3	27	90–92 (15)	1.4200
n-C_3H_7—	127–128 (21–22)[d]	50	1.4281	0.9177	144.2	144.9	12	103–105 (15)	1.4229
n-C_4H_9—	137–138 (16–17)[e]	44	1.4320	0.9096	158.2	158.3	27	117–118 (16)	1.4256
n-C_5H_{11}—	147–149 (16–17)[f]	48	1.4346	0.9022	172.3	172.4	28	129–131 (15)	1.4283
n-C_6H_{13}—	160–162 (16–17)[g]	51	1.4377	0.8982	186.3	186.2	30	141–144 (15–16)	1.4306

[a] Purified yield. [b] Crude yield. [c] The literature (ref. 6) gives b.p. 203–204°, [d] 125.5–126.5° (23 mm.), [e] 123–125° (22 mm.), [f] 131–135° (21 mm.), [g] 135–137° (19 mm.).

2-Ethyl-2-methylhexanoic acid was prepared using 102 g. of the ethyl ester, 180 g. of potassium hydroxide and 1020 ml. of diethylene glycol. The acid was obtained in 90.5% yield: 78.0 g.; b.p. 137–138° (16–17 mm.); n_D^{25} 1.4322; neut. equiv., 157 (calcd., 158.23).

2-Ethyl-2-methylheptanoic acid was prepared in 94% yield by boiling a mixture of 110 g. of the ethyl ester, 180 g. of potassium hydroxide, and 1020 ml. of diethylene glycol for 8 hr. The product boiled at 148–149° (17 mm.); 89.0 g.; n_D^{25} 1.4346; neut. equiv., 173 (calcd., 172.26).

Resolution of 2-ethyl-2-methylpentanoic acid with brucine. A mixture of 21.6 g. of the *dl*-acid, 59.1 g. of brucine, and 130 ml. of absolute ethanol was allowed to crystallize producing 39 g. of salt, m.p. 81–82°. Six more crystallizations furnished 13.8 g. of salt: m.p. 83°; $[\alpha]_D^{25}$ −38.06° (95% ethanol; c, 8). Decomposition of this brucine salt in hydrochloric acid, extraction with ether, and distillation gave 2.1 g. (10%) of *(+)-2-ethyl-2-methylpentanoic acid;* b.p. 127° (20 mm.); α_D^{25} +0.970° (homogeneous, 1 dm.); $[\alpha]_D^{25}$ +1.05°.

The mother liquors were concentrated according to the usual diamond scheme to give 29.0 g. of yellowish crystals: m.p. 80–81°, $[\alpha]_D^{25}$ −40.62° (95% ethanol; c, 8). Decomposition of this salt gave 2.7 g. of *(−)-2-ethyl-2-methylpentanoic acid;* b.p. 127° (20–21 mm.); $[\alpha]_D^{25}$ −0.58° (homogeneous).

An attempted resolution with quinine produced a 24% yield of quinine salt after seven crystallizations from ethanol: m.p. 131.5°; $[\alpha]$ −131.4° (95% ethanol; c, 8). Decomposition of this salt gave 2.3 g. of the acid: b.p. 128° (21 mm.); $[\alpha]_D^{25}$ −0.14°. The tail fraction gave the (+)-acid, $[\alpha]_D^{25}$ +0.12°. Cinchonine, strychnine, and (−)-α-phenylethylamine failed as resolving agents.

(+)-2-Ethyl-2-methylhexanoic acid was resolved in 5.1% yield by nine crystallizations of the brucine salt in ethyl acetate: the salt, m.p. 89°; the acid, b.p. 137° (17 mm.); α_D^{25} +1.12° (homogeneous, 1 dm.); $[\alpha]_D^{25}$ +1.23°.

The *(−)-acid* from the tail fraction had the value, $[\alpha]_D^{25}$ −0.58° (homogeneous).

(+)-2-Ethyl-2-methylheptanoic acid was resolved in 6.1% yield by eight crystallizations of the brucine salt from ethyl acetate: the salt; m.p. 73°; the acid, b.p. 148° (16–17 mm.); α_D^{25} +2.11° (homogeneous, 1 dm.); $[\alpha]_D^{25}$ +2.34°.

The tail fraction gave *(−)-acid,* $[\alpha]_D^{25}$ −1.13°.

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Substituted γ-Lactones. IV. Some Aldehyde Condensations with $\Delta^{\beta,\gamma}$-Angelica- and γ-Valerolactone[1]

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In connection with some previous work[4] we were interested in preparing γ-lactones with α-benzylidene or α-benzyl substituents. These compounds have potential value due to some of their pharmacological effects; they also serve as model compounds for further experiments directed towards the synthesis of lignans of the α,β-dibenzylbutyrolactone type.

In this note we describe some condensations of $\Delta^{\beta,\gamma}$-angelicalactone and γ-valerolactone with

(1) Paper III of this series, see J. Rothe and H. Zimmer, *J. Org. Chem.*, **24**, 586 (1959).

(2) Taken from the M.Sc. Thesis of D. G., Univ. of Cincinnati (1958).

(3) Chattanooga Medicine Company Post-Doctorate Research Fellow 1956–58.

(4) Part I, H. Zimmer and J. Rothe, *J. Org. Chem.*, **24**, 28 (1959).

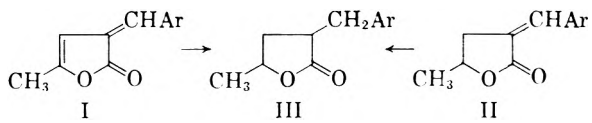
TABLE II

HYDROGENATION PRODUCTS, III

Cpd.	Yields from I	Yields from II	M.P.	Formula	Calcd. C	Calcd. H	Found C	Found H
IIIa	—	95	[a]	$C_{14}H_{19}NO_2$	72.07	8.21	71.28	8.25[d]
IIIb	70	97	62–64[b,c]	$C_{14}H_{18}O_4$	67.18	7.25	67.65	7.38
IIIc	41	90	68–69[c]	$C_{16}H_{22}O_4$	69.04	7.97	69.17	7.94

[a] B.p. 202–203°/4 mm. [b] B.p. 190–191°/1 mm. [c] Recrystallized from methanol. [d] Calcd.: N, 6.00. Found: N, 6.00.

certain aromatic aldehydes. Reactions of this type are known and give products of type I[5] and II.[6] In either case, 3-nitrobenzaldehyde furnished comparatively low yields of the desired condensation products, contaminated by large amounts of brown tars and resins. This fact confirm previous observations[4] regarding the influence of electron-withdrawing groups in the aromatic aldehyde on the result and yield of the reaction. Hydrogenations of either I or II led to α-benzyl-γ-valerolactones (III), the yields from II being comsiderably higher than from I.



I III II

a. Ar = 4-$CH_3NC_6H_4$; b. Ar = 3,4-$(CH_3O)_2C_6H_3$; c. Ar = 3,4-$(C_2H_5O)_2C_6H_3$; d. Ar = 3-$O_2NC_6H_4$.

The structures of type I and type II compounds have been established (a) by carbon, hydrogen analysis, (b) infrared spectra, and (c) by the fact that they lead to identical hydrogenation products of type III.

EXPERIMENTAL

Melting points are uncorrected. Microanalysis are by A. Bernhardt, Microanalytisches Laboratorium im Max-Planck-Institut, Mülheim/Ruhr, Germany.

Materials. Generally Eastman White Label products were employed without further purification.

α-(4-Dimethylaminobenzylidene)-Δ$^{\beta,\gamma}$-angelicalactone (Ia). Δ$^{\beta,\gamma}$-Angelicalactone[7] (0.08 mole), 4-dimethylaminobenzaldehyde (0.1 mole) and diethylamine (*ca.* 2 ml.) were heated on a water bath for 1 hr. After cooling to room temperature, the excess aldehyde was removed by shaking with sodium bisulfite solution. The remaining yellow solid was filtered and recrystallized from methanol–petroleum ether (2:1); yield 7.4 g. (40%), orange leaflets, m.p. 120–121°.

Anal. Calcd. for $C_{14}H_{15}NO_2$: N, 6.11. Found: N, 6.23.

α-(3,4-Dimethoxybenzylidene)-Δ$^{\beta,\gamma}$-angelicalactone (Ib) was prepared similarly from veratraldehyde, but in benzene solution (initial cooling with water, then 30 min. heating on a water bath with stirring), to give yellow prisms from methanol, m.p. 118–119°, yield 40%. The compound slowly turns orange under the influence of light.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.21; H, 5.64.

α-(3,4-Diethoxybenzylidene)-Δ$^{\beta,\gamma}$-angelicalactone (Ic) was prepared from 3,4-diethoxybenzaldehyde (no solvent, 40 min. heating on a water bath) to give yellow crystals from methanol, m.p. 100–101°, yield 43%.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.85; H, 6.69.

α-(3-Nitrobenzylidene)Δ$^{\beta,\gamma}$-angelicalactone (Id) was prepared from 3-nitrobenzaldehyde (no solvent, initial cooling with ice salt, then standing overnight). The crude resinous product was dissolved in methylene chloride and chromatographed on neutral alumina. A yield of 70%, as yellow needles from methanol, m.p. 154–155°, was obtained besides much noncrystalline material.

Anal. Calcd. for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.12; H, 3.97; N, 6.30.

α-(4-Dimethylaminobenzylidene)-γ-valerolactone (IIa) was obtained from the aldehyde and γ-valerolactone in benzene with sodium methoxide as condensing agent (1.5 hr. stirring at room temperature; yield 69%; see ref. 4) as yellow leaflets from methanol, m.p. 130–131°.

Anal. Calcd. for $C_{14}H_{17}NO_2$: N, 6.06. Found: N, 6.11.

Similarly, the following were prepared: *α-(3,4-dimethoxybenzylidene)-γ-valerolactone* (IIb), m.p. 116° (from methanol); yield 54%.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.51; H, 6.49.

α-(3,4-Diethoxybenzylidene)-γ-valerolactone (IIc), m.p. 110–112° (from methanol); yield 40%.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.68; H, 7.12.

α-(3-Nitrobenzylidene)-γ-valerolactone (IId), m.p. 110–112°, yellow crystals from methanol; the product was isolated in a small yield only and was separated from much resinous material by chromatography of its solution in methylene chloride on alumina.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.56; H, 4.89; N, 6.20.

Hydrogenations. These were performed using an Adams catalyst in methanol in a Parr apparatus (50 p.s.i. initial pressure). The results are tabulated below.

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2-Acetyl-6-methoxycoumaran-3-one. Benzylation at the Terminal Methyl Group[1]

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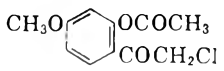
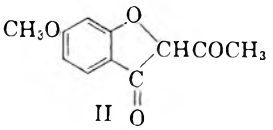
Wheeler and co-workers[2] have synthesized a number of coumaran-3-ones by rearrangement of the

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

appropriate *o*-acyloxy-ω-chloroacetophenone in dioxane by means of sodium hydride, which is a modification of the method of Auwers.[3] We have similarly effected the rearrangement of the *o*-acetoxy-ω-chloro-4-methoxyacetophenone (I) to form the coumaranone II in 80% yield.



I



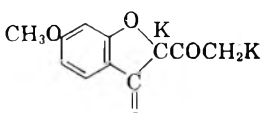
II

The coumaranone II was prepared for the purpose of studying the possibility of effecting condensations at its terminal methyl group similar to those realized recently[4] with certain simpler β-diketones. For example, acetylacetone was benzylated through its dipotassio salt III to form the terminal methyl derivative IV in 60% yield.[4]

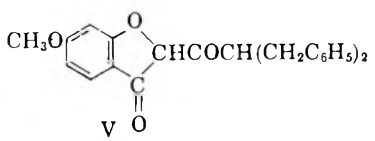
$CH_3COCH(K)COCH_2K$ III

$CH_3COCH_2COCH_2CH_2C_6H_5$ IV

The coumaranone II was added to two molecular equivalents of potassium amide in liquid ammonia to form presumably the dipotassio salt II′, which was treated with one equivalent of benzyl chloride. However, none of the corresponding monobenzyl derivative could be isolated. Instead, there was obtained the copper chelate of a product which, on the basis of analysis, was the dibenzyl derivative V. A considerable amount of the starting β-diketone II was recovered as its copper chelate.



II′



V

The possible dibenzyl derivative that might have resulted from alkylation at both the methyl and methinyl groups of II through II′ could not have formed a copper chelate. Another example of dibenzylation at the terminal methyl group has recently been observed with *o*-hydroxyacetophenone.[5]

An unsuccessful attempt was made to effect the benzoylation of dipotassio salt II′ with methyl benzoate under the conditions that were found satisfactory with dipotassio salt III.[4]

EXPERIMENTAL[6]

2-Acetoxy-ω-chloro-4-methoxyacetophenone (I). A solution of resorcinol dimethyl ether and chloracetyl chloride in carbon disulfide was treated with anhydrous aluminum chloride as described previously[7] to form ω-chloro-2-hydroxy-4-methoxyacetophenone.

A mixture of 20 g. (0.086 mole) of this compound, 40 ml. of acetic anhydride, and one drop of 70% perchloric acid was kept at room temperature for 1 hr., and then stirred with water for several hours (to hydrolyse the excess acetic anhydride). The resulting precipitate was collected on a funnel and washed with water. It was recrystallized from ethanol and then from ligroin to give 23 g. (95%) of the product I (white cubes), m.p. 99–100°.

Anal. Calcd. for $C_{11}H_{11}O_4Cl$: C, 54.44; H, 4.57; Cl, 14.61. Found: C, 54.47; H, 4.58; Cl, 14.59.

2-Acetyl-6-methoxycoumaran-3-one (II). To a stirred solution of 60 g. (0.252 mole) of 2-acetoxy-ω-chloro-4-methoxyacetophenone in 500 ml. of dioxane (purified by Vogel's method)[8] was added 15 g. of a 48.5% suspension of sodium hydride in mineral oil (0.32 mole of sodium hydride). The reaction mixture, which was kept under an atmosphere of nitrogen, was brought to a temperature of 50–60°, and the stirring was continued until hydrogen ceased to evolve (3–4 hr.). After adding a small quantity of methanol to destroy the excess sodium hydride, the precipitate of the sodium salt of the product was collected and washed with ether. It was dissolved in water and the cooled solution was acidified. The resulting precipitate was collected, washed with water, and dried to give 40.5 g. (80%) of crude 2-acetyl-6-methoxycoumaran-3-one. After recrystallization once from *n*-hexane and twice from ethanol the product was obtained as orange-brown cubes, m.p. 117–118°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.67; H, 4.8. Found: C, 64.53; H, 4.85.

The compound gave a green enol test with ferric chloride, and formed a green copper chelate which was washed with water, ethanol, and ether. Attempts to recrystallize the chelate from several solvents were unsuccessful. The dried chelate decomposed between 275 to 285°. Its infrared spectrum showed the following peaks: 3.4, 6.18, 6.28, 6.35, 6.53, 6.73, 6.93, 7.15, 7.4, 7.7, 7.85, 8.15, 8.5, 8.7, 9.15, 9.85, 10.6, 11.35, 12.25, 12.9, 13.15, 13.8, 14.3, 14.5μ.

Benzylation of II. To a stirred solution of 0.484 mole of potassium amide in liquid ammonia[4] was added in small portions 5 g. (0.0242 mole) of 2-acetyl-6-methoxycoumaranone (II). After stirring for 15–30 min., 3.08 g. (0.0242 mole) of benzyl chloride was added and the stirring was continued for 2 hr. An excess (2.5 g.) of solid ammonium chloride was added and the ammonia was evaporated as an equal volume of ether was added. The resulting ethereal suspension was shaken with water to dissolve the inorganic salts. The aqueous and ethereal layers were separated, the aqueous layer being discarded. The ethereal layer was extracted with a saturated aqueous solution of copper acetate to precipitate 3.3 g. of the copper chelate of the starting compound II which, after washing with water, ethanol, and ether, was identified by its infrared spectrum. The ethereal filtrate was evaporated to precipitate 2.3 g. (21%, based on benzyl chloride) of copper chelate of 2-dibenzylacetyl-6-methoxycoumaran-3-one (V) which, after recrystallization from ethanol, melted at 205–207°. Its infrared spectrum

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showed the following peaks: 3.3, 3.45, 6.18, 6.35, 6.55, 6.7, 6.95, 7.45, 7.75, 7.9, 8.2, 8.5, 8.7, 9.35, 12.15, 13.05, 13.4, 4.35μ (potassium bromide pellet).

Anal. Calcd. for $C_{30}H_{42}O_6Cu$: C, 71.98; H, 5.07; Cu, 7.62. Found: C, 71.80; H, 5.09; Cu, 7.52.

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The Nitration of 3-Chloro-4-iodonitrobenzene

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Halonitrobenzenes are important intermediates in the synthesis of a variety of compounds such as phenylhydrazine,[2] phenylsemicarbazide,[3] benzotriazole,[4,5] phenoxazine,[6] and anthranil.[7] In a program[8,9,10] on preparation of such compounds, the nitration of 3-chloro-4-iodonitrobenzene was undertaken for detailed investigation. Although it might give a mixture of dinitroisomers, only 1-iodo-2-chloro-4,6-dinitrobenzene[11] was isolated. It reacts with hydrazine hydrate to give 2-chloro-4,6-dinitrophenylhydrazine.[12]

EXPERIMENTAL[13]

Nitration of 3-chloro-4-iodonitrobenzene. To a suspension of 3-chloro-4-iodonitrobenzene (10 g.) in conc. sulfuric acid (42 ml., d., 1.82), fuming nitric acid (14 ml., d., 1.5) was added dropwise with vigorous shaking. When all the nitric acid was added, it was heated on a water bath for an hour and poured on crushed ice. The yellow crystalline solid was filtered and recrystallized successively from acetic acid, methanol, and ethanol to give 1-iodo-2-chloro-4,6-dinitrobenzene (7 g.) in yellow needles, m.p. 118°. Mixed melting point with an authentic sample of 1-iodo-2-chloro-4,6-dinitrobenzene remained undepressed.

Anal. Calcd. for $C_6H_2N_2O_4ClI$: Cl + I, 49.4. Found: Cl + I, 49.2.

2-Chloro-4,6-dinitrophenylhydrazine. To a cooled solution of 1-iodo-2-chloro-4,6-dinitrobenzene (1 g.) in ethanol twice the equivalent quantity of hydrazine hydrate was added. 2-Chloro-4,6-dinitrophenylhydrazine was filtered after an hour, m.p. 175° (lit.[12] m.p., 175°). After two recrystallizations from ethyl acetate, yellow needles (0.5 g.) melting at 190° were obtained.

Anal. Calcd. for $C_6H_5N_4O_4Cl$: Cl, 15.2. Found: Cl, 15.1.

The *acetyl* derivative prepared by the acetic acid–acetic anhydride method crystallized in lemon yellow needles from ethanol, m.p. 189°.

Anal. Calcd. for $C_8H_7N_4O_5Cl$: Cl, 12.9. Found: Cl, 12.7.

The *benzoyl* derivative prepared by the pyridine method crystallized in colorless needles from ethanol, m.p. 208°.

Anal. Calcd. for $C_{13}H_9N_4O_5Cl$: Cl, 10.5. Found: Cl, 10.2

Acknowledgment. The author wishes to express his gratitude to Dr. S. S. Joshi, D.Sc., Principal, Meerut College, Meerut (India) for his keen interest during the progress of this work.

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(13) All melting points are uncorrected.

Reactions of Nitrohydroxychalcones. Oxidation by Hydrogen Peroxide in Alkaline Medium

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Received September 3, 1959

In earlier publications,[3] we had communicated our observations regarding the isomerization of some nitrohydroxychalcones to flavanones and the conversion of nitrohydroxychalcones to flavones. The behavior of some of these chalcones towards alkaline hydrogen peroxide oxidation is now reported. The chalcones studied were 2′,4′-dihydroxy-3′-nitrochalcone derivatives (type I) and 2′,6′-dihydroxy-3′-nitrochalcone derivatives (type II). The type I chalcones on oxidation yielded the corresponding 3,7-dihydroxy-8-nitroflavone derivatives (type III), while the type II chalcones gave 2-benzylidene-4-hydroxy-7-nitro-3(2H)-benzofuranone derivatives (type IV). The constitutions were fully supported by color tests and analytical values.

The oxidation of type I chalcones gave products that gave a yellow coloration with concentrated sulfuric acid, and with ferric chloride a pale purplish-brown color characteristic of 3-hydroxy flavones. The enhanced halochromism of the 3-hydroxyflavones with *ortho* and *para* alkoxy substitution is shown in Table I.

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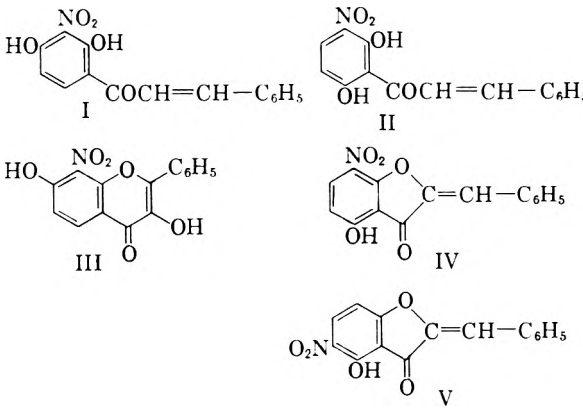
(3) S. Seshadri and P. L. Trivedi, *J. Org. Chem.*, **22**, 1633 (1957) and **23**, 1735 (1958).

TABLE I

LIST OF CHALCONES OXIDIZED AND THE REACTION PRODUCTS

Chalcone	Product of Oxidation	M.P., °c	$FeCl_3$	Conc. H_2SO_4	Formula	Analysis, % Found C	Found H	Calcd. C	Calcd. H
2′,4′-diOH-3′-NO_2	3,7-diOH-8-NO_2 flavone	234[a]	Brownish yellow	Yellow	$C_{15}H_9NO_6$	59.8	2.8	60.2	3.0
2′,4′-diOH-3′-NO_2-2-OCH_3	3,7-diOH-8-NO_2-2′-OCH_3 flavone	249[a]	Brownish yellow	Brownish yellow	$C_{16}H_{11}NO_7$	58.7	3.3	58.4	3.3
2′,4′-diOH-3′-NO_2-3-OCH_3	3,7-diOH-8-NO_2-3′-OCH_3 flavone	208–209[b]	Pinkish violet	Yellow	$C_{16}H_{11}NO_7$	58.4	3.3	58.4	3.3
2′,4′-diOH-3′-NO_2-4-OCH_3	3,7-diOH-8-NO_2-4′-OCH_3 flavone	252[a]	Brownish violet	Orange	$C_{16}H_{11}NO_7$	58.5	3.3	58.4	3.3
2′,4′-diOH-3′-NO_2-3:4-(O_2CH_2)	3,7-diOH-8-NO_2-3′:4′-(O_2CH_2) flavone	259[a]	Pale brown	Deep red	$C_{16}H_9NO_8$	56.4	2.7	56.0	2.6
2′,4′-diOH-3′-NO_2-4-CH_3	3,7-diOH-8-NO_2-4′-CH_3 flavone	223[a]	Violet	Yellow	$C_{16}H_{11}NO_6$	61.0	3.5	61.3	3.5
2′,6′-diOH-3′-NO_2	No product could be isolated	—	—	—	—	—	—	—	—
2′,6′-diOH-3′-NO_2-2-OCH_3	2-(2-OCH_3 benzylidene)-4-OH-7-NO_2-3(2H)-benzofuranone	255[b]	Deep brown	Purple	$C_{16}H_{11}NO_6$	61.3	3.2	61.3	3.5
	Acetate	207[b]	No color	—	$C_{18}H_{13}NO_7$	60.8	3.5	61.0	3.4
2′,6′-diOH-3′-NO_2-3-OCH_3	2-(3-OCH_3 benzylidene)-4-OH-7-NO_2-3(2H)-benzofuranone	225–226[b]	Deep brown	Blood red	$C_{16}H_{11}NO_6$	61.2	3.3	61.3	3.5
	Acetate	173–175[b]	No color	—	$C_{18}H_{13}NO_7$	60.6	3.6	61.0	3.4
2′,6′-diOH-3′-NO_2-4-OCH_3	2-(4-OCH_3 benzylidene)-4-OH-7-NO_2-3(2H)-benzofuranone	254[a]	Deep brown	Purple	$C_{16}H_{11}NO_6$	61.0	3.6	61.3	3.5
	Acetate	191–192[b]	No color	—	$C_{18}H_{13}NO_7$	60.7	3.5	61.0	3.4
2′,6′-diOH-3′-NO_2-3:4-(O_2CH_2)	2-(3:4O_2CH_2 benzylidene)-4-OH-7-NO_2-3(2H)-benzofuranone	278[a]	Deep brown	Purple	$C_{16}H_9NO_7$	58.7	2.7	58.4	2.4
	Acetate	208–210[b]	No color	—	$C_{18}H_{11}NO_9$	58.4	2.9	58.5	3.0

[a] Crystallized from acetic acid. [b] Crystallized from alcohol-acetic acid mixture. [c] The compounds generally underwent considerable decomposition at the melting point.



The products of oxidation of the type II chalcones, on the other hand, gave deep red colors with concentrated sulfuric acid, the colors being comparable to those given by the original chalcone itself. Because of the 4-hydroxy group they also gave a reddish-brown color with alcoholic ferric chloride. The alternative structure, 2-benzylidene-4-hydroxy-5-nitro-3(2H)-benzofuranone (V), was eliminated from a study of the reactivity of the hydroxyl group. Products could be acetylated even at room temperature by acetic anhydride and pyridine. Structure V contains a hindered hydroxyl group which will not undergo such ready acetylation. The reactivity of 5-hydroxy-8-nitroflavone and the nonreactivity of 5-hydroxy-6-nitroflavone towards acetylation of the hydroxyl group[4] may be cited as an analogous case.

The formation of 3-hydroxyflavones from chalcones of type I was expected as it has been shown that the nitro group does not affect the normal reaction to give 3-hydroxyflavones.[5]

The type II chalcones, however, possess a 6′-hydroxyl group which is chelated. A survey of the literature showed that oxidation of 6′-hydroxyl chalcones had not been carried out so far. On the basis of the mechanism of the abnormal reaction, postulated by Geissman,[6] the 6′-hydroxyl group should be expected to have the same influence as a 6′-methoxy or methyl group. Chalcones with a 6′-hydroxyl group should therefore be expected to give rise to 2-benzylidene-3(2H)-benzofuranones. The formation of the benzylidene benzofuranones shows that the nitro group does not alter the course of the abnormal reaction either.

EXPERIMENTAL

General procedure for oxidation of the chalcines. Sodium hydroxide solution (10 ml.; 10%) was added to the chalcone (0.5 g.). If an insoluble sodium salt formed (as in the case of type I chalcones), sufficient pyridine was added to dissolve it. Hydrogen peroxide solution (15 ml.; 20 vols.) was gradually added to this solution of the chalcone which was kept in ice. After addition, the reaction mixture was left in the refrigerator for 4 days and then for a day at room temperature (about 30°). The reaction mixture was then acidified by dilute hydrochloric acid and the precipitate obtained crystallized from a suitable solvent. Yields: 80 to 100 mg.

In the case of 2′,6′-dihydroxy-3′-nitrochalcone, the reaction mixture on acidifying gave a very small amount of yellowish white material which was very soluble in the usual solvents and could not be crystallized.

The benzylidene benzofuranones obtained from the type II chalcones were acetylated as follows: A 50-mg. sample of the compound was dissolved by heating in acetic anhydride (5 ml.) and a few drops of pyridine. The reaction mixture was then left at room temperature overnight. The solid obtained from the usual work-up was crystallized from a suitable solvent.

The physical and chemical properties of the compounds obtained and their analyses are given in Table I.

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Some Reactions of *N*-Hydroxymethyldodecanamide

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Several years ago we had occasion to prepare the then unknown *N*-hydroxymethyldodecanamide (Ia) for use as an analytical standard. Its straightforward preparation, elemental analysis, positive Eegriwe test for combined formaldehyde and infrared spectrum left little room for doubt as to its structure. However hydroxyl determinations by the usual method,[2,3] which involve acetylation at steam bath temperature, gave such reproducibly low results that further characterization of (Ia) seemed desirable.

The acetate was prepared and found to decompose at 100°, which makes the low OH values less surprising.

A puzzling phenomenon occurred when (Ia) was heated with 1-naphthyl isocyanate. Instead of the desired urethane derivative a good yield of a dehydration product, $C_{26}H_{52}N_2O_3$, was obtained in the first trial, and nothing but intractable mixtures in later trials. There are two possible simple dehydration products involving the loss of the elements of water between two molecules of Ia;

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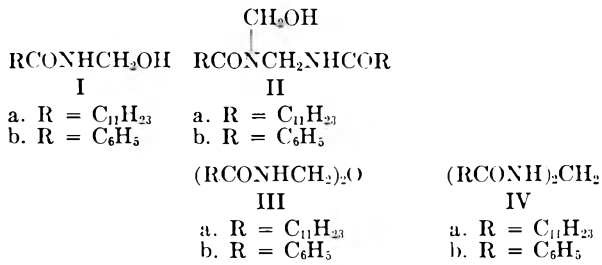
(2) S. Siggia, *Quantitative Organic Analyses via Functional Groups*, J. Wiley and Sons, Inc., New York, 1949, p. 4.

(3) Long-chain *N*-2-hydroxyethylamides have been analyzed successfully by this method. *Cf.* E. T. Roe, J. T. Scanlan, and D. Swern, *J. Am. Chem. Soc.*, **71**, 2215 (1949).

the hydroxymethylmethylenebisamide IIa and the ether IIIa.



I	II	III	IV
a. R = $C_{11}H_{23}$	a. R = $C_{11}H_{23}$	a. R = $C_{11}H_{23}$	a. R = $C_{11}H_{23}$
b. R = C_6H_5	b. R = C_6H_5	b. R = C_6H_5	b. R = C_6H_5

No report of any substance being formulated as III has been found and only four compounds seem to have been assigned structure II (with R = C_2H_5,[4] C_6H_5-, C_2H_5NH-, and C_2H_5O-[5]), all by Einhorn. Little is known about these compounds except that the phenyl compound liberates formaldehyde on pyrolysis and is easily converted to *N,N'*-methylenebisbenzamide(IVb). These slender facts can also be explained with structure IIIb, which would be much less stable than an ordinary ether.[6]

Our dehydration product is evidently of the same type as those of Einhorn as it could also be prepared from Ia by one of the unusual reactions by which IIb (or IIIb) was produced from Ib,[4] *viz.* by an attempted benzoylation under alkaline conditions.

A decision in favor of the hydroxymethylmethylenebisamide structure IIa was made after comparing the infrared spectrum of the dehydration product with the spectra of Ia and of IVa, which was prepared for this purpose (see Fig. 1). If the structure were IIIa there would probably be a stronger, broader absorption band in the 1060–1150 cm.$^{-1}$ region where CH_2OCH_2 absorbs[7] than is actually found, although this is not certain. The hydrogen-bonded OH stretching frequency in Ia is found at 3190 cm.$^{-1}$, and also appears as a poorly resolved but reproducible shoulder near 3200 cm.$^{-1}$ in the spectrum of the dehydration product. One or both of the 1052 and 1023 cm.$^{-1}$ bands is probably also caused by the primary alcohol group as somewhat similar bands are observed in the curve of Ia but not in that of IVa. The 3305, 3055, 1654, and 1545 cm.$^{-1}$ absorptions are normal for a secondary amide[7] and are at nearly the same frequencies in the other two curves.

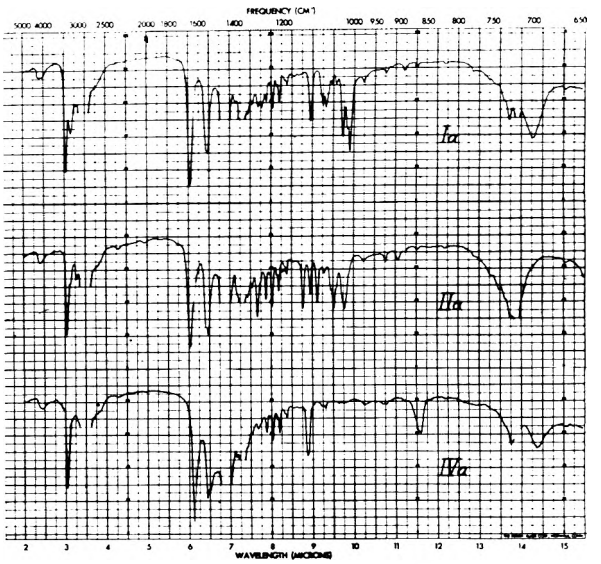


Fig. 1. Infrared absorption spectra of *N*-hydroxymethyldodecanamide (Ia), *N*-hydroxymethyl-*N,N'*-methylenebisdodecanamide(IIa), and *N,N'*-methylenebisdodecanamide (IVa) in Nujol mulls

EXPERIMENTAL[8]

N-Hydroxymethyldodecanamide (Ia). A brief report of the preparation of this compound in 70–80% yield appeared in Japanese[9] after we had developed our method. As our preparation gives a somewhat better yield details will be given. A solution of lauramide (10 g.), 36% aqueous formaldehyde (14 g.) 30% sodium hydroxide (1.15 ml.), and methanol (90 ml.) was heated to reflux for 2 hr. and allowed to cool.[10] The product separated as shiny colorless blades, m.p. 105–106°, yield, 10.1 g. (88%). Recrystallization from 95% ethanol raised the melting point to 110–111° (lit.[9] m.p. 109–110°). It gives a positive Eegriwe test,[11] and liberates formaldehyde at 170°. The infrared spectrum (Nujol) showed bands at 3285, 3190, 3060, 1654, 1545, 1118, 1082, 1073, 1028, 1016, and 1009 cm.$^{-1}$ (see Fig. 1).

Anal. Calcd. for $C_{13}H_{27}O_2N$: N, 6.11; OH, 7.43. Found: N, 5.99; OH[2], 3.25, 3.33.

A mixture of *N*-hydroxymethyldodecanamide (Ia) (0.5 g.), acetic anhydride (14 ml.), and acetic acid (19 ml.) was warmed to 40°, allowed to stand 2 days at room temperature, then poured onto ice. The crude product was taken up in benzene, washed with sodium carbonate (5%), then freed of benzene and water and leached with ether (15 ml.). The ether-soluble solid was crystallized from acetone-isopentane and from ethanol to give the pure *acetate*, m.p. 74°, which exhibited infrared absorption at 1750 cm.$^{-1}$ (ester C=O) and at 3290, 1715, and 1555 cm.$^{-1}$ (secondary amide).

Anal. Calcd. for $C_{15}H_{29}NO_3$: N, 5.16. Found: N, 4.85.

When heated at 100° an odor of acetic acid appeared, and when cooled after 0.5 hr., an unidentified solid, m.p. 80°, was obtained.

Reaction of Ia *with 1-naphthyl isocyanate.* When *N*-hydroxymethyldodecanamide (1.15 g.) was heated on a water bath with 1-naphthyl isocyanate (Eastman 1816) (0.9 g.) for 0.5 hr. an orange solid was produced. Spontaneous

(4) A. Einhorn, *Ann.*, **343**, 207 (1905).

(5) A. Einhorn, *Ann.*, **361**, 113 (1908).

(6) *Cf.* J. W. Weaver, H. A. Schuyten, J. G. Frick, Jr., and J. D. Reed, *J. Org. Chem.*, **16**, 1111 (1951), for the properties of ethers of the type $RCONHCH_2OR'$.

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., J. Wiley and Sons, Inc., New York, 1958.

(8) Elemental analyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, Calif. Melting points are uncorrected. Infrared spectra were run as Nujol mulls on a Perkin-Elmer Model 21 spectrometer (sodium chloride prism) by Mr. Everett P. Honorof.

(9) S. Sakakibara, K. Nambu, and S. Komori, *J. Oil Chemists' Soc. (Japan)*, **3**, 118 (1954).

(10) *Cf.* J. A. Shipp, U. S. Patent **2,232,485** (1941). Our method was evolved from one given by Shipp for *N*-hydroxymethyloctadecanamide, which gave only a 33% yield when applied to the synthesis of Ia.

(11) C. E. Bricker and H. R. Johnson, *Ind. Eng. Chem., Anal. Ed.*, **17**, 400 (1945).

evaporation of the ligroin (b.p. 90–120°) leachings yielded about 1 g. of *N-hydroxymethyl-N,N'-methylenebisdodecanamide* (IIa) as a colorless wax which melted at 106–106.5° after two crystallizations from alcohol and drying *in vacuo* at 55°.

Anal. Calcd. for $C_{26}H_{52}N_2O_3$: C, 70.86; H, 11.89. Found: C, 71.08; H, 11.82.

IIa gave a positive Eegriwe test, liberated formaldehyde at 220° and depressed the melting point of Ia by 23°. Three attempts to repeat this reaction, two using 1-naphthyl isocyanate from a different source (Matheson Coleman & Bell), and one employing purified isocyanate, b.p. 153.0–153.5°/20 mm., gave only colorless, low-melting mixtures in which no IIa could be detected; infrared evidence indicated that a good deal of unchanged Ia was present.

N-Hydroxymethyl-N,N'-methylenebisdodecanamide (IIa) was also obtained from Ia under Schotten-Bauman conditions.[4] When 10% aqueous potassium hydroxide (10 ml.) and benzoyl chloride (1 ml.) were added with shaking to *N*-hydroxymethyldodecanamide (1.0 g.) a vigorous reaction occurred. After cooling the colorless slurry was shaken mechanically for 1 hr. at room temperature. The solid was filtered and crystallized twice from 95% alcohol and once from chloroform. Evaporation of the chloroform mother liquors gave a solid, which was recrystallized from 100% alcohol to yield 80 mg. of colorless IIa, m.p. 104–105°, which proved to be identical with IIa from the aforedescribed reaction by mixed melting point and infrared spectrum (16 peaks checked).

N,N'-Methylenebisdodecanamide (III) has been prepared from lauroyl chloride in 20% yield[12] and, it has been claimed in the patent literature, from lauronitrile in "excellent" yield.[13] Using a variation of a convenient method of Einhorn,[4] a mixture of lauramide (1 g.), 36% aqueous formaldehyde (2 ml.), 5% sulfuric acid (1 ml.), and ethylene dichloride (10 ml.) was heated to reflux for 1.5 hr., cooled, filtered, and washed with water. The crude product, m.p. 145–148° (0.6 g., 57%), recrystallized from ethanol as colorless crystals, m.p. 155–156° (lit. 156–157°,[12] 154–155°[13]), infrared absorption (see Fig. 1) at 3310, 3055, 1633, 1553, 1535, 1128, and 863 cm.$^{-1}$, in apparent agreement with the literature.[12]

Anal. Calcd. for $C_{25}H_{50}O_2N_2$: N, 6.82. Found: N (Kjeldahl), 6.78.

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(12) A. Cannepin and A. Parisot, *Compt. rend.*, **239**, 180 (1954).

(13) D. T. Mowry, U. S. Patent **2,534,204** (1950).

Bromination Products of Mesitylglyoxal and Configuration of the Corresponding Monoximes

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Received November 16, 1959

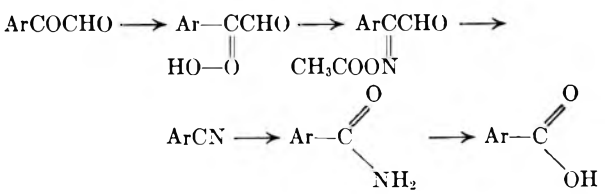
In the light of the behavior of benzene, toluene, the xylenes, and mesitylene toward bromine in polar solvents,[2,3] we decided to investigate phenylglyoxal and mesitylglyoxal under similar conditions.

(1) In partial fulfillment of the requirements for the M.S. degree.

(2) P. B. D. de la Mare and P. N. Robertson, *J. Chem. Soc.*, 279 (1943).

(3) R. Oda and K. Tumura, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **33**, No. 728, 129 (1937).

In both aqueous methanol and aqueous acetic acid, mesitylglyoxal underwent both mono- and dibromination, and the products proved to be identical with those obtained by Fuson *et al.*,[4,5] whereas phenylglyoxal did not undergo bromination. In aqueous acetic acid, both more rapid bromination and higher yields resulted than in aqueous methanol. Gray and Fuson[6] characterize the monoxime of mesitylglyoxal in terms of molecular formula and physical properties. We decided to investigate the configurations of the mono- and dibromoglyoxal monoximes. Thus we prepared the monoximes, acetylated them, and subjected the acetates to treatment with dilute aqueous sodium hydroxide.[7] These oximino esters underwent cleavage and not hydrolysis, thus indicating that they were of the α-configuration, and in terms of the products, that the oximino groups had replaced the ketocarbonyl oxygens.



Ar = 3-bromomesityl or 3,5-dibromomesityl

EXPERIMENTAL

Mesitylglyoxal and phenylgalyoxal were prepared according to the method of Gray and Fuson.[6]

Phenylglyoxal did not undergo bromination in aqueous methanol or aqueous acetic acid.

3-Bromomesitylglyoxal. To a 200-cc. 2-necked round bottom flask equipped with a mechanical stirrer, was added 5.3 g. (0.03 mole) of mesitylglyoxal dissolved in the minimum volume of cold methanol or glacial acetic acid. To this solution water was added to incipient cloudiness, followed by a few drops of the chosen solvent to give a clear solution. To the prepared solution 4.8 g. (0.03 mole) of bromine was added dropwise with vigorous stirring. The color of the bromine disappeared very rapidly. After the addition of the bromine, stirring was continued for some time. Finally enough water was added to produce slight turbidity, and the contents of the flask were chilled overnight. A pale yellow crystalline substance was obtained which when recrystallized from methanol exhibited the same physical and chemical properties as the compound obtained by Fuson and Soper.[4] A boiling aqueous solution of the glyoxal to which a few drops of methanol were added, on cooling, deposited the colorless hydrate. Both the glyoxal and its hydrate upon oxidation with alkaline hydrogen peroxide gave 3-bromomesitoic acid,[8] melting and mixed melting point with an authentic sample at 168°.

3,5-Dibromomesitylglyoxal was prepared by the same method as 3-bromomesitylglyoxal by using 2 moles of

(4) R. C. Fuson and Q. F. Soper, *J. Org. Chem.*, **9**, 193 (1944).

(5) R. C. Fuson, C. H. McBurney, and W. E. Holland, *J. Am. Chem. Soc.*, **61**, 3246 (1939).

(6) A. R. Gray and R. C. Fuson, *J. Am. Chem. Soc.*, **56**, 739 (1934).

(7) R. P. Barnes and A. H. Blatt, *J. Am. Chem. Soc.*, **57**, 1330 (1935).

(8) P. R. Shildneck and R. Adams, *J. Am. Chem. Soc.*, **53**, 347 (1931).

bromine per mole of mesitylglyoxal. It was obtained as the hydrate, exhibiting physical and chemical properties identical with those of the compound obtained by Fuson *et al.*,[5] yielding an identical semicarbazone, mesitylglycolic acid, and 3,5-dibromomesitoic acid.

The α-ketoxime of 3-bromomesitylglyoxal. An aqueous solution of 2.5 g. of hydroxylamine hydrochloride and 4 g. of sodium acetate in 10 cc. of water was prepared and heated to 40°. To this aqueous solution was added 2.5 g. of 3-bromomesitylglyoxal dissolved in 10 cc. of alcohol. The solution was warmed and shaken. In a few minutes a crystalline solid began to separate. When the reaction appeared to be complete, the mixture was chilled, filtered, washed first with water and finally twice with alcohol. On recrystallization from dilute alcohol, white crystals were obtained which melted at 135–136°.

Anal. Calcd. for $C_{11}H_{12}O_2BrN$: C, 48.89; H, 4.44. Found: C, 49.00; H, 4.49.

The α-ketoxime acetate of 3-bromomesitylglyoxal. A cold solution of 1.5 g. of the ketoxime in 5.5 cc. of acetic anhydride was shaken for about 1 hr. On chilling, pale yellow crystals separated. Upon filtering, drying, and recrystallization from methanol, white crystals melting at 87–88° were obtained.

Anal. Calcd. for $C_{13}H_{14}O_3BrN$: C, 50.00; H, 4.48. Found: C, 49.60; H, 4.56.

The α-ketoxime of 3,5-dibromomesitylglyoxal. This oxime was prepared in the same manner as the monobromooxime. It was obtained as white crystals, melting at 202–203°.

Anal. Calcd. for $C_{11}H_{11}O_2Br_2N$: C, 37.82; H, 3.15. Found: C, 37.99; H, 3.49.

The α-ketoxime acetate of 3,5-dibromomesitylglyoxal. This oxime acetate was prepared in the same manner as the monobromooxime acetate.

Anal. Calcd. for $C_{13}H_{13}O_3Br_2N$: C, 39.90; H, 3.33. Found: C, 39.72; H, 3.10.

Cleavage of the oxime acetates of the bromoglyoxals. One half g. of each of the oxime acetates was dissolved in 10 cc. of alcohol and shaken for several hours with 30 cc. of cold aqueous 5% sodium hydroxide. The solutions were diluted with water and extracted with ether. The ether was evaporated and the residues refluxed for several hours with 30% sodium hydroxide. The solutions were acidified with dilute hydrochloric acid and extracted with ether. The ethereal solutions were washed with water and dried over anhydrous sodium sulfate. Upon filtration and concentration by evaporation, each solution yielded a white crystalline solid. The monobromooximeacetate yielded 3-bromomesitoic acid and the dibromooxime acetate yielded 3,5-dibromomesitoic acid. Each acid was identified by comparison with an authentic sample.

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Some Derivatives of Cyanoethylated Isophorone

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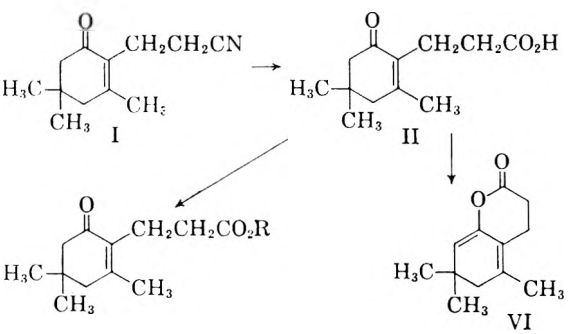
The base-catalyzed condensation of isophorone with acrylonitrile was reported by Bruson[1] to give mono-, di- and tricyanoethylation products. The structure of monocyanoethylated isophorone was shown to be 2-(2-cyanoethyl)-3,5,5-trimethyl-2-cyclohexencone (I) by Julia.[2] Hydrolysis of I to the corresponding acid (II)[1,2] and preparation of the methyl ester[2] appear to be the extent of utilization of this readily available keto nitrile. Herein is reported the synthesis of the allyl (III) decyl (IV), and vinyl (V) esters of II by conventional methods, as well as its conversion to the enol-lactone (VI) by dehydration with acetic anhydride. Similar dehydrations of 5-keto acids have been reported by Russian workers[3] to give monounsaturated enol-lactones.

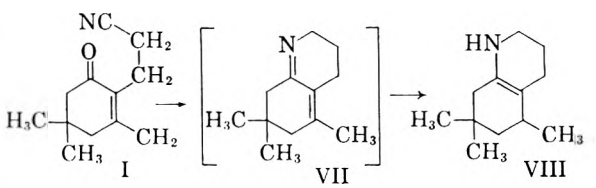


I, II, VI

III $-CH_2CH=CH_2$
IV $-C_{10}H_{21}$
V $-CH=CH_2$

We also report a further transformation of I to an octohydroquinoline system. Hydrogenation of I over Raney nickel in ammoniacal dioxane gave the novel cyclic enamine (VIII) in 59% yield. Reductive cyclization of 5-keto nitriles has been reported previously by Nazarov[4] to yield a saturated material.

A possible mode of formation of VIII may involve initial reduction and cyclodehydration to VII followed by 1,4-addition of hydrogen. It is not surprising that the resulting hindered internal double bond is resistant to further reduction.



I, VII, VIII

The general structure of VIII has been assigned on the basis of elemental analysis, acid equivalent, *N*-phenylurea derivative, and infrared spectrum. That the double bond is in the fully substituted position is indicated by very intense infrared bands at 6.12 and 6.21μ, which correspond to double bond and secondary amine absorptions, respectively, and are intensified as a result of interaction of the unshared pair of electrons on nitrogen with the double bond. Lack of absorption in the 12.4μ

(1) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, 75, 3585 (1953).

(2) S. Julia, *Compt. rend.*, **237**, 913 (1953).

(3) R. Y. Lovina, N. P. Shusherina, and M. Y. Lurye, *J. Gen. Chem. U.S.S.R.*, **24**, 1423 (1954).

(4) N. Nazarov G. A. Shvekhgeimer, and V. A. Rudenko, *J. Gen. Chem. U.S.S.R.*, **24**, 325 (1954).

region, which would indicate hydrogen attached to a double bond, excludes consideration of the double bond at the 4 or 8 positions.

The infrared spectrum of the residual product obtained after warming VIII with water and a drop of hydrochloric acid shows new bands indicating the presence of ketone (5.90 μ), primary amine, (3.02 and 11.1μ) and imine (6.02 μ). These data are in accord with the presence of an equilibrium mixture of the expected products, the isomeric cyclic imine and its hydrolytic cleavage product, the amino ketone.

EXPERIMENTAL[5]

2-(2-Cyanoethyl)-3,5,5-trimethyl-2-cyclohexeneone (I). The method of Bruson,[1] modified by the use of sodium methylate as catalyst, gave a 20% yield of I (b.p. 129–131°/2.4 mm., n_D^{30} 1.4908, d_{20}^{20} 0.9920).

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.40; H, 8.91; N, 7.34. Found: C, 75.42; H, 8.95; N, 7.38.

2-(2-Carboxyethyl)-3,5,5-trimethyl-2-cyclohexeneone (II). A mixture of 191 g. (1 mole) of I, 112 g. (2 moles) of potassium hydroxide and 1000 ml. of water was heated at reflux for 7 hr. The cooled mixture was then acidified with conc. hydrochloric acid to precipitate the product. Crystallization from heptane gave a 61% yield of refined II (m.p. 74.5–75.5°, reported[1] m.p. 76–77°).

2-(2-Carboallyloxyethyl)-3,5,5-trimethyl-2-cyclohexeneone (III). A mixture of 107 g. (0.51 mole) of II, 116 g. (2.0 moles) of allyl alcohol, 500 ml. of benzene, and 1.0 g. of *p*-toluenesulfonic acid was heated to reflux and the allyl alcohol-water-benzene azeotrope was taken off over a 5.5-hr. period. The reaction mixture was washed with 100 ml. of 20% aqueous sodium carbonate and then with 100 ml. of water. Distillation gave a 68% yield of III [b.p. 136°/1.7 mm., n_D^{30} 1.4861, d_{20}^{20} 1.0169. Infrared maxima at 3.24 μ (CH_2=), 5.8 μ (ester C=O), 6.03 μ (conj. ketone), 6.14 μ (conj. C=C), 7.24 and 7.32 μ [$(CH_3)_2C$], 8.7 μ (ester C—O—), 10.1 and 10.8 μ (CH_2=C)].

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 72.00; H, 8.80. Found: C, 71.61; H, 8.49.

2-(2-Carbo-"Oxo"-decyloxyethyl)-3,5,5-trimethyl-2-cyclohexeneone (IV). A mixture of 110 g. (0.52 mole) of II, 316 g. (2.0 moles) of Enjay Company "Oxo" decanol, 500 ml. of benzene, and 1.1 g. of *p*-toluenesulfonic acid was heated to reflux and water was removed as the benzene azeotrope over a 7-hr. period. The reaction mixture was washed with 10% aqueous sodium carbonate and then with water. Benzene was removed by distillation and IV was taken as residual dark oil in 99% yield [n_D^{30} 1.4739, d_{20}^{20} 0.9499. Infrared maxima at 5.80 μ (ester C=O). 6.03 (conj. ketone C=O), 6.13 μ (conj. C=C), 8.6 μ (ester C—O—), 14.4 μ (*cis* RCH=CHR')].

Anal. Calcd. for $C_{22}H_{38}O_3$: C, 75.5; H, 10.85. Found: C, 75.58; H, 10.87.

2-(2-Carbovinyloxyethyl)-3,5,5-trimethyl-2-cyclohexeneone (V). A mixture of 664 g. (3.15 moles) of II, 1376 g. (16 moles) of vinyl acetate, 10 g. of mercuric acetate, and 3.1 g. of conc. sulfuric acid was allowed to stand at ambient temperature for 72 hr. The catalyst was neutralized with 6 g. of anhydrous sodium acetate and the precipitate was removed by filtration. Distillation gave a 30% yield of V (b.p. 130°C./1.3 mm., n_D^{30} 1.4889).

Bromine titration of the vinyl group yielded a figure which was 102% of the calculated value. Infrared data was consistent with the assigned structure.

5,7,7-Trimethyl-3,4,6,7-tetrahydro-1,2-benzopyrone (VI). A mixture of 125 g. (0.596 mole) of II and 350 ml. of acetic anhydride was refluxed for 4 hr. during which time 105 ml. of distillate was removed. Distillation of the residual mixture gave 97 g., an 85% yield of VI [b.p. 125°/3.3 mm., n_D^{30} 1.5176, d_{20}^{20} 1.0571. Infrared maxima at 5.64 μ lactone C=O, strong), 6.1 μ (conj. C=C). Equivalent weight by saponification. Calcd.: 192. Found: 196].

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 75.1; H, 8.34. Found: C, 74.64; H, 8.12.

5,7,7-Trimethyl-1,2,3,4,5,6,7,8-octahydroquinoline (VIII). A mixture of 382 g. (2 moles) of I, 300 ml. of dioxane, 10 g. of wet Raney nickel (rinsed twice with dioxane), and 145 g. (8.5 moles) of anhydrous ammonia was hydrogenated in a stainless steel rocking autoclave at 160° and 1000 p.s.i.g. over a 5-hr. period. The cooled reaction mixture was filtered and fractionated to give 213 g., a 59% yield, of III [b.p. 85°/1.8 mm., n_D^{30} 1.5164, d_{20}^{20} 0.9495. Equivalent weight by perchloric acid in acetic acid titration. Calcd.: 179. Found: 179.5. Infrared maxima at 3.14 and 6.21 μ (—NH—), 6.12 μ (C=C), and 10.4 μ (—NH— out of plane)].

Anal. Calcd. for $C_{12}H_{21}N$: C, 80.4; H, 11.7; N, 7.84. Found: C, 80.6; H, 11.5; N, 7.95.

The *N*-phenylurea was prepared by treatment of VIII with phenyl isocyanate in ether and crystallized from ethanol (m.p. 115–116°).

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.6; H, 7.73; N, 9.40. Found: C, 77.0; H, 7.84; N, 9.75.

Hydrolysis of VIII. A mixture of 3.6 g. of VIII, 80 ml. of water, and one drop of conc. hydrochloric acid was warmed on steam bath overnight, cooled, and extracted with ether. The extract was dried over sodium sulfate and evaporated *in vacuo*. The residual oil, which quickly blackened on exposure to air, exhibited infrared maxima at 3.02 and 11.1 μ ($-NH_2$), 5.90 μ (C=O), 6.02 μ (C=N).

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(5) All temperatures are uncorrected.

Decomposition of Quaternary Salts. V. Stereospecificity in the Methadon Series

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Received April 23, 1959

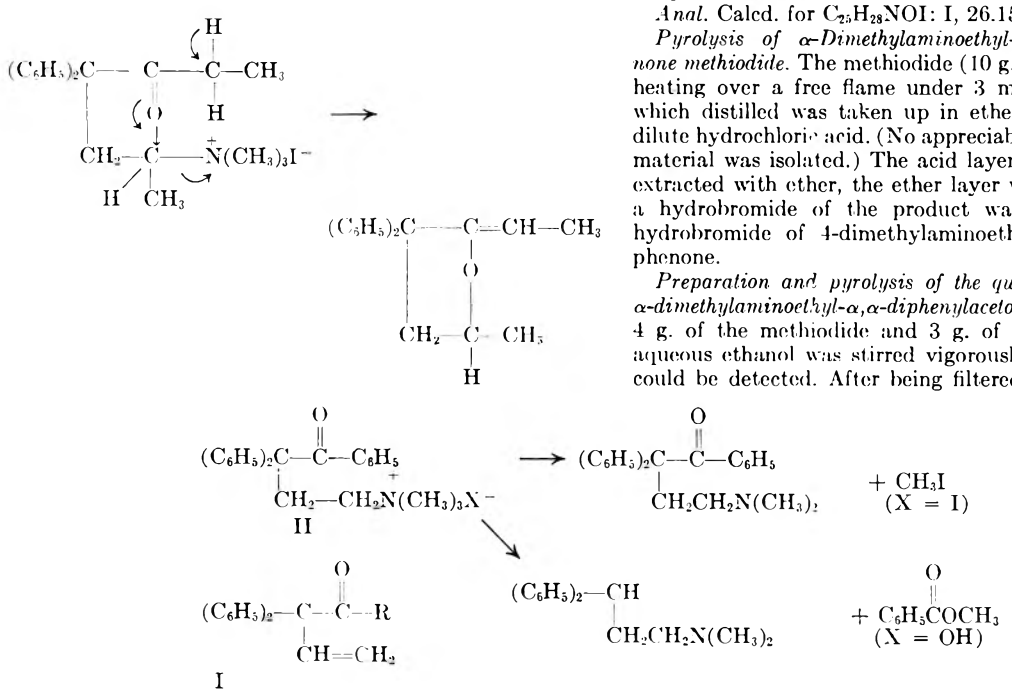
Previous papers[1] in this series have shown that ketones of the methadon type give ethylidenetetrahydrofurans on pyrolysis of their quaternary salts. It has also been shown[2] that this reaction does not proceed by an olefinic intermediate since the optical isomers of isomethadon give optically active products. We now wish to report that the optically active forms of the ethylidenetetrahydrofurans are obtained when the optically active forms of methadon methiodide are decomposed. This would indicate that a concerted reaction takes place and that at no time is a carbonium ion formed. The most

(1) Paper No. 4, S. J. Nelson, V. B. Fish, and N. R. Easton, *J. Am. Chem. Soc.*, **77**, 1908 (1955).

(2) N. R. Easton and V. B. Fish, *J. Am. Chem. Soc.*, **76**, 2836 (1954).

probable mechanism would be that of a rearward approach of the oxygen to the carbon attached to the nitrogen moiety, along with the cleavage of the nitrogen-carbon bond followed, or preceded, by the expulsion of the proton. Although it does not necessarily mean that inversion has taken place, the direction of the rotation is changed, the *d*- form of methadon methiodide gives the *l*- isomer of the cyclized compound. The optically active products were originally isolated as distillable oils which crystallized on long standing in the refrigerator. Although the *dl*- form is much higher melting and less soluble in methanol, none could be obtained in either reaction even by seeding alcoholic solutions of either oil with crystals of the *dl*- form. This indicates that very little, if any, racemization takes place during these pyrolyses.

In an attempt to prepare an unsaturated ketone of the type I several approaches were unsuccessful. The formation of this compound by the action of Grignard reagents on 4-bromo-2,2-diphenylbutanenitrile, 4-phenoxy-2,2-diphenylbutanenitrile or 2,2-diphenyl-3-butenenitrile was unsuccessful; in the second instance the phenoxy group was cleaved and in the third only the starting material and a nondistillable oil were obtained. It was hoped that by using a compound which contained no hydrogen atoms alpha to the carbonyl group, the cyclization could be prevented and the unsaturated ketone I would be obtained. When the methiodide of the



phenyl ketone (II) was decomposed in the usual way, methyl iodide was split off and the original ketone was obtained. However, where the quaternary hydroxide was decomposed an unexpected cleavage resulted. Methyl benzoate and 1,1-diphenyl-3-dimethylaminopropane were formed.

The pyrolysis of the quaternary hydroxide of methadon has been reported[3] to give 1,1-diphenyl-3-dimethylaminobutane but the other products were not isolated. However, no cleavage of this type was found in the isomethadon series or where the dimethylaminoethyl side chain was involved.

EXPERIMENTAL

The methiodides of *d*- and *l*-methadon were prepared in the usual manner, m.p. 170–171°.

Decomposition of d- and l-methadon quaternary iodides. These were decomposed[3] by pyrolysis under reduced pressure. The distillate was taken up in ether, washed with dilute hydrochloric acid, dried, and distilled.

l-3,3-Diphenyl-2-ethylidene-5-methyltetrahydrofuran was obtained from *d*-methadon, b.p. 130–134°/2 mm., $\alpha_D^{25} = -246°$ (c = 0.1026, ethanol).

Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.22; H, 7.60. From 15 g. of the methiodide 3.3 g. of the product was obtained.

d-3,3-Diphenyl-2-ethylidene-5-methyltetrahydrofuran was obtained from *l*-methadon, b.p. 129–133°/2 mm., $\alpha_D^{25} = 246°$ (c = 0.1014 ethanol).

Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.26; H, 7.70. From 15 g. of the methiodide 4.6 g. of the product was obtained.

Equal quantities of the *d*- and *l*- isomers were mixed in ethanol. Crystals formed, m.p. 78–80°, identical with the *dl*- form previously reported.[3] On long standing in the refrigerator each crystallized. The product was recrystallized from methanol, m.p. 55–56°.

Methiodide of α-dimethylaminoethyl-α,α-diphenylacetophenone. The methiodide was prepared from α-dimethylaminoethyl-α,α-diphenylacetophenone[4] in the usual way. After recrystallization from water it melted at 270–271° dec.

Anal. Calcd. for $C_{25}H_{28}NOI$: I, 26.15. Found: I, 26.02.

Pyrolysis of α-Dimethylaminoethyl-α,α-diphenylacetophenone methiodide. The methiodide (10 g.) was decomposed by heating over a free flame under 3 mm. pressure. The oil which distilled was taken up in ether and extracted with dilute hydrochloric acid. (No appreciable quantity of neutral material was isolated.) The acid layer was neutralized and extracted with ether, the ether layer was concentrated and a hydrobromide of the product was identical with the hydrobromide of 4-dimethylaminoethyl-2,2-diphenylacetophenone.

Preparation and pyrolysis of the quaternary hydroxide of α-dimethylaminoethyl-α,α-diphenylacetophenone. A mixture of 4 g. of the methiodide and 3 g. of silver oxide in warm aqueous ethanol was stirred vigorously until no iodide ion could be detected. After being filtered the precipitate was washed with water and with ethanol and the filtrate was concentrated under reduced pressure. After being trans-

(3) N. R. Easton, S. J. Nelson, V. B. Fish, and P. N. Craig, *J. Am. Chem. Soc.*, **75**, 3751 (1953).

(4) M. Bockmuhl and G. Ehrhart, *Ann.*, **561**, 52–85 (1948).

ferred to a Claisen flask it was subjected to a pyrolytic distillation under 20 mm. pressure. The oily product was dissolved in ether and washed with dilute hydrochloric acid. The ether solution was dried and concentrated and the residue distilled 50–55° at 3 mm. pressure. Its odor was similar to methyl benzoate. $n_D^{20} = 1.5190$. Lit. $n_D^{15} = 1.5181$. Hydrolysis gave benzoic acid, m.p. 121–121.5°; mixed with benzoic acid, m.p. 121–121.5°. The acid solution above was neutralized and extracted with ether. The ether layer was dried and alcoholic hydrogen chloride added; a precipitate formed (0.7 g.) which melted at 162–164°. After recrystallization from a mixture of ethanol, ethyl acetate, and isopropyl ether, it melted at 165–167°.

Anal. Calcd. for $C_{17}H_{22}NCl$: Cl, 12.85. Found: Cl, 12.73.

A mixed melting point with this compound and that prepared below showed no depression.

3-Dimethylamino-1,1-diphenylpropane. This was prepared by the treatment of 4-dimethylamino-2,2-diphenylbutanenitrile with sodium in isopropyl alcohol;[5] hydrochloride, m.p. 167–169°; methiodide, m.p. 190–192°.

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(5) N. R. Easton, L. R. Bartron, F. Meinhofer, and V. B. Fish, *J. Am. Chem. Soc.*, **75**, 2088 (1953).

Synthesis of Some Symmetrical Aliphatic Quaternary Ammonium Iodides

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As part of an investigation of the effect of ionic dimensions on electric conductance,[2] a series of aliphatic quaternary ammonium iodides has been prepared (Table I).

The principal quaternization procedure consisted in refluxing alcoholic solutions of primary or tertiary amines with the required alkyl iodides. In some instances, the reaction mixtures were maintained at a *p*H of approximately 9 by the periodic addition of ethanolic potassium hydroxide.

As the quaternary salts were to be used for conductivity studies, their purity was of critical importance. Anion impurities were detected by titration with aqueous silver nitrate using calomel and silver-silver chloride electrodes. The titration procedure was initially applied to the successive recrystallization liquors rather than to solutions of the recrystallized salts. This time-saving step was applicable as it was found that after repeated recrystallizations, no appreciable change in effect on ionic conductance of subsequent recrystallization liquors was noted. At this point the ultimate criterion of purity was established by titration of the quaternary salts in methanol after they had been subjected to further successive recrystallizations. If the conductance of samples from recrystallization to recrystallization differed by less than 5%, the salts were deemed sufficiently pure for the conductance work.

Repeated recrystallization of tetraoctylammonium iodide failed to provide a product having satisfactory ionic conductance properties or analytical characteristics. Subjecting tetrahexadecylammonium iodide to repeated recrystallizations finally gave a product, however, which showed no alteration in its ionic conductance from recrystallization to recrystallization, but which gave unsatisfactory analytical results.

Confirmation of the presence of a quaternary nitrogen atom in the latter compound was established by measurement of the change in its ionic conductance effected by silver hydroxide, as compared with similar measurements of authentic samples of a representative quaternary ammonium iodide, and representative secondary and tertiary amine hydroiodides.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses are by the Microanalytical Laboratory, Department of Chemistry, University of California.

Materials. The alkyl iodides which were not commercially available were prepared by the methods of Hartman, Byers, and Dickey[3a] and Finkelstein.[3b] The tertiary amines were obtained commercially or prepared by known methods.[4a,b]

General Procedures. The molecular amounts of reactants and other reaction data appear in Table I.

A. A mixture of the amine and the corresponding alkyl iodide was refluxed in a suitable solvent. Refluxing was discontinued intermittently, followed by cooling the reaction mixture and removing the reaction product.

B. Procedure A was modified in the following manner. After refluxing the reaction mixture was cooled, adjusted to *p*H 9 with 5% ethanolic potassium hydroxide, followed by the addition of an equal volume of water. The product was filtered and washed with water and ether. The yield of tetraheptylammonium iodide was increased to 31.4 g. (73%) by the addition of 50 ml. of commercial absolute ethanol and 12.5 g. (0.055 mole) of heptyl iodide to the diluted alkaline reaction filtrate and refluxing for 72 hr.

C. Procedure B was modified by maintaining the reaction mixture at a *p*H of approximately 9 by the periodic addition of 5% ethanolic potassium hydroxide. After refluxing, an equal volume of water was added and the mixture cooled.

D. A mixture of the tertiary amine and the alkyl iodide was heated in an open flask at 80°, following the procedure of Vernon and Masterson.[5]

E. Following the procedure described by Girard and Forneau,[6] ammonia gas was bubbled through the liquefied

(1) Taken from a dissertation submitted by Stuart P. Eriksen in partial fulfillment of the requirements for the Ph.D. degree in Pharmaceutical Chemistry, 1956.

(2) In preparation.

(3) (a) W. W. Hartman, J. R. Byers, and J. B. Dickey, in A. H. Blatt, *Org. Syntheses*, **Coll. Vol. II**, John Wiley and Sons, New York, N. Y., 1943, p. 322; (b) H. Finkelstein, *Ber.*, **43**, 1528 (1910).

(4) (a) M. R. McCorkle, *Iowa State Coll. Jour. Sci.*, **14**, 64 (1939); (b) A. W. Ralston, C. M. Hoerr, and P. L. DuBrow, *J. Org. Chem.*, **9**, 259 (1944).

(5) A. A. Vernon and J. P. Masterson, *J. Am. Chem. Soc.*, **64**, 2822 (1942).

(6) A. Girard and E. Forneau, *Bull. Soc. Chim.*, **37**, 1670 (1925).

TABLE I

TETRAALKYLAMMONIUM IODIDES $R_4N^+I^-$

No.[a]	R	Time, hr.	Solvent, ml.[b]	Millimoles Amine[c]	Millimoles RI	M.P., °	Yield, %	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Iodine Calcd.	Iodine Found
1A[d]	Hexyl	31	50	83	104	102–103	83	$C_{24}H_{52}NI$	2.91	2.89	26.35	26.10
2B	Heptyl	72	100	80	82	121–122	40	$C_{28}H_{60}NI$	2.61	2.51	23.60	23.80
3C	Octyl	96	200	84	271	127–128	30	$C_{32}H_{68}NI$	2.36	2.41 2.32	21.37	22.60 20.27
3D	Octyl	12	—	7.4	14.6	127–128	39	—	—	—	—	—
4A	Decyl	80	25	14	16	118–120	55	$C_{40}H_{84}NI$	1.98	1.98	17.98	17.71
4C	Decyl	48	200	85	280	118–120	38	—	—	—	—	—
5C	Dodecyl	96	200	65	200	116–117	38	$C_{48}H_{100}NI$	1.71	1.95	15.51	15.56
6C	Tetradecyl	96	100	80	339	114.5–115	36	$C_{56}H_{116}NI$	1.51	1.69	13.64	13.35
7E	Hexadecyl	96	50	29	17	110–111	15	$C_{64}H_{132}NI$	1.34	1.81	12.17	11.50

[a] Compounds 1 and 5 were recrystallized from ethanol-water; 4 from ethanol-water or ethyl acetate; 2 and 3 from ethyl acetate; 6 from ethanol; 7 from commercial absolute ethanol. [b] Reaction solvent for 1 and 6, ethanol; 2, 4A, and 4C, commercial absolute ethanol; 3C and 5, carbon dioxide-free commercial absolute ethanol; 7, benzene-ethanol 1:1. [c] Primary amines: 3C, 4C, 5C, 6C, and 7E. Tertiary amines: 1A, 2B, 3D, and 4A. [d] Letters refer to procedures.

alkyl iodide maintained at approximately 185°. The solid reaction mixture was first extracted with cold ether, followed by extraction with 100 ml. of boiling ether. On cooling the hot ether extract deposited 4 g. of crystalline solid; m.p. 79–80°. Girard and Forneau isolated a product melting at the same temperature which was claimed to be tetrahexadecylammonium iodide.

Evaporation of the combined cold ether extract and the filtrate from the hot ether extract gave 7.9 g. of crystalline residue; m.p. 42–43°. A mixture of 6.9 g. of this residue (0.029 mole, calculated on the basis of hexadecylamine; lit.,[7] m.p. 44–46°) and the alkyl iodide was refluxed in benzene-ethanol. After cooling, the resulting product was filtered and recrystallized.

A freshly prepared alcoholic paste of silver hydroxide was added to saturated ethanolic solutions of samples of the recrystallized product, tetrabutylammonium iodide, ditetradecylamine hydroiodide, and trioctylamine hydroiodide. The specific resistances increased on addition of the silver hydroxide by factors of 1.04, 1.18, 6.28, and 6.35, respectively. The two quaternary salts changed resistance only slightly, as there is no decrease in concentration of conducting species.

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(7) O. Westphal and D. Jerchal, *Ber.*, **73B**, 1002 (1940).

Pyridine-1-oxides. VI. Synthesis of Some 3-Styrylpyridine-1-oxides[1]

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During the course of an investigation of the chemistry of simple pyridine-1-oxides, it was found that 4-nitro-3-picoline-1-oxide condensed readily with benzaldehyde in ethanol or pyridine solution, in the presence of piperidine, to give 4-nitro-3-styrylpyridine-1-oxide.[2] Preliminary pharmacological screening of this compound indicated a high degree of antibacterial and antibiotic activity *in vitro*, and these findings prompted us to prepare a number of related 1-oxide derivatives.

4-Nitro-3-picoline-1-oxide was condensed with a number of other aromatic aldehydes, and the products formed are listed in Table I. All condensations could be carried out either in ethanol or in pyridine, with piperidine as catalyst. As pharmacological testing of many of these derivatives was difficult because of water insolubility, sodium salts of the phenolic derivatives were also prepared.

Treatment of 4-nitro-3-picoline-1-oxide with cinnamaldehyde, formaldehyde or glyoxal gave red, resinous materials, but no isolable products could be obtained. Attempts to condense 4-nitro-3-picoline-1-oxide with *p*-nitrosodimethylaniline failed.

Treatment of 4-nitro-3-styrylpyridine-1-oxide with acetyl chloride yielded 4-chloro-3-styrylpyridine-1-oxide. The action of thiourea in ethanol solution then gave the expected thiouronium salt, which on alkaline hydrolysis gave 4-mercapto-3-styrylpyridine-1-oxide along with a small amount of bis(1-oxy-3-styryl-4-pyridyl) sulfide.

It has already been pointed out by Jerchel and Heck[2] that neither 3-picoline, 4-nitro-3-picoline, nor 3-picoline-1-oxide gives a styryl derivative with benzaldehyde, and that both the 4-nitro and the 1-oxide groupings are therefore necessary for activation of the 3-methyl group. However, the 1-oxide grouping does effectively reduce electron density at the 3-position of the pyridine ring, as is clearly indicated by the observations that 3-amino-

(1) For the previous paper in this series, see E. C. Taylor and J. S. Driscoll, *J. Am. Chem. Soc.*, in press.

(2) Since this original observation was made (E. C. Taylor and A. J. Crovetti, Abstracts of Papers, 126th ACS Meeting, New York City, 1954, p. 24-N) the synthesis of 4-nitro-3-styrylpyridine-1-oxide has been reported (D. Jerchel and H. E. Heck, *Ann.*, **613**, 171 (1958)).

TABLE I

PRODUCTS FROM CONDENSATIONS OF 4-NITRO-3-PICOLINE-1-OXIDE AND AROMATIC ALDEHYDES

Compound No.	Ar	Reaction Time, Hr.	M.P., °	Recryst. solvent	Color	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	Phenyl	12	180–181	aq. DMF	Yellow-orange	73	$C_{13}H_{10}N_2O_3$	64.5	4.2	11.6	64.5	4.4	11.4
2	1-Naphthyl	8	254–255 dec.	aq. DMF	Orange	47	$C_{17}H_{13}N_2O_3$	69.9	4.1	9.6	69.9	4.3	9.8
3	4-Chlorophenyl	15	216–217	C_2H_5OH	Yellow	23	$C_{13}H_{19}ClN_2O_3$	56.4	3.3	10.1	56.7	3.2	9.8
4	4-Methoxyphenyl	16	196	aq. DMF	Orange	68	$C_{14}H_{12}N_2O_4$	61.8	4.4	10.3	61.9	4.3	10.4
5	2-Hydroxyphenyl	8	254 dec.	aq. DMF	Orange	47	$C_{13}H_{10}N_2O_4$	60.5	3.9	10.8	60.5	4.1	10.7
6	3,4-Methylenedioxyphenyl	11	238 dec.	aq. DMF	Orange	67	$C_{14}H_{10}N_2O_5$	58.8	3.5	9.8	59.1	3.4	9.5
7	3-Methoxy-4-hydroxyphenyl	4	237 dec.	aq. DMF	Red	27	$C_{14}H_{12}N_2O_5$	58.4	4.2	9.7	58.8	4.5	9.9
8	3,4-Dihydroxyphenyl	6	>360	aq. DMF	Red	11[a]	$C_{13}H_{10}N_2O_5$	56.9	3.7	10.2	57.1	3.5	10.3
9	4-Nitro-3-picoline-1-oxide												
10	4-Chloro-3-picoline-1-oxide												
11	4-Mercapto-3-styrylpyridine-1-oxide												
12	4-Chloro-3-styrylpyridine-1-oxide												

[a] Ethanol was used as solvent for the condensation. In all other cases, pyridine was used.

pyridine-1-oxide is a weaker base than 3-aminopyridine[3] and that 3-hydroxypyridine-1-oxide is a stronger acid than 3-hydroxypyridine.[4] 3-Aminopyridine-1-oxide fails to form an anil or an amide with acetoacetic ester, while 3-aminopyridine itself reacts readily.[3]

Compounds 1,2,4,6,9 and 11 (see Table I) showed some *in vitro* activity against *M. tuberculosis*. Compounds 1,2,4,7 and 8 were active *in vitro* against *Strep. pyogenes* C203. The inactivity of compound 3 against this microörganism indicates that 4-substituted 3-styrylpyridine-1-oxides are not uniformly active, and the low activity of compound 9 compared with a much higher activity of compound 1 points out the important activating influence of the styryl grouping. Slight *in vitro* activity was observed with compound 10 against *Pseud. aeruginosa*. Compound 6 was active *in vitro* against *Staph. aureus*. Slight amebiasis activity against *E. histolytics* was shown by compounds 1,2,3,4,6,7 (as the sodium salt), 9, 10, and 11. Unfortunately, none of the compounds tested showed sufficient *in vivo* activity to be of further interest.

EXPERIMENTAL[5]

Formation of styryl derivatives. The following procedures for the preparation of 4-nitro-3-styrylpyridine-1-oxide are illustrative of the methods used for all condensations of 4-nitro-3-picoline-1-oxide with aromatic aldehydes. Method A is similar to the previously published synthesis of 4-nitro-3-styrylpyridine-1-oxide.[2]

Method A. A mixture of 5.0 g. of 4-nitro-3-picoline-1-oxide,[6] 3.4 g. of purified benzaldehyde, 0.7 ml. of piperidine, and 15 ml. of absolute ethanol was heated under reflux for 3 hr. and then allowed to stand at room temperature for 8 hr. The resulting precipitate of yellow needles was collected by filtration, washed with ether, and recrystallized from ethanol to give 2.6 g. (47%, allowing for recovered starting material), of 4-nitro-3-styrylpyridine-1-oxide, m.p. 179–181°. This compound is reported to melt at 179–180°.[2] Concentration of both the ethereal and ethanolic filtrates gave 1.73 g. of crude starting material which, upon recrystallization from acetone, yielded 1.46 g. (29% recovery), m.p. 136–137°. This procedure was used successfully in runs of 25 g.

Method B. A mixture of 5.0 g. of 4-nitro-3-picoline-1-oxide, 10 ml. of reagent-grade pyridine, and 0.7 ml. of piperidine was heated on a steam bath for 12 hr. and then allowed to stand at room temperature for 12 hr. Filtration yielded 3.8 g. (73%, allowing for recovered starting material) of 4-nitro-3-styrylpyridine-1-oxide, m.p. 178–180°. Dilution of the filtrate with ether gave 1.7 g. of unchanged starting material. This procedure was also used successfully on runs of 25 g.

4-Chloro-3-styrylpyridine-1-oxide. A mixture of 12.0 g. of 4-nitro-3-styrylpyridine-1-oxide and 80 ml. of acetyl chloride was heated under reflux (hood) on a steam bath for 3 hr. The cooled reaction mixture was poured over ice with

(3) J. G. Murray and C. R. Hauser, *J. Org. Chem.*, **19**, 2008 (1954).

(4) E. Shaw, *J. Am. Chem. Soc.*, **71**, 67 (1949).

(5) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, New Jersey. All melting points are uncorrected.

(6) E. C. Taylor and A. J. Crovetti, *J. Am. Chem. Soc.*, **78**, 214 (1956).

vigorous stirring and the mixture was brought to a volume of 2 l. by the addition of water. During the dilution white crystals of product separated. Filtration yielded 9.6 g. (84%) of almost colorless product, m.p. 161–163° dec. The colorless analytical sample, m.p. 167–168° dec., was prepared by recrystallization from aqueous ethanol with the use of charcoal.

Anal. Calcd. for $C_{13}H_{10}NO$: C, 67.4; H, 4.35; N, 6.05. Found: C, 67.7; H, 4.7; N, 5.9.

4-Mercapto-3-styrylpyridine-1-oxide. A mixture of 2.0 g. of 4-chloro-3-styrylpyridine-1-oxide, 0.6 g. of thiourea, and 20 ml. of ethanol was heated under reflux for 1.5 hr. The mixture was then chilled and filtered to give 1.71 g. (68%) of the thiouronium hydrochloride salt, m.p. 162° dec. This salt was suspended in 10 ml. of water and 5 ml. of cold 10% sodium hydroxide added with shaking. The mixture was filtered (yellow residue, 0.3 g., m.p. 200° dec.), the filtrate acidified with acetic acid and the precipitated solid collected by filtration to give 0.83 g. (62%, based on the thiouronium salt) of 4-mercapto-3-styrylpyridine-1-oxide, m.p. 145–146°.

Anal. Calcd. for $C_{13}H_{11}NOS$: C, 68.1; H, 4.8; N, 6.1. Found: C, 68.3; H, 4.6; N, 6.0.

Bis(1-oxy-3-styryl-4-pyridyl)sulfide. The yellow residue obtained above was purified by dissolution in boiling aqueous acetic acid and reprecipitation with ammonium hydroxide. The analytical sample m.p. 198–200° dec. was prepared by recrystallization from dimethylformamide.

Anal. Calcd. for $C_{26}H_{20}N_2O_2S$: C, 73.6; H, 4.8; N, 6.6. Found: C, 73.2; H, 4.7; N, 6.8.

Acknowledgment. We are indebted to Parke, Davis and Company for carrying out the pharmacological screening of these compounds.

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Pyrazolines[1]

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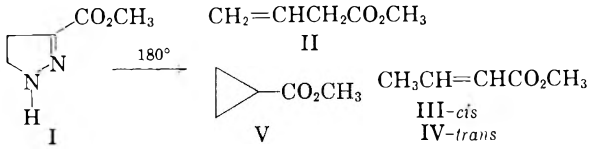
The pyrolysis of pyrazolines has long been regarded as a synthetic method for the preparation of derivatives of cyclopropane.[2] Particular use has been made of this method in the preparation of cyclopropanecarboxylic esters[3] and related compounds[4] where the pyrazoline is readily prepared by the addition of a diazoalkane to an α,β-unsaturated ester.

Of the methyl substituted 3-carbomethoxypyrazolines studied by von Auwers and Konig[3] only those which contained a methyl at the 3- position were found to give a cyclopropane product. A reinvestigation of this work which is now under way has shown that the products of pyrolysis of 3-carbomethoxypyrazolines are mixtures which contain in general α,β- and β,γ-unsaturated esters as well as the expected cyclopropanecarboxylic ester. A recent observation of the formation of a β,γ-unsaturated ketone from the pyrolysis of a pyrazoline in the steroid series has been reported.[5]

3-Carbomethoxypyrazoline (I), which was reported[3] to give in 81% yield methyl vinylacetate (II), has been shown to give a mixture in 80% yield of II, methyl *cis*-crotonate (III), methyl *trans*-crotonate (IV), and methyl cyclopropanecarboxylate in the ratio of 7:30:31:32, respectively.



Similarly methyl 2-methylcyclopropanecarboxylate has been isolated from the pyrolysis product from 4-methyl-3-carbomethoxypyrazoline and 5-methyl-3-carbomethoxypyrazoline in yields of 4 and 34%, respectively.[6]

That II, III, IV, and V were thermally stable under the reaction conditions was determined by heating each in a sealed tube for two hours at 195°. Not more than 2% rearrangement was observed. In the presence of iodine at 195° for five days, both II and IV gave an equilibrium mixture of the three olefins which contained 84% of IV, 12% of III, and 4% of II. These results would indicate that II and III are formed in the pyrolysis reaction by a kinetically controlled step and that although some isomerization may occur under the reaction conditions, it does not occur at a fast enough rate to give an equilibrium mixture.

It is hoped that by an extensive study of pyrazoline pyrolyses it will be possible to learn more about the mechanism[7] and the scope of the reaction as a synthetic method for the preparation of olefins and substituted cyclopropanes.

EXPERIMENTAL[8]

Pyrolysis of 3-carbomethoxypyrazoline (I). Thirteen g. of I (m.p. 65°, lit.[3] m.p. 66–68°) was placed in a 50-ml. round bottom flask fitted with a distilling head and heated in an oil bath. Pyrolysis began at 150° and was vigorous at 180°. The product distilled during pyrolysis and after 1 hr. 8 g. (80%) of a colorless liquid was collected.

Vapor chromatography of the product through a 10-ft. dinonyl phthalate column at 80° with a helium flow rate of 67 cc./min. gave four peaks at 20.8, 25.2, 32.4, and 36 min.

(1) Support for this work was received from the National Research Council of Canada and from the President's Committee on Research of the University of British Columbia.

(2) R. Huisgen, *Angew. Chem.*, **67**, 439 (1955).

(3) K. von Auwers and F. Konig, *Ann.*, **496**, 252 (1932).

(4) D. Gotkis and J. B. Cloke, *J. Am. Chem. Soc.*, **56**, 2710 (1934).

(5) H. L. Slates and N. L. Wender, *J. Am. Chem. Soc.*, **81**, 5472 (1959).

(6) Unpublished results from this laboratory.

(7) For proposals on the mechanism of this reaction see W. G. Young, L. J. Andrews, S. L. Lindenbaum, and S. J. Cristol, *J. Am. Chem. Soc.*, **66**, 810 (1944) and W. M. Jones, *J. Am. Chem. Soc.*, **81**, 3776 (1959).

(8) The instrument and columns for the vapor chromatograms were those available commercially under the trade name Aerograph.

which represented 7, 30, 32, and 31% of the product as determined by the weight of paper cuts of the peaks. Isolation of the four components was accomplished by fractionation through the vapor fractometer.

The 20.8-min. component, n_D^{23} 1.4083 (lit.[9] n_D^{20} 1.40909), was identical with an authentic sample of methyl vinylacetate (II) (prepared by the method of Corey[10]) as shown by their infrared spectra.

The 25.2-min. component, n_D^{23} 1.4223 (lit.[11] n_D^{20} 1.4225), was methyl *cis*-crotonate (III).

The 32.4-min. component, n_D^{23} 1.4182 (lit.[12] n_D^{20} 1.41866), was identical with an authentic sample of methyl cyclopropanecarboxylate V [prepared by the methylation of cyclopropanecarboxylic acid (Aldrich)] as shown by their infrared and NMR spectra.

The 36-min. component, n_D^{22} 1.4248 (lit.[9] n_D^{20} 1.42466), was identical with an authentic sample of methyl *trans*-crotonate (IV) (K and K Laboratories) as shown by their infrared and NMR spectra.

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(9) G. H. Jeffery and A. J. Vogel, *J. Chem. Soc.*, 658 (1948).

(10) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2251 (1953).

(11) J. L. H. Allan, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1862 (1955).

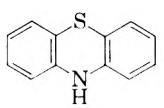
(12) G. H. Jeffery and A. J. Vogel, *J. Chem. Soc.*, 1804 (1948).

Preparation of Quinazolo[2,3-c]benzo[1,4]thiazine-12-(6H)one

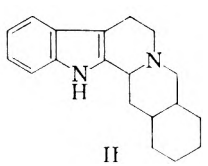
BETTY ANNE CARPENTER, JOHN E. MCCARTY, AND CALVIN A. VANDERWERF

Received August 13, 1959

During the course of an investigation of compounds with potential psychotherapeutic activity it appeared that derivatives of a ring system containing some of the features of phenothiazine (I)

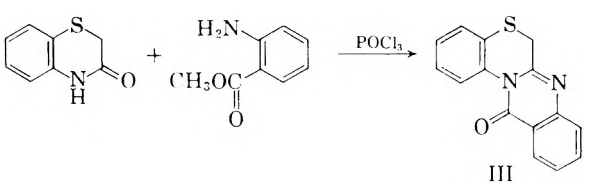


I



II

and benz[g]indole[2,3-a]quinolizine (II) (the reserpine nucleus) would be of interest. The quinazolo[2,3-c]benzo[1,4]thiazine system was selected and quinazolo[2,3-c]benzo[1,4]thiazine-12-(6H)one (III) was prepared by the method outlined below.



III

Preliminary pharmacological testing, however, indicates that this compound has negligible psychotherapeutic activity and the investigation in this area has been discontinued.

EXPERIMENTAL

Condensation of benzo[1,4]thiazine-3-one with methyl anthranilate. To a solution of 16.6 g. of benzo[1,4]thiazine-3-one dissolved in hot, anhydrous toluene, a solution of 30.4 g. of freshly distilled phosphorus oxychloride in 25 ml. of dry toluene was added slowly. After heating under reflux with rapid, mechanical stirring for 10 min., 30.2 g. of methyl anthranilate was added slowly and the resulting mixture heated under reflux for 8 hr. At the end of this time a yellow mass began to separate. The toluene was evaporated under reduced pressure, and the residue was dissolved in chloroform. The chloroform solution was dried over magnesium sulfate, filtered, and the chloroform evaporated on a steam bath. The residue was crystallized from 200 ml. of an 80% ethanol-water mixture.

The product was recrystallized twice from ethanol to give 12.5 g. (45%) of quinazolo[2,3-c]benzo[1,4]thiazine-12-(6H)one, yellow prisms, m.p. 154.5–156°.

Anal. Calcd. for $C_{15}H_{10}N_2OS$: C, 67.7; H, 3.8; N, 10.5; S, 12.0. Found: C, 67.8; H, 3.9; N, 10.4; S, 11.8.

Acknowledgment. We are grateful for the financial support by the Smith Kline and French Laboratories for a postdoctoral fellowship under which the work of one of us (J. E. M.) was performed.

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Amebicidal 8-Quinolinol Compounds

KONOMU MATSUMURA AND MOTOKO ITO

Received March 30, 1959

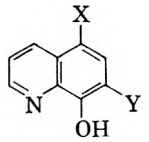
This note describes the preparation of several halogenated 8-quinolinol compounds which were made in the hope that they may be of therapeutic value.

The Results of Biological Study.[1] A number of 8-quinolinol compounds, including those reported in the present paper, has been tested against *Endamoeba histolytica in vitro*, and when indicated, against experimental amebiasis in guinea pigs. II was a hundred times as active as 5,7-diiodo-8-quinolinol in Balamuth media. Others (V and VIII) were somewhat more active than, or equal in activity to this standard. In animal assay, V and VIII possessed good antiamebic activity while II had no activity. It is noteworthy that V was of remarkably low toxicity when administered orally ($L.D._{50}$: 80 mg. per 20 g. body weight of a mouse).

(1) We are indebted to Dr. Akira Hirabayashi of our Institute who has kindly performed the biological testing and reported the results. Details of these test results will be published by A. Hirabayashi in a separate communication.

TABLE I

HALOGEN DERIVATIVES OF 8-QUINOLINOL COMPOUNDS



No.	X (5 position)	Y (7 position)	Yield, %	Solvent	Form[a]	M.p., °C.	Formula	Anal. N, % Calcd.	Found
I[b]	CH_3—CO—	I	90	EtOH	Needles	183 (dec.)	$C_{11}H_8INO_2$	4.47	4.44
II[b]	 -CO-	I	90	EtOH	Plates	209–210	$C_{16}H_{10}INO_2$	3.73	3.60
III[c]	Cl—CH_2—CO—	I	95	Glacial AcOH	Needles	227 (dec.)	$C_{11}H_7ClINO_2$	4.03	3.97
IV[d]	I—CH_2—CO—	H	96	C_6H_6	Plates	135 (dec.)	$C_{11}H_8INO_2$	4.47	4.56
V[e]	CCl_3—CH(OH)—	I	96	50% AcOH	Prisms	192 (dec.)	$C_{11}H_7Cl_3INO_2$	3.35	3.26
VI[f]	EtOOC—	I	98	EtOH	Needles	199–200	$C_{12}H_{10}INO_3$	4.08	4.21
VII[f]	BuOOC—	I	98	EtOH	Plates	155	$C_{14}H_{14}INO_3$	3.77	3.78
VIII[g]	HOOC—	I	70	EtOH	Prisms	228–229 (dec.)	$C_{10}H_6INO_3$	4.44	4.43
IX[h]	Cl	NO_2	80	EtOH	Needles	197 (dec.)	$C_9H_6ClN_2O_3$	12.47	12.90
X[i]	Cl	NH_2	86	Et_2O	Slightly brown prisms	162–163	$C_9H_7ClN_2O$	14.40	14.20
XI[j]	Cl	$NHCOCH_3$	76	C_6H_6	Colorless needles	201–202 (dec.)	$C_{11}H_9ClN_2O_2$	11.84	11.36

[a] Unless otherwise stated all crystal colors are orange. [b] Iodinated by method A-A1. [c] Iodinated by method B. [d] Prepared by method E. [e] Prepared by method C. [f] Iodinated by method A-A2. [g] Iodinated by method D. [h] Prepared by the addition of concentrated nitric acid (63%, 1 ml.) to a mixture of 5-chloro-8-quinolinol (1.8 g.) and glacial acetic acid (25 ml.) below 25°. [i] Made by stirring a mixture of IX (0.6 g.) pyridine (5 ml.) sodium hydrosulfite (4 g.) and water (20 ml.) at room temperature. [j] Made by allowing a mixture of X (0.4 g.) acetic anhydride (0.22 g.) freshly fused sodium acetate (0.4 g.) and ether (20 ml.) to stand at room temperature for 2 days.

EXPERIMENTAL

Method of Iodination. (A) 0.1 *N* Iodine–potassium iodide solution (20 ml.) was added dropwise into a solution of 5-substituted-8-quinolinol (0.001 mol.) and sodium acetate (0.25 g.) in methanol (40 ml.) at about 10° during 0.5 hr. After standing, excess iodine was destroyed by sulphur dioxide.

A1. The reaction mixture was evaporated on water bath to one-half volume and then made up to the original volume by addition of water. The resulting solid was crystallized from solvent.

A2. The product separated upon adding water (100 ml.) to the reaction mixture.

B. 0.1 *N* Methanolic iodine solution (20 ml.) was used and other conditions similar to that of A-A2.

C. One-half normal methanolic iodine solution (80 ml.) was added to a solution of 5-(α-hydroxy-3-trichloroethyl)-8-quinolinol (0.02 mol.) and sodium acetate (10 g.) in methanol (800 ml.) at about 10° during 1 hr.

Sulphur dioxide was added, if necessary, after the reaction mixture had stood overnight.

Most of the methanol was evaporated in vacuo below 50°. The product separated upon adding water (250 ml.) to the residual paste.

D. 0.1 *N* Iodine-iodide solution (20 ml.) was added dropwise with stirring to a solution of 5-carboxy-8-quinolinol (0.001 mol.) and sodium hydroxide (0.001 mol.) in water (50 ml.) at about 15° during 0.5 hr. The reaction mixture was acidified with acetic acid, the resulting solid filtered and dissolved in dilute sodium carbonate. The undissolved diiodo-8-quinolinol (0.05 g., m.p. 192–200°) which was formed as a byproduct was filtered off. The product separated upon adding acetic acid to the filtrate. It can be recrystallized from ethanol or glacial acetic acid.

E. A normal solution (4 ml.) of sodium iodide in acetone was added a little at a time to a mixture of 5-chloroacetyl-8-quinolinol (0.004 mol.) and acetone (30 ml.) with stirring at room temperature. After standing for a few hours, most of acetone was removed in vacuo. The product separated upon adding water to the residue.

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Chalcone-Type 8-Quinolinol Compounds

KONOMU MATSUMURA, MOTOKO ITO, AND SHEN TSO LEE

Received April 6, 1959

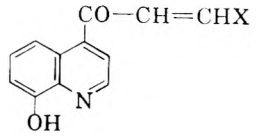
The compounds were prepared by condensation of 5-acetyl-8-quinolinol with aromatic aldehydes in the presence of potassium hydroxide or hydrochloric acid. None of them possessed any notable antituberculous or antiamebicidal activity.

EXPERIMENTAL

Method of condensation. A. In methanolic potassium hydroxide. To a solution of 5-acetyl-8-quinolinol (0.38 g., 0.002 mol.) and aromatic aldehyde (0.002 mol.) in methanol (6 ml.) was added a solution of potassium hydroxide (1 g.) in water (2 ml.) with stirring. The resulting solution was allowed to stand at room temperature or gently refluxed on a water bath. Then the reaction mixture was diluted with water, acidified with acetic acid, the separated solid filtered on standing and recrystallized.

TABLE I

CONDENSATION OF 5-ACETYL-8-QUINOLINOL WITH AROMATIC ALDEHYDE



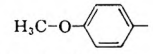
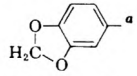
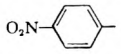
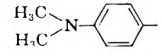
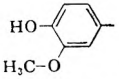
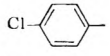
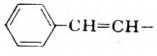
X	Reaction: Method	Reaction: Temp., °C.	Reaction: Time	Yield, %	Solvent	Form	M.P., °C.	Color in Concd. H_2SO_4	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
	A	30	24 hr.	73	EtOH	Plates	143–144	Orange yellow	$C_{18}H_{13}NO_2$	5.09	5.32
	B	60	4	73							
Hydrochloride					EtOH-HCl	Plates	252–254 (dec.)		$C_{18}H_{13}NO_2 \cdot HCl$	4.49	4.34
	A	60	5	80	Glacial AcOH	Needles	193 194	Red	$C_{19}H_{15}NO_3$	4.59	4.99
	B	60	3	64							
Hydrochloride					EtOH-HCl	Needles	271 (dec.)		$C_{19}H_{16}NO_3 \cdot HCl$	4.10	3.92
 [a]	A	20	24	94	EtOH	Prisms	180–181	Red			
	B	8	12 days	59							
Hydrochloride					EtOH-HCl	Needles	256				
	A	25	24 hr.	75	EtOH	Prisms	224	Orange yellow	$C_{18}H_{12}N_2O_4$	8.75	8.55
	B	60	17	89							
Hydrochloride					EtOH-HCl	Plates	280		$C_{18}H_{12}N_2O_4 \cdot HCl$	7.85	7.63
	A	60	10	31	EtOH	Prisms	191–192	Wine red	$C_{20}H_{18}N_2O_2$ [b]	8.81	9.01
	B	60	35	74							
Dihydrochloride					20% HCl	Needles	263–265 (dec.)		$C_{20}H_{18}N_2O_2 \cdot 2HCl$	7.16	7.04
	A	80	3	0	EtOH	Prisms	180–181	Red	$C_{19}H_{15}NO_4$	4.36	4.33
	B[c]	30	48	70							
Hydrochloride					Dil. HCl	Needles	268 (dec.)		$C_{19}H_{16}NO_4 \cdot HCl$	3.92	3.81
	A	60	3	76	EtOH	Cubes	193–195	Orange	$C_{18}H_{12}Cl\ NO_2$	4.52	4.52
	A	80	3	0	EtOH	Prisms	147	Purple red	$C_{20}H_{15}NO_2$	4.65	4.45
	B	8	3 days	70							
Hydrochloride					EtOH-HCl	Needles	257 (dec.)		$C_{20}H_{15}NO_2 \cdot HCl$	4.15	4.17
	A	8	24 hr.	89	EtOH	Plates	155–155.5	Reddish brown	$C_{16}H_{11}NO_3$	5.28	5.15

TABLE I (*Continued*)

X	Reaction			Yield, %	Solvent	Form	M.P., °C.	Color in Concd. H_2SO_4	Formula	Nitrogen, %	
	Method	Temp., C°.	Time							Calcd.	Found
	A	80	3	0	C_6H_6	Needles	271	Red	$C_{21}H_{14}N_2O_3$[d]	8.18	8.08
	B	60	17	80							
Dihydrochloride					Dil. HCl	Prisms	267 (dec.)		$C_{21}H_{14}N_2O_3 \cdot 2HCl$	6.75	6.77

[a] Lit. m.p. 178–179°, K. Matsumura and C. Sone, *J. Am. Chem. Soc.*, *53*, 1492 (1931). [b] Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.47; H, 5.66. Found: C, 75.19; H, 5.72. [c] In one lot, from the filtrate of recrystallization another isomer [yellow prisms, m.p. 276° (dec.), yield 20%, a red color in concd. H_2SO_4] was isolated, but not successfully repeated. *Anal.* Calcd. for $C_{19}H_{16}NO_4$: N, 4.36. Found: N, 4.37. *The hydrochloride* crystallized EtOH-HCl as yellow needles, m.p. 273–274° (dec.). *Anal.* Calcd. for $C_{19}H_{16}NO_4 \cdot HCl$: N, 3.92. Found: N, 4.11. [d] Calcd. for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.09. Found: C, 73.92; H, 4.40.

In the case of furfural, *N* sodium hydroxide (8 ml.) was added dropwise to a cooled solution of the components.

B. In concentrated hydrochloric acid. A mixture of 5-acetyl-8-quinolinol (0.38 g., 0.002 mol.) aromatic aldehyde (0.002 mol.) and concentrated hydrochloric acid (5 ml.) was allowed to stand in a sealed tube. After different periods of reaction time, the tube was opened, acid fume removed *in vacuo*, the product filtered, dissolved in water, and free base precipitated by adding sodium acetate to it.

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5-Carboxy-8-quinolinol Derivatives

MOTOKO ITO AND KONOMU MATSUMURA

Received April 16, 1959

This note describes the preparation of several derivatives of 5-carboxy-8-quinolinol in the hope that they may be of tuberculostatic activity. None of them, however, possessed any notable antituberculous activity *in vitro*.

EXPERIMENTAL

Condensation of 8-quinolinol with carbon tetrachloride. The Lippmann and Fleissner method[1] *was followed.* Starting from 20 g. of 8-quinolinol and with 13 hr. refluxing, 5.7 g. (22%) of 5-carboxy-8-quinolinol [m.p. 272° (dec.)] was isolated as the final product.

From dirty matter which was insoluble in dilute sodium carbonate, 4.7 g. of unreacted 8-quinolinol (m.p. 70–74°) was recovered by distillation with steam and 1.2 g. of 5-carboethoxy-8-quinolinol (m.p. 124.5–125.5°) isolated by carbon tetrachloride extraction of the residue of steam distillation and recrystallization of the extract from ethanol, the identity being ascertained by mixed m.p. method with an authentic specimen of 5-carboethoxy-8-quinolinol.

The hydrochloride formed light yellow needles, m.p. 263° (dec.).

Anal. Calcd. for $C_{12}H_{11}NO_3 \cdot HCl$: N, 5.53. Found: N, 5.71.

The carbon tetrachloride insoluble dark solid (*ca.* 5 g.) after three recrystallizations from dilute hydrochloric acid gave pure hydrochloride. It produced 0.62 g. of the free base on treating with dilute sodium carbonate.

It formed colorless prisms, m.p. 282–283° when recrystallized from nitrobenzene and then glacial acetic acid. The analytical figures corresponded to those of *bis*-8-quinolinol-5-yl ketone.

Anal. Calcd. for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.80; N, 8.86. Found: C, 72.26; H, 3.79; N, 8.61.

The hydrochloride crystallized from dilute hydrochloric acid as light yellow columns, m.p. 309–311° (dec.).

Anal. Calcd. for $C_{19}H_{12}N_2O_3 \cdot 2HCl$: N, 7.20. Found: N, 7.02.

Diacetyl derivative crystallized from dilute acetic acid as colorless prisms, m.p. 201–202°. In dilute ethanol, it gives no color reaction with ferric chloride but develops a green color on standing or warming.

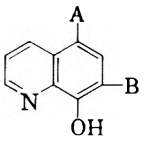
Anal. Calcd. for $C_{23}H_{16}N_2O_5$: N, 7.00. Found: N, 7.21.

8-Hydroxy-(XII) *and 8-chloro-*(XIII) *5-carbamoylquinoline.* A mixture of 5-carboxy-8-quinolinol (1.9 g., 0.01 mol.), phosphorus pentachloride (2.2 g., 0.011 mol.) and phosphorus oxychloride (2.9 g.) was heated at 100–105°

(1) E. Lippmann and F. Fleissner, *Ber.*, **19**, 2467 (1886).

TABLE I

DERIVATIVES OF 5-CARBOXY-8-QUINOLINOL



Compound	A	B	M.P., °C.	Form	Solvent	Formula	Nitrogen Calcd.	Nitrogen Found
I[a]	$-COOC_4H_9$	H	83	Slightly yellow rhombs	EtOH	$C_{14}H_{15}NO_3$	5.71	5.52
II[b]	$-COOC_2H_5$	$-NO_2$	285 (dec.)	Yellow needles	C_6H_6	$C_{12}H_{10}N_2O_5$	10.69	10.30
III[b]	$-COOC_4H_9$	$-NO_2$	220 (dec.)	Yellow columns	C_6H_6	$C_{14}H_{14}N_2O_5$	9.66	10.12
IV[c]	$-COOC_2H_5$	$-NH_2$	132–132.5	Garnet colored needles	Ether	$C_{12}H_{12}N_2O_3$	12.07	12.05
V[c]	$-COOC_4H_9$	$-NH_2$	139–140	Garnet colored columns	Ether	$C_{14}H_{16}N_2O_3$	10.77	10.81
VI[d]	IV Dihydrochloride		254 (dec.)	Orange needles	Dil. HCl	$C_{12}H_{12}N_2O_3 \cdot 2HCl$	9.18	8.76
VII[d]	V Dihydrochloride		211 (dec.)	Orange columns	Dil. HCl	$C_{14}H_{16}N_2O_3 \cdot 2HCl$	8.41	8.94
VIII[e]	$-COOC_2H_5$	$-NH^1COCH_3$	192	Slightly pink needles	C_6H_6	$C_{14}H_{14}N_2O_4$	10.22	10.24
IX[e]	$-COOC_4H_9$	$-NH^1COCH_3$	185–186	Slightly pink needles	C_6H_6	$C_{16}H_{18}N_2O_4$	9.27	9.41
X[f]	$-CONH^1NH_2$	H	268 (dec.)	Colorless needles	MeOH	$C_{10}H_9N_3O_2$	20.69	20.32
XI[d]	I Hydrochloride		239–240 (dec.)	Colorless needles	Dil. HCl	$C_{14}H_{15}NO_3 \cdot HCl$	4.97	5.20

[a] Made by heating a mixture of 5-carboxy-8-quinolinol (1.14 g.), butanol (5 ml.) and concentrated sulfuric acid (0.6 g.) at 120° for 16 hr. until clear dissolution effected, adding water and sodium acetate (2 g.) to the solution, removing butanol by steam distillation, dissolving the residual oil which soon solidified, in dilute hot hydrochloric acid (250 ml.) (just acid to congo red), filtering from dark green amorphous matter and precipitating the free ester (1.08 g., 73%) by sodium carbonate.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.12. Found: C, 68.14; H, 6.37.

[b] Made by heating a mixture of the corresponding ester (0.001 mol.) and 10% nitric acid (4 ml.) at 80° with stirring for 1 hr., yield 88% II and 84% III. [c] Made by stirring a mixture of the corresponding nitro compound (0.001 mol.), ethanol (10 ml.) 2% ammonium hydroxide (14 ml.) and sodium hydrosulfite (2 g.) for 1 hr. at room temperature, removing ethanol by evaporation on a water bath and filtering the resulting crystals on cooling, yield 60% IV and 80% V. [d] Made by concentrating a solution of the corresponding base in dilute hydrochloric acid *in vacuo* over potassium hydroxide at room temperature until crystals began to separate. [e] Made by adding acetic anhydride (0.11 g.) and freshly fused sodium acetate (0.25 g.) to a solution of the corresponding amine (0.001 mol.) in ether (65 ml.), letting the mixture stand at room temperature for 4 days, then evaporating the ether and washing the residue with water in almost quantitative yield. [f] Made by heating a mixture of I (0.25 g.) and 80% hydrazine hydrate (0.5 g.) at 100° for 13 hr. and washing the product with cold benzene, yield 59%.

for 1 hr., phosphorus oxychloride removed *in vacuo* and the residue treated with cold acetone (60 ml.) which had been saturated with ammonia at 0°. The reaction product on treating with dilute ammonia, 0.72 g. of 5-carboxy-8-quinolinol was recovered and the crude XII, when purified through the hydrochloride and finally recrystallized from 90% ethanol gave colorless glistening plates, m.p. 275–276° (dec.),[2] yield 0.32 g. It gives a deep green color with ferric chloride.

Anal. Calcd. for $C_{10}H_8N_2O_2$: N, 14.89. Found: N, 14.63.

On heating 5 hr. instead of 1 hr., the reaction product, on recrystallization from ethanol gave XII (0.17 g.) and from the filtrate of recrystallization XIII (0.4 g.) respectively. XIII gave colorless columns, m.p. 230–231° and no color reaction with ferric chloride.

Anal. Calcd. for $C_{10}H_7ClN_2O$: C, 58.11; H, 3.39; Cl, 17.19. Found: C, 57.91; H, 2.91; Cl, 17.27.

The picrate crystallized from ethanol as plates, m.p. 200–202°.

Anal. Calcd. for $C_{10}H_7ClN_2O \cdot C_6H_3N_3O_7$: N, 16.07. Found: N, 15.51.

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(2) Lit. m.p. 264–265° (dec.). G. R. Clemo and R. Howe, *J. Chem. Soc.*, **1955**, 3552.

Synthesis of *N*-Acetyl-5-methoxytryptamine

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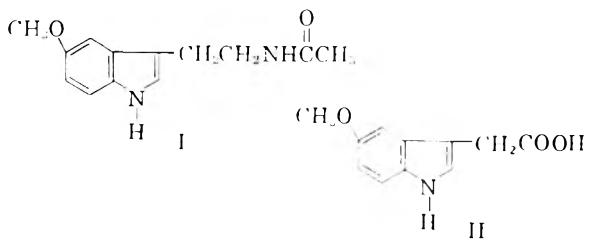
Lerner has reported the isolation[1] from pineal glands and peripheral nerves of an indole derivative, melatonin, which is the most potent agent

(1) A. B. Lerner, J. D. Case, Y. Takahashi, T. H. Lee, and W. Mori, *J. Am. Chem. Soc.*, **80**, 2587 (1958).

known in lightening frog skin. Melatonin and an inactive indole accompanying it in the isolation procedure have since been reported[2,3] to have the structures, 5-methoxy-*N*-acetyltryptamine (I) and 5-methoxyindole-3-acetic acid (II), respectively.

5-Methoxytryptamines seem to be of rare occurrence in nature, the only case we could find being 5 - methoxy - *N* - methyltryptamine, isolated from the grass *Phalaris arundinacea L.*[4]

The infrared spectrum of the methyl ester of naturally occurring II was found to be identical with that of the methyl ester of synthetic II described in the present paper. However, even though the evidence[3] for structure I is quite convincing, it has not been possible to characterize melatonin completely due to its availability from pineal glands in only microgram quantities and in an impure state.



In the present paper we would like to report the synthesis of I by two previously unreported routes. This material has the full activity of natural melatonin when tested on the frog skin.[5]

Previously, 5-methoxytryptamine has been prepared by reaction of *p*-methoxyphenylhydrazine with γ-aminobutyraldehyde diethyl acetal and zinc chloride,[6,7] from 5-methoxyindolemagnesium iodide and chloroacetonitrile[8] followed by reduction with sodium and alcohol,[9,10] and from *p*-methoxyphenyldiazonium chloride and 3-carbethoxy-2-piperidone followed by ring opening and decarboxylation.[11]

5-Methoxy-*N*-acetyltryptamine was used by Späth and Lederer[6] as an intermediate for the preparation of 10-methoxy-3-methyl-5,6-dihydro-4-carbolin, but it was neither purified nor characterized.

Our syntheses were chosen primarily because of the availability of appropriate starting materials. In the first synthesis 5-methoxyindole was converted to the corresponding gramine derivative, followed by displacement with cyanide, lithium aluminum hydride reduction, and acetylation. In the second synthesis, 5-methoxyindole-3-aldehyde was condensed with nitromethane and the resulting unsaturated nitro compound was reduced with lithium aluminum hydride and acetylated.

In connection with the identification of the second pineal-extract product II, we have repeated the preparation of 5-methoxyindole-3-acetic acid according to the literature[7] and converted it to its crystalline methyl ester. Previously II was prepared by alkaline hydrolysis of 5-methoxyindole-3-acetonitrile[12,13] and by the Japp-Klingeman method.[14] It was reported as a urinary excretion product of 5-methoxytryptamine in rats.[15]

EXPERIMENTAL

All melting points (capillary) are uncorrected. Ultraviolet spectra (in mμ) were determined in 95% ethanol using a Cary spectrophotometer, Model 14. Infrared spectra (in $cm.^{-1}$) were determined in Nujol using a Perkin-Elmer recording infrared spectrophotometer, Model 21.

5-Methoxyindole was purchased from Regis Chemical Co., Chicago, Ill.

5-Methoxygramine was prepared according to Cook[16]; m.p. 124–125° (lit., m.p. 124–125°); ultraviolet spectrum mμ (ε): 212 (29,850); 274 (6,250); 295 (4,950); f. 306 (3,700); infrared spectrum: NH: 3200 sh., 3090; *tert.* amine: 2800, 2770 sh.; C=C: 1625, 1590, 1545, 1490; C—O: 1250, 1220, 1070, 1038; aromatic substitution: 854, 830, 750.

5-Methoxyindole-3-acetonitrile was prepared according to the method used previously for the synthesis of indole-3-acetonitrile.[17] A solution of potassium cyanide (27.2 g.; 0.42 mole) in 55 ml. of water was added to a solution of 5-methoxygramine (43 g.; 0.21 mole) in 550 ml. of methanol. Methyl iodide (71 g.; 0.502 mole) was then added during 10 min., keeping the temperature below 20°. The reaction mixture was then stirred at 20–25° for 16 hr. The resulting suspension was evaporated at 35–40°. Water (300 ml.) and ether (500 ml.) were added and the suspension was filtered to give 25.9 g. of a colorless solid which proved to be impure tetramethylammonium iodide (infrared spectra). It was recrystallized from methanol, m.p. >320°.

Anal. Calcd. for $C_4H_{12}IN$: C, 23.89; H, 6.02; I, 63.12; N, 6.97. Found: C, 24.42; H, 6.25; I, 62.71; N, 6.92.

The ultraviolet (λ_{max} 219, ε 13,900) and infrared spectra were identical with those of an authentic sample of tetramethylammonium iodide.

The filtrate was separated into two layers and the ethereal solution was washed with 5% hydrochloric acid (4 × 100

(2) A. B. Lerner, J. D. Case, K. Biemann, R. V. Heinzelman, J. Szmuszkovicz, W. C. Anthony, and A. Krivis, *J. Am. Chem. Soc.*, **81**, 5264 (1959).

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(7) T. Hoshino and T. Kobayashi, *Ann.*, **516**, 81 (1935).

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(10) B. Asero, V. Coló, V. Erspamer, and A. Vercellone, *Ann.*, **576**, 69 (1952).

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(13) B. Asero, V. A. Coló, and A. Vercellone, *Il Farmaco (Pavia) Ed. Sci.*, **11**, 219 (1956); *Chem. Abstr.*, **50**, 13870[e] (1956).

(14) S. P. Findlay and G. Dougherty, *J. Org. Chem.*, **13**, 560 (1948).

(15) V. Erspamer, *J. Physiol. (London)*, **127**, 118 (1955).

(16) J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.*, 1203 (1951).

(17) M. B. Henbest, E. R. H. Jones, and G. F. Smith, *J. Chem. Soc.*, 3796 (1953).

ml.). A gummy impurity separated and after a few minutes was easily removed by decantation. The ether layer was washed in succession with water, sodium bicarbonate solution, water, and saturated salt solution and dried through sodium sulfate to give 25 g. (64% crude yield) of the nitrile as a yellow oil; ultraviolet spectrum: 218 (27,350); 273 (6,500); 295 (4,750); 306 (3,800); infrared spectrum: C≡N: 2240 (m); 2800? (w).

5-Methoxytryptamine. A solution of the crude 5-methoxyindole-3-acetonitrile (19 g., 0.102 mole) in 200 ml. of ether was added during 10 min. to a solution of lithium aluminum hydride (19 g.) in 1200 ml. of ether under nitrogen.

The resulting thick suspension was refluxed for 3 hr. and allowed to stand overnight. The mixture was cooled in ice and decomposed in succession with 20 ml. of water, 20 ml. of 15% aqueous sodium hydroxide, and 60 ml. of water. The resulting suspension was filtered and the cake washed well with ether.

The colorless filtrate was extracted with 5% hydrochloric acid (5 × 100 ml.). Some gummy material precipitated and was easily removed by decantation. The clear yellow extract was cooled in ice and made basic with 30% potassium hydroxide. The resulting oil was extracted three times with ether (total 500 ml.). The ether was washed with water followed by saturated salt solution; it was then dried through sodium sulfate and evaporated under reduced pressure to give a yellow solid, m.p. 119–122° (13.5 g.; 70% yield). Crystallization from benzene gave pale yellow prisms, m.p. 121.5–122.5° (lit.,[9] m.p. 121–122°); ultraviolet spectrum: 223 (25,250); 277 (6,300); 296 (5,050); f 308 (3,450); infrared spectrum: NH: 3310, 3250, 3080; aromatic C=C: 1620, 1585, 1495; C—O: 1240, 1220; aromatic substitution: 860, 850, 813, 793.

N-Acetyl-5-methoxytryptamine (I). 5-Methoxytryptamine (7.6 g.) was added to 35 ml. of acetic anhydride at room temperature. The resulting brown solution became warm and was allowed to stand under nitrogen for 23 hr. Water (200 ml.) was added and the mixture was stirred for 0.5 hr. It was then cooled in ice and neutralized partially by addition of solid sodium carbonate (28 g.). The resulting suspension was filtered and the solid washed with water. It was crystallized from benzene to give 7.6 g. (81.5% yield) of pale yellow leaflets, m.p. 116–118° unchanged on further recrystallization; ultraviolet spectrum: 223 (27,550); 278 (6,300); f. 297 (5,150); f. 308 (3,500); infrared spectrum: NH: 3240; C=O: amide I, 1627; amide II, 1555; aromatic C=C: 1620, 1587, 1492; C—O: 1217, 1180; aromatic substitution: 828, 810, 800.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.27; H, 6.79; N, 11.89.

5-Methoxy-β-indoleninideniumethyl nitronate. A solution of 22 g. of ammonium acetate, 6.0 ml. of acetic anhydride, and 17.6 ml. of acetic acid was stirred for 20 min. and a mixture of 30.0 g. (0.18 mole) of 5-methoxyindole-3-aldehyde (Regis Chemical Co.), 100 ml. of nitromethane, and 120 ml. of acetic acid was added. The solution was brought to reflux and 14 g. of sodium acetate was added. The mixture was refluxed for 2 hr. while 20 ml. of acetic anhydride was added dropwise. The solution was allowed to cool while 45 ml. of water was added dropwise. The mixture was refrigerated and filtered. After recrystallization from alcohol the product weighed 9.6 g. (25%) and melted at 157–158°; infrared spectra: NH/OH: 3215; C=C: 1612, 1585; —N<O, OH: 1297, 1255, 1212, 979; C—O: 1108, 1074; aromatic substitution: 954, 920, 815, 800, 783, 689; ultraviolet spectrum: 224 (19,700); 283 (9100); f. 292 (8250); f. 302 (6550); 405 (20,200).

Anal. Calcd. for $C_{\alpha\alpha}H_{10}N_2O_3$: C, 60.54; H, 4.61; N, 12.84. Found: C, 60.07; H, 4.30; N, 12.65.

5-Methoxytryptamine. A solution of 6.0 g. (0.027 mole) of the nitronate and 50 ml. of tetrahydrofuran was added dropwise to a refluxing mixture of 5.4 g. (0.14 mole) of lithium aluminum hydride and 100 ml. of tetrahydrofuran. The mixture was refluxed for 4 hr. after the addition was complete. It was then cooled and the excess lithium aluminum hydride was decomposed with wet ether followed by concd. potassium hydroxide solution. The solution was decanted and the residue washed thoroughly with ether and added to the original filtrate. The filtrate was dried over potassium carbonate and concentrated. The residue was dissolved in ethyl acetate, refluxed with Nuchar-190-N, and filtered. An approximately equal volume of Skellysolve B was added and the solution was refrigerated overnight. Filtration yielded 1.3 g. (27%) of product which melted at 115–117°. It was identical with the sample obtained by the gramine procedure (infrared, ultraviolet) and on acetylation gave I.

5-Methoxyindole-3-acetonitrile was prepared from the Grignard derivative with chloroacetonitrile.[8]

5-Methoxyindole-3-acetic acid was prepared by hydrolysis of the crude nitrile with aqueous methanolic potassium hydroxide.[12] The acid melted at 145–146°; ultraviolet spectrum: 221 (25,150); 276 (6,300); 296 (4,800); f. 308 (3.400); infrared spectrum: NH: 3,330; OH (carboxyl): 2640, 2560; C=O: 1690, 1670; C—O: 1215, 1175.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.20; H, 5.13; N, 6.62.

Methyl 5-methoxyindole-3-acetate. 5-Methoxy-3-indoleacetic acid (1.0 g.; 0.005 mole) was suspended in 100 ml. of ether and treated with three equivalents of diazomethane in ether. After 2 hr. 1.0 ml. of acetic acid was added. The solution was washed with water, sodium bicarbonate, and then with water. The solution was dried over potassium carbonate and concentrated to yield a dark red oil. This oil was subjected to distillation and the material boiling below 250°/0.03 mm. was collected. The resulting distillate solidified upon scratching. After crystallization from 50% benzene–Skellysolve B the product weighed 0.4 g. (35%) and melted at 73–74°; ultraviolet spectrum: 219 (25,800); 275 (6,350); f. 295 (4,850); f. 307 (3,500); infrared spectrum: NH: 3350; C=O: 1721; aromatic C=C: 1625, 1591, 1495; C—O: 1250, 1221, 1184, 1100, 1064, 1030; aromatic substitution: 825, 806.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.61; H, 5.83; N, 6.73.

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Tropine DL-α-Methyltropate (Methylatropine) and Its Optical Antipodes

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The loss of physiological activity on the ready racemization of natural *l*-hyoscyamine (I R= H)[1–4] led us to search for more stable active anal-

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(2) A. R. Cushny, *J. Physiol.*, 9, 4 P (1903).

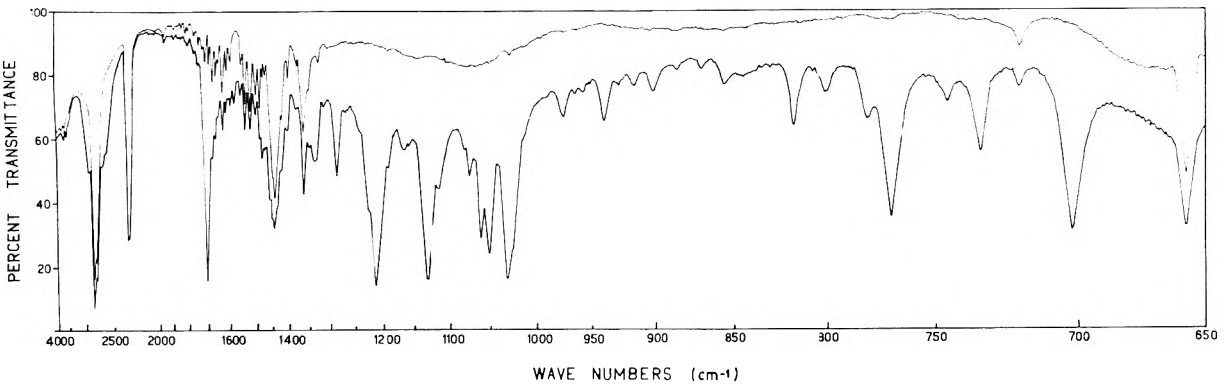


Fig. 1. Tropine *dl*-α-methyl tropate

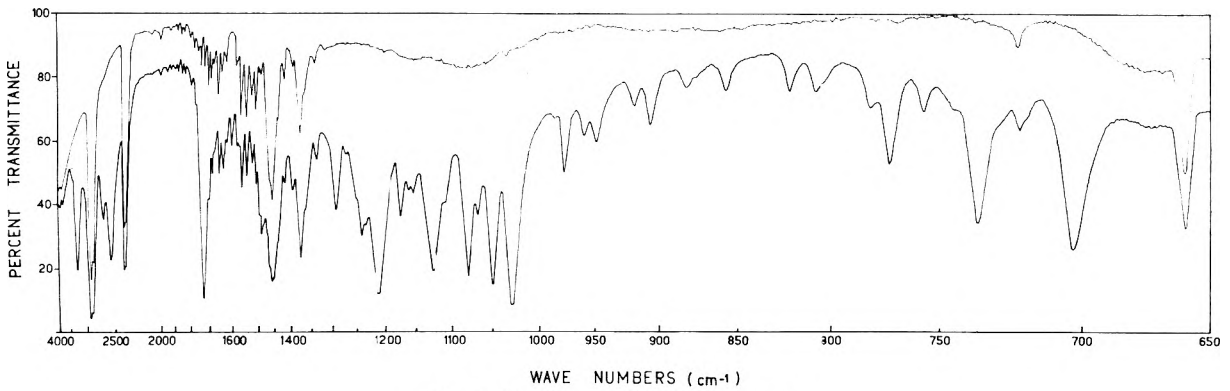
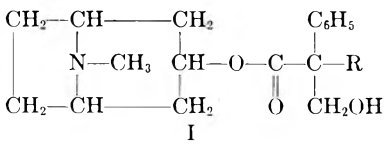


Fig. 2. Tropine (−)-α-methyl tropate

ogues. We have now resolved *dl*-α-methyltropic acid (II) the synthesis of which we recently described.[5,6a] The acids (*dl*, *d* and *l*) were converted to their *O*-acetyl chlorides, and these treated with tropine. Partial hydrolysis of the resulting ester



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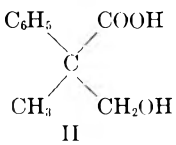

II

gave *dl*-methylatropine and the optically active α-methylhyoscyamines (I R = CH_3). Foster and Ing, who at first claimed to have synthesized α-methylatropine,[7] later recognized that they had actually synthesized the α-benzyl lactate of tropine.[8] Both racemic and optically active I (R = CH_3) are white crystals. Their infrared spectra are reported in Figs. 1 and 2. The optical dispersion curve of a 1% aqueous solution of (+) - methylhyoscyamine hydrochloride shows a gradual increase: at 700 mμ, 3°; at 500 mμ, 11°; 400 mμ, 23.5°; 375 mμ, 29°. The pharmacological activity of this product will be reported by Dr. G. Maffii and Cows. From the preliminary trials[9] α-methyl atropine seems as active as atropine and its (−) antipode [(−)-methylhyoscyamine] displays a higher activity than the (+) antipode.

EXPERIMENTAL

Resolution of α-methyltropic acid (II) *into its optical antipodes.* (a) (−)-α-*Methyltropic acid.* To 100 g. of *dl*-α-methyltropic acid,[5,6] m.p. 89–90°, and 185 g. of quinine free base dissolved in 450 ml. of warm absolute ethanol, was added 450 ml. of distilled water and the mixture heated for 5 min. on a boiling water bath. After 24 hr. at room temperature the crystalline precipitate was collected by suction, washed with 50% ethanol and dried: yield 118 g. of quinine (−)-α-methyltropate, m.p. 179.5°, $[\alpha]_D^{20}$ −120.7° (*c* = 2, ethanol). The recrystallization from 460 ml. of absolute ethanol and 460 ml. of distilled water gave 81.3 g. melting at 182–183°; $[\alpha]_D^{20}$ −123.4 (*c* = 2, ethanol). This product was further purified through a crystallization from 2350 ml. of a 9:1 mixture of ethyl acetate–95% ethanol with the addition of charcoal. The mixture was allowed to stand overnight at room temperature, then filtered. Yield, 60.5 g., m.p. 185–186°; $[\alpha]_D^{20}$ −121° (*c* = 2, ethanol). Further recrystallizations from different solvents did not raise the melting point or change the specific rotation value.

Anal. Calcd. for $C_{20}H_{24}N_2O_2;C_{10}H_{12}O_4$: N, 5.55. Found: N, 5.54.

The quinine (−)-α-methyltropate (60 g.) was suspended in 400 ml. of water and acidified to *p*H 1 with hydrochloric

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(4) M. Barrowcliff and F. Tutin, *J. Chem. Soc.*, **99**, 1966 (1909).

(5) A. Vecchi and G. Melone, *J. Org. Chem.*, **24**, 109 (1959).

(6) (a) E. Testa, L. Fontanella, G. F. Cristiani and F. Fava, *Ann.*, **619**, 47 (1958). (b) This acid has also been prepared in very poor yield by H. E. Zaugg and R. W. De Net [*J. Org. Chem.*, **23**, 498 (1958)].

(7) R. Foster and H. R. Ing, *J. Chem. Soc.*, 938 (1956).

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(9) G. Maffii, personal communication.

acid under cooling. The solution was extracted three times with ethyl ether; the ether extracts were washed with water, dried over sodium sulfate, and evaporated to dryness. The oily residue crystallized on standing; on recrystallization from 1800 ml. of benzene–petroleum ether (1:1) 15.8 g. of (−)-α-methyltropic acid were obtained, m.p. 89–90°; $[\alpha]_D^{20}$ −28.3° (*c* = 2, ethanol).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.60; H, 6.71. Found: C, 66.85; H, 6.87.

(b) (+)-α-*Methyltropic acid.* To a warm solution of 13.51 g. of *dl*-α-methyltropic acid,[5,6] m.p. 89–90°, in 54 ml. of absolute ethanol was added 20.6 g. of brucine free base in 54 ml. of warm water. The mixture was refluxed until complete solution was obtained, then allowed to stand overnight. The precipitate, 10 g., was collected by suction, dried *in vacuo* and recrystallized from 250 ml. of a 1:1 mixture of ethyl acetate–95% ethanol with the addition of charcoal. After standing some hours 4.6 g. of brucine (+)-α-methyltropate were collected; m.p. 209–212°; $[\alpha]_D^{20}$ −19.22° (c = 2, ethanol).

Anal. Calcd. for $C_{23}H_{26}N_2O_4{\cdot}C_{10}H_{12}O_3$: N, 4.87. Found: N, 5.11.

The brucine (+)-α-methyltropate may also be prepared from the mother liquors of the first crystallization of quinine (−)-α-methyltropate after separating the free acid by acidification.

The brucine (+)-α-methyltropate (3.8 g.) was treated as described above for quinine (−)-α-methyltropate. The crude product was recrystallized from 60 ml. of benzene–petroleum ether (1:1) with addition of charcoal. Yield 0.5 g. of colorless needles melting at 88–90°; $[\alpha]_D^{20}$ +27° (*c* = 2, ethanol).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.60; H, 6.71. Found: C, 66.46; H, 6.69.

β-*Acetoxy-α-methyl-α-phenylpropionyl chlorides. Example for dl-derivative.* A mixture of 13.5 g. of *dl*-α-methyltropic acid and 27 ml. of acetyl chloride was refluxed for 0.5 hour, then the excess of acetyl chloride was removed *in vacuo*. The oily residue was treated with 70 ml. of thionyl chloride and refluxed 1 hr. The excess thionyl chloride was distilled and the residue distilled from a Claisen flask to give 11.2 g. of product, b.p. 113–116°/1 mm. The distilled compound solidified on standing and was recrystallized from 70 ml. of petroleum ether: yield 10.6 g. (59%), m.p. 66–69°.

Anal. Calcd. for $C_{12}H_{13}ClO_3$: Cl, 14.74. Found: Cl, 14.51.

The (+)- and (−)-derivative were prepared, starting from the (+)- and (−)-α-methyltropic acid respectively, as described for the *dl*-derivative. The (+)- and (−)-isomers were not distilled from the Claisen flask and isolated in a pure state but employed as such for the following condensation with tropine.

α-*Methylatropine* (*tropine dl-α-methyltropate*). *dl*-β-Acetoxy-α-methyl-α-phenylpropionyl chloride (5.8 g.) and tropine free base[10] (4.2 g.), thoroughly mixed, were heated for 5 hr. at 150°. The mixture turned to brown and gas was evolved. After cooling to room temperature, the mixture was treated with 60 ml. of warm water, then with charcoal, and filtered from the scanty undissolved residue. The filtrate was adjusted to *p*H 9 with a saturated solution of sodium carbonate, extracted with ethyl ether and the ether extract dried over sodium sulfate and filtered. The filtrate was made acidic to Congo red by treatment with a saturated ether solution of hydrogen chloride. A thick oil separated, which was decanted from the ether and dissolved in 20 ml. of water. Two drops of 10% hydrochloric acid were added to this solution and the mixture was allowed to stand 15 hr. at room temperature, in order to hydrolyze the *O*-acetyl group. A saturated solution of sodium carbonate was then added, the separated oil extracted with ethyl ether, dried over sodium sulfate, and concentrated to a final volume of 20 ml. On cooling and rubbing α-methylatropine precipitated in the form of white fine crystals. Yield 0.9 g.: m.p. 131–133°.

Anal. Calcd. for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.30; N, 4.61. Found: C, 71.04; H, 8.29; N, 4.79.

(−)-α-*Methylhyoscyamine* [*tropine* (−)-α-*methyltropate*]. A mixture of 3.74 g. of tropine free base, 6.24 g. of (−)-β-acetoxy-α-methyl-α-phenylpropionyl chloride and 4 ml. of anhydrous toluene was heated for 4 hr. at 120–125°, then cooled, treated with 65 ml. of water and acidified to *p*H 1 with 10% hydrochloric acid. The mixture was extracted with ethyl ether,, the aqueous layer adjusted to *p*H 8.3 with a saturated solution of sodium carbonate and extracted with ethyl ether. This ether extract was dried over sodium sulfate, and acidified to *p*H 1 with a saturated ether solution of hydrogen chloride. The ether was decanted and the oily residue treated with 35 ml. of water, acidified with 5 drops of 10% hydrochloric acid, and allowed to stand 15 hr., to hydrolyze the *O*-acetyl group. The mixture was adjusted to *p*H 8.5 with a saturated solution of sodium carbonate, extracted with ethyl ether, the extract washed with water, dried over sodium sulfate and made acidic with a saturated ether solution of hydrogen chloride. The ether was decanted, the residual oil treated with boiling ethyl acetate with the addition of charcoal and filtered. After standing some days 0.470 g. of crystalline (−)-α-methylhyoscyamine hydrochloride were collected; m.p. 210–212°; $[\alpha]_D^{20}$ −6.8° (*c* = 1, water).

Anal. Calcd. for $C_{18}H_{25}NO_3{\cdot}HCl$: C, 63.51; H, 7.42; N, 4.12; Cl, 10.4. Found: C, 64.01; H, 7.50; N, 4.09; Cl, 10.2.

(+)-α-*Methylhyoscyamine* [*tropine* (+)-α-*methyltropate*] was prepared exactly as described for (−) isomer starting from 3.99 g. of tropine free base, 6.63 g. of (+)-β-acetoxy-α-methyl-α-phenylpropionyl chloride and 4 ml. of anhydrous toluene. Yield, 0.735 g. of crystalline (+)-α-methylhyoscyamine hydrochloride, m.p. 210–211.5°: $[\alpha]_D^{20}$ +7.3° (*c* = 1, water).

Anal. Calcd. for $C_{18}H_{25}NO_3{\cdot}HCl$: C, 63.61; H, 7.42; N, 4.12; Cl, 10.4. Found: C, 63.49; H, 7.95; N, 3.70; Cl, 10.85.

Acknowledgment. We wish to thank Prof. R. Fusco for the useful discussion on this subject during our experimental work and Dr. A. Wittgens for the assistance in the preparation of the manuscript. We also gratefully acknowledge Dr. G. G. Gallo and Mr. L. Chiesa who carried out the infrared spectra and measured the optical dispersion curve. The microanalyses have been carried out by Mr. Restelli of the Microanalytical Department of Lepetit S.p.A.

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(10) Fluka, A. G., Buchs (Switzerland)

Autoxidation of Trialkylboranes

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Received November 2, 1959

It has been postulated by Johnson and Van Campen[1] that the oxidation of trialkylboranes to the corresponding alkylboronates (II) proceeds through an intermediate (I) containing a boron

(1) J. R. Johnson and M. G. Van Campen, *J. Am. Chem. Soc.*, **60**, 121 (1938).

$$R_3B + O_2 \longrightarrow [R_3B \longleftarrow O_2] \longrightarrow RB(OR)_2$$
$$\text{I} \qquad \text{II}$$

oxygen dative bond. More recently it has been shown that peroxides of the structure, R_2BOOR, are also intermediates in this autoxidation.[2,3] We wish to describe some observations which indicate that a molecular complex between oxygen and the trialkylborane is an intermediate in the formation of the boron peroxides.

Studies were made on the rate of formation of peroxide in dilute hydrocarbon solutions of tri-*n*-butylborane through which oxygen had been bubbled. In these experiments a molar equivalent of oxygen was passed rapidly through the dilute boron alkyl solution. Nitrogen was then passed through the solution to remove unreacted, dissolved oxygen and to provide an inert atmosphere, whereupon aliquots were withdrawn at intervals and the yield of peroxide determined iodometrically. The results of a typical experiment are illustrated in Figure 1.

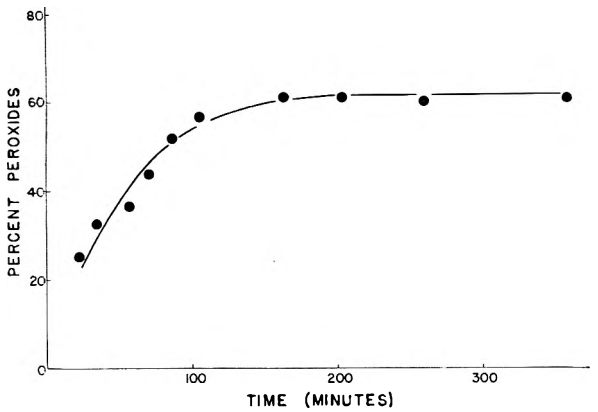

Fig. 1. Peroxide formation at 26°

Although there was presumably no dissolved oxygen in the system it is apparent that the yield of peroxide increased with time. This can best be explained by the initial and rapid formation of a nonperoxidic compound of oxygen with the trialkylborane, perhaps having the structure (I); followed by the slower rearrangement of this complex to the peroxide.

At temperatures of −10° or above in the presence of excess oxygen one mole of peroxide was produced per mole of boron alkyl (Table I). This is in agreement with the observations of Petry and Verhoek.[2] At lower temperatures, however, the stoichiometry is not so well defined, but it is apparent that considerably more than one mole of peroxide results. Another difference noticed at the lower temperatures was an increased rate of peroxide formation.

TABLE I

PREPARATION OF *n*-BUTYLBORON PEROXIDES BY THE PASSAGE OF A TEN-FOLD MOLAR EXCESS OF OXYGEN THROUGH A ONE-WEIGHT PER CENT SOLUTION OF TRI-*n*-BUTYLBORANE

Run	Solvent	Moles Peroxide / Moles Bu_3B	T, °
1	Benzene	0.96	26
2	Benzene	1.04	26
3	Iso-octane	1.00	−10
4	Iso-octane	1.05	−10
5	*n*-Heptane	1.92	−78
6	*n*-Heptane	1.55	−78

The reason for the more rapid formation of peroxide in increased yield at the lower temperatures is not evident from our data. It may indicate that at low temperatures where the concentration of oxygen is high the initial complex of boron and oxygen reacts further with oxygen to rapidly form a diperoxide.

The decomposition of one-weight per cent solutions of the resulting boron peroxide in iso-octane was also studied briefly. No significant decomposition was observed at 25° in fifty hours. However, at 50° and 100° the half-lives for the decomposition were forty-three and one and a half hours, respectively.

EXPERIMENTAL

Purification of materials. Reagent grade hydrocarbons were dried over sodium and distilled. Center cuts were used.

The tri-*n*-butylborane was obtained from the Callery Chemical Co. and distilled at reduced pressure. Center cuts were used, b.p. 48° at 0.5 mm.

The oxygen and nitrogen (Linde Co.) were of very high purity and used as obtained.

Preparation of peroxides. A 1-l., three-necked, round-bottomed flask which had an outer jacket for circulating liquid of the desired temperature was equipped with a "Tru-Bore" stirrer, a fritted glass gas delivery tube, a thermometer, and a Dry Ice condenser to catch vapors swept over by the incoming gas.

To this flask was added 495 g. of the desired solvent. This solvent was purged with nitrogen to rid it of any dissolved air. Then 5.0 g. of tri-*n*-butylborane was added. A known amount of oxygen was admitted through a flowmeter to the stirred solution. The amount of gas passing through the flask was noted on another flowmeter. The rate of oxygen passage was approximately 1 min. per molar equivalent of gas introduced. After the desired amount of oxygen had been passed into the flask the solution was well purged with nitrogen.

Analyses of solutions. The Dry Ice condenser was then replaced by a tube extending to the bottom of the flask which allowed a known volume of solution to be withdrawn from the flask. These aliquots were analyzed for peroxide iodometrically by the method of Siggia.[4]

Tri-*n*-butylborane, di-*n*-butyl(*n*-butoxy)borane, *n*-butyl(di-*n*-butoxy)borane and dissolved oxygen did not liberate iodine from sodium iodide under these conditions. The sol-

(2) R. C. Petry and F. H. Verhoek, *J. Am. Chem. Soc.*, **78**, 6416 (1956).

(3) A. G. Davies and M. H. Abraham, *Chem. & Ind. (London)*, 1622 (1957).

(4) S. Siggia, *Quantitative Organic Analyses Via Functional Groups*, John Wiley and Sons, Inc., New York, 1949, p. 101.

vents used did not form peroxides, as determined iodometrically, under experimental conditions.

Acknowledgment. The authors wish to acknowledge the valuable assistance of Mr. P. D. Wills.

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Reaction of 1-Bromo-2,3-epoxybutane with Phenol in the Presence of Boron Trifluoride

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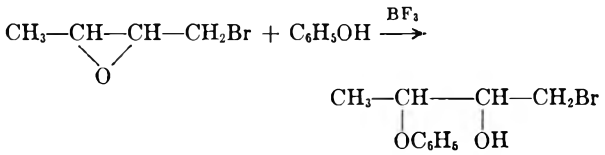
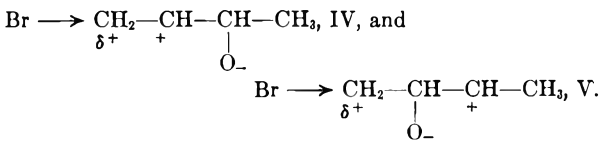
The reaction between 1-bromo-2,3-epoxybutane, I, and phenol in basic solution has been reported[1] to yield 3-phenoxy-1,2-epoxybutane.

In the present work phenol was allowed to react with I in the presence of boron trifluoride to find whether the direction of epoxide ring opening was the same as that reported for the reaction conducted in basic medium. The product of the acid-catalyzed reaction was found to consist chiefly of 1-bromo-3-phenoxy-2-butanol, II.



Dehydrobromination[2] of II at room temperature produced 3-phenoxy-1,2-epoxybutane, III. Upon treatment with silver oxide, III was oxidized to 2-phenoxypropionic acid.

The acid-catalyzed opening[3] of the epoxide ring of I may proceed in either direction, giving two possible carbonium ions:



Species IV would be predicted to be the less stable ion because of the presence of two positive charges (one real, one partial) on adjacent carbon atoms. Since V leads to the formation of II, the adjacent charge rule[3a,4] may be used to explain the predominant formation of that isomer. Such an interpretation is successful in accounting for the exclusive formation of 3-phenoxy-1-chloro-2-propanol[5] during the reaction of epichlorohydrin with phenol in the presence of boron trifluoride.

EXPERIMENTAL

Boiling points and melting points are uncorrected. 1-Bromo-2,3-epoxybutane, b.p. 143–145°, was prepared by the method of Petrov.[6]

Reaction of 1-bromo-2,3-epoxybutane, I, *with phenol.* In a 1-l., three-necked flask was placed a solution of 94 g. (1 mole) phenol and 1 g. boron trifluoride dissolved in 500 ml. benzene. While the temperature was maintained in the range −2° to +2°, 37.7 g. (0.25 mole) of I were added dropwise and with vigorous agitation. The addition required about 30 min. After the addition of I was complete, the solution was stirred for an additional 30 min. Water was then added to destroy the catalyst. The water was removed and the benzene was distilled at reduced pressure. At 15 mm. pressure phenol was removed by distillation in the range 78–90°. The product was 36.7 g. (60% yield) of clear, colorless oil, b.p. 100–105° at 0.3 mm., $n_D^{22°}$ 1.5500, which was found to be 1-bromo-3-phenoxy-2-butanol, II. An attempt to oxidize this compound with sodium hypoiodite was not successful.

Anal. Calcd. for $C_{10}H_{13}O_2Br$: C, 49.10; H, 5.35; Br, 32.60. Found: C, 49.78; H, 5.56; Br, 32.52.

Dehydrobromination of 1-bromo-3-phenoxy-2-butanol, II. A mixture of 35.2 g. of II, 200 ml. ethanol, and 50 ml. of 6*N* sodium hydroxide was shaken vigorously at room temperature for 1 hr. One liter of water was then added, and the product was removed by three extractions with diethyl ether. Analysis of the aqueous phase by the Mohr method indicated 96% removal of the bromine. The ether solution of epoxide was washed with water until neutral and dried over anhydrous calcium sulfate. The residue after removal of the ether was fractionated through a short Vigreux column to give 18.8 g. (80% yield) of 3-phenoxy-1,2-epoxybutane, III, b.p. 74–77° at 0.3 mm., $n_D^{21°}$ 1.5188. The residue was 3 g. of yellowish oil which gave a positive qualitative test for bromine.

Oxidation of 3-phenoxy-1,2-epoxybutane, III. Oxidation of III was carried out by stirring 3 g. of III with 17 g. silver oxide and 50 ml. of 10% sodium hydroxide solution for 18 hr. on the steam bath. The metallic silver was removed by filtration, and the solution was acidified with dilute hydrochloric acid. Several ether extractions yielded 3 g. of crude crystals upon evaporation of the ether. Recrystallization from hot water produced 2.4 g. (79% yield) of 2-phenoxypropionic acid, m.p. 115–116°. The amide and anilide were prepared and found to melt at 131° and 117–118°, respectively. These values are in good agreement with the literature values for 2-phenoxypropionic acid and derivatives.

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(1) R. L. Rowton and R. R. Russell, *J. Org. Chem.*, **23**, 1057 (1958).

(2) The presence of 1-bromo-2-phenoxy-3-butanol was neither proved nor disproved. A small quantity of bromine-containing material remained after treatment of II with sodium hydroxide, but no attempt was made to identify it.

(3) Unimolecular ring opening of the oxonium complex is often accepted as the mechanism of such reactions in acid media. (a) A. A. Petrov, *Chem. Tech. (Berlin)*, **6**, 639 (1954). (b) S. Winstein and R. B. Henderson, *Heterocyclic Compounds*, R. C. Elderfield, Ed., John Wiley & Sons, New York, N. Y., 1950, Vol. 1, p. 37.

(4) A. E. Remick, *Electronic Interpretations of Organic Chemistry*, 2nd Ed., John Wiley & Sons, New York, N. Y., 1950, p. 150.

(5) E. Levas, *Ann. chim.*, [12], **3**, 145 (1948).

(6) A. A. Petrov, *J. Gen. Chem. (U.S.S.R.)*, **11**, 713 (1941).

Reaction of Ethylene Oxide with Sulfur Trioxide

G. E. Ham

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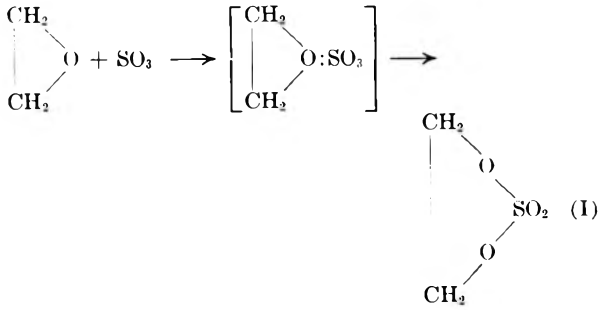
The reaction of certain aliphatic ethers with sulfur trioxide has been found to result in formation of the corresponding dialkyl sulfate. For example, Suter and Evans[1] report a yield of 85 to 90% of bis(2-chloroethyl) sulfate from bis(2-chloroethyl) ether and sulfur trioxide. They describe the reaction as proceeding through the formation of the ether coordination compound which undergoes rearrangement to the sulfate on heating. Should it be possible to form the sulfur trioxide–ethylene oxide coordination compound, one might expect this to rearrange easily to the five-membered ring compound, ethylene sulfate.



Ethylene oxide was treated with sulfur trioxide under a variety of conditions in an attempt to prepare ethylene sulfate. The only reaction system which did not result in excessive charring involved the use of 1,4-dioxane–sulfur trioxide addition compound in 1,4-dioxane. When one mole of ethylene oxide was treated with one mole of sulfur trioxide in 1,4-dioxane, a homogeneous solution was obtained which when mixed with cold water gave no acid. Removal of the solvent *in vacuo* gave a slightly colored, very viscous liquid. All attempts to crystallize this material failed. However, a 9.5% yield of the expected white crystalline ethylene sulfate could be sublimed *in vacuo* from the viscous liquid. On continued heating the heavy viscous liquid decomposed.

EXPERIMENTAL

To 200 ml. of dry redistilled 1,4-dioxane was added dropwise with cooling and stirring 19.3 g. (0.242 mole) of sulfur trioxide. By careful control of the temperature (*ca.* 10°) and rate of addition the sulfur trioxide could be added without charring. During addition the dioxane–sulfur trioxide addition compound precipitated from solution. After addition of sulfur trioxide was complete, ethylene oxide was passed slowly through the mixture which was stirred and cooled. When 0.25 mole of ethylene oxide had been added, the dioxane–sulfur trioxide addition compound had completely dissolved. The final volume of the reaction mixture was 210 ml.

A 5-ml. aliquot of this solution was added to about 50 ml. of water at room temperature and shaken vigorously. An oily layer separated from solution. This mixture was neutralized with less than 1 ml. of 0.100*N* sodium hydroxide solution.

The dioxane solution (50 ml.) was distilled under vacuum (2 mm.) until a pot temperature of 50° was reached. The residue (10.5 g.) was a dark viscous liquid. This material (1.69 g.) was heated to 70–80° in a micro sublimation apparatus at 2 mm. There was obtained 110 mg. (9.5%) of white crystalline ethylene sulfate, m.p. 96–97° (lit.,[2] m.p. 99°).

Anal. Calcd. for $C_2H_4O_4S$: C, 19.35; H, 3.25. Found: C, 19.86; H, 3.36.

Acknowledgment. The author wishes to thank Dr. O. C. Dermer for helpful discussions and S. A. Sims for able assistance.

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(1) C. M. Suter and P. B. Evans, *J. Am. Chem. Soc.*, 60, 536 (1938).

(2) Wilson Baker and F. B. Field, *J. Chem. Soc.*, 86 (1932).

Relative Basicities in the Series Dialkyl Sulfide, Sulfoxide, and Sulfone Toward Boron Trifluoride

Robert G. Laughlin

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Strong evidence has been obtained that in the series R-S-R′, R-SO-R′, R-SO_2R′ (R = *n*-$C_{12}H_{25}$, R′ = CH_3 or C_2H_5) the sulfoxide is considerably more basic toward the Lewis acid boron trifluoride than either the sulfide or sulfone. Each formed a 1:1 complex on passing boron trifluoride into a cold benzene solution, as indicated by abrupt saturation of the solution when close to one molar equivalent had been added. The benzene was then evaporated at aspirator pressure at or below room temperature. Only the sulfoxide formed a vacuum-stable complex. The starting sulfide and sulfone were recovered in the other two cases. Thus the dissociation of the sulfoxide complex must be much lower than that of the sulfide and sulfone complexes, *i.e.*, the sulfoxide is the strongest base towards boron trifluoride.

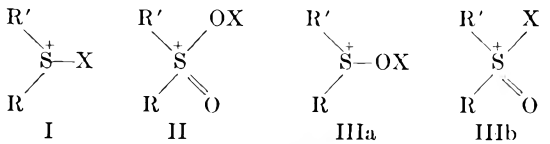
The order of basicity in this series toward boron trifluoride and toward protons will not necessarily correspond, especially if steric factors are involved.[1] However, Wimer[2] has obtained results from nonaqueous titrations which indicate that the order is the same. His data, combined with the known pK_A of protonated phosphine oxides (R_3POH^+),[3] would

(1) E. A. Braude and F. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press, Inc., N. Y., (1955), pp. 634ff.

(2) D. C. Wimer, *Anal. Chem.* 30, 2060 (1958).

suggest that the pK_A of R_2SOH^+ is probably slightly less than zero.[4]

The order of basicity in this series has a bearing on the structure of the sulfoxide complex. In the sulfide and sulfone complexes the acceptor atom (proton or boron trifluoride) is unambiguously on sulfur or on oxygen respectively (I and II), whereas it could be on either atom in the sulfoxide complex (IIIa or IIIb).



(X = —H or $—BF_3^-$)

However, a consistent picture of the observed trend in basicity is obtained only if the acceptor atom is assumed to reside on oxygen in the sulfoxide (IIIa). If it were on sulfur, the sulfoxide should be *less* basic than either the sulfide or sulfone.[5] In agreement with the inference above concerning the structure of the sulfoxide-acid complexes it has recently been demonstrated that the oxygen in dialkyl sulfoxides is more nucleophilic than the sulfur.[6]

It was observed that the hydrolysis of ethyl-*n*-dodecyl sulfoxide–boron trifluoride in water is readily reversible. If the complex is placed in water, a turbid suspension with a very low *p*H (1.6) is obtained. If this is extracted with chloroform, sulfoxide is recovered.[7] If the solution is freeze-dried, it is principally the complex that is recovered, as indicated by the infrared spectrum. These observations may be accounted for by the following equilibrium:

$$\underset{\displaystyle R'}{\overset{+}{R}SO\cdot\bar{B}F_3} + H_2O \rightleftharpoons \underset{\displaystyle R'}{R—SO} + H^+ + H\bar{O}BF_3$$

As this sulfoxide is insoluble in water, the equilibrium is probably driven far to the right (as indicated by the low *p*H) and the sulfoxide may be readily extracted. However, the removal of water by freeze-drying apparently shifts the equilibrium to the left. Hydroxyfluoboric acid, the postulated acidic product, is known to be a strong acid.[8]

EXPERIMENTAL

Preparation of compounds. Methyl- and ethyl-*n*-dodecyl sulfide were prepared by the method of Kuhn and Dann[9] from the lower alkyl mercaptan and dodecyl bromide.

The sulfoxides were prepared by nitric acid oxidation of the sulfide.[10] *Methyl-n-dodecyl sulfoxide* was found to melt at 59–61°.

Anal. Calcd. for $C_{13}H_{28}SO$: S, 13.8. Found: S, 13.7.

Ethyl-n-dodecyl sulfoxide was found to melt at 52–52.5°.

Anal. Calcd. for $C_{14}H_{30}SO$: S, 13.0. Found: S, 12.9.

The principal infrared band of these sulfoxides is at 9.9μ. The very intense sulfone bands at 7.9 and 9.0μ were absent. The infrared spectra were taken on mulls.

Methyl-n-dodecyl sulfone was prepared by heating the sulfide with a 50% excess of 10% hydrogen peroxide in aqueous acetic acid (prepared from 60% hydrogen peroxide and glacial acetic acid) on the steam bath for 1 hr., diluting with several volumes of water, filtering, and drying. The compound was found to melt at 80–82°.

Anal. Calcd. for $C_{13}H_{28}SO_2$: S, 12.9. Found: S, 12.7. The compound was transparent in the infrared at 9.9μ, indicating the absence of sulfoxide.

Reactions with boron trifluoride. Methyl-*n*-dodecyl sulfone (0.036 mole) was dissolved in 250 ml. of benzene in a 500 ml. 3-neck flask fitted with gas addition tube, stirrer, thermometer, and a drying tube on the open neck. Boron trifluoride was passed into the solution at 10–15°; when 0.043 mole (1.2 moles/mole of sulfone) had passed in, boron trifluoride fumes abruptly commenced emerging from the drying tube. When the amount used was corrected for the amount necessary to displace the air in the flask, the amount absorbed was one mole/mole sulfone within weighing error. When this solution was evaporated to dryness at room temperature and slightly below in a rotating Rinco evaporator at aspirator pressure, a crystalline solid was obtained which was shown by infrared to be essentially pure recovered sulfone.

Methyl-*n*-dodecyl sulfide behaved exactly like the sulfone. One mole of boron trifluoride was absorbed and the sulfide was recovered on evaporation of solvent.

Ethyl-*n*-dodecyl sulfoxide[11] also absorbed one mole of boron trifluoride. The residue, after evaporation of benzene, was semisolid at room temperature. It had two very broad infrared bands at 8.6–9μ and 11.3–11.6μ. Similar bands are found in dimethyldodecylamine-boron trifluoride (prepared in the same way as the sulfoxide complex) at 8.7 and 10.8–11.0μ.

Anal. of the sulfoxide complex: Calcd. for $C_{14}H_{30}SOBF_3$: S, 11.2; B, 3.45. Found: S, 10.3;[12] B, 3.5.

When the sulfoxide complex was mixed with water, the turbid solution extracted with chloroform, and the chloroform evaporated after drying over calcium sulfate, crystal-

(3) P. Nylen, *Z. Anorg. allgem. Chem.*, **246**, 227 (1941).

(4) F. G. Bordwell and P. J. Boutan [*J. Am. Chem. Soc.* **79**, 717 (1957)] have obtained evidence that sulfoxides are largely protonated by *ca.* 1.5% trifluoroacetic acid in acetic acid.

(5) The sulfur atom in the sulfoxide is electron deficient compared to the sulfide sulfur because of the highly polar S—O bond, whose bond moment (*ca.* 2.8 D) is directed towards oxygen. Therefore the sulfoxide should be *less* basic than the sulfide if the acceptor were on sulfur in the sulfoxide. Similarly, in comparing a sulfoxide complex with the acceptor on the electron deficient sulfur and the sulfone complex with the acceptor on an electron rich oxygen, one would expect from electrical considerations that the latter would be the stronger complex, *i.e.*, the sulfone would be the stronger base. The second predicted relationship is probably not so well founded as the first, because in the first the donor atom is sulfur in both cases, while in the second it is sulfur in one case and oxygen in the other. This does not alter, however, the electrical status of the atoms in being electron deficient or abundant, and this is assumed to play the major role.

(6) S. G. Smith and S. Winstein, *Tetrahedron* **3**, 317 (1958); R. Kuhn and H. Trischmann, *Ann.* **511**, 117 (1958).

(7) This observation, incidentally, provides evidence that the complex formation is a simple Lewis acid-base interaction.

(8) C. A. Wamser, *J. Am. Chem. Soc.* **70**, 1209 (1948).

(9) R. Kuhn and O. Dann, *Ber.* **73B**, 1092 (1940).

(10) I. D. Webb, U. S. Patent 2,787,595, April 2, 1957.

(11) Methyl-*n*-dodecyl sulfoxide behaved similarly but was not so extensively investigated.

(12) The compound exploded when mixed with sodium peroxide in the standard Parr-bomb analysis for sulfur. A successful analysis, although somewhat low, was obtained by enclosing the sample in a gelatin capsule before carrying out the oxidation.

line sulfoxide was recovered. Freeze-drying the turbid suspension re-formed the complex largely, as indicated by infrared spectra. A suspension of 0.5 g. of complex in 50 ml. of distilled water had a *p*H of 1.6.

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Derivatives of Sulfenic Acids. XL. Phenyl Migration during Sulfenylation of *trans*-Stilbene

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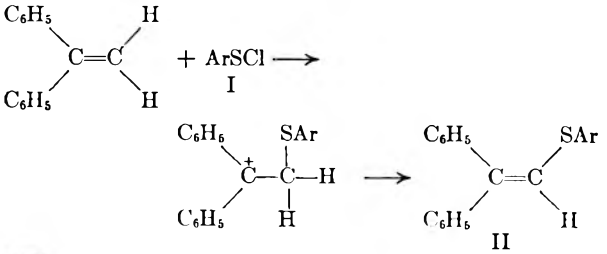
Received August 31, 1959

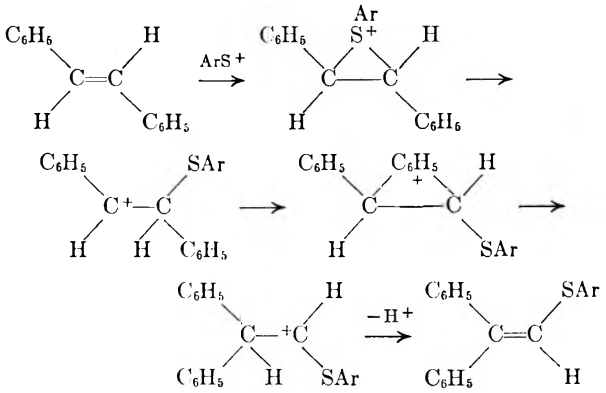
In connection with a study of the kinetics of addition of 2,4-dinitrobenzenesulfenyl chloride, I, to *cis* and *trans*-stilbene, we encountered a migration of the phenyl group in the reaction of I with *trans*-stilbene at elevated temperatures. To our knowledge, this is the first example of a phenyl group rearrangement during the course of addition of a sulfenyl halide to an olefin.

Previous studies[1] have shown deviations from 1:1 adduct formation with 2,4-dinitrobenzenesulfenyl chloride, I, and olefins. The product of the reaction of 4-methoxystyrene and I were governed by the reaction temperature, the vinyl sulfide being formed at the higher temperatures,[2] and olefins like 1,1-diphenylethylene were found also to lead to the vinyl sulfide.[1]

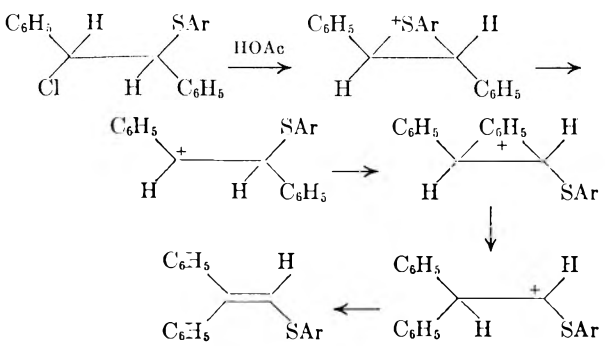
It has now been found that the product from the reaction of I with *trans*-stilbene in refluxing acetic acid was not the 1:1 adduct, but a vinyl sulfide. Oxidation of the vinyl sulfide to benzophenone and desulfuration of the vinyl sulfide with Raney nickel to 1,1-diphenylethane showed the vinyl sulfide to be 1,1-diphenyl-(2′,4′-dinitrophenylthio)-ethane, which is the expected product from 1,1-diphenylethylene assuming addition of ArS^+ and subsequent loss of a proton; Ar = 2,4-dinitrophenyl. The product from 1,1-diphenylethylene and the rearrangement product from *trans*-stilbene were shown to be identical.



The following sequence is suggested to explain the rearrangement with *trans*-stilbene, involving a cyclic episulfonium ion, subsequent participation by phenyl, followed by loss of a proton.



Since acetolysis of the 1:1 adducts of I and olefins have been postulated to proceed through a sulfonium ion with sulfur participation,[3] acetolysis of the 1:1 adduct in acetic acid would be expected to yield the vinyl sulfide. Acetolysis of the 1:1 adduct yielded the vinyl sulfide and some β-acetoxy compound while acetolysis with sodium acetate added yielded only the β-acetoxy compound. SN_2 acetolysis conditions with sodium acetate in anhydrous acetone, failed to give detectable reaction. The sequence leading to the same product, as shown above from *trans*-stilbene, is given below.



Systems such as those used in this study can thus permit interesting comparisons of the relative participations by neighboring sulfur and aryl groups.

EXPERIMENTAL

Reaction of 2,4-dinitrobenzenesulfenyl chloride, I, with trans-stilbene. To a refluxing solution of dry acetic acid was

(1) N. Kharasch, *J. Chem. Ed.*, **33**, 585 (1956); *Cf.* also, R. B. Langford and D. D. Lawson, *J. Chem. Ed.*, **34**, 510 (1957) and N. Kharasch, *Organic Sulfur Compounds, Vol. I*, Pergamon Press, New York–London. (In press).

(2) W. L. Orr and N. Kharasch, *J. Am. Chem. Soc.*, **78**, 1201 (1956).

(3) A. J. Havlik and N. Kharasch, *J. Am. Chem. Soc.*, **78**, 1207 (1956).

added *trans*-stilbene (2.31 g., 0.0128 mol.) and 3.74 g. of I. The reaction mixture was refluxed 2 hr., during which time the solution turned dark. The reaction mixture was aspirated to dryness, dissolved in benzene, and chromatographed on a column of alumina (2.5 × 20 cm.) using a 50% by volume mixture of benzene and mixed alkanes (b. range 50–60°) to elute the first fraction. Methanol was gradually added to elute the second fraction.

Fraction (1) gave 2.8 g., m.p. 133–134°.

Fraction (2) gave 0.7 g., m.p. 122–125°. The separations indicate that two distinct products are formed. Both products gave negative Beilstein tests, and had similar infrared spectra but 2 showed an absorption maximum in the 5.9μ region while 1 did not.

Elemental analysis of 1 indicated that it was the vinyl sulfide (compound II, in text).

Anal. Calcd. for $C_{20}H_{14}N_2O_4S$: C, 63.47; H, 3.73. Found C, 63.70; H, 3.55.

Elemental analysis of 2 indicated that it was the β-acetoxy compound.

Anal. Calcd. for $C_{22}H_{18}N_2O_6S$: C, 60.26; H, 4.14. Found: C, 60.33; H, 4.01.

Reaction of 2,4-dinitrobenzenesulfenyl chloride with 1,1-diphenylethylene. Reaction of 5.0 g. of I and 3.3 g. of 1,1-diphenylethylene, in 40 ml. of dry acetic acid for 24 hr. at room temperature yielded crude II, which after recrystallization from 95% ethanol yielded 5.5 g. of product, m.p. 134–135° (80%).

Anal. Calcd. for $C_{20}H_{14}N_2O_4S$: C, 63.47; H, 3.73. Found: C, 63.70; H, 3.55.

This product was identical with the one from *trans*-stilbene, as shown by infrared spectra and mixture melting point.

Acetolysis of the 1:1 adduct in refluxing acetic acid. To a refluxing solution of dry acetic acid was added 2.1 g. of 1:1 adduct. The reaction mixture was refluxed 4 hr. Employing a similar chromatographic procedure as above, it was found that the 1:1 adduct was converted into 70% vinyl sulfide, II, and 10% of the acetoxy compound of fraction 2. A 10% loss in work-up was sustained.

Acetolysis of the 1:1 adduct with sodium acetate and acetic acid. To a refluxing solution of dry acetic acid was added 5.0 g. of anhydrous sodium acetate and 1.6 g. of 1:1 adduct. The reaction mixture was refluxed 4 hr. The yellow reaction mixture was aspirated nearly to dryness and poured onto ice. The yellow material was collected and recrystallized from methanol. The product melted at 125–126°; yield, 1.4 g.; 89%.

Desulfuration and reduction of the vinyl sulfide with Raney nickel. A solution of 4.0 g. (0.011 mol.) of the vinyl sulfide was dissolved in 50 ml. of absolute ethanol containing 15 g. of Raney nickel. The solution was refluxed 2 hr. on the steam bath. About 5 g. more of catalyst was added, and refluxing continued an additional hour. The mixture was filtered through diatomaceous earth, and the catalyst washed with two 15-ml. portions of absolute ethanol. The washings were added to the filtrate, which was then concentrated in an air stream to dryness. The dark oil was distilled under reduced pressure yielding a colorless oil, b.p. 110°/2 mm., m.p. −8° (1.0 g., 57%).

Oxidation of the vinyl sulfide. The vinyl sulfide (4.0 g., 0.011 mol.) was added to an aqueous solution of potassium dichromate. Concentrated sulfuric acid was added to the solution. An hour later, the solution was poured onto ice. The white crystals were collected and reprecipitated from 95% ethanol with ice to give 1.6 g. of product, m.p. 47–48° (84%). This product was shown to be benzophenone by infrared spectra and mixture melting point.

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Organic Disulfides and Related Substances. II. 2,4,6-Triisopropylphenyl Disulfide, the 2,4,5-Isomer, and Related Compounds[1]

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The first disulfide named in the title is new, the second has been mistaken for the first, and in our opinion, the disulfides and related compounds deserve further study and comment.

Triisopropylbenzene made from propylene and benzene with sulfuric acid as a catalyst has been shown to consist mainly of the 1,2,4-isomer.[2] Evidently, Costanza and co-workers[3] believed that the commercial mixture was mainly the symmetrical 1,3,5-isomer for the properties of their sulfonyl chloride and disulfide made from the hydrocarbon, reported as the 2,4,6-isomers, agreed well with the physical properties of our 2,4,5-isomers. Our confidence in the correctness of the structures given here is based on three facts: (1) The equilibration of a trialkylbenzene with large amounts of aluminum chloride (which provided our 1,3,5-triisopropylbenzene) gives predominantly the symmetrical 1,3,5-isomer, as this isomer is the strongest Lewis base and forms the most stable Lewis salt.[2,4,5] (2) The hydrocarbon obtained from the equilibration in this work differed considerably in physical properties from the original hydrocarbon. And both hydrocarbons gave derivatives which had sharp melting ranges and were distinctly different from each other. (3) 2,4,5-Triisopropylbenzenesulfonyl chloride (I) and its 2,4,6-isomer (II) were made by the method of Newton and agreed well in physical properties and derivative formation with his descriptions.[6]

The study of models of 2,4,6-triisopropylbenzenesulfonyl chloride (II) suggested that the chlorosulfonyl group would be tilted out of the ring plane so that the rear of the group would be more exposed to the attack of a nucleophilic reagent than that of the 2,4,5-isomer which is in the plane of the ring and is hindered by a ring substituent. The solvolysis of such sulfonyl chlorides has been shown

(1) Supported in part by funds provided by the Office of Ordnance Research, U. S. Army. Abstracted from the M.S. thesis of D.C., Vanderbilt University, January, 1956. Paper I. L. Field and J. E. Lawson, *J. Am. Chem. Soc.*, **80**, 838 (1958).

(2) A. Newton, *J. Am. Chem. Soc.*, **65**, 320 (1943).

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

(4) J. P. Wibaut and B. Paulis, *Rec. trav. chim.*, **77**, 769 (1958).

(5) For references bearing on the general problem. D. A. McCaulay and A. P. Lien, *J. Am. Chem. Soc.*, **74**, 6246 (1952); **77**, 1803 (1955); **79**, 5953 (1957); H. C. Brown, B. A. Bolto, and F. R. Jensen, *J. Org. Chem.*, **23**, 417 (1958).

(6) A Newton, *J. Am. Chem. Soc.*, **65**, 2439 (1943).

to proceed by a concerted (SN-2) mechanism.[7] If one assumes that the steric inhibition of resonance of a sulfur atom with the benzene ring is a negligible influence[8] and that the attack of water is made on the sulfur atom on the side opposite to the chlorine atom, one would predict a faster rate of hydrolysis for the 2,4,6-isomer than for the 2,4,5-isomer. The results in the Experimental show that the 2,4,6-isomer does hydrolyze almost twice as rapidly as the 2,4,5-isomer.

The sulfonyl chlorides were reduced to the thiols by lithium aluminum hydride and the latter reoxidized without isolation to the disulfides. We were expecting that 2,4,6-triisopropylphenyl disulfide in comparison with phenyl disulfide would show a substantial difference in ease of formation from the thiol or in ultraviolet absorption properties. Neither expectation was realized. Both the 2,4,5- and 2,4,6-disulfides formed with ease, and the absorption spectra, given in the Experimental, showed differences that could be attributed merely to inductive properties of alkyl groups alone. Apparently, groups larger than an isopropyl or phenyl[9] are necessary to prevent or hinder disulfide formation.

EXPERIMENTAL[10]

1,2,4-Triisopropylbenzene. Triisopropylbenzene (Distillation Products Industries, Technical) was separated by very slow distillation through a 10-in. carborundum-packed column. The middle fractions of constant refractive index were taken as the desired compound, b.p. 238–240° (754 mm.), n_D^{20} 1.4915, reported[11] b.p. 240–242° at 753 mm., n_D^{20} 1.4924.

1,3,5-Triisopropylbenzene. 1,2,4-Triisopropylbenzene (n_D^{20} 1.4915) was isomerized to the 1,3,5 isomer by the method of Newton[2] and others.[4] The first isomerization with anhydrous aluminum chloride appeared to be incomplete as judged from refractive indices of the distillate. The distillate therefore was subjected to a second isomerization with aluminum chloride. The 1,3,5-triisopropylbenzene fraction obtained by isolation and distillation had b.p. 228–230° (754 mm.) and a constant refractive index, n_D^{20} 1.4884, reported[4] n_D^{20} 1.4882.

2,4,5-Triisopropylbenzenesulfonyl chloride (I). This compound, made by the method of Newton,[6] was less pure (m.p. 137–140°) than that of Newton, m.p. 141.5–142.2°. Derivatives of I, however, checked well with the literature[6]: sulfonamide m.p. 155–156°, sulfonanilide m.p. 187–188°. Recrystallization of I from isooctane proved wasteful, but small portions could be purified by partial hydrolysis. I (6 g.) was dissolved in 100 ml. of 80% aqueous acetone, and the solution held at 50° for 1 hr., diluted with water to the point of cloudiness, and cooled. After filtration, drying, and recrystallization from isooctane, 3.5 g. of I was obtained, m.p. 141–141.8°.

2,4,6-Triisopropylbenzenesulfonyl chloride (II). This compound, made by the method of Newton,[6] melted at 95–97°, reported[6] m.p. 97.2–98.4°. Derivatives checked well with the literature:[6] sulfonamide m.p. 118.5–119.5°; sulfonanilide m.p. 163–164°. Partial hydrolysis of 6 g. of II (as with I) gave 2.8 g. of pure II, m.p. 96.8–97.5°.

2,4,5-Triisopropylphenyl disulfide (III) *and the 2,4,6-isomer* (IV). Compound I (18 g., 0.06 mole) was dissolved in 180 ml. of absolute ether contained in a 3-necked flask fitted with condenser, stirrer, and dropping funnel and protected from moisture by calcium chloride tubes. Lithium aluminum hydride (5.3 g., 0.14 mole) in 115 ml. of ether was added dropwise over a period of 25 min. to the stirred solution of I. The initial hydride concentration in ether was determined by weighing the residue from a 5-ml. aliquot. Vigorous refluxing and hydrogen evolution were noted during the addition. After a reflux period of 4 hr., 50 ml. of an equal mixture of benzene and ethanol was cautiously added dropwise to destroy excess hydride. Following this addition, about 200 ml. of 10% aqueous sulfuric acid was added to dissolve the lithium salts, and 75 ml. of benzene was added to dissolve the thiol. The benzene solution was separated from the aqueous acid solution and washed free of acid with aqueous sodium bicarbonate. For oxidation to the disulfide, 8.8 g. (0.07 mole) of iodine in 50 ml. of benzene was added to the thiol in benzene. After standing for 8 hr., during which time it was washed twice with water to remove hydrogen iodide, the mixture was washed with a 5% sodium bisulfite solution to destroy excess iodine, dried with sodium sulfate, and evaporated. A dark oil was obtained which solidified after immersion in Dry Ice and scratching. Recrystallization from 40 ml. of methanol gave large yellow plates of III, 7 g., 50%, m.p. 75.4–76.2°.

Anal. Calcd. for $C_{30}H_{46}S_2$: C, 76.53; H, 9.85. Found: C, 76.64; H, 9.83.

2,4,6-Triisopropylphenyl disulfide (IV). IV was made in the same manner as the previous disulfide except that the compound crystallized without cooling in Dry Ice: light yellow plates, 8.4 g., 60%, m.p. 91.2–92.0°. Costanza *et al.* report m.p. 79–79.5°.[3]

Anal. Calcd. for $C_{30}H_{46}S_2$: C, 76.53; H, 9.85. Found: C, 76.90; H, 10.05.

Ethyl 2,4,5-triisopropylbenzenesulfonate (V) *and the 2,4,6-isomer* (VI). By dissolving the appropriate sulfonyl chloride in alcohol and allowing the solution to stand at 50° overnight, the ethyl ester was obtained in over 70% yields. The 2,4,5-ester (V), recrystallized from hexane, melted at 99–100°.

Anal. Calcd. for $C_{17}H_{28}O_3S$: C, 65.34; H, 9.03. Found: C, 65.61; H, 9.18.

The 2,4,6-isomer, recrystallized from hexane, melted at 58–59°.

Anal. Calcd. for $C_{17}H_{28}O_3S$: C, 65.34; H, 9.03. Found: C, 64.98; H, 8.87.

Hydrolysis rates of the sulfonyl chlorides, I *and* II. About 0.6 g. samples (weighed accurately) were added to 125 ml. of 80% by volume of acetone, 20% water held at 51.8°. Aliquots (25 ml.) were taken at .5 hour intervals at the beginning and hour intervals near the end of the hydrolysis. The aliquots were quenched with 25 ml. of acetone cooled to ice temperature and titrated with standard base using a *p*H meter to detect the end-point. Duplicate runs were made, and the average values, as pseudo first-order rate constants at 51.8° in 80% aqueous acetone, are given below:

Sulfonyl Chloride	k_1 (min.$^{-1}$)	Half-life (min.)
2,4,5-Triisopropylbenzene-(I)	2.3×10^{-3}	301
2,4,6-Triisopropylbenzene-(II)	3.9×10^{-3}	178
4-Bromobenzene-	15.0×10^{-3}	46

(7) E. Tommila and P. Hirsjarvi, *Acta Chem. Scand.*, **5**, 659 (1951); H. K. Hall, Jr., *J. Am. Chem. Soc.*, **78**, 1450 (1956).

(8) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **72**, 1292 (1950).

(9) K. Dimroth and G. Oosterloo, *Angew. Chem.*, **70**, 165 (1958).

(10) All melting points are corrected and boiling points uncorrected. Analyses were by Micro-Tech Analytical Laboratories, Skokie, Ill.

(11) G. Egloff, *Physical Constants of Hydrocarbons*, Reinhold Publishing Corp., New York, Vol. III, p. 167 (1946).

Ultraviolet spectra of disulfides. The ultraviolet spectra were obtained with the Beckman Recording Spectrophotometer, Model DK, using isooctane as a solvent. The curves are recorded in a thesis,[1] and the maxima: diphenyl disulfide, 241 (4.33), [λ, (log ε)] in mμ are: 272 (3.57), 302 (3.26); bis-(2,6-dimethylphenyl) disulfide, 225 (4.02), 260 (3.89), 305 (2.78); bis-(2,4,5-triisopropylphenyl) disulfide, 244 (4.18), 285 (3.56), 344 (284): bis-(2,4,6-triisopropylphenyl) disulfide, 232 (4.18), 270 (4.07), 310 (3.51). All of the disulfides except diphenyl show a low order of absorption (log ε *ca.* 0.2–0.4) at *ca.* 500–700 mμ, which increases as the ultraviolet region is approached, and are pale yellow. The absorption spectrum of diphenyl disulfide checked well with that recorded.[12]

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(12) H. P. Koch, *J. Chem. Soc.*, 397 (1949); G. Leandri and A. Tundo, *Ann. Chim.* (Rome) **45**, 180 (1955); [C.A. **49**, 12,960 (1955)]; R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, New York, 1951, p. 152.

Bis(2-aminoethyl) Dithiolcarbonate Dihydrochloride: Intermediate in the Hydrolysis of 2-Thiazoline-2-thiol

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The acid hydrolysis of 2-thiazoline-2-thiol (I) to 2-aminoethanethiol hydrochloride (II) has been known for some time.[2,3] When conducted in a sealed container at about 150°, a four to six hour reaction period generally sufficed to give quantitative yields of II. Because we desired some 2-aminoethanethiol hydrochloride, we undertook a study of the hydrolysis in refluxing, concentrated hydrochloric acid. At atmospheric pressure the reaction requires approximately two weeks for completion. Intermediate reaction periods produced a readily separable mixture of 2-aminoethanethiol hydrochloride and a hitherto unreported material, compound III. Reaction times of about twenty-four hours resulted in recovery of substantial amounts of starting material and gave good yields of compound III with practically no 2-aminoethanethiol hydrochloride. The results of several hydrolyses, as summarized in Table I, and the evidence which characterizes compound III as bis(2-aminoethyl) dithiolcarbonate dihydrochloride are reported in this paper.

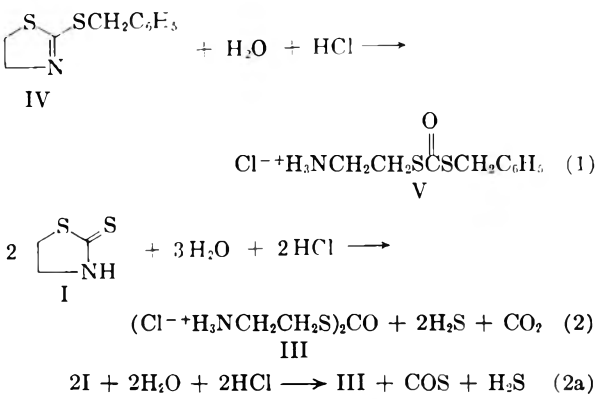
While the facile hydrolysis of 2-alkylthio- or 2-arylthio-2-thiazolines to the corresponding 2-aminoalkyl dithiolcarbonate hydrochlorides[4,5] (equation 1) is well known, the conversion of 2-thiazoline-2-thiol to a similar type of compound (equations 2 and 2a) has not been reported.

TABLE I

ACID HYDROLYSIS PRODUCTS OF 2-THIAZOLINE-2-THIOL

Time, Hrs.	Yield, % I	II[a]	III[a]
19.5	61.3	0.0	57.0
20[b]	60.2	9.9[c]	71.5
90	12.9	45.2	33.4
336	0.0	94.5	0.0

[a] Yields are corrected for recovered I. [b] Conducted with a mixture of 0.5 mole each of I and II. [c] Yield corrected for original II present.



Compound III can be obtained either as a crystalline hydrate or as an anhydrous salt. It is quite soluble in water but is only sparingly soluble in ethanol and common organic solvents. Microanalyses indicate an empirical formula of $C_5H_{14}ON_2S_2Cl_2$. Van Slyke amino nitrogen and Volhard chloride determinations further showed that compound III must be a dihydrochloride containing two primary amino groups. An equivalent weight of 126 (chloride content) and a neutral equivalent of 257 indicated that $C_5H_{14}ON_2S_2Cl_2$ (M.W. = 253) was very probably the molecular formula. The presence of a single oxygen atom in a carbonyl group was inferred from analytical data and the presence of a strong, infrared absorption band at 1645 cm.$^{-1}$

The chemical behavior of compound III, which at first may seem incongruous, can best be explained by its formulation as bis(2-aminoethyl) dithiolcarbonate dihydrochloride. It is obtained in highest yield and free from 2-aminoethanethiol hydrochloride in the early stages of the hydrolysis. Like aminoethyl alkyl dithiolcarbonate hydrochlorides generally[4-6] III is rather resistant to further acid

(1) Address correspondence to Department of Chemistry, John Carroll University, Cleveland 18, Ohio.

(2) S. Gabriel and E. Leupold, *Ber.*, **31**, 2832 (1898).

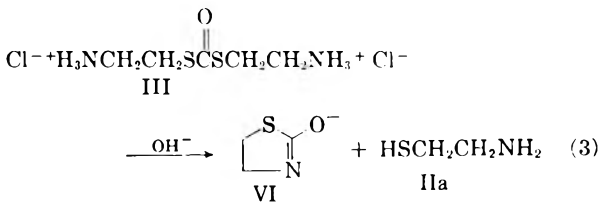
(3) E. J. Mills and M. T. Bogert, *J. Am. Chem. Soc.*, **62**, 1173 (1940).

(4) J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 3094 (1952).

(5) J. M. Sprague and A. H. Land, *Heterocyclic Compounds*, R. C. Elderfield, ed., John Wiley and Sons, New York, N. Y., 1957, Vol. 5, p. 696.

(6) H. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 2071 (1951).

hydrolysis; however, it ultimately is converted quantitatively to 2-aminoethanethiol hydrochloride. While a slightly acidic solution of III does not react with lead acetate or iodine,[7] in basic solution it undergoes an eliminative-recyclization reaction peculiar only to 2-aminoalkyl substituted dithiolcarbonates.[4,6] This reaction is illustrated in equation 3.



The formation of the anion of 2-thiazolidinone (VI) accounts for the neutral equivalent of III and the elimination of aminoethanethiol (IIa) gives rise to the quantitative reaction with iodine and a positive sodium nitroprusside test.[7]

Finally, authentic 2-aminoethylbenzyl dithiolcarbonate hydrochloride (V) was prepared and its infrared spectrum was compared with that of III. The correlation of the significant bands, presented in Table II, is excellent. Thus, there is little doubt that this new compound isolated from the acid hydrolysis of 2-thiazoline-2-thiol is bis(2-aminoethyl) dithiolcarbonate dihydrochloride (III).

TABLE II

INFRARED COMPARISON OF COMPOUNDS III AND V

III Bands ($cm.^{-1}$)	V Bands ($cm.^{-1}$)	Assignment
3360		OH stretch, present only in hydrate
1735	1740	Overtones of 875 and 885 bands respectively
1645	1655	C=O stretch
1600	1585	NH bending in NH_3^+
1525	1525	
875	885	S—C—S antisymmetric stretch

The isolation of III would seem to indicate that the hydrolysis of 2-thiazoline-2-thiol is considerably more complex than might be anticipated. The resistance of III to further acid hydrolysis may also be the reason for the over-all sluggishness of the reaction. The formation of bis(2-aminoethyl) dithiolcarbonate dihydrochloride in this reaction apparently requires more than one molecule of 2-thiazoline-2-thiol and raises interesting questions regarding the mechanistic path of the process. In the absence of a detailed kinetic examination of this reaction, we are not prepared to speculate further on the probable mechanism for the acid hydrolysis of 2-thiazoline-2-thiol to bis(2-aminoethyl) dithiolcarbonate dihydrochloride and 2-aminoethanethiol hydrochloride.

(7) N. D. Cheronis and J. B. Entricken, *Semimicro Qualitative Organic Analysis*, T. Y. Crowel Co., N. Y., 1947, pp. 140-141.

EXPERIMENTAL

Bis(2-aminoethyl) dithiolcarbonate dihydrochloride (III). A mixture of 119 g. (1.0 mole) of 2-thiazoline-2-thiol and 250 ml. of conc. hydrochloric acid was heated under reflux (115°) for 90 hr. The resulting solution, upon prolonged chilling, deposited 15.4 g. (12.9%) of starting material which was removed by vacuum filtration and washed with a small portion of ice-cold water. The filtrate and washings were combined and vacuum concentrated (*ca.* 90° and 20 mm.) to a pale yellow syrup. This was treated successively with 200 ml. of 1:1 ethanol-benzene, and two 100-ml. portions of ethanol with vacuum concentration after each treatment. The resulting solid was suspended in 100 ml. of hot absolute ethanol and filtered. The filter cake was washed with a total of 250 ml. of absolute ethanol and dried to give 36.8 g. (33.4% corrected for recovered I) of bis(2-aminoethyl) dithiolcarbonate dihydrochloride, m.p. 198.7–199.9° with gas evolution.

Vacuum concentration of the combined filtrate and ethanol wash liquor produced a yellow syrup. This was dissolved in 50 ml. of boiling, absolute ethanol, brought to the cloud-point with anhydrous ether and stored at 5° over night. The resulting, slightly yellow crystalline solid was removed by vacuum filtration, washed with two 100-ml. portions of anhydrous ether, and dried in a desiccator to give 44.7 g. (45.2% corrected for recovered I) of impure 2-aminoethanethiol hydrochloride, m.p. 65.4–67.4° (lit.[3] m.p. 70.2–70.9°).

A representative analytical sample of III was obtained by dissolving the product obtained in the 19.5 hr. reaction (*cf.* Table I), m.p. 204.6–205.6° with gas evolution, in a minimum of hot water, filtering, and diluting with approximately 10 volumes of 95% ethanol. After storage at 5°, the solution deposited a nicely crystalline hydrate (infrared band at 3360 $cm.^{-1}$) which, upon drying at 100° and 0.2 mm. for 24 hr., gave the anhydrous salt (no band at 3360 $cm.^{-1}$). Both forms melted at 204–205.2° with gas evolution.

Anal. Calcd. for $C_5H_{14}ON_2S_2Cl_2$: C, 23.72; H, 5.57; N, 11.06; S, 25.32; Cl, 28.00. Found: C. 23.94, 23.69; H, 5.28, 5.54; N, 11.09, 11.40 (Kjeldahl), 14.55, 14.62 (Van Slyke); S, 24.68, 24.97; Cl, 28.02, 28.94 (Carius), 27.68 (Volhard).

Neutral equivalent of III. A solution of 0.4658 g. of III was made basic by the addition of 45.0 ml. of 0.100*N* sodium hydroxide. After a brief storage period, the solution was back-titrated with 0.100*N* hydrochloric acid. A total of 26.9 ml. of acid was required to reach the break in the *p*H titration curve. This corresponds to an initial consumption of 18.1 ml. of base or a neutral equivalent of 257 ($C_5H_{14}ON_2S_2Cl_2$ = 253).

Titration with standard iodine solution. Bis(2-aminoethyl) dithiolcarbonate dihydrochloride (5.06 g.) was suspended in 150 ml. of 95% ethanol. The suspension was made basic by the addition of 80 ml. of 1*N* sodium hydroxide, then made up to 250 ml. with ethanol. After storage for 3 hr. at 25°, a 10 ml. aliquot was withdrawn and acidified with 3.3 ml. of 0.100*N* hydrochloric acid. This sample consumed 7.76 ml. of 0.0985*N* iodine solution which corresponds to the liberation of 95.6% of the theoretical amount of aminoethanethiol based on equation 3.

Attempted hydrolysis of III. A solution of 10.0 g. of III in 50 ml. of conc. hydrochloric acid was heated under reflux for 46 hr. The resulting solution was vacuum concentrated (90° and 20 mm.) to a yellow solid. This was treated successively with 100 ml. of 1:1 ethanol-benzene and 50 ml. of ethanol with vacuum concentration after each treatment. The resulting solid was suspended in 150 ml. of boiling ethanol and vacuum filtered. The filter cake was washed with

several portions of ethanol, then ether, and dried to give 5.8 g. (58%) of recovered III, m.p. 201.9–203° with gas evolution. Additional small quantities of III separated from the mother liquor; however, no crystalline 2-aminoethanethiol hydrochloride was isolated.

2-Aminoethylbenzyl dithiocarbonate hydrochloride (V). A solution of 2-benzylthio-2-thiazoline[8] (41.9 g., 0.2 mole) in 500 ml. of 6*N* hydrochloric acid was heated under reflux for 2 hr. After storage at 0° for 1 hr., the crystalline product was removed by suction filtration and dried in a vacuum desiccator. The yield of V, m.p. 172.2–175.2° (lit.,[4] m.p. 175°), was 43.6 g. (82.8%). A sample recrystallized from hot glacial acetic acid melted at 177.9–178.7°.

Acknowledgment. The authors wish to express their thanks to Mr. Norman Colthup for assistance in interpreting the infrared data and to Dr. Julius Kuck and the staff of the Microanalytical Laboratory for the microanalyses.

(8) A. H. Goddin, U. S. Patent 2,516,313.

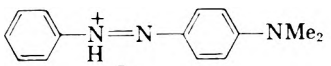
Absorption Spectra of the 4-Dimethylamino Derivatives of Azobenzene and Stilbene

G. E. Lewis

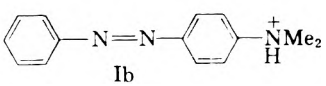
Received October 26, 1959

In neutral solution 4-dimethylaminoazobenzene displays a strong absorption band at 420 mμ which in acidic solution is replaced by one band at 520 mμ and another at 320 mμ.[1] Absorption in the 520 mμ region has been associated with the azonium cation (Ia) to which can be attributed a high degree of stabilization by charge-resonance[2] while the 320 mμ peak is considered to be due to the ammonium cation (Ib) essentially because azobenzene in neutral solution also absorbs strongly at 320 mμ.[1,3]

Further, it has been postulated[1,3] that both cations exist together in solution as a tautomeric equilibrium mixture (Ia⇌Ib); support for these interpretations has come from several sources.[4,5,6]



Ia



Ib

Klotz, Fiess, Chen Ho, and Mellody,[7] however, have questioned the validity of attributing the absorption at 520 mμ to the ion (Ia) and have attempted to reconcile addition of a proton solely at the dimethylamino- group (Ib) with an absorption shift to longer wave lengths. Criticisms of this view have already been raised by some authors.[4,8,9]

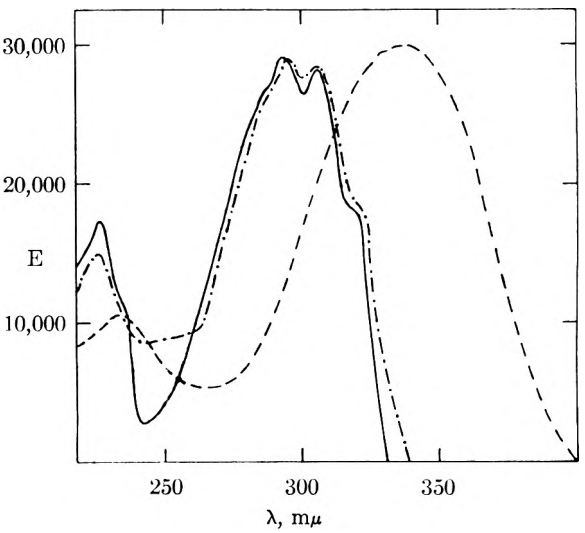
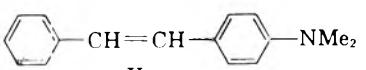


Fig. 1. Absorption spectra: Stilbene in neutral aqueous-ethanol (——); 4-Dimethylaminostilbene in neutral (– – –) and acidic (2*N* sulfuric acid) aqueous-ethanol (–·–·–)

In an attempt to bring fresh evidence to bear on this question the ultraviolet absorption spectrum of 4-dimethylaminostilbene (II) has been examined in 50% aqueous-ethanol under acidic (2*N* sulfuric acid) and neutral conditions and the separate curves have been compared with that of stilbene in neutral solution. (See Fig. 1.) 4-Dimethylaminostilbene is isosteric with 4-dimethylaminoazobenzene but unlike the azo-compound possesses only one basic center and should therefore add a proton only at the dimethylamino- group.



II

The spectrum of 4-dimethylaminostilbene, as shown, in acidic solution is very nearly identical with that of stilbene in neutral solution and definitely reveals no absorption at wave lengths higher than the main band of the parent free base. These observations fail to lend support to the spectral interpretations suggested by Klotz *et al.*[7] On the other hand the assignment of the 320 mμ band, shown by 4-dimethylaminoazobenzene in acidic solution, to the ammonium cation (Ib) is clearly reinforced.

EXPERIMENTAL

Absorption spectra. A Hilger Uvispek Spectrophotometer was used to determine the spectra. The appropriate solvent

(1) G. M. Badger, R. G. Buttery, and G. E. Lewis, *J. Chem. Soc.*, 1888 (1954).
(2) C. R. Bury, *J. Am. Chem. Soc.*, **57**, 2115 (1935).
(3) A. Hantzsch and A. Burawoy, *Ber.*, **63**, 1760 (1930).
(4) G. Cilento, E. C. Miller, and J. A. Miller, *J. Am. Chem. Soc.*, **78**, 1718 (1956).
(5) E. Sawicki, *J. Org. Chem.*, **21**, 605 (1956).
(6) H. H. Jaffe and Si-Jung Yeh, *J. Org. Chem.*, **22**, 1281 (1957).
(7) I. M. Klotz, H. A. Fiess, J. Y. Chen Ho, and M. Mellody, *J. Am. Chem. Soc.*, **76**, 5136 (1954).
(8) E. Sawicki, *J. Org. Chem.*, **22**, 365 (1957).
(9) I. N. Zhmurova, *J. Gen. Chem.* (*U.S.S.R.*), **27**, 2745 (1957).

in each case was prepared from equal volumes of absolute ethanol and either distilled water or 4N sulfuric acid. Immediately prior to use the samples of stilbene and 4-dimethylaminostilbene were purified by chromatography on alumina followed by recrystallization from ethanol thereby, ensuring that any traces of the *cis* isomers were removed.

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Liquid Scintillators. XII. Absorption and Fluorescence Spectra of 2,5-Diaryl-1,3,4-oxadiazoles[1]

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Received November 6, 1959

The importance of spectral properties of scintillators has been outlined,[2,3] at which time the absorption and emission spectra of a variety of aryl-substituted oxazoles were reported. Similar data have been obtained for another important class of liquid scintillator solutes, the 1,3,4-oxadizaoles. The synthesis[4] of these compounds and evaluation as liquid scintillator solutes[5] have been reported previously. Two new pyridyl derivatives are described in the Experimental.

The absorption and fluorescence data are presented in Table I; the mean wave length, $\bar{\lambda}$, is that wave length which bisects the area under the fluorescence spectrum.

The effect of an oxadiazole nucleus on the spectrum of an aromatic system is very similar to that of a *p*-phenylene group. *p*-Terphenyl (λ_{max} 280, ϵ 2.5 × 10^4), *p*-quaterphenyl (λ_{max} 300, ϵ 3.9 × 10^4), and *p*-quinquephenyl (λ_{max} 310, ϵ 6.3 × 10^4)[6] may be compared with the five analogous oxadiazoles having the equivalent number of rings.

(1) Work performed under the auspices of the U. S. Atomic Energy Commission.

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

(3) R. K. Swank, W. L. Buck, F. N. Hayes, and D. G. Ott, *Rev. Sci. Instr.*, **29**, 279 (1958).

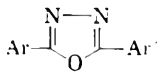
(4) F. N. Hayes, B. S. Rogers, and D. G. Ott, *J. Am. Chem. Soc.*, **77**, 1850 (1955).

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

(6) A. E. Gillam and D. H. Hey, *J. Chem. Soc.*, **1939**, 1170.

TABLE I

Absorption and Fluorescence Spectral Data[a]



Ar	Ar′	Absorption λ_{max}^{abs}	Absorption $\epsilon \times 10^{-4}$	Fluorescence λ_{max1}^{fl}	Fluorescence λ_{max2}^{fl}	$\bar{\lambda}$
C_6H_5	C_6H_5	282	2.6	336	350	360
C_6H_5	4-$C_6H_5C_6H_4$	300[b]	4.5	364	380	388
C_6H_5	1-$C_{10}H_7$	313	1.8	372	392	392
C_6H_5	2-$C_{10}H_7$	310	2.7	364	—	380
C_6H_5	2-Furyl	292	3.3	364	—	372
C_6H_5	2-Thienyl	298	2.4	373	—	388
C_6H_5	3-Pyridyl	285	2.3	355	—	362
C_6H_5	4-Pyridyl	284	2.5	335	353	360
p-$CH_3OC_6H_4$	4-$C_6H_5C_6H_4$	308	4.0	372	390	394
p-$CH_3OC_6H_4$	1-$C_{10}H_7$	317	2.3	380	396	402
p-$CH_3OC_6H_4$	2-$C_{10}H_7$	308	3.2	366	382	386
p-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	289	3.1	342	354	366
p-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	301	3.3	356	370	380
p-FC_6H_4	*p*-FC_6H_4	283	2.4	335	350	358
p-ClC_6H_4	*p*-ClC_6H_4	294	3.2	344	362	370
p-BrC_6H_4	*p*-BrC_6H_4	297	3.6	347	360	374
p-IC_6H_4	*p*-IC_6H_4	303	3.7	344	—	382
4-$C_6H_5C_6H_4$	4-$C_6H_5C_6H_4$	313[b]	6.1	378	396	396
$C_6H_5CH{=}CH$	$C_6H_5CH{=}CH$	331	3.6	406	422	442
2-Furyl	2-Furyl	297	2.6	355	370	378
2-Thienyl	2-Thienyl	313	2.4	377	390	420
1-$C_{10}H_7$	1-$C_{10}H_7$	335	2.3	392	408	412
2-$C_{10}H_7$	2-$C_{10}H_7$	332	3.3	370	388	388
5,5-Diphenyl-2,2′-bi-1,3,4-oxadiazole		298[b]	4.0	354	370	378
2,2′-*p*-Phenylenebis(5-phenyl-1,3,4-oxadiazole)		315[c]	4.8	373	390	392

[a] Wave lengths are in mμ; the solvent was cyclohexane for absorption and toluene for fluorescence unless otherwise indicated. [b] Solvent was 2% chloroform in cyclohexane. [c] Solvent was chloroform; a band at 325 mμ, ϵ 4.8 × 10^4, is also present.

Fluorescence and absorption maxima of the oxadiazoles occur at shorter wave lengths than for the corresponding oxazoles. Substituent groups influence the maxima in essentially the same manner for both types of compounds, and thus the discussions presented previously regarding correlation of spectra with structure of the oxazoles[2] apply, qualitatively, to the 1,3,4-oxadiazoles.

EXPERIMENTAL[7]

The following compounds were prepared by the procedures given previously[4]:

1-Benzoyl-2-nicotinoylhydrazine, m.p. 234–234.5°, after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60. Found: C, 64.69; H, 4.56.

3-[5-Phenyl-2-(1,3,4-oxadiazolyl)]pyridine, m.p. 121.5–122°, white needles from toluene-ligroin.

Anal. Calcd. for $C_{13}H_9N_3O$: C, 69.94; H, 4.06; N, 18.83. Found: C, 70.03; H, 4.24; N, 18.38.

1-Benzoyl-2-isonicotinoylhydrazine, m.p. 232–233.5°, white needles from toluene.

Anal. Found for $C_{13}H_{11}N_3O_2$: C, 64.77; H, 4.80.

4-[5-Phenyl-2-(1,3,4-oxadiazolyl)]pyridine, m.p. 142–143°, white needles from toluene.

Anal. Found for $C_{13}H_9N_3O$: C, 70.16; H, 3.98; N, 18.82.

Fluorescence and Absorption Spectra were obtained as described earlier.[2]

Acknowledgment. The authors are grateful for the technical assistance of Mrs. Ruth Lier.

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(7) Melting points are uncorrected. Microanalyses are by Micro-Tech Laboratories, Skokie, Illinois.

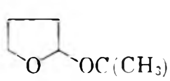
Communications TO THE EDITOR

Reaction of *t*-Butyl Peresters with Ethers

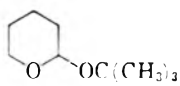
Sir:

In previous communications[1,2] the reactions of *t*-butyl peresters with olefins in the presence of copper salt catalysts were described. In subsequent work[3] the reactions of *t*-butyl peresters were extended to substrates containing activated hydrogen atoms other than olefins. Thus, *t*-butyl perbenzoate with dioxane yielded dioxanyl benzoate, and with phenyl allyl ether yielded 2-benzoyloxy-3-phenoxy-1-propene. In all these reactions the activated hydrogen atom is displaced by an acyloxy group and the *t*-butoxy radical is converted to *t*-butyl alcohol.

It has now been found that *t*-butyl peresters react with ethers containing only one ether function and two activated adjacent methylene groups, such as tetrahydrofurans, tetrahydropyran, and *n*-butyl ether. In addition to the expected acyloxy compounds, these reactions yield mainly 2-*t*-butoxytetrahydrofuran (I), 2-*t*-butoxytetrahydropyran (II), and 1-*t*-butoxy-1-*n*-butoxybutane (III).



I



II

$CH_3(CH_2)_2CHO(CH_2)_3CH_3$
|
$OC(CH_3)_3$
III

Specifically, the reaction of 0.3 mole of *t*-butyl peracetate with 1 mole of tetrahydrofuran in the presence of 0.35 mmole of cuprous bromide for 14 hr. at 67–84° yields 41% of compound I, b.p. 40°/11 mm., n_D^{25} 1.4186. *Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.80; H, 11.02; mol. wt., 144. Found: C, 66.78; H, 11.23; mol. wt., 146.

Similarly, the reaction of 0.3 mole of *t*-butyl perbenzoate and 1 mole of tetrahydrofuran with 0.35 mmole of cuprous bromide for 14 hr. at 67–84° yields 45% of compound I. The reaction of 0.2 mole of *t*-butyl perbenzoate with 0.5 mole of tetrahydropyran for 14 hr. at 86° yields 33% of II, b.p. 56°/13 mm.; n_D^{25} 1.4268. *Anal.* Calcd. for $C_9H_{18}O_2$: C, 68.30; H, 11.48; mol. wt., 158. Found: C, 68.65; H, 11.61; mol. wt., 154. The compound is identical in all respects with a sample prepared by the method of Paul.[4,5] The reaction of 0.1 mole of *t*-butyl perbenzoate with 0.35 mole of *n*-butyl ether for 48 hr. at 90° gives a 48% yield of III. b.p. 100°/17 mm.; n_D^{25} 1.4148. *Anal.* Calcd. for $C_{12}H_{26}O_2$: C, 71.20; H, 12.96; mol. wt., 202. Found: C, 71.15; H, 12.65; mol. wt., 195. If the reaction is stopped within 6 hr., it is possible to isolate substantial quantities of 2-acyloxy compounds. Due to their instability, these compounds could not be purified sufficiently for elemental analysis.

In the absence of a copper salt catalyst, the reaction of *t*-butyl peresters with ethers proceeds at a much slower rate.

A mechanism which accounts for the formation of the acetals I, II, and III is proposed on the basis of the following results. Dihydropyran reacts with acetic acid at 100° to give 2-acetoxytetrahydropyran.[6] We found that under similar conditions an equimolar mixture of dihydropyran, *t*-butyl alcohol, and either benzoic acid or acetic acid produces mainly the acetal II (40%) and only 13% of the acyloxy compounds. There is no reaction between dihydropyran and *t*-butyl alcohol in the presence of copper salt in the absence of acid. At 130°, 1 hr., 2-benzoyloxyfuran decomposes to 66% 2,3-dihydrofuran plus 69% benzoic acid. An equimolar mixture of 2-benzoyloxytetrahydropyran and *t*-butyl alcohol at 80°, 14 hr., yields compound II plus benzoic acid.

From these results it is reasonable to assume that the *t*-butyl peresters in the presence of copper salt catalysts react with tetrahydrofuran, tetrahydropyran, or *n*-butyl ether to form initially the corresponding acyloxy intermediates, which decompose at the chosen experimental conditions to give free organic acids and an unsaturated ether. This ether, in turn, adds *t*-butyl alcohol in the presence of the corresponding acid to give the observed products, I, II, or III, respectively.

The scope of the reactions of *t*-butyl peresters with ethers is currently being investigated, and the results will be reported at a later date.

The author is indebted to the Quaker Oats Company for free samples of dihydropyran and tetrahydropyran.

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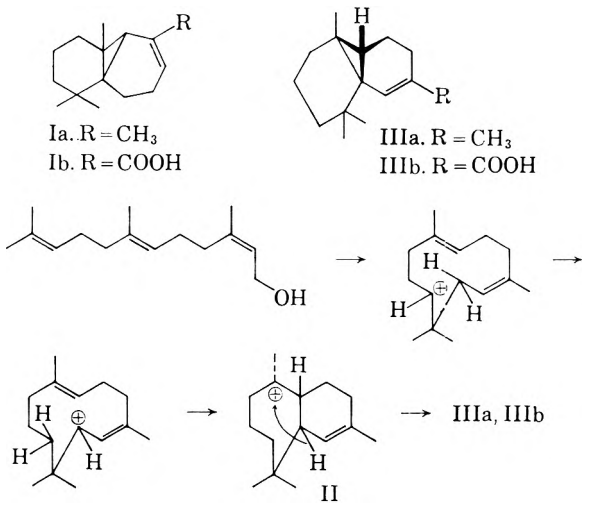
(1) M. S. Kharasch and George Sosnovsky, *J. Am. Chem. Soc.*, **80**, 756 (1958).
(2) M. S. Kharasch, George Sosnovsky, and N. C. Yang, *J. Am. Chem. Soc.*, **81**, 5819 (1959).
(3) George Sosnovsky and N. C. Yang, *J. Org. Chem.*, in press.
(4) R. Paul, *Bull. Soc. Chim.*, (5) **1**, 973 (1934).
(5) G. F. Woods and D. N. Kramer, *J. Am. Chem. Soc.*, **69**, 2246 (1947).
(6) J. G. M. Brenner and D. G. Jones, British Patent **606, 764** (Aug. 19, 1948). *Chem. Abstr.*, **43**, 1442 (1949).

Biogenetically Assigned Structures of Thujopsene and Hinokiic Acid

Sir:

The recent publication of Erdtman and Norin[1] on the tentative structures of thujopsene (Ia) and hinokiic acid (Ib) has prompted the authors to make a comment on the possible biogenesis of these sesquiterpenes.

In the light of the ingenious idea of Ruzicka's biogenetic isoprene-rule[2] as extended by Eschenmoser,[3] Hendrickson[4] and others, it is quite attractive to consider that both thujopsene and hinokiic acid are derived from *cis*-farnesol according to the following scheme.



The bicyclic cation (II) is a probable intermediate stage for the production of longifolene as suggested by Hendrickson.[4] Regarding the conversion of II into the tricyclic compounds (IIIa and IIIb), a proton elimination assisted by the positive charge situated at the γ-carbon is assumed. Though this type of a cyclization is not very common,[5] the sterically-forced proximity of the α- and γ-carbon atoms concerned should be the cause of this rather unusual formation of the cyclopropane ring.

Such a consideration leads to the predicted absolute configurations of IIIa and IIIb for thujopsene and hinokiic acid, respectively. Those formulas are supported by almost all of the known reactions of the sesquiterpenes.[1,6] Full details will be published elsewhere.

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Received February 19, 1960

(1) H. Erdtman and T. Norin, *Acta Chem. Scand.*, **13**, 1124 (1959). The formula (Ia) had already been assigned to thujopsene by H. Kobayashi, S. Nagahama, and S. Akiyoshi [*Bull. Chem. Soc. Japan*, **32**, 202 (1959)] prior to the publication of the Swedish authors.

(2) L. Ruzicka, A. Eschenmoser, and H. Heusser, *Experientia*, **9**, 357 (1953).

(3) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955). See also L. Ruzicka in Sir A. Todd, *Perspectives in Organic Chemistry*, Interscience, New York, 1956, p. 265.

(4) J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).

(5) The formation of nortricyclene from 2-*exo*-norbornyl derivatives may be cited as an example of such a mode of deprotonation. See P. von Ragué Schleyer, *J. Am. Chem. Soc.*, **80**, 1700 (1958).

(6) (a) S. Nagahama, H. Kobayashi, and S. Akiyoshi, *Bull. Chem. Soc. Japan*, **32**, 366 (1959) and earlier papers cited there. (b) O. Okuda, *J. Pharm. Soc. Japan*, **73**, 9 (1953) and earlier papers cited there.

Steroids and Related Natural Products. II. A Method for the Direct Conversion of Esters to Ethers[1,2]

Sir:

We wish to report a one-step procedure for converting an ester to its corresponding ether derivative. The reduction has been accomplishd employing a boron trifluoride etherate–lithium aluminum hydride reagent.[3] This novel reaction was first observed during the course of an investigation directed at determining the effect of boron trifluoride etherate–lithium aluminum hydride mixtures on the steroidal sapogenin spiroketal system.[4]

The ester in boron trifluoride etherate solution was added to a cooled suspension of lithium aluminum hydride in ethyl ether. After 45 min. at ice bath temperature followed by a 2-hr. period at reflux the product was isolated. This procedure has been used for the preparation of 3β-ethoxycholestane (0.17 g.),[5] colorless needles, $[\alpha]_D^{20}$ +23.8° (chloroform), m.p. 81–83° (*Anal.* Calcd. for $C_{29}H_{52}O$: C, 83.53; H, 12.58; O, 3.89. Found: C, 83.47; H, 12.56; O, 3.91), from 3β-acetoxycholestane (1.1 g.) and 3β-ethoxylanostane, colorless leaflets, m.p. 134–135°, $[\alpha]_D^{20}$ +53.2° (chloroform), 38% yield (*Anal.* Calcd. for $C_{32}H_{58}O$: C, 83.84; H, 12.66; O, 3.49. Found: C, 83.62; H, 12.47: O, 3.97), from

(1) Consult G. R. Pettit and W. J. Bowyer, *J. Org. Chem.*, **25**, 84 (1960), for the first contribution to this series.

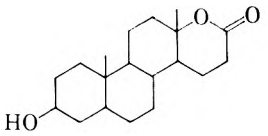
(2) This investigation was supported by Research Grants CY-4074(CI) and CY-4074(CISI), from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(3) Similar reagents have been used recently for the hydroboration of olefins and as general reducing agents. *Cf.*, H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **82**, 681 (1960); S. Winstein, E. L. Allred, and J. Sonnenberg, *J. Am. Chem. Soc.*, **81**, 5833 (1959); H. C. Brown and K. Murray, *J. Am. Chem. Soc.*, **81**, 4108 (1959); H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 4106 (1959); F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959); R. Dulou and Y. Chrétien-Bessière, *Bull. soc. chim. France*, 1362 (1959); S. P. Fore and W. G. Bickford, *J. Org. Chem.*, **24**, 920 (1959).

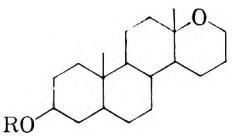
(4) *Cf.*, footnote 10 ref. 1.

(5) C. Djerassi, M. Shamma, and T. Y. Kan, *J. Am. Chem. Soc.*, **80**, 4723 (1958).

3β-acetoxylanostane.[6] Both products were found to be identical (mixture melting point and infrared spectral comparison) with authentic samples. An important application of this method involved reduction of 3β,13α-dihydroxy-13,17-secoandrostan-17-oic acid lactone (I)[7] to the tetrahydropyran IIa, colorless needles, m.p. 181–183°, $[\alpha]_D^{20}$ 0.00° (chloroform), 43% yield (*Anal.* Calcd. for $C_{19}H_{32}O_2$ (292): C, 78.03; H, 11.03; O, 10.94; active H, 0.34. Found: C, 77.54; H, 10.82; O, 11.56; active H, 0.28); mol. wt. (Rast), 297. Treating IIa with acetic anhydride–pyridine afforded the acetate derivative IIb, colorless rods, $[\alpha]_D^{20}$ −18.0° (chloroform)



I



II a, R = H
b, R = $OCOCH_3$

m.p. 145–146°. (*Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25; O, 14.35. Found: C, 75.64; H, 10.30; O, 14.29). The yields reported are based on chromatographically pure compounds.

The scope of this reaction is presently under investigation.

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