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Santonin and Related Compounds. XIX.[1] Some Transformation Reactions of 2-Bromo-α-tetrahydrosantonin

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The 2-bromo structure (II) for the monobromo derivative of α-tetrahydrosantonin (I) was definitely proved by the reaction sequence (II → IV → VI → VIII). The 2-bromoketone (II) on acetolysis afforded the more stable epimer (IX) of the ketol acetate, which was also prepared from I with lead tetraacetate in reflux acetic acid. When the latter reaction was performed at the lower temperature, the other epimer (X) was obtained almost quantitatively. Epimerization of X to IX was effected by refluxing with acetic acid. Both ketol acetates were reduced to the parent ketone (I) or 3-desoxy-α-tetrahydrosantonin (VII), respectively, with zinc dust-acetic acid or by the Clemmensen method. The dimethylene thioketals (XIV and XV) of the ketol acetates gave the 3-desoxy compound (VII) on reduction with Raney nickel. Compound XV could be easily epimerized to XIV.

It has been reported[2] that treating α-(I) and γ-tetrahydrosantonin[3] with bromine gave exclusively the 2-bromo compounds. The evidence for the 2-bromo structure of these derivatives was principally based on the fact that on collidine treatment, each of these bromoketones gave a Δ^1-dihydrosantonin (III) as the sole product isolated. However, because the yields of the dihydro compounds were small, the allocation of bromine in the bromoketones, though it appears very logical, cannot be considered conclusive. Moreover, previous work has shown that dehydrobromination of the 2-bromo derivative of 9-methyl-3-decalones with γ-collidine was always accompanied by rearrangement,[4,5] and that 4,9-dimethyl-3-decalones, both *cis*- and *trans*- fusions, were invariably brominated at the 4-position rather than the 2-position.[6,7] In view of these observations, the slight possibility of 4-bromination in the tetrahydrosantonins cannot be completely excluded. It seems to us worthwhile to unequivocally establish the structure of these bromoketones. The present paper reports on a study of the derivatives of α-tetrahydrosantonin (I), possessing the *trans*-decalin system.

The monobromo derivative of I was subjected to the same sequence of reactions (II→IV→VI→VIII) employed earlier for the proof of the position of bromine in the 2-bromo derivative of 9-methyl-3-decalone.[4,5b] Reduction of the bromoketone with sodium borohydride in ethanol at room temperature proceeded stereospecifically, and one of two possible bromohydrin isomers was obtained as a crystalline solid in a 74% yield. It is generally accepted that a *cis*-bromohydrin is converted by alkali to a ketone whereas its *trans*-isomer readily gives an epoxide. Upon treatment with methanolic potassium hydroxide, the present bromohydrin was unaffected at room temperature, but when heated to reflux, it was converted to the parent ketone (I) in a good yield. This result clearly favored the *cis*-structure (IV) for the bromohydrin.

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

(2) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955); *cf.* M. Yanagita and H. Ogura, *J. Org. Chem.*, **22**, 1092 (1957).

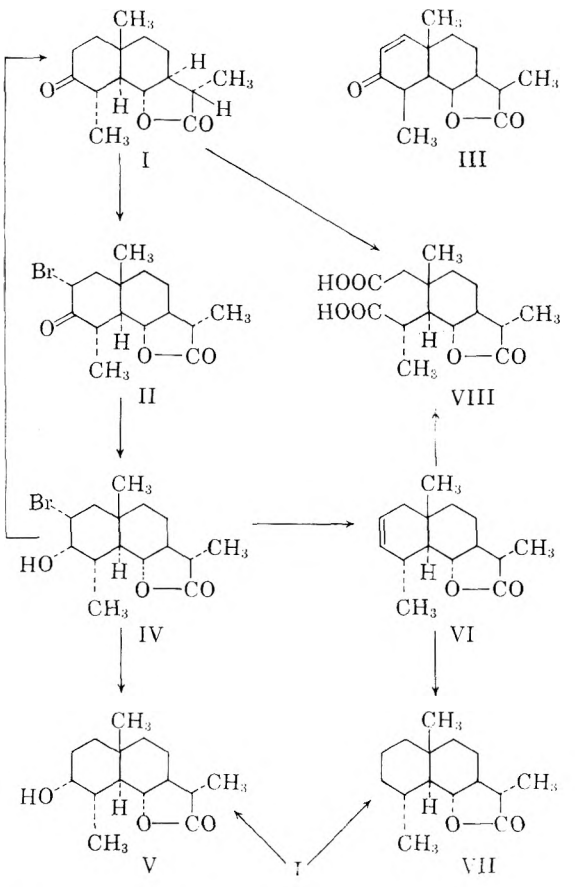
(3) The prefixes α and γ are used in this and following papers in conformity to the original paper in this series (ref. 2); *cf.* ref. 11b.

(4) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **22**, 291 (1957).

(5) (a) M. Yanagita and A. Tahara, *J. Org. Chem.*, **18**, 792 (1953); (b) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **21**, 500 (1956).

(6) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956).

(7) *Cf.* M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 443 (1958).



The equatorial orientation of bromine in the bromoketone (II), which was rendered likely from conformational analysis,[8] was established by the shifts of the carbonyl absorption in the ultraviolet ($\Delta\lambda_{max}$ -5.5 mμ)[9] and infrared spectra ($\Delta\nu$ $+23$ cm.$^{-1}$)[10] over the parent ketone (I). It is most likely that the bromine in the bromohydrin takes up the same equatorial position. Consequently, it is deduced that the hydroxyl group in the bromohydrin may be axially oriented. This deduction was confirmed by the observation that the bromohydrin was catalytically reduced to one isomer of the hexahydrosantonin, in which the axial character of the hydroxyl group at the 3-position has been established.[11] It is to be noted that the predominant formation of the *cis*-bromohydrin from the 2-bromoketone (II) with borohydride is in a remarkable contrast to the result of similar reduction of 2α-bromocholestan-3-one, which gave chiefly the *trans*-bromohydrin with the newly-formed hydroxyl group at the equatorial position.[12] This may be attributed to an increase in steric hindrance to the carbonyl group due to the combined effects of the two α-oriented, adjacent, bulky substituents, as suggested previously for explanation of the same stereochemical course of borohydride reduction of the 2α,4α-dihalo-3-ketosteroids.[13] This consideration was supported by the previous result[11a] that borohydride reduction of α-tetrahydrosantonin (I), unlike the case of II, reesulted in the predominant formation of an epimer of the hexahydrosantonin (V), carrying the equatorial hydroxyl group at the 3-position.

Reduction of the bromohydrin (IV) with zinc dust and acetic acid afforded in 67% yield an olefin (VI), which was differentiated from the known Δ^3-isomer[11b] by comparisons of the melting points and rotational data. It had the infrared absorption bands at 1662 and 678 cm.$^{-1}$, indicating the presence of a *cis*-disubstituted double bond.[4,5b,14] The olefin was quantitatively hydrogenated over platinic oxide to 3-desoxy-α-tetrahydrosantonin (VII) reported previously[15] Permanganate oxidation of the olefin was carried out in pyridine solution at low temperature with addition of magnesium sulfate in keeping the mixture neutral to litmus paper. There was obtained a diacid in 50% yield. The same acid was also formed in comparable yield directly from I by oxidation with hot concentrated nitric acid. From these modes of the preparation, it may be presumed that the diacid (VIII) preserved the original lactone ring, which is considerably stable to acid. The diacid was quantitatively recovered from the hot alkaline solution by acidification, showing that the lactone ring in the diacid possesses the most favorable of the possible isomeric structures.[16] Ozonolysis of the olefin (VI), which seems to be the most promising method for preparing the diacid, was attempted under various conditions, but even when methanol[17] was used as a solvent at low temperature, no crystalline products were obtained.[18]

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

(9) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(10) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).

(11) (a) B. Riniker, Thesis, E. T. H. Zürich, 1955. (b) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4549 (1956).

(12) L. F. Fieser and X. A. Dominguez, *J. Am. Chem. Soc.*, **75**, 1704 (1953); E. J. Corey, *J. Am. Chem. Soc.*, **75**, 4832 (1953); H. B. Henbest and T. I. Wrigle, *J. Chem. Soc.*, 4596 (1957); *Cf.* J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. F. Fieser [(*J. Am. Chem. Soc.*, **75**, 3500 (1953)] reported that borohydride hydrogenation of 2-chlorocholestan-3-one resulted in an epimeric mixture, consisting of almost an equal amount of *cis*- and *trans*-chlorohydrins.

(13) J. J. Beereboom and C. Djerassi, *J. Org. Chem.*, **19**, 1196 (1954).

(14) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954, p. 31.

(15) (a) Wedekind and K. Tettweiler, *Ber.*, **64**, 387 (1931). (b) Ö. Kovács, V. Herout, M. Herák, and F. Šorm, *Collection Czeckoslov. Chem. Commun.*, **21**, 225 (1956).

(16) With respect to this point, a more detailed argument including *cis*-series will be made in the following paper of this series XX.

(17) Methanol was reported to be an excellent solvent for ozonolysis; for example see P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956).

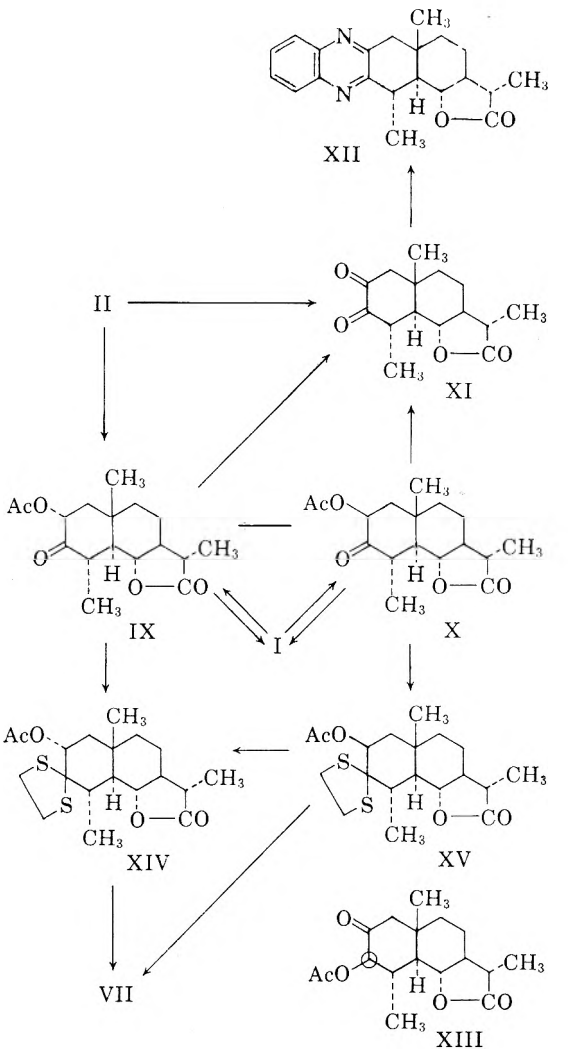
(18) A similar instance was found in a recent paper describing ozonolysis of the acetate of Δ^2-anhydroisodihydroresin, which gave only a poor yield of the oily ester of the diacid corresponding to VIII [C. Djerassi, F. W. Donovan, S. Burstein, and R. Mauli, *J. Am. Chem. Soc.*, **80**, 1972 (1958)].

The reaction sequence mentioned above clearly showed that the olefin (VI) has the double bond between the 2- and 3-positions, and hence, the previous formula (II) of the bromoketone is beyond doubt.

It is known that on acetolysis, the α-bromo-3-ketosteroids frequently yield rearranged product,[19] while the simple 2-bromo-3-decalone gives the normal ketol acetate.[4,5] It seems of interest to examine the reaction of the above bromoketone (II) with the acetate ion. Refluxing II with potassium acetate in glacial acetic acid led in 58% yield to one isomer, m.p. 199–200°, of the ketol acetate. The same compound could be quantitatively obtained in one step from I by oxidation with lead tetraacetate in refluxing glacial acetic acid. When the latter reaction was conduced on a water-bath, another isomer, m.p. 171.5–172.5°, was secured in 90% yield. That the discrepancy of the melting points of these two forms is due to isomerism rather than dimorphism was shown by comparisons of their infrared spectra and by preparation of dissimilar 2,4-dinitrophenylhydrazones. It is reasonably assumed that the acetoxyl group in the higher-melting epimer (IX) occupies an equatorial (*trans* to the angular methyl group) and the one in the lower-melting epimer (X) an axial conformation (*cis* to the angular methyl group). This assumption was confirmed by complete transformation of X into IX by refluxing with acetic acid for 6 hours, indicating that IX is the more stable compound. A similar instance in steroid chemistry is the oxidation of 23-bromo-22α,5α-spirostan-3-one with lead tetraacetate on the steam bath to give the 2α(axial)-acetoxyl compound.[20]

In order to hydrolyze the acetoxyl group, the ketol acetates (IX and X) were allowed to stand in 0.25*N* potassium hydroxide solution at room temperature for 2 hours. From either reaction mixture, the same α-diketone (XI), showing positive ferric chloride test, was isolated in good yield. It was characterized as a glyoxime and quinoxaline (XII). The bromoketone (II) on the same treatment with alkali afforded the identical diketone. There was no evidence for the expected α-ketol or diacid (VIII) in these reactions. Even when the alkaline hydrolysis of the bromoketone was conducted under a stream of nitrogen, the α-diketone (XI) was the only product isolated.

The slight possibility that the ketol acetate would have the structure XIII resulting from α-ketol rearrangement during acetolysis could not be excluded. It has been reported that in the ketol acetates of steroid[21] and of the simple cyclic compound,[22] which possess the carbonyl group in conjugation with the double bond, the acetoxyl group was readily eliminated by brief refluxing with zinc in acetic acid (or acetic anhydride). The same method of reduction was tried on ketol acetates IX and X, but both were completely recovered. When the refluxing time was prolonged to 24 hours, even the more stable ketol acetate (IX) was quantitatively reduced to the parent ketone (I). This completely eliminated XIII as a possible structure for the ketol acetate.



Hoping to prepare the 2-oxygenated compound by elimination of the carbonyl group, the ketol acetates (IX and X) were subjected to reduction by the Martin modification of Clemmensen method. Both reactions gave in good yields the same product, the 3-desoxy-tetrahydrosantonin (VII). This result was not unexpected, since some examples have been recorded involving elimination of only the hydroxyl group or the two oxygen functions of ketol (not its acetate) on reduction by the Clem-

(19) L. F. Fieser and M. A. Romero, *J. Am. Chem. Soc.*, **75**, 4716 (1953).

(20) J. Herran, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 5531 (1954).

(21) F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953).

(22) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4233 (1952).

mensen reaction or modifications of it.[23] Another possible route is the hydrogenolysis of the thioketal derivative of the ketol acetate. Unlike the parent ketone (I),[15b] both IX and X remained unaffected on treatment with ethane dithiol in acetic acid using *p*-toluenesulfonic acid as a catalyst. Replacement of toluenesulfonic acid by boron trifluoride–ether complex gave thioketals (XIV and XV) in quantative yields. It was found that the thioketal (XV) of the less stable ketol acetate was readily epimerized to XIV by refluxing with dioxane for 20 hours. By the same procedure, the ketol acetate (IX) itself was epimerized quantitatively to X. Such a ready epimerization of the thioketal merits attention, because, unlike the ketol acetate, this compound is devoid of the enolizable function adjacent to the migrating group. Upon desulfurization with Raney nickel in dioxane or ethanol by the conventional procedure, both thioketals were converted to the above 3-desoxy compound (VII) with simultaneous elimination of the acetoxyl group. This result is somewhat unexpected, but after completion of this experimentation, a similar observation on Raney nickel hydrogenation of the dimethylene thioketal of the 3β-acetoxy-2-keto-steroid was reported.[24]

EXPERIMENTAL[25]

All temperatures are uncorrected. Rotations were determined in a 0.5-dm. semimicro tube; infrared absorption spectra were measured with a Perkin-Elmer model 21 double-beam spectrophotometer.

α- and γ-Tetrahydrosantonins. According to the procedure described previously,[2] l-α-santonin was hydrogenated over palladium-charcoal. α-Tetrahydrosantonin (I), obtained in 56% yield, had m.p. 153–156°; $\lambda_{max}^{CHCl_3}$ 289 mμ (ε 21.2); $\nu_{C=O}^{Nujol}$ 1701 cm.$^{-1}$ (cyclohexanone ring) and 1777 cm.$^{-1}$ (γ-lactone).

γ-Tetrahydrosantonin, obtained in 22% yield, had m.p 100–103°; $\lambda_{max}^{CHCl_3}$ 289 mμ (ε 30) and λ_{max}^{EtOH} 286 mμ (ε 40); $\nu_{C=O}^{Nujol}$ 1709 (cyclohexanone ring) and 1764 cm.$^{-1}$ (γ-lactone).

2-Bromo-α-tetrahydrosantonin (II). This was prepared from α-tetrahydrosantonin (I) with bromine as described previously.[2] It had m.p. 144–146°; $\lambda_{max}^{CHCl_3}$ 283.5 mμ (ε 30.0); $\nu_{C=O}^{CHCl_3}$ 1733 (cyclohexanone ring) and 1776 cm.$^{-1}$ (γ-lactone), $\nu_{C=O}^{Nujol}$ 1727 (cyclohexanone ring), and 1770 cm.$^{-1}$ (γ-lactone).

Reduction of 2-bromo-α-tetrahydrosantonin (II) *with sodium borohydride.* To an ice-cooled solution of 1.0 g. of the bromoketone (II) in 80 cc. of ethanol was added, dropwise, a solution of 0.12 g. of sodium borohydride in 50 cc. of ethanol with stirring within about 30 min. The stirring was continued 6 hr. at room temperature, and the mixture was allowed to stand overnight. Evaporation of the ethanol at reduced pressure left a white solid, which was treated with 10% sulfuric acid and extracted with ether. The ether solution was washed with water, dried and evaporated to give a pale yellow oil (0.98 g.) which partly solidified in a refrigerator. Trituration with a small amount of 70% ethanol afforded 0.74 g. (74%) of the *2-bromohexahydrosantonin* (IV) as colorless prisms, melting in the range 84–93°. Recrystallization from the same solvent and then 99% ethanol gave colorless silky needles, m.p. 91–93°; $[\alpha]_D^{26}$ +12.7° ($CHCl_3$; *c* 1.57); $\nu_{OH}^{CHCl_3}$ 3497 cm.$^{-1}$ and $\nu_{C=O}^{CHCl_3}$ 1770 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{15}H_{23}BrO_3$: C, 54.38; H, 6.95. Found: C, 54.12; H, 7.29.

Reaction of the 2-bromohexahydrosantonin (IV) *with methanolic alkali.* (a) *At room temperature.* The above bromohydrin (IV, 0.09 g.) was allowed to stand in a solution of 0.05 g. of potassium hydroxide in 10 cc. of methanol 3 days. After acidification, the solution was evaporated under reduced pressure, and the residue was mixed with water and extracted with ether. Evaporation of the ether solution gave a pale yellow oil (0.07 g.), from which only the starting material, m.p. and mixed m.p. 90–93°, was isolated as a crystalline solid.

(b) *At reflux temperature.* The bromohydrin (IV, 0.20 g.) was refluxed 3 hr. in the same alkali solution described above in (a). The crystalline product (0.14 g., 93%), melting in the range 122–137°, was purified by passing the solution in benzene through alumina (5 g.) and then recrystallized from dilute ethanol to give colorless plates, m.p. 153–155°. It showed no depression of the melting point on admixture with α-tetrahydrosantonin (I).

Catalytic hydrogenation of the 2-bromohexahydrosantonin (IV) *in alkaline medium.* A solution of 0.20 g. of the bromohydrin (IV) and 1.5 g. of potassium hydroxide in 20 cc. of ethanol was shaken under an atmosphere of hydrogen in the presence of palladium-charcoal (prepared from 2 cc. of 1% palladium chloride solution and 0.04 g. of charcoal). Uptake of one equivalent of hydrogen required about 3 hr. After removal of the catalyst, the hydrogenation mixture was acidified and then evaporated under reduced pressure. The oily residue was mixed with water and extracted with ether, and the dried ether solution was evaporated to leave an oil (0.16 g.) which solidified partly. This was chromatographed on 5 g. of alumina, and elution with benzene gave crystals, m.p. 135–140°, which were recrystallized from ethanol to afford colorless needles, m.p. 143–144°. It showed no depression of the melting point on admixture with the hexahydrosantonin (V), m.p. 143–144°, prepared by catalytic hydrogenation of I with platinic oxide as reported previously.[11]

Reduction of the 2-bromohexahydrosantonin (IV) *with zinc dust and acetic acid.* A solution of 0.98 g. of the bromohydrin (IV) in 10 cc. of glacial acetic acid was refluxed with 1.7 g. of acid-washed zinc dust 3 hr. After removal on zinc by filtration, the reaction mixture was poured into ice water. There was obtained 0.465 g. (67%) of the Δ²-olefin (VI), m.p. 139–144.5°, which was crystallized from petroleum ether to give colorless plates, m.p. 143–144.5°; $[\alpha]_D^{22}$ +6.4° (EtOH, *c* 0.94); $\nu_{C=O}^{Nujol}$ 1776 cm.$^{-1}$ (γ-lactone) and $\nu_{C=C}^{Nujol}$ 1662 cm.$^{-1}$ (*cis*-CH=CH—), 720 and 687 cm.$^{-1}$ (*cis*-

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.09; H, 9.71.

Catalytic hydrogenation of the olefin (VI) in ethanol over platinic oxide gave in quantitative yield a crystalline product, melting in the range 120–135°. Recrystallization from ethanol furnished colorless plates, m.p. 150–153°; $\nu_{C=O}^{Nujol}$ 1770 cm.$^{-1}$ (γ-lactone). It showed no depression of the melting point on admixture with the 3-desoxy-α-tetrahydrosantonin (VII), prepared by the Clemmensen reduction of I was reported previously.[15]

Oxidation of the Δ²-olefin (VI) *with potassium permanganate.* A solution of 0.20 g. of the Δ²-olefin (VI) in 3.4 cc. of pyridine was mixed with a solution of 3.2 g. of manganese sulfate hydrate in 3.4 cc. of water. To this mixture was added, in

(23) V. Prelog, K. Shenker, and H. H. Gunthard, *Helv. Chim. Acta.*, **35**, 1598 (1952); M. N. Huffman and M. H. Lott, *J. Am. Chem. Soc.*, **75**, 4327 (1953); M. Cordon, J. D. Knight, and D. J. Cram, *J. Am. Chem. Soc.*, **76**, 1643 (1954).

(24) J. C. Sheehan and W. F. Erman, *J. Am. Chem. Soc.*, **79**, 6050 (1957).

(25) Microanalyses were carried out by Mrs. Ch. Inayama and the ultraviolet measurements by Miss M. Suzuki, both of this school.

small portions, 3.2 g. of powdered potassium permanganate with rigorous stirring cooling with ice. After the addition was completed in about 1.5 hr., the stirring was maintained 2 hr. with cooling and then at room temperature for 5 hr. After decomposition of an excess of permanganate and removal of the manganese dioxide, the yellow solution was evaporated under reduced pressure to a small volume, acidified with hydrochloric acid and extracted with ethyl acetate. The ethyl acetate solution was shaken with aqueous bicarbonate, and the bicarbonate solution was acidified and extracted with ethyl acetate. Evaporation of the dried ethyl acetate solution afforded a pale yellow viscous oil (0.23 g.) which partly solidified on standing in a refrigerator for a week. Trituration with a little ethyl acetate gave 0.145 g. (57%) of colorless prisms, melting in the range 179–183°. Recrystallization from water raised the melting point to 193–195°; $\nu_{C=O}^{Nujol}$ 1783 (γ-lactone) and 1715 cm.$^{-1}$ (carboxyl). It showed no depression of the melting point on admixture with the diacid (VIII) described in the following paragraph.

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.11; H, 7.17.

Oxidation of α-tetrahydrosantonin (I) *with nitric acid.* To 5 cc. of fuming nitric acid (d = 1.52) containing 0.02 g. of ammonium vanadate was slowly added 0.50 g. of α-tetrahydrosantonin (I), and soon an exothermic reaction took place under violent evolution of a brown-red gas. After standing overnight, the reaction mixture was diluted with 4 cc. of water and evaporated under reduced pressure to leave a red viscous oil, which was dissolved in ethyl acetate. The ethyl acetate solution was filtered, and the filtrate was repeatedly shaken with aqueous bicarbonate. Acidification of the combined bicarbonate solutions afforded 0.33 g. (55%) of colorless prisms (VIII), melting in the range 189–195°. Recrystallization from water raised the melting point to 193–195°; $[\alpha]_D^{26}$ −15.0° (EtOH; c 1.27). The infrared absorption spectrum of this sample was superimposable on that of the sample above mentioned.

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.00; H, 7.62.

A solution of the diacid (0.05 g.) in 5% sodium hydroxide (1 cc.) was warmed on a water bath for 30 min. Acidification of the alkaline solution gave back the parent material in a quantitative yield.

Reaction of 2-bromo-α-tetrahydrosantonin (II) *with anhydrous potassium acetate.* The 2-bromoketone (II, 0.30 g.) was heated to reflux with 0.45 g. of anhydrous potassium acetate in 3 cc. of glacial acetic acid 4 hr. The light-brown mixture was poured into 20 cc. of ice water and extracted with ether, and the ether solution was washed with 10% sodium carbonate and then with water. Evaporation of the dried ether solution left a pale yellow oil (0.24 g.), which soon solidified mostly. Trituration with ethanol gave 0.16 g. (57.5%) of the *trans-2-acetoxy-α-tetrahydrosantonin* (IX) as colorless plates, m.p. 191–196°. Recrystallization from ethanol raised the melting point to 198–200°; $[\alpha]_D^{26}$ +41.3° ($CHCl_3$; c 1.33) λ_{max}^{EtOH} 283 mμ (ϵ 26.2); $\nu_{C=O}^{CHCl_3}$ 1739 (acetyl), 1730 (cyclohexanone ring) and 1770 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.41; H, 7.65.

In the above reaction system, use of ethanol instead of acetic acid gave the same product (IX) in lower yield.

Oxidation of α-tetrahydrosantonin (I) *with lead tetraacetate in glacial acetic acid.* (a) *At reflux temperature.* The α-tetrahydrosantonin (I, 0.50 g.) was heated to reflux with 1.0 g. of lead tetraacetate in 100 cc. of glacial acetic acid for 6 hr. in an oil bath. After cooling, the acetic acid was mostly evaporated under reduced pressure, and the residue was mixed with aqueous bicarbonate and shaken with chloroform. After removal of the insoluble material by filtration, the chloroform extract was again washed with aqueous bicarbonate and then with water, and dried. Evaporation of the chloroform left 0.63 g. (quantitative) of the *trans*-ketol acetate (IX), melting in the range 180–198°. Recrystallization from ethanol afforded colorless plates, m.p. 199–200°, undepressed on admixture with the sample described in the preceding paragraph.

With Brady's reagent,[7] it formed in 76% yield a *2,4-dinitrophenylhydrazone* as yellow crystals, melting in the range 213–223° (dec.) which was recrystallized from ethanol to give yellow needles, m.p. 226–228° (dec.).

Anal. Calcd. for $C_{23}H_{28}N_4O_8$: C, 56.55; H, 5.78; N, 11.47. Found: C, 56.91; H, 5.97; N, 11.05.

(b) *On the boiling water bath.* A solution of 0.30 g. of the α-tetrahydrosantonin (I) in 100 cc. of glacial acetic acid was heated with 0.6 g. of lead tetraacetate 6 hr. on the boiling water bath. The reaction mixture was worked up as described above in (a), and there was obtained 0.335 g. (90%) of the *cis-2-acetoxy-α-tetrahydrosantonin* (X) as a crystalline solid, m.p. 166–172°. Recrystallization from ethanol gave colorless plates, m.p. 171.5–172.5°; $[\alpha]_D^{26}$ +49.7° ($CHCl_3$; c 1.53); λ_{max}^{EtOH} 285 mμ (ϵ 30.4); $\nu_{C=O}^{CHCl_3}$ 1739 (acetyl), 1730 (cyclohexanone ring) and 1770 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.17; H, 7.86.

With Brady's reagent, it formed in 85% yield a *2,4-dinitrophenylhydrazone,* melting in the range 162–175°. Recrystallization from ethanol afforded orange-yellow plates, m.p. 207–210°.

Anal. Calcd. for $C_{23}H_{28}N_4O_8$: C, 56.55; H, 5.78; N, 11.47. Found: C, 56.61; H, 5.47; N, 11.73.

Conversion of cis-2-acetoxy-α-tetrahydrosantonin (X) *into the trans-epimer* (IX). The *cis*-ketol acetate (X, 0.05 g.) was heated to reflux in 1.5 cc. of glacial acetic acid 6 hr. Evaporation of the acetic acid under reduced pressure gave quantitatively the *trans*-acetoxyketone (IX), melting in the range 188–200°. Recrystallization from ethanol furnished colorless prisms, m.p. and mixed m.p. 198–201°.

Alkali treatment of cis- and trans-2-acetoxy-α-tetrahydrosantonin (X *and* IX). The *trans*-ketol acetate (IX, 0.05 g.) was dissolved in 10 cc. of 0.25*N* ethanolic potassium hydroxide to give a clear solution, which showed a strong yellow fluorescence. On keeping the solution at room temperature 1 hr., the fluorescence disappeared. After standing an additional 1 hr., the pale yellow solution was acidified and evaporated under reduced pressure. The residue was mixed with water and extracted with ether. The ether extract was dried and evaporated to furnish 0.04 g. (94%) of a yellow viscous oil, which almost completely solidified in a refrigerator; m.p. 155–158°. Recrystallization from ethanol gave colorless prisms, m.p. 159–160°, undepressed on admixture with 2-keto-α-tetrahydrosantonin (XI), prepared from the bromoketone (II) as described in the following paragraph. It showed a dark violet coloration with ferric chloride.

The same treatment of the *cis*-ketol acetate (X) with alkali gave, in a comparable yield, the diketone (XI), m.p. and mixed m.p. 158–160°.

Alkali treatment of 2-bromo-α-tetrahydrosantonin (II). Essentially as described in the preceding paragraph, the bromoketone (II, 0.20 g.) was treated with 0.25*N* ethanolic potassium hydroxide (40 cc.). The alkali reaction showed the same yellow fluorescence as described with IX. Evaporation of the ether extract left 0.11 g. (73%) of *2-keto-α-tetrahydrosantonin* (XI), m.p. 148–156°. Recrystallization from ethanol furnished colorless prisms, m.p. 159–160°; $[\alpha]_D^{26}$ +108° ($CHCl_3$; c 1.33); λ_{max}^{EtOH} 278.5 mμ (ϵ 10,000); $\nu_{C=O}^{CHCl_3}$ 1642 (α,β-unsaturated ketone) and 1757 cm.$^{-1}$, $\nu_{C=C}^{CHCl_3}$ 1667 cm.$^{-1}$, and $\nu_{OH}^{CHCl_3}$ 3413 cm.$^{-1}$ The infrared spectrum indicated that the α-diketone exists chiefly in an enol form.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.93; H, 7.55.

It formed in good yield a *glyoxime,* m.p. 238–241° (dec.), by the conventional method. Recrystallization from ethanol gave colorless needles, m.p. 245–246° (dec.). It showed a pink coloration with nickel salt.

Anal. Calcd. for $C_{15}H_{22}N_2O_4$: C, 61.20; H, 7.53; N, 9.52. Found: C, 60.98; H, 7.69; N, 9.79.

According to the procedure reported by Sheehan and Erman,[24] the diketone (0.05 g.) was heated with the same amount of *o*-phenylenediamine at 150–160° 30 min. in a stream of nitrogen gas. The crude product, a light-brown viscous oil, was dissolved in ethyl acetate, and on standing overnight, the acetate solution deposited 0.03 g. (47%) of a *quinoxaline* (XII) as yellow crystals, melting in the range 250–265°. Recrystallization from ethyl acetate gave yellow silky needles, m.p. 268–271°.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.95; H, 7.32; N, 8.46.

In attempting to isolate an intermediate, an α-ketol, the alkali hydrolysis of II was conducted in a stream of nitrogen gas to avoid the air-oxidation. Unlike the above reactions, the strong fluorescence of the alkali solution did not disappear even after keeping the solution at room temperature 2 hr. The solution was immediately acidified, but the only product isolated was the α-diketone (XI) and no evidence for the α-ketol was found in the reaction mixture.

Reduction of the trans-2-acetoxy-α-tetrahydrosantonin (XI) *with zinc and acetic acid.* A solution of 0.10 g. of the *trans*-ketol acetate (IX) in 2 cc. of glacial acetic acid was heated to reflux with 1.0 g. of acid-washed zinc dust 24 hr. After removal of the zinc, the reaction mixture was evaporated under reduced pressure, and the residue was mixed with aqueous bicarbonate and extracted with ether. The ether solution was water washed, dried and evaporated to leave 0.08 g. (quantitative) of α-tetrahydrosantonin (I), melting in the range 128–144°. Recrystallization from ethanol gave colorless plates, m.p. and mixed m.p. 154–156°.

In preliminary experiments, attempts were made to remove the acetoxy group in the ketol acetate by the procedure reported earlier for related compounds.[20,21] Thus, each epimer (IX or X) of ketol acetate was heated to reflux with zinc dust in acetic acid (or acetic anhydride) 10 min., but the starting material was completely recovered. Even on prolongation of the reflux time to 1 hr., IX was completely recovered while X gave a mixture probably consisting of IX and X resulting from partial epimerization.

Clemmensen reduction of the cis- and trans-2-acetoxy-α-tetrahydrosantonin (IX *and* X). The above *trans*-ketol acetate (IX, 0.1 g.) in 2 cc. of toluene was refluxed for 8 hr. with 1.0 g. of zinc amalgam in 1.5 cc. of concentrated hydrochloric acid and 0.5 cc. of water. Then, 1.5 cc. each of concentrated hydrochloric acid was added to refluxed reaction 3 times at intervals of 4 hrs. After removal of zinc amalgam, the reaction mixture was salted out and extracted with ether. The organic layer was washed with water, dried, and evaporated under reduced pressure. There was obtained 0.06 g. (84%) of the above 3-desoxy compound (VII) of I, melting in the range 135–147°. Recrystallization from ethanol afforded colorless plates, m.p. and mixed m.p. 150–153°.

By the same procedure, the *cis*-ketol acetate (X) was reduced to VII in almost the same yield.

Dimethylene thioketal (XIV) *of the trans-2-acetoxy-α-tetrahydrosantonin* (IX). To a solution of 0.81 g. of the *trans*-ketol acetate (IX) in 10 cc. of glacial acetic acid was added 0.5 cc. of ethanedithiol and 1.0 cc. of boron trifluoride–ether complex. After standing at room temperature 5 hr., the mixture was poured into 100 cc. of ice water, and the separated solid (XIV, 1.05 g., quantitative), m.p. 214–217°, was recrystallized from ethanol to afford colorless plates, m.p. 219–220°; $[\alpha]_D^{26}$ +27.9° ($CHCl_3$; c 1.47); $\nu_{C=O}^{CHCl_3}$ 1736 cm.$^{-1}$ (acetyl) and 1767 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{19}H_{28}O_4S_2$: C, 59.36; H, 7.28. Found: C, 59.03; H, 7.25.

According to the procedure reported previously for α-tetrahydrosantonin (I),[15b] the *trans*-ketol acetate (IX, 1.0 g.) in glacial acetic acid was allowed to stand 5 hr. with ethanedithiol in the presence of *p*-toluenesulfonic acid. However, the starting material was substantially recovered.

Dimethylene thioketal (XV) *of the cis-2-acetoxy-α-tetrahydrosantonin* (X). Employing the conditions described above for the *trans*-epimer (IX), the *cis*-ketol acetate (X, 0.85 g.) was treated with ethanedithiol using boron trifluoride–ether complex as a catalyst. There was obtained white solid (XV, 0.99 g., 94%), melting in the range 160–194°. Recrystallization from ethanol afforded colorless plates, m.p. 200–203°; $[\alpha]_D^{26}$ +35.6° ($CHCl_3$; *c* 0.87); $\nu_{C=O}^{CHCl_3}$ 1733 (acetyl) and 1770 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{19}H_{28}O_4S_2$: C, 59.36; H, 7.28. Found: C, 59.49; H, 7.32.

Like IX, X remained unaffected on treatment with ethanedithiol in the presence of *p*-toluenesulfonic acid.

Conversion of the dimethylene thioketal (XV) *of X into the trans-epimer* (XIV). A solution of 0.05 g. of the *cis*-acetoxy thioketal (XV) in 6 cc. of dioxane was refluxed 20 hr. Evaporation of the reaction solution under reduced pressure gave 0.05 g. (quantitative) of the *trans*-epimer (XIV), m.p. and mixed m.p. 219–220°.

When the reflux time was shortened to 12 hr., XV was almost completely recovered.

Like the thioketal (XV), the less stable ketol acetate (X) was completely epimerized to IX by the same procedure (refluxing 20 hr.), and was recovered on shortening of the reflux time (10 hr.).

Reduction of the dimethylene thioketal of trans-2-acetoxy-α-tetrahydrosantonin (XIV) *with Raney nickel.* A solution of 0.25 g. of the *trans*-acetoxy thioketal (XIV) in 30 cc. of purified dioxane was heated to reflux with 2.5 g. of Raney nickel on a water bath 10 hr. After removal of nickel, evaporation of the reaction mixture under reduced pressure left 0.14 g. (77%) of the above 3-desoxy compound (VII), m.p. 141–145°. Recrystallization from ethanol gave colorless plates, m.p. and mixed m.p. 150–153°.

Substitution of dioxane by ethanol in this reduction led to almost the same result, but using of acetone as a solvent gave only substantial recovery of the starting material.

Reduction of the dimethylene thioketal of cis-2-acetoxy-α-tetrahydrosantonin (XV) *with Raney nickel.* Exactly as described above for the *trans*-epimer (XIV), the *cis*-acetoxy thioketal (XV, 0.25 g.) was treated with Raney nickel in dioxane to give 0.16 g. (88%) of VII, m.p. and mixed m.p. 150–152° (after recrystallization from ethanol). Using ethanol in place of dioxane reduced the yield of VII to 77%, while use of acetone gave a quantitative recovery of the starting material.

Acknowledgment. The author wishes to thank Professor M. Yanagita for his helpful suggestions and continued interest during the course of this work. The author is also indebted to Mr. K. Kotera and Mr. T. Takahashi, both of the Tanabe Seiyaku Co., Ltd., Osaka, Japan, for determination and interpretation of the infrared spectra in this work.

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[CONTRIBUTION FROM THE PHARMACEUTICAL LABORATORY, MEDICAL SCHOOL, KEIO UNIVERSITY]

Santonin and Related Compounds. XX.[1] Some Transformation Reactions of 2-Bromo-γ-tetrahydrosantonin[2]

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The monobromo derivative (II) of γ-tetrahydrosantonin (I) was submitted to the same reactions as reported earlier for the derivative of α-tetrahydrosantonin. The reaction sequence (II → III → IV → VII) gave conclusive evidence for the structure (II) of the bromoketone. The acid (VII) from the olefin (IV) was readily isomerized to IX with acid. Acetolysis of the bromoketone (II) led to the more stable epimer (XII) of the ketol acetate, while lead tetraacetate oxidation of I afforded only the less stable epimer (XIII). The transformations of these ketol acetates were undertaken as described for the α-isomer. Marked differences in reactivity were observed in various types of reaction of the isomeric pairs of the α- and γ-series, in which the isomers of the α- series were always more reactive. This steric situation is in accord with the generality suggested previously for the juncture isomers of the simpler decalin systems.

In an earlier paper of this series,[1] some reactions of the monobromo derivative of α-tetrahydrosantonin have been described, by which the 2-bromo structure for this compound was definitely proved. From the reasons discussed there[1] and for the purpose of comparison, it is desirable to extend the same sequence of reactions (II→III→IV→VII) to the monobromo derivative of γ-tetrahydrosantonin (I), which is of *cis*-decalin type.

Like the monobromide in the α-series,[1] the monobromo-γ-tetrahydrosantonin (II), prepared from I with bromine,[3] possesses the bromine atom in the equatorial position, as evidenced by the shift of absorption maxima in the ultraviolet ($\Delta\lambda_{max}^{CHCl_3}$ −37 mμ and $\Delta\lambda_{max}^{EtOH}$ −34 mμ)[4,5] and infrared spectra ($\Delta\nu_{C=O}$ +15 cm.$^{-1}$)[6] over those of the parent ketone (I). Sodium borohydride reduction of the bromoketone (II) resulted in an almost quantitative yield (95%) of one isomer (III) of the bromohydrin, and no evidence for the simultaneous production of the other isomer was obtained. This indicated that the borohydride reduction of II proceeded in more highly stereoselective manner than in the α-series.[1] The bromohydrin was refluxed with methanolic potassium hydroxide for 4 hr. to give the parent ketone (I), identified as the semicarbazone. From this, it is deduced that in the bromohydrin (III), the hydroxyl group at the 3-position is *cis*- to the bromine, assuming an axial conformation. The configuration of this hydroxyl group was further supported by the observation that catalytic hydrogenation of the bromohydrin with palladium-charcoal in an alkaline medium led quantitatively to the known hexahydrosantonin (VI), where the hydroxyl group was previously proved to be axial.[7] Zinc dust and acetic acid hydrogenation of III gave in 82% yield an olefin, but requiring much longer reaction period compared with the α-series.[1] The Δ²-structure (IV) for this olefin was based on the infrared spectrum, $\nu_{C=C}$ 1653 cm.$^{-1}$ and $\nu_{CH=}$ 718 and 697 cm.$^{-1}$ (*cis*-disubstituted double bond)[1,8] and the nonidentity with the Δ³-isomer reported previously.[9] Catalytic hydrogenation of IV gave the 3-desoxy-γ-tetrahydrosantonin (V),[9] prepared by the Clemmensen reduction of I. As compared with the Δ²-olefin in the α-series, IV was more difficulty oxidized with permanganate in pyridine solution in the presence of magnesium sulfate. The only product, isolated in 25% yield, was a diacid, m.p. 220–222°. When the oxidation period was shortened, a glycol (VIII), besides the diacid, was obtained in 10% yield, the structure of which followed from the analytical data and the mode of its formation.

In the α-series, the oxidation of tetrahydrosantonin with fuming nitric acid was shown to afford the diacid identical with the compound obtained from the Δ²-olefin with permanganate.[1] In contrast to this result, oxidation of γ-tetrahydrosantonin (I) with fuming nitric acid, which took place more slowly, led in a very low yield (17%) to a diacid, m.p. 248–250°, differing from the above acid. For these two diacids, three structures (VII, IX, X) are possible, of which the last one, assuming a boat form, appears most unlikely. On analogy with the α-series, the lower melting diacid may be assigned the structure (VII) retaining the original lactone ring, and hence, the other isomer the struc-

(1) Paper XIX, K. Yamakawa, *J. Org. Chem.*, **24**, 897 (1959).

(2) This work was supported in part by the Grant in Aid for Scientific Research from the Japanese Ministry of Education.

(3) (a) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955). (b) M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 1268 (1958) and related references cited there.

(4) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(5) Obviously, these decreases of the absorption maxima are unusual, but the similar anomaly has been reported with the ultraviolet spectrum of *cis*-9-methyl-3-decalone 2,4-dinitrophenylhydrazone (ref. 10).

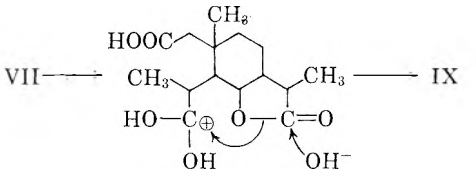
(6) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).

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

(8) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, Methuen & Co. Ltd., London, 1954, p. 33.

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

ture (IX) with the inverted lactone ring. These formulations are supported by comparison of the infrared spectra. The lower melting diacid exhibited a single carbonyl band ($\nu_{C=O}^{Nujol}$ 1709 cm.$^{-1}$), which is similar to those of the diacid in the α-series[1] and of *cis*- and *trans*-1-methylcyclohexane-1,2-diacetic acid.[10,11] On the other hand, the higher melting diacid exhibited the carbonyl band as a doublet ($\nu_{C=O}^{Nujol}$ 1704 and 1733 cm.$^{-1}$), presumably being attributed to the different properties of the two carbonyl groups. Since the more stable diacid (IX) was completely recovered unchanged from the warm alkali solution by acidification, the less stable isomer (VII) would be expected to be converted to IX on alkali treatment. However, this expectation was not realized, and acidification on the alkali solution of VII gave only an oil, which could not be induced to crystallize. It is presumed that these two isomeric lactones did not form the same triacid on alkali hydrolysis. This isomerization was found to be readily effected by warming of VII with concentrated hydrochloric acid, giving a quantitative yield of IX. For explanation of this isomerization, a mechanism based on attack of a proton on the carboxyl oxygen of the carbonyl group in VII and subsequent inversion of the lactone ring in the resulting carbonium ion (XI) to form IX was proposed.



XI

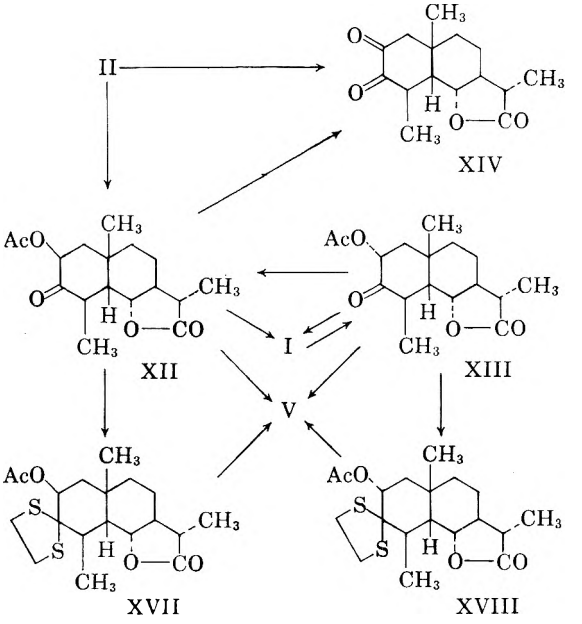
The foregoing result led to the conclusion that, like α-tetrahydrosantonin, the γ-isomer (I) was invariably attacked by electrophilic reagents (Br^+ or OH^+) at the 2-position, indicating the preference of the Δ^2- over the Δ^3-enolization of the carbonyl group at the 3-position.

Acetolysis of the 2-bromoketone (II) and lead tetraacetate oxidation of I were carried out as described with the corresponding compounds in the α-series. Refluxing of II with potassium acetate in acetic acid gave in 61% yield an epimer, m.p. 247°, of ketol acetate. Another epimer, m.p. 187–188.5°, was obtained from I by lead tetraacetate oxidation in glacial acetic acid. However, contrary to the case in the α-series,[1] the latter epimer was the only isoluble product even when the oxidation was conducted at the reflux temperature for 6 hr., and the lowering of the reaction temperature considerably reduced the yield of this product. On analogy with the formulation in the α-series,[1] the higher melting epimer of the ketol acetate is assigned the structure (XII) with the equatorial acetoxyl group, while the other epimer the structure (XIII) with the axial acetoxyl group. It was shown[1] that in the α-series, the ready conversion of the less stable ketol acetate into the other epimer was effected by refluxing in acetic acid for 6 hr. That XIII is inert to epimerization under these conditions is shown by the above observation on the lead tetraacetate oxidation of I. It was found, however, XIII was converted to XII completely after refluxing 24 hr. in acetic acid. This result gave conclusive evidence for the configuration of the acetoxyl group in the ketol acetates (XII and XIII). It seems of interest that on lead tetraacetate oxidation, both α-[1] and γ-tetrahydrosantonin were preferentially attacked at the 2-position by the acetoxyl radical from the axial side. Also, it is notable that each 2-bromoketone in both series on acetolysis gave, as the only isoluble product, the respective 2-ketol acetate bearing the acetoxyl group in the equatorial position. Though the yields of the ketol acetates were not so high (*ca.* 60%),

(10) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **21**, 500 (1956).

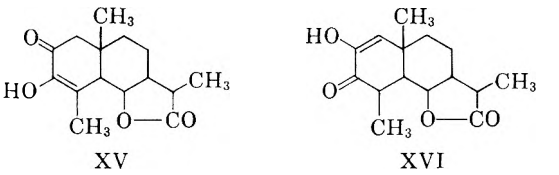
(11) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **22**, 291 (1957).

these acetolyses may be considered to occur in an stereospecific manner[12] and with no rearrangement. However, there remained a possibility that the acetolysis of the bromoketones would initially form the less stable epimer of the corresponding ketol acetate, followed by the complete epimerization to the other epimer. In the γ-series, this possibility can be excluded by the above observation that the less stable epimer (XIII) is inert to refluxing acetic acid under such conditions.



Reductive removal of the acetoxyl group in these ketol acetates with zinc dust in refluxing acetic acid proceeded much less readily, compared with that of the α-isomers.[1] Under the conditions employed for quantitative conversion of the more stable epimer of the α-ketol acetate into the parent ketone in the α-series, XIII was partly reduced to I, but XII was completely recovered unchanged. Even on prolonged reflux, the latter gave a 50% yield of I with a lesser amount of the recovered material. The similar difference in reactivity has been observed in reduction of the axial and equatorial acetoxyl groups in some ketol acetates of steroid.[13]

Clemmensen reduction or alkali treatment of the ketol acetates took place as in the case of the α-series,[1] giving, respectively the above 3-desoxy compound (V) or an α-diketone (XIV), as the single products isolated. The latter product, which was also obtained from the bromoketone II by treatment with alkali, showed positive ferric chloride test and gave a glyoxime, but, unlike the α-isomer,[1] no quinoxaline was formed on fusion with *o*-phenylenediamine. In the above hydrolysis of the acetate and the bromide, no evidence for formation of the expected ketol or diacid was obtained. The α-diketones in the α-and γ-series had, respectively, λ_{max}^{EtOH} 278.5 mμ (ε 10,000)[1] and 275.5 mμ (ε 6,600). For each of the α-diketones, two enol structures XV and XVI) are possible, whose maxima may be expected to be 280 mμ and 270 mμ, respectively.[11,14] From these data, it appears that both the α-diketones in the α- and γ-series exist predominantly in the Δ^3-enol structure (XV), and that the α-isomer tends mainly, but γ- isomer partly, to the enol form in keto-enol equilibration.



The ketol acetates (XII and XIII) were treated with ethane dithiol in the presence of boron trifluoride–ether complex to give the corresponding dimethylene thioketals (XVII and XVIII), both of which afforded the same 3-desoxy compound (V) on hydrogenolysis with Raney nickel. These sequences almost parallel those in the α-series.[1] However, unlike the α-isomer, XVIII could not be epimerized to XVII by refluxing with dioxane. Under more strenuous conditions it was converted to an untractable oil.

Previous works from our laboratory have shown that in the juncture isomers of the simple 9-methyl decalin compounds, the *cis*-isomer is always less reactive than the *trans* one.[11,15,16] In more complex decalin systems, a similar difference in reaction rates has been observed in bromination of the tetrahydrosantonins[3a] and their derivatives[17] in the α- and γ-series and of coprostan-3-one and cholestan-3-one.[18] Also, it has been reported by Evans and Shoppee[19] that methanolysis of tosylates of coprostanol proceeded more slowly than that of the

(12) It was reported [M. Provita, J. O. Jilek, L. Novk, E. Adlerover, V. Simak, and E. Knobloch, *Chem. Abstr.*, **50**, 4048 (1956)], that the α-monobromide of 2-methyl-2-carbethoxycyclohexanone afforded an epimeric mixture of the ketol acetate on acetolysis under similar conditions.

(13) For example see F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953).

(14) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd Ed., Reinhold Publishing Corp., New York, 1949, p. 195; F. E. King, T. J. King, and J. M. Ross, *J. Chem. Soc.*, 3995 (1954); N. L. Wendler and D. Taub, *Chem. & Ind. (London)*, 1237 (1957).

(15) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956).

(16) Futaki [*J. Org. Chem.*, **23**, 451 (1958)] claimed that the relative reactivity of the juncture isomers of 2,9-dimethyl-3-decalone toward bromine is opposite to this generalization. On reinvestigation, however, it was found that this observation is erroneous and no apparent difference in reactivities exists in these isomers.

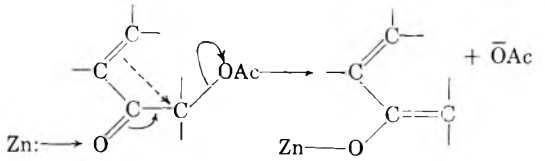
(17) M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 443 (1958).

(18) O. H. Wheeler and J. L. Mateos, *J. Org. Chem.*, **22**, 605 (1957).

(19) D. D. Evans and C. W. Shoppee, *J. Chem. Soc.*, 540 (1953).

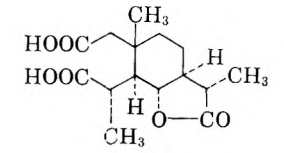
same derivatives of cholestanol. The present work added a number of examples involving the same relationship in reactivity of isomeric pairs in the α- and γ-tetrahydrosantonin series. This generality, however, which covers various types of reaction, is now referred only to the ring carbons at the 2- and 3-positions in the 9-methyl decalin systems. Furthermore, it is an outstanding problem whether the above generalization would be extended to the other positions in the 9-methyl decalin systems.[20,21]

It has been reported that the unsaturated ketol acetates with the double bond adjacent to the carbonyl group in the 9-methyl decalin systems were smoothly reduced to the ketone by treatment with zinc dust in hot acetic acid, acetic anhydride or xylene.[13,22,23] Compared with these previous results, the hydrogenolysis of the saturated ketol acetates of the tetrahydrosantonin, as described above, proceeded much less slowly under similar conditions. The greater reactivity of the unsaturated ketol acetate in this reaction can be readily rationalized by the assumption that in the unsaturated system (XIX), the ethylene double bond would accelerate the intermediate formation of the enol (XX) by the conjugation with the newly formed olefinic double bond and by its anchimeric assistance in the alkyl-oxygen fission, as pictured in XIX and XX.

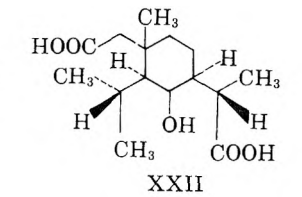


XIX XX

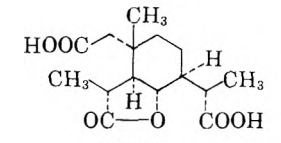
The marked difference in stabilities of the isomers of diacid lactone (XXI and VII, respectively) in the α- and γ-series, described above, will be discussed from a conformational viewpoint. In the triacid (XXII), resulting from the lactone ring opening of the α-isomer (XXI), the two α-propionic acid side chains are symmetrically arranged with respect to the hydroxyl group. Of these, the one at the 3-position should be strongly pushed by the adjacent bulky *gem*-substituents closer to the hydroxyl group than the other. This steric effect would prefer the formation of the inverted lactone (XXIII) rather than that of the original lactone (XXI). However, the former, which is represented by XXIV, is less favored than the latter (the conformation XXV) by a severe nonbonded interaction between the two methyl groups at the 4- and 5-position, the strength of which is nearly equivalent to the *meta*-diaxial effect. That the latter effect is much more significant than the steric interaction between the two substituents at the 2- and 5-positions, is shown by the reported results that XXI was completely recovered unchanged from the alkaline solution by acidification.[1] In the γ-series, the diacid-lactones (VII and IX) can be described by the conformations XXVI and XXVII, respectively. From the molecular models, it can seen that in XXVI, the axial α-propionic side chin should suffer severe steric repulsions by the adja-



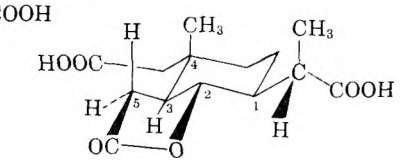
XXI



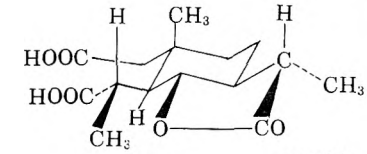
XXII



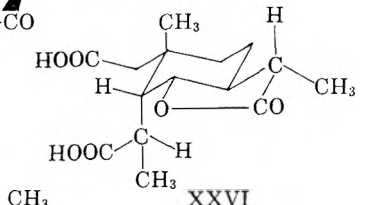
XXIII



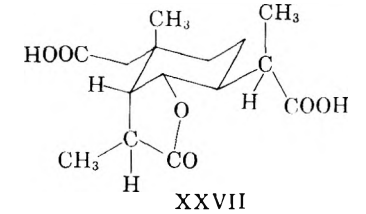
XXIV



XXV



XXVI

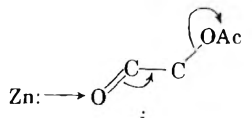


XXVII

(20) It has been recently reported [M. Idelson and E. I. Becker, *J. Am. Chem. Soc.*, **80**, 908 (1958)] that the tosylate of *cis*-9-hydroxylmethyldecalin is similarly resistant to hydrogenolysis with Raney nickel as the same derivatives of the *trans*- isomer, although the former appears more open than the latter. This indicates that the above generalization may not be extended at ease.

(21) It has been shown [H. B. Henbest and B. J. Lovell, *Chem. & Ind. (London)*, 278 (1956)] that on treatment with potassium bicarbonate, the percentage hydrolysis of each isomer of 3-acetoxy-5-hydroxy derivatives of coprostane. The relative reactivity of these compounds may be more strongly influenced by factors other than the present steric effect.

(22) R. B. Woodward *et al.* [*J. Am. Chem. Soc.*, **74**, 4223 (1952)] have offered an explanation for the mechanism of the facile removal of the acetoxyl group in the α-ketol acetate, as symbolized in i:

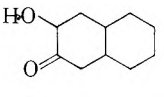


i

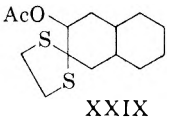
(23) C. Amendolla, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 1226 (1954); L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4377 (1953).

cent equatorial substituents as well as the axial *meta*-hydrogens on the cyclohexane ring. This interference would be greatly relieved by the formation of the lactone ring with the adjacent hydroxy group as in XXVII. Moreover, the rule that the *cis*-γ-lactone ring is more stable than the *trans*-one may strongly favor XXVII in stability over XXVI. These steric factors are responsible to the facile isomerization of VII into IX, cited here.

After the present work was completed, an interesting paper of Ali and Owen[24] has appeared describing the studies on the 2-hydroxy-3-decalone (decalin 2,3-ketol) bearing no substituent at the ring juncture. Certain properties reported for these ketols and their derivatives are markedly different from those of analogous compounds with the angular methyl group at the ring juncture which were described in the present and earlier papers[25] of this series. First, it was shown[24] that both *cis*- and *trans*-ketols (XXVIII) are rather stable to alkali, as indicated by the mode of its preparation involving the alkaline hydrolysis of the 2-chloro or 2-acetoxy-decalone. This is in a sharp contrast to the unsuccessful attempt on isolation of the ketol from hydrolysis of the analogous derivatives of 9-methyl-3-decalone[11,25] and tetrahydrosantonins. Second, each isomer of dimethylene thioketals



XXVIII



XXIX

(XXIX) of the ketol acetate was readily reduced with Raney nickel into the individual acetoxy compound in the usual manner, unlike the same derivatives (*e.g.* XVII and XVIII) of tetrahydrosantonins. From these observations, it is obvious that in the simpler 3-decalone systems, the angular methyl group at the 9-position exerts a significant influence on the course of reactions of these compounds, causing an increase in the reactivity of the substituent at the 2-position. Compared with the juncture isomers in the decalin systems, in this case, an enhancement in the steric compression of the whole molecule increases significantly the reactivity of the substituent.

EXPERIMENTAL[26]

All temperatures are uncorrected. Rotations were determined in a 0.5-dm. semimicro tube; infrared absorption spectra were measured with a Perkin-Elmer Model 21 double-beam spectrophotometer.

γ-Tetrahydrosantonin (I). According to the method reported by Cocker and McMurry,[7] sodium santoninate (from 2.5 g. of α-santonin) was hydrogenated over platinic oxide to give the tetrahydro acid (2.33 g.), melting in the range 95–100°. Recrystallization from dilute ethanol gave colorless plates (1.56 g., 62%), m.p. 194°. Reported,[7] m.p. 190–191°.

This acid (1.53 g.) was heated to reflux 2 hr. in benzene (30 cc.) with *p*-toluenesulfonic acid (0.4 g.). The reaction mixture was washed with sodium bicarbonate and water, and after drying, evaporated to leave 1.41 g. (99%) of γ-tetrahydrosantonin (I), melting in the range 94–103°. Recrystallization from dilute ethanol gave colorless prisms, m.p. and mixed m.p. 101–103°. The absorption spectra of I was given in a previous paper.[1]

2-Bromo-γ-tetrahydrosantonin (II). This was prepared from γ-tetrahydrosantonin (I) with bromine as described previously.[3a] It had m.p. 145.5–146° (dec.); $\lambda_{max}^{CHCl_3}$ 252 mμ (ε 71) and λ_{max}^{EtOH} 252 mμ (ε 65); $\nu_{C=O}$ 1770 (γ-lactone) and 1724 cm.$^{-1}$ (cyclohexanone ring) (Nujol). Reported,[3a] m.p. 144–146°.

Reduction of 2-bromo-γ-tetrahydrosantonin (II) *with sodium borohydride.* According to the procedure described earlier for 2-bromo-α-tetrahydrosantonin,[1] the 2-bromo-ketone (II, 1.0 g.) was reduced with sodium borohydride (0.12 g.). A white complex solid from the reaction was decomposed by refluxing 2 hr. in 50 cc. of benzene with 3 cc. of 10% hydrochloric acid. The benzene solution was washed with bicarbonate solution, and evaporated to give 0.95 g. (95%) of *2-bromo-hexahydrosantonin*, m.p. 210–214° (dec.). Recrystallization from ethanol afforded colorless needles, m.p. 215–217° (dec.); $[\alpha]_D^{26}$ −13.8° ($CHCl_3$; c 0.87); $\nu_{C=O}$ 1764 cm.$^{-1}$ (γ-lactone), and ν_{OH} 3472 and 1292 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{15}H_{23}BrO_3$: C, 54.38; H, 6.95. Found: C, 54.48; H, 6.69.

Reaction of the 2-bromohexahydrosantonin (III) *with methanolic alkali.* This was carried out similarly as described earlier for the 2-bromohexahydrosantonin in the α-series.[1] A solution of 0.14 g. of the bromohydrine (III) and 0.025 g. of potassium hydroxide in 5 cc. of methanol was heated to reflux 4 hr. The product was a viscous oil (0.11 g.) which could not be induced to crystallize. The oil formed 0.075 g. of a semicarbazone, melting in the range 205–215° (dec.). Recrystallization from ethanol afforded colorless plates, m.p. 240–242° (dec.), undepressed on admixture with the same derivative of γ-tetrahydrosantonin.[3a]

Anal. Calcd. for $C_{16}H_{25}O_3N_3$: N, 13.67. Found: N, 13.93.

Catalytic hydrogenation of the 2-bromohexahydrosantonin (III) *in basic medium.* Hydrogenation of 0.20 g. of the bromohydrin (III) over palladium-charcoal was carried out exactly as described earlier for the 2-bromohydrin in the α-series.[1] There was obtained 0.165 g. (98%) of crystalline solid, melting in the range 203–210°. Recrystallization from ethanol afforded colorless prisms, m.p. 210–212°. It showed no depression of the melting point on admixture with the hexahydrosantonin (VI), prepared by hydrogenation of γ-tetrahydrosantonin (I) with platinic oxide essentially by the method reported previously.[7]

Reduction of the 2-bromohexahydrosantonin (III) *with zinc dust and acetic acid.* Essentially as described earlier for the bromohydrin in the α- series,[1] 0.50 g. of the bromohydrin (III) was heated to reflux with zinc dust (1.0 g.) in glacial acetic acid (10 cc.), but the refluxing time was prolonged to 16 hr. There was obtained 0.29 g. (82%) of the Δ^2-olefin (IV) as colorless needles, melting in the range 82–90°. Recrystallization from petroleum ether gave colorless needles, m.p. 88–90°; $[\alpha]_D^{26}$ +20.0° ($CHCl_3$; *c* 1.40); $\nu_{C=O}$ 1770 cm.$^{-1}$, $\nu_{C=C}$ 1653 cm.$^{-1}$, $\nu_{HC=}$ 718 and 692 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.60; H, 9.56.

Catalytic hydrogenation of the olefin (IV) with platinic oxide gave quantitatively the 3-desoxy-γ-tetrahydrosantonin (V), melting in the range 75–83°. Recrystallization from ethanol afforded colorless plates, m.p. 85–86°. It showed no depression of the melting point on admixture with a sample, prepared by the Clemmensen reduction of I as reported previously.[9]

(24) M. E. Ali and L. N. Owen, *J. Chem. Soc.*, 2111 (1958).

(25) M. Yanagita and A. Tahara, *J. Org. Chem.*, **18**, 792 (1953); *cf.* reference 10.

(26) Microanalyses were carried out by Mrs. Ch. Inayama and ultraviolet measurement by Miss M. Suzuki, both of this school.

Oxidation of the Δ^2*-olefin* (IV) *with potassium permanganate.* Under the same conditions as described for the α-Δ^2-olefin,[1] 0.2 g. of the above olefin (IV) was oxidized with potassium permanganate, except the powdered permanganate was added in a period of 3.5 hr. and then the mixture was stirred 3 hr. in the ice bath. There was obtained 0.04 g. (25%) of the *diacid* (VII), melting in the range 204–216°. Recrystallization from water afforded colorless prisms, m.p. 220–222°; $[\alpha]_D^{26}$ −4.28° (EtOH; c 1.40); $\nu_{C=O}$ 1709 (carboxyl) and 1795 cm.$^{-1}$ (γ-lactone) (Nujol).

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.17; H, 7.59.

Hoping to raise the yield of VII, the oxidation was conducted under the milder conditions. Thus, to a cooled mixture of 0.48 g. of the olefin (IV) and 8.0 g. of magnesium sulfate hydrate in 8.5 cc. of pyridine was added 0.65 g. of potassium permanganate with vigorous stirring. The addition was completed in about 2 hr., and the stirring was continued for additional 1 hr. After an excess of permanganate was decomposed with methanol, the mixture was filtered, and the residual manganese dioxide was washed with 40 cc. of hot water. The wash water, combined with the filtrate, was allowed to stand in a refrigerator overnight. The separated *glycol* (VIII, 0.05 g.), melting in the range 140–165° was recrystallized from ethanol to give colorless prisms, m.p. 176°; $[\alpha]_D^{25}$ −24.2° ($CHCl_3$; c 0.33).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.19; H, 8.80.

The aqueous filtrate, removed from VIII, was worked up as described earlier for the olefin in the α-series.[1] There was obtained 0.08 g. of the diacid (VII), melting in the range 191–215°, which was recrystallized from water to give colorless prisms, m.p. and mixed m.p. 220–222°.

Oxidation of γ*-tetrahydrosantonin* (I) *with nitric acid.* This oxidation was carried out at higher temperatures than that described earlier for the α- isomer.[1] To a 2 cc. of fuming nitric acid (d = 1.52) containing 0.01 g. of ammonium vanadate was slowly added 0.2 g. of γ-tetrahydrosantonin (I). Contrary to the case of the α- isomer, the reaction at room temperature was only slightly exothermic and no apparent evolution of a red gas was observed. The mixture was heated 3 hr. on a water bath. The acidic oily product, which solidified partly, was triturated with a little ethyl acetate to give 0.04 g. (17%) of the *diacid* (IX), melting in the range 240–247°. Recrystallization from water afforded colorless prisms, m.p. 248–250°; $[\alpha]_D^{26}$ −22.4° (EtOH; c 1.07); $\nu_{C=O}$ 1704, 1733 (carboxyl), and 1770 cm.$^{-1}$ (γ-lactone) (Nujol).

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.11; H, 7.17.

A solution of 0.02 g. of IX in 0.5 cc. of 5% aqueous sodium hydroxide was heated on a water bath for 30 min. Acidification of the solution yielded 0.018 g. (90%) of the starting material.

Conversion of VII *into* IX *with acid.* The diacid (VII, 10 mg.) was heated 2 hr. in 0.2 cc. of concentrated hydrochloric acid. The solution was evaporated under reduced pressure to leave IX as pale yellow crystals, m.p. 238–245°. Recrystallization from water afforded colorless prisms, m.p. and mixed m.p. 247–250°.

Treatment of VII with alkali as described above for IX gave a viscous oil, which could not be induced to crystallize.

Reaction of 2-bromo-γ*-tetrahydrosantonin* (II) *with anhydrous potassium acetate.* Essentially as described for the α-isomer,[1] acetolysis of the bromoketone (II) was carried out, but the refluxing period in acetic acid was prolonged. Thus, a mixture of 1.0 g. of the 2-bromoketone (II) and 1.5 g. of anhydrous potassium acetate in 10 cc. of glacial acetic acid was refluxed 10 hr. The mixture was poured into ice water (60 cc.), and *cis-2-acetoxy-*γ*-tetrahydrosantonin*[27] (XII) separated as colorless crystals (0.57 g., 61%), melting in the range 197–206°. Recrystallization from ethanol afforded colorless needles, m.p. 247°; $[\alpha]_D^{26}$ −36.0° ($CHCl_3$; c 1.00); λ_{max}^{EtOH} 275 mμ (ϵ 45.0); $\nu_{C=O}$ 1770 (γ-lactone), 1745 (cyclohexanone ring), and 1733 cm.$^{-1}$ (acetyl) (in $CHCl_3$ solution).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.49; H, 7.72.

Oxidation of γ*-tetrahydrosantonin* (I) *with lead tetraacetate in glacial acetic acid.* (a) *On the boiling water bath.* As described earlier for α-tetrahydrosantonin, 0.10 g. of the γ-ketone (I) was heated 6 hr. with 0.20 g. of lead tetraacetate in 20 cc. of glacial acetic acid on the boiling water bath. There was obtained 15 mg. (12%) of *trans-2-acetoxy-*γ*-tetrahydrosantonin* (XIII), melting in the range 160–175°. Recrystallization from ethanol afforded colorless prisms, m.p. 187–188.5°; $[\alpha]_D^{26}$ −24.3° ($CHCl_3$; c 1.73); λ_{max}^{EtOH} 274 mμ (ϵ 90.0); $\nu_{C=O}$ 1776 (γ-lactone), 1770 (cyclohexanone ring), and 1733 cm.$^{-1}$ (acetyl) (in $CHCl_3$ solution).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.13; H, 7.84.

(b) *At reflux temperature.* As described earlier for the α-isomer,[1] the above reaction mixture was heated to reflux 6 hr. The *trans*-acetoxyketone (XIII, 0.05 g., 40%), melting in the range 170–184°, was obtained, which gave the pure sample, m.p. and mixed m.p. 187–188.5° (from ethanol).

Even when the reflux time was prolongated to 12 hr., the yield of XIII could not be improved.

Conversion of trans-2-acetoxy-γ*-tetrahydrosantonin* (XIII) *into the cis-epimer* (XII). The *trans*-ketol acetate (XIII, 0.02 g.) was heated to reflux 24 hr. in glacial acetic acid (3 cc.). Evaporation of the solution under reduced pressure gave quantitatively the *cis*-ketol acetate (XII), m.p. 235–241°, which was recrystallized from ethanol to give the pure sample, m.p. and mixed m.p. 246–248°.

Alkali treatment of cis- and trans-2-acetoxy-γ*-tetrahydrosantonin* (XII *and* XIII). As described earlier for the α-isomer,[1] a solution of the *cis*-ketol acetate (XII, 0.05 g.) in 0.25*N* ethanolic potassium hydroxide, which showed a strong yellow fluorescence, was allowed to stand 3 hr. at room temperature. There was obtained 0.03 g. (70%) of *2-keto-*γ*-tetrahydrosantonin* (XIV), melting in the range 140–150°. Recrystallization from ethanol gave colorless plates, m.p. 174–176°; $[\alpha]_D^{26}$ −190° ($CHCl_3$; c 0.60); λ_{max}^{EtOH} 275.5 mμ (ϵ 6600); $\nu_{C=O}$ 1684 (α,β-unsaturated ketone) and 1789 cm.$^{-1}$ (γ-lactone), $\nu_{C=C}$ 1658 cm.$^{-1}$ and ν_{OH} 3484 cm.$^{-1}$ (free) (in $CHCl_3$ solution). It showed a dark violet coloration with ferric chloride.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.99; H, 7.32.

A *glyoxime*, m.p. 220–226° (dec.), obtained in a moderate yield, was recrystallized from ethanol to give colorless prisms, m.p. 230–232° (dec.). It showed a light red coloration with nickel salt.

Anal. Calcd. for $C_{15}H_{22}N_2O_4$: C, 61.20; H, 7.53; N, 9.52. Found: C, 61.55; H, 7.39; N, 9.53.

Exactly as described above, the *trans*-ketol acetate (XIII 0.05 g.) was treated with alkali to give 0.015 g. (35%) of the same diketone (XIV), melting in the 160–170°; the pure sample, m.p. and mixed m.p. 175–176° (from ethanol).

Alkali treatment of 2-bromo-γ*-tetrahydrosantonin* (II). Treatment of the bromoketone (II, 0.20 g.) with alkali, exactly as described earlier for the α- isomer,[1] gave 0.05 g. (31%) of the above α-diketone (XIV), m.p. 166–173°; the pure sample, m.p. and mixed m.p. 174–176° (from ethanol).

Reduction of cis- and trans-2-acetoxy-γ*-tetrahydrosantonin* (XII *and* XIII) *with zinc and acetic acid.* As described earlier for *trans*-2-acetoxy-α-tetrahydrosantonin,[1] 0.05 g. of the *cis*-ketol acetate (XII) was heated to reflux 24 hr. with zinc dust (0.3 g.) in glacial acetic acid (2.5 cc.). There resulted complete recovery of the starting material, m.p. and mixed m.p. 235–247°. When the refluxing was continued 50 hr. with 0.5 g. of zinc dust in the above system,

(27) The term *cis-trans-* refers to the configuration of the acetoxyl group in relation with the angular methyl group at the 9- position; *cf.* ref. 1.

there was obtained an oil which solidified mostly. Fractional recrystallization from ethanol afforded 0.01 g. of the starting material (XII), m.p. 225–235°; the pure sample, m.p. and mixed m.p. 247–249°. On standing for a few days, the mother liquors of XII deposited 0.02 g. (50%) of γ-tetrahydrosantonin as colorless prisms, m.p. 88–94°; the pure sample, m.p. and mixed m.p. 98–100° (from dilute ethanol).

The *trans*-ketol acetate (0.05 g.), as described above, was refluxed 24 hr. with zinc dust to give an oil which solidified mostly. Trituration with a little methanol afforded 0.025 g. (62%) of γ-tetrahydrosantonin (I), m.p. 83–90°; the pure sample, m.p. and mixed m.p. 98–100° (from methanol).

Clemmensen reduction of cis- and trans-2-acetoxy-γ-tetrahydrosantonin (XII *and* XIII). Employing the conditions described earlier for 2-acetoxy-α-tetrahydrosantonin,[1] the *cis*-ketol acetate (XII, 0.10 g.) was reduced by the Martin modification of the Clemmensen method. There was obtained 0.07 g. (92%) of the 3-desoxy-γ-tetrahydrosantonin (V), m.p. 73–81°; the pure sample, m.p. and mixed m.p. 85–86° (from ethanol).

On a similar treatment, the *trans*-ketol acetate (XIII, 0.10 g.) gave 0.07 g. (92%) of the 3-desoxy compound (V), m.p. 69–76°; the pure sample, m.p. and mixed m.p. 85–86° (from ethanol).

Dimethylene thioketals of cis- and trans-2-acetoxy-γ-tetrahydrosantonin (XII *and* XIII). As described earlier for the 2-acetoxy-α-tetrahydrosantonin,[1] 0.34 g. of the *cis*-ketol acetate (XII) was allowed to stand 48 hr. with 0.3 cc. of ethane dithiol and 0.7 cc. of boron trifluorid-ether complex in 5 cc. of acetic acid. The crude dimethylene thioketal (XVII, quantitative), melting in the range 140–161°, was recrystallized from ethanol to give 0.22 g. (57%) of colorless prisms, m.p. 176–177.5°; $[\alpha]_D^{26}$ −58.3° ($CHCl_3$; *c* 1.27); $\nu_{C=O}$ 1783 (γ-lactone) and 1751 cm.$^{-1}$ (acetyl) (in $CHCl_3$ solution).

Anal. Calcd. for $C_{19}H_{28}O_4S_2$: C, 59.36; H, 7.28. Found: C, 59.61; H, 7.12.

By the same procedure, the *trans*-ketol acetate (XIII, 0.50 g.) formed the dimethylene thioketal (XVIII, 0.59 g., 95%), melting in the range 130–152°. Recrystallization from ethanol gave 0.46 g. (74%) of colorless prisms, m.p. 163–165.5°; $[\alpha]_D^{26}$ −32.3° ($CHCl_3$; *c* 1.33); $\nu_{C=O}$ 1779 (γ-lactone) and 1748 cm.$^{-1}$ (acetyl) (in $CHCl_3$ solution).

Anal. Calcd. for $C_{19}H_{28}O_4S_2$: C, 59.36; H, 7.28. Found: C, 59.25; H, 7.57.

Attempted epimerization of the dimethylene thioketal (XVIII) *of* XIII. Exactly as described earlier for the *cis*-acetoxy thioketal in the α- series,[1] the dimethylene thioketal (XVIII) was heated to reflux in dioxane, but the starting material was completely recovered. When the refluxing time was prolonged to 50 hr., XVIII was converted to an oil which could not be induced to crystallize.

Reduction of the dimethylene thioketals (XVII *and* XVIII) *of the ketol acetates with Raney nickel.* As described earlier for the same derivatives of the ketol acetate in the α-series,[1] 0.06 g. of the dimethylene thioketal (XVII) of the *cis*-ketol acetate was heated to reflux 30 hr. with Raney nickel (0.6 g.) in dioxane (10 cc.). There was obtained 0.03 g. (82%) of the above 3-desoxy-γ-tetrahydrosantonin (V), m.p. 63–72°; the pure sample, m.p. and mixed m.p. 85–86°.

By the same procedure, the dimethylene thioketal (XVII) of the *trans*-ketol acetate was converted to the 3-desoxy compound (V) in good yield.

Acknowledgment. The authors wish to thank Mr. K. Kotera of the Tanabe Seiyaku Co. Ltd., Osaka, Japan, for determination and interpretation of the infrared spectra in this work.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX S.A.]

Steroids. CXIX.[1] The Preparation of Some Vicinal Glycols in the Cortical Hormone Series

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Osmylation of Δ⁶-dehydrocortisone acetate and Δ⁶-dehydro-9α-fluorohydrocortisone acetate proceeds in dioxane solution to yield the corresponding 6α,7α-dihydroxy analogs of cortisone acetate and 9α-fluorohydrocortisone acetate. When Δ⁶-dehydroprednisone acetate is similarly treated a mixture of 6α,7α-dihydroxyprednisone acetate and 1α,2α-dihydroxy-Δ⁶-dehydrocortisone acetate is obtained.

The findings that in the cortical hormone series 16α-hydroxylation[2] as well as 16α,17α-acetal or ketal formation[3] markedly influence biological properties prompted us to investigate a number of steroid vicinal glycols. This paper reports the synthesis of four such compounds.

Thus when Δ⁶-dehydrocortisone acetate (Ia)[4] was allowed to stand for four or five days at room temperature in dioxane solution with osmium tetroxide there was obtained, following hydrogen sulfide decomposition of the osmic ester,[5] a mixture of starting material and 6α,7α-dihydroxycortisone acetate (IIa). This mixture was readily resolved by chromatography to provide the pure 6α,7α-dihydroxy compound (IIa), characterized as its 6α,7α-acetonide (III). In our hands the addition of small quantities of pyridine[2] to the osmylation mixture did not improve the yield.

An identical procedure with Δ⁶-dehydro-9α-

(1) Paper CXVIII. H. J. Ringold, J. Perez Ruelas, E. Batres, and C. Djerassi. *J. Am. Chem. Soc.*, in press.

(2) S. Bernstein, R. A. Lenhard, W. S. Allen, M. Heller, R. Littel, S. M. Stolar, L. I. Feldman, and R. H. Blank, *J. Am. Chem. Soc.*, **78**, 5693 (1956).

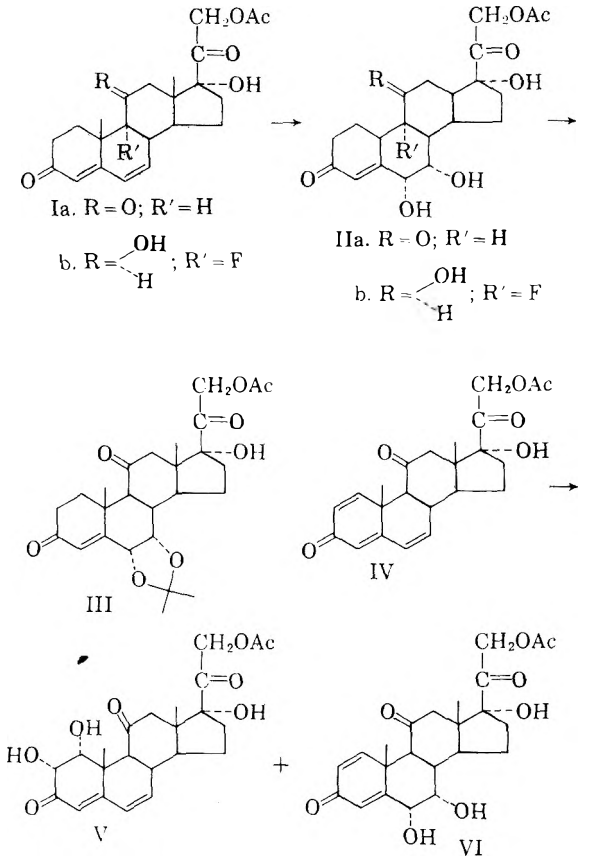
(3) J. Fried, A. Borman, W. B. Kessler, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **80**, 2338 (1958).

(4) V. R. Mattox, E. L. Woroch, G. A. Fleisher, and E. C. Kendall, *J. Biol. Chem.*, **197**, 261 (1952).

(5) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2090 (1956).

fluorohydrocortisone acetate (Ib)[6] led to the isolation of 6α,7α-dihydroxy-9α-fluorohydrocortisone acetate (IIb).

When Δ⁶-dehydroprednisone acetate (IV)[7] was treated under the above conditions a difficultly separable mixture of 1α,2α-dihydroxyΔ⁶-dehydrocortisone acetate (V) and 6α,7α-dihydroxyprednisone acetate (VI) resulted. While it was not possible to obtain satisfactory analytical results for the 1α,2α-dihydroxy compound (V), the spectral data proved to be in accord with the proposed structure.



The assignment of the α- configurations to the above products has been made solely on the basis that attack from the rear[8] is a more probable steric course considering the large bulk of osmium tetroxide.

Bioassays[9] of IIa, IIb, III, and VI indicate that all the compounds are considerably less potent than their parent steroids in terms of thymolytic and anti-inflammatory activity.

(6) R. F. Hirschman, R. Miller, R. E. Beyler, L. H. Sarett, and M. Tishler, *J. Am. Chem. Soc.*, **77**, 3166 (1955).

(7) D. Gould, E. L. Shapiro, H. L. Herzog, M. J. Gentles, E. B. Hershberg, W. Charney, M. Gilmore, S. Tolksdorf, M. Eisler, and P. Perlman, *J. Am. Chem. Soc.*, **79**, 502 (1957).

(8) L. F. Fieser, *Experientia*, **6**, 312 (1950); T. F. Gallagher and T. H. Kritchevsky, *J. Am. Chem. Soc.*, **72**, 882 (1950).

(9) We wish to thank Dr. R. I. Dorfman of the Worcester Foundation, Shrewsbury, Mass., for these assays.

EXPERIMENTAL[10]

6α,7α-Dihydroxycortisone acetate (IIa). Dioxane (50 ml.) containing 3.46 g. of Δ⁶-dehydrocortisone acetate (Ia)[4] and 3.46 ml. of pyridine was allowed to stand at room temperature for 5.5 days with 2.0 g. of osmium tetroxide. The mixture was then saturated with hydrogen sulfide and filtered through a pad of filter aid. The resultant colored filtrate was evaporated to dryness and taken up in 50 ml. of methanol. By stirring for 20 min. with 10 g. of neutral alumina and 2 g. of decolorizing carbon and then filtering, the solution was almost completely decolorized and gave upon evaporation to dryness 2.6 g. of noncrystalline material, λ_{max}^{EtOH} 238–240 and 280 mμ, log ε 3.84 and 4.00. Following adsorption on 50 g. of Florisil and elution with methylene chloride, 0.7 g. of crude starting material was recovered as indicated by its ultraviolet spectrum (λ_{max}^{EtOH} 280–282 mμ, log ε 4.21). Further elution with increasing polar mixtures of methylene chloride–acetone provided in the methylene chloride–acetone (1:1) fraction 1.06 g., m.p. 225–240°, λ_{max}^{EtOH} 236–238 mμ, log ε 3.81. By repeated recrystallizations from methanol–ethyl acetate 0.17 g. of pure 6α,7α-dihydroxycortisone acetate (IIa) was obtained, m.p. 273–276°, $[\alpha]_D$ +210° (pyridine), λ_{max}^{EtOH} 238–240 mμ, log ε 4.00.

Anal. Calcd. for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96; O, 29.46. Found: C, 64.05; H, 7.18; O, 28.98.

6α,7α-Dihydroxycortisone acetate 6,7-acetonide (III). To 20 ml. of acetone containing 150 mg. of 6α,7α-dihydroxycortisone acetate (IIa) was added 5 drops of 78% perchloric acid. After 1 hr. at room temperature 5 drops of pyridine was added and the resultant solution was evaporated to dryness under reduced pressure. Water (5 ml.) was added to the residue and it was then extracted several times with 10 ml. of ethyl acetate. The pooled extracts were washed to neutrality with water, dried over sodium sulfate, and evaporated to dryness. The residue upon trituration with methanol gave 60 mg. of crystals m.p. 273–277°. Four additional recrystallizations from the same solvent furnished the pure acetonide III m.p. 279–282°, $[\alpha]_D$ +242° (chloroform) λ_{max}^{EtOH} 240 mμ, log ε 4.11.

Anal. Calcd. for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22; O, 26.98. Found: C, 66.05; H, 7.15; O, 26.76.

6α,7α-Dihydroxy-9α-fluorohydrocortisone acetate (IIb). Following the procedure previously described, 1.0 g. of Δ⁶-dehydro-9α-fluorohydrocortisone acetate (Ib)[6] was treated for 5 days with a large excess of osmium tetroxide (1.0 g.). The resulting semicrystalline product, 1.0 g., λ_{max}^{EtOH} 238–240 mμ, log ε 3.92, was then chromatographed on 20 g. of silica gel. Elution with benzene–ether (2:3) and pure ether yielded 0.58 g. of crystals m.p. 223–227° which after repeated recrystallization from acetone–ether exhibited the m.p. 251–253°, $[\alpha]_D$ +68° (pyridine), λ_{max}^{EtOH} 238 mμ, log ε 3.95.

Anal. Calcd. for $C_{23}H_{31}O_8F$: C, 60.78; H, 6.87. Found: C, 61.23; H, 6.96.

1α,2α-Dihydroxy-Δ⁶-dehydrocortisone acetate (V) *and 6α,7α-dihydroxyprednisone acetate* (VI). To 100 ml. of dioxane containing 1.65 g. of Δ⁶-dehydroprednisone acetate (IV)[7] was added 1.0 g. of osmium tetroxide and the mixture was kept at room temperature for 4 days. Following saturation with hydrogen sulfide and filtration through a pad of filter aid there was obtained a clear solution which upon evaporation to dryness provided 1.40 g. of crystalline material. This was then adsorbed on 60 g. of Florisil whereupon elution with methylene chloride–acetone (8:2) and (1:1) provided 1.10 g. of crystals m.p. 239–241°, λ_{max}^{EtOH} 244 mμ and 276–280 mμ, log ε 3.94 and 4.06. After six recrystallizations from methanol 85 mg. of pure 6α,7α-dihydroxyprednisone acetate (VI) was obtained m.p. 290–292° dec., $[\alpha]_D$ +109° (pyridine), λ_{max}^{EtOH} 238 mμ, log ε 4.11.

(10) We are indebted to Dr. L. Throop and staff for all spectral and rotational determinations.

Anal. Calcd. for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53; O, 29.60. Found: C, 63.78; H, 6.81; O, 29.36.

Evaporation of the mother liquors from the first recrystallization yielded 0.5 g. of noncrystalline material λ_{max}^{EtOH} 234–238 mμ, log ε 3.88 whereas combination and evaporation of the mother liquors from the following two recrystallizations gave *ca.* 0.2 g. of crystals λ_{max}^{EtOH} 276–280 mμ, log ε 3.96. This latter substance was then adsorbed on 6 g. of silica gel from a solution of methylene chloride. Elution of the column with methylene chloride–acetone (9:1) led to 60 mg. of crystals which were recrystallized four times from acetone thus providing 1α,2α-dihydroxy-Δ⁶-dehydrocortisone acetate (V) m.p. 235–238°, $[\alpha]_D$ +230° (pyridine), λ_{max}^{EtOH} 280 mμ, log ε 4.32. The poor analytical results cannot be ascribed to dehydration since the substance gave no color with ferric chloride and the ultraviolet absorption spectra was not altered by addition of alkali.

Anal. Calcd. for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53. Found: C, 64.92; H, 6.83.

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MEXICO, D. F.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Alkaloids of Tobacco Smoke. I. Fractionation of Some Tobacco Alkaloids and of the Alkaloid Extract of Burley Cigarette Smoke by Gas Chromatography[1]

LOUIS D. QUIN

Received November 18, 1958

An alkaloid extract from Burley tobacco cigarette smoke was separated by gas chromatography on polyglycol columns. It was necessary to perform the separation under three sets of conditions to overcome difficulties associated with the wide boiling range of the mixture and the relatively massive amount of nicotine present. There appears to be a minimum of sixteen alkaloidal or basic compounds, in addition to nicotine, boiling above 150–170° in the extract. Besides its analytical features, the gas chromatographic method is valuable in isolation and purification of the alkaloids.

It has been known for many years that other alkaloids in small quantities accompany nicotine in tobacco smoke,[2] but much uncertainty exists as to the identity and amounts of these compounds. The recent paper chromatographic work of Kuffner, Schick, and Bühn[3] has done much to clarify in a qualitative manner the alkaloidal content of cigar smoke. They were able to show that many of the alkaloids in the smoke were present in the tobacco itself. However, definitive studies are lacking on cigarette smoke, which differs from cigar smoke in several respects. We have recently undertaken a study of the alkaloids in a continuation of our work on the chemical composition of cigarette smoke.[4]

It was anticipated that the tobacco alkaloids, generally boiling in the range 200–300°, might be subject to separation by the versatile technique of gas chromatography. This hope was realized and in a preliminary communication[5] we reported the successful application of gas chromatography to these compounds. It was found that good separation of a majority of the alkaloids studied could be achieved at moderate temperatures (about 190°) on 1 meter columns containing certain polyglycols as the stationary liquid phase. The list of known alkaloids studied has been extended since this initial report; a complete list with the retention times on three different columns is provided as Table I.

TABLE I

GAS CHROMATOGRAPHY OF INDIVIDUAL TOBACCO ALKALOIDS

Liquid Phase	Columns and Conditions: Polypropylene glycol[a]	Polybutylene glycol[b]	Polyethylene glycol[c]
Temp., °C.	190	180	190
He flow, ml./min.	45	50	48
	Retention Time, Min.		
3-Pyridyl methyl ketone	4.3	3.1	4.3
3-Pyridyl ethyl ketone	6.1	5.0	5.3
3-Pyridyl *n*-propyl ketone	8.1	7.0	6.6
Nicotine	8.6	8.2	5.2
Nornicotine	16.1	14.3	12.3
Myosmine	16.4	14.7	13.4
Anabasine	19.4	18.1	13.8
Nicotyrine	21.0	18.3	19.4
Metanicotine	23.5	20.9	16.5
Anatabine	25.2	22.5	21.1
2,3′-Dipyridyl	31	26	29
N-Methyl nicotinamide	42	30	64
Nornicotyrine	73	55	101
Cotinine	79	63	85

[a] Mol. wt. 1025. [b] Mol. wt. 1500. [c] Mol. wt. 20,000.

(1) Supported by a grant from the Damon Runyon Memorial Fund. Presented at the Twelfth Tobacco Chemists' Research Conference, October 23, 1958, Durham, N. C.

(2) The literature has been recently reviewed: A. I. Kosak in *The Biologic Effects of Tobacco*, ed. by E. L. Wynder, Little, Brown and Co., Boston, Mass., 1955, p. 15; A. I. Kosak, *Experientia*, 10, 69 (1954); L. Marion in *The Alkaloids*, ed. by R. H. F. Manske and H. L. Holmes, Acedemic Press, N. Y., N. Y., 1950, Vol. 1, p. 228.

(3) F. Kuffner, K. Schick, and H. Bühn, *Monatsh.*, 87, 749 (1956).

(4) Preceding paper: L. D. Quin and M. E. Hobbs, *Anal. Chem.*, 30, 1400 (1958).

(5) L. D. Quin, *Nature*, 182, 865 (1958).

The coverage of known tobacco alkaloids is seen to be quite broad. Only one alkaloid studied, oxynicotine, failed to be eluted under the conditions employed. The eluted substances in every case were shown by their ultraviolet absorption spectra to be identical with the starting compounds.

In the present paper, we describe the application of gas chromatography to the separation of the alkaloid-containing fraction of cigarette smoke. In the following paper,[6] the identification of a number of the alkaloids in this fraction is described.

Nicotine appears to account for 90% or more of the alkaloid fraction of cigarette smoke under consideration here;[7] the several other alkaloids are consequently present as trace constituents. It has been found expedient to perform the gas chromatographic separation of the gross mixture under three different sets of conditions to provide adequate overall resolution and overcome the interference of nicotine in the elution of neighboring peaks. Polypropylene glycol (mol. wt. 1025)) as the stationary liquid phase has given the most complete resolution of the mixture and was used in this study.

At a column temperature of 140–150°, the alkaloids or other bases emerging before nicotine were resolved on a 1 m. by 6 mm. column (Fig. 1).

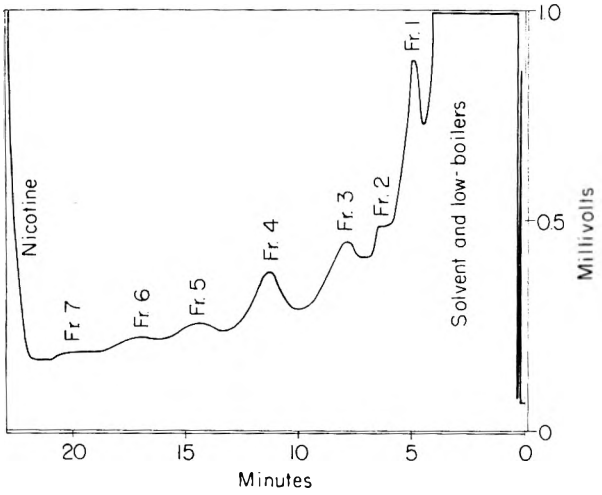

Fig. 1. Gas chromatogram of alkaloid fraction from smoke of 4.4 cigarettes, showing pre-nicotine peaks. Temp., 145°C. He flow, 47 ml. per min. Detector voltage, 8.0. Sensitivity, 1/2. Column, 1 m. × 6 mm. P.P.G. 1025

Seven peaks were noted (Fractions 1–7). These appear to be due to substances boiling above about 170°, as suggested by the elution of 2,4-lutidine (b.p. 157°) and collidine (b.p. 172°), when run separately under the same conditions, in shorter retention times than those of any of these peaks. Lower boiling bases are possibly present but are obscured here by the large solvent peak. At this relatively low temperature, the column is overloaded with nicotine, resulting in the elution of this compound in a broad, asymmetric peak. The run is terminated when nicotine breaks through.

At 190°, the alkaloids immediately following nicotine are resolved (Fig. 2). A column of wider diameter (10 mm. o.d.) was desirable for this portion of the separation, as it permitted a relatively large nicotine load to be placed on the column without an asymmetric, tailing peak resulting. The increased size of the column necessitated faster helium flow rates to obtain sample elution in reasonable times. Six peaks (Fractions 8–13) were readily detected after the nicotine had been eluted. The peaks appearing before nicotine (not shown on Fig. 2) differ somewhat in number and relative

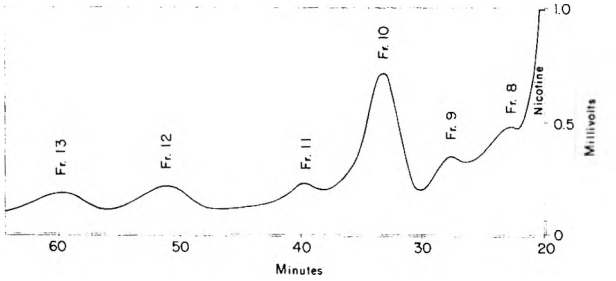

Fig. 2. Gas chromatogram of alkaloid fraction from smoke of 4.4 cigarettes, showing immediate post-nicotine peaks. Temp., 190°C. He flow, 73 ml. per min. Detector voltage, 8.0. Max. sensitivity. Column, 1 m. × 10 mm. P.P.G. 1025

position from those obtained in the previous separation as Fractions 1–7. Large differences in temperature, helium flow, and column diameter exist between the two separations, and some or all of these variables may be responsible for this fact.

The higher boiling alkaloids are more readily examined on the smaller diameter column; retention times are of a more desirable magnitude, and no interference by the nicotine occurs with these outlying peaks. At 190°, three peaks (Fig. 3, Fractions 14–16) appeared after the final peak recorded in the preceding portion of the separation.

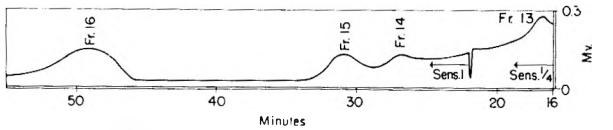

Fig. 3. Gas chromatogram of alkaloid fraction from smoke of 4.4 cigarettes, showing late post-nicotine peaks. Temp., 190°C. He flow, 72 ml. per min. Detector voltage, 8.0. Column, 1 m. × 6 mm. P.P.G. 1025

Tentatively assuming homogeneity of each peak, it is seen that a minimum of sixteen substances accompany nicotine in the alkaloid fraction of cigarette smoke. The possibilities exist that other

(6) L. D. Quin, *J. Org. Chem.*, 24, 914 (1959).

(7) The isolation procedure is specifically designed for the study of the high-boiling bases; low boilers such as pyridine, etc., are probably lost. It should be noted that all of the bases discovered in this work have not yet been established as being truly alkaloidal in the sense that they are pyridine derivatives. However for convenience this fraction will be referred to as the alkaloid fraction.

substances are present but in concentrations too small to be detected, or that some substances originally present are destroyed in the isolation or chromatographic procedures. It is also possible that alkaloids are present of too little volatility to be gas chromatographed under the conditions used so far.

The resolution provided by the above conditions is generally inadequate for obtaining pure samples of the eluted compounds. However, by re-chromatographing a collected eluate, a specimen free of forerunning compounds can generally be obtained for other studies. Even in an extreme case, such as Fraction 8, which is riding on the nicotine tail, collection and re-chromatography provided a nicotine-free sample (Fig. 4). In some cases, re-chromatography on a different column might be advantageous.

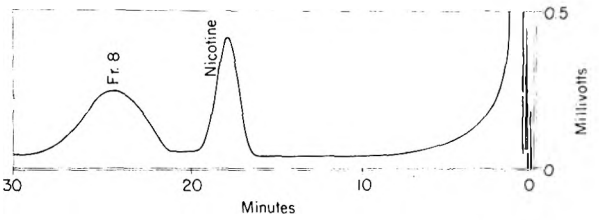

Fig. 4. Gas chromatogram of Fraction 8. Temp., 190°C. He flow, 72 ml. per min. Detector voltage, 8.0. Max. sensitivity. Column, 1 m. × 10 mm. P.P.G. 1025

The conditions developed in this study are subject to modification and improvement. Longer columns would improve the resolution of neighboring peaks. Also, it is likely that column packings having greater stability and better selectivity will be discovered. It is felt, however, that the present method provides satisfactory separation of a complex mixture of tobacco alkaloids, and should be useful in the study of such mixtures from sources other than cigarette smoke. It is also possible that certain other alkaloid families having slight volatility and good thermal stability will be separable by this or a related gas chromatographic technique.

EXPERIMENTAL

Isolation of alkaloid fraction of cigarette smoke. One hundred 70 mm. cigarettes of Burley tobacco, without additives, were humidified over a saturated sodium bromide solution for several days and smoked five at a time on an automatic machine to a butt length of 20 mm. Puffs of 2 seconds duration and 35 ml. volume were taken every minute. The smoke was passed through a 4.5 cm. circular glass-fiber filter of the type described by Wartman and Harlow.[8] The filter was replaced after each cycle. The particulate-free gas from the filter was passed through a trap chilled in Dry Ice-ethanol. The filters, trap, and connecting tubing were thoroughly washed with 1*N* HCl (400 ml. total) and this solution then continuously extracted with benzene for 3 days. The benzene was changed each day, stripped to 1 ml., and examined by gas chromatography to monitor removal of volatile acidic or neutral material. No evidence for such material was found after the third day of extraction. The acid solution was then made *p*H 11 with solid sodium hydroxide and the benzene extraction continued for three days. The extract was concentrated to 1.0 ml. and stored in the refrigerator for later use. This solution contains about 0.5 g. of total alkaloids.

Gas chromatographic equipment. The Perkin-Elmer Vapor Fractometer Model 154-B was used. A Fenwall Thermoswitch No. 17502 was installed to improve high-temperature stability of the instrument. The heater on the sample injection block was placed on line voltage to permit a temperature giving prompt sample vaporization. The vent line outside the thermostatted chamber was shortened to 6 in. and fitted with a Nichrome wire heater to prevent sample condensation therein. A Leeds and Northrup Speedomax type G recorder set at 1 mv. full scale deflection detected the elution peaks.

Samples were injected with either a syringe or the Perkin-Elmer "Micro dipper" pipets. For collection of eluted samples, 3 mm. o.d. glass U-tubes of 30 cm. total length were immersed in a Dry Ice bath and attached directly to the vent line.

The carrier gas was helium. The flow rate was measured with a soap-bubble meter.

Columns were U-tubes, 1 m. long, of 6 mm. or 10 mm. o.d. glass tubing. They were packed with mixtures of the stationary liquid phase on Firebrick (Fisher "Columpak") in the weight ratio of 1 to 4. Acidic material was first removed from the Firebrick by washing with 2% alcoholic potassium hydroxide; it was then washed with absolute alcohol and dried at 110°.

Column packings. Several materials were screened for suitability as the stationary liquid phase. The following gave sharp, symmetrical elution peaks for the alkaloids and were sufficiently stable and nonvolatile to permit their continued use for 2–3 weeks or more: polypropylene glycol, mol. wt. 1025 or 2025 (Union Carbide Chemicals Co.); polybutylene glycol, mol. wt. 1500 (Dow Chemical Co.); polyethylene glycol, mol. wt., 20,000 (Dow), or 4000 (Carbide). Polystyrene glycol, mol. wt. 750 (Dow) was found to be too volatile, and Hyprose SP 80 (Dow, octakis (2-hydroxypropyl) sucrose) too unstable, at 190°, but both gave satisfactory peaks and may find use at lower temperatures. Flexol R2H (Carbide, a polyester) and Apiezon M grease gave tailing peaks and poor selectivity.

Gas chromatography of individual alkaloids. Twenty μl. aliquots of benzene solutions each containing 5–10 mg. per ml. of a known alkaloid were chromatographed on three different columns. Conditions and retention times are given in Table I. The alkaloids were collected as eluted and dissolved in 95% ethanol to obtain solutions suitable for ultraviolet spectral analysis. The spectra, obtained on a Warren Spectracord, checked in every case with those of the known alkaloids run simultaneously.

Gas chromatography of cigarette smoke alkaloids. Samples of the concentrated benzene extract were run under numerous conditions during this study. Since the best resolution was obtained with a stationary liquid phase of polypropylene glycol, mol. wt. 1025, this material was used in the procedures finally adopted. Chromatography was performed under three sets of conditions on different aliquots of the benzene extract. Some typical conditions are summarized in Table II. In each case the injected sample was 50 μl. of the extract, representing about 25 mg. of total alkaloids, or the smoke of 4–5 cigarettes. All peaks were reproduced in different smoke preparations; typical chromatograms are presented as Figs. 1–3.

Purification by re-chromatography is illustrated with Fraction 8. This fraction was collected from three consecutive 50 μl. smoke extract samples, the trap rinsed with 1 ml. of benzene into a 3-in. testtube, and the solvent evaporated to

(8) W. B. Wartman and E. S. Harlow, presented before the Division of Agricultural and Food Chemistry, 133rd National Meeting of the American Chemical Society, San Francisco, April 15, 1958.

TABLE II

FRACTIONATION OF CIGARETTE SMOKE ALKALOIDS BY GAS CHROMATOGRAPHY

Separation Performed:	Pre-nicotine	Immediate Post-nicotine	Late Post-nicotine
Column[a]	1 m. × 6 mm.	1 m. × 10 mm.	1 m. × 6 mm.
Temp., °	145	190	190
He rate, ml./min.	47	75	60
Retention time of nicotine, min.	24[b]	18	5.5
Retention time of other peaks	4.9, 6.2, 7.9, 11.3, 14.4, 17.0, 20	23, 28, 33, 39, 51, 60	27, 31, 49

[a] Packed with polypropylene glycol, mol. wt. 1025, on Firebrick, 1:4. [b] On separately run sample.

about 50 μl. with a stream of nitrogen. This solution was then chromatographed under the same conditions used in collection of the original sample. The chromatogram is shown as Fig. 4.

Acknowledgment. The author expresses appreciation to Dr. Marcus E. Hobbs for his advice and interest during this work. The technical assistance of John M. Flowers, Jr., during portions of the work is acknowledged. Generous samples of tobacco alkaloids were supplied by the American Tobacco Co., Dr. R. F. Dawson of Columbia University, and Drs. R. N. Jeffrey and T. C. Tso of the U. S. Department of Agriculture. The cooperation of the Research Laboratory of the Liggett and Myers Tobacco Co. is acknowledged.

DURHAM, N. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Alkaloids of Tobacco Smoke. II. Identification of Some of the Alkaloids in Burley Cigarette Smoke[1]

LOUIS D. QUIN

Received November 18, 1958

By combinations of gas and paper chromatography and ultraviolet spectroscopy, myosmine, nornicotine, anabasine, anatabine, 2,3′-dipyridyl, and cotinine have been conclusively identified in Burley tobacco cigarette smoke. Rough determinations were made for the quantities of these substances and of nicotine in the smoke.

In the preceding paper,[2] a gas chromatographic method for the separation of an alkaloid extract obtained from Burley tobacco cigarette smoke was described. A number of the compounds producing the observed chromatographic peaks have been identified, some for the first time in cigarette smoke. Approximate figures for the amounts of the identified alkaloids were also obtained by the gas chromatographic method, providing the first published data on the secondary alkaloid content of tobacco smoke.

The gas chromatographic technique of separation was advantageous in that it easily provided crude samples of the individual alkaloids from a mixture by simply condensing them from the gas stream as they were eluted. These samples can then be purified by re-chromatography to remove impurities eluted in close proximity and collected simultaneously. Only when compounds are eluted at essentially the same time does this procedure fail to provide a pure specimen. This procedure avoided the time consuming and tedious operations of fractional crystallization, extraction, or distillation employed in the past for alkaloid separations. The specimens obtained generally contained a trace of the material used as the stationary liquid phase in the column, but this did not interfere with the subsequent work. This impurity could probably be removed if necessary.

The retention time of each gas chromatographic fraction from the alkaloid extract of cigarette smoke was observed on columns of polypropylene glycol (mol. wt. 1025) and of polyethylene glycol (mol. wt. 20,000). These were compared with the retention times of known alkaloids obtained under identical conditions. Checks on both columns between a known and a compound of smoke origin provided a tentative identification. The different retentive ability of the two columns for the various alkaloids[3] made this a reliable cross-checking procedure. In one case, this technique failed to provide distinction between two compounds; myosmine and nornicotine were eluted more or less together on

(1) Supported by a grant from the Damon Runyon Memorial Fund. Presented at the Twelfth Tobacco Chemists' Research Conference, October 23, 1958, Durham, N. C.

(2) L. D. Quin, *J. Org. Chem.*, **24**, 911 (1959).

(3) See Table I, ref. 2.

both columns, and a smoke alkaloid fraction having the same retention time could not be identified as one or the other of these two alkaloids. Paper chromatography, however, later proved the presence of both alkaloids in this fraction, In another case, a fraction thought to be homogeneous and indicated to be anabasine on the polypropylene glycol column actually was found to be a mixture when it gave two peaks on the polyethylene glycol column. Paper chromatography also indicated the presence of anabasine and another alkaloid in this fraction.

For final identification, the purified smoke alkaloid fraction was generally chromatographed on paper together with the known(s) suggested by gas chromatography. If the R_f values checked in the two solvent systems used, it was considered that conclusive identification of the smoke alkaloid was obtained. In two cases, ultraviolet absorption spectra were recorded for the alkaloids to assist in the identification work.

By the above techniques, it was shown that myosmine, nornicotine, anabasine, anatabine, 2,3′-dipyridyl, and cotinine are present in Burley tobacco cigarette smoke. The experimental data are summarized in Table I. The first two of these compounds constitute fraction 10 and the others, fractions 11, 12, 13, and 16, respectively, appearing on the gas chromatograms reproduced in the preceding paper.[2] Among these compounds, cotinine has never been reported as a constituent of tobacco smoke, although it has recently been found in tobacco.[4] Nornicotine, anabasine, 2,3′-dipyridyl, and anatabine have not been identified previously in cigarette smoke, but have been detected recently in cigar smoke[5] and are well known alkaloids of tobacco itself. Myosmine has been known for some time to be a constituent of cigar smoke;[6] it has recently been detected in the smoke of high nornicotine-content cigarettes.[7]

The other chromatographic peaks have not yet been associated with specific compounds. None correspond with some of the available knowns studied, namely, nicotyrine, metanicotine, *N*-methyl nicotinamide, and nornicotyrine. There is preliminary evidence that pyridyl alkyl ketones may be present; however, adequate proof of these has not yet been obtained.

The failure to detect nicotyrine in the smoke extract is interesting, since this compound has been reported to be a constituent of tobacco smoke.[5,8] It was considered possible that it may have been present in the smoke but was not recovered by the isolation procedure. That this may be true was found by the failure to detect nicotyrine in a synthetic mixture of alkaloids including this substance which had been subjected to the isolation procedure used in obtaining the smoke sample. Metanicotine also failed to survive the isolation procedure. The conclusion, therefore, cannot be drawn that a substance is absent from smoke unless it is known that the substance is recoverable under the experimental conditions.

The amount of cotinine in the smoke extract was determined by comparing the area of its gas chromatographic peak with the area from a sample of known, and approximately the same, concentration. A value of 57 micrograms of cotinine per cigarette smoked was thus obtained. A nicotine analysis performed similarly gave a value of 5.08 mg. per cigarette. The validity of this figure was demonstrated when a closely checking value (5.18 mg. per cigarette) was obtained for the extract by the established method for nicotine analysis of Cundiff and Markunas.[9]

Insufficient quantities of the pure individuals prevented a similar direct determination of the other identified alkaloids. However, a rough determination was made by relating the peak areas due to these compounds on a single chromatogram to the area obtained from chromatographing a known amount of myosmine under the same conditions. This procedure does not make allowance for any differences in area-weight relationships among the alkaloids, and the values must be considered as approximate for the present. The following values for micrograms per cigarette smoked were obtained: myosmine–nornicotine, 88; anabasine, 11;[10] anatabine, 14; 2,3′-dipyridyl, 7. It is hoped these values will be refined in future work, and that individual figures for myosmine, nornicotine, and anabasine can be obtained.

EXPERIMENTAL

Isolation and purification of smoke alkaloids. As described previously,[2] desired fractions were collected from the gas chromatographic separation of the alkaloid extract of Burley tobacco cigarette smoke and purified by re-chromatography. Generally, three 50 μl. aliquots, representing about 15 cigarettes smoked, were chromatographed to obtain sufficient material for further study. The final products of the isolation procedure were 50–100 μl. of benzene solutions of the alkaloids of interest.

Identification by comparative gas chromatography. Ten to 20 μl. aliquots of the above solutions were chromatographed on each of 1 m. by 6 mm. columns containing polypropylene glycol, mol. wt. 1025 and polypropylene glycol, mol. wt. 20,000, on alkali-washed Firebrick in the weight ratio of 1 to 4. Experimental conditions varied from one identification run to another, but the temperature was generally about 190° and helium flow about 40–55 ml. per min. Selected

(4) W. G. Frankenburg and A. A. Vaitekunas, *J. Am. Chem. Soc.*, **79**, 149 (1957).

(5) F. Kuffner, K. Schick, and H. Bühn, *Monatsh.*, **87**, 749 (1956).

(6) A. Wenusch and R. Schöller, *Fachl. Mitt. österr. Tabak-Regie*, **2**, 2 (1933).

(7) J. M. Moseley and C. H. Rayburn, Abstracts of Papers, Eleventh Tobacco Chemists' Research Conference, October 10–11, 1957, New Haven, Conn.

(8) A. Wenusch, *Der Tabakrauch*, A. Geist, Bremen, 1939.

(9) R. H. Cundiff and P. C. Markunas, *Anal. Chem.*, **27**, 1650 (1955).

(10) Including another alkaloid, unidentified, which is present in this fraction.

TABLE I

IDENTIFICATION OF SMOKE ALKALOIDS

	Retention Time, Min.		P_f Values		λ_{max}, mμ	
	I[a]	II[b]	I[c]	II[d]	First	Second
Fraction 10	13.5	13.9	18, 88	33, 61		
Nornicotine	13.3	13.2	18	33		
Myosmine	13.5	14.0	87	60		
Fraction 11	17.4	11.8, 13.6	18, 97	42, 90		
Anabasine	17.4	13.6	17	43		
Fraction 12	23.2	20.9	27	35		
Anatabine	23.0	20.8	27	35		
Fraction 13	20.0	23.2	[e]	[e]	274	238
2,3′-Dipyridyl	20.1	23.0	[e]	[e]	274[f]	238[f]
Fraction 16	49	52	88	70	260	
Cotinine	49	51	88	72	260	

[a] On polypropylene glycol. [b] On polyethylene glycol. [c] 1-Butanol-pyridine-water system. [d] 1-Butanol-benzene-acetate buffer system. [e] At solvent front. [f] See also R. L. Frank and J. V. Crawford, *Bull. soc. chim. France*, **1958**, 419.

known alkaloids were run individually at the same time as smoke fraction. The retention times of the smoke alkaloids and of the knowns indicated to be identical with these appear in Table I.

Identification by paper chromatography. Two solvent systems of Kuffner, Schick, and Bühn[6] were used: 1-butanol-pyridine-water, 3 to 1 to 3, v./v., and 1 butanol-benzene-acetate buffer,[11] 85 to 5 to 30, v./v. In each case the lower layer was placed in the bottom of a chromatographic chamber lined with paper, and the upper was retained for placement in troughs for descending chromatography. Whatman's No. 1 paper was sprayed lightly with 0.2*M* ammonium tartrate and with 0.2*M* ammonium chloride for use in the two systems, respectively. A 10–20 μl. aliquot of the benzene solution of the smoke alkaloid and of a known alkaloid thought to be identical were spotted on the paper and left 4 hr. in the chamber for equilibration. The solvent was then placed in the trough and the chromatograms developed overnight. After air-drying, the strips were sprayed with a 0.5% solution of benzidine in absolute ethanol and exposed to cyanogen bromide vapor. Spots were generally round with little streaking, except in the case of myosmine and cotinine in the second-named system. R_f values are recorded in Table I.

Identification by ultraviolet spectroscopy. Two purified smoke alkaloids (cotinine and 2,3′-dipyridyl) were dissolved in absolute ethanol and ultraviolet spectral measurements with a Warren Spectracord made. Results appear in Table I, along with data for the known compounds obtained similarly.

Quantitative analysis by gas chromatography. A. Cotinine. Conditions: 1 m. by 6 mm. column of polypropylene glycol, mol. wt. 1025, on Firebrick, 1: 4; 190°; helium flow, 55 ml. per min.; sensitivity, 1; recorder range, 1 mv. Samples: 50 μl. of smoke alkaloid extract of 1.70 ml. (from 150 cigarettes) and 20 μl. of a benzene solution containing 8.9 mg. cotinine per ml. Peak areas were measured with a planimeter. The smoke cotinine area was 1.4 times the known's area; the smoke extract thus contained 5.0 mg. cotinine per ml.

B. Nicotine. Conditions: 1 m. × 10 mm. column of polypropylene glycol, mol. wt. 1025, on Firebrick 1:4; 190°; helium flow, 75 ml. per min.; sensitivity, 1/32; recorder range, 1 mv. Samples: 20 μl. of the same smoke extract as above and 20 μl. of a benzene solution containing 0.397 g. of nicotine per ml. The smoke nicotine peak was 1.13 times the known's area; the former thus contained 0.449 g. per ml.

C. Other identified alkaloids. Twenty μl. of the same smoke sample was chromatographed as in the nicotine analysis, except at a sensitivity of 1. Twenty μl. of a benzene solution containing 10 mg. myosmine per ml. was also run. The myosmine-nornicotine peak of the former was 0.78 times the myosmine peak of the latter; the smoke extract thus contained 7.8 mg. of myosmine-nornicotine per ml. From chromatographing a 50 μl. sample of the smoke extract, the following peak area relationships were established: myosmine-nornicotine, 1; anabasine, 0.13[10]; anatabine, 0.16; 2,3′-dipyridyl, 0.075. The content of the latter three compounds is therefore 1.0, 1.2, and 0.59 mg. per ml., respectively.

Acknowledgment. The cooperation of the Research Laboratories of the Liggett and Myers Tobacco Company and The American Tobacco Company is gratefully acknowledged.

DURHAM, N. C.

(11) Prepared from 0.2 M acetic acid and 0.2 M sodium acetate, 1 to 10 v./v.

[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE AND THE UNIVERSITY OF ALABAMA MEDICAL SCHOOL]

Synthesis of 5,6,7-Trimethoxy-2,3-dihydroindole and 6,7-Dimethoxyindole

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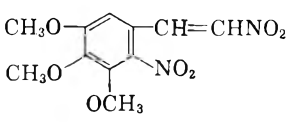
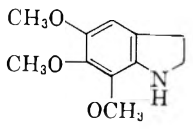
Received December 3, 1958

5,6,7-Trimethoxy-2,3-dihydroindole has been synthesized by catalytic hydrogenation of the corresponding indole. Several alternative routes to this dihydroindole were unsuccessful. The synthesis of 6,7-dimethoxyindole is also described.

In a previous communication,[3] we described the synthesis of 5,6,7-trimethoxyindole from 2-nitro-3,-4,5-trimethoxy-β-nitrostyrene (I) which was obtained in 9% yield by nitration of 3,4,5-trimethoxy-β-nitrostyrene. At that time, we indicated our interest in obtaining 5,6,7-trimethoxy-2,3-dihydroindole (II), a possible primary *in vivo* oxidative cyclization product of mescaline (3,4,5-trimethoxy-β-phenethylamine). The present study was undertaken with the idea of examining several alternative routes for the synthesis of II in better overall yield than would be expected from a two-step reduction of I.



I

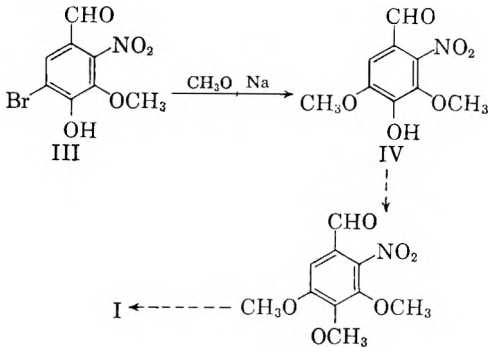


II

We had attempted unsuccessfully to synthesize the *N*-benzyl derivative of II[4] directly by the action of ethylene chlorobromide on *N*-benzyl-2,3,4-trimethoxyaniline; other routes were also sought for building up the 5,6,7-trimethoxyindole via the appropriate oxindole, dioxindole, and isatin derivatives[4] which were obtained from the aforementioned aniline. However, none of these approaches was deemed satisfactory for preparing II for the principal reason that cyclizations involving the open *ortho*- position to the amino group either occurred in poor yield or not at all. In an attempt to obtain *o*-bromo-*N*-benzylmescaline for other cyclization studies, debromination occurred when *o*-bromo-*N*-benzoylmescaline was treated with lithium aluminum hydride; the only product formed was *N*-benzylmescaline. *o*-Bromo-*N*-benzoylmescaline was obtained by bromination of *N*-benzoylmescaline with one mole equivalent of bromine in acetic acid.[5] Oxidation of this monobromo compound with alkaline permanganate gave a degradation product which was identified as 2-bromo-3,4,5-trimethoxybenzoic acid.[6]

Although the nuclear debromination of aromatic compounds by lithium aluminum hydride in ethers is somewhat unusual, it has been observed in several other instances. Erne and Ramirez[7] showed that 3,4-methylenedioxy-5-bromo-β-nitrostyrene is reduced to 3,4-methylendioxy-β-phenethylamine when refluxed with lithium aluminum hydride for 10 hr. Similarly, Gates and Tschudi[8] have noted that 1-bromocodeinone is simultaneously reduced and debrominated by this reagent. It is noteworthy that in all of these instances the halogen atom removed is originally present in an aromatic ring containing at least two alkoxy groups, one of which is either *ortho*- or *para*- to the halogen atom. In our recent work describing the syntheses of 4-halo-β-phenethylamines,[9] it was noted that the reduction of 4-halophenylacetonitriles could be carried out with lithium aluminum hydride without loss of the halogen atom.

In the following approach to the synthesis of II, in which improved yields of the intermediate I were hoped for, 2-nitro-5-bromovanillin[10] (III) was chosen as a starting material:



The possibility of replacing the bromine atom in III with methoxyl to form IV was suggested by the

(1) Battelle Memorial Institute.

(2) Department of Surgery, University of Alabama Medical School.

(3) R. D. Morin, F. Benington, and L. C. Clark, *J. Org. Chem.*, 22, 331 (1957).

(4) F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, 23, 19 (1958).

(5) A. Heffter, *Ber.*, 31, 1196 (1898) found that mescaline was converted to the corresponding 2,6-dibromo compound when treated with an excess of bromine.

(6) A. M. Hamburg, *Monatsh.*, 19, 589 (1898).

(7) M. Erne and F. Ramirez, *Helv. Chim. Acta*, 53, 912 (1950).

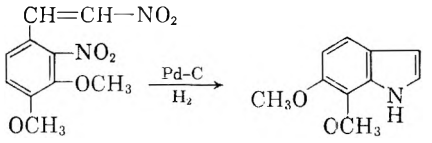
(8) M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, 74, 1109 (1952).

(9) F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, 23, 1979 (1958).

(10) L. C. Raiford and W. C. Strosser, *J. Am. Chem. Soc.*, 50, 2556 (1928).

fact that 5-bromovanillin has been converted to syringaldehyde[11] by the action of sodium methoxide and copper powder at elevated temperatures. It was thought that the presence of the nitro group in III would enhance the activity of the bromine atom. When a methanol solution of III was subjected to the action of sodium methoxide in the presence of copper powder under the conditions employed by Pepper and MacDonald,[11] only an intractable tar was formed from which none of the desired aldehyde (IV) could be isolated; carrying out the same reaction in refluxing methanol afforded only unchanged III.

The ready availability of 2-nitrovanillin, the precursor of III, did, however, offer a satisfactory route to the synthesis of the hitherto unknown 6,7-dimethoxyindole (VI). Methylation of 2-nitrovanillin gave 2-nitro-3,4-dimethoxybenzaldehyde,[12] which was condensed with nitromethane to form the β-nitrostyrene V. Reductive cyclization of V in accordance with the method of Huebner *et al.*[13] gave 6,7-dimethoxyindole (VI) in about 23% yield.



V VI

The indole VI exhibited a characteristic ultraviolet absorption spectrum and gave a positive Ehrlich color reaction. The possibility of preparing compounds having potential pharmacological activity from VI is currently being examined.

Because of these unsuccessful attempts to find new routes for the synthesis of 5,6,7-trimethoxy-2,3-dihydroindole (II), the possibility of selective reduction of the corresponding substituted indole was examined. Adkins and Coonradt[14] have reported that 2-methylindole undergoes hydrogenation (190°; 200–300 atm.) in the presence of a copper chromite catalyst to give largely 2-methyl-2,3-dihydroindole. These investigators also point out that hydrogenation at 230° over Raney nickel brings about perhydrogenation to 2-methyloctahydroindole. A later investigation reported by King *et al.*[15] states that indole in ethanol solution undergoes both perhydrogenation and alkylation with hydrogen and Raney nickel at temperatures above 150°, whereas, if the reaction is carried out at 90–100°, the primary reduction product is 2,3-dihydroindole. Previous work in this laboratory has shown that the aromatic ring in mescaline does not undergo hydrogenation in the presence of Raney nickel catalysts under the same conditions described by King. Accordingly, it was expected that the hydrogenation of 5,6,7-trimethoxyindole would stop at the point where one mole of hydrogen had been taken up by the pyrrole ring. The hydrogenation of this indole was done in ethanol solution with a commercial Raney nickel catalyst at 100° and at a hydrogen pressure of 1000 p.s.i.g. The behavior of the reaction product on distillation indicated that virtually no hydrogenation of the benzene ring had taken place, and the desired 5,6,7-trimethoxy-2,3-dihydroindole (II) was obtained in about 69% yield.

EXPERIMENTAL[16]

N-Benzoyl-2-bromo-3,4,5-trimethoxy-β-phenethylamine. To a solution of 20 g. of mescaline sulfate in 100 ml. of water was added 20 g. of NaOH and 14 g. of benzoyl chloride. Within a few minutes a solid began to deposit, and after warming on the steam bath for 10 min. and cooling, the crude *N*-benzoylmescaline was collected and recrystallized from alcohol-water; yield, 19.5 g. (86%); m.p. 123–124°; (reported,[17] 123°). To a solution of 19.5 g. of *N*-benzoylmescaline in 100 ml. of glacial acetic acid was added gradually a solution of 9.9 g. of Br_2 in 25 ml. of glacial acetic acid with swirling. Absorption of Br_2 was rapid, and immediately after addition of the Br_2 solution, the reaction mixture was poured into about 300 ml. of water. The colorless oil which separated was extracted with chloroform, and this extract was washed with $NaHCO_3$ solution and water. After drying over anhydrous $MgSO_4$, most of the chloroform was evaporated, and the residue was diluted with petroleum ether. A colorless crystalline solid was deposited which was collected and dried; yield, 23.1 g. (95%); m.p. 112–113°. After recrystallization from alcohol-water, an analytical specimen melted at 114–115°.

Anal. Calcd. for $C_{18}H_{20}BrNO_4$: Br, 20.3. Found: Br, 20.5.

Reduction of N-benzoyl-2-bromo-3,4,5-trimethoxy-β-phenethylamine with $LiAlH_4$. To a stirred solution of 7.7 g. of $LiAlH_4$ in 100 ml. of dry ether was added gradually a solution of 26.6 g. of *N*-benzoyl-2-bromo-3,4,5-trimethoxy-β-phenethylamine in 300 ml. of dry ether and 100 ml. of dry benzene. The mixture was then stirred and heated under reflux for 1.5 hr., cooled in an ice bath, and cautiously treated with ice water to hydrolyze the excess $LiAlH_4$ and the reaction complex. Precipitated inorganic salts were removed by filtration, and the filtrate was dried over anhydrous $MgSO_4$, filtered, and solvents were removed by distillation under reduced pressure. Distillation of the residue gave 16.8 g. (83%) of pale yellow oil, b.p. 210–220°/0.5 mm. This product contained no halogen, and analysis of the HCl salt, m.p. 158–159°, obtained by treatment of an ether solution with dry HCl gas and recrystallization from alcohol ether, showed this base to be *N*-benzylmescaline.

Anal. Calcd. for $C_{18}H_{24}ClNO_3$: C, 64.0; H, 7.1; Cl, 10.5; N, 4.15. Found: C, 63.6; H, 7.1; Cl, 11.2; N, 4.07.

To confirm the structure of 2-bromo-*N*-benzoylmescaline, a sample was oxidized to the known 2-bromo-3,4,5-trimethoxybenzoic acid[6] by refluxing 4 g. of the former with a solution of 8 g. of $KMnO_4$ and 1 ml. of 10% NaOH in 80 ml. of water for 5 hr. The mixture was filtered from MnO_2, extracted with chloroform and ether, and acidified with hydrochloric acid. On cooling, a nearly colorless solid slowly crystallized; m.p. 149–150°. For comparison, a small sample of authentic 2-bromo-3,4,5-trimethoxybenzoic acid

(11) J. M. Pepper and J. A. MacDonald, *Canadian J. Chem.*, **31**, 476 (1953).

(12) R. Pschorr and C. Sumuleanu, *Ber.*, **32**, 3409 (1899).

(13) C. F. Huebner, H. A. Troxell, D. C. Schroeder, *J. Am. Chem. Soc.*, **75**, 5887 (1953).

(14) H. Adkins and H. L. Coonradt, *J. Am. Chem. Soc.*, **63**, 1563 (1941).

(15) F. E. King, J. A. Barltrop, and R. J. Walley, *J. Chem. Soc.*, 277 (1945).

(16) All melting points are uncorrected.

(17) R. H. F. Manske and H. L. Holmes, *The Alkaloids*, Academic Press, Inc., New York, 1953, Vol. III, p. 325.

was prepared by bromination of 3,4,5-trimethoxybenzoic acid in acetic acid; m.p. 149–150° (reported,[6] 151°). The compound obtained by oxidation did not depress the melting point of the authentic 2-bromo-3,4,5-trimethoxybenzoic acid.

2-Nitro-5-bromovanillin (III). A mixture of 152 g. of vanillin and 150 ml. of acetic anhydride was refluxed for 3.5 hr., allowed to cool slightly, and poured with stirring into 1 l. of water. The oil which separated soon solidified and was collected and washed thoroughly with water; yield, 190 g. (98%); m.p. 73–74° (reported,[18] 77°). To 400 g. of fuming HNO_3 (d = 1.5) was added gradually 100 g. of acetylvanillin with stirring while maintaining the temperature at 2 to 6° with a cooling bath. After stirring an additional 10 min., the reaction mixture was poured into 1.5 l. of ice and water, and the yellow solid product collected and washed well with water. Without drying, the crude product was refluxed with a mixture of 50 ml. of CH_3OH, 50 ml. of water, and 60 ml. of 45% KOH for 15 min. Acidification with HCl gave a crude solid product which, after collection and drying, was stirred with 250 ml. of alcohol at room temperature; the solution was filtered from any insoluble material and concentrated under reduced pressure to permit crystallization of the 2-nitrovanillin; yield (2 crops), 62 g. (61%); m.p. 137–138°; (reported,[10] 136°). To a solution of 16.5 ml. of Br_2 in 200 ml. of glacial acetic acid was added 60 g. of 2-nitrovanillin and 1 g. of I_2. The mixture was warmed on a steam bath until all solid was dissolved and then allowed to stand overnight at room temperature. The mixture was poured into 1 l. of water, and the precipitated product collected, washed with water, and dried to obtain 79 g. (94%) of 2-nitro-5-bromovanillin (III) as a light tan powder, m.p. 152–153° (reported,[10] 150–151°), sufficiently pure for subsequent experiments.

Attempted conversion of III to 2-nitro-3,5-dimethoxy-4-hydroxybenzaldehyde (IV). Refluxing 27.6 g. of III with a solution of 5 g. of sodium in 100 ml. of absolute methanol for 5 hr. resulted in complete recovery of unchanged starting material on concentration and acidification. Heating 11 g. of III with a solution of 10 g. of sodium in 125 ml. of absolute methanol at 135° in a bomb for 2 hr. also resulted in recovery of unchanged starting material. Use of copper powder as a catalyst[11] under the latter conditions promoted extensive decomposition, but in all cases the products which could be isolated still contained bromine, and the desired replacement of Br by OCH_3 could not be achieved.

2-Nitro-3,4-dimethoxy-β-nitrostyrene (V). A solution of 52 g. of NaOH in 60 ml. of water was added gradually to a stirred mixture of 60 g. of 2-nitrovanillin, 80 ml. of alcohol, and 60 ml. of dimethyl sulfate while maintaining the reaction temperature at about 45–60°. An additional 20 ml. of dimethyl sulfate was added and the mixture was stirred for an hour longer, diluted with 800 ml. of water, and the oily product which separated was extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$, and the ether evaporated to give 57 g. (80%) of crude 2-nitroveratric aldehyde as a dark brown oil which refused to crystallize (reported m.p. 64°[12]). A mixture of 33 g. of the crude 2-nitroveratric aldehyde, 15 ml. of nitromethane, 9 g. of ammonium acetate, and 50 ml. of acetic acid was refluxed for 2 hr. and cooled. The yellow solid which crystallized was collected, washed with water, and dried; yield, 12.6 g. (32%); m.p. 170–171°. An analytical specimen recrystallized from $CHCl_3$-petroleum ether melted at 171–171.5°.

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: N, 11.0. Found: N, 10.9.

6,7-Dimethoxyindole (VI). To a solution of 18.7 g. of V 185 ml. of ethyl acetate, 20 ml. of alcohol, and 25 ml. of acetic acid in a Parr hydrogenation bottle was added 2 g. of 10% Pd-C catalyst, and the mixture was shaken with hydrogen at about 3 atmospheres until hydrogen was no longer absorbed (about 4 hr.). The catalyst was removed by filtration, and the filtrate was added to a mixture of ether and saturated aqueous $NaHCO_3$ and stirred to neutralize acetic acid. The organic layer was separated, washed 3 times with water, and dried over anhydrous Na_2CO_3. After concentrating to a volume of about 20 ml., 250 ml. of petroleum ether was added, and the solvent phase was decanted from a dark oil which separated. Evaporation of the solvent on a steam bath and cooling gave 3 g. (23%) of VI as light yellow needles, m.p. 102–103°, unchanged after recrystallization from petroleum ether-benzene; ultraviolet absorption, λ_{max} (log ϵ): 208 (4.67); 270 (3.90).

Anal. Calcd. for $C_{10}H_{11}NO_2$: N, 7.91. Found: N, 7.93.

5,6,7-Trimethoxy-2,3-dihydroindole (II). A mixture of a solution of 6.5 g. of 5,6,7-trimethoxyindole[3] in 75 ml. of alcohol and 10 g. of Raney nickel was hydrogenated for 16 hr. at 100° and 75 atm. of hydrogen. The catalyst was removed by filtration, the solvent was stripped from the filtrate and the residue was distilled to give 4.4 g. (67%) of a pale yellow oil, b.p. 133–134°/0.7 mm. Treatment of an ether solution with dry HCl gave 5,6,7-trimethoxy-2,3-dihydroindole hydrochloride, m.p. 205–206° after recrystallization from alcohol-ether.

Anal. Calcd. for $C_{11}H_{16}ClNO_3$: Cl, 14.5; N, 5.70. Found: Cl, 14.2; N, 5.88.

Acknowledgment. We are grateful to Mr. I. S. Ungar for the preparation of certain intermediates and for making the hydrogenation studies. This research was supported by Battelle Memorial Institute funds and by Public Health Service Grants M-600(R) and M-1588.

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(18) Tiemann and Nagai, *Ber.*, **11**, 647 (1878).

[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

Hydroboration of Fats. I. Positional Isomerism in the Methyl Oleate Hydroboration Reaction

SARA P. FORE AND W. G. BICKFORD

Received February 5, 1959

It has been found that addition of diborane to the ethylenic bond of methyl oleate proceeds smoothly without significant reduction of the carbomethoxy group. Alkaline hydrogen peroxide oxidation of the tris(carbomethoxyalkyl)borane resulted in the formation of an equimolar mixture of 9- and 10-hydroxyoctadecanoic acids, establishing that the hydroboration reaction proceeded nonselectively. Little or no isomerization occurred on heat treatment of these substituted trialkyl boranes.

Brown and Subba Rao have reported that a variety of olefins react readily with diborane in ether solution to form trialkyl boranes[2] which can be oxidized to the corresponding alochols with alkaline hydrogen peroxide. Oxidation of the trialkyl boranes derived from 1- and 2-hexenes with alkaline hydrogen peroxide resulted in formation of the primary alcohol only from the former compound and of 2- and 3-hexanol in a ratio of 2:1 from the latter. In addition, these authors found that heating the trialkyl boranes derived from internally unsaturated olefins resulted in migration of the boron moiety to the terminal position of the olefin chain.[3]

Reaction with diborane, followed by isomerization of the resultant substituted trialkyl boranes, appears to be a possible route to the preparation of α- or ω-hydroxy acids from internally monunsaturated fatty acids. Therefore, it was desirable to ascertain whether or not such unsaturated compounds could be hydroborated without significant reduction of the carboxyl group, whether or not the boron moiety adds preferentially to either carbon of the ethylenic bond, and the extent and direction of any isomerization which may occur on heating these substituted trialkyl boranes. For this purpose methyl oleate, which would be expected to be less susceptible than oleic acid to reduction by diborane,[4] was chosen as a model compound. The procedure of Brown and Subba Rao[2] was applied to the hydroboration of methyl oleate and a portion of the reaction mixture was refluxed for 24 hr. in an attempt to effect isomerization of the resultant tris(1-carbomethoxy-8(9)-heptadecyl)-boranes. The tris(1-carbomethoxyheptadecyl)boranes recovered from the reaction mixture before and after heating were converted to the corresponding hydroxyoctadecanoic acids by treatment first with alkaline hydrogen peroxide and then with hydrochloric acid. The unsaturated materials were removed from the hydroxy acids by extraction of the crude products with petroleum ether (b.p. 30–60°). The positions of the hydroxyl groups in the two samples of hydroxyoctadecanoic acids were determined by the following series of reactions: The hydroxyoctadecanoic acids were oxidized to the corresponding keto acids which were then converted to their oximes; the oximes were subjected to Beckmann rearrangement and the resultant amides were hydrolyzed under pressure with alkali; the mixed dicarboxylic acids recovered from the hydrolyzate were analyzed by application of elution chromatography employing a modification[5] of the method of Higuchi *et al.*[6]

The analyses performed on the unheated crude tris(1-carbomethoxy-8(9)-heptadecyl)borane and its derived hydroxyoctadecanoic acids indicated that hydroboration of most of the ethylenic bonds of methyl oleate was effected without material reduction of the ester group. Heat treatment of the crude tris(1-carbomethoxy-8(9)-heptadecyl)-borane resulted in an increase in both unsaturated and neutral material.

Application of the aforementioned series of reactions to the hydroxy acids from either the original or the heat-treated substituted trialkyl boranes resulted in the isolation of only two dicarboxylic acids, azelaic and sebacic acids, and these were present in approximately equimolar proportions. It was concluded, therefore, that the boron moiety added equally to the 9- and 10-positions of methyl oleate during hydroboration, and that little or no migration of this group occurred during heating. It is not impossible, however, that some isomerization occurred and was not detected, since the yield of azelaic and sebacic acids from this sample was less than that from the unheated sample, and since the hydroxyoctadecanoic acids in the petroleum ether soluble fraction were not examined. Additional work directed toward the isomerization of trialkyl boranes of this type is now in progress in this laboratory.

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1136 (1957).

(3) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1137 (1957).

(4) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1135 (1957).

(5) M. H. Chahine, E. R. Cousins, and R. O. Feuge, *J. Am. Oil Chemists' Soc.*, **35**, 396 (1958).

(6) T. Higuchi, N. C. Hill, and G. B. Corcoran, *Anal. Chem.*, **24**, 491 (1952).

EXPERIMENTAL

Since the structures of both the original and heat-treated tris(1-carbomethoxyheptadecyl)boranes were established by the same series of reactions, reaction conditions will be described for the former material only, pertinent data regarding the latter being given at the conclusion of each section.

Reagents. Methyl oleate (I.V., 85.5; diene, 1.5%) was prepared from the mixed methyl esters of pecan oil by low temperature fractional crystallization from acetone.[7]

Diglyme (diethylene glycol dimethyl ether) obtained from Ansul Chemical Co., Eastman's practical grade boron fluoride–ethyl ether, and Metal Hydrides' sodium borohydride were used without purification.[8]

Hydroboration of methyl oleate. The hydroboration of methyl oleate was carried out as described by Brown and Subbo Rao for 1-hexene.[2] Diborane gas (0.032 mole), generated during a period of 0.5 hr. by the dropwise addition of 2.13 g. of sodium borohydride dissolved in 50 ml. of diglyme to 11.4 ml. of boron trifluoride etherate dissolved in 21 ml. of diglyme, was bubbled through a solution of 53.3 g. (0.18 mole) of methyl oleate in 400 ml. of diglyme. The reaction was carried out in an all-glass apparatus with all joints sealed with glyptal resin. Dry nitrogen was employed as a sweep gas. Removal of the solvent from a 227 ml. portion of the reaction mixture (total volume, 470 ml.) at 35° under reduced pressure yielded 27.8 g. of a colorless viscous liquid having an iodine value of 6.9. This material began to oxidize immediately on exposure to the atmosphere.

Attempted isomerization of tris(1-carbomethoxy-8(9)-heptadecyl)borane. A 227 ml. portion of the reaction mixture was refluxed for 24 hr. Removal of the solvent under high vacuum at 60° yielded 27.2 g. of a colorless viscous oil having an iodine value of 13.8.

Hydroxyoctadecanoic acids. The substituted trialkyl boranes were subjected to oxidation with alkaline hydrogen peroxide,[9] enough alkali being used to saponify the methyl ester as well. A mixture of 26.8 g. of tris(1-carbomethoxy-8(9)-heptadecyl)borane, 8.0 g. of sodium hydroxide, 8.0 ml. of water and 120 ml. of ethanol was stirred and heated to about 60°. Heating was discontinued and 19.0 ml. of 30% hydrogen peroxide was added dropwise over a period of 0.5 hr. The reaction mixture was refluxed for 2 hr. and then was diluted with 400 ml. of distilled water containing 19.0 ml. of concentrated hydrochloric acid. Recovery of the product by the usual ether extraction procedure yielded 24.0 g. of crude hydroxy acids. An 18.0 g. sample of the hydroxy acids, upon treatment with petroleum ether (b.p. 30–60°) to remove unsaturated material, afforded 16.1 g. of hydroxyoctadecanoic acids, m.p. 78–82°.

Anal. Calcd. for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08; neut. equiv., 300.5. found: C, 72.00; H, 12.13; neut. equiv., 300.2.

The petroleum ether soluble fraction (1.86 g.) had a neutral equivalent of 310.5 and an iodine value of 38.9. Infrared analysis of this fraction indicated that approximately 66% of the ethylenic bonds were of the *trans*- configuration.

Similarly, the heat-treated sample yielded 24.2 g. of crude hydroxyoctadecanoic acids which on purification gave 15.9 g. of crystals, m.p. 77–82°.

Anal. Found: C, 72.48; H, 12.04; neut. equiv., 304.8.

The petroleum ether soluble fraction from the heat-treated sample (7.80 g.) had a neutral equivalent of 323.0 and an iodine value of 56.9. Infrared analysis of this fraction indicated that approximately 62% of the ethylenic bonds were of the *trans*- configuration.

Oxoöctadecanoic acids. A sample of the purified hydroxyoctadecanoic acids (14.0 g., 0.047 mole) in 25 ml. of glacial acetic acid was stirred and maintained at 32° during the dropwise addition of chromium trioxide (4.79 g., 0.048 mole) dissolved in 3.5 ml. of distilled water and 66 ml. of glacial acetic acid. After addition of the reagent, which required 2 hr., the sample was maintained at 35–40° for an additional 1.5 hr. The crystals which separated on dilution of the reaction mixture with water were boiled first with dilute hydrochloric acid and then with water. The keto acids thus obtained (13.84 g.) melted at 70–74°.

Anal. Calcd. for $C_{18}H_{34}O_3$: Carbonyl O, 5.36. Found: Carbonyl O, 5.3.

Oxidation of the hydroxy acid from the heat-treated sample in the same manner yielded 13.6 g. of keto acids, m.p. 66–72°.

Anal. Found: Carbonyl O, 5.3.

Oximes of oxoöctadecanoic acids. A solution of 8.73 g. (0.134 mole) of potassium hydroxide in 32 ml. of water was added to a mixture of 13.34 g. (0.0447 mole) of the keto acids, 6.21 g. (0.0894 mole) of hydroxylamine hydrochloride, and 160 ml. of ethanol. The mixture was stirred and refluxed for a period of 3 hr. After most of the ethanol had been removed at room temperature under vacuum in a rotary evaporator, the product was treated with 100 ml. of 1.5*N* hydrochloric acid. Separation of the organic material by ether extraction yielded 13.47 g. of oximes.

Anal. Calcd. for $C_{18}H_{35}NO_3$: N, 4.47. Found: N, 4.36.

Oximes (13.31 g.) were prepared as described above from keto acids (13.07 g.) derived from the heat-treated hydroboration product.

Anal. Found: N, 4.38.

The Beckmann rearrangement and hydrolysis of resultant amides. A portion of the oximes (6.56 g., 0.0209 mole) was stirred and heated at 100° for 1 hr. with 40 ml. of concentrated sulfuric acid. The reaction mixture was cooled to room temperature and poured into 400 ml. of cold distilled water which was maintained at less than 30° during this step by external cooling. The solid which separated was washed once with boiling water and then dried over sodium hydroxide in a vacuum desiccator.

The amides thus obtained (6.40 g., 0.0204 mole) were hydrolyzed by heating at 180–200° for 4 hr. with 11.9 g. of 86% potassium hydroxide in 40 ml. of water. The hydrolysis was carried out under a nitrogen atmosphere in a Parr[8] high pressure hydrogenator equipped with a glass liner.

Beckmann rearrangement of a portion of the oximes from the heat-treated sample (6.52 g., 0.0208 mole) and hydrolysis of the resultant amides (6.25 g., 0.0199 mole) were carried out as described above.

Dicarboxylic acids. The hydrolyzate was acidified with 33.5 ml. of concentrated hydrochloric acid in 50 ml. of distilled water and subjected to steam distillation for the removal of monocarboxylic acids. Ether extraction of the distillation residue yielded 2.35 g. of a light tan solid material containing the dicarboxylic acids. This fraction was extracted 5 times with 15-ml. portions of boiling water. The aqueous extract was concentrated to a volume of about 40 ml. and upon standing at room temperature deposited 1.45 g. of mixed dicarboxylic acids.

Similarly, 3.23 g. of crude and 1.15 g. of purified dicarboxylic acids were obtained from the heat-treated sample.

Chromatographic separation of the dicarboxylic acids. Duplicate samples of the mixed dicarboxylic acids (*ca.* 0.2 g., accurately weighed) were dissolved in 0.5 ml. of *t*-amyl alcohol and diluted to 10.0 ml. with chloroform. Aliquots (1.0 ml. each) of these solutions were added to a column prepared according to the procedure described by Higuchi, *et al.*[6] using 25.0 g. of dry silicic acid, 19.0 ml. of citrate buffer, *p*H 5.4, and 100 ml. of chloroform. The acids were eluted with successive 100-ml. portions of chloroform containing 0, 1.5, 3, 5, and 10% of *n*-butanol, and 10.0 ml. portions of the eluate were titrated with 0.0255*N* sodium

(7) S. P. Fore and W. G. Bickford, *J. Org. Chem.*, 24, 620 (1959).

(8) It is not the policy of the Department to recommend the products of one company over those of any others engaged in the same business.

(9) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, 78, 5694 (1956).

hydroxide solution. Only two fractions were encountered and these were identified by their peak eluant volumes as azelaic acid, 50.1 mole %, and sebacic acid, 49.9 mole %.

Application of the above described procedures to the dicarboxylic acids obtained from the heat-treated sample showed the mixture to be 48.8 mole percent azelaic and 51.2 mole percent sebacic acid.

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NEW ORLEANS 19, LA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MICHIGAN STATE UNIVERSITY]

Tetrazolopyrimidines: Their Synthesis and Structure[1]

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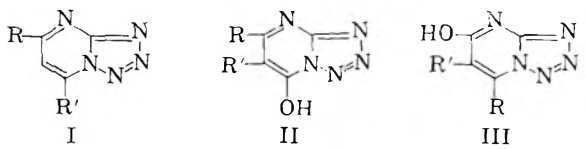
The reaction of 5-aminotetrazole with β-keto esters yields condensation products originally formulated as tetrazolo[*a*]-pyrimidines. The structure of this ring system has been substantiated through an alternative synthesis involving diazotization of 2-hydrazinopyrimidines and cyclization of the intermediate azidopyrimidines. Orientation of the substituents is supported by a study of the acylation of 5-aminotetrazole.

The formation of tetrazolopyrimidines by condensation of β-diketones and β-keto esters with 5-aminotetrazole was first described by Bülow.[3] The condensation with β-diketones in ethanol solution catalyzed with piperidine gave products assigned the structure I. With acetoacetic ester in glacial acetic acid a compound (IIa) was said to form; the possibility of formation of compounds of structure III was not considered. More recently Nachod and Steck[4] repeated Bülow's preparation of Ia for use in spectrographic studies without questioning the structure assignment. The arbitrary assignment of structures by Bülow made reinvestigation of this group of compounds desirable. Alternative methods of synthesis were devised with the object of demonstrating (1) the presence of the bicyclic system and (2) the orientation of the substituents according to II rather than III. The structural relationship of these compounds both to the purines and to bicyclic systems related to pentamethylenetetrazole made an extension of examples of this type of system attractive.



I II III

Ia. R = CH_3; R′ = CH_3
Ib. R = CH_3; R′ = C_6H_5
IIa. R = CH_3; R′ = H
IIb. R = C_6H_5; R′ = H
IIc. R = CH_3; R′ = CH_3
IId. R = CH_3; R′ = C_2H_5
IIe. R = CH_3; R′ = *n*-C_3H_7
IIf. R = CH_3; R′ = *iso*-C_3H_7
IIg. R = CH_3; R′ = *n*-C_4H_9
IIh. R—R′ = —$(CH_2)_4$—

The condensation of β-keto esters with 5-aminotetrazole was reinvestigated to determine the effect of solvents and catalysts on the reaction.It quickly became apparent that condensations in glacial acetic acid as recommended by Bülow[3] were not satisfactory. The product (IIa) obtained with acetoacetic ester was contaminated with large amounts of 5-acetamidotetrazole with which the product formed a molecular complex. The product described by Bülow as IIb, but for which no analysis was given, obtained with benzoylacetic ester under similar conditions proved to be 5-acetamidotetrazole. Using ethanol as solvent and piperidine as catalyst, as recommended for the condensation of β-diketones with 5-aminotetrazole,[3] greatly improved yields of tetrazolopyrimidines were obtained from β-keto esters. The condensation product (IIb) with benzoylacetic ester was actually obtained under these conditions. Similar condensations with a variety of alkylated acetoacetic esters gave the products IIc–IIh.

To establish the presence of a pyrimidine ring system in the products the procedure of Finnegan, Henry, and Lieber[5] for the synthesis of substituted 5-aminotetrazoles was adapted. These authors had shown that a variety of *S*-methyl thiuronium salts could be converted into 5-aminotetrazole derivatives by interaction successively with hydrazine to form aminoguanidines[6] and nitrous acid to form guanyl azides. The latter cyclized readily to form the tetrazoles. Considering 2-methylmercaptopyrimidines (IV) as cyclic *S*-

(1) Based on the doctoral thesis submitted to Michigan State University by Leonard E. Brady. Presented before the Division of Medicinal Chemistry at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 7–12, 1958.

(2) Present address: Abbott Laboratories, North Chicago, Ill.

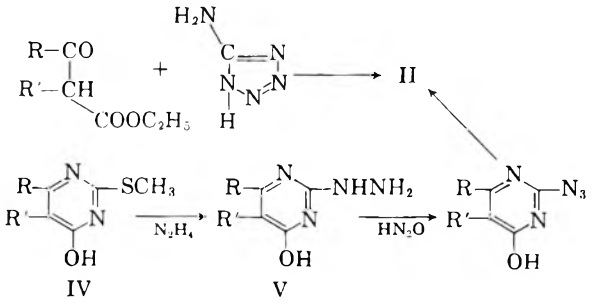
(3) C. Bülow, *Ber.*, **42**, 4429 (1909).

(4) F. C. Nachod and E. A. Steck, *J. Am. Chem. Soc.*, **70**, 2819 (1948).

(5) W. G. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).

(6) G. W. Kirsten and G. B. L. Smith, *J. Am. Chem. Soc.*, **58**, 800 (1936).

methyl thiuronium salts, it was found possible to convert them into 2-hydrazinopyrimidines (V) by interaction with hydrazine. Treatment of the hydrazinopyrimidines with nitrous acid completed the formation of the tetrazolopyrimidines (II) identical in all respects with the correspondingly substituted products obtained from alkylated acetoacetic esters and 5-aminotetrazole.



R and R′ defined as for II

The presence of the pyrimidine ring was also substantiated when 2-amino-4-methyl-6-hydroxypyrimidine was isolated as the result of attempts to reduce IIa in glacial acetic acid with hydrogen in the presence of platinum oxide. Neither hydrogenolysis of the tetrazole ring nor hydrogenation were observed in a similar attempt to reduce IIa in aqueous ethanol containing potassium hydroxide.

It remained to determine whether the orientation of the substituents in the tetrazolopyrimidines was in accord with II or III. Compounds of structure II would be expected if the initial reaction between β-keto esters and 5-aminotetrazole was azomethine formation. On the other hand, if the first step involved acylation of 5-aminotetrazole by the esters, compounds of structure III would be likely to result. With this in mind conditions for the acylation of 5-aminotetrazole were studied. Prolonged heating with an excess of carboxylic acid caused acylation of 5-aminotetrazole. The same products were obtained by interaction with the corresponding acyl chlorides or anhydrides. Direct interaction of 5-aminotetrazole with esters of carboxylic acids failed to cause acylation; starting materials could be recovered completely. On the other hand, interaction of 5-aminotetrazole with esters in glacial acetic acid solution gave modest yields (20–25%) of the acylaminotetrazole. Apparently acylation with esters is catalyzed in acetic acid solution. An attempt to induce acylation of 5-aminotetrazole with esters in ethanol solution in presence of piperidine was not successful.

Since piperidine failed to catalyze interaction of simple esters with 5-aminotetrazole in ethanol solution, whereas under similar conditions azomethine formation with simple carbonyl compounds has been shown to take place readily,[7,8] it seems likely that the initial step in the condensation of β-keto esters with 5-aminotetrazole involves azomethine formation. Subsequent elimination of the elements of ethanol from the azomethine would give tetrazolopyrimidines of structure II. Although structure III cannot be excluded unequivocally on the basis of available evidence, the formation of compounds of structure II seems more probable.

The tetrazolopyrimidines prepared from 5-aminotetrazole and β-keto esters are listed in Table I. With the exception of IIf all of these compounds were also prepared from the appropriate 2-methylmercaptopyrimidines. In addition 5,7-dimethyltetrazolo [*a*]pyrimidine (Ia) was prepared both from acetylacetone and 5-amino-tetrazole and from 2-methylmercapto-4,6-dimethylpyrimidine.

The requisite 2-methylmercaptopyrimidines (Table II) were prepared by interaction of S-methyl thiuronium iodide and appropriate β-keto esters in aqueous alcoholic solution in presence of potassium hydroxide.[9] 2-Hydrazinopyrimidines (Table III) were prepared by interaction in alcoholic solution of 2-methylmercaptopyrimidines and either anhydrous or 85% hydrazine hydrate. Benzal derivatives of the hydrazinopyrimidines are described in Table IV. The 2-hydrazinopyrimidines were converted into azido compounds or tetrazolopyrimidines by interaction with sodium nitrite in dilute, aqueous acid solution.

Screening of the compounds in Table I in the Parke, Davis Laboratories indicated no marked inhibitory action on growth in microbiological systems. When administered to mice intraperitoneally, IIa and IIh were lethal at dosage levels of 5 mg. per kg. The other compounds were slightly less toxic; IIb was tolerated up to 150 mg. per kg. No pronounced central nervous effects were observed below the lethal dose.[10] The compounds failed to show anticancer activity when screened by the Cancer Chemotherapy National Service Center.

EXPERIMENTAL[11]

5-Hydroxytetrazolo[a]pyrimidines were prepared by three methods: (A) the condensation of β-keto esters with 5-aminotetrazole in glacial acetic acid[3]; (B) the condensation of β-keto esters and 5-aminotetrazole in ethanolic solution in the presence of piperidine; (C) the diazotization of 2-hydrazino-6-hydroxypyrimidines.

(A) A mixture of 42.5 g. (0.5 mole) of anhydrous 5-aminotetrazole[12] and 78 g. (0.6 mole) of ethyl acetoacetate in 250 ml. of glacial acetic acid was heated under reflux for 48 hr. The solid which precipitated on cooling could be separated by repeated fractional crystallization from water into IIa

(7) R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, 76, 923 (1954).

(8) R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, 76, 926 (1954).

(9) H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, 29, 478 (1903).

(10) The cooperation of Dr. Graham M. Chen of the Parke, Davis Laboratories is gratefully acknowledged.

(11) Microanalyses on all compounds were done by Micro-Tech Laboratories, Skokie, Ill. All melting points were taken in open capillaries and are not corrected.

(12) R. M. Herbst and J. A. Garrison, *J. Org. Chem.*, 18, 941 (1953).

TABLE I

5-HYDROXY TETRAZOLO[*a*]PYRIMIDINES

Cpd. No.	R	R′	Method	Yield, %	M.P.	Formula	Analyses: Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
IIa	CH_3	H	A	17	247–248 dec.	$C_5H_6N_6O$	39.7	3.3	46.4	39.8	3.6	46.6
			B	40	247–248							
			C	52	247–248							
IIb	C_6H_5	H	B	21	224–225 dec.	$C_{10}H_7N_5O$	56.3	3.3	32.8	56.6	3.6	33.1
			C	71	224–225 dec.							
			A	0								
IIc	CH_3	CH_3	B	49	226 dec.	$C_6H_7N_5O$	43.6	4.3	42.4	43.9	4.5	42.3
			C	56	226 dec.							
IId	CH_3	C_2H_5	B	46	182–183	$C_7H_9N_5O$	46.9	5.1	39.1	46.8	5.1	39.0
			C	40	182–183							
IIe	CH_3	*n*-C_3H_7	B	52	145–146	$C_8H_{11}N_5O$	49.7	5.7	36.2	49.8	5.8	36.3
			C	60	145–146							
IIf	CH_3	*i*-C_3H_7	B	16	182–183	$C_8H_{11}N_5O$	49.7	5.7	36.2	49.7	5.6	36.2
IIg	CH_3	*n*-C_4H_9	B	30	151–152	$C_9H_{13}N_5O$	52.2	6.3	33.8	52.1	6.3	34.1
			C	63	151–152							
IIh	—$(CH_2)_4$—		B	26	199–200 dec.	$C_8H_9N_5O$	50.2	4.7	36.6	50.0	5.0	36.6
			C	31	199–200 dec.							

TABLE II

2-METHYLMERCAPTO-6-HYDROXYPYRIMIDINES

Cpd. No.	R	R′	Yield, %	M.P.	Formula	Analyses: Calculated C	Calculated H	Calculated N	Calculated S	Found C	Found H	Found N	Found S
IVa	CH_3	H	50	219	Ref. 9								
IVb	C_6H_5	H	14	238	Ref. 9								
IVc	CH_3	CH_3	19	216–217	$C_7H_{10}N_2OS$	49.4	5.9	16.5	18.8	49.4	5.9	16.5	17.0
IVd	CH_3	C_2H_5	16	201–202	Ref. 9								
IVe	CH_3	*n*-C_3H_7	6	181–182	$C_9H_{14}N_2OS$	54.5	7.1	14.1	16.2	54.5	7.2	13.9	16.0
IVg	CH_3	*n*-C_4H_9	9	159–160	$C_{10}H_{16}N_2OS$	56.6	7.6	13.2	15.1	56.6	7.6	13.4	15.1
IVh	—$(CH_2)_4$—		27	218–219	$C_9H_{12}N_2OS$	55.1	6.2	14.3	16.3	54.9	6.4	14.3	16.2

and a substance whose elemental analysis approximated that of a complex of two molecules of 5-acetamidotetrazole and one molecule of IIa; the complex melted at 238° with decomposition.

Anal. Calcd. for $(C_5H_5N_5O)(C_3H_5N_5O)_2$: C, 32.6; H, 3.7; N, 51.8. Found: C, 33.6; H, 3.7; N, 52.0.

The IIa prepared in this manner is described in Table I.

Interaction of ethyl benzoylacetate and 5-aminotetrazole in glacial acetic acid[3] gave a product, m.p. 267–268° with decomposition, identical in all respects with 5-acetamidotetrazole.

(B) The preparation of IIa will serve as an example. A solution of 8.5 g. (0.1 mole) of anhydrous 5-aminotetrazole, 19.5 g. (0.15 mole) of ethyl acetoacetate and 1 ml. of piperidine in 100 ml. of absolute ethanol was heated under reflux for 48 hr. The reaction mixture was evaporated to dryness on a steam bath and the residue recrystallized twice from hot water. Yields, melting points, and analytical data for compounds prepared by this method are given in Table I.

In the preparation of IIb from ethyl benzoylacetate and 5-aminotetrazole in the presence of piperidine, the piperidine salt of the product separated on cooling the reaction mixture. The piperidine salt crystallized from water, apparently as a hydrate, m.p. 119° (air dried) followed by resolidification and remelting at 144°; after drying at 100°, m.p. 144°.

Anal. Calcd. for $C_{15}H_{18}N_6O$: C, 60.4; H, 6.1; N, 28.2. Found: C, 60.3; H, 6.3; N, 28.2.

IIb was obtained by acidifying a hot aqueous solution of the piperidine salt with concentrated hydrochloric acid.

All the tetrazolopyrimidines in Table I can be crystallized from hot water or from aqueous ethanol.

(C) The preparation of IIa is typical of the series. To a solution of 5 ml. of concentrated hydrochloric acid in 30 ml. of water was added 4.0 g. of 2-hydrazino-4-methyl-6-hydroxypyrimidine (IVa). While stirring and cooling in an ice bath a saturated aqueous solution of sodium nitrite was added dropwise until the first excess was shown by the starch–potassium iodide end point. Stirring and cooling were continued for 15 min. when solid sodium carbonate was added until the mixture reached *p*H 8. At this point the material that had separated during the diazotization redissolved. The mixture was allowed to come to room temperature when it was acidified (*p*H 5) with hydrochloric acid. The solid which precipitated was recrystallized from hot water. IIa prepared in this way was shown to be identical with that prepared by Methods A and B by melting point and mixture melting point determinations and by comparison of infrared absorption spectra.

2-Methylmercaptopyrimidines were synthesized from S-methylisothiuronium iodide and the appropriate β-keto esters in aqueous ethanolic solution in the presence of potassium hydroxide.[9] The compounds prepared in this way are described in Table II.

2-Hydrazinopyrimidines were prepared by interaction of the 2-methylmercaptopyrimidines in ethanol solution with anhydrous hydrazine (Method A) or 85% hydrazine hydrate (Method B). 2-Hydrazino-4,5-dimethyl-6-hydroxypyrimidine (Vc) was prepared by both methods and will serve as an example. (A) A solution of 4.1 g. of 2-methylmercapto-4,5-dimethyl-6-hydroxypyrimidine and 8.2 g. of anhydrous hydrazine in 150 ml. of absolute ethanol was heated under reflux for 28 hr. The mixture was evaporated to dryness

TABLE III

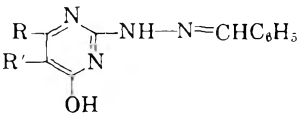
2-HYDRAZINO-6-HYDROXYPYRIMIDINES

Cpd. No.	R	R′	Method	Yield, %	M.P.	Formula	Analyses Calculated C	H	N	Found C	H	N
Va	CH_3	H	B	43	230–231 dec.	$C_5H_8N_4O$	42.8	5.8	40.0	43.1	5.7	39.8
Vb	C_6H_5	H	A	35	219–220 dec.	$C_{10}H_{10}N_4O$	59.4	5.0	27.7	59.6	5.0	27.7
Vc	CH_3	CH_3	A	19	333 dec.	$C_6H_{10}N_4O$	46.7	6.5	36.3	46.5	6.6	36.3
			B	41	333 dec.							
Vd	CH_3	C_2H_5	A	18	232[a]	$C_7H_{12}N_4O$	50.0	7.2	33.3	50.2	7.3	33.5
Ve	CH_3	n-C_3H_7	B	68	215–216[b]	$C_8H_{14}N_4O$	52.7	7.7	30.8	52.8	7.8	30.8
Vg	CH_3	n-C_4H_9	B	16	201–202	$C_9H_{16}N_4O$	55.1	8.2	28.6	55.3	8.4	28.8
Vh	—$(CH_2)_4$—		B	41	324 dec.	$C_8H_{12}N_4O$	53.3	6.7	31.1	53.2	6.8	31.4

[a] Resolidified and remelted at 320° with decomposition on continued heating. [b] Resolidified and remelted at 323° with decomposition on continued heating.

TABLE IV

2-BENZALHYDRAZINO-6-HYDROXYPYRIMIDINES



R	R′	Yield, %	M.P.	Formula	Analyses Calculated C	H	N	Found C	H	N
CH_3	H	44	228–229	$C_{12}H_{12}N_4O$	63.1	5.3	24.6	62.9	5.4	23.6
C_6H_5	H	56	261–262	$C_{17}H_{14}N_4O$	70.3	4.9	19.3	70.5	4.7	19.3
CH_3	CH_3	32	241–242	$C_{13}H_{14}N_4O$	64.4	5.8	23.1	64.2	5.9	23.0
CH_3	C_2H_5	17	228–229	$C_{14}H_{16}N_4O$	65.6	6.3	21.9	65.8	6.3	21.7
CH_3	n-C_3H_7	34	199–200	[a]	64.5	6.9	20.1	64.0	6.8	20.0
CH_3	n-C_4H_9	27	192–193	$C_{16}H_{20}N_4O$	67.6	7.1	19.7	67.4	7.2	19.6

[a] Calculated for the hemihydrate: $C_{15}H_{18}N_4O \cdot {}^1/_2H_2O$.

and the residue recrystallized from ethanol. (B) A solution of 4.3 g. of 2-methylmercapto-4,5-dimethyl-6-hydroxypyrimidine in 75 ml. of ethanol was stirred under reflux on a steam bath with 12.6 g. of 85% hydrazine hydrate. The evolution of methylmercaptan ceased after 60 hr. after which the solution was chilled and the solid that separated recrystallized from ethanol. The product was identical with the material prepared by Method A. In Table III are given yields, melting points and analytical data for compounds prepared in both ways.

2-Benzalhydrazinopyrimidines. A solution of 1.1 g. of benzaldehyde in 5 ml. of ethanol and 0.6 g. of glacial acetic acid was treated with water until faintly cloudy. To this mixture 0.7 g. of 2-hydrazino-4-methyl-6-hydroxypyrimidine was added. The mixture was heated in a beaker on a steam bath until evaporated to dryness and the residue recrystallized from absolute ethanol. Other benzal derivatives were prepared in a similar manner. Table IV gives melting points, yields and analytical data for the benzal derivatives.

5,7-Dimethyltetrazolo[a]pyrimidine (Ia) was prepared from acetylacetone and 5-aminotetrazole in ethanol with piperidine as catalyst,[3] yield 49%, m.p. 151–152° after crystallization from water.

Anal. Calcd. for $C_6H_7N_5$: C, 48.3; H, 4.7; N, 47.0. Found: C, 48.3; H, 4.6; N, 46.9.

The aqueous mother liquors from recrystallization of Ia deposited a second product on thorough chilling. The product crystallized from water as long, fine needles, m.p. 139–140°.

Anal. Found: C, 57.1; H, 5.5; N, 30.1.

The analysis corresponds with values calculated for a product formed by combination of one molecule of 5-aminotetrazole and two of acetylacetone with elimination of three molecules of water. It was not investigated further.

An alternate method of preparation involved interaction of 85% hydrazine hydrate and 2-methylmercapto-4,6-dimethylpyrimidine[13] in ethanol as described for the hydroxy analogs to form 2-hydrazino-4,6-dimethylpyrimidine, m.p. 165°, after crystallization from ethanol.

Anal. Calcd. for $C_6H_{10}N_4O$: C, 52.5; H, 7.3; N, 40.6. Found: C, 52.0; H, 7.2; N, 40.8.

The *benzal* derivative was crystallized from ethanol, m.p. 160°.

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.0; H, 6.2; N, 24.8. Found: C, 68.8; H, 6.2; N, 24.9.

Treatment of 2-hydrazino-4,6-dimethylpyrimidine with sodium nitrite in aqueous, acid solution as described for the hydrazinohydroxypyrimidines gave Ia, m.p. 151–152° after crystallization from ethanol. Mixture melting point determination and comparison of infrared spectra showed the product to be identical with the material prepared by Bülow's method.

Hydrogenolysis of 5-hydroxy-7-methyltetrazolo[a]pyrimidine. A solution of 3 g. of IIa in 150 ml. of glacial acetic acid was shaken with 175 mg. of platinum oxide at 65° for 24 hr. under 49 p.s.i. hydrogen pressure. After removal of the catalyst the solvent was evaporated and the residue recrystallized from water, m.p. 297° with decomposition. The product was identical with 2-amino-4-methyl-6-hydroxypyrimidine prepared by the method of Jaeger.[14]

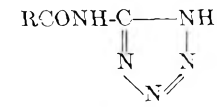
An attempt to hydrogenate IIa in 50% ethanol in the presence of 1.5 molar equivalents of potassium hydroxide with platinum oxide at room temperature and 49 p.s.i.

(13) H. L. Wheeler and G. S. Jamieson, *Am. Chem. J.*, 32, 342 (1904).

(14) J. Jaeger, *Ann.*, 262, 365 (1891).

TABLE V

5-ACYLAMINOTETRAZOLES



R	M.P.[a]	Method	Yield, %	Formula	Analyses					
					Calculated			Found		
					C	H	N	C	H	N
CH_3	268–269	A	36	$C_3H_5N_5O$	28.4	4.0	55.1	28.5	4.1	55.2
	Ref. 15	B	90							
C_2H_5	265	A	27	$C_4H_7N_5O$	34.0	5.0	49.6	34.0	5.2	49.4
	265	B	27							
n-C_3H_7	250	A	39	$C_5H_9N_5O$	38.7	5.8	45.1	38.7	5.8	45.2
	250	B	36							
$(C_2H_5)_2CH$	237–238	A	8							
	237–238	B	77	Ref. 16						
C_6H_5	280	B	54	Ref. 17						

[a] All melting points with decomposition.

hydrogen pressure was not successful. Only IIa was recovered from the reaction mixture.

Acylation of 5-aminotetrazole. (A) A mixture of 7.4 g. of anhydrous 5-aminotetrazole and 150 ml. of glacial acetic acid was boiled under reflux for 48 hr. After evaporation of the solvent the residue was recrystallized twice from water, yield 4 g. (36%) of 5-acetamidotetrazole, m.p. 268–269° with decomposition.[15] Similar preparations were done with propionic, *n*-butyric and diethylacetic acid. Yields, melting points and analytical data are given in Table V.

(B) Comparable acyl derivatives were obtained by warming anhydrous 5-aminotetrazole with acetic anhydride,[15] propionic anhydride, *n*-butyryl chloride, diethylacetyl chloride,[16] and benzoyl chloride.[17] Data for the products are included in Table V.

(C) A mixture of 15.8 g. (0.11 mole) of ethyl diethylacetate and 8.5 g. (0.1 mole) of anhydrous 5-aminotetrazole in 250 ml. of glacial acetic acid was boiled under reflux for 24 hr. The crystalline product that separated on cooling was recrystallized from water, yield 4.1 g., m.p. 238°, identical in all respects with 5-diethylacetamidotetrazole obtained in Methods A and B.

(D) Attempts to prepare the acyl derivatives by warming 5-aminotetrazole with ethyl acetate, ethyl propionate, ethyl *n*-butyrate, or ethyl benzoate alone or in ethanol or 1,4-dioxane solution in the presence of piperidine were unsuccessful. In each case 5-aminotetrazole was recovered completely.

EAST LANSING, MICH

(15) J. Thiele and H. Ingle, *Ann.*, **287**, 233 (1895).

(16) R. Stollé and O. Roser, *J. prakt. Chem.*, **136**, 314 (1933).

(17) R. Stollé and F. Henke-Stark, *J. prakt. Chem.*, **124**, 261 (1930).

[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY]

Synthesis of 1-Isobornyl-5-alkyl Tetrazoles[1]

CARLETON W. ROBERTS[2] AND MILTON L. MASKALERIS[3]

Received December 15, 1958

The reaction of nitriles with 1,1-disubstituted olefins in the presence of an acid catalyst to form *N*-substituted amides (Ritter Reaction) has been utilized to prepare a series of *N*-isobornylalkanamides from camphene and acetonitrile, propionitrile, *n*-butyronitrile, and *n*-valeronitrile. These amides have been converted by the von Braun procedure to the corresponding 1-isobornyl-5-alkyl tetrazoles. The first member in the series, 1-isobornyl-5-methyl tetrazole, possesses stimulatory activity toward rats at dosages of 10 mg./kg.

Gross and Featherstone[4] have studied the ultraviolet spectra of several series of pentamethylenetetrazoles and 1,5-disubstituted tetrazoles. The several series of compounds showed a surprising range of physiological activity, from strong sedatives to strong analeptics. On the basis of an admittedly empirical correlation, the authors conclude, "that without exception, substances possessing a potent and stimulatory action showed little or no absorption in the ultraviolet." Typical of the compounds studied in the 1,5-disubstituted

(1) From a thesis submitted to the Graduate School, Purdue University, in partial fulfillment of the requirements for the degree of Master of Science in Chemistry, August 1956.

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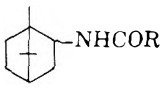
(4) F. W. Schueler, S. C. Wang, R. M. Featherstone, and E. G. Gross, *J. Pharmacol. Exptl. Therap.*, **97**, 266 (1949).

TABLE I

N-ISOBORNYL-*n*-ALKANAMIDES

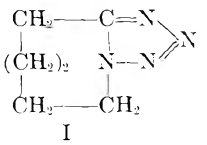


Group, R	M.P.	Yield, %	Percentage Composition					
			Carbon		Hydrogen		Nitrogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3-	141.0–141.5[a,b]	48	—	—	—	—	—	—
C_2H_5-	115.0–116.0[c]	58	—	—	—	—	—	—
n-C_3H_7-	89.0–90.5[d]	47	75.28	75.30	11.28	11.18	6.27	6.38
n-C_4H_9	107.5–108.5	71	75.90	75.94	11.47	11.30	5.90	5.87

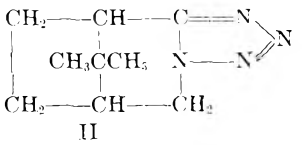
[a] M. O. Foster, *J. Chem. Soc.*, **73**, 395 (1898), reported m.p. 143°; M. O. Foster and J. Hart-Smith, *J. Chem. Soc.*, **77**, 1157 (1900), reported m.p. 144°; reference 6 reported m.p. 142–143°. [b] P. F. Frankland and F. Barrow, *J. Chem. Soc.*, **95**, 2025 (1909), reported m.p. 145.5°. [c] Reference *b* reported m.p. 117°. [d] Reference *b* reported m.p. 97°

tetrazole series were 1-cycohexyl-5-methyl tetrazole and 1-methyl-5-cyclohexyl tetrazole; both of these compounds were analeptics and showed no absorption in the ultraviolet. Other older and, in one instance, commercially interesting disubstituted tetrazoles are those possessing the pentamethylene structure [Metrazole, Cardiazole (I)], the "camphor tetrazole" (II), and compounds derived from the thujones.[5]

A consideration of the structure of the "camphor tetrazole" led to the conception of incorporating other types of bicyclic systems with the tetrazole nucleus. This paper reports the synthesis of four bicyclic substituted tetrazoles where the bicyclic moiety is attached to the 1-position of the tetrazole ring, and the 5-position of the tetrazole ring is reserved for alkyl substituents.



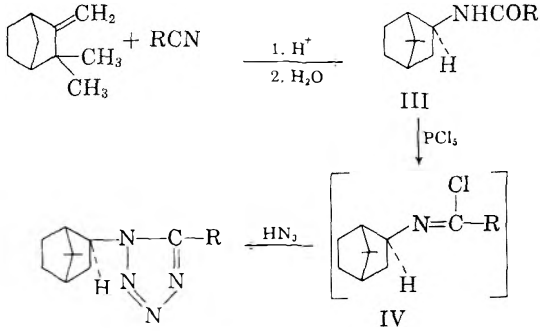
I



II

Ritter and co-workers[6] have described several examples of the reaction in which a nitrile reacts with an olefin or alcohol in the presence of an acid catalyst to give *N*-substituted amides. In the earliest reference, Ritter describes the reaction of acetonitrile with camphene to give *N*-isobornylacetamide (III) in excellent yield. Utilizing essentially a comparable procedure we have prepared a series of *N*-isobornyl alkanamides[7,10] from camphene and acetonitrile, propionitrile, *n*-butyronitrile, and *n*-valeronitrile.

The *N*-isobornyl alkanamides (Table I) were treated with phosphorus pentachloride in benzene to give the corresponding imino chlorides (IV); these intermediates were not isolated but, rather, were treated *in situ* with a benzene solution of hydrogen azide.[11–13] From the reaction mixtures were isolated the 1-isobornyl-5-alkyl tetrazoles (V) (Table II).



Spectra. The infrared spectra of the 1-isobornyl-5-alkyl tetrazoles showed absorption maxima in the 9.00 to 10.00μ region; the particular peaks were at 9.15, 9.30, 9.60, 9.70 and 9.9μ. These compare with the tetrazole ring peaks assigned[14] previously

(5) E. K. Harvill, C. W. Roberts, R. M. Herbst, *J. Org. Chem.*, **15**, 58 (1950).

(6) J. J. Ritter and co-workers, *J. Am. Chem. Soc.*, **70**, 4045 (1948); **71**, 4128 (1949); **73**, 4076 (1951); **74**, 763 (1952).

(7) Stein[8] and, subsequently, Luskin[9] reported that contrary to Ritter, the reaction of camphene with hydrogen cyanide gives 3-formamidoisocamphane. Higher alkyl nitriles do not appear to give the originally reported[6] rearrangement of the camphene to the isobornyl structures.

(8) G. A. Stein, M. Stelzinger, H. Arnold, D. Reinhold, W. Gaines, and K. Pfister, III, *J. Am. Chem. Soc.*, **78**, 1514 (1956).

(9) L. S. Luskin, A. J. McFaull, and G. E. Gantert, *J. Org. Chem.*, **21**, 1430 (1956).

(10) That the isobornyl moiety of the compounds described in this paper is correct is based on a comparison of the infrared spectra of *N*-isobornylacetamide (this paper) with the spectra of 2-formylisocamphane, *N*-formyl-*d*-bornylamine and *dl*-*N*-formylisobornylamine kindly supplied by Dr. G. A. Stein. Similar comparisons were made with spectra for formamidoisocamphane, isocyanatoisocamphane, and isobornyl isocyanate kindly supplied by Dr. L. S. Luskin. The authors wish to express their appreciation for the copies of these spectra.

(11) J. von Braun and W. Rudolph, *Ber.*, **74**, 264 (1941).

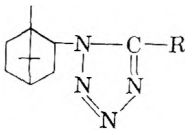
(12) E. K. Harvill, R. M. Herbst, E. C. Schreiner and C. W. Roberts, *J. Org. Chem.*, **15**, 662 (1950).

(13) R. M. Herbst, C. W. Roberts, H. T. F. Givens, and E. K. Harvill, *J. Org. Chem.*, **17**, 262 (1952).

(14) E. Lieber, D. R. Levering, and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

TABLE II

1-ISOBORNYL-5-ALKYL TETRAZOLES



Group, R	M.P.	Yield, %	Percentage Composition					
			Carbon		Hydrogen		Nitrogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3-	81.5–83.5	29	65.42	65.52	9.15	9.58	25.43	25.61
C_2H_5-	93 5–95.0	22	66.63	66.51	9.46	9.28	23.91	24.03
n-C_3H_7-	75.5–76.0	52	67.70	67.33	9.74	9.56	22.56	22.65
n-C_4H_9	63.5–65.0	62	68.66	68.64	9.99	9.75	21.35	21.41

at 9.40 to 10.10μ for 5-substituted tetrazoles, 9.14 to 9.20μ and 10.08 to 10.30μ for 1,5-disubstituted tetrazoles[15] where the substituents were methyl and chlorophenyl. In a recent report[16] several 5-dialkylaminoalkyl tetrazoles were reported to have associated peaks at 9.08μ.

No absorption was evidenced by the tetrazoles reported in this present paper in the ultraviolet region.

Pharmacological testing. Preliminary pharmacological testing was carried out by the authors. Interperitoneal injections of solutions of the 1-isobornyl-5-methyl tetrazole in sesame oil in rats at 10 mg./kg. of rat showed stimulation after 10 min.; these convulsive reactions lasted nearly 2 hr. In Amytal-sedated rats, a total dosage of 26 mg./kg. of rat of 1-isobornyl-5-methyl tetrazole was necessary to achieve the same order of convulsive reaction. The 1-isobornyl-5-ethyl tetrazole and the 5-alkyl tetrazoles containing larger alkyl groups appeared to effect sedation or to possess the opposite effect to that displayed by the first member of the series. The amides, *N*-isobornyl-acetamide (NSC 3681), *N*-isobornyl-*n*-butyramide (NSC 3680), and *N*-isobornyl-*n*-valeramide (NSC 3683) were tested against Sarcoma-180 and Ca-755.[17] *N*-Isobornylacetamide showed an acute toxicity at 150 mg./kg. in Swiss mice. The tetrazoles showed no activity when screened as analgesics, hypotensive agents, tranquilizers or diuretics.[18]

EXPERIMENTAL[19]

Typical experimental details are given for one series of preparations from the camphene to the tetrazole.

N-Isobornyl-n-valeramide. In a 500-ml., three necked flask equipped with a Claisen adapter, thermometer, dropping funnel, and a stirrer was placed 150 ml. (2.63 moles) of glacial acetic acid and 56 ml. (1.05 moles) of concentrated sulfuric acid. After cooling the mixture to 15°, 27.3 g. (0.33 mole) of *n*-valeronitrile was added during 20 min. maintaining the temperature below 20°. A solution of 40.8 g. (0.30 mole) of camphene in 35 ml. of glacial acetic acid was added dropwise during 30 min. at a temperature below 30°. After mixing was complete, the reaction mixture was warmed to 45° for 4 hr. and to 80° for 3 hr. The mixture was cooled to 30° and poured into a fourfold volume of cracked ice and water. Sufficient 6*N* sodium hydroxide was added to bring the *p*H to 5.0. The collected solid was washed twice with distilled water and air dried. The product, 69.2 g. (97.3%) was dissolved in 330 ml. of acetone, decolorized by refluxing with 10 g. of Norite, and filtered. The chilled filtrate was filtered to obtain the first crop of product. By careful concentration of the mother liquors, four subsequent crops were obtained; a total of 50.5 g. of pure product was isolated, m.p. 107–108.5° (71.7%). The data for the other *N*-isobornylalkanamides are in Table I.

1-Isobornyl-5-n-butyl tetrazole. In a 500-ml., round bottomed, three necked flask equipped with a dry port, thermometer, reflux condenser (protected with a Drierite tube) and stirrer was placed 22.3 g. (0.1 mole) of *N*-isobornyl-*n*-valeramide and 300 ml. of anhydrous benzene. Maintaining the temperature below 40°, 20.9° (0.1 mole) of phosphorus pentachloride was added portionwise through the dry port. As addition proceeded the amide appeared to react and dissolve; when the phosphorus pentachloride was all added the mixture was stirred for 30 min. at 40° to insure complete reaction. The Drierite tube exit was connected to a source of vacuum and sufficient vacuum was applied to remove the hydrogen chloride evolved from the reaction. The reaction mixture was then cooled to 20° and a solution of hydrogen azide (8.6 g., 0.2 mole; 5.56 g. hydrogen azide/100 ml. benzene) in benzene was added dropwise from a funnel replacing the dry port. Stirring was continued for 1 hr. at 25° and for 3 hr. at reflux (the condenser outlet was attached to an open T-tube to a vacuum source to prevent escape of hydrogen azide or hydrogen chloride to the hood or room) for 30 min. The cooled reaction mixture was treated with an aqueous solution of sodium hydroxide to *p*H 7. The benzene layer was separated and the aqueous layer extracted with two 25 ml. portions of benzene. The benzene

(15) C. W. Roberts, G. F. Fanta, and J. D. Martin, *J. Org. Chem.*, 24, 654 (1959).

(16) P. A. S. Smith and N. W. Kalenda, *J. Org. Chem.*, 23, 1599 (1958).

(17) Acknowledgment is gratefully made to the Cancer Screening Program, National Institutes of Health for the screening data on these compounds.

(18) Acknowledgment is gratefully made to the Lederle Laboratories, Pearl River, N. Y., for these preliminary data.

(19) All melting points are corrected (capillary). Microanalyses by Dr. C. T. Yeh and Mrs. D. W. Margerum, Purdue University. Infrared spectra by Mrs. B. Pollister using sodium chloride prisms on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra by Mr. E. Choplinski using a Cary spectrophotometer.

extracts were combined, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated to about 50 ml. and chilled; the semisolid residue was treated with 75 ml. of petroleum ether (b.p. 95–110°), rechilled and filtered to give 18.7 g. of crude product. After three recrystallizations from petroleum ether (b.p. 95–110°) there was obtained 16.1 g. (61.5%) of 1-isobornyl-5-*n*-butyl tetrazole, m.p. 63.5–65°. The data for the tetrazoles are in Table II.

WEST LAFAYETTE, IND.

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

Effect of Associated Salts and Amines on Polymerization of Butadiene by Amylsodium[1]

AVERY A. MORTON AND FRANK K. WARD

Received November 10, 1958

Triethyl amine and sodium hydroxide caused amylsodium to polymerize butadiene in a 1,4- rather than the usual 1,2-manner. The combination resembles in some aspects the alfin group of reagents but is less satisfactory with respect to the yield, size of polymer and freedom from gel of the polybutadiene. The conditions under which this combination operates are described.

Prior work has demonstrated that the association of sodium isopropoxide and sodium chloride with allylsodium caused the predominant polymerization of butadiene to change from a 1,2- to a 1,4-process. Similar effects were achieved with other straight chain alkenyl- or benzyl-sodium reagents. These combinations are known generally as alfin catalysts.[2] The organosodium components have unsaturation in the chain or the ring. No such change has been found, hitherto, when the organic moiety is saturated.[2a,3] The present paper reports that the association of triethyl amine and sodium hydroxide—sodium chloride happened to be present also—with amylsodium caused a similar alteration in the polymerization of butadiene. Alone, amylsodium polymerized butadiene largely in a 1,2-manner, the ratio of *trans*-1,4- to -1,2- structures being 0.3 or 0.4 (only 23–28% *trans*-1,4-), but with appropriate amounts of triethyl amine and sodium hydroxide the ratio became as high as 1.75 ,that is, 64% *trans*-1,4-structure, only a little less than the 75% achieved with a good alfin reagent which in turn is as much as in free radical polymerization.

Around 200 experiments (not all reported in this paper) were made in demonstrating this effect. Amylsodium was made from amyl chloride and sodium. Water was added in varying amounts to different preparations so that different ratios of sodium hydroxide to amylsodium were obtained. Then a specific quantity (usually 10 ml.) of each reagent was added to 30 ml. of butadiene in 200 ml. of solvent, said solvent being cyclohexane, triethyl amine, or mixtures of these two liquids. By this means a wide coverage of conditions was assured although the experiments by no means encompassed all possible variations. Adequate controls and tests with other components were made.

The principal results are shown in six graphs. In the first the highest proportion of 1,4-polymerization was realized when the ratio of sodium hydroxide to amylsodium was around 0.8 and the amine was approximately one half by volume of the total solvent. The bottom curve on the graph shows a control series where no amine was present; the proportion of 1,4-structure increased only a

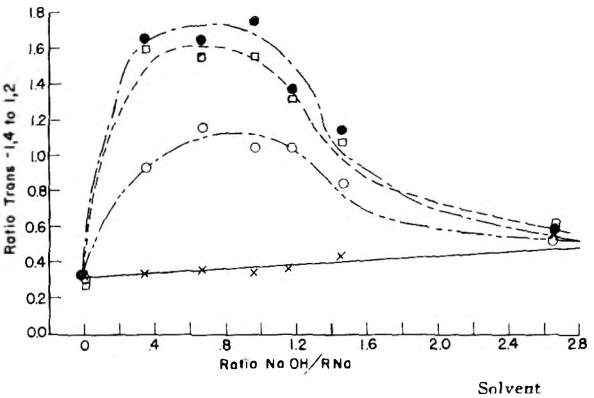


Fig. 1. Infrared ratio as a function of amine concentration and oxide ratio

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(1) This work was performed as part of a research project sponsored by the National Science Foundation.

(2) (a) A. A. Morton, E. E. Magat, and R. L. Letsinger, *J. Am. Chem. Soc.*, 69 950 (1947); (b) A. A. Morton, *Ind. Eng. Chem.*, **42**, 1488 (1950); (c) A. A. Morton, F. H. Bolton, F. W. Collins, and E. F. Cluff, *Ind. Eng. Chem.*, **44**, 2876 (1952); (d) A. A. Morton, I. Nelidow, and E. Schoenberg, *Proc. Third Rubber Tech. Conf.*, 108 (1954); (e) A. A. Morton, *Advances In Catalysis*, IX 745 (1957), Academic Press, Inc. New York.

(3) British Patent **782970**, Sept. 18, 1957, issued to Polymer Corp. Ltd., of Canada, describes the use of amylsodium with sodium isopropoxide and sodium chloride as a reagent which can cause a high proportion of 1,4- polymerization. However, their amylsodium was prepared in xylene, which would react at once to give xylylsodium.

trifle (0.3 to 0.5) as the proportion of hydroxide increased.

The second graph shows the effect of time on polymerization. The shortest time tested was 1 hr. although the 1,4- process was probably over within a few minutes. Thereafter the slower and longer lasting 1,2- process lowered the over-all value for the final product. Even after 24 hr., however, an area of optimum 1,4- activity could be seen. The curve at the bottom of the graph shows again the low ratio which was found in the absence of any triethyl amine.

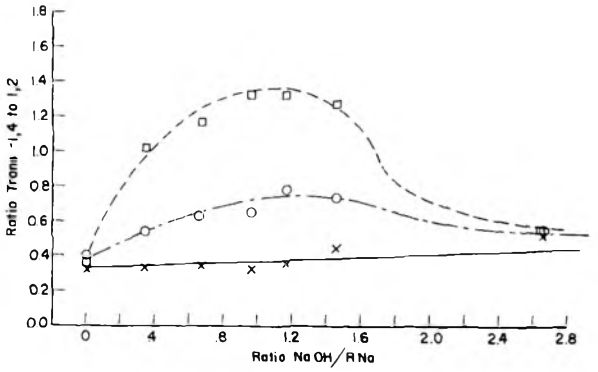


Fig. 2. Infrared ratio as a function of polymerization time and oxide ratio

The third graph shows that the same high ratio of *trans*-1,4- to -1,2-structure was realized by two different quantities of reagent but the proportion of sodium hydroxide to amylsodium had to be increased a little when more reagent was used. This result might be explained on the ground that some moisture was present on the walls of the glass bottle used as the polymerization vessel in spite of moderate heating and drying in dry nitrogen.

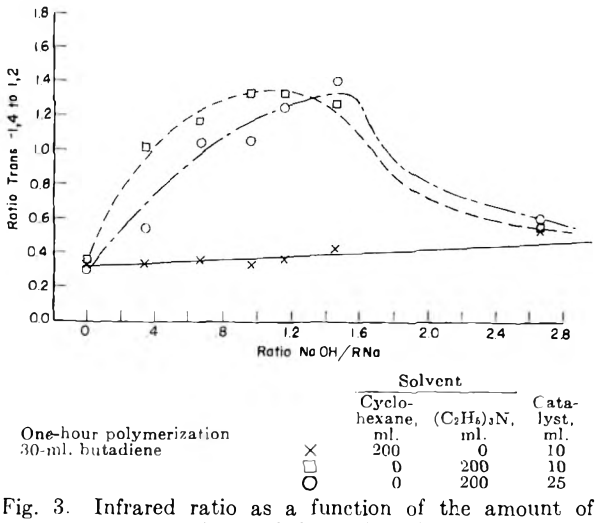


Fig. 3. Infrared ratio as a function of the amount of catalyst and the oxide ratio

This moisture would react with amylsodium to produce some sodium hydroxide *in situ*. When larger quantities of sodium reagent were used this loss by hydrolysis was proportionately less and more sodium hydroxide had to be added to get the proper proportion for high activity.

The three remaining graphs show the effect of changes in the components which make up the mixture of reagents. Neither sodium methoxide, sodium isopropoxide nor sodium *t*-butoxide could be used in place of sodium hydroxide (graph 4); in no case did the ratio rise above 0.7. Triethyl amine was the best of the three amines tried (see graph 5). Less than half of the polymerization in the presence of tributyl amine was 1,4-. Allylsodium, which was such an important component of the alfin catalyst, was relatively ineffective in this amine system, the ratio of *trans*-1,4- to -1,2-structures being not above 0.9 (see graph 6).

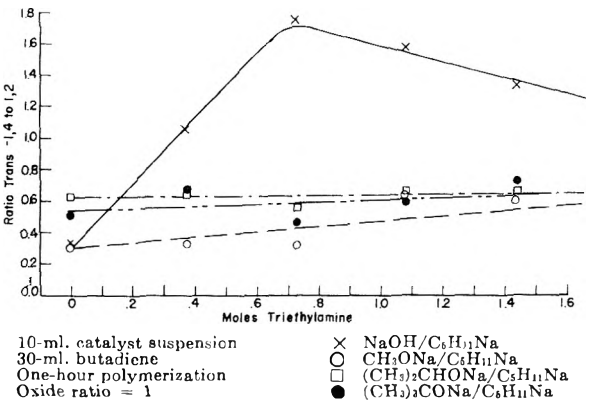


Fig. 4. Comparison of oxide components in the amine catalyst

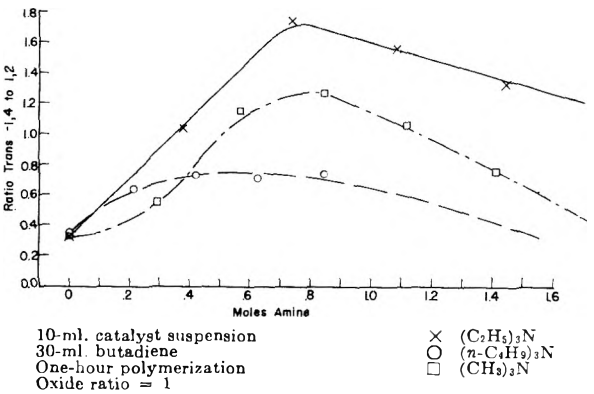


Fig. 5. Comparison of amines in the amine catalyst

Diethyl amine proved incapable of causing 1,4-polymerization either in the absence or presence of triethyl amine. If this amine, as a sodium salt (R_2NNa), caused any effect at all, it was toward more 1,2- structure and a lower viscosity polymer. This secondary amine might be assumed to have been formed by cleavage of triethyl amine with amylsodium. Another paper,[4] however, reports

(4) A. A. Morton and F. K. Ward, unpublished work

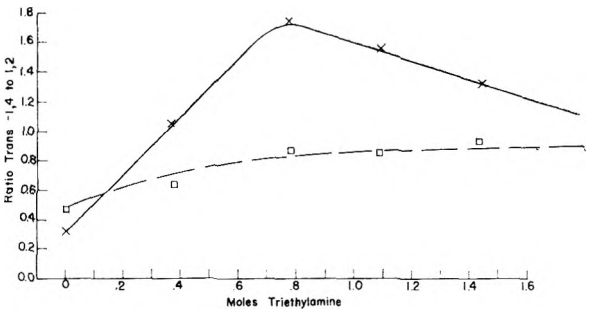


Fig. 6. Comparison of organosodium reagents in the amine catalyst

the failure to find any such cleavage and the present tests show that any diethylsodamide, if it had formed, would have been ineffective in causing 1,4-polymerization.

Table I shows a comparison of the hydroxide-amine-organosodium combination with the alfin system. Three different components have proved essential for each. If sodium chloride should happen to be required for a new system as it proved to be for the alfin combination,[2c] and if some olefin or butadiene remained coordinated with the reagent in the alfin catalyst, each might be regarded as a four component combination, broadly similar to the other. Specifically, however, some of the components show wide differences. A transposing of either the organosodium or the sodium oxide salt from one system to the other destroys the capacity for 1,4-polymerization. Sodium chloride is common to both. Triethyl amine is essential for the new system and can be present also with the alfin system without special harm.[5]

TABLE I

COMPARISON OF THE COMPOSITION OF THE AMINE WITH AN ALFIN SYSTEM

Components	Amine	Alfin
RNa salt	$C_5H_{11}Na$	$CH_2{=}CHCH_2Na$
Oxide salt	NaOH	$(CH_3)_2CHONa$
Halide salt	[NaCl][a]	NaCl
Coordinating agent	$(C_2H_5)_3N$	[C_4H_6 or C_nH_{2n}][b]

[a] Sodium chloride was introduced during the preparation of amylsodium but has not been proved to be essential. [b] No liquid coordinating agent has been proven to be a part of the alfin reagent but that role might be fulfilled by the olefin or diene itself.

Were it not for the differences in composition this new system, in its present state of development, might be called a very poor alfin catalyst. The viscosity (DSV) was 2.5 to 4 which is within the range shown by some of the alfin catalysts[2e] though far below the values of 10 and higher found with the best members of that group. The conversion (not above 1 or 2%) was very low but that value probably could be changed by more reagent or improvements in the conditions for polymerization. A major difficulty was the unusually high percentage of gel, often being 85–95%. Consequently the polymer rapidly enclosed the catalyst in an insoluble shell which retarded or stopped polymerization within a few minutes while the conversion was still low. Undoubtedly this tendency to form gel came from the very high metalating activity of amylsodium, because metalation has been shown to cross-link rubber.[6] The same trouble was experienced with the alfin catalyst where the gel was 100% when the reagent was first discovered but was gradually reduced to zero as the amount of reagent and the proportions of its components were adjusted. The problem seems unusually difficult in the present case because amylsodium is noted for its metalating[7] activity. However, the gel was reduced greatly —to around 6%— by the use of triethyl amine as the medium instead of a mixture of triethyl amine and cyclohexane but the use of more reagent thereafter in order to increase the yield caused a high gel again. Some improvement would be expected with butyl-, propyl-, or ethyl-sodium which are less active metalating agents[8] than the very powerful amylsodium but no time was available to investigate those and other possibilities. Another hundred or so experiments might have been required. The study was not intended as a survey of optimum conditions. The prime interest was theoretical.

This work was done with the idea of demonstrating that amylsodium could function as a radical pair and thereby could induce 1,4-polymerization of butadiene. Some details in the formation of radical pairs from sodium reagents[9] and of alfin polymerizations as a radical process[2d,e] have been published. The interpretation which this laboratory considers most suitable for the present case would parallel closely the prior explanations.

EXPERIMENTS

Preparation of amylsodium. Amylsodium was prepared in the usual way[10,11] from 0.5 mole of amyl chloride and 1 g.-

(5) Unpublished work with F. W. Collins.

(6) A. A. Morton and H. E. Ramsden, *J. Am. Chem. Soc.*, **70**, 3132 (1948); A. A. Morton, R. P. Welcher, F. Collins, S. E. Penner, and R. D. Coombs, *J. Am. Chem. Soc.*, **71**, 481 (1949).

(7) (a) A. A. Morton and C. E. Claff, Jr., *J. Am. Chem. Soc.*, **76**, 4933 (1954); (b) A. A. Morton and J. L. Eisenmann, *J. Org. Chem.*, **23**, 1469 (1958).

(8) A. A. Morton, G. M. Richardson, and A. T. Hallowell, *J. Am. Chem. Soc.*, **63**, 327 (1941).

(9) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **21**, 93 (1956).

(10) A. A. Morton and A. E. Brachman, *J. Am. Chem. Soc.*, **76**, 2980 (1954).

(11) A. A. Morton, F. D. Marsh, R. D. Coombs, A. L. Lyons, S. E. Penner, H. E. Ramsden, V. B. Baker, E. L. Little, Jr., and R. L. Letsinger, *J. Am. Chem. Soc.*, **72**, 3785 (1950).

atom of sodium sand in 500 ml. of n-heptane. Water, alcohol, or diethyl amine was added dropwise while the mixture was maintained at 0°. Then the mixture was stirred an additional hour at 0° before being transferred to a dry quart bottle which had been evacuated and filled with nitrogen. The reaction flask was rinsed twice with heptane and each time the rinsings were transferred to the bottle as before. Finally the volume of the suspension was adjusted to 800 ml. by addition of more heptane and the bottle was closed with a cork and sealed with glyptal cement. All operations of preparing and handling the suspension were carried out under an atmosphere of dry nitrogen. After 24 hr. the bottle was shaken and a 50-ml. aliquot was removed and carbonated in order to determine the carboxylic acids and thus the amount of sodium reagent. When the reagent was allylsodium the same technique was followed except that after the addition of water, propylene was passed into the flask in order to convert the remainder of the amylsodium to allylsodium.

In a series of 24 different preparations by the above means the average yield of combined organosodium reagent and sodium oxide (or amide) salt was 87.4% and the extremes were 80.7 and 93.8%, but some variation existed between classes of reagent. For instance, without any oxide salt the average yield in seven preparations was 83.8 and the extremes were 80.7–87.0. When sodium hydroxide was present the average yield from eight preparations was 89.3% and the extremes were 84.0–93.8. In the presence of diethylsodamide the average of six preparations was 89.5% and the extremes were 83.8–93.0%. Single preparations only were made with sodium methoxide, sodium isopropoxide, and sodium *t*-butoxide and the respective yields were 90.2, 86.4, and 85%. It is unlikely that these differences can be attributed to a small amount of reaction between water, alcohol or amine, and small bits of sodium metal left over because of the incompleteness of the reaction between amyl chloride and sodium, because diethyl amine does not react with sodium metal. An alternative idea, particularly applicable to sodium hydroxide, is that the salt helped to stabilize the amylsodium against decomposition, even as it had made it less reactive in other work.[7b] Possibly some of the variations are typical for heterogeneous systems.

In any event the ratio of oxide salt to organosodium reagent was calculated from the total sodium salt (oxide salt plus organosodium reagent), the reasonable assumption being made that the reaction between amylsodium and the active hydrogen of water, alcohol or amine was complete.

Polymerizations. The usual practice was to add 10 ml. of the amylsodium reagent to 30 ml. of Phillips research grade of butadiene to each of five 12-oz. beverage bottles each containing 200 ml. of liquid. This liquid was cyclohexane, triethyl amine, or mixtures of the two. The amount of triethyl amine varied progressively from 0, 50, 100, 150 to 200 ml. while the cyclohexane correspondingly decreased. The bottles were capped after addition of the reagent, shaken by hand a few times to mix the contents, and then allowed to stand at room temperature. At the end of a given time (usually 1 hr.) the contents were poured into 500 ml. of methanol. The precipitated polymer was collected, washed, and dried over night at 40°/1 mm.

For analysis an aliquot of this polymer was suspended in toluene and shaken gently for 48 hr. before filtering through silk gauze in order to separate the gel. An aliquot of this filtrate was evaporated and the residue weighed in order to determine the proportion of soluble polymer. The difference between the total polymer and this soluble product was credited as gel. The dilute solution viscosity (DSV) was determined on this soluble portion.

Another part of the polymer was suspended in carbon disulfide, shaken gently for 48 hr., filtered, and concentrated. Its infrared absorption was determined in a Baird Double Beam recording spectrophotometer, model B, with particular attention to the values at 965 cm.$^{-1}$ and 910 cm.$^{-1}$ favorable to measurements of the *trans*-1,4- and -1,2-structures, respectively.[2d] A ratio of *trans*-1,4- to 1,2-structure exceeding 1 indicated that over half of the polymerization was 1,4-. The *cis*-1,4- was not measured chiefly because only a very small amount was present, organosodium reagents being very active in converting *cis* to *trans* structure.[12]

Drying of the triethyl amine. The initial tests with amylsodium were made with triethyl amine which had stood over potassium hydroxide pellets for several months. A ratio of *trans*-1,4- to -1,2- structure of 1.5 was obtained but the progressively lower yield as more and more triethyl amine was used suggested three questions: (1) Was a reaction product of amylsodium with triethyl amine responsible; (2) Did moisture in the triethyl amine cause the high ratio; or (3) Did some impurity such as diethyl amine react with amylsodium? Accordingly, triethyl amine was pretreated with amylsodium. Thereafter in two separate series in which the amine progressively replaced cyclohexane as the medium, the ratio of trans-1,4- to -1,2- structures ranged from 0.30 to 0.42. These tests eliminated the first possibility and showed that the cause of the unusual polymerization lay in either the second or third proposition.

Potassium hydroxide alone was effective as a drying agent when the mixture was stirred in the high-speed stirring apparatus for 4 days. In that way the hydroxide was broken into small particles and the surface coating was removed. After decantation the amine was used in varying proportions with cyclohexane as already described. The ratio of *trans*-1,4- to -1,2- structures varied 0.3–0.35. This test eliminated the possibility that dissolved potassium hydroxide could have been responsible for the high ratio and also eliminated the second possibility above, namely that diethyl amine had been present, because potassium hydroxide would not react with the secondary amine. Water alone, which would react with amylsodium and form sodium hydroxide *in situ*, was responsible for the special activity; and this idea was reinforced by positive evidence from vapor phase chromatography (silicon oil on firebrick at 80°) that a small amount of water remained in the amine dried over sodium hydride but was absent in the liquid dried by long stirring over potassium hydroxide.

Drying by filtration through a 4-ft. column filled with calcium sulfate (Drierite) and potassium hydroxide was tested also. That the ratio varied 0.32–0.52 suggested that this method of drying was almost as good as the other two. A longer column probably would have given entirely satisfactory results.

In subsequent experiments the triethyl amine was dried over amylsodium.

1,2- Polymerizations. Some of the experiments in cyclohexane which resulted in 1,2- polymerization are recorded in Table II. As the proportion of sodium hydroxide increased (column 3) the yield per milliequivalent of amylsodium generally decreased (column 6) while the viscosity (DSV in column 7) correspondingly increased. The infrared ratio also increased a little. Diethylsodamide behaved a little differently. The yield, viscosity, and infrared ratio all tended to decrease as the proportion of diethylsodamide increased. Also the yield per milliequivalent in the presence of diethylsodamide seemed a little higher than with the corresponding amount of sodium hydroxide.

Table III shows 1,2- polymerization in triethyl amine. The yields and viscosities were considerably lowered in this medium. The tendency to form gel was also greater. The results discourage the idea that solution of the reagent was much of a factor. The yield was decreased rather than increased. In this medium diethylsodamide increased slightly the yield per milliequivalent.

1,4- Polymerizations. The most significant results have been presented already in the graphs. Table IV records, however, the yields and other information in triethyl amine as the medium. The yields per milliequivalent were much

(12) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, 20, 839 (1955).

TABLE II

1,2- POLYMERIZATION OF BUTADIENE IN CYCLOHEXANE BY AMYLSODIUM IN THE PRESENCE OF SODIUM HYDROXIDE OR DIETHYLSODAMIDE

RNa,[a] Me.	Assoc. Salt[b] Type	Me.	Yield,[c] G.	%	G./Me.	DSV	Gel, %	I.R.[d] Ratios
5.1	N		18.0[e]	93	3.6	0.60	0	0.32
5.3	N		18.2[f]	93	3.4	0.62	0	0.30
5.1	N		15.4[g]	79	3.0	0.45	0	0.33
5.1	N		10.0[h]	51	2.0			0.30
5.1	N		0.1[i]	1	.1			0.52
4.0	H	111	9.2	47	2.3	0.50	0.3	0.34
3.2	H	167	6.5	33	2.0	0.57	1.6	0.37
2.9	H	222	7.7	39	2.6	0.70	0.8	0.33
2.7	H	250	5.5	28	2.0	0.59	6.0	0.39
2.4	H	278	4.4	22	1.8	0.95	0	0.44
1.6	H	333	0.6	3	0.4	1.20	3.3	0.56
4.5	A	67	12.5	64	2.8	0.51	0	0.37
3.9	A	150	11.6	60	3.0	0.64	0	0.34
3.8	A	205	11.3	58	3.0	0.30	0	0.29
3.1	A	273	8.3	43	2.7	0.28	0.1	0.30
2.7	A	342	6.8	35	2.5	0.19	0.1	0.30
1.9	A	411	4.5	23	2.4	0.18	0.1	0.29

[a] R signifies amyl. [b] N, H, and A are abbreviations for none, hydroxide and amide and signify, respectively, no other salt, sodium hydroxide and diethylsodamide. The milliequivalents listed for these added salts is the amount added to the preparation of amylsodium from 500 me, of amyl chloride and 1 g.-atom of sodium metal. [c] Yield after 1 hr. unless otherwise specified. [d] Ratio of *trans*-1,4- to -1,2-structures as determined by infrared measurements. [e,f,g,h,i] represent respectively 4, 24, 2, 1/3, and 1/6 hr. reaction time. The last named experiment was done in order to demonstrate that a yield of 1% or less was not responsible for IR ratios greater than 1.

TABLE III

1,2-POLYMERIZATION OF BUTADIENE IN TRIETHYL AMINE BY AMYLSODIUM WITH AND WITHOUT DIETHYLSODAMIDE

RNa,[a] Me.	Amide,[b] Me.	Yield[c] G.	%	G./me.	DSV	Gel, %	IR Ratio
5.1	0	0.1[d]	0.7	0.03	2.1	39	0.52
5.1	0	2.2[e]	11.2	0.42	0.2	18	0.35
5.3	0	5.7[f]	29.1	1.08	0.7	23	0.38
5.3	0	2.7	14	0.52	0.2		0.31
3.0	0	2.6	13	0.87	0.1		0.40
4.4	67	4.8	25	1.1	0.2		0.39
3.6	150	4.0	20	1.1	0.2		0.41
3.7	205	3.8	20	1.2	0.2	1	0.39
2.2	273	3.0	15	1.4	0.2	6	0.41
1.5	342	2.5	13	1.7	0.2	11	0.38
1.4	411	1.0	5	0.7	0.21	14	0.36

[a] R signifies amyl. [b] This column records the milliequivalents of diethyl amine added to the preparation of amylsodium. [c] Yield after 1 hr. polymerization unless otherwise specified. [d] The reaction time was four hours and the triethyl amine was dried by passage through a column filled with potassium hydroxide and Drierite. [e] The reaction time was 2 hr. and the triethyl amine was dried by high-speed stirring with potassium hydroxide. [f] The reaction time was 24 hr.

TABLE IV

EFFECT OF AMOUNT OF REAGENT IN POLYMERIZATION OF BUTADIENE IN TRIETHYL AMINE

Molal ratio, NaOH/RNa		0.95		1.15		1.46	
Reagent	Ml.	10	25	10	25	10	25
	Me.	2.9	7.3	2.7	6.8	2.4	6.0
Yield	G.	0.05	0.07	0.04	0.09	0.03	0.13
	%	0.3	0.5	0.2	0.5	0.2	0.7
	G./me.	0.02	0.02	0.01	0.03	0.01	0.05
DSV		3.2	2.4	2.9	2.6	2.7	2.9
Gel	%	6	44	8	73	3	89
I.R. ratio		1.31	1.05	1.31	1.25	1.29	1.40

lower than in the 1,2- polymerizations recorded in Table III but this feature is probably an illusion. Actually, kernels of 1,4- polymer were formed within 5 min. They were insoluble and enclosed the reagent, thereby shutting off 1,4- and also 1,2- polymerization. By contrast, the product from 1,2-polymerization (Table III) was soluble and generally free from gel; hence that reagent was free to continue its action. The low conversion of butadiene by 1,4- polymerization

could have been increased by the use of more reagent as shown by comparison of the yields with 25 ml. and 10 ml. of reagent, but little would be gained thereby. A better reagent and its more efficient use would have to be developed, and the final result would probably be no better than is achieved by the present alfin catalyst.

Acknowledgment. The authors are indebted to Elizabeth Driscoll Ward for the measurements of viscosity and to Prof. N. A. Nelson for the infrared values.

CAMBRIDGE 39, MASS.

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

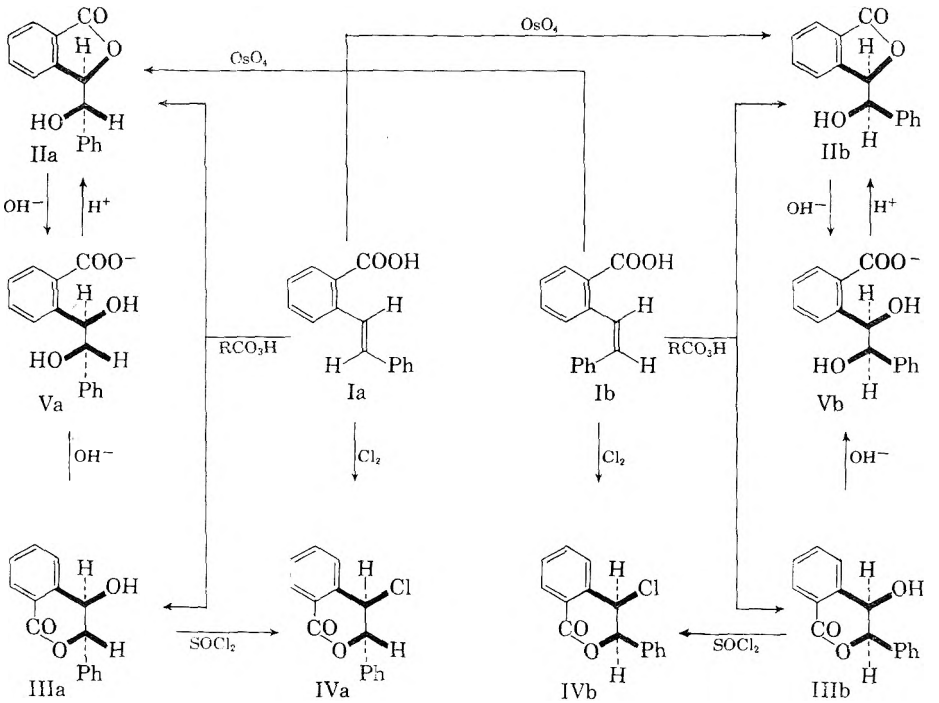
The Reaction of *cis*- and *trans*-Stilbene-2-carboxylic Acids with Peroxyacids[1]

GIANCARLO BERTI

Received January 5, 1959

The reaction of derivatives of *o*-vinylbenzoic acid with organic peroxyacids does not lead to the corresponding epoxides, hydroxylactones being the main products. The stereochemistry of this reaction was investigated, using the *cis*- and *trans*-forms of stilbene-2-carboxylic acid. The products were either the diastereomeric racemates of 3-phenyl-4-hydroxy-3,4-dihydroisocoumarin, or those of 3-(α-hydroxybenzyl)phthalide, higher temperatures or the presence of stronger acids favoring the formation of the former. A complete stereospecificity was observed, the products having the configurations to be expected from a *trans*- addition to the ethylenic double bond of a hydroxyl and of the carboxyl group. The possible mechanisms are discussed.

In continuation of earlier work on the formation of lactones from unsaturated acids, the reaction of *trans*- and *cis*-stilbene-2-carboxylic acid (Ia and Ib) with organic peroxyacids was investigated. When the acids Ia and Ib were treated with peroxyphthalic acid, no evidence was found for the formation of the corresponding epoxides, and the only identified products were two isomeric lactones, $C_{15}H_{12}O_3$, which were not identical with the diastereomeric 3-(α-hydroxybenzyl)phthalides (IIa and IIb), previously prepared by a different method,[2] but were transformed into them by a treatment with alkali, followed by one with acid. Such behavior led to the identification of the lactones as the two racemates of 3-phenyl-4-hydroxy-3,4-dihydroisocoumarin (IIIa and IIIb), whose rings were opened during the treatment with alkali to give the salts Va and Vb, which under acidic conditions were transformed into the more stable γ-lactones (IIa and IIb). A further proof was given by the fact that thionyl chloride transformed the two lactones into the compounds IVa and IVb,

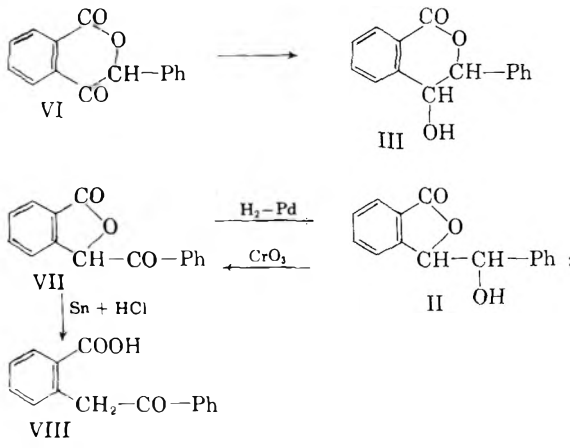


(1) Presented in part at the 16th International Congress of Pure and Applied Chemistry, Paris, 1957

(2) G. Berti, *Tetrahedron*, 4, 393 (1958).

previously obtained by chlorination of the acids Ia and Ib, whose structures and configurations had been proved beyond doubt.[2] Furthermore, the I.R. spectra of the two new lactones have a carbonyl peak at 5.91μ; in the isomeric phthalides (IIa and IIb) this band is shifted to 5.77μ, in good agreement with the well known fact that in γ-lactones the carbonyl stretching shows up at lower wave length than in the corresponding δ-lactones.[3]

Although the proofs appeared rather convincing, there still remained some doubt, as Wanag and Walbe[4] obtained in the reduction of a ketolactone, formulated as VI, a compound to which they assigned the structure III, whose melting point is quite different from those of our lactones. When this work was repeated, it was found that the keto-



lactone was 3-benzoylphthalide (VII), instead of the compound VI, because it was also obtained by oxidizing the hydroxyphthalide IIa with chromic acid, and retransformed into IIa by catalytic reduction. The compound, m.p. 162°, which Wanag and Walbe obtained from the reduction of the ketolactone with tin and hydrochloric acid, was not even a lactone, but had acidic character and was identified as *o*-phenacylbenzoic acid (VIII),[5] evidently formed by hydrogenolysis of the lactone ring.

The configurations of the two lactones III are easily derived from those of the compounds II, whose stereochemistry had been clarified[2] by means of osmium tetroxide oxidations of the acids Ia and Ib. It can be assumed safely that the opening of the lactone rings with base and their reclosure with acid does not involve any inversion.

Hydroxylactones are the main products also of the reactions of the stilbene-2-carboxylic acids with peroxybenzoic and peroxyformic acid. However, with peroxybenzoic acid in chloroform, at, or below room temperature the lactones were predominantly of the γ-type (IIa and IIb), while, if the reaction was carried out at reflux temperature, the dihydroisocoumarins (IIIa and IIIb) were isolated in fairly good yields. When the peroxidations with peroxybenzoic acid were performed in the presence of trichloroacetic acid, the latter lactones were formed exclusively, in very good yields, even in the cold. This seems to be the best method for the preparation of these compounds.

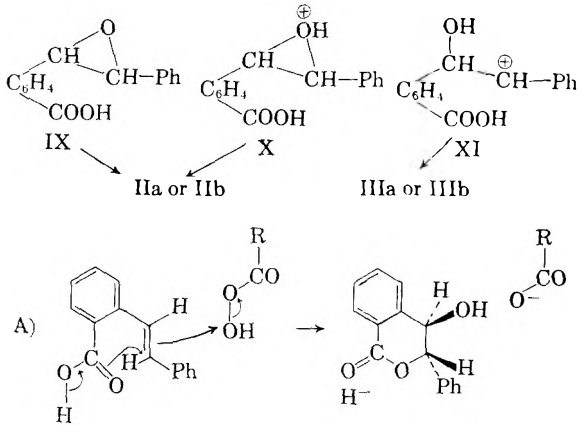
Peroxyformic acid in formic acid solution yielded δ-lactones (IIIa and IIIb), together with significant amounts of oily by-products, which on hydrolysis with sodium hydroxide gave rise to sodium formate and to the sodium salts of the acids Va and Vb. These oily materials were not investigated further, but they probably were formic esters of the compounds II or III. Similar esters of benzoic acid were obtained in smaller amounts in the reactions with peroxybenzoic acid. Hydroxylactones of type III were also formed, when the methyl esters of the stilbene-2-carboxylic acids were reacted with peroxybenzoic or peroxyformic acid.

All the lactonization reactions described above are characterized by a complete stereospecificity. When the *trans*-acid (Ia) or its methyl ester are treated with any of the three peroxyacids, the products, no matter which is their nature (five- or six-membered hydroxylactones or their esters), all give, after hydrolysis with alkali, the salt of *erythro*-α,α'-dihydroxybibenzyl-2-carboxylic acid (Va), while the salt of the *threo*-acid (Vb) is obtained if the *cis*-acid (Ib) or its ester is the starting material. The products are those that can be expected from a *trans*-addition of the $-COO^-$ and OH^+ groups to the ethylenic double bond. Such a stereospecificity is not at all common in addition reactions to stilbene derivatives.[6] Any mechanistic interpretation must account for such stereospecificity. Although the complete mechanism of the reactions of peroxyacids with olephins is still matter of discussion,[7] it certainly involves an electrophilic attack on the double bond, leading to an epoxide, which, in some cases, if an excess of an acid, such as acetic or formic acid, is present, can react further, yielding the monoester of the corresponding α-glycol. In our case only the hydroxylactones were isolated, and their formation can be explained in several different ways. One can assume that a true epoxide (IX) is the intermediate which reacts further by a rapid attack of the carboxyl or carbomethoxyl group on the oxirane ring. Against this hypothesis could stand the fact that epoxides normally react only slowly with weak acids, and not at all with esters. Furthermore, *trans*- opening of the ring is by no means a rule with stilbene epoxides: several recent and older cases in the literature[8]

(3) L. J. Bellamy, *The Infra-Red Spectra of Complex Molecules*, Methuen, London, 1954, p. 153.
(4) G. Wanag and U. Walbe, *Ber.*, **71**, 1448 (1938).
(5) S. Gabriel, *Ber.*, **18**, 2446 (1885).
(6) G. W. Wheland, *Advanced Organic Chemistry*, 2nd ed., J. Wiley and Sons, New York, 1949, p. 292.
(7) D. Swern in *Organic Reactions*, Vol. VII, J. Wiley and Sons, New York, 1953, p. 385; B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).

show that very often such additions take place in a *cis*- way or are not stereospecific. These objections, however, are not sufficient to rule out the intermediate formation of epoxides in our case, first, because a favorable neighboring group effect could greatly increase the rate of attack by the carboxyl group, as was found, for instance, in the hydrolysis of phthalamic acid[9]; secondly, because the stereochemistry of an intramolecular reaction may be different from that of an intermolecular one.

Alternatively, the lactonization step could involve a more reactive intermediate of the type X or XI, provided that in the latter case the cyclization be faster than a rotation around the α,β-bond, to account for the stereospecificity. Finally, the reaction could take place in a single step, through a concerted mechanism, represented by



(A) for the *trans*- acid, in which the electrophilic attack of the peroxyacid is assisted by the simultaneous nucleophilic attack by the carboxyl group.

The fact that an increase in temperature or in acidity leads to δ- instead of γ-lactones could be explained by assuming that different intermediates are involved, in analogy with the hypothesis made to account for the changes in the way of hydrolytic splitting of normal epoxide rings in solutions of decreasing *p*H.[10] The alternative formation of hydroxy γ- or δ-lactones can be determined by a lower electron density on the α- or β-carbon atom. If the actual intermediate in the cyclization step is of the type IX or X, ring-closure is more likely to occur on the α-carbon, which is influenced more by the electron-attracting effect of the carboxyl group. On the other hand, a δ-lactone should be formed, if the intermediate is a carbonium ion (because XI is more stable than the corresponding ion with the charge on the α-position), or if the concerted mechanism (A) is involved (the mesomeric effect of the carboxyl group should reduce the electron density on the β-carbon; similarly, cynnamic acid, of which the acids Ia and Ib are benzologs, is known to add nucleophilic groups on the β-carbon atom[11]).

A final decision about the mechanisms outlined above is not yet possible, but further work which is now in progress, involving kinetic measurements and the extension of the reaction to other unsaturated acids, may give the answer.

It has been found that, beside the stilbene-2-carboxylic acids, several other olephinic acids yielded only hydroxylactones with peroxybenzoic acid. Table I summarizes some of the results: only γ-lactones were formed; this was proved by the fact that they were recovered unchanged after hydrolysis with base, followed by acidification. δ-Lactones, subjected to the same treatment, would have been transformed into the more stable γ-lactones. The alkaline hydrolysis must be very mild, as it was found that one of the lactones, 3 - phenyl - 3 - (α - hydroxyethyl)phthalide, when heated for some time with ethanolic potassium hydroxide, suffered a carbon-carbon splitting, with formation of 3-phenylphthalide and of polymers of acetaldehyde.

Very recently there have been several reports of the formation of hydroxylactones in the reactions of some acids derived from octahydronaphthalene,[12] *endo*-methylenecyclohexene[13] and benzocycloheptene[14] with peroxyacids. This seems to point to a rather general character of the reaction.

EXPERIMENTAL[15]

3-Phenyl-4-hydroxy-3,4-dihydroisocoumarins (IIIa and IIIb) *and 3-(α-hydroxybenzyl)phthalides* (IIa and IIb). (a) *With monoperoxyphthalic acid.* A solution of 5 g. (0.022 moles) of *trans*-stilbene-2-carboxylic acid[16] (Ia) in ether (100 ml.) was treated with 150 ml of a 6.5% solution of peroxyphthalic acid[17] (0.053 mole) in ether and refluxed for 3 hr. After storage at room temperature for 24 hr., the solution was filtered, washed with sodium carbonate solution, dried over magnesium sulfate, and evaporated to dryness. The residue, after crystallization from benzene, gave 3.2 g (60%) of *trans*-3-phenyl-4-hydroxy-3,4-dihydroisocoumarin (IIIa), which presented two different crystalline

(8) J. Boeseken and G. Elsen, *Rec. trav. chim.*, **47**, 694 (1928); J. Boeseken and G. C. C. C. Schneider, *J. prakt. Chem.*, **131**, 285 (1931); J. H. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956); R. C. Cookson and J. Hudec, *Proc. Chem. Soc.*, 24 (1957); B. Witkop and C. M. Foltz, *J. Am. Chem. Soc.*, **79**, 197 (1957); D. Y. Curtin, A. Bradley, and Y. G. Hendrickson, *J. Am. Chem. Soc.*, **78**, 4064 (1956); D. R. Campbell, J. O. Edwards, J. Maclachlan, and K. Polgar, *J. Am. Chem. Soc.*, **80**, 5308 (1959).

(9) M. L. Bender, Yuang-Lang Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958).

(10) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, 1953, p. 341.

(11) R. Fittig and F. Binder, *Ann.*, **195**, 131 (1879); C. Liebermann, *Ber.*, **23**, 141 (1890).

(12) I. N. Nazarov, V. F. Kucherov, and V. M. Andreev, *Izvest. Akad. Nauk S.S.R., Otdel. Khim. Nauk*, 471 (1957) [*Chem. Abstr.*, **51**, 16378 (1957)].

(13) I. N. Nazarov, V. F. Kucherov, and V. G. Bukharov, *Izvest. Akad. Nauk S.S.R., Otdel. Khim. Nauk*, 328 (1958) [*Chem. Abstr.*, **52**, 14543 (1958)].

(14) T. A. Crabb and K. Schofield, *Chem. and Ind. (London)*, 102 (1958).

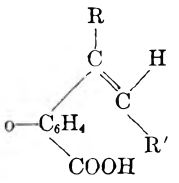
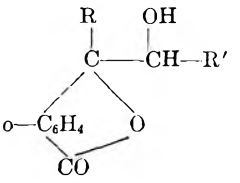
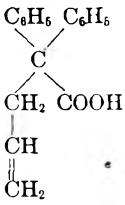
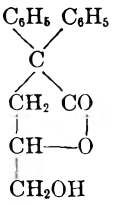
(15) Melting points were taken on a Kofler block and were not corrected. Infrared spectra were kindly determined on Nujol mulls by Dr. P. Bertolaccini.

(16) S. Gabriel and T. Posner, *Ber.*, **27**, 2492 (1894).

(17) H. Boehme, *Org. Syntheses*, **20**, 70 (1940).

TABLE I

HYDROXYLACTONES OBTAINED WITH PEROXYBENZOIC ACID

Starting Acid	Product	M.P.	% Yield	Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
							
R R′	R R′						
CH_3 H[a]	CH_3 H	118–119	82	67.40	67.09	5.66	5.49
H CH_3[b]	H CH_3	90–91	42	67.40	67.63	5.66	5.46
C_6H_5 H[c]	C_6H_5 H	123–124	90	74.99	74.83	5.03	5.41
C_6H_5 CH_3[d]	C_6H_5 CH_3	123–124	92	75.57	74.95	5.55	5.46
		82–85	60	76.10	76.00	6.01	5.89

[a] J. M. van der Zanden and A. P. ter Borg, *Rec. trav. chim.*, **75**, 1115 (1956). [b] The preparation of this acid will be described elsewhere. [c] E. Bergmann, *J. Org. Chem.*, **4**, 1 (1939). [d] G. Berti, *Gazz. chim. ital.*, **81**, 428 (1951). [e] R. T. Arnold and S. Searles, *J. Am. Chem. Soc.*, **71**, 1150 (1949).

TABLE II

REACTIONS OF THE STILBENE-2-CARBOXYLIC ACID WITH PEROXYBENZOIC ACID

Compound	Reaction Conditions	Products and Yields
Ia	3 Days at 0° in $CHCl_3$	IIa (42%), IIIa (18%), esters (10%)[a]
Ia	36 Hr. at r.t.[b] in $CHCl_3$	IIa (40%), IIIa (40%), esters (6%)[a]
Ia	2 Hr. reflux in $CHCl_3$	IIa (5%), IIIa (85%), esters (5%)[a]
Ia	3 Days at 0° in ether	IIa (5%), starting material (80%)
Ia	3 Days at r.t.[b] in $CHCl_3$ + CCl_3COOH	IIIa (90%)
Ia, methyl ester	3 Days at 0° in $CHCl_3$	IIIa (40%), IIa (10%), esters (40%)[a]
Ib	3 Days at 0° in $CHCl_3$	IIb (50%), esters (20%)[a]
Ib	2 Days at r.t.[b] in $CHCl_3$	IIb (70%), esters (10%)[a]
Ib	2 Hr. reflux in $CHCl_3$	IIb (10%), IIIb (30%), esters (40%)[a]
Ib	3 Days at 0° in ether	IIb (10%), starting material (60%)
Ib	3 Days at r.t.[b] in $CHCl_3$ + CCl_3COOH	IIIb (85%), esters (10%)[a]
Ib, methyl ester	3 Days at 0° in $CHCl_3$	IIIb (20%), esters (50%)[a]

[a] The name esters is used for the impure oily by-products, which, upon saponification gave the salts Va and Vb and sodium benzoate. [b] R.t. = room temperature, 20° ± 5.

forms: opaque hemispheres, m.p. 117–119°, or transparent clusters of prisms, m.p. 125–127°. Its I.R. spectrum showed a strong peak at 5.91 μ.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.29; H, 5.34.

When the same reaction was carried out with the *cis*-acid[8] (Ib), *cis*-3-phenyl-4-hydroxy-3,4-dihydroisocoumarin (IIIb) was obtained in 30% yield, as clusters of needles, m.p. 135–136°. It showed a strong I.R. peak at 5.91 μ.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.55; H, 5.03.

Large amounts of neutral oily by-products were formed in both reactions and particularly in the second one. They were not investigated further. The alkaline washings of the ether solutions contained, beside sodium phthalate, small amounts of unreacted stilbene-2-carboxylic acid, but it was not possible to detect any epoxy acid in them.

(b) *With peroxybenzoic acid.* The following general method was used: a 5 to 10% solution of the stilbene-2-carboxylic acid, or of its methyl ester, in chloroform was treated with a 10% excess of the equimolar quantity of a titrated peroxybenzoic acid solution in chloroform. After a variable time the solution was washed with sodium carbonate solution, distilled to a small volume and treated with petroleum ether. The products usually separated as crystalline solids, if the right proportions of the two solvents were used. When the product was a mixture, it was allowed to crystallize very slowly, by spontaneous evaporation of a benzene solution. Large, different crystals were formed, which could be separated mechanically. It was thus possible to isolate, beside the lactones IIIa and IIIb, those IIa, m.p. 148–149°, and IIb, m.p. 102–103°[2]. The two latter lactones showed strong peaks at 5.77 μ in their I.R. spectra. They can be differentiated easily from the δ-lactones of type III, because with sulfuric acid they give a yellow color, which after a few minutes turns red, with a violet fluorescence, while in the same conditions IIIa and IIIb show only a stable faint yellow color. The last mother-liquors of the fractional crystallizations contained the more soluble oily esters. These were saponified by boiling for 1 min. with 5% methanolic po-

tassium hydroxide, the solution was then diluted with water, acidified and the precipitate thus formed extracted with sodium carbonate solution. The alkaline extract contained sodium benzoate, while the insoluble part was compound IIa, if the starting material was the acid Ia, or compound IIb, if one had started from the acid Ib. In some of the runs the reaction with peroxybenzoic acid was carried out in ether, but yields were very poor. In others, 0.5 g. of trichloroacetic acid were added to the chloroform solution for each gram of stilbene-2-carboxylic acid. Table II summarizes the results of several reactions conducted under different conditions. The yields were evaluated on the basis of accurate fractional crystallizations, and, in the case of inseparable mixtures, from melting-point diagrams. They should be accurate within ±5%.

(c) *With peroxyformic acid.* A suspension of 1 g. of the acid Ia in 10 ml. of 98% formic acid was treated with 0.5 ml. of 35% hydrogen peroxide and heated during 20 min. on a steam bath. After 6 hr. at room temperature, the formic acid was distilled off under reduced pressure, the residue was dissolved in ether, washed with sodium carbonate solution and dried over magnesium sulfate. After elimination of the ether and crystallization from benzene-ligroin, 0.45 g. of the lactone IIIa were obtained. The mother-liquor was evaporated to dryness and the residue refluxed for 5 min. with 10 ml. of 5% ethanolic potassium hydroxide, diluted with water and acidified with sulfuric acid: 0.3 g. of the lactone IIa separated out. The filtrate gave a formic acid containing distillate.

When the same reaction was carried out with 1 g. of the acid Ib, 0.30 g. of IIIb and, after saponification, 0.45 g. of IIb were obtained. The methyl ester of the acid Ia gave similarly IIIa (50% yield) and IIa (30%); the methyl ester of Ib yielded IIIb (40%) and IIb (40%).

Reactions of other unsaturated acids with peroxybenzoic acid. Table I summarizes the results obtained with other unsaturated acids, which were left with peroxybenzoic acid in chloroform at room temperature, until a starch-iodide test showed that the peroxyacid had disappeared. The products were isolated as described above and obtained pure after one crystallization from benzene or from a benzene-ligroin mixture.

Saponification of the lactones. A solution of 0.1 g. of each of the lactones in 2 ml. of methanol was treated with 2 ml. of 10% methanolic potassium hydroxide and left at room temperature until a clear solution was obtained upon dilution with water. The aqueous solution was acidified with concentrated hydrochloric acid and the precipitate was collected, or, if the lactone did not precipitate, it was extracted with ether. The following results were obtained: the lactones IIa and IIb, and all those of Table I, were recovered unchanged. The lactones IIIa and IIIb were transformed into those IIa and IIb, respectively. When 3-phenyl-3-(α-hydroxyethyl)-phthalide was refluxed for 15 min. with 10% ethanolic potassium hydroxide the solution became brown. Dilution with water produced some precipitate, which was extracted with ether. Acidification of the aqueous layer gave a solid, which, after crystallization from carbon tetrachloride, yielded needles, m.p. and mixed m.p. with 3-phenylphthalide[18] 115°.

3-Phenyl-4-chloro-3,4-dihydroisocoumarins (IVa and IVb). The lactone IIIa (0.3 g.) was treated with 2 ml. of thionyl chloride and refluxed for 10 min. The excess thionyl chloride was then evaporated under reduced pressure and the residue, after crystallization from benzene–petroleum ether, gave 0.1 g. of prisms, m.p. 108–110°, of IVa.[2]

The same reaction, starting from the lactone IIIb, led to the chlorolactone IVb, m.p. 146–147°.[2]

3-Benzoylphthalide. A solution of the lactone IIa (0.2 g.) in 5 ml. of glacial acetic acid was treated with 0.2 g. of chromium trioxide and heated for 30 min. on a steam bath. On cooling a precipitate separated out, which, after crystallization from ethanol, gave prisms, m.p. 148° (0.1 g.). This product did not depress the melting point of the compound prepared by the treatment of 2,3-diphenyl-1,4-diketo-1,2,3,4-tetrahydroisoquinoline with hydrochloric acid, which, according to Wanag and Walbe[4] should be 3-phenylisochroman-1,4-dione.

A solution of 0.5 g. of 3-benzoylphthalide in 30 ml. of glacial acetic acid was shaken with hydrogen in the presence of 0.3 g. of 5% palladium on charcoal, until the absorption of hydrogen stopped (1 hr.). After filtration and dilution with 200 ml. of water, the solution was extracted with ether, the ether extract was washed with sodium carbonate solution, dried over magnesium sulfate and evaporated. The residue, after crystallization from benzene-ligroin, gave 0.25 g. of IIa, m.p. 148–149°. When the reduction was carried out according to Wanag and Walbe,[2] with tin powder and hydrochloric acid in ethanol, the product was an acid, m.p. 162° with decomposition, whose melting-point was not depressed in a mixture with *o*-phenacylbenzoic acid.[5]

PISA, ITALY

(18) F. Ullmann, *Ann.*, **291**, 17 (1896).

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

Birch Reduction of 2-Naphthoic and of *ortho*-Methoxynaphthoic Acids

ERNEST L. ELIEL AND TROY E. HOOVER

Received January 6, 1959

The Birch reduction of 2-naphthoic acid and its 1- and 3-methoxy derivative gives mainly 1,2,3,4-tetrahydro-2-naphthoic acid or 1,2,3,4,5,8-hexahydronaphthoic acid, depending on conditions and proportions of reagents. The methoxyl group, where present, is lost in these reductions. 2-Methoxy-1-naphthoic acid, on the other hand, gives mainly 2-methoxy-1,4,5,8-tetrahydro-1-naphthoic acid without loss of the methoxyl group.

In connection with another problem we were interested to find out whether an *o*-methoxybenzoic acid could be submitted to the Birch reduction[1] without loss of either the carboxyl or the methoxyl function. By "Birch reduction" is meant the reduction of an aromatic compound, usually to a 1,4-cyclohexadiene derivative, by means of an alkali metal–liquid ammonia–alcohol combination. The reaction was originally discovered by Wooster[2]

(1) (a) A. J. Birch, *Quart. Revs.*, **4**, 69 (1950). (b) See also G. W. Watt, *Chem. Revs.*, **46**, 317 (1950).

(2) C. B. Wooster, U. S. Patent, **2,182,242** (Dec. 5, 1939); *Chem. Abstr.*, **34**, 1993 (1940); C. B. Wooster and K. L. Godfrey, *J. Am. Chem. Soc.*, **59**, 596 (1937).

but has been investigated particularly extensively by Birch in the period 1944–55; a very useful experimental modification was described by Wilds and Nelson in 1953.[3] The reduction of anisole[1a,3] is one of the classical examples of the Birch reduction and leads to 1-methoxy-1,4-cyclohexadiene, addition of hydrogen taking place at positions other than that occupied by the methoxyl substituent. The reduction of benzoic acids has also been studied;[4] in this case the hydrogen seeks the position occupied by the electron-withdrawing group and a 1-carboxy-2,5-cyclohexadiene results. The sodium salt of 1-naphthoic acid has similarly been reduced to 1,4-dihydro-1-naphthoic acid,[5] but the reduction is atypical in that no proton donor such as alcohol was present during the reduction.

A few examples of the reduction of methoxybenzoic acids are on record.[6] To the extent that one may generalize from these few instances, it seems that a methoxyl group *para-* to the carboxyl group is eliminated in the Birch reduction, but a methoxyl group *meta-* to the carboxyl group is preserved. Thus, veratric acid (3,4-dimethoxybenzoic acid) yields, after hydrolysis of the intermediate enol ether, cyclohexanone-3-carboxylic acid. Surprisingly enough, the same product is obtained from *m*-methoxybenzoic acid, indicating that the intermediate reduction product was a methoxytetrahydrobenzoic acid instead of the expected methoxydihydrobenzoic acid. 3,4,5-Trimethoxybenzoic acid upon reduction and hydrolysis yields 1,3-cyclohexanedione-5-carboxylic acid, presumably *via* 1,4-dihydro-3,5-dimethoxybenzoic acid; the *p*-methoxyl group is eliminated.

The significance of these observations is not, however, entirely unambiguous; for previously[7] it had been found that the central methoxyl group in *pyrogallol trimethyl ether* (1,2,3-trimethoxybenzene) is completely lost in the Birch reduction and one of the two methoxyl groups in veratrole (1,2-dimethoxybenzene) is partly lost. Thus, it is possible that similar loss of methoxyl functions in polymethoxybenzoic acids is caused mainly by the adjacent methoxyl group rather than by the carboxyl group in the *para-* position. The reduction of 5,6,7,8-tetrahydro-3-methoxy-2-naphthoic acid and 5,6,7,8-tetrahydro-1-methoxy-2-naphthoic acid[8] might have settled this question; but in the former case the (major) acidic product was not characterized, and in the latter case it was identified only tentatively as 2,5,6,7,8,10-hexahydro-2-naphthoic acid, since chromic acid oxidation of the crude acidic product gave 5,6,7,8-tetrahydro-2-naphthoic acid. The reduction of *o-* and *p*-methoxybenzoic acid has been mentioned without experimental details in several papers by Birch[6,8] as involving loss of the methoxyl function. Recently, however, the reduction of *o*-methoxybenzoic acid with sodium and methanol in liquid ammonia has been found[9] to give 2-methoxy-1,4-dihydrobenzoic acid (isolated in the form of derivatives) *without* loss of the methoxyl function.

The present work is concerned with the reduction of 2-naphthoic acid (I), 1-methoxy-2-naphthoic acid (II), 3-methoxy-2-naphthoic acid (III), and 2-methoxy-1-naphthoic acid (IV). The method of reduction was that of Wilds and Nelson,[3] using liquid ammonia with ether as a co-solvent, lithium as the reducing metal and anhydrous ethanol as the proton source. In most instances, 10 g.-atoms of lithium were employed per mole of compound to be reduced, but in some runs the amount of reducing agent was deliberately limited.

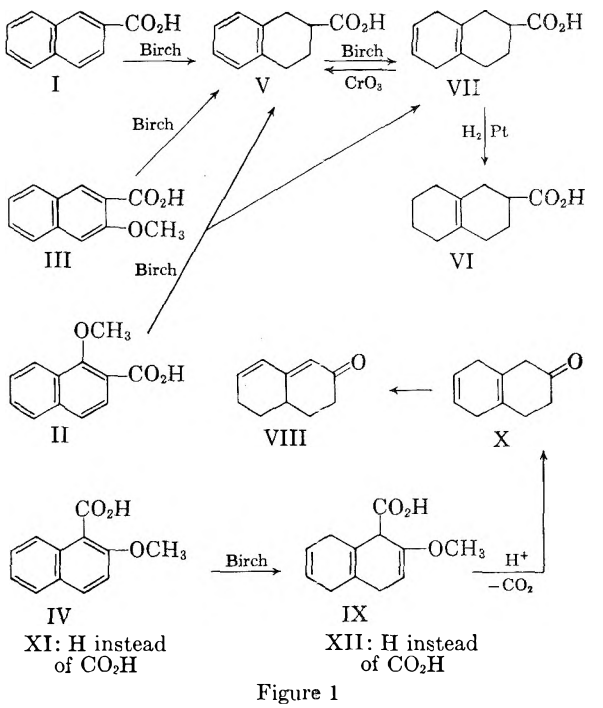


Figure 1

The reduction of 2-naphthoic acid (I) with an excess of lithium gave a hexahydro-2-naphthoic acid which was transparent in the ultraviolet region of the spectrum and did not react with maleic anhydride, indicating that the double bonds were nonconjugated. Oxidation of this material with chromium trioxide yielded 1,2,3,4-tetrahydro-2-naphthoic acid (V), suggesting that the two double bonds in the hexahydro acid were in the unsub-

(3) A. Wilds and N. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953).

(4) Unpublished results by A. J. Birch quoted in ref. 1. The reduction of *o*-toluic acid to 1,4-dihydro-2-methylbenzoic acid has been described by A. J. Birch, *J. Chem. Soc.*, 1551 (1950).

(5) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

(6) A. J. Birch, P. Hextall, and S. Sternhell, *Aust. J. Chem.*, **7**, 256 (1954).

(7) A. J. Birch, *J. Chem. Soc.*, 102 (1947).

(8) A. J. Birch, A. R. Murray, and H. Smith, *J. Chem. Soc.*, 1945 (1951).

(9) M. E. McEntee and A. R. Pinder, *J. Chem. Soc.*, 4419 (1957). This report appeared after the present work was completed.

stituted ring. Hydrogenation of the hexahydro acid with platinum in ethanol yielded an octahydro-2-naphthoic acid, characterized by its blue nitroso chloride derivative. Bedause of failue of this material to undergo further hydrogenation and because it formed a nitroso chloride rather than an oxime upon treatment with nitrosyl chloride,[5] it was assigned the structure 1,2,3,4,5,6,7,8-octahydro-2-naphthoic acid (VI) and the original reduction product is therefore 1,2,3,4,5,8-hexahydro-2-naphthoic acid (VII).

Reduction of 2-naphthoic acid with a limited amount of lithium (4 g.-atoms per mole) gave the known 1,2,3,4-tetrahydro-2-naphthoic acid (V). Compound V is probably an intermediate in the reduction of I to VII, since it could, in turn, be reduced to VII by means of the Birch procedure.

The reduction of 1-methoxy-2-naphthoic acid (II) with excess lithium gave, on one occasion, 1,2,3,4-tetrahydro-2-naphthoic acid (V) and on another 1,2,3,4,5,8-hexahydro-2-naphthoic acid (VII). Since the yields were not very high, it is possible that in both instances mixtures were obtained. It seems that here, again, the tetrahydro-acid (V) is the primary product and is then further reduced to the hexahydroacid (VII).

From the reduction of 3-methoxy-2-naphthoic acid (III) with excess lithium, only the tetrahydroacid V was isolated, though in poor yield. The concomitant formation of some hexahydroacid VII is not excluded.

Whereas the reduction of the 1- and 3-methoxy-2-naphthoic acids thus proceeded with elimination of the methoxyl function, a different result was observed in the reaction of 2-methoxy-1-naphthoic acid (IV). Reduction of this material produced, in respectable yield, an acidic tetrahydro derivative which still contained the methoxyl function. The ultraviolet spectrum of this material indicated the absence of conjugated double bonds, although a moderately strong maximum was found at 209 mμ, possibly due to an enol ether function. The infrared spectrum showed a carbonyl band (carboxylic acid) at 5.90μ and a doublet at 6.01 and 6.11μ, as is to be expected for an enol ether.[3] Treatment of this material with 2,4-dinitrophenylhydrazine in acid produced, depending on conditions, either an unconjugated or a conjugated 2,4-dinitrophenylhydrazone. The melting point of the conjugated derivative agreed with that reported[7] for the 2,4-dinitrophenylhydrazone of 2-keto-2,3,4,5,6,10-hexahydronaphthalene (VIII). On this basis, the reduction-product was assigned structure IX, 1,4,5,8-tetrahydro-2-methoxy-1-naphthoic acid. The unconjugated dinitrophenylhydrazone is probably a derivative of 2-keto-1,2,3,4,5,8-hexahydronaphthalene (X), even though it melted slightly lower than the known derivative of this ketone,[8] possibly because of geometric isomerism.

The fact that the derivatives of 2-naphthoic acid (II and III) lose their methoxyl substituent upon Birch reduction whereas the derivative of 1-naphthoic acid (IV) does not is of interest. An explanation for the loss of methoxyl is suggested in Fig. 2. This explanation is based on

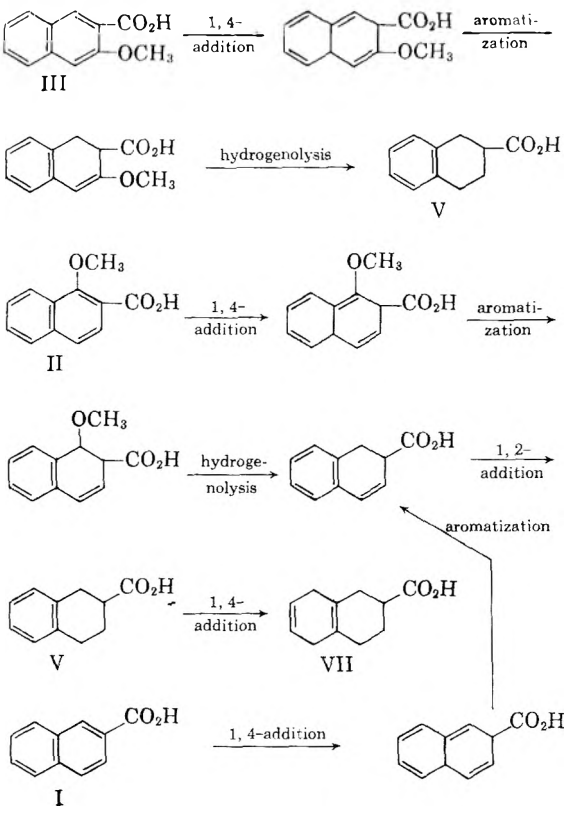


Figure 2

the following known facts: (1) The metal (lithium) in the Birch reduction adds most readily to the carboxyl-substituted carbon and the carbon *para*-to its[6]; (2) if the primary reduction product is a methylenecyclohexadiene, it rearranges readily to a benzene derivative[10]; (3) a methoxyl group in a β-methoxystyrene and in a benzyl ether is readily hydrogenolyzed,[11] whereas other types of methoxyl groups evidently survive the conditions of the Birch reduction.

The reduction of 2-methoxy-1-naphthoic acid (IV) to the tetrahydroderivative IX is in close analogy with the known reduction of 2-naphthyl methyl ether (XI) to 1,4,5,8-tetrahydro-2-naphthyl methyl ether (XII).[8] In this case, as in the case of anisole[1a,3,5] and *o*-methoxybenzoic acid,[9] there is no obvious reason why the methoxy group should be

(10) *Cf.* W. J. Bailey and J. Rosenberg, *J. Am. Chem. Soc.*, **77**, 73 (1955).

(11) R. Stoermer and Th. Biesenbach, *Ber.*, **38**, 1964 (1905) have described the hydrogenolysis of phenyl β-styryl ether, $C_6H_5OCH{=}CHC_6H_5$ to phenol and ethylbenzene by means of sodium and ethanol; and A. Klages, *Ber.*, **39**, 2587 (1906) has described the hydrogenolysis of benzyl alcohol to toluene under the same conditions; benzyl alkyl ethers would probably be reduced similarly.

lost. Upon treatment with acid, XII is known to give rise first to 1,2,3,4,5,8-hexahydro-2-ketonaphthalene (X) and then to 2,3,4,5,6,10-hexahydro-2-ketonaphthalene (VIII).[8]

Also shown in Fig. 2 is what we believe to be the sequence of events in the reduction of 2-naphthoic acid. 1,4-Addition in the carboxyl-substituted 2- and the 10-position gives 2,10-dihydro-2-naphthoic acid which rearomatizes itself to 1,2-dihydro-2-naphthoic acid. The latter then undergoes reduction at the styrene-type double bond[1b] to give the isolated product 1,2,3,4-tetrahydro-2-naphthoic acid (V).[12] Further 1,4-addition may then proceed in the second benzene ring to give the hexahydroacid VII. There are several analogies in the literature suggesting that such addition will avoid the alkyl-substituted positions, the most closely similar case being the reduction of tetralin to 1,2,3,4,5,8-hexahydronaphthalene.[5]

EXPERIMENTAL

Melting points are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Reduction of 2-naphthoic acid. (I) (a) *Using excess lithium.* To a suspension of 8.6 g. (0.05 mole) of 2-naphthoic acid and 2.42 g. (0.35 g.-atom) of lithium wire in 200-ml. liquid ammonia and 40-ml. anhydrous ethyl ether contained in a three necked flask was added 25 ml. of anhydrous ethanol over a 20-min. period with good mechanical stirring. The ammonia was allowed to evaporate and more ether was added. The reaction mixture was cooled in an ice bath and 35 ml. water was added, followed by 120 ml. of 3*N* hydrochloric acid. The ether layer was separated and the acid layer extracted with two more portions of ether. The combined ether layers were washed with water and brine, dried over sodium sulfate, and concentrated until crystallization commenced. The solution was chilled and filtered to yield a first crop of crystals weighing 4.84 g., m.p. 77–79° and a second crop weighing 2.49 g., m.p. 67–73°. Two recrystallizations of the first crop from petroleum ether (b.p. 90–120°) returned 3.52 g. of 1,2,3,4,5,8-hexahydro-2-naphthoic acid (VII) melting at 80–81°. Two further recrystallizations from aqueous methanol raised the melting point to 81–82°.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.18; H, 7.92; neut. equiv., 178.2. Found: C, 74.40; H, 8.06; neut. equiv., 178.6.

The ultraviolet spectrum of this material showed only a very low maximum at 273 mμ (ethanol), $\epsilon = 15$. The substance was recovered from an attempted reaction with maleic anhydride.

Further material was recovered from the second crop. A second reduction produced essentially the same result.

(b) *Using four equivalents of lithium.* This reduction was carried out using 0.34 g. (0.002 mole) of 2-naphthoic acid, 7 ml. ether, 25 ml. ammonia, 0.06 g. (0.008 g.-atom) lithium and enough anhydrous ethanol to decolorize the solution. The isolation procedure was as described above and there was obtained 0.24 g. of product which, after recrystallization from petroleum ether (b.p. 60–65°) weighed 0.11 g. and melted at 95.5–96.5°. This material was 1,2,3,4-tetrahydro-2-naphthoic acid (V) since its melting point was undepressed by admixture of an authentic sample of V kindly made available by Professor Melvin S. Newman of Ohio State University.

Reduction of 1,2,3,4-tetrahydro-2-naphthoic acid (V). This reduction was carried out as described for 2-naphthoic acid using 0.60 g. (0.0033 mole) of V, 10 ml. of anhydrous ether, 50 ml. of liquid ammonia, 0.21 g. (0.03 g.-atom) of lithium, and sufficient ethanol to produce decolorization. The residue of this reaction, worked up as described before, weighed 0.53 g. Two recrystallizations from petroleum ether (b.p 60–65°) returned 0.20 g. of 1,2,3,4,5,8-hexahydro-2-naphthoic acid (VII), m.p. 82–83° undepressed by admixture of the analytical sample described earlier.

Chromic acid oxidation of 1,2,3,4,5,8-hexahydro-2-naphthoic acid (VII). A 1-g. sample (0.006 mole) of VII obtained in the Birch reduction of I was oxidized by means of 0.6 g. chromium trioxide in 5 ml. glacial acetic acid using the method of Birch.[5] After the exothermic reaction was over, the reaction mixture was diluted with 15 ml. of water and the solid product was collected and crystallized twice from aqueous ethanol to give 0.40 g. of 1,2,3,4-tetrahydro-2-naphthoic acid (V), m.p. 96–97°, undepressed by admixture of the authentic specimen described above

Catalytic hydrogenation of 1,2,3,4,5,8-hexahydro-2-naphthoic acid (VII). A 3.50-g. sample (0.0195 mole) of VII, m.p. 80–81° in 60 ml. anhydrous ethanol was hydrogenated for 8 hr. using 0.15 g. of platinum oxide as catalyst at an initial hydrogen pressure of 40 p.s.i. The catalyst was removed by filtration and the residue concentrated under reduced pressure to give 3.28 g. of a sticky, pleasant-smelling solid. Four recrystallizations from petroleum ether (b.p. 60–90°) returned 0.58 g. melting at 111.5–113°. Further recrystallization from aqueous methanol raised the melting point to 114–115°. The mixed melting point with a sample of the all-*cis*-decahydro-2-naphthoic acid, m.p. 105–106° (kindly provided by Professor William G. Dauben of the University of California) was depressed to 88–97°. The analysis of the material indicated it to be an octahydronaphthoic acid (VI).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95 Found: C, 73.53; H, 8.82.

Essentially the same result was obtained in a second hydrogenation extended to 40 hr., except that an increased amount of a nonacidic, pleasant-smelling oil was obtained. The acid is apparently partially esterified under the conditions of the reduction. When the hydrogenation was carried out in glacial acetic acid, the product (perhaps a mixture of diastereoisomeric decahydroacids?) did not crystallize.

Nitroso chloride of VI. To 9.5 g. of sodium nitrite in 37 ml. water was added dropwise, at 0°, a mixture of 2.5 ml. water, 3.4 ml. of concentrated sulfuric acid, and 11 g. of amyl alcohol. The aqueous layer was separated and the amyl nitrite washed with 2.5 ml. of sodium bicarbonate–sodium chloride solution. To a mixture of 0.154 g. (0.00085 mole) of VI and 0.25 g. (0.00175 mole) of amyl nitrite at −15° was added 0.15 ml. of concentrated hydrochloric acid. A small amount of acetone was added and the solvent removed by vacuum evaporation. This left a blue solid, m.p 108–111°. Two recrystallizations from acetone returned 0.038 g. of blue material, m.p. 127–128°.

Anal. Calcd. for $C_{11}H_{16}ClNO_3$: C, 63.68; H, 6.60. Found: C, 63.76; H, 6.80.

1-Methoxy-2-naphthoic acid (II). This acid was prepared as previously described.[13] Distillation of the crude product (m.p. 115–118°) in a sausage flask through a short column at reduced pressure followed by crystallization from benzene gave material melting at 127.0–127.5° (lit.[13] 126–127°).

Reduction of 1-methoxy-2-naphthoic acid (II). (a) To a well stirred suspension of 9.26 g. (0.046 mole) of II in 20 ml. ether

(12) The scheme proposed here is not unique. Alternative means of reducing the substituted ring in 2-naphthoic acid and its 1- and 3-methoxy derivatives, possibly without disturbing the aromatic character of the unsubstituted ring even temporarily, can be envisaged. The loss of the methoxyl function in II and III might involve β-elimination of methanol from the 1,2,3,4-tetrahydro acid corresponding to II and III.

(13) E. Bretscher, H. G. Rule, and J. Spence, *J. Chem. Soc.*, 1493 (1928).

and 225 ml. liquid ammonia was added 3.2 g. (0.46 g.-atom) of lithium wire over a 15-min. period. After stirring for 15 more min., another 50 ml. of liquid ammonia was added, followed by the slow addition of 22 ml. anhydrous ethanol. The product was isolated as described for the reduction of 2-naphthoic acid, using 105 ml. 4*N* hydrochloric acid in the extraction. The residue weighed 9.08 g. Recrystallization from aqueous ethanol returned 7.02 g., m.p. 71–76°. Recrystallization of 6 g. of this material from petroleum ether (b.p. 39–45°) and from aqueous ethanol gave a total of 2.25 g., m.p. 93–94° and 94–95°. This material did not depress the melting point of a sample of 1,2,3,4-tetrahydro-2-naphthoic acid (V) obtained in the reduction of 3-methoxy-2-naphthoic acid (see below). The literature[14] gives 96.0–96.6° as the melting point of V.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.04; H, 6.87; neut. equiv., 176.2. Found: C, 75.32, 75.22; H, 6.89, 7.01; neut. equiv., 176.7.

The ultraviolet spectrum of this material, λ_{max} 266 mμ, ϵ_{max} 450; λ_{max} 273.5 mμ, ϵ_{max} 500 (ethanol) closely resembles the spectrum of tetralin.[15]

The amide of this product melted at 135–136° (lit.[14] 138.0–138.8°).

(b) The above experiment was repeated under apparently similar conditions, using 8.22 g. (0.041 mole) of II, 35 ml. ether, 225 ml. liquid ammonia, 2.8 g. (0.4 g.-atom) lithium wire, and 20 ml. anhydrous ethanol. The residue this time weighed 6.46 g. and melted at 56–74°. Three recrystallizations from petroleum ether (b.p. 60–65°) returned 3.08 g., m.p. 79–81°. Further recrystallizations from the same solvent failed to raise the melting point beyond 80.5–81°. This material was 1,2,3,4,5,8-hexahydro-2-naphthoic acid (VII), since it did not depress the melting point of the analytically pure sample of VII obtained in the reduction of 2-naphthoic acid (see above).

Reduction of 3-methoxy-2-naphthoic acid (III). A sample of 3.03 g. (0.015 mole) of III[16] was reduced using 20 ml. anhydrous ether, 100 ml. liquid ammonia, 1.04 g. (0.15 g.-atom) lithium wire, and *ca.* 3 ml. anhydrous ethanol. Acidification was effected using 18 ml. of 6*N* hydrochloric acid and the red, semisolid residue after ether extraction and concentration weighed 2.53 g. Recrystallization of this material from petroleum ether gave 0.475 g., m.p. 95–97°, 0.381 g., m.p. 89–91° and 0.117 g. (after sublimation), m.p. 87–91°. Further recrystallization from petroleum ether (b.p. 39–45°), petroleum ether–acetone and aqueous methanol gave material melting at 96.5–97.5° whose melting point was undepressed by admixture of an authentic sample of 1,2,3,4-tetrahydro-2-naphthoic acid (V) (see above), lit.[14] m.p. 96.0–96.6°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.04; H, 6.87. Found: C, 74.93; H, 6.92.

The reduction was repeated with essentially the same result.

The amide of V obtained in the above reduction melted at 137.5–138° (lit.[14] 138.0–138.8°) and, upon admixture, did not depress the melting point of an authentic sample kindly provided by Professor M. S. Newman.

2-Methoxy-1-naphthoic acid (IV). 2-Hydroxy-1-naphthaldehyde was methylated by the published procedure.[17] The product, m.p. 83.5–84.5° (lit.[17] 84°) was oxidized as previously described[18] to IV, m.p. 174–176° (lit.[18] 176–177°).

Reduction of 2-methoxy-1-naphthoic acid (IV). The reduction of 12.95 g. (0.064 mole) of IV in 90 ml. anhydrous ether and 300 ml. liquid ammonia was effected using 4.5 g. (0.65 g.-atom) lithium wire and sufficient anhydrous ethanol to decolorize the solution. The reaction and isolation were effected as described for 2-naphthoic acid, 125 ml. of 4*N* hydrochloric acid being employed in the acidification step.[19] The residue from the reaction weighed 11.4 g. Treatment of this material with diethyl ether and filtration gave 6.7 g. of 1,4,5,8-tetrahydro-2-methoxy-1-naphthoic acid (IX), m.p. 133.5–134.5°. Low-temperature crystallization from absolute ethanol did not change the melting point.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; neut. equiv., 206. Found: C, 70.09; H, 6.80; neut. equiv., 210.

The ultraviolet spectrum of the material showed a maximum in ethanol at 209 mμ, ϵ = 2000 and was otherwise transparent except for a slight shoulder at 250–255 mμ.

A 208-mg. sample (0.001 mole) of the above acid dissolved in 100 ml. 95% ethanol was treated with 4 ml. of a 0.25*M* 2,4-dinitrophenylhydrazine reagent in phosphoric acid. After 40 hr. the precipitated derivative was collected; it weighed 289 mg., m.p. 138–141°. After two recrystallizations from ethanol–ethyl acetate the material melted at 162–163° (lit.[8] m.p. 171° for the dinitrophenylhydrazone of X).

Anal. Calcd. for $C_{16}H_{16}N_4O_6$: C, 58.53; H, 4.91. Found: C, 58.56; H, 4.99.

The material was orange in color and absorbed in the ultraviolet at 230 mμ, ϵ = 17,000 and at 360 mμ, ϵ = 20,000 (ethanol).

When the derivative was prepared from a 50-mg. sample of IX by heating with 2 ml. of a 2,4-dinitrophenylhydrazine–sulfuric acid solution in 95% ethanol,[20] the originally orange precipitate changed in color to red and melted at 189–191° (59 mg.). Two recrystallizations from ethanol–ethyl acetate raised the melting point to 202–204° (lit.[8] m.p. 202° for the dinitrophenylhydrazone of VIII).

Anal. Calcd. for $C_{16}H_{16}N_4O_6$: C, 58.53; H, 4.91. Found: C, 58.72; H, 4.99.

The material absorbed in the ultraviolet at 267 mμ, ϵ = 17,500 and at 302 mμ, ϵ = 15,000 and in the visible at 405 mμ, ϵ = 49,000.

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NOTRE DAME, IND.

(14) M. Newman and J. Mangham, *J. Am. Chem. Soc.*, **71**, 3342 (1949).

(15) M. Soffer, R. Stewart, and G. Smith, *J. Am. Chem. Soc.*, **74**, 1556 (1952).

(16) Prepared by the method of G. B. Jambuserwala, S. Holt, and F. A. Mason, *J. Chem. Soc.*, 373 (1931), m.p. 133–134° (lit.[13] 133–134°). We were not able to duplicate the high yield claimed by these investigators.

(17) G. Barger and W. Starling, *J. Chem. Soc.*, **99**, 2030 (1911).

(18) F. L. Warren, M. Gindy, and F. G. Baddar, *J. Chem. Soc.*, 687 (1941).

(19) Ether extraction of the ammoniacal solution after addition of water but before acidification yielded 0.21 g. of neutral material. Similarly small amounts of neutral material were isolated in several of the other reductions described earlier in this paper.

(20) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, Inc., New York, 4th ed., (1956), p. 219.

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

Alkyl Substituent and Solvent Effects in the "Principal" Ultraviolet Transition of Some Positive Ions

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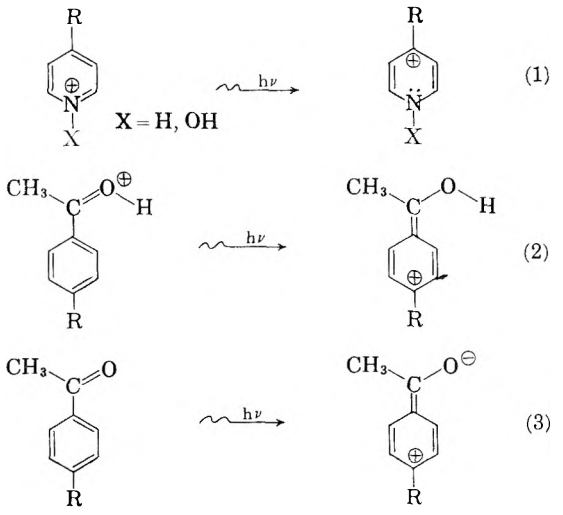
The energy of the "principal" electronic transition has been determined for the conjugate acids of *p*-alkylnitrobenzenes, the conjugate acids and acylonium ions of 4-alkyl-2,6-dimethylbenzoic acids, the conjugate acids of *p*-alkylacetophenones, 4-alkylpyridinium ions, and 4-alkyl-1-hydroxypyridinium ions. The excitation energies of the latter three series of compounds were measured in a number of solvents. For all the series and in all solvents, stabilization of the excited state relative to the ground state was in the inductive order, indicating that C—H hyperconjugation is *not* the most important mode of electron release by alkyl groups in these highly electron-demanding transitions. In keeping with the nature of the transitions, solvent effects in shifting the spectra or changing the excitation energy spreads between members of a series were small.

This paper deals with the effect of changing alkyl substituent and changing solvent upon the "principal" electronic transition of a number of positive ions, including 4-alkylpyridinium and 4-alkyl-1-hydroxypyridinium ions, conjugate acids of *p*-alkylacetophenones and *p*-alkylnitrobenzenes, and conjugate acids and acylonium ions of 4-alkyl-2,6-dimethylbenzoic acids. The "principal" transition involves a redistribution of charge, with the transition moment lying in the long axis of the molecule, and is represented approximately by Equations 1 and 2.[2]



In a previous study of the principal electronic transition of neutral *p*-alkylnitrobenzenes and *p*-alkylacetophenones (Equation 3) it was found that: (1) in the gas phase the order of excitation energies is H (greatest)>>Me>Et>iPr>tBu[3] and (2) basic solvents tended to invert the gas phase order, giving a resultant jumbled order of excitation energies. It was concluded that the *order* of inherent electron release by alkyl, in such electron demanding transitions at least, is the inductive one; *i.e.*, that C—H hyperconjugation is *not* a predominant mode of electron release. The Baker-Nathan Effect[4] on the excitation energies in basic solvents was ascribed to steric hindrance to solvation *near* the alkyl substituent. This factor would tend to invert the inductive order of excitation energies since solvent stabilization of the excited state relative to the ground state would be decreased with increasing bulk of the substituent.[3]

It appeared of interest to determine, if possible, whether the inductive order of inherent electron release also would prevail in principal electronic transitions of the types of Equations 1 and 2, since these are presumably even more demanding of electron release by the substituent. It also was considered necessary to study the effect of changing solvent on the excitation energies of a number of the positive ions, since previous experience has shown that the order of inherent substituent effects may be masked by solvent.[3]

EXPERIMENTAL

Materials. The preparation and purification of the *p*-alkylacetophenones,[3] *p*-alkylnitrobenzenes,[3] 4-alkyl-2,6-dimethylbenzoic acids,[6] and of pyridine, 4-methylpyridine, 4-ethylpyridine, and their perchloric acid salts[2] has been described. Fractional distillation through a 40-plate spinning band column was used to purify 4-isopropylpyridine,[7] b.p. 122° (127 mm.), $n_D^{25.5}$ 1.4941, and 4-*t*-butylpyridine,[7] b.p. 135° (131 mm.), $n_D^{25.5}$ 1.4934. The perchloric acid salts were prepared and purified by the method used previously.[2] The 4-isopropylpyridinium perchlorate melted at 60.1–60.8°.

(1) National Science Foundation Predoctoral Fellow, 1956–58.

(2) W. M. Schubert and J. Robins, *J. Am. Chem. Soc.*, **80**, 559 (1958).

(3) W. M. Schubert, J. Robins, and J. L. Haun, *J. Am. Chem. Soc.*, **79**, 910 (1957).

(4) The term "Baker-Nathan Effect" is defined as an order of *experimental quantities* that either corresponds with or tends to correspond with the number of α-hydrogens on the alkyl substituent.[5]

(5) W. M. Schubert and W. A. Sweeney, *J. Org. Chem.*, **21**, 119 (1956).

(6) W. M. Schubert, J. Donohue, and J. D. Gardner, *J. Am. Chem. Soc.*, **76**, 9 (1954).

(7) H. C. Brown and W. A. Murphey, *J. Am. Chem. Soc.*, **73**, 3308 (1951).

TABLE I

VALUES OF ν_{max} (CM.$^{-1}$) FOR THE PRINCIPAL BAND OF 4-ALKYLPYRIDINIUM PERCHLORATES IN VARIOUS SOLVENTS[a,b,c]

Group	98% H_2SO_4	70% $HClO_4$	50% $HClO_4$	36% $HClO_4$	1% $HClO_4$[c]	MeOH[e]	EtOH[e]
H	+3820	+3760	+3720	+3650	+3620	+3100	+2320
Me	45660	45620	45790	45980	46080[d]	45980	46020
Et	−430	−380	−340	−430	−400	−320	−340
i-Pr	−650	−520	−540	−650	−630	−480	−480
t-Bu	−900	−720	−720	−790	−770	−630	−610

[a] The absolute value of ν_{max} is given for the 4-methyl compound; the ν_{max} values of the other compounds are relative to the methyl compound. [b] Average of 2 runs, duplicable to ±20 cm.$^{-1}$ [c] Negligible amount of free pyridine in any of the solvents (H. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.*, **77**, 1725 (1955). [d] Has λ_{max} = 217.0 mμ, ϵ_{max} = 5400. [e] Contain 1% by volume of H_2SO_4.

TABLE II

VALUES OF ν_{max} (CM.$^{-1}$) FOR THE PRINCIPAL BAND OF 4-ALKYL-1-HYDROXYPYRIDINIUM IONS IN ACIDIC MEDIA[a,b,c]

Group	98% H_2SO_4	62% H_2SO_4	70% $HClO_4$	9% $HClO_4$	MeOH[e]	EtOH[e]
H	+2010	+1830	+2130	+1680	+1420	+1290
Me	44400	44250	44400	44000[d]	43670	43560
Et	−410		−340	−250	−230	−230
i-Pr	−620		−480	−350	−320	−330
t-Bu	−750		−630	−480	−380	−370

[a] Protonation to the 1-hydroxypyridinium ion greater than 90% complete in 9% $HClO_4$ (H. H. Jaffé and G. O. Doak, *J. Am. Chem. Soc.*, **77**, 4441 (1955). [b] The absolute value of ν_{max} is given for the 4-methyl compound; the ν_{max} values of the other compounds are relative to the methyl compound. [c] Average of 2 runs, duplicable to ±20 cm.$^{-1}$ [d] Has λ_{max} = 227.3 mμ, ϵ_{max} = 8500. [e] Contain 10% by weight of H_2SO_4.

Anal. Calcd. for $C_8H_{12}NO_4Cl$: C, 43.67; H, 5.46. Found: C, 43.41; H, 5.35.

The 4-*t*-butylpyridinium perchlorate melted at 100.8–101.2°.

Anal. Calcd. for $C_9H_{14}NO_4Cl$: C, 46.20; H, 5.99. Found: C, 46.44; H, 5.97.

Preparation and purification of pyridine-1-oxide and 4-methylpyridine-1-oxide were described previously.[2] The same procedure was used to prepare the other pyridine oxides. The 4-ethylpyridine oxide melted at 111.0–111.5°.

Anal. Calcd. for C_7H_9NO: C, 68.26; H, 7.36. Found: C, 68.21; H, 7.20.

The 4-isopropylpyridine oxide melted at 78–79°.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08. Found: C, 69.40; H, 7.83.

The 4-*t*-butylpyridine oxide melted at 103.9–104.3°.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.48; H, 8.66. Found: C, 70.86; H, 8.26.

Spectral determinations. Spectral measurements were made at room temperature as previously described. The instrument used was a Beckman DU spectrophotometer, equipped with a photomultiplier and a special fused quartz prism that extended the wave-length range to 185 mμ. Values of ν_{max} were determined in the graphical manner previously described.[3]

RESULTS

Plotted in Fig. 1 are the spectra of 4-methylpyridinium perchlorate in 1% perchloric acid, 4-methyl-1-hydroxypyridinium ion in 9% perchloric acid, and *p*-methylacetophenone conjugate-acid in 92.1% sulfuric acid. These spectra are representative of each class of compound and display well defined symmetrical bands. On variation of the 4-substituent of each class of compound the position of the band was shifted but did not change in shape. Values of ν_{max} in various solvents are given for 4-alkylpyridinium ions in Table I, for 4-alkyl-1-hydroxypyridinium ions in Table II, and for *p*-alkylacetophenone conjugate acids in Table III. Table IV lists ν_{max} and ϵ_{max} values for *p*-alkylnitrobenzene conjugate acids in 101.5% sulfuric acid. Table V lists ν_{max} and ϵ_{max} values for the conjugate acids (in 88% H_2SO_4) and acylonium ions (101% H_2SO_4) of 4-alkyl-2,6-dimethylbenzoic acids.

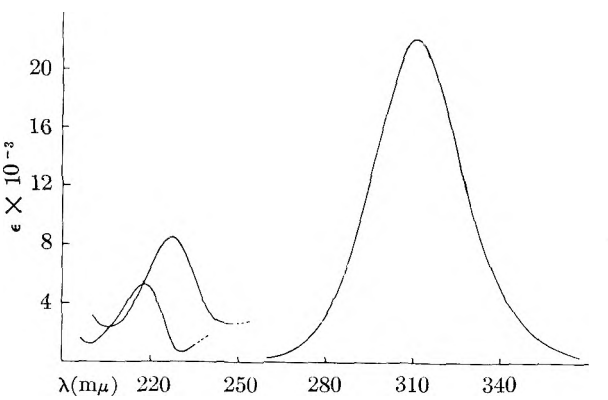


Fig. 1. Spectra of 4 methylpyridinium perchlorate in 1% $HClO_4$, 4-methyl-1-hydroxypyridinium perchlorate in 9% $HClO_4$ and *p*-methylacetophenone conjugate acid in 92.1% H_2SO_4 (reading from left to right).

DISCUSSION

Solvent effects. A main feature of the results of Tables I, II, and III is the fact that changing solvent has very little effect on the principal band

TABLE III

VALUES OF ν_{max} (Cm.$^{-1}$) FOR THE PRINCIPAL BAND OF *p*-ALKYLACETOPHENONES IN CONCENTRATED H_2SO_4[a,b,c]

Group	99.0% H_2SO_4	92.1% H_2SO_4	85.2% H_2SO_4
H	+1840	+1900	+1940
Me	32030	32110[d]	32270
t-Bu	−380	−330	−310

[a] Protonation to conjugate acid practically complete in all solvents (M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957). [b] The absolute value of ν_{max} is given for the *p*-methyl compound; the ν_{max} of the other compounds are relative to the methyl compound. [c] Average of 2 runs, duplicable to ±20 cm.$^{-1}$ [d] Has λ_{max} = 311.4 mμ, ϵ_{max} = 22100.

TABLE IV

VALUES OF ν_{max} (Cm.$^{-1}$) AND ϵ_{max} FOR THE PRINCIPAL BAND *p*-ALKYLNITROBENZENES IN 101.5% H_2SO_4[a]

p-Group	ν_{max}[b,c]	$\epsilon_{max} \times 10^{-3}$[d,e]
Me	26610[d]	15.3
Et	−210	16.8
i-Pr	−240	16.0
t-Bu	−370	17.7

[a] The nitrobenzenes are 97–99% in the form of their conjugate acids (J. C. D. Brand, *J. Chem. Soc.*, 997 (1950)). [b] Absolute value given for methyl compound; the others are relative to methyl. [c] Average of two or more determinations, duplicable to ±30 cm.$^{-1}$ [d] λ_{max} = 375.8 mμ. [e] Estimated accuracy, ±5%. Spectra determined quickly due to slow sulfonation.

TABLE V

VALUES OF ν_{max} (Cm.$^{-1}$) AND ϵ_{max} FOR THE PRINCIPAL BAND OF 4-ALKYL-2,6-DIMETHYLBENZOIC ACIDS IN STRONG H_2SO_4

p-Group	88% H_2SO_4[a] ν_{max}[c]	88% H_2SO_4[a] $\epsilon_{max} \times 10^{-3}$[d]	101% H_2SO_4[b] ν_{max}[c]	101% H_2SO_4[b] $\epsilon_{max} \times 10^{-3}$[d]
Me	35460[e]	7.2	35520	20.0
Et	35340	8.2	35270	21.7
i-Pr	35270	7.9	35150	22.2

[a] Substrate primarily in the form of the conjugate acid, $ArCO_2^+H_2$.[6] [b] Substrate practically completely in the form of the acylonium ion, $ArCO^+$.[6] [c] Determined to ±60 cm.$^{-1}$ [d] Estimated accuracy, ±3%. [e] λ_{max} = 282 mμ.

position of each compound; *i.e.*, the *difference* between solvent stabilization of ground and excited states is not very sensitive to a change in medium.[8] This is not surprising since the transitions involve a redistribution of positive charge (Equations 1 and 2). The Franck-Condon Principle applies, of course, which means that there is practically no movement of the solvent atomic nuclei in the short time of the electronic excitation. Solvent stabilization at the functional group (*e.g.*, H-bonding to the acidic proton) is less in the excited state than in the ground state, since the positive charge at the functional group is decreased in the excitation. This factor acts to raise the excitation energy (relative to the gas phase). However, solvent stabilization of the ring is greater in the excited than in the ground state, since the positive charge in the ring is increased in the excitation, and this would act to lower the excitation energy. These two solvation forces appear to be approximately balanced.

There are only slight differences in the solvent shifts for the three series of compounds. For example, compare the effect of decreasing strength of aqueous mineral acid. As aqueous solvent basicity is increased, the excitation energies of the 1-hydroxypyridinium ions decrease slightly (Table II), those of the pyridinum ions increase slightly (Table I) and those of the acetophenone conjugate acids increase somewhat more rapidly (Table III). In other words, the quantity, solvent stabilization of the excited state *minus* solvent stabilization of the ground state, increases slightly for the hydroxypyridinium ions, decreases slightly for the pyridinium ions and decreases to greater degree for the acetophenone conjugate acids. Since the Franck-Condon Principle applies, which means that the orientation of solvent molecules in the excited state is that fixed by the ground state, interpretation of these small differences in behavior between the three series of compounds is difficult. However, the results imply that as one proceeds from the hydroxypyridinium ions to the pyridinium ions to the acetophenone conjugate acids, there is a reduction in the importance of solvation of the ground state at sites that increase in positivity in the excitation *relative to* solvation at sites that decrease in positivity. This may mean that the positive charge in the ground state of the ions is dispersed to the greatest extent in the hydroxypyridinium ions and to the least extent in the acetophenone conjugate acids. Such a conclusion is perhaps an oversimplification, however.

Substituent effects. For each series of positive ions (some of them incomplete) the principal band excitation energies follow the inductive order (Tables I–V). Furthermore, in those instances in which the solvent was varied (Tables I–III), this order is maintained and solvent shifts on the spectrum of a particular compound are small. Therefore, it is safe to conclude that the *order* of inherent electron release in these highly electron demanding transitions is the inductive one. Thus, as in the principal electronic transitions of neutral *p*-alkyl-nitrobenzenes and acetophenones,[3] C—H hyperconjugation is not the most important factor in the total electron release effects of the alkyl groups.

As the solvent is changed there are no dramatic changes in the spreads between excitation energies of the compounds of Tables I, II, and III such as were found for the neutral nitrobenzenes and aceto-

(8) By contrast, the principal band of *p*-nitrotoluene, *e.g.*, changes by 2080 cm.$^{-1}$, or 5.9 Kcal., from water to 70% perchloric acid as the solvent.[3]

phenones.[3] Since the total *difference* between solvent stabilization of the excited and ground states is changed very little with solvent, one would not expect the factor of steric hindrance to solvation near the alkyl group to greatly influence the excitation energy spreads from solvent to solvent. Certain minor trends possibly attributable to this factor may be discernible, although speculation seems unwarranted.

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SEATTLE 5, WASH.

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Synthesis of Deuterated Biphenyls[1]

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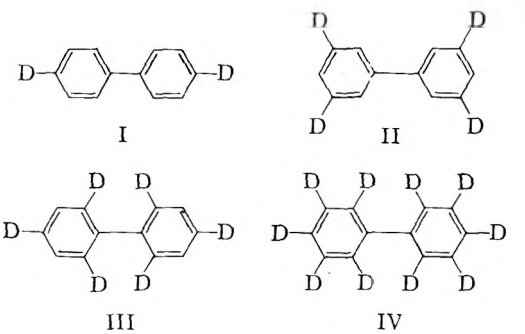
The preparation of four deuterated analogs of biphenyl, biphenyl-4,4′-d_2, biphenyl-3,3′,5,5′-d_4, biphenyl-2,2′,4,4′,6,6′-d_6, and biphenyl-d_{10} is described. The first compound was synthesized from 4,4-dibromobiphenyl, and the other three were formed by coupling the Grignard reagent of the appropriate deuterated bromobenzene.

Deuterium labeling has proved of great value for studies of substitution reactions in organic compounds.[2] Examination of the fragmentation of organic compounds by ionizing radiation[3,4] and the determination of molecular configuration by infrared spectrometry[5] have also been facilitated by deuterium labeling. Furthermore, the use of properly deuterated molecules greatly simplifies the interpretation of mass spectra of organic molecules[4,6] by enabling identification of the ionized fragments produced and analysis of the processes taking place.

In this laboratory we are studying aromatic hydrocarbons of the polyphenyl type by several of the above methods—irradiation, vibrational analysis, and mass spectrometry. Biphenyl, which is the simplest member of the polyphenyl series, is the simplest aromatic compound containing only benzene rings which has nonequivalent carbon-hydrogen bonds. This nonequivalence has been demonstrated in the substitution reactions of biphenyl, since the rates of reaction differ at the positions *ortho*, *meta*, and *para* to the bond joining the two rings.[7] Replacing hydrogen atoms by deuterium atoms at various sites in the biphenyl molecule allows the techniques mentioned above to furnish more information about the molecule. Consequently we have prepared four deuterium-substituted biphenyls: biphenyl-4,4′-d_2 (I), which has deuterium atoms in the two *para* positions; biphenyl-3,3′,5,5′-d_4 (II), which has deuterium atoms in the four *meta* positions; biphenyl-2,2′,4,4′,6,6′-d_6 (III), which has deuterium atoms in the four *ortho* and two *para* positions; and biphenyl-d_{10} (IV), which is completely deuterated. It can be seen that no molecular symmetry is lost in these deuterated biphenyls (in contrast to the case of the partially deuterated benzenes[5]), and therefore there is no increase in complexity of the vibrational spectra of the deuterated biphenyls over that of biphenyl itself.



Synthetic procedures. Deuterated benzenes and toluenes have been prepared by treatment of Grignard reagents[8] and organolithium compounds[9]

(1) This work was performed under AEC Contract AT(11-1)-GEN-8.

(2) J. G. Burr, Jr., *Tracer Applications for the Study of Organic Reactions*, Interscience Publishers, Inc., New York, 1957; L. C. S. Melander, *The Use of Nuclides in the Determination of Organic Mechanisms*, University of Notre Dame Press, Notre Dame, Ind., 1955.

(3) S. Gordon and M. Burton, *Discussions Faraday Soc.*, No. 12, 88 (1952); P. V. Phung and M. Burton, *Radiation Research*, **7**, 199 (1957).

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(5) W. R. Angus, C. R. Bailey, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.*, 912 (1936); C. R. Bailey, C. K. Ingold, H. G. Poole, and C. L. Wilson, *J. Chem. Soc.*, 222 (1946).

(6) P. N. Rylander, S. Meyerson, and H. M. Grubb, *J. Am. Chem. Soc.*, **79**, 842 (1957); G. A. Ropp and C. E. Melton, *J. Am. Chem. Soc.*, **80**, 3509 (1958).

(7) G. W. Wheland, *Resonance in Organic Chemistry*, J. Wiley & Sons, Inc., New York, 1955, pp. 493–494.

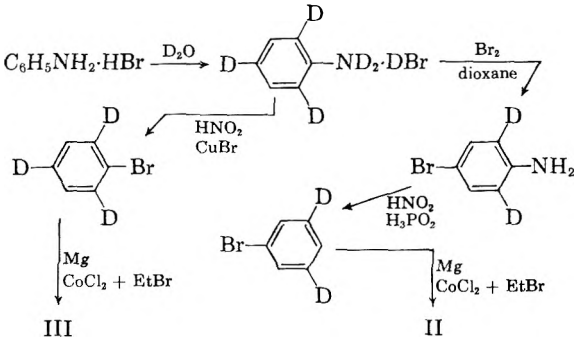
(8) L. H. P. Weldon and C. L. Wilson, *J. Chem. Soc.*, 235 (1946); J. Turkevich, H. A. McKenzie, L. Friedman, and R. Spurr, *J. Am. Chem. Soc.*, **71**, 4045 (1949); T. J. Prosser and E. L. Eliel, *J. Am. Chem. Soc.*, **79**, 2544 (1957).

(9) W. M. Lauer and W. E. Noland, *J. Am. Chem. Soc.*, **75**, 3689 (1953).

with deuterium oxide. Several attempts to prepare the difunctional Grignard reagent from 4,4′-dibromobiphenyl, either with magnesium iodide as promoter[10] or with ethyl iodide by the entrainment method, gave low yields. *Dilithium* compounds have been prepared previously from 4,4′-dibromobiphenyl[11] and 3,3′-dibromobiphenyl.[12] The exchange reaction between 4,4′-dibromobiphenyl and *n*-butyllithium reagent was first carried out in aliphatic hydrocarbon solvents.[11] Better yields and a purer product were obtained by the use of ethyl ether as the reaction solvent.[12] The 4,4′-dibromobiphenyl was treated with excess *n*-butyllithium reagent, and the reaction mixture hydrolyzed with 99.7% deuterium oxide; the yield of biphenyl 4,4′-d_2 was 63%.

The other three deuterated biphenyls were prepared by converting the appropriately deuterated bromobenzene to its Grignard reagent; this was coupled to form biphenyl by cobaltous chloride in the presence of ethyl bromide, according to the method of Kharasch and Fields.[13]

For the synthesis of biphenyl-3,3′,5,5′-d_4, aniline hydrobromide was converted by six successive exchanges with 99.7% deuterium oxide to aniline-*N*,*N*,2,4,6-d_5 hydrobromide-d by a modification of the method of Best and Wilson.[14] Bromination to 2,4,6-tribromoaniline and examination of its infrared spectrum showed the absence of deuterium in the 3- and 5-positions of the deuterated aniline.[15] The aniline-*N*,*N*,2,4,6-d_5 hydrobromide-d was brominated by the bromine-dioxane complex[16] to 4-bromoaniline-2,6-d_2, which was diazotized and reduced by hypophosphorous acid to bromobenzene-3,5-d_2.[17] The Grignard reagent formed from this was then coupled to biphenyl-3,3′,5,5′-d_4.



The over-all yield for the bromination, reduction, and coupling was 22%.

The preparation of biphenyl-2,2′,4,4′,6,6′-d_6 has not been previously accomplished; Shatenshteĭn, Kalinachenko, and Varshavskiĭ[18] have determined, however, by measuring rates of exchange, that six hydrogens of biphenyl can be exchanged for deuterium in liquid deuterium bromide. No product was isolated, and the positions which underwent exchange (presumably the *ortho*- and *para*-positions) were not determined.

In the present work, biphenyl-2,2′,4,4′,6,6′-d_6 was prepared from aniline-*N*,*N*,2,4,6-d_5 hydrobromide-d. The deuterated aniline was converted by the Sandmeyer reaction[19] to bromobenzene-2,4,6-d_3. The Grignard reagent was prepared and and coupled as above. The yield for these two steps was 41%.

The completely deuterated compound, biphenyl-d_{10}, has been obtained by treating biphenyl in liquid ammonia-d_3 in the presence of potassium amide-d_2.[20] Several experiments were carried out[21] to determine if biphenyl-d_{10} could be synthesized by exchange between biphenyl and sulfuric acid-d_2. These included shaking biphenyl alone (at room temperature or above its melting point) or dissolved in benzene or carbon tetrachloride with sulfuric acid-d_2 of varying concentrations. In those cases where exchange took place, the rate of sulfonation of biphenyl was too great to permit isolation of sufficient deuterated material. Hence, benzene was converted by exchange with sulfuric acid-d_2 to benzene-d_6 by the procedure of Ingold, Raisin, and Wilson.[22] This was brominated by stirring with aqueous hypobromous acid to bromobenzene-d_5.[14] The Grignard reagent was prepared and coupled as above to biphenyl-d_{10}. The yield for the bromination and coupling was 38%.

The various deuterated biphenyls were analyzed by gas chromatography, and were found to be free of chemical impurities. The infrared spectra and the mass patterns were obtained. The isotopic content of the preparations was determined by mass spectrometry at an ionizing voltage great enough to ionize the molecules but too small to remove hydrogen atoms from the molecules.[23] The isotopic purities obtained in this manner are shown in

(10) R. Gibert, *Compt. rend.*, **205**, 443 (1937).

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

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(13) M. S. Kharasch and E. K. Fields, *J. Am. Chem. Soc.*, **63**, 2316 (1941).

(14) A. P. Best and C. L. Wilson, *J. Chem. Soc.*, 239 (1946).

(15) A. P. Best and C. L. Wilson, *J. Chem. Soc.*, 28 (1938).

(16) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **75**, 3596 (1953).

(17) N. Kornblum, *Org. React.*, **2**, 262 (1944).

(18) A. I. Shatenshteĭn, V. R. Kalinachenko, and Ya. M. Varshavskiĭ, *Zhur. Fiz. Khim.*, **30**, 2093 (1956); *Chem. Abstr.*, **51**, 11025f (1957).

(19) J. L. Hartwell, *Org. Syntheses*, Coll. Vol. III, 185 (1955).

(20) G. S. Landsberg, A. I. Shatenshteĭn, G. V. Peregudiv, E. A. Israilevich, and L. A. Novikova, *Izvest. Akad. Nauk S.S.S.R., Ser. Fiz.*, **18**, 669 (1954); *Chem. Abstr.*, **50**, 7585h (1956).

(21) These experiments were conducted by Dr. R. H. Shudde of this laboratory.

(22) C. K. Ingold, C. G. Raisin, and C. L. Wilson, *J. Chem. Soc.*, 915 (1936).

(23) D. P. Stevenson and C. D. Wagner, *J. Am. Chem. Soc.*, **72**, 5612 (1950).

Table I. Since the D_2O used in the preparations contained 0.3 atom % hydrogen, the theoretical maximum purity is given in the last column of Table I.

TABLE I

ISOTOPIC COMPOSITION OF DEUTERATED BIPHENYLS

Compound	Isotopic Composition		Theoretical Maximum Purity
Biphenyl-d_2	$C_{12}H_8D_2$-	97.4%	99.4%
	$C_{12}H_9D$-	2.2%	
	$C_{12}H_{10}$-	0.4%	
Biphenyl-d_4	$C_{12}H_6D_4$-	98.0%	98.8%
	$C_{12}H_7D_3$-	1.8%	
	$C_{12}H_8D_2$-	0.2%	
Biphenyl-d_6	$C_{12}H_4D_6$-	95.2%	98.2%
	$C_{12}H_5D_5$-	4.6%	
	$C_{12}H_6D_4$-	0.2%	
Biphenyl-d_{10}	$C_{12}D_{10}$-	95.1%	97.0%
	$C_{12}HD_9$-	4.7%	
	$C_{12}H_2D_8$-	0.2%	

EXPERIMENTAL[24]

4,4'-Dibromobiphenyl was prepared by bromination of biphenyl.[25]

n-Butyllithium reagent was prepared in ethyl ether[26] and used directly upon completion of the reaction. The reagent was analyzed only for the total base present.

Biphenyl-4,4'-d_2. To a mixture of 43.1 g. (0.138 mole) of 4,4'-dibromobiphenyl and 400 ml. of anhydrous ethyl ether in an inert atmosphere in a 3-neck flask was added rapidly, with stirring, 520 ml. of *n*-butyllithium reagent (containing 0.55 mole of total base). The mixture refluxed slowly for a short time. It was stirred 17 hr. at room temperature, refluxed for 1 hr., and treated, drop by drop, with approximately 20 ml. of 99.7% pure deuterium oxide. The ether phase was separated, washed twice with water, and dried over potassium carbonate. The solvent was evaporated and the residual material distilled twice *in vacuo*. The fraction collected (b.p. 120–121° at 11.5 mm., m.p. 64.5–66°) was sublimed *in vacuo*. A yield of 13.5 g. (63%) of white crystals m.p. 68–69°, was obtained.

Aniline-N,N,2,4,6-d_5 hydrobromide-d was prepared from aniline hydrobromide by the method used by Best and Wilson[14] to deuterate aniline hydrochloride. The progress of the deuteration was followed by converting samples to aniline and analyzing the infrared spectrum. The ratio of absorbance for C-D stretching to C-H stretching became constant during the last three equilibrations, indicating that maximum deuteration had been achieved. A sample of the final product was brominated to 2,4,6-tribromoaniline, and its infrared spectrum was examined; no C-D absorption was found, indicating that exchange takes place only in the *ortho-* and *para-* positions.

Bromobenzene-3,5-d_2. A mixture of 72.0 g. (0.400 mole) of aniline-*N,N*,2,4,6-d_5 hydrobromide-d and 120 ml. of dioxane was treated slowly with a solution of 44.8 g. (0.800 mole) of potassium hydroxide in 80 ml. of water. The mixture was cooled below 5° while a solution of 64 g. (0.40 mole) of bromine in 640 ml. of dioxane was added with stirring. The mixture was filtered, the filtrate was washed with 60 ml. of 40% (w/w) potassium hydroxide in water, and the solvent was distilled *in vacuo*. The dark, viscous residue was dissolved in anhydrous ethyl ether, and anhydrous hydrogen chloride was passed in until precipitate no longer formed. The precipitate was separated, washed with ethyl ether, and dried; it weighed 71.6 g. The crude hydrochloride in 50 ml. of water and 100 ml. of concentrated hydrochloric acid was diazotized with 24.7 g. of sodium nitrite in 60 ml. of water, the temperature being kept below 5°. The diazonium solution was treated with 530 ml. of cold 50% hypophosphorous acid (5.1 moles) and was kept at about 0° overnight. The lower organic phase was separated. The aqueous phase was extracted with ethyl ether, and the extract was combined with the organic phase, washed with sodium hydroxide solution and water, and dried over potassium carbonate. Distillation gave 21.8 g. (0.137 mole) of bromobenzene-3,5-d_2, a 34% yield.

Biphenyl-3,3',5,5'-d_4. The Grignard reagent prepared from 21.5 g. (0.135 mole) of bromobenzene-3,5-d_2, 4.1 g. (0.169 gram-atom) of magnesium, and 55 ml. of anhydrous ethyl ether, was added with stirring to a mixture of 1.6 g. (0.012 mole) of anhydrous cobaltous chloride, 16.3 g. (0.150 mole) of ethyl bromide, and 15 ml. of anhydrous ether at such a rate that the mixture refluxed. After the addition was completed, the reaction mixture was refluxed for another hour and then poured into ice and water. The mixture was treated with 20 ml. of acetic acid. The organic phase was separated, washed with sodium bicarbonate solution and water, and dried over potassium carbonate. The solvent was distilled, and the residue was sublimed *in vacuo*. The yield of 6.8 g. (0.043 mole) of biphenyl-3,3',5,5'-d_4, m.p. 68–69°, is 64%.

Bromobenzene-2,4,6-d_3. A mixture of 36.0 g. (0.2 mole) of aniline-*N,N*,2,4,6-d_5 hydrobromide-d and 48 ml. of 48% hydrobromic acid was treated with 13.8 g. of sodium nitrite in 25 ml. of water, the temperature being kept below 10°. The reaction mixture was added to a boiling mixture of 17.2 g. of cuprous bromide and 16 ml. of 48% hydrobromic acid at such a rate that the product steam distilled from the reaction mixture. The distillate was extracted with ethyl ether, and the extract was washed with dilute sulfuric acid, water, dilute sodium hydroxide solution, and water, and dried over potassium carbonate. Upon distillation, 20.2 g. (63%) of product (b.p. 155–156°) was obtained.

Biphenyl-2,2',4,4',6,6'-d_6 was prepared from bromobenzene-2,4,6-d_3 by the procedure used for biphenyl-3,3',5,5'-d_4.

Benzene-d_6 was prepared by shaking benzene several times with 51 mole % sulfuric acid-d_2 in 99.7% deuterium oxide until the hydrogen content was about 0.4 atom %. The product was analyzed by infrared spectrometry using standards analyzed by mass spectrometry.

Bromobenzene-d_5 was prepared by brominating benzene-d_6 by the method of Best and Wilson.[14]

Biphenyl-d_{10} was prepared from bromobenzene-d_5 by the procedure used for biphenyl-3,3',5,5'-d_4.

Gas chromatography. The various intermediates and the deuterated biphenyls were analyzed for chemical purity with a Perkin-Elmer model 154B Vapor Fractometer. Two columns, a two meter column of didecyl phthalate on Celite, and a two meter column of silicone oil on Celite, were used to analyze the biphenyls. The former column, on which biphenyl has a retention time of about 41 min. at 175°, was used to check for impurities more volatile than biphenyl, and the latter column, on which biphenyl has a retention time of about 8 min. at 150°, was used to check for impurities less volatile than biphenyl. The intermediates were analyzed on the first column. Under these conditions, biphenyl and the various deuterated biphenyls are not separated.

Infrared spectrometry. The infrared spectra were measured with a Perkin-Elmer model 21 double-beam recording infrared spectrophotometer. The strong absorption peaks found in the spectra of the deuterated biphenyls and biphenyl

(24) Melting points and boiling points are uncorrected.

(25) R. E. Buckles and N. G. Wheeler, *Org. Syntheses*, **31**, 29 (1951).

(26) R. G. Jones and H. Gilman, *Org. Reactions*, 6, 352 (1951).

TABLE II

INFRARED ABSORPTION PEAKS OF BIPHENYLS

Biphenyl	Biphenyl-d_2	Biphenyl-d_4	Biphenyl-d_6	Biphenyl-d_{10}
3 29 microns	3.29	3.26	3.28	4.41
6.27	4.41 (mod)[a]	4.42	4.43	7.44
6.75	5.22	5.46	5.44	7.60
6.98	6.29	6.32	7.03	
9.32	6.81	7.02	7.12	
9.58	7.16	7.22	7.27	
11.07	9.02	9.06	10.87	
	9.63	9.15		
		10.9–11.3 (band)		

[a] This absorption peak, caused by C-D stretching, is only moderately strong.

itself (measured in carbon tetrachloride solution, 200 mg. per ml. of solution) in the range 1.5–11.5 microns are given in Table II.

Mass spectrometry. The mass spectra of the deuterated biphenyls were determined with a modified Consolidated Electrodynamics Corporation model 21-620 mass spectrometer. The mass spectra of the compounds are discussed elsewhere.[27]

CANOGA PARK, CALIF.

(27) J. M. Scarborough, J. G. Burr, and R. H. Shudde, to be published.

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

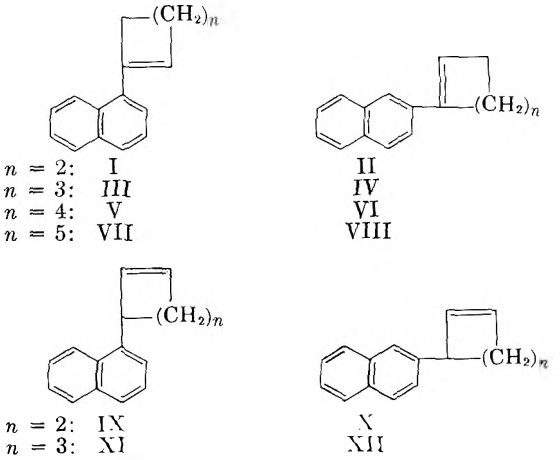
Syntheses and Ultraviolet Spectra of Eight Naphthylcycloalkenes[1-3]

L. H. KLEMM, B. T. HO, C. D. LIND, B. I. MACGOWAN,[4] AND E. Y. K. MAK[5]

Received November 24, 1958

Syntheses of 1-(1- and 2-naphthyl)cycloheptenes and -cyclo-octenes and of 3-(1- and 2-naphthyl)cyclopentenes and -cyclohexenes are described. Correlation of ultraviolet spectra of these compounds with structure is made.

In previous papers[6-9] we reported syntheses and ultraviolet absorption spectra of a number of conjugated naphthylalkenes, including I–IV. The present paper concerns an extension of these studies to the higher homologs V–VIII and the unconjugated isomers IX–XII. Compounds V–VIII were prepared by dehydration of the carbinols resulting from interaction of the appropriate naphthyl-magnesium bromides and cycloalkanones, while IX–XII resulted from the same Grignard reagents acting on 3-bromocyclohexene and 3-chlorocyclopentene. That the double bond had not migrated into the conjugated position during the preparative process was indicated by the isolation of crystalline polynitroaromatic complexes of IX–XI which were different (as determined by melting point and mixture melting point) from the corresponding complexes of the conjugated isomers I–III and by the fact that the ultraviolet spectra of X and XII were significantly different from those of II and IV, respectively.



(1) Presented, in part, at the Northwest Regional Meeting of the American Chemical Society, Portland, Ore., June 1958. Paper X in the series on Chemical Reactivities of Arylcycloalkenes. For paper IX see L. H. Klemm, D. Reed, and C. D. Lind, *J. Org. Chem.*, **22**, 739 (1957).

(2) Performed under the sponsorship of the Office of Ordnance Research, U. S. Army contract No. DA-04-200-ORD-176.

(3) Abstracted largely from the M.A. dissertation of B. T. Ho, University of Oregon, 1959, and the Ph.D. dissertation of C. D. Lind, University of Oregon, 1956.

(4) Research assistant, 1956.

(5) Research assistant, 1956–1957.

(6) L. H. Klemm and W. Hodes, *J. Am. Chem. Soc.*, **73**, 5181 (1951).

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

(8) L. H. Klemm, H. Ziffer, J. W. Sprague, and W. Hodes, *J. Org. Chem.*, **20**, 190 (1955).

(9) L. H. Klemm, J. W. Sprague, and E. Y. K. Mak, *J. Org. Chem.*, **22**, 161 (1957).

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA FOR EIGHT NAPHTHYLCYCLOALKENES[a]

V[b]		VI[c]		VII[d]		VIII[d]		IX[d]		X[d]		XI[b]		XII[d]	
λ_{max}, mμ	log ε	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε
225	4.78			224.5	4.79	(225)	4.70	224	4.87	226	5.04	226	4.94	227	5.13
		246	4.54			243–245	4.96								
								268	3.60	(270)	3.71	(263)	3.63	(268)	3.54
(273)	3.99	278	3.96	(273)	3.92	277	4.37	275	3.68	276	3.74	273	3.84	275–276	3.72
283	4.07	286	3.98	281–282	3.99	286	4.43	285	3.79	(284)	3.59	283	3.92	(284)	3.58
(294)	4.02	298	3.89	(291)	3.93	298	4.34	(290–293)	3.62			(292)	3.74		
								315	2.60	306[e]	2.67	315[f]	2.74	304[e]	2.66

[a] Determined on analytically pure samples by means of a Beckman DU spectrophotometer for V, VI, and IX–XII and a Beckman DK-2 spectrophotometer for VII and VIII. Parenthesized values of λ_{max} represent shoulders rather than true maxima. [b] Solvent, cyclohexane. [c] Solvent, 95% ethanol. [d] Solvent, isooctane. [e] Spectrum investigated only to 310 mμ; others, to 320 mμ. [f] This value is approximate only.

Pertinent data on the ultraviolet absorption maxima of V–XII are presented in Table I. As expected,[8] the spectra of IX and XI are virtually superimposable on the spectrum of 1-methylnaphthalene[10]; and those of X and XII, likewise on the spectrum of 2-methylnaphthalene.[10] The only clear difference between the spectrum of 1-methylnaphthalene and the nearly identical spectra of the 1-compounds I, III, V, and VII is the presence of the minor maximum at about 313 mμ in 1-methylnaphthalene. This close similarity is consistent with the suggestion[8] that electronic conjugation[11] is virtually absent in these structurally conjugated 1-compounds due to the presence of large angles of twist (between the planes of the naphthalene ring and the cycloalkenyl double bond) in the molecules. On the other hand the spectra of the 2-compounds II, IV, VI, and VIII differ markedly from the spectrum of 1-methylnaphthalene in the region of their major maxima (220–260 mμ). Of the spectra for this group, II exhibits the most fine structure, IV and VI are virtually identical, and VIII differs from IV principally only in having a shoulder at 225 mμ. Following our earlier interpretations[8] we then propose that VI and VIII should have θ'-distributions (sterically unrestricted angles of twist) similar to those of IV but with detectably increased prevalence (225 mμ shoulder) of molecules in the $90° - \beta$ to $90° + \beta$ spectral region for the cyclooctenyl compound VIII.

(10) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, Inc., New York, 1951.

(11) For clarity we have used the terms "conjugation" or "structural conjugation" in the classical sense of denoting alternate single and double bonds. The term "electronic conjugation" has been reserved for those structurally conjugated molecules which display special electronic properties due to such bond alternation.

EXPERIMENTAL[12]

Titration of picrates. For those cases where neutral equivalents of picrates are reported these were determined on 0.2- to 0.4-g. samples dissolved in 125 ml. of 40% (by volume) acetone, using 0.1*N* sodium hydroxide and ethyl bis(2,4-dinitrophenyl)acetate as indicator.[13]

1-(2-Naphthyl)cycloheptene (VI). To the Grignard reagent prepared from 20 g. (0.097 mole) of 2-bromonaphthalene, 2.4 g. (0.099 g.-atom) of magnesium turnings, and 60 ml. of ether was added slowly, at room temperature, a solution of 11 g. (0.098 mole) of cycloheptanone[14] in 25 ml. of ether. The reaction mixture was stirred for 1 hr., hydrolyzed with cold aqueous ammonium chloride, and extracted with ether. The residue from evaporation of the dried (magnesium sulfate) ethereal extract was dehydrated by stirring with 30 ml. of anhydrous formic acid for 20 min. at room temperature and then for 1 hr. on a steam bath. Combined ethereal extracts of the diluted acidic mixture were washed with 10% aqueous sodium hydroxide and evaporated. The residue was steam distilled to remove naphthalene, collected in ether (dried), and fractionally distilled twice, yield 8 g. (37%) of almost colorless liquid, b.p. 140–145° (1 mm.). Treatment with an equimolar quantity of picric acid in absolute ethanol solution precipitated the picrate, recrystallized from methanol to constant m.p. 82–84°, obtained as orange needles.

Anal. Calcd. for $C_{17}H_{18}\cdot C_6H_3N_3O_7$: Neut. equiv. 451.4. Found: Neut. equiv. 457.

Chromatographic dissociation of the picrate *via* silicic acid–celite[7] and three fractional distillations of the effluent in an atmosphere of nitrogen produced purified VI, b.p. 146.5–147.5° (0.8 mm.), m.p. *ca.* 30°.

Anal. Calcd. for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 92.09; H, 8.09.

1-(1-Naphthyl)cycloheptene (V). Repetition of the foregoing procedure but with 1-bromonaphthalene instead of its 2-isomer gave 19 g. (88%) of light yellow liquid, b.p. 139–144° (0.9 mm.), converted to the picrate, obtained as orange needles from methanol, m.p. 107–109°.

(12) Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(13) Adapted from the method of the Staff of Hopkin and Williams Research Laboratory, *Organic Reagents for Organic Analysis*, Chemical Publishing Co., Brooklyn, 1950, pp. 112–13.

(14) H. J. Dauben, H. J. Ringold, R. H. Wade, D. L. Pearson, and A. G. Anderson, *Org. Syntheses*, **34**, 19 (1954).

Anal. Calcd. for $C_{17}H_{18}\cdot C_6H_3N_3O_7$: Neut. equiv. 451.4. Found: Neut. equiv. 459.

Chromatographic dissociation of the picrate *via* alumina-Celite[9] and two fractional distillations of the effluent gave purified V, b.p. 146–147° (1.0 mm.).

Anal. Calcd. for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.57; H, 8.31.

1-(1-Naphthyl)cyclo-octene (VII). Following the general procedure for VI, but with 0.079-molar quantities of magnesium, 1-bromonaphthalene, and cyclo-octanone (10 g., Fluka), gave 4.5 g. (24%) of liquid, b.p. 141–148° (0.3 mm.), converted to the picrate, obtained as yellow prisms from absolute ethanol, m.p. 114–115° (not analytically pure). Purified VII boiled at 139–142° (0.3 mm.).

Anal. Calcd. for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.49; H, 8.73.

1-(2-Naphthyl)cyclo-octene (VIII). By the preceding method (but with 2-bromonaphthalene instead of its isomer) there was obtained 8.8 g. (47%) of crude liquid. After purification (picrate obtained as bright orange prisms from absolute ethanol, m.p. 79–110°) the product boiled at 148–152° (0.3 mm.).

Anal. Calcd. for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.22; H, 8.71.

3-(2-Naphthyl)cyclopentene (X). To the cold (−20°), stirred Grignard reagent prepared from 11 g. (0.45 g.-atom) of magnesium turnings, 93.2 g. (0.45 mole) of 2-bromonaphthalene, and 400 ml. of ether was added slowly (over 1–1.5 hr.) a freshly prepared, cold (Dry Ice bath temperature) solution of crude 3-chlorocyclopentene[15] (*ca.* 47 g.) in 150 ml. of ether. The mixture was allowed to warm to room temperature and then was added, with stirring, to a mixture of 30 g. of ammonium chloride, ice, and water. The ethereal layer was washed first with saturated aqueous sodium carbonate solution and then with water and evaporated. The residue was steam distilled. The ethereal extract of the nonvolatile organic residue was dried and distilled twice, yield 25.8 g. (30%) of liquid, b.p. 123–136° (1.2 mm.). One recrystallization from absolute ethanol of the picrate, which was formed in the same solvent, gave 26.5 g. (14% over-all) of orange needles, m.p. 86–87.5°, mixture m.p. with an authentic sample of II picrate[6] (m.p. 103–104°) 81–96°.

Anal. Calcd. for $C_{21}H_{17}N_3O_7$: C, 59.57; H, 4.05; N, 9.93. Found: C, 59.26, H, 4.13; N, 10.08.

Chromatographic dissociation[9] of the picrate gave purified X, b.p. 110.5–111.5° (0.6 mm.).

Anal. Calcd. for $C_{15}H_{14}$: C, 92.74; H, 7.26. Found: C, 92.48; H, 7.29.

(15) R. B. Moffett, *Org. Syntheses*, **32**, 41 (1952).

3-(1-Naphthyl)cyclopentene (IX). Using the same procedure as for X, except with 1-bromonaphthalene rather than 2-bromonaphthalene and without steam distillation, there was obtained 25.7 g. (30%) of pale yellow liquid, b.p. 96–102° (0.15 mm.). It was stored as its 1,3,5-trinitrobenzene derivative, m.p. 75–110° (not analytically pure). The recovered[9] purified IX was colorless, b.p. 106–107° (0.15 mm.).

Anal. Calcd. for $C_{15}H_{14}$: C, 92.74; H, 7.26. Found: C, 92.47; H, 7.38.

In a small-scale preliminary run (which could not be reproduced) the trinitrobenzene derivative of IX was obtained as yellow needles, m.p. 72.5–74.5°, after one recrystallization from methanol, mixture m.p. with the correspondingly formed trinitrobenzene derivative of I (m.p. 79–80°) 70–75.5°.

Anal. Calcd. for $C_{21}H_{17}N_3O_6$: C, 61.91; H, 4.21; N, 10.32. Found: C, 62.27; H, 4.26; N, 10.23.

3-(1-Naphthyl)cyclohexene (XI). This preparation was conducted in a manner similar to that used for IX. From 68.7 g. (0.33 mole) of 1-bromonaphthalene, 8.1 g. (0.33 g.-atom) of magnesium shavings, and 53.4 g. (0.33 mole) of freshly prepared, distilled 3-bromocyclohexene[16] (used instead of 3-chlorocylopentene) was obtained 39.7 g. (58%) of pale yellow liquid, b.p. 144–157° (1.3 mm.). The picrate, formed in glacial acetic acid, was recrystallized thrice from the same solvent to give orange prisms, m.p. 99.5–100.5°, depressed on admixture with III picrate[6] of m.p. 126.5–127°.

Anal. Calcd. for $C_{16}H_{16}\cdot C_6H_3N_3O_7$: Neut. equiv. 437.3. Found: Neut. equiv. 443.

The purified hydrocarbon (colorless) boiled at 140–141° (1.6 mm.).

Anal. Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.38; H, 7.64.

3-(2-Naphthyl)cyclohexene (XII). This compound, prepared in a manner analogous to that used for XI, was obtained as a pale yellow liquid, b.p. 137–148° (1 mm.), yield 21.1 g. (31%), converted to a yellow picrate, m.p. 81–107°, after two recrystallizations from absolute ethanol.

Anal. Calcd. for $C_{16}H_{16}\cdot C_6H_3N_3O_7$: Neut. equiv. 437.3. Found: Neut. equiv. 427.

The purified hydrocarbon (colorless) boiled at 119.5–121.5° (1 mm.).

Anal. Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.43; H, 7.82.

EUGENE, ORE.

(16) K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann, *Ann.*, **551**, 80 (1942).

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF INDIANA UNIVERSITY AND THE UNIVERSITY OF OREGON]

Benzoylation of 2,6-Dimethoxyphenol[1,2]

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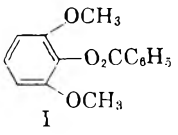
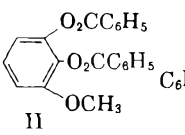
Received December 15, 1958

The effects of varying the solvent and the catalyst on the nature of the products formed from reaction of benzoyl chloride with 2,6-dimethoxyphenol were studied. It was found that, in general, as the reaction conditions are made increasingly strenuous one gets a transition from *O*-benzoylation (esterification) first to C-benzoylation (ring substitution) and then to demethylation plus O- or C-benzoylation. The structural assignment 2,3-dihydroxy-4-methoxybenzophenone was made to a yellow product previously reported as 3,4-dihydroxy-5-methoxybenzophenone by Mauthner. The undemethylated ketone 2,4-dimethoxy-3-hydroxybenzophenone was isolated for the first time.

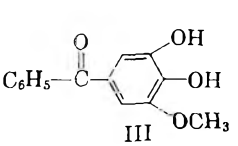
Using unspecified reaction conditons Herzig and Klimosch[4] isolated two white crystalline compounds, 2,6-dimethoxyphenyl benzoate (I) and 2,3-dibenzoyloxyanisole (II), from treatment of 2,6-dimethoxyphenol (DMP) with benzoyl chloride. Later Mauthner[5] reported the formation of I and a yellow ketone (A), m.p. 168°, for which he suggested structure III, by treating the same reactants with aluminum chloride in nitrobenzene at 2–25°. To us, however, the color[6] of Mauthner's



I

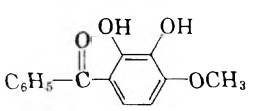


II

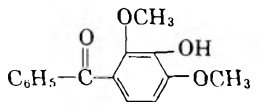


III

ketone, coupled with the fact that the production of his compound must involve both demethylation and ring benzoylation,[7] seemed inconsistent with structure III but readily correlatable with structure IV. It was the purpose of the present research to investigate further the benzoylation of DMP in order to clarify the structure of Mauthner's ketone and to develop, if possible, a method for benzoylation of the ring without accompanying demethylation.



IV



VII

A search of the literature revealed that a bright yellow compound (B), m.p. 165°, assigned either the structure of IV or that of 2,4-dihydroxy-3-methoxybenzophenone (V),[8] had been reported both by Graebe and Eichengrün[9] and by Motylewski[10] as the product from limited[11] methylation of the known 2,3,4-trihydroxybenzophenone. The alternative that B was actually 3,4-dihydroxy-2-methoxybenzophenone was rejected by Motylewski on the basis that he could monomethylate B to 2-hydroxy-3,4-dimethoxybenzophenone (VI), of proved structure.[10,12]

We have now established that A and B are identical by repetition of the preceding syntheses and comparison of the resultant products by the criteria of melting points (same) and mixture melting point (undepressed). *Prima facie* this identity might be considered evidence in favor of structure IV for A (and B), inasmuch as formation of V *via* benzoylation would necessitate the migration of a methyl group during the process whereas formation of IV would not. More definite evidence for the correctness of structure IV was obtained by examination of the ultraviolet absorption spectrum

(1) Abstracted (in part) from the M.A. thesis of H. J. Wolbert, Indiana University, August 1950.

(2) This investigation was supported (in part) by research grant No. CY-3097 from the National Cancer Institute, Public Health Service.

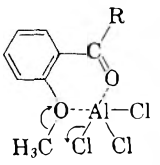
(3) Research assistant, 1957–1958.

(4) J. Herzig and K. Klimosch, *Monatsh.* **30**, 527 (1909).

(5) F. Mauthner, *J. prakt. Chem.*, **133**, 126 (1932).

(6) A check of I. Heilbron [*Dictionary of Organic Compounds*, Oxford University Press, New York, 1953, pp. 211–212] indicates that of the twelve possible dihydroxybenzophenones only the 2,3- and 2,5- isomers are definitely yellow.

(7) C. A. Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, Reinhold Publishing Corp., New York, 1941, pp. 727–28. It seems likely that the process of demethylation attendant to the acylation of an aromatic ring *ortho*- to a methoxy group is fostered by the formation of a chelate ring, thus



(8) *Cf. Beilsteins Handbuch der Organischen Chemie*, Julius Springer, Berlin, 1925, Vol. VIII, pp. 417–18.

(9) C. Graebe and A. Eichengrün, *Ann.*, **269**, 295 (1892).

(10) S. Motylewski, *Ber.*, **42**, 3148 (1909).

(11) There appears to be a typographical error in the directions of Motylewski, since he reported the formation of (a) a monomethyl derivative from treatment of 2,3,4-trihydroxybenzophenone with two molar quantities each of sodium hydroxide and dimethyl sulfate and (b) a dimethyl derivative from treatment of 2,3-dihydroxy-4-methoxybenzophenone with an equimolar quantity each of sodium hydroxide and dimethyl sulfate. On repetition of (a) we obtained 3,4-dimethoxy-2-hydroxybenzophenone.

(12) Proof of the structure of VI also established that of 2,3,4-trihydroxybenzophenone.

of the *2,4-DNP* of A. This spectrum showed a $\lambda_{max}^{CHCl_3}$ of 396–398 mμ. On the basis of observations by Johnson[13] one would expect a λ_{max} of 398 mμ for IV.2,4-DNP but of only 392 mμ for V.2,4-DNP. It might be noted, in connection with Motylewski's thoughts, that the infrared absorption spectrum of A in dilute carbon tetrachloride solution exhibits bands at 2.72μ (free hydroxyl) and 3.05–3.07μ (presumably due to hydroxyl *ortho* to a carbonyl group).[14]

In a series of experiments on reaction of DMP with benzoyl chloride under various conditions (*cf.* Table I) it was found possible to prepare a fourth product, Z, m.p. 114°, alkali soluble, white, and with the elemental composition expected for a monohydroxydimethoxybenzophenone. Z is assigned structure VII on the basis of the following considerations: (1) Z can be methylated with aqueous sodium hydroxide and dimethyl sulfate to a neutral compound of m.p. 54°, consistent with that reported for 2,3,4-trimethoxybenzophenone.[4] This neutral compound, moreover, differs from authentic 3,4,5-trimethoxybenzophenone (m.p. 78°) prepared by reaction of phenylmagnesium bromide on the known 3,4,5-trimethoxybenzonitrile.[15] (2) Z differs from 3,4-dimethoxy-2-hydroxybenzophenone (m.p. 131°, obtained by methylation of IV) in that the latter will not undergo methylation under the conditions employed successfully with Z itself.[16] (3) The alternative structure of 2,3-dimethoxy-4-hydroxybenzophenone (though not excluded completely) would necessitate methyl migration during the benzoylation reaction.

Observation of Table I shows that results of the benzoylation are apparently dependent on the strenuousness of the reaction conditions, as based on the solvent and catalyst used. Thus aluminum chloride, a strong Lewis acid, fosters benzoylation of the DMP ring and demethylation to a greater extent than occurs for stannic chloride, a milder Lewis acid. A polar solvent, nitrobenzene alone or with added tetrachloroethane, should favor the formation of ionic or polarized intermediates, probably of more importance in ring benzoylation than in esterification and of considerable importance in demethylation.[7] The nonpolar solvents, on the other hand, yield mainly esterification. In the latter regard the facile esterification occurring through catalysis by stannic chloride in benzene is especially noteworthy.

TABLE I

REACTION OF 2,6-DIMETHOXYPHENOL WITH BENZOYL CHLORIDE[a]

Run No.[b]	Catalyst	Solvent	Yield of Product[c] (in %) IV	II	VII	I
1	$AlCl_3$	ϕNO_2–$Cl_2CHCHCl_2$	19[d]	16		
2[e]	$AlCl_3$	ϕNO_2	6–12			Much
3	$SnCl_4$	ϕNO_2–$Cl_2CHCHCl_2$			24	5
4	$SnCl_4$	ϕNO_2			28	18
5[f]	$AlCl_3$	CS_2				50
6	$SnCl_4$	CS_2			3	30
7	$SnCl_4$	ϕH				92

[a] Generally the dimethoxyphenol, benzoyl chloride, and catalyst were used in approximately equimolar quantities. The temperature was 0–5°. [b] Listed in approximate expected order of decreasing strenuousness of reaction conditions. [c] Isolated as crystals. [d] Crude crystals. [e] Experiment of Mauthner.[5] [f] Also 12% of dimethoxyphenol was recovered.

EXPERIMENTAL[17]

3,4,5-Trimethoxybenzophenone. To the cold Grignard reagent prepared from 2.7 ml. of bromobenzene, 0.6 g. of magnesium, and 15 ml. of anhydrous ether was added a solution of 3.7 g. of 3,4,5-trimethoxybenzonitrile[15] in 40 ml. of anhydrous toluene. The stirred mixture (containing a yellow precipitate) was heated gradually to 35–40°, which temperature was maintained for 3 hr. After 13 more hours at room temperature the mixture was poured into ice and concentrated hydrochloric acid. From the organic layer was recovered 1.0 g. of nitrile. The acid layer was refluxed for 2 hr. and extracted with chloroform. The washed (5% aqueous sodium hydroxide and then water) chloroform solution was dried (magnesium sulfate) and evaporated to leave 2 g. (38%) of product, m.p. 60–70°. Recrystallization from methanol gave needles, m.p. 77–78°; reported[18] needles, m.p. 78–79°. In carbon tetrachloride (3 × $10^{-4}M$) it showed a carbonyl band at 6.12μ (broad).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: *C, 70.40; H, 6.05.*

The *2,4-dinitrophenylhydrazone*[19] formed orange needles from ethanol-ethyl acetate, m.p. 237–239°; $\lambda_{max}^{CHCl_3}$ predicted[13] 396 mμ (log ε 4.5), found 395 mμ (log ε 4.48); reported[18] orange needles from alcohol, m.p. 200–202°.

Anal. Calcd. for $C_{22}H_{20}N_4O_7$: C, 58.40; H, 4.46; N, 12.39. Found: C, 58.35; H, 4.17; N, 12.14.

4,3,5(?)-Hydroxydimethoxybenzophenone. A solution of 0.8 g. of the preceding trimethoxybenzophenone (m.p. 70–71°) in 4 ml. of concentrated sulfuric acid was maintained at 40° for 17 hr. and then poured onto ice. Combined solids from filtration and extraction (chloroform) of the filtrate were recrystallized from 60% ethanol, yield 0.65 g. (85%), m.p. *ca.* 118°, soluble in 5% aqueous sodium hydroxide. Recrystallization from the same solvent gave *needles, m.p.* 124.5–126°; reported[18] plates from ether-ligroin, m.p. 124–126°. In carbon tetrachloride (1 × $10^{-3}M$) it showed strong absorption at 2.73μ.

(13) G. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953). For this calculation additivity of the incremental effects on λ_{max} of substituents on the same phenyl ring in the basic structure of benzophenone.2,4-DNP is assumed. Such increments are 2 —OH, Δλ = 2 mμ; 3 —OH = 3 —OCH_3, Δλ = 0; 4 —OH, Δλ = 3; 4 —OCH_3, Δλ = 9.

(14) M. Tsuboi, *Bull. Chem. Soc. Japan*, **25**, 60 (1952).

(15) C. D. Hurd and H. E. Winberg, *J. Am. Chem. Soc.*, **64**, 2085 (1942).

(16) In addition, the failure to effect methylation of 3,4-dimethoxy-2-hydroxybenzophenone by means of potassium hydroxide, methyl iodide, and methanol has been noted by Graebe and Eichengrün (ref. 9).

(17) Unless otherwise indicated microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. Ultraviolet absorption spectra were determined by means of a Beckman DU instrument and infrared spectra by means of a Perkin-Elmer Infracord. Complete infrared spectra for three of the benzophenones taken in potassium bromide wafers are reported in the catalog of *Sadtler Standard Spectra.*

(18) C. F. Koelsch and R. N. Flesch, *J. Org. Chem.*, **20**, 1270 (1955).

(19) G. D. Johnson, *J. Am. Chem. Soc.*, **73**, 5888 (1951)

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.46; H, 5.58.

Methylation of 2,3,4-trihydroxybenzophenone.[11] A solution of 5 g. (0.022 mole) of 2,3,4-trihydroxybenzophenone[20] in 25 ml. of 4% aqueous sodium hydroxide was refluxed with 3 g. (0.024 mole) of dimethyl sulfate for 2 hr. The acidified solution was extracted with chloroform. The residue from evaporation of the chloroform was distilled (20 mm. pressure) and crystallized from methanol as bright yellow prisms of *2,3-dihydroxy-4-methoxybenzophenone*, yield 0.8 g. (15%), m.p. 166–167°, undepressed on admixture with the corresponding product from benzoylation of 2,6-dimethoxyphenol.

Repetition of the preceding methylation but with 8% aqueous sodium hydroxide and 6 g. of dimethyl sulfate gave pale yellow needles (from ethanol) of *3,4-dimethoxy-2-hydroxybenzophenone*, m.p. 130–131° [reported[21] prisms, m.p. 130–131°], undepressed on admixture with a sample from similar methylation of IV, obtained from benzoylation.

Benzoylation of 2,6-dimethoxyphenol. (a) *Using aluminum chloride in nitrobenzene-tetrachloroethane.* To the stirred cold (3–4°) solution of 100 g. (0.65 mole) of 2,6-dimethoxyphenol[22] in 475 ml. of purified[23] tetrachloroethane maintained in an atmosphere of nitrogen was first added, over a period of 1.5 hr., a solution of 78.5 g. of anhydrous aluminum chloride in 130 ml. of nitrobenzene and 200 ml. of tetrachloroethane and then, over a period of 2.5 hr., a solution of 78.5 g. (total 1.2 moles) of aluminum chloride and 92 g. (0.65 mole) of benzoyl chloride in 100 ml. of nitrobenzene and 240 ml. of tetrachloroethane. The reaction mixture was kept cold for 4 days, treated with 700 ml. of 1.7*M* hydrochloric acid, and steam distilled. The combined solid residues from the distillation flask and from evaporation of a chloroform extract of the distillate were pulverized and treated with methanol in a Soxhlet extractor. Crystallization of the insoluble portion from ethanol gave 35 g. (16%, based on dimethoxyphenol used) of *2,3-dibenzoyloxyanisole* (II), obtained as platelets, m.p. 154–156°; reported[4] m.p. 156–158°.

Anal.[24] Calcd. for $C_{21}H_{16}O_5$: C, 72.40; H, 4.63. Found: C, 72.70; H, 4.83.

II was further identified by saponification to benzoic acid (more than a one-molar quantity isolated, m.p. 119–120°, undepressed on admixture with an authentic specimen) and other alkali-soluble crystals, m.p. 38–40°, presumably 2,3-dihydroxyanisole; reported[25] m.p. 38–41°.[26]

From the cold methanolic extract were deposited 30 g. of yellow crystals, m.p. *ca.* 165–169°. For further purification a 5-g. sample of the crystals, dissolved in chloroform, was added to a chromatographic column of silicic acid–Celite (3:1 by volume) and eluted with 30–60° petroleum ether–chloroform (4:1 by volume). The first fraction of effluent contained additional II. Recrystallization from methanol of the main fraction obtained by elution of the yellow zone, gave 3 g. of bright yellow needles of *2,3-dihydroxy-4-methoxybenzophenone* (IV), m.p. 167.5–168.5°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.87; H, 4.88.

(20) German patent 54661, *Ber.*, 24c, 378 (1891).

(21) P. Bartolotti, *Gazz. chim. ital.*, 26 II, 433 (1896).

(22) We are indebted to Cliffs Dow Chemical Co., Marquette, Mich. for a generous sample of this compound.

(23) L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed. D. C. Heath and Co., New York, 1941, p. 366.

(24) Analysis by Mrs. G. White.

(25) J. Herzig and J. Pollak, *Monatsh.*, 25, 808 (1904).

(26) Herzig and Pollak (ref. 25) report a m.p. of 85–87° for 1,3-dihydroxy-2-methoxybenzene.

The *2,4-dinitrophenylhydrazone*[19] was obtained as red needles from ethyl acetate, m.p. 265–266.5° (dec.); $\lambda_{max}^{CHCl_3}$ predicted[13] 398 mμ (log ε 4.5), found 396–398 mμ (log ε 4.47).

Anal. Calcd. for $C_{20}H_{16}N_4O_7$: C, 56.60, H, 3.80; N, 13.20. Found: C, 56.73; H, 3.98; N, 13.51.

(b) *Using stannic chloride in nitrobenzene.* To a cold (−10 to 0°), stirred solution of 20 g. (0.13 mole) of 2,6-dimethoxyphenol in 100 ml. of nitrobenzene was added slowly 20 ml. (0.17 mole) of anhydrous stannic chloride and then 20 g. (0.14 mole) of benzoyl chloride. After 3 more hours the mixture was allowed to warm to room temperature and was then treated with ice and concentrated hydrochloric acid (10 ml.). The residue from steam distillation of the mixture was extracted with ether. The ethereal extract was washed first with excess 5% aqueous sodium bicarbonate (discarded) and then with excess 5% aqueous sodium hydroxide. Evaporation of the ethereal solution yielded 6 g. (18%) of *2,6-dimethoxyphenyl benzoate*, (I) obtained as needles, m.p. 114–117°. Recrystallization from ethanol raised the m.p. to 116–117°, undepressed on admixture with an authentic specimen of the same compound, m.p. 117–118°, prepared by reaction of benzoyl chloride with 2,6-dimethoxyphenol in the presence of pyridine.[27]

Anal.[24] Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.93; H, 5.65.

The preceding sodium hydroxide wash was acidified with hydrochloric acid and extracted with chloroform. The residue from evaporation of the chloroform was recrystallized from methanol to yield 9.5 g. (28%) of tan *2,4-dimethoxy-3-hydroxybenzophenone* (VII), m.p. 107–109°. Further recrystallization from methanol gave white prisms, m.p. 113–114° [m.m.p. with 4,3,5(?)-hydroxydimethoxybenzophenone 103–112.5°]; strong absorption at 2.71μ (free hydroxyl), weak at 2.83μ (methoxy-bonded hydroxyl),[14] and strong at 5.80μ (carbonyl) in $1 \times 10^{-3}M$ solution in carbon tetrachloride.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.23; H, 5.27.

For further identification, a sample of the preceding ketone was methylated (using aqueous sodium hydroxide and dimethyl sulfate) to the neutral compound *2,3,4-trimethoxybenzophenone*, obtained as fluffy crystals from methanol, m.p. 53–54°; reported[4] prisms from dilute ethanol, m.p. 55°.

(c) *Using stannic chloride in benzene.* To a cold (1–5°) solution of 15.4 g. (0.1 mole) of 2,6-dimethoxyphenol in 100 ml. of anhydrous benzene was added dropwise, with shaking, first a solution of 11.7 ml. (0.1 mole) of anhydrous stannic chloride in 25 ml. of benzene and then a solution of 11.5 ml. (0.1 mole) of benzoyl chloride in 25 ml. of benzene. The almost colorless complex which had precipitated on addition of the stannic chloride turned red and partially dissolved upon addition of the acid chloride. Hydrogen chloride was evolved. The mixture was kept cold for 2 days and then poured into ice and dilute hydrochloric acid. The combined organic layer and benzene extracts of the aqueous layer were washed with 5% aqueous sodium hydroxide and then with water, dried (magnesium sulfate), and evaporated to yield 23.7 g. (92%) of cream colored *2,6-dimethoxyphenyl benzoate* (I), m.p. 114.5–116°, identified by recrystallization and mixture m.p. as in part (b).

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(27) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., J. Wiley and Sons, New York, 1956, p. 212.

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

Substituted Styrenes. V. Reaction of Styrene and α-Methylstyrene with Dihalocarbenes

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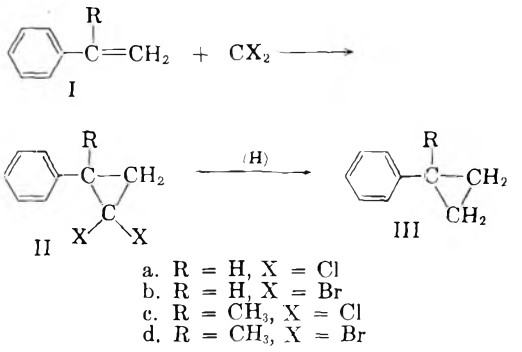
Optimum experimental conditions have been determined for the reaction of styrene with dichlorocarbene. Under the conditions described, a 76% yield of (2,2-dichlorocyclopropyl)benzene was obtained. The reactions of styrene with dibromocarbene and of α-methylstyrene with dichloro- and dibromocarbene gave the corresponding *gem*-dihalocyclopropyl compounds in yields of 72–81%. Reduction of the products yielded cyclopropanes.

In an effort to find confirmatory experimental evidence for the formation of dichlorocarbene as an intermediate in the alkaline hydrolysis of chloroform, Doering and Hoffmann[1] treated chloroform with cyclohexene in the presence of potassium *t*-butoxide and obtained 7,7-dichlorobicyclo[4.1.0]-heptane. Other olefins were found by these workers to react similarly with chloroform and bromoform in the presence of strong bases to give *gem*-dihalocyclopropanes and further examples of this reaction have been reported by Parham,[2] Skell,[3] and their co-workers.

In view of the ease with which dihalocarbenes can be generated in the presence of olefins, it would appear that the application of these reagents to the preparation of cyclopropane derivatives would be limited only by the availability of suitable olefins. Another aspect of the problem is encountered, however, when one considers the electrophilic character of carbenes. Olefins in which the nucleophilic character of the double bond has been reduced by electron-withdrawing groups should react less readily with carbenes than those in which the nucleophilic character has been increased by electron-donating groups. Some evidence in support of this view has been presented by Parham and Wright,[2c] Woodworth and Skell,[3c] and Doering and Henderson.[4]

Numerous investigations in our laboratory have been concerned with the effect of the nature and position of ring substituents on the chemistry of substituted styrenes.[5] The usual nucleophilic character of the double bond of styrene can be greatly diminished or even converted completely to one of electrophilic character, by placing a negative group, such as the nitro group, in the *ortho*- or *para*- position of the styrene nucleus. It is felt that a study of the reactions of dihalocarbenes with styrenes will throw additional light on the general reaction of carbenes with olefins, as well as in the formation of previously unreported cyclopropanes.

In the present study, dichloro- and dibromocarbene have been allowed to react with styrene (Ia) and α-methylstyrene (Ic) and the products have been reduced to phenylcyclopropanes by sodium and methanol.



a. R = H, X = Cl
b. R = H, X = Br
c. R = CH_3, X = Cl
d. R = CH_3, X = Br

Optimum conditions for the reaction of styrenes with carbenes were first determined by a study of the reaction of styrene itself with dichlorocarbene. The conditions were varied as to reaction time, temperature, solvent and ratio of styrene to dichlorocarbene. The best yields (71–76%) of (2,2-dichlorocyclopropyl)benzene (IIa) were obtained when an excess of styrene was used as the solvent for the reaction, the styrene being present in a molar ratio, to the dichlorocarbene, of from 4:1 – 6:1. Long reaction times (18–24 hr.) and low temperatures (−5 to −10°) were also found to increase the yields. These conditions were used to advantage in

(1) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954).

(2) (a) W. E. Parham, H. E. Reiff, and P. Swartzentruber, *J. Am. Chem. Soc.*, **78**, 1437 (1956). (b) W. E. Parham and R. R. Twelves, *J. Org. Chem.*, **22**, 730 (1957). (c) W. E. Parham and C. D. Wright, *J. Org. Chem.*, **22**, 1473 (1957).

(3) (a) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 3409 (1956). (b) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 5430 (1956). (c) R. C. Woodworth and P. S. Skell, *J. Am. Chem. Soc.*, **79**, 2542 (1957).

(4) W. von E. Doering and W. A. Henderson, *J. Am. Chem. Soc.*, **80**, 5274 (1958).

(5) (a) W. J. Dale, *J. Am. Chem. Soc.*, **76**, 6172 (1954). (b) W. J. Dale and G. Buell, *J. Org. Chem.*, **21**, 45 (1956). (c) W. J. Dale and L. Levine, Abstracts of the Organic Division of the 128th Meeting of the American Chemical Society, Minneapolis, 1955. (d) W. J. Dale and H. E. Hennis, *J. Am. Chem. Soc.*, **80**, 3645 (1958). (e) W. J. Dale and H. E. Hennis, *J. Am. Chem. Soc.*, **81**, 2143 (1959). (f) W. J. Dale and G. W. Eigenmann, Abstracts of the Organic Division of the 132nd Meeting of the American Chemical Society, New York, 1957.

subsequent reactions to give good yields of products in every case. (2,2-Dibromocyclopropyl)benzene (IIb) was obtained in a 72% yield from the reaction of styrene with dibromocarbene. The reactions of α-methylstyrene (Ic) with dichlorocarbene and dibromocarbene gave (2,2-dichloro-1-methylcyclopropyl)benzene (IIc, 75%) and (2,2-dibromo-1-methylcyclopropyl)benzene (IId, 81%), respectively. It is evident from these results that the increased steric factor presented by the α-methyl group is not sufficiently great to cause a decrease in the yield of product. Rather, the increased yield of IId might be attributed to the increased nucleophilic character of the double bond due to the presence of the methyl group.

Each of the above *gem*-dihalocyclopropanes underwent reduction when allowed to react with sodium metal and wet methanol. Thus, (2,2-dichlorocyclopropyl)benzene (IIa) and (2,2-dibromocyclopropyl)benzene(IIb) yielded identical products (cyclopropylbenzene, IIIa), in 74% and 69% yields, respectively. Similarly, (2,2-dichloro-1-methylcyclopropyl)benzene (IIc) and (2,2-dibromo-1-methylcyclopropyl)benzene (IId) were reduced to the same product, (1-methylcyclopropyl)benzene (IIIc), in 54% and 40% yields, respectively.

An attempt was made to hydrolyze (2,2-dichlorocyclopropyl)benzene (IIa) using the method employed successfully by Schmerling[6] for the hydrolysis of *gem*-dichlorides to ketones. When the compound was heated with water in a sealed Pyrex tube at 200–205° for 4½ hr., however, only black polymeric material was obtained. Under less drastic conditions (105–110° for 4 hr.), only starting material was recovered, even in the presence of sodium carbonate.

EXPERIMENTAL

All boiling points and melting points are uncorrected.

The reaction of styrene, chloroform, and potassium t-butoxide. (2,2-Dichlorocyclopropyl)benzene (IIa). Potassium *t*-butoxide was prepared by the addition of 10.0 g. (0.256 g. atom) of clean potassium metal to an excess of refluxing anhydrous *t*-butyl alcohol. Following complete solution of the metal, the excess *t*-butyl alcohol was removed by distillation under reduced pressure. The solid cake of white salt which remained was broken into fine pieces by means of a glass rod. An atmosphere of nitrogen was maintained in the reaction flask during the preparation of the potassium *t*-butoxide and its subsequent reaction with the styrene and haloform.

The flask containing the potassium *t*-butoxide was cooled in an ice–salt bath (−5° to −10°) and 156 g. (1.50 moles) of freshly distilled styrene was added.[6] The bright green color which developed when the styrene came in contact with the potassium *t*-butoxide was due to the presence of 4-*t*-butylpyrocatechol, added to the styrene as an inhibitor. Dry, freshly distilled chloroform (29.9 g., 0.250 mole) was then added, dropwise, to the well stirred mixture over a period of 1 hour. When the addition of the chloroform was complete, the mixture was stirred in the ice–salt bath for an additional 3 hr. The flask was then stoppered and placed in a refrigerator at 10° for 18 hr.

(6) L. Schmerling, *J. Am. Chem. Soc.*, 68, 1350 (1946).

The reaction mixture was then allowed to come to room temperature and 200 ml. of water was added. The slightly basic mixture was carefully neutralized with dilute hydrochloric acid and the organic and aqueous layers were separated. The aqueous layer was extracted three times with light petroleum ether (b.p. 80–86°), the combined extracts and original organic layer were washed with two 100-ml. portions of water, and the solution was dried over Drierite. The solvent was removed by distillation at atmospheric pressure and the remaining material was fractionally distilled under vacuum. The product, (2,2-dichlorocyclopropyl)benzene (IIa), (35.7 g., 76%) was obtained as a colorless, sweet smelling liquid, b.p. 78–83° (2 mm.), n_D^{25} 1.5498–1.5500.

Refractionation through a Todd Precise Fractionation Assembly gave a pure sample boiling at 114° (13 mm.), n_D^{23} 1.5501. Infrared absorption maxima occur at 3.45 (m), 6.27(m), 6.66(s), 6.88(s), 7.00(s), 8.13(s), 8.38(m), 8.95(s), 9.26(s), 9.55(s), 9.75(s), 10.54(m), 10.74(m), 11.00(w), 11.46(w), 12.86–12.93(s), 13.32(s), 13.60–13.67(s), and 14.33–14.40(s)μ.

Anal. Calcd. for $C_9H_8Cl_2$: C, 57.78; H, 4.31. Found: C, 57.69; H, 4.62.

The procedure described above was found to give the best yield of IIa. Variations on this procedure gave the following results: (a) When the chloroform was added to the mixture of styrene and potassium *t*-butoxide over a period of 30 min. at 0°, and the reaction mixture was stirred for an additional 45 min., only a 50% yield of product was obtained. (b) When the temperature of the exothermic reaction was permitted to rise to 60–80°, the other conditions being similar to (a), a yield of only 26% was obtained. This low yield is probably due to the loss of chloroform by evaporation before the reaction can take place. (c) When the procedure was varied only by reducing the molar ratio of styrene to dichlorocarbene from 6:1 to 4:1, the yield was reduced from 76% to 71%. Reducing the ratio to a point (1:1.3) where another solvent (benzene) was necessary, reduced the yield of product to 15%.

The reaction of styrene, bromoform, and potassium t-butoxide. (2,2-Dibromocyclopropyl)benzene (IIb). The reaction was performed as described in detail above for (2,2-dichlorocyclopropyl)benzene, using potassium *t*-butoxide prepared from 10.0 g. (0.256 g. atom) of potassium metal, freshly distilled bromoform (63.2 g., 0.250 mole), and styrene (156 g., 1.50 moles). Fractional distillation of the reaction product yielded 49.9 g. (72%) of (2,2-dibromocyclopropyl)benzene (IIb) obtained as a colorless liquid, b.p. 88–98° (1 mm.), n_D^{22} 1.5982–1.5989. Refractionation through a 10-cm. Vigreux column yielded a middle fraction boiling at 97° (1 mm.), n_D^{22} 1.5988 (lit.,[3b] b.p. 94° (2 mm.), n_D^{25} 1.5963). The infrared spectrum exhibits bands at 3.20(m), 6.24(m), 6.67(s), 6.90(s), 7.04(m), 8.15(w), 8.98(s), 9.23(m), 9.58(s), 9.72(s), 10.66(m), 10.79(m), 13.01(s), 13.58(s), 14.27–14.35(s), and 14.63–14.77(s)μ.

Anal. Calcd. for $C_9H_8Br_2$: C, 39.17; H, 2.92. Found: C, 39.30; H, 3.16.

The reaction of α-methylstyrene, chloroform, and potassium t-butoxide. (2,2-Dichloro-1-methylcyclopropyl)benzene (IIc). In the manner described for the analogous reaction of styrene, 29.9 g. (0.250 mole) of chloroform was added dropwise to a cold (about −5°), well stirred mixture of α-methylstyrene (Ic) (177 g., 1.50 moles) and potassium *t*-butoxide, prepared from 10.0 g. (0.256 g. atom) of potassium. Following the addition of the chloroform (about 45 min.), the mixture was stirred an additional 4 hr. at −5° and then placed in a refrigerator at 10° for 38 hr. The product was isolated as described above. The yellow liquid obtained was fractionated under reduced pressure to give 37.9 g. (75%) of (2,2-dichloro-1-methylcyclopropyl)benzene (IIc) as a colorless liquid, b.p. 77–81° (5 mm.), n_D^{22} 1.5404–1.5406. Redistillation through a 15-cm. Vigreux column yielded a middle fraction boiling at 75–77° (1 mm.), n_D^{22} 1.5406. Absorption maxima occur in the infrared at 3.25(m), 3.29(m), 3.33(m), 3.40(m), 3.47(m), 6.24(m), 6.69(s), 6.93(s), 7.03(m), 7.24(m),

7.95(w), 8.97(m), 9.16(m), 9.28(s), 9.54(s), 9.67(s), 10.68(m), 10.95(w), 11.28(m), 12.86–12.98(s), 13.25(s), and 14.20–14.33(s)μ.

Anal. Calcd. for $C_{10}H_{10}Cl_2$: C, 59.72; H, 5.01. Found: C, 59.85; H, 5.28.

The reaction of α-methylstyrene, bromoform, and potassium t-butoxide. (2,2-Dibromo-1-methylcyclopropyl)benzene (IId). α-Methylstyrene (177 g., 1.50 moles) was reacted with 63.2 g. (0.250 mole) of bromoform and potassium *t*-butoxide, from 10.0 g. (0.256 g. atom) of potassium, in the manner described for the reaction of α-methylstyrene and chloroform. The reaction product, (2,2-dibromo-1-methylcyclopropyl)benzene (IId) (58.9 g., 81%) was obtained as a colorless liquid, b.p 94–100° (2 mm.), n_D^{22} 1.5831–1.5848. A refractionation of the product through a 15-cm. Vigreux column yielded a middle fraction boiling at 91–92° (1 mm.), n_D^{22} 1.5842. The product solidified upon cooling, m.p. 35.5–36°. The infrared spectrum exhibits absorption maxima at 3.28(m), 3.31(m), 3.38(s), 3.43(m), 3.50(m), 6.24(m), 6.32(w), 6.69(s), 6.94(s), 7.00(s), 7.24(m), 7.57(w), 7.66(w), 7.98(w), 8.71(m), 8.99(m), 9.32(s), 9.42(s), 9.80(s), 10.73(m), 10.97(m), 11.59(m), 11.79(m), 13.10(s), and 14.30–14.41 (s)μ.

Anal. Calcd. for $C_{10}H_{10}Br_2$: C, 41.41; H, 3.48. Found: C, 41.55; H, 3.55.

The reduction of (2,2-Dichlorocyclopropyl)benzene with sodium and methanol. Cyclopropylbenzene (IIIa). The method described by Doering and Hoffmann[1] for the reduction of 7,7-dibromobicyclo[4.1.0] heptane was employed with only slight modification. Following the complete reaction of the sodium metal (46 g., 2.0 g. atoms) with the wet methanol (10 ml. of water to 300 ml. of methanol), 200 ml. of water was added, the layers were separated, and the aqueous layer was neutralized with hydrochloric acid before being extracted with ether. From 18.7 g. (0.100 mole) of (2,2-dichlorocyclopropyl)benzene (IIa) there was obtained 8.7 g. (74%) of cyclopropylbenzene as a colorless liquid, b.p. 64–70° (18 mm.). A redistillation of the product through a Todd Precise Fractionation Assembly yielded a middle fraction boiling at 69° (12 mm.), n_D^{22} 1.5316, d_4^{20} 0.936; M_D calcd. 38.8, M_D found 39.1 (lit., b.p. 60–63° (11 mm.), 7 n_D^{20} 1.5320,[7] d_D^{25} 0.9374[8]). Absorption maxima were observed in the infrared at 3.24(s), 6.22(s), 6.64(s), 6.80(s), 6.89(m), 6.97(m), 8.18(m), 8.49(w), 9.05(w), 9.22(s), 9.53(s), 9.74(s), 10.03(w), 11.11(s), 12.28(s), 13.26–13.37(s), and 14.30–14.39(s)μ.

Anal. Calcd. for C_9H_{10}: C, 91.47; H, 8.53. Found: C, 91.21; H, 8.51.

The reduction of (2,2-dibromomocyclopropyl)benzene with sodium and methanol. Cyclopropylbenzene (IIIa). (2,2-Dibromocyclopropyl)-benzene (IIb) (27.6 g., 0.100 mole) was reduced with 46 g. (2.0 g. atoms) of sodium and 300 ml. of wet methanol in the above manner. The product obtained (8.1 g., 69%) was identical with that obtained from the dichloro compound as evidenced by both boiling point (65° at 17 mm.) and refractive index (n_D^{22} 1.5315).

The reduction of (2,2-dichloro-1-methylcyclopropyl)benzene and (2,2-dibromo-1-methylcyclopropyl)benzene with sodium and methanol. (1-Methylcyclopropyl)benzene (IIIc). By the method described above, 10.1 g. (0.050 mole) of (2,2-dichloro-1-methylcyclopropyl)benzene (IIc) was reduced with 23 g. (1.0 g. atom) of sodium and 200 ml. of wet methanol to give 3.5 g. (54%) of colorless (1-methylcyclopropyl)-benzene (IIIc), b.p. 72–77° (22 mm.), n_D^{21} 1.5146–1.5150. Refractionation of the product through a 10-cm. Vigreux column yielded a middle fraction boiling at 69° (18 mm.), n_D^{21} 1.5151. The reduction of 21.8 g. (0.075 mole) of (2,2-dibromo-1-methylcyclopropyl)benzene (IId) by 32 g. (1.4 g. atoms) of sodium and 300 ml. of wet methanol yielded 4.0 g. (40%) of (1-methylcyclopropyl)benzene (IIIc), b.p. 70–74° (22 mm.), n_D^{21} 1.5152–1.5157. Redistillation of the product through a 10-cm. Vigreux column yielded a middle fraction boiling at 71° (20 mm.), n_D^{21} 1.5152. The infrared absorption spectrum of the product exhibits maxima at 3.22(s), 3.29(s), 3.35(s), 3.45(m), 6.22(s), 6.31(w), 6.66(s), 6.86(s), 6.92(s), 7.00 (m), 7.23(m), 7.42(w), 8.93(s), 9.24(w), 9.33(m), 9.71(s), 9.86(s), 10.72(m), 11.07(w), 11.61(w), 11.81(s), 12.73(w), 13.13–13.23(s), and 14.24–14.35(s)μ.

Anal. Calcd. for $C_{10}H_{12}$: C, 90.85; H, 9.15. Found: C, 90.56; H, 9.04.

COLUMBIA, MO.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Preparation of Polymers Containing Pyridine Units from Polyvinyl Ketones

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Poly(methyl vinyl ketone) was converted to the polyoxime and this polymer, under the conditions of the Knoevenagel 1,5-dioxime ring closure, gave a copolymer of methyl vinyl ketone with some 2,6-dimethylpyridine units which consisted of 76.2 mole % of the latter. Similarly a copolymer of phenyl vinyl ketone and phenyl vinyl ketoxime containing 70.2 mole % ketoxime units was converted to a copolymer of phenyl vinyl ketone and 2,6-diphenylpyridine units which consisted of 50.3 mole % of the latter. Neither copolymer was thermally stable.

The marked thermal and chemical stability of the pyridine nucleus prompted an investigation of the heat resistance of polymers which incorporate a pyridine ring as a structural feature of the polymer chain. A promising approach to the desired polymers was suggested by the work of Marvel and Levesque[2] on the structure of low molecular weight poly(methyl vinyl ketone). During this

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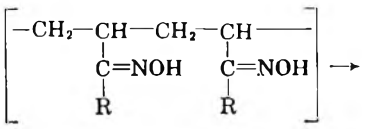
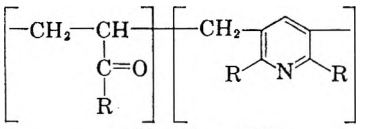
(2) (a) C. S. Marvel and C. L. Levesque, *J. Am. Chem. Soc.*, 60, 280 (1938). (b) C. S. Marvel and C. L. Levesque, *J. Am. Chem. Soc.*, 61, 3234 (1939).

study a material possessing the correct elemental composition for copolymer IIa was obtained by application of the Knoevenagel ring closure of 1,5-dioximes[3] to polymethyl vinyl ketoxime (Ia).



Ia. R = CH_3
Ib. R = C_6H_5



IIa. R = CH_3
IIb. R = C_6H_5

The limited information available on the copolymer necessitated a re-examination of this work to provide additional evidence as to the presence of a pyridine moiety in the polymer and to determine if such a copolymer were heat stable.

In order to insure the molecular weight and consequently the potential stability of the pyridine-containing copolymer, it was essential to polymerize the precursor vinyl ketone to the highest possible molecular weight polymer which still possessed the required solubility properties. To this end, a number of procedures for the polymerization of methyl vinyl ketone was examined. Bulk polymerization with benzoyl peroxide produced polyketones having an average inherent viscosity of 0.65. Standard emulsion polymerization techniques were found to be unsuccessful, but when the water solubility of the monomer was decreased by including varying amounts of sodium chloride in polymerization recipes employing solutions of potassium caproate, it was possible to prepare methyl vinyl ketone polymers having inherent viscosities in the range 0.83–1.45. A summary of the results obtained by use of this procedure is included in Table I. Considerably higher molecular weight polyketones were obtained with a modification of the potassium persulfate-silver nitrate aqueous solution procedure reported by Whitby and co-workers.[4]

With this technique poly(methyl vinyl ketones) possessing inherent viscosities of 1.27–2.60 (usual range 1.9–2.0) could be prepared at 5°, and polymers having inherent viscosities of 2.00–2.99 could be obtained at −15° (Table II). By comparison with the intrinsic viscosity–osmotic pressure molecular weight reported by Guillet and Norrish,[5] it can be estimated that methyl vinyl ketone polymers of inherent viscosity 2 to 3 should have molecular weights of the order of 3–4 × 10.[5] Infrared analysis of the polyketone disclosed bands consistent with the expected vinyl polymer, but in addition, weak bands were found at 3620–3500 cm.$^{-1}$ and 3380 cm.$^{-1}$ which appeared to be due to strongy adsorbed water which was not removed by the drying procedure; this is in accord with the consistently low carbon analyses.

TABLE I

POLYMERIZATION OF METHYL VINYL KETONE IN POTASSIUM CAPROATE–SODIUM CHLORIDE SOLUTION

No.	Time, Hr.	Temp.	Conversion, %	Salt Concentration, G.	Inherent Viscosity[a]
72	64	26	20	0.10	1.24
73	16	50	61	0.10	1.45
74	20	50	67	0.10	0.83
75	62	26	14	0.25	1.08
76	14	50	51	0.25	1.20
77	19	50	66	0.25	1.19
78	110	26	49	0.35	1.23
79	19	50	61	0.35	1.21
80	14	50	53	0.35	1.25

[a] Inherent viscosities were determined in methyl ethyl ketone.

TABLE II

POLYMERIZATION OF METHYL VINYL KETONE

(Water Azeotrope Initiated by Potassium Persulfate-Silver Nitrate)

No.	Time, Hr.	Temp.	Conversion, %	Inherent Viscosity[a]
7	5	26	87	0.83
10	8	26	90	0.85
9	8	5	93	1.45
8	18	5	96	2.60
11	19	5	86	1.27
12	20	5	95	1.92
15	20	5	94	1.91
13	21	5	96	1.95
14	21	5	100	2.03
16	21	5	96	1.99
18	24	−15	82	2.00
19	36	−15	88	2.17
17	40	−15	100	2.45
20	42	−15	67	2.99
21[b]	24	−15	85	2.88
23	36	−15	69	2.55

[a] Inherent viscosities were determined in methyl ethyl ketone. [b] Runs 21 and 23 used one half the usual amount of potassium persulfate.

Conversion of the high molecular weight polymethyl vinyl ketone to polymethyl vinyl ketoxime (Ia) was effected by use of a modification of the procedure of Marvel and Levesque.[2a] Treatment of this material with an ethanolic hydrogen chloride solution produced a copolymer of methyl vinyl ketone and 2,6-dimethylpyridine units (IIa) containing 76.2 mole % of pyridine units. From poly-

(3) (a) E. Knoevenagel and R. Weissberger, *Ber.*, **26**, 436 (1893). (b) E. Knoevenagel, *Ann.*, **281**, 25 (1894). (c) J. Wislicenus, *Ann.*, **302**, 235, 241 (1898). (d) E. E. Blaise and M. Montagne, *Compt. rend.*, **180**, 1760 (1925). (e) B. D. Shaw, *J. Chem. Soc.*, 300 (1937).

(4) G. S. Whitby, M. D. Gross, J. R. Miller, and A. J. Costanza, *J. Polymer Sci.*, **16**, 549 (1955).

(5) J. E. Guillet and R. Norrish, *Proc. Roy. Soc.*, **233A**, 153 (1955).

methyl vinyl ketoximes of inherent viscosity 3.2–3.6 in dimethyl sulfoxide, copolymers were obtained which possessed inherent viscosities in chloroform of 0.11–0.14. Infrared spectra of the copolymer in chloroform revealed pertinent absorption bands at 1708 (C=O), 1599, 1562 cm.$^{-1}$, and a weak shoulder at 1500 cm.$^{-1}$ (pyridine C=C and C=N bands). In addition a band of very weak intensity was noted at 3300–3160 cm.$^{-1}$ (—OH). The results of the elemental analysis eliminate the possibility of this absorption being due to the hydroxyl group of a residual oxime or an aldol condensation, and suggest the observed band was again due to residual water. This is consistent with the hygroscopic nature of the copolymer and the frequently low carbon analyses. The possibility of amide formation by rearrangement of the oxime functions under the conditions of the ring closure was excluded by treatment of the copolymer with 20% sulfuric acid at reflux temperature. The infrared spectrum of the material isolated from this reaction was identical at all significant points with the spectrum of the starting material. Comparison of the ultraviolet spectrum of the copolymer with spectra reported for a number of methyl substituted pyridines provided additional evidence for the presence of a recurring pyridine unit in the polymer. The general shapes of the curves were quite similar, a bathochromic shift being observed with increasing alkyl substitution. A summary of these data is presented in Table III. An average neutralization equivalent of 117.0 for the basic unit of the copolymer was obtained by titration of the polymer with perchloric acid in a nonaqueous system; this represents a 1.8% deviation from the theoretical value of 119.1.

TABLE III

COMPARISON OF ULTRAVIOLET ABSORPTION OF METHYLPYRIDINES WITH COPOLYMER IIa[a]

Compound	λ_{max} mμ)	ε
2,6-Dimethylpyridine	269–270	7,600
2,3,5-Trimethylpyridine	273–273.5	6,820
2,3,6-Trimethylpyridine	274.5–275	8,480
2,3,5,6-Tetramethylpyridine	279.5	10,060
Copolymer IIa	281.5	8,980

[a] Data used for comparison were taken from ref. 6; these values correspond to others reported in the lit.[7] Spectra were determined in 0.2*N* H_2SO_4.

Since the practicality of this route to a pyridine-containing polymer had been successfully demonstrated by the preparation of copolymer IIa, it was desirable to extend this series of reactions to the analogous aromatic system, poly(phenyl vinyl ketoxime). As a preliminary to this work, an examination of the ring closure reaction was carried out on a comparable monomeric system. It was found that 2,6-diphenylpyridine could be prepared from the dioxime of 1,3-dibenzoylpropane in a yield of 97.5%; therefore, it was evidently feasible to extend this reaction to poly(phenyl vinyl ketoxime).

The first point of attack in this phase of the work involved a series of experiments designed to uncover the optimum conditions for the preparation of high molecular weight poly(phenyl vinyl ketone). Solution polymerization of phenyl vinyl ketone initiated by benzoyl peroxide or azo-*bis*-isobutyronitrile produced polymers with inherent viscosities in the range 0.11–0.26 (Table IV). With a potassium persulfate system emulsified with Triton X-301, polymers of inherent viscosity 0.14–0.17 were obtained at temperatures of 5°–55°. The addition of silver nitrate to this system as an activator raised the inherent viscosity range to 0.21–0.30 for experiments carried out at 5°. Similar results were obtained with a potassium persulfate–ORR soap system containing 5% of emulsifier and 0.37% of initiator; polymers prepared by this procedure possessed viscosities of 0.16–0.31. Lowering the initiator concentration to 0.2% and raising the soap concentration to 7.5% changed the viscosity range to 0.41–0.65. A summary of these polymerizations is recorded in Table V.

TABLE IV

SOLUTION POLYMERIZATION OF PHENYL VINYL KETONE

No.	Procedure	Time, Hr.	Temp.	Conversion, %	Inherent Viscosity[a]
87	A	6	55	58	0.19
88	A	10	55	44	0.19
89	B	10	55	73	0.26
90	B	11	55	84	0.19
98	B	25	55	70	0.11

[a] Inherent viscosities of poly(phenyl vinyl ketone) were determined in benzene.

TABLE V

EMULSION POLYMERIZATION OF PHENYL VINYL KETONE

No.	Procedure	Time, Hr.	Temp.	Conversion, %	Inherent Viscosity
92	A	3	55	41	0.17
91	A	12	26	9	0.14
93	A	13	5	11	0.16
99	B	36	5	26	0.21
100	B	62.5	5	52	0.30
95	C	4	55	52	0.25
94	C	12	26	50	0.31
96	C	13	5	34	0.16
109	D	5	50	86	0.59
110	D	10	50	100	0.41
108	D	24	26	69	0.65

(6) N. Ikekawa, M. Maruyama, and Y. Sato, *Pharm. Bull. (Japan)*, **2**, 209 (1954).

(7) (a) R. J. L. Andon, J. D. Cox, and E. F. Herington, *Trans. Faraday Soc.*, **50**, 918 (1954). (b) J. I. Jones, *J. Chem. Soc. Ind. (London)*, **69**, 99 (1950). (c) H. E. Podall, *Anal. Chem.*, **29**, 1423 (1957).

TABLE VI

ANIONIC POLYMERIZATION OF PHENYL VINYL KETONE

No.	Initiator	G.	Solvent	Temp.	Conversion, %	Inherent Viscosity
104	Sodium	0.01	Liquid ammonia	−78	66	0.09
113	Sodium	0.005	Liquid ammonia	−78	56	0.06
114	Lithium	0.005	Liquid ammonia	−78	68	0.03
105	Sodium ethoxide	0.03	Dimethylformamide	−78	10	Insoluble
106	Sodium ethoxide	0.03	Tetrahydrofuran	−78	100	0.03
115	Sodium cyanide	0.005	Dimethylformamide	−78	24	0.06
116	Sodium cyanide	0.01	Dimethylformamide	−78	20	0.08
118	Sodium cyanide	0.005	Dimethylsulfoxide	24	100	0.08
117	Potassium cyanide	0.005	Dimethylformamide	−78	28	0.10

Under anionic conditions, low molecular weight material was obtained with a number of initiator systems. Physically, these polymers varied from tacky semisolids to powders while the inherent viscosities ranged from 0.03–0.10. Comparison of the infrared spectra of the soluble polymers with spectra of authentic samples of poly(phenyl vinyl ketone) indicated the polymers were similarly constituted. Representative results of these polymerizations are summarized in Table VI.

A sample of the higher molecular weight poly(phenyl vinyl ketone) prepared under emulsion conditions was converted to a copolymer of phenyl vinyl ketone and phenyl vinyl ketoxime containing 70.2 mole per cent ketoxime units by oximation of the polyketone under very mild conditions. Infrared analysis was consistent with the proposed copolymer structure with pertinent bands at 3500–3260 cm.$^{-1}$ (—OH); 1665 cm.$^{-1}$ (ArC=O); 1635 cm.$^{-1}$ (C=N); 1600 cm.$^{-1}$, 1580 cm.$^{-1}$, and 1498 cm.$^{-1}$ (aromatic); 914 cm.$^{-1}$

When this copolymer was subjected to the conditions designed to effect ring closure of the 1,5-dioxime groups to a pyridine moiety, a polymer was obtained which dissolved slowly in dilute hydrochloric acid and was insoluble in sodium hydroxide solution. By contrast the precursor polyketone was completely insoluble in acid. On the basis of the elemental analysis it was possible to estimate that the "pyridine" copolymer consisted of 49.7 mole % phenyl vinyl ketone and 50.3 mole % 2,6-diphenylpyridine units (IIb). Infrared analysis indicated the absence of hydroxyl functions (no residual oxime) and showed a new absorption band at 1547–1545 cm.$^{-1}$ This absorption is somewhat lower than would be expected for a 2,6-diphenylpyridine nucleus but is in the general region for C=C, C=N aromatic absorption (*cf.* 2,6-diphenylpyridine: 1605, 1592, 1568, and 1497 cm.$^{-1}$; phenyl and pyridine C=C and C=N bands). Additional evidence consistent with the assignment of a 2,6-diphenylpyridine moiety to the copolymer was provided by a comparison of the ultraviolet spectrum of the polymer with the spectrum of 2,6-diphenylpyridine. In dioxane, absorption maxima for the monomeric pyridine occurred at 245 mμ (ε 28,200), 285 mμ (shoulder, ε 12,280) and 302 mμ (ε 11,200). In the same solvent, a similar spectrum was obtained for the copolymer containing 50.3 mole % 2,6-diphenylpyridine units. The maxima were found to have undergone a considerable hypsochromic shift with the long wave length bands compressed to a single maximum at 285 mμ (ε 11,200) and the main absorption shifted to 236 mμ (ε 20,900). Extinction coefficients for the pyridine units of the copolymer were calculated by subtracting the contribution expected from the phenyl vinyl ketone units at the wave lengths of the observed maxima; this contribution was determined from a spectrum of polyphenyl vinyl ketone in dioxane (λ 236, ε 7,760; λ285, ε 870).

Thermal stability tests on the pyridine-containing copolymers revealed that neither polymer was appreciably stable. At 225° the copolymer with 2,6-dimethylpyridine units (IIa) lost 3.2% of its weight in 12 hr. and the copolymer with 2,6-diphenylpyridine units (IIb) lost 2.7% of its weight in the same time. At 300° both polymers exhibited a steady weight loss; after 12 hr. polymer IIa had lost 21.6% of its original weight and IIb had lost 9.9%.

EXPERIMENTAL

Bulk polymerization of methyl vinyl ketone. Pure methyl vinyl ketone was obtained by treating the water azeotrope of methyl vinyl ketone (85% monomer) with an equal weight of acetic anhydride for 24 hr. at room temperature; the monomer was recovered by careful fractionation of this mixture under nitrogen at atmospheric pressure using a 30-cm. column packed with glass helices; b.p. 81–81.4°, $n_D^{20.7}$ 1.4096 (premature polymerization was prevented by collecting the distillate in Dry Ice–acetone). Polymerization was effected by adding 0.5% of benzoyl peroxide to 10 g. of freshly distilled monomer, flushing the system with nitrogen, and placing the samples in a constant temperature bath at 26° for 40 hr. The viscous, light yellow semisolid product was purified by successive reprecipitations from acetone into water. After drying at 50° for 48 hr., approximately 40% yields of a hard material soluble in acetone, methyl ethyl ketone, and dioxane were obtained. Inherent viscosities in methyl ethyl ketone averaged 0.65.

Polymerization of methyl vinyl ketone in potassium caproate–sodium chloride solution. Pure methyl vinyl ketone (10.0 g.), potassium caproate (20.0 g. of a 2.5% aqueous solution),

sodium chloride (as indicated in Table I), Hooker's lauryl mercaptan (0.005 g.), and potassium persulfate (0.2 g.; 5 ml. of a solution containing 4 g. of potassium persulfate in 100 ml. of oxygen-free water) were added to 4-ounce screw-cap bottles equipped with self-sealing rubber gaskets. After bubbling nitrogen through the solutions, the bottles were capped and tumbled end-over-end in constant temperature baths. The polymers were recovered by slowly pouring the reaction mixtures into reagent grade methanol with rapid stirring followed by the addition of sufficient hydrochloric acid to adjust the solution *p*H to approximately 2. Purification was accomplished as previously described.

Polymerization of water azeotrope of methyl vinyl ketone initiated by potassium persulfate–silver nitrate. Methyl vinyl ketone was polymerized by the following modification of the procedure reported by Whitby *et al.*[4]

Into 4-ounce screw-cap bottles equipped with self-sealing rubber gaskets were placed 11.7 g. of methyl vinyl ketone water azeotrope (freshly distilled under nitrogen; approximately 10 g. of monomer) and 80 ml. of oxygen-free water. To this solution was added 0.2 g. of potassium persulfate (5 ml. of a solution containing 4 g. of potassium persulfate in 100 ml. of water). After bubbling nitrogen through the solutions, the bottles were capped and brought to the desired temperature. Silver nitrate (0.0105 g., 1 ml. of a solution containing 1.050 g. of silver nitrate in 100 ml. of water) was then added, the bottles swept out with nitrogen, recapped, and returned to constant temperature baths. Alternatively, the silver nitrate solution was injected with a hypodermic syringe through a puncture in the metal cap. For polymerizations at 26° or 5° the polymers were recovered by slowly pouring the white suspensions into reagent grade methanol. For polymerizations at −15° the polymers were isolated by allowing the samples to warm to room temperature, decanting the supernatant liquid and dissolving the solid in reagent grade acetone. Purification was effected as described above; samples for microanalysis were dried for three days over phosphorus pentoxide at 80° (0.75 mm.). Significant infrared bands (film): 3620–3500, 3380 (weak); 1710 (C=O), 1435, 1363 cm.$^{-1}$

Anal. Calcd. for $(C_4H_6O)n$: C, 68.54; H, 8.63. Found: C, 68.17, 68.09; H, 8.71, 8.33.

Polymethyl vinyl ketoxime. To a solution of 4.88 g. (0.070 mole) of hydroxylamine hydrochloride in 125 ml. of ethanol was added 5.82 g. (0.071 mole) of anhydrous sodium acetate in 190 ml. of ethanol. After 5 min. the precipitated sodium chloride was removed by filtration and the alcohol solution diluted with 80 ml. of redistilled dioxane. The solution was heated at reflux temperature with vigorous stirring while 2.46 g. (0.035 mole) of high molecular weight polymethyl vinyl ketone in 125 ml. of dioxane was added over a period of 45 min. The reaction mixture was stirred at this temperature for an additional 7 hr. during which time a large amount of the product precipitated. After allowing the mixture to stand at room temperature for 12 hr., the polymer was collected on a filter, washed thoroughly with water and methanol, and purified by reprecipitation from redistilled dimethyl sulfoxide into water; yield 2.6 g. (87%) of white powder; softening range 246–280°. Inherent viscosity in dimethyl sulfoxide: 3.59. Samples for microanalysis were dissolved in dimethyl sulfoxide, the solutions filtered, and the polymer recovered by pouring the solution into water (repeated three times). After washing with a large volume of water the samples were dried 4 days at 80° (0.1 mm.). Significant infrared bands (Nujol): 3400–3180 (—OH), 1658 (C=N), 955–935 cm.$^{-1}$ (characteristic of oximes[8]).

Anal. Calcd. for $(C_4H_7NO)n$: C, 56.45; H, 8.29; N, 16.46. Found. C, 56.24; H, 8.51; N, 15.86; residue, 0.88. Adjusted to account for residue. C, 56.86; H, 8.58; N, 16.00.

Copolymer of methyl vinyl ketone and "2,6-dimethylpyridine" (IIa). Poly(methyl vinyl ketoxime) (1.044 g., 0.0122 mole) was dissolved in 16 ml. of concentrated hydrochloric acid by adding the powdered oxime slowly to the well stirred acid. To this was added a solution of 44.4 g. (1.2 moles) of hydrogen chloride in 165 ml. of absolute ethanol. The resultant cloudy yellow solution was heated under reflux with stirring for 24 hr. At the end of this period the red-orange solution was concentrated under reduced pressure to 20 ml., diluted with water, and made basic with concentrated ammonium hydroxide. The precipitated polymer was collected on a filter and washed with 200 ml. of distilled water. Purification was effected as follows: The polymer was dissolved in dilute hydrochloric acid, insoluble material was removed by filtration, and the polymer recovered by reprecipitation with sodium carbonate solution (repeated four times). The material was then alternately suspended in distilled water and filtered until three complete washings gave negative chloride tests with silver nitrate. Following this, the solid was dried at 100° for 1 hr. Finally, the polymer was dissolved in reagent grade chloroform, insoluble material was removed by filtration, and the polymer recovered by slowly adding the chloroform solution to petroleum ether (b.p. 30–60°) (repeated four times). Yield: 0.65 g. (88%); decomp. 190°, partial melting 460°. Samples for analysis were dried at 100° (0.25 mm.) for 48 hr. Pertinent infrared bands (chloroform): 3400–3160, very weak (—OH); 1708 (C=O); 1599, 1562, and a weak shoulder at 1500 (pyridine C=C and C=N bands); 1445; 1365 cm.$^{-1}$ (C—CH_3). Ultraviolet maximum (0.2*N* H_2SO_4): λ_{max} 281.5 mμ (ϵ 8980).

Anal. Calcd. for $(C_8H_9N)_{0.762}$-$(C_4H_6O)_{0.238}$: C, 78.74; H, 7.76; N, 9.93.[9] *Found:* C, 79.05; H, 8.01; N, 9.87.[10]

Neutralization equivalent of the basic moiety in the methyl vinyl ketone-"2,6-dimethylpyridine" copolymer (IIa). A sample of pure methyl vinyl ketone-"2,6-dimethylpyridine" copolymer was dried at 100° (0.25 mm.) for 2 days. Immediately upon removal of the material from the drying apparatus, a 47.519-mg. sample was placed in a 25-ml. volumetric flask and diluted to volume with reagent grade chloroform. From this solution, 2-ml. aliquots were removed, diluted with 30 ml. of glacial acetic acid, and titrated with 0.00288*N* perchloric acid (in acetic acid; standardized with potassium acid phthalate to a crystal violet end point). When crystal violet was used to determine the end point of the polymer titration, 9.40 ml. (average value) of standard acid was required; with methyl violet as the indicator, 9.65 ml. (average value) was required. These values correspond to equivalent weights of 118.5 and 115.5, respectively (theoretical: 119.1). For the calculation of the equivalent weight, it was assumed the polymer was 84.46 gram per cent C_8H_9N; this is the result of the hydrolysis of 13.53% of the ketoxime groups during the ring closure.[5]

Dioxime of 1,3-dibenzoylpropane. (a) *Glutaryl chloride.* Glutaric acid (30 g., 0.23 mole) was mixed with phosphorus pentachloride (94.4 g., 0.46 mole). After the reaction had started, the mixture was heated on the steam bath for 1 hr. The phosphorus oxychloride was then removed by distillation at atmospheric pressure and the residue fractionated under reduced pressure; b.p. 105–106° (18 mm.), [lit., 107–108° (16 mm.)[12]]. The yield was 34.5 g. (90%).

(b) *1,3-Dibenzoylpropane.* A mixture of 59.6 g. (0.448 mole) of anhydrous aluminum chloride in 300 ml. of dried, distilled benzene was cooled in an ice bath and 34.5 g. (0.204 mole) of freshly distilled glutaryl chloride was added dropwise with stirring over a period of 15 min. When all the acid chloride had been added, the ice bath was removed and the

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(9) The percentage composition of this polymer was calculated on the basis of the assumed hydrolysis of 13.53% of the ketoxime groups during the reaction *i.e.* for 0.4324 mole C_8H_9N and 0.1353 mole of C_4H_6O.[2b,11]

(10) The hygroscopic nature of the polymer necessitated drying the sample to a constant weight prior to analysis.

(11) P. J. Flory, *J. Am. Chem. Soc.*, **61**, 1518 (1939).

(12) K. v. Auwers and M. Schmidt, *Ber.*, **46**, 457 (1913).

reaction stirred at room temperature for 2 hr. The solution was then poured slowly onto a mixture of cracked ice and 40 ml. of concentrated hydrochloric acid; 400 ml. of benzene was added and the organic layer separated. After washing with an equal volume of sodium bicarbonate solution and then with water, the benzene was evaporated under reduced pressure leaving a heavy oil which solidified on cooling. Upon recrystallization from ethanol-petroleum ether (b.p. 30–60°), 38.1 g. (74%) of pure 1,3-dibenzoylpropane was obtained; m.p. 65–66° [lit., 62–63°,[13a] 67.5°[13b]]. Infrared analysis (chloroform): 1683 (ArC=O); 1601, 1584, 1495–1490 (aromatic); 1453; 685 cm.$^{-1}$ (monosubstituted phenyl). Ultraviolet maximum (absolute ethanol): λ_{max} 243 mμ (ε 25,200).

(c) *Dioxime of 1,3-dibenzoylpropane.* To 25.4 g. (0.31 mole) of anhydrous sodium acetate in 425 ml. of ethanol were added at equivalent rates a solution of 1,3-dibenzoylpropane (25.2 g., 0.10 mole) in 350 ml. of ethanol and a solution of 20.9 g. (0.30 mole) of hydroxylamine hydrochloride in 300 ml. of ethanol. After the reaction had been heated at reflux temperature for 4 hr., the hot mixture was filtered, and the filtrate concentrated to one half its original volume and diluted with water to precipitate 27.6 g. of crude product (98%). Two recrystallizations from ethanol-water yielded 22.3 g. (79%) of 1,3-dibenzoylpropane dioxime; m.p. 163–164° [lit., 165–166° (dec.)[14]]. Infrared analysis (Nujol): 3100 (—OH); 1625–1620 (C=N); 1600 (shoulder), 1575, 1499 (aromatic); 938 (oxime); 770–765, and 700 cm.$^{-1}$ (monosubstituted phenyl).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.32; H, 6.33; N, 9.71.

2,6-Diphenylpyridine. A solution of 100 g. of hydrogen chloride in 400 ml. of absolute ethanol was added to 2.82 g. (0.01 mole) of the dioxime of 1,3-dibenzoylpropane in 40 ml. of absolute ethanol and the resulting solution heated at reflux for 19 hr. The light pink reaction mixture was then concentrated to 30 ml., cooled, and neutralized with ammonium hydroxide. An additional 100 ml. of water was added to the mixture, the precipitate collected on a filter, washed well with water, and dried; crude yield: 2.25 g. (97.5%); m.p. 80–81.6°. After treatment with Darco in absolute ethanol, the yield of pure 2,6-diphenylpyridine was 1.68 g. (73%); m.p. 81.5–82° [lit., 81–82°[15]]. Infrared analysis (chloroform): 3035; 1605 (shoulder), 1592, 1568, and 1497 (pyridine and phenyl, C=C and C=N); 1457; 1444; 1268; and in Nujol: 826; 778, 758, 742; and 697 cm.$^{-1}$ Ultraviolet maxima (absolute ethanol): λ_{max} 245 mμ (ε 28,200), λ_{max} 285 mμ (ε 12,280), λ_{max} 302 mμ (ε 11,200).

Anal. Calcd. for $C_{17}H_{13}N$: C, 88.28; H, 5.67; N, 6.06. Found: C, 88.34; H, 5.60; N, 5.92.

Phenyl vinyl ketone. (a) *β-Chloropropiophenone.* β-Chloropropiophenone was prepared by a modification of the procedures used by Allen and Barker[16] and Hale and Britton.[17] With this procedure 60–74% yields of pure β-chloropropiophenone were obtained if the reaction was carried out on ½ molar amounts or less, but when the reaction scale was increased the product was found to be contaminated with 30–38% of β-phenylpropiophenone. Higher yields of pure product were obtained with the following procedure.

Anhydrous aluminum chloride (83 g., 0.62 mole) was cooled in an ice bath and 69.9 g. (0.55 mole) of β-chloropropionyl chloride in 140 ml. of reagent grade carbon disulfide was added with stirring. With continued cooling, 42.9 g. (0.55 mole) of dry distilled benzene in 100 ml. of carbon disulfide was added over a period of 10 min.; at this point a large amount of solid was present in the reaction flask. The reaction was stirred at 0° for 1 hr. and then heated to reflux for ½ hr. at which time the clear solution was poured onto cracked ice. Chloroform was added, and the two phases separated. The aqueous layer was extracted with two 50-ml. portions of chloroform which were combined with the original organic layer. The combined organic phases were then washed with four 200-ml. portions of water and finally with 100 ml. of a saturated sodium chloride solution. After drying the yellow chloroform solution over sodium sulfate, the solvent was removed under reduced pressure, never allowing the solution to become warm. The resulting solid was pulverized and dried in air; crude yield: 89.4 g. (96%). One recrystallization from petroleum ether (b.p. 30–60°) produced 78.5 g. (85%) of β-chloropropiophenone; m.p. 49–50° [lit., 49–50°[18]].

Anal. Calcd. for C_9H_9OCl: C, 64.11; H, 5.38. Found: C, 64.22; H, 5.39.

(b) *Phenyl vinyl ketone.* Phenyl vinyl ketone was prepared in 69% yield according to the procedure of Allen *et al.*[19] by the dehydrohalogenation of β-chloropropiophenone; b.p. 37–38° (0.05 mm.); n_D^{20} 1.5588; phenylhydrazine derivative (1,3-diphenyl-Δ²-pyrazoline) m.p. 152.5–153° [lit., 152–153°[20]]. Phenyl vinyl ketone can be stored at Dry Ice temperature for at least 3 weeks without change in the refractive index of the material.

Solution polymerization of phenyl vinyl ketone. Polymerizations were carried out in 21 × 70 mm. screw-cap vials fitted with rubber gaskets. The reagents were added in the order listed, the vials swept out with nitrogen, capped, and placed in constant temperature baths for the indicated times. The polymers were recovered by evaporating the solvent and triturating the residue with methanol. Purification was effected by dissolving the polymers in benzene and reprecipitating into petroleum ether (b.p. 30–60°).

Procedure A: Phenyl vinyl ketone, 2.0 g.; benzoyl peroxide, 0.0125 g. (10-ml. aliquot of a solution containing 0.125 g. of benzoyl peroxide in 100 ml. of benzene).

Procedure B: Phenyl vinyl ketone, 2.0 g.; azo-*bis*-isobutyronitrile, 0.0125 g. (10-ml. aliquot of a solution containing 0.125 g. of AIBN in 100 ml. of benzene). Table IV lists the results of these polymerizations.

Emulsion polymerization of phenyl vinyl ketone. The polymerization samples were prepared in the same manner as in the solution polymerizations described above, and then tumbled in constant temperature baths for the indicated periods. The polymers were recovered by pouring the emulsions into methanol with stirring. Purification was accomplished by dissolving the solid in benzene, removing any insoluble material by filtration, recovering the polymers by slowly adding the benzene solutions to low boiling petroleum ether, and finally freeze-drying the polymers from benzene.

Procedure A: Phenyl vinyl ketone, 2.0 g.; Triton X-301, 0.1 g.; potassium persulfate, 0.0075 g. (0.37%; 3-ml. aliquot of a solution containing 0.250 g. of potassium persulfate in 100 ml. of oxygen-free water).

Procedure B: Phenyl vinyl ketone, 2.0 g.; Triton X-301, 0.1 g.; potassium persulfate, 0.0125 g. (0.62%; 5-ml. aliquot of a solution containing 0.250 g. of potassium persulfate in 100 ml. of oxygen-free water); silver nitrate, 0.0005 g.

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(14) G. Ponzio and M. Fornaseri, *Gazz. chim. ital.*, **66**, 813 (1936).

(15) (a) M. Scholtz, *Ber.*, **28**, 1726 (1895). (b) O. Döbner and P. Kuntz, *Ann.*, **252**, 349 (1889). (c) C. G. Overberger, J. G. Lombardino, and R. G. Hiskey, *J. Am. Chem. Soc.*, **79**, 6430 (1957).

(16) C. F. H. Allen and W. E. Barker, *J. Am. Chem. Soc.*, **54**, 740 (1932).

(17) W. Hale and E. Britton, *J. Am. Chem. Soc.*, **41**, 845 (1919).

(18) J. B. Conant and W. R. Kirner, *J. Am. Chem. Soc.*, **46**, 240 (1924).

(19) C. F. H. Allen, A. C. Bell, Alan Bell, and J. Van Allen, *J. Am. Chem. Soc.*, **62**, 656 (1940).

(20) (a) F. Ramirez and A. Kirby, *J. Am. Chem. Soc.*, **75**, 6026 (1953). (b) T. Matsumoto and K. Hata, *J. Am. Chem. Soc.*, **79**, 5506 (1957).

(0.03%; 1-ml. aliquot of a solution containing 0.050 g. of silver nitrate in 100 ml. of oxygen-free water).

Procedure C: Phenyl vinyl ketone, 2.0 g.; ORR soap, 3.6 g. (2.8% solution, 5%); potassium persulfate, 0.0075 g. (as in procedure A above).

Procedure D: Phenyl vinyl ketone, 2.0 g.; ORR soap, 5.4 g. (2.8% solution, 7.5%); potassium persulfate, 0.004 g. (0.2%; 3-ml. aliquot of a solution containing 0.133 g. of potassium persulfate in 100 ml. of oxygen-free water).

Pertinent infrared bands (chloroform): 3000; 2905; 1677 (ArC=O); 1600, 1585 (aromatic); 1454; 1263; 1225; 1005; 976; 695 cm.$^{-1}$

Anal. Calcd. for $(C_9H_8O)_n$: C, 81.79; H, 6.10. Found: 81.81, 81.83; H, 6.28, 6.24.

Representative results of these polymerizations are recorded *in Table V.*

Anionic polymerization of phenyl vinyl ketone. All anionic polymerizations were performed as follows: A mixture of 25 ml. of the solvent and the initiator was placed in a 50-ml. flask and brought to the desired polymerization temperature. To this mixture, 2.0 g. of monomer was added at once and the reaction mixtures allowed to warm to room temperature. In runs using dimethylformamide, solution of the monomer did not occur until the solvent melted as it warmed to room temperature. The polymers were isolated from the indicated solvents by use of the following techniques: (a) Liquid ammonia: ammonia allowed to evaporate and residue dissolved in benzene; (b) Tetrahydrofuran: reaction mixture precipitated by pouring into water; (c) Dimethylformamide: reaction mixture precipitated by *pouring into isopropyl alcohol; (d) Dimethylsulfoxide:* reaction mixture precipitated by pouring into isopropyl alcohol. Purification was accomplished as previously described. The results of these polymerizations are recorded in Table VI.

Copolymer of phenyl vinyl ketone and phenyl vinyl ketoxime. Polyphenyl vinyl ketone (0.39 g., 0.003 mole) in 50 ml. of dioxane, hydroxylamine hydrochloride (2.09 g., 0.030 mole) in 30 ml. of dioxane to 50 ml. of ethanol, and anhydrous sodium acetate (2.46 g., 0.030 mole) in 20 ml. of dioxane to 50 ml. of ethanol were mixed and allowed to stand at room temperature for 52 days. The inorganic precipitate was removed by filtration and the filtrate added slowly to water to precipitate the polymer. The product was collected on a filter, washed well with water, dried briefly in air, and dis*solved in pure tetrahydrofuran.* Purification was accomplished by reprecipitating the polymer from tetrahydrofuran into low boiling petroleum ether (repeated 4 times); *yield of copolymer: 0.405 g.* Significant infrared bands (Nujol): 3500–3260 (—OH); 1665 (ArC=O); 1635 (C=N); 1600, 1580, 1498 (aromatic); 914; 765, 694 cm.$^{-1}$ (monosubstituted phenyl).

Anal. Calcd. for $(C_9H_8O)_{0.298}$—$(C_9H_9NO)_{0.702}$: C, 75.75; H, 6.14; N, 6.89. Found: C, 75.69; H, 6.03; N, 6.89.

On the basis of the analytical results it was concluded that this polymer was 70.2 mole per cent phenyl vinyl ketoxime.

Copolymer of phenyl vinyl ketone and "2,6-diphenylpyridine" (IIb). A solution of 35 g. of hydrogen chloride in 100 ml. of ethanol was gradually added to 10 ml. of pure tetrahydrofuran containing 0.3023 g. of a copolymer of phenyl vinyl ketone and phenyl vinyl ketoxime which consisted of 70.2 mole per cent ketoxime units. After the reaction had been stirred at reflux temperature for 48 hr., the red solution was concentrated to 20 ml. and a sodium carbonate solution was added dropwise until the *p*H reached 8–9. The mixture was diluted with water and extracted with two 50-ml. portions of chloroform. Traces of insoluble material were removed from the chloroform by filtration, the solution was concentrated to 20 ml. and then added slowly to low boiling petroleum ether to precipitate the product. The polymer was purified by reprecipitation from chloroform into low boiling petroleum ether (five times); yield: 0.1089 g.; softening range: 200–235°. Significant infrared bands (chloroform): 3040 (shoulder); 2950; 1673 (ArC=O); 1593, 1577, 1547–1545, 1492 (aromatic C=C and C=N); 1440; 1072; 1016; 693 cm.$^{-1}$ Ultraviolet maxima (dioxane): λ_{max} 236 mμ (ε 20,900), λ_{max} 285 mμ (ε 11,200).

Anal. Calcd. for $(C_9H_8O)_{0.497}$—$(C_{18}H_{13}N)_{0.503}$: C, 86.39; H, 5.64; N, 3.75. Found: C, 86.09; H, 5.60; N, 4.03.

Thermal stability of copolymers IIa *and* IIb. Previously dried samples of the two polymers were heated in air in aluminum cups and the weight loss was determined at given intervals during the heating period; the results of these tests have been described above.

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URBANA, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF APPLIED CHEMISTRY, SCHOOL OF SCIENCE AND ENGINEERING, WASEDA UNIVERSITY]

Reaction of Hydrazine Hydrate and Phenylhydrazine with Malononitrile

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The condensation products from hydrazine hydrate and phenylhydrazine with malononitrile were examined and are believed to be derivatives of 3-amino-4-cyano-5-(cyanomethyl)pyrazole rather than of 3,5-diaminopyrazole as reported by Rothenberg. Evidence is given for the proposed structures, and the chemical properties are described.

Rothenberg reported that the reaction of malononitrile with hydrazine and phenylhydrazine yielded oily substances which were assumed to be diaminopyrazole derivatives Ia and Ib, on the basis of the elementary analyses of their derivatives.[1]

As a result of repeating his procedure in our laboratory, however, the reaction seemed to proceed not in the way assumed by him and detailed study on the reaction products under various experimental conditions indicated a different process for the reaction. The reaction was studied under

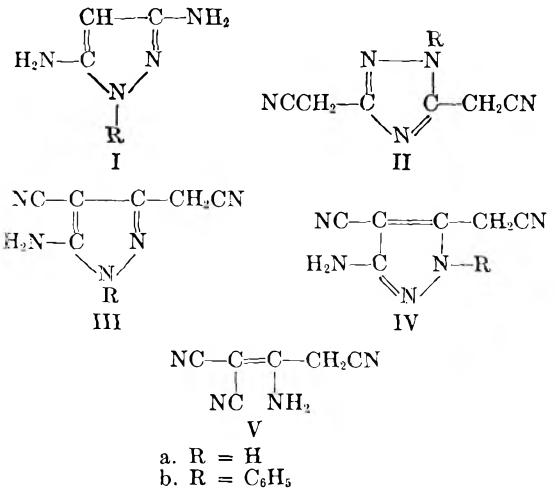
(1) R. v. Rothenberg, *J. prakt. Chem.*, 52, 45 (1895).

three experimental conditions changing the molar ratio of malononitrile to hydrazine. When the molar ratio was 1.0 (the same ratio used in the experiment by Rothenberg), crystals of $C_6H_5N_5$ (named compound A in this report) and an oily substance (named compound B) were obtained with a liberation of ammonia. The chemical composition of compound A indicated that it was produced by a reaction between two moles of malononitrile and one mole of hydrazine with a loss of ammonia. Although the further purification of the oily substance (compound B) was not successful, its hydrochloride and hydrobromide were obtained in crystalline form. These salts had compositions represented by $C_3H_7N_5.2HCl$ and $C_3H_7N_5.2HBr$, respectively, which indicates that the reaction takes place between two moles of hydrazine and one mole of malononitrile.

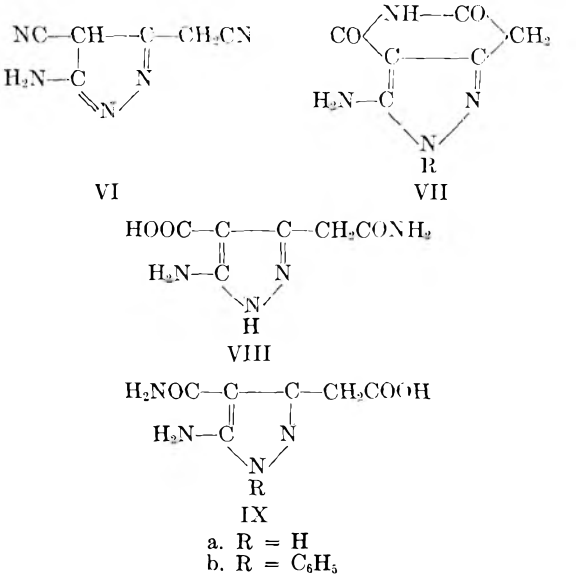
The decrease of the molar ratio to 0.5 afforded only the oily substance B, and the increase of the ratio to 2.0 gave the crystalline compound A alone, although, in the latter case, the yield was low owing to the formation of large quantities of amorphous by-product.

When phenylhydrazine was used in place of hydrazine hydrate, a compound having the composition of $C_{12}H_9N_5$ was obtained (named compound C). This chemical composition indicates the formation of the phenyl derivative of compound A. A notable fact observed in the experiment with phenylhydrazine was that no substance corresponding to compound B was obtained, even when a large amount of phenylhydrazine was used.

The molecular formulas of the compounds A and C suggest that structures II, III, and IV can be considered for these products. The infrared spectra of A and C showed the bands of NH_2, C=C, and both conjugated and nonconjugated C=N. The spectra of the monoacetyl derivatives showed the N–H band of a secondary amide, which also indicated the existence of primary amino group in A and C. Further evidence against structure II is found in the recent experimental result by Carboni Coffman, and Howard,[2] who obtained compounds having the same melting points and analytical values as those of A and C, by condensing malononitrile dimer V with hydrazine derivatives, although these authors do not reach any conclusions as to whether these compounds have structures III or IV. Although IIIa and IVa are interconvertible with A by a tautomeric shift of hydrogen, such an interconversion is not possible when the hydrogen on the ring was replaced by a phenyl group. That structure IIIb is preferable to structure IVb for C was inferred from comparison of the basicity of A and C. Compound C is a weak base, being soluble in concentrated hydrochloric acid and can be recovered unchanged by diluting this solution with water, whereas A is not basic and is insoluble even in concentrated hydrochloric acid. The nonbasic property of A is considered to result from the formation of the tautomeric structures IVa and VI, in which the C=N group in the ring may give the direct influence on the amino group. The basic property of C can, therefore, be explained more reasonably with structure IIIb, in which such a direct effect on amino group is absent.



Acid hydrolysis of A and C gave yellow crystals of $C_6H_6N_4O_2$ and $C_{12}H_{10}N_4O_2$, respectively. The cyclic imide structures VIIa and VIIb may be assigned to these products, since the infrared spectra showed the presence of NH_2, C=C, and CONH (doublet in the amide carbonyl region).



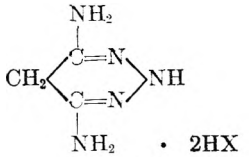
Alkaline hydrolysis of either the compound A or VIIa gave an identical compound, $C_6H_8N_4O_3$. Treatment of the hydrolyzed product with hydrochloric acid afforded VIIa. The infrared spectrum of the alkaline-hydrolyzed product showed the presence of NH_2, C=C, COOH, and CONH, so that the product is apparently either VIII or IXa. In structure VIII, the acidity of the carboxyl group may be

(2) R. A. Carboni, D. D. Coffman, and E. G. Howard, *J. Am. Chem. Soc.*, **80**, 2838 (1958).

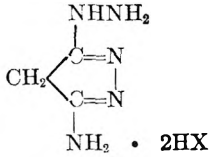
reduced owing to the influence of the neighboring amino group, while, in structure IXa, it may be strengthened by the effect of the C=N group in the ring. The pK_a value of the product formed by the alkaline hydrolysis was 3.5, being smaller (stronger in acidity) than that of acetic or benzoic acid. The assignment of structure IXa was also supported by the presence of C=O band of nonconjugated aliphatic carboxyl which was located at 1706 cm.$^{-1}$ for this compound.

Treatment of compound C and VIIb with alkali afforded an acid. The infrared spectra supported structure IXb, but the elemental analysis did not coincide with the calculated value.

The hydrochloride or hydrobromide of the oily substance B showed the infrared absorption bands of NH_2, CH_2, C=C, or C=N. The Schotten-



X



XI

Baumann benzoylation of these salts afforded tribenzoyl derivatives, but acetone did not react even with their free base. From these facts, the dihydrotriazine structure X seems to be most probable for this compound, although the isomeric pyrazole structure XI cannot be excluded at the present stage of investigation.

EXPERIMENTAL

3-Amino-4-cyano-5-(cyanomethyl)pyrazole (compound A). A solution of 6.6 g. of malononitrile in 20 ml. of ethanol was added to 5 ml. of 80% hydrazine hydrate. After the mixture was kept below 40° for 3 hr., ethanol was removed under reduced pressure. The residual slurry was washed with a little amount of ethanol to remove an oily substance B. Recrystallization from water afforded needles, m.p. 197°.

Anal. Calcd. for $C_6H_5N_5$: C, 48.98; H, 3.40; N, 47.62. Found: C, 48.35; H, 3.61; N, 47.03.

The infrared spectrum showed the presence of NH_2 (3420, 3360, 3230, 1654), nonconjugated C≡N (2245), conjugated C≡N (2200), and C=C (1598 cm.$^{-1}$).

An acetyl derivative was prepared by treating A with acetic anhydride in the presence of a trace of sulfuric acid and recrystallized from acetic acid, m.p. 276°.

Anal. Calcd. for $C_8H_7N_5O$: C, 50.79; H, 3.70; N, 37.03. Found: C, 50.50; H, 3.86, N, 36.77.

The infrared spectrum showed the N—H band of a secondary amide at 3280 cm.$^{-1}$.

4,6-Diamino-2,5-dihydro-1,2,3-triazine dihydrochloride (X). From the ethanol washing obtained in the above procedure, ethanol was removed under reduced pressure. To the residual red oil, concentrated hydrochloric acid was gradually added with cooling. The solid was recrystallized from 18% hydrochloric acid, m.p. 205° (dec.).

Anal. Calcd. for $C_3H_9Cl_2N_5$: C, 19.36, H, 4.84, N, 37.64. Found: C, 19.11; H, 4.78; N, 37.65.

The infrared spectrum showed the presence of NH_2 (3440, 3360, 1640), CH_2 (2920, 1458) and C=C or C=N (1600 cm.$^{-1}$).

A dihydrobromide was obtained by using hydrobromic acid in place of hydrochloric acid in the above procedure, m.p. 205° (dec.).

Anal. Calcd. for $C_3H_9Br_2N_5$: N, 25.43. Found: N, 25.89.

Benzoylation of the hydrochloride in water with benzoyl chloride and sodium hydroxide gave a gummy substance which was chromatographed from benzene on alumina. Elution with ethanol afforded tribenzoyl derivative of X which was recrystallized twice from dilute ethanol, m.p. 239°.

Anal. Calcd. for $C_{24}H_{19}N_5O_3$: C, 67.76; H, 4.47; N, 16.47. Found: C, 66.63; H, 4.51; N, 16.85.

3-Amino-4-cyano-5-(cyanomethyl)-2(or 1)-phenylpyrazole (compound C). A mixture of 26 g. of malononitrile and 22 g. of phenylhydrazine in 40 ml. of ethanol was heated at reflux for 3 hr. The solution was concentrated under reduced pressure and water was added. The resulting solid was recrystallized from ethanol, m.p. 169°.

Anal. Calcd. for $C_{12}H_9N_5$: N, 31.39. Found: N, 30.97.

The infrared spectrum showed the presence of NH_2 (3492, 3368, 3200, 1629), nonconjugated C≡N (2233), conjugated C≡N (2195), and C=C (1591 cm.$^{-1}$).

An acetyl derivative was prepared by treating C with acetic anhydride in the presence of a trace of sulfuric acid for 30 min., m.p. 168°.

Anal. Calcd. for $C_{14}H_{11}N_5O$: C, 63.39; H, 4.15; N, 26.41. Found: C, 63.04; H, 4.41; N, 26.36.

The infrared spectrum showed the N—H band of a secondary amide at 3280 cm.$^{-1}$.

A benzal derivative was prepared by heating with benzaldehyde in glacial acetic acid and recrystallizing from ethanol, m.p. 117°.

Anal. Calcd. for $C_{19}H_{13}N_5$: N, 22.51. Found: N, 22.77.

Acid hydrolysis of compound A and its alkaline hydrolysis product (IXa). A suspension of 2 g. of A or IXa (see below) in 25 ml. of concentrated hydrochloric acid was heated at reflux for 3 hr. Most of the starting solid material dissolved within 15 min., but other crystals soon appeared. Recrystallization from 18% hydrochloric acid gave the hydrochloride of VIIa, m.p. >360°.

Anal. Calcd. for $C_6H_7ClN_4O_2$: N, 27.66. Found: N, 28.10.

Treatment of the hydrochloride with water afforded free base which was recrystallized from water, m.p. >360°.

Anal. Calcd. for $C_6H_6N_4O_2$: C, 43.37; H, 3.62; N, 33.74. Found: C, 42.93; H, 3.45; N, 32.25.

The infrared spectrum showed the presence of NH_2 (3430, 3380, 3210, 1640), C=C (1595) and amide C=O (1700, 1682 cm.$^{-1}$).

Acid hydrolysis of compound C. A solution of 2 g. of C in 25 ml. of concentrated hydrochloric acid was heated at reflux for 2 hr., and neutralized with 10% sodium hydroxide. Recrystallization of the resulting solid from dilute acetic acid afforded crystals of VIIa, m.p. 258°.

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.51; H, 4.13; N, 23.14. Found: C, 59.41; H, 4.42; N, 23.15.

The infrared spectrum showed the presence of NH_2 (3468, 3380, 3180, 1620), C=C (1595) and amide C=O (1688, 1670 cm.$^{-1}$).

Alkaline hydrolysis of compound A and its acid hydrolysis product (VIIa). A solution of 7 g. of A or VIIa in 35 ml. of 10% sodium hydroxide was heated at reflux for 3 hr. The solution was neutralized with 10% hydrochloric acid and concentrated under reduced pressure to about 10 ml. of volume. Recrystallization of the resulting solid from water afforded the compound IXa, m.p. 208° (dec.).

Anal. Calcd. for $C_6H_8N_4O_3$: C, 39.13; H, 4.35; N, 30.44. Found: C, 39.37; H, 4.64; N, 30.68.

The infrared spectrum showed the presence of NH_2 (3455, 3370, 3200, 1640), C=C (1600), carboxyl C=O (1706), carboxyl OH (2600–2800), and amide C=O (1666 cm.$^{-1}$).

The infrared absorption shown in this report was observed in nujol or in KBr disks with a Koken Infrared Recording Spectrophotometer, Model DS 301.

Acknowledgment. The author is indebted to Prof. M. Ohta of Tokyo Institute of Technology for many helpful suggestions and to A. Kondo for the microanalyses of substances described in this report.

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[CONTRIBUTION FROM THE CAROTHERS RESEARCH LABORATORY, E. I. DU PONT DE NEMOURS AND CO.]

Synthesis of Diarylphosphine Oxides by the Friedel-Crafts Method

ARLEN W. FRANK

Received January 22, 1959

The reaction of mesitylene, durene, or pentamethylbenzene with phosphorus trichloride and aluminum chloride catalyst under conditions normally employed for the synthesis of primary phosphonous dichlorides gave instead good yields of secondary phosphine oxides (after hydrolysis). Small amounts of secondary phosphinic acids were obtained as by-products. The three new phosphine oxides were found to be exceptionally stable to oxidation. With a simpler aromatic hydrocarbon, ethylbenzene, the only secondary product obtained was the phosphinic acid.

Very few secondary phosphine oxides[1] (I) have been reported in the literature. Early attempts to prepare them by careful hydrolysis of phosphinous chlorides,[2] esters,[3] or amides[4] showed that they disproportionated readily, even under the mildest conditions, into equal parts of phosphine (II) and phosphinic acid (III).[5] When atmospheric oxygen was not excluded, the phosphine was oxidized and the only product found was the phosphinic acid.

$$\underset{\text{I}}{2R_2P(O)H} \longrightarrow \underset{\text{II}}{R_2PH} + \underset{\text{III}}{R_2P(O)OH}$$

In only two instances were secondary phosphine oxides obtained which were apparently stable to air. They were obtained by hydrolysis of the corresponding phosphinous chlorides (V). The reaction of phosphorus trichloride with dimethylaniline[6] at reflux temperature gave, among other products, a small amount of bis(*p*-dimethylaminophenyl)-phosphine oxide (I, R = $Me_2NC_6H_4$-): and 9,10-dihydro-10-phenophosphazine oxide[7] was isolated from the products of the reaction of phosphorus trichloride and diphenylamine[8] in a sealed tube at 200°.

A synthesis of aliphatic secondary phosphine oxides by treatment of dibutyl phosphite with the appropriate Grignard reagent was described by Williams and Hamilton,[9] but their attempts to extend this reaction to the aromatic series were unsuccessful. The synthesis of aromatic secondary phosphine oxides was recently accomplished by treatment of diethyl phosphite with a Grignard reagent[10] or an aryllithium compound.[11] The three phosphine oxides obtained by these methods (I, R = C_6H_5-, o-$MeOC_6H_4$- and *p*-$MeOC_6H_4$-) were readily oxidizable by hydrogen peroxide.

In the present work a series of diarylphosphine oxides of high oxidative stability were prepared by a method based on the Friedel-Crafts synthesis of aromatic phosphonous dichlorides (IV).[12]

$$RH + PCl_3 \longrightarrow \underset{\text{IV}}{RPCl_2} + \underset{\text{V}}{R_2PCl}$$

When this synthesis was applied without modification to durene, none of the expected product (IV, R = 2,3,5,6-Me_4C_6H-) was found. From the gum which was coprecipitated with the $AlCl_3$·-$POCl_3$ complex there were isolated two crystalline compounds, one acidic and the other neutral, identified as bis(2,3,5,6-tetramethylphenyl)phosphinic acid (III, R = 2,3,5,6-Me_4C_6H-) and bis-(2,3,5,6-tetramethylphenyl)phosphine oxide (I, R = 2,3,5,6-Me_4C_6H-), respectively. The acidic com-

(1) In the report of the ACS Nomenclature Committee on organophosphorus compounds, *Chem. Eng. News*, **30**, 4515 (1952), these compounds were named phosphine oxides when written $R_2P(O)H$ and phosphinous acids when written R_2POH. In this article they have been named as P^{IV} compounds rather than P^{III}, in keeping with their chemical character.

(2) A. Michaelis and L. Gleichmann, *Ber.*, **15**, 801 (1882).

(3) A. Michaelis and W. LaCoste, *Ber.*, **18**, 2109 (1885).

(4) A. Michaelis, *Ann.*, **315**, 43 (1901).

(5) The hydrolysis of di-*n*-octylphosphinous bromide and diphenylphosphinous chloride to the corresponding phosphine oxide without disproportionation was recently accomplished by R. C. Miller, private communication.

(6) R. K. Robins and B. E. Christensen, *J. Org. Chem.*, **16**, 324 (1951); see also M. Bourneuf, *Bull. soc. chim. France*, **33**, 1808 (1923); H. Raudnitz, *Ber.*, **60**, 743 (1927); G. M. Kosolapoff and J. S. Powell, *J. Chem. Soc.*, 3535 (1950).

(7) This compound has also been called 10-hydroxy-5(or 9),10-dihydrophenophosphazine.

(8) P. G. Sergeev and D. G. Kudryashov, *J. Gen. Chem. (U.S.S.R.)*, **8**, 266 (1938); see also A. Michaelis and A. Schenk, *Ber.*, **21**, 1497 (1888); *Ann.*, **260**, 1 (1890).

(9) R. H. Williams and L. A. Hamilton, *J. Am. Chem. Soc.*, **74**, 5418 (1952); **77**, 3411 (1955).

(10) B. B. Hunt and B. C. Saunders, *J. Chem. Soc.*, 2413 (1957).

(11) J. L. Willans, *Chem. & Ind. (London)*, **1957**, 235.

(12) B. Buchner and L. B. Lockhart, Jr., *Org. Syntheses*, **31**, 88 (1951); *J. Am. Chem. Soc.*, **73**, 755 (1951).

pound, obtained in much smaller amount, was considered to be a by-product of the hydrolysis of the intermediate phosphinous chloride to the phosphine oxide. Similar results were obtained when the phosphonous dichloride synthesis was applied to mesitylene or pentamethylbenzene.

Michaelis recognized many years ago that secondary organophosphorus compounds were sometimes produced in the Friedel-Crafts reaction of aromatic hydrocarbons with phosphorus trichloride. Diarylphosphinic acids were isolated from the petroleum ether–insoluble fractions of the reactions with ethylbenzene,[13] cumene,[14] and pseudocumene.[14] The yield from pseudocumene amounted to 20%. Since the experimental procedures have been considerably improved since Michaelis' time, particularly with respect to the removal of the aluminum chloride, it was of interest to see whether a secondary phosphine oxide could be isolated from one of these hydrocarbons, *e.g.*, ethylbenzene, with the aid of the newer techniques.[15]

When the phosphonous dichloride synthesis[12] was applied to ethylbenzene under the same conditions as for durene, the diaryl fraction isolated from the $AlCl_3 \cdot POCl_3$ complex was found to be completely alkali-soluble, and therefore contained no phosphine oxide.

The stability of the diarylphosphine oxides toward oxidizing agents increased markedly with increasing methyl substitution on the ring. The mesityl compound (I, R = $Me_3C_6H_2$-) was completely oxidized by alkaline ferricyanide in 30 min. at 80–90° and the duryl compound (I, R = Me_4C_6H-) in 2 hr., but the pentamethylphenyl compound (I, R = Me_5C_6) was only 14% oxidized in 17 hr.

The secondary phosphine oxides reported in the literature have sometimes been called phosphinous acids, and written with the phosphorus atom in the trivalent form. The chemical evidence accumulated in this article, including the very method of their isolation, supports the tetracovalent form for the phosphine oxides. Also, their infrared spectra (Table I) clearly show the presence of bands assigned[16] to P—H and to P→O and the absence of the P—OH band.

The phosphinic acid, bis(2,3,5,6-tetramethylphenyl)phosphinic acid, exhibited the same *P→O* doublet as the corresponding phosphine oxide, but the P—H band was replaced by the P—OH band.

TABLE I

INFRARED SPECTRA OF SECONDARY PHOSPHORUS COMPOUNDS

No.	R	P—H[a]	P → O[b]	P—OH[c]
I	$Me_3C_6H_2$-	2335	1175, 1189	—
I	Me_4C_6H-	2380	1160, 1190	—
I	Me_5C_6-	2340	1170	—
III	Me_4C_6H-	—	1160, 1175[d]	2500–2780

[a] Assigned[16] frequency, 2280–2440 cm.$^{-1}$ [b] 1200–1300 cm.$^{-1}$ [c] 2650–2700 cm.$^{-1}$ [d] This doublet was clearly resolved in a pressed potassium bromide disk spectrum.

EXPERIMENTAL

All of the reagents were the best commercially available and were used without further purification. The experiments were conducted in a well ventilated hood because of the possible toxicity of the phosphorus compounds, and where moisture-sensitive compounds were involved the operations were carried out as rapidly as possible. Melting points were not corrected. The infrared spectra were determined in Nujol mulls.

Phosphonous dichlorides, $RPCl_2$. The procedure described in *Organic Syntheses*[12] for the synthesis of phenylphosphonous dichloride from benzene was applied without modification to ethylbenzene, mesitylene, durene, and pentamethylbenzene. The aromatic hydrocarbon (0.3 mole) was mixed with 105 ml. (1.2 mole) of phosphorus trichloride and 53.3 g. (0.4 mole) of anhydrous aluminum chloride, and heated under reflux for 4 hr. with stirring and exclusion of moisture. The heat source was then removed and 37 ml. (0.4 mole) of phosphorus oxychloride was run in from a dropping funnel at a rate sufficiently rapid to maintain reflux. This caused the separation of a partly granular, partly gummy $AlCl_3 \cdot POCl_3$ complex. The mixture was heated another 30 min. to complete the reaction, allowed to cool, and diluted with 300 ml. of low boiling (30–60°) petroleum ether. The liquid was decanted through a sintered glass filter into a large round bottom flask under suction. The gummy $AlCl_3 \cdot POCl_3$ complex was washed twice with 100-ml. portions of petroleum ether and the washings added to the filtrate. These extractions were performed as rapidly as possible. The solids were saved for the isolation of the diaryl compounds, described below.

The low boiling liquids in the filtrate, mostly petroleum ether, phosphorus trichloride, and phosphorus oxychloride, were removed by distillation at atmospheric pressure. The phosphonous dichloride was then distilled through a 20 cm. Vigreux column under vacuum.

Ethylphenylphosphonous dichloride. Colorless liquid, 32.3 g. (52% yield), distilling at 70–82°/0.8 mm.

No phosphonous dichlorides were obtained under these conditions[17] from mesitylene, durene, or pentamethylbenzene. The recovery of unchanged hydrocarbon from mesitylene and pentamethylbenzene was 11.4 g. (32%) and 15.6 g. (35%), respectively, but from durene there was recovered only 5.7 g. of a low boiling liquid, b.p. 53°/5 mm., which did not crystallize when seeded with durene and was probably a mixture of isomerized hydrocarbons.[18]

Phosphinic acids, $RPH(O)OH$. Hydrolysis of 0.1 mole of the ethylphenylphosphonous dichloride with ethanol-water, carried out as described for phenylphosphonous dichloride,[19]

(13) A. Michaelis, *Ann.*, **293**, 261 (1896).

(14) A. Michaelis, *Ann.*, **294**, 1 (1897).

(15) A method for the quantitative determination of the ratio of primary to secondary products in the phosphonous dichloride synthesis, developed by G. M. Kosolapoff and W. F. Huber, *J. Am. Chem. Soc.*, **69**, 2020 (1947), does not distinguish phosphine oxides from phosphinic acids.

(16) D. E. C. Corbridge, *J. Appl. Chem. (London)*, **6**, 456 (1956).

(17) Using much longer reaction times (30–36 hr.) and different proportions of reagents, Michaelis[14] and W. C. Davies, *J. Chem. Soc.*, 462 (1935), have prepared mesitylphosphonous dichloride in 5 to 8% yield.

(18) Durene is known to isomerize under the influence of aluminum chloride; see D. Nightingale and F. Wadsworth, *J. Am. Chem. Soc.*, **63**, 3514 (1941).

(19) G. M. Kosolapoff and J. S. Powell, *J. Am. Chem. Soc.*, **72**, 4291 (1950).

gave an oily mixture of ethylphenylphosphinic acid isomers, from which the crystalline *p*- isomer was isolated by taking advantage of the insolubility of its sodium salt in acetone.[20]

p-Ethylphenylphosphinic acid. White crystals, 5.9 g. (35% yield), melting at 64–65.5°. The melting point was raised to 67–68° by recrystallization from benzene.[21] The acid formed a white crystalline sodium salt which was insoluble in acetone.

o- and m-Ethylphenylphosphinic acid. Colorless oil, 8.9 g. (52% yield). The sodium salt was also an oil and was soluble in acetone.

Phosphine oxides, $R_2P(O)H$. The diaryl compounds produced as by-products of the phosphonous dichloride synthesis described above were found to be coprecipitated with the granular $AlCl_3 \cdot POCl_3$ complex as gums. The smaller the amount of diaryl compounds produced, the more cleanly granular the complex. Whether the diaryl compounds, presumably in the form of phosphinous chlorides, were present in the free state (and simply insoluble in petroleum ether) or as $R_2PCl \cdot AlCl_3$ complexes was not determined. The phosphine oxides were isolated as follows.

The residue containing the $AlCl_3 \cdot POCl_3$ complex was decomposed cautiously by adding it in small portions to 1 l. of water in an open beaker. The reaction was vigorous and exothermic, and fumes of petroleum ether and hydrogen chloride were evolved. At the end of the addition a yellow gummy substance remained undissolved. The liquid was decanted, extracted with three 100-ml. portions of benzene and discarded. The gummy residue was rubbed with small portions of benzene until it dissolved. The benzene solutions and extracts were then combined, washed three times with water to remove most of the hydrogen chloride, extracted with dilute sodium hydroxide solution, again washed with water, filtered, and evaporated to dryness. The sodium hydroxide extracts were saved for the recovery of the diarylphosphinic acids.

Bis(2,4,6-trimethylphenyl)phosphine oxide. An almost colorless viscous oil, 25.5 g. (59% yield), soluble in benzene and ethanol but insoluble in water or sodium hydroxide solution.

Anal. Calcd. for $C_{18}H_{23}OP$: C, 75.50; H, 8.10; P, 10.82. Found: C, 74.83, 74.86; H, 7.87, 8.05; P, 10.53, 10.66.

Bis(2,3,5,6-tetramethylphenyl)phosphine oxide. A white crystalline solid, 20.1 g. (43% yield), soluble in benzene, ethanol, and chloroform, and insoluble in ethyl acetate, water, and sodium hydroxide solution. After two recrystallizations from benzene, the compound melted with decomposition at about 150°.

Anal. Calcd. for $C_{20}H_{27}OP$: C, 76.40; H, 8.66; P, 9.85. Found: C, 76.48, 76.19; H, 8.79, 8.34; P, 9.66, 9.60.

Bis(pentamethylphenyl)phosphine oxide. A white crystalline solid, 13.8 g. (27% yield). After two recrystallizations from benzene the compound melted with decomposition at 240°.

Anal. Calcd. for $C_{22}H_{31}OP$: C, 77.16; H, 9.12; P, 9.05. Found: C, 77.57, 77.32; H, 9.08, 9.27; P, 9.57, 9.34.

No phosphine oxide was obtained from ethylbenzene, as the diaryl fraction was completely soluble in alkali.

Phosphinic acids, $R_2P(O)OH$. The diarylphosphinic acids were isolated from the sodium hydroxide extracts (see above) by acidification with dilute hydrochloric acid and extraction with benzene.

Bis(ethylphenyl)phosphinic acid. A yellow gum, 15.0 g. (36% yield), probably a mixture of isomers. The acid formed a pale blue crystalline copper salt, as described by Michaelis.[13]

Bis(2,4,6-trimethylphenyl)phosphinic acid. A white crystalline solid, 2.4 g. (5% yield). After two recrystallizations from benzene the acid melted at 167–168°.

Anal. Calcd. for $C_{18}H_{23}O_2P$: C, 71.50; H, 7.67; P, 10.25. Found: C, 73.77; H, 8.00; P, 9.82.

Bis(2,3,5,6-tetramethylphenyl)phosphinic acid. A white crystalline solid, 2.0 g. (4% yield). After two recrystallizations from benzene the acid melted at 234–235°. It was soluble in hot benzene and hot ethanol, and insoluble in water.

Anal. Calcd. for $C_{20}H_{27}O_2P$: C, 72.70; H, 8.24; P, 9.38. Found: C, 72.71, 72.88; H, 8.41, 8.54; P, 9.38, 9.36.

In an earlier experiment the acid was prepared from the phosphine oxide by fractional crystallization from benzene, the acid being much the less soluble.

Bis(pentamethylphenyl)phosphinic acid. An amorphous substance, 2.3 g. (4% yield), which frothed when dried under reduced pressure.

Oxidation of the phosphine oxides. The oxidation of the phosphine oxides described above was desired to establish their relationship with the phosphinic acids. The initial experiments were performed on the duryl compound, bis-(2,3,5,6-tetramethylphenyl)phosphine oxide.

An attempted oxidation with alkaline hydrogen peroxide according to a method used with other phosphine oxides[10,11] failed, the phosphine oxide being recovered unchanged in almost quantitative yield. Another attempt with alkaline permanganate also failed because the oxidant was too vigorous. Oxidation was finally found to proceed smoothly with alkaline ferricyanide. At room temperature, a 70% yield of bis(2,3,5,6-tetramethylphenyl)phosphinic acid was obtained after 27 hr. and 26% of the phosphine oxide was recovered. At 80–90° the oxidation was complete in 2 hr. Details of the experimental procedure follow.

The diarylphosphine oxide (1 mmole) was slurried with a solution of 0.40 g. of sodium hydroxide and 0.66 g. (2 mmoles) of potassium ferricyanide in 50 ml. of water. The mixture was heated with stirring to 80–90° and held at that temperature until the phosphine oxide was all dissolved. The solution was then cooled, filtered to remove a small amount of rust-colored solid, acidified with hydrochloric acid, and extracted three times with benzene. The benzene extracts were combined, extracted twice with water, filtered, and evaporated to dryness.

The mesityl compound required 30 min. for complete oxidation, the duryl compound 2 hr., but the pentamethylphenyl compound was only 14% oxidized in 14 hr. The products in each case were identical to the acids isolated as by-products of the Friedel-Crafts reactions.

Acknowledgment. The author wishes to thank Miss R. A. Staszesky for taking and interpreting the infrared spectra, and Dr. J. O. Corner for his encouragement and interest.

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(20) An approximate measure of the ratio of isomers in the ethylbenzene reaction was also reported by G. M. Kosolapoff, *J. Am. Chem. Soc.*, **74**, 4119 (1952), using another method.

(21) Michaelis[13] gives m.p. 63–64°.

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

Studies in Organosilicon Chemistry. XXXVII. The Preparation of Dimethylsiloxy and Trimethylsiloxy Derivatives of Naphthalene

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By the action of trimethylchlorosilane and dimethyldichlorosilane, in the presence of pyridine, on 1-naphthol, 2-naphthol, and several dihydroxynaphthalenes, a series of ten methylsiloxynaphthalenes has been prepared in good yields.

By the interaction of trimethylchlorosilane, pyridine, and the appropriate naphthol or dinaphthol, the following compounds have been prepared and characterized: 1-trimethylsiloxynaphthalene (I), 2-trimethylsiloxynaphthalene (II), 5,8-dichloro-1-trimethylsiloxynaphthalene (III), bis(1,5-trimethylsiloxy)naphthalene (IV), bis(1,6-trimethylsiloxy)naphthalene (V), bis(2,3-trimethylsiloxy)naphthalene (VI) and bis(2,7-trimethylsiloxy)naphthalene (VII). From dimethyldichlorosilane there have been prepared dimethylbis(1-naphthoxy)silane (VIII), dimethylbis(2-naphthoxy)silane (IX) and dimethylbis(5,8-dichloro-1-naphthoxy)silane (X). Infrared absorption curves have been determined for each of these products.

Infrared absorption curves were determined for all ten products. Bellamy[3] has assigned the region 900–700 cm.$^{-1}$ to silicon-carbon absorption, 1250, 841, 756–754 cm.$^{-1}$ to trimethylsilyl and 1259, 814–800 cm.$^{-1}$ to dimethylsilylene. These correspond to 11.8–14.3, 8.0, 11.8, 13.2, 7.9, and 12.2–12.5 microns, respectively. Prominent bands in all of these assigned regions have been observed and are reported herein wherever they are not masked by solvent effects.

TABLE I

PHYSICAL PROPERTIES

	B.P.	Mm.	M.P.	n_D^{20}	d_4^t
I	98.0–102.3	3		1.5596	1.011 (24°)
	271.0–272.0	742 (1)		1.5590 (1)	1.000 (20°) (1)
II	98.2–101.0	8		1.5559	1.006 (24°)
III	174.8–177.5	4		1.5885	1.215 (25°)
IV			87		
V	167.2–169.0	5		1.5330	1.003 (25°)
VI	153.8–156.0	5	60–61		
VII			51–53		
VIII	155–160	11 (2)	55–57		
IX			60–61		
X			117–118		

Langer, Connell and Wender[1] have reported the formation of a number of trimethylsilyl ethers including 1-trimethylsiloxynaphthalene. Larsson[2] caused 1-naphthol to react with dimethyldiethoxysilane, obtaining dimethylbis(1-naphthoxy)silane.

In this work, three compounds have been prepared of the formula $ROSi(CH_3)_3$, four of the formula $R'(OSi(CH_3)_3)_2$ and three of the formula $(RO)_2Si(CH_3)_2$ where R is $C_{10}H_7$ or $C_{10}H_5Cl_2$ and R′ is $C_{10}H_6$ or $C_{10}H_4Cl_2$. Anhydrous benzene or diethyl ether was used as the solvent and anhydrous pyridine as the proton acceptor. As outlined in the experimental part, hydrolytic tests on 1-trimethylsiloxynaphthalene and 2-trimethylsiloxynaphthalene with water and with sodium hydroxide demonstrated unexpected resistance and stability. Hydrochloric acid, however, caused hydrolysis to the original naphthol and an insoluble silicon compound which was not identified.

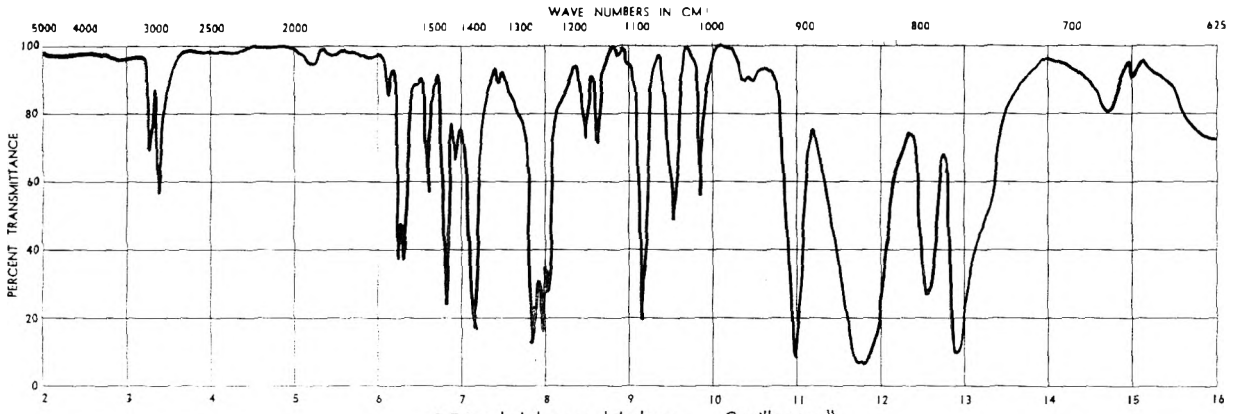
EXPERIMENTAL

1-Trimethylsiloxynaphthalene. 1-Naphthol (30.0 g., 0.208 mole) in 300 cc. of anhydrous ethyl ether in a 500 cc. three necked flask equipped with mercury sealed stirrer, thermometer, condenser, and calcium chloride tube, was treated with 24.7 g. (0.313 mole) of anhydrous pyridine, then dropwise with 33.7 g. (0.313 mole) of trimethylchlorosilane, with stirring. An immediate reaction occurred with the formation of a heavy white precipitate accompanied by a rise in temperature. The mixture was refluxed for 2 hr., then allowed to stand overnight. The precipitate of pyridine hydrochloride was filtered off and ether distilled from the filtrate. Distillation at reduced pressure first removed unreacted pyridine, then 1-trimethylsiloxynaphthalene distilled over, b.p. (found) 98.0–102.3° (2 mm.), (lit.) (1) 271.0–272.0°; n_D^{20} (found) 1.5596, (lit.) (1) 1.5590; d_4^{25} (found) 1.011, d_4^{20} (lit.) (1) 1.000.

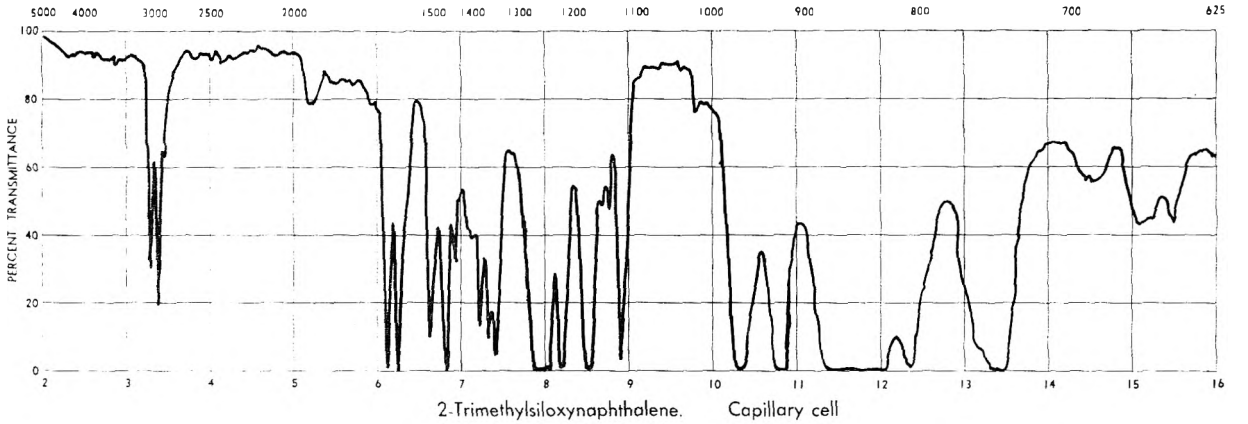
(1) S. H. Langer, S. Connell, and I. Wender, *J. Org. Chem.*, **23**, 50 (1958).

(2) E. Larsson, *Chem. Ber.*, **86**, 1382 (1953).

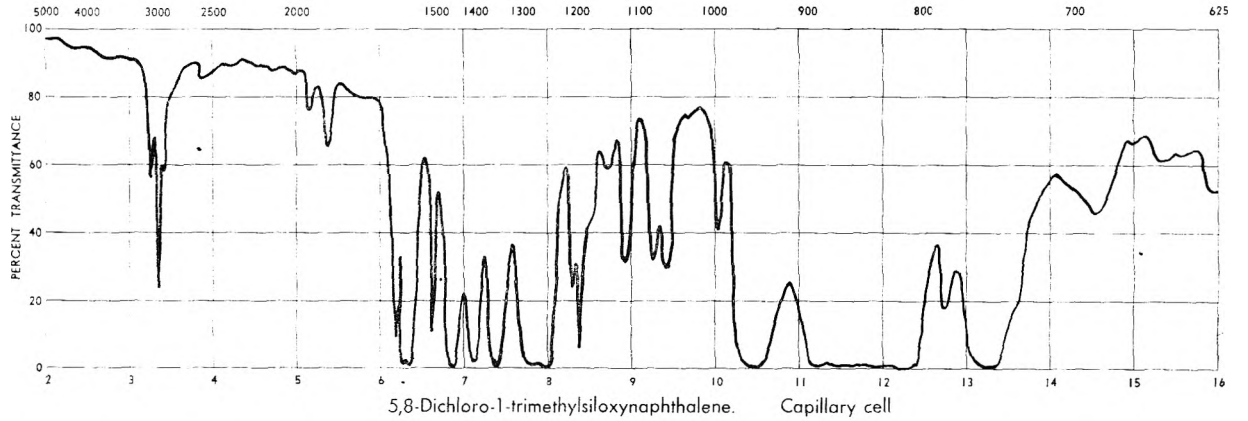
(3) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc. (1954).



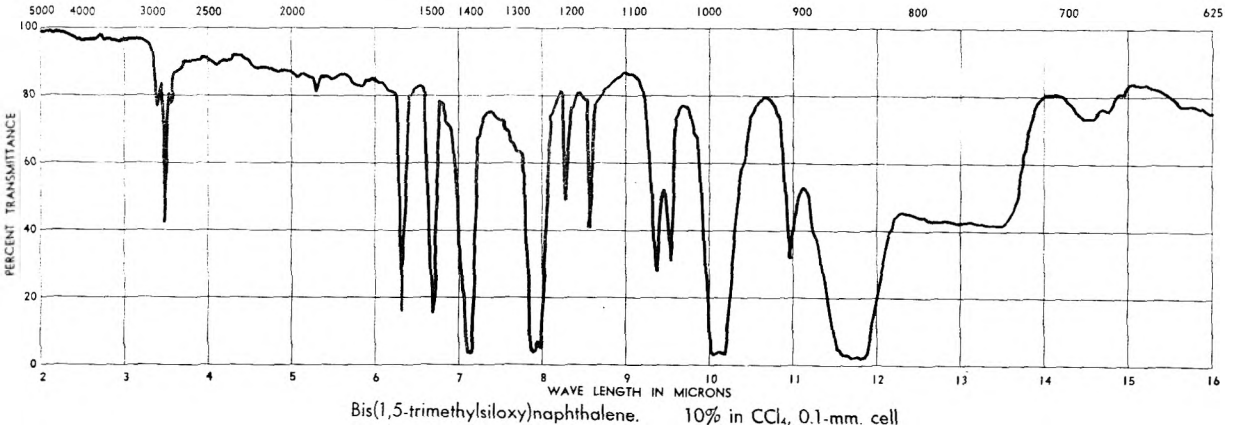
1-Trimethylsiloxynaphthalene. Capillary cell



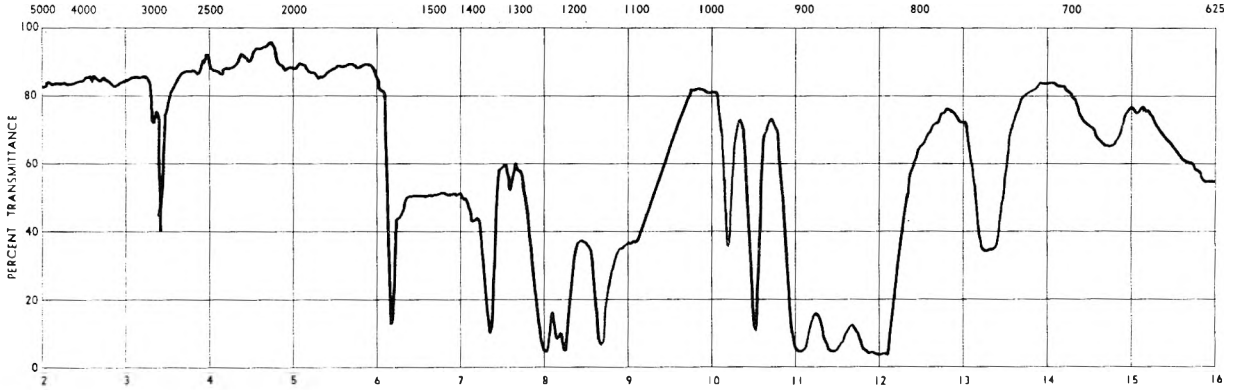
2-Trimethylsiloxynaphthalene. Capillary cell



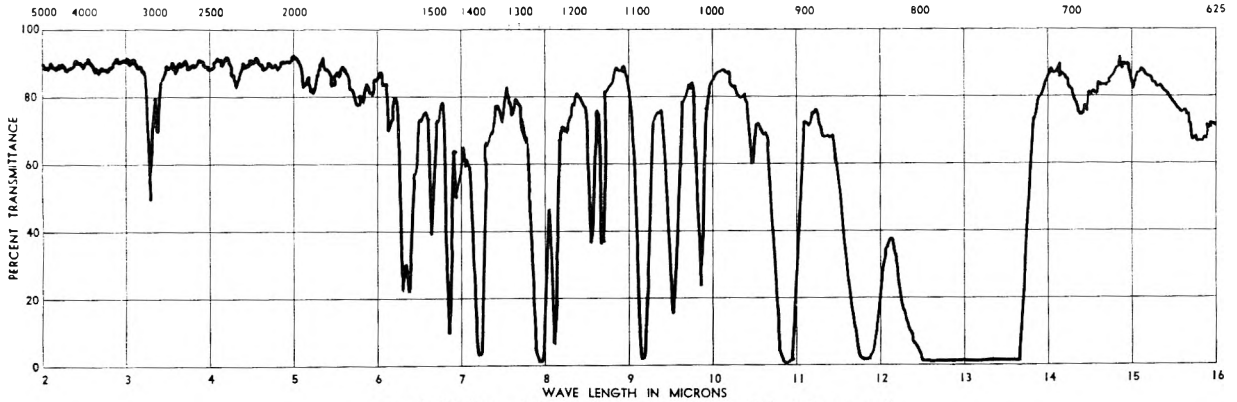
5,8-Dichloro-1-trimethylsiloxynaphthalene. Capillary cell



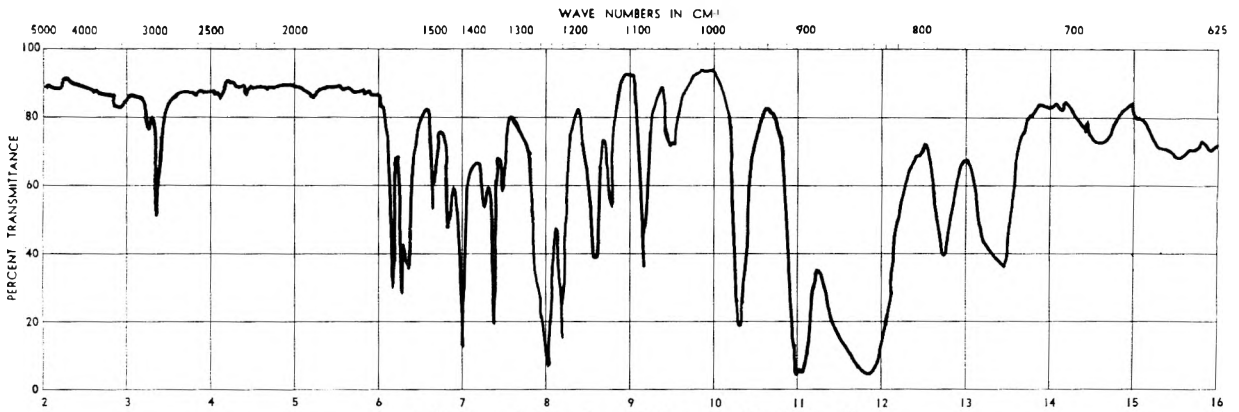
Bis(1,5-trimethylsiloxy)naphthalene. 10% in CCl_4, 0.1-mm. cell



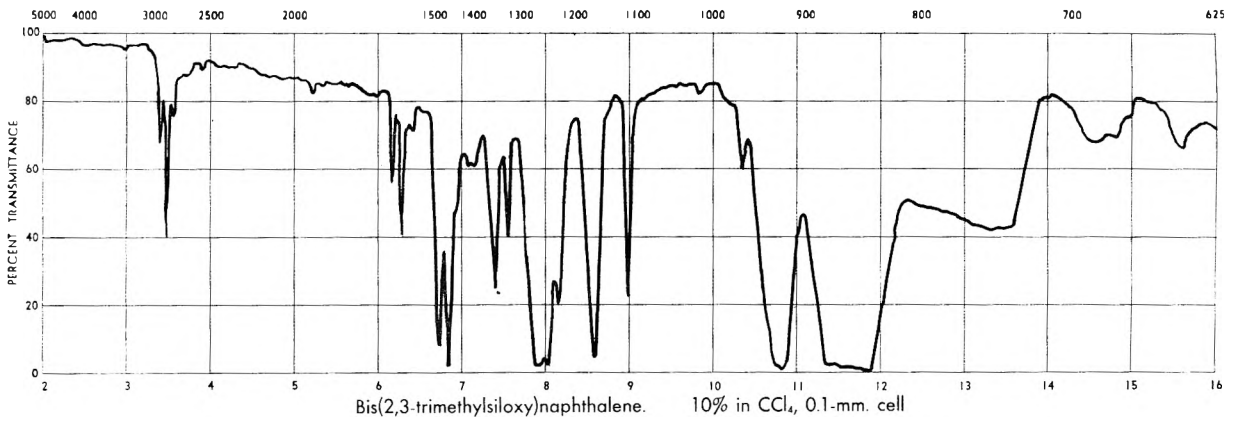
Bis(2,7-trimethylsiloxy)naphthalene. 5% in CS_2, 0.2-mm. cell



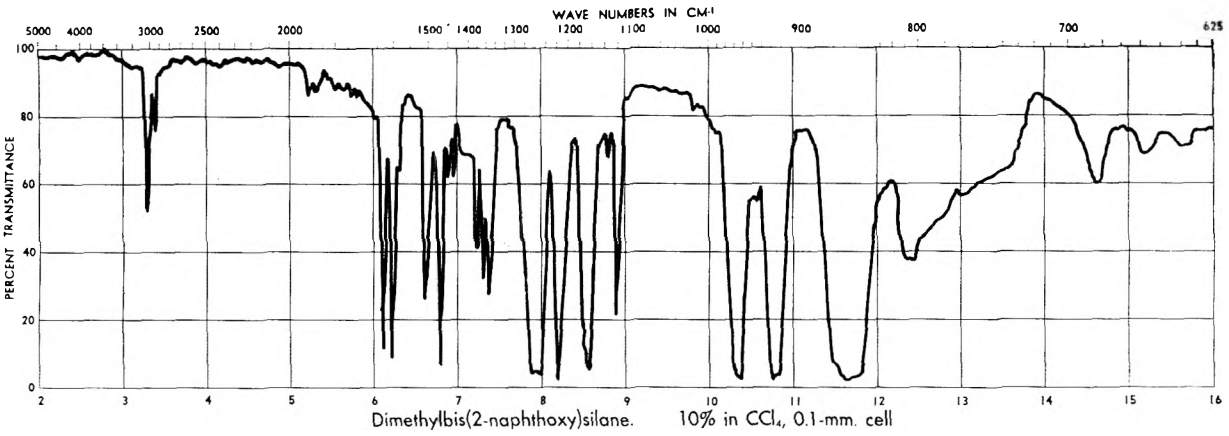
Dimethylbis(1-naphthoxy)silane. 10% in CCl_4, 0.1-mm. cell



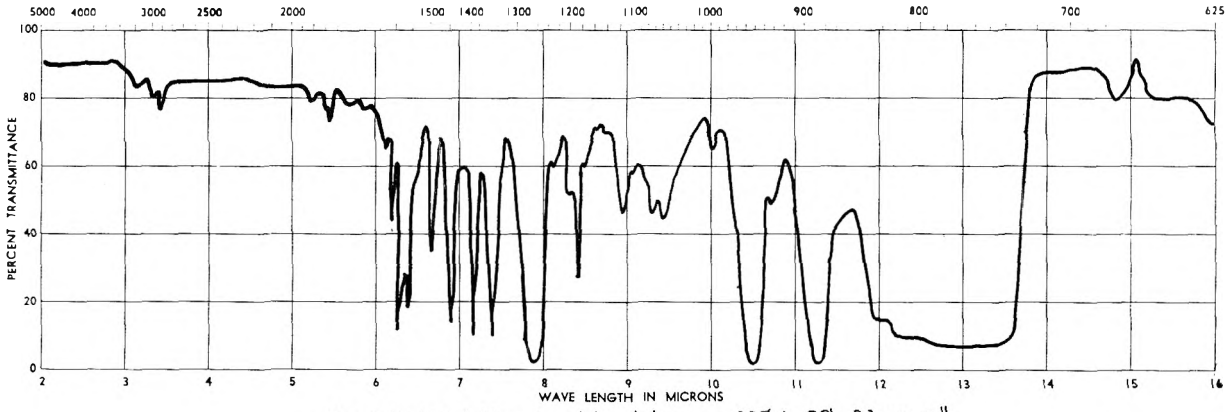
Bis(1,6-trimethylsiloxy)naphthalene. Capillary cell



Bis(2,3-trimethylsiloxy)naphthalene. 10% in CCl_4, 0.1-mm. cell



Dimethylbis(2-naphthoxy)silane. 10% in CCl_4, 0.1-mm. cell



Dimethylbis(5,8-dichloro-1-naphthoxy)silane. 10% in CCl_4, 0.1-mm. cell

TABLE II

ANALYTICAL DATA

	Si		Mol. Wt.		M.R.		Yield,	Cl	
	Calcd.	Found	Calcd.	Found	Calcd.	Found	%	Calcd.	Found
I	12.97	12.9 12.7	216	206	68.4	69.0	67		
II	12.97	12.6 12.7	216	203	68.4	68.9	71		
III	9.86	9.6 9.8	285	274	78.1	78.8	57	28.4	27.8 27.7
IV	18.42	18.4 18.5	304	297			5 4		
V	18.42	18.4 18.3	304	289	93.2	93.8	81		
VI	18.42	18.4 18.5	304	287			30		
VII	18.42	18.3 18.2	304	287			22		
VIII	8.14	8.1 8.2	344	330			35		
IX	8.14	8.1 8.2	344	326			30		
X	5.82	6.0 6.0	482	443			16	29.4	29.6 29.5

Anal. Calcd. for $C_{13}H_{16}OSi$: Si, 12.97; mol. wt., 216 M.R., 68.4. Found: Si, 12.9, 12.7; mol. wt., 206, M.R., 69.0.

The preparation of the other products followed the same general procedure. Benzene (300 cc.) was used as the solvent in the synthesis of compounds IV, V, and VI.

Hydrolytic tests. To 1-cc. portions of trimethylsiloxynaphthalene and its 2-isomer, was added respectively, 2 cc. of each of the following: distilled water, 0.08% sodium hydroxide (*p*H 13), 1% hydrochloric acid (C.P. 35%). Each was allowed to stand at room temperatures for 4 hr. One portion using water was kept at 110° in an oven for

the 4-hr. period. Each hydrolytic system was extracted with 5 cc. of chloroform and infrared curves were determined on the chloroform extract, after drying with a molecular sieve. No change in the infrared curves could be observed in any of the solutions except that from the action of hydrochloric acid in which a white precipitate had formed and absorption data here indicated the presence of the original naphthol as well as the silicon ether.

Trimethylchlorosilane and dimethyldichlorosilane were purchased from Dow Corning Corp. of Midland, Mich., and were always freshly distilled before using. Pyridine was obtained from Brothers Chemical Co., Orange, N. J., and made anhydrous by distilling and storing over potassium hydroxide pellets and a molecular sieve. Naphthalene derivatives were obtained through the courtesy of National Aniline Division, Allied Chemical and Dye Corp., Buffalo, N. Y.

Molecular weights were determined cryoscopically in benzene.

Molecular refractions were calculated from data supplied by Warrick.[4]

BUFFALO, N. Y.

(4) E. Warrick, *J. Am. Chem. Soc.*, 68, 2455 (1946).

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

Chlorination of Alkyl Disulfides and the Preparation of Thiolsulfonate Esters[1]

IRWIN B. DOUGLASS AND BASIL SAID FARAH

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Methyl methanethiolsulfonate has been prepared by the addition of 2 moles of chlorine to a cold mixture containing molar quantities of methyl disulfide and acetic acid, followed by the addition of 2 moles of water. During the chlorination reaction methanesulfenyl, acetyl and methanesulfinyl chlorides are formed. Hydrolysis of the latter forms methanesulfinic acid which combines immediately with methanesulfenyl chloride to form the thiolsulfonate ester. Mixed thiolsulfonate esters can be prepared by adding water to a reaction mixture containing sulfinyl and sulfenyl chlorides having different alkyl radicals.

The chlorination of mercaptans, disulfides, and other organosulfur compounds in the presence of water, or glacial or aqueous acetic acid has long been recognized as a superior method for the preparation of sulfonyl chlorides.[2-4] Occasionally, however, slight modifications in procedure have resulted in the formation of thiolsulfonate esters, RSO_2SR.[3-6]

Anhydrous chlorine acts on mercaptans and disulfides to form a variety of substances. The aromatic sulfenyl chlorides, RSCl, have been known for many years but only since World War II have the alkanesulfenyl chlorides been studied to any extent. The last decade has also seen the discovery of the organosulfur trichlorides, $RSCl_3$.[7,8] These latter compounds have been found to decompose into 1-chloroalkanesulfenyl chlorides, RCHClSCl, and to undergo solvolysis with the formation of sulfinyl chlorides, RSOCl,[9] and sulfinic acids, RSO_2H.

Disulfides, thus, can be transformed into sulfonyl chlorides, thiolsulfonate esters, sulfenyl chlorides, organosulfur trichlorides, 1-chloroalkanesulfenyl chlorides, sulfinyl chlorides, and sulfinic acids. The inter-relationships of these compounds and the reactions by which they are formed have been unfolding over the past few years but were not fully understood until recently when Stirling clearly established that thiolsulfonate esters are produced by the reaction of sulfenyl chlorides with sulfinic acids.[10,11]

The following diagram, modified from that of Stirling, represents the inter-relationships of the products from chlorinating alkyl disulfides. This chart emphasizes our finding that sulfinyl chlorides are intermediate solvolytic products between organosulfur trichlorides and sulfinic acids.[12] With few exceptions, the yields are nearly quantitative if the quantities of reactants are carefully controlled.

(1) Presented before the Organic Division of the A.C.S. at the 134th Meeting in Chicago, Ill., September 11, 1958.

(2) Th. Zincke and W. Frohneberg, *Ber.*, 42, 2721 (1909).

(3) I. B. Douglass and T. B. Johnson, *J. Am. Chem. Soc.*, 60, 1486 (1938).

(4) S. W. Lee and G. Dougherty, *J. Org. Chem.*, 5, 81 (1940).

(5) D. Barnard, *J. Chem. Soc.*, 1957, 4673.

(6) J. M. Stewart and H. P. Cordts, *J. Am. Chem. Soc.*, 74, 5880 (1953).

(7) K. R. Brower and I. B. Douglass, *J. Am. Chem. Soc.*, 73, 5787 (1951).

(8) I. B. Douglass, K. R. Brower, and F. T. Martin, *J. Am. Chem. Soc.*, 74, 5770 (1952).

(9) I. B. Douglass and D. R. Poole, *J. Org. Chem.*, 22, 536 (1957).

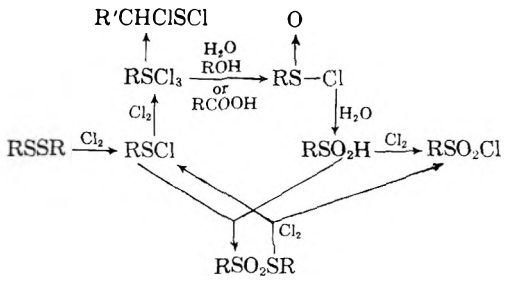
(10) C. J. M. Stirling, *J. Chem. Soc.*, 1957, 3597.

(11) Shortly before the appearance of the paper by Stirling, D. Barnard told the senior author he had observed that sulfenyl chlorides combine with sulfinic acids to form thiolsulfonate esters. Barnard's comment suggested the work reported in this paper.

(12) It is interesting that Zincke and Frohneberg[2] suggested, without experimental proof, that the transformation of 1,4-benzenedithiol into the corresponding disulfonyl chloride by treatment with chlorine in glacial acetic acid takes place through the intermediate steps:

$$(SC_6H_4S)_n \longrightarrow C_6H_4(SCl_3)_2 \longrightarrow C_6H_4(SOCl)_2 \longrightarrow C_6H_4(SO_2Cl)_2$$

thus anticipating the formation of organosulfur trichlorides and their solvolysis to sulfinyl chlorides.



The present paper is concerned with an excellent method for obtaining thiolsulfonate esters, utilizing sulfinyl chlorides, and the improved procedure which makes them so readily available.[13] In its simplest form the new method consists of allowing a sulfenyl chloride to react with a sulfinic acid produced by the action of water on a sulfinyl chloride. As described in the experimental part, the reaction may be carried out in various ways. Water can be added to an equimolar mixture of an alkanesulfenyl chloride and an alkanesulfinyl chloride. If both compounds contain the same alkyl radical a simple thiolsulfonate ester results, but if the sulfenyl and sulfinyl chlorides contain different alkyl radicals, mixed thiolsulfonate esters are formed. The products obtained by this method are practically colorless.

It is not necessary that the sulfenyl and sulfinyl chlorides be prepared separately before carrying out the reaction. If exactly 2 moles of chlorine is passed into a cold mixture containing 1 mole of disulfide and 1 mole of glacial acetic acid, the resulting reaction mixture contains both the sulfinyl and sulfenyl chlorides necessary for the subsequent hydrolysis and metathetical reactions:

$$CH_3SSCH_3 + CH_3COOH + 2Cl_2 \longrightarrow CH_3SOCl + CH_3SCl + CH_2COCl + HCl$$

$$CH_3SOCl + CH_3SCl + CH_2COCl + 2H_2O \longrightarrow CH_3SO_2SCH_3 + CH_3COOH + 3HCl$$

Such a procedure can be carried out rapidly and conveniently but the resulting product must be separated from acetic acid and is apt to be colored by unidentified yellow impurities which boil only slightly lower than the desired thiolsulfonate esters.

To prepare an unsymmetrical thiolsulfonate ester, the above procedure is modified by using three moles of chlorine to convert 1 mole of disulfide to the sulfinyl chloride. Then 1 mole of a different disulfide is added and chlorinated with one mole of chlorine to the sulfenyl chloride stage. Finally, addition of water hydrolyzes the sulfinyl chloride and forms the mixed thiolsulfonate ester.

The constitutions of the mixed thiolsulfonate esters, methyl ethanethiolsulfonate, $C_2H_5SO_2SCH_3$, and ethyl methanethiolsulfonate, $CH_3SO_2SC_2H_5$, were established by the use of a reaction reported by Douglass and Osborne.[14] The thiolsulfonate ester was chlorinated in inert solvent, forming a sulfonyl chloride and an organosulfur trichloride. The organosulfur trichloride was hydrolyzed, neutralized, and the resulting sodium alkanesulfinate caused to react with α-chlorotoluene to form an alkyl benzyl sulfone. The sulfonyl chloride, in turn, was treated with *p*-toluidine and identified through the resulting sulfon-*p*-toluidide.

EXPERIMENTAL

Preparation of methyl methanethiolsulfonate. In a three-neck flask, fitted with a stirrer and an outlet tube leading to a hydrogen chloride absorption trap were placed 47.1 g. of methyl disulfide (0.5 mole) and 30.0 g. of glacial acetic acid (0.5 mole) and the mixture was cooled to $-10°$ by an acetone–solid carbon dioxide bath. Exactly 71.0 g. of chlorine (1.0 mole) was condensed in a large test tube cooled to the temperature of Dry Ice, and the tube then connected to the inlet tube of the reaction flask. The liquid chlorine was allowed to boil spontaneously as it absorbed heat from the atmosphere or from the hand and the gas was introduced into the space above the surface of the reaction mixture.

When all of the liquid chlorine had evaporated the reaction mixture was reddish in color from the presence of methanesulfenyl chloride. At this time 19 ml. of water was slowly introduced into the cold reaction mixture while vigorous stirring was maintained. Immediate reaction ensued with the evolution of a large volume of hydrogen chloride. When the last of the water had been added, the color of the reaction mixture was only faintly yellow and, as stirring continued, faded to colorless. The cold bath was removed and stirring was continued while the reaction mixture warmed to room temperature.

The mixture was finally distilled under reduced pressure through a 12-in. Vigreux column and, after removal of acetic acid, yielded 55 g. (87%) of yellow product boiling 116–118° (16 mm.). Redistillation gave a colorless product boiling 114° (13 mm.) and having n_D^{25} 1.5112, d_4^{25} 1.3311, d_4^0 1.3567 and strong infrared absorption at about 1310, 1130, 955, and 750 cm.$^{-1}$

Anal. Calcd. for $C_2H_6O_2S_2$: C, 19.04; H, 4.68; S, 50.82. Found: C, 19.4, 19.64; H, 4.8, 4.7; S, 50.3, 50.5.

Preparation of ethyl methanethiosulfonate. Into the reaction flask previously described were introduced 23.5 g. methyl disulfide (0.25 mole) and 30.0 g. glacial acetic acid (0.5 mole), and the mixture was cooled to about $-10°$. In the same manner as previously described, 53.3 g. (0.75 mole) of chlorine was condensed in a large test tube and then allowed to evaporate into the reaction flask. When all the chlorine had been added the reaction mixture was only faintly yellow and consisted of methanesulfinyl and acetyl chloride together with dissolved hydrogen chloride.

Without disturbing the flask 30.6 g. of ethyl disulfide (0.25 mole) was added to the reaction mixture and an additional 17.8 g. of chlorine (0.25 mole), condensed as previously described, was allowed to evaporate into the flask. When all the chlorine had been added, 19 ml. of water (1.05 mole) was added slowly and the reaction mixture treated as previously described. Distillation under reduced pressure gave 57.6 g. (82%) of yellow liquid boiling 119–121° (16 mm.). Repeated redistillation gave a colorless product boiling at 115° (11 mm.) and having n_D^{25} 1.5018, d_4^{25} 1.2469, D_4^0 1.2721 and showing strong infrared absorption at about 1310, 1130, 955, and 750 cm.$^{-1}$

Anal. Calcd. for $C_3H_8O_2S_2$: S, 45.73. Found: S, 45.3, 45.7.

(13) I. B. Douglass and B. S. Farah, *J. Org. Chem.*, **23**, 330 (1958).

(14) I. B. Douglass and C. E. Osborne, *J. Am. Chem. Soc.*, **75**, 4582 (1953).

The structure of this liquid was established by chlorinolysis. Into two large test tubes, both cooled to the temperature of solid carbon dioxide, were weighed, respectively, 6.2 g. of the liquid believed to be ethyl methanethiolsulfonate and 5.7 g. of liquid chlorine. To each tube was added 15 ml. of previously chilled methylene chloride, and then the chlorine solution was quickly added to the solution of thiol ester. At first there was no evidence of reaction but slowly crystals began to form and in 20 min. the reaction appeared to be complete.

The resulting slurry of white crystals was quickly filtered by suction through a sintered glass crucible which had been chilled to the temperature of Dry Ice. The crystals were dissolved in glacial acetic acid, the solution was neutralized with aqueous sodium bicarbonate, and the alkaline solution refluxed for several hours with 4 ml. of benzyl chloride. On cooling, a solid separated, which, after recrystallizing from water, melted at 83–84° and at 84° when mixed with authentic ethyl benzyl sulfone.

The filtrate from the chlorination step was diluted with ether and treated with *p*-toluidine in presence of sodium bicarbonate solution. Alkaline extraction and acidification of the extract yielded methanesulfon-*p*-toluidide, melting at 103–104° and unchanging when mixed with an authentic sample.

Preparation of methyl ethanethiolsulfonate. The same procedure was followed as that described above for preparing ethyl methanethiolsulfonate except that the order of adding the disulfides was reversed. Ethyl disulfide (0.25 mole) was converted to ethanesulfinyl chloride and then methyl disulfide (0.25 mole) was added and chlorinated to methanesulfenyl chloride. Addition of water allowed the reaction to go to completion as already described. Distillation of the reaction mixture gave 58.6 g. (84% yield) of yellow product boiling at 120–122° (14 mm.). Repeated redistillation gave a colorless liquid boiling at 119° (13 mm.) and having n_D^{25} 1.5054, D_4^{25} 1.2593, D_4^0 1.2840 and showing strong infrared absorption at about 1310, 1125, 775, and 700 cm.$^{-1}$

Anal. Calcd. for $C_3H_8O_2S_2$: C, 25.70; H, 5.75; S, 45.73. Found: C, 25.5, 25.65; H, 5.94, 5.62; S, 45.7, 46.0.

The liquid thus obtained was shown to be methyl ethanethiolsulfonate by chlorinolysis as described above and by conversion of the chlorination products to ethanesulfon-*p*-toluidide, melting at 80–81° and methyl benzyl sulfone, melting at 125–126°. Both derivatives melted unchanged when mixed with authentic samples.

Preparation of methanesulfenyl chloride. Chlorine gas was led from a test tube, in which liquid chlorine (42.5 g., 0.6 mole) had been condensed, into 56.5 g. (0.6 mole) of well stirred methyl disulfide contained in a 500-ml. three-neck flask and held at −20° or lower. The chlorine inlet tube terminated well above the surface of the disulfide so that it would not become clogged with methylsulfur trichloride. When the last of the liquid chlorine had evaporated, the cold reaction vessel was shaken to bring unreacted methyl disulfide in contact with solid methylsulfur trichloride in order to convert both to methanesulfenyl chloride. Disappearance of solid indicated that the reaction was complete.

The product was not distilled but was kept at the temperature of solid carbon dioxide until used. The yield was nearly quantitative.

Preparation of methyl ethanethiolsulfonate (alternative methods). Ethanesulfinyl chloride[13] (22.5 g., 0.2 mole) and methanesulfenyl chloride (16.6 g., 0.2 mole) were mixed in the reaction flask already described and cooled to −10°. Exactly 3.6 g. of water (0.2 mole) was then added slowly from a medicine dropper and caused the reaction mixture to lose its color.

The mixture was warmed with stirring to room temperature and distilled through a 12-in. Vigreux column under reduced pressure. After 1.1 g. of slightly colored forerun there was obtained 21.4 g. (76.4%) of nearly colorless methyl ethanethiolsulfonate boiling at 125° (18 mm.).

Variations in procedure in which (1) the sulfenyl chloride was added dropwise to the hydrolyzed sulfinyl chloride and (2) the hydrolyzed sulfinyl chloride was added to the sulfenyl chloride made no significant difference in either yield or quality of product.

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ORONO, ME.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF KENTUCKY]

N-Sulfinyl Amines. Reaction with Carboxylic Acids[1]

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The previously reported reaction of *N*-sulfinylaniline with carboxylic acids to give acyl anilides has been shown to require the presence of hydrogen chloride. The sequence of steps involved in the overall reaction and the role of hydrogen chloride are described.

Carré and Libermann[2] reported that carboxylic acids react with *N*-sulfinylaniline to form the corresponding anilides:

$$C_6H_5NSO + RCO_2H \longrightarrow C_6H_5NHC(=O)-R + SO_2$$

As part of our study of the chemistry of *N*-sulfinyl amines, attempts were made to carry out the above reaction. It was found that when a solution of *N*-sulfinylaniline in acetic acid was refluxed as described by Carré and Libermann no sulfur dioxide was evolved and no acetanilide could be isolated from the solution. Since these results were contrary to those reported by Carré and Libermann, variations in the reaction conditions were studied and various other acids which reportedly reacted with *N*-sulfinylaniline were also tried, but without success.

N-Sulfinylaniline may be prepared by the action of thionyl chloride on aniline hydrochloride. This suggests the possibility that traces of either thionyl chloride or hydrogen chloride, or both, might be present as impurities in *N*-sulfinylaniline. To test the possibility that one of these impurities might have been acting as a catalyst in the experiments of Carré and Libermann the following experiments were performed.

When a mixture of *N*-sulfinylaniline and acetic acid containing a small amount of thionyl chloride was refluxed, there was obtained a 90% yield of acetanilide.

To show the possible catalytic effect of hydrogen chloride a mixture of *N*-sulfinylaniline and acetic acid was exposed to dry hydrogen chloride gas for a few minutes and then allowed to stand with suitable protection from moisture. A precipitate which almost immediately started to form completely dissolved in three days. At the end of seven days a new precipitate had formed. This second precipitate was identified as acetanilide and represented an 83% yield.

These results thus show the catalytic effect of both thionyl chloride and hydrogen chloride on the reaction of *N*-sulfinylaniline with acetic acid. Since thionyl chloride reacts with the carboxylic acid to give hydrogen chloride as one of the products, it appears that the catalytic effect of thionyl chloride is simply due to the fact that it does give rise to hydrogen chloride under the conditions used in the reaction.

A consideration of the possible role of hydrogen chloride as a catalyst for these reactions leads to the following possibilities:

I.
$$RCO_2H + HCl \rightleftharpoons RC(=O)-Cl + H_2O$$
$$C_6H_5NSO + H_2O \xrightarrow{HCl} C_6H_5NH_2\cdot HCl + SO_2$$
$$C_6H_5NH_2\cdot HCl + RC(=O)-Cl \longrightarrow C_6H_5NHC(=O)-R + 2HC$$

The possibility of the first step's taking place has to be considered, since the removal of water by reaction with C_6H_5NSO in the second step could drive the equilibrium of the first step to completion:

II.
$$C_6H_5NSO + HCl \longrightarrow C_6H_5NHS(=O)-Cl$$
$$C_6H_5NHS(=O)-Cl + RC(=O)-OH \longrightarrow$$
$$C_6H_5NHS(=O)-OH + RC(=O)-Cl$$
$$C_6H_5NHS(=O)-OH \xrightarrow{HCl} C_6H_5NH_2\cdot HCl + SO_2$$
$$C_6H_5NH_2\cdot HCl + RC(=O)-Cl \longrightarrow$$
$$C_6H_5NHC(=O)-R + 2HCl$$

III. In a variation of sequence II the initial step need not be represented as above, but simply as the formation of a "complex" between hydrogen chloride and *N*-sulfinylaniline. $C_6H_5NSO + HCl \rightarrow C_6H_5NSO\cdot HCl$. This complex, which may or may not have the structure shown in sequence II, might then react directly with the carboxylic acid

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under contract No. AF49(638)-49. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) P. Carré and D. Libermann, *Compt. rend.*, 194, 2218 (1932).

(3) A. Michaelis, *Ber.*, 24, 745 (1891).

$$C_6H_5NSO\cdot HCl + RCO_2H \longrightarrow C_6H_5NHC(=O)R + HCl$$

IV. $$C_6H_5NSO + 3HCl \longrightarrow C_6H_5NH_2\cdot HCl + SOCl_2$$

$$RCO_2H + SOCl_2 \longrightarrow RC(=O)Cl + SO_2 + HCl$$

$$C_6H_5NH_2\cdot HCl + RC(=O)Cl \longrightarrow C_6H_5NHC(=O)R + 2HCl$$

The first step in this sequence is essentially the reverse of the reaction usually used to prepare *N*-sulfinylaniline. It has been reported[2,3] that this reverse reaction does take place when dry hydrogen chloride is passed into pure *N*-sulfinylaniline. The subsequent steps are known reactions.

Of the above four sequences, three (I, II, and IV) postulate the presence of aniline hydrochloride as an intermediate. Several experiments indicate that aniline hydrochloride is indeed formed prior to the formation of acetanilide in the catalyzed reaction of *N*-sulfinylaniline with acetic acid. When a slight excess of thionyl chloride was added to a solution of *N*-sulfinylaniline in acetic acid there was almost immediate formation of crystals. These crystals were shown to be aniline hydrochloride. When this same mixture was allowed to stand overnight and then worked up as described above, acetanilide was obtained. These results explain the observations described earlier for the hydrogen chloride catalyzed reaction of *N*-sulfinylaniline with acetic acid in which the precipitate which formed at the start of the reaction later dissolved and was replaced by a new precipitate.

In an experiment under the above conditions, it was shown that in less than 15 min. a 64% yield of aniline hydrochloride was obtained. This result is particularly significant in demonstrating that aniline hydrochloride is an intermediate in the formation of acetanilide because this yield of aniline hydrochloride is nearly as great as would have been the yield of acetanilide if the reaction had been allowed to continue.

In a similar experiment the passage of dry hydrogen chloride into a solution of *N*-sulfinylaniline in xylene gave an 88% yield of aniline hydrochloride.

The above experiments established the presence of aniline hydrochloride as an intermediate in the overall sequence of reactions. On this basis, sequence III can be ruled out. Of the remaining possibilities only sequence IV involves the intermediate formation of thionyl chloride. Efforts to isolate thionyl chloride from some of the experiments described above in which aniline hydrochloride was formed were inconclusive. In order to show that thionyl chloride is formed from *N*-sulfinylaniline, a solution of *N*-sulfinylaniline in cyclohexane was exposed to dry hydrogen chloride for a short while and then distilled. The presence of thionyl chloride in the distillate was shown by means of vapor phase chromatography. To show that thionyl chloride is also formed in acetic acid the cyclohexane of the above experiment was replaced by acetic acid with essentially the same results.

The above experiments confirm the earlier observations[3,4] that the reaction given in step 1 of sequence IV can take place. Moreover, our experiments show that this reaction can occur under the same conditions in which *N*-sulfinylaniline reacts with carboxylic acids.

Since sequence IV is the only sequence in which both aniline hydrochloride and thionyl chloride are intermediates, it can be concluded that the steps involved in the reaction of *N*-sulfinyl amines with carboxylic acids are correctly described by sequence IV. It is not necessary that all of the acetanilide be formed from the reaction of aniline hydrochloride with acetyl chloride, since some reaction may take place directly with the acetic acid.

Anilides of the following acids were obtained by refluxing the acid with *N*-sulfinylaniline and a drop of thionyl chloride: formic, 44% yield; benzoic, 30% yield; chloroacetic, 65% yield, glutaric, trace of dianilide. These reactions are not peculiar to *N*-sulfinylaniline. The *N*-sulfinyl derivatives of *p*-nitroaniline and cyclohexyl amine are converted to the corresponding *N*-acetyl derivatives by refluxing in acetic acid containing a trace of thionyl chloride. The reaction of *p*-nitro-*N*-sulfinylaniline with acetic acid is more vigorous than the corresponding reaction of *N*-sulfinylaniline. Immediate reaction is noted and a 92% yield of *p*-nitroacetanilide is obtained. *N*-sulfinylcyclohexylamine gives only a 31% yield under similar conditions.

EXPERIMENTAL[5]

Acetanilide from N-sulfinylaniline and acetic acid. Thionyl chloride catalyst. To a solution of 5 g. (0.036 mole) of *N*-sulfinylaniline[3] in 15 ml. of glacial acetic acid was added 0.2 ml. (0.33 g., 0.003 mole) of thionyl chloride. The solution was refluxed for 2 hr., poured into water, and extracted with chloroform to give 4.4 g. (90%) of acetanilide, m.p. 113–114°, undepressed by mixture with an authentic sample.

Miscellaneous anilides. The following anilides were prepared as above from 1.2 g. of *N*-sulfinylaniline, 1 drop of thionyl chloride and the indicated amount of acid. Formanilide, m.p. 45–46° (44%) from 5 ml. formic acid. Benzanilide, m.p. 156–160° (30%) from 2.17 g. benzoic acid. ω-Chloroacetanilide, m.p. 133–134° (65%) from 1.76 g. chloroacetic acid. Glutaric dianilide, m.p. 221–223° (trace) from 0.94 g. glutaric acid.

Acetanilide from N-sulfinylaniline and acetic acid. Hydrogen chloride catalyst. A solution containing 1.2 g. (0.009 mole) of *N*-sulfinylaniline in 5 ml. of acetic acid was exposed to dry hydrogen chloride for 10 min. The solution was protected from moisture and allowed to stand. A precipitate which started to form almost immediately had completely dis-

(4) P. Carré and D. Libermann, *Bull. soc. chim. France*, 6, 579 (1939).

(5) Melting points were taken on a Fisher-Johns melting point block and are corrected.

solved at the end of 3 days. At the end of 7 days a new precipitate had formed. The mixture was then poured into water and extracted with chloroform to give 1.0 g. (83%) of acetanilide, m.p. 113–114°.

p-Nitroacetanilide from p-nitro-N-sulfinylaniline. To 5 ml. of glacial acetic acid and 0.1 ml. (0.17 g., 0.0015 mole) of thionyl chloride was added 1 g. (0.005 mole) of *p*-nitro-*N*-sulfinylaniline.[3] Immediate formation of crystals was noted, and after 15 min. of heating the mixture was completely solid. An additional 5 ml. of acetic acid was added and the mixture was allowed to stand for 30 min. The reaction mixture was then diluted with 100 ml. of water and extracted with chloroform. The solid which did not dissolve was removed by filtration and combined with that obtained from evaporation of the chloroform to give 0.9 g. (92%) of *p*-nitroacetanilide, m.p. 215–216°.[6]

N-Cyclohexylacetamide. A mixture of 5 ml. of acetic acid, 1.09 g. (0.0075 mole) of *N*-sulfinylcyclohexyl amine[7] and 0.1 ml. (0.17 g., 0.0015 mole) of thionyl chloride was refluxed for 2 hr., cooled, and extracted with chloroform to give 0.33 g. (31%) of *N*-cyclohexylacetamide, m.p. 103–104°.[8]

Aniline hydrochloride from N-sulfinylaniline. To a solution of 1.2 g. (0.009 mole) of *N*-sulfinylaniline in 5 ml. of acetic acid at 25° was added 1.65 g. (0.017 mole) of thionyl chloride. There was an immediate vigorous reaction resulting in the precipitation of 0.85 g. (74%) of aniline hydrochloride, m.p. 195–198°, undepressed by mixture with an authentic sample.

In another experiment a slow stream of dry hydrogen chloride was passed for 1 hr. into 10 g. (0.07 mole) of *N*-sulfinylaniline dissolved in 30 ml. of dry xylene at 25° to give 8.2 g. (88%) of aniline hydrochloride.

Detection of thionyl chloride. Solutions of *N*-sulfinylaniline in cyclohexane and in acetic acid were exposed to dry hydrogen chloride for 15 min. and then distilled. Vapor phase chromatography of both distillates and of authentic mixtures showed the presence of thionyl chloride.

LEXINGTON, KY.

(6) A. Kaufmann, *Ber.*, **42**, 3482 (1909).

(7) Donald Trimnell, Thesis, University of Kentucky, 1958.

(8) A. Baeyer, *Ann.*, **278**, 104 (1894).

[CONTRIBUTION FROM THE PIONEERING RESEARCH DIVISION, TEXTILE FIBERS DEPARTMENT, E. I. DU PONT DE NEMOURS & CO., INC.]

Reaction of an Isocyanate and a Carboxylic Acid in Dimethyl Sulfoxide

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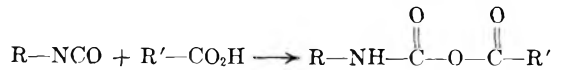
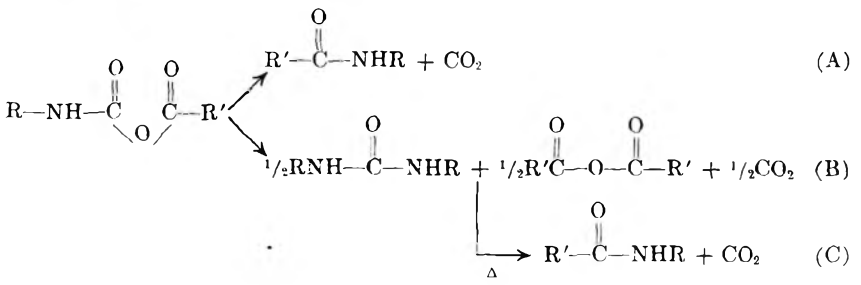
The reaction of an aromatic isocyanate or diisocyanate with benzoic acid in dimethyl sulfoxide as solvent has been found to give the urea or high molecular weight polyurea derived from the amine or diamine precursor of the isocyanate. The dimethyl sulfoxide takes part in the reaction also, forming the methylthiomethyl ester of benzoic acid. This fact, plus the observed stoichiometry of the reaction (2:1:1 for isocyanate:carboxylic acid:sulfoxide), precludes the operation in this case of the usual isocyanate-carboxylic reaction. A mechanism is proposed which accounts for the products formed.

Previous work[1] on the reaction of an isocyanate with a carboxylic acid in equimolar amounts has shown that the first product of the reaction is a mixed carbamic-carboxylic anhydride, which, in most cases, is not stable but in some instances can be isolated:



The decomposition of the mixed anhydride proceeds by two paths to give an amide in A (below), and in B a symmetrical urea and the anhydride of the acid.[2] Carbon dioxide is evolved in both cases. The products of path B, on heating to higher temperatures (135° or more) can react with each other to give the amide, path C.[2] Thus, under forcing conditions, the ultimate product of the reaction is the amide:



This over-all reaction has been used to prepare amides in good yields.[3]

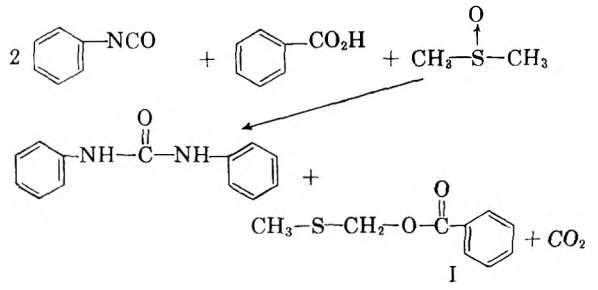
We would like to report here an unusual variant of the above reactions. If two moles of phenyl

(1) W. Dieckmann and F. Breest, *Ber.*, **39**, 3052 (1906).

(2) C. Naegli and A. Tyabji, *Helv. Chim. Acta*, **17**, 931 (1934); **18**, 142 (1935).

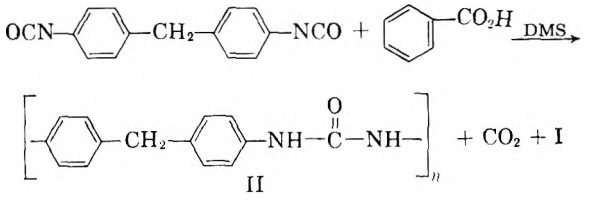
(3) C. L. Ayre, G. Dinga, and R. Pflaum, *J. Org. Chem.*, **20**, 695 (1955).

isocyanate, one mole of benzoic acid and one mole of dimethyl sulfoxide (DMS) are warmed together in benzene, *sym*-diphenyl urea, carbon dioxide and α-benzoyloxydimethyl sulfide I may be isolated.



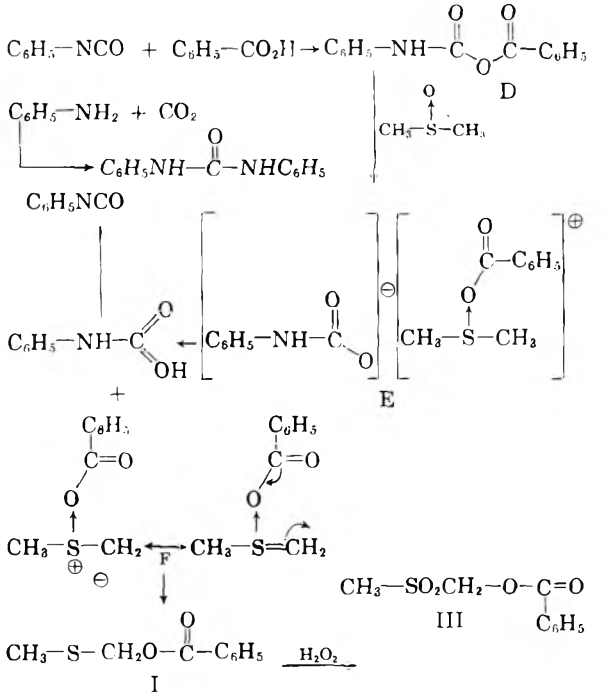
The sulfide-ester I was identified by elementary analysis, saponification equivalent, infrared absorption, oxidation to the corresponding sulfone (III). The melting point of the urea was undepressed in mixed melting with an authentic sample of *sym*-diphenyl urea. The yield of the urea was 70%, of I, 50%.

To demonstrate that the reaction is actually one of very high efficiency, one mole of methylene bis(4-phenyl isocyanate) and one mole of benzoic acid were brought together under strictly anhydrous conditions in excess DMS as solvent at room temperature. The reaction proceeded exothermally with evolution of carbon dioxide and formation of a viscous solution. The polyurea (II) was formed quantitatively in high molecular weight (inherent viscosity of 1.0, see Experimental). Tough films could be formed from the as-made solution by casting on a glass plate and drying in vacuum. The polyurea was identical with authentic II (see Experimental) in its infrared spectrum. No attempt was made to isolate the sulfide-ester I from this reaction.

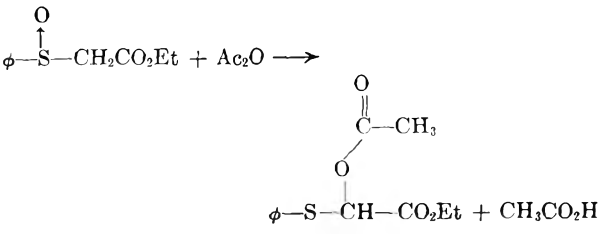


It is significant to note that the stoichiometry of the reaction reported here precludes the operation of path B of the usual isocyanate-acid reaction discussed originally in the formation of the products observed here. Where DMS is present, the stoichiometry of two —NCO groups to one —CO_2H is followed. Benzoic acid above this amount could be recovered from the polymer-forming reaction. A lesser quantity gave only low polymer. In the normal reaction one —NCO to one —CO_2H is required to form products in high yield. Unlike the normal reaction which produces an amide as the ultimate product, a urea is the ultimate product in our case. The quantitative formation of a high molecular weight polyurea in the case of the diisocyanate shows that the reaction must proceed uniformly by one course without side reactions, since high polymer-forming reactions are extremely sensitive to impurities, imbalances of reactants and chain terminating reactions. For example, any amide formation here would be a chain terminating reaction since a benzamide link would be the result.

A reasonable mechanism to account for the course of our reaction involves formation of a mixed carboxylic-carbamic anhydride, D, which subsequently reacts with DMS to give E, which decomposes to phenyl carbamic acid and resonance-stabilized F. The latter, by a cyclic process, rearranges to the sulfide ester (I). Phenyl carbamic acid decarboxylates to give aniline, which reacts with the second mole of isocyanate to form the urea. It is this part of the sequence that accounts for polymer formation in the case of the diisocyanate.



This reaction is similar to that of DMS with acid chlorides to give α-chlorodimethyl sulfide as noted by Bordwell,[4] and also to the reaction of carbethoxymethylphenyl sulfoxide with acetic anhydride as found by Pummerer.[5]



(4) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955).

(5) R. Pummerer, *Ber.*, **43**, 1401 (1901).

EXPERIMENTAL

α-Benzoyloxydimethyl sulfide (I). In 250 ml. dry benzene was placed 24.2 g. (0.2 mole) benzoic acid, 47.6 g. (0.4 mole) phenyl isocyanate, and 15.6 g. dimethyl sulfoxide. The mixture was refluxed overnight on a steam bath. After cooling, the solid was filtered and recrystallized from benzene-ether. It had a m.p. of 240–241° and was undepressed on admixture with authentic *sym*-diphenylurea. The melting point of the latter is given as 240° in the literature. The yield was 29.5 g. (70%).

The benzene filtrate was extracted once with 100 ml. of 10% sodium bicarbonate solution, and once with 100 ml. of water. Ten g. of benzoic acid was recovered by acidifying the extract. The benzene solution was dried over $MgSO_4$ and the benzene distilled off. The residue was distilled at reduced pressure to a slightly yellow liquid of b.p. 85–86°/0.1 mm. The weight was 10.5 g., or 50% yield based on unrecovered benzoic acid.

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.34; H, 5.48; S, 17.58; sapon. equiv., 182. Found: C, 59.4, 59.4; H, 5.2, 5.3; S, 17.6, 17.7; sapon. equiv., 176, 175.

The infrared spectrum of this compound had bonds at 3.3, 6.27, 6.34 and 6.74μ, indicative of an aromatic ring; at 5.83, 8.0, and 9.2μ for an aromatic ester; at 3.4–3.48μ for aliphatic C—H.

α-Benzoyloxydimethyl sulfone (III). Five g. of I was dissolved in 20 ml. *t*-butyl alcohol and heated to 85-90° in an oil bath. Ten ml. of 30% hydrogen peroxide was added and heating continued 1 hr. and 15 min. The *t*-butyl alcohol was distilled off at reduced pressure. The residue solidified on cooling. It was recrystallized three times from absolute ethanol to give 2.5 g. (43%) of the sulfone, melting at 105–106°.

Anal. Calcd. for $C_9H_{10}O_4S$: C, 50.46; H, 4.67; S, 14.95. Found: C, 50.4, 50.4; H, 4.5, 4.4; S, 14.7, 14.5.

Poly-bis(4-aminophenyl)methane carbonamide (II). In 20 ml. dry dimethyl sulfoxide was dissolved 2.42 g. (0.02 mole) benzoic acid. To it was added 5.0 g. (0.02 mole) methylene bis(4-phenylisocyanate). The reaction was allowed to proceed at room temperature with occasional shaking. The vessel was protected from moisture with a drying tube. In 3–4 hr., a clear, viscous yellow solution resulted. Clear, tough films were obtained by casting on glass plates and drying at 80° in a vacuum oven.

In another run, the polymer was precipitated into water, washed with water and methanol, then dried. The yield, 4.4 g., was quantitative. The inherent viscosity ($\eta inh = \frac{1}{c} \ln \frac{n}{n_0}$, where concentration is 0.5% in dimethyl sulfoxide at 25°) was 1.0.

The infrared spectrum obtained on a sample of the above film was identical to that of films of the polyurea obtained by mixing equimolar amounts of the diisocyanate and bis-(4-aminophenyl)methane in dimethylformamide and casting similarly.

If twice the amount of benzoic acid was used as given above, the reaction proceeded as above. The polymer was precipitated in methylene chloride, filtered, and washed thoroughly with more methylene chloride. The weight of polymer was again 4.4 g. The combined methylene chloride was extracted with 5% aqueous sodium bicarbonate solution, which was, in turn, extracted with ether. Acidification of the aqueous layer precipitated 2.2 g. of benzoic acid, virtually all that was in excess. When this procedure was carried out on a polymer solution made as described originally, with no excess benzoic acid present, no benzoic acid was recovered.

When benzoic acid was added portionwise to a solution of the diisocyanate in DMS, a maximum solution viscosity was achieved at 1:1 molar equivalence, beyond which no viscosity change occurred nor carbon dioxide evolved.

That carbon dioxide was evolved from the reaction was established by passing the evolved gas from a typical reaction through a calcium hydroxide solution. The familiar milky precipitate formed. No quantitative measure was made.

WILMINGTON, DEL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Synthesis of Urushenol, the Mono-olefinic Component of the Allergenic Principles of Poison Ivy and Japanese Lac

BERNARD LOEV[1] AND CHARLES R. DAWSON

Received January 12, 1959

The synthesis of urushenol has made available for clinical study for the first time one of the olefinic catechols that make up the allergenic principle of poison ivy and Japanese lac. The catechol hydroxyl groups are protected by benzylation during the construction of the olefinic side chain. The benzyl ethers are subsequently cleaved, and a double bond of the styrene type is simultaneously reduced, by means of sodium and butanol. The desired Δ8 olefinic bond is not altered during the reductive cleavage. It is believed that the method will be adaptable to the synthesis of the higher olefinic components of poison ivy urushiol.

It has been known for over twenty years that the toxic principle of poison ivy is chemically similar to Japanese lac urushiol.[2,3] Only recently, however, has the complete structure of each of these allergenic oils been elaborated.[4,5] Because of the extreme sensitivity of these compounds and for other

(1) This paper is based on a portion of the thesis submitted by Bernard Loev in 1952 to Columbia University in partial fulfillment of the requirements for the Ph.D. degree in Chemistry. Present address: Smith Kline and French Laboratories, Philadelphia, Pa.

(2) R. Majima and co-workers, *Ber.*, **55**, 172 (1922) and preceding papers.

(3) G. A. Hill, V. Mattacotti, and W. D. Graham, *J. Am. Chem. Soc.*, **56**, 2736 (1934).

(4) W. F. Symes and C. R. Dawson, *J. Am. Chem. Soc.*, **76**, 2959 (1954).

(5) S. V. Sunthankar and C. R. Dawson, *J. Am. Chem. Soc.*, **76**, 5070 (1954).

reasons pointed out previously,[6,7] none of the pure olefinic components of the poison ivy principle has been available heretofore, either from natural sources or by synthetic means, for clinical investigation. Consequently there has been interest in the development of a method of synthesis for such alkenyl phenols. The primary obstacle has been the extreme sensitivity of these compounds to polymerization by heat and acids. Recently a method of protecting phenolic groups by benzylation followed by removal of the benzyl groups by reductive cleavage using sodium and butanol has been described.[7] This development has made possible the synthesis of urushenol, described in this communication.

Urushenol,[8] the mono-olefinic component of both the lac and poison ivy urushiols has been shown to have the structure of 3-(8′-pentadecenyl)catechol[4,5] (V in Fig. 1). The olefinic bond in the side chain has the *cis* configuration, as do the higher olefinic components of the poison ivy "urushiol".[6]

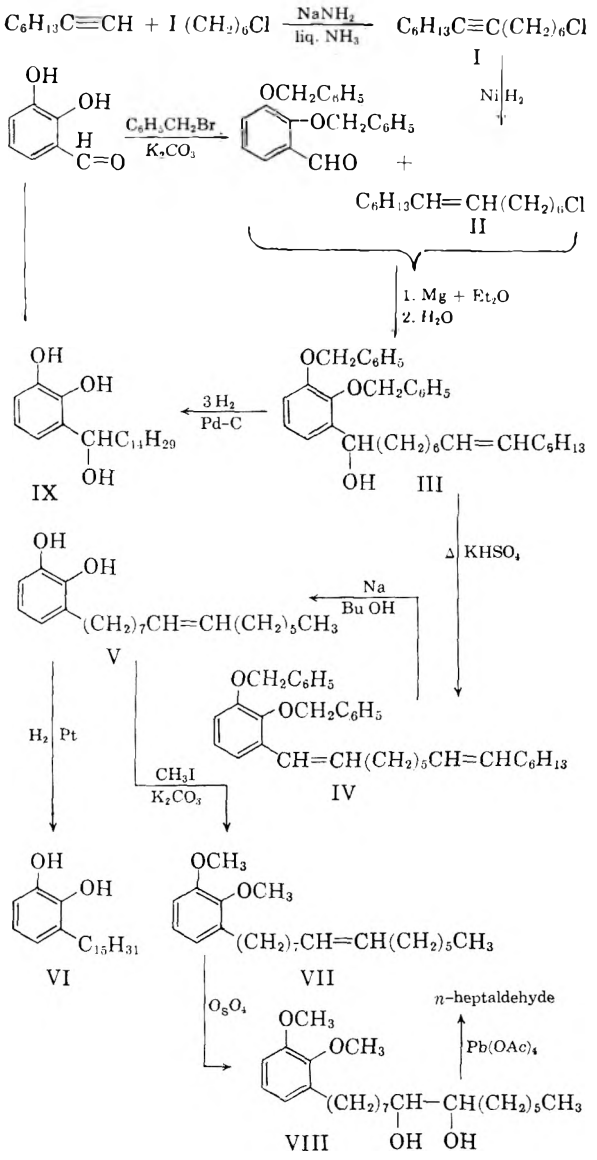


Fig. 1. Schematic diagram of the synthesis and confirmation of structure of urushenol (V)

The method of synthesis (Fig. 1), is partly based on a route developed earlier[6] in these laboratories for the synthesis of ethers of alkenyl phenols.[9] Most noteworthy in our synthesis is the use of benzyl rather than methyl ethers for protecting the phenolic hydroxyl groups during the Grignard reaction (see formation of III), and the subsequent removal of the benzyl groups by reaction with sodium and butanol with *simultaneous* reduction of the styrene type double bond[7] *without affecting the isolated olefinic bond* (IV → V). In the new synthesis, the olefinic side chain (II) is made up before utilizing the Grignard reaction, whereas in the earlier syntheses[9] of urushenol dimethyl ether the side chain was built up stepwise after introduction on the ring.

The acetylenic chloride (I), synthesized in a manner similar to that frequently used in the synthesis of unsaturated fatty acids,[10] exhibited some very interesting properties. Although it readily absorbed two moles of hydrogen on catalytic hydrogenation to give tetradecyl chloride, its infrared spectrum showed no absorption peak at 4.5 μ, the point where many acetylenes show absorption.[11] Furthermore it reacted only very slowly with bromine and was extremely resistant to permanganate oxidation and to ozonolysis. (Stearolic acid resisted bromination and ozonolysis under the same conditions.) The acetylenic chloride could not be induced to form the Grignard reagent even after careful purification nor when activated magnesium[12] and extensive refluxing were employed.

Similar peculiar properties of non-terminal acetylenes have previously been described.[13] Thus Wotiz and Miller[14] reported that the infrared ab-

(6) B. Loev and C. R. Dawson, *J. Am. Chem. Soc.*, **78**, 1180 (1956).

(7) B. Loev and C. R. Dawson, *J. Am. Chem. Soc.*, **78**, 6095 (1956).

(8) See footnote 5 in ref. (6) for discussion of nomenclature.

(9) For another method of synthesis of alkenylveratroles and anisoles see D. Wasserman and C. R. Dawson, *J. Org. Chem.*, **8**, 73 (1943) and M. Sletzinger and C. R. Dawson, *J. Org. Chem.*, **14**, 849 (1949).

(10) K. Ahmad, F. M. Bumpus, and F. M. Strong, *J. Am. Chem. Soc.*, **70**, 3391 (1948); W. R. Taylor and F. M. Strong, *J. Am. Chem. Soc.*, **72**, 4263 (1950); W. F. Huber, *J. Am. Chem. Soc.*, **73**, 2730 (1951).

(11) These spectra are available in the dissertation of Bernard Loev, a microfilm copy of which may be obtained from the Columbia University Library.

(12) H. W. Underwood and J. C. Gale, *J. Am. Chem. Soc.*, **56**, 2117 (1934); H. Gilman and R. H. Kirby, *Rec. trav. chim.*, **54**, 577 (1935).

(13) A. W. Ralston, *Fatty Acids and their Derivatives*, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 163; R. Kuhn and K. Meyer, *Z. Physiol. Chem.*, **185**, 195 (1929); A. Steger and J. Van Loon, *Rec. trav. chim.*, **52**, 593 (1933).

(14) J. H. Wotiz and F. A. Miller, *J. Am. Chem. Soc.*, **71**, 3441 (1949).

sorption of the C≡C bond is most intense when the triple bond is near the end of the chain. When the triple bond is more than three positions from the end of the chain its infrared absorption becomes practically undetectable.

The olefinic chloride (II), prepared by the controlled reduction of I, behaved in a normal manner, *i.e.*, the olefinic bond was readily detected in the infrared, and II rapidly decolorized bromine. The olefinic chloride was readily oxidized by permanganate and ozone but formed the Grignard reagent rather slowly.

Partial reduction of the acetylene (I) using 10% palladium-on-charcoal, or 5% palladium-on-calcium carbonate as prepared by the method of Busch and Stove,[15] gave a mixture containing a large quantity of *trans* olefin, as indicated by the intense absorption at 10.4 μ in the infrared spectrum of the reduction product.

Partial reduction of I using either Raney nickel W-5 catalyst[16] or a palladium-on-calcium carbonate catalyst as described by Lindlar[17] gave predominantly the *cis* olefin. The presence of a small amount of *trans* olefin in the reduction product was revealed by a small 10.4 μ peak in the infrared spectrum.[11]

Preparation of the Grignard reagent of II required a twenty-four hour refluxing period under strictly anhydrous conditions. Addition of the 2,3-dibenzyloxybenzaldehyde to the refluxing Grignard reagent produced the expected olefinic alcohol (III) in better than 80% yield. A sample of III, purified by chromatography on alumina, was catalytically hydrogenated. The product (IX) proved to be identical to the alcohol obtained by direct reaction of tetradecylmagnesium bromide with 2,3-dihydroxybenzaldehyde.[18]

The crude olefinic alcohol (III) was dehydrated by heating with potassium bisulfate in a nitrogen atmosphere. We had previously shown that these dehydrating conditions have no effect on the position or configuration of the isolated double bond in the $\Delta 8$ position.[6] Treatment of a butanol solution of the crude diene (IV) with excess sodium caused simultaneous reduction of the olefinic bond conjugated with the ring and reductive cleavage of the benzyl ether groupings. The crude product (V), 3-(pentadecenyl-8′)-catechol or "urushenol," was obtained in excellent yield. However, on vacuum distillation a large portion polymerized to a black solid residue. Despite the large loss at this step the overall yield in the synthesis from II to purified V was 28%. The urushenol as distilled was practically colorless, but rapidly became a pale golden yellow in the receiver. On exposure to air it soon turned dark.

The structure of the synthetic urushenol (V) was confirmed in a number of ways. On catalytic reduction, V absorbed one mole of hydrogen to give hydrourushiol (3-pentadecylcatechol), VI, identified by mixed melting point with an authentic sample. Methylation of V gave dimethylurushenol (VII) having a refractive index in good agreement with that reported by Symes and Dawson[4] for the dimethyl ether of natural urushenol. The position of the double bond in the side chain of V was established by the method of synthesis, by the conversion of V to the known solid glycol VIII, and by oxidation of this glycol to give a quantitative yield of *n*-heptaldehyde.

The ultraviolet absorption spectra of the synthetic poison ivy urushenol (V) and of hydrourushiol (VI) were found to be identical, and characterized by an absorption band at 277 mμ. The dimethyl ethers of the natural and the synthetic urushenols also had identical ultraviolet absorption spectra, characterized by two bands, at 272 mμ and 278 mμ.[11]

The infrared absorption spectra of the synthetic urushenol and of hydrourushiol were very similar. Likewise the infrared absorption spectra of the dimethyl ethers of the natural and the synthetic urushenols were essentially identical except for the presence of a small absorption band at 10.4 μ in the synthetic material.[11] The intensity of this band was about the same as found in the spectra of the olefinic halide (II) used for the Grignard reaction. Consequently it may be inferred that no significant isomerization of the double bond occurred during steps in the synthesis subsequent to the Grignard reaction.

V gave a momentary green color rapidly turning black, when treated with ferric chloride solution, and gave a dense white precipitate with methanolic lead acetate solution. On application to the skin (B.L.) it caused within a few hours the marked edema and blistering characteristic of poison ivy dermatitis. Each of these properties is the same as has been observed with the natural urushiol. Treatment of the synthetic urushenol (V) with dilute aqueous mineral acid caused extensive isomerization from the *cis* to *trans* configuration of the olefinic bond as evidenced by the appearance of a large absorption peak at 10.4 μ in the infrared spectra.[11] The isomerized (*trans*) material caused a typical poison ivy rash and the pale golden

(15) M. Busch and H. Stove, *Ber.*, **49**, 1063 (1916).

(16) H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, **70**, 695 (1948).

(17) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(18) We had originally hoped to be able to carry out the synthesis *without* the use of any protecting group. In order to test this route, we carried out the synthesis of IX by reaction of myristyl magnesium bromide with unprotected 2,3-dihydroxybenzaldehyde (see Exptl.). Although this first step proceeded in a surprisingly good yield, this route had to be abandoned when all attempts to dehydrate IX led only to polymeric materials,[7,19] even though dehydration of the corresponding monohydric phenols had been successfully carried out.[19]

(19) B. Loev and C. R. Dawson, *J. Am. Chem. Soc.*, **78**, 4083 (1956).

liquid solidified at about 10° (the *cis* isomer remains liquid when maintained at this temperature).

EXPERIMENTAL

1-Chlorotetradecyne-7 (I). Into a solution of 0.15 g. hydrated ferric nitrate in 1 l. of liquid ammonia was added portionwise a total of 8.6 g. (0.375 mole) of sodium. When all the sodium had been converted to sodamide[20] (90 min.) the color of the mixture was a gray-brown. After stirring the mixture for an additional hour, 41 g. (0.375 mole) of octyne-1[21] (b.p. 122–126°, n_D^{27} 1.440) was added over a period of 2 hr. The thick white precipitate which gradually formed during the addition was stirred for another hour before adding, dropwise, 92.3 g. (0.375 mole) of 1-chloro-6-iodohexane [b.p. 83–84° (2 mm.), n_D^{25} 1.5178] prepared as described by Gensler *et al.*[22] The mixture, which soon became transparent and colorless with a dark brown gum coating the sides of the flask, was stirred overnight (volume 300 cc.). On the slow addition of a cold dilute ammonium chloride solution a white precipitate formed which dissolved as more solution was added. The mixture then separated into a brown organic layer and a colorless aqueous layer. The organic material was taken up in ether, washed several times with water, once with dilute hydrochloric acid, and once with sodium thiosulphate. The ethereal solution was dried, and the ether and unreacted octyne-1 were removed by distillation, *in vacuo*, leaving 75.5 g. of an orange oil. Distillation of this oil gave 62.4 (73% yield) of I, b.p. 117–122° (2 mm.). This material was redistilled through a 23″ Widmer fractionating column, giving the 1-chlorotetradecyne-7 as a colorless liquid, b.p. 121–22° (1.5 mm.), n_D^{22} 1.4628.

Anal. Calcd. for $C_{14}H_{25}Cl$: C, 73.49; H, 11.01; Cl, 15.50. Found: C, 73.43; H, 11.01; Cl, 15.67.

A sample of I on prolonged reduction with W-5 nickel catalyst[16] or palladium-on-charcoal, absorbed two equivalents of hydrogen, giving tetradecyl chloride, n_D^{24} 1.4439 (lit.[23] n_D^{20} 1.4450).

A solution of I and potassium permanganate in acetone was refluxed for 1 hr. Upon working up the reaction mixture, I was recovered almost quantitatively. I was also recovered unchanged from refluxing aqueous alkaline permanganate solution.

A solution of I in carbon tetrachloride was treated with a drop of bromine. The color disappeared after standing about 30 min. in the dark. Although I absorbed a large quantity of bromine in this manner, the reaction was very slow.

When ozone (3%) was passed through a solution of I in ethyl acetate at 5°, no absorption of ozone occurred (as indicated by the immediate quantitative liberation of iodine from a potassium iodide solution in series with the solution of I).

When stearolic acid was used instead of I in the bromine and the ozone experiments, the results were the same as with I.

All attempts at the preparation of a Grignard reagent using I were unsuccessful.

A sample of I was converted to the iodide by refluxing with a solution of sodium iodide in acetone for 24 hr. When the iodide was used for the preparation of the Grignard reagent, apparently only coupling occurred for a large quantity of alcohol insoluble material was obtained.

1-Chlorotetradecene-7 (II). (*a*) *Reduction of I using various palladium catalysts.* Reduction of a 0.5 g. sample of I in ethyl acetate, using the palladium-on-calcium carbonate catalyst, as prepared by the method of Lindlar,[17] required 90 min., and practically ceased with the absorption of one equivalent of hydrogen. Removal of the catalyst and solvent left the *cis* olefin, II, n_D^{29} 1.4550. This reduction product showed a small infrared absorption at 10.4 μ, showing the presence of a small amount of *trans* olefin in the product.

When the reduction of I was carried out using either palladium-on-carbon or the palladium-on-calcium carbonate catalyst of Busch and Stove,[15] the reduction was stopped after one equivalent of hydrogen had been absorbed. The reduction products (n_D^{24} 1.4564 and n_D^{25} 1.4557, respectively) both showed an intense absorption at 10.4 μ, indicating the presence of a considerable amount of *trans* olefin in the reduction product.

(*b*) *Reduction of I using the Nickel W-5 catalyst.*[16] The reduction using this catalyst proceeded rapidly and the rate slowed down somewhat after one equivalent of hydrogen had been absorbed. A 40 g. sample of I in absolute alcohol was reduced in 45 min., the reduction being interrupted after one equivalent of hydrogen had been absorbed. The reduction product (II) was a colorless liquid, b.p. 113–114° (0.6 mm.), $n_D^{22.5}$ 1.4559. It showed a small absorption band in the infrared at 10.5 μ of about the same intensity as that of the product obtained using the palladium-on-calcium carbonate catalyst as prepared by Lindlar.[17]

A sample of II reacted rapidly with bromine and with permanganate. On ozonolysis, the theoretical quantity of ozone was absorbed, and the product smelled strongly of heptaldehyde, but the aldehyde was not isolated.

A sample of II was further hydrogenated using a palladium-on-charcoal catalyst. Exactly one equivalent of hydrogen was absorbed giving a quantitative yield of myristyl chloride.

3-(1′-Hydroxypentadecenyl-8′)-catechol dibenzyl ether (III). Approximately 50 cc. of anhydrous ether, prepared by refluxing with butyl Grignard reagent, was distilled into a well flamed vessel containing 3.35 g. (0.147 mole) magnesium. An equivalent amount (33.6 g.) of the halide (II) was added; one third at once and then the remainder dropwise over 2 hr. as the ether was maintained at reflux temperature. The volume of the solution was maintained at about 150 cc. by distilling in ether as necessary. After several hours a white suspension formed, and after 24 hr. most of the magnesium had disappeared. A 46.7 g. sample (0.147 mole) of 2,3-dihydroxybenzaldehyde dibenzyl ether, prepared as previously described,[7] was placed in the condenser supported by a plug of glass wool so that the refluxing ether slowly dissolved it. When all of the aldehyde had dissolved the solution was a dark yellow color with a greenish fluorescence. After another hour of heating, the Grignard complex was hydrolyzed by pouring the reaction solution into cold ammonium chloride solution (containing a small amount of acetic acid). The pale yellow organic layer was washed, dried, and the solvent removed leaving 76.5 g. of an oil having an odor of benzyl bromide. The oil was dissolved in 300 cc. of hot ethanol and a 3 g. precipitate of unreacted 2,3-dihydroxybenzaldehyde dibenzyl ether formed on cooling, m.p. 92–93.5°. After filtering and removing the solvent, *in vacuo*, 73.5 g. of III was obtained as a dark orange oil, n_D^{28} 1.5349. A small sample of III was chromatographed on alumina, using ligroin as the solvent, and a yellow oil of n_D^{28} 1.5517–1.5549 (λ_{max} 268 mμ) was collected. Also isolated from the column was a small amount of unreacted II. The chromatography experiment revealed that the 73.5 g. of product contained about 82% III corresponding to an 81% yield.

The identity of III was confirmed when a sample of the chromatographed III, on hydrogenation over palladium-on-carbon in ethyl acetate, absorbed three moles of hydrogen to give IX, m.p. 88–90°, identical to a sample of IX, m.p. 89.6–90.5°, prepared by the reaction of 2,3-dihydroxybenzaldehyde with myristyl magnesium bromide (see below).

(20) T. H. Vaughn, G. F. Hennion, R. R. Vogt, and J. A. Nieuwland, *J. Org. Chem.*, **2**, 1 (1937).

(21) Purchased from Farchan Research Laboratories, Cleveland, Ohio.

(22) W. J. Gensler and G. R. Thomas, *J. Am. Chem. Soc.*, **73**, 4601 (1951).

(23) L. R. Drake and C. S. Marvel, *J. Org. Chem.*, **2**, 387 (1937).

3-(1'-Hydroxypentadecyl)catechol (IX). To a chilled solution containing the Grignard reagent prepared from 147.7 g. (0.49 mole) tetradecylbromide, was slowly added a solution of 16.4 g. (0.122 mole) of 2,3-dihydroxybenzaldehyde in anhydrous ether containing sufficient anhydrous benzene to bring the aldehyde into solution. The mixture was refluxed for several hours and then hydrolyzed by pouring into dilute acetic acid containing a little sodium hydrosulfite. After washing several times with dilute hydrosulfite solution, the ether was distilled. The remaining brown liquid was dissolved in boiling ethanol and then chilled. The octacosane that precipitated on cooling was filtered and the liquid tetradecane which oiled out of the ethanol was separated. Removal of the ethanol left a pink oil that solidified on cooling. Recrystallization from ligroin gave 22.9 g. (56%) of the carbinol (IX), as feathery white crystals, m.p. 89.6–90.5°; λ_{max} 280 mμ; green color with ferric chloride. The use of three equivalents of the Grignard reagent per mole of aldehyde resulted in a lower (40.5%) yield of the carbinol.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.98; H, 11.05.

IX, prepared as described above, proved to be identical to IX previously prepared by catalytic reduction of 2,3-dibenzyloxyphenyl tetradecyl carbinol.[7]

3-(1',8'-Pentadecadienyl)-catechol dibenzyl ether (IV). The crude III (70 g.) was heated to 175° in a nitrogen atmosphere with a small amount of potassium bisulfate until the vigorous bubbling ceased. The resulting oil was taken up in ether, washed with water, treated with a little charcoal and alumina, and filtered. The solvent was removed, leaving 61 g. IV as a dark oil, n_D^{23} 1.5481, λ_{max} 256 mμ. The crude IV was used for the next step without purification.

3-(Pentadecenyl-8')-catechol (urushenol) (V). Sodium, 61 g., was added as rapidly as refluxing would permit to a solution of 30.7 g. of IV in 600 cc. hot anhydrous butyl alcohol. The solution immediately turned dark blue-green. This color soon changed to a dark red-brown, and then proceeded to a pale yellow color, during the first 5 min. of the reaction. When all of the sodium had reacted (2 hr.), the solution was allowed to cool to room temperature under nitrogen. Cold water, containing a little hydrosulfite, was cautiously added causing vigorous boiling. As more water was added, a precipitate formed and then redissolved. A cold dilute solution of slightly more than the theoretical quantity of acetic acid required to neutralize the sodium hydroxide (and containing a little sodium hydrosulfite) was added. The solution was then saturated with sodium chloride and separated. The organic layer was washed with saturated salt solution containing some bicarbonate and hydrosulfite, and then with a small quantity of distilled water. Another 28 g. of IV was reductively cleaved in the same fashion and the solutions were combined. The solvent and any unreacted halide which had been carried through were removed by distillation under nitrogen, *in vacuo*, leaving 37.2 g. of V as a dark brown oil, a small sample of which gave a dense precipitate with methanolic lead acetate.

On vacuum distillation there was obtained, following a small forerun of low boiling material, 13.4 g. of a pale yellow oil (V) of b.p. 207–208° (0.8 mm., bath at 265–290°) corresponding to a 28.5% overall yield from II. The product, n_D^{25} 1.4970, darkened rapidly on standing in air but remained pale yellow for a long period when stored in an evacuated or nitrogen-filled sealed vial. The residue in the distilling flask polymerized to a viscous black mass.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.20; H, 10.76. Found: C, 79.30; H, 10.86.

A solid derivative of V, the di-naphthylurethan, was made by heating a mixture of 0.3 g. V, 0.3 cc. of α-naphthyl isocyanate, and 3 drops of pyridine for 5 min. on a steam bath. The resulting solid was triturated with hexane, filtered, and recrystallized from benzene-hexane, 0.34 g., m.p. 139–141°.

Anal. Calcd. for $C_{43}H_{48}O_4N_2$: C, 78.49; H, 7.51. Found: C, 78.10; H, 7.62.

Mixed melting point with the di-naphthylurethan of hydrourushiol, m.p. 149–150° (from $CHCl_3$), showed a marked depression.

On treatment with ferric chloride solution, V gave a momentary green color changing rapidly to black. A small sample of V on catalytic hydrogenation absorbed slightly more than the theoretical quantity of hydrogen for a mono-olefin and gave, after one recrystallization from petroleum ether, hydrourushiol (VI) as a pale yellow solid of m.p. 57.5–58.5°. A mixed melting point with an authentic sample of hydrourushiol showed no depression.

Chromatographic purification of urushenol (V).[24] As the result of subsequent investigations in this laboratory involving the mono-olefinic component of poison ivy "urushiol" as isolated from natural sources, it became apparent from refractive index values that the synthetic urushenol (V) was contaminated with material which did not significantly affect the analysis data, the double bond value, or the ultraviolet or infrared spectra. The refractive index of V (n_D^{25} 1.4970) was considerably lower than that of the natural product (n_D^{25} 1.5083). Considering the method of synthesis of V it seemed possible that the contaminating material was a side product of the Grignard reaction, *i.e.* the R-R coupling product octacosadiene-7,21.

It had recently been found in these laboratories[25] that alkenylphenols in ligroin can be adsorbed on acid washed Alumina, Grade III (Merck), and then quantitatively eluted with anhydrous diethyl ether. Consequently a small sample of V was placed on an acid washed alumina column and washed repeatedly with ligroin. The eluate contained a colorless oil (n_D^{25} 1.4584). This oil gave negative tests for the catechol nucleus, had no ultraviolet spectrum above 220 mμ and its infrared spectrum showed only those peaks expected of an unsaturated hydrocarbon,[26] and also present in the natural and synthetic mono-olefin, 3-pentadecenyl-8'-catechol. Extraction of the column with anhydrous diethyl ether gave a 72% recovery of a brown wax, n_D^{25} 1.5108. This material was molecularly distilled to give a light yellow oil of n_D^{25} 1.5081, which crystallized on standing at 0°. On warming it starts to soften at 22° and melts at 33°. Its ultraviolet and infrared spectra, as well as its refractive index, were identical with those of the mono-olefinic component isolated from poison ivy urushiol.[27]

Dimethyl urushenol (VII). A 3 g. sample of V was refluxed for 24 hr. with excess methyl iodide and potassium carbonate in acetone.[28] The precipitated salts were filtered and the solvent distilled. The product was a pale yellow oil, 1.5 g., n_D^{25} 1.4870. It was insoluble in alcohol and gave a negative ferric chloride test. A sample of this material was chromatographed on alumina (grade I) using ligroin as solvent. The resulting product was made up of fractions having refractive index n_D^{25} 1.4940–1.4950 in satisfactory agreement with the product derived from poison ivy (n_D^{25} 1.4930–1.4945).[4]

Hydroxylation of VII *with osmium tetraoxide.* A 0.5 g. sample of VII was treated with osmium tetraoxide as previously described.[6] The resulting 0.43 g. of glycol, VIII, melted at 95–96°, and the melting point of a mixture of VIII and the glycol obtained in a similar manner from the natural dimethyl urushenol (m.p. 94–95°)[6] also melted at 95–96°. Cleavage of VIII by means of lead tetra-acetate[28] gave heptaldehyde which was steam distilled from the reaction

(24) Experimental work by K. H. Markiewitz.

(25) V. J. Paul, unpublished observations, Columbia University (1956).

(26) The presence of significant quantities of this hydrocarbon would not materially change the analysis.

(27) A method for isolating the various olefinic components of Poison Ivy "Urushiol" in their free phenolic and allergenically active form has recently been developed by K. H. Markiewitz in these laboratories.

(28) L. Claisen and O. Eisleb, *Ann.*, 401, 21 (1913).

mixture and identified as the 2,4-dinitrophenylhydrazone, melting sharply at 106.5–107°, and showing no depression when mixed with an authentic sample of the 2,4-dinitrophenylhydrazone of *n*-heptaldehyde.

Acknowledgment. The authors are indebted to the Lederle Laboratories Division of the American Cyanamid Co. for a grant to Columbia University for support of this investigation. They also wish to thank Dr. Kenneth H. Markiewitz for technical aid.

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Notes

A department for short papers of immediate interest.

Ring Derivatives of Phenothiazine. IV. Further Studies on the Thionation Reaction, and the Synthesis of Phenothiazinols

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The synthesis of 2-, 3-, and 4-derivatives of phenothiazine by the thionation of diphenylamines in a solvent was studied and found to offer some advantages over thionation without solvent. The 1-, 2-, and 3-phenothiazinols were prepared by cleavage of the corresponding methyl ethers with pyridine hydrochloride. The phenols were further characterized, by the preparation of suitable derivatives.

The synthesis of 1-substituted ring derivatives of phenothiazine has been studied using *o*-dichlorobenzene as a solvent,[3] and this procedure was shown to afford certain advantages. It, therefore, seemed desirable to extend these studies to the syntheses of ring derivatives of phenothiazine with substituents in other positions by thionation of the corresponding diphenylamines.

It has been found that the use of solvent makes the process quite convenient in the isolation and purification of the products, particularly, where isomers are formed. However, as in the case without solvent,[4] 3-methoxydiphenylamine gave only 2-methoxyphenothiazine, no 4-isomer being isolated. Derivatives containing substituents in both rings also thionated smoothly using solvent.

The phenothiazinols were prepared by smooth demethylation of the corresponding methoxy derivatives, using pyridine hydrochloride.[5] These phenols were further identified through the diacetyl derivatives, both the amino hydrogen and the phenolic hydrogen being replaced by acetyl groups.

Although xanthydrol reacts with phenothiazine in hot glacial acetic acid to yield the 10-(9-xanthenyl) derivative, the susceptibility of the latter to heat, and its high melting point made it unsuitable as a derivative.

The use of isopropenyl acetate,[6] with boron trifluoride as a catalyst, was found to give better results as an acetylating agent than acetic anhydride and pyridine in the case of 1-substituted phenothiazines, where difficulties were encountered earlier in the preparation of 1-chloro-10-acetylphenothiazine.[3]

These compounds were submitted to the Sloan-Kettering Institute and the Upjohn Drug Company for physiological testing; results will be reported elsewhere.

EXPERIMENTAL[7]

Anthranilic acids.[8] The *meta*- and *para*-chloro-, and methoxy- and methylanthranilic acids were prepared in the usual manner[3,9] from the corresponding anilines and o-chlorobenzoic acid in 50–60% yields. The *m*-anisidine needed for the synthesis of *N*-*m*-anisylanthranilic acid was prepared by the direct methylation of *m*-aminophenol.[10]

The *N*-*p*-anisyl-*m*-chloroanthranilic acid was prepared from the corresponding potassium salt.[11]

Diphenylamines. These were prepared in good yield by decarboxylation of the corresponding anthranilic acids at 210–260° for 1–2 hr. The liquid diphenylamines were then distilled directly; in the case of the solids, they were taken up in ether, the ethereal solutions extracted with 10% sodium carbonate solution, the ether removed, and the residues crystallized from ethanol, benzene, or benzene-petroleum ether.

Thionation of diphenylamines. The reaction was carried out in the usual manner,[3] by heating a mixture of the diphenylamine (0.1 mole), sulfur (0.2 mole), and 0.7 g. of iodine in 20 ml. of refluxing *o*-dichlorobenzene for 1 hr. On cooling, a crystalline mass separated from the reaction mixture, and was filtered and recrystallized from petroleum ether-benzene mixture. In some cases further purification was effected by sublimation or a second crystallization.

In cases where isomers were present, petroleum ether was added to the reaction mixture. The 2-isomer separated, and was filtered from the mixture. The 4-isomer was recovered from the filtrate. The results are given in Table I.

Anal. Calcd. for $C_{13}H_{10}ONSCl$: S, 12.17. Found: S, 12.23

1-Hydroxyphenothiazine.[12] A mixture of 22.9 g. (0.1 mole) of 1-methoxyphenothiazine[3] and 57.8 g. (0.5 mole) of pyridine hydrochloride was heated for 5 hr. in a flask surrounded by an oil bath maintained at 200°. The melt was cooled, poured into an excess of cold water, and extracted with ether. After treatment with Norite, the ethereal solution was dried over anhydrous magnesium sulfate, and the ether was

(1) Present address: Department of Chemistry, Brown University, Providence, R. I.

(2) To whom inquiries should be sent.

(3) S. P. Massie and P. K. Kadaba, *J. Org. Chem.*, 21, 347 (1956).

(4) P. Charpentier, P. Gaillot, R. Jacob, J. Gaudechon, and P. Buisson, *Compt. rend.*, 235, 59 (1952).

(5) V. Prey, *Ber.*, 75, 445 (1942).

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(7) All melting points are uncorrected. Analyses are by Midwest Microlab, Inc., Indianapolis, Ind.

(8) Some of these acids were prepared by Helen Peoples.

(9) C. Allen and G. McKee, *Org. Syntheses*, Coll. Vol. II, 15 (1943).

(10) P. K. Kadaba and Samuel P. Massie, *J. Org. Chem.*, 22, 333 (1957).

(11) This salt was purchased from the Winthrop Chemical Co., New York, N.Y.

(12) Some of this work was carried out by Eugene A. White.

TABLE I

PHENOTHIAZINES BY THIONATION

Substituent	Yield, %[a]	M.P.
2-Methyl-	38	190–191°[b]
4-Methyl-	3	129–132°[c]
2-Chloro-	26	197–199°[d]
4-Chloro-	Unable to purify	
2-Methoxy-	16	185–188°[e]
4-Methoxy-	Unable to isolate	
3-Methyl-	47	166–167°
3-Methoxy-	48	155–157°[f]
3-Chloro-	[g]	
2-Chloro-7-methoxy	35	173–174°

[a] These yields represent purified yields. For example, in the thionation of 3-methyldiphenylamine, a crude yield of 80% of the 2-isomer, melting at 175–177°, is obtained, and a crude yield of 20% of the 4-isomer, melting at 125–127°. [b] Charpentier *et. al., loc. cit.*, reported a melting point of 187–188°. [c] Charpentier *et al.*, m.p., 114–118°. As noted above, our crude product melted at 125–127°. [d] Charpentier, *et al.*, m.p., 196–197°. [e] Charpentier, *et al.*, m.p., 179–180°. [f] Gilman and Shirley, *J. Am. Chem. Soc.*, 66, 888 (1944) and Kehrmann and Nossenko, *Ber.*, 46, 2809 (1913) report a melting point of 158–159°; Pummerer and Gassner, *Ber.*, 46, 2322 (1916) report 163°. [g] 3-Chlorophenothiazine could not be obtained by this procedure. Complete loss of chlorine resulted and good yields of phenothiazine were obtained as the only reaction product. A similar loss occurred to some extent in the preparation of 1-chlorophenothiazine.[4]

removed by distillation. There was obtained 20.4 g. (95%) of a yellow product, melting at 135–136°.

An analytical sample was obtained by recrystallization from benzene. Colorless glistening crystals, melting at 136–137°, were obtained. On standing or exposure to air, the compound slowly turned green.

Anal. Calcd. for $C_{12}H_9ONS$: C, 67.0; H, 4.19. Found: C, 66.8; H, 4.25.

1-Aceloxy-10-acetylphenothiazine. A mixture of 0.6 g. of 1-hydroxyphenothiazine, 4 ml. of acetic anhydride, and a few drops of pyridine was refluxed for 4 hr. On cooling the mixture, colorless crystals settled out. Recrystallization from benzene gave 0.4 g. (60%) of colorless crystals, m.p., 208–209°.

Anal. Calcd. for $C_{16}H_{13}O_3NS$: S, 10.70. Found: S, 10.34.

1-Ethoxyphenothiazine.[12] A mixture of 3 g. of 1-hydroxyphenothiazine, 3 ml. of ethyl bromide, and 10 g. of anhydrous potassium carbonate in 150 ml. of dry acetone was refluxed for 24 hr. The hot reaction mixture was filtered, and the filtrate evaporated. The residue, which was insoluble in alkali, was recrystallized from ethanol to give 2.1 g. (62%) of colorless crystals, m.p., 81–82.

Anal.[13] Calcd. for $C_{14}H_{13}ONS$: C, 68.8; H, 5.35. Found: C, 68.0; H, 5.36.

2-Acetoxy-10-acetylphenothiazine. A mixture of 2 g. of 2-methoxyphenothiazine and 6 g. of pyridine hydrochloride was heated at 200° for 5 hr. When the melt was worked up as described under 1-hydroxyphenothiazine, an oil was obtained which could not be crystallized. The oil was, therefore, by a procedure similar to that for the 1-hydroxy derivative, converted into 2-acetoxy-10-acetylphenothiazine. This was crystallized with difficulty from benzene–petroleum ether to give 0.6 g. (35%) of colorless crystals, m.p., 138–140°.

Anal. Calcd. for $C_{16}H_{13}O_3NS$: S, 10.70. Found: S, 10.23.

(13) Analysis by C. Beames, N. Mexico Highlands University, Las Vegas, N. M.

(14) This compound has been reported to melt at 172–174° by D. F. Houston, E. B. Kester, and F. DeEds, *J. Am. Chem. Soc.*, 71, 3816 (1949), who prepared it by the thionation of p-anilinophenol.

3-Hydroxyphenothiazine.[14] The demethylation of 3 g. of 3-methoxyphenothiazine with 12 g. of pyridine hydrochloride was carried out as described for the 1-hydroxy derivative. Recrystallization from benzene acetone mixture gave 2.2 g. (76%) of steel-gray crystals, m.p. 187–188°. Because of the ease of oxidation, to a purple colored solid, the product was not analyzed but was converted, as described under the 1-derivative, into 3-acetoxy-10-acetylphenothiazine, which crystallized with difficulty from benzene–petroleum ether mixture to give a white powder, m.p., 111–116°.

Anal. Calcd. for $C_{16}H_{13}O_3NS$: S, 10.70. Found: S, 10.21.

2-Chloro-7-hydroxyphenothiazine. Demethylation of 2 g. of 2-chloro-7-methoxyphenothiazine in the usual manner gave a product which crystallized from benzene to give 1 g. (52%) of light purple crystals, m.p. 224–226°, turning deep purple on standing.

Anal. Calcd. for $C_{12}H_8ONSCl$: S, 12.83. Found S, 13.14.

10-(9-Xanthenyl)-phenothiazine. A mixture of 0.5 g. of phenothiazine, 0.5 g. of xanthydrol and 6 ml. of glacial acetic acid was heated to reflux. On cooling to room temperature, a white crystalline solid separated. Filtration and recrystallization from ethanol-acetone mixture gave a colorless solid, m.p., 205–212°, sintering at 195°. It turned violet on standing.

Anal.[13] Calcd. for $C_{25}H_{17}NOS$: C, 79.2; H, 4.48. Found C, 78.6; H, 4.86.

1-Chloro-10-acetylphenothiazine.[3] To 1.0 g. of 1-chlorophenothiazine was added 1 ml. of isopropenyl acetate[15] and 5 drops of boron trifluoride ethereate. The mixture was heated with stirring in a boiling water for a few minutes. The dark residue was cooled and triturated in ethanol to remove colored impurities. The colorless amide was filtered and recrystallized from ethyl acetate to give 1.3 g. of colorless crystals, m.p., 135–136°. By adapting the same procedure, the 10-acetyl derivatives of 1-methyl phenothiazine and 1-methoxyphenothiazine were also prepared.

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(15) This material was kindly supplied by the Tennessee Eastman Co., courtesy, Dr. J. B. Dickey.

Hexagonal Urea from Acetone-Urea Adduct

DEMETRIOS KYRIACOU

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It is reported in the literature that when a urea adduct decomposes, the urea reverts to its natural tetragonal structure.[1] Urea adducts are crystalline molecular compounds of hexagonal structure.[2] We have found that a small part of the urea obtained from the decomposition of an acetone urea adduct existed in the hexagonal form. X-ray dif-

(1) R. T. Holman, W. O. Lundberg, T. Malkin, *Progress in the Chemistry of Fats and Lipids*, Pergamon Press, Ltd., London, 1954, Vol. 2.

(2) A. E. Smith, *J. Chem. Phys.* 18, 150 (1950).

fraction patterns were obtained, showing that a small amount, probably less than 5%, possessed hexagonal structure. The urea obtained from acetone urea adduct after the adduct was decomposed by heat at 55° was found to form fatty acid urea adducts readily in the absence of any urea solvent.

EXPERIMENTAL

Preparation of acetone activated urea.[3] Into a beaker containing *ca.* 150 ml. of acetone was added exactly 200 g. of urea of about 150 mesh, and the mixture was left to stand for 1 hr. at room temperature. The excess acetone was removed by suction filtration and the solid adduct was placed in a 55° oven until the original weight of urea was obtained. At this point decomposition of the acetone urea adduct was considered to be complete.[4]

Reactivity of acetone activated urea. To 100 g. of the above urea was added 25 g. of oleic acid, U.S.P. grade, and the mixture was left to stand for 2 hr. with occasional stirring. From the adduct formed, 24 g. of fatty acid was recovered after decomposition of the adduct by hot water. Other fatty acids and their methyl or ethyl esters reacted equally well.

Rate study. Urea, 200 g., was treated as in the first experiment. To this urea was added 370 ml. of toluene to which 40 g. of stearic acid, N.F. grade, had been dissolved, and immediately mechanical agitation was started. Small samples were taken out at definite intervals, were rapidly filtered *via* a cotton plug and of the clear liquid an aliquot was titrated in isopropyl alcohol with standard sodium hydroxide solution to a phenolphthalein end point so that the molarity of the stearic acid toluene solution could be determined at each interval. The results were plotted and fitted well the first order equation:

$$2.3 \log c/c_0 = kt$$

where c_0 = initial concentration of stearic acid
c = concentration of stearic acid after lapse of time, t
t = time, min.
k = specific reaction velocity constant

Fig. 1 represents this curve.

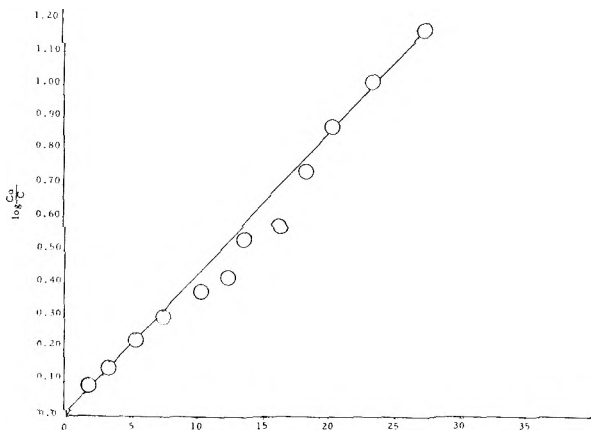


Fig. 1. First order reaction of stearic acid–acetone activated urea

Comparison of rates of acetone activated and ordinary urea. Urea, 200 g. of *ca.* 200 mesh, was reacted with stearic acid dissolved in toluene in the same manner as the acetone activated urea in the previous example. Practically no reaction took place. Fig. 2 shows the results.

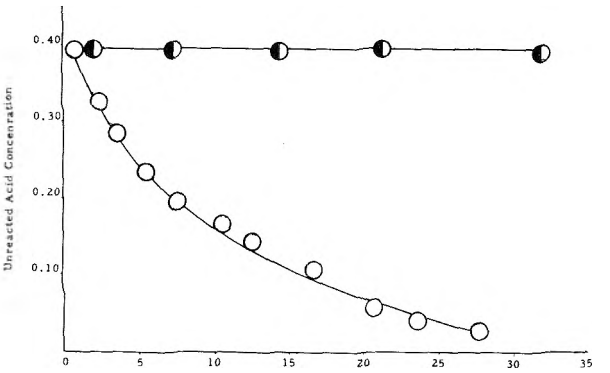
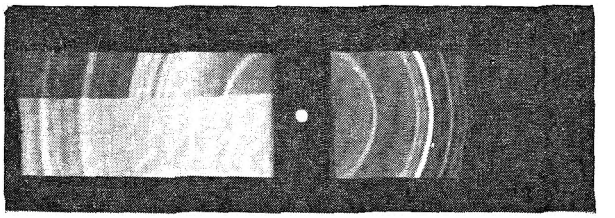


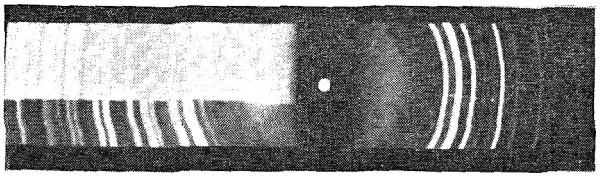
Fig. 2. Rate comparison: acetone activated urea–stearic acid, O; ordinary urea–stearic acid, ◐

X-ray diffraction patterns. Powder diffraction patterns were obtained with copper target and wedge sample holder in a Debye-Sherrer type camera.

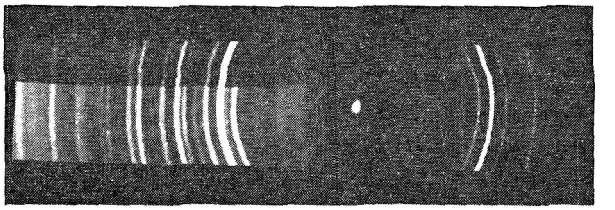
1. Sample exposed for 1.5 hr. Film #23
2. Sample exposed for 2 hr. Film #42
3. Hexagonal urea (ethyloleate adduct)[5] Film #35



Film #35. Hexagonal urea (ethyl oleate adduct)



Film #42. 2 hr. exposure. Just to left of heavy line is weak line of hexagonal urea



Film #23. Exposure 1.5 hr.

Figure 3

(3) Urea from decomposed acetone adduct.

(4) The urea was weighed to the nearest tenth of a mg. to make sure that no acetone or acetone adduct was present when this urea was caused to react with the fatty substances. Small traces of acetone or acetone adduct might still be present; however, these small traces could not have catalyzed the reaction to any great extent. It was found that when ordinary urea, 100 g., was mixed with 25 g. of oleic acid in the presence of *ca.* 0.5 g. acetone adduct and 0.5 ml. of acetone, less than 3 g. of oleic acid had reacted after 2 hr. at room temperature. It is not probable that traces of free acetone or acetone adduct could have catalyzed the reaction of acetone activated urea with the fatty acids or their esters, in these experiments.

(5) This adduct was freshly made in saturated urea methanol solution with excess ethyl oleate.

Exactly 5 g. of urea, C.P., was caused to react with excess acetone as in the first experiment. A specimen of this urea was investigated. Film #23 did not show much evidence for hexagonal urea. Film #42 did show a weak line at about 21° 12/(20). This corresponds to the most intense line of the hexagonal urea adduct, Film #35. The intense line of tetragonal urea was very dark on the film because of the long exposure. A densitometer was used to compare the line of the hexagonal with the intense line of the tetragonal urea. Only an estimate could be made on account of the high darkening of the tetragonal line. This estimate put the amount of hexagonal urea at probably less than 5%. Diffraction patterns are shown in Fig. 3.

DISCUSSION

The existence of the small portion of hexagonal urea, after the acetone urea adduct is decomposed by heating the adduct, could perhaps justify a conjecture that the hexagonal channels of urea do not all collapse instantly upon the escape of the acetone molecules. Some of them may retain their hexagonal configuration or assume some metastable structure before reverting to the natural tetragonal form. Such a crystalline configuration would favor adduct formation with adduct forming substances without the use of a urea solvent. A phenomenon similar to adsorption[6] may take place when acetone activated urea is contacted with a substance such as oleic acid. The catalytic effect of acetone, and perhaps of other ketones, may be explainable not only on the basis that acetone is a mutual solvent for both urea and adduct forming substances but also that it forms its urea adduct which decomposes to provide *in situ* acetone activated urea.

Acknowledgment. We thank Mr. H. D. Orcutt of the Physics Research Dept. of Aerojet General Corp., who did the x-ray work, for his interest and helpful advice. We also express gratitude to Pacific Vegetable Oil Corp., for offering to us the opportunity to become interested in this study.

AEROJET-GENERAL CORP.
SACRAMENTO, CALIF.

(6) W. J. Zimmerchied, R. A. Dinerstein, A. W. Weitkamp, and Robert F. Marschner, *Ind. Eng. Chem.*, **42**, 1300 (1950).

New Simple Preparation of Diphenylsilanediol and Its Condensation Products; Cyclodiphenylsiloxanes

TOSHIO TAKIGUCHI

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In the previous works[1-7] related to the preparation of diphenylsilanediol (hereafter called diol) from diphenyldichlorosilane, the hydrolysis of the chlorosilane under carefully controlled mild conditions to minimize the formation of high polymers has generally been aimed at for successful preparation.

The author now finds that diol in pure form can be obtained readily from the reaction of diphenyldichlorosilane with ammonium carbonate monohydrate, the yield being 90–94%.

The new method can be represented summarily by the following equation:

$$(C_6H_5)_2SiCl_2 + (NH_4)_2CO_3\text{-}H_2O \longrightarrow (C_6H_5)_2Si(OH)_2 + 2NH_4Cl + CO_2$$

When 1 mole of diphenyldichlorosilane was added to 1.2–1.5 mole of ammonium carbonate monohydrate covered with an inert anhydrous organic solvent preheated at 50–60°, the ammonium salt decomposed readily, evolving carbon dioxide, and ammonium chloride precipitated as fine crystals. After cooling to room temperature, the reaction product was filtered, whereupon pure diol was obtained from the filtrate upon evaporation. The most effective result was obtained by use of acetone as the reaction medium: The hydrophilic character of this would make the first stage of the reaction, hydrolysis of diphenyldichlorosilane with water produced by the decomposition of ammonium carbonate, fairly homogeneous.

The proposed method has the advantage that throughout the preparation procedure no by-products other than ammonium chloride and carbon dioxide were produced. Both of these have no disadvantageous effect on the hydrolysed product and can be separated easily from the liquid part, allowing ready isolation of diol.

As has been described by Burkhard,[4] diol was converted readily into cyclodiphenylsiloxanes on being refluxed in an appropriate solvent in the presence of acid or caustic alkali as catalyser; hydrochloric acid and sodium hydroxide gave hexaphenylcyclotrisiloxane and octaphenylcyclotetrasiloxane, respectively.

EXPERIMENTAL

Reagents. Reagent grade ammonium carbonate monohydrate was used after prolonged drying in a vacuum desiccator. Highest purity diphenyldichlorosilane was received from the Shin-etsu Chemical Industrial Co. Acetone was purified according to the ordinary method.

Preparation and some properties of diol. In a 2-l. flask surrounded by a water bath heated at 50° was placed 80 g.

(1) G. Martin, *Ber.*, **45**, 403 (1912).
(2) F. S. Kipping, *J. Chem. Soc.*, **101**, 2108 (1912).
(3) F. S. Kipping and R. Robinson, *J. Chem. Soc.*, **105**, 487 (1914).
(4) C. A. Burkhard, *J. Am. Chem. Soc.*, **67**, 2173 (1945).
(5) J. F. Hyde and R. C. DeLong, *J. Am. Chem. Soc.*, **63**, 1194 (1941).
(6) S. Fukukawa, *Science & Industry (Japan)*, **30**, 71 (1956).
(7) T. Takiguchi, "Studies on organochlorosilanes, VII," *J. Chem. Soc. Japan (Ind. Chem. Sect.)*, in press.

(0.7 mole) of finely powdered ammonium carbonate monohydrate and 400 ml. of acetone. From a dropping funnel, 126 g. (0.5 mole) of diphenyldichlorosilane dissolved in 150 ml. of acetone was added portionwise into the flask, which was shaken gently during the addition. By the addition, ammonium chloride precipitated as fine white crystals and carbon dioxide was evolved readily; the gas evolved from the reaction mixture immediately precipitated barium carbonate when it was led into barium hydroxide aqueous solution. After the addition was complete, the contents were refluxed gently for about 1 hr. The product was filtered by suction after cooling and the colorless filtrate was then evaporated to dryness on a water bath; a white needle crystalline mass melting at 122–126° was obtained. Further purification was effected by recrystallization from purified methylacetate; 100 g. (93%) of white needles were obtained.

Anal. Calcd. for $C_{12}H_{12}SiO_2$: C, 66.62; H, 5.59; Si, 12.97; mol. wt., 216; OH/molecule, 2.00. Found: C, 66.3; H, 5.20; Si, 12.8; mol. wt., 190–198 (glacial acetic acid); OH/molecule, 1.97 (Karl Fischer titration[8]).

Density of a single crystal when measured in calcium chloride aqueous solution of matched density was 1.16 (at 25°).

The infrared absorption data were in complete agreement with those given by Tatlock and Rochow.[9]

Regarding the melting point of this diol, the well known abnormality was confirmed: For example, needles obtained from acetone ether melted at 155°, needles from methylacetate melted at 147–148°; moreover, some needles which melted at 131–133°, 142–144°, 158–160° were also found during many measurements. Melting was always accompanied by formation of liquid decomposition products and the measurement of melting point was always carried out using clean Pyrex capillary tube and at the rate of heating 5° per min., the bath being preheated at about 110°.

Further investigations on the possible existence of poly- or mesomorphism of this diol are being undertaken by using x-ray technique.

Cyclodiphenylsiloxanes. (A) *Trimer.* The crude crystalline mass obtained in the procedure described above was dissolved in 1000 ml. of ether, and 30 ml. of concentrated hydrochloric acid was added. The mixture was gently refluxed or about 2 hr. and then evaporated to dryness on a water bath. Recrystallization from ethanol benzene gave 75 g. (77%) of hexaphenylcyclotrisiloxane melting at 189°.

(B) *Tetramer.* The filtrate obtained in the above procedure was concentrated in the presence of a small grain of sodium hydroxide. White crystals precipitated upon cooling; recrystallization from ethylacetate gave 81 g. (82%) of octaphenylcyclotetrasiloxane melting at 201°.

These cyclodiphenylsiloxanes were well identified by their x-ray powder pattern data.[10]

Acknowledgment. The author thanks the Shinetsu Chemical Industrial Co. for supply of pure diphenyldichlorosilane.

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(8) H. Gilman and L. S. Miller, *J. Am. Chem. Soc.*, **73**, 2367 (1951).

(9) W. S. Tatlock and E. G. Rochow, *J. Org. Chem.*, **17**, 1555 (1952).

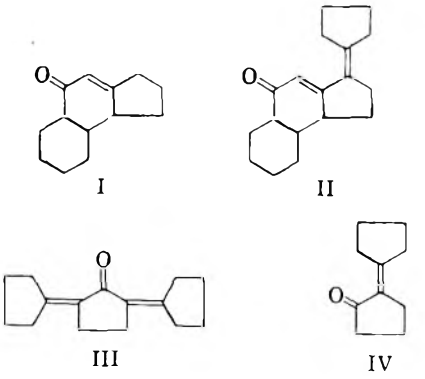
(10) J. F. Hyde, L. K. Frevel, H. S. Nutting, P. S. Petrie, and M. A. Purcell, *J. Am. Chem. Soc.*, **69**, 488 (1947).

Steroidal Hormone Relatives. VI. The Condensation of Cyclopentanone with 1-Acetylcyclohexene[1]

J. H. Burckhalter and P. Kurath[2]

Received November 24, 1958

This report describes part of a continuing program in the synthesis of model compounds which contain a carbonyl group in a position corresponding to the 11-keto of cortisone.[3] In the present approach, 1-acetylcyclohexene was condensed with cyclopentanone under alkaline conditions in an effort to obtain a Michael reaction product which would then undergo an aldol type reaction to give 5-keto-$\Delta^{3a(4)}$-decahydro-1-benz[*e*]indene (I).[4] Compound I would offer a possibility for bromination



I II III IV

in the allylic position[5] corresponding to C-17 of the steroids and thus open a route to the dihydroxyacetone side chain of cortisone.

Various attempts to obtain I by the condensation of 1-acetylcyclohexene and cyclopentanone in the presence of sodamide in ether,[4a] lithium amide in ether,[4b] sodium in an excess of cyclopentanone,[4c] and potassium isopropoxide in pyridine,[4d] yielded instead of I a mixture of 3-cyclopentylidene-5-keto-$\Delta^{3a(4)}$-decahydro-1-benz[*e*]indene (II) and 2,5-dicyclopentylidenecyclopentanone (III).

It has been pointed out by Wallach that cyclopentanone condenses with itself in the presence of sodium ethoxide to form III and 2-cyclopentylidenecyclopentanone (IV).[6] It appears that under the conditions employed to prepare the alkali metal

(1) Aided by the General Research Fund, University of Kansas.

(2) Abbott Laboratories, North Chicago, Ill.

(3) J. H. Burckhalter and P. Kurath, *J. Am. Chem. Soc.*, **81**, 395 (1959).

(4) Earlier approaches in this direction may be seen in the studies of Robinson and others: (a) W. S. Rapson and R. Robinson, *J. Chem. Soc.*, 1285 (1935); (b) A. J. Birch and R. Robinson, *J. Chem. Soc.*, 503 (1944); (c) C. A. Friedmann and R. Robinson, *Chem. and Ind. (London)*, 777 (1951); and (d) W. Huber, *Ber.*, **71**, 725 (1938).

(5) C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).

(6) (a) O. Wallach, *Ber.*, **29**, 2955 (1896); (b) R. Mayer, *Ber.*, **89**, 1443 (1956).

derivative of cyclopentanone, the latter underwent self-condensation to form III and IV. The 2-cyclopentylidenecyclopentanone (IV) then reacted with 1-acetylcyclohexene to give II. As a confirmation of structure, IV was prepared[6] and treated with 1-acetylcyclohexene in the presence of sodamide by analog with earlier work[4] to form II in 40% yield. A 2,4-dinitrophenylhydrazone of II was prepared. Also, the absorption maximum of II in the ultraviolet was found to be at 308 mμ; a value of 316 was calculated by the rule of Woodward for conjugated dienones.[7]

Compound II is a substituted α-decalone prepared under alkaline conditions where only the *trans*- form has been considered to be stable.[8] Thus, II may have *trans*- ring fusion between the rings corresponding to rings B and C in the steroid series where the same stereochemical arrangement was established. However, since no proof is available, it is preferred to leave the question open.

EXPERIMENTAL

Attempted synthesis of 5-keto-$\Delta^{3a(4)}$-decahydro-1-benz[e]indene (I). Cyclopentanone and 1-acetylcyclohexene[9] in 0.08 molar amounts were used under conditions suggested by the work of Birch and Robinson.[4b] Distillation of the ether soluble material gave 5 g. of a yellow oil which distilled at 75–150° (0.3 mm.). Redistillation gave 2 g. of oil of b.p. 125° (0.3 mm.) which solidified, m.p. 82–84°. After several recrystallizations from methyl alcohol the yellow *2,5-dicyclopentylidenecyclopentanone* (III) melted at 89–90°. Admixture of this compound with III of the same melting point, obtained from cyclopentanone in the presence of sodium ethoxide[6], did not depress the melting point [lit., b.p. 190° (12 mm.)[6a]; m.p. 76–77°[6a]; b.p. 198–200° (12 mm.)[6b]; m.p. 81.5–82°[6b]]. The substance would not readily form a ketonic derivative, and, after a few days, it darkened badly.

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.02; H, 9.35.

Continued distillation at 150–170° (0.3 mm.) gave 1 g. of highly viscous, oily *3-cyclopentylidene-5-keto-$\Delta^{3a(4)}$-decahydro-1-benz[e]indene* (II) which crystallized upon treatment with acetone, m.p. 161–164°. After several recrystallizations from acetone, the white needles melted at 167–169°.

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.48; H, 9.41.

3-Cyclopentylidene-5-keto-$\Delta^{3a(4)}$-decahydro-1-benz[e]indene (II). To a suspension of 3 g. (0.077 mole) of sodamide in 180 ml. of dry ether in a nitrogen atmosphere, 11.6 g. (0.073 mole) of 2-cyclopentylidenecyclopentanone (IV)[6] was added with stirring and cooling during a period of 15 min. The mixture stood then for 6 hr. at room temperature and was finally refluxed for 1 hr. With stirring and cooling 9.6 g. (0.077 mole) of 1-acetylcyclohexene was added. After standing overnight, the mixture was treated with 60 ml. of dilute sulfuric acid and then extracted with ether. The extract was handled in the usual manner to give 7.9 g. (40% yield) of crude II, b.p. 155–184° (0.3 mm.). After several recrystallizations from acetone, it melted at 167–169° and the melting point was not depressed by samples obtained earlier (*vide supra*). (λ_{max}^{EtOH} 308 mμ, ϵ 1.42 × 10^5; λ_{min}^{EtOH} 250 mμ, ϵ 4.03 × 10^4.)

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.52; H, 9.54.

The *2,4-dinitrophenylhydrazone of II* was prepared and recrystallized from chloroform as a red crystalline solid, m.p. 243–245° dec.

Anal. Calcd. for $C_{24}H_{28}N_4O_4$: C, 66.03; H, 6.47. Found: C, 65.87; H, 6.52.

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(7) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 192.

(8) (a) W. Hückel, *Ann.*, **441**, 1 (1925); (b) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *J. Am. Chem. Soc.*, **64**, 1985 (1942); (c) R. P. Linstead, S. R. Davis, and R. R. Whetstone, *J. Am. Chem. Soc.*, **64**, 2009 (1942).

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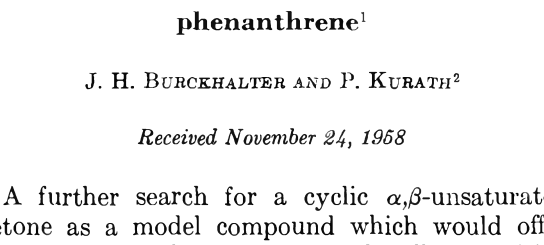
Steroidal Hormone Relatives. VII. Allylic Bromination of *trans*-9-Keto-Δ^{10},-decahydrophenanthrene[1]

J. H. BURCKHALTER AND P. KURATH[2]

Received November 24, 1958

A further search for a cyclic α,β-unsaturated ketone as a model compound which would offer a possibility for bromination in the allylic position corresponding to C-17 of the steroids[3] resulted in the selection of *trans*-9-keto-Δ^{10}-dodecahydrophenanthrene (I).[4]



I II III

Reaction of I with *N*-bromosuccinimide in the absence of ultraviolet irradiation, according to the experimental procedure of Meystre and Wettstein,[5] followed by treatment of the crude bromination product with cuprous cyanide,[6] yielded a mixture from which no pure product was isolated. However, since hydrogen bromide was formed during the bromination step, it was decided that bromination had occurred and was followed by the introduction into I of a second carbon-to-carbon double bond.

A repetition of the bromination experiment, followed by a dehydrobromination procedure em-

(1) Aided by the General Research Fund, University of Kansas.

(2) Present address: Abbott Laboratories, North Chicago, Ill.

(3) J. H. Burckhalter and P. Kurath, *J. Org. Chem.*, **24**, 990 (1959).

(4) W. S. Rapson and R. Robinson, *J. Chem. Soc.*, 1285 (1935); R. P. Linstead, S. B. Davis, and R. R. Whetstone, *J. Am. Chem. Soc.*, **64**, 2009 (1942).

(5) C. Meystre and A. Wettstein, *Experientia*, **2**, 408 (1946); C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).

(6) J. V. Supniewsky and P. L. Salzberg, *Org. Syntheses*, Coll. Vol. I, 46 (1941).

ploying pyridine,[7] gave a mixture which was separated through distillation and recrystallization into two isomeric compounds considered to be 9-keto-$\Delta^{1,10}$-decahydrophenanthrene (II) and *sym*-octahydro-9-phenanthrol (III).

Mixed melting point determinations showed that I, II and III were distinct. Although neither product gave a positive ferric chloride test, the phenolic compound (III) was slightly soluble in 10% sodium hydroxide solution and had the same melting point as the previously described III prepared by different procedures.[8] Also, the infrared absorption spectrum of III showed a strong peak at 3.13 μ, indicative of a hydroxyl, and weaker peaks at 6.20, 6.32, and 6.67, indicative of a monohydroxyphenyl grouping. II showed strong carbonyl absorption (6.13 μ) in the infrared and absorption of less intensity at 6.33 suggestive of conjugated C=C groupings. Absorption maximum of II in the ultraviolet was at 286 mμ, which compares favorably with the value of 280 calculated by the rule of Woodward and found for the analogous $\Delta^{3,5}$-cholestadiene-7-one.[9] It is possible that II may have a double bond between positions 4 and 4a instead of 1 and 2. However, Woodward's rule gives 298, a less favorable value than 280.

The isolation of compounds of structures II and III suggests that the allylic bromination of I occurred at positions 1 and 4a. II probably arises from loss of hydrogen bromide at positions 1 and 2 and III from loss at 4a and 5a.

EXPERIMENTAL

Reaction of trans-9-keto-Δ^{10}-dodecahydrophenanthrene (I) *with N-bromosuccinimide.* A mixture of 6 g. (0.029 mole) of I, 15.8 g. (0.066 mole) of *N*-bromosuccinimide and 100 ml. of carbon tetrachloride was heated at reflux temperature for 90 min. The solvent was removed by distillation and replaced with 100 ml. of pyridine, whereupon heating at boiling temperature was continued for 2 hr. The pyridine was removed under reduced pressure and the residue dissolved in ether. After the ether extract was washed with 2*N* hydrochloric acid and then water, it was dried over magnesium sulfate and the ether removed. Upon distillation of the residue, 3 g. of crude 9-keto-$\Delta^{1,10}$-decahydrophenanthrene (II) was obtained at 145–150° (0.2 mm.). The solidified residue was recrystallized first from methyl alcohol and then from acetone, m.p. 119–121° (λ_{max}^{EtOH} 286 mμ, ϵ 1 × 10^4; λ_{min}^{EtOH} 270 mμ).

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.11; H, 8.97. Found: C, 83.03; H, 9.55.

Continued distillation at 150–155° (0.2 mm.) gave 1 g. of oil which solidified. After removal of the mother liquors from the isolation of II, the residue was combined with the solid distillate and distilled to give 2.1 g. of solid product, b.p. 155° (0.2 mm.). Upon recrystallization from methyl alcohol, a small amount of II separated. On standing, the filtrate yielded a higher melting compound. Recrystallization from dilute methyl alcohol gave a small amount of *sym*-octahydro-9-phenanthrol (III), m.p. 133–134° (lit.[8] 133°).

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.11; H, 8.97. Found: C, 83.66; H, 9.12.

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(7) Pl. A. Plattner, Kd. Meier, and H. Heusser, *Helv. Chim. Acta.*, **30**, 905 (1947).

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The Synthesis of 7-Halogeno-1-hydroxy-2-naphthoic Acids

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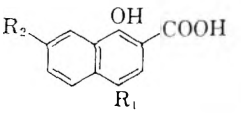
This report deals with the preparation of 1-naphthol derivatives with substitutions in the difficultly accessible 7-position.[1,2] The procedure employed for the preparation of the desired compounds involved the cyclization of a γ-substituted phenylbutyric acid to a 7-substituted-1-tetralone, followed by bromination and dehydrobromination to the naphthol. This product was carboxylated by a modified Kolbe procedure with subsequent chlorination in the 4-position.

Although somewhat lengthy, the procedure adopted has given unequivocally the desired modified naphthoic acids. Of special interest is the action of dimethyl formamide and lithium chloride as a dehydrohalogenating agent. This reagent was employed by Holyz[3] for introducing α, β-unsaturation in 3-keto steroids, and has recently been used by Gabel and Binkley[4] in the dehydrobromination of bromodihydropyrimidines to pyrimidines. The present application to bromotetralones indicates the general usefulness of this method. According to Holyz the lithium chloride is an obligatory factor for the activation of the bromine atom.

Four new 1-hydroxy-2-naphthoic acids have been synthesized and characterized. The effect of these



R_1 = hydrogen or chlorine
R_2 = bromine or chlorine

compounds and their derivatives on oxidative phosphorylation in rat brain mitochondria was studied and it was observed that both a free carboxyl group and a free hydroxyl group were necessary for inhibition of this process.

(1) H. Franzen and G. Stäuble, *J. prakt. Chem.*, **103**, 352 (1922).

(2) H. Erdmann and R. Kirchhoff, *Ann.*, **247**, 366 (1888).

(3) R. P. Holyz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

(4) N. W. Gabel and S. B. Binkley, *J. Org. Chem.*, **23**, 643 (1958).

EXPERIMENTAL

All melting points are uncorrected. Carbon and hydrogen analyses were made by Spang Microanalytical Laboratories, Ann Arbor, Mich.

3,4-Dihydro-7-halo-1(2H)naphthalenones. These tetralones were prepared according to the procedure of Fieser and Seligman.[5]

2-Bromo-3,4-dihydro-7-halo-1(2H)naphthalenones. These compounds were prepared according to the procedures of Coulson,[6] and Fieser and Dunn.[7] These 2-bromo-1-tetralones are very irritating to the skin.[8] Prolonged contact can lead to severe dermatitis.

7-Halo-1-naphthols.[3] Lithium chloride (3.23 g., 0.0762 mole) was dissolved in dimethylformamide (75 ml.) by heating to 70–80°. 7-Chloro-2-bromo-3,4-dihydro-1(2H)-naphthalenone (6.6 g., 0.025 mole) was dissolved in dimethylformamide (25 ml.) and added to the lithium chloride solution. This resulting solution was heated on a steam bath for 3.5 hr. The solution was cooled and transferred to a separatory funnel. Ether (150 ml.) was added and the dimethyl formamide and lithium chloride were extracted with a 75 ml. portion of water. The aqueous layer was diluted with an equal amount of water and extracted with 50 ml. of ether. The ether layers were combined and washed four more times with 75 ml. portions of water, dried over magnesium sulfate, filtered, and the ether removed *in vacuo*. The residue was recrystallized from hot benzene and the light tan needles were washed with petr. ether. Yield, 2.41 g. (56%) m.p. 120–122° (lit. 123° (2)). Picrate, m.p. 139–140° (Lit. 139° (2)).

2,7-Dibromo-3,4-dihydro-1(2H) naphthalenone (26 g., 0.085 moles) was dissolved in 150 ml. of dimethylformamide. Lithium chloride (10.9 g., 0.256 moles) was added and the solution was heated at reflux temperature for 120 hr. The product was obtained by following the procedure outlined above and recrystallized from benzene-petr. ether to give rose colored crystals which darkened upon standing. Yield, 14.5 g. (76%) m.p. 101–105° (lit. 105.5–106.5°[9]).

7-Halo-1-hydroxy-2-naphthoic acids. These acids were prepared according to the procedures of Baine *et al.*,[10] and Cameron *et al.*[11]

The 7-halogeno-1-naphthol was mixed with three equivalents of anhyd. potassium carbonate in a high pressure hydrogenation apparatus. Samples of naphthol from 1–10 g. were employed. The reaction was effected at 150° under 1500 p.s.i. of carbon dioxide for 4 hr. The cooled reaction charge was dissolved in hot water and filtered rapidly. Prolonged heating resulted in decarboxylation and formation of tars. The filtrate was acidified with 6*N* hydrochloric acid. The yields were consistently in the range of 65–70%.

7-Chloro-1-hydroxy-2-naphthoic acid was purified by solution in hot 95% alcohol and reprecipitation by the addition of water. Slow recrystallization did not remove the colored contaminant from the product. Three consecutive reprecipitations gave a product which decomposed with the evolution of carbon dioxide[12] at 212–213.5°. The acid gave a blue green color with ferric chloride. A determination of the neutralization equivalent gave a value of 224 (calcd. neut. equiv., 222.5).

Anal. Calcd. for $C_{11}H_7O_3Cl$: C, 59.34; H, 3.17. Found: C, 59.47; 59.55; H, 3.34; 3.38.

The methyl ester derivatives of the carboxylic acids were prepared by the reaction of excess diazomethane with the acids suspended in ether. The excess diazomethane does not attack the free hydroxyl group in the ortho position.[12] The esters were recrystallized from 95% ethanol. Methyl 7-chloro-1-hydroxy-2-naphthoate melted at 107°.

Anal. Calcd. for $C_{12}H_9O_3Cl$: C, 60.90; H, 3.83. Found; C, 61.04; 60.97; H, 3.97; 3.88.

7-Bromo-1-hydroxy-2-naphthoic acid was purified by slow recrystallization from aqueous ethanol to give a product which decomposed at 214.5–215°. Neut. equiv., 267 (Calcd. neut. equiv., 267).

Anal. Calcd. for $C_{11}H_7O_3Br$: C, 49.46; H, 2.64. Found: C, 49.56; 49.52; H, 2.86; 3.29.

Methyl 7-bromo-1-hydroxy-2-naphthoate m.p. 115–117°.

Anal. Calcd. for $C_{12}H_9O_3Br$: C, 51.27; H, 3.23. Found: C, 51.46; 5.35; H, 3.38; 3.29.

Methyl 1-acetoxy-7-bromo-2-naphthoate was prepared by heating isopropenyl acetate and methyl 7-bromo-1-hydroxy-2-naphthoate at reflux temperature in the presence of catalytic amounts of sulfuric acid. The product was recrystallized from absolute alcohol. M.p. 136–137°.

4-Chloro-7-halogeno-1-hydroxy-2-naphthoic acids.[13] 7-Chloro-1-hydroxy-2-naphthoic acid (3.5 g., 0.0157 mole) was treated at reflux temperature with about 20 ml. of glacial acetic acid in a 25 ml. three necked flask fitted with a stirrer, and condenser with a calcium chloride tube. Chlorine was passed over the surface of the stirred solution for about 20 min. whereupon the product precipitated. The solvent was evaporated and the residue was dissolved in sodium carbonate solution and filtered. The residue was extracted with dilute sodium hydroxide and filtered. The two filtrates were combined, decolorized with charcoal, filtered, and acidified with 6*N* hydrochloric acid. Yield, 1.0 g. (25%) m. 235–236° dec. This product was purified by reprecipitation from hot aqueous alcohol four times to give a compound which decomposed at 242°. Neut. equiv., 257 (Calcd. neut. equiv., 257).

Anal. Calcd. for $C_{11}H_6O_3Cl_2$: C, 51.39; H, 2.35. Found: C, 50.88; 50.94; H, 2.63; 2.71.

Methyl-4,7-dichloro-1-hydroxy-2-naphthoate. m.p. 155°.

Anal. Calcd. for $C_{12}H_8O_3Cl_2$: C, 53.16; H, 2.97. Found: C, 53.23; 53.29; H, 3.11; 3.15.

7-Bromo-1-hydroxy-2-naphthoic acid (2 g., 0.0075 mole) was chlorinated by the procedure described above. The product which had separated was removed by filtration and dissolved in 95% ethanol. The solution was decolorized with charcoal, filtered, and cooled, whereupon crystals formed. Yield, 1.83 g. (81%) dec. 240°. This compound was recrystallized twice from aqueous alcohol to give a product which decomposed at 249–250°. Neut. equiv., 298.5 (Calcd. neut. equiv., 301.5).

Anal. Calcd. for $C_{11}H_6O_3BrCl$: C, 43.81; H, 2.01. Found: 43.88; 43.89; H, 2.25; 2.19.

Methyl 7-bromo-4-chloro-1-hydroxy-2-naphthoate. m.p. 147–148°.

Anal. Calcd. for $C_{12}H_8O_3BrCl$: C, 45.67; H, 2.56. Found: C, 45.54; 45.59; H, 2.71; 2.62.

Acetate (acid) m.p. 184.5°.

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A Simple Synthesis of Piperitenone

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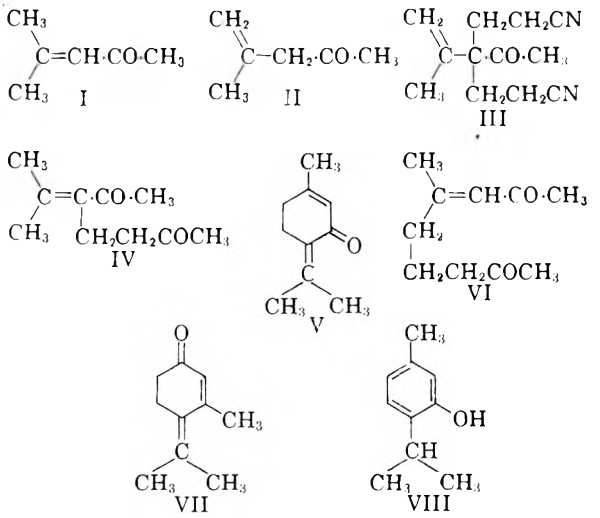
In view of its tendency to appear in an allyl-isomeric form (II), mesityl oxide (I) can act both as acceptor and as donor in Michael reactions. Thus, acrylonitrile gives with mesityl oxide a mono- and a diadduct,[1,2] the constitution of the latter having been proved unambiguously. The dimerization of mesityl oxide can be formulated as a Michael reaction, though Braude and co-workers[3] consider it to be a normal diene addition. It was our intention to elucidate whether in monoadducts of mesityl oxide with suitable acceptors the α-methylene group of II or one of the *gem.* methyl groups of I is the point of attack. That these methyl groups are activated by the carbonyl, has been known from various condensation reactions.[4,5]

When mesityl oxide was condensed with one mole of methyl vinyl ketone under the influence of sodium *t*-pentoxide in toluene solution, it could be shown that the adduct resulted from an attack at the α-methylene group. The adduct had lost one mole of water and had thus evidently undergone cyclization. If the α-methylene group had been the point of attack, V or VII would have formed *via* IV; in case of reaction at a terminal methyl group, an eight-membered ring would result from the cyclization of VI. The product is, in fact, *dl*-piperitenone (V). This can be deduced from the infrared (1661 cm.$^{-1}$) and the ultraviolet spectra (238 mμ; 295.5 mμ), as a compound such as VII should absorb at 1670 cm.$^{-1}$ [6] and 285 mμ,[6a] respectively. Furthermore, the product is decomposed by boiling formic acid into 3-methylcyclohex-2-enone and acetone, a reaction characteristic of compounds of type V,[7] and, finally, heating with palladium transformed it into thymol (VIII).[7a] The latter reaction takes place, when one attempts to hydrogenate the compound catalytically. In this case, thymol is formed together with menthone and menthols.

While the chemical reactions of our product are identical with those reported by Naves and co-workers[8,9] for natural piperitenone, the ultraviolet spectrum observed by these authors (243; 279; 353 mμ) is at variance with our observations. In fact, Naves works with mixtures of piperitenone, isopiperitenone, and pulegone and claims that the product used for the determination of the spectrum was almost free of these contaminations.



EXPERIMENTAL

Piperitenone (V). In a nitrogen-filled flask of 1-l. capacity, mounted with stirrer, reflux condenser, and dropping funnel, a mixture of 35 g. of mesityl oxide, 25 g. of methyl vinyl ketone, and 150 ml. of toluene is cooled to 0°, and a solution of sodium *t*-pentoxide is added, prepared from 4.0 g. of sodium, 15.5 g. of *t*-amyl alcohol and 150 ml. of toluene. After 45 min., the mixture is heated at 60° for 15 min. and poured into water, containing 15 ml. of glacial acetic acid. The organic layer is washed with a 5% sodium carbonate solution and water, dried, and distilled. After recovery of 10 g. of unchanged mesityl oxide, 22 g. (41%) of piperitenone distill at 80–83° (0.05 mm.) or 130–134° (24 mm.).

Anal. Calcd. for $C_{10}H_{14}O$: C, 80.0; H, 9.4. Found: C, 79.6; H, 9.7.

2,4-Dinitrophenylhydrazone, from isobutanol dark red fine needles of m.p. 152°, $\lambda_{max}^{CHCl_3}$ 414 mμ (4.28).

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.2; H, 5.5; N, 17.0. Found: C, 58.6; H, 6.0; N, 17.3.

A higher-boiling fraction [135–138° (0.05 mm.)] was also obtained in small quantities, probably formed from 1 mole of mesityl oxide and 2 moles of methyl vinyl ketone.

Degradation with formic acid. A mixture of 12 g. of V and 30 g. of 90% formic acid was heated at 110–120° in a short column for 24 hr. so that no formic acid distilled over. Thus, 2.0 g. of acetone was obtained, which was characterized as 2,4-dinitrophenylhydrazone, from methanol m.p. 126–127°. The distillation residue was poured into a mixture of concentrated sodium chloride solution and ether and made alkaline with potassium carbonate. Distillation of the ethereal layer gave 5 g. of a distillate of b.p. 95–100° (3.5 mm.) and some unchanged V. The first fraction was identified as 3-methylcyclohex-2-en-1-one through the semi-

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carbazone, from methanol m.p. 201° (lit.,[10] 201°) and the 2,4-dinitrophenylhydrazone, from methanol, m.p. 172° (lit.,[10] 170–173°).

Isomerization of V. A mixture of 8 g. of V and 0.5 g. of palladium-charcoal was heated at 180–190° for 3 hr. The product was extracted with sodium hydroxide solution (10%), from which thymol (3.3 g.; 40%) was recovered by acidification, extraction with low-boiling petroleum ether, and distillation, b.p. 130° (35 mm.). When the material, insoluble in alkali, was subjected to the same treatment, some more (1 g., 12%) thymol was isolated. The phenol was characterized by its infrared spectrum (3350 cm.$^{-1}$ (OH), 815 cm.$^{-1}$ (trisubstituted benzene)) and through thymoxy-acetic acid, from water m.p. 146° (lit.,[11] 145°).

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A Rearrangement of Diaryltrichloromethylcarbinols

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In view of the fact that diaryltrifluoromethylcarbinols rearrange in their halochromic solutions in concentrated sulfuric acid to yield fluorene derivatives,[1,2] it seemed of interest to study the behavior of the recently[3] described diaryltrichloromethylcarbinols (I) under similar conditions. When the solutions of these compounds in concentrated sulfuric acid are poured into water or alcohol, yellow crystalline compounds precipitate, which were identified as the corresponding benzils (II).

$(X\cdot C_6H_4)_2C(OH)\cdot CCl_3$ (I) $\qquad X\cdot C_6H_4\cdot CO\cdot CO\cdot C_6H_4\cdot X$ (II)

X = H, F, Cl (*para*)

Rearrangement of asymmetric to symmetric diarylethanes and -ethylenes occurs in many cases; in particular one would recall the transformation of 1,1-diaryl-2,2-dichloro- or 1,2,2,2-tetrachloro-ethanes into chlorinated bibenzyls,[4–6] the preparation of α,α,β-trifluorobibenzyls from 1,1-diaryl-2,2,2-trichloroethanes under the influence of hydrogen fluoride and mercuric oxide,[7,8] and particularly the conversion of 1,1-di-(*p*-chlorophenyl) 2,2,2-trichloro- and 1,2,2,2-tetrachloroethane into 4,4′-dichlorobenzil under the influence of concentrated sulfuric acid.[9] The mechanism of the observed rearrangement can be formulated as follows in accordance with Barry and Boyer[9]:

$$Ar_2C(OH)\cdot CCl_3 \xrightarrow{H_2SO_4} Ar_2\overset{+}{C}\cdot CCl_3 \qquad (1)$$

$$Ar_2\overset{+}{C}\cdot CCl_3 \longrightarrow (Ar)(Cl)\overset{+}{C}\cdot CCl_2Ar \qquad (2)$$

$$(Ar)(Cl)\overset{+}{C}\cdot CCl_2Ar \longrightarrow Ar\cdot\overset{+}{C}(OH)\,CCl_2Ar \qquad (3)$$

$$Ar\cdot\overset{+}{C}(OH)\cdot CCl_2Ar \longrightarrow Ar\cdot CO\cdot CCl_2Ar + H^+ \qquad (4)$$

$$ArCO\cdot CCl_2Ar \longrightarrow ArCO\cdot COAr \qquad (5)$$

This mechanism is analogous to that accepted for the transformation of, *e.g.*, diphenylglycolaldehyde into benzoin.[10]

EXPERIMENTAL

The diaryl-trichloromethyl-carbinols (I) and their acetates were obtained as described earlier.[3] In the preparation of [I (X = H)], a yield of 84% (instead of the previously reported 56%) was obtained when the preparation was carried out on a larger scale. The acetates of I may be saponified directly (without prior isolation) by refluxing the filtered reaction mixture with dilute sulfuric acid for 1.5–2 hr.

Nitration of diphenyl-trichloromethyl-carbinol (I, X = H). At −5 to −10°, a solution of 6.0 g. of diphenyl-trichloromethyl-carbinol in 15 ml. of chloroform was added dropwise, during 30 min., to a well stirred mixture of 20 ml. of nitric acid (d. 1.5) and 5 ml. of concentrated sulfuric acid. The stirring was continued for another half hour at −10° and for 4 hr. at room temperature, and the organic layer separated, washed with sodium bicarbonate solution and water and evaporated, yielding 8 g. of a yellow, very viscous product. As it could not be obtained in a crystalline state, it was acetylated by an excess of boiling acetic anhydride and 2 drops of concentrated sulfuric acid. The acetate so obtained melted at 115–130° and was a mixture of several isomers. By a number of tedious recrystallizations from acetic acid, toluene, and ethanol a small amount of colorless crystals of 154–156° was obtained. Their quantity did not suffice for the determination of the position of the two nitro groups.

Anal. Calcd. for $C_{16}H_{11}Cl_3N_2O_6$: C, 44.3; H, 2.6. Found: C, 44.3; H, 2.8.

Action of concentrated sulfuric acid on the carbinols (I). *4,4-Difluorobenzil* (II, X = F). To 2.3 g. of 1,1-di-(*p*-fluorophenyl)-1-acetoxy-2,2,2-trichloroethane, 25 ml. of concentrated sulfuric acid was added. The red color of the solution quickly turned greenish brown. The mixture was shaken for 2 hr. in a stoppered bottle and poured into cold water. The yellow 4,4′-difluorobenzil (0.6 g.; 40%), m.p. 114–120°, was recrystallized from petroleum ether (60–90°) and methanol and melted at 121.5–122.5° (lit.[6] 123–123.5°).

Anal. Calcd. for $C_{14}H_8F_2O_2$: C, 68.3; H, 3.3. Found: C, 68.1; H, 3.6.

Analogously, from the blue-violet solution of diphenyl-trichloromethyl-carbinol (I, X = H) or its acetate, *benzil*,

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m.p. and mixed m.p. 94–96° (yield, 48%), and from the red solution of di-(*p*-chlorophenyl)-trichloromethyl-carbinol (I, X = Cl), 4,4′-dichlorobenzil (yield, 36%), m.p. and mixed m.p. 200–201°,[6] was obtained. In these two cases, part of the starting material failed to dissolve in the acid and was recovered unchanged by filtration.

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Basic Alcoholysis of Diarylperfluoroalkylmethanes

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It has been reported[1] that diaryltrifluoromethylmethanes $Ar_2CH \cdot CF_3$ undergo facile alcoholysis in sodium alkoxide solution to yield the alkyl ester of the corresponding diarylacetic acid *via* the corresponding diarylketene dialkylacetal. It became of interest to investigate the behavior of diarylpentafluoroethylmethanes (I) and diarylheptafluoropropylmethanes (II) under similar conditions.

The reaction between I and sodium methoxide in anhydrous methanol, under mild conditions, caused dehydrofluorination of I and formation of the corresponding 1,1-diaryl-2,3,3,3-tetrafluoro-1-propene (III). However, when I (Ar = *p*-C_6H_4Cl) was refluxed with a five-fold excess of sodium methoxide and for an extended period of time, a compound (IV) different from (III) was isolated. IV was also obtained from III and boiling sodium methoxide solution. According to the analysis, one fluorine atom in (III) has been exchanged for a methoxyl group; the most likely formula for IV is, then, 1,1-di-(*p*-chlorophenyl)-2-methoxy-3,3,3-trifluoro-1-propene. Both III and IV were oxidized to 4,4′-dichlorobenzophenone by chromic acid; this lends support to the formula. The following reaction mechanism is suggested.

$$\underset{\text{I}}{Ar_2CH\cdot CF_2\cdot CF_3} + OCH_3^- \longrightarrow [Ar_2C\cdot CF_2\cdot CF_3]^- \xrightarrow{-F^-}$$

$$\underset{\text{III}}{Ar_2C{=}CF\cdot CF_3} \xrightarrow{+OCH_3^-} [Ar_2C\cdot CF(OCH)\cdot CF_3]^- \xrightarrow{-F^-}$$

$$\underset{\text{IV}}{Ar_2C{=}C(OCH)\cdot CF_3}$$

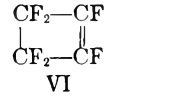
Di-(*p*-chlorophenyl)heptafluoropropylmethane (II) is even less reactive than the diarylpentafluoroethylmethanes (I); its reactivity amounts to about 60% of that of II in the reaction with boiling sodium methoxide solution, and only slowly V, the analog of IV, is formed.

An interesting parallel to these observations is the fact that perfluorocyclobutene (VI) is converted by methylalcoholic sodium hydroxide into 1,2 - dimethoxy - 3,3,4,4 - tetrafluorocyclobutene (VII).[2]

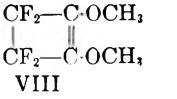
Examination of the infrared spectra of III and IV (Ar = *p*-C_6H_4Cl) shows that the 720–740 cm.$^{-1}$ frequency of the CF—CF_3 grouping in (III)[3] is absent in IV, while the latter possesses a band at 1000 cm.$^{-1}$

II $Ar_2CH\cdot CF_2\cdot CF_2\cdot CF_3$

V $Ar_2C{=}C(OCH_3)\cdot CF_2\cdot CF_3$



VI



VIII

EXPERIMENTAL

All m.p.'s were determined on a Kofler microstage; the b.p.'s are uncorrected.

β, β, γ, γ, γ-Pentafluoropropiophenone. To a Grignard solution prepared from 118 g. (0.75 mole) of bromobenzene and 18.2 g. of magnesium turnings in 250 ml. of ether, 41 g. (0.25 mole) of pentafluoropropionic acid in 70 ml. of ether was added at 5–10° over a period of 60 min. After decomposition with ice and sulfuric acid and distillation of the ether extract, 34.5 g. (61%) of pentafluoropropiophenone was obtained, b.p. 157–159° (lit.: 161–162°[4]; 158–161°[5]).

Phenylpentafluoroethylcarbinol. A quantity of 22.4 g. (0.1 mole) of the above ketone in 60 ml. of anhydrous ether was added with cooling and stirring to a suspension of 3 g. of lithium aluminum hydride in 100 ml. of ether. Ten min. later, 10 ml. of ethyl acetate was slowly added, followed by a cold solution of 100 ml. of 20% sulfuric acid. The ethereal layer was separated, dried and subjected to distillation. Yield, 15.0 g. (66%), b.p. 108–110° (42 mm.); 183–185° (760 mm.); n_D^{27} 1.4329; d_{27}^{27} 1.371; MR calcd., 42.96; MR found, 42.85.

Anal. Calcd. for $C_9H_7F_5O$: C, 47.8; H, 3.1. Found: C, 48.0; H, 3.0.

1,1-Diphenyl-2,2,3,3,3-pentafluoropropane (I, Ar = C_6H_5). When 8.2 g. (0.036 mole) of phenylpentafluoroethylcarbinol in 10 ml. of benzene was added, with stirring, to a mixture of 15 ml. of concentrated sulfuric acid and 1.5 ml. of 60% oleum within 15 min., the temperature rose from 25 to 50°. After 3 hr. of stirring at room temperature, the mixture was poured onto crushed ice and extracted with ether. Distillation gave 7.9 g. (76%) of the propane, b.p. 102–105° (2 mm.), which had been prepared previously by the reduction of diphenylpentafluoroethylcarbinol.[6]

1,1-Diphenyl-2,3,3,3-tetrafluoro-1-propene (III, Ar = C_6H_5). When 4.5 g. (0.015 mole) of I in 10 ml. of methanol was refluxed with 17.3 ml. (0.03 mole) of 1.65*N* sodium methoxide solution for 1.5 hr., some solid material precipitated which was removed by filtration. Most of the solvent was distilled off, and the resulting liquid filtered from white crystals of sodium fluoride (0.59 g.). The filtrate was then neutralized and extracted with petroleum ether (40–60°). Distillation yielded 2.4 g. (60%) of 1,1-diphenyl-2,3,3,3-

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tetrafluoro-1-propene (III, Ar = C_6H_5), b.p. 147–149° (30 mm.). n_D^{30} 1.5180; d_{30}^{30} 1.235; MR calcd., 65.10; MR found, 65.30.

Anal. Calcd. for $C_{15}H_{10}F_4$: C, 67.7; H, 3.8. Found: C, 67.5; H, 4.2.

Oxidation of III (Ar = C_6H_5) with chromic anhydride in boiling acetic acid gave benzophenone (identified as its dinitrophenylhydrazone, m.p. 236–238°).

p-Chlorophenyl pentafluoroethyl ketone. This ketone was prepared by the above described procedure using 288 g. of *p*-chlorobromobenzene, 36.4 g. of magnesium and 82 g. of pentafluoropropionic acid. Yield, 54.9 g. (42%), b.p. 186–188°.

Anal. Calcd. for $C_9H_4ClF_5O$: C, 41.8; H, 1.6. Found: C, 41.6; H, 1.7. The *dinitrophenylhydrazone* melts at 180–182° (from methanol).

Anal. Calcd. for $C_{15}H_8ClF_5N_4O_4$: C, 41.1; H, 1.8. Found: C, 41.0; H, 2.1.

(p-Chlorophenyl)pentafluoroethyl-carbinol. Reduction of the foregoing ketone (25.9 g.) with lithium aluminum hydride (3.0 g.) as described above, afforded 20.3 g. (78%) of the carbinol, b.p. 115–125° (30 mm.). It solidified and was recrystallized from petroleum ether (40–60°); m.p. 41–42°.

Anal. Calcd. for $C_9H_6ClF_5O$: C, 41.5; H, 2.3. Found: C, 40.8; H, 2.6.

1,1-Di(p-chlorophenyl)-2,2,3,3,3-pentafluoropropane (I, Ar = *p*-C_6H_4Cl). A solution of 19.7 g. (0.075 mole) of (*p*-chlorophenyl)pentafluoroethylcarbinol and 5 ml. of chlorobenzene was added to a mixture of 11 ml. of chlorobenzene, 37 ml. of 95% sulfuric acid and 3.7 ml. of 60% oleum, in the manner described before. After the usual procedure, 22 g. (83%) of the propane was obtained, b.p. 148–152° (5–6 mm.), m.p. 46–50° (from methanol). An analytical sample was obtained by recrystallization from petroleum ether (40–60°), b.p. 52–53°.

Anal. Calcd. for $C_{15}H_9Cl_2F_5$: C, 50.7; H, 2.5. Found: C, 51.0; H, 2.8.

The same compound was obtained in 48% yield by refluxing for 250 hr. 7.4 g. of di-(*p*-chlorophenyl)pentafluoroethylcarbinol[5] with 2 g. of red phosphorus and 0.8 g. of iodine in 20 ml. of glacial acetic acid and 0.5 ml. of water.

Alkaline alcoholysis of 1,1-di-(p-chlorophenyl)-2,2,3,3,3-pentafluoropropane (I, Ar = *p*-C_6H_4Cl). (a). A mixture of 14.2 g. (0.04 mole) of I (Ar = *p*-C_6H_4Cl) and 24.2 ml. of 1.65*M* sodium methoxide was refluxed for 2 hr., cooled, and filtered. The white precipitate of sodium fluoride weighed 1.55 g. Titration of the filtrate showed that 4% of the sodium methoxide had not reacted. After removal of the solvent, the residue was distilled under reduced pressure to yield 10.2 g. (76%) of 1,1-di-(*p*-chlorophenyl)-2,3,3,3-tetrafluoro-1-propene (III, Ar = *p*-C_6H_4Cl), b.p. 130–132° (4 mm.). It solidified slowly and was recrystallized from methanol or petroleum ether; m.p. 40–41°.

Anal. Calcd. for $C_{15}H_8Cl_2F_4$: C, 53.8; H, 2.4. Found: C, 53.9; H, 2.2.

Oxidation with chromic anhydride in hot acetic acid yielded 4,4′-dichlorobenzophenone, m.p. and mixed m.p. with an authentic sample 146–147°.

(b) The same operation was repeated, using a five-fold excess of sodium methoxide solution and a reflux period of 4 hr. Thus, 6.9 g. (50%) of the well crystallized 1.1-di-(*p*-chlorophenyl)-2-methoxy-3,3,3-trifluoro-1-propene (IV, Ar = *p*-C_6H_4Cl) was obtained; m.p. 58–59° (from petroleum ether).

Anal. Calcd. for $C_{16}H_{11}Cl_2F_3O$: C, 55.3; H, 3.2; F, 16.4; OCH_3, 8.9. Found: C, 55.3; H, 2.9; F, 16.8; OCH_3, 9.0.

(c) A mixture of 6.7 g. (0.02 mole) of di-(*p*-chlorophenyl)-2,3,3,3-tetrafluoro-1-propene (III, Ar = *p*-C_6H_4Cl) and 30.4 ml. of 1.65*N* sodium methoxide solution was refluxed for 2 hr. After cooling, the solution was filtered from sodium fluoride (0.80 g.); titration of the filtrate showed that 38% of the sodium methoxide employed had reacted. Upon dilution with water, 1,1-di-(*p*-chlorophenyl)-2-methoxy-3,3,3-trifluoro-1-propene (IV, Ar = *p*-C_6H_4Cl) precipitated; it solidified quickly and was recrystallized from methanol. Yield, 5.9 g. (85%), m.p. 56–58°.

Oxidation of IV (Ar = *p*-C_6H_4Cl) by chromic anhydride in hot acetic acid yielded 4,4′-dichlorobenzophenone. It may be noted that I (Ar = *p*-C_6H_4Cl) is refractory to this treatment and is recovered unchanged.

1,1-Di(p-chlorophenyl)-2,2,3,3,4,4,4-heptafluorobutane (II). A quantity of 10.5 g. (0.025 mole) of di-(*p*-chlorophenyl)-heptafluoropropylcarbinol[6] was reduced with red phosphorus and iodine in aqueous acetic acid as described above. Thus, 6.6 g. (65%) of II was obtained; b.p. 155–160° (4 mm.). The distillate solidified on standing and was recrystallized from methanol; m.p. 58–59°.

Anal. Calcd. for $C_{16}H_9Cl_2F_7$: C, 47.4; H, 2.2. Found: C, 47.0; H, 2.5.

Alkaline alcoholysis of II. When 2.1 g. of II was refluxed for 2 hr. with 3 ml. of 1.65*N* sodium methoxide solution, 0.12 g. (58% of theory) of sodium fluoride was obtained and 33% of the methoxide had not reacted. The oily product which was precipitated by addition of water, was refluxed again for 4 hr. with 10 ml. of 1.65*N* sodium methoxide solution; the solvent was evaporated after neutralization and the residue extracted with ether and fractionated. The fraction (0.7 g.), boiling at 172–175° (5 mm.), n_D^{30} 1.5312, was mainly the methoxy olefin V.

Anal. Calcd. for $C_{17}H_{10}Cl_2F_5O$: C, 51.5; H, 2.5; F, 24.0. Found: C, 51.2; H, 2.6; F, 25.8.

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Pteridines. XXI. A One-Step Synthesis of 4-Aminopteridines[1,2]

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Received December 8, 1958

A facile synthesis of 2-substituted adenines has recently been described[3] which involves the isomerization of an amidine salt of isonitrosomalononitrile (I) in an appropriate basic solvent to a 2-substituted 4,6-diamino-5-nitrosopyrimidine (II), followed by reduction to III, formylation to IV and dehydration to V in a single operation by treatment with a mixture of formamide, formic acid, and sodium hydrosulfite. The conversion of I to V may be carried out in one step by employing formamide as the solvent for the initial isomerization of I to II. Since 4,5-diaminopyrimidines (III) may be converted to pteridines by reaction with α-diketones,[4] it was apparent that the above reaction sequence leading to purines might be adapted to the synthesis of pteridines by emplcying a solvent for the isomerization which could not react

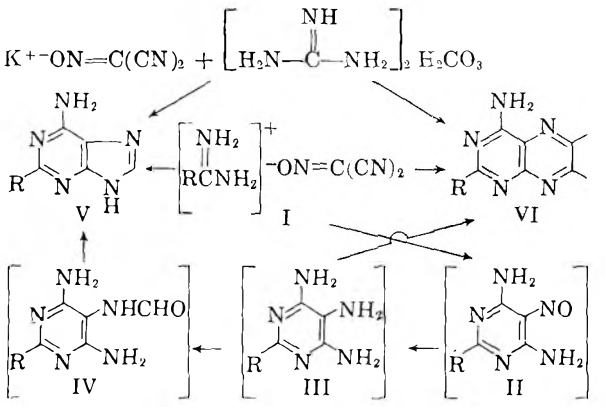
(1) This investigation was supported by a research grant (C-2551) to Princeton University from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) For the previous paper in this series, see E. C. Taylor, O. Vogl and P. K. Loeffler, *J. Am. Chem. Soc.*, 81, 2479 (1959).

(3) E. C. Taylor, O. Vogl, and C. C. Cheng, *J. Am. Chem. Soc.*, 81, 2442 (1959).

(4) A. Albert, *Quart. Rev.*, 6, 197 (1952).

with any subsequent intermediates, and by adding an α-diketone to the reaction mixture after III had been formed. In accordance with this expectation, it has been found that 4-aminopteridines (VI) may conveniently be prepared by heating amidine salts of isonitrosomalononitrile (I) in an appropriate solvent until isomerization to II is complete,



adding water and sodium hydrosulfite (thus giving III), and finally adding an α-diketone. The pteridines thus formed generally crystallize directly from the reaction mixture and are chromatographically pure (see Table I) without further purification except as indicated in the Experimental. Prior formation of the amidine salt I is not necessary in every instance. Thus, 2,4-diaminopteridines (VI. R = $-NH_2$) may be prepared directly from guanidine carbonate and the potassium salt of isonitrosomalononitrile by a reaction sequence analogous to the previously described one-step synthesis of 2,6-diaminopurine (V. R = $-NH_2$).[3]

TABLE I

R_f VALUES, DESCENDING METHOD (22°)[a]

Pteridine	4% Sodium citrate	3% NH_4Cl	*n*-BuOH/5*N* HOAc (2:1)	*n*-PrOH/1% NH_4OH (2:1)
2,4-Diamino-6,7-dimethyl-	0.25	0.54	0.43	0.65
2,4-Diamino-6,7-diphenyl-	0.08	0.17	0.73	0.88
2,4-Diamino-	0.27	0.54	0.28	0.51
2,4-Diamino-5,7-dihydroxypyrimido(5,4-g)-	0.23	~0	~0	~0
4-Amino-2,6,7-triphenyl-	~0		0.88	~1

[a] All spots are fluorescent.

EXPERIMENTAL[5]

2,4-Diamino-6,7-dimethylpteridine. A mixture of 1.0 g. of the potassium salt of isonitrosomalononitrile and 1.1 g. of guanidine carbonate in 10 ml. of ethylene glycol was warmed gently for 3 min. to give a clear, deep red solution. The mixture was diluted with 10 ml. of water, 0.6 g. of sodium hydrosulfite dihydrate added, and the mixture heated on a water bath for 20 min. until a clear, light yellow solution resulted. It was acidified to *p*H 6 with hydrochloric acid, 1 ml. of biacetyl was added, and the mixture was warmed on a water bath for 15 min. Dilution with 20 ml. of ethanol and chilling yielded 1.07 g. (75%) of a yellow crystalline solid which was identical with an authentic sample of 2,4-diamino-6,7-dimethylpteridine formed by the method of Mallette, Taylor, and Cain.[6]

2,4-Diamino-6,7-diphenylpteridine. A mixture of 1.5 g. of the potassium salt of isonitrosomalononitrile, 1.5 g. of guanidine carbonate and 12 ml. of ethylene glycol was heated for 3 min. and then reduced with 1.0 g. of sodium hydrosulfite dihydrate as described above. To the alkaline solution was added 2.2 g. of benzil dissolved in a mixture of 10 ml. of ethyl methyl ketone and 5 ml. of ethanol, and the mixture was heated under reflux for 1 hr. Filtration yielded a small amount of impurity, and the filtrate was chilled to give 1.02 g. (29%) of a yellow crystalline solid which was identical with an authentic sample of 2,4-diamino-6,7-diphenylpteridine.[6]

2,4-Diaminopteridine. A mixture of 3 g. of the potassium salt of isonitrosomalononitrile, 3.3 g. of guanidine carbonate and 20 ml. of ethylene glycol was heated for a few minutes and then reduced with 1.8 g. of sodium hydrosulfite dihydrate, as described above. The light yellow solution was acidified to *p*H 3 with hydrochloric acid and then treated with a solution of 7.5 g. of glyoxal bisulfite in 50 ml. of water. After 40 min. of stirring at 110°, the reaction mixture was allowed to stand at room temperature overnight, made alkaline with ammonium hydroxide, acidified again with glacial acetic acid and filtered. The collected light yellow solid (3.55 g., 97%) was purified by sublimation at 240°/0.05 mm. The product was shown to be 2,4-diaminopteridine by comparison with an authentic sample.[6]

2,4-Diamino-5,7-dihydroxypyrimido(5,4-g)pteridine. A mixture of 2.0 g. of the potassium salt of isonitrosomalononitrile and 2.2 g. of guanidine carbonate was isomerized and then reduced as described above. To the light yellow reduction solution was added 20 ml. of 1*N* hydrochloric acid followed by 2.0 g. of alloxan. The reaction mixture immediately became deep purple, but on shaking it gradually turned orange with the simultaneous separation of an orange solid. The reaction mixture was adjusted to *p*H 9 with potassium hydroxide, heated at 110° for 10 min., reacidified to *p*H 6 with hydrochloric acid and chilled to give 2.8 g. (76%) of an orange solid, m.p. >350°. The product was shown to be identical with an authentic sample of 2,4-diamino-5,7-dihydroxypyrimido(5,4-g.)pteridine prepared by the method of Taylor, Cain, and Loux.[7]

4-Amino-2,6,7-triphenylpteridine. A mixture of 2.0 g. of the benzamidine salt of isonitrosomalononitrile[3] and 10 ml. of 2-picoline was heated at 135° for 30 min. The reaction mixture was diluted with 20 ml. of water and the bluish green suspension was evaporated to dryness under reduced pressure. The residue was treated with 25 ml. of water, heated to 90–100° and treated portionwise with 1.6 g. of sodium hydrosulfite dihydrate. The resulting light brownish-yellow solution was stirred for 20 min., treated with 2 g. of benzil dissolved in a mixture of 15 ml. of ethyl methyl ketone and 15 ml. of ethanol and heated under reflux for 2 hr. Cooling of the reaction mixture yielded a yellow solid which was recrystallized from aqueous ethanol to give 1.9 g. (54.5%) of light yellow, fluffy needles, m.p. 255°.

(5) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J.

(6) F. M. Mallette, E. C. Taylor, and C. K. Cain, *J. Am. Chem. Soc.*, **69**, 1814 (1947).

(7) E. C. Taylor, C. K. Cain, and H. M. Loux, *J. Am. Chem. Soc.*, **76**, 1874 (1954).

λ_{max}^{EtOH} 290, 377 mμ; log ε 4.53, 4.23.
Anal. Calcd. for $C_{24}H_{17}N_5$: C, 76.8; H, 4.6; N, 18.7. Found: C, 76.7; H, 4.4; N, 19.0.

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Phenyl and Chlorophenyl Derivatives of 1,4-Dihydro-2-pyrimidinethiol

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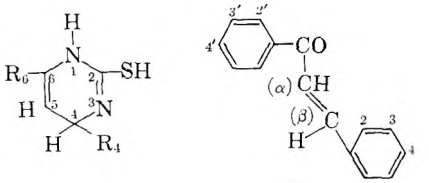
In order to facilitate continued studies[1] on the potential anticancer activity of mercaptopyrimidines,[2] we have prepared and characterized five new mono- and dichloro-derivatives (formulas I–V) of 1,4-dihydro-4,6-diphenyl-2-pyrimidinethiol, and one new dichlorochalcone (X). Such dihydropyrimidinethiols are conveniently prepared by the general procedures of Mathes *et al.*[3,4] and of Robbins,[5] the latter being suitable for derivatives such as I with no substituent on nitrogen. The needed mono and dichloro chalcone intermediates were prepared by alkaline condensation of appropriate acetophenone and benzaldehyde derivatives.

The effect of these five new thiols (and of eighteen similar but previously known thiols) on the mean survival time of Webster-Swiss mice inoculated with the Ehrlich ascites tumor is now being examined, and the results will be reported elsewhere. In previously reported tests[1] in our laboratory on thirty other dihydropyrimidinethiols, marginal activity was found in several cases.

These compounds are of interest not only because of their structural similarity to the well known antileukemic agent, 6-mercaptopurine, but also because of the recent finding[6] that dihydropyrimidines may be intermediates in the catabolism of pyrimidines.



I. R_4 = *o*-Cl-Phenyl, R_6 = Phenyl
II. R_4 = *m*-Cl-Phenyl, R_6 = Phenyl
III. R_4 = *p*-Cl-Phenyl, R_6 = Phenyl
IV. R_4 = Phenyl, R_6 = p-Cl-Phenyl
V. R_4 = *o*-Cl-Phenyl, R_6 = p-Cl-Phenyl
VI. 2-Chloro
VII. 3-Chloro
VIII. 4-Chloro
IX. 4′-Chloro
X. 2,4′-Dichloro

EXPERIMENTAL

All melting and boiling points have been corrected. Melting points were determined with a *Monoscop* micro hot stage. Microanalyses by the Micro-Tech Laboratories, Skokie, Ill., and by Weiler and Strauss, Oxford, England.

2,4′-Dichlorochalcone (X). To a solution of 5.7 g. of sodium hydroxide in 60 ml. of methanol at 25° was added gradually with stirring a solution of 18 g. of *o*-chlorobenzaldehyde and 20 g. of *p*-chloroacetophenone in 100 ml. of methanol. The precipitate which separated almost immediately was collected by filtration, washed with ice cold methanol, and dried, giving 32 g. (90%) of crude product, m.p. not determined. A sample recrystallized from ethanol for analysis (pale yellow needles) melted sharply at 85–86°.

Anal. Calcd. for $C_{15}H_{10}Cl_2O$: C, 65.00; H, 3.64: Cl, 25.59. Found: C, 64.54; H, 3.58: Cl, 26.00.

4-o-Chlorophenyl-1,4-dihydro-6-phenyl-2-pyrimidinethiol (I). To 36.4 g. of 2-chlorochalcone (VI, m.p. 46–52°, reported[7] m.p. 50–52°) was added 15.2 g. of anhydrous ammonium thiocyanate, 80 ml. of anhydrous commercial xylene (isomer mixture) and 15 ml. of cyclohexanol, and the mixture boiled under reflux until (24 hr.) the formation of water had almost ceased. The liberated water was collected and measured by means of a Stark and Dean trap. After cooling, the liquid phase was decanted from the crystalline residue of unreacted ammonium thiocyanate, and vacuum distilled. The viscous, syrupy residue was stirred with 100 ml. of acetone, and the mixture chilled overnight. The crystalline product which separated was collected by filtration, and dried, giving 14.0 g. (31%) of material melting at 182–184°. A sample recrystallized for analysis (colorless needles) melted at 184–184.5°.

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.88: H, 4.36; Cl, 11.79, Found: C, 63.81: H, 4.45; Cl, 11.47.

The infrared spectra were recorded for this compound and for the other pyrimidinethiols described below. The spectra were very complex, and showed only slight changes from one isomer, or analog, to another.

4-m-Chlorophenyl-1,4-dihydro-6-phenyl-2-pyrimidinethiol (II). From 16.0 g. of 3-chlorochalcone (VII, m.p. 74–76°, reported[8] m.p. 75°) by a similar procedure (reflux time 40 hr.) there was obtained 7.2 g. (36%) of crude II, m.p. 196–199°. A sample recrystallized from ethanol (colorless needles) melted at 202–204°.

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.88: H, 4.36: Cl, 11.79. Found: C, 64.11: H, 4.43: Cl, 11.82.

4-p-Chlorophenyl-1,4-dihydro-6-phenyl-2-pyrimidinethiol (III). From 20.2 g. of 4-chlorochalcone (VIII, m.p. 113–115°, reported[8] m.p. 114.5°) by a similar procedure (reflux time 20 hr.) there was obtained 6.2 g. of III.

In order to improve the yield, the syrupy residue obtained by evaporation of the mother liquor was recycled with additional ammonium thiocyanate (7.6 g.), xylene and cyclohexanol, giving 4.0 g. of additional crude product,

(1) For reports of previous tests, see A. Furst, W. Cutting, and Hudi Gross, *Proc. Am. Assn. Cancer Res.*, Vol. 2, April, 1956.

(2) For anticancer studies on certain 2- and 6-pyrimidinethiols (not dihydro) see: (a) A. di Marco and M. Gaetani, *Estratto da Tumori*, 42, 531 (1956); (b) E. J. Modest and H. N. Schlein, *Abstracts of Papers*, April 1955 Meeting American Chemical Society, page 7-M; (c) J. F. Holland *et al. Cancer Research*, 18, 776 (1958).

(3) R. A. Mathes, *J. Am. Chem. Soc.*, 75, 1747 (1953).

(4) R. A. Mathes, F. Stewart, and F. Swedish, *J. Am. Chem. Soc.*, 70, 1452 (1948). (*Note:* The " . . . 4,6,6-trimethylpyrimidines" mentioned in this publication should apparently have been designated ". . . *1,4-dihydro*-4,4,6-trimethylpyrimidines."

(5) T. E. Robbins, U. S. Patent 2,539,480, January 30, 1951.

(6) R. M. Fink, R. E. Cline, and H. M. Koch, *Federation Proc.*, Vol. 13, March, 1954.

(7) C. L. Bickel, *J. Am. Chem. Soc.*, 68, 865 (1946).

(8) J. F. J. Dippy and R. H. Lewis, *Rec. trav. chim.*, 56, 1000 (1937).

m.p. the same. The total yield was thus 10.2 g. (41%). A sample recrystallized from ethanol for analysis melted at 169–170° (colorless needles).

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.88: H, 4.36: Cl, 11.79. Found: C, 64.11: H, 4.40: Cl, 11.40.

6-p-Chlorophenyl-1,4-dihydro-4-phenyl-2-pyrimidinethiol[9] (IV). From 17.8 g. of 4'-chlorochalcone (IX, m.p. 94–96°, reported[10] m.p. 96°) by a procedure similar to that used for I there was obtained 5.6 g. (25%) of crude product, m.p. 212–216°. A sample recrystallized from ethanol was obtained as colorless needles, m.p. 218–220°.

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.88: H, 4.36: Cl, 11.79. Found: C, 64.08: H, 4.37: Cl, 11.81.

4-o-Chlorophenyl-6-p-chlorophenyl-1,4-dihydro-2-pyrimidinethiol (V). From 20.0 g. of recrystallized 2,4'-dichlorochalcone (X, m.p. 85–86°) by similar procedure (20 hr. reflux time) there was obtained 7.2 g. (30%) of crude V, m.p. 206–208°. The analytic sample, colorless needles, melted at 207–209°.

Anal. Calcd. for $C_{16}H_{12}Cl_2N_2S$: C, 57.32: H, 3.61: Cl, 21.15. Found: C, 57.64: H, 3.76: Cl, 20.67.

Acknowledgment. This work was aided by a grant C-2798(C) from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service, and by an American Cancer Society Institutional Grant to Stanford University.

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(9) It is of interest that the isomeric phenylchlorophenyldihydropyrimidine-thiols III and IV might in principle be interconverted by an allylic rearrangement, or 1,3 prototropic shift. However, no such interconversion has been noted under the conditions thus far employed.

(10) C. F. H. Allen and G. F. Frame, *Can. J. Res.*, 6, 605 (1932).

Some Urea and Picrate Derivatives of Pyridoxamine

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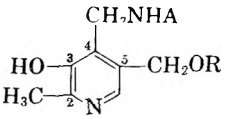
In order to facilitate continued studies[1] on cancer chemotherapy, we have synthesized pyridoxurea hydrochloride[2] (formula II), a derivative of the well known vitamin pyridoxamine (I), in which the primary amino group is replaced by a ureido group. Pyridoxamine free base when briefly heated with equimolar amounts of potassium cyanate and dilute hydrochloric acid reacted to form the desired urea. This product could conveniently be isolated only by conversion to its monopicrate (II.HPic). The picrate, being presumably too toxic for therapeutic use, was converted in the usual manner to the corresponding monohydrochloride (II.HCl), a colorless, stable crystalline solid.

Attempted regeneration of the picrate with an anhydrous solution[3] of hydrogen chloride in acetic acid caused simultaneous acetylation of the primary alcohol group, giving the urea 5-O-acetate monohydrochloride (III.HCl).

In order to facilitate characterization of the urea picrate, the previously unreported pyridoxamine monopicrate (I.HPic) was prepared and characterized. Although pyridoxamine free base (I) and the corresponding dipicrate (I.2HPic) have been reported previously,[4,5] it appears that the first detailed and explicit account of their preparation is that now given.



I. R = A = H
II. R = H, A = $-CONH_2$
III. R = $-COCH_3$, A = $-CONH_2$

Numerous attempts to prepare the thiourea analog of II, using various suitable reagents, have led to no useful result. To obtain this derivative it might be necessary to introduce temporary protective groups to prevent possible interference by the phenolic or primary alcohol functional groups.

Biological tests of the various compounds described below against the Ehrlich ascites tumor in Swiss-Webster mice, and other chemotherapeutic tests, are now in progress and will be reported elsewhere.

EXPERIMENTAL

All melting and boiling points have been corrected Melting points were determined with a *Monoscop* micro hot-stage. Microanalyses by the Micro-Tech Laboratories, Skokie, Ill.

4-Aminomethyl-3-hydroxy-2-methyl-5-pyridinemethanol (pyridoxamine free base). To a solution of 2.02 g. of sodium bicarbonate in 20 ml. of water was added 2.41 g. of pyridoxamine dihydrochloride, with stirring. The resulting clear solution on standing overnight deposited a crystalline precipitate, which was collected, washed with water, and dried, giving 1.4 g. (83%) of colorless, flaky lumps, very difficult to pulverize. Under the microscope, colorless needles were visible.

This material was recrystallized from absolute ethanol (35 ml./g.; filter hot), giving 0.9 g. of colorless crystals, m.p. 190–191°, reported[4] m.p. 193.5°. The crystals become discolored on prolonged exposure to air and light.

4-Aminomethyl-3-hydroxy-2-methyl-5-pyridinemethanol picrate (pyridoxamine monopicrate). To 168 mg. of pyridoxamine free base in 10 ml. of boiling absolute ethanol was

(1) For previous publication, see G. E. McCasland, Erwin Blanz, Jr., and Arthur Furst, *J. Org. Chem.*, 23, 1570 (1958).

(2) *Pyridoxurea* is here used as a trivial name for the derivative of pyridoxamine in which a ureido group has replaced the amino group.

(3) This reagent is most conveniently prepared by adding acetic anhydride to concentrated hydrochloric acid. See ref. 1.

(4) S. A. Harris, D. Heyl, and K. Folkers, *J. Am. Chem. Soc.*, 66, 2088 (1944).

(5) E. E. Snell, *J. Am. Chem. Soc.*, 67, 194 (1945).

added a solution of 229 mg. of picric acid[6] in 3.0 ml. of hot absolute ethanol. After cooling, the yellow crystalline product was collected by filtration, washed, and dried (weight 335 mg.).

The material was recrystallized from absolute ethanol (150 ml./g.). After one or two days, there were obtained sheaves of yellow needles, dry weight 221 mg. (56%) m.p. 177–181° (gradually turns to dark viscous liquid).

Anal. Calcd. for $C_{14}H_{13}N_6O_9$: C, 42.32; H, 3.81. Found: C, 41.97; H, 3.66.

4-Aminomethyl-3-hydroxy-2-methyl-5-pyridinemethanol dipicrate (pyridoxamine dipicrate). (A) To pyridoxamine free base (84 mg.) in 6 ml. of boiling ethanol was added a solution of 229 mg. of picric acid[6] in 5 ml. of hot ethanol. The yellow precipitate was collected, washed, dried, and recrystallized from absolute ethanol (220 ml./g.), giving 139 mg. (44%) of glistening yellow leaflets, m.p. 189–192° (gradually changes to dark liquid). The reported[5] (capillary) melting point is 201° (dec.).

This picrate when recrystallized from water separates in the form of long yellow needles.

(B) In an attempted preparation of pyridoxamine thiourea picrate, a solution of 964 mg. of pyridoxamine dihydrochloride, 583 mg. of anhydrous potassium thiocyanate, and 336 mg. of sodium bicarbonate, in 5.0 ml. of water was boiled 10 min. A solution of 1.01 g. of picric acid[6] in 20 ml. of boiling water was then added. The yellow crystals which separated on cooling were collected, washed, and dried (weight 1.3 g.). The material was recrystallized from water (57 ml./g.), giving 1.15 g. (dry weight) of long yellow needles, consisting of starting material dipicrate. The melting behavior was identical with that of the product in Part A (above).

Anal. Calcd. for $C_{20}H_{18}N_8O_{16}$: C, 38.34; H, 2.90; N, 17.88. Found: C, 38.23; H, 2.71; N, 17.56.

3-Hydroxy-2-methyl-4-ureidomethyl-5-pyridinemethanol picrate (pyridoxurea monopicrate). To 336 mg. of pyridoxamine free base was successively added 162 mg. of potassium cyanate, 5.0 ml. of water, and 0.33 ml. of 6*M* hydrochloric acid, with stirring. The resulting mixture was heated to boiling, giving a clear solution, which was boiled under reflux for an additional 10 min.

A 458 mg. portion of crystalline picric acid[6] was added all at once, and the mixture boiled for 5 min. On cooling, there separated yellow crystals, which were collected by filtration, washed with two 5-ml. portions of water, and dried, giving 750 mg. (85%) of crude product.

For analysis, a portion of this material was recrystallized from absolute ethanol (175 ml./g.). After 24 hr. a good recovery was obtained of long yellow needles, m.p. 198–203° (dec.). (It was later found that 50% ethanol, 37 ml./g., is a more convenient crystallizing solvent.).

Anal. Calcd. for $C_{15}H_{16}N_6O_{10}$: C, 40.91; H, 3.66; N, 19.09. Found: C, 41.05; H, 3.41; N, 18.59.

From the mother liquors on standing there separated yellow prisms, which have not yet been characterized.

3-Hydroxy-2-methyl-4-ureidomethyl-5-pyridinemethanol hydrochloride (pyridoxurea monohydrochloride). A 1.55-g. portion of the urea picrate was dissolved in 10.0 ml. of 6*M* hydrochloric acid, and the solution extracted twice with 25 ml. portions of benzene. The acidic aqueous phase was separated, and vacuum distilled to dryness. The residue was recrystallized from 1:1 absolute ethanol–methanol, and dried, giving 560 mg. (64%) of colorless needles, m.p. 205–208° (dec.).

Anal. Calcd. for $C_9H_{14}ClN_3O_3$: C, 43.64; H, 5.70; Found: C, 43.62; H, 5.87.

5-Acetoxymethyl-3-hydroxy-2-methyl-4-ureidomethylpyridine hydrochloride (pyridoxurea 5-O-acetate monohydrochloride). To 440 mg. of the above urea picrate there was added 2.05 ml. of a 2.44*M* solution of hydrogen chloride[3] in glacial acetic acid, with stirring. Within a few minutes the yellow crystals changed into a nearly colorless oil. The mixture was allowed to stand for 24 hr., and 5.0 ml. of benzene was then added, with stirring.

After 30 min. the yellowish crystals were removed by filtration and washed repeatedly with additional 5 ml. portions of benzene until colorless. The crude vacuum-dried (over sodium hydroxide) product weighed 2.5 mg. and melted with decomposition at 190–210°.

To the product in 5.4 ml. of boiling absolute ethanol (slight residue) was added sufficient water (5–10 drops) to give a clear (yellow) solution. On cooling there was obtained 86 mg., dry weight (30%), of flat colorless needles, m.p. 200–208 (dec.).

For analysis this material was again recrystallized, from 95% ethanol, giving sheaves of colorless needles, m.p. 203–206° (dec.).

Anal. Calcd. for $C_{11}H_{16}ClN_3O_4$: C, 45.60; H, 5.57; N, 14.50. Found: C, 45.50; H, 5.42; N, 14.40.

A sample when tested for phenolic hydroxyl with ferric chloride gave an immediate deep red brown color (positive test). A control test on pyridoxamine dihydrochloride gave a similar color. An additional control test on 3-amino-5-aminomethyl-4-ethoxymethyl-2-methylpyridine[7] (which has no phenolic group) did not give any color.

The infrared spectrum (determined with a Perkin-Elmer Model 21 Recording Spectrophotometer, using a potassium bromide pellet) showed a strong absorption maximum at 1730 cm.$^{-1}$. This peak presumably represents the stretching vibration of the ester carbonyl group,[8] and is missing in the spectrum of the nonacetylated urea hydrochloride (II.HCl). A comparison spectrum on pyridoxamine dihydrochloride itself likewise had no absorption maximum in this region.

Acknowledgment. This work was aided by a grant C-2798-C from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service, and by an American Cancer Society Institutional Grant to Stanford University. Pyridoxamine dihydrochloride was supplied by Dr. Howard W. Bond and Dr. Ronald B. Ross of the Cancer Chemotherapy National Service Center.

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(6) The commercial picric acid used presumably contains up to 10% of added water; it is unfortunate that the manufacturers seldom, if ever, specify on the label the added water content of this reagent.

(7) S. A. Harris and K. Folkers, *J. Am. Chem. Soc.*, 61, 1245 (1939).

(8) Although acylation of a urea primary amino group is sometimes possible, we believe that the strongly acidic conditions here used would prevent amine acylation, and at the same time would favor esterification. Under strongly acidic conditions acyl groups, even if originally attached to nitrogen, tend to migrate to oxygen.

Some Sulfones of the Anthraquinone Series

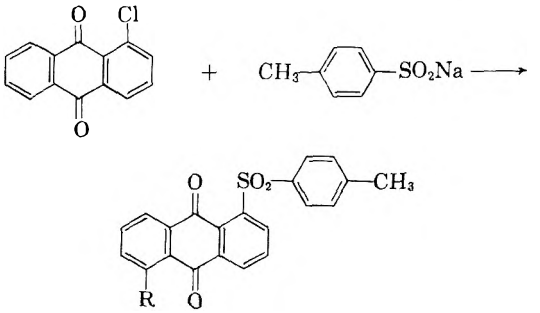
ERWIN KLINGSBERG

Received December 18, 1958

Anthraquinonyl sulfones are usually prepared by oxidation of the corresponding thioethers, which are obtainable from haloanthraquinones, either di-

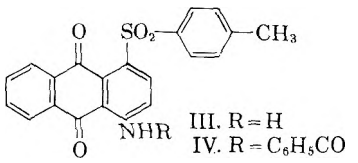
rectly or *via* the mercaptans. The reaction of a haloanthraquinone with an alkali sulfinate, to give the sulfone in one step, has apparently never been tried.

1-Chloroanthraquinone did, in fact, react smoothly with sodium *p*-toluenesulfinate in refluxing diethylene glycol monoethyl ether to give the sulfone (I). 5-Benzamido-1-chloroanthraquinone reacted similarly to give II, though in poorer yield.



I. R = H
II. R = $NHCOC_6H_5$

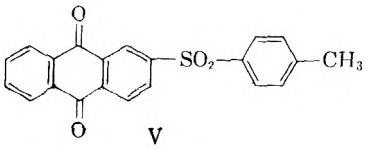
With 4-benzamido-1-chloroanthraquinone, results were not very reproducible, although it was possible to isolate the debenzoylated sulfone (III) in rather poor yield; this could be benzoylated to IV.



III. R = H
IV. R = C_6H_5CO

The sulfone group is removed by syrupy phosphoric acid, converting III to 1-aminoanthraquinone.

As would be expected, 2-chloro derivatives proved less reactive. 2-Chloro-3-anthraquinonecarboxylic acid gave a poor yield of the decarboxylated sulfone (V), while 2-chloroanthraquinone gave a



V

reaction mixture containing unchanged starting material and sulfone (V). The latter was not isolated but was identified by infrared comparison with the pure compound.

Ultraviolet and visual spectra. Table I gives wave lengths and molecular extinction coefficients for all absorption peaks shown by these sulfones in the visual and ultraviolet range, measured in methylene dichloride. The positions of the peaks of highest wave length were then correlated (Table II) by the recent method of Labhart.[1] In his analysis, the energy difference between the ground state and the first excited state, considered as a function of the nature and position of the substituents, is expanded in a Taylor series through the square terms. This gives rise to two sets of parameters, of which the ring position parameters are called α's and the substituent parameters, b's. In this way, Labhart made fairly accurate wave-length computations for anthraquinone derivatives containing no more than two substituents.

TABLE I

VISUAL AND ULTRAVIOLET ABSORPTION[a]

Sulfone	Band 1		Band 2		Band 3	
	λ_{max}	ϵ	λ_{max}	ϵ	λ_{max}	ϵ
I	325	4500	255	39,000	...	...
II	425	6800	252	44,000	...	...
III[b]	448	4940	306	11,500	248	38,100
IV	400	4600	310	22,700	265	40,400
V	325	6600	258	49,000	...	...

[a] The spectra were measured at 10 mg./l. concn. in dichloromethane, the visual with a modified Hardy-type and the ultraviolet with a Cary recording spectrophotometer. [b] Shoulder at 275 mμ (ϵ = 15,600).

TABLE II

FIRST ABSORPTION MAXIMA

Sulfone	λ_{max} (mμ)		ΔE (eV)	
	Found	Calcd.	Found	Calcd.
I[a]	325	...	3.83	...
II	425	414	2.92	3.00
III	448	462	2.77	2.68
IV	400	410	3.10	3.02
V	325	325	3.82	3.82

[a] The calculation of the parameter b = −0.03 for the *p*-toluenesulfonyl group is based on this compound; this value is used in turn to compute λ_{max} and ΔE for the remaining compounds.

Table II shows the moderately successful predictions of the first absorption peaks for these sulfones; it might be said that they do not constitute a very severe test of Labhart's equation, inasmuch as the *p*-toluenesulfonyl group does not affect absorption very strongly. Its feebly hypsochromic influence is reflected in the low negative value of −0.03 for its parameter, which causes the square terms to vanish in the energy expansion. Nevertheless, it is interesting to incorporate these compounds in the Labhart scheme, which was naturally based almost exclusively on the far commoner bathochromic substituents. It is of the nature of this scheme that each addition to it multiplies the scope of its predictive power.

EXPERIMENTAL[2]

1-(p-Toluenesulfonyl)anthraquinone (I). A mixture of 2.4 g. (0.010 mole) 1-chloroanthraquinone and 2.0 g. (0.011 mole) sodium *p*-toluenesulfinate in 75 ml. of diethylene glycol monoethyl ether was stirred for 5 hr. at 180–190° and then cooled and diluted with water, giving 2.8 g. (78%

(1) H. Labhart, *Helv. Chim. Acta*, **40**, 1410 (1957).

(2) Melting points are corrected.

yield) of yellow solid, m.p. 248–251°. (Additional product was obtainable by further dilution.) Crystallization from acetic acid or xylene raised the m.p. to 257–258°.

Anal. Calcd. for $C_{21}H_{14}O_4S$: C, 69.6; H, 3.9; S, 8.8. Found: C, 69.4; H, 3.6; S, 8.8.

5-Benzamido-1-(p-toluenesulfonyl)anthraquinone (II). 5-Benzamido-1-chloroanthraquinone crystallized from acetic acid as orange-yellow needles, m.p. 221.5–222.5°.

Anal. Calcd. for $C_{21}H_{12}ClNO_3$: C, 69.7; H, 3.3; Cl, 9.8; N, 3.9. Found: C, 69.8; H, 3.4; Cl, 9.8; N, 3.7.

A mixture of 1.8 g. (5.0 mmol.) 5-benzamido-1-chloroanthraquinone and 1.0 g. (5.6 mmol.) sodium *p*-toluenesulfinate in 25 ml. of diethylene glycol monoethyl ether was stirred under reflux for 7 hr. in an oil bath at 195–200°, cooled partially, diluted with about 3 ml. of water, cooled to room temperature, and filtered. The orange-yellow product was crystallized from 40 ml. xylene, giving a yield of 1.40 g. (58%) with m.p. 257–260°. Crystallization from acetic acid or xylene raised the m.p. to 259–260°.

Anal. Calcd. for $C_{28}H_{19}NO_5S$: C, 69.8; H, 4.0; N, 2.9; S, 6.6. Found: C, 69.7; H, 3.7; N, 3.2; S, 6.8.

4-Amino-1-(p-toluenesulfonyl)anthraquinone (III). 4-Benzamido-1-chloroanthraquinone crystallized from acetic acid as yellow needles of m.p. 234.5–236°.

Anal. Calcd. for $C_{21}H_{12}ClNO_3$: C, 69.7; H, 3.3; Cl, 9.8; N, 3.9. Found: C, 69.5; H, 3.5; Cl, 9.9; N, 3.9.

A mixture of 5.0 g. (0.014 mole) 4-benzamido-1-chloroanthraquinone, 3.0 g. (0.017 mole) sodium *p*-toluenesulfinate, and 50 ml. of diethylene glycol monoethyl ether was stirred and refluxed for 16 hr., cooled slightly, diluted with 5 ml. of water, cooled to room temperature, and filtered. The product was washed with a little methanol and crystallized from 500 ml. of xylene, giving 2.6 g. (50%) of orange solid, m.p. 254–259°. Crystallization from acetic acid raised the m.p. to 260–261°.

Anal. Calcd. for $C_{21}H_{15}NO_4S$: C, 66.9; H, 4.0; S, 8.5. Found: C, 67.2; H, 3.8; S, 8.6.

As with others of these sulfones, yields were lower on larger runs. On 5 hr. refluxing in sirupy phosphoric acid, this product is converted to 1-aminoanthraquinone, identified by m.p., analysis, and formation of the benzoyl derivative.

The *N*-benzoyl derivative (IV) of the sulfone was prepared by 3 hr. refluxing with benzoyl chloride in *o*-dichlorobenzene. It crystallized from acetic acid in fine yellow needles, m.p. 273–275°.

Anal. Calcd. for $C_{28}H_{19}NO_5S$: C, 69.8; H, 4.0; N, 2.9; O, 16.6; S, 6.6. Found: C, 70.0; H, 4.0; N, 2.8; O, 16.5; S, 6.7.

2-(p-Toluenesulfonyl)anthraquinone (V). A mixture of 2.9 g. (0.010 mole) 2-chloro-3-anthraquinonecarboxylic acid and 6.0 g. (0.034 mole) sodium *p*-toluenesulfinate in 75 ml. of diethylene glycol monoethyl ether was stirred under reflux for 24 hr. in an oil bath at 190–195°. After cooling, dilution with water, and filtration, the product was crystallized from 30 ml. of acetic acid containing 4 ml. of water, giving 0.95 g. (26% yield) yellow solid, m.p. 194–205°. Further crystallization from acetic acid alternating with mixed amyl alcohols gave 0.60 g. (17% yield) of white product, m.p. 211.5–212.5°. It was insoluble in ammonium or sodium hydroxide.

Anal. Calcd. for $C_{21}H_{14}O_4S$: C, 69.6; H, 3.9; S, 8.8. Found: C, 69.5; H, 3.8; S, 8.8.

A mixture of 2.4 g. (0.010 mole) 2-chloroanthraquinone and 2.0 g. (0.011 mole) sodium *p*-toluenesulfinate in 75 ml. of diethylene glycol monoethyl ether, stirred and refluxed at 185–195° for 5 hr., gave 2.1 g. yellow solid, m.p. approximately 175–190°, unchanged upon crystallization first from acetic acid and then from ethylene glycol monomethyl ether. The presence of the sulfone in the mixture was indicated by a prominent infrared absorption band at 1143 cm.$^{-1}$, which is in the region characteristic of sulfone absorption,[3] and is also shown by the pure sulfone but not by 2-chloroanthraquinone.

Elementary analysis for chlorine and sulfur was in agreement with a mixture containing 47% sulfone and 53% 2-chloroanthraquinone.

Anal. Calcd. for 47% $C_{21}H_{14}O_4S$ and 53% $C_{14}H_7ClO_2$: Cl, 7.7; S, 4.1. Found: Cl, 7.9; S, 4.1.

When the reaction was run for 24 hr. with a 3:1 mole ratio of sodium *p*-toluenesulfinate to 2-chloroanthraquinone, a chlorine-free mixture was obtained, again too low in sulfur content for the sulfone.

Acknowledgments. The author is indebted to F. C. Dexter for visual and ultraviolet absorption data, to Miss J. L. Gove for infrared data, and to O. E. Sundberg and his associates for microanalyses.

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(3) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2d. ed., J. Wiley & Sons, Inc., New York, 1958, p. 361.

Nitrosation of α-Aceto-γ-butyrolactone. Isolation of an *O*-Acetyloximino Intermediate

ANTHONY E. LANZILOTTI AND MARTIN J. WEISS

Received December 22, 1958

In the course of some synthetic work in the amino acid field we had occasion to prepare α-oximino-γ-butyrolactone (IV). When this preparation was carried out by the method of Feofilaktov and Onishchenko,[1] a procedure which involves the reaction of nitrous acid with α-aceto-γ-butyrolactone (I), an intermediate compound, not previously described by the Russian workers, was isolated. This white, crystalline product (m.p. 89–90°) is sensitive to solvolytic action and thus is slowly hydrolyzed in the presence of moisture to form the desired α-oximino-γ-butyrolactone (IV) with the liberation of acetic acid. Hydrolysis with dilute hydrochloric acid readily converts this intermediate compound to IV in 68% yield.[2]

From similar experiments, Sudo and co-workers[3] and also Reppe and co-workers[4] reported the isolation of an intermediate compound (m.p. 88°) which appears to be identical to the one described above. These investigators assumed that this compound was α-aceto-α-nitroso-γ-butyrolactone (II). The compound isolated in our laboratory showed infrared absorption bands at 5.98μ and 8.50μ. The presence of these bands, which were interpreted as corresponding to a C=N grouping and to

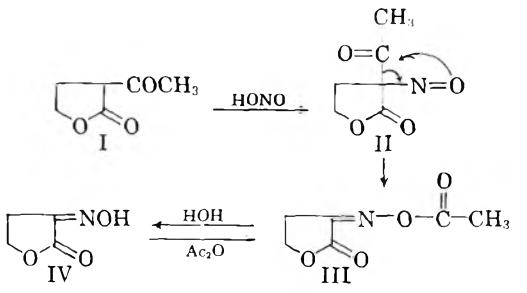
(1) V. Feofilaktov and A. Onishchenko, *J. Gen. Chem. (U.S.S.R.)*, **9**, 304 (1939); *Chem. Abstr.*, **34**, 378 (1940).

(2) Gas evolution was observed during the course of this hydrolysis. It is possible that some of the lactone is opened and the resulting α-oximino (or α-keto) acid undergoes decarboxylation to produce β-hydroxypropionaldehyde or the corresponding oxime.

(3) R. Sudo, Y. Akiyama, T. Kato, and M. Ohta, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **74**, 1009 (1953); *Chem. Abstr.*, **49**, 6829 (1955).

(4) W. Reppe and co-workers, *Ann.*, **596**, 164 (1955).

an acetoxy group of the enol acetate type, respectively, and the apparent absence of a nitroso band in the spectrum indicated that this compound was probably not the nitroso derivative II, as claimed by the previous workers,[3,4] but was rather *O*-acetyl-α-oximino-γ-butyrolactone (III). Furthermore, this product showed an ultraviolet absorption maximum in acetonitrile solution at 210 mμ (ϵ = 13,400) indicating the presence of a conjugated chromophoric grouping. The presence of such a group is consistent with structure III but not with structure II. Isolation of unchanged III from acetonitrile solution indicated that the ultraviolet absorption was due to the oximino acetate III and not to its hydrolytic product IV (λ_{max}^{MeCN} 218 mμ, ϵ = 11,200). Confirming evidence for structure III was obtained by comparison with a sample of III, prepared by acetylation of α-oximino-γ-butyrolactone (IV).



The formation of the *O*-acetyloximino derivative may be interpreted as proceeding *via* an intramolecular 1,3-rearrangement of the initially formed α-aceto-α-nitroso-γ-butyrolactone (II). This rearrangement may be considered analogous to the prototropic isomerization of a nitroso compound to its tautomeric oxime.[5]

It is interesting to note that Feofilaktov and Onishchenko[6] similarly observed the formation of *O*-acetyl-α-oximino-γ-chloromethyl-γ-butyrolactone on nitrous acid treatment of α-aceto-γ-chloromethyl-γ-butyrolactone. These workers considered the formation of the *O*-acetate as indicative of an anomalous course of reaction. However, in view of our results it is probable that the *O*-acetate is the usual intermediate for this type of reaction. Indeed, we would point out that these results are suggestive of a possible mechanism for the general reaction[7] whereby nitrous acid treatment of an α-substituted β-keto ester, malonic acid or ester, or cyanoacetic ester results in the replacement of an acyl group by an oximino group. It is possible that these reactions all involve an initial nitrosation followed by a rearrangement to a readily-solvolyzable *O*-acyloximino intermediate.

EXPERIMENTAL[8]

O-Acetyl-α-oximino-γ-butyrolactone (III). (A) *Nitrosation of α-aceto-γ-butyrolactone.* To a cooled (+5°) solution of α-aceto-γ-butyrolactone (I, 250 g., 1.95 mole) and sodium nitrite (160 g., 2.32 mole) in 400 ml. of water was added 400 ml. of 6*N* aqueous hydrochloric acid over a period of 1 hr. The reaction mixture was allowed to stand at +5° for an additional 3 hrs. and the precipitate which had formed was collected by filtration, washed with cold (+5°) water and dried *in vacuo* over phosphorus pentoxide to give 235 g. (77%) of crude III as tacky yellow crystals. Several recrystallizations from isopropanol gave 90 g. (29%) of III as colorless crystals, m.p. 89–90° ($\lambda_{max}^{CHCl_3}$, 5.56μ, 5.60μ, 5.98μ, 8.50μ; λ_{max}^{MeCN} 210 mμ; ϵ = 13,400).

Anal. Calcd. for $C_6H_7NO_4$: C, 45.9; H, 4.49; N, 8.92. Found: C, 46.0; H, 4.58; N, 8.97.

(B) *Acetylation of α-oximino-γ-butyrolactone* (IV). A suspension of α-oximino-γ-butyrolactone (IV, 3.45 g., 0.03 mole) in 25 ml. of acetic anhydride was heated for 15 min. at 90°. The resulting solution was allowed to cool slowly to room temperature over a period of 1 hr. and concentrated *in vacuo* on a water bath (50°). The residual oil was poured into 50 ml. of ethyl ether and the resulting solid was collected by filtration and dried *in vacuo* over phosphorus pentoxide to give 4.50 g. (95%) of colorless crystals, m.p. 86–89°. Recrystallization from isopropanol gave 4.15 g. of III, m.p. 89–90°. The infrared spectrum for this material was identical with that of the product obtained *via* the nitrosation of α-aceto-γ-butyrolactone (III) and admixture melting point gave no depression.

α-Oximino-γ-butyrolactone (IV). A suspension of *O*-acetyl-α-oximino-γ-butyrolactone (III, 70 g., 0.45 mole) in 250 ml. of 2*N* hydrochloric acid was heated to 50° for 30 min. and cooled to 10°. The precipitate which formed was collected by filtration, washed with water, and dried *in vacuo* at 50° to give 35.0 g. (68%) of IV as colorless crystals, m.p. 180–183°; λ_{max}^{MeCN} 218 mμ, ϵ = 11,200. Feofilaktov and Onishchenko[1] report m.p. 192–193°; Sudo *et al.*,[3] report m.p. 183°; Snyder *et al*,[9] report m.p. 183–185°.

Acknowledgment: We wish to thank Mr. O. Sundberg and staff for microanalyses and Mr. W. Fulmer for spectral interpretations.

ORGANIC CHEMICAL RESEARCH SECTION
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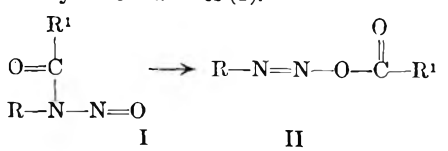
(5) A. Streitweiser and W. D. Schaeffer [*J. Am. Chem. Soc.*, 79, 2893 (1957)] have postulated that rearrangement to a diazoester (II) represents the first step in the decomposition of acylnitroso amines (I).



We wish to thank one of the referees of this manuscript for calling this analogous rearrangement to our attention.

(6) V. Feofilaktov and A. Onishchenko, *Compt. rend. acad. sci., U.R.S.S.*, 20, 133 (1938); *Chem. Abstr.*, 33, 1725 (1939).

(7) For a review of this reaction see O. Touster, *Org. Reactions*, VII, 336 (1953).

(8) Melting points are uncorrected.

(9) H. R. Snyder, J. H. Andreen, G. W. Cannon, and C. P. Peters, *J. Am. Chem. Soc.*, 64, 2082 (1942).

The Preparation of 2,2-Bis(hydroxymethyl)-3-butene-1-ol and 2-(Hydroxymethyl)-2-methyl-3-butene-1-ol and Their Acetates and Nitrates

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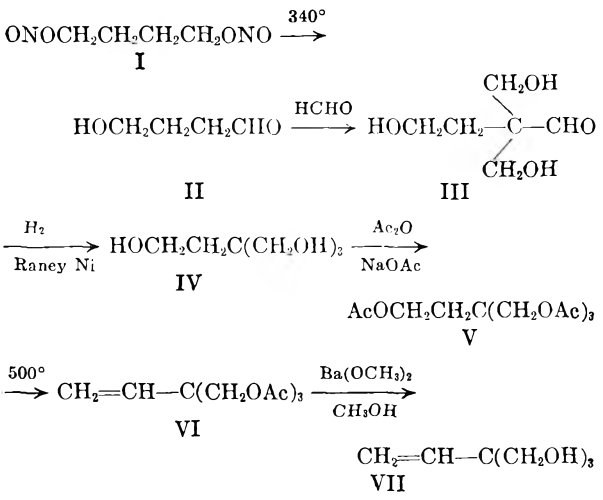
2,2-Bis(hydroxymethyl)-3-butene-1-ol (VII) was prepared by the following sequence of reactions:



II was prepared by adapting the pyrolysis of 1,4-butanediol dinitrite[1] as a synthetic method. Yields were lower than those reported by Kuhn and DeAngelis since the nitrite was pyrolyzed more rapidly and in large quantities, causing an increase in side reactions.

Attempted preparation of IV from II by condensation with formaldehyde followed by a crossed Cannizzaro reaction (as in the well-known synthesis of pentaerythritol[2]) led to the formation of uncrystallizable sirups and large amounts of gummy solid. IV was successfully prepared by condensing II with formaldehyde to form III, then hydrogenating[3] III catalytically to give IV. The crude IV was not isolated as such but was acetylated to give V, which was distilled. This was found to be the best way to work up the reaction mixture without large losses. Also, the next step, introduction of the double bond, required that IV be in the form of its acetate, since the trimethylol configuration is thermally unstable[4] and IV probably could not be dehydrated as such to give VII in reasonable yield. A small sample of IV was prepared and characterized by catalytic deacetylation of V.

2-(Hydroxymethyl)-2-methyl-3-butene-1-ol (VIII) was prepared from 4-hydroxy-3-(hydroxymethyl)-3-methyl-2-butanone[5] through reactions analogous to those used to prepare VII. The overall yields of VIII and VII (based on methyl ethyl ketone and on II) were 16.1 and 11.1%, respectively.

The nitrate esters of VII and VIII were prepared in a fairly pure state and their physical properties determined. In order to avoid the formation of nitro compounds and other side reactions it was found necessary to keep the reaction time to a minimum and to dilute the nitrating mixture with more acetic acid than is customary. The nitrates had negligible infrared absorption at 5.8 and 6.4 microns (carbonyl and nitro regions) and retained the absorption at 3.24 microns characteristic of C—H stretching in vinyl compounds.

EXPERIMENTAL

Preparation of 2,2-bis(hydroxymethyl)-3-butene-1-ol (VII).

γ-Hydroxybutyraldehyde. The pyrolysis of I was carried out in a vertical pyrex tube, 3 × 57 cm., with a side arm near the top for admitting nitrogen. The central 23-cm. portion of the tube was packed with glass helices and kept at 340° by means of an electric furnace, and a slow stream of nitrogen swept the pyrolyzate into two traps, the first cooled with ice and the second with Dry Ice. The system was maintained at 10–20 mm. by means of a water pump, and liquid I was added at a rate of 1 drop per 3 sec. The pyrolyzate was taken up in twice its volume of ether, washed with 5% sodium carbonate solution and dried over magnesium sulfate. After removal of the ether the product was distilled through a Vigreux column. The average yield of hydroxybutyraldehyde, b.p. 55–60° (9 mm.), was 43%.

2,2-Bis(hydroxymethyl)-4-hydroxybutyraldehyde (III). Into a 1-l., three necked flask equipped with a stirrer, thermometer, and gas inlet and outlet tubes were added 119 g. (1.35 moles) γ-hydroxybutyraldehyde, 232 g. 36% formaldehyde (2.79 moles), and 210 ml. of water. The mixture was cooled to 15° and 49.7 g. of sodium carbonate was added in small portions over 35 min. The solution was allowed to come to room temperature and after 1 hr. was heated to 45° and stirred at this temperature overnight. The reaction was carried out in a nitrogen atmosphere. The reaction mixture was then cooled and brought to a *p*H of 8 with 6*N* HCl. The water was distilled off under vacuum, leaving a paste which was treated with acetone and filtered to remove sodium chloride. The filtrate was evaporated to a small volume and treated with 700 ml. of acetone. The solution was kept cold overnight. More solid precipitated, which was filtered off. Evaporation of the filtrate yielded 179 g. crude III, whose infrared spectrum has no band in the carbonyl region, indicating that it exists in the form of its cyclic hemiacetal.

2,2-Bis(acetoxymethyl)-1,4-diacetoxybutane (V). The crude III was dissolved in 380 ml. absolute alcohol, 60 ml. W-7 Raney nickel catalyst was added, and the solution was hydro-

(1) L. P. Kuhn, R. Wright, and L. DeAngelis, *J. Am. Chem. Soc.*, **78**, 2719 (1956).

(2) Gilman and Blatt, ed., *Org. Syntheses*, Coll. Vol. I, 2nd ed., 425 (1941).

(3) An alternate procedure would be to reduce the III with sodium borohydride and then acetylate.

(4) R. W. Brown and G. Dougherty, *J. Org. Chem.*, **13**, 173 (1948).

(5) W. Grimme and J. Wöllner, German Patent 924,803 (1955); *Chem. Abstr.*, **52**, 3853a (1958).

genated at 150° and 1000 p.s.i. for 3 hr. The catalyst was filtered off and the alcohol was removed at reduced pressure to leave a thick sirup (presumably IV) which was acetylated by refluxing for 2 hr. with 650 ml. of acetic anhydride and 70 g. freshly fused sodium acetate. After cooling, the reaction mixture was poured into 4 l. of ice water. The oily layer was separated and the aqueous layer, after standing 2 hr., was neutralized with sodium carbonate and extracted with ether. Extract and oil were washed acid free with 10% sodium carbonate solution and dried over calcium chloride. Removal of the ether and distillation of the product through a spinning band column gave 3 fractions: 16.5 g. b.p. < 125° (0.07 mm.), 28.4 g. impure acetate b.p. 125–147° (0.07 mm.), $n_D^{19.5}$ 1.4480, and 124 g. pure V, b.p. 153–156° (0.07 mm.), $n_D^{19.5}$ 1.4501, $d^{19.5°}$ 1.164. Calcd. MR, 73.46. Found, 73.47. The yield of pure product is 29%, based on the hydroxybutyraldehyde.

Anal. Calcd. for $C_{14}H_{22}O_8$: C, 52.81; H, 6.97. Found: C, 52.65; H, 6.83.

2,2-Bis(hydroxymethyl)-1,4-butanediol (IV). A solution of 1.3 g. V in 50 ml. dry methanol containing 3 ml. 0.2 *M* methanolic barium methylate was refluxed for 15 min., then cooled, neutralized with Dry Ice, and the methanol evaporated. It was necessary to repeat the entire process in order to secure complete deacetylation.

The residue was dissolved in acetone and centrifuged to remove barium salts. Evaporation of the acetone left crude product, m.p. 74–87°. One recrystallization from acetone gave 0.5 g. IV (82% yield), m.p. 87–88°.

Anal. Calcd. for $C_6H_{14}O_4$: C, 47.98; H, 9.39. Found: C, 48.02; H, 9.33.

4-Acetoxy-3,3-bis(acetoxymethyl)-1-butene (VI). Using the same apparatus described in the preparation of hydroxybutyraldehyde, 119 g. V were introduced at a rate of 1 drop per 3 sec. The temperature was 500° and a slow stream of nitrogen was passed through the system at atmospheric pressure. The pyrolyzate was taken up in ether, washed with 10% sodium carbonate solution until acid free and then with water and dried over calcium chloride. After removal of the ether the product was distilled through a spinning band column. The yield of VI was 51 g. (53% yield), b.p. 99–103° (0.1 mm.), $n_D^{20°}$ 1.4504, d^{20} 1.119. MR Calcd., 62.06. Found, 62.11.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.79; H, 7.02. Found: C, 56.09; H, 6.85.

2,2-Bis(hydroxymethyl)-3-butene-1-ol (VII). VI (8.9 g.) was deacetylated in the same manner as was V, using 80 ml. dry methanol and 4 ml. 0.2*M* methanolic barium methylate, and repeating the entire process. After removal of the barium salts and evaporation of the acetone, the residue was dissolved in 80 ml. hot chloroform and the solution was allowed to cool and set in the refrigerator overnight. The crystals which had formed were separated from the solvent by decantation of the solvent, and washed with cold chloroform and dried at reduced pressure. The yield of VII was 3.3 g. (72%), m.p. 16–19°, n_D^{20} 1.4980.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.51; H, 9.15. Found: C, 54.21; H, 9.34.

Proof of structure of 2,2-bis(hydroxymethyl)-3-butene-1-ol. One gram of VII was dissolved in 50 ml. absolute alcohol and hydrogenated for 3 hr. at 40 p.s.i., using 0.15 g. 10% Pd on charcoal catalyst. Filtration and evaporation left 1.0 g. crude 1,1,1-trimethylolpropane, m.p. 48–57°. After recrystallization from a mixture of acetone and ether, the product melted at 54–58° and showed no depression when mixed with a commercial sample of trimethylolpropane, m.p. 54–58°.

4-Nitrato-3,3-bis(nitratomethyl)-1-butene. With the temperature kept below 10°, 11.4 ml. (0.27 mole) 100% nitric acid was added slowly to a mixture of 8.1 ml. acetic anhydride and 19.5 ml. acetic acid. To this nitrating mixture 2.3 g. (0.0174 mole) VII dissolved in 7 ml. acetic acid were added slowly and with good stirring over a 5-min. period, the temperature being kept at −5 to −10°. After stirring for an additional 10 min. at this temperature the solution was poured into 200 ml. ice water. The mixture was extracted with ether and the extract was washed free of acid with 10% sodium carbonate solution, then was washed several times with water and dried over calcium chloride. Removal of the ether left 4.2 g. nitrate (91% yield), n_D^{21} 1.4876.

Anal. (of crude nitrate). Calcd. for $C_6H_9N_3O_9$: C, 26.98; H, 3.40; N, 15.73. Found: C, 26.33; H, 3.12; N, 15.31.

Preparation of 2-(hydroxymethyl)-2-methyl-3-butene-1-ol (VIII).

4-Hydroxy-3-(hydroxymethyl)-3-methyl-2-butanone (IX). This compound was prepared by a modification of the method of Grimme and Wöllner.[5] To 1.89 g. calcium hydroxide in 1290 ml. water were added simultaneously over a 5-min. period 600 g. (6 moles) 30% formaldehyde solution and 216 g. (3.0 moles) methyl ethyl ketone. The mixture was stirred vigorously and held at 10–15° for an additional 12 hr. After 6 hr. no free calcium hydroxide remained so an additional 0.4 g. were added. After 12 hr. the calcium hydroxide was neutralized with Dry Ice and the calcium carbonate was removed by filtration. The filtrate was concentrated at reduced pressure to a sirup which, upon distillation, gave 224 g. IX (57%), b.p. 138–140° (16 mm.), lit. 138–140° (16 mm.).[6]

2-(Hydroxymethyl)-2-methyl-1,3-butanediol (X). Two hundred twenty-four g. of IX were dissolved in 350 ml. absolute alcohol and hydrogenated for 2 hr. at 150° and 1300 p.s.i., using 24 g. copper chromite catalyst. Filtration to remove the catalyst and evaporation of the solvent at reduced pressure left crude X, which was used directly in the next step.

2-(Acetoxymethyl)-2-methyl-1,3-diacetoxybutane (XI). X was acetylated in the same manner as was IV. Distillation gave 253 g. XI (57% yield based on IX), b.p. 108° (0.1 mm.), n_D^{20} 1.4382, d^{20} 1.097. MR Calcd., 62.58. Found, 62.31.

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.35; H, 7.74. Found: C, 55.11; H, 7.61.

4-Acetoxy-3-(acetoxymethyl)-3-methyl-1-butene (XII). XI (252.8 g.) was pyrolyzed in the same manner as was V. Distillation gave 149 g. of XII (76% yield), b.p. 64–66° (0.6 mm.), n_D^{21} 1.4378, d^{21} 1.026, MR Calcd., 51.22; Found, 51.19.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.04. Found: C, 59.96; H, 7.80.

2-(Hydroxymethyl)-2-methyl-3-butene-1-ol (VIII). XII (70 g.) was deacetylated in the same manner as was V, using 320 ml. methanol and 12 ml. 0.2*M* barium methylate. The residue was distilled directly after removal of the methanol, giving 28 g. VIII (69% yield), b.p. 88–90° (2.4 mm.), m.p. 24–26°.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.07; H, 10.33. Found: C, 62.13; H, 10.36.

3-Methyl-4-nitrato-3-(nitratomethyl)-1-butene. VIII was nitrated in the same manner as was VII, using 13.1 ml. (0.311 mole) 100% nitric acid, 8.7 ml. acetic anhydride, and 19.8 ml. acetic acid. Three g. (0.0259 mole) of VIII in 9 ml. acetic acid were added. The yield of nitrate was 5.3 g. or 100%. Distillation gave two fractions: (1) 1.5 g., b.p. < 75° (0.05 mm.), n_D^{26} 1.4620; and (2) 2.3 g., b.p. 75° (0.05 mm.), n_D^{26} 1.4633. Fraction (2) had d^{22} 1.285, n_D^{22} 1.4648. MR Calcd., 45.21. Found: 44.35.

Anal. Calcd. for $C_6H_{10}N_2O_6$: C, 34.95; H, 4.89; N, 13.59. Found: (crude nitrate) C, 34.53; H, 4.77; N, 13.46. Fr. 2 dist. nitrate: C, 34.46; H, 4.80; N, 13.58.

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Some Nitropyridine Derivatives[1]

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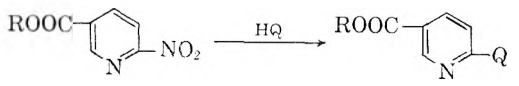
During the study of possible synthetic routes to a pyridine analog of Chloromycetin[2] several nitropyridine derivatives were prepared. 5-Nitropyridine-2-carboxaldehyde was prepared by the selenium dioxide oxidation of 2-methyl-5-nitropyridine but the yield was low and this approach was not followed further. 2-Nitropyridine-5-carboxylic acid was prepared and its esterification and subsequent use in ester-type condensations was investigated. The 2-nitro group proved to be very labile toward nucleophilic substitution. It was replaced by chloro, hydroxy, methoxy, and amino groups with ease.



R = H or CH_3
Q = Cl, OH, OCH_3, NH_2

Because of this, successful Claisen ester type condensations of methyl 2-nitropyridine-5-carboxylate were not realized.

The reaction of 2-nitropyridine-5-carboxylic acid with sulfuric acid in ethanol, or hydrochloric acid in methanol, led to the displacement of the 2-nitro group by the hydroxyl or chloro group, in addition to esterification. Displacement also occurred when 2-nitropyridine-5-carboxylic acid was heated in aqueous sulfuric or hydrochloric acid. The synthesis of methyl 2-nitropyridine-5-carboxylate was achieved by the use of diazomethane. In attempts to condense methyl 2-nitropyridine-5-carboxylate with ethyl acetate in the presence of sodium methoxide, the product obtained was methyl 2-methoxypyridine-5-carboxaldehyde.

Displacement of the 2-nitro group has been reported in the reactions of potassium hydroxide and sodium ethoxide with 2-nitropyridine,[3] hydrobromic acid with 2-nitro-5-ethoxypyridine and 2,6-dinitro-3,5-diethoxypyridine,[4] acetyl chloride and 2-nitropyridine-N-oxide,[5] and ammonia with 2-nitro-5-bromopyridine and 2-nitro-5-ethoxypyridine.[6] Similar reactions of 4-nitropyridine derivatives have been reported.[3,7] No reports of the displacement of a 3-nitro group from the pyridine ring were found.

The similarity in substitution reactions of many pyridine compounds and the corresponding nitrobenzene derivatives is well known.[8] Displacements of nitro groups from tri- and tetra-nitrobenzene under strong acidic conditions and of nitro groups from dinitro- and dinitrohalo-benzenes by basic reagents have been reviewed.[9] Such reactions are in contrast to the inert character of mononitrobenzene derivatives towards such displacement reactions. The reactivity of the 2-nitro group in the pyridine ring is readily rationalized according to the general mechanism of aromatic nucleophilic displacements.[9-11]

EXPERIMENTAL[12]

2-Methyl-5-nitropyridine.[13] To a solution of diethyl malonate (41.0 g., 0.26 mole) in anhydrous ether (500 ml.) was added sodium hydride (6.2 g., 0.26 mole) under a nitrogen atmosphere. When the evolution of hydrogen had subsided, 2-chloro-5-nitropyridine[14] (40.0 g., 0.26 mole) was added with stirring, followed by the removal of ether by distillation. The red, tarry residue was heated by an oil bath to 110° for 1 hr., then refluxed in 12 N sulfuric acid (300 ml.) for 9 hr., during which time the product was removed by continuous steam distillation. This was accomplished by placing a reflux condenser almost horizontally, allowing the solid to remain in the condenser while the water flowed back into the flask; the white crystalline product, 2-methyl-5-nitropyridine (23.1 g., 65% yield), melted at 108–110°.

5-Nitropyridine-2-carboxaldehyde. The oxidation of 2-methyl-5-nitropyridine to the aldehyde was accomplished, after extensive exploration, by a procedure similar to that of Baumgarten,[15] who reported the preparation of 3-nitropyridine-4-carboxaldehyde. 2-Methyl-5-nitropyridine (1.00 g., 0.0072 mole) and freshly prepared selenium dioxide (0.80 g., 0.0072 mole) were dissolved in ethanol (20 ml., 95%) and refluxed for 5.5 hr. Some black selenium (0.10 g.) was removed by filtration. Xylene (30 ml.) was added and the ethanol was removed by distillation over a two hour period. A tarry precipitate (0.63 g.) containing selenium was removed by filtration and the filtrate was extracted with 6N hydrochloric acid (3 × 15 ml.). The extract was filtered through Celite and made basic with sodium bicarbonate, filtered again to remove a small amount of red precipitate and the filtrate extracted with chloroform (3 × 20 ml.). The extract was dried over anhydrous magnesium sulfate,

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evaporated to an oily residue (0.46 g.) which was distilled at 100° and 30 mm. to give a white, crystalline solid (0.19 g., 17% yield), m.p. 54–57°. The infrared spectrum had a carbonyl band at 5.86 microns. This material stained the skin dark green.

Anal. Calcd. for $C_6H_4N_2O_3$: C, 47.38; H, 2.65; N, 18.42. Found: C, 47.31; H, 2.78; N, 18.36.

The oxime was white, m.p. 190–191°; the 2,4-dinitrophenylhydrazone was chrome yellow, m.p. 250–252° with sintering at 228–232°; the thiosemicarbazide was yellow, m.p. 177–179°.

2-Nitropyridine-5-carboxylic acid. 2-Nitro-5-methylpyridine, m.p. 93–95°, (average yield 66%) was prepared from 2-amino-5-methyl pyridine,[16] and oxidized by permanganate[17] to 2-nitropyridine-5-carboxylic acid, m.p. 178–180°, yield 41–89% (average 66%) based on unrecovered starting material.

Methyl 2-nitropyridine-5-carboxylate. 2-Nitropyridine-5-carboxylic acid (8.3 g., 0.0494 mole) was dissolved in refluxing absolute ether (1000 ml.), cooled to 25°, and treated with diazomethane in ether. Evaporation left a residue of white crystalline methyl 2-nitropyridine-5-carboxylate (8.3 g., 92% yield) m.p. 130–131°, strong carbonyl band at 5.85 μ.

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.27; H, 3.45; N, 15.15.

Ethyl 2-hydroxypyridine-5-carboxylate. Concentrated sulfuric acid (25 ml.) was added with cooling to a solution of 2-nitropyridine-5-carboxylic acid (20.0 g., 0.119 mole) in absolute ethanol (50 ml.). The solution was heated on a steam bath for 3 hr., cooled, poured on ice (about 300 g.), made basic with ammonium hydroxide (70 ml.), and chilled. The solid which precipitated was collected by filtration, combined with the residue from chloroform extraction of the filtrate, and recrystallized from ethyl acetate to give white crystalline ethyl 2-hydroxypyridine-5-carboxylate (14.4 g., 72%) m.p. 149–151° (lit.[18] m.p. 149–150°), strong hydroxyl band at 2.90 μ and carbonyl band at 5.89 μ.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.58; H, 5.54; N, 8.48.

2-Hydroxypyridine-5-carboxylic acid. 2-Nitropyridine-5-carboxylic acid (0.75 g.) was refluxed 1 hr. in a solution of 6*N* sulfuric acid (10 ml.) and ethanol (5 ml.); crystalline 2-hydroxypyridine-5-carboxylic acid, m.p. 300° *dec.* (lit.[16] m.p. 301–302° *dec.*), precipitated on cooling.

Methyl 2-chloropyridine-5-carboxylate. 2-Nitropyridine-5-carboxylic acid (26.5 g., 0.158 mole) was dissolved in absolute methanol (265 ml.), and a slow stream of hydrogen chloride was introduced with stirring and chilling during 90 min. and then kept at 0° for 12 hr. The solution became golden yellow after 1 hr., indicating the formation of nitric oxide. The reaction mixture was evaporated under reduced pressure, neutralized with sodium carbonate at 0° and the white precipitate which formed was collected by filtration and combined with the residue from the chloroform extract of the filtrate. The product was recrystallized from benzene-petroleum ether to give a white crystalline chlorine containing compound shown to be methyl 2-chloropyridine-5-carboxylate (17.5 g., 65% yield) m.p. 86–87° (lit.[19] m.p. 86–89°). The infrared spectrum indicated the absence of nitro or hydroxyl functions.

2-Chloropyridine-5-carboxylic acid. A mixture of 2-nitropyridine-5-carboxylic acid (0.75 g.) and concentrated hydrochloric acid (5 ml.) was boiled for 5 min.; nitric oxide was evolved. Evaporation to dryness gave white crystalline 2-chloropyridine-5-carboxylic acid (0.70 g.) m.p. 195–200° (lit.[20] m.p. 199° *dec.*). Esterification according to the previous experiment gave the methyl ester, m.p. 86–87°; a mixture melting point with sample prepared in the previous experiment was undepressed.

Methyl 2-methoxypyridine-5-carboxylate. Methyl 2-nitropyridine-5-carboxylate (0.14 g.) and methanol (0.10 ml.) were dissolved in benzene (10 ml.). Sodium hydride (0.14 g.) was added, and the mixture was refluxed 4 hr. A solid was collected by filtration which gave brown fumes on acidification, and a positive "brown ring test" with ferrous sulfate and concentrated sulfuric acid, indicating the presence of nitrite ion. The filtrate residue was sublimed to long white needles of methyl 2-methoxypyridine-5-carboxylate (0.09 g.) m.p. 48–49° (lit.[21] m.p. 42°).

Anal. Calcd. for $C_8H_{10}O_3N$: OCH_3 37.1. Found: 36.5.

Under the same conditions, but without the addition of methanol, sodium hydride was recovered by filtration and methyl 2-nitropyridine-5-carboxylate by evaporation of the filtrate. With sodium methylate in methanol the same product was obtained on sublimation but the yield was lower.

2-Aminopyridine-5-carboxylic acid. Methyl 2-nitropyridine-5-carboxylate (0.60 g.) was added to a sodium amide suspension prepared by the addition of sodium (0.08 g.) to liquid ammonia (50 ml.). The mixture immediately became deep purple, then slowly faded to brown. Evaporation of the ammonia left an amorphous gray water-soluble powder, which evolved nitric oxide upon acidification with 3*N* hydrochloric acid. From the acid solution, a small amount (10 mg.) of crystalline 2-aminopyridine-5-carboxylic acid was obtained, m.p. 290–310° dec. (lit.[22] 312° dec.).

Attempted condensations with ethyl acetate using sodium hydride, sodium amide or sodium triphenylmethyl in inert solvents were unsuccessful.

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The Synthesis of 5-Azaindole[1]

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Since 7-azaindole and 7-azatryptophan[3] have exhibited interesting biological activity in a number of systems,[4] a synthesis of 5-azaindole and deriva-

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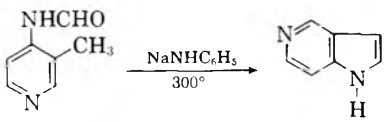
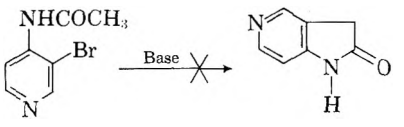
tives seemed desirable. 5-Azaindole itself was first prepared by Möller and Süs[5] by a photochemical ring contraction of 3-diazo-1,6-naphthyridin-4-(3*H*)-one and decarboxylation of the resulting 5-azaindole-3-carboxylic acid. Earlier unsuccessful attempts to prepare the heterocycle included application of the Madelung cyclization of 4-formamido-3-picoline,[6] as well as a Bischler-Napieralski-type reaction of 2-(2-formamidoethyl)-pyrrole.[7] Since 7-azaindole could be prepared in greatly improved yield by use of sodium anilide[3] in the Madelung reaction, rather than sodium ethoxide,[8] it was thought that a reinvestigation of the cyclization using the former reagent might be fruitful. A further inducement to this study stemmed from the fact that Clemo and Swan[6] attempted the synthesis employing an impure, noncrystalline preparation of 4-formamido-3-picoline. Preliminary studies on the formylation of 4-aminopyridine produced the hitherto unreported 4-formamidopyridine and made possible the selection of reaction conditions which led to 4-formamido-3-picoline in good yield and in crystalline form. Cyclization of the latter by the procedure employed for 7-azaindole[3,9] afforded 5-azaindole in 21% yield. The product was identical with the compound prepared by Möller and Süs.[10]



Several attempts were made to convert 5-azaindole to 5-azatryptophan. The substance, however, differs appreciably in its reactivities from 7-azaindole and the reaction sequence employed with the latter was unsuccessful. Thus attempted conversion to "5-azagramine" by several modifications of the Mannich reaction led to materials which could not be crystallized or purified. Further, no well characterized compounds could be isolated on treatment of the crude Mannich reaction product with acetamidomalonic ester, nor was it possible to isolate any crystalline substance from the direct treatment of 5-azaindole with diethyl piperidinomethylformamidomalonate.[11]

5-Azaindole differs in other respects from its 7-aza analog. Thus, attempted atmospheric-pressure hydrogenation in acidic medium over Adams' catalyst did not take place.[12] A considerably lower absorption value for the longer wave-length ultraviolet absorption maximum compared to the 7-azaindole[3] and 4-methyl-5-azaindole[7] maxima was also noted. The identity of the products prepared by the two different syntheses, however, together with the analytical data, molecular weight determinations and characteristic color reactions (*vide infra*) allow no other expression for the product.

Another possible approach to the synthesis of the 5-azaindole ring system involves the creation of an intermediate "pyridyne" species, so substituted that an adjacent nucleophilic center might add intramolecularly. This method of synthesis of heterocyclic compounds was first elucidated by Hrutfiord and Bunnett.[13,14] Experiments were first carried out with 4-acetamido-3-bromopyridine, a derivative which is relatively easily available. It may be noted, however, that attempts to prepare the compound by bromination of 4-acetamidopyridine were unsuccessful, starting material being recovered. The substance was obtained *via* 3-bromopyridine-*N*-oxide by nitration, reduction and acetylation. Treatment of the product with a wide variety of basic reagents did not result in the desired cyclization to 5-azaindole. In all cases starting material was recovered or dehalogenation or hydrolysis was observed. It was thought that salt formation involving the active hydrogen of the amide group might be interfering with the cyclization, and accordingly attempts were made to prepare the acetyl derivative of 4-benzylamino-3-bromopyridine. It was found that 4-benzylaminopyridine can be prepared in good yield by treatment of 4-aminopyridine with benzaldehyde and subsequent reduction with formic acid.



No well characterized products were obtained on bromination of the amine, however. The desired combination of halogen and benzylamino groups was finally attained by treatment of 4-amino-3-bromopyridine with benzyl alcohol and potassium hydroxide.[15] The resulting 4-benzylamino-3-bromopyridine, which was isolated as the picrate was not investigated further because of the termination of the project.

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(15) *Cf.* I. Hirao and M. Hayashi, *J. Pharm. Soc. Japan*, **74**, 853 (1954), *Chem. Abstr.*, **49**, 10308 (1955).

EXPERIMENTAL[16,17]

4-Formamidopyridine. A formylating mixture, prepared by heating 2.5 ml. of 98% formic acid and 6.3 ml. of acetic anhydride at 50° for 2 hr., was cooled to ice-bath temperature and a solution of 1.88 g. of 4-aminopyridine in 40 ml. of dry tetrahydrofuran was added slowly with cooling. The mixture was allowed to stand at room temperature for 2 days, another anhydride solution prepared by heating 1.7 ml. of formic acid and 4.2 ml. of acetic anhydride was added and the reaction was allowed to stand one more day. It was then evaporated to dryness *in vacuo* and the residue was washed with ether and recrystallized from acetone. The 1.98 g. (80%) of white sand melted at 160–162°. The analytical sample, prepared by two more recrystallizations from acetone, melted at 162–163°.

Anal. Calcd. for $C_6H_6N_2O$: N, 22.92. Found: N, 22.94.

4-Formamido-3-picoline. The 4-amino-3-picoline was prepared on a large scale by a modification of the two-step reduction of 4-nitro-3-picoline-N-oxide.[18] It was found that the intermediate 4-nitro-3-picoline could be hydrogenated on a 22-g. scale in 90% yield at 1–3 atmospheres pressure, provided that the shaker bottle was cooled continuously during the early, exothermic stage of the hydrogenation by a stream of running water. In the absence of such cooling some undesired side reaction took place and almost none of the desired product was obtained. A solution of 32.2 g. of the amine in 200 ml. of dry tetrahydrofuran was added slowly to a formylating mixture prepared, as in the 4-formamidopyridine preparation, from 38 ml. of formic acid and 95 ml. of acetic anhydride. After standing and treatment with a second portion of anhydride solution, prepare from one half the above quantities of reagents, the reaction mixture was worked up as in the previous case. The residue from the evaporation was triturated with 200 ml. of dry ether and the resulting 33 g. of white solid was purified by chromatography on 300 g. of alumina.[19] Elution with about 1000 ml. of 2:1 benzene-acetone afforded, after recrystallization from benzene, 22.9 g. of white needles, m.p. 141°. About 10 g. of crude material, obtained from the mother liquors, from the earlier ether washings and from later chromatogram fractions was chromatographed again on 125 g. of alumina. By this procedure an additional 5.13 g. of white needles, m.p. 140–141°, was obtained. Thus, the total yield was 69%. The analytical sample, m.p. 142–143°, was prepared by sublimation at 140° (0.2 mm.).

Anal. Calcd. for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.75; H, 5.71; N, 20.53.

The picrate formed yellow needles from ethanol, m.p. 199–200° (reported[6] m.p. 199–200°).

5-Azaindole. The cyclization of the amide was effected by the procedure used for 7-azaindole.[3,9] In the single large scale reaction carried out, 42.4 g. of amide was cyclized using appropriate quantities of sodium hydride and aniline,[9] the only variation in procedure being the use of 44.5 g. of dry *sodium* formate, instead of the potassium salt. It has been found that the sodium salt is more satisfactory for 7-azaindole preparations, as well. The usual reaction workup afforded, in the final distillation, 14.1 g. of red oil, b.p. 163–166° (0.5 mm.). After the oil had partially crystallized the solid was separated by filtration and recrystallized from ether-petroleum ether. The 2.48 g. of white solid melted at 105–107°. Chilling of the oil yielded more solid, which after two recrystallizations weighed 1.32 g. and melted at 110–111°. The combined oils and materials from the mother liquors were purified by chromatography on 150 g. of alumina.[19] Elution with about 800 ml. of 4:1 ether-acetone afforded, after recrystallization, 2.96 g. of additional product. Rechromatography of the crude fractions through another 100-g. alumina column produced a final fraction of 1.03 g. of 5-azaindole. The total yield was 7.79 g. or 21%. The analytical sample was prepared by recrystallizations from benzene-cyclohexane, from chloroform-hexane and from water and by sublimation at 105° (0.3 mm.). The white solid melted at 111.5–112.5° and the melting point was undepressed on admixture with a sample prepared by Möller and Süs. 5-Azaindole gives a negative Ehrlich test, but a dark blue-green color on treatment with sodium nitroprusside and alkali, as does 7-azaindole.[3] The ultraviolet spectrum shows a minimum at 238 mμ (log ε 3.13) and a maximun at 265 mμ (log ε 3.62). The corresponding values determined from the sample provided by Möller and Süs were λ_{min} 237 mμ (3.16) and λ_{max} 265 mμ (3.63). The equivalent weight of the substance was determined by perchloric acid titration of an acetic acid solution using crystal violet indicator, while the molecular weight was approximated by a crude semimicro Rast procedure.[20]

Anal. Calcd. for $C_7H_6N_2$: C, 71.19; H, 5.09; N, 23.73; mol. wt. 118. Found: C, 71.41; H, 5.16; N, 23.86; neut. equiv., 118; mol. wt., 141.

4-Amino-3-bromopyridine. This known material was prepared from 3-bromopyridine by nitration of the N-oxide and reduction. A number of improvements were made in the steps. Räth[21] reported the preparation of 3-bromopyridine in 56% yield by diazotization of 3-aminopyridine in sulfuric acid–hydrobromic acid and treatment with copper powder. Since, in our hands, this method gave a yield of only 28%, the reaction was run in a mixture of 3 volumes of 48% hydrobromic acid and 1 volume of water. By this modification the yield was increased to 41–53%. Den Hertog[22] prepared 4-amino-3-bromopyridine in approximately 23% yield from the 3-bromo compound. This over-all yield was approximately doubled by: (1) Use of peracetic acid, rather than perphthalic acid in the oxidation, and isolation of 3-bromopyridine-N-oxide as the hydrochloride. (2) Nitration of the hydrochloride salt. (3) Prolonged extraction of the iron–acetic acid reduction product into ether in a continuous extraction apparatus.

4-Benzylamino-3-bromopyridine picrate. A mixture of 0.43 g. of 4-amino-3-bromopyridine, 0.30 g. of benzyl alcohol, 0.30 g. of potassium hydroxide, and 5 ml. of xylene was refluxed 7 hr., cooled, and added to 30 ml. of ether. Insoluble material was separated by filtration and the organic layer was evaporated *in vacuo*. Since the residual oil afforded no crystalline material on chromatography, a picrate was formed in ethanol. The 0.61 g. of yellow needles melted at 160–165°. After recrystallizations from absolute ethanol the compound had m.p. 163–165°.

Anal. Calcd. for $C_{18}H_{14}N_5O_7Br$: N, 14.23. Found: N, 14.30.

4-Acetamido-3-bromopyridine. A mixture of 3.1 g. of the amine and 30 ml. of acetic anhydride was refluxed 6 hr. and evaporated *in vacuo*. The residue was dissolved in 150 ml. of ether and extracted with three 150 ml. portions of cold 3% aqueous sodium hydroxide.[23] The sodium hydroxide solution was saturated with carbon dioxide and the resulting precipitate was washed with cold water and dried. The 2.88 g. (75%) of 4-acetamido-3-bromopyridine had m.p. 96–100°. Recrystallization from ether-petroleum ether afforded white needles, m.p. 86–87°. Thorough drying of

(16) Melting points are corrected, boiling points uncorrected.

(17) Analyses by Weiler and Strauss, Oxford, England, except for some nitrogen analyses which were carried out by a semimicro Kjeldahl technique in this laboratory.

(18) W. Herz and L. Tsai, *J. Am. Chem. Soc.*, **76**, 4184 (1954).

(19) Fisher adsorption alumina was used.

(20) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 55.

(21) C. Räth, *Ann.*, **486**, 100 (1931).

(22) H. J. Den Hertog and J. Overhoff, *Rec. trav. chim.*, **69**, 468 (1950).

(23) The solubility of amides of 2- and 4-aminopyridine in strong aqueous base is general when the amide nitrogen is unsubstituted.

these crystals at 70° caused a change to prisms, m.p. 102.5–103.5°. The analytical sample, prepared by further recrystallizations from the same solvent pair, had m.p. 86–87°, which changed to 101–102.5° after storage of the product for one month at room temperature.

Anal. Calcd. for $C_7H_7N_2OBr$: N, 13.03. Found: N, 12.96.

No cyclization products were obtained from reactions in which the substance was treated with potassium amide in liquid ammonia, with sodium ethoxide in ethanol at 150–160°, with sodium hydride in refluxing xylene or with sodium amide in refluxing cumene.

4-Benzylaminopyridine. A mixture of 3 g. of 4-aminopyridine, 4.5 g. of benzaldehyde and 10 ml. of cumene was refluxed for 2 hr., during which period water was removed periodically by co-distillation with cumene. The mixture was cooled, then after addition of 6 ml. of 98% formic acid it was refluxed again for 17 hr. Fifty ml. of water was added to the two-phase system after cooling and the aqueous layer was separated, washed with three 25-ml. portions of ether, then made alkaline with saturated aqueous sodium carbonate. The precipitated white solid weighed 4.19 g. and melted at 107.5–109.5°. Recrystallizations from ether-petroleum ether afforded 3.99 g. (69%) of white prisms, m.p. 110.5–111°. The picrate was formed in methanol and recrystallized from the same solvent, m.p. 138.5–139.5°.[24]

Absorption spectra. The ultraviolet spectra of the 5-azaindole samples were determined from $10^{-4}M$ solutions in 95% ethanol. Measurements were carried out with either a Beckman model DU spectrophotometer or a Beckman model DK-1 instrument.

Acknowledgments. The authors wish to express their sincere appreciation to Mrs. Bonnie L. Robison, who advised on the Madelung cyclization and rendered other assistance, to Mr. Robert Eisenthal, who carried out early work on the 5-azaindole synthesis, to Mr. Michael A. Simon who undertook preliminary investigations of the formylation reaction, and to Mr. Louis Dorfman at CIBA Pharmaceutical Products, Inc., who determined the ultraviolet spectrum of Möller and Süs's azaindole sample and provided valuable advice on the spectra.

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(24) T. Kahto and M. Ohta, *J. Pharm. Soc. Japan*, **71**, 217 (1951) report m.p. 108–109.5° for the amine and m.p. 140–142° for the picrate.

Reaction of Styrene Oxide with 2-Naphthalenethiol

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Styrene oxide has been shown by Gilman and Fullhart[2] to react with potassium methyl mercaptide and form the secondary alcohol, $C_6H_5CHOH-CH_2SCH_3$. More recently Rondestvedt[3] reported that the reaction of styrene oxide with potassium benzyl mercaptide in dioxane gave the corresponding secondary alcohol. This direction of ring opening was considered normal by these investigators.

Since styrene oxide had been found to react with sodium 2-naphthoxide in water predominantly by nuclear attack, forming 2-(2-hydroxy-1-naphthyl)-2-phenylethanol,[4] and since the analogous compound that would result from a comparable reaction between styrene oxide and 2-naphthalenethiol was now sought, the latter compounds were subjected to appropriate reaction conditions. This was undertaken in spite of the known lack of nucleophilic reactivity of the ring in such thiophenols.[5] The substance that was isolated, in 80% yield, was shown to have structure I. The reaction in aqueous

$$\begin{array}{l} C_6H_5—CH—CH_2OH \\ \quad\quad | \\ \quad\quad SC_{10}H_7 \\ \quad\quad I \end{array}$$

medium with excess sodium hydroxide present was relatively rapid at 0–5°. Little, if any, of the secondary alcohol could have been formed. Both of the possible isomeric alcohols were synthesized by reliable methods for structure proof as reported in the experimental portion.

The direction of ring opening of styrene oxide in aqueous alkali is thus the same with 2-naphthol and 2-naphthalenethiol. For these two compounds differences in the rate of reaction and structure of products seem to result, in part, from the nature of the nucleophilic species.[5,6] It is our conjecture that solvent effects are partially responsible for the difference in the direction of ring opening of styrene oxide observed by us and the aforementioned investigators.[7] In an experiment not reported here the reaction of styrene oxide with the sodium salt of 2-naphthalenethiol in dioxane evidently formed the secondary alcohol predominantly.

EXPERIMENTAL[8]

Reaction of styrene oxide with 2-naphthalenethiol in aqueous sodium hydroxide. A mixture of 2-naphthalenethiol (11.0 g., 0.069 mole, Eastman product recrystallized to m.p. 80–82°) in sodium hydroxide (5.0 g., 0.125 mole) and water (75 ml.) was stirred under nitrogen with warming to aid dissolution of the thiol. This was then cooled in an ice bath to below 5° prior to the addition of styrene oxide (4.0 g., 0.033 mole, b.p. 45° (2 mm.), n_D^{20} 1.5345) in portions in 5 min. A reaction occurred almost immediately as evidenced by the appearance of a fine precipitate. After 2 hr. the mixture was allowed to warm to room temperature, filtered, washed by

(1) Taken in part from the M.S. thesis of Herbert S. Wilgus III, December 1955.

(2) H. Gilman and L. Fullhart, *J. Am. Chem. Soc.*, **71**, 1478 (1949).

(3) C. S. Rondestvedt, Jr., *J. Org. Chem.*, **21**, 911 (1956).

(4) C. O. Guss and L. H. Jules, *J. Am. Chem. Soc.*, **72**, 3878 (1950).

(5) *Eg.*, D. S. Tarbell, and A. H. Herz, *J. Am. Chem. Soc.*, **75**, 1668 (1953) and references mentioned there.

(6) O. R. Quale and E. E. Royals, *J. Am. Chem. Soc.*, **64**, 226 (1942); J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **76**, 3011 (1954).

(7) C. O. Guss and H. R. Williams, *J. Org. Chem.*, **16**, 1809 (1951).

(8) Temperature measurements are uncorrected.

dispersion in water until the filtrate was no longer turbid when acidified, and dried to obtain 9.0 g. (96.8%), m.p. 87–98°. Acidification of the first filtrate gave 5.7 g. of recovered thiol, m.p. 75–82°.

Two recrystallizations from heptane[9] gave 7.4 g. (80%), m.p. 100–103°. The pure 2-(2-naphthylmercapto)-2-phenylethanol (I) melted at 102–103°, from dilute ethanol.

Anal. Calcd. for $C_{18}H_{16}OS$: C, 77.11; H, 5.75. Found: C, 77.29; H, 6.04.

p-Nitrobenzoate was prepared as cream colored leaves from dilute ethanol, m.p. 106–108°.

Anal. Calcd. for $C_{25}H_{19}NO_4S$: C, 69.90; H, 4.46. Found: C, 70.17; H, 4.60.

Synthesis of α-(2-naphthylmercapto)phenylacetic acid. From 2-naphthalenethiol and mandelic acid. A mixture of 2-naphthalenethiol (8.0 g., 0.05 mole) and mandelic acid (6.1 g., 0.04 mole) was heated in a large test tube under nitrogen at an oil bath temperature of 190–195° for one hour.[10] The warm, amber colored reaction mixture, still liquid, was transferred by means of ethanol (100 ml.) to a beaker, and the resulting slurry warmed with 8 g. sodium bicarbonate in 250 ml. water to form the sodium salt. Some insoluble dinaphthyl disulfide was filtered off. Air was then bubbled through the aqueous filtrate at about 40° for 4 hr. to oxidize unreacted thiol to disulfide, finally giving 2.4 g. of the recrystallized disulfide, m.p. 137–139°, reported[11] m.p. 139°. Acidification of the aqueous mixture with concentrated hydrochloric acid produced 7.35 g. solid which, after three recrystallizations from dilute acetic acid (carbon black), gave 5.4 g. (45.9%), m.p. 169–171°. The analytical sample, from dilute ethanol, melted at 171–172°.

Anal. Calcd. for $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79. Found: C, 73.52; H, 4.97.

Anilide was prepared by heating the acid with aniline at 150–170° under nitrogen for 2 hr. and found to melt at 173.5–174.5°, fine white needles from dilute ethanol.

Anal. Calcd. for $C_{24}H_{19}NOS$: C, 78.03; H, 5.18. Found: C, 78.09; H, 5.52.

p-Bromoanilide, similarly prepared, was a better derivative since its melting point was 188–189°, white needles from dilute ethanol.

Anal. Calcd. for $C_{24}H_{18}BrNOS$: C, 64.28; H, 4.05. Found: C, 64.43; H, 4.32.

From 2-naphthalenethiol and ethyl α-bromophenylacetate. Ethyl α-bromophenylacetate (6.1 g., 0.025 mole, n_D^{20} 1.5385) was added slowly to a stirred mixture of 2-naphthalenethiol (4.0 g., 0.025 mole) in sodium hydroxide (2.0 g., 0.05 mole) dissolved in water (50 ml.) under nitrogen. A precipitate began to appear after 20 min. at room temperature. At the end of 2 hr. the reaction mixture was transferred to a boiling flask containing 10 g. sodium hydroxide in water. The total volume was finally 200 ml. This was refluxed 2 hr. to produce a clear solution. The warm solution was treated with carbon black, being careful to keep the solution warm enough to prevent the crystallization of the sodium salt. Acidification of the filtrate with concentrated hydrochloric acid and recrystallization of the resulting solid from dilute acetic acid gave 6.6 g. (90.4%) fine, white needles, m.p. 169–172°. A mixed melting point of this acid and that prepared by the alternate method showed no depression.

Reduction of α-(2-naphthylmercapto)phenylacetic acid to I. Tetrahydrofuran was preferred to ether as the solvent because the acid was insoluble in ether. The α-(2-naphthylmercapto)phenylacetic acid (4.4 g., 0.015 mole, m.p. 169–117°) in tetrahydrofuran (30 ml.) was added to lithium aluminum hydride (1.0 g., 0.026 mole) in tetrahydrofuran (25 ml.) over a 15-min. period. After an additional 30 min. the mixture was treated with 10 ml. concentrated hydrochloric acid in 40 ml. water. The organic layer was taken up in ether and washed with 4% aqueous sodium hydroxide to remove some acid that was not reduced. After the ether solution was dried over anhydrous potassium carbonate and the solvent removed, the product was recrystallized from heptane[9] (carbon black) to yield 3.1 g. (73.8%), m.p. 100–103°. A mixture melting point with pure 2-(2-naphthylmercapto)-2-phenylethanol (I) from the reaction of styrene oxide with 2-naphthalenethiol was 101–103°.

Synthesis of 2-(2-naphthylmercapto)-1-phenylethanol. The preparation of α-(2-naphthylmercapto)acetophenone from phenacyl chloride and 2-naphthalenethiol followed the procedure of Long.[12] A nearly theoretical yield was obtained, m.p. 97–98°, white needles from ethanol.

Anal. Calcd. for $C_{18}H_{14}OS$: C, 77.66; H, 5.07. Found: C, 77.41; H, 5.41.

The *2,4-dinitrophenylhydrazone* melted at 209–210°, reddish orange needles from ethyl acetate–benzene.

Anal. Calcd. for $C_{24}H_{18}N_4O_4S$: C, 62.87; H, 3.96. Found: C, 63.03; H, 4.21.

Reduction of this ketone with excess lithium aluminum hydride by the conventional procedure provided an oil that soon solidified to a solid, m.p. 57–60° in quantitative yield. Recrystallization from a mixture of heptane[9] and benzene gave fine, white needles, m.p. 59–60°.

Anal. Calcd. for $C_{18}H_{16}OS$: C, 77.11; H, 5.75. Found: C, 77.16; H, 6.11.

The *p-nitrobenzoate* of this alcohol melted at 114–115°, yellow, from dilute ethanol.

Anal. Calcd. for $C_{25}H_{19}NO_4S$: C, 69.90; H, 4.46. Found: C, 69.80; H, 4.81.

Acknowledgment. The authors are grateful to the Research Corp. for a Frederick Gardner Cottrell grant in support of this work.

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(9) Eastman Organic Chemicals, P 2215.

(10) B. I. Arventi and M. Robu-Burnuz, *Ann. sci. univ. Jassy,* 26, 602 (1940).

(11) K. Fries and G. Schurmann, *Ber.,* 47, 1195 (1914).

(12) L. M. Long, *J. Am. Chem. Soc.,* 68, 2159 (1946).

Reaction of Phenols with Phosphorus Pentachloride[1]

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Although the reaction of alcohols with phosphorus pentachloride is a standard method for the preparation of alkyl chlorides, little is known concerning the mechanism.[2] Gerrard and Phillips have postulated the formation of $ROPCl_4$ as an intermediate in this reaction.[3] This intermediate can be used to explain the formation of the alkyl chloride and phosphorus-containing by-products which are also obtained.[3] Although such alkoxyphosphorus tetrachlorides have never been isolated to our

(1) Presented at the Southwest Regional Meeting of the American Chemical Society, San Antonio, Tex., Dec. 4–6, 1958.

(2) For a comprehensive review of earlier work and further work on the mechanism, see W. Gerrard, *J. Chem. Soc.,* 741 (1946).

(3) W. Gerrard and R. J. Phillips, *Chem. & Ind. (London),* 540 (1952).

knowledge, it is of interest that analogous aryloxy compounds from the reaction of phenols with phosphorus pentachloride have been obtained.[4] Aryloxyphosphorus tetrachlorides[5] can also be prepared by the reaction of aryloxyphosphorus dichlorides with chlorine.[4,6]

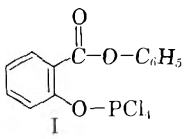
$$ArOH + PCl_5 \xrightarrow{-HCl} ArOPCl_4 \longleftarrow ArOPCl_2 + Cl_2$$

It is of considerable mechanistic interest that aryloxyphosphorus tetrachlorides decompose on heating to aryl chlorides and phosphorus oxychloride.[7,8]

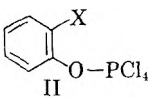
$$ArOPCl_4 \longrightarrow ArCl + POCl_3$$

A thorough study of this decomposition would be of interest not only from the standpoint of mechanism, but also since this reaction furnishes a means for converting phenols into aryl chlorides.[9] The main drawback to such a study is the reported[4,6] instability of aryloxyphosphorus tetrachlorides with respect to moisture.

In this connection, the related product (I)[10] from the reaction of phenyl salicylate and phosphorus pentachloride was of interest since it was reported[8] to be quite stable. Thus, it was the initial object of the present investigation to prepare other *ortho*-substituted compounds of this type (II) in the expectation of obtaining a series of stable compounds suitable for use in the studies outlined above.



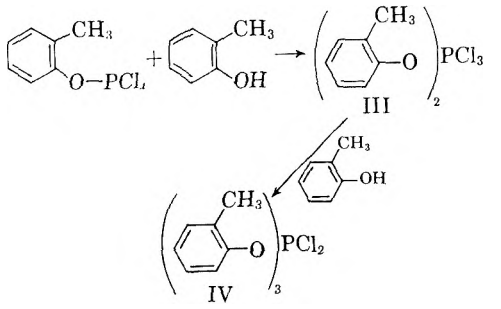
I



II

RESULTS

ortho-Substituted phenols. When X was the aldehydo (—C(=O)H) group, the product of the reaction was unstable to both moisture and oxygen since it hydrolyzed easily and turned a dark blood-red color on standing.[11] When X was phenyl or methyl, the product hydrolyzed rapidly in contact with air. With *ortho*-cresol, further reactions were carried out to determine whether more highly substituted compounds (III and IV) might be more stable; however, these compounds were also unstable to atmospheric moisture.



The stoichiometry of the reaction with *ortho*-nitrophenol[12] was more complicated than a simple 1:1 reaction. When the reaction mixture was hydrolyzed, a mixture of products was obtained instead of the *ortho*-nitrophenyl phosphate (V) expected. From this mixture, it was possible to isolate the trisubstituted phosphate:tris(*ortho*-nitrophenyl)phosphate (VI). It would be expected that the mono- and disubstituted phosphates (V and VII) would also be present. Recrystallization of the crude product into pure compounds was not accomplished because of the unusual solubility characteristics of these compounds. In view of the experimental conditions used in carrying out the reactions (see experimental part) in which the formation of polysubstituted products was minimized by keeping phosphorus pentachloride in excess during the reaction, these results were somewhat surprising. Kosolapoff suggests[7] that disproportionation can take place during hydrolysis. Another possibility is the further reaction of $ArOPCl_4$ with the phenol to produce products which on hydrolysis would yield the corresponding mono- and diaryloxyphosphates (as outlined below). Because of the experimental procedure used in the present work, however, such reactions could only take place if the chlorines in $ArOPCl_4$ were more reactive than those in phosphorus pentachloride. The latter explanation seems plausible since the tris-compound was obtained *before* the hydrolysis was carried out (see experimental part). Furthermore, the latter explanation is substantiated by the work of Rydon and Tonge[4c] on disproportionation reactions of aryloxyphosphorus halides.

(4) A summary of earlier work can be found in the following references: (a) G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley & Sons, Inc., New York, N. Y., 1950, p. 325; (b) D. G. Coe, S. R. Landauer, and H. N. Rydon, *J. Chem. Soc.*, 2281 (1954); (c) H. N. Rydon and B. L. Tonge, *J. Chem. Soc.*, 3043 (1956).

(5) In view of recent work showing (on the basis of conductivity studies) that various aryloxyphosphorus halides are dimeric [G. S. Harris and D. S. Payne, *J. Chem. Soc.*, 3038 (1956) and ref. (4) (c)], it is probable that aryloxyphosphorus tetrahalides are also dimeric.

(6) R. Anschütz and W. D. Emery, *Ann.*, **239**, 301 (1887); R. Anschütz and C. D. Moore, *Ann.*, **239**, 314 (1887); L. Anschütz, F. Koenig, and H. Walbrecht, *Ann.*, **525**, 297 (1936).

(7) Ref. (4) (a), p. 328.

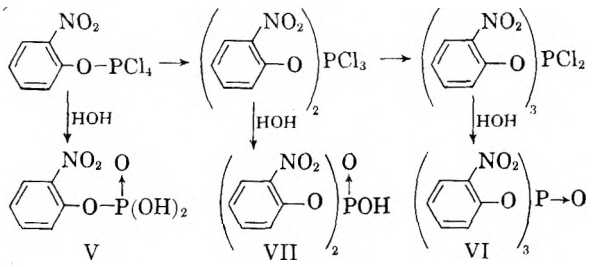
(8) A. Michaelis and W. Kerkhof, *Ber.*, **31**, 2172 (1898).

(9) After the work reported in this paper was complete, a method for accomplishing this in good yields by the thermal decomposition of tetraaryloxyphosphorus monohalides was reported: D. G. Coe, H. N. Rydon, and B. L. Tonge, *J. Chem. Soc.*, 323 (1957).

(10) See, however, A. G. Pinkus, P. G. Waldrep, and P. H. Ko, Abstracts, 134th meeting of the American Chemical Society, Chicago, Ill., Sept. 8–12, 1958.

(11) The authors wish to acknowledge the aid of Mr. Jack Goodwyn in carrying out this experiment.

(12) The authors acknowledge the aid of Mr. Luis Ramos in this experiment.



Di-ortho-substituted phenols. In view of the instability to moisture of the *ortho*-substituted phenols discussed above, it seemed that perhaps the more hindered 2,6-disubstituted phenols might form more stable compounds. One of the most hindered compounds of this type, 2,6-di-*tert*-butyl-*p*-cresol, was studied because of its ready availability.[13] However, even under vigorous reflux conditions in benzene or carbon tetrachloride, no reaction appeared to take place.

As further examples of di-*ortho*-substituted types, the reactions of 2,4,6-trihalophenols with phosphorus pentachloride were investigated. The trichlorophenol reacted at room temperature whereas the tribromo- and triiodophenols required heat. The products of these reactions appeared to be somewhat more stable to atmospheric moisture than the mono-*ortho*-substituted compounds previously investigated; however, the stability was not outstanding.

At the present time, in view of the more interesting results obtained in related work,[10] we do not contemplate any further work along the lines discussed in this paper.

EXPERIMENTAL

Reaction of phenols with phosphorus pentachlorides. The general procedure used in all of the reactions is described. In order to minimize polysubstitution of phosphorus pentachloride and to favor the formation of the monosubstituted compound, the reactions were run in such a way as to keep the concentration of the phenol at a minimum at all times, and to keep phosphorus pentachloride in excess during the reaction. This was done by adding the phenol dropwise to the phosphorus pentachloride.

A solution of 0.100 mole of the phenol dissolved in approximately[14] 50 ml. of purified ACS grade benzene was added dropwise by means of a dropping funnel to a stirred suspension of 0.100 mole of phosphorus pentachloride in approximately 50 ml. of benzene in a three-neck flask. The flask was equipped with a condenser which was attached to a calcium chloride drying tube which led in turn to a safety bottle and then to a solution of sodium hydroxide for absorption of hydrogen chloride. By the completion of the addition, the phosphorus pentachloride had reacted and gone into solution. The reaction mixture was allowed to stir for about 1–3 hr. after the completion of addition. The benzene solution was then transferred to a one-neck flask and the solvent removed *in vacuo* to obtain the crude product.

Since the present investigation was an exploratory study, no elaborate precautions were taken to exclude atmospheric moisture in the handling of the compounds. Thus, the results are of a qualitative nature. Since the compounds prepared were very hygroscopic—some liquefying almost immediately on contact with atmospheric moisture—the melting points and analyses are not reported because of the questionable purity of the compounds. In order to obtain pure compounds for reliable melting points and analyses, rigorous dry box techniques are recommended.

With the exception of the compound obtained from salicylaldehyde, which was an oily liquid, all of the other compounds were white solids.

Reaction of ortho-nitrophenol. The reaction was carried out according to the general procedure above. After standing for several days, a solid deposited from the benzene solution (before removal of solvent). The benzene solution was decanted and the solid collected, tris(*ortho*-nitrophenyl)-phosphate (VI) and weighed 2.0 g. after drying. The melting point, after recrystallization from purified isopropyl alcohol, was 126.4–128.0° (total immersion thermometer) (lit.[15] 126°). The benzene solution from the decantation, was evaporated *in vacuo* leaving a solid mass weighing 13.4 g. The solid was unstable to moisture. It was hydrolyzed by adding ice. A vigorous reaction took place with evolution of hydrogen chloride and formation of a brown oil which solidified on standing for about 2 hr. The solid was collected by filtration and washed with water. The wash water appeared to hydrolyze and dissolve the solid on the Büchner funnel, since after drying over calcium chloride only 1.2 g. of the solid remained. A comparison of the ultraviolet spectrum of the yellow filtrate with that of an aqueous solution of *ortho*-nitrophenol confirmed the presence of this compound in the filtrate. Thus it would appear that the solid which is probably the mono- and diphosphate esters, is readily hydrolyzed by water into *ortho*-nitrophenol and phosphoric acid. The molybdate test for phosphate showed its presence in the filtrate. The solid from the hydrolysis melted 164.5–166.0°. Attempts made to recrystallize the compound were unsuccessful since the compound was either too soluble or too insoluble in the many solvents tried. No combination of mixed solvents was found to be satisfactory. The compound decomposed into *ortho*-nitrophenol during an attempted sublimation under reduced pressure. Chromatography over silica gel was unsuccessful.

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(13) The authors express thanks to Shell Chemical Corp. and to Koppers Co., Inc. for samples of this compound.

(14) If necessary to dissolve the phenol completely, larger volumes of benzene were occasionally used.

(15) A. Engelhardt and P. Latschinow, *J. Russ. Phys. Chem. Soc.*, 2, 116; *Z. für Chemie*, 1870, 230; (*Beilsteins Handbuch der Organischen Chemie, Band*, 6, vierte auflage, Verlag von Julius Springer, Berlin, 1923, p. 222) prepared this compound by heating *ortho*-nitrophenol and phosphorus pentachloride and treating the reaction product with water.

Infrared Spectra of Acid Azides[1]

EUGENE LIEBER[2] AND EDWIN OFTEDAHL

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Recent investigations[3,4] have demonstrated that reactions which theoretically should lead to thiocar-

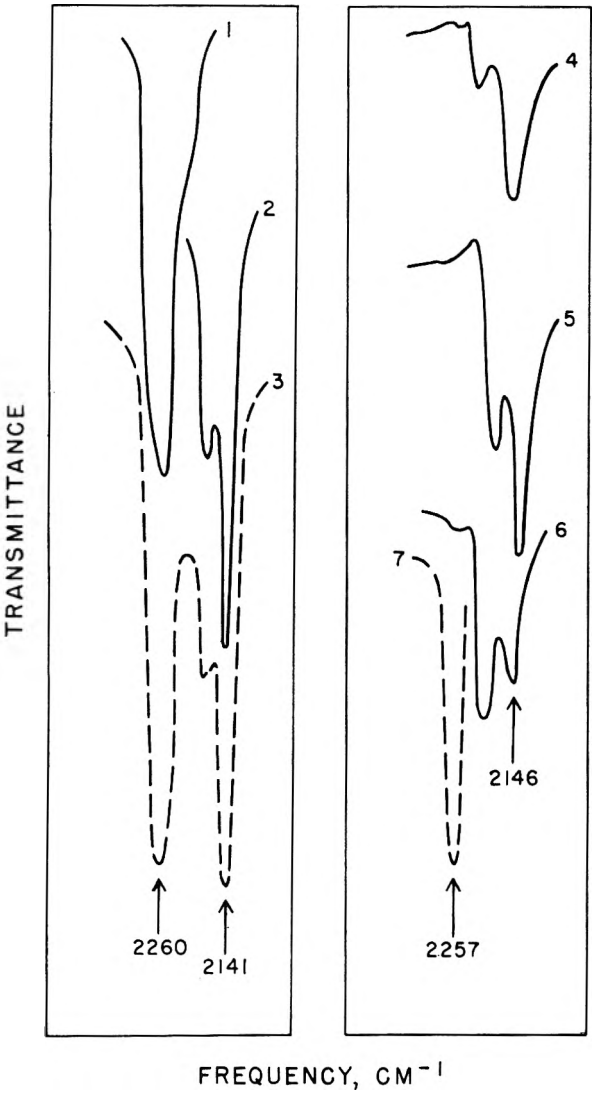
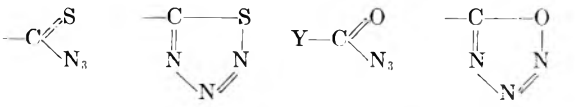


Fig. 1. (1) Phenylisocyanate by decomposition of benzazide. (2) Benzazide. (3) An equal mixture of phenylisocyanate and benzazide. (4) 3,5-Dinitrobenzazide. (5) *para*-Nitrobenzazide. (6) *meta*-Nitrobenzazide. (7) *meta*-Nitrophenylisocyanate by decomposition of *meta*-nitrobenzazide.

bamyl azides (I) are in reality derivatives of the thiatriazole ring system (II). Evidence for this observation was discovered simultaneously and independently by Scott,[3] Lieber,[4] Smith,[5a] and Jensen[5b] by infrared absorption spectroscopy, although chemical evidence is now available[4,5] to support this conclusion. On the other hand, chemical and spectroscopic evidence,[3,6] while limited, clearly demonstrates the azide structure of carbamyl azides (III).



I II III. Y = N IV. Y = alkyl or aryl V

In reviewing the evidence for structure III, infrared absorption data were also sought for organic acid azides (IV). There has been no systematic study[7] on the infrared spectra of organic acid azides of structure IV, although this is not surprising since acid azides are explosives of varying degree of sensitivity[8] and are usually used as intermediates without isolation.[8b] Nevertheless, in spite of their sensitive nature, it was deemed of interest to examine the infrared absorption spectra of the more readily accessible and purifiable acid azides to determine the possibility of their existence as oxatriazoles (V) and/or possible group frequency shifts due to the proximity of the strong electron-withdrawing carbonyl group. This communication reports upon the preliminary results of this study. Table I and Figure 1 summarize the data obtained. All spectrum were obtained as mulls.

TABLE I

FREQUENCIES, CM.$^{-1}$

RN_3 R =	N_3 (Asym)		N_3 (Sym)	C=O
$C_6H_5C(O)$-	2179 (m)	2141 (s)	1238 (s)	1709 (s)
3-NO_2-$C_6H_4C(O)$-	2203 (s)	2146 (m)	1241 (m)	1701 (s)
4-NO_2-$C_6H_4C(O)$-	2193 (s)	2146 (s)	1233 (s)	1701 (s)
3,5-$(NO_2)_2$-$C_6H_3C(O)$-	2237 (m)	2155 (s)	1258 (s)	1692 (s)

The surprising feature of the data (Table I) is the observation that the asymmetric N=N=N stretching absorption, hitherto, always observed as a strong single band[7] now appears as a doublet (Fig. 1). In first observing this for benzazide (IV. Y = C_6H_5-) (curve 2 of Fig. 1) it was thought that the product had decomposed from the time involved in its preparation to the taking of the spectrum and that the doublet was that of phenylisocyanate as reported by Hoyer[9] (at 2277 and 2262 cm.$^{-1}$). Accordingly, a freshly prepared specimen of benzazide was divided into three portions and one por-

(1) The authors gratefully acknowledge sponsorship of this research by the Office of Ordnance Research, U. S. Army.

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(3) F. L. Scott, *Experienta*, **13**, 275 (1957).

(4) E. Lieber *et. al.*, (a) *J. Org. Chem.*, **22**, 441 (1957); (b) *J. Org. Chem.*, **22**, 1750 (1957); (c) *Can. J. Chem.*, **35**, 832 (1957); (d) *Can. J. Chem.*, **36**, 801 (1958); (e) *Chem. and Ind.*, **1958**, 893.

(5) Private communications from: (a) Professor P. A. S. Smith, University of Michigan; and, (b) Professor K. A. Jensen, University of Copenhagen.

(6) F. L. Scott, A. Koczarski, and J. Reilly, *Nature*, **170**, 922 (1952).

(7) (a) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., Ltd., London, 1958; (b) E. Lieber *et al.*, *Anal. Chem.*, **29**, 916 (1957).

(8) (a) N. V. Sidgwick, *The Organic Chemistry of Nitrogen*, Oxford Clarendon Press, 1937; (b) P. A. S. Smith, *The Curtius Reaction* in *Organic Reactions*, vol. III, J. Wiley and Sons, Inc., New York, 1946.

(9) H. Hoyer, *Chem. Ber.*, **89**, 2677 (1956).

tion decomposed[8b] to phenylisocyanate and its spectrum taken together with that of its admixture with benzazide. Curves 1, 2, and 3 of Fig. 1 clearly demonstrated that the doublet for benzazide was, indeed, real. Curves 4, 5, and 6 of Fig. 1 show similar doublets for three additional acid azides. Curve 7 is for *m*-nitrophenylisocyanate prepared by decomposition of the *m*-nitrobenzazide. It can be clearly noted from curves 4, 5, and 6 that traces of isocyanate are present in each case. Accordingly, the spectrum between 2500 to 2000 cm.$^{-1}$ serves as a powerful method for establishing the purity of acid azides. The benzazide as finally prepared showed no trace of isocyanate impurity by this method.

References relating to the infrared absorption spectra of organic acid azides are difficult to find since such data that have been noted were incidental insertions in a larger work. Ungnade[10] examined the spectra of a series of α-nitroacetazides ($O_2NCR^1R^2C(O)N_3$ where R^1 and R^2 were H and CH_3) in solution and reported a single band for the N_3 absorption at 2155 cm.$^{-1}$ and 2150 cm.$^{-1}$ No characterizations of the α-nitroacetrazides were attempted. Boyer *et al.*[11] reported a strong singlet N_3 absorption for methane sulfonyl azide at 2137 cm.$^{-1}$ Lucien[12] has reported the azide absorption frequencies at 2180 cm.$^{-1}$ (asym.) and 1350 cm.$^{-1}$ (sym.) for nitrosyl azide.

The present investigation continues particularly with extension to the more sensitive acid azides and to an examination of the effect of increasing conjugation on possible group frequency shifts in organic acid azides.

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(10) H. E. Ungnade and L. W. Kissinger, *J. Am. Chem. Soc.*, **79**, 1662 (1957).
(11) J. H. Boyer *et al.*, *J. Org. Chem.*, **23**, 1051 (1958).
(12) H. W. Lucien, *J. Am. Chem. Soc.*, **80**, 4458 (1958).

Chemistry of Merimines. II. Reductive Alkylation

William B. Wright, Jr.

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The preparation and properties of a number of derivatives of merimine, 2,3-dihydro-1H-pyrrolo-[3,4-*c*]-pyridine, were described in the first paper of this series.[1] Additional merimine derivatives have now been prepared by the reductive alkylation of 2-unsubstituted merimines.

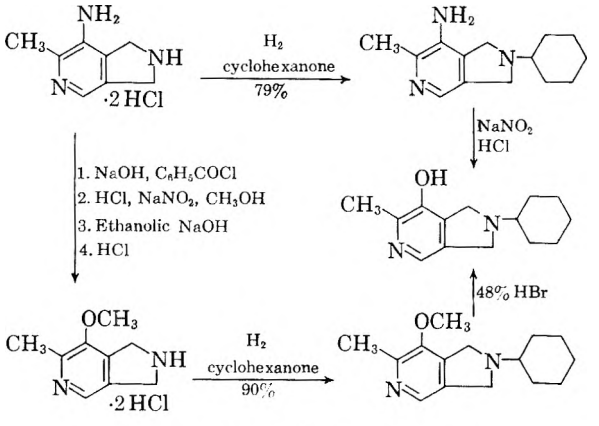
A review by Emerson[2] of the preparation of amines by reductive alkylation states that only poor yields are obtained in the preparation of tertiary amines from aliphatic secondary amines and ketones. It is interesting, therefore, that excellent yields of tertiary amines were obtained when 2-unsubstituted merimine derivatives were reductively alkylated with either aldehydes or ketones.

When the alkylation was stopped after absorption of about 1 molar equivalent of hydrogen, substitution occurred almost entirely in the 2-position even when 7-amino-6-methylmerimine dihydrochloride was alkylated with a large excess of the carbonyl compound. It was possible, however, to prepare a trimethyl derivative of 7-amino-6-methylmerimine dihydrochloride by allowing the alkylation to continue for 29 hr. In this experiment, 7-dimethylamino-2,6-dimethylmerimine dihydrochloride was obtained in 75% yield.

The position of monoalkylation has been established by conversion of 7-amino-2,6-dimethylmerimine dihydrochloride to the corresponding 7-bromo and 7-chloro analogs. These products would not be obtained if the 7-amino group were methylated. In the 2-cyclohexylmerimine series the structure has been proved by the sequence of reactions pictured below.

The preparation of the 7-methoxy-6-methylmerimine dihydrochloride has been previously described.[1]

The compounds prepared are described in Table I.



EXPERIMENTAL

Two general procedures were employed for the alkylations. When aldehydes or acetone were the alkylating agents, a 5% palladium-on-carbon catalyst was used. With higher ketones, a mixture of 5% palladium-on-carbon and 10% platinum-on-carbon catalysts gave faster reaction and higher yields. The following preparations serve to illustrate these procedures.

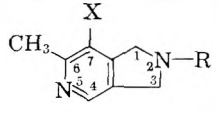
Procedure A. 7-Amino-2,6-dimethylmerimine. A mixture of 22.2 g. (0.1 mole) of 7-amino-6-methylmerimine dihydrochloride,[1] 8.25 ml. (0.11 mole) of 37% formaldehyde, 2.0 g. of 5% palladium-on-carbon catalyst and 200 ml. of water was shaken in the Parr hydrogenator under hydrogen pressure of about 3 atmospheres until 0.1 mole of hydrogen was absorbed. This usually required less than 30 min. The catalyst was filtered off and the filtrate was concentrated to dryness. The product was washed onto a filter with ethanol and then recrystallized from dilute ethanol. The yield of pure 7-amino-2,6-dimethylmerimine dihydrochloride, m.p. >300°, was 80%.

The base, m.p. 155–157°, was obtained when the dihydrochloride was treated with 2 equivalents of 5*N* sodium hydroxide and the aqueous layer was extracted with chloroform.

(1) W. B. Wright, Jr., J. S. Webb, and J. M. Smith, Jr., *J. Am. Chem. Soc.*, **79**, 2199 (1957).
(2) W. S. Emerson, *Org. Reactions*, **IV**, 195 (1948).

TABLE I

7-SUBSTITUTED-2-ALKYL-6-METHYLMERIMINES



R	X	Yield, %[a]	Characterized As	M.P., °C.[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	NH_2	80[c]	2HCl	>300	$C_9H_{15}Cl_2N_3$	45.8	45.5	6.4	6.5	30.0	29.9	17.8	18.1
			Base	155–157	$C_9H_{13}N_3$	66.2	65.8	8.0	8.2			25.7	25.7
Methyl	Dimethylamino	75	2HCl	246 dec.	$C_{11}H_{19}Cl_2N_3$	50.0	49.6	7.3	7.5	26.8	26.9	15.9	15.8
Methyl	OH	80[c]	2HCl	246–248	$C_9H_{14}Cl_2N_2O$	45.6	45.6	6.0	6.3	29.9	29.5	11.8	11.9
Methyl	Cl	33[d]	2HCl	264 dec.	$C_9H_{13}Cl_3N_2$	42.3	42.2	5.1	5.3	41.6	41.4	11.0	11.1
Methyl	Br	43[d,e]	2HCl	269 dec.	$C_9H_{13}BrCl_2N_2$	36.0	35.8	4.4	4.5	23.6	23.5	9.3	9.6
2-Propyl	NH_2	88[c,f]	2HCl	>300	$C_{11}H_{19}Cl_2N_3$	50.0	50.0	7.2	7.3	26.8	27.1	15.9	16.3
1-Butyl	NH_2	88[c,g]	Base[h]	128–130	$C_{12}H_{19}N_3$	70.2	70.3	9.3	9.5			20.5	20.2
			2HCl	>300	$C_{12}H_{21}Cl_2N_3$	51.8	52.1	7.6	7.9	25.4	25.7	15.2	15.5
3-Pentyl	NH_2	67[f]	Base[h]	119–121	$C_{13}H_{21}N_3$	71.2	70.9	9.7	9.8			19.2	19.6
Cyclohexyl	NH_2	79[f,j]	Base	181–182	$C_{14}H_{21}N_3$	72.7	72.8	9.2	9.3			18.2	18.5
			2HCl	>300	$C_{14}H_{23}Cl_2N_3$	55.3	55.0	7.6	7.7	23.3	23.5	13.8	13.7
Cyclohexyl	OCH_3	90[f]	2HCl	216 dec.	$C_{15}H_{24}Cl_2N_2O$	56.4	56.1	7.6	7.8	22.2	21.9	8.8	8.8
Cyclohexyl	HO	100[k,l]	2HBr	320 dec.	$C_{14}H_{22}Br_2N_2O$	42.7	42.7	5.6	5.9			7.1	7.3
		50[d]	Base	253–255	$C_{14}H_{20}N_2O$	72.4	72.2	8.7	8.9			12.1	11.8

[a] Unless otherwise noted, yields are after recrystallization. [b] Melting points are uncorrected. [c] Procedure A. [d] By diazotization of the 7-amino analog. [e] Bromine: calcd. 26.6, found 26.7. [f] Used 2 equivalents of acetone. [g] Used 2 equivalents of butyraldehyde and isolated as the base. [h] Recrystallized from ethyl acetate. [i] Procedure B. [j] Crude yield, m.p. 178–180°, was 97%. [k] By cleavage of the 7-methoxy analog. [l] Yield before recrystallization.

Procedure B. 7-Amino-2-cyclohexyl-6-methylmerimine. A mixture of 22.2 g. (0.1 mole) of 7-amino-6-methylmerimine dihydrochloride, 25 ml. (0.24 mole) of cyclohexanone, 2 g. of 5% palladium on carbon catalyst, 2 g. of 10% platinum-on-carbon catalyst and 230 ml. of water was shaken in the Parr hydrogenator under hydrogen pressure of about 3 atmospheres until about 0.13 mole of hydrogen was absorbed. The catalyst was filtered off, and the filtrate was concentrated and then treated with 25 ml. of 50% potassium hydroxide. The crystals which separated were filtered, washed with water, and dried. The crude yield of 7-amino-2-cyclohexyl-6-methylmerimine, m.p. 178–180°, was 97%. On recrystallization from ethanol, a 79% yield of pure product, m.p. 181–182°, was obtained.

When the above base was treated with two equivalents of ethanolic hydrogen chloride, 7-amino-2-cyclohexyl-6-methylmerimine dihydrochloride, m.p. 300°, was obtained. This compound was purified by recrystallization from dilute ethanol.

7-Chloro-2,6-dimethylmerimine dihydrochloride. A solution of 7.25 g. of sodium nitrite in 60 ml. of water was added over 5 min. to a mixture of 23.6 g. (0.1 mole) of 7-amino-2,6-dimethylmerimine dihydrochloride, 100 ml. of 4*N* hydrochloric acid and 600 ml. of water. The reaction mixture was held at 0 to −2° during this addition and for 10 min. longer and then poured into a mixture of 10 g. of cuprous chloride and 150 ml. of 4*N* hydrochloric acid. The mixture was allowed to warm up to 30° over a 3-hr. period and was then treated with hydrogen sulfide. The precipitate was filtered off and the filtrate was treated with activated charcoal. The clear solution was concentrated to dryness and the product was washed onto a filter with ethanol. The yield of salt and crude product was 20.1 g. The estimated product was 14.3 g. (56%). This mixture was stirred with 6.2 g. of sodium methylate and 400 ml. of ethanol for 2 hr. The salt was filtered off and the filtrate was treated with activated carbon and then concentrated to dryness. On addition of alcoholic hydrogen chloride, a precipitate separated. This product was filtered off and recrystallized twice from 90% ethanol. The yield, including recoveries, of pure 7-chloro-2,6-dimethylmerimine dihydrochloride, m.p. 264° dec., was 8.1 g. (33%).

7-Bromo-2,6-dimethylmerimine dihydrochloride. A mixture of 23.6 g. (0.1 mole) of 7-amino-2,6-dimethylmerimine dihydrochloride, 11.2 g. of sodium methylate and 400 ml. of anhydrous ethanol was stirred at room temperature for 2 hr. and then filtered to remove the salt. The filtrate was concentrated under reduced pressure to a white solid. A mixture of 400 ml. of water and 50 ml. of 40% hydrobromic acid was added and the solution was cooled to −2°. A solution of 7.25 g. of sodium nitrite in 60 ml. of water was added over a 5-min. period at 0 to −2°. The reaction mixture was held at this temperature for 10 more min. and then poured into a cold mixture of 17.5 g. of cuprous bromide, 70 ml. of 40% hydrobromic acid and 40 ml. of water. After 19 hr., hydrogen sulfide was passed in and the dark precipitate was filtered off. The filtrate was treated with activated carbon, concentrated to dryness, and the product was washed onto a filter with ethanol. The dried filter cake was added to an excess of 5*N* sodium hydroxide and extracted with chloroform. After drying over magnesium sulfate, the chloroform layer was mixed with 37 ml. of 4*N* ethanolic hydrogen chloride and the product which separated was filtered off and recrystallized from 90% ethanol. The yield of 7-bromo-2,6-dimethylmerimine dihydrochloride, m.p. 269° dec., was 43%.

7-Dimethylamino-2,6-dimethylmerimine dihydrochloride. A mixture of 22.2 g. (0.1 mole) of 7-amino-6-methylmerimine dihydrochloride, 40.5 g. (0.5 mole) of 37% formaldehyde, 160 ml. of water and 2 g. of 10% palladium-on-carbon catalyst was shaken in the Parr hydrogenator under an initial hydrogen pressure of about 3 atmospheres. Hydrogen absorption was rapid at first and 0.1 mole was absorbed in 25 min. The reaction rate then dropped sharply and the absorption was only 0.23 moles at the end of 22 hr. An additional 2 g. of 10% palladium-on-carbon catalyst was added and the reduction was continued until the total hydrogen absorption was 0.3 moles. The total reaction time was 29 hr. The reaction mixture was filtered, concentrated, treated with aqueous sodium hydroxide, and extracted with chloroform. The chloroform layer was distilled and the portion which boiled at 102–108° (0.2 mm.), n_D^{23} 2.544, was collected. This oil was treated with ethanolic hydrogen chloride and ether, and the crystals which separated were recrystallized from ethanol by the addition of ether. The yield of pure 7-dimethylamino-2,6-dimethylmerimine dihydrochloride, m.p. 246° dec., was 19.7 g. (75%).

2-Cyclohexyl-7-hydroxy-6-methylmerimine. (A) *From 7-amino-2-cyclohexyl-6-methylmerimine.* A solution of 3.8 g. of sodium nitrite in 30 ml. of water was added over a 30-min. period at 93–97° to a rapidly stirred solution of 11.5 g. (0.05 mole) of 7-amino-2-cyclohexyl-6-methylmerimine in 600 ml. of 0.05*N* hydrochloric acid. The reddish solution was held at the same temperature for 20 min. longer and then treated with activated carbon. The filtrate was concentrated to about 100 ml. and treated with excess sodium carbonate. The tan product which separated was filtered and washed with water, and the moist cake was recrystallized twice from ethanol. The yield of 2-cyclohexyl-7-hydroxy-6-methylmerimine, m.p. 253–255°, was 3.7 g. (32%). Recoveries from the alcoholic filtrates increased the yield to 50%.

(B) *From 2-Cyclohexyl-7-methoxy-6-methylmerimine.* A solution of 2.0 g. of 2-cyclohexyl-7-methoxy-6-methylmerimine, m.p. 58–60° but not analyzed, in 20 ml. of 48% hydrobromic acid was heated on the steam bath for 30 hr. and then concentrated to dryness. The residue was washed onto a filter with ethanol and dried. The yield of 2-cyclohexyl-7-hydroxy-6-methylmerimine dihydrobromide, m.p. *ca.* 320° dec., was 3.2 g. (100%). Recrystallization from ethanol improved the color but did not change the decomposition point.

When the dihydrobromide was dissolved in water and treated with sodium carbonate, the base was obtained. After recrystallization from ethanol it was identical by melting point, mixture melting point, and infrared spectra to the 2-cyclohexyl-7-hydroxy-6-methylmerimine prepared by method A above.

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Alkyl *N*,*N*-Dialkyl Methylphosphonamidates[1]

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In a series of recent publications Razumov *et al.*[3] describe the preparation and biological properties of

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(3) A. I. Razumov, O. A. Mukhacheva, and E. A. Markovich, *Khim. i Primenie Fosfororgan. Soedinenii, Akad. Nauk S.S.S.R., Trudy l-oi Konferents.*, 194 (1955) (published 1957); and *Zhur. Obschei Khim.*, **27**, 2389 (1957); A. I. Razumov, *Trudy Kazan. Khim. Technol. Inst. im. S. M. Kirova*, **23**, 205 (1957).

TABLE I

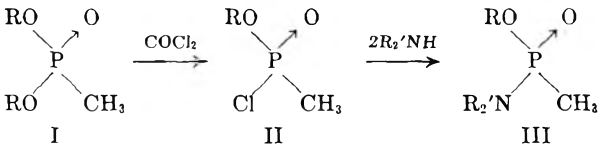
ALKYL *N,N*-DIALKYL METHYLPHOSPHONAMIDATES

Formula	°C./mm.	n_D/t°C.	Yield, %	Carbon		Hydrogen	
				Calcd.	Found	Calcd.	Found
$CH_3P(O)(OC_2H_5)N(CH_3)_2$	55/1.0	1.4303/24	70	39.7	39.4	9.3	9.0
$CH_3P(O)(n\text{-}C_3H_7)N(CH_3)_2$	62/1.0	1.4320/25	60	43.6	43.4	9.8	9.6
$CH_3P(O)(Oi\text{-}C_3H_7)N(CH_3)_2$	43/0.04	1.4300/22	56	43.6	43.5	9.8	9.7
$CH_3P(O)(On\text{-}C_4H_9)N(CH_3)_2$	64/0.5	1.4341/26	59	46.9	46.6	10.0	9.9
$CH_3P(O)(On\text{-}C_5H_{11})N(CH_3)_2$	91/1.0	1.4362/21	63	49.7	49.6	10.4	10.1
$CH_3P(O)(OC_2H_5)N(C_2H_5)_2$	54/1.0	1.4360/21	62	46.9	46.7	10.0	9.9
$CH_3P(O)(Oi\text{-}C_3H_7)(NC_5H_{10})^a$	90/1.0	1.4590/16	63	53.0	53.2	9.8	9.5
$CH_3P(O)(Oi\text{-}C_3H_7)(NC_4H_8O)^b$	86/1.0	1.4596/18	62	46.3	46.1	8.7	8.7

Derived from [a] piperidine and [b] morpholine.

a number of alkyl *N,N*-dialkyl ethylphosphonamidates. We have synthesized a number of similar compounds based on methylphosphonamidic acid by a different and apparently more convenient route.

Dialkyl methylphosphonates (I) were treated with phosgene by the procedure of Coe *et al.*[4] to give the alkyl methylphosphonochloridates (II). These compounds which are thermally unstable were obtained sufficiently pure by this method to be used without distillation. Reaction of the chloridates with two equivalents of the appropriate amine gave the corresponding alkyl *N,N*-dialkyl methylphosphonamidate (III) in yields ranging from 60–70% after distillation. Similarly by using piperidine and morpholine, with isopropyl methylphosphonochloridate, the isopropyl methyl phosphonopiperidate and morpholidate were obtained respectively.



These compounds, the data for which are given in Table I, were tested as insecticides and found to have pronounced systemic activity but very low mammalian toxicity.[5]

EXPERIMENTAL

n-Propyl N,N-dimethyl methylphosphonamidate. Dry phosgene was bubbled slowly through 60 g. (0.33 mole) of di-*n*-propyl methylphosphonate for 18 hr. with water cooling during the first 3 hr. Volatile products were removed by degassing at 30° and 10 mm. On analysis it was found that the chlorine content of the residue was within 0.5% of that required for $CH_3PO(OC_3H_7)Cl$. The chloridate was dissolved in 250 ml. of dry ether, and into it passed 30 g. (0.7 mole) of anhydrous dimethylamine, with continuous stirring and ice cooling. After standing for 3 hr. at room temperature the mixture was filtered and the ether removed under reduced pressure. The residue was fractionally distilled to yield 33 g. (60%) of *n*-propyl *N*-dimethyl methylphosphonamidate, b.p. 62° at 1 mm.; n_D^{25} 1.4320.

Anal. Calcd. for $C_6H_{16}O_2NP$: C, 43.61; H, 9.75. Found: C, 43.38; H, 9.60.

SUFFIELD EXPERIMENTAL STATION
RALSTON, ALBERTA

(4) D. G. Coe, B. J. Perry, and R. K. Brown, *J. Chem. Soc.*, 3604 (1957).

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Diosmetin Triacetate from 3-Bromohesperetin Triacetate and Silver Acetate-Acetic Anhydride[1,2]

J. H. LOOKER AND MYRON J. HOLM[3]

Received January 16, 1959

In an investigation of hesperetin (I) as a potential synthetic precursor of quercetin 4′-monomethyl ether, the reaction of the 3-bromohesperetin triacetate (II) of Zemplen and Bognar[4] with silver acetate in acetic anhydride, reported to give 3-acetoxyhesperetin triacetate,[4] was investigated. The present note reports that this reaction leads to diosmetin triacetate (III).

3-Bromohesperetin triacetate (II) was prepared by the general method of Zemplen and Bognar.[4] The quality of the absolute chloroform used in their procedure was found to be extraordinarily critical. Repeated attempts were made to carry out the reported synthesis of 3-acetoxyhesperetin triacetate by reaction of II with silver acetate in acetic anhydride. There was obtained, however, in yields up to 75%, III, identical with a product obtained from

(1) From the M.S. thesis (1956) of Myron James Holm.

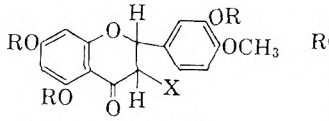
(2) This investigation was supported in part by a research grant (E-1703) from the National Institute of Allergic and Infectious Diseases, Public Health Service.

(3) Du Pont Postgraduate Teaching Assistant, 1956–57; Standard Oil of Indiana Foundation Fellow, 1957–58.

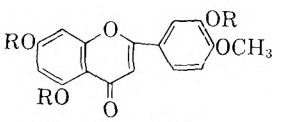
(4) G. Zemplen and R. Bognar, *Ber.*, **76B**, 454 (1943).

the action of NBS on hesperetin triacetate.[5] Characterization of III involved both acidic and basic hydrolysis to give diosmetin (IV), in turn characterized by reacetylation to III, and demethylation followed by acetylation to give luteolin tetraacetate. The IV thus obtained had an ultraviolet absorption spectrum identical with that previously reported.[6]

Our observation is similar to that of Robertson, Cavill and co-workers,[7] who attempted to prepare 3-acetoxy-7-methoxyflavanone by reaction of silver acetate with 3-bromo-7-methoxyflavanone. 7-Methoxyflavone was the sole reaction product.



I. X = H; R = H
II. X = Br; R = $COCH_3$



III. R = $COCH_3$
IV. R = H

EXPERIMENTAL

3-Bromohesperetin triacetate. Numerous experiments proved the quality of the absolute chloroform to be critical. Reagent grade chloroform was washed twice with conc. sulfuric acid, and then five or six times with water (at least twice after the chloroform layer becomes clear). The chloroform was shaken with anhydrous calcium chloride, decanted onto fresh calcium chloride, and allowed to stand for several hours. The chloroform was then distilled, and the first distillate fraction tested for phosgene by addition of silver nitrate. If any cloudiness whatsoever appeared, all of the chloroform, both distillate and residue, was discarded. If no cloudiness appeared, approximately 1/4 of the chloroform was distilled and discarded. The middle portion was then collected, and usually distilled over a 0.2° boiling range. If the boiling range was greater than 0.4°, all of the chloroform was discarded. The chloroform thus purified was used within a few hours.

A 1-g. quantity of hesperetin triacetate, m.p. 143.5–144.5°,[8] was brominated in absolute chloroform solution in a Vycor flask under irradiation with a Hanovia Model 30600 quartz mercury vapor lamp under the general conditions of Zemplen and Bognar. A total quantity of 720 mg. of crude, crystalline bromination product (two crops, second by crystallization of residual oil from ether) was obtained. Recrystallization of the total crude from 4 ml. of chloroform and 12 ml. of absolute ethanol gave 510 mg. of product, m.p. 170–190°. Three additional crystallizations from chloroform-ethanol gave 270 mg. of 3-bromohesperetin triacetate, m.p. 196–198° (lit.[4] m.p. 190–191°). The high loss upon recrystallization necessitated reworking of the mother liquors.

Anal.[9] Calcd for $C_{22}H_{19}BrO_9$: Br, 15.7. Found: Br, 15.6.

An alcoholic solution of 3-bromohesperetin triacetate gave no turbidity with aqueous silver nitrate at room temperature, but slowly became turbid at the boiling point. In acetonitrile, no silver bromide was obtained with silver nitrate in two weeks.

Reaction of 3-bromohesperetin triacetate with silver acetate. A 0.6 g. quantity of 3-bromohesperetin triacetate, 800 mg. of silver acetate, and 8 ml. of anhydrous acetic anhydride were heated on a steam bath for 2 hr., then for 1 hr. at 130° in an oil bath. The reaction mixture then was poured into water and allowed to stand overnight. The resulting solid was collected, extracted with three 20 ml. portions of chloroform, and the solvent subsequently evaporated. The residual oil was crystallized twice from acetone-alcohol, to give 320 mg. (75%) (two crops), of diosmetin triacetate, m.p. 195–197° (lit.[10] m.p. 195–196°). The infrared spectrum (KBr pellet) was identical with that of diosmetin triacetate obtained by NBS dehydrogenation of hesperetin triacetate, and contained strong or medium absorption bands at 1767, 1645, 1631, 1613, 1520, 1434, 1373, 1343, 1284, 1262, 1199, 1147, 1103, 1091, 1038, 1024, and 910 $cm.^{-1}$

In view of the previous report[4,11] that this substance is 3-acetoxyhesperetin triacetate, additional characterization was carried out. Basic hydrolysis of 50 mg. of product (diosmetin triacetate) in 2.5 ml. of 95% ethanol was effected by addition of 0.3 ml. of 3% aqueous sodium hydroxide, heating 5 min. on a steam bath, diluting with water, and acidifying to *p*H *ca.* 4.5. Further dilution gave a precipitate, m.p. 185–187° (positive test with magnesium–hydrochloric acid). This product was redissolved in 2.5 ml. of 95% ethanol and 0.3 ml. of 3% sodium hydroxide added. Immediate precipitation of yellow solid ensued, and solution was effected by addition of water. After warming 10 min., the solution was diluted and acidified to give diosmetin, m.p. 252° (lit.[10] m.p. 253–254°).

Acid hydrolysis was carried out by dissolving 200 mg. of diosmetin triacetate in 16 ml. of 97.5% ethanol, adding 0.4 ml. of concentrated hydrochloric acid and heating the resulting mixture under reflux 1 hr. under nitrogen. Dilution with 24 ml. of water, and cooling overnight gave a flocculent precipitate of diosmetin, which became orange colored during collection by filtration, even under nitrogen; yield, 140 mg., m.p. 255–258°. Acetylation of 50 mg. of this product in 3 ml. of acetic anhydride containing 250 mg. of anhydrous sodium acetate by heating under reflux for 3 hr. gave diosmetin triacetate, m.p. 196–197°. Demethylation of the crude diosmetin was effected by dissolving 50 mg. in 1 ml. of glacial acetic acid, adding 0.5 ml. of hydriodic acid (d. 1.7), and heating under reflux for 3 hr. The crude luteolin (*ca.* 40 mg.) was isolated by pouring the reaction mixture into ice water, collecting the precipitate by filtration and air drying; m.p. 326° (lit.[12] m.p. 327–329°). The luteolin thus obtained was acetylated by boiling 1 hr. with 40 mg. of anhydrous sodium acetate and 2 ml. of acetic anhydride. The mixture was poured into water, and the precipitated solid collected and recrystallized from 95% ethanol; m.p. 230° (lit.[13] m.p. 226–227°).

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(5) J. H. Looker and M. J. Holm, *J. Org. Chem.*, 24, 567 (1959).

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(9) Previous analytical characterization (ref. 4) was restricted to methoxyl determination.

(10) A. Lovecy, R. Robinson, and S. Sugasawa, *J. Chem. Soc.*, 817 (1930).

(11) Zemplen and Bognar (ref. 4) reported m.p. 193–194°, and observed OCH_3 = 6.84 for 3-acetoxyhesperetin triacetate (calcd. OCH_3 = 6.40). M.p. of diosmetin triacetate is 195–196°, and theoretical OCH_3 = 7.28.

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Electrochemical Fluorination of S-Methylthioglycollic Acid Chloride[1]

JOHN A. YOUNG AND RICHARD D. DRESDNER

Received January 16, 1959

Perfluoroalkyl sulfur pentafluorides, R_fSF_5, react with unsaturated fluorocarbon derivatives to add $R_F\cdot$ and F· across the double bond,[2,3] as shown in Equations 1 and 2.

$$CF_3SF_5 + CF_3CF{=}CF_2 \longrightarrow C_4F_{10} \text{ isomers} \quad (1)$$

$$CF_3SF_5 + CF_3N{=}CF_2 \longrightarrow (CF_3)_3N \quad (2)$$

In hopes of extending the scope of this reaction to more useful R_F groups, it was decided to investigate the reaction of SF_5CF_2COF under similar conditions. Haszeldine[4] has shown that electrochemical fluorination of thioglycollic acid gives an extremely low yield of SF_5CF_2COF; however, since dialkyl sulfides have been found to cleave during this process to give good yields of R_FSF_5,[5,6] it was thought that the desired compound might be obtained by electrochemical fluorination of CH_3SCH_2COCl. The absence of active hydrogens such as —COOH and —SH in this compound would be expected to improve cell performance over that shown by thioglycollic acid. The results of the fluorination of CH_3SCH_2COCl are reported in this paper.

Identification of the materials obtained by fractionation of the crude cell product after conclusion of the run showed that although considerable cleavage had occurred, loss of the methyl group alone had not taken place. The two products found in greatest abundance were CF_3SF_5 and $(CF_3)_2SF_4$. A large fraction was obtained which had values (b.p. 14–20°, mol. wt. 211–228) near those reported for SF_5CF_2COF (b.p. 22°, mol. wt. 224), but by chromatographic separation it was found that this material was merely a mixture containing $(CF_3)_2SF_4$ and smaller amounts of unidentified incompletely fluorinated substances.

Two compounds were isolated which largely retained the original structure. These were $CF_3SF_4CF_2CF_3$ and $CF_3SF_4CF_2COF$, each representing about 7% of the total cell product. These were identified by infrared and nuclear magnetic resonance (NMR) spectra, and by analysis of the methyl ester of the latter. Retention of the entire structure in $CF_3SF_4CF_2COF$ is rather surprising, and indicates that fluorocarbon acids containing sulfur as well as those containing nitrogen[7] can be made by this method, although the yields in both cases are quite poor.

The most novel compound was a liquid (b.p. 88°, m.w. 352) whose analysis corresponded to $C_2F_{14}S_2$, mol. wt. 354. The three possible structures for this formula are $CF_3SF_4CF_2SF_5$ (I), $SF_5CF_2CF_2SF_5$ (II), and $CF_3SF_4SF_4CF_3$ (III). The first can be eliminated on the basis of the NMR spectrum, which showed all the fluorines on carbon and 6 or 8 of those on sulfur to be identical. The δ-value for the single C-F peak (a triplet) was −5.5 (ref. CF_3COOH). This is in the normal region for CF_3 attached to SF_4 ($CF_3SF_4CF_2CF_3$ −9.8) and considerably removed from that for CF_2 between CF_3 and SF_4 or SF_5. Chemical shifts for the latter configuration run roughly from +15 to +25, on the basis of information obtained in this laboratory or from the literature,[8] concerning half a dozen compounds of this type. The resonance of the fluorine on sulfur was quite complex, two of the peaks being split into five or seven, but the δ-values of −95.5 and −116 correspond better with SF_4 (−94.8, −123 in $O(CF_2CF_2)_2SF_4$)[8] than with SF_5 (−118.7 to 137.5).[8] Because of the symmetry, presence of CF_3 and SF_5 in the same molecule is prohibited, and structure III, $CF_3SF_4SF_4CF_3$, is therefore the most probable. This is the first reported instance of two vicinal SF_4 groups in a fluorocarbon derivative, and this compound cannot be made by electrochemical fluorination of dimethyl disulfide.[6]

EXPERIMENTAL

The apparatus and procedures for the electrochemical fluorination process have been previously described.[5,6] From 615 g. of CH_3SCH_2COCl, made by methylation of thioglycollic acid with methyl sulfate and conversion to the acid chloride by means of either PCl_3 or $SOCl_2$,[9] a total of 436 g. product boiling above −80° was obtained, including 30 g. recovered as a second phase when the cell was drained after the run. The concentration of solute during the operation was roughly 2 mole %. Fractionation was performed in columns appropriate for the temperatures involved and packed with nickel helices. Although the five principal fractions described below were the only ones identified, forerun and intercuts were relatively large, and small amounts of material boiling as high as 35°/2 mm. were obtained.

Fraction A. Boiling point −23 to −18°, 64 g., mol. wt. 195, chromatographic purity 93%. The infrared spectrum of a center cut was identical with that of CF_3SF_5, b.p. −20°, mol. wt. 196.

(1) This material was presented at the Meeting-in-Miniature of the Florida Section of the American Chemical Society, Lakeland, Fla., May 9–10, 1958. The work was supported by the Office of Naval Research, and reproduction of all or any part of this paper is permitted for purposes of the United States Government.

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(3) R. D. Dresdner, *J. Am. Chem. Soc.*, **79**, 69 (1957).

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(7) J. A. Young and R. D. Dresdner, *J. Am. Chem. Soc.*, **80**, 1889 (1958).

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(9) A. Mooradian, C. J. Cavallito, A. J. Bergman, E. J. Lawson, and C. M. Sutter, *J. Am. Chem. Soc.*, **71**, 3372 (1949).

Fraction B. Boiling point 16–20°, 85 g., mol. wt. 219–228; reported[4] for SF_5CF_2COF, b.p. 22°, mol. wt. 224. Since a gas chromatograph showed four to six components over this boiling range a 2 g. sample was quantitatively chromatographed, using a stationary phase of the ethyl ester of Kel-F acid 8114, on Celite. About 75% of this amount, representing approximately 63 g. of the whole fraction, was recovered as one peak, mol. wt. 250, and was identified as $(CF_3)_2SF_4$ by comparison of its infrared spectrum with that of known $(CF_3)_2SF_4$, b.p. 20°, mol. wt. 246. The remainder of the chromatographed material had an average mol. wt. of only 148.

Fraction C. Boiling point 47.5°, 24 g., mol. wt. 297, purity 99%. An infrared spectrum showed all peaks found in the spectrum of $CF_3SF_4CF_2CF_3$, b.p. 47.1°, mol. wt. 296, but also additional lines at 10.80–10.85 and 12.25, and an elemental analysis was therefore made.

Anal. Calcd. for $C_3F_{12}S$: C, 12.2; F, 77.1; S, 10.8. Found: C, 12.4; F, 76.8; S, 11.0.

Fraction D. Boiling point 55°, 39 g., mol. wt. 279 (calcd. for $CF_2SF_4CF_2COF$ 274), purity 83%. An infrared spectrum showed a sharp peak for −COF at 5.27. Because of the impurities present, this compound was converted for analysis to the methyl ester (67% yield) by refluxing with methanol. The ester had b.p. 123°, n_D^{30} 1.3259.

Anal. Calcd. for $C_4H_9H_3O_2$: C, 16.8; F, 59.7; H, 1.1; S, 11.2. Found: C, 17.1; F, 59.0; H, 1.1; S, 10.9.

Principal infrared lines for these two new compounds are: $CF_3SF_4CF_2COF$ 5.27, 7.80, 7.90–7.95, 8.06, 9.70, 10.12 (w), 10.83, 11.32 (w), 11.65–11.80, 12.50, 14.00–14.05, 14.85–14.95; $CF_3SF_4CF_2COOCH_3$ (in CCl_4) 5.60, 6.95, 7.62, 8.00–8.05, 8.17, 8.63–8.73, 9.95, 11.90–12.00, 12.18, 14.50.

Fraction E. Boiling point 87–88°, 10 g., mol. wt. 352, n_D^{28} 1.2964, purity 95%. Refluxing with 30% aqueous KOH did not change the mol. wt. and no sign of reaction was observed. Identified by NMR, as discussed above. Principle infrared lines for this compound are 7.95, 8.63, 10.85–11.05, 11.65–11.75, 12.75, 14.25–14.50.

Anal. Calcd. for $C_2F_{14}S_2$: F, 75.2; S, 18.0 mol. wt. 354. Found: F, 75.1; S, 18.0; mol. wt. 352.

Acknowledgment. The authors are indebted to Dr. Max Rogers of Michigan State University for the NMR studies.

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Structure of the Reaction Product of Phenyl Vinyl Ketone and Hydroxylamine

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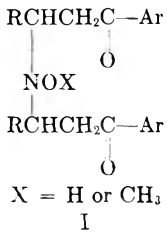
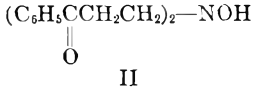
Under the proper conditions, the reaction of certain α,β-unsaturated aryl ketones (or a precursor of the unsaturated ketone) with methoxyamine, substituted hydroxylamines, or hydroxylamine has been reported to yield bisketoamines analogous to structure I.[2]



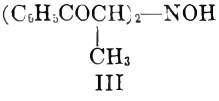
I

In line with this, Auwers and Müller[3] have described a compound melting at 140° to which they assigned the structure bis(β-benzoylethyl)hydroxylamine (II). This material was prepared from the



II

corresponding dioxime, which in turn resulted from the treatment of β-chloropropiophenone with free hydroxylamine and excess alkali. Shortly before this, Danilowa and Danilow[4] had reported a compound melting at 122.5° (obtained from the reaction of a 1:1 ratio of phenyl vinyl ketone and free hydroxylamine) to which they assigned structure III. Both groups reported a compound melting at



III

153–154° which they described as the dioxime of the respective dicarbonyl compounds (II and III).

In the present work, the reaction of phenyl vinyl ketone with hydroxylamine hydrochloride in the presence of sodium acetate produced compounds which were demonstrated to be bis(β-benzoylethyl)-hydroxylamine (II), m.p. 120.5–121°, or the dioxime (m.p. 148–149°) of this compound. With hydroxylamine hydrochloride and sodium acetate the dicarbonyl compound could be readily converted into the dioxime, but repeated recrystallizations from three different solvents failed to raise the melting point of the dioxime (148–149°) to the value reported by Auwers[3] and Danilowa.[4] In order to clarify the structure of these compounds two similar compounds were prepared for a comparative nuclear magnetic resonance study; bis(β-benzoylethyl)methoxyamine (IV) was produced in 53% yield from phenyl vinyl ketone and methoxyamine hydrochloride and bis[β-(*p*-methoxybenzoyl)ethyl]-

(1) The work discussed herein was supported by Contracts AF 33(616)-3772 and -5486 with the Materials Laboratory of Wright Air Development Center, Wright-Patterson Air Force Base, Ohio. Reproduction of this paper in whole or in part is permitted for any purpose of the United States Government. The paper is based on portions of a thesis submitted by Donald J. Casey to the Graduate College of the University of Illinois in partial fulfillment of the requirements of Doctor of Philosophy.

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TABLE I

NUCLEAR MAGNETIC RESONANCE DATA FOR SUBSTITUTED HYDROXYLAMINES

	$\Delta\nu$[a]	Area[b] Ratio	Assignment	$\Delta\nu$	Area Ratio	Assignment	$\Delta\nu$	Area Ratio	Assignment	$\Delta\nu$	Area Ratio	Assignment
II	57.6	1.28 (1.25)	$-CH_2-$									
Acetate of II	53.5	1.24 (1.25)	$-CH_2-$	109.6	2.74 (2.67)	CH_3CO						
IV	57.3	1.24 (1.25)	$-CH_2-$				47.1	3.17 (3.33)	$NOCH_3$			
V	58.0	0.98 (1.0)	$-CH_2-$				46.1	2.72 (2.66)	$NOCH_3$	32.9	1.44 (1.33)	$ArOCH_3$

[a] Expressed in cycles/second from water at a frequency of 40 M.c.p.s. The sign convention is such that positive values of $\Delta\nu$ represent signals observed at a higher field than that of water. [b] Area ratio: aromatic peaks (at −83 to −143)/observed peak; ( ) is the theoretical values for compounds having structure.

$$(YC_6H_4COCH_2CH_2)_2—NOX$$

Y = H or CH_3O

X = H, CH_3, or $COCH_3$

methoxyamine (V) was produced in 28% yield from *p*-methoxyphenyl vinyl ketone and methoxyamine hydrochloride.

$$(C_6H_5\overset{\overset{O}{\|}}{C}CH_2CH_2)_2—NOCH_3$$

IV

$$(p\text{-}CH_3OC_6H_4\overset{\overset{O}{\|}}{C}CH_2CH_2)_2—NOCH_3$$

V

An examination of these compounds by nuclear magnetic resonance produced rather anomalous results. For compounds having structure I (where R = H), significantly different chemical shifts would be expected for the chemically different methylene groups. In the spectra of II, the acetate of II, IV, and V, this distinction was not observed; in all cases a single sharp peak assignable to the methylene groups was found. Comparison of the integrated area of the peaks produced by the aromatic hydrogens with the areas of peaks resulting from the other hydrogens provided strong support for the presence of a $-CH_2—CH_2-$ grouping in these molecules. These data are summarized in Table I. The area measurements were also found to be internally consistent for a given compound. For the acetate of II, the ratio $—CH_2—/CH_3CO$ was 2.74 (theoretical: 2.67 for 8/3). For compound IV, the ratio $—CH_2—/NOCH_3$ was 2.55 (theoretical: 2.67 for 8/3). And for compound V the area ratios were: $—CH_2—/NOCH_3$, 2.77 (theoretical: 2.67 for 8/3); $—CH_2—/ArOCH_3$, 1.47 (theoretical: 1.33 for 8/6); $ArOCH_3/NOCH_3$, 1.88 (theoretical: 2.0 for 6/3).

Substantial proof for two of these structural assignments was provided by the Clemmenson reduction of II to bis(γ-phenylpropyl)amine which was isolated and identified as the hydrochloride. This established the structure of II and the dioxime of II, and when considered in conjunction with the similarities in manner of synthesis, comparable infrared data, and nuclear magnetic resonance data, constituted strong support for the structural assignments offered for IV and V.

EXPERIMENTAL

Bis(β-benzoylethyl)hydroxylamine (II). To 3.77 g. (0.046 mole) of anhydrous sodium acetate dissolved in 75 ml. of water was added 2.0 g. (0.015 mole) of phenyl vinyl ketone[5] suspended in 80 ml. of water and 10 ml. of ethanol. Stirring was started and the solution was cooled to 0°; 3.12 g. (0.045 mole) of hydroxylamine hydrochloride in 75 ml. of water was then added to the vigorously stirred mixture during 10 min. After 90 min. at 0°, the precipitated white solid was collected on a filter and air dried. Crude yield: 1.92 g. (86.4%), m.p. 115–118°. Recrystallization from absolute ethanol produced fine white crystals, m.p. 120.5–121°. Significant infrared bands (chloroform): 3420–3300 (—OH); 1680 (ArC=O); 1602, 1586, 1497 (aromatic); 1455; 1374; 1325; 1282; 975; and 685 cm.$^{-1}$ Ultraviolet maxima (absolute ethanol): λ_{max} 242 mμ (ε 23,700), λ_{max} 280 mμ (ε 2,390). Nuclear magnetic resonance data have been summarized in Table I.

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71; O, 16.14. Found: C, 72.63; H, 6.50; N, 4.78; O, 16.18. Mol. wt. calcd.: 297. Mol. wt. (ebullioscopic in butanone): 302.

Acetate of bis(β-benzoylethyl)hydroxylamine. bis(β-Benzoylethyl)hydroxylamine (0.300 g., 0.001 mole) dissolved in 14 ml. of chloroform was allowed to react with 0.122 g. (0.0012 mole) of acetic anhydride in 5 ml. of glacial acetic acid at 0°. After 0.5 hr. at 0°, the reaction was stirred at room temperature for 16 hr. The mixture was then washed with a dilute solution of sodium bicarbonate, the chloroform layer separated, dried over sodium sulfate, and evaporated to dryness. The residue was recrystallized from absolute ethanol; yield: 0.240 g. (71%); m.p. 90–91°. Significant infrared

(5) C. S. Marvel and Donald J. Casey, *J. Org. Chem.*, in press.

bands (chloroform): 2995, 2900, 2860, 1755, 1682, 1600, 1583, 1452, 1370, 1326, 1194, 1004, 970, 917, and 687 cm.$^{-1}$ Nuclear magnetic resonance data have been listed in Table I.

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.80; H, 6.43; N, 4.04.

Dioxime of bis(β-benzoylethyl)hydroxylamine. Solutions of 2.0 g. (0.015 mole) of phenyl vinyl ketone in 50 ml. of ethanol and 2.38 g. (0.029 mole) of anhydrous sodium acetate in 75 ml. of ethanol were added at equivalent rates to a stirred solution of 2.09 g. (0.030 mole) of hydroxylamine hydrochloride in 50 ml. of ethanol at 0°; addition time: 15 min. The mixture was stirred at 0° for 90 min., allowed to warm to room temperature, and the inorganic salt removed by filtration. The ethanol solution was then concentrated under reduced pressure to 25 ml., and 150 ml. of water was added gradually to precipitate 2.26 g. (92%) of crude product. This material was washed thoroughly with chloroform and recrystallized from methanol to yield 1.72 g. (70%) of pure dioxime; m.p. 148–149°. Pertinent infrared bands (Nujol): 3310, 1630 (weak), 1600 (weak), 1577 (weak), 1503, 1323, 1312, 1024, 933, 810, 765, 758, and 688 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{21}N_3O_3$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.77; H, 6.52; N, 12.75. Mol. wt. calcd.: 327. Mol. wt. (ebullioscopic in butanone): 346.

Bis(β-benzoylethyl)hydroxylamine was converted to the dioxime by treatment with slightly more than a two-fold excess of hydroxylamine hydrochloride and sodium acetate in ethanol at room temperature. The yield was 80%.

Bis(β-benzoylethyl)methoxyamine (IV). Anhydrous sodium acetate (2.38 g., 0.029 mole) in 50 ml. of ethanol and methoxyamine hydrochloride (2.42 g., 0.029 mole) in 50 ml. of ethanol were added at equivalent rates to a stirred solution of phenyl vinyl ketone (3.6 g., 0.027 mole) in 50 ml. of ethanol at 0°; addition time: 15 min. After 1 hr. at 0°, the precipitated sodium chloride was removed by filtration and the ethanol solution concentrated to 20 ml. under reduced pressure. The precipitated solid was collected on a filter, washed well with water, and recrystallized from absolute ethanol; yield: 2.24 g. (53%); m.p. 93–94. Significant infrared bands (chloroform): 3000, 2935, 2890, 1680, 1598, 1582, 1463 (shoulder), 1452, 1371, 1324, 1180, 1035, 1003, 973, and 687 cm.$^{-1}$ The spectrum was strikingly similar to that of bis(β-benzoylethyl)hydroxylamine. Nuclear magnetic resonance data have been presented in Table I.

Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.31; H, 6.68; N, 4.71.

p-Methoxy-β-chloropropiophenone. *p*-Methoxy-β-chloropropiophenone was prepared by a modification of the procedure of Davies and Powell.[6] To 83 g. (0.62 mole) of anhydrous aluminum chloride was added with stirring and cooling in an ice bath a solution of 69.9 g. (0.55 mole) of β-chloropropionyl chloride in 90 ml. of carbon disulfide, followed by 67.2 g. (0.62 mole) of freshly distilled anisole in 120 ml. of carbon disulfide. The ice bath was removed and the reaction heated under reflux for 1 hr. after which the mixture was poured onto cracked ice with stirring. Chloroform was added and the layers separated. The aqueous layer was extracted with chloroform and the washings combined with the original organic phase which was then washed with water and dried over sodium sulfate. Evaporation of the solvent under reduced pressure left a solid which was recrystallized from a 70:30 mixture of medium high boiling (b.p. 60–90°) and low boiling (b.p. 30–60°) petroleum ether; yield: 88 g. (81%); m.p. 63–64° [lit., 63,[6] 63–64[7]]. Significant infrared bands (chloroform): 3000 (shoulder), 2960, 2835, 1673, 1600, 1578, 1513, 1465, 1425, 1365–1353, 1310, 1260, 1243, 1170, 1114, 1030, 982, and 835 cm.$^{-1}$.

Bis[β-(p-methoxybenzoyl)ethyl]methoxyamine (V). Solutions of *p*-methoxy-β-chloropropiophenone (5.88 g., 0.0296 mole) in 25 ml. of ethanol and potassium acetate (2.90 g., 0.0296 mole) in 25 ml. of ethanol were mixed and heated briefly. After 45 min. the precipitated potassium chloride was removed by filtration. To this ethanol solution of *p*-methoxyphenyl vinyl ketone was added at once 2.47 g. (0.0296 mole) of methoxyamine hydrochloride in 50 ml. of ethanol. Stirring was started and 2.43 g. (0.0296 mole) of sodium acetate in 50 ml. of ethanol was added over a period of 10 min.; the reaction was then stirred at room temperature for 2 hr. The precipitated sodium chloride was removed, the ethanol solution concentrated to 10 ml., and the resulting solid collected on a filter. This material was recrystallized once from medium high boiling petroleum ether (b.p. 60–90°) and then from absolute ethanol. Yield: 1.55 g. (28%); m.p. 111.5–112.6°. A 34% yield of the same product was obtained by substituting a drop of concentrated hydrochloric acid for the sodium acetate in the above procedure. Pertinent infrared bands (chloroform): 3000 (shoulder), 2930, 2830, 1671, 1598, 1575, 1510, 1464, 1445, 1421, 1369, 1313, 1260, 1240–1220, 1168, 1113, 1030, 981, and 835 cm.$^{-1}$. Nuclear magnetic resonance data have been recorded in Table I.

Anal. Calcd. for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.79; H, 6.81; N, 3.62.

Reduction of bis(β-*benzoylethylhydroxylamine*). Zinc dust (7.2 g., 0.11 mole), mercuric chloride (0.72 g., 0.0026 mole), 1 ml. of concentrated hydrochloric acid, and 10 ml. of water were shaken together for 5 min.; the supernatant liquid was then decanted and discarded. To the amalgamated zinc were added in order: 4.5 ml. of water, 10.5 ml. of concentrated hydrochloric acid, and 0.997 g. (0.0034 mole) of bis-(β-benzoylethyl)hydroxylamine in 15 ml. of reagent grade benzene. The mixture was then heated at reflux temperature for 24 hr. with an additional 1.5 ml. of concentrated hydrochloric acid being added every 6 hr. At the end of this period the reaction mixture was cooled and the solution decanted. The insoluble oil clinging to the walls of the reaction flask was dissolved in ethanol, the ethanol solution filtered to remove particles of zinc, and the solvent evaporated. The residual oil was treated with dilute sodium hydroxide solution, the basic solution extracted with chloroform, and the chloroform solution evaporated to dryness. The residual yellow oil was repeatedly extracted with hot dilute hydrochloric acid and the combined acid solutions evaporated to dryness leaving small white plates. After 5 recrystallizations from water, 0.155 g. (16%) of bis(γ-phenylpropyl)amine hydrochloride was obtained; m.p. 214.5–215.5° (lit., 203°[8]). An additional 0.394 g. of intractable oil was also isolated. Pertinent infrared bands (chloroform): 3400 (very weak), 3010 (shoulder), 2950, 2760, 2460, 1653 (very weak), 1600 (shoulder), 1582, 1494, 1465 (shoulder), 1453, 969, and 690 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{24}NCl$: C, 74.59; H, 8.34; N, 4.83; Cl, 12.23. Found: C, 74.63; H, 8.08; N, 4.69; Cl, 12.04. Mol. wt. calcd.: 290. Mol. wt. (Signer[9] in chloroform): 309.

Acknowledgment. Microanalyses were performed by Mr. Jozsef Nemeth, Miss C. Higham, Mrs. F. Ju, and Mrs. M. Stingl. Infrared spectra were determined by Mr. Paul McMahon and Miss M. DeMott. Nuclear magnetic resonance spectra were obtained by Mr. Ben Shoulders.

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Catalytic Synthesis of Heterocycles. XI.[1] Dehydrocyclization of *o*-Ethylbenzeneselenol to Selenonaphthene[2]

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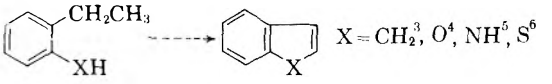
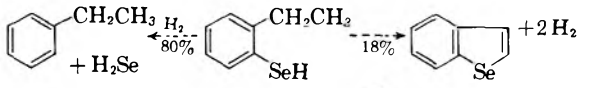
A procedure for the synthesis of *o*-ethylbenzeneselenol has been developed. The vapor phase catalytic dehydrogenation of this benzeneselenol to selenonaphthene in 18% yield is discussed.

In continuing our work on the catalytic synthesis of heterocycles it was decided to attempt to extend ring closures of the type to selenium compounds.



Of the four types of ring closures indicated above, those involving the thiol group go most easily and in best yield. With chromium oxide catalysts the thiophene ring forms *via* dehydrogenation at temperatures of 425–450° while temperatures of 525–625° are necessary for the formation of the furan, pyrrole, and cyclopentadiene rings. With sulfur compounds, a side reaction which may be serious is the hydrogenolysis of the C—S bond to hydrogen sulfide and the hydrocarbon. Thus, from the work with other heterocycles it was expected that *o*-ethylbenzeneneselenol would dehydrocyclize at relatively low temperatures of around 400°, but it was also expected that hydrogenolysis might predominate over dehydrocyclization. This proved to be true. Under the best conditions about 80% hydrogenolysis occurred along with 18% cyclization. Although part of the hydrogen for the hydrogenolysis indicated in Equation B below could be obtained from reaction A, this would not be sufficient.



Some of the hydrogen must come from the conversion of the ethyl group to a vinyl group and no doubt considerable styrene formed along with the ethylbenzene, although no attempt was made to determine the amount. No unreacted *o*-ethylbenzeneselenol was found.

EXPERIMENTAL

o-Bromoethylbenzene. In a 2-l. beaker was placed 121 g. of commercial grade of *o*-ethylaniline and 225 ml. of 48% hydrobromic acid. The mixture was warmed to dissolve the salt and then quickly cooled with stirring to 0°. The resulting slurry was diazotized with a solution of 69 g. of sodium nitrite in 125 ml. of water. Although the temperature was held below 5° during this process, considerable amounts of ethylphenol were observed to form. After the diazotization was completed the diazonium solution was poured onto a solution of cuprous bromide made from 250 g. of $CuSO_4$-$5H_2O$.[7]

The cuprous bromide so made was dissolved in 75 ml. of 48% hydrobromic acid. The cold diazonium salt was added to a cold solution of the cuprous bromide with stirring and the mixture allowed to come slowly to room temperature. It was then warmed and finally steam distilled. The organic layer was separated from the distillate and washed first with sodium hydroxide solution, then concentrated sulfuric acid, and then water. After the solution was dried over calcium chloride, it was distilled. The yield was 104.5 g. (56.5%) b.p. 195–197°/730 mm. A boiling point of 199.5° has been reported for material made by another procedure.[8]

o-Ethylbenzeneselenol. In the synthesis of this compound the general procedure of Foster[9] was used. The Grignard reagent from 55 g. of o-bromoethylbenzene was prepared in 250 ml. of dry ether in a three-neck flask fitted with a dropping funnel, a reflux condenser, and a sealed stirrer. After the reagent was prepared the dropping funnel was removed and an addition tube with 22 g. of selenium attached. During the preparation of the Grignard reagent as well as during the preparation of the beneneselenol, the system was kept under a nitrogen atmosphere. The ether solution of the Grignard reagent was brought to the boiling point and the selenium was added slowly over a period of about 45 min. with good stirring. Stirring and refluxing were continued for an additional 45 min. and then the mixture was poured onto crushed ice. After acidification with hydrochloric acid it was filtered through glass wool into a separatory funnel. The product was extracted with ether and the ether extracts were combined and dried over magnesium sulfate. Evaporation of the ether and distillation gave 26.5 g. (48.2%) of *o*-ethylbenzeneselenol b.p. 61–67°/0.9 mm. A center cut showed n_D^{25} 1.5728.

Anal. Calcd. for $C_8H_{10}Se$: C, 51.90; H, 5.45. Found: C, 51.96; H, 5.88.

Selenonaphthene. The procedure for the dehydrogenation was similar to that previously described.[10] Two different catalysts were investigated. One consisted of 1% platinum on coconut charcoal supplied commercially by the Baker Company and the other was a copper-chromium-charcoal catalyst used in our earlier work.[8] Essentially the same yield was obtained with each catalyst. In a typical experiment 10 g. of *o*-ethylbenzeneneselenol was dissolved in 25 ml. of dry thiophene-free benzene. This solution was then passed over the catalyst at a temperature of 425° during the course of 30 min. The gas evolved in the dehydrogenation was passed through a weighed ascarite tube to remove any hydrogen selenide and then measured in a wet test meter. (After the run the system was swept out with hydrogen to

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(2) This research was supported by a grant from the National Science Foundation.

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insure that all the hydrogen selenide was absorbed by the ascarite.) The rate of gas evolution remained almost constant during the 30-min. period with the copper-chromium catalyst, indicating that at least a rapid rate of poisoning did not occur. The platinum catalyst was much more susceptible to poisoning and at the end of 20 min. the rate of hydrogen evolution was less than one third of an initial rate more rapid than that of the copper-chromium catalyst. Running the benzeneselenol over the catalyst at slower rates or higher or low temperatures did not increase the yield. In a typical experiment (using 10 g. of *o*-ethylbenzeneselenol) with the copper-chromium catalyst, the ascarite tube gained 0.355 g. which would indicate that about 80% of the benzeneselenol underwent hydrogenolysis to give hydrogen selenide. After the run the catalyst tube was washed with benzene which was allowed to run down into the condensate. The benzene solution was then washed with dilute sodium hydroxide and then water. After the solution was dried over magnesium sulfate most of the benzene was removed by distillation through an efficient column. The residue which still contained some benzene was flash distilled to give first a forerun of benzene with some selenonaphthene. The material which boiled above 200° was collected and after crystallization from methanol, 1.72 g. of material of m.p. 50–51° was obtained. The picrate of this material melted at 155–157°. When the forerun from the distillation was treated with picric acid, 0.4 g. of picrate of m.p. 151–153° was obtained. The melting point of selenonaphthene has been reported as 50–51° and its picrate as 156–157°.[11]

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III. Synthesis of Dihydrosphingosine-1,3-cyclophosphate[1]

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In a previous communication,[2] it was reported that in the preparation of dihydrosphingosine-1-phosphate from sphingosine which is D-erythro-1,3-dihydroxy-2-amino-4-trans-octadecene,[3] *N*-carbobenzoxydihydrosphingosine reacted with only 1 mole of diphenylphosphoryl chloride to yield *N*-carbobenzoxy-1-diphenylphosphoryl dihydrosphingosine. It was thought that knowledge of this reaction would possibly be utilized in the synthesis of several phosphate diesters in which the primary hydroxyl group of dihydrosphingosine and another nitrogen-containing moiety, such as ethanolamine, choline, or serine, are esterified with phosphoric acid. In a series of reactions under a variety of conditions, *N*-carbobenzoxydihydrosphingosine-1-phenylphosphoryl *N*-carbobenzoxyethanolamine, the desired intermediate in the preparation of dihydrosphingosine-1-phosphoryl-ethanolamine, could not be obtained by the addition of *N*-carbobenzoxyethanolamine to *N*-carbobenzoxydihydrosphingosine and phenylphosphoryl dichloride. Similar results were obtained when choline chloride was substituted for the protected ethanolamine in the above reaction. However, from each reaction mixture a crystalline derivative was isolated in reasonable yield. These derivatives had the same melting point and similar contents of nitrogen and phosphorus. Removal of the protective groups by catalytic hydrogenolysis over platinum yielded a monophosphate ester of dihydrosphingosine. Since this compound consumed no periodic acid under conditions that cleaved dihydrosphingosine-1-phosphate, it was concluded to be dihydrosphingosine-1,3-cyclophosphate and its immediate precursor thus was *N*-carbobenzoxydihydrosphingosine-1,3-phenylcyclophosphate. Further confirmation of this structure was provided by its conversion to the phosphate monoester by opening of the diester ring after acid hydrolysis. This yielded essentially the 1-isomer, the 3-isomer being undetected, which was ascertained by the finding of palmitaldehyde after periodic acid oxidation of the isolated phosphate monoester.

EXPERIMENTAL

N-Carbobenzoxydihydrosphingosine-1,3-phenylcyclophosphate (I). A chilled solution of 6.5 g. of *N*-carbobenzoxydihydrosphingosine[2] in 30 ml. of anhydrous pyridine was added with vigorous stirring for 3–5 min. to 3.2 g. of phenylphosphoryl dichloride[4] in 10 ml. of pyridine surrounded by an ice bath. After standing for 30 min. at 0°, the reaction mixture, upon attaining room temperature, was poured into 500 ml. of crushed ice water. When the precipitate aggregated, it was removed by suction filtration, dried over phosphorus pentoxide *in vacuo*, and crystallized from 200 ml. of n-heptane; yield 3.1 g. (36% of theory); m.p., 81–82°.

Anal. Calcd. for $C_{32}H_{48}O_6NP$ (573.4): C, 66.87; H, 8.44; N, 2.44; P, 5.40. Found: C, 66.86; H, 8.72; N, 2.45; P, 5.47.

Dihydrosphingosine-1,3-cyclophosphate (II). 2.0 g. of I were dissolved in 50 ml. of glacial acetic acid containing 200 mg. of platinum oxide and hydrogenated under slightly above atmospheric pressure and room temperature. When the uptake of hydrogen ceased, the reaction mixture was filtered; the filtrate was diluted with 6 volumes of water and brought to *p*H 4.0–5.0 (*p*H paper) with 5*N* NaOH. After chilling the solution in an ice bath, the precipitate was removed, dried over phosphorus pentoxide, and crystallized from 100 ml. of 85% ethanol. The moist precipitate obtained after crystallization was washed successively on the filter with 20 ml. portions of ethanol (twice), acetone, and ether; yield 0.45 g. (35% of theory). Dihydrosphingosine-1,3-cyclophosphate is insoluble in water and most organic solvents but soluble in glacial acetic acid and acid or alkaline ethanol. It consumed no periodic acid.

Anal. Calcd. for $C_{18}H_{38}O_4NP$ (363.3): C, 59.45, H, 10.54, N, 3.85, P, 8.53. Found: C, 59.72, H, 10.63, N, 3.78, P, 8.56.

Conversion of dihydrosphingosine-1,3-cyclophosphate to dihydrosphingosine-1-phosphate (III). 151. 8 mg. of dihydrosphingosine-1,3 cyclophosphate were heated under reflux for 18 hr. in a solvent mixture consisting of 5 ml. of glacial acetic acid, 15 ml. of 34% hydrobromic acid, and 5 ml. of

(1) This investigation was supported in part by research grant No. B-341 (C5 and C6) from the Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

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water. After cooling to room temperature, the reaction mixture was diluted with 2 volumes of water and chilled in an ice bath. The flocculent white precipitate was removed by suction filtration and washed successively on the filter with 75 ml. portions of water, acetone, and ether; yield 142.7 mg. The entire 142.7 mg. of dihydrosphingosine-1-phosphate, 0.418 mM, were oxidized with periodic acid as previously described.[2] The consumption of periodate was 0.384 mM. This result indicates 92% completion of the reaction. The palmitaldehyde, isolated as the 2,4-dinitrophenylhydrazone, melted at 105–106°; yield 42 mg.

Acknowledgment. The author wishes to acknowledge the assistance of Mr. Wilson Woodbeck in the preparation of the beef spinal cord sphingolipides. Mrs. Florence Brand in the nitrogen determinations, Mrs Sonia Braun in the phosphorus analyses, and Miss Mary Veralli, Miss Leona Crook, Mr. James Clark, and Dr. Paula Raizman in preparing the sphingosine sulfate employed in this investigation.

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Some Observations on the Iodoform Test

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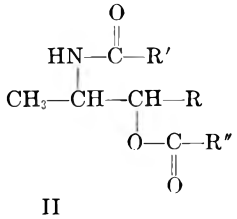
The reactivity of various hypohalite solutions on organic compounds and the scope of this reactivity



II

IIa. R = CH_2OCH_3; R′, R″ = CH_3

IIb. R, R′, R″ = C_2H_5

IIc. R, R′, R″ = CH_3

was adequately reviewed by Fuson and Bull[3] in 1934, and since that time relatively few new structure types have been found to give a positive iodoform test (Lieben's Reaction). These new structures which gave the iodoform test could nevertheless always be explained by hydrolysis, cleavage, or oxidation. Thus α,β-unsaturated ketones not having the requisite methyl ketone or methyl carbinol grouping, could yet yield iodoform if they are capable of forming acetaldehyde or saturated methyl ketones upon a reverse aldol condensation.[4] Upon treatment with sodium hypoiodite 5-methyl-2-furoic acid also yielded iodoform.[5]

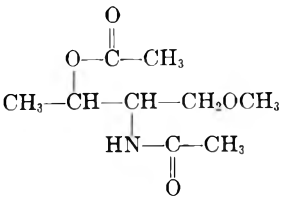
In the course of an investigation on the structure of Elaiomycin,[6] the iodoform test was used in an attempt to distinguish between two possible structures of a degradation product, *N*-(2-hydroxy-1-methylenemethoxypropyl)acetamide, acetate ester (I) and *N*-(2-hydroxy-3-methoxy-1-methylpropyl)-acetamide, acetate ester (IIa).

Distinction between these two structures by the iodoform test was discovered impossible when synthetic IIa yielded iodoform.

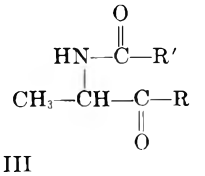
While systems which contain the group CH_3-$CHNH_2$— are known to give a positive test,[3] the conditions of the iodoform test employed in this work were not vigorous enough to hydrolyze an acylated amine. Alanine and isopropylamine which gave a positive test were acetylated to *N*-acetylalanine and *N*-isopropylacetamide, respectively, and the iodoform test failed.

That the esterified methyl carbinol system was hydrolyzed under the standard conditions to give the requisite grouping for iodoform formation was demonstrated by positive tests on *O*-acetyl lactic acid and *N*-(2-hydroxy-1-methylpropyl)acetamide, acetate ester (IIc).

Treatment of *N*-(3-methoxy-1-methylacetonyl)-



I



III

IIIa. R = CH_2OCH_3; R′ = CH_3
IIIb. R, R′ = C_2H_5

acetamide (IIIa) with sodium hypoiodite also resulted in the formation of iodoform. The ketone IIIa would be formed in the hydrolysis and oxidation of IIa with sodium hypoiodite. Further, *N*-(1-

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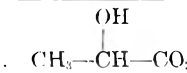
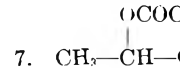
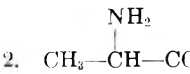
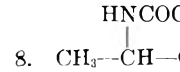
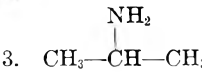
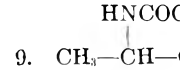
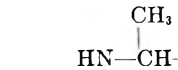
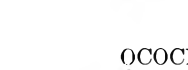
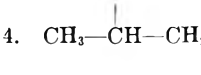
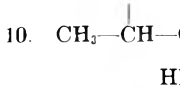
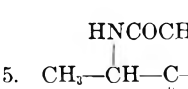
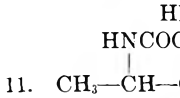
COMPOUNDS TESTED[7]

		Iodoform			Iodoform
1.		(+)	7.		(+)
2.		(+)	8.		(−)
3.		(+)	9.		(−)
4.		(+)	10.	 (IIc)	(+)
5.	 (IIIa)	(+)	11.	 (IIa)	(+)
6.	 (IIIb)	(+)	12.	 (IIb)	(+)

methylbutan-2-onyl)propionamide (IIIb) and *N*-(2-hydroxy-1-methylbutyl)propionamide, propionate ester (IIb) with a similar structural arrangement also gave positive iodoform tests.

Thus, compounds with the general structure III or those compounds which can produce this structural grouping under the conditions of the iodoform test represent a new structure type capable of positive results in the iodoform test.

The observed reaction is postulated to occur by oxidation of III in the α-position. Subsequent decomposition can then occur leading to a reactive methyl ketone.

EXPERIMENTAL[8]

Iodoform tests. All iodoform tests were performed according to the procedure of McElvain[7] using 7 drops of sample, 2.5 ml. of water, 5 ml. of 5% sodium hydroxide solution, and the required amount of iodine–potassium iodide solution necessary to give an iodine color. The iodoform obtained was identified by melting point and mixture melting point determinations. Samples 1, 2, 3, and 4 were available compounds of reagent grade.

O-Acetyl lactic acid. Lactic acid was acetylated according to the procedure of Filachione[9] and a 67% yield of *O*-acetyl lactic acid, b.p. 85–88° (0.8 mm.), n_D^{25} 1.4230, d^{25} 1.4320, d^{25} 1.175 was obtained.

*N-Acetyl-*DL*-alanine.* DL-Alanine was acetylated with acetic anhydride by the method described in *Organic Syntheses* for glycine.[10] The *N*-acetyl-DL-alanine prepared melted 136–137°.[11]

N-Isopropylacetamide. Low temperature acylation of isopropylamine with excess acetic anhydride followed by distillation resulted in a quantitative yield of *N*-isopropylacetamide, b.p. 201–203°, n_D^{25} 1.4273, d^{25} 0.912.

N-(2-Hydroxy-1-methylpropyl)acetamide, acetate ester (IIc). Hydrogenation of 3-acetamido-2-butanone[12] (11.5 g., 0.088 mole) with platinum oxide in ethanol yielded 10 g. (87%) of *N*-(2-hydroxy-1-methylpropyl)acetamide, b.p. 112–115° (0.3 mm.), n_D^{25} 1.4664. Ten g. of this alcohol was treated with cold acetic anhydride and then warmed gently for 8 hr. Volatile material was removed under reduced pressure and on distillation there was obtained 10 g. (76%) of IIc,[13] b.p. 50° (5–8 μ), n_D^{25} 1.4526, d^{25} 1.055.

N-(3-Methoxy-1-methylacetonyl)acetamide (IIIa). Methoxyacetic anhydride, b.p. 74–77° (2 mm.), n_D^{25} 1.4259 was prepared from methoxyacetic acid, thionyl chloride, and pyridine at −15°.[14] In a 100-ml. flask equipped with condenser was placed 23 g. (0.1418 mole) of methoxyacetic anhydride, 11.3 g. (0.1418 mole) of pyridine, and 6.55 g. (0.05 mole) of *N*-acetylalanine. The reaction mixture was heated several hours on the steam bath. The mixture was then distilled to yield 3.84 g. (48%) of IIIa, b.p. 48° (5 μ), n_D^{25} 1.4562, d^{25} 1.126.

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.81; H, 8.23. Found: C, 53.23, H, 7.88.

N-(2-Hydroxy-3-methoxy-1-methylpropyl)acetamide, acetate ester (IIa). Two g. (0.0125 mole) of IIIa was reduced in absolute ethanol with 0.3 g. of prereduced platinum oxide and 0.85 equivalent of hydrogen was absorbed. Filtration of the mixture and removal of the ethanol from the filtrate under reduced pressure left a residue which was treated with excess acetic anhydride. Subsequent removal of the excess acetic anhydride and acetic acid after heating and distillation yielded 1.90 g. (75%) of IIa, b.p. 60° (0.3 μ), n_D^{25} 1.4502, d^{25} 1.109. The infrared spectrum of this compound was in agreement with the assigned structure.

Anal. Calcd. for $C_9H_{17}NO_4$: C, 53.18; H, 8.43. Found: C, 52.98; H, 8.11.

(7) The procedure in S. M. McElvain, *The Characterization of Organic Compounds*, The MacMillan Co., New York, 1949, pp. 137, was utilized.

(8) Melting points and boiling points are uncorrected.

(9) E. M. Filachione, *Ind. Eng. Chem.*, **36**, 472 (1944).

(10) A. H. Blatt, *Org. Syntheses*, **Coll. Vol. 2**, 11, 1943.

(11) W. Shive and G. W. Shive, *J. Am. Chem. Soc.*, **68**, 117 (1946).

(12) C. C. Price, *Org. Syntheses*, **33**, 1 (1953).

(13) F. H. Dickey, W. Fickett, and H. J. Lucas, *J. Am. Chem. Soc.*, **74**, 944 (1952) report the DL-*threo*-, *erythro*-, D(+)-*threo*- and L(−)-*erythro*- forms.

(14) W. Gerrard and A. M. Thrush, *J. Chem. Soc.*, 741 (1952).

N-(1-Methylbutan-2-onyl)propionamide (IIIb). The procedure for the preparation of 3-acetamido-2-butanone[12] was utilized. Treatment of 20 g. (0.224 mole) of DL-alanine with 95 g. (1.2 moles) of pyridine and 174.8 g. (1.344 moles) of propionic anhydride yielded 20.2 g. (58.5%) of IIIb, b.p. 79–81° (0.1 mm.), n_D^{25} 1.4547, d^{25} 1.016.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.11; H, 9.61. Found: C, 61.30; H, 9.48.

N-(2-Hydroxy-1-methylbutyl)propionamide, propionate ester (IIb). To 4 g. (0.0254 mole) of IIIb in methanol was added slowly with swirling 750 mg. of sodium borohydride. The reaction mixture was allowed to stand overnight. Ammonium hydroxide was added to the solution. The solution was extracted with ether and the ether extracts dried over anhydrous sodium sulfate, filtered, and evaporated to leave a white solid. Recrystallization of the solid from petroleum ether–acetone yielded 2.663 g. (66%) of *N*-(2-hydroxy-1-methylbutyl)-propionamide, m.p. 113–114°. A solution of 2.563 g. of this alcohol in pyridine was added to an excess of propionyl chloride in pyridine and the mixture was allowed to stand overnight, then poured onto cracked ice. The aqueous mixture was extracted with ether and the ether extract was washed successively with dilute hydrochloric acid, water, sodium bicarbonate, and water. The ether solution was dried and then distilled to yield 1.752 g. (51%) of IIb, b.p. 101–103° (0.1 mm.), n_D^{25} 1.4523, d^{25} 1.004. The infrared spectrum of this compound was in agreement with the assigned structure.

Anal. Calcd. for $C_{11}H_{21}NO_3$: C, 61.36; H, 9.83; N, 6.51. Found: C, 61.12; H, 9.80; N, 6.45.

DEPARTMENT OF CHEMISTRY
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Derivatives of Sulfenic Acids. XXIV. Synthesis of Certain Thiophenols by Cleavage of Unsymmetrical Disulfides[1]

NORMAN KHARASCH AND ALAN JAMES PARKER[2]

Received January 28, 1959

In a preceding paper of this series[3] a new synthesis of thiophenols was recorded, involving alkaline cleavage of aryl 2,4-dinitrophenol sulfides:

$$(NO_2)_2C_6H_3SAr + OCH_3^- \longrightarrow ArS^- + (NO_2)_2C_6H_3{-}OCH_3 \quad (1)$$

We now wish to describe another new method for preparing certain thiophenols, which was an outgrowth of our interests in the mechanisms of scission of the sulfur-sulfur bond.

It is well known[4] that many disulfides are cleaved by nucleophilic reagents such as CN^-, RS^-, SO_3^{--}, $(C_6H_5)_3P$, AsH_5, $S_2O_3^{--}$, *etc.* These reactions are simply nucleophilic displacements from bivalent sulfur, of a mercaptide ion, by a base with more affinity for sulfur. The reactions involve equilibria, which may be represented as in (2), where B^- is a base such as those above, and R and R′ are any groups (not necessarily different), which form a covalent bond with sulfur which is less susceptible to cleavage than the =S—S—bond.

$$R{-}S{-}S{-}R' + B^- \rightleftharpoons RS^- + R'S{-}B \quad (2)$$

In many cases, equilibrium *b* lies well to the left because of the high affinity of RS^- for sulfur, and, in other cases, the alternate scission (3) may compete with (2). If, however, B^- is a strong

$$R{-}S{-}S{-}R' + B^- \rightleftharpoons RS{-}B + R'S^- \quad (3)$$

displacing anion, and R is a strong electron withdrawing group (such as 2,4-dinitrophenyl or 2-nitro-4-chlororophenyl), the reactivity of RS^- in reaction (2) will be less than that of B^- and this will cause equilibrium (*b*) to lie to the right. Also, if R is considerably more electron withdrawing than R′, RS^- will be the more easily displaced mercaptide group, so that primarily reaction (2) and not (3), will occur. With these conditions in mind, reaction (2) can be adapted to a convenient synthesis of certain thiophenols, RSH, starting with sulfenyl chlorides, RSCl, in which R is a strong electronegative group, and choosing a less electronegative group, R′, so that R′SB, or its decomposition products, are readily soluble in water, or are volatile.

We selected 2-mercaptosuccinic acid (thiomalic acid) as the source for the group R′S, and hydroxide ion as the nucleophilic reagent for general use; ethyl mercaptan, mercaptoacetic acid, and β-mercaptoethanol are equally effective sources of the R′S group. It is also known[4] that cyanide ion and triphenylphosphine are much more powerful displacing nucleophiles for reaction (1) than is hydroxide ion, and—although less convenient—should be chosen when cleaving disulfides (RSSR′) in which R is not as strongly electron withdrawing as it is in the case of 2,4-dinitrophenyl or 2-nitro-4-chlorophenyl. In one reaction (R = 2-nitrophenyl), the use of cyanide ion as the displacing anion increased the yield of 2-nitrothiophenol by 35% over that obtained with hydroxide ion as nucleophile.

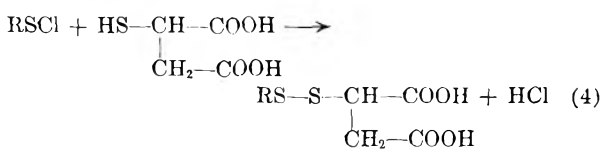
The reactions are easy to perform and lead to the desired thiophenols quickly. The sulfenyl chloride is converted almost quantitatively to the thiomalic acid derivative (Equation 4), which is a stable, odorless, crystalline disulfide. Like the aryl 2,4-dinitrophenyl sulfides of Equation (1), these disulfides cleaved rapidly to yield the thiophenol.

(1) This study was carried out, in part, under sponsorship of the Office of Ordnance Research, United States Army, Contract DA-04-495-Ord. 901.

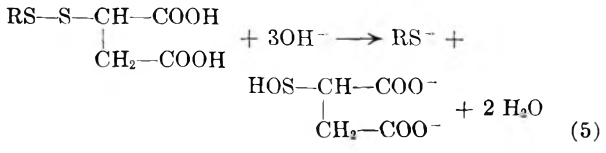
(2) Australian Commonwealth Scientific and Industrial Research Organization post-doctoral fellow at the University of Southern California, 1958–1959.

(3) N. Kharasch and R. Swidler, *J. Org. Chem.*, 19, 1704 (1954).

(4) *Cf.* the reviews by O. Foss in *Organic Sulfur Compounds*, edited by N. Kharasch, Vol. 1, Pergamon Press, 1959; and A. J. Parker and N. Kharasch, *Chem. Revs.*, in press.



Addition of alkali, followed by warming in some cases, dissolves the disulfide and displaces RS^- (Equation 5). Filtration and acidification of the



filtrate precipitates the thiophenol, leaving the other reaction products in solution.

The general procedure, described below, was used to prepare 2,4-dinitrothiophenol, m.p. 128–130°, in 95% yield; 2-nitrothiophenol, m.p. 56°, in 50% yield (with alkali) and in 85% yield (with cyanide as nucleophile); 4-chloro-2-nitrothiophenol, m.p. 122°, in 60% yield; and pentachlorothiophenol, m.p. 232–233°, in 55% yield. The yields are based on the amount of sulfenyl chloride used.

It is, of course, recognized that the required sulfenyl chlorides can, themselves, often best be prepared from thiophenols,[5] so that the conversion ArSCl → ArSH is not always important for synthetic use; and, of course, other routes to the thiophenols listed are available.[6] Nevertheless, the present method is quite convenient, especially when stocks of the stable intermediate disulfides are available, for preparing—as required—quantities of reactive thiols. For example, 2,4-dinitrothiophenol is frequently desired as a reagent for characterizing halides,[7] and it is convenient to prepare it in small amounts, as described above, because of its great tendency to oxidize to the very insoluble disulfide, if not stored quite properly.

The mechanistic factors involved in nucleophilic scission of unsymmetrical disulfides have been discussed at some length in ref. (4). It may be noted that the yields of thiophenols (RSH) recorded agree with the expected effect of electron withdrawing substituents in R on the relative affinities of RS^- and B^- for sulfur (Equation 2), and, hence, on the ease of displacement of RS^-.

EXPERIMENTAL

General procedure. The sulfenyl chloride RSCl (0.1 mole) was dissolved in 100 ml. dry acetic and 0.1 mole of thiomalic acid, suspended in 50 ml. acetic acid, was added, with stirring. The solution was warmed to 70–80° for a few minutes and the acetic acid then removed under reduced pressure to yield the crude disulfide of Equation 4. Without further purification, the thiol was displaced from the above disulfide, by adding an excess of the appropriate nucleophile, as described below.

(a) *Displacement by alkali.* The solid residue was dissolved in 100 ml. 4*N* alkali and refluxed, preferably under nitrogen, for 30 min. The reaction mixture was filtered, cooled, the filtrate acidified with hydrochloric acid and the precipitated thiol collected immediately and recrystallized from ligroin. Thorough drying, and storage under nitrogen, permits the thiols to be stored for long periods without oxidation to disulfide. If considerably stronger alkali is used for the displacement, refluxing is not necessary and a purer product results on acidification. It is probable that some redox reactions of the nitrothiophenoxide ions can occur on heating.

(b) *Displacement by cyanide.* The disulfide obtained by reaction of the sulfenyl chloride and thiomalic acid, by the general procedure above, was dissolved in dilute alkali and 0.1 mole of solid sodium cyanide was added. The reaction mixture was warmed for a few minutes, filtered, and the filtrate acidified (CAUTION: HCN) with hydrochloric acid. The precipitated thiol was purified as described above.

Acknowledgment. We are indebted to the National Aniline Division of the Allied Chemical and Dye Corporation for a generous sample of thiomalic acid and to the Australian Commonwealth Scientific and Industrial Research Organization for a studentship to one of us (A.J.P.).

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(5) N. Kharasch, S. J. Potempa, and H. L. Wehrmeister, *Chem. Revs.*, **39**, 269 (1946).

(6) Houben-Weyl, *Methoden der Organischen Chemie*, Georg Thieme Verlag, Stuttgart, 4th ed. Vol. 9 (1955).

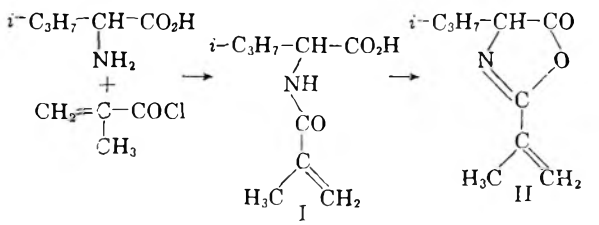
(7) R. W. Bost, P. K. Starnes, and E. L. Wood, *J. Am. Chem. Soc.*, **72**, 1968 (1951).

A Vinyl Azlactone

John W. Lynn

Received January 28, 1959

A novel vinyl-polymerizable azlactone, 2-isopropenyl-4-isopropyl-2-oxazolin-5-one (II), was prepared by the cyclodehydration of 2-methacrylamido-3-methylbutyric acid (I), which was prepared by acylation of *dl*-valine with methacrylyl chloride.



Both in homopolymerization and in copolymerization with vinylidene chloride II proved to be a very reactive vinyl monomer. Copolymers of II possess a pendant azlactone group which may provide a site for crosslinking or chemical modification of a resin.

EXPERIMENTAL[1]

2-Methacrylamido-3-methylbutyric acid (I). A mixture of 117 g. (1 mole) of *dl*-valine (Dow), 400 ml. of water and 80 g. (2 moles) of sodium hydroxide was stirred at 10–15° and 105 g. (1 mole) of methacrylyl chloride (Monomer and Polymer Co.) was added over a 1.5-hour period. The mixture was then treated with 1 mole of concentrated hydrochloric acid. The voluminous precipitate, which formed on standing, was removed by filtration, washed with water, and then recrystallized from benzene to give 141 g., a 75% yield, of I (m.p. 99–100°).

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.4; H, 8.10; N, 7.56. Found: C, 58.36; H, 8.08; N, 7.65.

2-Isopropenyl-4-isopropyl-2-oxazolin-5-one (II). The technique of Cleaver and Pratt[2] was employed for this closure. A mixture of 18.5 g. (0.1 mole) of I and 51 g. (0.5 mole) of acetic anhydride was added rapidly to 51 g. (0.5 mole) of acetic anhydride at 100°. The mixture was held at 100° for 10 min. and then distilled to give 6.8 g., a 40.5% yield, of II (b.p. 81°/10.5 mm., n_D^{30} 1.4550).

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.78; N, 8.38. Found: C, 64.25; H, 7.68; N, 8.21.

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(1) All temperatures are uncorrected.

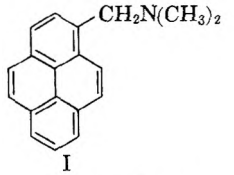
(2) C. S. Cleaver and B. C. Pratt, *J. Am. Chem. Soc.*, **77**, 1544 (1955).

Some Dimethylaminomethyl Derivatives of Polycyclic Aromatic Hydrocarbons

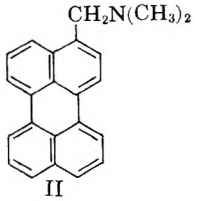
E. MARCUS AND J. T. FITZPATRICK

Received January 28, 1959

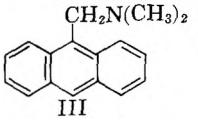
The preparation of dialkylaminomethylbenzenes from aromatic aldehydes and dialkylformamides by the Leuckart reaction has been described previously.[1] We wish to report the extension of the Leuckart reaction to the synthesis of the dimethylaminomethyl derivatives of pyrene, perylene, anthracene, and naphthacene (I–IV).



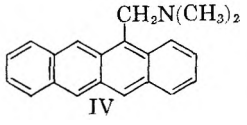
I



II



III



IV

(1) (a) O. Wallach, *Ann.*, **343**, 54 (1905); (b) E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949); (c) M. Mousseron, R. Jacquier, and R. Zagdoun, *Bull. soc. chim.*, 974 (1953); (d) M. L. Moore, *Org. Reactions*, **5**, 301 (1952).

The corresponding aldehydes can be obtained readily by formylation of the hydrocarbons with *N*-methylformanilide or dimethylformamide and phosphorus oxychloride. Refluxing a solution of the aldehyde in dimethylformamide in the presence of formic acid gave fair to good yields of the desired compounds. When the reaction of pyrenecarboxaldehyde with dimethylformamide was carried out in the absence of formic acid, no product at all was obtained. The compounds were isolated as their hydrochlorides.

An alternative route *via* the corresponding chloromethyl derivatives is less satisfactory, because direct chloromethylation of such highly active polycyclic hydrocarbons often leads to diarylmethane-type compounds and bis(chloromethyl) derivatives.[2] When 9-(chloromethyl)anthracene was needed as an intermediate in some recent work, it was made by a three-step synthesis.[3]

EXPERIMENTAL

All melting points are uncorrected. The neutralization equivalents of the amine hydrochlorides were determined by titration with sodium hydroxide using phenolphthalein as indicator; the values are estimated to be accurate within 2 or 3%.

The aldehydes were prepared according to methods described in the literature.[4–7] The melting point of crude 5-naphthacenecarboxaldehyde (m.p. 157–161°) agreed better with the data for analytically pure material reported by Buu-Hoï and Lavit[8] (m.p. 164°) than by Martynoff[7] (m.p 148°). Buu-Hoï and Eckert[9] reported they could use dimethylformamide in place of *N*-methylformanilide for the preparation of 1-pyrenecarboxaldehyde. We found that a fair yield of 1-pyrenecarboxaldehyde could be obtained with dimethylformamide by heating the reaction mixture for 3 hr. at 105°.

As an example for the synthesis of the amines the preparation of *N,N*-dimethyl-1-pyrenemethylamine hydrochloride is described. The hydrochlorides of *N,N*-dimethyl-3-perylenemethylamine, *N,N*-dimethyl-9-anthracenemethylamine, and *N,N*-dimethyl-5-naphthacenemethylamine were made in a similar fashion (Table I).

N,N-Dimethyl-1-pyrenemethylamine hydrochloride. A mixture of 11.5 g. (0.05 mole) of 1-pyrenecarboxaldehyde, 27.5 g. (0.38 mole) of dimethylformamide, and 2.5 ml. of 90% formic acid was refluxed for 4 hr. at about 150°. After removal of the excess of dimethylformamide and formic acid by distillation the residual oil was dissolved in ethyl ether, dried over sodium sulfate, and filtered. Introduction of gaseous hydrogen chloride into the ethereal solution pre-

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TABLE I

PHYSICAL DATA, ANALYSES, AND YIELDS OF DIMETHYLAMINOMETHYL DERIVATIVES

Compound		Analyses C	H	N	Cl	Neutral Equivalent	Color	M.P.[a]	Yield, %[b]
I	Found:[b]	77.00	6.43	4.70		299[b]	White	270–277[b]	72
	Calcd.:	77.14	6.13	4.74		296			
II[d]	Found:[e]	79.68	5.67	4.10	10.00	346[b]	Yellow	290–305[e]	50
	Calcd.:	79.90	5.79	4.05	10.25	346			
III	Found:[c]	75.30	6.67	5.33		275[b]	White	241–242[c]	81
	Calcd.:	75.12	6.67	5.15		272			
IV[d,f]	Found:[e]	77.62	6.19	4.24	10.30	319[e]	Yellow-brown	220–237[e]	61
	Calcd.:	78.36	6.27	4.35	11.02	322			

[a] All samples melted with decomposition. [b] Crude product. [c] After recrystallization from a mixture of concentrated hydrochloric acid and water (1:1) with the aid of charcoal. [d] After removal of the excess of dimethylformamide and formic acid a solid remained. Most of this solid was soluble in a very large amount of ethyl ether. A solid by-product, corresponding in weight to about 20% of the aldehyde used as starting material, was insoluble and was discarded. [e] The sample had been purified by dissolving the material in a very large amount of hot water, filtration, and addition of hydrochloric acid to the filtrate. [f] The analytical data indicate the presence of an impurity. However, there is little doubt that the product has predominantly the assigned structure.

cipitated 10.7 g. (72%) of white *N,N*-dimethyl-1-pyrenemethylamine hydrochloride, m.p. 270–277° with decomposition; it had a neutral equivalent of 299 (Calcd. 296).

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Pyridoxine *N*-Oxide[1]

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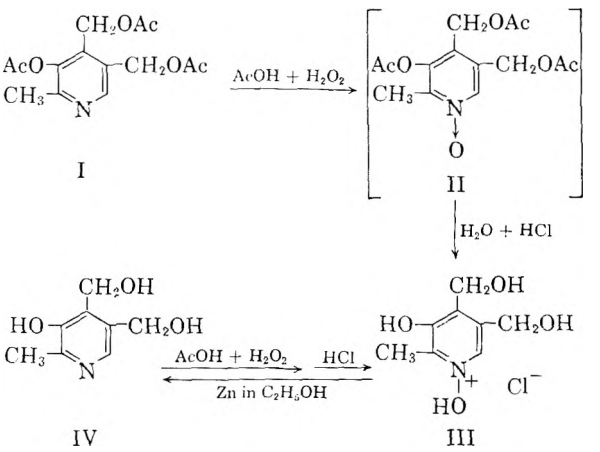
Upon treatment with acetic acid–hydrogen peroxide, a variety of pyridine derivatives form *N*-oxides.[2] It seemed possible, in a similar manner, to convert pyridoxine (IV) to pyridoxine *N*-oxide (III), which is of interest because of the following two possibilities: (a) pyridoxine *N*-oxide (III) may act as an antimetabolite, or (b) pyridoxine *N*-oxide (III) may serve as a source of vitamin B_6 *in vivo*. It has been reported that pyridine *N*-oxide was reduced to pyridine by baker's yeast, although an analogous reaction did not occur with 4-picoline *N*-oxide.[3]

In the present study, 3,4,5-triacetylpyridoxine (I) was treated with a mixture of glacial acetic acid and hydrogen peroxide at 37° for 72 hr., or at 60–70° for 8 hr. The intermediate, possibly 3,4,5-triacetylpyridoxine *N*-oxide (II), was hydrolyzed by refluxing in 65% ethanol containing 4.5% hydrogen chloride. The resulting product contained a considerable amount of pyridoxine. A longer reaction time and the use of an oxidation mixture which consisted of acetic acid–acetic anhydride–hydrogen peroxide failed to complete the oxidation. The *N*-oxide hydrochloride (III), however, was far more soluble than pyridoxine hydrochloride in 1-propanol, 2-propanol, and 1-butanol and could thus be purified by solvent fractionation. Pyridoxine (IV) was regenerated from pyridoxine *N*-oxide (III) upon refluxing in 95% ethanol in the presence of zinc dust. The identity of the reduced material was established by mixed melting point with an authentic specimen of pyridoxine, paper chromatography, and the biological activity to support growth of *Saccharomyces carlsbergensis*. For paper chromatography, the solvent systems reported by Rodwell *et al.*[4] and Snyder *et al.*[5] were satisfactory.



Free pyridoxine base (IV) also formed pyridoxine *N*-oxide (III), although the yield was considerably lower. It has been shown that under certain conditions, a portion of pyridoxine is oxidized to pyri-

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doxal when treated with hydrogen peroxide,[6] and that pyridoxal is readily reduced to pyridoxine upon treatment with zinc in boiling ethanol.[7] When the pyridoxine *N*-oxide (III) as prepared was treated with 1% phenylhydrazine in acetic acid, no yellow color developed, indicating the absence of possible contamination with pyridoxal. The mixture of acetic acid–hydrogen peroxide containing free pyridoxine base (IV) was also tested from time to time during the course of oxidation by paper chromatography. The only spots detected were that of pyridoxine (IV) and pyridoxine *N*-oxide (III), and thus the possibility of pyridoxal formation was excluded. On the other hand, pyridoxine hydrochloride failed to form the *N*-oxide (III) under the oxidation conditions, and in two cases, the recovery of pure pyridoxine hydrochloride was 65–70%.

The results of the bioautography and microbiological assay using *S. carlsbergensis* indicated that pyridoxine *N*-oxide (III) was not growth inhibitory. It retained 15% of the vitamin B_6 activity as compared with equimolar amounts of pyridoxine.

The preparation of pyridoxine *N*-oxide (III) (2–3 mg.) was refluxed in 0.5 ml. of distilled water, 5*N* hydrochloric acid or 5*N* aqueous sodium hydroxide for 1 hr., and the resulting solution was applied for paper chromatography. In all cases, the chromatographic patterns were identical with that of the original pyridoxine *N*-oxide (III).

EXPERIMENTAL[8]

Paper chromatography. The following two solvent systems were used: Solvent A, a mixture of water, acetone, *tert*-butanol, and diethylamine (20:35:40:5, *v/v*),[4] and Solvent B, the upper layer of a mixture of water, isoamyl alcohol, and pyridine (40:40:20, *v/v*).[5] Throughout this investigation, a descending system on Whatman No. 1 filter paper was employed at room temperature. The spots were detected by spraying a 0.1% benzene solution of *N*,2,6-trichloro-*p*-quinoneimine followed by exposure to ammonia vapor, or by spraying a 4% ethanolic solution of ferric chloride. The spots were also detectable on the papergram under ultraviolet light. Typical R_f values for pyridoxine (IV) and pyridoxine *N*-oxide (III) were 0.48 and 0.30, respectively, with Solvent A, and were 0.40 and 0.11, respectively, with Solvent B. The R_f value of pyridoxal with Solvent A was 0.67.

Assay with Saccharomyces carlsbergensis (A.T.C.C. 4228). The method reported by Atkin *et al.*[9] was employed. For bioautography, a papergram which had been developed with Solvent A was applied.

Pyridoxine N-oxide hydrochloride (III) *from 3,4,5-triacetylpyridoxine* (I). Two grams of triacetylpyridoxine (I)[10] was dissolved in a mixture of 25 ml. glacial acetic acid and 10 ml. of 30% hydrogen peroxide. After maintaining the solution at 37° for 72 hr., the volatile portion was removed *in vacuo* as much as possible. The residual oil was refluxed in 50 ml. of 65% ethanol containing 4.5% hydrochloric acid for 30 min., and the solvent was removed until dryness under diminished pressure. The product was taken up in 5 ml. of ethanol and ether was added. The white precipitate was collected, dissolved in 10 ml. of warm 1-propanol, and kept at −5° for 20 hr. The solid portion was removed by filtration and thoroughly washed with cold 1-butanol. The filtrate and the butanol washings were combined, and the product separated upon addition of ether. The compound thus isolated was essentially free from pyridoxine. The crystalline product was again shaken in 10 ml. of 1-butanol at room temperature for approximately 5 min., and a small amount of insoluble matter was removed by filtration. Upon addition of ether, pyridoxine *N*-oxide hydrochloride (III) crystallized. Recrystallization was effected from 1-butanol–ethyl acetate. Yield 0.45 g. (33%). M.p. 145.5–146.0°.

Anal. Calcd. for $C_8H_{11}NO_4 \cdot HCl$: C, 43.35; H, 5.00; N, 6.32; Cl, 16.02. Found: C, 43.11; H, 5.20; N, 6.40; Cl, 16.44.

The precipitate, which had been separated from 1-propanol and washed with 1-butanol as described, was recrystallized from 95% ethanol. One recrystallization was sufficient to recover pure pyridoxine hydrochloride (0.1 g.).

Comparable results were also obtained by carrying out the oxidation at 60–70° for 8 hr.

Pyridoxine N-oxide (III) *from pyridoxine* (IV). Free pyrodixine base (IV) (2.1 g.) was dissolved in a mixture of 30 ml. of glacial acetic acid and 12 ml. of 30% hydrogen peroxide, and allowed to stand at 37° for 144 hr. The volatile portion was removed *in vacuo*, and the residue was taken up in 10 ml. of ethanol containing dry hydrogen chloride. Upon addition of ether, a mixture of pyridoxine hydrochloride and pyridoxine *N*-oxide hydrochloride (III) separated. The product thus isolated was shaken, at room temperature, in 15 ml. of 1-propanol, and cooled at −5° for 5 hr. The insoluble portion (0.4 g.), which mainly consisted of pyridoxine hydrochloride, was removed by filtration. The crystals which had been separated after addition of ether, were shaken in 10 ml. of 1-butanol at room temperature for 5 min. A small amount of insoluble material was removed, and pyridoxine *N*-oxide hydrochloride (III) precipitated by adding ether. Recrystallization was effected from 1-propanol–ethyl acetate. Yield 0.25 g. (9%). M.p. 145.0–145.5° Mixed melting point with the pyridoxine *N*-oxide hydrochloride (III) obtained from triacetylpyridoxine (I) was 145.0–145.5° C. The identity of these two preparations was also recognized by paper chromatography.

Similar results were obtained by conducting the oxidation at 60–70° for 8 hr.

Pyridoxine hydrochloride (IV) *from pyridoxine N-oxide hydrochloride* (III). One hundred twenty mg. of pyridoxine *N*-oxide hydrochloride (III) was dissolved in 10 ml. of 95% ethanol and refluxed for 2 hr. in the presence of 500 mg. zinc dust. The reaction mixture was filtered, and the filtrate acidified with dry hydrogen chloride. The product crystallized upon addition of ether, and was recrystallized from methanol–ether. Yield 45 mg. (40%). M.p. 206.0–208.0° (dec.). Mixed melting point with an authentic specimen of pyridoxine hydrochloride was 208.0–208.5° C. (dec.).

This product was free from pyridoxine *N*-oxide (III) as proved by paper chromatography and was as active as an authentic sample of pyridoxine hydrochloride in supporting growth of *Saccharomyces carlsbergensis*.

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Communications TO THE EDITOR

A Convenient Modification of the Brown Hydration Reaction. Hydration of Unsaturated Steroids

Sir:

Recently H. C. Brown and co-workers have described an excellent method for the anti-Markownikoff hydration of double bonds, through conversion to the trialkylborane and subsequent oxidation. The method used for carrying out the hydroboration step involved passing diborane (generated from sodium borohydride and boron trifluoride etherate in diglyme) into a solution of the olefin in an ether[1] or alternatively allowing the olefin to react *in situ* with sodium borohydride and aluminum chloride[2] or boron trifluoride[3] in diglyme solution.

Diglyme (the dimethyl ether of diethylene glycol) not being available to us, we studied the *in situ* reaction of olefins with lithium aluminum hydride and boron trifluoride in ether solution, since the latter hydride (unlike sodium borohydride) is ether soluble and this combination is known also to generate diborane.[4] This modification when applied to simple olefins was found to give as excellent results as the original procedures. Thus 1-octene and cyclohexene by this method after oxidation with alkaline hydrogen peroxide furnished 1-octanol and cyclohexanol, respectively, in over 80% yield. In this way the necessity of generating diborane separately, or using the high boiling diglyme [b.p. 160–162° (740 mm.)] *in situ* is avoided.

We have successfully applied the Brown hydration method to steroids. By use of our modification, Δ^4-cholestene gave 60% of cholestan-4α-ol [m.p. 187–188°, $[\alpha]_D$ +3° (all rotations in chloroform)] and Δ^5-cholestene gave 75% of cholestan-6α-ol (m.p. 128–129°, $[\alpha]_D$ +35°). No isomeric alcohols were detected (the remainder was mainly unchanged starting material in each case)and these results confirm the conclusion that the hydration proceeds by *cis* addition from the less hindered side of the double bond.[1b] The yields of the cholestanols were 30% and 40%, respectively, when the hydroboration was carried out by passing diborane into the sterols dissolved in ether.[5]

Cholesterol by either method after acetylation furnished 70% of cholestane-3β,6α-diol diacetate (m.p. 104–105°, $[\alpha]_D$ +41°) and 15–20% of coprostane-3β,6β-diol diacetate (m.p. 136–138°, $[\alpha]_D$ +16°).[6] Cholesterol 2-(2′-tetrahydropyranyl) ether by our modification after acid treatment and acetylation gave these diacetates in 45% and 35% yield, respectively. It is of interest to note that the direction of attack of the Δ^5-double bond appears to depend on the bulk of the substituent at C-3.

Other unsaturated steroids have also been hydrated by the lithium aluminum hydride–boron trifluoride method, as will be reported in the full paper. In addition, the method has been found to proceed well and stereospecifically in the decalin series, *e.g.* 7,7,10-trimethyl-$\Delta^{1(9)}$-octalin gave 7,7,10-trimethyl-*cis*-decal-1β-ol (m.p. 82–83°) in 80% yield.

The following hydration of cholesterol is typical. A solution of 0.6 g. of lithium aluminum hydride in 30 cc. of dry ether was added dropwise to a solution containing 2 g. of cholesterol and 3.0 g. of boron trifluoride etherate in 75 cc. of ether under nitrogen. After 1 hr. at room temperature, the mixture was treated with a saturated sodium sulfate solution and solid sodium sulfate, and was filtered and evaporated. The residue in tetra hydrofuran was then oxidized with 30% aqueous hydrogen peroxide and alcoholic sodium hydroxide,[1,2] and the product was isolated with ether, acetylated and chromatographed on alumina.

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