resembling that of hexachloro-ethane, and boiled at about 210° with decomposition and evolution of hydrogen chloride.

m-**Tolyl Orthoformate,** $CH(O.C_6H_4.CH_3)_3$.—This compound was prepared from potassium *m*-cresolate at 110–120°, and was isolated as described above. It was purified by recrystallization first from pentane, and finally from alcohol containing a little water, being thus obtained as a silky mass of long, slender, colorless prisms. It is extremely soluble in all common organic solvents, but is comparatively sparingly soluble in 80% alcohol; m. p., 50°.

Anal. Calc. for $C_{22}H_{22}O_3$: C, 79.04; H, 6.59; mol. wt., 334. Found: C, 78.80; H, 6.56; mol. wt. in freezing benzene, 305.

The author wishes to express his thanks to Professor F. S. Kipping, F.R.S., for his encouragement and interest in this work, and to Dr. W. A. Richardson for examining microscopically the *p*-tolyl ester.

Summary

1. The action of chloroform on the potassium derivatives of the cresols has been investigated. The three isomeric tolyl orthoformates have been isolated and described.

2. A new mechanism is suggested for the formation of cyclic ketones by the action of chloroform on alkaline solutions of phenols.

NOTTINGHAM, ENGLAND

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

PRESSOR ANESTHETICS. I

BY C. S. MARVEL AND V. DU VIGNEAUD

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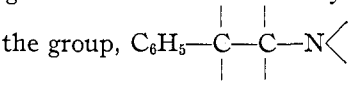
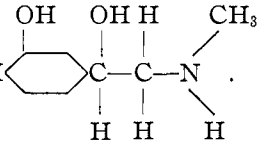
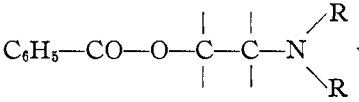
In medical practice, a pressor drug is always used with a local anesthetic in order to localize and prolong its action. The pressor substance also helps to reduce bleeding if an operation is performed. Since the chemical structures that produce pressor action and that produce local anesthesia are well known, an attempt was made to combine these two pharmacological properties in one molecule.

The work of Barger and Dale[1] has shown very clearly that pressor action is associated with the group,  and reaches a maximum in adrenaline,  . The pressor action is not strong in the compounds which do not contain a phenolic hydroxyl and the primary and secondary amines have been shown to have the greatest action.

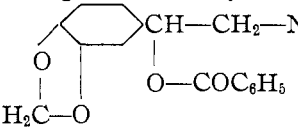
[1] (a) *J. Physiol.*, **41**, 19 (1910). (b) See also Pyman, *J. Chem. Soc.*, **111**, 1121 (1917).

Local anesthetics of various types are known but the most important synthetic products are of the alkylamine ester type and contain the group,

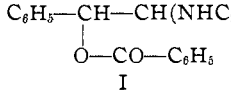


which is found in cocaine.[2]

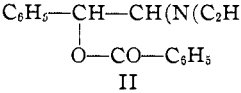
A few compounds are reported in which both of these characteristic linkages occur. Pyman[3] has prepared a compound of the formula



but found that while it had considerable anesthetic action, it was toxic and an irritant. The benzoyl esters of ethyl mydriatine (I) and diethyl mydriatine (II)



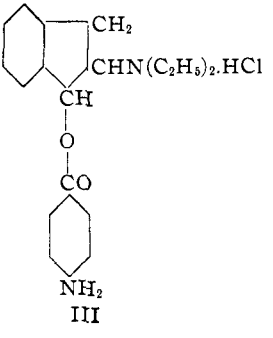
I



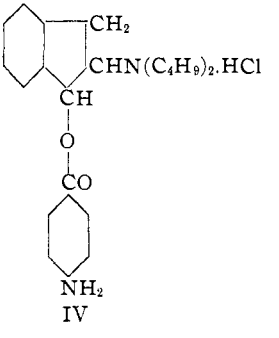
II

have been patented[4] as local anesthetics. No mention could be found in the literature concerning the pressor action of any of these compounds.

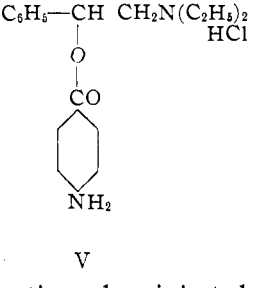
The initial work, which is reported in this paper, has to do with compounds that may be considered as derivatives of β-phenyl-ethylamine. The two characteristic groups of atoms previously mentioned have been combined in the following compounds: β-diethylamino-*p*-aminobenzoyl-α-hydroxyhydrindene hydrochloride (III), β-di-*n*-butylamino-*p*-aminobenzoyl-α-hydroxyhydrindene hydrochloride (IV), and α-phenyl-β-diethylamino-ethyl-*p*-aminobenzoate hydrochloride (V).



III



IV



V

None of these esters showed appreciable pressor action when injected intravenously into an etherized dog.[5] In fact the hydrindene derivatives

[2] For discussion see Pyman, *J. Chem. Soc.*, (a) **93**, 1796 (1908). (b) Ref. 1 b.

[3] Ref. 2 a.

[4] U. S. pat. 1,399,312.

[5] The authors are indebted to the Abbott Laboratories for the pharmacological data given here.

(III and IV) produced the opposite effect to a slight degree. The hydrindene derivatives have only a very slight anesthetic action which seems to be greater in the case of the diethylamino compound (III). Phenyl procaine (V) has a strong anesthetic action and seems to be of low toxicity.

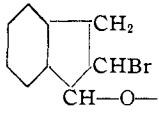
Compounds III and IV were synthesized from α-hydroxy-β-bromo-hydrindene,  , which was easily obtained from indene by the method of Pope and Read.[6] The first method of preparing the desired compounds that was tried, was the condensation of the *p*-nitro-benzoyl ester of the bromohydroxy compound with the desired secondary amine. This method was unsuccessful. The products were obtained by reacting bromohydroxy-hydrindene with the secondary amine to give the desired amino alcohol. This was then converted to the *p*-nitrobenzoyl ester and reduced with iron.

Compound V was prepared by condensing chloro-acetophenone with diethylamine. The amino ketone thus formed was reduced catalytically by the method of Adams and Voorhees.[7] The amino alcohol was treated with *p*-nitrobenzoyl chloride and the ester hydrochloride reduced in the usual way.

An interesting discovery was made in this investigation. The nitrate of α-phenyl-β-diethylamino-ethyl-*p*-nitrobenzoate was found to be quite insoluble. It gives some promise of usefulness in the determination of the nitrate radical. This will be considered further in a later paper.

The study of compounds that should have both pressor and local anesthetic action is being continued. The synthesis of a derivative of catechol which will be closely related to adrenaline is now under way.

Experimental Part

β-Bromo-*p*-nitrobenzoyl-α-hydroxyhydrindene, 

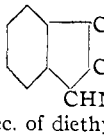
A mixture of 20 g. of β-bromo-α-hydroxyhydrindene, 25 g. of *p*-nitrobenzoyl chloride and 6 cc. of pyridine dissolved in 300 cc. of benzene was heated on a steam-bath under a reflux condenser for about eight hours. A small amount of *p*-nitrobenzoic acid which separated was filtered off. The filtrate was washed with water, dil. sodium hydroxide solution and finally again with water to remove pyridine salts and *p*-nitrobenzoic acid. The benzene was then evaporated and the resulting solid was recrystallized from about 800 cc. of alcohol; yield of ester, 28 to 29 g., or 83–85%; m. p., 131°.

Anal. (Parr bomb). Subs., 0.5280: 14.43 cc. of 0.1001 *N* $AgNO_3$. Calc. for $C_{16}H_{12}O_4NBr$: Br, 22.08. Found: 21.88.

[6] Pope and Read, *J. Chem. Soc.*, **101**, 760 (1912).

[7] Adams and Voorhees, THIS JOURNAL, **44**, 1397 (1922). See Adams and Shriner, *ibid.*, **45**, 2171 (1923), for the best method of preparing the catalyst.

Attempt to Condense β-Bromo-*p*-nitrobenzoyl-α-hydroxyhydrindene with Diethylamine.—The bromo ester was treated with an excess of diethylamine without a solvent and in turn with ether, benzene, toluene and acetone (containing a little sodium iodide) solutions at various temperatures but nothing could be isolated from the reaction mixture except the original materials. A trial reaction was made in a sealed tube at 110° but only a tar was obtained.

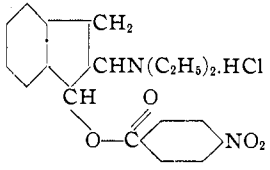
β-Diethylamino-α-hydroxyhydrindene,  —A mixture of 120 g. of β-bromo-α-hydroxyhydrindene and 130 cc. of diethylamine was refluxed on a steam-bath for 24 hours, then dissolved in dil. hydrochloric acid, and the unreacted bromo-hydroxy compound and tar were extracted with ether. The acid solution was made strongly alkaline with sodium hydroxide and the oil that separated was dissolved in ether, dried over a little solid sodium hydroxide and distilled under reduced pressure. The yield of amino alcohol boiling at 165–167° at 15 mm. was 65 to 70 g., or 56–60%. The amino alcohol is a thick, viscous, colorless liquid turning red on exposure to the air; d_{20}, 1.043; $n_D^{20°}$, 1.5393.

Anal. (Kjeldahl). Subs., 0.9726, 0.9467: 8.4, 8.23 cc. of 0.559 *N* HCl. Calc. for $C_{13}H_{19}ON$: N, 6.82. Found: 6.72, 6.76.

The hydrochloride was prepared by dissolving 10 g. of the amine in dry ether and then passing dry hydrogen chloride into this solution. The salt was filtered off and recrystallized from butyl alcohol. The yield was 10 to 10.5 g., or 85–90%, of pure white product; m. p., 175°.

Anal. Subs., 0.6184: 2.568 cc. of *N* $AgNO_3$. Calc. for $C_{13}H_{20}O_2NCl$: Cl, 14.75. Found: 14.72.

β-Diethylamino-*p*-nitrobenzoyl-α-hydroxyhydrindene Hydrochloride.—



A solution of 20 g. of the amino alcohol and 20 g. of *p*-nitrobenzoyl chloride in 150 cc. of benzene was heated under a reflux condenser on a steam-bath for one hour. On cooling, a solid separated. An equal volume of ether was added and the solid filtered off and recrystallized from *n*-butyl alcohol until white. Two or three crystallizations were necessary; yield, 18 to 22 g., or 51–62%; m. p., 210–212°.

Anal. Subs., 0.5729: 14.53 cc. of 0.1000 *N* $AgNO_3$. Calc. for $C_{20}H_{23}O_4N_2Cl$: Cl, 9.07. Found: 9.01.

The free amino ester was obtained by dissolving some of the hydrochloride in water, adding sodium hydroxide solution and extracting with ether. The ether was evaporated and the product recrystallized from hot alcohol. Bright yellow crystals, melting at 85°, were obtained.

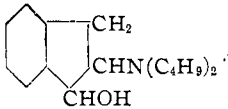
Anal. (Dumas). Subs., 0.2502: 18 cc. of N_2 (29°, 748 mm.). Calc. for $C_{20}H_{22}O_4N_2$: N, 7.90. Found: 7.87.

The free ester was also obtained by condensing *p*-nitrobenzoyl chloride with β-diethylamino-α-hydroxyhydrindene in the presence of pyridine. Twenty g. of amino alcohol, 20 g. of *p*-nitrobenzoyl chloride and 6 cc. of pyridine were mixed in benzene solu-

tion. Heat was evolved, the solution turned dark red and a solid separated. The reaction mixture was warmed for one hour and then filtered. The solid was washed with sodium hydroxide to remove *p*-nitrobenzoic acid and was then recrystallized from alcohol; yield, 17–20 g., or 50–59%; m. p., 85°.

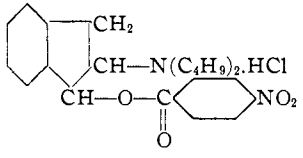
β-Diethylamino-*p*-aminobenzoyl-α-hydroxyhydrindene Hydrochloride (III).—Fifteen g. of β-diethylamino-*p*-nitrobenzoyl-α-hydroxyhydrindene hydrochloride was mixed with 100 g. of iron filings and enough water was added to form a thick paste. No heat was evolved, so the mixture was heated on a steam-bath for three to four hours, kept well stirred during this heating period, and water was added as necessary to keep the paste of the same consistency. A small amount of sodium carbonate solution was then added and the mixture extracted twice with benzene or with ether. The solvent was evaporated and the remaining material dissolved in ethyl alcohol. Dil. hydrochloric acid was added until the solution was neutral to litmus. After concentrating the alcohol solution the ester hydrochloride separated. It was recrystallized from *n*-butyl alcohol. The compound obtained turned black and melted at 206°; yield, 6.6 g., or 48%.

Anal. Subs., 0.5570: 15.43 cc. of 0.1000 *N* $AgNO_3$. Calc. for $C_{20}H_{25}O_2N_2Cl$: Cl, 9.83. Found: 9.83.

β-Di-*n*-butylamino-α-hydroxyhydrindene,  .—A solution of 80 g. of β-bromo-α-hydroxyhydrindene and 110 cc. of di-*n*-butylamine in 100 cc. of benzene was placed in a flask fitted with a reflux condenser and a mechanical stirrer. The mixture was stirred and heated on a steam-bath for 24 hours. It was then washed with water to take out dibutylamine hydrochloride and the benzene layer was distilled under reduced pressure, giving first benzene, then some unchanged dibutylamine. The amino alcohol was collected at 155–165° (7 mm.). Low pressures were necessary during distillation to prevent much decomposition; yield, 59 to 61 g., or 63–65%. β-Di-*n*-butylamino-α-hydroxyhydrindene was a thick, viscous liquid, colorless when first distilled but turning dark red very quickly; $n_D^{29°}$, 1.493.

Anal. (Kjeldahl). Subs., 1.1219: 9.00 cc. of 0.4649 *N* HCl. Calc. for $C_{17}H_{27}ON$: N, 5.33. Found: 5.22.

β-Di-*n*-butylamino-*p*-nitrobenzoyl-α-hydroxyhydrindene Hydrochloride.—



A solution of 45 g. of the amino alcohol and 45 g. of *p*-nitrobenzoyl chloride in 300 cc. of benzene was placed in a flask fitted with a reflux condenser and a mechanical stirrer, stirred and heated on a steam-bath for 24 hours. A very deep red color developed. The benzene was distilled under reduced pressure, leaving a dark, thick, tarry mass. This material was washed repeatedly with 100cc. portions of ether which removed the tar, leaving a light brown solid. Usually 1.5 to 2 liters of ether was required. The solid was recrystallized from butyl alcohol and washed again with ether, thus yielding a white crystalline product; m. p., 155–156°; yield, 41 to 45 g., or 60 to 67%.

Anal. (Parr bomb). Subs., 0.7465: 13.47 cc. of 0.101 *N* $AgNO_3$. Calc. for $C_{24}H_{31}O_4N_2Cl$: Cl, 7.94. Found: 7.93.

β-Di-*n*-butylamino-*p*-aminobenzoyl-α-hydroxyhydrindene (IV).—Thirty g. of the

nitro ester hydrochloride was mixed with 250 g. of iron filings and enough water to form a paste. A few drops of dil. hydrochloric acid were added to help start the reaction. No apparent reaction took place, so the mixture was heated for about three hours on a water-bath and continually stirred. The temperature was held at about 50°. Water was added as was necessary to keep the paste of the proper consistency. After the specified time the reaction mixture was cooled, 5 g. of sodium carbonate was added and the amino ester was extracted with hot benzene. The benzene was evaporated leaving a thick, viscous liquid which solidified when it was cooled and stirred. This solid was recrystallized two or three times from hot alcohol, finally giving white crystals; m. p., 74°; yield, 18 to 20 g., or 72–85%.

Anal. (Kjeldahl). Subs., 0.5207: 5.85 cc. of 0.4649 *N* HCl. Calc. for $C_{24}H_{32}O_2N_2$: N, 7.36. Found: 7.31.

The monohydrochloride was prepared by dissolving 15 g. of the free amino compound in dil. hydrochloric acid and adding dil. sodium hydroxide solution until the solution was barely acid to litmus. The monohydrochloride separated. After filtering, it was recrystallized from about 20% alcohol; yield, 12–14 g., or 75–87%; m. p., 229–230°.

Anal. Subs., 0.5189: 12.15 cc. of 0.101 *N* $AgNO_3$. Calc. for $C_{24}H_{33}O_2N_2Cl$: Cl, 8.45. Found: 8.37.

The acid sulfate was prepared by treating 10 g. of the free amino ester with 50 cc. of dil. sulfuric acid. A solid separated almost immediately. After one or two recrystallizations from ethyl alcohol, the product melted at 200–201°; yield, 10.5 to 11 g., or 81–87%.

Anal. Subs., 0.9988: $BaSO_4$, 0.4770. Calc. for $C_{24}H_{34}O_6N_2S$: SO_4, 20.07. Found: 19.84.

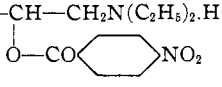
α-Diethylamino-acetophenone, $C_6H_5—COCH_2N(C_2H_5)_2$.—A solution of 154 g. of α-chloro-acetophenone in 500 cc. of benzene was added to a solution of 150 g. of diethylamine in 150 cc. of benzene. Some heat was evolved. After about two days, the calculated amount of diethylamine hydrochloride which separated was filtered off. The benzene was evaporated and the residue distilled under reduced pressure. The product was collected at 148–152° (30 mm.); yield, 125 g., or 65%; n_D^{23}, 1.5180.

Anal. (Kjeldahl). Subs., 0.6930: 36.37 cc. of 0.0964 *N* HCl. Calc. for $C_{12}H_{17}ON$: N, 7.32. Found: 7.10.

α-Phenyl-β-diethylamino-ethanol, $C_6H_5CHOHCH_2N(C_2H_5)_2$.—The amino ketone was reduced to the alcohol with hydrogen in the presence of the platinum catalyst described by Adams and Voorhees.[7] A solution of 50 g. of amino ketone in 100 cc. of alcohol was treated with the catalyst from 2.3 g. of chloroplatinic acid. The reduction was run overnight although it was 90% complete, as shown by the absorption of hydrogen, after five hours. The catalyst was filtered off and the alcohol was removed by heating on a steam-bath. The residue was distilled under reduced pressure. A small fraction which was insoluble in acids distilled below 149° at 22 mm.; yield, 37–38 g., or 73–75%; n_D^{26}, 1.507.

Anal. (Kjeldahl). Subs., 0.6920: 36.42 cc. of 0.0964 *N* HCl. Calc. for $C_{12}H_{19}ON$: N, 7.25. Found: 7.10.

α-Phenyl-β-diethylamino-ethyl-*p*-nitrobenzoate Hydrochloride.



.—A solution of 60 g. of *p*-nitrobenzoyl chloride and 35 g. of the amino alcohol in 250 cc. of benzene was placed in a flask fitted with a reflux condenser and a mechanical stirrer. The solution turned red and heat was given off. After about ten minutes of stirring, crystals began to separate. The mixture was stirred for

about three hours while the temperature was kept at about 50–55°. The ester hydrochloride was collected upon a filter and washed with ether. The product thus obtained was pure white; m. p., 155–156°. It was crystallized from ethyl alcohol without changing the melting point; yield, 59 to 61 g., or 89–91%.

Anal. Subs., 0.4817: 13.41 cc. of 0.930 *N* $AgNO_3$. Calc. for $C_{19}H_{23}O_4N_2Cl$: Cl, 9.34. Found: 9.18.

The nitrate was prepared by dissolving 5 g. of the hydrochloride in 25 cc. of water and adding dil. nitric acid. The nitrate, which is quite insoluble, precipitated and was filtered off. After recrystallization from alcohol, it was obtained in long needles; m. p., 161.5°; yield, 5 g., or 92%.

Anal. (Kjeldahl). Subs., 0.6993: 56.66 cc. of 0.0964 *N* HCl. Calc. for $C_{19}H_{23}O_7N_3$: N, 11.20. Found: 10.93.

α-Phenyl-β-diethylamino-ethyl-*p*-aminobenzoate (V).—Thirty g. of the nitro ester hydrochloride was mixed with 180 g. of iron filings and enough water was added to form a paste. The mixture was stirred constantly throughout the reduction. The reaction proceeded with the evolution of heat and care had to be taken to keep the temperature around 50°. The reaction slowed down after one hour. Eighty g. of iron filings was added and the mixture kept at 45–50° for another half-hour. During the reaction, water was added to keep the paste at the proper consistency. The reduction mixture was treated with 5 g. of sodium carbonate and extracted with hot benzene. The benzene was evaporated and the thick, viscous liquid that remained solidified when cooled and stirred. This product may be used directly for the preparation of the hydrochloride. It may be recrystallized from alcohol; in this manner a white solid melting at 88–89° is obtained.

Anal. (Kjeldahl). Subs., 0.6218: 40.64 cc. of 0.0964 *N* HCl. Calc. for $C_{19}H_{24}O_2N_2$: N, 8.97. Found: 8.82.

The hydrochloride was prepared by dissolving the crude amino ester, from a reduction performed as described above, in 25 cc. of alcohol and treating this solution with alcoholic hydrochloric acid until neutral to litmus. On standing, the salt crystallized from the solution. It was recrystallized from a mixture of 75% alcohol and 25% ethyl acetate; yield, 21 to 22 g., or 77–81%. It was a white product that melted at 210–212°.

Anal. Subs., 0.5795: 17.65 cc. of 0.930 *N* $AgNO_3$. Calc. for $C_{19}H_{25}O_2N_2Cl$: Cl, 10.16. Found: 10.05.

Summary

1. Three compounds containing the characteristic groups of atoms that produce local anesthetic and pressor actions have been prepared.

2. All of these compounds have some anesthetic action but none has pressor action.

URBANA, ILLINOIS