equivalents of ammonium carbonate (cubes) and the mixtures were heated at 58–60° for ten to twenty hours. In most cases, part of the hydantoin separated as a white, almost pure solid from the warm solution and chilling caused practically all of the hydantoin to crystallize from the reaction solution. The hydantoins were recrystallized from alcohol–water or acetone–water; in general, the melting point of the crude material was not raised as much as 2° by repeated recrystallization.

Although these new hydantoins are amphoteric, their basic properties are more pronounced than are the acidic. Certain pertinent data for the hydantoins have been collected in Table III.

Summary

1. There have been re-synthesized 1-chloro-4-phenylbutanol-2 and 1-chloro-4-phenylbutanone-2; certain physical properties determined for these compounds are not entirely in agreement with those previously reported in the literature.

2. Six new disubstituted amino ketones have been prepared.

3. Seven new disubstituted aminomethylphenethylhydantoins have been obtained.

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

1-Alkyl 2-Dialkylaminoalkyl 3-Aminophthalates as Local Anesthetics

BY F. F. BLICKE AND CHIEKO OTSUKI[1]

Many years ago Pyman[2a] stated that the hydrochloride of the bis-(β-diethylaminoethyl) ester of phthalic acid (I) lacks local anesthetic properties. However, methyl β-diethylaminoethyl phthalate (II) has been described in a German patent[2b] as a very good local anesthetic.

It seemed to us that more satisfactory products would be obtained if a nuclear amino group were introduced into esters of type II, consequently, we prepared a series of 1-alkyl 2-dialkylaminoalkyl 3-aminophthalates (III).

Our expectation that these esters would be found to be strong anesthetics proved to be correct. In fact, many of them were shown to be more potent than cocaine when tested on the rabbit cornea. Especially active are the 1-*n*-butyl, 1-*n*-amyl and 1-*n*-hexyl 2-diethylaminoethyl 3-aminophthalates.

The esters were tested by L. W. Rowe in the Parke, Davis and Company Laboratories. A detailed pharmacological report will be published by him in another journal.

Three different methods (A, B and C), illustrated in the case of 1-ethyl 2-(β-diethylaminoethyl) 3-aminophthalate, were employed for the preparation of the diesters.

The monoesters V, IX and XI were synthesized by interaction of 3-nitrophthalic acid with the required alcohol and sulfuric acid (V), and from reaction of 3-nitrophthalic anhydride with a dialkylaminoalkanol (IX) or with ethylene bromohydrin (XI).

In order to obtain the diesters, a compound of type V was heated with a dialkylaminoalkyl chloride whereupon an ester of type VI was formed in good yield. This latter procedure is one which Horenstein and Pählicke[3] used originally for the preparation of dialkylaminoalkyl esters of hydroxy acids. The diesters (VI and XIII) were obtained also from the monoesters IX and XI by treatment of the ester-acid chlorides (X and XII) with an alcohol.

Reduction of the nitro diester to the corresponding amino compound was effected with stannous chloride and hydrogen chloride in acetic acid solution.[4]

Experimental Part

1-Ethyl 2-(β-Diethylaminoethyl) 3-Nitrophthalate Hydrochloride

Method A.—3-Nitrophthalic acid[5] (IV) was converted into 1-ethyl 3-nitroacidphthalate[6] (V). A solution of 11.9 g. (0.050 mole) of the highly purified monoester and 6.5 g. (0.048 mole) of β-diethylaminoethyl chloride[7] in 30 cc. of isopropyl alcohol, which had been treated with sodium and distilled, was refluxed for twelve hours. The solvent was removed by distillation under reduced pressure and the

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[1] This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by Chieko Otsuki in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

[2] (a) Pyman, *J. Chem. Soc.*, **93**, 1796 (1908); (b) see also German Patent 371,046 (*Frdl.*, **14**, 1244).

(3) Horenstein and Pählicke, *Ber.*, **71**, 1644 (1938).

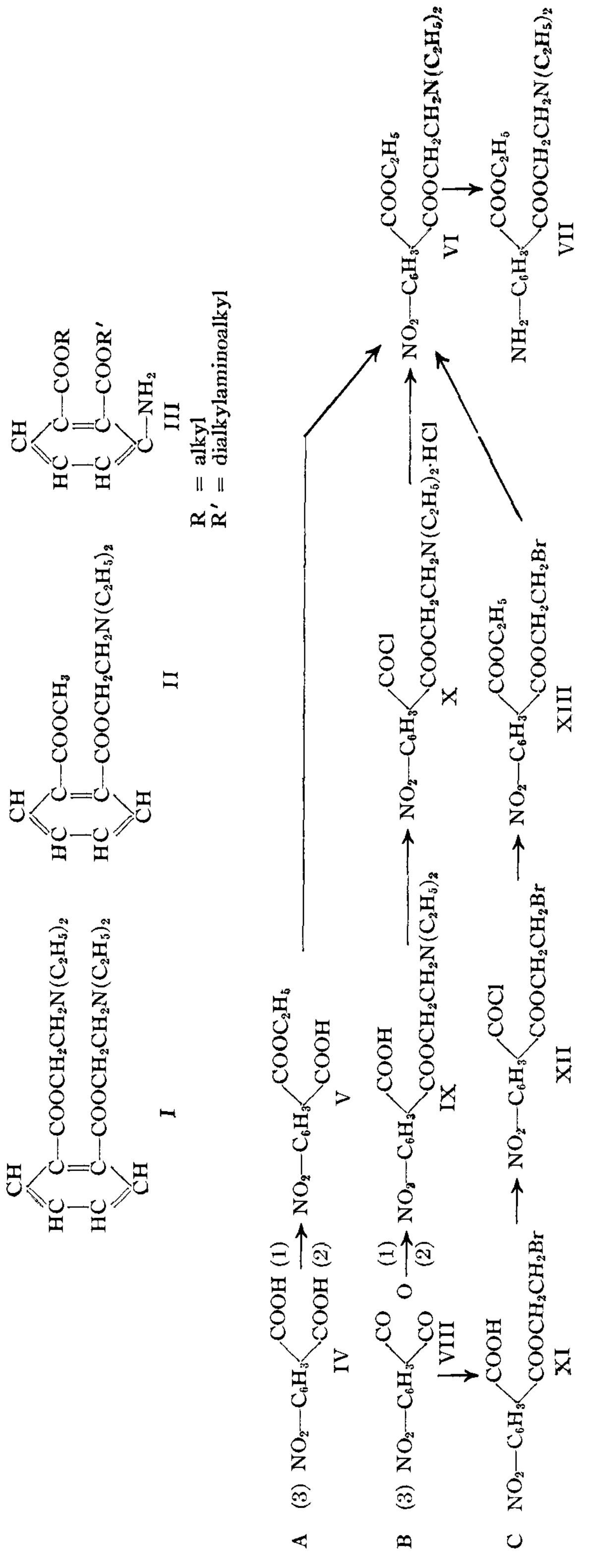
(4) Blicke and Parke, THIS JOURNAL, **61**, 1201 (1939).

(5) "Organic Syntheses," Coll. Vol. I, p. 399.

(6) Cohen, Woodroffe and Anderson, *J. Chem. Soc.*, **109**, 232 (1916). These investigators also described the 1-methyl and the 1-propyl ester.

(7) The chloride hydrochloride has been described by Slotta and Behnisch, *Ber.*, **68**, 758 (1935). The base was liberated from an aqueous solution of the hydrochloride and used immediately,

residue of 1-ethyl 2-(β-diethylaminoethyl) 3-nitrophthalate hydrochloride (VI) washed with absolute ether; yield 14 g. (75%).



Method B. 2-(β-Diethylaminoethyl) 3-Nitroacidphthalate (IX).—Thirty-five and one-tenth grams (0.03 mole) of β-diethylaminoethyl alcohol was added, in portions, through a condenser to 59.7 g. (0.03 mole) of 3-nitrophthalic anhydride,[8] dissolved in 500 cc. of hot, dry benzene and the mixture refluxed for three hours. The 2-(β-diethylaminoethyl) 3-nitroacidphthalate (IX), which precipitated from the cold solution, was filtered and recrystallized from alcohol; yield 82.5 g. (89%); m. p. 167–168°.

Anal. Calcd. for $C_{14}H_{18}O_6N_2$: N, 9.03. Found: N, 9.00.

A mixture of 3.1 g. (0.01 mole) of the monoester and 3.6 g. (0.03 mole) of thionyl chloride (practical) was refluxed for one hour, the excess thionyl chloride removed by distillation under reduced pressure and the gummy residue washed with absolute ether. The crude acid chloride hydrochloride (X) was used in the next experiment.

To the chloride hydrochloride there was added 5 cc. of ethyl alcohol, the mixture refluxed for twenty minutes and the excess alcohol removed under reduced pressure. The residue was rubbed under ether whereupon the hydrochloride of 1-ethyl 2-(β-diethylaminoethyl) 3-nitrophthalate (VI) became crystalline; yield 3.3 g. (94%).

Method C. 2-(β-Bromoethyl) 3-Nitroacidphthalate (XI).—A mixture of 19.3 g. (0.01 mole) of 3-nitrophthalic anhydride, 37.5 g. (0.03 mole) of ethylene bromohydrin and 360 cc. of benzene was refluxed on a steam-bath for ten hours. After removal of the solvent and excess ethylene bromohydrin by distillation under diminished pressure, the crystalline residue was washed with water, filtered, treated with 10% sodium carbonate solution, filtered again and the filtrate acidified. The precipitated product, which weighed 15.5 g., was recrystallized from dilute alcohol; m. p. 172–175°.

Anal. Calcd. for $C_{10}H_8O_6NBr$: Br, 25.12. Found: Br, 24.89.

A mixture of 10.1 g. (0.032 mole) of 2-(β-bromoethyl) 3-nitroacidphthalate and 11.4 g. (0.96 mole) of thionyl chloride was refluxed for one hour, the excess thionyl chloride removed under diminished pressure and 10 cc. of absolute alcohol added to the gummy residue. The material was heated on a steam-bath for one hour and the oily residue of 1-ethyl 2-(β-bromoethyl) 3-nitrophthalate (XIII), obtained after removal of the excess alcohol, was used immediately in the following experiment.

The diester was dissolved in 100 cc. of toluene, the solution poured into a magnesium citrate bottle, 5.9 g. (0.0128 mole) of diethylamine added and the mixture heated in a water-bath for three hours. The precipitated diethylamine hydrobromide (3.8 g. or 95% of the calcd. amount) was filtered and the solvent removed by distillation under diminished pressure. To the oily base, which weighed 9.7 g. (79%), there was added 2.29 cc. of hydrochloric acid (sp. gr. 1.19). The mixture was rubbed under anhydrous ether whereupon the hydrochloride of 1-ethyl 2-(β-diethylaminoethyl) 3-nitrophthalate (VI) became crystalline.

In a few instances in which we were unable to obtain a crystalline hydrochloride or hydrobromide of a nitro diester, the methiodide was prepared. For example, a mixture of 3.4 g. (0.0092 mole) of 1-isobutyl 2-(β-diethyl-

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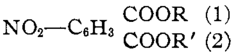
[8] "Organic Syntheses," Coll. Vol. 1, p. 402.

TABLE I

1-ALKYL 2-DIALKYLAMINOALKYL 3-NITROPHTHALATE SALTS: (3) $NO_2{-}C_6H_3$



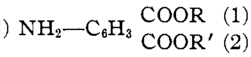
$NO_2{-}C_6H_3\begin{matrix}COOR\ (1)\\ COOR'\ (2)\end{matrix}$

	R	R'		M. p., °C.[c]	Formula	Halogen, % Calcd.	Found
1	CH_3	$CH_2CH_2N(C_2H_5)_2$	A[a]	139–140	$C_{15}H_{21}O_6N_2Cl$	9.83	9.88
2	CH_2CH_3	$CH_2CH_2N(C_2H_5)_2$	A, B[a], C[a]	126–128	$C_{16}H_{23}O_6N_2Cl$	9.46	9.64
3	$CH_2CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	A	93–95	$C_{17}H_{25}O_6N_2Cl$	9.12	9.30
4	$CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	B	110–111	$C_{17}H_{25}O_6N_2Br$	18.44	18.50
5	$CH_2CH_2CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	B	73–75	$C_{18}H_{27}O_6N_2Br$	17.86	17.93
6	$CH_2CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	B	155–156	$C_{19}H_{29}O_6N_2I$[b]	24.96	24.68
7	$CH(CH_3)CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	B	86–88	$C_{18}H_{27}O_6N_2Br$	17.86	17.90
8	$CH_2(CH_2)_3CH_3$	$CH_2CH_2N(C_2H_5)_2$	B	91–93	$C_{19}H_{29}O_6N_2Br$	17.32	17.27
9	$CH_2(CH_2)_4CH_3$	$CH_2CH_2N(C_2H_5)_2$	B	50–53	$C_{21}H_{33}O_6N_2I$[b]	23.66	23.30
10	$CH_2CH_2CH_3$	$CH_2C(CH_3)_2CH_2N(CH_3)_2$	A	164–166	$C_{18}H_{27}O_6N_2Br$	17.86	17.84

[a] Preparative method. [b] Methiodide. [c] Compounds, 1, 2, 6 and 10 were recrystallized from a mixture of ethyl acetate and absolute alcohol; compounds 3, 4, 5 and 7 from ethyl acetate; compound 8 from benzene and compound 9 from a mixture of benzene and acetone.

TABLE II

1-ALKYL 2-DIALKYLAMINOALKYL 3-AMINOPHTHALATE SALTS: (3) $NH_2{-}C_6H_3$



$NH_2{-}C_6H_3\begin{matrix}COOR\ (1)\\ COOR'\ (2)\end{matrix}$

	R	R'	M. p., °C.[b]	Formula	Halogen, % Calcd.	Found
1	CH_3	$CH_2CH_2N(C_2H_5)_2$	114–115	$C_{15}H_{23}O_4N_2Cl$	10.72	10.84
2	CH_2CH_3	$CH_2CH_2N(C_2H_5)_2$	112–113	$C_{16}H_{25}O_4N_2Br$	20.52	20.60
3	$CH_2CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	107–108	$C_{17}H_{27}O_4N_2Br$	19.81	19.94
4	$CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	86–89	$C_{23}H_{34}O_{11}N_2$[a]	(N 5.44	5.51)
5	$CH_2CH_2CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	91–92	$C_{18}H_{29}O_4N_2Br$	19.14	19.33
6	$CH_2CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	110–112	$C_{18}H_{29}O_4N_2Br$	19.14	19.35
7	$CH(CH_3)CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	92–95	$C_{24}H_{36}O_{11}N_2$[a]	(N 5.30	5.45)
8	$CH_2(CH_2)_3CH_3$	$CH_2CH_2N(C_2H_5)_2$	81–83	$C_{25}H_{38}O_{11}N_2$[a]	(N 5.16	5.32)
9	$CH_2(CH_2)_4CH_3$	$CH_2CH_2N(C_2H_5)_2$	79–81	$C_{26}H_{40}O_{11}N_2$[a]	(N 5.03	5.13)
10	$CH_2CH_2CH_3$	$CH_2C(CH_3)_2CH_2N(CH_3)_2$	145–146	$C_{24}H_{36}O_{11}N_2$[a]	(N 5.30	5.39)

[a] Citrate. [b] All of the salts were recrystallized from a mixture of ethyl acetate and absolute alcohol except compound 10 which was purified with the aid of absolute alcohol.

aminoethyl) 3-nitrophthalate, 3.9 g. (0.0276 mole) of methyl iodide and 50 cc. of absolute alcohol was poured into a magnesium citrate bottle and heated in a water-bath at 90° for one hour. The mixture was evaporated to dryness and the residue washed with ether.

Citrates of the amino diesters were obtained when equivalent molecular amounts of the ester and citric acid monohydrate were heated in absolute alcohol for one-half hour on a steam-bath. After removal of the solvent, the residues were washed with absolute ether whereupon they were obtained in crystalline state.

β,β-Dimethyl-γ-dimethylaminopropyl Chloride Hydrobromide.—To a solution of 5 g. of β,β-dimethyl-γ-dimethylaminopropyl alcohol[9] in 25 cc. of benzene there was added 15 cc. of thionyl chloride. The mixture was refluxed for one hour, the excess thionyl chloride and benzene removed by distillation under reduced pressure and the residue washed with dry ether. The gummy chloride hydrochloride, which refused to crystallize, was dissolved in water, the solution made alkaline with sodium carbonate, the base extracted with ether and the solution dried with fused sodium sulfate. After removal of the solvent the base was titrated with the calcd. amount of hydrobromic acid (48%) and then rubbed under ether. The chloride hydrobromide was recrystallized from a mixture of ethyl acetate and absolute alcohol; m. p. 157–158°[10]; yield 61%.

The free base was used immediately after liberation from the salt.

Anal. Calcd. for $C_7H_{17}NClBr$: Br, 34.55. Found: Br, 34.63.

Summary

A number of 1-alkyl 2-dialkylaminoalkyl 3-aminophthalates have been described. Many of these products proved to be strong local anesthetics when tested on the rabbit cornea.

ANN ARBOR, MICHIGAN RECEIVED MAY 20, 1941

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[9] Mannich, Lesser and Silten, *Ber.*, **65**, 381 (1932).

[10] The hydrobromide of the alcohol, obtained by addition of the calcd. amount of 48% hydrobromic acid to the latter, melts at 157–159° after recrystallization from a mixture of ethyl acetate and absolute alcohol; mixed with the alcohol hydrobromide, the chloride hydrobromide melted at 138–157°.