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

1-Alkyl 2-Dialkylaminoalkyl 4-Aminophthalates as Local Anesthetics

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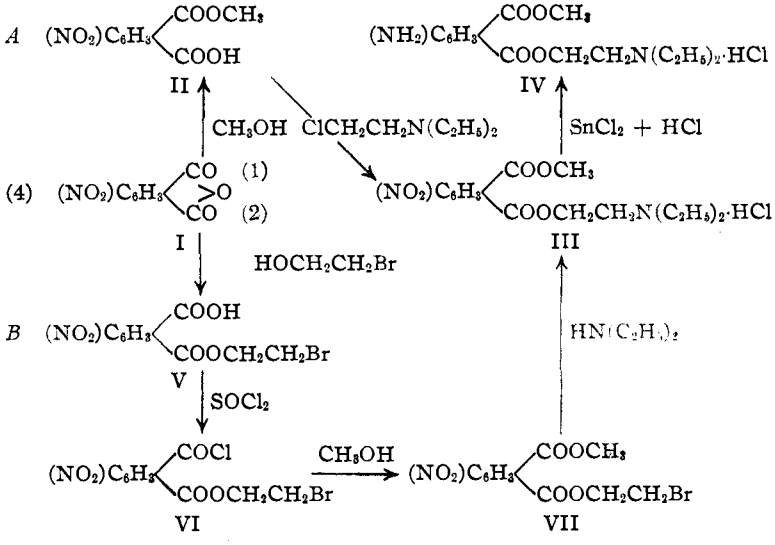
Diesters of the types represented by 1-alkyl 2-dialkylaminoalkyl[2] and 1-dialkylaminoalkyl 2-alkyl 3-aminophthalates[3] have been found to be strong local anesthetics.

This paper deals with 1-alkyl 2-dialkylaminoalkyl 4-aminophthalates which were obtained by two procedures, A and B. These are illustrated in the case of 1-methyl 2-(β-diethylaminoethyl) 4-aminophthalate.

REACTION SCHEME



From 4-nitrophthalic anhydride and ethylene bromohydrin we expected to obtain 1-(β-bromoethyl) 4-nitroacidphthalate which could be converted, by means of a series of reactions such as outlined in scheme B, into 1-dialkylaminoalkyl 2-alkyl 4-aminophthalates. However, since the transformation of the monoester into the ester-acid chloride, treatment of the latter with methyl alcohol to form the bromo diester and, finally, replacement of the bromine by diethylamine yielded a diester identical with 1-methyl 2-(β-diethylaminoethyl) 4-nitrophthalate, the monoester which we obtained from 4-nitrophthalic anhydride and ethylene bromohydrin was 2-(β-bromoethyl) 4-nitroacidphthalate and not the 1-(β-bromoethyl) ester. Furthermore, the ethyl, propyl, isopropyl β-diethylaminoethyl 4-nitrophthalates, obtained by scheme A, proved to be identical with the corresponding esters prepared by the bromohydrin method.

The structures of 1-methyl and 1-ethyl 4-nitroacidphthalate have been proven by Wegscheider and co-workers.[4]

All of the diesters of 4-aminophthalic acid listed in Table II were tested pharmacologically by L. W. Rowe in the Parke, Davis and Company Laboratories and a detailed report will be published by him in another journal. It may be said that preliminary results indicate that this series, the most active member of which seems to be the hydrochloride of 1-*s*-butyl 2-(β-diethylaminoethyl) 4-aminophthalate, is inferior to the group of 1-dialkylaminoalkyl 2-alkyl 3-aminophthalates, described previously, as far as local anesthetic action is concerned.

Experimental

Alkyl 4-Nitroacidphthalates (II and V).—A mixture of 0.3 mole of 4-nitrophthalic anhydride[5] and 5 moles of the required alcohol was heated on a steam-bath two to ten hours,[6] the excess alcohol removed by distillation under reduced pressure and the oily residue washed thoroughly with water whereupon the product usually crystallized. The latter was treated with 10% sodium carbonate solution, filtered and the cold filtrate acidified. The precipitated oily ester was cooled for several hours and after it had become crystalline it was recrystallized a number of times from water or benzene. The average yield of crude ester was about 50% of the calcd. amount.

The propyl ester melted at 73–75° after recrystallization from benzene.

The isopropyl ester, after recrystallization from water, melted at 149–150°.

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by Esperanza R. Castro in partial fulfillment of the requirements of the Degree of Doctor of Philosophy in the University of Michigan.

(2) Blicke and Otsuki, THIS JOURNAL, **63**, 1945 (1941).

(3) Blicke and Otsuki, *ibid.*, **63**, 2435 (1941).

(4) Wegscheider, Kusy and Dubrav, *Monatsh.*, **24**, 805 (1903); Wegscheider and Bondi, *ibid.*, **26**, 1093 (1905).

(5) Prepared from 4-nitrophthalic acid ("Organic Syntheses," Vol. 16, p. 56) and acetic anhydride by the procedure described in "Organic Syntheses," Coll. Vol. I, p. 402, for 3-nitrophthalic anhydride.

(6) In the case of the methyl ester, described by Wegscheider and Lipschitz, *Monatsh.*, **21**, 805 (1900), and the ethyl ester, synthesized by Wegscheider and Bondi, *ibid.*, **26**, 1048 (1905), the mixture was heated for ten hours. We heated 4-nitrophthalic anhydride and *s*-butyl alcohol for six hours.

TABLE I

1-ALKYL 2-DIALKYLAMINOALKYL 4-NITROPHTHALATE SALTS

(4) NO_2–C_6H_3 COOR (1), COOR′ (2)

	R	R′	M. p., °C.	Formula	Halogen, % Calcd.	Found
1	CH_3	$CH_2CH_2N(C_2H_5)_2$ A,[a] B[a]	164–165	$C_{15}H_{21}O_6N_2Cl$	9.84	9.52
2	CH_2CH_3	$CH_2CH_2N(C_2H_5)_2$ A, B	143–144	$C_{16}H_{23}O_6N_2Cl$	9.48	9.62
3	$CH_2CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$ A, B	146–147	$C_{17}H_{25}O_6N_2Cl$	9.14	9.24
4	$CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$ A, B	136–137	$C_{17}H_{25}O_6N_2Cl$	9.14	9.21
5	$CH_2CH_2CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$ A	116–117	$C_{18}H_{27}O_6N_2Br$	17.90	17.88
6	$CH_2CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$ A	105–106	$C_{18}H_{27}O_6N_2Cl$	8.82	8.83
7	$CH(CH_3)CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$ A, B	132–133	$C_{18}H_{27}O_6N_2Cl$	8.82	8.86
8	CH_2CH_3	$CH_2CH_2N(C_3H_7)_2$ B	143–144	$C_{18}H_{27}O_6N_2Cl$	8.82	8.96
9	CH_2CH_3	$CH_2CH_2NC_5H_{10}$ B	155–156	$C_{17}H_{23}O_6N_2Cl$	9.18	9.13
10	CH_2CH_3	$CH_2CH_2NC_4H_8O$ B	120–121	$C_{16}H_{21}O_7N_2Cl$	9.13	9.19

[a] Method of preparation: Compounds 1 to 7 were obtained by the esterification of the anhydride with the corresponding alcohols. Compounds 8 to 10 were prepared by the ethylene bromohydrin synthesis. Compounds 1 to 9 were recrystallized from a mixture of ethyl acetate and alcohol; compound 10 from absolute alcohol.

TABLE II

1-ALKYL 2-DIALKYLAMINOALKYL 4-AMINOPHTHALATE SALTS

(4) NH_2–C_6H_3 COOR (1), COOR′ (2)

	R	R′	M. p., °C.	Formula	Halogen, % Calcd.	Found
1	CH_3	$CH_2CH_2N(C_2H_5)_2$	166–168	$C_{15}H_{23}O_4N_2Cl$	10.74	10.81
2	CH_2CH_3	$CH_2CH_2N(C_2H_5)_2$	152–153	$C_{16}H_{25}O_4N_2Cl$	10.31	10.41
3	$CH_2CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	117–118	$C_{17}H_{27}O_4N_2Br$	19.85	19.97
4	$CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	97–99	$C_{28}H_{34}O_{11}N_2$[a]	(N 5.45	5.67)
5	$CH_2CH_2CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	93–94	$C_{24}H_{36}O_{11}N_2$[a]	(N 5.30	5.52)
6	$CH_2CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	102–104	$C_{24}H_{36}O_{11}N_2$[a]	(N 5.30	5.66)
7	$CH(CH_3)CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	79–83	$C_{25}H_{35}O_4N_2I$[b]	22.92	22.59
8	CH_2CH_3	$CH_2CH_2N(C_3H_7)_2$	114–116	$C_{18}H_{29}O_4N_2Cl$	9.53	9.66
9	CH_2CH_3	$CH_2CH_2NC_5H_{10}$	182–183	$C_{17}H_{25}O_4N_2Cl$	9.96	10.10
10	CH_2CH_3	$CH_2CH_2NC_4H_8O$	181–182	$C_{16}H_{23}O_6N_2Cl$	9.90	10.01

[a] Citrate. [b] Benzyl iodide addition product. Compounds 1, 2, 8, 9 and 10 were prepared by the ethylene bromohydrin synthesis; compounds 3, 4, 5, 6 and 7, by the interaction of the anhydride with the alcohols. Compounds 1 to 6, 8 and 9 were recrystallized from a mixture of ethyl acetate and alcohol; compound 7 from ether and compound 10 from absolute alcohol. Compound 7 was analyzed as the benzyl iodide addition product but the oily base was tested for anesthetic activity.

Anal. Calcd. for $C_{11}H_{11}O_6N$: N, 5.54. Found: N, 5.78.

The butyl ester was obtained as an oil.

The isobutyl ester was recrystallized from water; m. p. 108–109°.

Anal. Calcd. for $C_{12}H_{13}O_6N$: N, 5.25. Found: N, 5.49.

The *s*-butyl ester melted at 112–114° after recrystallization from benzene.

Anal. Calcd. for $C_{12}H_{13}O_6N$: N, 5.25. Found: N, 5.47.

In order to obtain 2-(β-bromoethyl) 4-nitroacidphthalate, 193.0 g. (1 mole) of 4-nitrophthalic anhydride, 200 cc. of dry benzene and 131.1 g. (1.05 mole) of ethylene bromohydrin was heated on a steam-bath for one hour, the solvent removed under reduced pressure and the red, oily residue washed with water and then treated with 10% sodium carbonate solution. The alkaline solution was shaken with ether, the ether layer discarded, and the solution cooled and neutralized with hydrochloric acid. The oily precipitate solidified after several hours in an ice-bath. The ester melted at 99–101°; yield 200 g.

Anal. Calcd. for $C_{10}H_8O_6NBr$: Br, 25.15. Found: Br, 25.07.

Prepared in an analogous manner with the aid of ethylene chlorohydrin, 2-(β-chloroethyl) 4-nitroacidphthalate melted at 97–98°.

Anal. Calcd. for $C_{10}H_8O_6NCl$: Cl, 12.98. Found: Cl, 12.97.

1-Alkyl 2-(β-Bromoethyl) 4-Nitrophthalates (VII).—Thirteen grams of 2-(β-bromoethyl) 4-nitroacidphthalate and 25 g. of thionyl chloride were heated in a Claisen flask on a steam-bath for three hours. The excess thionyl chloride was removed under reduced pressure and the crude oily acid chloride used in the next experiment.

A mixture of ten grams of the acid chloride, 20 cc. of dry benzene and 25 cc. of the required alcohol (methyl, ethyl, propyl or isopropyl) was refluxed for two hours and the solvent and excess alcohol removed under diminished pressure. The oily residue was washed with 10% sodium

carbonate solution, then with water and dissolved in ether. The ether solution was dried with fused sodium sulfate and the solvent removed. All the esters were oils and were obtained in about 10 g. yields.

1-Alkyl 2-(β-Diethylaminoethyl) 4-Nitrophthalate (III).—(a) One-hundredth mole of the 1-alkyl 4-nitroacidphthalate, 0.01 mole of β-diethylaminoethyl chloride[7] and 30 cc. of isopropyl alcohol were heated for ten hours on a steam-bath. The solvent was removed under reduced pressure and the oily ester hydrochloride washed with anhydrous ether whereupon it usually solidified. The salt was recrystallized from a mixture of alcohol and ethyl acetate.

In the event that the hydrochloride could not be obtained in a crystalline state, the base was liberated and the hydrobromide or methiodide was prepared.

(b) A mixture of 0.056 mole of the 1-alkyl 2-(β-bromoethyl) 4-nitrophthalate, 20 cc. of dry toluene and 16.5 g. of diethylamine was heated in a magnesium citrate bottle at 95° in a water-bath for three hours. After filtration of the precipitated diethylamine hydrobromide, the solvent and the excess amine were removed under reduced pressure. The residue was washed with water, dissolved in 5% hydrochloric acid, the mixture filtered, the filtrate made alkaline with 10% sodium carbonate solution and the ester extracted with ether. After the ether extract had been dried with fused sodium sulfate, the solvent was removed and the oily, basic ester was rubbed with the calcd. amount of 38% hydrochloric acid required for the formation of the hydrochloride. The product became crystalline after it had been washed thoroughly with dry ether.

Esters which contained the 2-(β-dipropylaminoethyl), 2-(β-piperidinoethyl) or 2-β-(4-morpholyl)-ethyl group were prepared by substitution of dipropylamine, piperidine or morpholine for diethylamine in the above procedure. The hydrochlorides of these esters were obtained by the addition of the required amount of alcoholic hydrogen chloride to the base.

1-Alkyl 2-(β-Diethylaminoethyl) 4-Aminophthalate (IV).—All of the nitro esters listed in Table I were reduced to the corresponding amino compounds with stannous chloride and hydrogen chloride in acetic acid solution.[8]

(7) Slotta and Behnisch, *Ber.*, **68**, 758 (1935).

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

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Summary

A number of 1-alkyl 2-dialkylaminoalkyl 4-aminophthalates have been described. Most of them exhibit a fair degree of local anesthetic activity when tested on the rabbit cornea.

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

Structure of Gossypol. XXVI. Gossypolic Acid[1]

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With one exception, all of the significant degradation products of gossypol have been discussed in previous papers and their structures explained satisfactorily on the basis of the postulated formula for gossypol (I).[3] The exception is gossypolic acid, reported by Karrer and Tobler[4] to be formed by ozonization of gossypol along with oxalic acid. Unfortunately the conditions for preparation and isolation of gossypolic acid were not well established and the inability of these authors to obtain more than very small amounts of material prevented them from making an exhaustive study of this substance. They suggested, however, that it was probably an aromatic *o*-hydroxy acid as determined by its solubility in aqueous sodium bicarbonate and the color reaction with alcoholic ferric chloride. On the basis of analytical data, it was assigned the formula $(C_{12}H_{14}O_4)_x$. Molecular weight determinations gave values half-way between those expected, if $x = 1$ and $x = 2$.

Gossypolic acid with diazomethane was converted into a molecule with two methoxyl groups per unit $(C_{11}H_{12}O{\cdot}OCH_3{\cdot}COOCH_3)_x$, one of which was saponified readily by alkali to give an aqueous bicarbonate soluble product $(C_{11}H_{12}O{\cdot}OCH_3{\cdot}COOH)_x$. The molecular weight of the methyl ether methyl ester gave a value between 10 and 15% too low for a substance in which $x = 2$.

After many experiments, it was found possible in this investigation to obtain a small amount of gossypolic acid. Even the successful ozonolyses under carefully observed conditions could not be duplicated more than occasionally. As a consequence, the experiments have been limited in scope. The reactions of Karrer and Tobler on gossypolic acid were repeated in all details. Complete analyses on the three products and a molecular weight determination on the methyl ether methyl ester were performed. From the results,

(1) For previous paper in this series, see Adams and Baker, THIS JOURNAL, **63**, 535 (1941).

(2) An abstract of a thesis submitted in partial fulfillment for the degree of Doctor of Philosophy in Chemistry; Solvay Process Co. fellow 1940–1941.

(3) Adams, Morris, Geissman, Butterbaugh and Kirkpatrick, THIS JOURNAL, **60**, 2193 (1938).

(4) Karrer and Tobler, *Helv. Chim. Acta*, **15**, 1204 (1932).