amount as corresponding acid. The acids were identified by mixed melting point determinations.

Summary

A new method for the esterification of certain sterically hindered acids is described. This method consists in pouring a 100% sulfuric acid solution of the acid to be esterified into the desired alcohol.

Theoretical considerations concerning the behavior of organic substances in sulfuric acid are discussed.

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

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

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

Recently we described a series of 1-alkyl 2-dialkylaminoalkyl 3-aminophthalates[2] and reported that a number of them are strong local anesthetics.

This paper deals with the preparation of 1-dialkylaminoalkyl 2-alkyl 3-aminophthalates which were obtained by a series of simple reactions: conversion of 3-nitrophthalic anhydride into a 2-alkyl 3-nitroacidphthalate by means of an alkanol; treatment of the monoester with a dialkylaminoalkyl chloride whereupon a 1-dialkylaminoalkyl 2-alkyl 3-nitrophthalate hydrochloride was formed; reduction of the nitro group in the diester with stannous chloride and hydrogen chloride in acetic acid solution.

Many of the products were found to be more active than cocaine when tested on the rabbit cornea; the salts of 1-(β-diethylaminoethyl) 2-amyl and 1-(β-diethylaminoethyl) 2-hexyl 3-aminophthalate are especially strong local anesthetics. A detailed pharmacological report will be published later by L. W. Rowe, who examined the esters in the Parke, Davis and Company Laboratories.

Experimental

2-Alkyl 3-Nitroacidphthalates.[3]—A mixture of 0.25 mole of 3-nitrophthalic anhydride[4] and 1.25 moles of the required alcohol was heated on a steam-bath for five hours, the excess alcohol removed by distillation under reduced pressure and the residue treated with 10% sodium carbonate solution. The mixture was filtered, the filtrate acidified, the precipitated monoester filtered and recrystallized from a suitable solvent—water, alcohol, dilute alcohol or benzene.

In order to obtain the monolauryl and the monostearyl esters, the nitro anhydride was heated in xylene solution with 1:1 molecular quantity of the alcohol for six hours at 145–150°.

The esters must be highly purified before use.

1-(β-Diethylaminoethyl) 2-Alkyl 3-Nitrophthalate Hydrochloride.—A mixture of 0.05 mole of 2-alkyl 3-nitroacidphthalate. 0.45 mole of β-diethylaminoethyl chloride[5] and 30 cc. of dry *iso*propyl alcohol[6] was heated on a steam-bath for five hours and the solvent removed by distillation under reduced pressure. The crude hydrochloride was purified by recrystallization.

The 3-amino esters were obtained in the manner described previously.[7]

Several cases were noticed in which the hydrochlorides of the isomeric esters possessed identical or very similar melting points: thus, both 1-ethyl 2-(β-diethylaminoethyl) 3-nitrophthalate hydrochloride and 1-(β-diethylaminoethyl) 2-ethyl 3-nitrophthalate hydrochloride melt at 126–128°; however, the mixed melting point was found to be 114–124°.

In a few instances in which the hydrochloride of the nitro or the amino ester could not be obtained in crystalline form, the hydrobromide, citrate or methiodide[2] was prepared.

γ-Dibutylaminopropyl chloride hydrochloride was obtained when a mixture of 18.7 g. of γ-dibutylaminopropyl alcohol, 75 cc. of chloroform and 25 cc. of thionyl chloride was heated for two hours on a steam-bath and the solvent and excess thionyl chloride removed under diminished pressure. The crude salt was dissolved in water, the basic chloride liberated with sodium bicarbonate, the product extracted with ether, the solution dried and the solvent removed. The material was used immediately.

The chloroaurate, obtained as yellow needles after recrystallization from dilute alcohol, melted at 143–146°.

Anal. Calcd. for $C_{11}H_{25}NCl_5Au$: Au, 36.13. Found: Au, 36.06.

The preparation of γ-dimethylamino β,β-dimethylpropyl chloride hydrobromide has been published[2] and γ-piperidinopropyl bromide hydrobromide will be described later.

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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 fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

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

(3) A long series of these esters has been described by Dickinson, Crosson and Copenhaver, *ibid.*, **59**, 1094 (1937).

(4) "Organic Syntheses," Coll. Vol. I, p. 402.

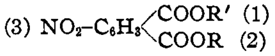
(5) Slotta and Behnisch, *Ber.*, **68**, 758 (1935).

(6) In the case of 2-lauryl and the 2-stearyl esters, xylene was used as a solvent and the mixture was heated for five hours at 120–130°.

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

TABLE I

1-DIALKYLAMINOALKYL 2-ALKYL 3-NITROPHTHALATE SALTS



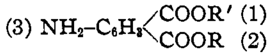
$$(3)\ NO_2{-}C_6H_3\begin{array}{l}\diagup COOR'\ (1)\\ \diagdown COOR\ \ (2)\end{array}$$

	R	R′	M. p., °C.	Formula	Halogen, % Calcd.	Halogen, % Found
1	CH_3	$CH_2CH_2N(C_2H_5)_2$	145–146	$C_{15}H_{21}O_6N_2Cl$	9.83	9.87
2	CH_2CH_3	$CH_2CH_2N(C_2H_5)_2$	126–128	$C_{16}H_{23}O_6N_2Cl$	9.46	9.42
3	$CH_2CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	111–112	$C_{17}H_{25}O_6N_2Cl$	9.12	9.24
4	$CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	124–126	$C_{17}H_{25}O_6N_2Cl$	9.12	9.23
5	$CH_2CH_2CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	80–82	$C_{18}H_{27}O_6N_2Cl$	8.80	8.76
6	$CH_2CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	125–127	$C_{18}H_{27}O_6N_2Cl$	8.80	8.85
7	$CH(CH_3)CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	. . .[a]	$C_{18}H_{27}O_6N_2Br$	17.86	17.78
8	$CH_2(CH_2)_3CH_3$	$CH_2CH_2N(C_2H_5)_2$	71–73	$C_{19}H_{29}O_6N_2Cl$	8.50	8.53
9	$CH_2(CH_2)_4CH_3$	$CH_2CH_2N(C_2H_5)_2$	64–66	$C_{20}H_{31}O_6N_2Cl$	8.23	8.48
10	$CH_2(CH_2)_{10}CH_3$	$CH_2CH_2N(C_2H_5)_2$	84–86	$C_{26}H_{43}O_6N_2Cl$	6.88	7.17
11	$CH_2(CH_2)_{16}CH_3$	$CH_2CH_2N(C_2H_5)_2$	89–90	$C_{32}H_{35}O_6N_2Cl$	5.92	6.08
12	$CH_2CH_2CH_3$	$CH_2CH_2CH_2NC_5H_{10}$	137–139	$C_{19}H_{27}O_6N_2Br$	17.40	17.59
13	$CH_2CH_2CH_3$	$CH_2CH_2CH_2N(C_4H_9)_2$	155–156	$C_{23}H_{37}O_6N_2I$[b]	22.48	22.57
14	$CH_2CH_2CH_3$	$CH_2C(CH_3)_2CH_2N(CH_3)_2$	164–165	$C_{19}H_{29}O_6N_2I$[b]	24.97	24.77

[a] Hygroscopic. [b] Methiodide. Compounds 1, 2, 3, 12, 13 and 14 were recrystallized from a mixture of ethyl acetate and absolute alcohol; compounds 4, 5, 6, 10 and 11 from ethyl acetate; compounds 7 and 8 from benzene and compound 9 from a mixture of benzene and pet. ether (90–100°).

TABLE II

1-DIALKYLAMINOALKYL 2-ALKYL 3-AMINOPHTHALATE SALTS



$$(3)\ NH_2{-}C_6H_3\begin{array}{l}\diagup COOR'\ (1)\\ \diagdown COOR\ \ (2)\end{array}$$

	R	R′	M. p., °C.	Formula	Halogen, % Calcd.	Halogen, % Found
1	CH_3	$CH_2CH_2N(C_2H_5)_2$	150–152	$C_{15}H_{23}O_4N_2Cl$	10.72	10.81
2	CH_2CH_3	$CH_2CH_2N(C_2H_5)_2$	139–140	$C_{16}H_{25}O_4N_2Cl$	10.28	10.44
3	$CH_2CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	129–130	$C_{17}H_{27}O_4N_2Cl$	9.88	9.96
4	$CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	153–154	$C_{17}H_{27}O_4N_2Cl$	9.88	10.03
5	$CH_2CH_2CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	117–118	$C_{18}H_{29}O_4N_2Cl$	9.51	9.63
6	$CH_2CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	118–119	$C_{16}H_{29}O_4N_2Cl$	9.51	9.66
7	$CH(CH_3)CH_2CH_3$	$CH_2CH_2N(C_2H_5)_2$	117–118	$C_{18}H_{29}O_4N_2Br$	19.14	18.94
8	$CH_2(CH_2)_3CH_3$	$CH_2CH_2N(C_2H_5)_2$	86–88	$C_{19}H_{31}O_4N_2Br$	18.57	18.71
9	$CH_2(CH_2)_4CH_3$	$CH_2CH_2N(C_2H_5)_2$	72–74	$C_{26}H_{40}O_{11}N_2$[a]	(N 5.03	5.21)
10	$CH_2(CH_2)_{10}CH_3$	$CH_2CH_2N(C_2H_5)_2$	84–86	$C_{32}H_{52}O_{11}N_2$[a]	(N 4.37	4.46)
11	$CH_2(CH_2)_{16}CH_3$	$CH_2CH_2N(C_2H_5)_2$	45–46	$C_{32}H_{56}O_4N_2$[b]	(N 5.26	5.33)
12	$CH_2CH_2CH_3$	$CH_2CH_2CH_2NC_5H_{10}$	123–124	$C_{19}H_{29}O_4N_2Cl$	9.22	9.17
13	$CH_2CH_2CH_3$	$CH_2CH_2CH_2N(C_4H_9)_2$	115–116	$C_{22}H_{37}O_4N_2Br$	16.88	17.14
14	$CH_2CH_2CH_3$	$CH_2C(CH_3)_2CH_2N(CH_3)_2$	139–141	$C_{18}H_{29}O_4N_2Br$	19.16	19.15

[a] Citrate. [b] Base. Compound 1 was recrystallized from absolute alcohol; compounds 2, 3, 5, 6, 7, 8, 9, 12, 13 and 14 from a mixture of ethyl acetate and abs. alcohol; compounds 4 and 10 from ethyl acetate and compound 11 from dilute alcohol.

Summary

A number of 1-dialkylaminoalkyl 2-alkyl 3-aminophthalates have been described. Many of these esters have been found to be strong local anesthetics.

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