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Esters of Halogenated Aminobenzoic Acids

BY MARTIN RUBIN, H. C. MARKS, H. WISHINSKY AND A. LANZILOTTI

The alkanolamine esters of certain halogenated aminobenzoic acids have been described as potent local anesthetics.[1] These compounds suffer variously the disadvantages of high toxicity, poor solubility, or instability in aqueous solution. The possibility that the antibacterial activity and the non-interference with the bacteriostatic action of the sulfonamide drugs characteristic of some of the parent acids of this class[2,3,4] might also be true of the esters, led us to prepare some new members of this class of compounds.

and esterification of 2-chloro-4-acetamidobenzoic acid by reflux in the appropriate alkanol with hydrogen chloride (Procedure II).

The detailed pharmacological study of the compounds prepared in this study will be the subject of a separate report by others. In agreement with previous workers, it has been found that halogenation of the benzene ring increases the local anesthetic activity. The effect of the halogenation on the toxicity of the compounds is less uniform. As in a previously reported example[4]

TABLE I

ESTERS OF HALOGENATED AMINOBENZOIC ACIDS, X-4-$NH_2C_6H_3COOR$

	R[f]	X	Prepn.	M. p., °C.	Formula	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
1	CH_3	2-Cl	II	107–108	$C_8H_8O_2NCl$	51.77	4.34			51.70	4.37		
2	C_2H_5	2-Cl	II	110–111	$C_9H_{10}O_2NCl$				17.77				17.84
3	n-C_3H_7	2-Cl	I	76–77	$C_{10}H_{12}O_2NCl$	56.20	5.66			56.50	5.51		
4	i-C_3H_7	2-Cl	I	110–111	$C_{10}H_{12}O_2NCl$	56.20	5.66			56.10	5.60		
5	n-C_4H_9	2-Cl	II	77–78	$C_{11}H_{14}O_2NCl$	58.01	6.20			57.85	6.13		
6	$CH_2CH_2CH_2N(C_2H_5)_2$[a,g]	2-Cl	I	197–198	$C_{14}H_{22}O_2N_2Cl_2$	52.02	6.90			52.46	6.96		
7	$CH_2C(CH_3)_2NH(n$-$C_4H_9)$[b,c]	2-Cl	I	189–190	$C_{15}H_{25}O_2N_2Cl_3$			7.54				7.65	
8	$CH_2C(CH_3)_2NH(n$-$C_5H_{11})$[b,c]	2-Cl	I	202–203	$C_{16}H_{27}O_2N_2Cl_3$	49.81	7.05		27.57	50.30	7.14		27.53
9	$CH_2C(CH_3)_2NH(i$-$C_5H_{11})$[b,c]	2-Cl	I	186–187	$C_{16}H_{27}O_2N_2Cl_3$			7.26				7.35	
10	$CH_2CH_2N(C_2H_5)_2$[a]	2-Cl	I	171–172	$C_{13}H_{20}O_2N_2Cl_2$	50.82	6.56			50.90	6.57		
11	$CH_2CH_2N(C_4H_9)_2$[a]	2-Cl	I	185–186	$C_{17}H_{28}O_2N_2Cl_2$	56.20	7.77			56.32	7.91		
12	$CH_2CH_2NC_4H_8O$[d,d]	2-Cl	I	227–228	$C_{13}H_{15}O_3N_2Cl_2$			8.72	22.08			8.75	22.47
13	$CH_2CH_2NC_5H_{10}$[b,e]	2-Cl	I	210.5–211	$C_{14}H_{21}O_2N_2Cl_3$			7.88				7.99	
14	$CH_2CH_2N(CH_3)_2$[b]	2-Cl	I	197–198	$C_{11}H_{17}O_2N_2Cl_3$	41.86	5.43			41.90	5.88		
15	$CH_2CH_2N(C_2H_5)_2$[a]	3-Cl	I	149–150	$C_{13}H_{20}O_2N_2Cl_2$			9.12				8.97	
16	$CH_2CH_2OCH_2CH_2N(C_2H_5)_2$[a,c]	2-Cl	I	137–138	$C_{15}H_{24}O_3N_2Cl_2$			7.97				8.05	
17	$CH_2CH_2N(C_2H_5)_2$[a]	2-F	I	134–135	$C_{13}H_{20}O_2N_2ClF$			9.64				9.58	
18	$CH_2CH_2N(C_2H_5)_2$[a]	3-F		142–143	$C_{13}H_{20}O_2N_2ClF$			9.64				10.24	

[a] Hydrochloride. [b] Dihydrochloride. [c] Preparation of the amino alcohols 7, 8 and 9 was according to Pierce, Salsbury, Haden and Willis, THIS JOURNAL, **64**, 2884 (1942); 16 was according to Horne and Shriner, THIS JOURNAL, **54**, 2925–2930 (1932). [d] NC_4H_8O = Morpholino. [e] NC_5H_{10} = Piperidino. [f] Compounds 1, 2, 3 and 4 were recrystallized from aqueous ethanol; 5 from petroleum ether (60–90°); 8, 10, 11, 12 from absolute ethanol; 7, 9, 14, 17 from absolute ethanol–ethylacetate mixture; 15 and 16 from dioxane; 6 and 13 were precipitated from ethanol with ether. [g] Diethylaminoethyl 2-chloro-4-aminobenzoate hydrochloride is more stable than procaine to hydrolysis in aqueous solution.

The diethylaminoethyl ester of 3-fluoro-4-aminobenzoic acid was prepared through 3-fluoro-4-nitrobenzoyl chloride by reaction with diethylaminoethanol in benzene, followed by catalytic reduction of the nitro group. The esters of 2-chloro, 3-chloro and 2-fluoro-4-aminobenzoic acids (Table I) were prepared through their corresponding amino acids by the elegant procedure of Blicke and Lilienfeld[5] (Procedure I). For the preparation of certain of the alkyl esters of 2-chloro-4-aminobenzoic acid, it was found advantageous to carry out simultaneous hydrolysis

the determination of the toxicity in terms of the fatal subcutaneous dose indicates a toxicity equal or less than that of procaine. Determination of the toxicity by the intraperitoneal route indicates a higher toxicity but nevertheless a more favorable therapeutic ratio compared to procaine. We wish to thank Dr. O. Wyss for an examination of the biochemical characteristics of these compounds. He has demonstrated that under suitable experimental conditions the esters exhibit the bacteriostatic and non-sulfonamide inhibiting characteristics of the parent acids.

Experimental

Diethylaminoethyl-3-fluoro-4-nitrobenzoate Hydrochloride.—A mixture of 2 g. of 3-fluoro-4-nitrobenzoic acid,[4] 5 cc. of thionyl chloride and 20 cc. of benzene was refluxed for four hours. The benzene and excess thionyl chloride was removed by distillation *in vacuo*. To the cooled residue dissolved in 20 cc. of dry benzene was added 2 g. of diethylaminoethyl alcohol. After standing overnight the mixture was poured into cold dilute hydrochloric acid. The aqueous portion was extracted with ether and then

(1) (a) Moore and Volwiler, THIS JOURNAL, **62**, 2799 (1940); (b) Schering-Kahlbaum A. G., British Patent 321,968 (1928); (c) Morel, Leulier and Deuoyel, *Bull. soc. chim.*, [4] **45**, 457–463 (1929); (d) Fosdick and Dodds, THIS JOURNAL, **65**, 2305 (1943); (e) Frejka and Vymetal, *Coll. Czechoslov. Chem. Commun.*, **7**, 436–443 (1935); *C. A.*, **30**, 1370–1371 (1936).

(2) Wyss, Rubin and Strandskov, *Proc. Soc. Expil. Biol. Med.*, **52**, 155 (1943).

(3) Johnson, Green and Pauli, *J. Biol. Chem.*, **153**, 37 (1944).

(4) Schmelkes and Rubin, THIS JOURNAL, **66**, 1631 (1944).

(5) Blicke and Lilienfeld, *ibid*, **65**, 2283 (1943).

made alkaline with sodium carbonate. The oil which separated was extracted twice with ether and the combined ethereal extracts washed with water and dried over anhydrous potassium carbonate. The ester hydrochloride separated as a fine crystalline precipitate upon addition of dry hydrogen chloride to the filtered ethereal solution. The collected precipitate was recrystallized from absolute ethanol; m. p. 190–191°.

Anal. Calcd. for $C_{13}H_{18}O_4N_2ClF$: N, 8.74. Found: N, 8.72.

Diethylaminoethyl-3-fluoro-4-aminobenzoate Hydrochloride.—A solution of 1 g. of diethylaminoethyl-3-fluoro-4-nitrobenzoate in 100 ml. of absolute ethanol absorbed the theoretical quantity of hydrogen in fifteen minutes using Adams platinum oxide catalyst at a pressure of 2 atmospheres at room temperature. The catalyst was recovered by filtration and the solvent removed by distillation *in vacuo*. The product after recrystallization from a mixture of alcohol and ether melted at 142–143°.

Anal. Calcd. for $C_{13}H_{20}O_2N_2ClF$: N, 9.64. Found: N, 10.24.

Procedure I.—Following the procedure of Blicke and Lilienfeld[5] the acid chloride hydrochlorides of 2-chloro-4-aminobenzoic acid,[6] 3-chloro-4-aminobenzoic acid[3] and 2-fluoro-4-aminobenzoic acid[4] were prepared. These unstable compounds were immediately esterified by reaction with the appropriate alkanol or alkanolamine hydrochloride.

Procedure II.—Hydrogen chloride was passed for three hours through a refluxing solution of 20 g. (0.1 mole) of 2-chloro-4-acetamidobenzoic acid in 200 cc. of the appropriate alkanol. The mixture was then poured onto ice and excess sodium carbonate. The precipitated ester was removed by filtration and purified by recrystallization.

Summary

The preparation of various esters of 2-chloro-4-aminobenzoic acid and the diethylaminoethyl esters of 3-chloro- and 2- and 3-fluoro-4-aminobenzoic acids has been described.

(6) Kunckell and Richartz, *Ber.*, **40**, 3395 (1907).

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The Preparation of Substituted Diphenylethylamines and Diphenylethanolamines

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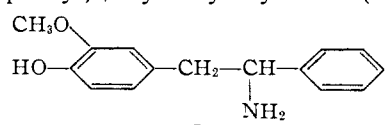
In 1943, Dodds, Lawson and Williams[1a] published a note on the morphine-like properties of diphenylethylamine and five related compounds. In a later publication[2] the study was extended to include nine compounds not previously tested, several of which had hydroxyl or methoxyl groups in the aromatic rings. The most active substances of the English workers were the hydrochlorides of α,β-diphenyl-β-hydroxyethylamine, α,β-diphenylethylamine and dimethyldesylamine. These three were tested clinically in a small number of patients, the first substance giving results which indicated that it might be useful as a general analgesic.

The present project was undertaken in order to ascertain the effect of alkoxyl and hydroxyl substituents in the β-phenyl groups of diphenylethylamine and diphenylethanolamine. After our synthetic work had been completed, there appeared a third publication[3] of the English group stating that α,β-diphenyl-β-hydroxyethylamine, which was the most active substance they had tested and which had been found to be effective in relieving pain due to pressure on nerves in patients with inoperable tumors, "has no universal analgesic action and cannot be used generally as a substitute for morphine." We had prepared α,β-diphenyl-β-hydroxyethylamine and under the conditions of our tests[4] this compound does not show analgesic activity. When the third publication[3] appeared, it was apparent, however, from the methods of synthesis that a different stereoisomer was studied in each series of tests. The English workers employed the isomer of m. p. 163° obtained from benzoin oxime while we studied the more easily prepared Erlenmeyer base of m. p. 129°.[5]

Pharmacological tests employing electrical stimulation in dogs indicate, however, that several of the compounds of the present series have definite analgesic properties. The most effective are the hydrochlorides of α-phenyl-β-(3-methoxy-4-hydroxyphenyl)-ethylamine (I) and α-phenyl-β-(4-hydroxyphenyl)-β-hydroxyethylamine (II).



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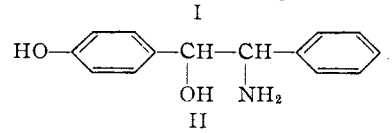

II

The action of these compounds appears to be somewhat different from that of morphine. The substances exert a prolonged effect at peak activity whereas the effect of morphine tapers off quite regularly from the peak.

The first synthetic approach considered was the condensation of suitably substituted aromatic aldehydes with phenylnitromethane to form substituted α-nitrostilbenes and reduction of the latter to substituted diphenylethylamines. While

(1) At present, Ensign, U. S. N. R.

(1a) Dodds, Lawson and Williams, *Nature*, **151**, 614 (1943).

(2) Dodds, Lawson and Williams, *Proc. Roy. Soc.* (London), **B132**, 119 (1944).

(3) Dodds, Lawson and Williams, *Nature*, **154**, 514 (1944).

(4) The pharmacological tests were carried out under the direction of Dr. T. J. Becker of these Laboratories and will be reported elsewhere.

(5) *Cf.* Read and Steele, *J. Chem. Soc.*, 910 (1927).