LOCAL ANÆSTHETIC ACTIVITY OF 4-ALKOXYBENZAMIDES

BY P. KOLOSY, P. TEYSSIÉ AND H. VANDERHAEGHE

From Recherche et Industrie Thérapeutiques, Genval, Belgium

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CONSIDERING the large number of esters whose local anæsthetic properties have been reported, it is surprising that only a few amides appear to have been tested.

Among the local anæsthetics used clinically, cinchocaine is the most powerful when tested with laboratory methods.[1] This product was selected from a series of 2-alkoxyquinolin-4-carboxamides[2]. Sievers and McIntyre[3] have examined diethylaminoethylamides of α-substituted cinnamic acids. These substances do possess moderate activity but are locally irritating. More recently, Büchi and collaborators[4] have compared a number of dialkylaminoethyl-esters and amides of 3-butoxy-4-aminobenzoic acid. Both groups were found to have nearly the same anæsthetic potency so far as nerve conduction is concerned, but the surface anæsthesia is lower and the tissue irritation is increased with the amides. Several esters and amides of 2:6-dialkoxypyridine-4-carboxylic acid were also investigated by the same group[5,6]. In these series the amides were rather more active than the esters, but all substances were very irritating locally. Having investigated previously a group of esters of 4-alkoxybenzoic acid[7], we decided to examine the corresponding amides, but limiting the study to the diethylaminoethylamides, since in the ester group, variations in the side-chain produced only small quantitative differences in the pharmacological properties[7,8].

PHARMACOLOGICAL ACTIVITY

Surface and infiltration anæsthesia, tissue irritation and hæmolytic activity were determined by the methods described previously[7]. All results are summarised in Table I.

These results show that the amides are less active than the corresponding esters. The maximum surface anæsthetic activity is obtained with the butoxybenzamide (IV), whereas with the esters there is a regular increase of activity up to the hexylderivative (XII). The infiltration anæsthesia is greatly reduced in the amides, whereas the local irritation remains of the same order of magnitude as with the esters. It may be concluded that the compounds of these series offer no prospect of therapeutic significance.

PREPARATION

NN-*Diethylethylenediamine.* A simple modification of a method described in the literature[9,10] was used to prepare this amine.

Diethylaminoethanol was transformed into diethylaminoethyl chloride in 80 per cent. over-all yield[11,12]. 35 g. (0·19 mole) of potassium phthalimide was added to a solution of 18·5 g. (0·14 mole) of diethylaminoethyl chloride in 100 ml. of anhydrous xylene, and the mixture

was refluxed for 16 hours. After cooling the solution was filtered, and the filtrate was extracted with 150 ml. of 5 N hydrochloric acid. The aqueous solution was refluxed for 2 hours, and, after cooling, the phthalic acid was filtered. The filtrate was evaporated to dryness, and the residue treated with an ice-cold concentrated solution of potassium hydroxide and extracted with ether. The ether solution was dried with potassium

TABLE I

A COMPARISON OF THE PHARMACOLOGICAL ACTIVITIES OF THE AMIDE AND ESTER DERIVATIVES

		Corneal anæsthesia				Infiltration anæsthesia in guinea-pigs		Tissue toxicity		
		Duration with 1 per cent. solution				Duration with 0·1 per cent. solution		Rating* and diameter (mm.) of reaction zone		
		Rabbits		Guinea-pigs						
	R	Minutes	Potency ratio cocaine = 1	Minutes	Potency ratio cocaine = 1	Minutes	Potency ratio procaine = 1	0·5 per cent. solution	1 per cent. solution	Hæmolytic concentration
										
I.	CH_3O	0	—	0	—	0	—	+ (2)	+ (3)	>1/100
II.	C_2H_5O	0	—	0	—	0	—	+ (2)	+ (4)	>1/100
III.	n-C_3H_7O	15	2·1	18	1·0	6	0·4	+ (2)	+ (3)	1/200
IV.	n-C_4H_9O	21	3·0	24	1·3	8	0·5	+ (2)	+ (3)	1/400
V.	n-$C_5H_{11}O$	6†	0·9	15	0·8	9	0·6	+++ (5)	+++ (9)	1/2000
VI.	n-$C_6H_{13}O$	9†	1·3	21	1·1	12	0·8	+++ (6)	+++ (10)	1/3500
										
VII.	CH_3O	0	—	0	—	0	—	+ (3)	++ (4)	>1/100
VIII.	C_2H_5	9	1·3	24	1·3	33	2·2	0	0	>1/100
IX.	n-C_3H_7O	12	1·7	26	1·4	24	1·6	+ (4)	++ (7)	1/200
X.	n-C_4H_9O	19	2·7	42	2·3	28	1·9	0	++ (6)	1/200
XI.	n-$C_5H_{11}O$	25	3·6	45	2·5	37	2·5	++ (5)	+++ (8)	1/2000
XII.	n-$C_6H_{13}O$	44	6·3	95	3·3	56	3·7	+++ (9)	+++ (10)	1/3000
	Procaine	0	—	0	—	15	1·0	0	+ (3)	>1/100
	Cocaine	7	1·0	18	1·0	27	1·8	+ (2)	+ (5)	—

* + Erythema.
++ Erythema with petechiæ.
+++ Erythema with ulceration.

† These products were irritating for the eye.

carbonate, and after removing the solvent, the product distilled. Yield: 10·5 g. (67 per cent.). B.pt. 144 to 147° C.

p-*Alkoxybenzoyl-diethylaminoethylamides.* No reaction was observed between methyl *p*-ethoxybenzoate and *NN*-diethylethylenediamine in methanol or water. For this reason all products were prepared by the following method. 0·04 mole of *NN*-diethylethylenediamine and 0·04

TABLE II

	M.pt. ° C.*	Per cent. nitrogen†		
		Calculated	Found	
I.	110 to 111°	9·77	9·78	9·75
II.	151 to 152°	9·31	9·31	9·30
III.	128 to 130°	8·90	8·88	8·91
IV.	112 to 113°	8·52	8·54	8·54
V.	98 to 99°	8·17	8·19	8·17
VI.	93 to 94°	7·85	7·84	7·84

* Most products are hygroscopic.
† The elementary analyses were made by Dr. A. Konovalov in the Laboratory of General Chemistry, University of Louvain.

mole of the acid chloride were dissolved separately each in 20 ml. of benzene. The two solutions were mixed with cooling, and subsequently heated for 4 hours on the water bath. When the product did crystallise on cooling, it was filtered and recrystallised. Otherwise, the solution was evaporated to dryness, *in vacuo*, and the residue was crystallised from acetone or methylethylketone.

Table II lists the melting points and elementary analyses of these preparations.

SUMMARY

The diethylaminoethylamides of several *p*-alkoxybenzoic acids were prepared. The study of their pharmacological properties has shown that they possess a smaller anæsthetic activity, but nearly the same toxicity as the corresponding esters.

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