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Local Anaesthetic Studies with Some Alkoxy-dialkylaminoalkoxyanilines

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During the course of an investigation of compounds for local anaesthetic activity, it was found that some substituted diethylaminoethoxyanilines had pronounced activity and relatively low irritancy. This was not unexpected since arylalkamine ethers have been found to possess local anaesthetic activity[1-5] and, as pointed out by Ing and Ormerod, 'it is well known that alkamines which contain a sufficiently hydrophobic radical (e.g. an aryl group or a long-chain alkyl group) possess local anaesthetic properties'.[2] What is uncommon is to find high local anaesthetic activity combined with a relatively low irritancy (local anaesthetic activity/irritancy ratios higher than that of procaine). Because this pharmacological pattern has been found so far almost exclusively among esters, thioesters and amides, it was of interest to investigate the effect of some structural changes on the local anaesthetic activity, toxicity and irritancy of dialkylalkoxyanilines. This paper deals with the results of this investigation.

Methods

Chemical synthesis. The alkoxy-dialkylaminoalkoxy anilines were prepared as follows: Catechol was alkylated with the appropriate alkyl benzenesulphonate to a 1,2-dialkoxybenzene, which in turn was nitrated to yield a 1,2-dialkoxy-4-nitrobenzene. Displacement of the 1-alkoxy group by means of an aqueous potassium hydroxide solution gave the corresponding 2-alkoxy-4-nitrophenol. Bromination of the phenols with bromine or pyridinium

bromide perbromide, or chlorination with gaseous chlorine, gave the 2-alkoxy-6-halogeno-4-nitrophenols. The latter were then alkylated by a dialkylaminoalkyl chloride, and the resulting 1-halogeno-2-dialkylaminoalkoxy-3-alkoxy-5-nitrobenzenes were reduced to the desired 3-halogeno-4-dialkylaminoalkoxy-5-alkoxy-anilines by means of iron and hydrochloric acid.

Pharmacology. Sixteen compounds were studied. *Local anaesthetic activity* was determined by the method of Bülbring and Wajda.[6] The Threshold Anaesthetic Concentration$_5$ (TAC_5) was estimated as previously described.[7] Each compound was tested in parallel with procaine hydrochloride on the two wheals on the guinea pig's back: one was raised with a procaine solution and the other with a solution of one of the experimental compounds. The concentrations of the solutions were graded at 0·3 log intervals. Each solution was tested on 8 or more guinea pigs.

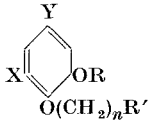
Approximately linear dose–effect curves were obtained by plotting the mean anaesthetic score against the log of the concentration. The TAC_5 was estimated from the dose–effect curve.

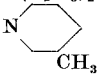
The mean of the 16 TAC_5 values obtained with procaine is shown in Table I. The procaine ratio was obtained by dividing the mean procaine TAC_5 by that of the compound. The TAC_5 and the procaine ratio for each compound are shown in Table I.

Intravenous toxicity in mice and *intradermal irritancy* in rabbits (Trypan Blue method) were determined as previously described.[8, 9] The procaine TIC_4 (Threshold Irritant Concentration$_4$) and the LD_{50} values obtained by pooling all the results obtained in this laboratory were used to calculate the corresponding procaine ratios in Table II.

Duration of intradermal anaesthesia was determined in guinea pigs using the technique of Bülbring and Wajda[6] but taking readings every 10 minutes until the anaesthesia disappeared.[10] Ten guinea pigs were used in each parallel test. The maximal anaesthetic score that can be obtained at each reading is 6 (Bülbring and Wajda's technique). The duration of anaesthesia for each wheal was obtained by plotting the anaesthetic score at each reading against time and estimating by interpolation the time at which the line on the ordinates, which corresponds to score 3, was crossed. The average of the values thus obtained (Tables III and IV) had been called $mean_2$ in a previous publication.[11]

Table I. Chemical structure and local anaesthetic activity



Compound no.	Structure					Salt	Local anaesthetic activity		
							Threshold anaesthetic concentration$_5$ (TAC_5)		Molar procaine ratio
	Y	X	R	n	R′		%, (in terms of bases)	millimolar	
I	$-NH_2$	Br	$-CH_3$	2	$-N(C_2H_5)_2$	HCl	0·077	2·43	3·5
II	$-NH_2$	Br	$-C_2H_5$	2	,,	HCl	0·036	1·08	8·0
III	$-NH_2$	Br	$-C_3H_7$	2	,,	2 HCl	0·017	0·53	16·0
IV	$-NH_2$	Br	$-C_4H_9$	2	,,	2 HCl	0·011	0·30	28·6
V	$-NH_2$	Br	$-C_6H_{13}$	2	,,	2 HCl	0·0056	0·14	60·0
VI	$-NH_2$	Br	$-CH_2C_6H_5$	2	,,	2 HCl	0·022	0·56	15·0
VII	$-NHCOCH_3$	Br	$-C_2H_5$	2	,,	HCl	0·45	12·2	0·7
VIII	$-NHCOCH_3$	Cl	$-CH_3$	2	,,	HCl	0·68	21·6	0·4
IX	$-NH_2$	Cl	$-CH_3$	2	,,	HCl	0·046	1·68	5·1
X	$-NH_2$	Cl	$-C_2H_5$	2	,,	HCl	0·024	0·84	10·3
XI	$-NH_2$	Cl	$-CH_3$	2	$-N(CH_3)_2$	HCl	0·085	3·49	2·5
XII	$-NH_2$	Cl	$-CH_3$	3	,,	HCl	0·055	2·13	4·0
XIII	$-NH_2$	Cl	$-CH_3$	3	$-N(C_2H_5)_2$	HCl	0·031	1·08	8·0
XIV	$-NH_2$	Cl	$-CH_3$	2		HCl	0·027	0·89	9·7
XV	$-NH_2$	Cl	$-CH_3$	3	,,	HCl	0·030	0·94	9·1
XVI	$-NH_2$	Cl	$-C_2H_5$	3	$-N(C_2H_5)_2$	HCl	0·014	0·46	18·6
Procaine						HCl	0·20[a]	8·59[a]	1·0
Propoxycaine						HCl	0·023	0·81	10·6

[a] Mean of 16 ED_{50} values.

Table II. Toxicity and irritancy

Compound no.	Intravenous toxicity in mice			Irritancy (Trypan Blue test)			Local anaesthetic activity/irritancy ratio, procaine = 1
				Threshold irritant conc.$_4$ (TIC_4)			
	$LD_{50} \pm$ s.e., mg/kg (in terms of bases)	LD_{50}, μmoles/kg	Molar procaine ratio	%, (in terms of bases)	millimolar	Molar procaine ratio	
I	17·0 ± 0·9	53·7	4·1	2·2	61·8	2·8	1·3
II	7·8 ± 0·6	23·4	9·5	1·3	39·4	4·4	1·8
III	4·1 ± 0·3	12·0	18·5	1·0	28·7	6·0	2·7
IV	2·3 ± 0·18	6·5	34·0	0·46	12·7	13·6	2·1
V	1·1 ± 0·08	2·8	80·0	0·14	3·9	44·0	1·4
VI	2·8 ± 0·27	7·2	31·0	0·34	8·6	20·0	0·75
VII	62·0 ± 3·6	166·0	1·3	1·8	48·7	3·6	0·2
VIII	82·0 ± 9·9	290·0	0·76	2·4	75·4	2·3	0·17
IX	23·0 ± 0·7	86·0	2·6	3·1	113·0	1·5	3·4
X	10·6 ± 0·7	37·1	6·0	1·8	61·0	2·8	3·7
XI	44·0 ± 2·6	178·0	1·3	3·7	149·0	1·2	2·1
XII	29·0 ± 4·6	112·0	2·0	1·8	71·0	2·4	1·7
XIII	18·0 ± 1·2	62·0	3·6	1·3	46·4	3·7	2·2
XIV	10·9 ± 0·45	39·4	5·6	1·2	38·7	4·5	2·2
XV	6·9 ± 0·54	24·9	8·9	1·3	40·0	4·3	2·1
XVI	5·8 ± 0·4	19·3	11·5	1·4	46·0	3·8	4·1
Procaine	52·7 ± 2·1	222·0	1·0	4·2	173·0	1·0	1·0
Propoxycaine	6·6 ± 0·3	22·0	10·0	2·2	75·0	2·3	4·6

Table III. Duration of intradermal anaesthesia produced by diethylaminoethoxy anilines in solutions containing *laevo*-nordefrin 1:80,000

Expt. no.	Compounds	Conc., %[a]	Duration of anaesthesia	
			Mean ± s.e.	% (propoxycaine HCl + *l*-nordefrin = 100)
1	I	0·63	59 ± 3·2	39
	P[b]	0·25	152 ± 11·6	100
2	II	0·35	131 ± 11·6	69
	P	0·25	193 ± 12·8	100
3	III	0·166	201 ± 12·9	95
	P	0·25	211 ± 6·3	100
4	IV	0·1	160 ± 14·1	102
	P	0·25	157 ± 8·0	100
5	V	0·061	174 ± 9·5	90
	P	0·25	193 ± 7·1	100

[a] Concentrations, expressed in terms of the salts, are approximately equi-active. [b] P = Propoxycaine.

Table IV. Duration of intradermal anaesthesia[a]

Solution	Active agents	Concentration	Average duration of anaesthesia, min Mean ± s.e.
1	Propoxycaine·HCl	0·25%	
	Compound I	0·63%	96 ± 6·5
	laevo-Nordefrin	1:80,000	
2	Propoxycaine·HCl	0·25%	176 ± 10
	laevo-Nordefrin	1:80,000	

[a] Parallel test run on 10 guinea pigs.

Results and Discussion

Only 2 of the 16 compounds studied (VII and VIII) were less active than procaine (Table I). The activities of the other 14 compounds varied from 2·5 to 60 times that of procaine, on a molar basis, and with one exception (compound VI) their local anaesthetic activity/irritancy ratios were greater than that of procaine (Table II).

The effect of lengthening the 5-alkoxy side chain on local anaesthetic activity, toxicity and irritancy was studied on the series of five homologues (compounds I–V). Both activity and toxicity increased approximately at the same geometric rate up to the butoxy homologue, each compound being about twice as active as the next lower member of the series (Fig. 1). From the

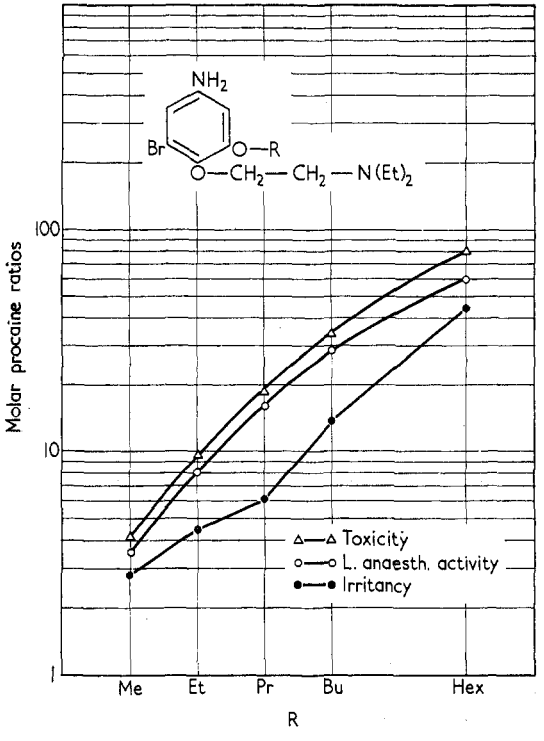


Fig. 1. Local anaesthetic activity, toxicity and irritancy.

butoxy to the hexoxy homologue, the increase in activity and toxicity was reduced. The changes in irritancy were nearly parallel, but the increase in irritancy was greater from the propoxy to the butoxy homologue.

Replacing the NH_2 group by $NHCOCH_3$ had little effect on irritancy but the activity and toxicity were greatly reduced.

In the two cases where chlorine was substituted for bromine

(compounds I *vs.* IX and II *vs.* X) the chloro analogue was less irritating and somewhat more active.

A moderate increase in activity, toxicity and irritancy was obtained by substituting a diethylamino for a dimethylamino group (compounds IX *vs.* XI and XII *vs.* XIII).

The effect of lengthening the 5-alkoxy side-chain (compounds I–V) on the duration of intradermal anaesthesia in the presence of a vasoconstrictor was determined by testing equi-active solutions of the compounds. The strength ratios of the solutions were based on the activity ratios (TAC_5 ratios). The concentration of the vasoconstrictor (*laevo*-nordefrin) in the solution was 1:80,000, in terms of the base. Each solution was tested in parallel with a solution containing 0·25 per cent of propoxycaine hydrochloride (2-diethylamino-4-amino-2-propoxybenzoate hydrochloride) plus *laevo*-nordefrin (1:80,000). The results summarized in Table III show that the methoxy homologue (compound I) was very short-acting and that the duration of anaesthesia increased with the length of the 5-alkoxy side-chain up to the propoxy homologue, and no further increase was observed with the higher homologues. This indicates a more rapid diffusion of the more water-soluble homologues, and/or vasoconstrictor antagonism. It was surprising to find that even the hexoxy homologue (compound V), which is considerably more active and irritating than propoxycaine, produced anaesthesia of approximately the same duration when tested in parallel with this drug in equi-active concentrations in solutions with the same vasoconstrictor strength (Table III).

The results in Table III show that the duration of anaesthesia produced by compound II was approximately 69 per cent of that of the control solution [propoxycaine (0·25 per cent) + *laevo*-nordefrin (1:80,000)].

Compound II has not been compared directly with procaine in parallel duration tests, but in a previous study it was found that the duration of action of mixed solutions of procaine hydrochloride + epinephrine (1:100,000) was 35 to 40 per cent shorter than that of propoxycaine hydrochloride solutions containing the same concentration of epinephrine. From these results, we may deduce that in regard to duration of intradermal anaesthesia, compound II is approximately as short-acting as procaine. Compound I, the methoxy homologue, is even shorter-acting than compound II.

Compound I added to a solution containing propoxycaine and epinephrine produced approximately a 45 per cent reduction in its duration of action (Table IV). As reported previously, procaine hydrochloride had the same effect when added to a solution of propoxycaine and epinephrine.

The toxicity of the compounds in this series showed a high degree of correlation with local anaesthetic activity, in agreement with the significant correlation found between these two properties in a previous study with 57 compounds.[12] Some of the compounds studied may be of clinical interest in view of their short duration of action and their high potency/irritancy ratios in relation to that of procaine.

Summary. (1) Five 5-alkoxy-3-bromo-4-(2-diethylaminoethoxy)-aniline homologues and 11 chemically related compounds were tested for local anaesthetic activity (intradermal anaesthesia in guinea pigs), intravenous toxicity in mice and intradermal irritancy in rabbits (Tryptan Blue Test.)

(2) In the homologous series, activity, toxicity and irritancy increased with the length of the 5-alkoxy side-chain. The methoxy homologue was approximately 3·5 times, and the hexoxy 60 times, more active than procaine, on a molar basis.

(3) When the members of the homologous series were mixed with a vasoconstrictor (*laevo*-nordefrin), the average duration of intradermal anaesthesia produced by equi-active concentrations increased with the length of the 3-alkoxy side-chain up to the propoxy homologue.

(4) Substitution of chlorine for bromine in the phenyl ring decreased the irritancy without any important change in local anaesthetic activity. Replacing the amino with an acetamido group greatly reduced the activity and toxicity. The decrease in irritancy was considerably smaller.

(5) With the exception of the 1-acetamido compounds, all the compounds tested were more active than procaine.

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