ESTERS OF *N*-METHYLPYRROLIDINYLALKANOLS AS LOCAL ANAESTHETICS

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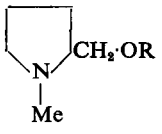
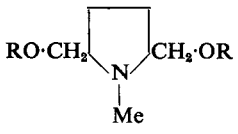
Three new pyrrolidylalkanol esters, 2-*p*-methoxybenzoyloxymethyl-1-methyl-, 2,5-di(*p*-methoxybenzoyloxymethyl)-1-methyl- and 2,5-di(2-*p*-methoxybenzoyloxypropyl)-1-methyl-pyrrolidine have been prepared and tested as local anaesthetics. The activity of the last compound has been shown to be almost identical with that of cocaine by the intracutaneous route, though it is without action on the cornea.

The preparation of a number of esters and phenylcarbonates of the 1-methylpyrrolidinylalkanols (R=H) I, II and III has been described[1].



(I)



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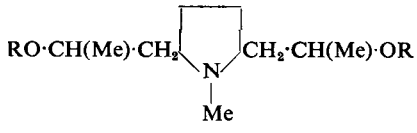

(III)

R = C_6H_5·CO–, C_6H_5CH:CH·CO–, *p*-NH_2·C_6H_4·CO–, C_6H_5·NH·CO–

Preliminary pharmacological tests indicated that local anaesthetic activity was present in all three series of compounds and this paper reports the preparation and activity of the *p*-methoxybenzoates (I, II and III where R = *p*-MeO·C_6H_4·CO–).

2-Hydroxymethyl-1-methylpyrrolidine (1; R = H) was prepared by the method of Blicke and Chi Jung Lu[2], and this with anisoyl chloride in dry benzene gave the hydrochloride of 2-*p*-methoxybenzoyloxymethyl-1-methylpyrrolidine directly. The preparation of 2,5-di(hydroxymethyl)-1-methylpyrrolidine (II; R = H) and of 2,5-di(2-hydroxypropyl)-1-methylpyrrolidine (III; R = H) has been described[1]. These were treated in acetone solution with anisoyl chloride and excess sodium hydroxide solution to give the esters (II and III; R = *p*-MeOC_6H_4·CO–), which were converted to the hydrochlorides.

EXPERIMENTAL

All m.p.s. are uncorrected. Microanalyses are by Mr. G. S. Crouch, School of Pharmacy, University of London.

(I) 2-*p-Methoxybenzoyloxymethyl*-1-*methylpyrrolidine hy drochloride.* A Mixture of 0·86 g. of 2-hydroxymethyl-1-methylpyrrolidineand 1·54 g. of anisoyl chloride was refluxed for 1 hour in 20 ml. of dry benzene and left overnight. The deposited solid was recrystallised from isopropanol/light petroleum to give 1·47 g. of *product*, m.p. 204°. Found: C, 59·0; H, 7·0; N, 4·9. $C_{19}H_{20}O_3N$, Cl requires C, 58·83; H, 7·06; N, 4·90 per cent.

Picrate. Yellow needles from ethanol, m.p. 208–209° (decomp.).

(II) 2,5-*Di*(*p-methoxybenzoyloxymethyl*)-1-*methylpyrrolidine hydrochloride.* 2,5-di(hydroxymethyl)-1-methylpyrrolidine (II; R = H) (1·45 g.) was dissolved in acetone (20 ml.) and anisoyl chloride (6·8 g.) added. The solution was cooled, made strongly alkaline with 20 per cent NaOH solution (30 ml.) and shaken at intervals for 2 hours. After dilution with water the solution was extracted with ether, the ether dried (Na_2SO_4), the solvent removed, and the residue taken up in dry ether. Treatment with dry hydrogen chloride gave a colourless oil which solidified on scratching. Recrystallisation from isopropanol gave fine white needles (2·7 g.) of m.p. 193°. Found: C, 60·5; H, 6·1; N, 3·3. $C_{23}H_{28}O_6NCl$ requires C, 61·40; H, 6·24; N, 3·12 per cent.

Picrate. Yellow needles from ethanol, m.p. 140–141° (decomp.).

(III) 2,5-*Di*(2-*p-methoxybenzoyloxypropyl*)-1-*methyl-pyrrolidine hydro*)-*chloride.* This was prepared in a similar manner to the previous compound from 2,5-di(2-hydroxypropyl)-1-methylpyrrolidine (III; R = H) (1·57 g.) and anisoyl chloride (5·4 g.), as white needles from isopropanol, m.p. 140–142°. Yield, 1·8 g. Found: C, 64·6; H, 7·1; N, 2·7. $C_{27}H_{36}O_6$ requires C, 64·06; H, 7·17;
N, 2·77 per cent.

Picrate. Yellow needles from ethanol, m.p. 220° (decomp.).

TABLE I

EFFECTS ON MICE

Ester HCl	Dose in mg. by intraperitoneal route	Number of animals dead	Other effects
(I)	20	4/4	Convulsions, death in 2 to 3 min.
	10	0/4	Slight tremors
	4	0/4	Sedation
(II)	10	0/4	—
(III)	10	0/4	Marked sedation
Cocaine HCl	5	4/4	Convulsions, rapid death
	2	4/4	Convulsions, rapid death
	1	2/4	Tremors
	0·5	1/4	Tremors

PHARMACOLOGY

By courtesy of Professor G. A. H. Buttle, School of Pharmacy, University of London.

Effects in Mice

The compounds were injected intraperitoneally into groups of 4 animals all weighing between 20 to 22 g. The effects of 20, 10 and 4 mg. of compound I and of 10 mg. of compounds II and III are compared in Table I with the effects produced by cocaine hydrochloride, 5, 2, 1 and 0·5 mg. i.p.

Effects in the Eye

Solutions, in water, of the ester hydrochloride, 5 mg./ml., were prepared by warming (with III there was a tendency to recrystallise on cooling). One drop of each solution was placed in the eye of a guinea pig. In no case was any anaesthetic effect noted. Compound III caused some slight irritation. A solution of III in glycerol also produced no local anaesthetic effect.

Intracutaneous Method

The substances were compared by intracutaneous injection into guinea pigs, the backs of the animals being shaved the day before the test. Positive response was counted as the failure to elicit a squeak from the animal when a pin was applied to the weal produced by the injection. Six pricks were made to each weal at 5-minute intervals after injection. The number of pricks failing to cause a squeak (out of a total of 36) was taken as the degree of local anaesthesia present. The results are shown in Table II.

TABLE II

INTRACUTANEOUS METHOD WITH GUINEA PIGS

Time min.	Number of pinpricks (out of 6) failing to elicit squeak				
	Cocaine HCl 0·5 mg./ml.		1 mg./ml. (I)	1 mg./ml. (II)	1 m.g/ml. (III)
	(i)	(ii)			
5	6	6	6	6	6
10	6	5	6	6	6
15	5	4	6	6	6
20	6	4	6	6	5
25	5	0	5	6	6
30	5	0	5	6	6

From the results all three compounds appear to have a local anaesthetic activity of at least half that of cocaine.

A further assessment of the local anaesthetic activity of compound III was made by the guinea pig weal method. Preparation of the solution in saline was desirable as distilled water was found to have a marked anaesthetic effect, however, the presence of NaCl depressed the solution of the drug so dextrose, 5 per cent, was used, which did not itself have any degree of anaesthesia. Cocaine hydrochloride was also dissolved in 5 per cent dextrose. The results are shown in Table III.

TABLE III

ASSESSMENT OF COMPOUND III BY GUINEA PIG WEAL METHOD

Time min.	Number of pinpricks (out of 6) failing to elicit squeak)											
	Compound III						Cocaine HCl					
	mg./ml.						mg./ml.					
	0·5		0·25		0·125		0·5		0·25		0·125	
	(i)	(ii)	(i)	(ii)	(i)	(ii)	(i)	(ii)	(i)	(ii)	(i)	(ii)
5	6	6	6	6	6	6	6	6	6	6	6	6
10	6	6	6	6	4	6	6	6	6	5	5	6
15	6	6	6	5	2	5	6	6	6	4	2	5
20	6	6	5	4	0	4	6	6	5	4	1	5
25	6	6	5	1	—	1	6	6	5	3	0	4
30	6	6	4	1	—	1	6	6	5	2	—	0
Total	72		55		35		72		57		40	

CONCLUSIONS

Compound III, the hydrochloride of 2,5-di(2-*p*-methoxybenzoyloxypropyl)-1-methylpyrrolidine has local anaesthetic activity almost identical with that of cocaine when injected intracutaneously into guinea pigs. It differs from cocaine in having no effect in anaesthetising the cornea.

REFERENCES

1. Linnell and Perks, *J. chem. soc.* (in the press).
2. Blicke and Chi Jung Lu, *J. Amer. chem. Soc.*, 1952, **74**, 3933.