213. *Derivatives of Pyrrolidine Alcohols as Local Anæsthetics.*

By W. H. Linnell and F. Perks.

The preparation of three series of esters and phenylurethanes of pyrrolidine alcohols as local anæsthetics is described. Their configurations are discussed on the basis of their pK_a values.

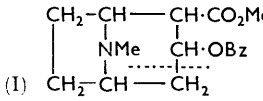
Many types of compound related to cocaine have been studied as local anæsthetics, but few derivatives of pyrrolidine have been prepared for this purpose,[1] other than pyrrolidino-derivatives.

Fission of the piperidine ring of cocaine (I), as shown, gives rise to a pyrrolidine derivative of the general type (II), the methoxycarbonyl group not being essential for local anæsthetic activity as it is absent in tropacocaine.[2] A consideration of the factors influencing local anæsthetic activity led to the conclusions that such activity might be introduced or enhanced in such compounds by (*a*) varying the esterifying acid, (*b*) extending and branching the alkylene side chain, and (*c*) " doubling " the molecule. Accordingly,

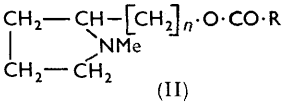
[1] Morgenroth, *Ber. pharm. Ges.*, 1919, **29**, 233; Blicke and Chi-Jung Lu, *J. Amer. Chem. Soc.*, 1955, **77**, 29; Doyle, Mehta, Sach, and Pearson, *J.*, 1958, 4458.

[2] Liebermann, *Ber.*, 1891, **24**, 2336, 2587.

the benzoate, cinnamate, *p*-aminobenzoate, and phenylurethane of 2-hydroxymethyl- (III), 2,5-bishydroxymethyl- (IV), and 2,5-di-(2-hydroxypropyl)-1-methylpyrrolidine (V) were prepared, and where possible, converted into their hydrochlorides.

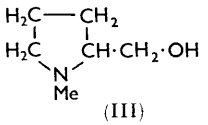


(I)

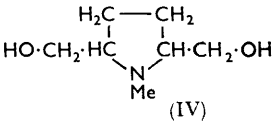


(II)

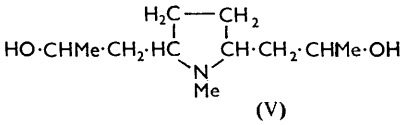
Butyl pyroglutamate, prepared from butan-1-ol, glutamic acid, and concentrated sulphuric acid by Segel's method,[3] was reduced with lithium aluminium hydride to 2-hydroxymethylpyrrolidine which was converted by the method of Blicke and Chi-Jung Lu [4] to 2-hydroxymethyl-1-methylpyrrolidine (III).



(III)



(IV)



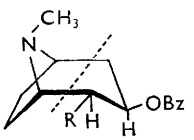
(V)

Crystalline ethyl *meso*-dibromoadipate [5] was converted into 1-methylpyrrolidine-2,5-dicarboxylic ester by the method of von Braun and Seemann.[6] The use of purified methylamine [7] gave an increased yield, no pyrrolidine-2,5-dicarboxyamide encountered by von Braun *et al.* then being formed. The pyrrolidine ester was reduced with lithium aluminium hydride in excellent yield (cf. ref. 6) to the dialcohol (IV).

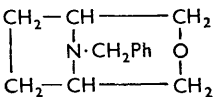
Interaction of acetoacetic acid, methylamine hydrochloride, and succindialdehyde in a buffer solution of pH 5 by the procedure of Schöpf and Lehmann [8] gave 2,5-diacetonyl-1-methylpyrrolidine which was reduced to the dialcohol (V).

Fodor and Kovács [9] and Findlay [10] have shown the configuration of (—)-cocaine to be (VI). Cleavage as shown gives rise to a pyrrolidine structure with substituents in positions 2 and 5 on the same side of the ring. Two series of compounds, *viz.*, derivatives of (IV) and (V) prepared in this work, have 2,5-substituents and it was desirable to determine their configurations and to relate them to local anæsthetic activity.

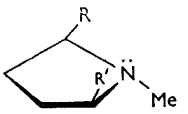
2,5-Bishydroxymethyl-1-methylpyrrolidine (IV) has been assigned the *cis*-configuration. This is probable since its precursor, 1-methylpyrrolidine-2,5-dicarboxylic ester, is formed by ring closure of *meso*-dibromoadipic ester with methylamine. Further, von Braun [6] has shown that the corresponding 1-benzyl derivative could be dehydrated to a bridged morpholine derivative (VII). Hence the dialcohol (IV) and its derivatives are assigned structure (VIII), the lone pair of electrons on the nitrogen atom being on the side adjacent



(VI; R = CO_2Me)



(VII)



(VIII)

to the groups R, because the relative order of size is CH_3 > lone pair > H atom. This is supported because on the proposed structure proton addition must take place from the

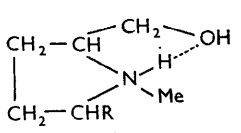
[3] Segel, *J. Amer. Chem. Soc.*, 1952, **74**, 851.
[4] Blicke and Chi-Jung Lu, *ibid.*, p. 3933.
[5] Ingold, *J.*, 1921, **119**, 951.
[6] von Braun and Seemann, *Ber.*, 1923, **56**, 1840.
[7] Philips, *Manuf. Chem.*, 1953, 207.
[8] Schöpf and Lehmann, *Annalen*, 1935, **518**, 1.
[9] Fodor and Kovács, *J.*, 1953, 724.
[10] Findlay, *J. Amer. Chem. Soc.*, 1953, **75**, 4624.

hindered side and the compounds will be weak bases as they are revealed to be by their pK_a values (see Table).

pK_a *values of pyrrolidine derivatives* (VIII).

Series 1 (R = R′)			Series 2 (R = H)			Series 3 (R = R′)		
No.	R = R′	pK_a	No.	R′	pK_a	No.	R = R′	pK_a
1	CO_2Et	4·3	4	CH_2Cl	8·1	7	CH_2·COMe	8·0
2	CH_2·OH	8·5	5	CH_2·OH	9·5	8	CH_2·CHMe·OH	9·3
3	CH_2·OBz	5·2	6	CH_2·OBz	8·5	9	CH_2·CHMe·OBz	7·0

Proton addition to the compounds tabulated may be considered in terms of (*a*) electronic factors, (*b*) steric factors, and (*c*) hydrogen bonding. Compound 1 shows a base-weakening, electron-withdrawal effect, further enhanced by the steric effect of the two ethoxycarbonyl groups on the same side of the molecule. Hence it is a weak base (pK_a 4·3). The low pK_a value of 5·2 for compound 3 indicates the importance of the steric effect since here electron-withdrawal is virtually absent. Compound 2 has approximately the same steric effect as compounds 1 and 3, but no electron-withdrawal. In addition, hydrogen bonding can occur here, as shown in (IX) where R = CH_2·OH and this markedly enhances the base strength (pK_a 8·5).



(IX)

Compound 8 (pK_a 9·3) is an even stronger base than compound 2 though similar in all respects except that it has a *trans*-configuration; thus the second alcoholic group is on the opposite side of the molecule and its steric effect cannot operate.

Series 2 compounds exhibit only slight steric hindrance from the one substituent present and are all therefore fairly strong bases. In compound 5 (IX; R = H) hydrogen bonding can again occur and this is the strongest of our bases, no opposing steric effect being possible.

The pK_a values of compounds of series 3 closely resemble those of series 2 and differ considerably from those of series 1. They therefore possess the *trans*-configuration. Thus for compound 7 the pK_a is 8·0 and for compound 4 pK_a is 8·1, where only the steric factor can operate. Again, compounds 8 and 5 have pK_a values of 9·3 and 9·5 respectively, with a comparable base-strengthening effect due to hydrogen bonding and a steric factor from not too dissimilar substituents.

From the above evidence therefore, 2,5-di-(2-hydroxypropyl)-1-methylpyrrolidine (V) and its derivatives are assigned a *trans*-configuration.

It is of interest that compounds of all three series exhibited at least half the local anæsthetic effect of cocaine hydrochloride in preliminary pharmacological tests, whereas, by analogy with the structure of cocaine (VI), those compounds of a *cis*-configuration might have been expected to be the more active.

Experimental

2-Hydroxymethyl-1-methylpyrrolidine.—Prepared by the method of Blicke and Chi-Jung Lu [4] but with butyl pyroglutamate [3] instead of ethyl 5-oxopyrrolidine-2-carboxylate. Its methiodide (from propan-2-ol) had m. p. 296—297° (lit.,[4] m. p. 293—294°).

2-Hydroxymethyl-1-methylpyrrolidine (0·53 g.) and cinnamoyl chloride (0·93 g.) were refluxed for 1 hr. in dry benzene (15 ml.) and left overnight. The *cinnamoyl ester hydrochloride* crystallised from propan-2-ol as needles, m. p. 181·5° (Found: C, 63·7; H, 7·0; N, 5·05. $C_{15}H_{20}O_2NCl$ requires C, 63·9; H, 7·2; N, 5·0%).

In a similar manner was prepared the benzoate hydrochloride, m. p. 166—168° (Found: C, 61·5; H, 6·9; N, 5·5. Calc. for $C_{13}H_{18}O_2NCl$: C, 61·05; H, 7·1; N, 5·5%), and *p*-nitrobenzoate hydrochloride, m. p. 217—218° (Found: C, 52·2; H, 5·7; N, 9·3. Calc. for $C_{13}H_{17}O_4N_2Cl$: C, 51·9; H, 5·7; N, 9·3%).

The *p*-nitrobenzoate hydrochloride was reduced to the corresponding aminobenzoate with iron filings and hydrochloric acid in ethanolic solution by West's method [11] and converted into

[11] West, *J.*, 1925, **127**, 494.

the hydrochloride by ethereal hydrogen chloride. Recrystallisation from propan-2-ol gave buff needles, m. p. 175—177° (Found: C, 56·7; H, 7·1; N, 10·2. Calc. for $C_{13}H_{19}O_2N_2Cl$: C, 57·6; H, 7·1; N, 10·35%).

The alcohol (0·75 g.) and phenyl isocyanate (0·75 g.) were refluxed together in sodium-dried ether for 2 hr. A small quantity of diphenylurea (m. p. 237°) was deposited overnight. The filtrate was treated with gaseous hydrogen chloride and the *phenyl urethane hydrochloride* recrystallised from propan-2-ol–ether as needles, m. p. 181—182° (Found: C, 57·2; H, 7·2; N, 10·4. $C_{13}H_{19}O_2N_2Cl$ requires C, 57·6; H, 7·2; N, 10·35%).

2,5-*Bishydroxymethyl*-1-*methylpyrrolidine* (IV).—Ethyl *meso*-dibromoadipate [5] with methylamine in benzene gave diethyl 1-methylpyrrolidine-2,5-dicarboxylate,[6] b. p. 114—116°/1 mm. (lit.,[8] 142—146°/11 mm.), and this was reduced with lithium aluminium hydride to 2,5-bishydroxymethyl-1-methylpyrrolidine (75% yield), b. p. 96—98°/0·25 mm. (lit.,[6] 120—130°/12 mm.) (Found: C, 57·6; H, 10·3; N, 9·4. Calc. for $C_7H_{15}O_2N$: C, 57·9; H, 10·4; N, 9·65%).

The benzene solution of methylamine was prepared by liberating the gas from a 25% commercial aqueous solution by means of solid sodium hydroxide and drying it by passage through a tower of sodium hydroxide and yellow mercuric oxide (to remove ammonia as mercuri-ammine) before absorption in benzene.[7]

The following esters were prepared from the dialcohol (IV) and the appropriate acid chloride in 20% excess in acetone solution and an excess of sodium hydroxide solution. The basic ester was isolated by ether-extraction, drying (Na_2SO_4), and removal of the ether. Hydrochlorides were obtained by treatment of an ethanolic or ethereal solution of the base with hydrogen chloride.

Dibenzoate hydrochloride, needles (from dilute hydrochloric acid), m. p. 183° (Found: C, 65·7; H, 6·35; N, 3·5. $C_{21}H_{24}O_4NCl$ requires C, 64·7; H, 6·2; N, 3·6%); this gave the *dibenzoate nitrate*, plates, m. p. 149° (decomp.) (Found: C, 60·4; H, 5·6; N, 7·4. $C_{21}H_{24}O_7N_2$ requires C, 60·6; H, 5·8; N, 6·7%). The *dibenzoate picrate* formed yellow needles (from ethanol), m. p. 180—181° (decomp.) (Found: C, 56·0; H, 4·6; N, 9·8. $C_{26}H_{26}O_{11}N_4$ requires C, 56·1; H, 4·7; N, 9·7%).

Dicinnamate hydrochloride, needles (from propan-2-ol), m. p. 191° (Found: C, 68·4; H, 6·4; N, 3·2. $C_{25}H_{28}O_4NCl$ requires C, 68·0; H, 6·4; N, 3·2%).

Di-p-*nitrobenzoate*, cream-coloured needles (from propan-2-ol), m. p. 143·5° (Found: C, 57·1; H, 4·8; N, 9·3. $C_{21}H_{21}O_8N_3$ requires C, 56·9; H, 4·8; N, 9·5%). Reduction as above gave the *di*-p-*aminobenzoate*, needles (from ethanol), m. p. 170° (Found: C, 65·7; H, 6·3; N, 11·0. $C_{21}H_{25}O_4N_3$ requires C, 65·8; H, 6·6; N, 11·0%). This gave a *dihydrochloride* as needles (from ethanol), m. p. 212° (decomp.) (Found: N, 9·3; Cl, 15·9. $C_{21}H_{25}O_4N_3,2HCl$ requires N, 9·2; Cl, 15·5%).

The alcohol (IV) (0·5 g.) and phenyl isocyanate (0·8 ml.) in boiling dry benzene (10 ml.) (1 hr.) gave the *bisphenylurethane*, prisms (from aqueous ethanol), m. p. indefinite with gas evolution, softening from 92° (Found: C, 65·6; H, 6·6; N, 10·9. $C_{21}H_{25}O_4N_3$ requires C, 65·8; H, 6·6; N, 11·0%), which gave a *hydrochloride* as needles (from propan-2-ol–ether), m. p. 130—132°, softening from 124° (Found: C, 60·1; H, 6·2; N, 10·1. $C_{21}H_{26}O_4N_3Cl$ requires C, 60·0; H, 6·2; N, 10·0%).

2,5-*Di*-(2-*hydroxypropyl*)-1-*methylpyrrolidine* (V).—2,5-Diacetonyl-1-methylpyrrolidine [8] after four recrystallisations from light petroleum (b. p. 60—80°) formed needles, m. p. 55° (lit.,[8] 57°), b. p. 90°/0·05 mm. The succindialdehyde for its preparation was obtained by shaking 2,5-diethoxytetrahydrofuran with twice its volume of 0·1N-hydrochloric acid for 24 hr. Reduction of the diketone with lithium aluminium hydride gave 2,5-*di*-(2-*hydroxypropyl*)-1-*methylpyrrolidine*, b. p. 102—106°/0·05 mm. (Found: C, 65·5; H, 11·4; N, 7·1. $C_{11}H_{23}O_2N$ requires C, 65·6; H, 11·5; N, 7·0%).

The following derivatives were prepared.

Dibenzoate, b. p. 200—204°/0·005 mm. (Found: C, 72·0; H, 7·6; N, 3·4. $C_{25}H_{31}O_4N$ requires C, 73·3; H, 7·2; N, 3·4%), which gave a *picrate*, needles (from ethanol), m. p. 148° (decomp.) (Found: C, 58·0; H, 5·2; N, 8·5. $C_{31}H_{34}O_{11}N_4$ requires C, 58·3; H, 5·4; N, 8·8%), and a *hydrochloride monohydrate*, needles (from propan-2-ol), m. p. 134—135° (Found: C, 64·3, 64·2; H, 7·3; N, 3·0; Cl, 7·6. $C_{25}H_{32}O_4NCl,H_2O$ requires C, 64·7; H, 7·4; N, 3·0; Cl, 7·6%).

Dicinnamate, b. p. 240—246°/0·1 mm., giving a *picrate*, needles (from ethanol and then acetone), m. p. 201·5° (decomp.) (Found: 60·3; H, 5·5; N, 8·0. $C_{35}H_{38}O_{11}N_4$ requires C, 60·9; H, 5·55; N, 8·1%). The hydrochloride was an oil.

Di-p-*nitrobenzoate*, cream-coloured needles (from ethanol), m. p. 184° (Found: C, 59·9; H, 5·8; N, 8·4. $C_{25}H_{29}O_8N_3$ requires C, 60·1; H, 5·85; N, 8·4%).

The derived di-*p*-aminobenzoate did not crystallise, but gave a NN′-*di*-p-*nitrobenzoyl derivative*, cream-coloured needles (from acetone), m. p. 210° (Found: C, 63·4; H, 5·2; N, 9·55. $C_{39}H_{39}O_{10}N_5$ requires C, 63·5; H, 5·3; N, 9·5%).

The *bisphenylurethane* formed prisms (from ethanol), m. p. 128° (Found: C, 68·7; H, 7·6; N, 9·55. $C_{25}H_{33}O_4N_3$ requires C, 68·3; H, 7·55; N, 9·55%); its hydrochloride was an oil.

Measurement of pK_a *Values*.—pK_a values were measured by using a Cambridge pH meter and glass electrode with calomel reference electrode. Solutions, in 30% ethanol, of the free base or hydrochloride were titrated with 0·1N-hydrochloric acid or 0·1N-sodium hydroxide. Graphs were plotted of the pH of the solution against volume of titrant added, and the pK_a values calculated from the points of half-neutralisation.

Microanalyses were performed by Mr. G. S. Crouch of the School of Pharmacy, University of London. One of us (F. P.) thanks the Pharmaceutical Society of Gt. Britain and the University of London for grants from their Research Funds. We also thank Messrs. T. and H. Smith, Edinburgh, for the gift of 2,5-diethoxytetrahydrofuran.

THE PHARMACEUTICAL CHEMISTRY LABORATORY, COLLEGE OF TECHNOLOGY, PORTSMOUTH.
SCHOOL OF PHARMACY, UNIVERSITY OF LONDON. [*Received, July 27th*, 1959.]