# A NOTE ON THE SYNTHESIS OF ESTERS OF *N*-METHYLPYRROLIDINYLALKANOLS

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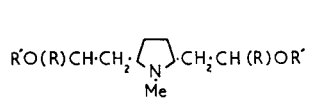
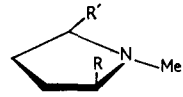
The preparation of a series of esters of 1-methyl-2,5-di-2-hydroxy-2-phenylethyl)pyrrolidine is described. They are assigned *trans* configurations on the basis of their $pK_a$ values.

Esters of *N*-methylpyrrolidinylalkanols of the type I (where R = Me and R′ = Ph·CO–, Ph·CH : CH·CO–, *p*-$NH_2$·$C_6H_4$·CO–, *p*-MeO·$C_6H_4$·CO– and Ph·NH·CO–) have been described by Linnell and Perks (1960 a, b), and found to possess local anaesthetic activity.




(I)




(II)

It was therefore of interest to prepare a similar series of compounds but having R = Ph–, in order to determine the effect of replacing the methyl group of the alkanol side chains by the phenyl group.

1-Methyl-2,5-diphenacylpyrrolidine hydrochloride was prepared by the method of Schöpf and Lehmann (1935) and, after conversion to the free base, reduced with lithium aluminium hydride to 1-methyl-2,5-di(2-hydroxy-2-phenylethyl)-pyrrolidine. This was treated in acetone solution with the appropriate acid chloride and excess sodium hydroxide solution to give the pyrrolidinylalkanol esters (I; R = Ph–; R′ = Ph·CO–, Ph·CH : CH·CO–, *p*-MeO·$C_6H_4$·CO– and *p*-$NO_2$·$C_6H_4$·CO–). These were all viscous oils and were converted to their picrates for analysis. No soluble salts suitable for pharmacological testing could be prepared.

## Experimental

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

1-Methyl-2,5-diphenacylpyrrolidine hydrochloride, prepared according to Schöpf and Lehmann (1935) had m.p. 200° and this was converted into the free base, m.p. 62°, by treatment with potassium hydroxide solution.

1-*Methyl*-2,5-*di*(2-*hydroxy*-2-*phenylethyl*)*pyrrolidine*. A suspension of 1-methyl-2,5-diphenacylpyrrolidine (75 g.) in dry ether (1·5 litre) (in which it is only slightly soluble), was stirred vigorously under reflux whilst a slurry of lithium aluminium hydride (10 g.) in dry ether (250 ml.) was added in small portions. The mixture was then refluxed and stirred

for 4 hr. and allowed to stand overnight. After destroying the excess lithium aluminium hydride with ethyl acetate, there was isolated in the usual manner 72 g. of the desired product as a yellow, viscous oil, b.p. 202–205° at 0·25 mm. Hg.

TABLE I

PICRATES OF PYRROLIDINYL ALKANOL ESTERS

| Ester | m.p. °C of picrate | Analysis of picrate | | | | | |
|---|---|---|---|---|---|---|---|
| | | Found (per cent) | | | Required (per cent) | | |
| | | C | H | N | C | H | N |
| Dibenzoate | 185° (decomp.) | 64·4 | 5·2 | 7·3 | 64·6 | 5·0 | 7·35 |
| Dicinnamate | 213° (decomp.) | 66·2 | 5·1 | 6·8 | 66·3 | 5·2 | 6·9 |
| Di-*p*-methoxybenzoate | 201–3° (decomp.) | 62·5 | 5·4 | 7·0 | 62·7 | 5·2 | 6·8 |
| Di-*p*-nitrobenzoate | 233–4° (decomp.) | 57·4 | 4·4 | 9·9 | 57·7 | 4·3 | 9·85 |

The following *pyrrolidinylalkanol esters* (see Table I) were prepared from the above pyrrolidinylalkanol and the appropriate acid chloride (20 per cent excess) in acetone solution and an excess of sodium hydroxide solution. The basic esters were isolated by ether extraction, drying ($Na_2SO_4$), and removal of the ether. In all instances the products were viscous oils which were dissolved in dry benzene and passed through a short column of alumina, followed by removal of the solvent. For analyses the picrates were prepared from alcoholic solutions of the ester and picric acid. The di-*p*-nitrobenzoate could not be reduced to the corresponding aminobenzoate, all attempts giving intractable tars.

TABLE II

$pK_a$ VALUES OF PYRROLIDINE DERIVATIVES (II) R = R′

| Series A | | Series B | | Series C | |
|---|---|---|---|---|---|
| No. | $pK_a$ | No. | $pK_a$ | No. | $pK_a$ |
| 1 $CO_2Et$ | 4·3 | 4 $CH_2$·COMe | 8·0 | 7 $CH_2$·CO·Ph | 6·9 |
| 2 $CH_2OH$ | 8·5 | 5 $CH_2$·CHMe·OH | 9·3 | 8 $CH_2$·CHPh·OH | 7·8 |
| 3 $CH_2OBz$ | 5·2 | 6 $CH_2$·CHMe·OBz | 7·0 | 9 $CH_2$·CHPh·OBz | 6·8 |

*Measurement of $pK_a$ values.* $pK_a$ values were measured using a Cambridge pH meter and glass electrode with calomel reference electrode. Solutions of the bases in 30 per cent ethanol were titrated with 0·1N hydrochloric acid. 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.

## DISCUSSION

The present series of compounds is believed to have a *trans* configuration like the previous series (Linnell and Perks (1960 a, b), on the basis of their $pK_a$ values (see Table II). This was to be expected, since the parent compound (II.R = R′ = $-CH_2$·CO·Ph) is prepared by a similar method to the corresponding diketone of the previous series (II, R = R′ = $-CH_2$:CO·Me).

The compounds of series A, included for comparison, have been shown to have the *cis* configuration and those of series B to have the *trans* configuration by considering proton addition to the ring nitrogen in terms of steric factors and hydrogen bonding (Linnell and Perks, 1960a).

Of the present series C, compound No. 7 is a comparatively strong base ($pK_a$ 6·9) though somewhat weaker than compound No. 4 ($pK_a$ 8·0) due to the more effective shielding of the basic centre by the bulkier substituent. This may be compared with the much weaker base No. 1 ($pK_a$ 4·3) where there is much more efficient shielding by two much smaller substituents in the *cis* configuration. Compound No. 8 ($pK_a$ 7·8) is a stronger base than No. 7, because of the base-strengthening hydrogen bonding effect, the steric factor being very similar in each case. In compound No. 9, the hydrogen bonding effect is lost and there is a fall in base strength ($pK_a$ 6·8). This is very near to the value for compound No. 6 ($pK_a$ 7·0) and it would seem that with substituting groups of such size and complexity, the steric effect has reached a maximum, larger groups being no more effective in shielding the basic centre.

Compounds of series C therefore, 1-methyl-2,5-diphenacylpyrrolidine and its derivatives are assigned the *trans* configuration.

## References

Linnell, W. H. and Perks, F. (1960a). *J. chem. Soc.*, **213**, 1036–1040.
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Schöpf, C. and Lehmann, G. (1935). *Annalen*, **518**, 1.