STEREOCHEMICAL INFLUENCES ON THE ANTINOCICEPTIVE POTENCY OF 2,3-DIMETHYL ANALOGUES OF THE REVERSED ESTER OF PETHIDINE

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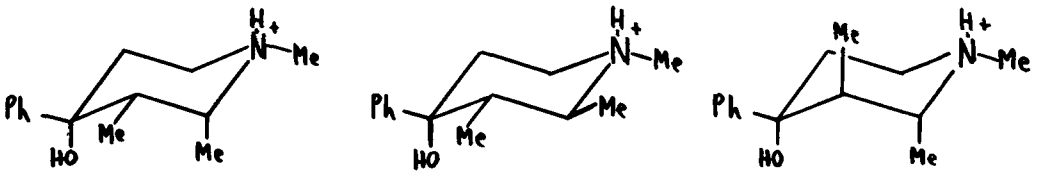
During the past 10 years efforts have been made to rationalise potency variations among mono- and di-C-methyl analogues of the reversed ester of pethidine with emphasis on stereochemistry (Casy 1978). The present report on 2,3-dimethyl congeners, compounds described in 1961 (Mistryukov & Shvetsov) without evidence of stereochemistry, completes work on relative configuration for the entire group. X-Ray analyses of the α-base, β-base and γ-HCl (obtained by fractionation of the mixture derived from 1,2,3-trimethyl-4-piperidone and lithium phenyl) established the relative configuration and solid-state conformations shown below (only 4R antipodes drawn):



α
c-2Me, c-3Me, r-4OH

β
t-2Me, c3Me, r-4OH

γ
c-2Me, t-3Me, r-4OH

Spectroscopic evidence (^{1}H, ^{13}C NMR, IR) shows that solute and solid state conformations of α- and β-alcohol bases are similar but skewboats are favoured for the γ-base as solute (intramolecular H-bonding detected); equatorial 4-phenyl chairs are preferred for acetate and propionate esters of all three alcohols as HCl salts in $CDCl_3$ (interpretations of spectral data are based on principles presented elsewhere, Casy et al 1981).

Potency rankings of propionate esters in antinociceptive assays were γ>α>β (ED_{50}mg/kg: mouse, hot-plate s.c. γ 0.28; α 1.6; β 30.7; rat, tail-withdrawal, i.v. γ 0.04; α 1.25; β 10).

These results correlate with previous stereo-structure/activity speculations based on a receptor-events interpretation (Casy 1978). Thus the low potency of the β-ester compared with γ-promedol (a 2,5-dimethyl isomer of similar geometry) accords with established absolute configurational preferences for equatorial ring methyls, while the higher activity of the α-ester provides a further example of the potency raising action of axial methyl adjacent to nitrogen. The advantageous influence of axial methyls is especially clear in assay data for the γ-isomer, the most potent ester of the group.

We thank Dr. F.R. Ahmed (NRC, Ottawa) for the X-ray analyses and Dr. A.E. Jacobson (NIH, Bethesda) and Mr. K. Schellekens (Janssen Pharmaceutica, Beerse) for the pharmacological results.

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0022-3573/81/120082P-01$02.50/0