Crystal Structures of the (±)-β- and (±)-γ-Promedol Alcohols

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Summary *X*-Ray analyses have shown that the isomeric β- and γ-promedol alcohols (1 2 5-trimethyl-4-phenylpiperidin-4-ol) differ only in having the phenyl group oriented axially in the former and equatorially in the latter

THE promedols are propionate esters of the isomeric 1,2,5-trimethyl-4-phenylpiperidin-4-ols The former are widely used as analgesics, as are their 1,3-dimethyl analogues, the prodines [1,2] Both the prodines and promedols have greater analgesic activity than pethidine [3] The most active of the known promedols is the β-isomer, and the least active is the γ-isomer While it is of great interest to correlate the activity to the molecular structures, previous studies[3–5] of the stereochemistry of the promedols have led to contradictory assignments The present *X*-ray analyses have been carried out on crystals kindly provided by Prof A F Casy The β-promedol alcohol has been found to form monoclinic crystals $P2_1/n$ the results of which are presented here and rhombohedral crystals $R\bar{3}$ which are currently under study

Crystal data (±)-β-promedol alcohol $C_{14}H_{21}NO$, m p 90 5—91 0°, monoclinic, $P2_1/n$, $a = 13\ 298$ $b = 7\ 721$ $c = 12\ 776$ Å, $\beta = 90\ 09°$ $V = 1312$ Å^3, $Z = 4$

(±)-γ-Promedol alcohol, $C_{14}H_{21}NO$, m p 104 0—105 0°, monoclinic, $P2_1/c$, $a = 10\ 806$, $b = 11\ 569$, $c = 10\ 460$ Å, $\beta = 98\ 75°$, $V = 1292$ Å^3, $Z = 4$

The crystal structures have been determined by the direct method of symbolic addition, and have been refined by block-diagonal least-squares utilizing 1585 and 1565 observed reflections for the β- and γ-isomers, respectively The H atoms have been located from difference Fourier maps The final agreement residuals are 0 055 and 0 043 for the β- and γ-isomers, respectively

The molecular structures are presented in Figures 1 and 2 Both molecules have the piperidine ring in the chair conformation with the three methyl substituents in equatorial positions However, the substituents on C(4) are reversed in the two isomers It should be noted that the β-isomer, which is the most analgesically active promedol alcohol, has its phenyl ring in an axial position similar to the conformation around the piperidine ring of both morphine[6] and codeine [7] As shown in Figures 1 and 2, the

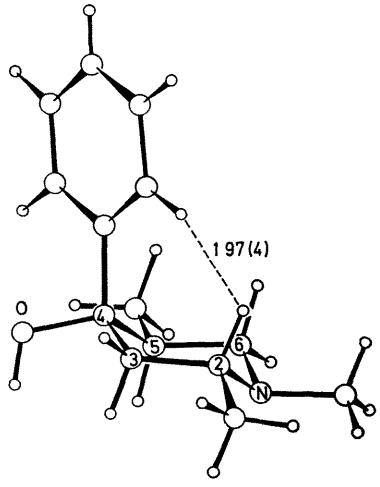

FIGURE 1 *Molecular structure of the monoclinic (±)-β promedol alcohol the most analgesically active*

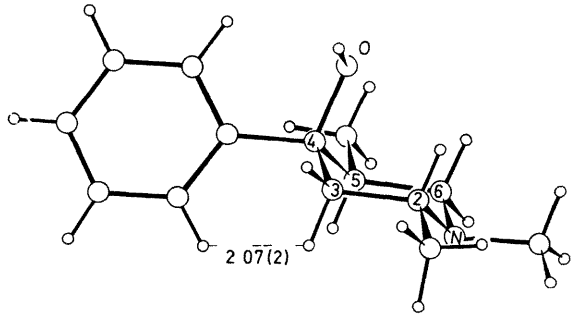

FIGURE 2 *Molecular structure of (±)-γ promedol alcohol, the least analgesically active*

β-isomer has a particularly short intramolecular H · H contact of 1·97 ($\sigma = 0\ 04$) Å, while the shortest similar

contact in the γ-isomer is 2·07 (σ = 0·02) Å. The normal H · · · H van der Waals contact is 2·4 Å. Bond lengths and angles of both molecules are within the range of expected values. Although the molecules of alphaprodine and γ-promedol alcohol are quite similar, no prodine appears to have been synthesized with a conformation similar to that of β-promedol alcohol.

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