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COMMUNICATIONS

Racemic and optically active *trans* 2,6-dimethyl analogues of the reversed ester of pethidine

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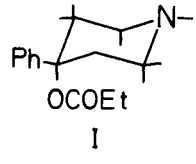
The preparation and stereochemical characterization of (±)-1,*trans* 2,6-trimethyl-4-phenyl-4-propionoxypiperidine hydrochloride and its (+)- and (−)-antipodes are described. The absolute configurations of the antipodes were established by X-ray analysis of the corresponding (−)-4-piperidinol hydrobromide. In antinociceptive tests on mice and rats, the (+)-2*S*,6*S* ester proved the more potent antipode by factors of at least 10 (rats) and 20 (mice), a result consistent with earlier proposals made about the probable uptake conformation of pethidine reversed esters at opioid receptors.

In a recent analysis of the effect of alkyl substitution in the piperidine ring of 4-phenylpiperidine analgesics, a consistent stereochemical structure-activity pattern was developed on the basis of 4-phenylpiperidine ligands associating with opioid receptors in the form of equatorial 4-phenyl chair conformations (Casy 1982). The absolute orientations of methyl substituents that favour or have minor influence on the ligand-receptor interactions were identified and are as illustrated in I.



I

Solid lines denote positions of permitted methyl substitution.

If this analysis is valid, it follows that antipodal forms of the *trans* 2,6-dimethyl analogue of the reversed ester of pethidine (II, R=COEt) should display a large antinociceptive potency difference and the more active form should have the absolute configuration 2*S*, 6*S* (III). This paper describes an investigation of these esters, relative configurations of which have previously been reported (Casy et al 1976).

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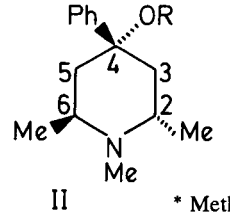
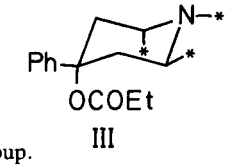
Chemistry and X-ray crystallography

The racemic acetate (II, R=COMe), obtained from 2,6-dimethyl-4-piperidone (Casy et al 1976), was reduced with lithium aluminium hydride to give the corresponding 4-piperidinol (II, R=H) which was resolved with a molar quantity of (−)-dibenzoyl-L-tartaric acid (solvent methanol). Optical activity of the salt, determined on 1% solutions in methanol was constant after three recrystallizations: $[\alpha]^{20}$ − 76·0 (589 nm), −351 (365 nm). The (−)-4-piperidinol base recovered from the salt had $[\alpha]^{20}$ −17·0 (589 nm), −44·0 (365 nm). The base II (R=H) recovered from mother liquors of the (−)-dibenzoyltartrates was mixed with a molar quantity of (+)-dibenzoyl-D-tartaric acid and the salt crystallized from ethanol and then methanol. The diastereoisomeric salt so obtained had $[\alpha]^{20}$ +71·0 (589 nm), +352 (365 nm), and the derived (+)-4-piperidinol base $[\alpha]^{20}$ +13·0 (589 nm) +41·0 (365 nm). Attempts to resolve the esters II (R=COMe) were unsuccessful. Conventional attempts to esterify the 4-piperidinols II (R=H) with propionic anhydride (Casy & McErlane 1972) gave dehydrated products, but reaction at room temperature (20 °C) in the presence of 4-dimethylaminopyridine was successful. Thus a mixture of racemic II (R=H) (0·5 g), 4-dimethylaminopyridine (0·15 g) and propionic anhydride (5 ml) was kept at room temperature for 24 h and then poured into 50% acetic acid in water (50 ml). The base (0·46 g), recovered as usual in ether and freed from 4-dimethylaminopyridine by washing the extract with water, was converted to racemic II (R=COEt) *hydrochloride,* m.p. 186–187 °C (found: C, 65·3; H, 8·4; N, 4·3; $C_{17}H_{26}NO_2Cl$ requires C, 65·5; H, 8·4; N, 4·5%). The



II



III

* Methyl group.

same treatment of the (+)-4-piperidinol gave (+)-II (R=COEt) *hydrochloride*, m.p. 187·5 °C, $[\alpha]^{20}$ +9·0 (589 nm), +19 (365 nm) (found: C, 65·2; H, 8·4; N, 4·3%) and the (−)-4-piperidinol gave (−)-II (R=COEt) *hydrochloride*, m.p. 186 °C, $[\alpha]^{20}$ −7·0 (589 nm), −21·0 (365 nm) (found: C, 65·5; H, 8·4; N, 4·3%).

X-ray crystallography

The X-ray analysis was performed on the hydrobromide salt of (−)-1,2,6-trimethyl-4-phenyl-4-piperidinol, $C_{14}H_{21}NO.HBr$, M_r = 300·25. Its crystals are orthorhombic, space group $P_{2_12_12_1}$, a = 13·714 (5), b = 12.363 (5), c = 8·707 (3) Å, V = 1476 Å^3 and D_x = 1·35 g cm^{-3}. The structure was solved by the heavy-atom method and refined by block-diagonal least-squares to a final R = 0·035 for 841 reflections classed as observed. The absolute configuration was established by comparison of weighted R-values for each of the two enantiomers at equal stages of refinement. Application of the R-factor ratio test indicated that the correct absolute configuration at C(2) and C(6) is R in both cases (Fig. 1). Full details of the crystal structure determination will be published elsewhere.

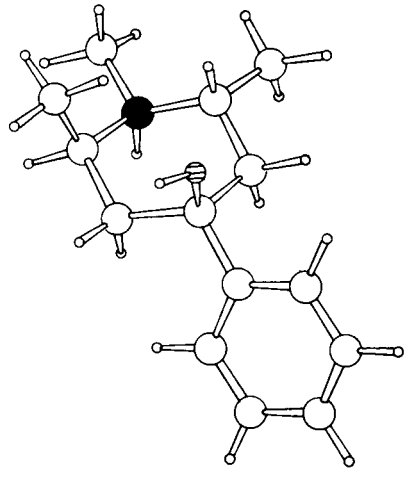


FIG. 1. The conformation and absolute configuration of (−)-1, *trans* 2,6-trimethyl-4-phenyl-4-piperidinol hydrobromide as determined from single crystal X-ray studies. See formula II for ring numbering: large open circles are carbons, the black circle nitrogen and the shaded circle oxygen. Chiral centres 2 and 6 both have the R-configuration (C-4 is achiral since it is linked to two substituents which, while differing in conformation, are of identical configuration).

Since the (−)-4-piperidinol yields the (−)- and the (+)-4-piperidinol the (+)-esters II (R=COEt), the ester configurations are 2R, 6R for the (−)- and 2S, 6S for the (+)-antipode.

Pharmacology and discussion

In mice antinociceptive ED50 values (mg kg^{-1}, s.c.) of the ester II (R=COEt) hydrochlorides were as follows: *hot-plate test* racemic mixture 1·5 (1·1–2·1), (+)-antipode 1·1 (0·9–1·3), (−)-antipode inactive at 5 and 20; *tail-flick test* racemic mixture 2·7 (1·0–7·5), (+)-antipode 0·7 (0·2–2·0), (−)-antipode 11·0 (6·8–17·8); *phenylquinone writhing* racemic mixture 0·1 (0·03–0·5), (+)-antipode 0·2 (0·07–0·7), (−)-antipode 3·0 (1·9–4·7). Both racemic and (+)-II (R=COEt) caused Straub tails in mice at dose levels of 20 mg kg^{-1}, while none of the three forms antagonized the action of morphine in the tail-flick test. In rats (tail-withdrawal test, i.v.) ED50 values (mg kg^{-1}) were 0·31 for the (+)-antipode and >2·5 for the (−)-isomer. Thus (+)-2S,6S II (R=COEt) is about 4 times as active as pethidine in mice (cf hot-plate ED50 4·1 mg kg^{-1}) and 20 times as potent as the same standard (ED50 6·15 mg kg^{-1}) in rats, and at least 20 times in mice and 10 times in rats more potent than its (−)-2R, 6R-antipode.

The results are thus consistent with the probable uptake conformation of pethidine reversed esters at opioid receptors (Casy 1982) and illustrate the fine degree of receptor discrimination for ligands in that the two antipodes differ merely in the relative placements of axial and equatorial methyl α- to the basic centre. The findings also complement conclusions drawn from data upon 3,3-dimethyl analogues of the reversed ester of pethidine recently reported (Ahmed et al 1985).

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