Table III. Protection from Intravenous Histamine Lethality in Guinea Pigs

compd	ED_{50}, mg/kg: hours after oral administrn			
	3	24	48	96
37	0.16	0.12	0.25	nt[a]
astemizole	0.33 (0.25–0.43)[b]	0.07 (0.05–0.09)[b]	0.04 (0.03–0.07)[b]	0.19 (0.10–0.35)[b]

[a] Not tested = nt. [b] Confidence limits.

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Registry No. **1a**, 100-46-9; **2**, 140-75-0; **3**, 5470-18-8; **3a**, 3723-70-4; **3b**, 73733-74-1; **4a**, 32282-07-8; **4b**, 73733-75-2; **5**, 73733-70-7; **6a**, 73733-83-2; **6b**, 75971-36-7; **7a**, 73734-02-8; **7b**, 73733-99-0; **8a**, 76031-50-0; **8a**·2HCl, 73734-21-1; **8b**, 75979-00-9; **8b**·2HCl, 73734-27-7; **9**, 73735-95-2; **10**, 73736-00-2; **11**, 73735-17-8; **12**, 73735-27-0; **13**, 73735-99-6; **14**, 73735-22-5; **15**, 73735-12-3; **16**, 75970-98-8; **17**, 73735-25-8; **18**, 73735-18-9; **19**, 73755-86-9; **20**, 75971-13-0; **21**, 73735-26-9; **22**, 98331-30-7; **23**, 73735-19-0; **24**, 73735-74-7; **25**, 73735-21-4; **26**, 98331-31-8; **27**, 73735-24-7; **28**, 98331-32-9; **29**, 73735-94-1; **30**, 73734-48-2; **31**, 73734-78-8; **32**, 73734-60-8; **33**, 73735-68-9; **34**, 73735-00-9; **35**, 73735-72-5; **36**, 73735-33-8; **37**, 73755-88-1; **38**, 98331-33-0; **39**, 73755-85-8; 4-methoxyphenylethanol methanesulfonate (ester), 73735-36-1; 2-vinylpyridine, 100-69-6; acetone, 67-64-1; acetaldehyde, 75-07-0; cyclohexanecarboxaldehyde, 2043-61-0; butanaldehyde, 123-72-8; (phenoxymethyl)oxirane, 122-60-1.

Notes

Racemic and Optically Active 1,3,3-Trimethyl-4-phenyl-4-(propionyloxy)piperidine

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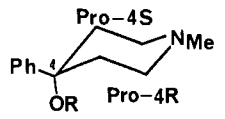
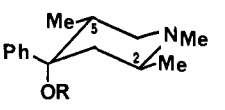
The preparation and resolution of 1,3,3-trimethyl-4-phenyl-4-(propionyloxy)piperidine (**5**, 3-methylprodine) are described, and the results of the antinociceptive activities of the products by hot-plate (mice) and tail-withdrawal (rats) tests are shown to support proposals made from a recent analysis of the stereochemical structure–activity relationships of *C*-methyl derivatives of the reversed ester of meperidine. Data of absolute configuration were obtained by X-ray crystallography of a hydrobromide salt.

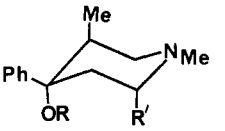
The effect of alkyl substitution in the piperidine ring of 4-phenylpiperidine analgesics has attracted much interest ever since the 3-methyl analogues of the reversed ester of meperidine were described in the late 1940s.[1] Since that time many 3-alkyl and all possible mono- and nongeminal di-*C*-methyl derivatives of the reversed ester have been reported, and much data have accrued on potency variations among isomeric sets and their relative and absolute geometries. In a recent analysis of these results[2] a consistent stereochemical structure–activity pattern was developed on the basis of 4-phenylpiperidine ligands associating with the opiate receptor in the form of equatorial 4-phenyl chair conformations. Thus, the fact of the preferred placement of methyl α and β to nitrogen in the Pro-4*R* and Pro-4*S* edges respectively of the unsubstituted reversed ester **1**[3,4] is consistent with the absolute stereochemistry of the more active γ-2,5-dimethyl analogue (*d*-γ-promedol (**2**))[5] and the inactivities of the β-2,3-dimethyl (either antipode must present one unfavorably positioned substituent) and *cis*-2,6- and *cis*-3,5-dimethyl analogues.[6,7] The same steric correlation obtains between the more active antipodal forms of β-prodine (**3**, R′ = H) and α-promedol (**3**, R′ = Me).[3,8] These and other results of stereochemical analyses of *C*-methyl reversed esters of meperidine allow the absolute orientations of methyl



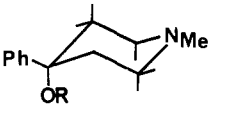
1, R = COEt throughout



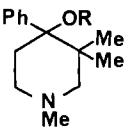
2



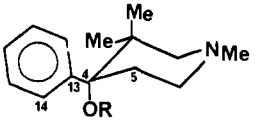
3



4 (solid lines denote positions of permitted Me substitution)



5



6 (4*R* isomer)

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[‡] Visitor from Department of Pharmacy, University of Otago Medical School, Dunedin, New Zealand.
[§] Visitor from College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

(1) Randall, L. O.; Lehman, G. *J. Pharmacol. Exp. Ther.* **1948**, *93*, 314.

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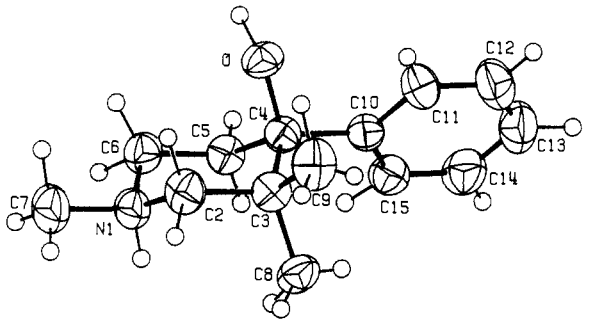

Figure 1. Perspective drawing of (−)-1,3,3-trimethyl-4-phenyl-4-piperidinol hydrobromide showing its conformation and absolute configuration.

substituents that favor or have minor influence on the ligand–receptor interactions to be identified, and these are summarized in **4**. To challenge further these conclusions, antipodal forms of the 3-methyl analogue of prodine **5** have now been examined; if the proposals are valid, the activity of the racemic mixture should reside in the *R* isomer **6** and the *S* form should be inactive or of low potency.[9]

Chemistry. 1,3,3-Trimethyl-4-piperidone, the precursor of **5**, was made from isobutyraldehyde by a reported procedure.[10] Reaction of the ketone with phenyllithium followed by propionic anhydride gave *RS*-**5**. The same reaction, with omission of the anhydride, gave the corresponding 4-piperidinol which was resolved by fractional crystallization of its dibenzoyl-L-tartaric acid salt. Antipodal 4-piperidinols were converted to propionate ester **5** hydrochlorides by treatment with propionyl chloride in toluene at the reflux temperature. Product and intermediate identities were confirmed by ^{13}C NMR spectroscopy.

X-ray Crystallography. The drawing in Figure 1 depicts the molecular structure and absolute configuration of the *l*-4-piperidinol hydrobromide corresponding to the inactive antipodal form of **5**, as determined from the present X-ray crystal structure analysis. Thus, in the solid state, the piperidine ring has the chair conformation with the phenyl ring equatorial and the hydroxyl group axial. The absolute configuration is 4*S*, assuming the priority sequence O > C(3) > C(10) > C(5), and consequently the active epimer has the configuration (+)-4*R*.

The phenyl ring is planar χ^2 ($=\sum\Delta^2/\sigma^2$) = 9.0 and makes a dihedral angle of 33.4 (5)° with the N(1), C(4), O plane, compared to 27.4° for the α-prodine with an equatorial 3-methyl and 45.2° for the β-prodine with an axial 3-methyl.[11] The C(11)–C(10)–C(4)–C(5) torsion angle is 153.5 (4)° for this levorotatory antipode.

In the crystal structure, each Br forms two hydrogen bonds N–H···Br···H′–O′ that interlink the molecules into chains along the *y* axis. These chains are separated by normal van der Waals interactions. The bond lengths and valence angles are comparable to those observed in related compounds.[11]

Pharmacology. In rodents, the antinociceptive activities of the *RS* ester **5** were 7–10 times greater than that of meperidine. ED_{50} values (mg/kg) were as follows: mice (hot-plate test, sc)[12] 0.61 (0.41–0.89), cf. meperidine 4.1 (2.8–6.1); rats (tail-withdrawal test, iv)[13] 0.63, cf. meperidine 6.15. In rats the *R*-(+) antipode **6** had ED_{50} 0.5 mg/kg while the *S*-(−) isomer was inactive at a dose level of 10 mg/kg. In exploratory experiments, *RS*-**5** produced Straub tails in mice at doses of 5 and 20 mg/kg.

The results establish that 3,3-dimethyl substitution in the Pro-4*S* edge of the meperidine reversed ester as depicted in **1** yields a potent antinociceptive agent while placement in the Pro-4*R* edge abolishes activity in this respect. The data are thus consistent with proposals made about the probable binding conformations of meperidine reversed esters at opioid receptors.[2] The hot-plate potency of *RS*-**5** in mice was intermediate between that of racemic α- and β-prodine (α, 0.92 mg/kg; β, 0.18 mg/kg; desmethylprodine, 0.85 mg/kg (determined by the same method in the same laboratory although not concurrently))[14] in accord with a balance between the potency enhancing and diminishing effects respectively of axial and equatorial 3-methyl substituents in reversed esters of meperidine. From examination of the solid-state conformation of (−)-1,3,3-trimethyl-4-phenyl-4-piperidinol hydrobromide, it is likely that a C(14)–C(13)–C(4)–C(5) torsion angle in the range −128 to −167° is favored for the (+) ester **6**, as is the case for the more active antipodes of a variety of chiral 4-phenylpiperidine analgesics.[15] The significance of the orientation of the phenyl and piperidine rings in absolute terms (governed by the 3-substituent placement) is doubtful, however, since as has been pointed out[16] the corresponding value for the relatively weak and nonstereoselective analgesic (+)-β-allylprodine is also negative and within the range found for potent agents. Furthermore, activity differences between antipodal forms of the β-2-methyl reversed ester cannot be accounted for in this manner because the *C*-methyl substituent is too far removed from C(4) to influence the orientation of the aromatic substituent.[4]

Experimental Section

Melting points are uncorrected. ^{13}C NMR data were obtained with a JEOL FX 90Q spectrometer operating at 22.5 MHz under conditions described elsewhere;[17] the solvent was $CDCl_3$, and chemical shifts are expressed in ppm from Me_4Si. Microanalytical data (values for C, H, and N were within 0.4% of theory) are from Janssen Pharmaceutica (J. V. Rompay). Optical rotations were obtained with an Optical Activity polarimeter.

1,3,3-Trimethyl-4-piperidone [bp 62–70 °C (16 mm) (reported bp 69 °C (16 mm))[10]; ^{13}C NMR δ 212.2 (C(4)), 68.6 (C(2)), 56.4 (C(6)), 45.8 (NMe), 45.4 (C(3)), 38.1 (C(5)), 23.8 (CMe_2)] was obtained by a described procedure.[10] Yields at all stages were lower than those reported, and it was found important to keep the temperature below 20 °C during the oxidation step using permanganate. Intermediates characterized by ^{13}C NMR were methyl 2,2-dimethyl-3-(methylamino)propionate [δ 177.5 (CO), 61.3 (CH_2), 51.4 (OMe), 43.5 (C_q), 37.3 (NMe), 23.7 (CMe_2)] and

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its product of condensation with methyl accrylate [δ 177.7, 172.7 (CO), 66.9 (Me_2CCH_2), 55.2 (NCH_2CH_2), 51.3 (OMe), 44.2 (C_q), 43.6 (NMe), 32.8 (NCH_2CH_2), 23.7 (CMe_2)].

1,3,3-Trimethyl-4-phenyl-4-(propionyloxy)piperidine and Related 4-Piperidinol. 1,3,3-Trimethyl-4-piperidone (5 g) in Et_2O was added to phenyllithium in Et_2O prepared from lithium (0.54 g) and bromobenzene (6.1 g), and the mixture was stirred for 1 h. Propionic anhydride (5 mL) was added, and the mixture was well stirred and then poured on a mixture of ice and HOAc. The aqueous phase was washed with Et_2O, made alkaline with NH_4OH, and extracted with Et_2O. Base recovered from the dried extract (8 g) was the 4-propionate **5**, mp 56–57 °C, from petroleum ether (60–80 °C): ^{13}C NMR δ 171.9 (CO), 140.4, 127.4, 126.8, 126.6 (Ar), 85.3 (C(4)), 65.1 (C(2)), 51.7 (C(6)), 46.4 (NMe), 39.3 (C(3)), 28.8, 28.0 (C(5) and $COCH_2$), 23.6, 22.1 (CMe_2), 9.4 ($COCH_2Me$). Anal. ($C_{17}H_{25}NO_2$) C, H, N. It gave a *hydrochloride*, mp 250 °C, from EtOH–Et_2O. Anal. ($C_{17}H_{26}NO_2Cl$) C, H, N. Repetition of the reaction with omission of propionic anhydride gave *1,3,3-trimethyl-4-phenyl-4-piperidinol* (7.3 g), mp 121–123 °C, from petroleum ether (40–60 °C). Anal. ($C_{14}H_{21}NO$) C, H, N.

Optical Resolution of 1,3,3-Trimethyl-4-phenyl-4-piperidinol. The 4-piperidinol (4.05 g) and dibenzoyl-L-tartaric acid (6.95 g) were each warmed to solution in a mixture of Me_2CO (75 mL) and MeOH (12.5 mL), and the solutions were mixed. Crystals (5.14 g) that separated overnight at room temperature were recrystallized twice from MeOH to give a product: 1.06 g; $[\alpha]^{24}_D$ +100.3° (*c* 1.0, MeOH). The 4-piperidinol recovered from this salt was converted to the (–) *hydrochloride*: 0.3 g; mp 265 °C from EtOH–Et_2O; $[\alpha]^{27}_D$ –64.2 (*c* 1.0, MeOH). Anal. ($C_{14}H_{22}NOCl·H_2O$) C, H, N, Cl. Treatment of *l*-4-piperidinol with excess of ethanolic hydrogen bromide gave the (–) hydrobromide, mp 230–232 °C, from ethanol, $[\alpha]^{20}_D$ –58.3 (*c* 1.0, MeOH), used for X-ray crystallography. Reaction of *l*-4-piperidinol (1.3 g) with propionyl chloride in hot toluene gave (–)-**5**·HCl: 1.29 g; mp 200–201 °C from Et-OH–Et_2O; $[\alpha]^{22}_D$ –71.4° (*c* 1.0, MeOH). Anal. ($C_{17}H_{26}NO_4Cl$) C, H, N. Crops of dibenzoyl tartrate (3.0 g) from mother liquors (excluding that of the first recrystallization) had $[\alpha]^{27}_D$ –99.8° (*c* 1.0, MeOH), and the recovered 4-piperidinol (1.2 g) was converted to (+)-**5**·HCl, mp 199–201 °C from EtOH–Et_2O, $[\alpha]^{22}_D$ +71.5 (*c* 1.0, MeOH), by the same method. Anal. ($C_{17}H_{26}NO_2Cl$) C, H, N.

X-ray Crystallography. The X-ray analysis was performed on the hydrobromide salt of (–)-1,3,3-trimethyl-4-phenyl-4-piperidinol; $C_{14}H_{21}NO·HBr$, M_r = 300.25. Its crystals are prismatic, orthorhombic, space group $P2_12_12_1$, with a = 12.387 (1) Å, b = 12.610 (1) Å, c = 9.576 (1) Å, V = 1495.8 Å^3, Z = 4, D_{measd} = 1.329 and D_{calcd} = 1.333 Mg m^{-3}, μ(Cu Kα) = 3.645 mm^{-1}, and $F(000)$ = 624. The cell parameters and intensity data were measured on a Nonius CAD-4 diffractometer using Ni-filtered Cu radiation and a crystal of dimensions 0.13 × 0.13 × (0.30–0.43) mm mounted along its length (the *y* axis). Each of the 1769 unique *hkl* reflections with $2\theta < 150°$, indexed in a right-handed system of axes, was scanned in the ω–2θ mode with $\Delta\omega = (0.8 + 0.14 \tan \theta)°$ plus 25% at each end for the background. Three standard reflections measured every hour fluctuated within ±4%. The net intensities were corrected for the scale fluctuation, the Lorentz and polarization effects, and absorption as evaluated by the Gaussian integration method[18] (transmission factors 0.422–0.656). The analysis was conducted on 1691 reflections with $I \geq 2\sigma(I)$. For determination of the absolute configuration, the intensities of the nonzonal reflections with $2\theta < 40°$ were measured consecutively in the eight octants, and each set of four equivalent measurements was averaged. Of these, 17 Friedel pairs showed significant dispersion effect with $[\langle I(hkl)\rangle - \langle I(\bar{h}\bar{k}\bar{l})\rangle]/\langle I(hkl)\rangle$ higher than 5%, and the corresponding $\langle I(hkl)\rangle/\langle I(\bar{h}\bar{k}\bar{l})\rangle$ ratios were in the range 0.61–1.27.

The structure was determined by the heavy-atom method utilizing Patterson and Fourier maps, and the H atoms were located from a difference map. Refinement was by block-diagonal least squares with anisotropic thermal parameters (isotropic for H), minimizing $\sum w(|F_o| - |F_c|)^2$ where $w = \{1 + [(|F_o| - 5)/15]^2\}^{-1}$ and excluding the strong reflections (200, 002, 122) showing extinction effect. After refinement of both enantiomorphs, the agreement among the observed reflections was significantly better, according to the Hamilton test,[19] for the enantiomorph presented in Figure 1 (R = 0.039 for this enantiomorph and 0.047 for the other). The $[|F_c(hkl)|/|F_c(\bar{h}\bar{k}\bar{l})|]^2$ ratios also were consistently comparable to the observed intensity ratios for the 17 Friedel pairs mentioned earlier.

The refinement converged at R = 0.039 for the 1688 reflections employed in the refinement, $R_w = [\sum w(F_o - F_c)^2/\sum wF_o^2]^{1/2}$ = 0.046, $S = [\sum w(F_o - F_c)^2/(m - n)]^{1/2}$ = 0.68, and maximum parameter shift 0.20σ (0.55σ for H). The residual peaks in the final difference map were within –0.36 and 0.31 e Å^{-3}. The atomic parameters are given in Table I and the bond lengths and angles are listed in Table II (see paragraph at the end of paper concerning supplementary material). The scattering factors[20,21] included the anomalous dispersion for Br. The computations were performed with the NRC system of programs,[22] and Figure 1 was produced by ORTEP.[23]

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Supplementary Material Available: Tables I and II containing the atomic parameters and the bond lengths and valence angles with estimated standard deviations (4 pages). Ordering information is given on any current masthead page.

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