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Reversed ester analogues of pethidine: isomeric 4-acetoxy-1,2,6-trimethyl-4-phenylpiperidines

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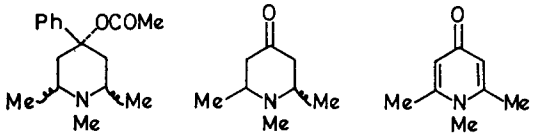
The preparation and stereochemical characterization of all three isomeric forms of 4-acetoxy-1,2,6-trimethyl-4-phenylpiperidine is described. Of these, only the *t*-2-Me,*c*-6-Me,*r*-4-OCOMe isomer was an effective analgesic in mice (2·3 × pethidine) as judged by the hot-plate test. The results, together with reported data, demonstrate the potency raising effects of axial methyl α- to nitrogen and the lowering action of equatorial α-methyl substituents in reversed esters of pethidine.

As part of our interest in the effects of methyl substituents on the analgesic activity of the reversed ester of pethidine (Casy & McErlane, 1972; Iorio, Damia & Casy, 1973; Iorio, Casy & May, 1975) we have prepared all three isomers of 4-acetoxy-1,2,6-trimethyl-4-phenylpiperidine



I II III

Two of the isomeric 4-propionyloxy analogues of I have been reported (Nazarov & Sorokin, 1960) as well as the corresponding *N*-phenethylpiperidin-4-ols (Harper, Beckett & Balon, 1960) but no pharmacological comparison of an isomeric trio has been made.

CHEMISTRY

The intermediate 4-piperidone (II) was obtained by two procedures. The product derived from dimethyl acetonedicarboxylate, acetaldehyde and methylamine hydrochloride, following work on the *N*-phenethyl analogue of (II) (Harper & others, 1960), was a 2:3 *cis-trans* mixture as judged by integrals of the 2,6-dimethyl ^{1}H nmr signals of the sample. The 4-piperidone synthesis of Nazarov & Sorokin (1960), which involves the catalytic reduction of 1,2,6-trimethyl-4(1H)-pyridone (III) followed by oxidation of the resultant 4-piperidinol mixture, gave a product chiefly composed of *cis* (II). Reaction between the piperidone mixture (II) and phenyl lithium followed by acetic anhydride gave a mixture of esters (I) from which the *t*-2-Me, *c*-6-Me, *r*-4-OCOMe isomer (IV) separated as the hydrochloride salt; this configuration follows from the non-equivalence of ^{13}C (Jones, Casy & McErlane, 1973) and ^{1}H nmr resonances in spectra of (IV) and the corresponding 4-piperidinol. The solid state conformation of the acetate hydrobromide (V) (Hayakawa & James, 1973) is probably maintained in the solute condition because one of the C-methyl ^{1}H resonances of the related 4-piperidinol displays a pronounced downfield shift (Δδ 0·31 or 0·43 ppm) when

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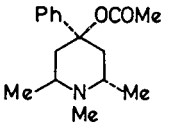
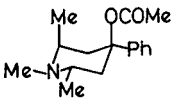


IV



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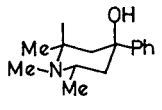
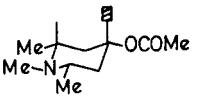


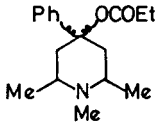
VI

solvent $CDCl_3$ is replaced by pyridine-d_5, a result diagnostic of a *syn* diaxial 1,3Me/OH arrangement (Demarco, Farkas & others, 1968). Since the two *cis* 2,6-dimethyl analogues of (IV) could not be isolated from the residual mixture of esters, a product free from the *trans* 2,6-dimethyl derivative (IV) was prepared by treating the *cis* 4-piperidone (II) with phenyl lithium-acetic anhydride. Hydrochlorides isolated from this material were composed of mixtures of the two *cis* isomers (^{1}H nmr evidence) which could not be fractionated. The free base recovered from such hydrochlorides deposited pure *t* 2,6-dimethyl-4-phenylpiperidin-*r*-4-ol (VI) from light petroleum–acetone and this alcohol was re-esterified with acetyl chloride. The stereochemistry (VI) is confirmed by the significant solvent shift ($\Delta\delta$ 0·38 ppm) suffered by the 2,6 methine ^{1}H nmr resonance when solvent $CDCl_3$ was replaced by pyridine d_5 (*cf.* above). Fractionation of material in the mother liquors gave the final ester, the *c*-2,6,-dimethyl-*r*-4-acetoxy derivative (VII). This derivative was characterized sterically by its high field OCO*Me* ^{1}H resonance (δ1·84), typical of acetates of 4 phenylpiperidin-4-ols with preferred axial phenyl chair conformations (Casy & McErlane, 1972), and low field 3(5) equatorial methine resonance (δ2·83, broad doublet, ^2J 12Hz) (eq 3,5-hydrogens fall in the deshielding zone of the adjacent axial phenyl group when orientated as in VII).

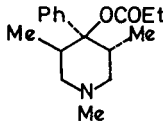
Preferred conformation with plane of Ph ring at right angles to that passing through a line joining N and C–4 of piperidine ring.



VII



VIII



IX

PHARMACOLOGY AND DISCUSSION

Of the three acetates (I), only the *t*-2-Me, *c*-6-Me, *r*-4-OCOMe isomer (IV) proved an effective analgesic at a low dose level in mice as assessed by the hot-plate procedure [ED50 2·0 (1·6–2·5) mg kg^{-1}] being about 2·3 times as potent as pethidine (ED50 4·7 mg kg^{-1}) and 1·8 times as potent as the des-2,6-dimethyl analogue, 4-acetoxy-1-methyl-4-phenylpiperidine (ED50 3·62 mg kg^{-1}) (Casy & McErlane, 1972). The *t*-2,6-di-Me,*r*-4-OCOMe isomer (V) [ED50 18·5 (13·4–25·7) mg kg^{-1}] was only a quarter as potent as pethidine, while (VII) (*c*-2,6-di-Me,*r*-4-OCOMe) was almost without activity in doses up to the toxic level of 100 mg kg^{-1}. Time features of the action of (IV) (activity onset 3·5 min, peak 17·7 min, and duration 118·9 min) were close to mean values observed for a series of reversed esters of pethidine (Iorio & others, 1975). These results accord with the report that the two *cis* 2,6-dimethyl isomers of the propionates (VIII) have little or no pain-relieving properties (Nazarov & Sorokin, 1960), while the *N*-phenethyl analogue of (IV) has significant analgesic properties (Balon, 1959).

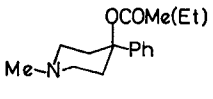
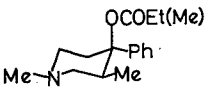
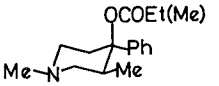
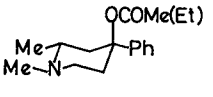
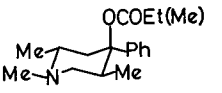
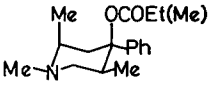
Results already published demonstrate the detrimental influence of equatorially placed methyl substituents α- to nitrogen upon the potency of 4-phenylpiperidine analgesics in mice (Table 1, items 1 and 2). The higher potency of (IV) compared with 4-acetoxy-1-methyl-4-phenylpiperidine shows, however, that an axial α-methyl group enhances the potency of the parent derivative and offsets the adverse influence of the equatorial C-methyl group. The same influence of axial α-methyl is seen in data upon α-prodine and α-promedol (Table 1, item 3). Stereochemical-activity relationships among the isomers (I) are similar to those of 3,5-dimethyl analogues, only the *trans* 3,5-dimethyl isomer (IX) being an effective analgesic in animal tests (Sorokin, 1961; Portoghese, Gomaa & Larson, 1973).

Preparation

Melting points are uncorrected. ^{1}H nmr spectra were recorded on 60 MHz Varian (A–60D) or 90 MHz Perkin Elmer (R32) spectrophotometers in deuteriochloroform with tetramethylsilane as internal standard unless otherwise stated. Nmr chemical shifts are given in ppm (δ scale) and the abbreviations s (singlet), d (doublet), and m (multiplet) are employed.

1,2,6-Trimethyl-4-piperidone (II). Methylamine hydrochloride (36·8 g) in water (40 ml) was added to a stirred, cooled, mixture of acetaldehyde (64 ml) and dimethyl acetonedicarboxylate (87 g). Next day most of the water and excess of acetaldehyde were evaporated. After addition of acetone (1–2 ml) the residual oil solidified on storage to give isomeric 3,5-dicarbomethoxy-1,2,6-trimethyl-4-piperidone hydrochlorides, m.p. 143–145° from ethanol–ether (Found: C, 48·3; H, 6·73; N, 4·96. $C_{12}H_{20}ClNO_5$ requires C, 49·07; H, 6·8; N, 4·8%) δ 1·5–2·0 (m, overlapping doublets due to 2,6-C-Me protons). A mixture of the crude product, water (150 ml) and concentrated hydrochloric acid (250 ml) was heated on a steam bath for 7 h in an open beaker. The product (300 ml volume) was then transferred to a shallow dish and further concentrated over a steam bath to give a malt-like product after 4 h; this was stirred with excess of concentrated aqueous potash and extracted with chloroform.

Table 1. *Hot-plate ED50 values in mice of some 4-phenylpiperidine derivatives*.*

Item	1	2	3
Preferred Conformation**			
	3·62(0·85)†	α–prodine 0·92(6·0)‡	α–prodine 0·92(6·0)‡
			
	4·9(1·4)†	γ–promedol 1·6(6·2)‡	α–promedol 0·58(2·6)‡

* All assays carried out at National Institutes of Health, Bethesda, U.S.A., under the direction of Dr. E. L. May, see Casy & McErlane (1971, 1972), Iorio & others (1975); McErlane & Casy (1972).

** Only one enantiomorph shown for chiral examples although both forms are equally populated since such derivatives were tested as racemic mixtures. ED50 in mg kg^{-1} by subcutaneous route given beneath formulae.

† For propionate.

‡ For acetate. The corresponding inverted chair and skew boat probably contribute significantly to the conformational equilibrium of this derivative (Jones, Beeman & others, 1973).

The chloroform was decanted, dried (Na_2SO_4) and evaporated giving a mixture of liquid and gum. The liquid was decanted and distilled to give a *c–t* mixture of 1,2,6-trimethyl-4-piperidone (18·3 g), b.p. 78–110°/20 mm (b.p. 80° on redistillation), δ 2·38 (*t*), 2·28 (*c*) (s, NMe), 1·18 (*c*), 1·03 (*t*) (d, *J* 6–7 Hz, C–Me). The preparation of the *cis* 4-piperidone (II) involved the following intermediates: 2,6-dimethyl-4H-pyran-4-one (93% yield), m.p. 130–132° (Nazarov & Sorokin, 1960, give 130·5–132·5°), product extracted with chloroform instead of ether; 1,2,6-trimethyl-4(1H)-pyridone (III) (77% yield by Elkaschef & Nosseir's method, 1960), m.p. 110° then solidified and remelted at 240° (Nazarov & Sorokin, 1960, give 249·5–250·5°; Elkaschef & Nosseir, 1960, give 110°); isomeric 1,2,6-trimethyl-4-piperidinols were obtained by hydrogenation of a mixture of III (20 g), Raney nickel (about 10 ml drained sludge, washed with ethanol) and ethanol (100 ml) enclosed in a Magnadrive Autoclave at 1400 psi and 110° for 26 h. The crude 4-piperidinols (13·3 g) had δ 2·27, 2·22 (s, NMe), 1·17, 1·12 (d, 2, 6 C–Me) [6·17 resonance of III (3, 5 H) absent]. Oxidation of the 4-piperidinols (13·3 g) in concentrated sulphuric acid (12·5 ml) and water (50 ml) with chromium trioxide (7·6 g) in water (20 ml) gave a product (9·2 g) which was distilled twice to give the *cis* 4-piperidone II, b.p. 95–102°/24 mm (Nazarov & Sorokin, 1960, give 92–100°/17 mm), ν_{max} 1720 cm^{-1}, film (C=O), δ 2·25 (s, NMe) 1·16 (d, *J* 6 Hz, C–Me), 1·0 (low intensity d due to C–Me of *trans* II or 4-piperidinol). It gave a hydrochloride, m.p. 175–176·5° (d.) from acetonitrile–dioxane (Nazarov & Sorokin, 1960, give 159–159·5° from ethyl acetate–methanol) (Found: C, 54·51; H, 9·35; N, 7·84. $C_8H_{16}ClNO$ requires C, 54·08; H, 9·08; N, 7·88%).

Isomeric 4-acetoxy-1,2,6-trimethyl-4-phenylpiperidines(I). *c–t* 1,2,6-trimethyl-4-piperidone (18·3 g) in ether was added to phenyl lithium in ether prepared from lithium (2 g) and bromobenzene (22·4 g) and the product decomposed with acetic anhydride (29 ml) (Casy, Beckett & Armstrong, 1961). The basic residue (23 g), recovered after pouring the reaction mixture on to acetic acid (20 ml) and ice, was acidified with ethanolic hydrogen chloride and the solution diluted with ether. The solid which separated after storage at 5° was t-*2-methyl*-c-*6-methyl*-r-*4-acetoxy-4-phenylpiperidine hydrochloride* (5·6 g), m.p. 198–199° from ethanol–ether (Found: C, 64·44; H, 8·25; N, 4·53. $C_{16}H_{24}ClNO_2$ requires C, 64·54; H, 8·07; N, 4·71%), δ (free base) 2·37 (s, NMe), 2·0 (s, OCOMe), 1·2, 1·07 (d, *J* 6–7 Hz, 2,6–C–Me). The base gave a *hydrobromide*, m.p. 187–188° (Found: C, 56·57; H, 7·02. $C_{16}H_{24}BrNO_2$ requires C, 56·14; H, 7·02%) that was used for X-ray crystallography (Hayakawa & James, 1973), and a *methiodide*, m.p. 245–247° (Found: C, 50·53; H, 6·63; N, 3·60 $C_{17}H_{26}INO_2$ requires C, 50·62; H, 6·45; N, 3·47%). Further crops of the same isomer deposited from the mother liquors. Treatment of the *c*–t 4-piperidone (II) (15·3 g) with phenyl lithium prepared from lithium (2 g) and bromobenzene (22·4 g) gave a mixture of isomeric 4-piperidinols (20 g) corresponding with (I) which partially solidified on storage. The oily component was decanted and the residual solid recrystallized from light petroleum (b.p. 30–60°)—acetone to give t-*2-methyl*-c-*6-methyl-4-phenylpiperidin*-r-*4-ol* (1 g), m.p. 95° (Found: C, 76·91; H, 9·62; N, 6·45. $C_{14}H_{21}NO$ required C, 76·72; H, 9·59; N, 6·39%), δ 3·2 (centre of broad m, 2,6–H), 2·33 (s, NMe), 1·27, 1·05 (d, *J* 6–7 Hz, 2,6 C–Me); (pyridine-d_5) 3·3 (centre of broad m, 2,6–H), 2·4 (s, NMe), 1·5, 1·1 (d, *J* 6–7 Hz, 2,6 C–Me).

The *cis* 4-piperidone (II) (13·4 g) was treated with phenyl lithium, from lithium (1·54 g) and bromobenzene (17·3 g), followed by acetic anhydride (22·4 ml) as usual. The recovered base (19 g) with ethanolic hydrogen chloride gave several crops of

crystals which were mixtures of the *c*- and *t*- 2,6-dimethyl-*r*-4-acetoxypiperidines (II) as hydrochlorides, δ ($CDCl_3$–D_2O) 2·68 (s, NMe), 2·09, 1·87 (s, OCOMe), 1·55 (poorly resolved d, 2,6 C–Me) (in $CDCl_3$ alone the spectrum was more complex because of signals from epimeric conjugate acids); free base 2·29, 2·14 (s, NMe), 2·0, 1·82 (s, OCOMe), 1·15 (centre of 2 closely overlapping d, *J* 6–7 Hz, 2,6 C–Me). The free base (7·4 g) from the mixed hydrochlorides solidified when stirred with light petroleum (bp 30–40°) and was recrystallized from the same solvent and acetone to give t-*2,6-dimethyl-4-phenylpiperidin*-r-*4-ol*, m.p. 129–130°. (Found: C, 77·43; H, 9·61; N, 6·68. $C_{14}H_{21}$-NO requires C, 76·72; H, 9·59; N, 6·39%), δ 2·58 (centre of broad m, 2, 6–H), 2·27 (s, NMe), 1·11 (d, *J* 6–7 Hz, 2,6 C–Me); (pyridine-d_5) 2·96 (centre of m, 2,6–H), 2·3 (s, NMe), 1·12 (d, *J* 6–7 Hz, 2,6 C–Me).

A mixture of the 4-piperidinol (VI) hydrochloride (0·5 g), acetyl chloride (1 ml) and toluene (30 ml) was heated under reflux for 72 h. Next day the solid component was collected and crystallized from ethanol–ether to give t-*2-methyl*-t-*6-methyl*-r-*4-acetoxy-4-phenylpiperidine hydrochloride* (0·28 g), m.p. 203–204° (Found: C, 64·34; H, 8·24; N, 4·95. $C_{16}H_{24}ClNO_2$ requires C, 64·54; H, 8·07; N, 4·71%), ν_{max} 1735 cm^{-1} (ester CO), δ ($CDCl_3$-D_2O) 2·1 (s, OCOMe), 1·58 (d, *J* 6–7 Hz, 2,6 C–Me) (spectrum in $CDCl_3$ alone shows duplicate NMe and C–Me signals due to epimeric conjugate acids); free base 2·29 (s, NMe), 2·02 (s, OCOMe), 1·15 (d, *J* 6–7 Hz, C–Me). Fractionation of the original mother liquors gave more piperidinol base (VI), an ester–piperidinol mixture, and finally c-*2-methyl*-c-*6-methyl*-r-*4-acetoxy-4-phenylpiperidine* (0·83 g), m.p. 97–98° (Found: C, 73·62; H, 8·77; N, 5·67. $C_{16}H_{23}NO_2$ requires C, 73·57; H, 8·81; N, 5·36%), ν_{max} 1735 cm^{-1} (ester CO), δ 2·83 (broad d, *J* 12 Hz, probably equatorial 3,5–H), 2·18 (s, NMe), 1·86 (s, OCOMe), 1·16 (d, *J* 6 Hz, 2,6 C–Me). It gave an *acid succinate*, m.p. 145–150°. (Found: C, 63·19; H, 7·65; N, 3·67. $C_{20}H_{29}NO_6$ requires C, 63·33; H, 7·65; N, 3·69%), ν_{max} 1735, 1710 cm^{-1} (ester and acid CO).

Acknowledgements

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