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Phenolic analogues of diastereoisomeric 2-methyl reversed esters of pethidine

A. F. CASY, G. H. DEWAR, R. A. PASCOE, *School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath, BA2 7AY, UK*

Abstract—The preparation and stereochemical characterization of α- and β-isomers of 1,2-dimethyl-4-*m*-hydroxyphenyl-4-propionyloxypiperidine are described. Both the α (axial 4-aryl/chair) and β (equatorial 4-aryl/chair) isomers were of low potency or inactive in mice antinociceptive tests. Shortcomings of the α-isomer as a model for the 4-arylpiperidine moiety of morphine are discussed.

Proposals that central analgesics of the 4-arylpiperidine class bind to opioid receptors in the axial-4-aryl chair conformation have been discounted for reversed esters of pethidine (*1a*, Ar = Ph, and 3-methyl analogues) on the basis of conformational studies using NMR and computational methods (Jones et al 1973; Froimowitz 1982; Froimowitz & Kollman 1984; Branch & Casy 1988).

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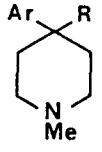

(a) R = OCOEt
(b) R = CO_2Et
(c) R = COEt
(d) R = Me

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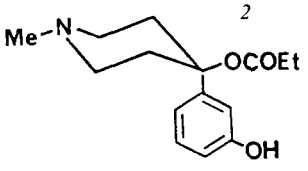

In addition, the activity of such esters is abolished rather than enhanced following insertion of a *meta*-placed phenolic hydroxyl which mimics the placement of the phenolic hydroxyl of morphine in the axial 4-aryl chair *2* (Portoghese et al 1981; Casy & Ogungbamila 1985). However, energy differences between chair invertomers of certain 4-arylpiperidine opioids with C-4 carbon functions are less than those calculated for reversed esters of pethidine (axial 4-aryl chairs are in fact preferred for *1d*) (Froimowitz 1982), while the potencies of pethidine (*1b*, Ar = Ph) and the ketone *1c* (Ar = Ph) are raised when Ar is *m*-hydroxylphenyl (Bergel & Morrison 1948). To ascertain whether the differing structure-activity relationships of C-4-oxygen and C-4-carbon 4-arylpiperidines with regard to phenolic substitution are due to conformational factors or otherwise, the synthesis of the 2-methylpiperidine esters, *3c*, was undertaken.

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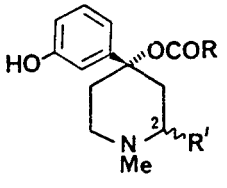

	R	R′
(a)	Me	H
(b)	Et	H
(c)	Et	Me (α and β)

There is chemical and NMR evidence that the β-isomer of 4-piperidinols related to *3c* (Ar = Ph) has a preferred equatorial 4-aryl chair conformation *4* while the corresponding α-isomer favours the 4-aryl chair *5* (Casy & McErlane 1972; Jones et al 1973).

Synthesis and stereochemistry

Sequential treatment of 1,2-dimethyl-4-piperidone with a lithium derivative prepared from the tetrahydropyranyl ether of *m*-bromophenol and butyl lithium, then propionic anhydride gave a diastereoisomeric mixture of the THP ethers of *3c*. The β-isomer separated as a solid propionate salt when the reaction mixture was diluted with ether; the α-isomer was recovered from the mother liquors as its free base. THP ethers were converted to their corresponding phenolic hydrochloridess *3c*, by treatment with excess of ethanolic hydrogen chloride.

Previous NMR evidence of the stereochemistry of related isomeric 1,2-dimethyl-4-phenyl-4-piperidinols was based upon relative ^{13}C chemical shifts of piperidine C-6 and aromatic C-quaternary (Cq) resonance (Jones et al 1973) as well as ^1H shifts of the acyl resonances of derived esters (Casy & McErlane 1972). Thus the similar C-6 chemical shifts of α-*5* (52·8 ppm), β-*4* (52·7 ppm) and the des-2-methyl-4-piperidinol analogue (51·7 ppm) showed that this carbon was not subject to steric polarization by 2-methyl in either isomer hence 2-Me must have an equatorial conformation.

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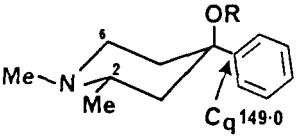
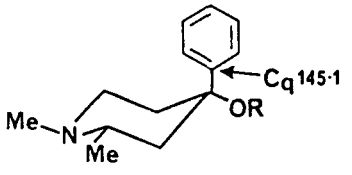


(β, *t* 2-Me, *r* 4-OR)

5



(α, *c* 2-Me, *r* 4-OR)

C-q shifts (shown for 4-piperidinols in *4* and *5*) provided evidence for phenyl conformation axial in the α- and equatorial in the β-isomer. ^{13}C NMR evidence of a similar kind was obtained for the phenolic analogues *3c* which defined the configuration and conformation of the isomeric bases (Table 1). ^1H NMR spectra run at high field (270, 400 MHz) complement the ^{13}C NMR data (Table 2). Thus the α-ester methylene and methyl protons, shielded by axial aryl in *5* (Casy & McErlane 1972), have higher field resonances than the corresponding β-resonances. Certain signals due to protons of the piperidine ring were resolved and have been assigned. The relative resonance positions of the isomeric axial 3-H signals (α lower field) accord with the proximity of axial 3-H to the deshielding acylcarbonyl function in the proposed α-geometry *5* (R = COEt); further, the

Table 1. ^{13}C shifts of 4-acyloxy-1-methyl-4-*m*-hydroxypiperidines [a,b]

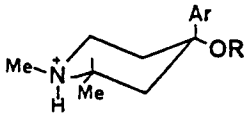
Comp.	C-2	C-3	C-4	C-5	C-6	2-Me	N-Me	C-q[c]
3a	51·2	35·0	79·3	35·0	51·2	—	45·7	145·6, 156·9
3b	51·2	35·0	79·3	35·0	51·2	—	45·7	145·6, 157·1
THP[d] ether of α *3c*	55·6	42·3	80·7	36·5	52·6	19·7	42·3	142·8, 156·8
THP ether of β *3c*	54·4	42·6	80·8	35·1	52·3	20·4	42·6	146·2, 157·2
α*3c*	55·8	42·8	80·5	35·9	52·0	18·9	41·9	142·6, 156·6
β*3c*	53·8	42·9	79·8	33·8	51·2	18·8	41·5	144·9, 155·8

[a] Bases in $CDCl_3$; chemical shifts in ppm (nearest tenth) from TMS. Assignments are based on comparisons with model compounds, established chemical shift parameters and DEPT experiments which reveal orders of protonation.
[b] Signals near 9·2 (Me), 28·0 (CH_2) and 170 (CO) are common to all propionate esters (22·1 Me of acetate).
[c] Aromatic quaternary carbons at positions 1′ (higher field) and 3′ (lower fied).
[d] Tetrahydropyranyl; signals CH_2: 62·1, 30·3, 25·1, 18·9; CH 96·5.

Correspondence to: A. F. Casy, School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK.

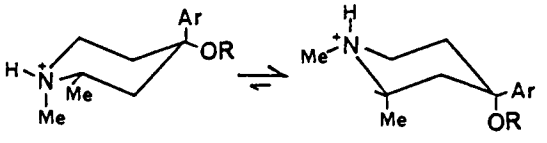
magnitudes of the couplings of these isomeric signals establish that they both arise from an axial proton adjacent to an axial 2-H, equatorial 2-Me system.

The striking feature of the spectrum of α-*3c* hydrochloride in D_2O is that it shows that the salt exists as a mixture of N-protonated epimers with one form predominant. Thus duplicate aryl, N-Me, 2-Me, and acyl (OCOEt) signals were seen together with pairs of ring proton resonances. Piperidine bases with preferred axial-aryl chair conformations often exist as epimeric mixtures when protonated (Casy et al 1970; Casy & McErlane 1972) since non-bonded interactions in the equatorially protonated epimer may be relieved by inversion. Evidence that *6* is the favoured conformation of the major epimer was obtained by observation of the 2-H resonance after irradiation of the major 2-Me signal (multiplet near 3·25 ppm→double doublet 11 and 2·8 Hz.



6

(major epimer)



(minor epimer) *7*

When the minor 2-Me signal as irradiated, the corresponding 2-H signal (m near 3·8 ppm) collapsed to a triplet with small separations showing it to arise from an equatorial proton in a chair or distorted chair conformation (see *7*). No minor epimeric signals could be detected in the spectrum of β-*3c* hydrochloride in D_2O. Magnitudes of separations of resolved equatorial 2-H, axial 2-H and equatorial 3-H signals supported the chair *4*, a solute conformation similar to that of the solid state form of a β-2-methyl-4-phenylacetate analogue established by X-ray crystallography (Fries et al 1982).

Pharmacology and discussion

Details of the antinociceptive activities in mice of RS diastereoisomeric forms of the phenolic propionates *3c* are given in Table 3. Previous data on isomeric 4-phenyl analogues (footnote *b* of Table 3) show that the hot-plate potencies of both α- and β-isomers are much reduced after insertion of a *meta*-hydroxyl in the 4-aryl substituent, while the activities of the isomeric phenols are each of a low order in the tail-flick and writhing procedures. The result for the β-isomer was anticipated since this isomer shares the equatorial 4-aryl chair conformation of the reversed ester of pethidine and its isomeric 3-methyl analogues. However, the fact that the α-phenol *3c* likewise displayed low levels of activity in these tests, in spite of its preference for the axial-aryl chair conformation, indicates that steroic factors thus far investigated are not responsible for the differential binding of C-4-carbon (activity enhanced by phenolic OH) and C-4-oxygen-arylpiperidines (activity depressed by phenolic OH) at opioid

Table 2. ^{1}H Chemical shifts of some 1,2-dimethyl-4-propionyloxy-4-m-hydroxypiperidines[a].

Compound	2-H	3-H	5-H	6-H	2-Me	N-Me	CH_2(acyl)	Me (acyl)	Ar[b]
α *3c*	2·29 unres. m	ax: 2·03 dd (14·3, 11·4) eq: 2·76 unres. m	ax/eq: unres.	ax/eq: unres.	1·16d (6·4)	2·28 s	2·19 q (7·1)	1·0 t (7·1)	7·26–6·67
β *3c*	unres.	ax: 1·73 dd (14·3, 11·4) eq: unres.	ax: 2·01 dt (15·7, 15·7, 3·3) eq: unres.	ax: unres. eq: 2·78 ddd (11·4, 5·7, 2·0)	1·09d (6·0)	2·295	2·30 q (7)	1·05 t (7)	7·10–6·56
α *3c* HCl[c]	3·25 m (dd, 11, 2·8)[d] [3·8 m (t, 3·9, 3·9)][d]	unres.	unres.	unres.	1·37d (6·4) [1·44d (6·4)]	2·77s [2·81s]	2·24 q (7·1) [2·37 q (7·1)]	0·89 t (7·1) [0·98t (7·1)]	5′-H t 7·29 [7·26] 6′-H d 7·1 [6·96] 2′-H t 7·0 [6·86] 4′-H dd 6·85 [6·81]
β *3c* HCl	3·55 overlaps eq 6-H signal	ax 2·05 dd (17,12) eq: 2·72 dd (17,2)	ax: 2·25 ddd (15·7, 14·3, 4·3) eq: overlaps 2·72 signal[e]	ax: 3·40 dt (12·8, 12·8 2·0) eq: 3·5 dd (12·8, 2·0)	1·37d (6)	2·89s	2·41q (7·3)	1·01 t (7·3)	7·3–6·8

[a] Bases in $CDCl_3$, hydrochlorides in D_2O; chemical shifts in ppm from TMS (referred to HDO signal at 4·8 ppm in D_2O); coupling constants or line separations (Hz) in parentheses following chemical shift.

Abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet, plus combinations, e.g., dt doublet of triplets; unres, unresolved. Most data recorded at 400 MHz Assignments based on shielding considerations, spin decoupling experiments and the expectation of large vicinal couplings for axial (ax) and small couplings for equatorial (eq) protons.

[b] Aromatic resonances, details for β *3c* HCl (typical of all): 5′-H 7·26 t (8·0), 6′-H 6·95 broad d (8·3); 2′-H 6·86 narrow t, 4′-H 6·82 dd (8·3,2). Corresponding resonances of minor epimer of α *3c* HCl were close to these values.

[c] Mixture of protonated epimers, data for minor epimer in square brackets.

[d] After irradiation of corresponding 2-Me doublet.

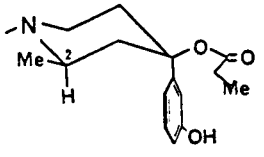
[e] broad d, separation 17 ~Hz.

Table 3. Antinociceptive activities in mice of α- and β-1,2-dimethyl-4-*m*-hydroxyphenyl-4-propionyloxypiperidine hydrochloride[a]

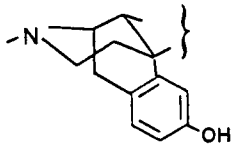
Compound	Hot-plate test	Tail-flick test	Phenylquinone writhing test
α *3c* HCl[b]	0% at 5 50% at 20	32·8 (16·2–66·5)	2·97 (1·22–7·23)
β *3c* HCl[b]	0% at 5 and 20	4% at 1·0 28% at 10·0 31% at 30	3·7 (1·6–8·1)
pethidine HCl	4·1	7·8 (3·0–20·6)	0·8 (0·32–2·2)

[a] ED50 values mg kg^{-1} sc given where measurable.
[b] 4-Phenyl analogues: hot-plate ED50 mg kg^{-1} α, 1.3; β 1.4; pethidine 4·7 (Casy & McErlane 1972).

receptors. An additional consideration may be that α-diastereoisomers of type *5* are inadequate as models of the 4-arylpiperidine moiety of morphine and related polycyclic opioids due to a difference between the mutual orientation of the two rings in these systems. Thus the aromatic ring of *5* is probably at right angles to the mean plane of the piperidine ring in the lowest energy conformer of the axial 4-aryl chair (*8*) (Allinger & Tribble 1971; Hodgson et al 1985), i.e. the two rings bear a relationship orthogonal to that which obtains in the rigid skeleton of morphine (*9*).



(end on view of aromatic ring)



(partial formula)

Similar considerations have been put forward by Loew et al (1987). The fact that α2-H (axial) and acyl methylene and methyl resonance lie at higher field than the corresponding β-signals of the isomers *3c* (Table 2) provides ^{1}H NMR evidence in support of an α-conformation of type *8* which places all these protons within the aromatic shielding zone.

Preparative work

Melting points are uncorrected. ^{13}C NMR spectra were recorded at 67·8 MHz using a Jeol GX270 MHz NMR spectrometer. The number of protons attached to carbons were established from DEPT experiments. ^{1}H NMR spectra were recorded on Jeol GX270 and 400 MHz spectrometers. Details are included in the Tables 1 and 2.

α- and β-1,2-Dimethyl-4-propionyloxy-m-(2-tetrahydropyranyloxy)phenylpiperidine and corresponding free phenols (3c). *n*-Butyl lithium (6·5 g) in hexane (10 mL) was added (20 min) to the tetrahydropyranyl (THP) ether of *m*-bromophenol (20 g) (Casy & Ogungbamila 1985) in tetrahydrofuran (100 mL) under N_2 at −55°C. The mixture was stirred (2 h −50°C) then 1,2-dimethyl-4-piperidone (10 g) in tetrahydrofuran added dropwise at −45°C. After stirring (1 h at 25°C), propionic anhydride (15 g) in tetrahydrofuran (30 mL) was added. After stirring (3 h), excess ether was added to the mixture and the solid which precipitated collected by filtration. The solid was dissolved in ethanol, diluted with ether, filtered (to remove inorganic material) and the filtrate evaporated. The residual solid was crystallized from acetone to yield *β-1,2-dimethyl-4-propionyloxyl-4-m-(2-tetrahydropyranyloxy)phenylpiperidine* as the *propionate* salt (6·4 g) m.p. 270°C (Found: C, 66·3; H, 8·3; N, 2·9.$C_{24}H_{37}NO_6$ requires C,66·2; H, 8·5; N, 3·2%) ^{13}C NMR, Table 1. The base recovered by ether extraction of the original mother liquors (after concentration and treatment with ice-NH_3) was crystallized from light petroleum (b.p. 60–80°C) to give the *α-isomer* (free base) (4·1 g) m.p. 128°C (Found: C, 69·6; H, 8·8; N, 4·2. $C_{21}H_{31}NO_4$ requires C,69·8; H, 8·6; N, 3·9%) ^{13}C NMR Table 1. The α-THP ether (4 g) in ethanol was treated with excess of ethanolic-HCl and the mixture concentrated. Crystallization from acetone gave *α-3c hydrochloride* (0·82 g) m.p. 165°C (Found: C, 58·4; H, 7·4; N, 4·0.C_{16} H_{24} NO_3Cl. H_2 requires C, 57·9; H, 7·8; N, 4·2%). The *β-3c hydrochloride* m.p. 264°C was similarly prepared (Found: C, 61·0; H, 7·7; N, 4·2. C_{16} H_{24} NO_3Cl requires C, 61·2; H, 7·7; N, 4·5%) ^{13}C NMR Table 1, ^{1}H NMR Table 2.

The des-2-methyl esters *3a*, *hydrochloride* m.p. 203°C, from ethanol (Found: C, 58·8; H, 7·1; N, 5·0.C_{14} $H_{20}NO_3Cl$ requires C, 58·8; H, 7·0; N, 4·9%) and *3b*, hydrochloride m.p. 204°C (Casy & Ogunbamila 1985 report m.p. 205–206°C) were similarly prepared using 1-methyl-4-piperidone and the appropriate acid anhydride (^{13}C NMR Table 1).

We thank Dr A. E. Jacobson (NIH, Bethesda) for the hot-plate data, Drs M. Aceto and L.S. Harris (Medical College of Virginia, Richmond) for the tail-flick and phenylquinone writhing data, and Mr R Hartell for skilled technical assistance.

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