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COMMUNICATIONS

Phenolic analogues of reversed esters of pethidine

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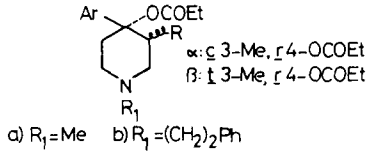
The preparation and stereochemical characterization of phenolic analogues of the reversed ester of pethidine, α- and β-prodine and a 1-phenethyl congener are described. All the compounds were weakly active or inactive as agonists in rodent antinociceptive tests and failed to antagonize fentanyl in rats. The results substantiate the view that the morphine and 4-phenylpiperidine groups of analgesics differ in their modes of interaction with opiate receptors, except possibly when the piperidine derivative carries a C-4 carbon substituent.

Introduction of *m*-hydroxyl into the phenyl substitutent of a 4-phenylpiperidine analgesic should enhance its activity if it interacts with opiate receptors in a similar manner to that of morphine and related polycyclic derivatives for which the presence of a free phenolic group is mandatory if high levels of activity are to be displayed (Reden et al 1979). Such is the case when C-4 carbon substituents are present, for example, ethoxycarbonyl (in pethidine), propionyl (in bemidone) and lower alkyl (Beckett & Casy 1962; McElvain & Clemens 1958). Data for some reversed ester analogues of pethidine, all of which carry the C-4 oxygen substituent propionyloxy (OCOEt) are now presented in extension of an earlier report (Casy & Ogungbamila, 1983).

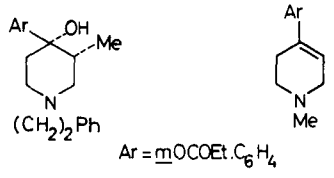
Chemistry

The phenolic esters **1** were made by treating the appropriate 4-piperidone with a Grignard reagent formed from *m*-hydroxybromobenzene with its phenolic function protected by etherification with dihydropyran.



1

Decomposition of the resultant complexes with propionic anhydride followed by ethanolic hydrogen chloride gave the free phenols **1** directly as hydrochloride salts. When 1-phenethyl-3-methyl-4-piperidone was used, a mixture of the 4-propionate **1b** and corresponding 4-piperidinol resulted. Treatment of the 4-piperidinol with propionic anhydride-pyridine gave a product **2** acylated at the phenolic function after a 3 h reaction period, while a longer reaction time produced the desired ester **1b**. The ^{13}C chemical shift of the C-4 carbon was a valuable aid to the characterization of the reaction products since piperidinol carbon resonances shift to lower field by about 10 ppm after acylation (Jones et al 1973). The 4-piperidinol derived from 1-methyl-4-piperidone gave the tetrahydropyridine **3** after treatment with propionyl chloride and toluene at the reflux temperature.



2 **3**

Use of 1,3-dimethyl-4-piperidone led to a mixture of diastereoisomeric esters **1a** (R=Me) in the approximate ratio 18 : 1 (from 3-Me ^1H nmr integrals). The major (α) isomer was isolated by fractional crystallization of the hydrochloride salts while the minor (β) form was obtained by crystallization involving malate salts. The stereochemistry of the products (see **1**) was established from their ^{13}C nmr characteristics (also used to monitor isomeric separation), notably those of the 3-Me and C-5 shifts (Table 1). The single 1-phenethyl-3-methyl ester **1b** (R=Me) also proved to have the *c*-3-Me,*r*-4-OCOEt configuration. Treatment of 1,3-dimethyl-4-piperidone with lithium *m*-methoxyphenyl followed by propionic anhydride gave a mixture of the corresponding 4-*m*-methoxyphenyl analogues of α-prodine (α-**1a**,R=Me, Ar=*m*-MeO.C_6H_4) and α-prodinol.

* Correspondence.

Table 1. ^{13}C Chemical shifts of phenolic analogues of reversed esters of pethidine and related compounds.[a,b]

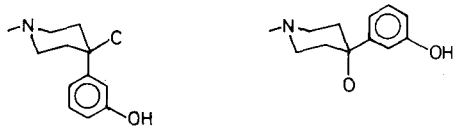
Item	Compound	C-2	C-3	C-4	C-5	C-6	1-Me	3-Me	C-q[c]
1	**1a** (R=H)	51·6	35·6	79·7	35·6	51·6	45·9	—	146·0, 157·4
2	α**1a** (R=Me)	58·9	42·1	83·3	32·3	51·2	45·7	12·6	143·2, 156·9
3	β**1a** (R=Me)	58·0	40·6	82·7	26·1[d]	51·6	46·4	15·1[e]	145·1, 157·2
4	α**1b** (R=Me)	57·1	42·5	83·9	32·9	49·2	60.0, 33·6[f]	12·4	143·8, 157·2
5	**3** HCl	51·6	116·5[g]	134·2[g]	24·2	50·2	42·3	—	139·9, 151·1
6	4-piperidinol corresponding to α**1b** (R=Me)	56·6	40 3	73·0	39·5	49·2	63·0, 33·3[f]	12·5	150·1, 157·0
7	**2**	57·1	40·9	74·0[h]	39·7	49·6	60·5, 34·0[f]	12·4	149·8, 151·4
8	3′-Methoxy analogue of α**1a** (R=Me)	59·2	42·7	83·2	32·8	51·3	46·0	12·7	143·6, 159·5[i]
9	**1a** (R=H) HCl in D_2O	50·7	32·9	77·5	32·9	50·7	43·5	—	145·2, 157·5

[a] Bases in $CDCl_3$ unless otherwise stated; chemical shifts in ppm (nearest tenth) from TMS. Assignments are based on comparisons with model compounds, established chemical shift parameters and off-resonance decoupled spectra.
[b] Signals near 9·2, 28·7 and 172·5 ppm are common to all propionate esters and due to Me, CH_2 and CO respectively.
[c] Aromatic quaternary carbons at position 3′ (lower field) and 1′; the 3′ resonance moves up field when the phenolic group is acylated (cf 3′-C of items 6 and 7).
[d] The higher field position of this resonance relative to those of C-5 items 1 and 2 is evidence that this carbon is subject to steric polarization by an axial substituent at C-3 (Casy et al 1981).
[e] The lower field position of the β-relative to the α-Me (item 2) is evidence that the former has an axial conformation (Casy et al 1981).
[f] Methylene carbons of 1-phenethyl side chain.
[g] Alkenic carbon.
[h] Chemical shift typical of 4-piperidinol (cf C-4 of item 4).
[i] 55·0 ppm (OMe).

Pharmacology and discussion

In rats the four phenols **1a** (R=H, α-Me, and β-Me) and **1b** (R=α-Me) were inactive either as agonists (tail-withdrawal test) or antagonists of fentanyl (Iorio & Casy 1978); dose levels of 2·5 mg kg^{-1} (also 10 mg kg^{-1} for α-**1a**, R=Me) by the i.v. route were employed. The phenolic analogue of α-prodine (**1a**, R=α-Me) also proved of a low activity in mice by the hot-plate test (ED50 16·9 mg kg^{-1}, cf. pethidine 4·1 mg kg^{-1}) and was less active than the corresponding 3-methoxyphenyl derivative (ED50 10·7 mg kg^{-1}), in sharp contrast with the activity rankings of OH–OMe pairs in the morphine group. The 4-phenyl analogues of these phenols have potencies equal to or greater than that of morphine in antinociceptive tests (Beckett & Casy 1962). Similar results were reported for phenolic analogues of 3-allylprodines (Portoghese et al 1981) although an uncharacterized β-prodine analogue (**1a**, R=β-Me) was claimed to be a weak antagonist of morphine in mice (Zimmerman et al 1978).

The results suggest that phenolic groups radically disrupt binding of reversed ester ligands **1** to opiate receptors even when the activity-enhancing 1-phenethyl or 3-α-allyl groups are present. Hence the view that analgesics of this class do not mimic morphine in their receptor interactions, previously indicated by the fact that 1-allyl and 1-cyclopropylmethyl congeners are opiate agonists rather than antagonists (Casy et al 1968), is supported. Differing influences of phenolic hydroxy on activities of the esters **1** and piperidines with C-4 carbon substituents may be related to conformation factors. Energy calculations for pethidine and ketobemidone reveal little difference between axial and equatorial 4-phenyl chairs while the axial phenyl conformation is preferred for 1,4-dimethyl-4-phenylpiperidine; in contrast equatorial 4-phenyl conformers are the lower energy species for all C-4 OCOEt derivatives (Froimowitz 1982). Phenolic hydroxyl would thus be expected to enhance activity of C-4 carbon piperidines which may mimic morphine sterically (**4**), but not piperidines



(partial formulae)

4 **5**

with C-4 oxygen functions which position the aryl group in a markedly different manner (**5**).

The possibility of activity differences between reversed esters of pethidine and their phenolic congeners being due to a greater liability of the latter derivatives to hydrolysis, was discounted by the result of monitoring over 6 days the ^{13}C nmr spectrum of **1a** (R=H) as a solute in D_2O; the spectrum of a freshly prepared solution displayed the requisite 13 resonances (Table 1, item 9) and was unchanged over the period of observation.

Preparative work

Melting points are uncorrected. Proton noise and off-resonance ^{13}C nmr spectra were recorded on JEOL X 90Q spectrometer operating at 22·5 MHz under conditions described elsewhere (Casy et al 1981).

4-*m*-Hydroxyphenyl-1-methyl-4-propionyloxypiperidine (**1a**, R=H). Minor modification of a reported procedure (Lednicer et al 1981) gave the tetrahydropyranyl (THP) ether of *m*-bromophenol as a solid m.p. 39–40 °C from hexane (Found: C, 51·51; H, 5·26. $C_{11}H_{13}O_2Br$ requires C, 51·38; H, 5·06%). A Grignard reagent prepared from the same THP ether (20 g), magnesium (2·1 g) and tetrahydrofuran (THF) (50 ml) (reaction initiated by addition of a few crystals of iodine and/or warming to 45 °C) was treated dropwise with 1-methyl-4-piperidone (8·8 g) in THF and the mixture stirred for 3 h. Propionic anhydride (11·9 g) in THF was added to the mixture which, after being stirred for 1 h, was poured on ice-aqueous ammonium chloride. The base (19·1 g), isolated from an ethereal extract of the mixture, was treated with ethanolic hydrogen chloride to give **1a** (R=H) *hydrochloride* (12·5 g), m.p. 205–206 °C from methanol (Portoghese et al 1981 report m.p. 196–198 °C for hemihydrate prepared by a different method) (Found: C, 60·45; H, 7·4; N, 4·64. Calc. for $C_{15}H_{22}NO_3Cl$: C, 60·09; H, 7·39; N, 4·67%) (^{13}C nmr, Table 1 item 1).

Treatment of the THP ether of 1-methyl-4-*m*-hydroxyphenyl-4-piperidinol with propionyl chloride and toluene at the reflux temperature (Casy et al 1982) gave the *tetrahydropyridine* **3** *hydrochloride*, m.p. 130–131 °C (Found: C, 60·85; H, 7·29; N, 4·72. $C_{15}H_{20}NO_2Cl.H_2O$ requires C, 60·39; H, 7·38; N, 4·67%) (^{13}C nmr, Table 1 item 5) ν_{max} 1765 cm^{-1}.

4-m-Hydroxyphenyl-1,3-dimethyl-4-propionyloxypiperidines (**1a**, R=Me) *and related compounds.* A similar Grignard reaction of 1,3-dimethyl-4-piperidone (12·5 g) gave an impure mixture of isomeric THP ethers of **1a** (R=Me) (24·8 g). Fractional crystallization of the base after acidification with ethanolic hydrogen chloride gave α-**1a** (R=Me) *hydrochloride* (8·6 g), m.p. 168–170 °C from ethanol–ether (Found: C, 60·8; H, 7·55; N, 4·4. $C_{16}H_{24}NO_3Cl$ requires C, 61·2; H, 7·7; N, 4·4%). Free base (6·8 g) recovered from the mother liquors was acidified with malic acid in acetone and the solid which separated (mainly the α-malate) collected. Free base from the filtrate gave β-**1a** (R=Me) *hydrochloride* (0·95 g), m.p. 206–207 °C (Found: C, 61·33; H, 7·78; N, 4·31%) ^{13}C nmr, Table 1 items 2(α) and 3(β).

Treatment of 3-methyl-1-phenethyl-4-piperidone (18 g) with the same Grignard reagent followed by propionic anhydride (39 g) gave a basic product which after acidification with ethanolic hydrogen chloride gave α-**1b** (R=Me) *hydrochloride* (10·2 g), m.p. 204–205 °C (Found: C, 68·65; H, 7·3; N, 3·43. $C_{23}H_{30}NO_3Cl$ requires C, 68·38; H, 7·48; N, 3·46%) (^{13}C nmr, Table 1 item 4). The corresponding 4-piperidionol (2 g) (^{13}C nmr, Table 1 item 6), isolated from the aqueous phase of the reaction mixture, was heated under reflux with propionic anhydride (3 g) and pyridine (15 ml) for 3 h. Solvents were removed under reduced pressure and the product acidified with ethanolic hydrogen chloride and crystallized to give the *4-(3-propionyloxyphenyl)-4-piperidinol* **2** *hydrochloride*, m.p. 254–255 °C (Found : C, 68·51; H, 7·73; N, 3·49. $C_{23}H_{30}NO_3Cl$ requires C, 68·38; H, 7·48; N, 3·46%), ν_{max} 1790 cm^{-1}, (^{13}C nmr, Table 1 item 7). The same procedure prolonged to a 12 h reflux period resulted in isolation of a product identical with the α-ester **1b** (R=Me) hydrochloride described above with ν_{max} 1726 cm^{-1}.

Treatment of 1,3-dimethyl-4-piperidone (23 g) with lithium *m*-methoxyphenyl, from 3-bromoanisole (56 g) in THF (180 ml) and a slight excess of lithium butyl (1·45 M in hexane), followed by propionic anhydride (15 g) gave a mixture of the corresponding 4-piperidinol and 4-propionate from which the latter was isolated as the α-*hydrochloride,* m.p. 171–172 °C (Found: C, 61·86; H, 8·0; N, 4·22; Cl, 10·99. $C_{17}H_{26}NO_3Cl$ requires C, 62·28; H, 7·99; N, 4·27; Cl, 10·81%) (Table 1 item 8).

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