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Opioid Properties of Some Derivatives of Pethidine Based on Tropane

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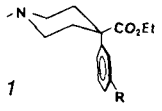
Abstract—The preparation of some tropane analogues of pethidine and its reversed ester, chiefly with preferred 3α-*m*-hydroxyphenyl chair conformations, is described. The former were secured from tropan-3-one in a sequence of reactions involving cyanide attack, hydrolysis, Grignard attack and then rearrangements. The reversed ester was obtained by treating tropan-3-one with lithium phenyl, followed by acylation. Configurational and conformational assignments follow from NMR analysis. The antinociceptive potencies of these compounds in mice are reported, and discussed in relation to non-phenolic congeners and the 4-arylpiperidine moiety of morphine.

This paper reports the synthesis and pharmacological evaluation of some tropane analogues of pethidine to study the influence of *m*-hydroxylation on opioid ligands of the 4-arylpiperidine class which show preference for axial-aryl chair conformations (*1*) (Casy 1989; Casy et al 1989).



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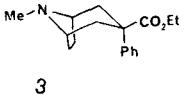

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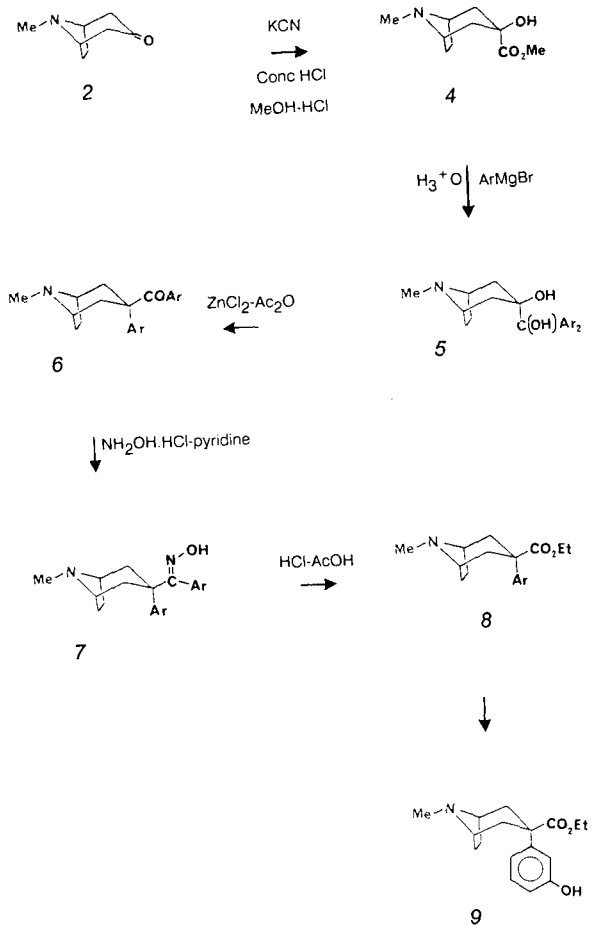
Chemistry

Chemistry

Bell & Archer (1960) described the conversion of 3-tropanone (*2*) to the α-phenyltropane analogue of pethidine (*3*) by a multistep route which was subsequently re-investigated with provision of spectroscopic evidence of stereochemistry (Casy & Coates 1974). Repetition of the procedure, using a Grignard reagent derived from 3-bromoanisole and magnesium, led successfully to the α-aryl-β-carboethoxyl derivative (*8*) as detailed in Scheme 1. The intermediate *8* was *O*-demethylated with boron tribromide

a R = H
b R = propyl
c R = CH_2-cC_3H_5
d R = ethylphenyl

to give the free phenol (*9*) and *N*-demethylated with 2,2,2-trichloroethylchloroformate to give the *sec*-amine *10*a(Ar = *m*-hydroxyphenyl). Alkylation of *10a* by standard methods gave the *t*-amines, *10b–d*, subsequently *O*-demethylated in poor yield. The ^{1}H NMR features of *9* were similar to those of the non-phenolic analogue *3* (HCl salts in D_2O) in



2 *4* *6* *5* *7* *8* *9*

SCHEME 1

respect of width of the 1(*5*) signal which was narrow and of a magnitude (W1/2 = 8 Hz), indicative of a preferred chair rather than boat conformation (Casy & Coates 1974). In accord, 2(*4*) H signals displayed no large ^{3}J coupling values, while 6(*7*) resonances were well separated at 270 MHz (2

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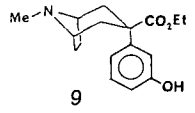

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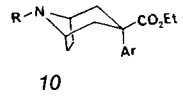

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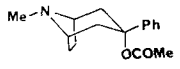
multiplets, $\Delta\ \delta$ 0·33) indicative of the shielding influence of the 3α-aryl substituent. The *m*-methoxyphenyl substitution pattern of the aromatic protons was retained during the rearrangement step (*5*–*6*).



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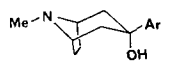

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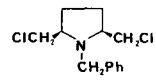

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The β-phenyl derivative, *11*, an analogue of the reversed ester of pethidine, was obtained by treating 3-tropanone

Ar = *m*-methoxyphenyl

with lithium phenyl followed by acetic anhydride. No α-epimer could be detected. The configuration *11* followed from knowledge of the geometry of the parent *t*-alcohol (Casy & Coates 1974) and dimensions of its 1(5)H NMR resonance (W1/2 = 9·9 Hz). The *t*-alcohol, *12*, similarly prepared stereospecifically from 3-tropanone, proved resistant to esterification as did also its lithium complex. Attempts to obtain the α-phenyl analogue of *11* by oxidative acetylation of 3-α-phenyl-*N*-methyltropane were unsuccessful. Daum et al (1975) obtained the pethidine analogue (*3*) in both forms by condensing benzylcyanide with the pyrrolidine, *13*, and subsequent elaboration. In our hands all attempts to cyclize *13* with *m*-methoxybenzylcyanide failed; the iodo analogue of *13* was similarly unreactive.

Preparative work

Melting points are uncorrected. ^{13}C NMR spectra were recorded at 67·8 MHz using a Joel GX 270 MHz NMR spectrometer. The number of protons associated with each carbon atom was established from DEPT experiments. ^{1}H NMR spectra were also recorded on a Joel GX 270 spectrometer. Abbreviations for data quoted are: d, doublet; t, triplet; q, quartet; m, multiplet; W1/2 width at half maximum height. Mass spectra were measured on a VG Micromass 7070E Mass Spectrometer operating at 70 eV (EI). IR spectra, recorded for liquids as films and for solids as KBr discs or nujol mulls, were obtained using a Unicam SP 1025 spectrometer. Routine spectroscopic and MS data, consistent with structure in all cases, are not quoted and may be obtained from the authors on request. Elemental analyses were carried out by Butterworth Laboratories Ltd, Middlesex, UK (Table 1). Dry solvents were used throughout. Hydrochloride salts were obtained by treating bases with excess of HCl in ethanol or ether.

*3α-Bis(*m*-methoxyphenyl)hydroxymethyl-3β-tropanol* (5)

α-Ecgonine methyl ester (*4*, 8·0 g) was heated under reflux for 90 min with the Grignard reagent prepared from 3-bromoanisole (56·8 g) and magnesium (8·0 g) in tetrahydrofuran (200 mL). The mixture was stirred at room temperature (21°C) overnight, and then poured onto ice and acetic acid (50 mL) and extracted with ether (3 × 75 mL). The aqueous phase was made basic with NH_3 solution and extracted with $CHCl_3$ (3 × 100 mL), and the combined extracts were washed, dried over $MgSO_4$ and evaporated to give the diol 5 (13·8 g; 90%) as a light yellow oil, characterized as a hydrochloride mp 239–241°C on recrystallization from acetone.

*3α-*m*-Methoxyphenyl-3β-tropanyl-*m*-methoxyphenyl ketoxime* (7)

A suspension of the diol 5 HCl (10 g) and fused powdered $ZnCl_2$ (30 g) in acetic anhydride (30 mL) was stirred for 24 h at room temperature (solution was complete within 40 min). The solution was poured into NaOH solution (15%, 400 mL) and extracted with $CHCl_3$ (3 × 100 mL); the dried extract was evaporated to give the impure ketone *6* (7·5 g, 86%) as a dark brown oil. A mixture of *6* (10 g), hydroxylamine hydrochloride (8 g), pyridine (50 mL) and propan-1-ol (200 mL) was heated under reflux for 16 h. The solid which separated on cooling was collected and recrystallized from water to give the oxime *7* hydrochloride (4·2 g, 37%), mp 280–282°C.

Table 1. Microanalytical data for tropane analogues of pethidine.

		Required			Found		
Compound	Formula	C	H	N	C	H	N
5 HCl	$C_{23}H_{30}NO_4Cl$	65·8	7·2	3·3	65·8	7·4	3·2
7 HCl	$C_{23}H_{29}N_2O_3Cl,H_2O$	63·5	7·1	6·4	63·0	7·2	6·4
8 HCl[a]	$C_{16}H_{22}NO_3Cl$	61·6	7·1	4·5	61·5	7·4	4·2
8 HCl	$C_{18}H_{26}NO_3Cl,H_2O$	60·7	7·6	3·9	61·0	8·0	3·8
9 HCl	$C_{17}H_{24}NO_3Cl$	62·7	7·4	4·3	62·9	7·6	4·2
10a HCl[b]	$C_{17}H_{24}NO_3Cl$	62·7	7·4	4·3	62·8	7·6	4·1
10c HCl[b]	$C_{21}H_{30}NO_3Cl$	66·4	7·9	3·7	66·7	7·8	3·7
10c HCl[c]	$C_{20}H_{28}NO_3Cl$	65·7	7·7	3·8	66·1	7·3	3·8
10b HCl[b]	$C_{20}H_{28}NO_3Cl$	65·7	7·7	3·8	65·5	7·5	3·8
10b HCl[c]	$C_{19}H_{26}NO_3Cl$	64·9	7·4	4·0	64·6	7·2	3·8
10d HCl[b]	$C_{25}H_{32}NO_3Cl$	69·8	7·5	3·3	70·0	7·3	3·0
10d HCl[c]	$C_{24}H_{30}NO_3Cl$	69·3	7·2	3·4	69·0	7·0	3·5
11 HCl	$C_{16}H_{22}NO_2Cl,H_2O$	61·3	7·7	4·5	60·5	7·6	4·7
12 base[b]	$C_{15}H_{21}NO_2$	72·9	8·5	5·7	72·8	8·7	5·5
12 HCl[c]	$C_{14}H_{20}NO_2Cl$	62·3	7·4	5·2	62·5	7·5	5·1

[a] ($CO_2C_2H_5$ replaced by CO_2H). [b] Ar = *m*-$CH_3OC_6H_4$. [c] Ar = *m*-OHC_6H_4.

3α-m-Methoxyphenyl-3β-tropane carboxylic acid and corresponding ethyl ester (8)
Dry HCl was passed into a suspension of the oxime 7 HCl (10 g) in glacial acetic acid (100 mL). After a few min, complete solution occurred and the whole was heated on a steam bath for 2 h while HCl was slowly passed through the solution. The product was evaporated in-vacuo and the residue boiled with acetone to yield the amino acid *8* ($CO_2C_2H_5$ replaced by CO_2H) hydrochloride (3·6 g, 48%), mp 210°C recrystallized from methanol-ether. A solution of this product (10 g) in absolute ethanol (200 mL) was saturated with dry HCl and heated under reflux for 24 h. Removal of solvent gave the ethyl ester *8* hydrochloride monohydrate (6·3 g, 58%), mp 135°C recrystallized from ethanol-ether.

Ethyl 3α-m-hydroxyphenyl-3β-tropane carboxylate (9)
Boron tribromide in CH_2Cl_2 (1·0 M, 10 mL) was added to a solution of the *O*-methyl derivative *8* (base, 1·0 g) in $CHCl_3$ (5 mL). The mixture was stirred for 2 h at room temperature and then poured onto NH_3-ice. The free phenol, 9, isolated via a $CHCl_3$ extract, formed a hydrochloride (0·45 g, 41%), mp 208–209°C.

Ethyl 3α-m-methoxyphenyl-3β-nortropane carboxylate (10a, *Ar* = m-$OCH_3C_6H_4$)
A mixture of the *N*-methyltropane *9* (base, 5·0 g), trichloroethylchloroformate (6·0 g), anhydrous K_2CO_3 (2·0 g) and dry toluene (100 mL) was heated under reflux for 2 days, cooled and diluted with ether (200 mL). The solution was washed with NaOH solution (5 M, 2 × 80 mL) and then with water (3 × 50 mL), and the organic layer separated, dried over $MgSO_4$ and evaporated. The residual gum solidified after removal of volatile reagents in-vacuo; it was dissolved in acetic acid (90%, 150 mL) and the solution stirred with powdered zinc (1·5 g) at room temperature for 16 h. The mixture was made basic with NH_3 solution and extracted with $CHCl_3$ (4 × 250 mL). The washed extracts were dried over $MgSO_4$ and evaporated to yield the nortropane 10a (Ar = *m*-OHC_6H_4), isolated as a hydrochloride (3·2 g, 60%), mp 201–204°C recrystallized from ethanol.

Ethyl N-cyclopropylmethyl-3α-m-methoxyphenyl-3β-nortropane carboxylate (10c, *Ar* = m-$CH_3OC_6H_4$)
A mixture of the nor-ester *10a* (Ar = *m*-$CH_3OC_6H_4$) (1·5 g), cyclopropylmethyl bromide (1·8 g), K_2CO_3 (2·9 g) and ethanol (90 mL) was heated under reflux for 2 days, cooled and diluted with ether (200 mL). Solid material was removed by filtration and the filtrate washed, dried over $MgSO_4$ and evaporated to give *10b* (Ar = *m*-$CH_3OC_6H_4$); this solid formed a hydrochloride (1·1 g, 56%), mp 184–185°C recrystallized from acetone. The corresponding free phenol 10c (Ar = OHC_6H_4), obtained by the *O*-demethylation procedure described above for the conversion of *8* to *9*, was isolated in low yield (66 mg from 0·8 g of methoxy derivative) as a hydrochloride, mp 238°C recrystallized from ethanol.

Ethyl N-allyl-3α-m-methoxyphenyl-3β-nortropane carboxylate (10b, *Ar* = m-$CH_3OC_6H_4$)
A mixture of the nor-ester *10a* (Ar = *m*-$CH_3OC_6H_4$) (1·5 g), allyl bromide (1·3 g), K_2CO_3 (2·9 g) and ethanol (90 mL) was treated as described above for the synthesis of *10c* (Ar = *m*-$CH_3OC_6H_4$), to give the corresponding *N*-allyl ester hydrochloride (0·7 g, 37%), mp 175°C recrystallized from acetone. The *O*-demethylated product *10c* (Ar = *m*-OHC_6H_4) (52 mg from 0·6 g precursor) formed a hydrochloride, mp 199–201°C recrystallized from ethanol.

Ethyl N-phenethyl-3α-methoxyphenyl-3β-nortropane carboxylate (10d, *Ar* = m-$CH_3OC_6H_4$)
N-Alkylation of the nor-ester *10a* (Ar = *m*-$CH_3OC_6H_4$) (1·5 g) with phenethyl bromide (1·4 g) by the usual method gave the corresponding *N*-phenethyl ester hydrochloride (1·2 g), mp 194°C recrystallized from acetone, itself converted by the BBr_3 procedure to the free phenol *10d* (Ar = *m*-OHC_6H_4) hydrochloride (113 mg from 0·6 g precursor), mp 214–215°C recrystallized from ethanol.

3α-Acetoxy-3β-phenyltropane (11)
Tropan-3-one (10 g) in ether (50 mL) was added to lithium phenyl, prepared from bromobenzene (46 g) and lithium (2·2 g) in ether (100 mL), and the mixture stirred overnight, followed by heating under reflux for 1 h. The cooled mixture was treated with acetic anhydride (50 mL), stirred for 5 h and then poured onto ice–acetic acid (50 mL). The aqueous phase was separated, washed with ether and then extracted with $CHCl_3$ after basification with K_2CO_3. The extract was dried over $MgSO_4$ and evaporated to yield the oily acetoxy ester *11*, isolated as a hydrochloride monohydrate (9·3 g, 44%), mp 198°C.

3α-Hydroxy-3β-m-methoxyphenyltropane (12, *Ar* = m-$CH_3OC_6H_4$)
n-Butyl lithium (7·7 g) in hexane was added to 3-bromoanisole (22·4 g) in tetrahydrofuran (100 mL) under N_2 at −55°C. The mixture was stirred at −50°C for 2 h, and then tropan-3-one (10 g) was added. After a further period of stirring (−45°C for 30 min, then 25°C for 1 h) the mixture was cooled to −10°C and then quenched with ice-water. The product was acidified with 6 M HCl and extracted with ether (3 × 100 mL). The aqueous phase was separated, made basic with 5 M NaOH and extracted with ether (3 × 100 mL). The ether extract was washed, dried over $MgSO_4$ and evaporated to leave a yellow oil from which the *t*-alcohol 12, mp 125–126°C, separated (5·4 g, 30%) following addition of ether (50 mL).

The corresponding free phenol *12* (Ar = *m*-$OHCC_6H_4$) was obtained by treating tropan-3-one with the lithium salt of the tetrahydropyranyl ether of *m*-bromophenol as in work on piperidine analogues (Casy et al 1989); it formed a hydrochloride, mp 254°C recrystallized from ethanol.

Pharmacology Results and Discussion

The pharmacological data was prepared by Dr A. E. Jacobson at the National Institutes of Health (Bethesda, MD, USA). Antinociceptive potency data in mice for five of our tropanes, together with two standard opioids, are given in Table 2. Tests applied were the tail-flick (TF) and *p*-phenylquinone-induced abdominal constriction (PPQ) procedures (see footnotes to Table 2). The phenolic analogue, *9*, proved far less effective than its non-phenolic parent, *3*, in both TF (no ED50 value could be measured) and PPQ (one-ninth as active) procedures; its *O*-methyl precursor, *8*, unexpectedly retained almost half the potency of the α-phenyl derivative in both tests. The enhanced activity of the

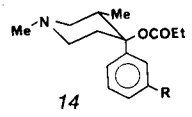
Table 2. Biological activity data in mice, for tropane analogues of pethidine.

Compound	Mouse tail-flick[a,b] ED50 (mg kg^{-1} subcutaneous)	Phenylquinone abdominal constriction test[b] ED50 (mg kg^{-1} subcutaneous)
3 HCl 3α-Ph	4·0 (3·6–4·3)	0·5 (0·2–1·7)
8 HCl 3α-*m*-$CH_3OC_6H_4$	9·8 (6·0–16·0)	1·1 (0·2–5·1)
9 HCl 3α-*m*-OHC_6H_4	11% at 30	4·5 (1·0–19·3)
10b HCl 3α-*m*-OHC_6H_4	—	7·7 (2·3–26·2)
10d HCl 3α-*m*-OHC_6H_4	2·5 (1·2–5·2)	1·0 (0·5–2·0)
Morphine SO_4^{2-}	5·8 (5·7–5·9)	0·23 (0·20–0·25)
Pethidine HCl	7·8 (3·0–20·6)	0·8 (0·3–2·2)

[a] Dewey et al (1970). [b] All the tropanes failed to block the antinociceptive actions of morphine in the tail-flick test (Harris & Pierson 1964). [c] Hendershot & Forsaith (1959).

phenol *10*d (Ar = *m*-methoxyphenyl), in the TF assay (1·6 times that of 3) may be attributed to the well-known advantageous effect of replacing *N*-methyl by *N*-phenethyl in many classes of opioid (Janssen & Eddy 1960; Casy & Parfitt 1986). The *N*-allyl congener *10b* (Ar = *m*-OHC_6H_4) failed to antagonize morphine in the TF test (as did all other tropanes examined) and behaved as a weak agonist in the PPQ procedure (one-fifteenth as potent as *3*).

The failure of a *m*-hydroxyl group to elevate the potency of the pethidine analogue *3* was also observed in the case of the α-2-methyl reversed ester *14*, in which an axial aryl-chair is



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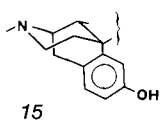
likewise of significant population (Casy et al 1989). These results indicate that receptor interactions of phenolic hydroxyl in rigid opioids such as morphine differ from those of the 4-arylpiperidine and 3-aryltropane class even when their overall geometries are similar. The relative orientations of the saturated heterocyclic and aromatic ring planes in opiates (Ar plane approximately coplanar to that bisecting the piperidine ring through N and C13, and held rigid, see *15*) is unfavoured in simple piperidines and tropanes whose Ar



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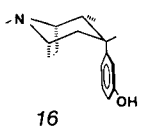

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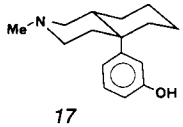

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group is free to rotate about the C_q—C_4 (C_3 for tropanes; see *16*) bond (Allinger & Tribble 1971; Hodgson et al 1985). It must be admitted, however, that activities above those of morphine were reported for the decahydroisoquinoline *17* in which the same considerations of rotational freedom in respect of the Ar group apply (Zimmerman 1988).

The antinociceptive action of the tropane derivative, *11*, an analogue of the reversed ester of pethidine, exceeded that of pethidine itself and was about a third that of morphine in mice by the hot-plate procedure (ED50 values, mg kg^{-1} subcutaneously: *11*, 3·4; pethidine, 4·7; morphine, 1·2).

Acknowledgements

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