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Opioid Properties of Some Isomeric Derivatives of Phencyclidine

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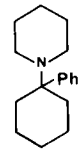
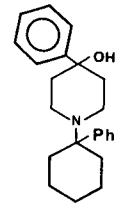
Abstract—The phencyclidine analogues (±)-α-, (±)-β-, and (+)-α- and (−)-α-4-hydroxy-3-methyl-4-phenyl-1-(1-phenylcyclohexyl)piperidine, all with known relative and absolute stereochemistry, have been prepared, and their analgesic potencies related to corresponding prodines. In contrast to the prodines, the (±)-α-phencyclidine analogue was a more potent analgesic than its diastereoisomer, while in agreement with observations in the prodine series, the 3*R*, 4*S*-α-enantiomer displayed substantially greater potency than its mirror image form.

Phencyclidine (*1*) has an array of pharmacological properties that makes it difficult to classify. Thus, it displays analgesic, stimulant, depressant and hallucinogenic effects. Phencyclidine, like *N*-allylnormetazocine (SKF 10, 047), is known to bind to σ-receptors (Vaupel & Jasinski 1979), but evidence is available to suggest that it has its own specific receptor (Casy 1989).



1

Introduction of a phenyl and hydroxyl substituent at position 4 of the piperidine ring of phencyclidine, as in *2*, an agent structurally similar to the precursor alcohol of the reverse ester, *3*, of pethidine, significantly enhances the affinity for specific opiate receptors (Itzhak et al 1981a, b). Compound *2* is approximately twice as potent as morphine in hot-plate and writhing tests, and, unusually, its corresponding propanoyl ester is less active (approx. 10 and 20 times less potent, respectively, in the above tests) (Itzhak et al 1981a).



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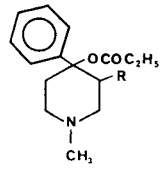
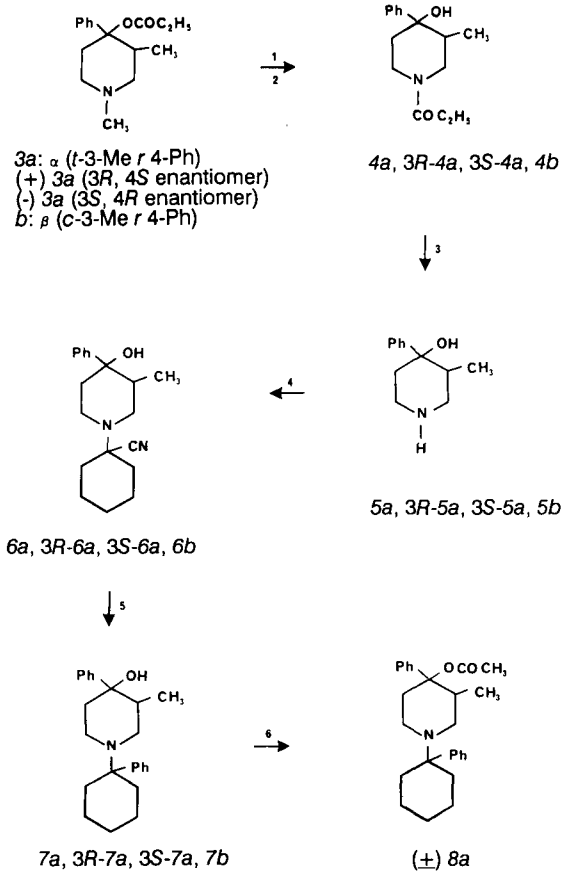


3: R = H
3a: R = Me: α
3b: R = Me: β

Introduction of a methyl group at position 3 of the piperidine ring in *3* (the prodines; *3a* and *3b*) greatly enhances potency: the α-isomer (*t*-3-Me *r*-4-Ph) is equipotent with morphine, whereas the β-isomer (*c*-3-Me, *r*-4-Ph) is approximately five times more active (Casy 1973). In this paper we describe the synthesis and pharmacological properties of the corresponding 3-methyl analogues of *2* (compounds *7a* and *b* in Scheme 1), to establish whether or not any parallel exists between these two compounds and the related prodines. The α-isomer, *7a*, has also been resolved, via α-prodine, and the properties of the two enantiomorphs are presented.



3a: α (*t*-3-Me *r* 4-Ph)
(+) *3a* (3*R*, 4*S* enantiomer)
(-) *3a* (3*S*, 4*R* enantiomer)
b: β (*c*-3-Me *r* 4-Ph)

4a, 3*R*-*4a*, 3*S*-*4a*, *4b*

5a, 3*R*-*5a*, 3*S*-*5a*, *5b*

6a, 3*R*-*6a*, 3*S*-*6a*, *6b*

7a, 3*R*-*7a*, 3*S*-*7a*, *7b*

(±) *8a*

SCHEME 1. Reagents: 1. $CCl_3CH_2OCOCl_2$; 2. Zn/acetic acid; 3. KOH/*i*spropanol; 4. cyclohexanone/KCN/HCl; 5. phenyl magnesium bromide; 6. acetyl chloride. Reaction 6 is on compound *7a* only.

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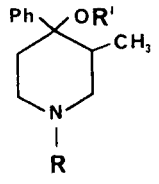
Chemistry

Scheme 1 outlines the synthesis of *7a*, (+)- and (−)-*7a*, and *7b*, starting from corresponding α-, resolved α- and β-prodines. Standard *N*-demethylation methods on the various prodine isomers gave, in all cases, amide alcohols, *4*, by acyl transfer. Hydrolysis yielded the required secondary amines, *5*, and standard Strecker reactions afforded the aminonitriles, *6*. Nitrile displacement using phenyl magnesium bromide gave the required phencyclidine analogues, *7*. *7a* Racemate alone was acetylated to *8*. See Tables 1 and 2 for physical data.

Table 1. Physical data for some isomeric piperidines.



	R	R′	Absolute stereochemistry	mp[a] (°C)	Yield (%)
*	$COOCH_2CCl_3$	COEt	—	—	95
*	$COOCH_2CCl_3$	COEt	3*R*, 4*S*	—	81
			3*S*, 4*R*	—	82
4b	COEt	H	—	146–148	43
4a	COEt	H	3*R*, 4*S*	162–163	40
			3*S*, 4*R*	171–172	42
5b	H	H	—	156[b,d]	54
5a	H	H	3*R*, 4*S*	134–135[b]	60
			3*S*, 4*R*	142–143[b]	64
6b	C_6H_{10}-CN[e]	H	—	134–135[b]	73
6a	C_6H_{10}-CN[e]	H	3*R*, 4*S*	144–145[b]	71
			3*S*, 4*R*	138–139[b]	72
7b	C_6H_{10}-Ph[f]	H	—	230–231[c]	76
7a	C_6H_{10}-Ph[f]	H	3*R*, 4*S*	238–239[c]	72
			3*S*, 4*R*	236–237[c]	75

[a]Solvents as for (±)-α-series; [b]free base; [c]hydrochloride salt; [d]Lit. (Henecka & Schubert 1967): 150–151; [e]1-cyanocylohexyl; [f]1-phenylcyclohexyl. *Intermediate carbamates to *4*.

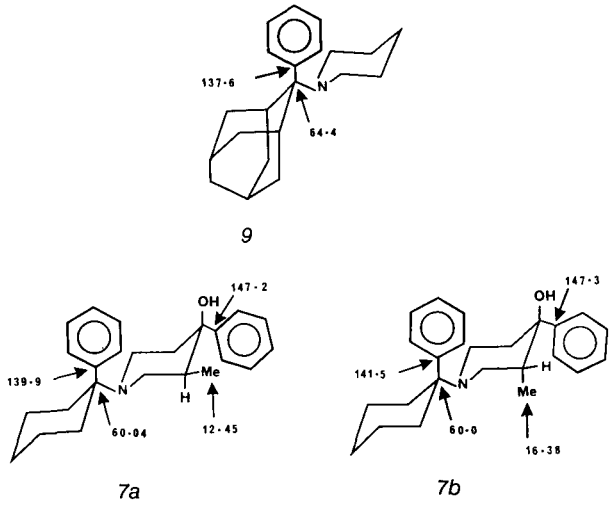


FIG. 1. The figures relate to ^{13}C NMR resonances in ppm downfield of TMS for the atoms shown. (All data from solutions of free base in $CDCl_3$).

Table 2. Microanalytical data for prepared isomeric piperidines (as hydrochlorides except compounds marked *, which are hemihydrates).

		Microanalysis (%)					
		Required			Found		
Compound	Formula	C	H	N	C	H	N
(±)-*4a*		72·8	8·6	5·7	72·6	8·8	5·6
3*R*, 4*S*-*4a*	$C_{15}H_{21}NO_2$	72·8	8·6	5·7	72·4	8·4	5·5
3*S*, 4*R*-*4a*		72·8	8·6	5·7	72·6	8·5	5·4
(±)-*4b*		72·8	8·6	5·7	72·6	8·5	5·6
(±)-*5a*		63·3	8·0	6·2	63·1	7·9	6·1
3*R*, 4*S*-*5a*	$C_{12}H_{18}NOCl$	63·3	8·0	6·2	63·0	7·8	6·0
3*S*, 4*R*-*5a*		63·3	8·0	6·2	62·9	7·8	6·1
(±)-*5b**		61·0	7·7	6·0	61·3	7·8	6·1
(±)-*6a*		65·7	8·8	9·0	65·6	8·7	9·0
3*R*, 4*S*-*6a**	$C_{17}H_{27}N_2OCl$	63·8	8·5	8·8	64·1	8·9	8·9
3*S*, 4*R*-*6a*		65·7	8·8	9·0	65·4	8·9	8·8
(±)-*6b**		63·8	8·5	8·8	63·8	8·8	8·8
(±)-*7a**		73·0	8·2	3·6	73·1	8·2	3·4
3*R*, 4*S*-*7a*	$C_{24}H_{32}NOCl$	74·7	8·4	3·6	74·7	8·3	3·8
3*S*, 4*R*-*7a*		74·7	8·4	3·6	74·9	8·2	3·6
(±)-*7b**		73·0	8·2	3·6	73·4	8·3	3·5
(±)-*8a**	$C_{26}H_{34}NO_2Cl$	71·5	7·8	3·2	71·1	7·8	3·2

Evidence for maintenance of stereochemical integrity through the reaction pathway from the prodines will now be presented. The aspect of relative stereochemistry as it applies to the piperidine ring will be considered first. In both α-prodine (*3a*) and β-prodine (*3b*), the preferred conformation is the one in which the position 4-phenyl is equatorially placed. It follows that in *3a*, the position 3-Me (*trans* to 4-Ph) is also equatorial, whereas in *3b* the 3-Me (*cis* to 4-Ph) must, of necessity, be axial. ^{13}C NMR is invaluable in distinguishing between these diastereoisomers: the 3-CH_3 resonance in *3b* is downfield of the corresponding signal in *3a* (by 3 ppm; see Table 3) of deshielding influences of *cis*-placed phenyl at position 4, and because the axial 3-Me in *3b* exerts steric compression on C-5 (a γ gauche effect) which results in an upfield shift (of ~6 ppm; see Table 3) compared with the corresponding carbon atom in *3a* (Casy 1971; Casy et al 1987). Table 3 provides ^{13}C NMR data that emphasizes this trend in compounds intermediate to, and including, *7*. By utilization of relevant ^{13}C values quoted for the adamantane derivative *9*, whose conformational features have been established unequivocally by X-ray analysis (Eaton et al 1983), it is suggested that the relative stereochemistry and conformation of *7a* and *7b* is as shown in Fig. 1 (axial phenyl quaternary C to higher field because of greater steric polarization (Grant & Paul 1964; Dalling & Grant 1967).

With regard to reactions undertaken on (+)- and (−)-*3a*, it was observed that all compounds intermediate to, and including, *7a* retained the optical rotatory sign (at 589 nm) of the parent prodine, with varying magnitudes.

Pharmacology and Discussion

Table 4 shows rat tail-withdrawal data, mouse tail-flick data, and certain in-vitro experimental values for (±)-*7a*, (+)- and (−)-*7a*, (±)-*7b*, and (±)-*8a*.

In the rat tail-withdrawal test the α-form *7a* was approximately three times as potent as morphine, while the β-

Table 3. C^3-CH_3 and C^5- ^{13}C NMR resonance for some substituted piperidines.

Compound	C^3-CH_3 (ppm)	C^5 (ppm)
3a	11·69	31·77
3b	14·68	25·41
5a	12·65	39·70
5b	14·83	31·89
6a	12·36	40·59
6b	15·89	31·40
7a	12·45	40·25
7b	16·38	33·44

* In $CDCl_3$, TMS internal standard. *4a,b* were omitted because they lacked $CDCl_3$ solubility. The resonance positions of interest differed little between the isomers in other solvents (DMSO-d_6; CD_3OD).

diastereoisomer *7b* was ineffective at an i.v. dosage of 2·5 mg kg^{-1} (failure of a compound to elicit signs of an antinociceptive response at this dose level corresponds to a high ED50 value) (Schellekens, private communication). This result contrasts with observations made on the prodines, where greater activity is seen in the β-form (Casy 1973). However, in tests on antipodal forms of the α-diastereoisomer *7a*, activity was found to reside in the 3*R*, 4*S* isomer in agreement with results noted for antipodes of α-prodine (the 3*R*, 4*S* isomer was about 25 times as active as the 3*S*, 4*R* form in the mouse hot-plate test) (Larson & Portoghese 1973).

In the mouse tail-flick test, 3*R*, 4*S*-*7a* displayed twice the activity of (±)-*7a*, and its antipode was inactive. Acetylation of (±)-*7a* lowered its potency in the rat test to 2·5 mg kg^{-1}— in the prodines an acyl group is an essential requirement for activity. The difference in activity between the *t*-alcohol *7a* and the ester *8a* is small and may be the result of pharmacokinetic factors.

Under the in-vitro conditions of the mouse vas deferens test, (±)-*7a* proved several times less effective than morphine suggesting that its superior potency in the rat tail-withdrawal procedure might be due to its greater ease of penetration of the central nervous system. Its action in the mouse vas deferens test resembled that of a μ-ligand since its effects were not seen in tissue pretreated with βFNA (the amide of fumaric acid mono-methyl ester and β-naltrexamine which selectively blocks μ-sites) but were unchanged in the presence of the selective δ-antagonist ICI-174864 (*N,N*-diallyl-Tyr-Aib-Aib-Phe-Leu-OH). The (±)-α preparation *7a* displaced tritiated etorphine (a universal opioid ligand) from rat brain membranes, but competed less well than morphine, in agreement with results of the mouse vas deferens experiment. Its K_i value vs the selective μ-ligand DAGO (D-Ala^2, $MePhe^4$, Gly-ol^5]enkephalin) was a tenth of that against etorphine, as further evidence of its μ-affinity.

The affinity of (±)-*7a* for phencyclidine receptors was very low, since it failed to displace the selective ligand [^{3}H]TCP (1-[1-(2-thienyl)cyclohexyl]piperidine) from rat brain membranes at a concentration of 1000 nM (cf phencyclidine, $K_i = 60$ nM) (Sircar & Zukin 1985).

It is concluded that the hybrid phencyclidine/4-aryl piperidines, *7*, associate with opioid (probably of the μ-subtype) rather than phencyclidine receptors, but with a binding mode that differs from that of pethidine reversed esters. It is possible that derivatives, *7*, may relate more closely to opioids in which 4-phenyl-4-piperidinol is linked through nitrogen to a CH_2 CH (H or CH_3) N (COEt) Ph chain (activity was also reduced on *O*-acylation) (Carabateas et al 1963; Fancher et al 1964).

Table 4. Biological activity data for phencyclidine analogues.

Compound	TWR[a] ED50 (mg kg^{-1} i.v.)	TFM[b] ED50 (mg kg^{-1} s.c.)	Binding[c] EC50 (nM)	MVD[d] EC50 (mM)
(±)-*7a* (α)	1·0	15·3 (5·7–41·1)	680	1·42[e]
3*R*, 4*S* (+)-*7a*	1·25	8·7 (4·1–18·3)	—	—
3*S*, 4*R* (−)-*7a*	>2·5	essentially inactive	—	—
(±)-*7b* (β)	>2·5	—	—	—
(±)-*8a*	2·5	—	—	—
Morphine	3·15	5·8	23·6	0·395

[a]Rat tail-withdrawal test (Janssen et al 1963). [b]Mouse tail-flick, (Dewey et al 1970). [c]Using 0·5 nM [^{3}H]etorphine in cerebral membranes from rat brain suspended in 50 mM Tris HCl buffer (pH 7·4) containing 150 nM NaCl (Woods et al 1988). [d]Mouse vas deferens test (Woods et al 1988). [e]Action blocked by naltrexone.

Preparative Work

^{13}C NMR spectra were recorded at 67·8 MHz using a Jeol GX270 MHz NMR spectrometer. The number of protons associated with each carbon atom was established from DEPT experiments. ^1H NMR spectra were recorded on a Jeol GX270 spectrometer. Unless stated otherwise, TMS was employed as internal standard, and $CDCl_3$ as solvent. Routine ^{13}C and ^1H NMR data, consistent with structure in all cases, are not quoted and may be obtained from the authors on request. Abbreviations for data quoted are: d, doublet; t, triplet; q, quartet; m, multiplet, plus combinations of dt, doublet of triplets.

Infrared spectra, recorded for liquids as films and for solids as KBr discs, were obtained using a Unicam SP1020 spectrometer.

Optical rotation readings were recorded on an Optical Activity Ltd AA-10 Polarimeter at the sodium D line (589 nm).

Elemental analyses were performed by Butterworth Laboratories Ltd, Middlesex and the Chemistry Department, University of Bath. Melting points are uncorrected.

Starting materials

α- and β-Prodine were obtained starting from 1,3-dimethylpiperidone (Howton 1945) by the method of Ziering & Lee (1947). α-Prodine was resolved into its (+) and (−) antipodes by crystallization of (+)- and (−)-tartrate salts, respectively, by the method described by Larson & Portoghese (1973).

(+)-*3a*, (+)-Tartrate salt: mp 163–164°C, $[\alpha]_D^{25}$ +13·5°C (c = 1, H_2O).

[Lit. (Larson & Portoghese 1973) mp 162–163°C, $[\alpha]_D^{25}$ +13·5° C (c = 1, H_2O)].

(+)-*3a* Base: mp 89–90°C, $[\alpha]_D^{25}$ +11·5°C (c = 1, Me_2CO). [Lit. (Larson & Portoghese 1973) mp 90–91°C, $[\alpha]_D^{25}$ +11·8°C (c = 1, Me_2CO)].

(−)-*3a*, (−)-Tartrate salt: mp 161–162°C, $[\alpha]_D^{25}$ −13·0°C (c = 1, H_2O). [Lit. (Larson & Portoghese 1973) mp 163–164°C, $[\alpha]_D^{25}$ −12·9°C (c = 1, H_2O)].

(−)-*3a* Base: mp 88–89°C, $[\alpha]_D^{25}$ −12·5°C (c = 1, Me_2CO). [Lit. (Larson & Portoghese 1973) mp 89–90°C $[\alpha]_D^{25}$ −12·0°C (c = 1, Me_2CO)].

(±)-α-4-Hydroxy-3-methyl-4-phenylpiperidine (5a)

A suspension of (±)- *3a* (20 g), 2,2,2-trichloroethylchloroformate (26 g) and K_2CO_3 (5·5 g) in dry toluene (250 mL) was refluxed for 2 h, and then stirred at room temperature (21°C) for 24 h. The reaction mixture was diluted with $CHCl_3$ (500 mL), washed with NaOH solution (2 M; 2 × 50 mL), water (2 × 50 mL), HCl (2 M; 2 × 30 mL) and finally water (2 × 100 mL). The organic layer was dried ($MgSO_4$) and evaporated in-vacuo to yield α-3-methyl-4-phenyl-4-propanoyloxy-1-(2,2,2-trichloroethyl-carbonyl)piperidine (25 g), as an oil. Addition of petroleum ether (bp 60–80°C) gave a solid which was recrystallized from the same solvent to give pure carbamate as colourless crystals (mp 158°C ν_{max}: 1740 cm^{-1} (CO str.)).

Zinc dust (12·5 g) was added a portion at a time to a stirred solution of the above carbamate (25 g) in glacial acetic acid (400 mL; 99%). The reaction mixture was refluxed for 2 h, and then stirred at room temperature for 12 h. The solid was filtered off and washed with methanol (20 mL). The organic solvents were evaporated in-vacuo and the oily residue dissolved in dichloromethane (400 mL). This solution was washed with NaOH (2 M; 3 × 50 mL), water (2 × 70 mL) and then dried ($MgSO_4$). Evaporation in-vacuo gave α-4-hydroxy-3-methyl-4-phenyl-1-propanoylpiperidine (*4a*; 5·9 g) as an oil, which solidified on addition of ether. Crystallization from ether gave pure *4a* as a colourless solid (mp 154–155°C; ν_{max}: 1640 cm^{-1} (CO str.). M^+ 247 (85%)); δ_H (ppm) (DMSO-d_6): 7·15–7·50 (m; Ar-*H*); 4·38 and 3·75 (2 × brd; C2-H_{eq}); 4·28 and 3·61 (2 × dd; C6-H_{eq}); 3·41 and 2·91 (2 × dt; C6-H_{ax}); 3·11 and 2·62 (2 × brt; C2-H_{ax}); 2·35 (dq; NCOCH_2) 1·97 (m; C5-H_{eq}); 1·84 (m; C3-*H*); 1·62 (m; C5-H_{ax}); 1·20 (t; amide CH_3); 0·52 (t; C3-CH_3).

KOH (5 g) was added in portions to a stirred solution of amide *4a* (5 g) in isopropanol (60 mL), and the reaction mixture refluxed for 48 h. The solution was cooled, and the solvent removed in-vacuo to leave an oily residue which was taken up in dichloromethane (50 mL). The inorganic solid was filtered off, and the combined layers extracted with HCl (2 M; 2 × 20 mL). The aqueous layer was basified with strong ammonia and extracted with $CHCl_3$ (3 × 40 mL). The $CHCl_3$ extract was washed with water (1 × 15 mL), dried ($MgSO_4$) and evaporated to yield *5a* (2 g), as an oil. Crystallization from petroleum ether (bp 60–80°C) gave pure secondary amine as a colourless solid (mp 130–131°C (Lit. (Henecka & Schubert 1967) mp 125–126°C)).

(±)-α-1-(1-Cyanocyclohexyl)-4-hydroxy-3-methyl-4-phenylpiperidine (6a)

To a solution of (±)-α-4-hydroxy-3-methyl-4-phenylpiperidine (4 g) in water (30 mL) was added a few drops of dilute hydrochloric acid. Cyclohexanone (2 mL) was added, followed by ethanol (95%; 1 mL) which, after stirring, rendered the mixture homogeneous. A solution of KCN (1·8 g) in water (10 mL) was added dropwise, and vigorous stirring continued for 72 h. The resulting mixture was basified with NaOH solution (5 M) and extracted with $CHCl_3$ (4 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give *6a* as an oil. Trituration with petroleum ether (60–80°C) gave a solid which was recrystallized from the same solvent.

The pure material (3·5 g; 67%) had mp 138°C, ν_{max}: 2250 (CN str.); M^+ 298 (28%).

(±)-α-4-Hydroxy-3-methyl-4-phenyl-1-(1-phenylcyclohexyl) piperidine (7a)

A solution of (±)-α-1-(l-cyanocyclohexyl)-4-hydroxy-3-methyl-4-phenylpiperidine (2·5 g) in dry THF (15 mL) was added dropwise to phenylmagnesium bromide [from Mg (1·8 g) and bromobenzene (11·0 g) in dry THF (100 mL)]. The reaction mixture was refluxed for 2 h, and then stirred at room temperature for 24 h. The solution was diluted with ether (200 mL), and added to a mixture of crushed ice (100 g) and glacial acetic acid (15 mL). The organic layer was separated, washed with NaOH solution (3 M; 3 × 30 mL), dried ($MgSO_4$) and evaporated in-vacuo to give the title compound (2·3 g; 76%), as an oil. Treatment of the oil with ethereal HCl gave the hydrochloride, mp 230–231°C (methanol) M^+ 349 (49%).

The corresponding β form, *7b*, and the *α-3R, 4S* and *α-3S, 4R* enantiomers, were synthesized from appropriate prodines (Scheme 1) by the above route. Relevant data are summarized in Tables 1 and 2. Microanalytical data for all compounds described above are also presented in Table 2.

(±)-α-4-Acetoxy-3-methyl-4-phenyl-1-(1-phenylcylohexyl) piperidine (8a)

Acetyl chloride (15 mL) was added dropwise to a stirred solution of (±)-α-*7a* (0·5 g) in dry THF (10 mL), and the reaction mixture refluxed for 12 h. The solution was cooled and excess of acetyl chloride and THF removed in-vacuo to give the hydrochloride salt of *8a* (0·3 g; 60%), mp 210–213°C (ethanol-ether).

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References

Carabateas, P. M., Wetterau, W. F., Grunbach, L. (1963) Strong analgesics: some *N*-(piperidinoalkyl) anilides. J. Med. Chem. 6: 355–357

Casy, A. F. (1971) Studies of alicyclic derivatives containing nitrogen. In: PMR Spectroscopy in Medicinal and Biological Chemistry. Academic Press, London, pp 135–169

Casy, A. F. (1973) Analgesic receptors. In: Featherstone, R.M. (ed.) Guide to Molecular Pharmacology and Toxicology. Dekker, New York, pp 217–278

Casy, A. F. (1989) Opioid receptors and their ligands: recent developments. Adv. Drug Res. 18: 178–289

Casy, A. F., Iorio, M. A., Madani, A. E. (1987) Stereochemical studies of 3-aryl-3-methylpiperidines of potential opioid ligand activities by high resolution ^{1}H and ^{13}C NMR spectroscopy. Magn. Reson. Chem. 25: 524–530

Dalling, D. K., Grant, D. M. (1967) Carbon-13 magnetic resonance. IX. The methylcyclohexanes. J. Am. Chem. Soc. 89: 6612–6622

Dewey, W. L., Harris, L. S., Howes, J. F., Nuite, J. A. (1970) The effect of various neurohumoral modulators on the activity of morphine and the narcotic antagonists in the tail-flick and phenylquinone tests. J. Pharm. Exp. Ther. 175: 435–442

Eaton, T. A., Houk, K. N., Watkins, S. F., Fronczek, S. F. (1983) Geometries and conformational processes in phencyclidine and a rigid adamantyl analogue: variable temperature NMR, X-ray crystallographic, and molecular mechanics studies. J. Med. Chem. 26: 479–486

Fancher, O. E., Hayao, S., Strycher, W. G., Sancilio, L. F. (1964) New analgesic *N*-substituted carboxamides. Ibid. 7: 721–725

Grant, D. M., Paul, E. G. (1964) Carbon-13 magnetic resonance II. Chemical shift data for the alkanes. J. Am. Chem. Soc. 86: 2984–2990

Henecka, H., Schubert, H. W. (1967) 4-Hydroxypiperidines. Fr. Patent 1, 470, 065

Howton, D. R. (1945) 1,3-Dimethylpiperidone-4. J. Org. Chem. 10: 277–282

Itzhak, Y., Kalir, A., Weissman, B. A., Cohen, S. (1981a) New analgesic drugs derived from phencyclidine. J. Med. Chem. 24: 496–499

Itzhak, Y., Kalir, A., Weissman, B. A., Cohen, S. (1981b) Receptor binding and antinociceptive properties of phencyclidine opiate-like derivatives. Eur. J. Pharmacol. 72: 305–311

Janssen, P. A. J., Niemegeers, C. J. E., Dony, J. G. H. (1963) The inhibitory effect of fentanyl and other morphine-like analgesics on the warm water-induced tail withdrawal reflex in rats. Arzneim. Forsch. 13: 502–506

Larson, D. I., Portoghese, P. S. (1973) Stereochemical studies on medicinal agents 12. The distinction of enantiotopic groups in the interaction of 1-methyl-4-phenylpropionoxypiperidine with analgesic receptors. J. Med. Chem. 16: 195–198

Sircar, R., Zukin, S. R. (1985) Quantitative localization of [^{3}H] TCP binding in rat brain by light microscopy autoradiography. Brain Res. 344: 142–145

Vaupel, D. B., Jasinski, D. R. (1979) Acute single dose effects of phencyclidine (PCP) in the dog. Fed. Proc. 38: p. 435

Woods, J. H., Medzihradsky, F., Smith, C. B., Winger, G. D., France, C. P. (1988) Evaluation of new compounds for opioid activity. Annual Report of the Committee on Problems of Drug Dependence: 1–48

Ziering, A., Lee, J. (1947) Piperidine derivatives. V. 1,3-Dialkyl-4-aryl-4-acyloxypiperidines. J. Org. Chem. 12: 911–914