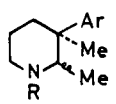
Isomeric 2,3-dimethyl-3-arylpiperidines with morphine-and nalorphine-like properties

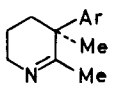
Kugita, Oine & others (1965) previously reported that single isomeric forms of the 2,3-dimethyl-3-arylpiperidines Ia (R = CH_2CH_2Ph and CH_2COPh) were about half as active as morphine in mice (hot-plate test) while the corresponding *N*-allyl derivative antagonized the analgesic effects of morphine in the same animal (see also Nurimoto & Hayashi, 1973). We obtained both *RS*-diastereoisomers (termed α- and β-) of the parent secondary amine Ib (R = H) by hydrogenation of the tetrahydropyridine II.



I

a) Ar = *m*-OH·C_6H_4

b) Ar = *m*-OMe·C_6H_4



II

The configurations α: *c*-2-Me-*r*-3-Ar and β: *t*-2-Me-*r*-3-Ar were established by analysis of differences in the ^1H nmr spectra of isomeric pairs, particularly of *N*-benzyl and *N*-acetyl derivatives (Casy & Iorio, 1974). *O*-Demethylation of the derivatives Ib (R = Me, CH_2CH_2Ph, and $CH_2CH:CH_2$) was achieved by treating the methoxy compound (1 g) with hydrogen bromide (10 ml, 48% in water) at the reflux temperature for 45 min under nitrogen, and the recovered base converted to a hydrochloride salt. Details of phenolic derivatives so prepared are given in Table 1.

In both hot-plate and Nilsen tests for analgesia in mice (Perrine, Atwell & others, 1972), the *N*-phenethyl pair (Ia, R = CH_2CH_2Ph) was significantly active (α: 0·7 ×, β: 0·3 to 0·4 × pethidine) (Table 2), while *N*-methyl and *N*-allyl analogues were very weak or inactive.

In rats the *N*-allyl isomers (Ia, R = $CH_2.CH:CH_2$) had no morphine-like properties but antagonized fentanyl-induced effects: the β-isomer (twice as active as nalorphine) was 4 times more effective than the α-form. In morphine-dependent monkeys the same derivatives precipitated a dose-related withdrawal syndrome with the β-isomer again the more effective agent.

Since certain *N*-allyl and *N*-cyclopropylmethyl 4-arylpiperidines (analogues of pethidine and its reversed ester and of ketobemidone) are analgesic "agonists" rather than antagonists (Casy, Simmonds & Staniforth, 1968; Oh-ishi & May, 1973), it is probable that, of the two classes, 3-arylpiperidines interact with opiate receptors in the more morphine-like manner. Flexible (boat) conformers of 3-arylpiperidines

Table 1. *2,3-Dimethyl-3*-m-*hydroxyphenylpiperidine (Ia) hydrochlorides.*

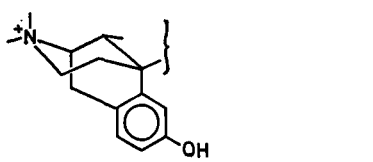
1-substituent (R in Ia)	Isomer	m.p. °	Molec. formula		Analysis C	H	N
Me	α	248–249[1]	$C_{14}H_{22}ClNO$	Found	65·78	8·77	5·49
				Required	65·74	8·66	5·47
Me	β	286–287[2]	$C_{14}H_{22}ClNO$	Found	65·77	8·68	5·47
$(CH_2)_2Ph$	α	215–217[1]	$C_{21}H_{28}ClNO$	Found	72·54	8·13	4·12
				Required	72·91	8·15	4·04
$(CH_2)_2Ph$	β	224–225[1]	$C_{21}H_{28}ClNO$ 0·5 H_2O	Found	71·19	8·23	3·90
				Required	71·07	8·23	3·95
$CH_2.CH:CH_2$	α	206–207[2]	$C_{16}H_{24}ClNO$	Found	68·42	8·62	5·00
				Required	68·18	8·58	4·96
$CH_2.CH:CH_2$	β	233–235[2]	$C_{16}H_{24}ClNO$	Found	68·11	8·71	4·70

[1] From ethanol–ether.
[2] From ethanol.

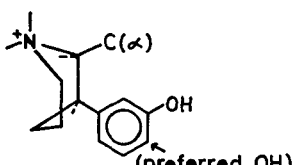
Table 2. *Nilsen and hot-plate ED50 values in mice for 2,3-dimethyl-3-*m*-hydroxyphenylpiperidines (Ia) and related compounds.*

Compound[1]	Isomer	ED50 mg kg^{-1}, s.c. Nilsen method	Hot-plate method
Ia(R = CH_2CH_2Ph)	α	4·6 (2·5–8·5))	7·0 (4·8–12·2)
	β	11·3 (7·0–18·1)	10·6 (7·7–14·6)
Ia(R = Me)	β	39·3 (22·7–68·2)	[2]
VI	—	6·4 (3·1–13·1)	13·0 (8·8–19·1)
Pethidine[3]	—	3·5 (2·3–5·4)	4·7 (4·2–5·4)

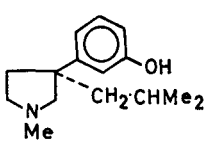
[1]All hydrochlorides.
[2]Indeterminate.
[3]Perrine & others (1972).



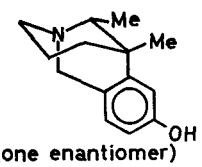
III
(morphine etc. partial structure)



IV



V



VI

most clearly reveal the relation to the 3-dimensional skeleton of the morphine, morphinan, and benzomorphan classes of analgesic (III and IV). It is of interest that analgesically active derivatives of 3-arylpyrrolidines, e.g. V are converted to morphine antagonists when the ring nitrogen carries an allyl or cyclopropylmethyl substituent (Bowman, Collier & others, 1973a, b). These derivatives may also adopt conformations in which the basic and aromatic features are orientated similarly to those in flexible forms of 3-arylpiperidines. Such comparisons emphasize the necessity for a β-arylethyl moiety (present in all structural types discussed except 4-arylpiperidines) in analgesics capable of conversion to narcotic antagonists.

The 1-aza-des-*N*-6,7-benzomorphan VI, m.p. 210–211° from acetone–ether (Found: C, 76·46; H, 8·88; N, 6·54. $C_{14}H_{19}NO$ requires: C, 77·38; H, 8·81; N, 6·45%), hydrochloride, m.p. 108–109° from ethanol–ether (Found: C, 61·81; H, 8·04; N, 5·17. $C_{14}H_{20}ClNO \cdot H_2O$ requires: C, 61·87; H, 8·15; N, 5·15%), derived from α-Ib (R = H) and formaldehyde-formic acid (Iorio & Casy, 1974) followed by *O*-demethylation, was about half and a third as active as pethidine in mice by Nilsen and hot-plate tests respectively (Table 2), and equi-active in rats by the tail withdrawal reflex.

We thank Dr. P. A. J. Janssen for testing the *N*-allyl isomers and VI in rats, Dr. E. L. May for accommodating one of us (M.A.I.) in his laboratory, and Drs L. Harris & M. Aceto (Virginia Medical College) for performing the antagonistic tests in monkeys.

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The isolation and enumeration of *Pseudomonas aeruginosa* from oily cream

The recovery of micro-organisms from topical non-sterile pharmaceuticals presents many problems for the analyst engaged in the microbiological quality control of such products. Variations of the membrane filtration technique developed by Sokolski & Chidester (1964) are widely used in the pharmaceutical and cosmetic industry to recover micro-organisms from topical preparations. Many solvents have been utilized to dissolve or disperse the ointment before membrane filtration. These include isopropyl myristate (IPM) (Sokolski & Chidester, 1964), n-hexane (White, Bowman & Kirshbaum, 1968), light liquid paraffin (British Pharmacopoeia, 1968) polyethylene glycol ether (Millipore Ltd., 1969), white spirit (Smith, personal communication) and carbon tetrachloride (Tall, personal communication). Recently Hambleton & Allwood (1972 & 1973) reported using a variety of solvents to recover *Bacillus megaterium* spores and *Escherichia coli* from white soft paraffin.

P. aeruginosa has been found as a common contaminant in topical preparations (Savin, 1967) and was isolated from oily cream by Simmons (1969). This report describes the recovery of *P. aeruginosa* from oily cream using a membrane filtration technique and a variety of solvent and dispersion systems.

P. aeruginosa NCTC 7244 was grown for 18h at 35° in nutrient broth (Oxoid Ltd., London) and found to contain approx. 5×10^8 cells ml^{-1}. The culture was diluted in sterile distilled water and 0·1 ml of a suitable dilution was incorporated into 2·0 g of oily cream by adequate mixing using a sterile spatula. The inoculated cream contained approx. 5×10^2 cells g^{-1}.

The following solvents were used in an attempt to recover *P. aeruginosa* cells from the cream; isopropyl myristate (Price's Chemicals Ltd., Bebington, Wirral, Cheshire),