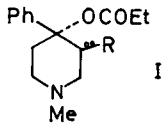
Influence of 3-alkyl substitution on the analgesic potency of the reversed ester of pethidine

We report here the results of analgesic assays in mice of the reversed ester of pethidine (Ia) and its 3-substituted analogues (Ib-Ie) each of which were obtained in separate RS-diastereoisomeric forms.



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(a) R=H; (b) R=Me; (c) R=Et; (d) R=Pr^n; (e) R=CH_2·CH=CH_2

A standardized hot-plate procedure carried out under the direction of Dr. E. L. May was employed, hence the data may be used meaningfully for comparative purposes. The original report on Ib, Ic and Ie (Ziering, Motchane & Lee, 1957) lacks data on Ia and Id and presents configurational assignments now known to be incorrect (Casy, 1970). There is unequivocal evidence for the stereochemistry of the 3-methyl (Ib) (Kartha, Ahmed & Barnes, 1960; Ahmed, Barnes & Masironi, 1963) and 3-allyl (Ie) isomeric pairs (Bell & Portoghese, 1973; Iorio, Damia & Casy, 1973) and we have now established the configurations of the 3-ethyl derivatives (Ic) by analysis of ester methyl and methylene Pmr chemical shifts (cf. Casy, 1966). The isomeric pair (Ic) (m.p. α 235–236°, β 200–201°, derived from 3-ethyl-1-methyl-4-piperidone), together with the 3-propyl analogues (Id) obtained by catalytic reduction of the 3-allyl isomers (Ie) of known configuration, completes the series Ia–Ie.

Pharmacological data for these compounds are given in Table 1. In the α-series (3-*R* equatorial in preferred chair conformation) the 3-methyl little alters the potency of Ia, 3-ethyl and 3-propyl groups depress activity, while the 3-allyl group sharply raises potency. In the β-series (3-R axial) both 3-methyl and 3-ethyl groups elevate, while 3-propyl and 3-allyl groups markedly depress the potency of the parent reversed ester. The β-member has the greater activity in pairs Ib and Ic while the α-form is the superior analgesic in pairs Id and Ie. Thus the configurational selectivity of the analgesic receptor is inverted when the 3-substituent is increased from 2 to 3 carbon atoms in a linear manner.

Experimental details and further consideration of structure-activity relationships will be given elsewhere.

Table 1. *Hot-plate ED50 values for reversed esters of pethidine (I)*[1].

R in (I)	Isomer[2]	ED50 in mice mg kg^{-1}, s.c.
H	—	0·85
Me	α	0·92
Me	β	0·18
Et	α[3]	3·5
Et	β	0·4
Pr^n	α	2·0
Pr^n	β	14·7
CH_2·CH=CH_2	α	0·09
CH_2·CH=CH_2	β	11·7
Pethidine	—	4·7

[1] The less pronounced α:β potency ratios earlier reported for the pairs Ic and Ie (Ziering & others, 1957) are possibly due to a lack of isomeric purity.

[2] Configurations: α *c*-3-R, *r*-OCOEt; β *t*-3-R, *r*-OCOEt. Original assignments for the pairs Ib, Ic and Ie are reversed.

[3] Enantiomorphic forms of α-Ic have recently been reported (Bell & Portoghese, 1974).

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The effect of massing time on drug concentration in different sized granules

Lachman & Sylwestrowicz (1964) have shown that granules of different size fractions may have different drug concentrations. Their results were obtained using a poorly soluble drug, massed for a given length of time. The results presented below show the effect of varying the massing time on the distribution of borax within a batch of granules.

Borax, of mean particle size 3·6 μm (Analar grade, BDH Chemicals, Poole), and lactose B.P., of mean particle size 2·5 μm (Hopkins and Williams, Essex), were mixed together in a Z blade mixer (Morton Machines Ltd., Wishaw, Scotland), for 2 min. The overall concentration of borax in the mixer was 2·0%. The contents of the mix were emptied onto a tile and subdivided into ten portions. Each of these portions was assayed for its borax content by titration with 0·01N HCl and the results are in Table 1.

Similar proportions of lactose and borax were placed in a Z blade mixer, mixed for 2 min and then massed with water. The mass was forced through a twelve mesh

Table 1. *The distribution of borax in lactose in a Z blade mixer after 2 min mixing (each portion is the mean of twenty analyses).*

Portion number	Mean % borax	Standard deviation
1	2·04	0·079
2	2·01	0·071
3	1·95	0·072
4	1·98	0·071
5	2·00	0·076
6	1·98	0·079
7	2·00	0·077
8	2·02	0·077
9	2·01	0·079
10	1·99	0·071