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1-Allyl and 1-(3,3-dimethylallyl) analogues of pethidine and its reversed ester

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The preparation of some 1-allyl and 1-(3,3-dimethylallyl)-4-phenylpiperidines related to pethidine and its reversed ester is described and the hot-plate activities in mice of these compounds reported. All six derivatives displayed morphine-like properties in mice, four being more potent (1·5–6 times) than morphine, but failed to act as analgesic antagonists in rats. The results are contrasted with the properties of similarly *N*-substituted fused-ring analgesics and differences discussed in terms of drug-receptor interaction modes.

THE aim of this work was to investigate the effect of replacing the methyl group in position 1 of 4-phenylpiperidine analgesics, such as pethidine and its reversed ester, by an allyl or 3,3-dimethylallyl group. In morphine, levorphanol and metazocine (analgesics with fused-ring skeletons), the same structural modification causes a striking change in pharmacological properties, the *N*-allyl (and *N*-substituted allyl) derivatives being analgesic antagonists (the *N*-allyl compounds have a potent action and the *N*-3,3-dimethylallyl compounds a weak action) which are devoid of activity in most of the usual tests for analgesia in animals. In man, however, some of these derivatives are effective analgesics, and one of them, pentazocine, has been developed as a clinically useful non-addicting analgesic (Keats & Telford, 1964; Archer & Harris, 1965).

Chemistry

The pethidine analogue I was obtained by alkylating norpethidine with 1-chloro-3-methylbut-2-ene. The 1-allyl-4-piperidones II (R = H or Me) required for the synthesis of the reversed esters III were made by Dieckmann cyclizations of the appropriate acyclic amino-diesters. Treatment of these piperidones with phenyl-lithium followed by propionic anhydride gave the esters III. In the case of the 3-methyl derivative III (R = Me), only one of the two diastereoisomeric esters was isolated and this was assigned a *trans* 3-Me/4-Ph configuration from a consideration of the nmr data (the secondary Me chemical shift of this ester suffered only a minor downfield shift upon base protonation) (Casy, 1966). The 1-(3,3-dimethylallyl) derivatives IV were obtained by alkylating the corresponding 4-phenyl-4-piperidinols with 1-chloro-3-methylbut-2-ene (or acylating with 3,3-dimethylacryloyl chloride and then reducing the amide formed) and esterifying the resulting piperidinol with propionic anhydride.

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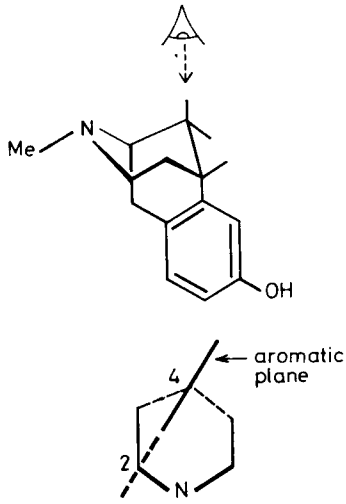
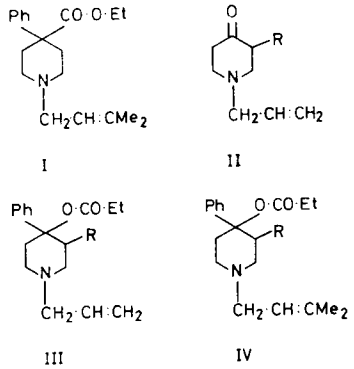


Diagram of the 4-phenylpiperidine moiety of fused-ring analgesics. In the lower drawing the piperidine and aromatic rings are depicted as viewed from above the piperidine and aromatic rings by an observer whose eye is placed in the position shown.



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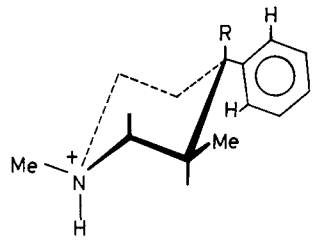
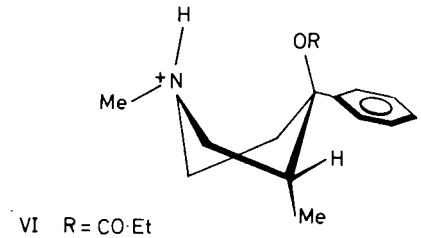


V R=O·CO·Et

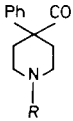
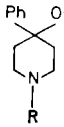
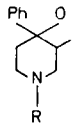


VI R = CO·Et

Pharmacology and discussion

The analgesic activity of the pethidine congener I and the reversed esters III and IV (R = H or Me) was assessed in mice by the hot-plate

TABLE 1. HOT-PLATE ACTIVITIES OF SOME 1-ALLYL- AND 1-(3,3-DIMETHYLALLYL)-4-PHENYLPIPERIDINES IN MICE*

Structure	ED50 mg/kg	
	R = CH_2·CH = CH_2	R = CH_2·CH = CMe_2
	63†	40
	15	7·5
	7·5‡	32

* Determined after subcutaneous administration by Janssen & Jageneau's method (1957)—by this procedure ED50 values for morphine and pethidine are 11 and 23 mg/kg respectively.
† Janssen (personal communication).
‡ ED50 for alphaprodine is 5·5 mg/kg approx. (Beckett, Casy & others, 1957).

test (Table 1). A result for the *N*-allyl analogue of pethidine, a compound previously reported to be without effect upon analgesia produced by methadone, alphaprodine and pethidine as assessed by a test in rats (Costa & Bonnycastle, 1955) is included. Nalorphine-like antagonistic properties were evaluated in rats using morphine (40 mg/kg subcutaneously) as the reference agonist. The test compound, given intravenously 1 hr after morphine, was considered to have nalorphine-like activity only if the morphine-induced rigidity and inhibition of the corneal and pinnal reflexes were antagonized immediately. By this criterion, all the

compounds tested were devoid of nalorphine-like properties. Thanks are due to Dr. Paul Janssen for making these tests.

The six compounds listed in Table 1 displayed morphine-like properties in mice, as shown by their mydriatic and behavioural effects (excitation and Straub tail) and significant hot-plate ED50 values (some of the compounds were more potent than morphine) but failed to act as analgesic antagonists in rats. The *N*-3,3-dimethylallyl analogue of ketobemidone is also a significantly active analgesic in mice (hot-plate ED50 = 4·6, cf. ketobemidone ED50 = 1·6) while it fails to display typical nalorphine-like effects in normal monkeys (Dr. J. E. Villarreal, personal communication). In 1-methyl-4-phenylpiperidine compounds with analgesic activity, therefore, no radical pharmacological change results when the methyl group in position 1 is replaced by allyl functions, a result in marked contrast to findings relating to cyclic analgesics of greater molecular rigidity such as morphine.

Although it is generally true that *N*-substituents have similar influences upon analgesic activity in the two classes of compounds (e.g. the potency-raising effect of the *N*-phenethyl group), discrepancies have been reported. Thus, while replacement of the methyl group in position 1 by a cinnamyl or 3-phenylpropyl group gives potent pethidine analogues (Elpern, Carabateus & others, 1959; Elpern, Gardner & others, 1957), the corresponding normorphinan derivatives are inactive (Eddy, Besendorf & Pellmont, 1958). Conversely, although *N*-phenacylnormorphinan is 6·5 times as potent as levorphanol, the same norpethidine derivative is only one tenth as active as the parent 1-methyl compound (Janssen & Eddy, 1960). The two classes also show different structure-activity relations with regard to oxygen functions. In analgesics based on morphine, morphinan and benzomorphan, a free phenolic group is an important, and often essential, feature for activity (its removal or etherification* result in sharp falls in potency) but the same function is not a prerequisite for high potency in 4-phenylpiperidine analgesics, although it may be advantageous (e.g. ketobemidone); on the other hand, all potent analgesics of the latter class possess non-aromatic oxygenated functions (e.g. CO·O·Et, O·CO·Et) (Beckett & Casy, 1965 and refs. there cited).

While both analgesic types appear to interact at a common site (evidence from analgesic antagonists), their differing structure-activity relations, as outlined above, indicate that they probably vary in their association modes with the receptor. Similar conclusions have been reached for two classes of acyclic analgesics, represented by methadone and diampromid respectively, which differ both in basic-group structure and stereospecificity (Casy & Hassan, 1967). The 4-phenylpiperidine unit is common to simple piperidine derivatives such as pethidine and alphaprodine and to morphine, morphinan, and benzomorphan analgesics. This fact allows a superficial correlation between rigid and non-rigid

* Esterification often leads to an enhancement of potency, but a study of diamorphine (heroin) indicates that the pharmacological effects of such esters are mediated primarily by the free phenols (Way, Kemp & others, 1960; Way, 1967).

cyclic analgesics but should not be interpreted too narrowly in terms of molecular geometry. In rigid analgesics the 4-phenylpiperidine moiety is constrained to an axial-phenyl chair conformation with the aromatic plane parallel with one passing through a line joining C–2 and C–4 of the heterocyclic ring (Diagram). In simple 4-phenylpiperidines, however, likely conformations for pethidine and alphaprodine (V) and for betaprodine (VI) as solutes in water have been proposed (Casy, 1966, 1968) in which the piperidine–aromatic ring orientations (deemed a key factor in agonist–receptor association, as this unit contains both the electrostatic and van der Waals' binding centres) differ markedly from that shown in the diagram. Thus, if flexible piperidine analgesics are to present the orientation shown in the diagram to the receptor, they must adopt highly unfavoured conformations, and it seems more reasonable to postulate a receptor capable of adapting itself to a variety of agonist conformations of varying binding efficiencies.

Experimental

1-*Allyl*-4-*piperidone.* A mixture of allylamine (19 g), ethyl acrylate (36·5 g) and ethanol (500 ml) was left to stand for two days, and then fractionally distilled to give ethyl β-(allylamino)-propionate (79 g), b.p. 66°/1·6 mm (Speziale & Jaworski, 1960, give b.p. 56°/1·2 mm). It formed a *hydrogen oxalate*, m.p. 184–6°, from acetone-ether (Found: C, 48·3; H, 7·0; N, 5·6. $C_{10}H_{17}NO_6$ requires: C, 48·6; H, 6·9; N, 5·7%). The aminoester (35 g) and ethyl acrylate (24·5 g) in ethanol (250 ml) were heated under reflux for 12 hr, and then fractionally distilled to give *N*-allyldi(2-ethoxycarbonylethyl)amine (48 g), b.p. 112–4°/2 mm. It formed a *hydrogen oxalate*, m.p. 87°, from acetone-ether (Found: C, 51·7; H, 7·2; N, 4·3. $C_{15}H_{25}NO_8$ requires: C, 51·9; H, 7·2; N, 4·0). The tertiary amine diester (103 g) was cyclized with sodium hydride (20·5 g) in benzene (2 litres) containing ethanol (1 ml) and then decarboxylated with HCl by the usual procedures (Casy, Birnbaum & others, 1965) to give *1-allyl-4-piperidone* (39·5 g), b.p. 60–63°/3 mm, n_D^{19} 1·4783 (Found: C, 68·7; H, 9·3; N, 9·7; $C_8H_{13}NO$ requires: C, 69·0; H, 9·4; N, 10·1%).

1-*Allyl*-3-*methyl*-4-*piperidone.* A mixture of allylamine (19 g), methyl methacrylate (36·7 g) and ethanol (100 ml) was stirred for 6 hr, and then heated under reflux for 16 hr. The product was fractionally distilled to give *methyl β-allylamino-α-methylpropionate* (30 g), b.p. 74°/0·65 mm (Found: C, 61·5; H, 9·9; N, 8·8. $C_8H_{15}NO_2$ requires: C, 61·1; H, 9·6; N, 8·9%). The amino-ester (42 g) and ethyl acrylate (29·4 g) in ethanol (150 ml) were heated under reflux for 24 hr and fractionally distilled to give *N*-allyl-*N*-(2-ethoxycarbonylethyl) (2-methoxycarbonylpropyl)amine (61·5 g), b.p. 104–116°/0·35 mm, n_D^{20} 1·4512. It gave an *oxalate*, m.p. 176°, from acetone-ether (Found: C, 55·6; H, 9·0. $C_{28}H_{48}N_2O_{12}$ requires: C, 55·6; H, 9·4%). The tertiary amine diester (78·5 g) was cyclized and decarboxylated as before to give 1-allyl-3-methyl-4-piperidone (28 g), b.p. 65°/0·4 mm (Found: C, 69·8; H, 9·65. $C_9H_{15}NO$ requires:

C, 70·55; H, 9·9%). It gave a *hydrobromide*, m.p. 141° (Found: C, 46·0; H, 6·7; N, 6·1. $C_9H_{16}BrNO$ requires: C, 46·2; H, 6·9; N, 6·0%).

1-*Allyl*-4-*phenyl*-4-*propionyloxypiperidine and its* 3-*methyl analogue.* 1-Allyl-4-piperidone (14 g) in ether (100 ml) was added to a cooled ethereal solution of phenyl-lithium prepared from lithium (4·4 g) and bromobenzene (50·2 g), the mixture heated under reflux for 2 hr, and then treated with propionic anhydride (91 g). After stirring for 16 hr, the mixture was poured onto ice and aqueous NaOH, and the ethereal phase separated and extracted with aqueous HCl. The base recovered from this extract was distilled to give 1-allyl-4-phenyl-4-propionyloxypiperidine (16 g), b.p. 179/1 mm. It gave a *hydrobromide*, m.p. 193°, from isopropanol (Found: C, 57·8; H, 6·7; N, 4·1. $C_{17}H_{24}BrNO_2$ requires: C, 57·6; H, 6·5; N, 4·0%) and a *toluene*-p-*sulphonate*, m.p. 140°, from ethyl acetate (Found: C, 64·1; H, 6·9; N, 3·1. $C_{24}H_{31}NO_5S$ requires: C, 64·7; H, 7·0; N, 3·1%). Similar treatment of 1-allyl-3-methyl-4-piperidone (10 g) gave 1-allyl-3-methyl-4-phenyl-4-propionyloxypiperidine (11 g), b.p. 148°/0·7 mm. It gave a *hydrobromide*, m.p. 210°, from isopropanol (Found: C, 58·9; H, 7·0; N, 3·8. $C_{18}H_{26}BrNO_2$ requires: C, 58·7; H, 6·8; N, 3·8%).

1-(3,3-*Dimethylallyl*)*norpethidine.* Norpethidine (10 g) and 1-chloro-3-methylbut-2-ene were dissolved in acetone (200 ml) through which CO_2-free nitrogen had been passed, and the mixture was stirred at the reflux temperature with Na_2CO_3 (13·6 g) for 48 hr. The filtered mixture was evaporated and the residue distilled to give 1-(3,3-dimethylallyl)-norpethidine (8 g), b.p. 170–172°/2 mm. It gave a *hydrobromide*, m.p. 199°, from isopropanol (Found: C, 59·7; H, 7·4; N, 3·5. $C_{19}H_{28}BrNO_2$ requires: C, 59·7; H, 7·4; N, 3·7%).

1-(3,3-*Dimethylallyl*)-4-*phenyl*-4-*propionyloxypiperidine and its* 3-*methyl analogue.* 1-Chloro-3-methylbut-2-ene (5·8 g) was added dropwise to a stirred mixture of 4-phenyl-4-piperidinol (9 g), benzene (150 ml), acetone (100 ml) and Na_2CO_3 (16 g). The mixture, after heating under reflux for 6 hr, was filtered and the filtrate fractionally distilled to give 1-(3,3-dimethylallyl)-4-phenyl-4-piperidinol (7 g), b.p. 142°/0·9 mm. This alcohol (6 g) was also obtained by reducing 1-($\beta\beta$-dimethylacryloyl)-4-phenyl-4-piperidinol (10 g) with aluminium lithium hydride (1·5 g) in tetrahydrofuran (150 ml); this *amide* (6 g), m.p. 104°, from chloroform (Found: C, 73·7; H, 7·95; N, 5·1. $C_{16}H_{21}NO_2$ requires: C, 74·1; H, 8·1; N, 5·4%) was obtained by treating 4-phenyl-4-piperidinol (8 g) with $\beta\beta$-dimethylacryloyl chloride (5·3 g) (Smith & Englehart, 1949) in the presence of Na_2CO_3 (10 g). A mixture of 1-(3,3-dimethylallyl)-4-phenyl-4-piperidinol (2 g), pyridine (3 ml) and propionic anhydride (3 ml) was heated under reflux for 3 hr and the product then decolorized with charcoal, filtered and evaporated. The residue, neutralized with 10% HBr in isopropanol and diluted with ether, gave 1-(3,3-*dimethylallyl*)-4-*phenyl*-4-*propionyloxypiperidine hydrobromide* (1·6 g), m.p. 181°, from isopropanol (Found: C, 60·0; H, 7·2; N, 3·9. $C_{19}H_{28}BrNO_2$ requires C, 59·7; H, 7·4; N, 3·7%). 3-Methyl-4-phenyl-4-piperidinol (15 g) Carabateas & others, 1963) treated with 1-chloro-3-methylbut-2-ene (9 g)

and $NaHCO_3$ (20 g), as previously described, gave 1-(3,3-*dimethylallyl*)-3-*methyl*-4-*phenyl*-4-*piperidinol* (6 g), b.p. 180–190°/1·5 mm (Found: C, 78·8; H, 9·3; N, 5·5; equiv. wt 261. $C_{17}H_{25}NO$ requires: C, 78·7; H, 9·7; N, 5·4%; equiv. wt 259). This alcohol (3 g), esterified with propionic anhydride (5 ml) and pyridine (5 ml), as previously described, gave 1-(3,3-*dimethylallyl*)- 3 -*methyl*- 4 -*phenyl*- 4 -*propionyloxypiperidine hydrobromide*, m.p. 169°, from isopropanol (Found: N, 3·7. $C_{20}H_{30}BrNO_2$ requires: N, 3·5%). Nmr characteristics of the 3-methyl substituent: Base, doublet 40 cycles/sec (J 6·7 cycles/sec); HBr, doublet 42 cycles/sec (J 6 cycles/sec) from tetramethylsilane.

Nmr spectra were recorded at 60 megacycles/sec on a Perkin-Elmer R-10 instrument, using $CDCl_3$ as solvent and tetramethylsilane as internal standard.

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