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Structure-activity relations in analgesics based on 4-anilinopiperidine

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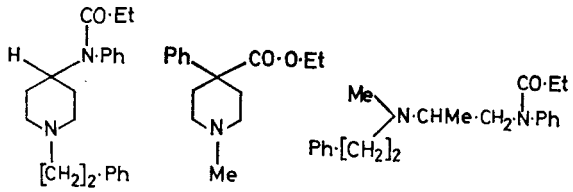
The synthesis of some 1-alkyl and 1-aralkyl-4-(*N*-phenylpropionamido)piperidines and related derivatives is described and the hot-plate activities in mice of these compounds reported. Activity variations among 1-methyl, 1-benzyl, and 1-phenethyl derivatives resemble those of corresponding open-chain anilide rather than 4-phenyl-piperidine analgesics. Infrared and nmr data show the two nitrogen atoms of the 4-anilinopiperidine derivatives to be further apart than those of open-chain anilides in their respective preferred conformations; these results, together with the extreme potency difference between the *N*-phenethyl derivatives diampromide and fentanyl, show that the two classes are best regarded as mutually distinct types of analgesic.

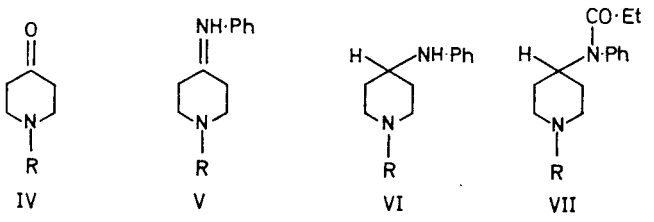
The analgesic fentanyl (I), introduced early this decade (Janssen, 1962), has proved a useful agent for the relief of pain and for neurolept analgesia, an anaesthetic technique in which an analgesic-tranquillizer mixture is given intravenously usually as an adjunct to nitrous oxide (Gorodetzky & Martin, 1965). It shows characteristic morphine-like effects e.g. Straub tail, mydriasis, and constipation in mice, and respiratory depression in dogs and cats, and appears to be a typical narcotic analgesic (Gardocki & Yelnosky, 1964; Gardocki, Yelnoksy & others, 1964). Fentanyl possesses molecular features of both 4-phenylpiperidine analgesics (e.g. pethidine, II) and open-chain basic anilides (e.g. diampromide, III, and its 2-thienyl analogue), and the present structure-activity study of 1-substituted 4-(*N*-phenylpropionamido)piperidines was made to obtain data which may help to establish more clearly its structural classification. This type of correlation among compounds with analgesic properties is of value, as it may lead to a better understanding of drug-receptor uptake modes and characteristics of the analgesic receptor (Portoghese, 1965; Casy, Simmonds & Staniforth, 1968).



I II III

CHEMISTRY

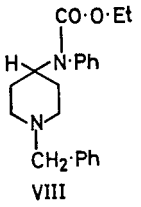
The 1 substituted 4-(*N*-phenylpropionamido)piperidines VII were obtained from 1-alkyl-or 1-aralkyl-4-piperidones IV by the three stage process IV to VII based upon a patent procedure (Janssen, 1964). Toluene-*p*-sulphonic acid was used as catalyst for



IV V VI VII

R= a) Me, b) CH_2·Ph, c) $[CH_2]_2$·Ph, d) CH_2·CH:CH_2,
e) NMe_2, f) CH_2·CH:CMe_2, g) H

most piperidone-aniline condensations, but a better yield of the Schiff base Vb followed the use of zinc chloride, recently reported as a good catalyst for the synthesis of cyclohexane analogues (Bull, Hey & others, 1967). The Schiff bases V, characterized by strong ν_{CN} absorption bands at 1660 cm^{-1}, were acid-labile, the precursor piperidone (isolated as the diethyl acetal salt) being regenerated after attempts to make the hydrochloride of the Schiff base Vc. 4-(*N*-Phenylpropionamido)piperidine VIIg, obtained by catalytic debenzylation of the anilide VIIb, was also sensitive to acid, as shown by the loss of its acyl group after treatment with a slight excess of ethanolic hydrogen bromide. The ester VIII was prepared by reaction between 4-anilino-1-benzylpiperidine VIb and ethyl chloroformate, while the 1-allyl derivatives VIId and f were obtained by alkenylating 4-(*N*-phenylpropionamido)piperidine VIIg with the appropriate alkenyl halide.



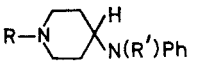
VIII

PHARMACOLOGY AND DISCUSSION

The analgesic properties of the 4-acylaminopiperidines VII and related compounds were assessed in mice (Jacobson & May, 1965) by the hot-plate test (Table 1); thanks are due to Dr. E. L. May, National Institutes of Health, Bethesda, Maryland, for arranging these tests. Structure-activity relations are compared below with those of 4-phenylpiperidine analgesics and open-chain basic anilide analgesics.

Influences of the 1-substituent upon activity within compounds 1 (methyl), 3 (benzyl) and 5 (phenethyl) (Table 1) are not typical of 4-phenylpiperidine analgesics, as in these, 1-methyl derivatives commonly have significant potencies while 1-benzyl analogues are, at the most, only feebly active (Beckett & Casy, 1965). It is true that replacement of a 1-methyl group by a 1-phenethyl group enhances activity in compounds of the same class but the increases, typically 3–4 fold (Janssen & Eddy, 1960), are not nearly so great as that seen in the 4-anilinopiperidines (Table 1). Activity variations amongst compounds 1, 3 and 5 more closely follow those of corresponding open-chain basic anilides, in which aralkyl-amino-substituents are essential for high activity, and dimethylamino-derivatives have only feeble analgesic properties (Table 2). However,

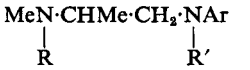
Table 1. *Analgesic activities of some 4-anilinopiperidines measured by the hot-plate test in mice after subcutaneous injection**



No.	R	R′	ED50 mg/kg
1	Me	CO·Et	Inactive (100 mg/kg)
2	Me	H	7·5
3	CH_2·Ph	CO·Et	10·45
4	CH_2·Ph	CO·O·Et	78·0
5 (Fentanyl)	$[CH_2]_2$·Ph	CO·Et	0·01
6	CH_2·CH : CH_2	CO·Et	12·1
7	CH_2·CH : CMe_2	CO·Et	9·8
8	NMe_2	CO·Et	inactive (100 mg/kg)

* Method of Jacobson & May (1965); *cf.* pethidine ED50 4·7 mg/kg

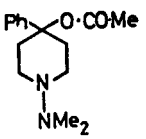
Table 2. *Analgesic activities of some open-chain basic anilides*



			Activity (mg/kg)	
Ar	R	R′	AD50 (tail flick)*	ED50 (hot plate)†‡
Ph	Me	CO·Et	—	50
Ph	CH_2·Ph	CO·Et	8	15
Ph	$[CH_3]_2$·Ph	CO·Et	3·7	—
2-Thienyl	Me	CO·Et	—	46·5
2-Thienyl	CH_2·Ph	CO·Et	—	29·9
2-Thienyl	$[CH_2]_2$·Ph§	CO·Et	—	7·1
2-Thienyl	$[CH_2]_2$·Ph	CO·O·Et	—	>100

* In rats (Wright and Hardy, 1963); pethidine AD50 = 11 mg/kg
† in mice (Casy and Hassan, 1967); pethidine ED50 = 23 mg/kg
‡ Thienyl derivatives: in mice (Sugimoto & others, 1962); morphine hydrochloride ED50 = 6·8 mg/kg
§ MeNR·CHMe·$[CH_2]_2$·NR′Ar analogue, ED50 57·7 mg/kg

although replacement of a 1-benzyl group by a 1-phenethyl group enhances activity in both the 4-anilinopiperidines and the open-chain basic anilides, the degree of potency rise is far greater in the 4-anilinopiperidines (the potency rise is 2–4 fold in the open-chain basic anilides but over 800 in the 4-anilinopiperidines). The dimethylamino-piperidine derivative IX related to a reversed ester of pethidine is about two-thirds as active as pethidine in the mouse hot-plate test (Beckett & Greenhill, 1961), a result in contrast with the complete inactivity of the 4-anilinopiperidine compound 8 (Table 1). The large decrease in activity following replacement of the *N*-propionyl group in compound 3 by the ethoxycarbonyl group (compound 4) is also seen in open-chain basic anilides (Table 2).



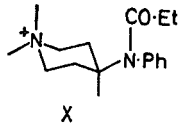
IX

The significant activity of the 1-allyl and the 1-(3-methylbut-2-enyl) derivatives, compounds 6 and 7 (Table 1), distinguishes the 4-anilinopiperidine analgesics from the morphine, morphinan and benzomorphan class, *N*-allyl derivatives of which are analgesic antagonists rather than agonists in animals. The analgesic potencies of compounds 6 and 7 are, however, considerably lower than those of comparable 4-phenylpiperidines (Casy & others, 1968).

The relative potencies of compounds 1 and 2 are unusual in that the compound lacking an *N*-propionyl function [established as the optional substituent in open-chain basic anilide analgesics (Sugimoto, Okumura & others, 1962)] is only slightly less active than pethidine, while its *N*-acylated analogue is completely inactive. Further data upon the analgesic properties of related diamines are being sought.

It is concluded from these pharmacological results that heterocyclic-substituted anilide analgesics based on 4-anilinopiperidine are more closely related to open-chain basic anilide analgesics than to 4-phenylpiperidine analgesics; the two classes of anilide differ, however, in the large potency discrepancy between the heterocyclic and open chain 1-phenethyl derivatives.

Further evidence bearing upon the common classification of open-chain basic and heterocyclic-substituted anilide analgesics may be obtained by a comparison of their preferred conformations. If the relative orientations of key functions in the two classes prove to be alike, support is provided for their having similar uptake modes at the receptor. Although agonists do not necessarily associate with their receptors in the more stable conformations (binding forces offsetting conformational energy barriers), it seems reasonable, as an initial approach, to compare conformers that are likely to be the more highly populated under physiological conditions. On steric grounds more favoured conformers of 4-anilinopiperidine derivatives are predicted to be piperidine-chairs with equatorial anilido-groups (X), and support for this conclusion

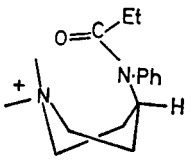


X

is provided from the following spectroscopic evidence. In the nmr spectra of bases and salts of the derivatives VIIa, VIIb and VIIc, 4-methine proton signals near 5τ are resolvable because they are moved downfield from ring proton signals, etc. by the adjacent deshielding anilide substituent. All the methine signals are broad multiplets of about 36 Hz width, clear nonets being obtained for the 1-methyl and 1-phenethyl bases from which coupling constants near 4–5 and 11·0 Hz may be abstracted (assuming an approximately first order system). Signal widths and coupling constants of these orders are consistent with the operation of 2 axial-axial and 2 axial-equatorial spin-spin coupling interactions regarding the 4-methine signal (Bhacca & Williams, 1964; Chen & Le Fèvre, 1965) and support X as the preferred conformation of 4-anilinopiperidine derivatives. This conclusion refers to bases and hydrochloride salts as solutes in $CDCl_3$; data in water would be of greater pharmacological significance but unfortunately the methine signals of hydrochloride salts in D_2O were obscured by the residual water signal.

In open-chain basic anilides (e.g. III), evidence for the proximity of the two nitrogen atoms was provided by the significantly greater $\nu_{C=O}$ stretching frequency values of hydrochloride salts compared with those of free bases (Casy & Hassan, 1967). In

contrast, the hydrochloride and base of the heterocyclic-substituted anilide VIIb had almost identical $\nu_{C=O}$ values as solutes in $CHCl_3$ (see experimental) and this result shows that the population of flexible conformers of type XI (where the protonated nitrogen atom may be close enough to the anilido-nitrogen atom to influence the $\nu_{C=O}$ value) must be low.



XI

As noted above, there is evidence that the two nitrogen atoms of open-chain basic anilides (separated by a two-carbon chain) are close together in their preferred conformations* and the *N*-to-*N* distance may well have a significant influence upon activity in the open-chain class as analogues in which the nitrogen atoms are separated by a three-carbon chain are only feebly active (Table 2). A carbon chain of the same length connects the nitrogen atoms of fentanyl and its congeners but these centres may approach each other if the molecule adopts the skew-boat conformation XI. Spectroscopic evidence already given, however, clearly supports the chair form X and provides no support for flexible conformers.

Conformational considerations do not, therefore, uphold the like classification of open-chain basic and heterocyclic-substituted anilide analgesics and this evidence, together with the extreme potency difference between the *N*-phenethyl derivatives diampromide and fentanyl, show that the two classes are best regarded as mutually distinct types of analgesic.

EXPERIMENTAL

Salts crystallized from acetone or ethanol-ether unless otherwise stated.

1-Benzyl-4-(N-phenylpropionamido)piperidine and related compounds. A mixture of 1-benzyl-4-piperidone IVb (28·5 g), aniline (18 g), toluene-*p*-sulphonic acid (15 mg) and toluene (240 ml) was heated under reflux for 15 h and then fractionally distilled to give the Schiff base Vb (10·5 g, 37%), b.p. 210°/0·5 mm (Janssen, 1964, gives b.p. 170°/0·05 mm) (Found: C, 81·5; H, 7:8; N, 10·4. $C_{18}H_{20}N_2$ requires: C, 81·8; H, 7·6; N, 10·6%). A mixture of IVb (57 g), aniline (36 g), zinc chloride (0·1 g) and xylene (500 ml) gave the Schiff base Vb in 53% yield (42 g) after a 24 h reflux period. A mixture of Vb (31·2 g), lithium aluminium hydride (9·6 g) and ether (500 ml) was heated under reflux for 5 h, then cooled, decomposed with water and filtered. The product, 4-anilino-1-benzylipiperidine VIb (35 g), m.p. 85–86° (Janssen, 1964, gives m.p. 84·8–86°) gave a *dihydrochloride*, m.p. 318–319° (Found: C, 64·3; H, 7·3. $C_{18}H_{24}Cl_2N_2$ requires C, 63·7; H, 7·1%). A mixture of VIb (15 g), propionic anhydride (10 g) and benzene (200 ml) gave 1-benzyl-4-(*N*-phenylpropionamido)piperidine VIIb (18 g) after a 3 h reflux period. It formed a *hydrochloride*, m.p. 235–237° (Found: C, 70·7; H, 7·6; N, 7·6. $C_{21}H_{27}ClN_2O$ requires: C, 70·3, H, 7·6; N, 7·8%). The following related compounds were prepared similarly:

* The physical possibility of the two nitrogen atoms being in juxtaposition has been demonstrated by an X-ray analysis of (+)-*N*-[2-(benzylmethylamino)propyl]propionanilide hydrobromide, in which the *N*–*N* distance (3·02 Å) barely exceeds the sum of the two van der Waals' radii (3·0 Å) (Ahmed, personal communication).

1-*Methyl*-4-(N-*phenylpropionamido*)*piperidine* VIIa, b.p. 126–128°/0·1 mm (Found: C, 73·6; H, 9·2; N, 11·6. $C_{15}H_{22}N_2O$ requires: C, 73·1; H, 9·0; N, 11·4%), *hydrochloride*, m.p. 265–266° (Found: C, 62·0; H, 8·5; N, 10·3. $C_{15}H_{23}ClN_2O$ requires: C, 62·1; H, 8·6; N, 10·35%) from the *Schiff base* Va, b.p. 134–136°/0·5 mm (Found: C, 76·5; H, 9·0; N, 15·0. $C_{12}H_{16}N_2$ requires: C, 76·5; H, 8·6; N, 14·9%) and 4-*anilino*-1-*methylpiperidine* VIa, m.p. 81–82° from aqueous ethanol (Found: C, 75·5, H, 9·5; N, 14·9. $C_{12}H_{18}N_2$ requires: C, 75·7; H, 9·5; N, 14·7%), *dihydrochloride*, m.p. 260–262° (Found: C, 54·3; H, 7·8; N, 10·35. $C_{12}H_{20}Cl_2N_2$ requires: C, 54·75; H, 7·7; N, 10·6%).

1-*Phenethyl*-4-(N-*phenylproprionamido*)*piperidine* VIIc, m.p. 82–84° (Janssen, 1964, gives m.p. 83–84°), *hydrochloride*, m.p. 254–255 (Found: C, 71·0; H, 7·75; N, 7·3. $C_{22}H_{29}ClN_2O$ requires: C, 70·9; H, 7·8; N, 7·5%) from the Schiff base Vc, b.p. 198–200°/0·4 mm and 4-*anilino*-1-*phenethylpiperidine* VIc, m.p. 90–91° from light petroleum (b.p. 60–80°) (Found: C, 80·9; H, 8·65; N, 9·95. $C_{19}H_{24}N_2$ requires: C, 81·4; H, 8·6; N, 10·0%), *dihydrochloride*, m.p. 261–262° from methanol (Found: C, 64·4; H, 7·4; N, 7·9. $C_{19}H_{26}Cl_2N_2$ requires: C, 64·6; H, 7·4; N, 7·9%).

The 1-*Dimethylamino*-4-(N-*phenylpropionamido*)*piperidine* VIIe, b.p. 183°/1 mm (Found: C, 69·4; H, 9·1; N, 15·3. $C_{16}H_{25}N_3O$ requires: C, 69·8; H, 9·1; N, 15·3%), *hydrobromide*, m.p. 193° (Found: C, 53·9; H, 7·1; N, 11·9. $C_{16}H_{26}BrN_3O$ requires: C, 53·9; H, 7·3; N, 11·8%) from the *Schiff base* Ve, b.p. 180°/1·3 mm (Found: C, 71·2; H, 9·1. $C_{13}H_{19}N_3$ requires: C, 71·8; H, 8·8%) and 4-*anilino*-1-*dimethylaminopiperidine* VIe, b.p. 189°/2 mm (Found: C, 70·6; H, 9·4. $C_{13}H_{21}N_3$ requires C, 71·2; H, 9·6; *hydrobromide*, m.p. 220° (Found: C, 52·1; H, 7·4; N, 13·8. $C_{13}H_{22}BrN_3$ requires: C, 52·0; H, 7·4; N, 14·0%).

The Schiff base Vc was converted to the diethyl acetal hydrochloride of 1-phenethyl-4-piperidone IVc, m.p. 184–186° (Beckett & others, 1959, give m.p. 178–179°) (Found: C, 64·7; H, 8·9; N, 4·5. Calc. for $C_{17}H_{28}ClNO_2$: C, 65·1; H, 9·0; N, 4·5%) on treatment with ethanolic hydrogen chloride.

1-*Alkylations of* 4-N-*phenylpropionamidopiperidine*. A mixture of 1-benzyl-4-(*N*-phenylpropionamido)piperidine VIIb (13 g), palladized charcoal (2 g, 5%) and ethanol (200 ml) was shaken with hydrogen (room temperature, atmospheric pressure) until gas absorption ceased. The suspension was filtered and the filtrate evaporated to give 4-(*N*-phenylpropionamido)piperidine VIIg (7 g), m.p. 84–85° (Janssen, 1964, gives m.p. 83–85°). It was converted to 4-*anilinopiperidine* (VIg) *dihydrobromide*, m.p. 266–268° (Found: C, 39·9; H, 5·65; N, 8·9. $C_{11}H_{18}Br_2N_2$ requires: C, 39·1; H, 5·4; N, 8·3%) on treatment with ethanolic hydrogen bromide. A mixture of VIIg (7 g), allyl bromide (4 g), sodium bicarbonate (13 g) and acetone (200 ml) was stirred and heated under reflux for 11 h. The cooled mixture was filtered, the filtrate evaporated and the residue acidified with hydrogen bromide in isopropanol to give 1-*allyl*-4-(N-*phenylpropionamido*)*piperidine* (VIId) *hydrobromide*, m.p. 199° (Found: C, 57·8; H, 6·9; N, 7·6. $C_{17}H_{25}BrN_2O$ requires: C, 57·8; H, 7·1; N, 7·9%). A similar alkylation of VIIg with 1-chloro-3-methylbut-2-ene gave 1-(3-*methylbut*-2-*enyl*)-4-(N-*phenylpropionamido*)*piperidine* (VIIf) *hydrobromide*, m.p. 233 (Found: C, 59·6; H, 7·2; N, 7·5. $C_{19}H_{29}BrN_2O$ requires: C, 59·8; H, 7·1; N, 7·4%).

1-*Benzyl*-4-(N-*ethoxycarbonyl*-N-*phenylamino*)*piperidine*. A mixture of 4-anilino-1-benzylpiperidine VIb (13·3 g), ethyl chloroformate (7·65 g) and benzene (50 ml) was heated under reflux for 3 h and then evaporated to dryness. The residue was made

alkaline with aqueous potassium hydroxide solution and extracted with ether. The *N*-ethoxycarbonyl derivative VIII (9·5 g), recovered from the extract, formed a *hydrochloride*, m.p. 229–230° (Found: C, 67·4; H, 7·2; N, 7·2. $C_{21}H_{27}ClNO_2$ requires: C, 67·3; H, 7·3; N, 7·5%).

Infrared data upon 1-*benzyl*-4(*N-phenylpropionamido*) *piperidine.*

Base $\nu_{C=O}$ 1650 cm^{-1} (film), 1637 cm^{-1} (10, 5, 3 and 1% solution in chloroform).

Hydrochloride $\nu_{C=O}$ 1654 cm^{-1} (Nujol mull), 1636 $\pm$ 1 cm^{-1} (10, 5, 3, 1, 0·5, 0·3 and 0·1% solution in chloroform).

Infrared spectra were recorded on a Unicam S.P. 100 spectrometer and nmr spectra on a Varian A-60 spectrophotometer using deuterochloroform as solvent and TMS as internal standard.

Acknowledgement

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