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3-Allyl analogues of fentanyl

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The proposal that the narcotic analgesic fentanyl represents a variant of 4-arylpiperidine analgesics and may thus be classified with pethidine and its reversed ester (Casy 1978), is supported by the fact that the influence of 3-methyl substituents on potency (substantial rise for methyl *cis* to the 4-aryl group while a *trans* substituent has little influence) is the same in the two classes of analgesic (Casy 1973; Van Bever et al 1974). Since the effect on potency of 3-allyl in reversed esters of pethidine differs radically from that of methyl (potency raised over ten fold by allyl *trans* to 4-aryl and depressed by a *cis* substituent) (Bell & Portoghese 1973; Iorio et al 1973), we have examined the 3-allyl analogue of fentanyl to investigate further comparative structure-activity relationships in the two groups of analgesic.

The 3-allyl analogue (5a), m.p. 106–108 °C (Found: C, 70·07; H, 7·69: N, 6·34. $C_{25}H_{33}N_2OCl.H_2O$ requires C, 69·60; H, 8·12; N, 6·50%) was made from 1-carbethoxy-4-piperidone by the sequence (1) through (5a). The corresponding *N*-methyl derivative (5b), m.p. 135–136 °C (Found: C, 66·74: H, 8·67; N, 8·62. $C_{18}H_{27}N_2OCl$ requires C, 66·96; H, 8·43; N, 8·68%) was made similarly from 3-allyl-1-methyl-4-piperidone (Bell & Portoghese 1973). Reduction of the anil (3) was highly stereoselective and only the *cis* 3-allyl diastereoisomer was isolated in each case. Details of synthesis and evidence of stereochemistry (based on ^1H and ^{13}C n.m.r. data) will be reported elsewhere.

The *cis* 3-allyl analogue of fentanyl (5a) proved to be 0·13 to 0·14 times as potent as the parent compound (ED50 mg kg^{-1} 0·08 for 5a and 0·011 for fentanyl, iv route) in rats by the tail-withdrawal test, a result in close correspondence with the influence of a *cis* 3-allyl group on the potency of the reversed ester of pethidine (approx. 10 fold decrease). The substantially lower activity of the *N*-methyl derivative (5b) in the same test (ED50 10 mg kg^{-1}) further illustrates the importance of the contribution of the *N*-phenethyl feature of fentanyl to activity (Casy et al 1969).

Thus data on the effects of 3-substitution (methyl and allyl) so far available support the view of fentanyl and pethidine-related analgesics sharing common drug-receptor association modes. Results on studies of phenolic analogues of the two series further corroborate this argument in that 3-hydroxyphenyl congeners of fentanyl (Lobbezoo et al 1980), the reversed ester of pethidine (Portoghese et al 1981) and alphaprodine (unpublished results) are all inferior in opiate receptor affinity and/or antinociceptive potency to respective parent compounds with unsubstituted phenyl substituents. These last results are in sharp contrast to findings in rigid analgesics of the morphine, morphinan and 6,7-benzomorphan class in which the presence of a meta-placed phenolic group is essential if high potency is to be achieved.

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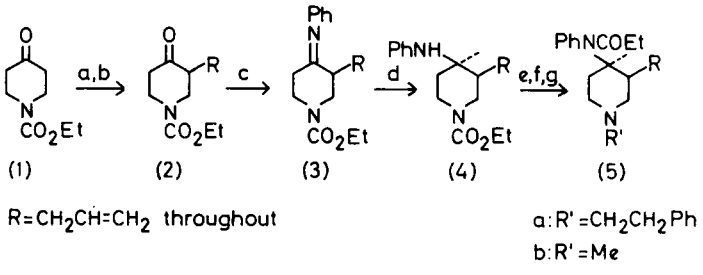

Reagents: (a) pyrrolidine (gives enamine); (b) allyl bromide; (c) aniline-*p*-toluene sulphonic acid; (d) $NaBH_4$; (e) KOH-isopropanol; (f) $PhCH_2CH_2Br$-K_2CO_3; (g) $(EtCO)_2O$.

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