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Agonist and antagonist potencies of isomeric 2,3-dimethyl-3-aryl-piperidines

Iorio & Casy (1975) recently reported on the antinociceptive effects of diastereoisomers of 2,3-dimethyl-3-aryl-piperidines and on their antagonist properties in rats and monkeys. These compounds have now been assayed on the guinea-pig isolated ileum by the method previously described (Kosterlitz & Watt, 1968). The results (Table 1) indicate general agreement with the observations obtained *in vivo*. The *N*-phenethyl isomers have relatively weak agonist activity, the α-isomer being more potent than the β-isomer. The *N*-allyl isomers are devoid of agonist activity. The antagonist potencies of all 4 compounds are low, the β-isomer of the allyl analogues being more active than the α-isomer while the reverse relationship holds for the phenethyl analogues. These observations agree with the data obtained on morphine-dependent monkeys.

Table 1. *Assessment of 2,3-dimethyl-3-*m*-hydroxyphenyl-1-R_1-piperidines*

R_1	Isomer	ID50 (nM)	Ke (nM)	Relative agonist potencies (morphine or normorphine = 1) Ileum	Nilsen	Relative antagonist potencies (naloxone = 1) Ileum	Dependent monkey
Phenethyl	α	291 ± 51	99·7 ± 10·3	0·21 ± 0·01	0·17	0·012 ± 0·001	Mild-intermediate withdrawal
Phenethyl	β	2138 ± 354	389 ± 57	0·03 ± 0·005	0·07	0·003 ± 0·001	Very mild withdrawal
Allyl	α	infinite	141 ± 16	0	0	0·009 ± 0·001	<0·05
Allyl	β	infinite	56·7 ± 7·9	0	0	0·023 ± 0·003	0·05–0·1

The values are the means ±s.e. of 4 observations (5 with α-allyl). α is cis and β trans in respect of Me_3/Ph_3. The results on the morphine-dependent monkey (Dr. E. L. Harris & Dr. M. Aceto, Virginia Medical College) and those of the Nilsen antinociceptive tests in mice have been supplied by Dr. M. A. Iorio and Dr. E. L. May.

Iorio & Casy (1975) point out that certain *N*-allyl 4-aryl-piperidines (analogues of pethidine and its reversed ester and of ketobemidone) are *in vivo* agonists without antagonist action. In agreement with these observations it has been shown that, in the guinea-pig ileum, the *N*-allyl analogues of alphaprodine (ST47; Dr. D. H. Staniforth) and of betaprodine (ST121) have no antagonist activity (Kosterlitz & Waterfield, 1975). Similar findings were obtained with *N*-allyl-4-phenyl-4-propionyl-oxy-piperidine (ST46), *N*-(3,3-dimethylallyl)-4-(*N*-phenyl)-4-propionamido-piperidine (ST71), *N*-allyl-4-(*N*-phenyl)-4-propionamido-piperidine (ST87) and *N*-(3,3-dimethyl-allyl)-norpethidine (ST48) (Kosterlitz, Waterfield & Berthoud, 1973). On the other hand, the *N*-hexyl- and *N*-heptylnorketobemidones have antagonist potencies similar to those found for the *N*-allyl derivatives shown in Table 1 (Kosterlitz, Leslie & Waterfield, 1975).

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