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Stereochemical correlation of the more active antipodal forms of opiate antagonists based on 3-*m*-hydroxyphenyl derivatives of pyrrolidine and piperidine

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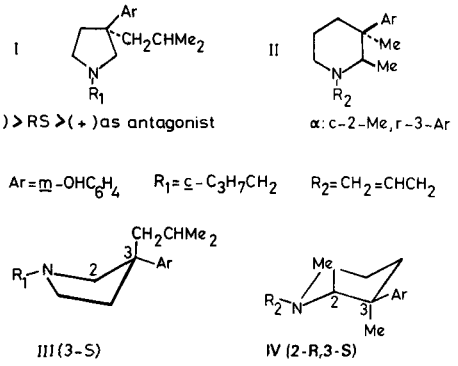
Analgesics related to 3-phenylpyrrolidine and 3-phenylpiperidine share two important structure-activity relationships with the morphine-morphinan-6,7-benzomorphan group, namely (1) a phenolic hydroxyl of meta orientation in the aromatic ring, and (2) the antagonist properties of derivatives with allyl or cyclopropylmethyl substituents attached to the basic centre (Bowman et al 1973: Iorio & Casy 1978).

Receptor stereoselectivity as found for (I) is reported here for α-1-allyl-2,3-dimethyl-3-(*m*-hydroxyphenyl)-



piperidine (II), a 3-arylpiperidine with a potency close to that of nalorphine as an antagonist of fentanyl (Iorio & Casy 1975). Antipodal forms of II were obtained from fractionally crystallized (+)- and (−)-tartrates of the corresponding 3-methoxyphenyl secondary base with specific rotations of −26·4 and +25·0 respectively ($[\alpha]_D^{20}$ *c* 1·1 in MeOH, HCl salts m.p. 223–224 °C), by N-allylation followed by O-demethylation as reported for racemic material (Iorio & Casy 1975). α-(+)-II HCl had m.p. 216–217 °C, $[\alpha]_D^{20}$ +9·5 (*c* 1 in EtOH) (Found: C, 66·3; H, 9·0; N, 4·65. $C_{16}H_{24}ClNO\ 0.5H_2O$ requires C, 66·1; H, 8·7; N, 4·8%) and α-(−)-II HCl m.p. 218–219 °C, $[\alpha]_D^{20}$ −8·3 (*c* 1 in MeOH) (Found: C, 66·45; H, 9·0; N, 4·7%). The antipodes were tested as antagonists of fentanyl in rats and the data (Table 1) clearly show that the laevo isomer is the more potent.

The absolute configurations of the more active antipodes (−)-I and (−)-II were established by X-ray diffraction analyses of corresponding HBr salts and are shown diagramatically in III and IV respectively (details will be published elsewhere). (−)-I HBr had m.p. 158–159 °C (Found: C, 60·8; H, 8·1; N, 3·9. $C_{18}H_{28}$-

* Correspondence.

Table 1. Antagonism of fentanyl (0·63 mg kg^{-1} s.c.)-induced effects in rats by antipodal forms of α-1-allyl-2,3-dimethyl-3-((*m*-hydroxyphenyl)piperidine (II) hydrochloride after i.v. injection.*

Antipode	Parameters	2·5 mg kg^{-1}	0·63 mg kg^{-1}	0·16 mg kg^{-1}	0·04 mg kg^{-1}
(+)-II	respiration	†††	†††	0	
	right. reflex	†††	0	0	
	rigidity	†††	††	0	
	tail withdr.	††	0	0	
	reflex duration	<30′	<30′		
(−)-II	respiration	†††	†††	†††	†
	right. reflex	†††	†††	0	0
	rigidity	†††	†††	†††	0
	tail withdr.	†††	†††	0	0
	reflex duration	30′–60′	<30′	<30′	

Key: ††† fully active; †† active; † very weak; 0 not active.
* See Iorio & Casy (1978) for details.

BrNO requires C, 61·1; H, 7·9; N, 3·95%) and (−)-II HBr m.p. 215–216 °C (Found: C, 58·7; H, 7·4; N, 4·1. $C_{16}H_{24}BrNO$ requires C, 58·9; H, 7·4; N, 4·3%). The crystallographic analysis of (−)-II confirms the relative configuration of the α-diastereoisomer deduced from n.m.r. evidence (Casy & Iorio 1974; Casy et al 1981).

Both (−)-I and (−)-II may adopt conformations close to that of the near-rigid analgesic α-(−)-metazocine, a model typical of the morphine group (Fig. 1). The best arrangement of the piperidine derivative in this respect is a boat form in which steric interactions of the axial methyls of the chain IV are relieved, and hence reasonable on energetic grounds. In all these conformations, distances between nitrogen and the aromatic feature (with centre of ring or OH function as point of

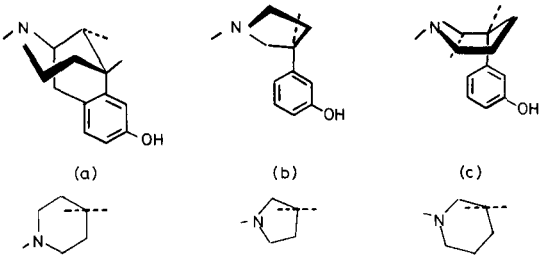


FIG. 1. Diagrams of the possible active conformations of laevo isomers of α-metazocine (a), the pyrrolidine I (b) and piperidine II (c). Substituent groups are omitted for clarity. Single, dotted and heavy lines denote bonds that lie approximately in, behind and above the plane of the paper respectively. Views of heterocyclic rings looking down on the molecules are beneath each structure: the dotted lines represent the end-on views of the aromatic moiety.

reference) are similar (Horn & Rodgers 1976). Further, a bimethylene chain projects in front of the aromatic plane when this is orientated in relation to the heterocyclic ring as it is in the benzomorphan (see views looking down on the molecules). In the dextro antipodal forms, projection of heterocyclic carbons in front of the aromatic plane is less extensive and this différence may be a key factor in determining the degree of interaction with the opiate receptor either in the provision of binding sites (perhaps to fit the 'cavity' originally proposed in 1954 by Beckett & Casy) or avoidance of a receptor area intolerant to non-polar elements. An alternative model for (−)-I and (−)-II is the 1-aza analogue of the benzomorphan of Fig. 1 (with N and C-1 interchanged) which, as a racemate, has a half to a third the potency of pethidine in mice antinociceptive tests and is significantly active in a binding assay (Iorio & Casy 1975; Iorio & Klee unpublished results). These facts demonstrate that the anionic site of the opiate receptor herein involved has some degree of tolerance to the siting of the cationic centre of the ligand (Fries & Portoghese 1976).

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Thyroid hormones do not alter rat brain benzodiazepine receptor function in-vivo

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It has recently been reported that thyroid hormones and their derivatives inhibit benzodiazepine receptor binding in a stereospecific manner in rat brain membranes in-vitro (Nagy & Lajtha 1983). The endocrinologically inactive isomer D-thyroxine was found to be the most potent inhibitor with both L-thyroxine (L-T_4) and L-triiodothyronine (L-T_3) being considerably less potent. It was also of interest that audiogenic-seizure susceptible mice (DBA/2J) have both high serum thyroxine concentrations (Seyfried et al 1978, 1979) and increased benzodiazepine receptor binding (Robertson 1980) during the seizure-susceptible period of development. These reports prompted us to investigate whether these thyroid hormones possess anticonvulsant properties in mature rats since they might have clinical relevance in the treatment of epilepsy. Furthermore, since high affinity benzodiazepine receptor ligands that antagonize the anticonvulsant effect of benzodiazepines have recently been reported (Hunkeler et al 1981; Nutt et al 1982) we have investigated whether these drugs modify in any way the anticonvulsant effects of the water-soluble benzodiazepine, flurazepam, and the proconvulsant properties of FG 7142, the methylamide of ethyl β-carboline 3-carboxylate, which also acts via the benzodiazepine receptor (Petersen et al 1982).

* Correspondence

Method

Seizure thresholds were measured using an intravenous infusion method (Nutt et al 1980) at various times following the acute or chronic administration of either D-thyroxine (D-T_4) or L-triiodothyronine (L-T_3) or their respective vehicles. In addition the effects of these compounds on the flurazepam-induced increase and the FG 7142-induced decrease in seizure threshold were evaluated (for details see Table 1). Rats weighed 130–150 g for the acute experiments and 190–210 g at the end of the chronic treatment.

Results and discussion

From Table 1, it can be seen that very large doses (approximately 100 times the dose required to restore thyroid function in hypothyroid rats) of the thyroid hormones had no effect on pentetrazol seizure thresholds, a system which is quite sensitive to the anticonvulsant effect of benzodiazepines (Nutt et al 1982). Seizure thresholds were unaltered at times when brain penetration was thought to be maximal (Ford & Cramer 1977; Vigoroux et al 1979) and 24 h later. Furthermore, the failure of these hormones to alter in any way the anticonvulsant effects of various doses of flurazepam or the proconvulsant effects of FG 7142 argued against their having any benzodiazepine receptor antagonist