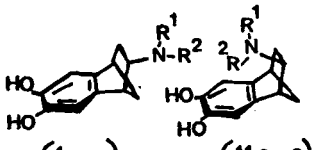
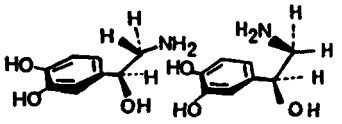
α-ADRENOCEPTOR PROPERTIES OF SOME DIHYDROXYBENZONORBORNENES DESIGNED AS RIGID CATECHOLAMINES

P. Burn, P.A. Crooks, C. Waldron† & P.E. Hicks†. Depts of Pharmacy, Pharmacology, Materia Medica & Therapeutics†, University of Manchester, M13 9PT, U.K.





a) $R^1 = R^2 = H$ b) $R^1 = CH_3$, $R^2 = H$ c) $R^1 = R^2 = CH_3$

The neurotransmitter noradrenaline (NA) is a flexible molecule that can exist in a number of conformational forms. In order to study the conformational requirements for the interaction of NA at α_2-receptors, we have synthesised a series of substituted exo-(I) and endo-(2)-aminobenzonorbornenes (II) which are structurally rigid molecules and which provide spatial approximations of the anti (III) and gauche (IV) forms of the NA molecule. A determination of adrenergic activities of these compounds is of particular interest since they also represent rigid analogues of the potent α_2-adrenoceptor agonist 2(N,N-dimethyl)6,7-dihydroxy-amino-tetraline (TL99; Hicks & Cannon 1980). Compounds Ia-c and IIa-c were prepared from 6,7-dimethoxybenzonorbornene, utilizing stereo specific synthetic routes, described for the aromatic unsubstituted compounds to the exo- and endo-series (Burn et al 1980).

Compounds were tested for α_2-adrenoceptor agonist activity in the stimulated guinea-pig ileum in vitro and in the pithed rat preparation in vivo as vasoconstrictor agents (Table 1). In the guinea-pig ileum the pA_2 for rauwolscine against Ib or TL99 was similar, 7.52 (7.26-7.78) and 8.06 (7.53-8.59) respectively, and indicates that these agonists act at the same receptor. This study suggests that a fully extended conformation of NA is necessary for α_2-adrenoceptor interaction. Interesting differences in agonist activity are shown for N-substituted derivatives of exo-amines Ia-Ic.

Table 1. Agonist potencies of N-substituted 2-aminobenzonobornenes

Agonist	guinea-pig ileum IC_{50} (μM)	pithed rat$^+$ EC_{50} (μg/kg)
TL99	0.03 (0.02 - 0.04)	1.68 (1.37 - 1.99)
I a	>52*	272 (209 - 354)
b	14 (9 - 21)	175 (117 - 263)
c	21 (12 - 37)	2722 (2187 - 3388)
II a-c	inactive 228-261	inactive 20,000

IC_{50} = 50% inhibition of stimulation., EC_{50} = 50 mmHg rise in Diastolic B.P., n = 4-9, † propranolol treated, * >52 μM causes contractile effects.

Hicks, P.E. & Cannon, J.G. (1980) J. Pharm. Pharmacol. 32: 786-788
Burn, P. et al (1980) Ibid. 32: 87-91

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