PREPARATION OF A SERIES OF NOVEL ANALOGUES OF OCTOPAMINE AND SYNEPHRINE

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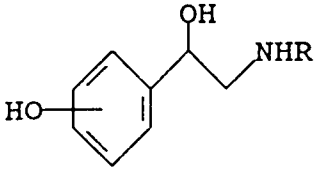
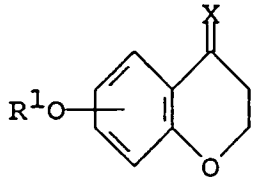
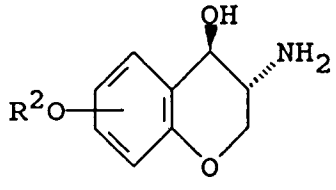
Increased activity at β-adrenergic receptors has been achieved by conformationally restricting the β-hydroxyamine moiety within the molecule (Nishikawa et al 1974). The more active analogues of adrenaline exist in the trans-diequatorial arrangement.
Octopamine (I, R=H), structurally related to noradrenaline, also possesses the β-hydroxyamine function and it is thought that activity of these compounds could be increased by similarily restricting this freely rotating function, by the formation of structures of type II.



I



II



III

Substituted 3-aminochromanol (III, R^2=H,CH_3) derivatives, which are conformationally restricted analogues of isomeric octopamines, have been prepared in order to test them for alpha, beta and octopaminergic (1, 2A and 2B) activity. These aminochromanols have been prepared from the 6-, 7-, and 8-methoxychromanones (II, X=O, R^1=CH_3) by the cyclization of the corresponding 3-(methoxyphenoxy) propionic acid with polyphosphoric acid (Glennon 1982). The 5-methoxychromanone was obtained by preparing the perchlorate salt of the chromone, liberation of the parent molecule by ion-exchange and hydrogenation in the prescence of 10% Pd/C to give the required chromanone. All monomethoxychromanones were converted to the corresponding tosyloximes, (II, X=NOTs, R^1=CH_3) via preparation of the oxime and the action of tosyl chloride.
The Neber rearrangement (O'Brien 1964) of the tosyl oximes in sodium ethoxide gave the 3-aminochromanones. The resultant ketoamines were then demethylated using 47% hydrobromic acid to give the required octopamine analogues. Subsequent reduction of the 3-amino-hydroxychromanones can yield either the cis or trans isomer. Initial attempts using sodium borohydride to give exclusively the trans isomers did not prove successful. Hydrogenation of the chromanones in either acidic or basic conditions gave the pure cis or trans isomers (Sugihara et al 1977).Cis and trans isomers can be clearly distinguished from each other by the NMR signal arising from the proton at C4. The spectra of the cis and trans amino-alcohols show the doublet at δ4.2-4.6 to a have coupling constant, J=5-6, 3-4Hz respectively(Lap et al 1979). JW and JMM wish to thank the Royal Pharmaceutical Society of Great Britain for finanicial support.

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