03.4-4 STRUCTURAL FACTORS GOVERNING AGONIST AND ANTAGONIST ACTIVITY IN THE GABA\(_A\) SYSTEM.

By G.W. Pooley and E.G. Steward, Molecular Medicine Group, The City University, London, U.K.

By comparing various semi-rigid GABA\(_A\) agonists and antagonists we can categorise separate structural requirements for GABA\(_A\) agonist and antagonist activity in three distinct ways:

(i) The arrangement of charge centres - corresponding to \(\mathrm{H}^+\) and \(\mathrm{COO}^-\) in GABA (G.W. Pooley and E.G. Steward, J. Molec. Struct., (1987) in press).

(ii) The presence of a suitably located benzene ring - for potent specific antagonist action.

(iii) The presence of steric bulk in the positive nitrogen region.

The possession of (ii) and (iii) in a drug appears to give it structural requirements for antagonist activity (Matsumoto et al., J. Med. Chem., 1987, 30, 354-358).

There are two crystal forms of hordenine sulfate: one, of lower symmetry, has been solved by the direct method (Johnson, Acta Crystallogr., Sec. B, 1983, 39, 222). The other, of higher symmetry, has been solved by the heavy-atom method (Johnson, Acta Crystallogr., Sec. B, 1983, 39, 222). The two molecules in the crystal and molecular structure are related by a crystallographic inversion centre.

Previous studies on the crystal structures of hordenine sulfate and related alkaloids have revealed the most likely geometry of the drug-receptor interactions of the non-hydrogen atoms with 3247 reflections has led to an R value of 0.11. The ethylamine sidechain in both the molecules adopt extended trans conformation (i.e. the torsion angle \(\tau_1\) is around \(90^\circ\), and \(\tau_2\) is around \(180^\circ\)). The plane of the phenyl ring is oriented at right angles to the plane of the side chain and these inter-planar angles are 59.6° and 78.5° respectively in the two molecules. In both the hordenine molecules, the \(\mathrm{N}\) atom is protonated and the distances and heights from the respective benzene rings are in conformity with those observed in other sympathomimetic amines. The structure is stabilised by a three-dimensional network of hydrogen bonds.

03.4-5 MOLECULAR RECOGNITION IN STRYCHNINE ALKALOID SALTS.

By R.G. Gould, P. Taylor and M.D. Walkinshaw, Chemistry Department, University of Edinburgh, United Kingdom.

Brucine and strychnine (Fig. 1) are two naturally occurring alkaloids, both of which have striking physiological activity, and both of which are powerful resolving agents for chiral anions.

These two functions are examples of molecular recognition. We have co-crystallised the alkaloid cations with several anionic amino acid derivatives in order to highlight the particular features in alkaloid molecules responsible for their chiral specificity. Nearly all of the structures we have studied exhibit alternating layers of alkaloid and peptide. We have analysed these packing types, and will illustrate the contact surfaces between peptide and alkaloid.