03.4-4 STRUCTURAL FACTORS GOVERNING AGONIST AND ANTAGONIST ACTIVITY IN THE $GABA_A$ SYSTEM.
By G.W.Pooler 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 N^+ and COO^- in GABA (G.W. Pooler and E.G. Steward, J. Molec. Struct., (1987) in press).

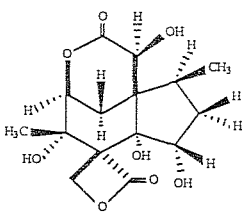
(ii) The presence of a suitably located benzene ring - for potent specific antagonist action.

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

The possession of (ii) and (iii) in a drug appears to be sufficient to preclude agonist activity, since GABA antagonists with these features (e.g. bicuculline and SR95103 (J.P. Chambon et al, Proc. Natl. Acad. Sci. USA, (1985) 82, 1832-1836)) are devoid of agonist activity. In addition, fulfilling just the first, 'linear', requirement for antagonist activity tends to yield GABA analogues which are inactive (e.g. iso-muscimol) or only weak antagonists (e.g. iso-THIP).

03.4-5 THE CRYSTAL STRUCTURE OF ANISATIN, A POTENT CONVULSANT. By J.M. Gulbis and M.F. Mackay, Department of Chemistry, La Trobe University, Bundoora, Victoria, Australia 3083.

Anisatin (1) is a very potent convulsant isolated from the seeds of *Illicium Anisatum L.* Present evidence indicates that its pharmacological effects are caused by interaction with the "picrotoxinin" binding site within the GABA-benzodiazepine chloride ionophore (Shinozaki, Ishida and Kudo, *Brain Res.*, 1981, 222, 401; Matsumuto and Fukuda, *ibid.*, 1983, 270, 103). Previous studies on the plant alkaloid, picrotoxinin, which is thought to bind at the same site, have revealed the most likely active conformation (Mackay and Sadek, *Aust. J. Chem.*, 1983, 36, 2211; Andrews, Iskander, Jones and Winkler, *ibid*; 1983, 36, 2219). The X-ray analysis of an ethyl-acetate solvate of anisatin was carried out to assist in the identification of the geometric requirements of the picrotoxinin binding site in collaboration with theoretical conformational analyses by Dr. M.G. Wong and co-workers at The Victorian College of Pharmacy Ltd.



(1)

Crystal data:
(1).$\frac{1}{3}$ ($C_4H_8O_2$), $C_{15}H_{20}O_8$, $P6_1$, a = 14.168(5), c = 14.609(2) Å, Z = 6, R = 0.048 for 1760 data ($I \geq \sigma I$).

03.4-6 STRUCTURE OF A SYMPATHOMIMETIC AMINE, HORDENINE SULFATE, $(C_{10}H_{15}NO)_2.H_2SO_4.2H_2O$. By S.Ghose and J.K.Dattagupta, Crystallography and Molecular Biology Division, Saha Institute of Nuclear Physics, 1/AF Bidhan Nagar, Calcutta 700 064, India.

It is generally assumed that the stereo-chemistry of the small drug molecules can be used to obtain indirect information about the topography of the active site of the receptor. Hordenine is a sympathomimetic amine and the crystal and molecular structure of hordenine sulfate has been studied to obtain some idea about the nature of the drug-receptor interactions of this class of comp-ounds. The structure has been solved using diffractometric data and direct methods. There are two molecules of hordenine in the asymmetric unit, and anisotropic refinement of the non-hydrogen atoms with 5247 reflec-tions 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 τ_1 is around 90° , and τ_2 is around 180°). The plane of the phenyl ring is oriented approximately at right angles to the plane of the side chain and these inter-planar angles are 69.6° and 78.5° respecti-vely in the two molecules. In both the hordenine molecules, the 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.

03.4-7 MOLECULAR RECOGNITION IN STRYCHNINE ALKALOID SALTS, By R.O. 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.

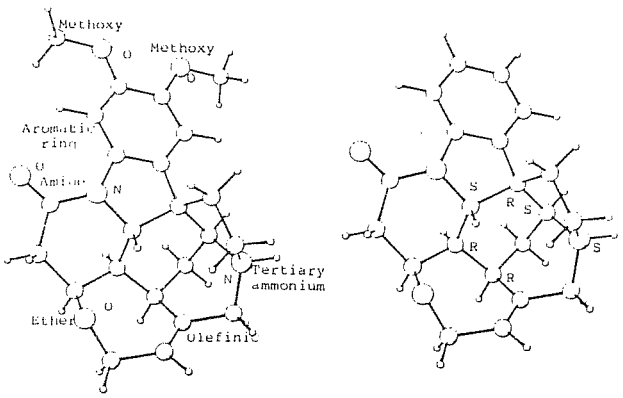


Fig. 1. Brucine with functions and strychnine with chiral centres.

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 alkaloid packing types, and will illustrate the contact surfaces between peptide and alkaloid.