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).

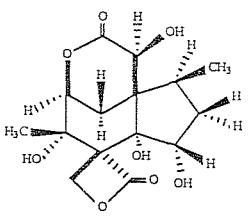
(ii) The presence of a suitably located benzene ring - for potent specific antagonist action.

(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.

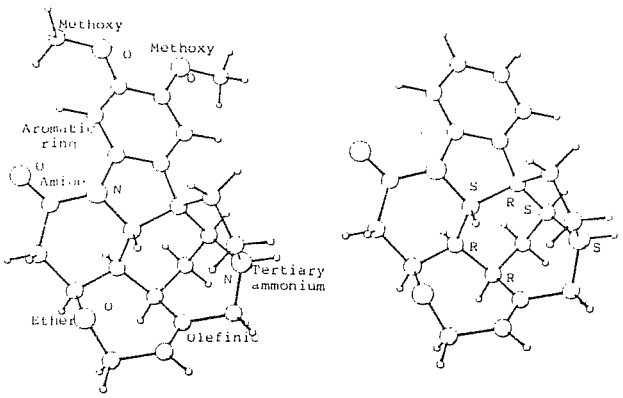


Fig. 1. Brucine with functions and strychnine with chiral centres.

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.

Strychnine crystallises with a variety of anions in two structural types (Fig. 2).

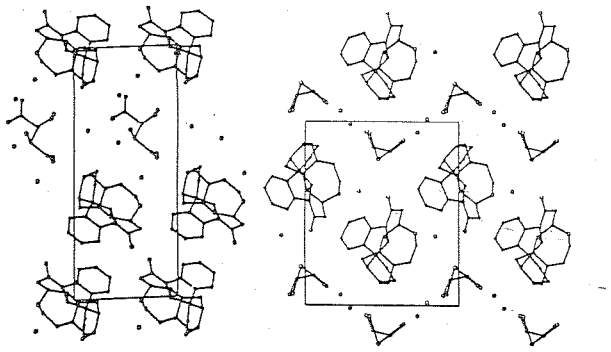


Fig. 2. Packing in strychnine (+) tartrate and strychnine (-) bitartrate.

They may both be described as bilayers with the strychnine molecules projecting hydrophilic portions toward one surface or the other. The bilayers differ in the extent of "grooving" to accommodate hydrophobic parts of counterions.

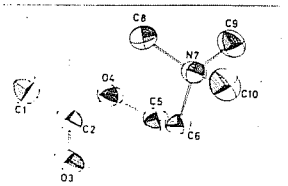
Brucine complexes are more widely used in resolutions than strychnine ones, and show greater variety. They can, however, normally be classed as corrugated monolayers of three types: channelled head-to-head, channelled head-to-tail, and offset head-to-tail. A range of examples will be presented and discussed.

03.4-8 MODELS FOR THE BINDING TO DNA OF CIS-PLATINUM DERIVATIVES CONTAINING BIDENTATE TERTIARY AMINES. By Max R. Taylor, Sally L. Birch, Sharon E. Lawton, Lisa J. Keefe and Louise M. Vilkins, School of Physical Sciences, The Flinders University of South Australia, Bedford Park, S.A. 5042, Australia, and John D. Orbell, St. Vincents Institute of Medical Research, 41 Victoria Pde., Fitzroy, Victoria, 3065, Australia.

The binding of the cis-$A_2Pt(II)$ cationic moiety (A = a monodentate amine or A_2 = a bidentate amine) to two adjacent guanine residues on the same strand of DNA, i.e. the formation of an intrastrand crosslinkage, is a leading hypothesis concerning the mode of action of cis-platinum antitumour agents. The effectiveness of these drugs is strongly influenced by the nature of the amine ligands(s) A or A_2. For example, the cytotoxic activity of these compounds is found to decrease along the series $A = NH_3 \approx NH_2R > NHR_2 > NR_3$. This may be wholly or in part due to intramolecular steric effects which would be expected to influence the formation and subsequent geometry of cis-platinum adducts with DNA.
To date, crystallographic investigations of model systems for an intrastrand cross linkage have involved compounds where two nucleobase derivatives are cis-coordinated to $A_2Pt(II)$, where A or A_2 are primary amines; representative of effective oncolytic agents. There is a paucity of structural information on model systems for cis-platinum derivatives which are ineffective due to the amines being secondary or tertiary - this requires the presence of relative bulky substituents on the coordinated nitrogen atoms.
The complexes
cis-[(TMED)Pt(9-methylguanine)$_2$]$(PF_6)_2$.$2H_2O$,
cis-[(TMED)Pt(9-ethylguanine)$_2$]$(ClO_4)_2$.$2H_2O$,
cis-[(TMED)Pt(1,3-dimethylxanthine)$_2$]$(PF_6)_2$.$4H_2O$ and
cis-[(TMED)Pt(1,3,9-trimethylxanthine)$_2$]$(PF_6)_2$.$\times H_2O$ where TMED = N,N,N^1,N^1-tetramethylethylenediamine have been prepared and structurally characterised by x-ray methods. Least-squares refinement has given R values of 0.020, 0.045, 0.059 and 0.09 respectively. Each [(TMED)Pt(Base)$_2$]$^{2+}$ cation shows square-planar geometry with the two crystallographically independent purine ligands coordinated through N(7) and arranged in a head-to-tail conformation so that the cation has approximately C_2 symmetry.
The structures are compared with each other and with related compounds in terms of their base/base and base/coordination plane dihedral angles, and their different crystalline environments.

03.5-1 PICRATES OF ACETYLCHOLINE AND METHOXYCARBONYLCHOLINE. By Karla Frydenvang and Birthe Jensen, Department of Chemistry BC, The Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark.

The title compounds have been studied at 105 K as part of a series of salts of acetylcholine and related compounds. A very clear correlation is found between conformation and geometry. The magnitude of the angle O4-C5-C6 varies from ∿100° in a fully extended choline ester to ∿113° in the most folded conformers.



Packing patterns in crystals may reveal preferred types of interaction between choline derivatives and neighbouring groups. Acetylcholine as well as methoxycarbonylcholine form a great number of contacts to oxygen atoms. Contacts from the quaternary ammonium group do not seem to be of greater importance than contacts from the acetyl- or methoxycarbonyl-moiety. Direct contacts between aromatic rings and the quaternary ammonium group in acetylcholine have been observed by NMR-techniques (Minch et al., J. Org. Chem., 1979, 44, 3247-3252). This type of contact is not found in the picrates. Their possible importance in crystals is being studied, based on data retrieved from the Cambridge Database (Allen et al., Acc. Chem. Res., 1983, 16, 146-155).