03. X–15 ANALYSIS AND DESIGN OF PROTEINS AND PEPTIDE DRUGS. By B. Robson, University of Manchester Medical School, Manchester M60, England.

There has recently been considerable interest in applying the lessons, learned from conformational analysis of peptide systems, to the design of artificial peptides. The chemical fourmulae are being sought which will give the required properties in vitro (eg. artificial enzymes) and in vivo (eg. as drugs such as neuropetide agonists or antagonists). An even more recent interest is being shown in the design of artificial vaccines. Calculation of the conformations and conformational behaviour of peptides is obviously an important part of the design procedure, and indeed the classic problem of predicting the native structures of natural proteins and oligopeptides may appear as part of that procedure. For example, one may need to predict the structure of a natural enzyme to design a peptide inhibitor to it, or of an oncogene product to design artificial vaccines against it. Examples will be drawn from work in our laboratory, including studies on TRH and analogues, neurotensin, chemotaxic factors, thrombin, and oncogene products. These studies span from detailed calculations on smaller oligopeptides to rapid approximate methods for calculation of the three dimensional structures of proteins 70-350 residues in length, and involve new advances in calculation technique.

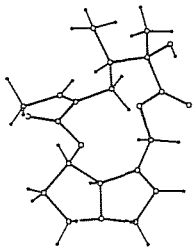
03. 1–1 CONFORMATIONAL STUDIES OF HEPATOTOXIC PYRROLIZIDINE ALKALOIDS. By M.F. Mackay, Department of Physical Chemistry, La Trobe University, Bundoora, Victoria, Australia 3083 and C.C.J. Culvenor, CSIRO, Division of Animal Health, Parkville, Victoria, Australia 3052.

Awareness of widespread human exposure in many countries to the hepatotoxic and carcinogenic pyrrolizidine alkaloids is increasing and with it the need to understand the degree of toxic hazard they pose. Crystallographic studies are being used to gain insights into the structural and conformational aspects which influence toxicity. The similarity between conformation in the solid state and solution can be gauged from nuclear magnetic resonance measurements.

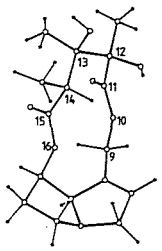
Toxicity of the alkaloids is dependent on protection of the ester groups from esterase attack, the protection being usually ascribed to steric hindrance by the highly substituted esterifying acids. In the macrocyclic diesters, the degree of protection is increased by the restricted rotation of bonds and by the ring itself hindering approach to the carbon end of the carbonyl groups. This is most marked in several alkaloids with a 12-membered ring such as senecionine (I), in which the carbonyls are *anti*-parallel and directed outwards from the ring. Even in the alkaloids with an 11-membered ring such as monocrotaline (II), in which the carbonyls are *syn*-parallel, substantial protection should occur.

A comparison of closely related alkaloids with a similar conformation, crispatine, fulvine (Sussman & Wodak, *Acta Cryst.* (1973) B29, 2918) and monocrotaline (Stoeckli-Evans, *Acta Cryst.* (1979) B35 231; Wang, *Sci. Sin.* (1981) 24, 497), the toxicity of which decreases in this order, suggests that lipophilic character rather than conformational difference is the main influence in determining their relative toxicity. Crispatine is more soluble than fulvine in lipid solvents, apparently because the stereochemistry of the 13α-OH permits an intramolecular H-bond with the secondary ester carbonyl; fulvine has a 13β-OH which cannot bond in this way. Monocrotaline with 2 OH groups has the lowest lipid solubility.

The toxicity of pyrrolizidine alkaloids is exerted through a reactive pyrrole metabolite (Huxtable, *Trends Pharmacol. Sci.* (1980) 1, 299). The metabolite from senecionine, dehydrosenecionine, has a conformation that closely resembles that in the parent alkaloid apart from the flattening of the pyrrolizidine nucleus. Thus a similar protection against esterases is afforded although direct hydrolysis by water will occur. In the active metabolite of monocrotaline, dehydromonocrotaline, the conformation of the 11-membered macroring is significantly different from that in the parent alkaloid, the perturbation of the macroring being revealed most notably in the conformation around the primary ester system.



(I)



(II)

03. 1–2 THE STRUCTURAL COMPARISON OF PHENYL ETHYL BIGUANIDE HYDROCHLORIDE WITH SYMPATHOMIMETIC AMINES. By P. Roychowdhury, Department of Physics, University College of Science, Calcutta, and Sandhya Roychowdhury and B. N. Das, X-ray Laboratory, Presidency College, Calcutta, and S. Chaudhuri, R.S.I.C., Bose Institute, Calcutta.

Studies of a number of sympathomimetic compounds suggested tnat a molecule with an aromatic six membered ring or ring system and an attached ethylamine side chain generally exhibit sympathomimetic activity provided this molecule assume a preferred configuration. The structure of the title compound was determined mainly to compare its phenyl-ethyl-amine moiety with the similar group present in sympathomimetic drug.

The crystal data are : cryst. sys. = monoclinic; sp. g. = $P2_1/c$; cell dim. a=14.913(3), b=9.372(2), c=20.338(5), β=116.69°; z=8 (2 independent molecules per asymmetric unit); dens.=1.26 g.cm^{-3}; calc. dens.= 1.27 g.cm^{-3}.

X-ray data were collected on a Nonius CAD-4 diffractometer using copper radiation. The structure was solved by Patterson synthesis and refined anisotropically using full matrix least squares to a final R of 0.048 for 2,800 reflections.

It is interesting to note that the conformation of the phen-ethyl-amine moiety **in** this compound show considerable resemblance with the preferred one usually adopted by sympathomimetic drugs even though the degree of agreement is different for the two molecules in the asymmetric unit that form a hydrogen bonded dimer with relatively different configuration. The torsion angles clearly indicate that in both the molecules the