03. CRYSTALLOGRAPHY IN BIOCHEMISTRY AND PHARMACOLOGY

03.X–15 ANALYSIS AND DESIGN OF PROTEINS AND PEPTIDE DRUGS. By B. Robson, University of Manchester Medical School, Manchester H60, 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 features are being sought which will give the required properties in vitro (eg. artificial enzymes) and in vivo (eg. as drugs such as sympathomimetic agents). 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 oncoprotein 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 oncogenes and oncoproteins. 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.P. Import, 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 carcino genic 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 new 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 ether group 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 carboxyl groups. This is most marked in several alkaloids with a 12-membered ring such as senecionine (I), in which the carboxyls are syn-parallel and directed outwards from the ring. Even in the alkaloids with an 11-membered ring such as monocrotaline (II) in which the carboxyls are syn-parallel, substantial protection should occur.

A comparison of closely related alkaloids with a similar conformation, crispamine, fulvine (Sussman & Wodak, Acta Cryst. (1973) B29, 2918) and monomericine (Stoeckli-Evans, Acta Cryst. (1979) B35 231; Wang, Scz. 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. Crispamine is more soluble than fulvine in lipid solvents, apparently because the stereochemistry of the 13a-OH permits an intramolecular H-bond with the secondary ester carbonyl; fulvine has a 13b-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, Prad&l; Pharmaeutol. Ser. (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 macrocoring is significantly different from that in the parent alkaloid, the perturbation of the macrocoring being revealed most notably in the conformation around the primary ester system.

03.1–2 THE STRUCTURAL COMPARISON OF FRONTAL ETHYL RICINUS HYDROCHLORIDE WITH SYMPATHOMIMETIC AMINES. By P. Roychowdury, Department of Physics, University College of Science, Calcutta, and Sandhya Roychowdury 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 that a molecule with an aromatic six membered ring or ring system and an attached ethylamine side chain generally exhibit sympathomimetic activity. The structural studies in our laboratory, using X-ray and neutron diffraction methods for calculation of the three-dimensional structures of proteins 70–350 residues in length, and involve new advances in calculation technique.

The crystal data are: crystal sys. = monoclinic; sp. g. = 1.1; cell dim. a=4.9,13(3), b=9.27(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.

The crystal 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 2,500 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 the need to understand the degree of toxic hazard they pose.