

## 03.1-14 CONFORMATION ANALYSIS OF NEUROLEPTICS LIKE PHENOTHIAZINE (DIPHENYLSULPHUR DERIVATIVES).

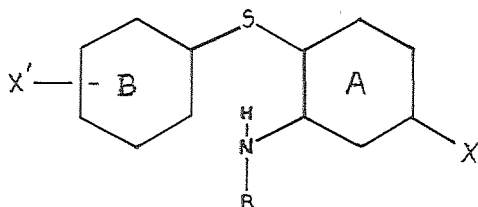
by P.Marsau, M.Alléaume, Y.Barrans and M.Cotrait, Laboratoire de Cristallographie, Université de Bordeaux I, 33405 - Talence-Cedex - France.

Numerous diphenylsulphur derivatives have been synthesized. They constitute neuroleptic phenothiazine analogs where one of the C-N bonds of the central nucleus is broken, and where the partial rigidity of the phenothiazine molecule was decreased.

The X-ray crystallographic study of 9 derivatives shows that for some of them the aminoaliphatic chain R has a tendency to fold up over the B ring. Such a conformation cannot exist in phenothiazine derivatives. This folding can be modified by the nature of substituent located on the rings, especially in 1 position.

- quantum mechanic calculations have been performed in order to evaluate the energy levels of the various conformations.
- semi-empirical methods have been used in order to define the parameters of freedom of these isolated molecules, in comparison with the crystallographic conformation.

In relation with the molecular structure, biological studies have been performed (binding on the dopamine receptor).



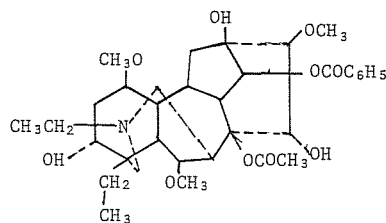
## 03.1-15 STRUCTURAL MODELS FOR THE ACTION OF ACONITINE ON SODIUM CHANNELS. By Penelope W. Coddling, Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4.

Although aconitine(I) and batrachotoxin(II) appear to be structurally unrelated, both are potent, lipid-soluble neurotoxins which demonstrate competitive interaction in neuroblastoma cells. Aconitine is a diterpenoid alkaloid isolated from *aconitum napelles* and other plants; whereas batrachotoxin is a steroidal alkaloid found in the venom of the Columbian frog *Phylllobates aurotaenia* and other species.

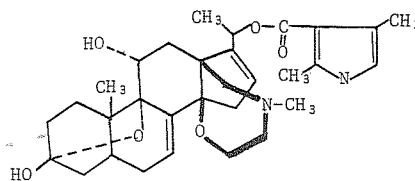
A recent review by Cattrell (Ann. Rev. Pharmacol. Toxicol. (1980) 20:15-43) indicates that the wide variety of pharmacological effects of these toxins results from the depolarization of nerve and muscle due to increased  $\text{Na}^+$  permeability of the excitable membrane. Ion flux experiments have defined a common receptor site for aconitine and batrachotoxin.

We have recently determined the structure of aconitine and several of its congeners. The structure of batrachotoxin has been published (Karle and Karle, Acta Cryst. (1969) B25 428-434). Since the evidence suggests that the two alkaloids interact with the same receptor site, a three dimensional mapping of the active portions of the two molecules will delineate some of the structural requirements of the receptor. In addition, specific models of the receptor can be tested against the 3-dimensional structures of the two toxins.

Crystal Data: Aconitine,  $M = 646$ ; Space group,  $P2_12_12_1$ ,  $a = 15.616(6)$ ,  $b = 17.069(7)$ ,  $c = 12.243(4)$  Å,  $Z = 4$ ,  $R = .099$



(I)



(II)

## 03.1-16 BESTATIN: CRYSTAL AND MOLECULAR STRUCTURE J. Ricci, A. Bousvaros, and A. Taylor, Chemistry Department, Williams College, Williamstown, MA 01267 and Brookhaven National Laboratory, Upton, NY 11973, USA, and H. Umezawa, Institute of Microbial Chemistry, Tokyo, Japan.

The x-ray crystal structure of bestatin, [(2S,3R)-3-amino-2-hydroxy-4-phenylbutanoyl]-L-leucine,  $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_4$ , has been determined.

It crystallizes with one molecule of 2-methyl-2,4-pentanediol and two molecules of water in  $P2_12_12_1$  with  $Z = 4$ . Unit cell

dimensions are  $a = 6.653(1)$ ,  $b = 15.150(3)$  and  $c = 27.309(4)$  Å. Solvent disorder results in a final  $R_F = 8.5\%$  based on 2871 independent structure amplitudes. In addition to the usual functional groups needed for binding to leucine aminopeptidase, LAP, bestatin includes a tetrahedral carbon, C-8, as might be found in the putative transition state intermediate. The structure indicates that the nonpolar side chains are oppositely disposed and separated by  $\sim 10$  Å. The peptide bond is trans and there is no H bonding between OH on C-8 and the adjacent carbonyl. These data suggest possible modes of binding of this transition state analog to LAP and should be useful in the interpretation of our ongoing crystallographic studies of the enzyme. The treatment of disorder and the hydrogen bonding will be described.

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