03. CRYSTALLOGRAPHY IN BIOCHEMISTRY AND PHARMACOLOGY

03.3-05 CRYSTAL STRUCTURES OF TWO PTERIDINES WITH DIURETIC AND ANTIFOLATE ACTIVITY. By C.H. Schwalbe and D.S.W. Williams, Department of Pharmacy, University of Aston, Birmingham, England, and Department of Chemistry, Brookhaven National Laboratory, Upton, N.Y. 11973, U.S.A.

Clinically valuable diuretics such as triamterene and antifolates such as amethopterin both contain the 2,4-diaminopteridine moiety. We report here the crystal structures of 2,4-diaminopteridine monohydrate (I) and a protonated derivative, 2,4-diamino-6,7-dimethylpteridine hydrochloride monohydrate (III), which themselves are effective diuretics with some antifolate activity.

Data were collected on an Enraf-Nonius CAD4 system and refined to R = 0.059 for 3300 observed reflections with I and R = 0.059 for 3300 observed reflections with II.

Corresponding bond distances and angles in the two independent molecules of II are identical within 0.006 Å and 0.6°. Relative to Z, the effect of protonation at N(1) of II is chiefly to lengthen the ring bonds to N(3), shorten the bridge bond and the exocyclic C=N bond, and decrease the adjacent endocyclic angles. A hydrogen-bonded water molecule acts as a proton donor near N(3) of I but as a proton acceptor near N(1) of II. Both species form hydrogen-bonded pairs about a center or pseudo-center of symmetry but use different parts of the molecule.

The phenyl rings of the tosyl groups in (I) are nearly coplanar to the phenyl rings of dibenzooxadiazanine. This causes an intramolecular charge-transfer interaction.

03.3-06 THE CRYSTAL STRUCTURES OF (3) AND (R) BACLOFEN AND CARBAMAZEPINE By Chang-Hwan Chang, Daniel S.C. Yang, Chung Soo Yoo, Bi-Chen Wang, James Pletcher and Martin Sax, Department of Crystallography, University of Pittsburgh, PA 15260 and Brookhaven Crystallography Lab., VA Medical Center, Pittsburgh, PA 15240.

The crystal structures of the three title compounds have been determined. All of the three are used as a muscle relaxant for the relief of spasticity with varying degrees of activity. The relationship between the drug activity and three-dimensional structure among these three compounds has been investigated.

The baclofen crystals are orthorhombic, space group P2_12_1_2, a = 6.378(1), b = 7.319(1), c = 25.689(4) and Z = 4. The structures were determined by a combination of direct methods and Fourier techniques yielding final R factor of 2.9% for the R form and 4.0% for the R2 form. The absolute configurations were determined using anomalous scattering techniques. The side chain assumes a gauche conformation with respect to the C3 - C4 bond.

The carbamazepine crystal is triclinic, space group P1, a = 9.001(3), b = 7.441(2), c = 13.755(3), α = 119.48(2), β = 98.96(2), γ = 101.61(2) and Z = 4. The structure was solved by MULTAN and the R factor is 5.9% at this stage. The angle between the benzene rings is 120°. There is good three-dimensional overlap between the carbamazepine and baclofen(R,S).

03.3-07 CRYSTAL STUDIES OF DIBENZOOXADIAZINE-9-NINE DERIVATIVES. A. Steplewski, E. Waismann, Dept. of Crystallography, Institute of Chemistry, University of Łódz, Nowotki 18, 91-416 Łódz, Poland, and R. Glinka, Institute of Chemistry and Technology of Drugs, School of Medicine, 90-145 Łódz, Poland.

Pharmacological investigations of the family of compounds given in the title have shown their action on the central nervous system and especially their neuroleptic action. The strongest pharmacological action is shown by N,N'-ditosyl and N,N'-ditrimethoxybenzoyl derivatives.

Two compounds have been investigated:

03.3-08 THE CRYSTAL AND MOLECULAR STRUCTURE OF (3S,6S)-6-METHYL-5-OXO-THIOMORPHOLIN-3-CARBONYL-L-HIS-L-PRO-NH_2. By Emil Eckle and John J. Stezowski, Institut für Organische Chemie, Biochemie und Isotopenforschung der Universität Stuttgart, Pfaffenweiding 55, D-7000 Stuttgart 80, Federal Republic of Germany.

The crystal structure determination of the title compound, L, presents a continuation of our study of the conformational properties of TRH analogs. In addition to its thyrotropin releasing activity, TRH is also a central nervous system (CNS) stimulant. L displays much greater CNS activity than TRH but only about 20% of that of its 6-epimer, II for which we reported a crystal structure earlier (Stezowski, J. J. and Eckle, E., 1980 Abstracts, 6th European Crystallography Meeting, 215).

I crystallizes as a tetrahydrate with space group symmetry P2_12_1_2, a = 8.510(1) Å, b = 11.507(1) Å, c = 23.735(3) Å, β = 90°; Z = 4. A total of 4656 data contributed to the refinement of 417 variables to give R = 0.043, R_w = 0.049 and σ = 1.12.

A quantitative comparison of the conformation of I and II will be presented.