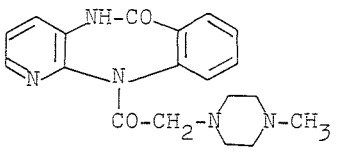
03.1-11 GEOMETRIC AND ELECTRONIC FACTORS IN THE STRUCTURE-ACTIVITY RELATIONSHIP OF SOME 5-PHENYL-1,4-BENZODIAZEPINES. By P. Chananont and T. A. Hamor, Department of Chemistry, University of Birmingham, Birmingham, England, and I. L. Martin, M.R.C. Neuropharmacology Unit, Department of Pharmacology, The Medical School, Birmingham B15 2TJ, England.

MNDO molecular orbital calculations were made on sixteen 5-phenyl-1,4-benzodiazepines of known crystal structure and covering a wide range of biological activity. Electronic properties, including net atomic π-electron charge-densities, dipole moment, and HOMO and LEMO energies have been obtained. Geometrical features derived from the X-ray analyses have been tabulated. These include parameters relating to the overall conformation, shape and size of the molecule as well as bond length data. Biological activities are based on the affinities of the specific benzodiazepine receptor in the brain for the compounds (Squires and Braestrup, Nature (1977) 266, 732; European J. Pharmacol. (1978) 48, 263) which correlate well with their efficacies as antianxiety and anticonvulsant agents.

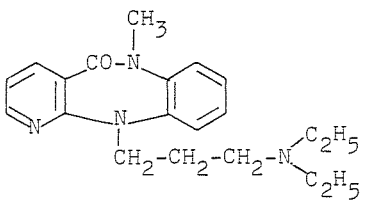
The results of statistical analyses of the data will be presented. Correlations between activity and various calculated electronic quantities postulated previously (Blair and Webb, J. Med. Chem. (1977) 20, 1206; Gilli et al., Abstracts ECM4, Oxford, 1977 pp. 38-39; Lucek et al., Fed. Proc. (1979) 38, 541) have not been substantiated. There appears, however, to be some correlation when $E_{HOMO} + E_{LEMO}$ is considered.

03.1-12 STRUCTURAL STUDIES OF SOME NEW TRICYCLIC DRUGS. By P. Luger, Institut für Kristallographie, FU Berlin, West Germany.

Tricyclic drugs are widely used in pharmacy, where they are known to have central as well as peripheral activity. Their molecular skeleton consists in principle of three structural elements, a tricyclic ring system, a more or less linear side chain and a basic substituent (see formulae (I) and (II)). Since it was found that minor chemical modifications lead to considerable alterations in the pharmacological activity, a systematic study of the structures of these types of drugs becameinteresting in order to get more information on their structure-activity relationships.



(I)



(II)

Recently two new dibenzazepine derivatives, 5-11-dihydro-11[(4-methyl-piperazine-1-yl)acetyl]-6H-pyrido [2,3-b] [1,4] benzodiazepine-6-on (Pirenzepin, trade name: Gastrozepin®)-(I)- and 11-(3-diethylaminopropyl)-6,11-dihydro-6-methyl-5H-pyrido [2,3-b] [1,5]-benzodiazepine-5-on -(II)- have been synthesized in the research laboratories of the Dr. Karl Thomae GmbH, Biberach, West Germany.
(I) is a first representative having peripheral but no central activity, it acts as a highly specific antagonist of muscarinic receptors. (II) is known to have peripheral activity, too, however it is still unknown whether it acts on the central nervous system or not. From the unusual pharmacological properties of these drugs the knowledge of their molecular structures seemed to be useful. We executed X-ray analyses of the hydrochloride of (I) and the hydrobromide of (II) and we shall present a study of the molecular conformations together with a comparison with a number of thus far investigated related tricyclic drugs.

The author is indebted to Drs. G. Schmidt and W. Eberlein for helpful discussions and to the Dr. Karl Thomae GmbH, Biberach, for the samples of the crystalline material.

03.1-13 CRYSTAL AND MOLECULAR STRUCTURE OF SINTAMIL - [10-(3-DIMETHYLAMINOPROPYL)-2-NITRODIBENZ[b,f][1,4] OXAZEPIN-11(10H)ONE (2)HYDROCHLORIDE]. R. Usha, M.M. Bhadbhade and K. Venkatesan, Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, and K. Nagarajan, CIBA-Geigy Research Center, Bombay 400 063, India.

Sintamil, $C_{18}H_{20}N_3O_4Cl.H_2O$, a new antidepressant has a heteroatom seven-membered central ring and the side chain emanates from the nitrogen atom of the two atom bridge in contrast to the widely used tricyclics like imipramine or amitriptyline. Crystals are orthorhombic, space group $Pn2_1a$, a = 7.710(3), b = 11.455(4) and c = 21.199(5) Å. Structure was solved by direct method program SHELX-76 and refined by block-diagonal least-squares procedures to an R = 0.045 for 1747 significant reflections ($|F_{obs}| \geq 2\sigma(|F_{obs}|)$). Angle between least-squares planes through benzene rings is 125.0° whereas in imipramine these angles are 123.0° and 130.3° for the two independent molecules in the asymmetric unit. The side chain folding is similar to one of the independent molecules in imipramine. Distances from the terminal nitrogen atom to the geometric centers of benzene rings are 7.70 Å and 6.76 Å. Conformations of tricyclic antidepressants active at receptor sites for norepinephrine will be discussed on the basis of present X-ray study and other tricyclic antidepressants.