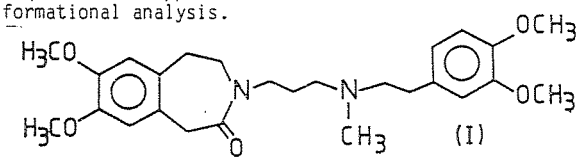
03.1-7 CONFORMATIONAL ASPECTS OF UL-FS 49, A NEW SPECIFIC BRADICARDIC AGENT.

By P. Luger, Institut für Kristallographie, Freie Universität Berlin; P. Müller, M. Reiffen and A. Prox, Chemical Research Department, Dr. Karl Thomae GmbH, Biberach, Federal Republic of Germany

Coronary heart disease is a major cause of morbidity and mortality in Western countries. In the last years cardiovascular drugs with a new pharmacological profile have been described by us as "specific bradicardic" agents. Recently a major breakthrough was made by a novel type of structure, represented by the seven membered ring compound, coded UL-FS 49 (I). Due to the long aliphatic chain, which connects the benzazepinone system with the substituted phenyl ring this compound shows a high conformational flexibility. Therefore, the deduction of its pharmacologically active conformer requested the application of different methods of conformational analysis.



X-ray analysis of the protonated and non protonated form of the molecule in the solid state, revealed a rather unusual U-shaped geometry (Fig. 1), in which both phenyl rings are only about 3 Å apart from each other. However, according to the results of photoelectronic-(PE)-spectroscopy, an extend form was derived for the gas phase. NMR-experiments, to elucidate the most stable conformation in solution, are currently under investigations. Empirical (MMI, MMPI, ECEPP) and semiempirical (PCILO, MNDO) calculations confirmed both the extended as well as the globular conformation as energetically favoured with an energy difference of less than 6 kcal. By comparing the conformational shape of UL-FS 49 and related compounds with their experimentally obtained pharmacological data, we conclude that there is a strong correlation between the molecular conformation and bradi cardic activity, with the most potent conformer being very close to the structure found in X-ray analysis.

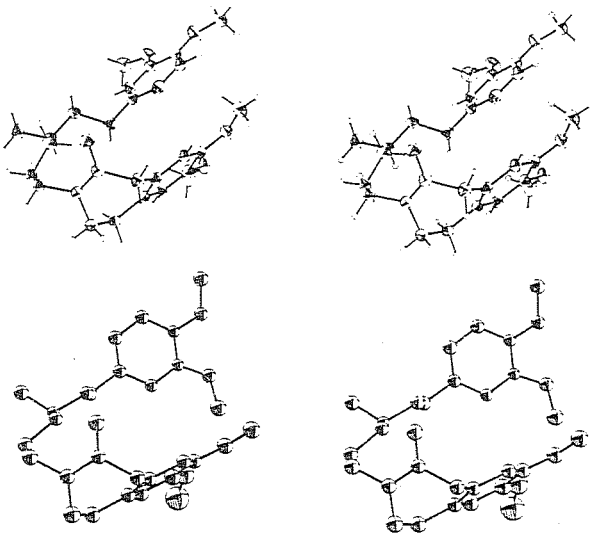


Fig. 1. Protonated (above) and nonprotonated form (below) of UL-FS 49

03.1-8 STRUCTURE-ACTIVITY RELATIONSHIP IN FUROCOUMARIN DERIVATIVES.

By F. Benetollo[a], G. Bombieri[b], A. Del Pra[b] and L. Mosti[c] (a) Istituto di Chimica e Tecnologia dei Radioelementi del C.N.R. Padova, Italy. (b) Istituto di Chimica Farmaceutica, Universita' di Milano, Italy. (c) Istituto di Scienze Farmaceutiche, Universita' di Genova, Italy.

Investigations on the molecular conformation of substituted furocoumarins have been carried out in order to elucidate the role of the substituents with respect to their differing ability to form molecular complexes with DNA in the ground state, where the ligands could undergo intercalation between two base pairs of the macromolecule. Among those ligands which have proved to be biologically active, the following have been characterized by X-ray diffraction analysis in order to correlate molecular structure with their biological activities.

3-chloro-4-morpholinoangelicin. Monoclinic system, space group $P2_1/n$, Z=4, cell dimensions a = 11.776(2), b = 13.832(2), c = 8.793(1) Å, β = 110.73(2)°.

3-chloro-4-aminomethylphenyl-7-tioangelicin. Monoclinic system, space group $P2_1/a$, Z=4, cell dimensions a = 18.313(3), b = 6.123(1), c = 14.124(2) Å, β = 93.41(2)°.

3-phenylangelicin. Trigonal system, space group $R\bar{3}$, cell dimensions a=b=40.964(10), c=3.881(2) Å, Z=18 (hexagonal axes).

Conformational analysis by X-ray crystallography, and pharmacological activity of these new furocoumarins will be discussed.

03.1-9 CRYSTAL AND MOLECULAR STRUCTURE OF 1,4-DIHYDRO-6-METHOXY-7-BENZOYLOXY ISOCOUMARIN.

By K. Sivakumar, K. Subramanian, and S. Natarajan, Department of Physics, Anna University, Madras 600 025, India.

In continuation of our work on coumarins involved in the biological metabolism and selected dye laser activities, the crystal structure of 1,4-dihydro-6-methoxy-7-benzoyloxy isocoumarin has been determined. The title compound, $C_{17}H_{16}O_4$ crystallises in the space group $P2_1/c$ with a=10.822(1), b=13.961(1), c=10.047(1) Å and β = 109.57(1); Z=4, D_m=1.312, D_x=1.320 gcm^{-3}. The structure was solved by direct methods using CuK_α diffractometer intensity data. The coumarin ring system was seen in the E-map with the highest figure of merit. The rest of the non-hydrogen atoms were located in the subsequent difference Fourier maps. The present R factor for 2080 unique reflections is 0.063.

The characteristic feature of the molecule is the system formed by the aromatic ring in benzoyloxy group and the hetro ring in coumarin ring system. The conformation of the coumarin ring system is typical of that of other molecules in the series. The hetro ring is in sofa conformation [ΔC_s =1.1]. The orientation of the aromatic ring of the benzoyloxy group normal to the coumarin plane is an interesting feature. This has been found in flavonoids and correlated to the biological activity. The methoxy group present in the structure is approximately contained in the plane of the aromatic ring to which it is attached.

Packing in the unit cell emphasizes the non-associated nature of the molecules. The conformational features will be analysed and compared with other structurally related biomolecules in the light of a model for structural activity at receptor site, and the results will be presented in the congress.