C – 74 03. CRYSTALLOGRAPHY IN BIOCHEMISTRY AND PHARMACOLOGY

03.3-5 STRUCTURAL STUDIES OF OXAZOLO-1,4-BENZODI-AZEPINES: POLYMORPHISM AND OPTICAL ACTIVITY OF HALOXAZOLAM. By <u>S.Sato</u>, K.Kawazoe, T.Hata, *T.Takebayashi, *Y.Okada, **T.Miyadera and C.Tamura, Analytical and Metabolic Research Laboratories, *Product Development Laboratories, and **Chemical Research Laboratories, Sankyo Co,. Ltd., Tokyo, Japan.

A number of benzodiazepine derivatives have been synthesized in many laboratories for searching tranqulizing agents. (L.O.Randall, W.Schallek, G.A.Heise, E.F.Keith and R.E.Bagdon: J.Pharmacol.Exptl.Therap. 129, 163 (1960)). Our research laboratories have succeeded in developing the three tetrahydrooxazolo-1,4-benzodi-

azepines (Serenal $^{\mathbb{R}}$, Sepazon $^{\mathbb{R}}$ and Somelin $^{\mathbb{R}}$). The third

drug, the title compound, used as a sleep inducer has a polymorphism of three types under the following crystallizing conditions. Although the α -form could be obtained from methanol in slow evaporation, the β -form was produced in rather rapid evaporation from the same solvent. The γ -form was produced by recrystallization from acetone. As shown in Figure, the molecular conformation of the α -form differs from the β and γ -forms related to a rotation of the o-fluorophenyl ring. The molecular packings of these three crystals are due to chain NH...O=C hydrogen bonds. Interestingly the α -form obtained under the chemically and physically achiral conditions showed

a high opitical activity ((a) $_{\rm D}^{25}$ ±ca.320°, 0.2% dioxane).

Conformational aspects of the three types of crystals and racemization mechanism for producing the optically active products will be described.

Haloxazolam (C₁₇H₁₄N₂O₂FBr=377.2) 10-bromo-11b-

(2-fluoropheny1)-2,3,7,1lb-tetrahydrooxazolo(3,2-d)(1,4) benzodiazepin-6(5H)-one.

Crystal Data

	orthorhombic ^{P2} 1 ² 1 ² 1	β monoclinic P2 ₁ /c	monoclinic P2 ₁ /c
a(A) b c ß(°) Z	10.333(3) 7.209(2) 21.287(6) 4	11.616(3) 7.243(2) 38.652(9) 91.10(6) 8	12.617(3) 14.100(4) 8.903(2) 104.84(8) 4
V(A ³)	1585.7	3252.4	1531.0
$Dx(gcm^{-3})$	1.58	1.54	1.64



Figure Molecular structures projected on each bromophenyl plane. 03.3-6 STRUCTURE AND INTERACTIONS OF ANTI-INFLAMMATORY ANALGESICS. CRYSTAL STRUCTURE OF A 1:1 COMPLEX BETWEEN MECLOFENAMIC ACID AND CHOLINE. By <u>V.Dhanaraj</u> and M.Vijayan, Molecular Biophysics Unit, Indian Institute of Science, Bangalore-560 012, India.

As part of a continuing programme of structural studies of anti-inflammatory analgesics, which are believed to act through the inhibition of prostablandin biosynthesis, and their inter-actions, the crystal structure of a hydrated crystalline complex between the important analgetic fenamate 2-(2,6-dichloro-3-methyl-phenyl) aminobenzoic acid, generally known as meclofenamic acid, and choline has been determined (Pna21, a=9.637, b=12.962, c=33.009 %,Z=8,R=0.068 for 1942 observed reflections). The two sets of crystallographically independent molecules in the structure have nearly the same geometry. Complex formation is achieved primarily through ionic interactions between the deprotonated negatively charged carboxylate group in meclofenamic acid and the positively charged trimethylamine group in choline. The invariant structural features of free fenamates (Acta Cryst. 1979, B35, 262; 1981, B37, 1102; 1982, B38, 315), namely, the coplanarity of the carboxylate group and the six-membered ring bearing it, and the internal hydrogen bond between the carboxylate group and the imino nitrogen atom that bridges the two six-membered rings, are retained in the complex also. The hydroxyl group is gauche to the trimethylamino group, in the choline molecule. The crystal structure contains polar columns, made up of carboxylate groups, choline molecules and water molecules, surroun-

03.3-7 STRUCTURE OF HYDPOCHLORO [1-(3,4 METHYLEN-DIOXY-BENZOYLOXY-3-ISOPROPYLAMINOPPOPAN-2-OL]. By Herman Ammon, <u>Karimat E1-Sayed</u> and Macchia Bruno, Maryland University, U.S.A. and Ain Shams University, Cairo, Egypt

The structure of the β -adrenergic drug; C_{14} H₂₀ N⁺O₅ Cl⁻ is triclinic; PI, a = 7.301 (1), b = 7.483 (2), c = 15.241 (4) ^OA, α = 88.278 , β = 77.283 , γ = 84.297 and Z = 2. The structure was solved with direct method and refined with full matrix least square techniques to R indices of 0.039. The CH(OH)-CH₂-NH(R) section of the side chain shows the gauche conformation. The Cl⁻ ion is responsible with the Vander-Waals forces for the crystalline cohesion.