

03.3-15 STEREOCHEMICAL CHARACTERISTICS OF DOPAMINE AGONIST: MOLECULAR STRUCTURES OF PERGOLIDE AND TL-140-HBr.

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Crystals of pergolide ( $C_{19}H_{26}N_2S$ ) are orthorhombic with cell dimensions  $a=7.038(5)$ ,  $b=12.109(8)$  and  $c=20.430(10)$  Å, space group  $P2_12_12_1$  with four formula units per cell. The residual  $R=7.37\%$  for 887 observed reflections. The absolute configuration was determined by applying Hamilton's test and was found to be the same as the active form of bromocriptine methanesulfonate. Crystals of TL-140-HBr ( $C_{16}H_{24}NO_2Br$ ) are monoclinic with cell dimensions  $a=13.907(7)$ ,  $b=7.856(5)$ ,  $c=15.357(8)$  Å and  $\beta=93.21(8)^\circ$ , space group  $P2_1/c$  with four formula units per cell. The residual  $R=6.21\%$  for 1541 observed reflections. The two molecular structures are compared to each other and to apomorphine and bromocriptine.

03.3-16 THE STRUCTURES OF A NEW ANTITUMORAL AGENT:  $\alpha$  AND  $\beta$  TGT ( $C_{12}H_{15}N_3O_2$ ).

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$\alpha$  and  $\beta$  stereoisomers of 1,3,5-Triglycidyl-S-Triazinetrione (TGT) both display a high therapeutic activity against P388 and L1210 mouse leukemias. The structures were solved by MULTAN 80.  
 $\alpha$  Stereoisomer:  $M_r=297$ , orthorhombic,  $Pna2_1$ ,  $a=9.198(5)$ ,  $b=9.475(6)$ ,  $c=15.507(8)$  Å,  $V=1351$  Å<sup>3</sup>,  $Z=4$ ,  $CuK\alpha$  rad., 981 intensities with I's GE 3 $\sigma$ , final  $R=6.9\%$ .  
 $\beta$  Stereoisomer: rhombohedral,  $R\bar{3}$ ,  $a=8.964(5)$  Å,  $\alpha=103.15(7)^\circ$ ,  $V=652$ ,  $Z=2$ ,  $CuK\alpha$  rad., 730 intensities with I's GE 3 $\sigma$ , final  $R=6.1\%$ .

The  $\alpha$  stereoisomer has the absolute configuration R,R,S/S,S,R with melting point  $105^\circ$  C and its therapeutic activity is superior to that of  $\beta$  form. The crystals of  $\beta$  form with melting point of  $155^\circ$  C consist of R,R,R/S,S,S enantiomers. This significant difference in the melting points and solubility in water (1.01 and 0.053% at  $20^\circ$  C) is easily explained when the two crystal structures are compared. The molecules of the  $\alpha$  form are packed in the crystal with mainly van der Waals contacts between them. Packing in  $\beta$  is drastically different: the molecules form dimers with full overlapping of the triazinetrione rings at a distance of 3.4 Å. Such contacts are possible because the three glycidyl branches are on the same side of the triazinetrione ring, as opposed to the orthorhombic  $\alpha$  form where they are not.

03.3-17 STRUCTURE OF  $\beta$ -CYCLODEXTRIN-PHENOBARBITAL COMPLEX. By Isao Nakanishi, Takaji Fujiwara and Ken-ichi Tomita, Faculty of Pharmaceutical Sciences, Osaka University, Suita, Osaka, 565, Japan.

Cyclodextrins (CyDs) are circular oligomers of  $\alpha$ -1,4 linked D-glucopyranose and include various guest molecules in their hydrophobic cavities. CyDs have been often used as the structural model for enzymes or membranes, and their application to medicinal chemistry is also attractive. It is desirable for drug design to elucidate the detailed molecular structure of CyD inclusion complex with various drugs. We chose phenobarbital (5-ethyl-5-phenyl barbituric acid) as a guest molecule, because of its pharmaceutical significance and its unique molecular geometry.

The inclusion complex of  $\beta$ -CyD (heptamer) with phenobarbital was crystallized by slow cooling of hot aqueous solution. Intensity data were collected up to  $2\theta=125^\circ$  with the graphite monochromatized  $CuK\alpha$  radiation using the Rigaku AFC-5 four-circle diffractometer. The crystal is monoclinic, space group  $P2_1$  with  $a=15.562(1)$ ,  $b=33.189(3)$ ,  $c=15.229(1)$  Å,  $\beta=104.854(7)^\circ$  and  $Z=2$ . The cell dimensions are similar to those of the  $\beta$ -CyD-p-ethylaniline complex (Acta Cryst. B37, 1158 (1981)). The structure was solved by R-map method using the dimeric  $\beta$ -CyD model complex with 3,4-xylidine, which were oriented by interpretation of Patterson map. It was refined by the full-matrix least-squares method (ORXFLS4) applying the restraint to the bond distance and angle. At the present stage, the R factor is 16.0% for the 3710 reflections with  $\sin\theta/\lambda < 0.6\text{Å}^{-1}$  using isotropic thermal parameters for all the non-hydrogen atoms.

The structure is shown in Fig.1. Two  $\beta$ -CyD molecules form a head to head type dimer linked by hydrogen bonds between secondary hydroxy groups of dimeric  $\beta$ -CyDs and include two guest molecules: One phenobarbital molecule was entirely buried into a hydrophobic cavity which was formed by  $\beta$ -CyD dimer. On the other hand, another one plunged only its phenyl group into the cavity, and the pyrimidine ring was outside of the hydrophobicity. The former type of host-guest interaction is often seen in  $\beta$ -CyD complexes of aromatic organic compounds, but the latter which is rare, is probably due to the size of the guest molecule, i.e. the diameter of  $\beta$ -CyD cavity is smaller than that of phenobarbital and the hydrophobic sphere is too narrow to accept two guest molecules, so the latter guest molecule could not be fully placed into the cavity. This result may exhibit the hydrophobic selectivity of  $\beta$ -CyD cavity.

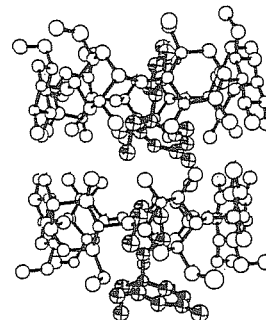


Fig. 1