

Fig.a

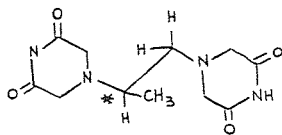
Fig.b

In the crystal structure of 8-butoxy-psoralen-thymine, psoralen and thymine rings are not parallel (Fig.b) and the angle between the planes is 73° .

- (1) LERMAN L.S. (1961) J.Mol.Biol. 3, 18
- (2) SONG P.S. and TAPLEY K.J. (1979) Photochem. Photo-biol. 29, 1177.

03.1-06 ANTI-CANCER AGENTS: STRUCTURES OF ICRF-159, THE CHIRAL STEREOISOMER SCRIF, AND CIS AND TRANS FIXED CONFORMATION ANALOGUES. By A. Hempel and N. Camerman, Department of Biochemistry, University of Toronto, Toronto, Ont., Canada, and A. Camerman, Departments of Medicine (Neurology) and Pharmacology, University of Washington, Seattle, Wash., U.S.A.

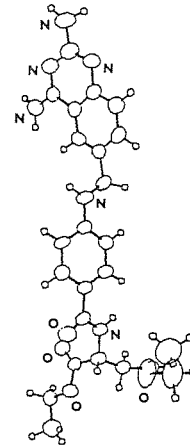
The compound ICRF-159 has demonstrated activity against cancer cells *in vitro* and *in vivo*, seemingly working by inhibiting tumor blood vessel development. In a study using fixed geometry analogues [J. Med. Chem. 21, 1974 (1978)] activity was shown to reside in the *cis*-conformation only. We have determined the crystal and molecular structures of ICRF-159 and its optically pure enantiomer SCRIF, and of the fixed-geometry compounds employed in the biological tests. The SCRIF has a linear *trans* conformation in the crystal, while ICRF adopts the *cis* arrangement, very similar to the conformation of the fixed-geometry *cis* analogue. Conformational comparisons of the four compounds will be described. Crystallographic data: ICRF-159, triclinic, $P\bar{1}$, $a=6.93$, $b=11.93$, $c=8.58\text{\AA}$, $\alpha=101.1$, $\beta=108.0$, $\gamma=97.5^\circ$, $Z=2$; SCRIF, monoclinic, $P2_1$, $a=10.58$, $b=9.46$, $c=6.59\text{\AA}$, $\beta=95.0^\circ$, $Z=2$; *cis* analogue, orthorhombic, $Pna2_1$, $a=9.73$, $b=7.08$, $c=18.21\text{\AA}$, $Z=4$; *trans* analogue, monoclinic, Cc , $a=19.17$, $b=6.65$, $c=9.85\text{\AA}$, $\beta=109.4^\circ$, $Z=4$.



03.1-07 MOLECULAR STRUCTURE OF A QUINAZOLINE ANALOG OF AMINOPTERIN. Donald Mastropalo, H. Warren Smith & Arthur Camerman, Depts. of Neurology & Pharmacology, U. of Washington, Seattle, WA, & Norman Camerman, Dept. of Biochemistry, U. of Toronto, Toronto, Canada.

Aminopterin is a folate antagonist that strongly inhibits dihydrofolate reductase (DHFR) and can inhibit tumor cell growth. Although such drugs as aminopterin and methotrexate are useful in the treatment of various forms of cancer, they also interfere with normal cell growth and cause severe side effects. Much research is currently aimed at developing folate antagonists which could preferentially inhibit tumor cell DHFR. Detailed stereochemical information on folates and folate antagonists is essential to the understanding of their enzyme binding properties and could aid in the search for better anticancer agents.

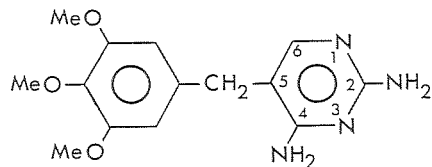
N-[p-[(2,4-Diamino-6-quinazyl methyl)amino]benzoyl]diethyl-aspartate, a close analog of aminopterin is an inhibitor of both DHFR and thymidylate synthetase. Crystals of this compound were obtained from a water-ethanol mixture and its structure was investigated. The unit cell is monoclinic, space group C_2 , with parameters $a=32.77(1)$, $b=7.529(9)$, $c=11.064(3)\text{\AA}$, $\beta=109.34(2)^\circ$, $Z=4$. The structure was solved by direct methods and refined to an R-factor of .079. The molecular conformations of the title compound, folic acid and methotrexate will be compared and stereochemical features important for enzyme binding will be discussed.



03.1-08 COMPARISON OF THE BINDING OF TRIMETHOPRIM AND TRIMETHOPRIM ANALOGUES TO BACTERIAL DIHYDROFOLATE REDUCTASE. By D.J.Baker, C.R.Beddell, J.N.Champness, P.J.Goodford, F.E.Norrington, B.Roth(*) and D.K.Stammers. Wellcome Research Laboratories, Langley Court, Beckenham, Kent, BR3 3BS, U.K. and (*) Wellcome Research Laboratories, 3030 Cornwallis Road, Research Triangle Park, N.C.27709, U.S.A.

Trimethoprim (TMP) is a widely used anti-bacterial drug, a potent inhibitor of bacterial dihydrofolate reductases (DHFRs) but a much weaker inhibitor of the vertebrate enzymes. To provide information on the action of this drug at the molecular level, we have determined the structure of the binary complex of *E.coli* (strain RT500) DHFR with TMP and compared it with those of two related complexes each incorporating an analogue of TMP. The enzyme crystallizes in space group $P6_1$ with unit cell dimensions $a=b=93.6\text{\AA}$, $c=73.9\text{\AA}$ and the asymmetric unit contains two protein molecules. Two heavy atom derivatives were used in the solution of the structure to 2.8\AA resolution.

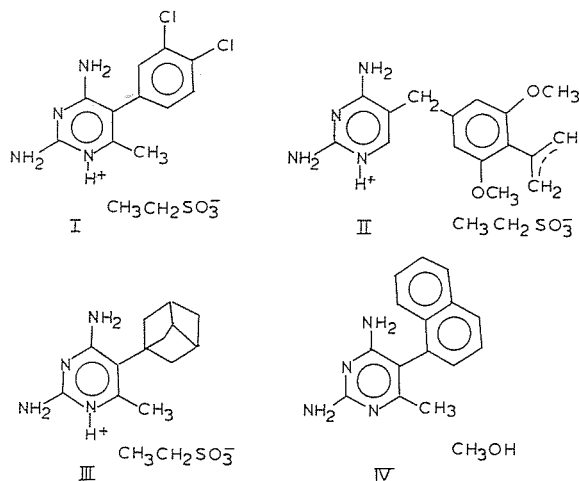
The overall folding of the polypeptide backbone is substantially in accord with that described by Matthews et al. (Science (1977) 197, 452) for the *E.coli* (MB142B) DHFR-Methotrexate (MTX) complex even though there are differences in the amino acid sequence between the enzymes of the two strains of *E.coli*. The structure incorporates an eight-stranded β -sheet beginning at the N-terminus and ending, with its only antiparallel strand, at the C-terminus.



The binding of TMP is similar in each of the two molecules in the asymmetric unit; it lies in a prominent cleft, the face of the β -sheet closing the cleft at the rear. The 4-amino group, C2 and N3 of the pyrimidine group are all close to the first β -strand, in the region of residues 5, 6 and 7, and N1 and the 2-amino group of TMP are about 3\AA from the carboxyl oxygens of Asp 27. The other enzyme/drug interactions are largely hydrophobic in nature: the trimethoxybenzyl group of TMP is directed outwards from the enzyme cleft and is close to the side chains of Ile 50, Leu 28 and Phe 31.

The two analogues of TMP involve a substitution of N3 by CH and a substitution with methyl at C6. These modifications respectively affect the thermal vibration and conformation of the bound ligand.

The analysis of these data shows that all but IV are protonated at N1, all but III have coplanar 2,4-diaminopyrimidine rings and all have similar hydrogen bonding patterns with a base-pair hydrogen bond between N4...N3 of inversion-related molecules. The conformation of the 5-substituent in molecules I, III and IV is such that the two ring systems are rotated 108° , -8° , -87° , respectively. The torsion angles about the bridging carbon in (II) are $-153^\circ/-98^\circ$, respectively. The conformational and hydrogen bonding patterns exhibited by these structures may help explain binding affinity and dihydrofolate inhibition differences among these antifolates and distinguish structural features that control species specificity.



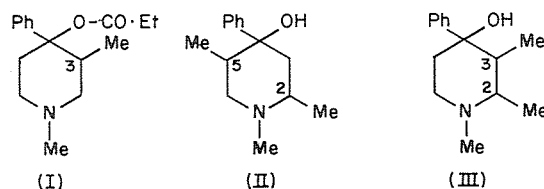
This research was supported by DHEW Grant No. RR-05716.

03.1-09 STRUCTURE-FUNCTION RELATIONSHIPS AMONG 2,4-DIAMINOPYRIMIDINE ANTIFOLATES. By Vivian Cody, Medical Foundation of Buffalo, Inc., Buffalo, NY 14203, U.S.A.

It has been shown that the essential features required for tight binding of antifolates to dihydrofolate reductase are a 2,4-diaminopyrimidine or s-triazine structure. In particular, those compounds with a lipophilic group at position five appear to act as antineoplastic agents while other compounds of this class have antibacterial or antimalarial activity. Some of these compounds also show species specificity in their antifolate activity. It has also been suggested that the enhanced binding of these antifolates compared to that of the natural folic acid substrates may be related to the activity of the 2,4-diaminopyrimidine (1) to achieve and maintain a specific hydrogen bonding pattern in the active site of the enzyme in contrast to the 2-amino, 4-oxo groups of folates, or (2) to contribute to electronic interactions such as charge-transfer or electron donation due to the increased basicity of N1 in the 2,4-diaminopyrimidines. Thus the crystal structures of the following lipophilic 5-substituted 2,4-diaminopyrimidines have been undertaken to investigate the conformational aspects of drug specificity. (I) 2,4-Diamino-5-(3,4-dichlorophenyl)-6-methyl pyrimidine ethyl sulfonate ($\text{C}_{13}\text{H}_{16}\text{N}_4\text{O}_2\text{Cl}_2\text{S}$; PI, $Z=2$, $a=10.6021(7)$, $b=12.7180(2)$, $c=7.5180(6)$ \AA , $\alpha=96.35(1)$, $\beta=103.59(7)$, $\gamma=117.57(1)^\circ$), (II) 2,4-diamino-5-((3,5-dimethoxy-4-propene)benzyl)pyrimidine ethyl sulfonate ($\text{C}_{16}\text{H}_{26}\text{N}_4\text{O}_5\text{S}$; PI, $Z=2$, $a=9.400(1)$, $b=19.563(2)$, $c=5.420(1)$ \AA , $\alpha=93.29(1)$, $\beta=94.11(1)$, $\gamma=103.95(1)^\circ$), (III) 2,4-diamino-5-(1-adamantyl)-6-methyl pyrimidine ethyl sulfonate ($\text{C}_{15}\text{H}_{22}\text{N}_4\text{O}_3\text{S}$; PI, $Z=2$, $a=10.309(1)$, $b=4.536(2)$, $c=6.486(1)$ \AA , $\alpha=91.76(2)$, $\beta=94.98(1)$, $\gamma=109.75(1)^\circ$), and (IV) 2,4-diamino-5-(1-naphthyl)-6-methyl pyrimidine methanol complex ($\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}$; C2/c, $Z=8$, $a=18.542(8)$, $b=10.990(4)$, $c=14.721(9)$ \AA , $\beta=91.91(5)^\circ$) [Cody & Zakrzewski; ACA Abstracts, 7, 13; 8, 35, 1980].

03.1-10 STRUCTURE-POTENCY RELATIONSHIPS FOR THE 2,3-DIMETHYL ANALOGS OF THE PROMEDOL ALCOHOLS. By M. Cygler and F.R. Ahmed, National Research Council of Canada, Ottawa K1A 0R6, Canada; A.F. Casy and F.O. Ogungbamila, University of Bath, Bath BA2 7AY, England.

The structure-potency relationships of the isomeric prodines (I) and the isomeric promedol alcohols (II) were summarized by Ahmed & De Camp (Acta Cryst. (1972), B28, 3489-3494), and a more general article on analgesics and their antagonists has been published by Casy (Progress in Drug Research. (1978) 22, 149-227). The present work extends these relationships to the three isomers of the 2,3-dimethyl analogs (III) of the prodine alcohols.



The isomers of (III) are confirmed to have the activity ranking $\gamma > \alpha > \beta$. The configurations of the α - and β -isomers have been determined from ^1H - and ^{13}C -NMR data and confirmed by the X-ray results. The configuration of the γ -isomer and the solid-state conformations of all three isomers have been elucidated from the crystal structures.

The potency-configuration relationships among the three isomers of (III) are found to follow the same pattern as for the isomers of (II), and are not affected by having a methyl substituent on C(3) instead of C(5). Only the isomers with the highest potency in (II) and in (III) crystallize in opposite conformations.