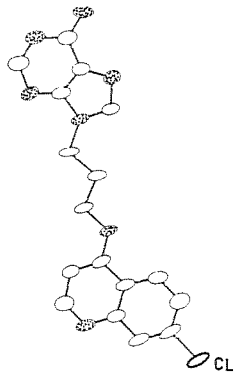


Fig.a

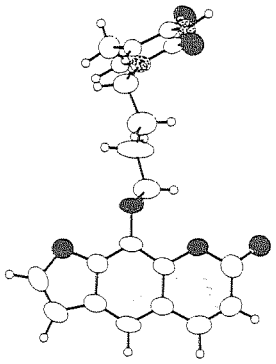


Fig.b

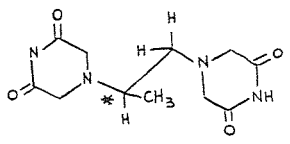
In the crystal structure of 8 butoxy-psoralen-thymine, psoralen and thymine rings are not parallel (Fig.b) and the angle between the planes is 73°.

(1) LERMAN L.S. (1961) J.Mol.Biol. 3, 18

(2) SONG P.S. and TAPLEY K.J. (1979) Photochem. Photobiol. 29, 1177.

03.1-06 ANTI-CANCER AGENTS: STRUCTURES OF ICRF-159, THE CHIRAL STEREOISOMER SCRF, 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.

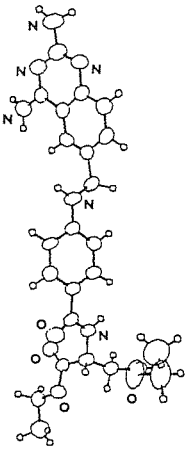
The compound ICRF-159 has demonstrated activity against cancer cells in vitro and in vivo, seemingly working by inhibiting tumor blood vessel development. In a study using fixed geometry analogues [J. Med. Chem. 21, 1974 (1978)] activity was shown to reside in the cis-conformation only. We have determined the crystal and molecular structures of ICRF-159 and its optically pure enantiomer SCRF, and of the fixed-geometry compounds employed in the biological tests. The SCRF 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=8.58Å, α=101.1, β=108.0, γ=97.5°, Z=2; SCRF, monoclinic, $P2_1$, a=10.58, b=9.46, c=6.59Å, β=95.0°, Z=2; cis analogue, orthorhombic, $Pna2_1$, a=9.73, b=7.08, c=18.21Å, Z=4; trans analogue, monoclinic, Cc, a=19.17, b=6.65, c=9.85Å, β109.4°, Z=4.



03.1-07 MOLECULAR STRUCTURE OF A QUINAZOLINE ANALOG OF AMINOPTERIN. Donald Mastropaolo, 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)Å, β=109.34(2)°, 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=93.6Å, c=73.9Å and the asymmetric unit contains two protein molecules. Two heavy atom derivatives were used in the solution of the structure to 2.8Å 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 (MB1428) 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.