Brassinolide (I) is an extremely potent naturally occurring plant growth promoting steroid. The structure of brassinolide, which was obtained in minute quantities from large amounts of rape pollen, was established by an x-ray single crystal analysis (M. D. Grove et al. Nature, 281, 216-217 (1979)). The seven-membered lactone moiety found for the B-ring in brassinolide was unprecedented in a natural steroid.

Since the structure was published, several groups of chemists have synthesized brassinolide. However, the synthesis is costly and time consuming and the yields are quite low. Therefore, other researchers are searching for isomers and analogs of brassinolide which are more easily synthesized, yet still exhibit a physiological activity similar to that of the natural product. Several such molecules have been synthesized (B. N. Mandava, USDA, Beltsville, Maryland, USA) and the structures of four of these materials have been determined. All four molecules differ from brassinolide in the stereochemistry of the C20-C25 side chain. In addition, two of the molecules have slightly modified structures, i.e. substitution of a -C\(_2\)H\(_5\) moiety for the -CH\(_3\) group on C24 and in one molecule the lactone group on ring B is flipped from what it was in brassinolide, i.e. -06-07 instead of -05-07.

All of these compounds show the same type of physiological activity as the natural product but are less potent. The structures of these molecules will be compared in an effort to understand the relationship between their structures and relative activities. They will also be compared to other physiologically active steroids which have been isolated from plants and animals.

The title compound (FIAC) is one of the most potent new antiviral agents. It has excellent activity against herpes simplex viruses I and II as well as against Herpes Zoster; it is currently undergoing clinical trials. An X-ray analysis was undertaken in order to determine details of its geometry and conformation, this being the first such study of a fluorinated nucleoside. Crystals of FIAC (from methanol) belong to the monoclinic space group \(P2_1\) with cell dimensions \(a = 4.747, b = 14.017, c = 18.514\) \(\text{Å}\), \(\beta = 90.28^\circ\). There are two molecules in the asymmetric unit which are related by a pseudo-twofold screw axis, making the structure pseudo-orthorhombic \((P2_1;2_1;2_1)\). At the present stage of the refinement \(R = 6.5\%\). The conformation of the two independent molecules is almost identical: anti about the glycosidic bond and (C\(^3\)) endo \((\text{E})\) pucker of the sugar ring. The \(-\text{CH}_2\text{OH}\) side chain is disordered, with equal contributions of the gauche-gauche \((g+g)\) and gauche-trans \((g-t)\) rotamers. This conformation will be compared with that derived by \(1\)H NMR spectroscopy. Details of this structure will be correlated with those of other arabinosides as well as with other antiviral nucleosides.

### 03.1-05 SYNTHETIC MODELS RELATED TO DNA-INTERCALATING MOLECULES: THE CRYSTAL AND MOLECULAR STRUCTURE OF CHLORO-QUINOLINE-PROPYL-ADENINE AND 8-BUTOXY-PSORALEN-THYMINE

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A number of studies have shown that many planar heteroaromatic molecules bind with nucleic acids. The binding has been frequently interpreted in terms of the intercalation model first proposed by Lerman (1) in which the interacting molecule is intercalated between two adjacent base pairs.

In order to investigate this specific problem of ring stacking interaction, we have studied compounds in which two interacting rings are linked by a flexible hydrocarbon chain: chlorinated ring of chloroquinine-adenine and psoralen ring-thymine. Furthermore psoralen binds photochemically to nucleic acids by photocyclization with the pyrimidine bases (2). Quinoline-propyl-adenine and 8-butoxy-psoralen crystallize respectively in space group \(P2_1\) with \(a = 8.309(2)\) \(\text{Å}\), \(b = 9.563(2)\) \(\text{Å}\), \(c = 14.547(6)\) \(\text{Å}\), \(\alpha = 97.57(2)^\circ\), \(\beta = 91.45(2)^\circ\), \(\gamma = 107.95(2)^\circ\) and \(a = 8.646(3)\) \(\text{Å}\), \(b = 25.692(6)\) \(\text{Å}\), \(c = 8.599(3)\) \(\text{Å}\), \(\alpha = 113.81(5)^\circ\).

The two structures were solved by direct methods. Quinoline-propyl-adenine crystallizes with five water molecules, shown in extended form with adenine and quinoline rings parallel (Fig.a) and important stacking between quinoline and adenine rings.
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°.


03.1.06 ANTI-CANCER AGENTS: STRUCTURES OF ICRF-159, THE CITRAL STEREOISOMER SCRF, AND CIS AND TRANS FIXED CONFORMATION ANALOGUES. By A. Kempel 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, a=6.95, b=11.53, c=6.583, α=101.1, β=108.0, γ=97.5°, Z=2; SCRF, monoclinic, P21, a=10.58, b=9.46, c=6.594, β=95.0°, Z=2; cis analogue, orthorhombic, Pna21, a=9.73, b=7.08, c=18.214, Z=4; trans analogue, monoclinic, Cc, a=19.17, b=6.65, c=9.854, β=109.4°, Z=4.


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 C21, with parameters a=32.771, b=7.529, c=11.066(3)Å, β=109.34(2)°, Z=4. The structure was solved by direct methods and refined to an R-factor of 0.079. 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 DHYDROFOLATE REDUCTASE. By D.J. Baker, C.R. Reddell, J.N. Champness, P.J. Goodford, P.J. Snowington, R.B.'s laboratories, Wellcome Research Laboratories, Langley Court, Beverley, 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, with unit cell dimensions a=b=93.6Å, c=73.5Å 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.