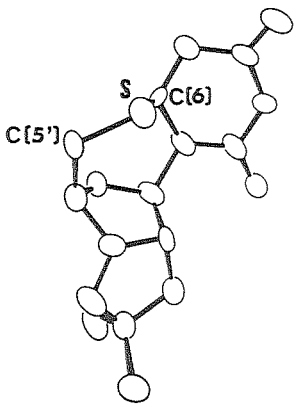
03.2–8 POSSIBLE RELEVANCE OF THE MOLECULAR STRUCTURES OF TWO MODIFIED NUCLEOSIDES TO THE ACTION OF THYMIDYLATE SYNTHETASE By N.Gautham and M.A.Viswamitra Department of Physics and ICMR Centre on Genetics and Cell Biology, Indian Institute of Science, Bangalore 560 012, India.

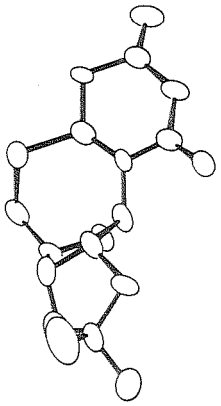
We have recently solved the crystal structures of (i) 5'-deoxy-5',6-epithio-5,6-dihydro-2',3'-O-isopropylidene-3-methyluridine and (ii) 5'-deoxy-5',6-epithio-5,6-dihydro-2',3'-O-isopropylideneuridine. These compounds were synthesized (by Drs.D.M.Brown and S.A.Salisbury, University of Cambridge) as they provided useful models for understanding some structural aspects of the action of the thymidylate synthetase enzyme. The point of interest was whether sulphur occupied an axial or equatorial position with respect to the dihydrouracil base.

Compound (i) crystallizes in the space group $P2_12_12_1$ with $a = 39.526(4)$, $b = 6.607(2)$ and $c = 5.661(2)$ Å. The molecular conformation is anti about the glycosidic bond sugar pucker is C(4')-endo, O(1')-exo. Compound (ii) crystallizes in the space group P1 with $a = 5.635(2)$, $b = 11.077(2)$, $c = 11.582(2)$ Å, $\alpha = 70.48(1)$, $\beta = 88.16(3)$ and $\gamma = 80.56(3)^{\circ}$. There are two independent molecules in the unit cell. Both molecules have an anti conformation about the glycosidic bond and a C(4')-endo, O(1')-exo sugar pucker.

The position of sulphur in compound (i) is equatorial with respect to the dihydrouracil base, i.e. the C(5)-S bond is almost in the plane of the base. In compound (ii) sulphur is axial in one molecule and equatorial in the other (see figure). In the thymidylate synthetase system additions of S at C(6) and CH_3 at C(5) of the dUMP substrate are thought to occur with both S and CH_3 axial to the base. Since in the product, i.e. dTMP, the methyl group at C(5) is equatorial, a conformational inversion may be necessary to take both S and CH_3 from axial to equatorial position. The present structures show that both equatorial and axial sites are equally possible in the case of sulphur.



Molecule A. Sulphur is axial



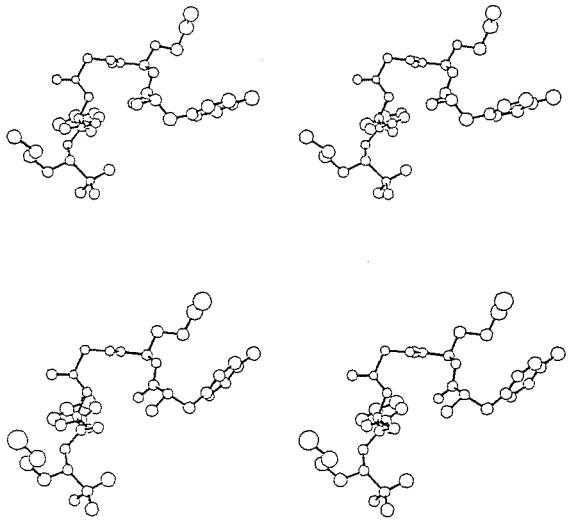
Molecule B. Sulphur is equatorial

03.2–9 THE CRYSTAL AND MOLECULAR STRUCTURE OF THE ENKEPHALIN ANALOG Tyr-D-Nle-Gly-Phe-NleS. Emil Eckle and John J. Stezowski, Institut für Organische Chemie, Biochemie und Isotopenforschung der Universität Stuttgart, 7000 Stuttgart 80 Federal Republic of Germany and S. Bajusz, Institute for Drug Research, P.O. Box 82, Budapest Hungary.

The natural enkephalins: Tyr-Gly-Gly-Phe-Leu and Tyr-Gly-Gly-Phe-Met are endogenous peptides that interact with opiate receptors[1]. We report a crystal structure determination for a synthetic analog in which the gly residue at position 2 and the carboxylate terminal residue have been substituted by D-norleucine and by the sulfonic acid analog of L-norleucine, respectively. This enkephalin analog displays a high preference for δ-sites as evidenced by its MVD/GPI potency ratio of 40.5[2].

The title compound crystallizes from an ethanol:water solution in space group $P2_1$, $a = 8.588(7)$, $b = 30.265(38)$, $c = 15.024(18)$ A, $\beta = 96.94(7)^{\circ}$ for a crystal at ∿120 K. There are two enkephalin analog molecules, five water molecules and an ethanol molecule per asymmetric unit. At present, $R = 0.098$ with 5831 reflections (Mo Kα radiation) contributing to the refinement of 881 variables.

Both enkephalin analog molecules are in a D-Nle[2]-Gly[3]-β-bend conformation stabilized by intramolecular Tyr[1](carbonyl)-Phe[4](amide) and Tyr[1](amide)-Phe[4](carbonyl) hydrogen bonds.



Stereoscopic projections of the two independent molecules of Tyr-D-Nle-Gly-Phe-Nles.

[1]J. Hughes, T.W. Smith, H.W. Kosterlitz, L.A. Fothergill, B.A. Morgan and H.R. Moris, Nature, 258, 577 (1975).
[2]S. Bajusz, in "Steric Effects in Biomolecules" G. Náray-Szabó (Ed). Akadémiai Kiadó, Budapest, 1982, pp 149-167.