Preparation and Structure of a Photodimer of 1-Methylthymine

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INTEREST in the u.v. photodimerization of thymine has arisen largely because of the biological importance of this phenomenon in DNA, where the dimer is considered to be formed only from neighbouring thymidylyl residues of the polymer.[1] The thymine photo-product from DNA has been shown by various means to be a *cis–syn*-cyclobutane derivative.[2] Irradiation of solutions and frozen solutions[3] or of crystals[4] of thymine and its derivatives may give rise to cyclobutane photoproducts[5] which have different configurations about the cyclobutane ring. Wulff and Fraenkel[6] have pointed out that four stereoisomers are possible. The four stereoisomers of thymine dimer, obtained from various starting materials, have been separated chromatographically and identified with the corresponding Wulff and Fraenkel structures.[3] We report the first X-ray crystal structure determination of one of these photodimers.[†] Our results provide a conclusive demonstration of the cyclobutane ring structure for the dimer and structural details of the molecule.

The photo-product, 1-methylthymine dimer (M.T.D.), was obtained by irradiation of frozen solutions of 1-methylthymine (M.T.). The preparation and isolation were done according to the method of Wulff and Fraenkel.[6] Crystals were obtained from concentrated aqueous solution by precipitation in the cold. A number of crystals in the form of elongated prisms were examined with X-rays. Preliminary investigation proved all of them to be identical, with monoclinic unit-cell dimensions $a = 7{\cdot}542 \pm 0{\cdot}001$, $b = 6{\cdot}228 \pm 0{\cdot}001$, $c = 14{\cdot}463 \pm 0{\cdot}0015$ Å, $\beta = 117{\cdot}04° \pm 0{\cdot}01°$, space group $P2_1/c$, with $Z = 2$ dimers per unit cell. Hence, the dimer molecules are centrosymmetric, and can correspond to none but isomer (IV) (*trans–anti*) of Wulff and Fraenkel.[6] We have not attempted to determine whether the photo-product solution contains other isomers of M.T.D.

Three-dimensional X-ray data were collected from one crystal on the Oak Ridge Computer-Controlled Diffractometer[7] with Cu-K_α radiation to a minimum crystal spacing of 0·84 Å. No absorption or extinction corrections were made.

The structure was solved by the symbolic addition procedure[8] with the use of the computer program "MAGIC".[9] After initial refinement of the structure, a difference Fourier, based on the coordinates of the C, N, and O atoms, clearly showed all the hydrogen atoms. The refinement was continued by using a modification of the full-matrix least-squares program "ORLFS",[10] in which the thermal motions of the C, N, and O atoms were treated anisotropically, while those of the H atoms were treated isotropically. Based on 1048 independent reflections, a value of 5% has been obtained for the reliability index $R_1(F)$. The refinement is being continued, and full results will be presented elsewhere.

The molecular structure viewed in a direction nearly perpendicular to the pyrimidine rings is shown in the Figure. It contains the expected cyclobutane ring, which is planar (dihedral angle = 0°) and substituted in a *trans–anti*-configuration, as required by the centre of symmetry. In other cyclobutane derivatives, dihedral angles from 0° to 51° have been found for the cyclobutane moieties.[11] The cyclobutane ring is approximately square, with bond lengths of 1·543 and 1·571 Å (e.s.d. 0·004 Å) and bond angles of 90·4° and 89·6° (e.s.d. 0·2°). All other bond lengths and angles fall within normal

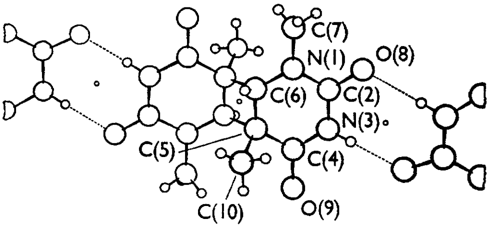

FIGURE. *Structure of the* trans–anti-*isomer of 1-methylthymine dimer. The Figure shows one complete dimer molecule and parts of two neighbouring molecules in the crystal. The smallest circles represent centres of symmetry in the crystal. The next-smallest, unlabelled circles represent hydrogen atoms. Hydrogen bonding between neighbouring molecules in the crystal is indicated by broken lines.*

[†] After completion of this work, we received from N. Cameron and S. C. Nyburg a preliminary account, which is to be published in *Tetrahedron Letters*, of an X-ray crystal structure determination of the *trans–anti*-isomer of thymine photodimer. Through subsequent communication with those authors, we have been able to compare the corresponding bond lengths and angles of the two different molecules, at the present stages of refinement, and have found no appreciable differences. The unit cells and molecular packing are quite different, however.

ranges. The pyrimidine rings, having lost the C(5)–C(6) double bonds present in the monomer, are not nearly so planar as in M.T.,[12] or in thymine,[13] but have a maximum deviation of 0·14 Å out of the least-squares "best" plane. The tetrahedral configuration about C(5) causes the attached methyl carbon, C(10), to lie 1·41 Å out of the pyrimidine "best" plane rather than very close to it, as in M.T.[12] and in thymine.[13] The dihedral angle between (normals to) the pyrimidine "best" plane and the cyclobutane plane is 54°. Neighbouring dimers are bonded together by hydrogen bonds between N(3) and O(8), with pairs of these bonds being related by centres of symmetry.

We can offer no explanation at this time for the formation of isomer (IV) instead of the other isomeric forms, since we have no definite knowledge of the monomer packing in the frozen solution. Stewart has discussed photodimerization in one crystalline form of M.T. and has shown that with this form it is reasonable to expect the formation of isomer (II).[4] His argument is based on the assumption that monomer linking takes place between nearest pairs of 5,6-double bonds in the monomer crystal. However, the crystal form he discussed is only one of two forms obtained on cooling hot solutions of M.T. to room temperature, the other being the form that crystallizes first.[12] The latter crystal form (the structure of which is unknown) and/or still other crystal forms of M.T., such as hydrates, might possibly exist in frozen solutions.

We thank Dr. H. A. Levy for use of the Oak Ridge Computer-Controlled *X*-ray Diffractometer, and both Dr. Levy and Dr. R. D. Ellison for assistance in using this instrument. This research was jointly sponsored by the National Cancer Institute, and the U.S. Atomic Energy Commission under contract with the Union Carbide Corporation.

(*Received, August* 14*th*, 1967; *Com.* 865.)

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