Crystal and Molecular Structure of Thalidomide

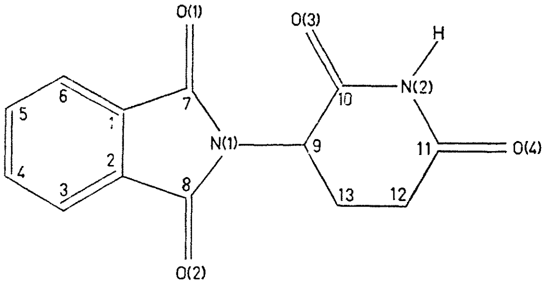
By F H ALLEN and JAMES TROTTER*
(*Department of Chemistry, University of British Columbia, Vancouver 8, B C , Canada*)

Summary Crystal structure analysis of Thalidomide has established the molecular conformation and dimensions, the glutarimido-residue is twisted 81 3° relative to the phthalimide moiety

---

THE *N*-(α-glutarimido)-derivative of phthalimide [structure (I), in which the numbering is for convenience in the crystal analysis] was first synthesized in 1953, and was marketed as the sedative Thalidomide in 1957[1] The deleterious effect of Thalidomide on the human foetus was first suggested in 1961,[2] and the overwhelming medical evidence led to its withdrawal throughout the world in 1962 The mode of action of the drug *in vivo* is not yet clear, but the general similarity of the molecular shape to that of the nucleosides[3] and the similarity of the glutarimido-residue to the barbiturate radical, have led us to determine the crystal structure, in order to study the molecular conformation in the solid state A short communication on the crystal structure (in projection) of the 4-bromo-derivative has been published,[4] we have chosen the unsubstituted compound for our study since the mode of packing in the crystal must be affected by the incorporation of a heavy atom Crystal data *N* (α-glutarimido)phthalimide, $C_{13}H_{10}N_2O_4$, $M =$ 258 26, m p 269—271° Monoclinic, space-group $P2_1/n$, $a = 8\ 233(1)$, $b = 10\ 070(2)$, $c = 14\ 865(2)$ Å $\beta =$ 102 53(2)°, $U = 1203\ 0$ Å^3 $D_m = 1\ 43$ g cm^{-3}, $Z = 4$, $D_c = 1\ 426$ g cm^{-3}, μ(Cu K_α) = 9 22 cm^{-1}

The intensities of the 2256 independent *X*-ray reflections with $2\theta \leqslant 140°$ were measured on a G E XRD 6 diffractometer, using a θ–2θ scan at 2°/min in 2θ The structure was solved using the direct sign-determining procedure programmed by Long[5] and based on Sayre's equation[6] All 19 non-hydrogen atoms were easily located from the first three-dimensional '*E*-map', and the ten hydrogens were found in a subsequent difference map Full-matrix least-squares refinement, with anisotropic thermal parameters for C, N, and O and isotropic values for H, has reduced R to 0·056 for the 1855 observed data not affected by extinction.



A view of the structure down the c^* axis is shown in the Figure. The atoms of the benzene ring are closely coplanar (maximum deviations: 1·7σ for C, 3σ for H), but the five-membered ring is somewhat puckered. This means that the phthalimide residue, as a whole, is not planar, contradicting the report of Furberg *et al.*;[3,4] a mean-plane calculation for all eleven atoms shows an average deviation of 0·029 Å (*ca.* 10σ) with maxima of 0·06 Å (30σ) at N(1) and O(2). The five-membered ring is best described as a very shallow envelope with N(1) at the flap, an effect caused by a trigonal pyramidal configuration at N(1) which is 0·12 Å above the C(7)–C(8)–C(9) plane. It should be noted however that both C(sp^2) atoms, C(7), C(8), have strictly planar configurations.

The glutarimido-residue is not planar; C(13) deviates by 0·65 Å from the mean plane through the other ring atoms. There is also some puckering in the remainder of the ring: the four-atom groupings centred on N(2) and C(11) are essentially planar but make an angle of 5·1° with each other, and there is a further dihedral twist of 4·5° about C(10)–N(2).

The mean plane through the eleven non-hydrogen atoms of the phthalimide residue makes an angle of 81·3° with that through the eight glutarimido-atoms. As pointed out by Furberg[3] the degree of twist about N(1)–C(9) is determined by the intramolecular van der Waals contacts between O(1) and O(3) (3·15 Å) and O(1) and one of the hydrogens at C(13) (2·59 Å). He also notes the similarity of this angle to that found between the base and sugar moieties in many nucleosides.

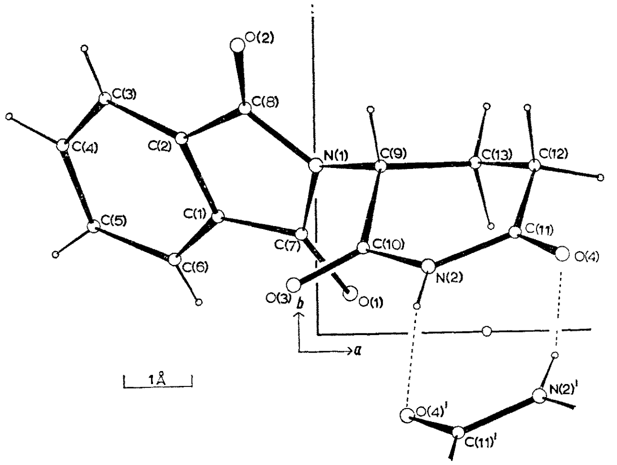


FIGURE. *View of the thalidomide structure down* c*; *the centre of symmetry shown is at* $z = \frac{1}{2}$.

The Figure shows that pairs of centrosymmetrically related molecules form dimers through N(2)–H · · · · O(4′) hydrogen bonds of 2·93 Å. The N(2)–H distance is 0·82 Å, H · · · · O(4′) is 2·12 Å and the angle at H is 171·8°. These parameters are in agreement with data from other crystallographic studies.[7]

(*Received, April* 27*th*, 1970; *Com.* 620.)

---

[1] Chemie Grunenthal, G.m.b.H., B.P., 1957, 768,821.

[2] W. Lenz, *Deutsch. med. Wochenschr.*, 1961, **86**, 2555; *Lancet*, 1962, **1**, 45 and 271; W. G. McBride, *ibid.*, 1962, **2**, 1358.

[3] S. Furberg, *Acta Chem. Scand.*, 1965, **19**, 1266.

[4] S. Furberg and C. S. Petersen, *Acta Chem. Scand.*, 1965, **19**, 253.

[5] R. E. Long, Ph.D. Thesis, University of California at Los Angeles, 1965.

[6] D. Sayre, *Acta Cryst.*, 1952, **5**, 60.

[7] W. C. Hamilton and J. A. Ibers, "Hydrogen Bonding in Solids," Benjamin, New York, 1968, ch. 5.