Structural Relationship between Thalidomide and Nucleosides

SVEN FURBERG

Institute of Chemistry, University of Oslo, Blindern, Oslo 3, Norway

We have recently determined the crystal structure of 4-bromo-thalidomide by X-ray crystallographic methods.[1] From this work the main structural features of the thalidomide molecule (Fig. 1 a) may by inferred. It can briefly be described as follows:

The phthalimide part of the molecule is essentially planar, the glutarimide ring non-planar, with atom C(2′) about 0.5 Å out of the mean plane of the other ring atoms. The central C—N bond lies nearly in the plane of the phthalimide and forms approximately tetrahedral angles with the adjacent bonds in the glutarimide part. The phthalimide plane and the mean glutarimide plane are nearly perpendicular to each other. The bond C(2′)—C(3′) is parallel to the phthalimide plane and only about 10° off the N—C direction. A study of models shows that the relative orientation of the two rings around the N—C bond is governed by van der Waals forces mainly between one of the phthalimide oxygens and the oxygen O(5′) and one of the hydrogens at C(2′) in glutarimide.

We would like to draw attention to the fact that this structure has a general resemblance to that of the nucleosides. In the first place, the stereochemistry of the central N—C bond is the same in the two types of compounds, namely planar arrangement at the nitrogen atom and tetrahedral at the carbon atom.[2] A roughly perpendicular relationship between the two parts of the molecule is characteristic also for the nucleosides, although the van der Waals forces are different because ribose lacks an atom corresponding to O(5′) in glutarimide. Furthermore, the atoms C(2′) and C(3′), as well as atoms linked to C(2′) and C(3′), are similarly situated in the two cases, especially if ribose (or deoxyribose) has the conformation found in crystals of cytidylic acid.[3] In this conformation the atom C(2′) is 0.5 Å from the mean plane of the other ring atoms of ribose, and the bond C(2′)—C(3′) forms an angle of roughly 20° with the glycosidic linkage.

In Fig. 1 thalidomide is compared with two nucleosides, *viz.* deoxycytidine and deoxyadenosine. The figure shows projections of large-scale wire models based on bond lengths and angles from related crystal structures.[4-6] A van der Waals radius of 1.2 Å is assigned to the hydrogen atoms and of 1.4 Å to the oxygen and nitrogen atoms. The sugar has the conformation described above. As seen from the figure, the dimensions of the three molecules are approximately the

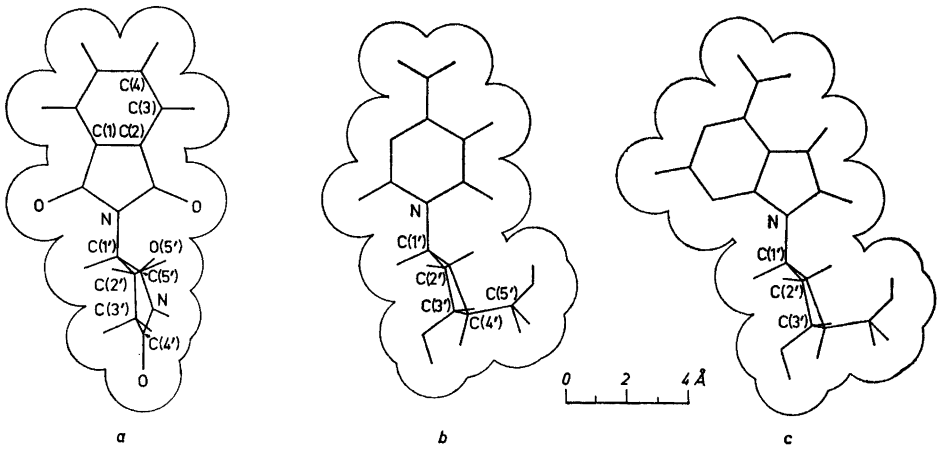

Fig. 1. The structures of a) thalidomide, b) deoxycytidine, and c) deoxyadenosine projected perpendicularly to the aromatic planes.

same, apart from the difference between $CO \cdot NH \cdot CO$ in glutarimide and $O \cdot CH \cdot CH_2OH$ in ribose. It is evident that the thalidomide molecule is similar in size and shape to those of the nucleosides. There is also resemblance in the general distribution of polar groups. On the other hand, the compounds differ widely in chemical behaviour and ability to form hydrogen bonds.

It would appear worth while to consider the possibility that the biological effects of thalidomide may in part be related to its structural resemblance with nucleosides. Perhaps thalidomide is an antagonist to one or more nucleosides and/or nucleotides. It could, because of its similar shape, size and van der Waals field of force, partially block an enzyme, causing interference with nucleic acid and protein synthesis, or with other metabolic processes involving nucleosidic structures. Less likely, it may also be conceived that thalidomide interacts directly with nucleic acid structure, either temporarily, or by intercalation of its phthalimide part between bases in a manner resembling that proposed for proflavine.[7] This would be due to attraction between the planar parts of the molecules. The similarity in the disposition of the hydrogen atoms at C(2′) and C(3′) may also play a role.

A number of investigations of the influence of thalidomide on embryonic development has been carried out and several theories proposed,[8-10] but its mode of action still appears to be unknown.

1. Furberg, S. and Petersen, C. S. *Acta Chem. Scand.* **19** (1965) 253.
2. Furberg, S. *Acta Chem. Scand.* **4** (1950) 751.
3. Alver, E. and Furberg, S. *Acta Chem. Scand.* **13** (1959) 910.
4. Brown, R. N. *Acta Cryst.* **14** (1961) 711.
5. Haschmeyer, A. E. V. and Sobell, H. M. *Acta Cryst.* **18** (1965) 525.
6. Furberg, S., Petersen, C. S. and Römming, Chr. *Acta Cryst.* **18** (1965) 313.
7. Lerman, L. S. *J. Mol. Biol.* **3** (1961) 18.
8. Faigle, J. W., Keberle, H., Riess, W. and Schmid, K. *Experientia* **18** (1962) 389.
9. Nyström, C. *Scand. Clin. Lab. Invest.* **15** (1963) 102.
10. Frank, O., Baker, H., Ziffer, H., Aaronson, S., Hutner, S. H. and Leevy, C. M. *Science* **139** (1963) 110.

Received May 19, 1965.

Chemical Constituents of the Genus *Dahlia*

Two Polyacetylenic Compounds from *Dahlia scapigera* Link et Otto

FRANTZ KAUFMANN and JØRGEN LAM

Department of Chemistry, University of Aarhus, Aarhus C., Denmark

A recent communication by Bohlmann and Kleine [1] on acetylenes from *Dahlia merckii* Lehm. prompts us to report on two acetylenes which we have isolated independently.

By chromatography of a light petroleum extract of the roots and tubers of *Dahlia scapigera* (A. Dietr.) Link et Otto var. *scapigera forma merckii* (Lehm.) Sherff, two colourless acetylenic compounds A and B were eluted. Both are present in large amounts (A: 0.1 %, B: 0.1 %, based on the weight of fresh material).

Compound A is eluted easily with light petroleum and melts at 29.5–31.0°. In the ultraviolet region it has the following peaks: 250, 266.5, 280, 296.5, 315, and 336 mμ (ε: 29 400, 25 800, 15 100, 26 100, 35 300, and 26 100). (The molecular extinctions are calculated on basis of molecular weights corresponding to C_{13}-compounds).

Compound B is more polar and can be eluted with a mixture of light petroleum and ether. After purification by preparative thin-layer chromatography the compound melts at 111.0–111.5° and exhibits an ultraviolet spectrum nearly identical with that of compound A: 250, 266.5, 280, 296.5, 315, and 336 mμ (ε: 31 500, 27 950, 16 500, 28 700, 39 100, and 28 800).

The infrared spectrum of A is indicative of an acetoxygroup (1750 cm^{-1}, 1240 cm^{-1}) and that of B of a primary alcohol group (3630 cm^{-1}, 1050 cm^{-1}, 1290 cm^{-1}). Further bands observed for A are: $-C\equiv C-$ (2210 cm^{-1}, 2140 cm^{-1}), *trans* $-CH=CH-$ (945 cm^{-1}) and *trans-trans* $-(CH=CH)_2-$ (1640 cm^{-1}, 980 cm^{-1}). The spectrum of compound B shows $-C\equiv C-$ (2200 cm^{-1}, 2130 cm^{-1}), *trans* $-CH=CH-$ (949 cm^{-1}), and *trans-trans* $-(CH=CH)_2-$ (1635 cm^{-1}, 985 cm^{-1}) absorptions.

Hydrolysis of A (purified by preparative thin-layer chromatography) with methanolic potassium hydroxide afforded a compound with m.p. 110.5–111.5° and