Crystal and Molecular Structure of Cyclophosphamide Hydrate

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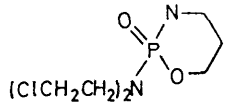
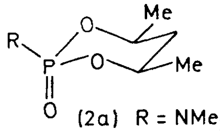
Summary The *X*-ray structure of cyclophosphamide (**1**) shows that the chair-form ring possesses an equatorial dialkyl amino-group and an axial phosphoryl oxygen in contrast to the opposite phosphorus stereochemistry reported for structures of similar systems wherein a variety of other groups replace the dialkyl amino-ring substituent.

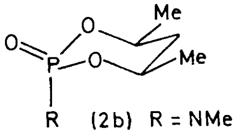
THE carcinostatic properties of cyclophosphamide (**1**) in the treatment of various *in vivo* tumours have been widely studied [1]



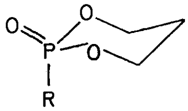
(1)



(2a) R = NMe_2
(3a) R = OMe



(2b) R = NMe_2
(3b) R = OMe



(4)

The presence of the ring in (**1**) implies that the phosphorus substituents can assume axial or equatorial positions. Compound (**2**) is more stable as isomer (**a**) than as isomer (**b**) in solution[2] contrary to earlier findings with (**3**).[3] Moreover solid-state structural results[3a] on six systems of type (**4**) (in which the ring carbons may or may not possess alkyl substituents) indicated the presence of isomer (**b**) even when large R groups such as Ph and OPh were present. It was therefore important to ascertain whether the equatorial dialkyl amino-group–axial phosphoryl oxygen stereochemistry which appears to be more stable in solution persists in the solid state.

Crystals of (**1**) grown by slow evaporation of an ether–heptane solution were found to be triclinic $a = 8{\cdot}65(1)$, $b = 13{\cdot}39(1)$, $c = 6{\cdot}01(1)$ Å, $\alpha = 96{\cdot}3(1)$, $\beta = 100{\cdot}3(1)$, $\gamma = 106{\cdot}7(1)^\circ$, $Z = 2$, space group $P\bar{1}$. After correction for experimental effects a total of 1601 diffractometer measured intensities (Mo-K_α radiation, $\theta_{\max}$ 30°) were observed. Phases were assigned by an iterative application of Sayre's equation and all fourteen non-hydrogen atoms of the molecule were apparent in the subsequent E synthesis. A water molecule was discovered in the subsequent F synthesis. Least-squares refinement converged rapidly to $R = 8{\cdot}7\%$. All 17 hydrogen atoms were located in a subsequent difference map and refinement continued to the present minimum of $7{\cdot}2\%$.

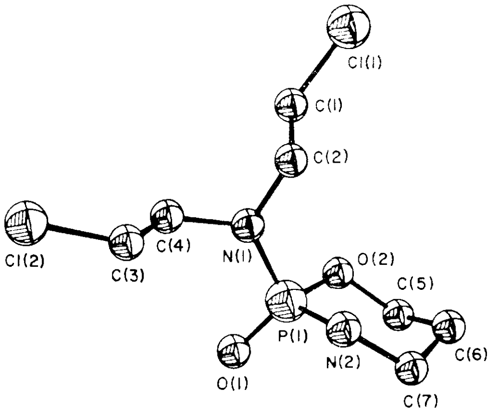


FIGURE.

The configuration of (**1**) (Figure) shows that the more stable axial oxygen–equatorial dialkyl amino-group stereochemistry inferred from solution studies of (**2**)[2] is also found in the solid state of (**1**). The near planarity of the exocyclic and ring nitrogens and their respective substituent atoms is common in solid state structural studies of aminophosphorus compounds[5,6] where steric factors are absent.[7] The staggered conformation of the C_2NP plane with respect to the nitrogen and oxygen atoms in the ring is also typical of amino-difluoro-phosphine systems.[5,6] All the bond-lengths and angles agree with generally accepted values.†

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† The crystal and molecular structure have also been solved by Drs. Aurea Perales and Garcia-Blanco of the Instituto De Quimica Fisica "Roscolano," Serrano 119, Madrid 6, Spain.

[1] See for example Cancer Chemotherapy Reports, 1967, **51**. This entire issue is devoted to chemical and clinical research on (**1**)

[2] J. A. Mosbo and J. G. Verkade, *J. Amer. Chem. Soc.*, 1972, **94**, in the press.

[3] (a) D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc.* (*B*), 1971, **1454**; (b) W. G. Bentrude and K. C. Yee, *Tetrahedron Letters*, 1970, 3999; (c) W. G. Bentrude, K. C. Yee, R. D. Bertrand, and D. M. Grant, *J. Amer. Chem. Soc.*, 1971, **93**, 797.

[4] See references to crystallographic work in ref 3(a).

[5] G. C. Holywell, D. W. H. Rankin, B. Beagley, and J. M. Freeman, *J. Chem. Soc. A*, 1971, 785, and references therein.

[6] A. H. Brittain, J. E. Smith, P. L. Lee, K. Cohn, and R. H. Schwendeman, *J. Amer. Chem. Soc.*, 1971, **93**, 6772 and references therein.

[7] J. G. Verkade, *Co-ordidation Chem. Rev.*, 1972, **9**, in the press.

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