SYNTHESIS AND STRUCTURE OF 5-PHENYLCYCLOPHOSPHAMIDES

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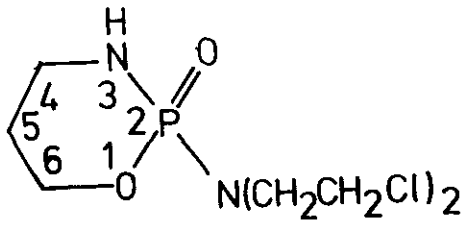
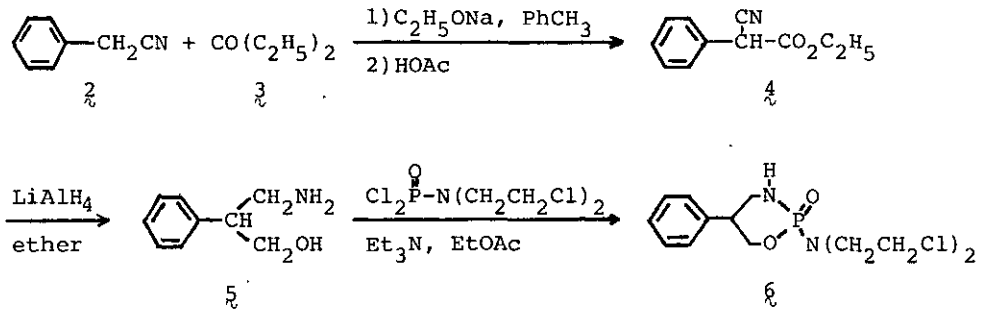
Abstract ——5-Phenylcyclophosphamides have been synthesized from benzyl cyanide via carbethoxylation, reduction, and finally condensation with bis(2-chloroethyl)-phosphoramidic dichloride. The two diastereomers have been separated and their structures have been assigned on the basis of ir, P-31 nmr and X-ray crystallography.

Racemic cyclophosphamide, 1, is a widely used drug for the treatment of human cancers. The metabolisms, pharmacokinetics, and mechanism of action of 1 have been extensively studied.[1] The synthesis of oxazaphosphorinane derivatives is interesting not only for medical purposes but also for intrinsical molecular structures.

Recently, a series of 4-arylcyclophosphamides have been synthesized, whose antitumor activity and X-ray studies have been reported.[2-4] Both 4-phenylcyclophosphamides and 4-tolylcyclophosphamides have the twisted chair conformation. It is our aim to extend the synthesis and structure studies to 5-arylcyclophosphamides, where aryl is phenyl in this report. Monosubstitution at C-5 generates a second chiral center in addition to P-2, resulting in a pair of diastereomers, i.e., RR/SS = trans and RS/SR = cis for phenyl and P=O moieties.



Cyclophosphamide, 1



The synthetic scheme started from benzyl cyanide, 2, which was reacted with equimolar freshly prepared sodium ethoxide and 5-fold dry diethyl carbonate, 3, to give pure ethyl phenylcyanoacetate, 4, bp 129-131^{0}C/5mm Hg, in 81.0% yield (lit. bp 125-135^{0}C/3-5mm Hg, yield 70-78%).[5] 4 was reduced with 3 mole equivalents of lithium aluminum hydride in refluxing ether to form 3-amino-2-phenyl-1-propanol, 5, bp 150-160^{0}C/4mm Hg in 11.2% yield (lit. bp 114-115^{0}C/0.5mm Hg).[6] 5 was allowed to react at room temperature with equimolar amount of bis(2-chloroethyl)-phosphoramidic dichloride[7] and 2 mole equivalents of triethylamine in dry ethyl acetate. The reaction mixture was stirred for 48 h and then filtered to remove triethylamine hydrochloride. The clear solution was rotarily evaporated and the residue was chromatographed on silica gel, eluting with chloroform. Two isomers were obtained in nearly equal amount (The fast migrating 6A, yield 35.0%, and the slow migrating 6B, yield 39.7%, are according to their relative mobilities on column chromatography). 6A was recrystallized from n-hexane as needles, while 6B recrystallized from n-hexane-benzene, also as needles but much smaller. With the same mass spectra, 6A and 6B were found to have different mp's, ir, and nmr spectra. Relevant data and those of similar compounds were shown in Table 1.

Table 1.

Characteristic Data of 5-Phenylcyclophosphamides and Similar Compounds

Compound[a]	mp (°C)	Mass Spectra (M+)	ir, νP=O[b] (cm^{-1})	P-31 nmr[c] (δ)	Reference
6A[d]	69.4	336, 338	1218	12.46	this report
6B[d]	118.1	336, 338	1234	11.07	this report
7A	130.5-132	336, 338	1230	8.89	2
7B	114-116	336, 338	1212	13.2	2
8A	129-131	316	1224	9.78(C_6D_6)	10
8B	173-175	316	1226	6.69	10

a. A: Fast migrating, B: Slow migrating.
b. Recorded on a Perkin Elmer model 297 Infrared Spectrophotometer using KBr tablets.
c. Recorded on a Jeol FX100 FT nmr using $CDCl_3$ as solvent. The chemical shifts are reported in ppm downfield from external H_3PO_4.
d. New compounds with satisfactory elementary analysis.

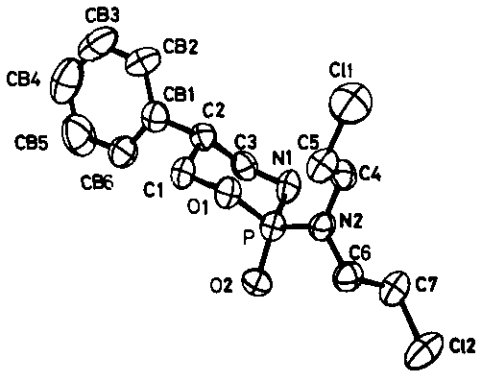


Figure 1. ORTEP drawing of 6A with thermal ellipsoids at 50% level. Hydrogen atoms are omitted.

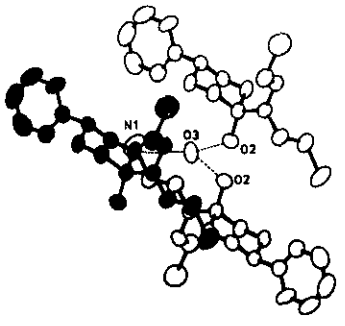


Figure 2. ORTEP plot to show the hydrogen bonding interactions. One of the three 6A molecules is darkened for clarity.

A crystal of 6A suitable for X-ray structure analysis was obtained. It was found to crystallize in the monoclinic space group C2/c with Z=8 and cell dimensions a=20.213(3)Å, b=5.993(3)Å, c=28.802(4)Å, β=93.71(1)°. Intensity data up to $2\theta \leq 50^{\circ}$ were collected using a Nonius CAD-4 automated diffractometer equipped with monochromated Mo-K_{α} radiation employing the θ-2θ scan method. The structure was solved by direct methods and successive Fourier maps, and it was refined with a weighted least squares routine. 6A was found to be mono-hydrated in the crystalline state. All nonhydrogen atoms were refined anisotropically, and hydrogen atoms were fixed at calculated positions isotropically, resulting in final R=0.057 and R_{ω}=0.049 for 1213 observations out of 2876 measurements (2σ data). The quantity minimized was $\Sigma w||F_o|-|F_c||^2$, where F_o, F_c were observed and calculated structure factors, respectively, and w, the weight, was given by $1/(\sigma^2(F)+0.00005|F|^2)$.

An ORTEP drawing[8] of 6A with atom names is presented in Figure 1, revealing a chair like structure with an equatorially disposed phenyl substituent. More importantly, the X-ray structure is seen to possess an RS/SR relationship, i.e., 6A has a cis configuration. In the crystalline state, the RS and SR 6A's are paired up by the crystallographic requirements, manipulated through strong hydrogen bonding interactions as seen in Figure 2. The hydrogen bonding systems for hydrate oxygen are: O3 to N1 of a 6A, O3 to O2 of a second 6A, and O3 to O2 of a third 6A, and vice versa for one 6A to 3 hydrate oxygen atoms, i.e., without any direct cyclophosphamide to cyclophosphamide hydrogen bonding interactions which are commonly seen in other cyclophosphamide structures.[3,4,9] Discussion on other structural parameters is to be detailed elsewhere.

6A has a lower P=O stretching frequency than 6B, indicating a lower P=O stretching force constant for 6A due to less deformation of cyclophosphamide ring. With equatorially disposed phenyl substitution, trans-4-phenyl-cyclophosphamide, 7B, also has a less deformed ring similar to 6A structurally. 7B also shows a lower P=O stretching frequency than cis-4-phenylcyclophosphamide, 7A, as revealed in Table 1. The P-31 nmr chemical shift of 7A is remarkably at higher field than that of 7B, showing the large difference of P environment because of deformation of cyclophosphamide ring. Correspondingly, that of 6B is at higher field than that of 6A, though the difference is less enhanced. The

same trend has been reported recently for 2-oxo-2-(dimethylamino)-3,5-diphenyl-1,3,2-oxazaphosphorinane, 8A and 8B.[10]

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REFERENCES

1. (a) D. L. Hill, In "A Review of Cyclophosphamide", Charles C. Thomas: Springfield, IL, 1975, pp 9-59.
   (b) L. B. Grochow and M. Colvin, Clin. Pharmacokinet., 1979, 4, 380. M. Colvin and J. Hilton, Cancer Treat. Rep., 1981, 65(Suppl. 3) 89.
   (c) G. Zon, Progr. Med. Chem., 1982, 19, 205.
2. (a) Y. E. Shih, J. S. Wang, and C. T. Chen, Heterocycles, 1978, 9, 1277.
   (b) J. S. Wang, Y. E. Shih, and C. T. Chen, Bull. Inst. Chem., Academia Sinica, 1979, 26, 87.
3. (a) V. L. Boyd, G. Zon, V. L. Himes, J. K. Stalick, A. D. Mighell, and H. V. Secor, J. Med. Chem., 1980, 23, 372.
   (b) V. L. Himes, A, D, Mighell, J. K. Stalick, and G. Zon, Acta Cryst., 1982, B38, 1009.
4. (a) L. K. Liu and C. J. Wang, Bull. Inst. Chem., Academia Sinica, 1983 30, 19.
   (b) L. K. Liu, J. Chinese Chem. Soc., 1984, 31, 125.
5. E. C. Horning and A. F. Finell, Org. Synth., 1950, 30, 43.
6. E. Testa, L. Fontanella, G. Cristiani, and L. Moriani, Ann., 1961, 639, 166; cf Chem. Abstr., 1961, 55, 27004b.
7. O. M. Friedman and A. M. Seligman J. Am. Chem. Soc., 1954, 76, 655.
8. C. K. Johnson, "ORTEP: A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations," Oak Ridge National Laboratory, ORNL 3794.
9. I. L. Karle, J. M. Karle, W. Egan, G. Zon, and J. A. Brandt, J. Am. Chem. Soc., 1977, 99, 4803.
10. W. G. Bentrude, R. O. Day, J. M. Holmes, G. S. Quin, W. N. Setzer, A. E. Sopchik, and R. R. Holmes, J. Am. Chem. Soc., 1984, 106, 106.

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