SYNTHESIS AND STRUCTURE OF 6-PHENYLCYCLOPHOSPHAMIDES

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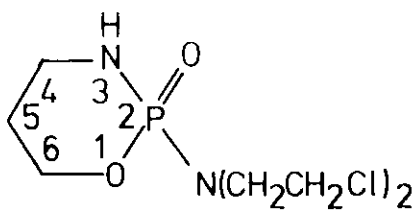
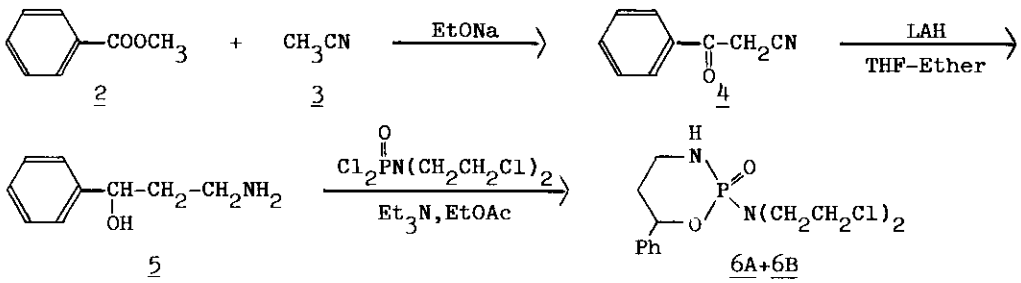
Abstract— 6-Phenylcyclophosphamides have been synthesized from methyl benzoate and acetonitrile to benzoyl acetonitrile followed by reduction to amino alcohol and condensation with bis(2-chloroethyl)phosphoramidic dichloride. The two diastereomers have been separated and their structures have been assigned 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 pharmacology, pharmacokinetics, and structure-activity relationship 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.



Cyclophosphamide, 1

As 4-arylcyclophosphamides and 5-arylcyclophosphamides have been synthesized, their structures have accumulated a lot of information concerning the conformation of oxazaphosphorinane ring.[2] It is our aim to extend the synthesis and structure studies to 6-arylcyclophosphamides, where aryl is phenyl in this report. Monosubstitution at C-6 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.



The synthetic scheme started from methyl benzoate, 2, which was reacted with equimolar freshly prepared sodium ethoxide and a slight excess of acetonitrile, 3, at 105°C for 18 h with continuous stirring to give the pure benzoyl acetonitrile, 4, which was recrystallized from n-hexane/benzene in 65.1% yield, mp 83.5°C, (lit. mp 80-81°C);[3] ir(cm^{-1}) 1682 (C=O), 2240 (C≡N); ^1H nmr(ppm) 4.1 (s, 2H), 7.5-7.9(m, 5H). Compound 4 was reduced with 4 mole equivalents of lithium aluminum hydride in refluxing ether-THF mixture to form 3-amino-1-phenyl- 1-propanol, 5, in 94.7% yield, mp 60-61°C (lit. mp 63-64°C, 40% yield with ether/benzene mixed solvent).[4] Compound 5 crystallized to give white needles after vacuum distillation, ms M^+ 151; ir(cm^{-1}) 3150-3450 (OH, NH), no carbonyl or nitrile bands. Compound 5 was allowed to react at room temperature with equimolar amount of bis(2-chloroethyl)phosphoramidic dichloride 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 crude product 6 was column chromatographed on silica gel, eluting with chloroform.

Two isomers were obtained in nearly equal amount (The fast migrating 6A, yield 29.0%, and the slow migrating 6B, yield 33.8%, are according to their relative mobilities on column chromatography and also on tlc developed with 10:1 ethyl acetate/n-hexane). Compound 6A was recrystallized from 1:1 ethyl acetate/n-hexane while 6B from benzene, both as prisms. 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.

A crystal of 6B suitable for X-ray structure analysis was obtained. It was found to crystallize in the monoclinic space group $P2_1/a$ with Z=4 and cell dimensions a=10.274(3)Å, b=12.474(3)Å, c=12.840(4)Å, β=105.58(3)°. Intensity data up to $2\theta \leq 60^0$ 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. Compound 6B was found to have hydrogen-bonded pairs in the crystalline state. All nonhydrogen atoms were refined with anisotropic temperature factors and hydrogen atoms were refined isotropically, resulting in final R=0.039 and R_ω=0.027 for 2616 observations out of 4616 measurements (2.5σ data). The quantity minimized was $\Sigma w||Fo|-|Fc||^2$, where Fo, Fc were observed and calculated structure factors, respectively, and w, the weight, was given by counting statistics only.

An ORTEP drawing[5] of 6B with atom names is presented in Figure 1, revealing a chair like structure with an equatorially disposed phenyl substituent and an axially P=O moiety. More importantly, this X-ray structure is seen to possess an RR/SS relationship, i.e., 6B has a trans configuration. In the crystalline state, the RR and SS 6B's are paired up by the crystallographic requirements, manipulated through strong hydrogen bonding interactions as seen also in Figure 1: N3 to O2 of a second 6B with opposite chirality, and vice versa O2 to N3 of the same second 6B, i.e., a direct cyclophosphamide to cyclophosphamide hydrogen bonding interactions same as in both cis- and trans-4-tolylcyclophosphamide structures.[6] Discussion on other structural parameters is to be detailed elsewhere.

Table 1.

Characteristic Data of 4-, 5-, and 6-Phenylcyclophosphamides

Compound[a]	mp (°C)	Mass Spectra (M+)	ir, P=O[b] (cm^{-1})	P-31 nmr[c] (ppm)	Reference
6A[d]	122-123	336, 338	1232	10.83	this report
6B[d]	133-134	336, 338	1214	13.37	this report
7A	130.5-132	336, 338	1230	8.89	2(a)
7B	114-116	336, 338	1212	13.2	2(a)
8A	69.4	336, 338	1218	12.46	2(b)
8B	118.1	336, 338	1234	11.07	2(b)

a. 6A and 6B 6-phenyl-; 7A cis-4-phenyl-; 7B trans-4-phenyl-; 8A cis-5-phenyl-; 8B trans-5-phenyl-; and 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.
Calcd. C, 46.29; H, 5.64; Cl, 21.07; N, 8.31; P, 9.20
Found. 6A: C, 46.47; H, 5.74; Cl, 20.81; N, 8.27; P, 9.27
Found. 6B: C, 46.77; H, 5.73; Cl, 20.93; N, 8.30; P, 9.19

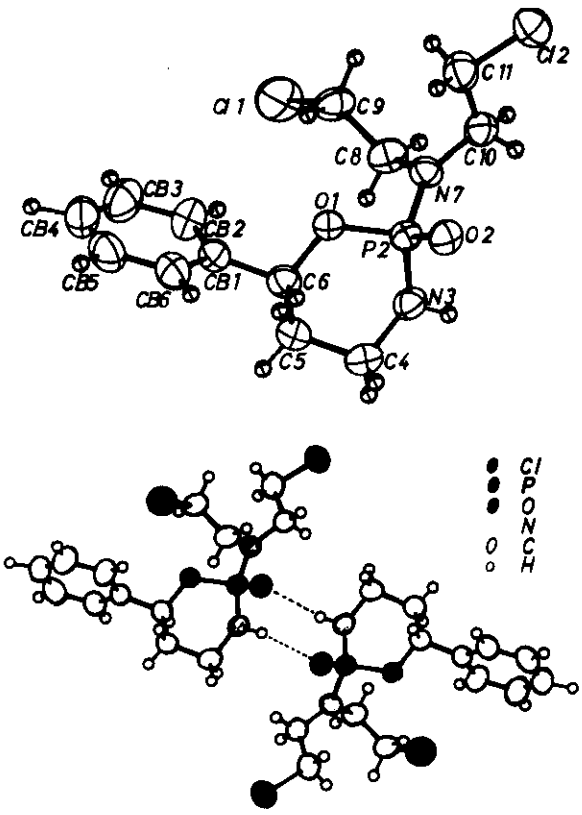


Figure 1.

(a) ORTEP drawing of 6B with thermal ellipsoids at 50% level. (b) The hydrogen bonding interactions. An inversion center is seen for this pair of 6B.

Compound 6B has a lower P=O stretching frequency than 6A, indicating a lower P=O stretching force constant for 6B due to less deformation of cyclophosphamide ring: the phenyl substituent being equatorially disposed quite easily without deforming moieties around P-2. Structural correlation could be made by comparing with 4- and 5-phenylcyclophosphamides. With a less deformed ring similar to 6B structurally, 7B and 8A also show a lower P=O stretching frequency than 7A and 8B respectively, as revealed in Table 1. The P-31 nmr chemical shifts follow the seeming pattern: those of 6B, 7B, and 8A at down fields while those of 6A, 7A, and 8B at up fields. It might be safe to conclude that a less deformed cyclophosphamide ring has a lower P=O stretching frequency and a less shielding P-31 nmr signal.

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