

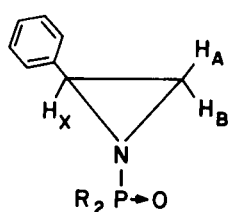
P.M.R. Analysis of Several Phosphorylated Aziridines

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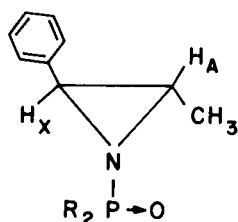
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Several new phosphorylated aziridines of related structure were prepared. P.m.r. analysis *via* decoupling experiments provided *cis* H-H, *trans* H-H, *gem* H-H and PNCH coupling values. Similar to simple aziridines, the *cis* H-H coupling is larger than *trans* H-H coupling (on vicinal ring carbons) which in turn is larger than *gem* H-H coupling. In one example operating at 100 MHz and 0° it was possible to detect the presence of two invertomers.

The value of several phosphorylated aziridines in the treatment of leukemia and other disorders is well documented (1). To our knowledge the identification of such aziridines by a systematic p.m.r. study of the J values for correlation with structure has not been reported for phosphorylated aziridines as evidenced by a recent and extensive review (2). To be sure, p.m.r. data is available on simple aziridines (1,3a-c). In connection with a separate investigation of certain aziridines (4), phosphorylated aziridines 1-5 were synthesized and analyzed *via* p.m.r. spectroscopy.



- 1 $R = C_6H_5 -$
 2 $R = C_2H_5O -$
 3 $R = (C_2H_5)_2N -$



- 4 $R = C_6H_5 -$
 5 $R = C_2H_5O -$

In the p.m.r. spectra of 1-3, one would expect four different types of couplings—*gem*, *cis*, *trans* and PNCH couplings. In the p.m.r. spectra of 1-5 the aziridine ring protons are shifted downfield compared to the parent 2-phenylaziridine (6) or *trans*-2-phenyl-3-methylaziridine (7). This is very likely due to the deshielding influence of the strong electron withdrawing groups, *i.e.* $(C_6H_5)_2P \rightarrow O$, $(C_2H_5O)_2P \rightarrow O$, and $[(C_2H_5)_2N]_2P \rightarrow O$ (Table I).

Evidence exists which suggests that *cis* coupling is larger than the *trans* coupling which in turn is larger than the *gem* coupling (2) in some simple aziridines. We conclude from the present study that a similar trend occurs

in this series of phosphorylated aziridines, PNCH coupling varies from 13 to 18 Hz (Table II).

Proton decoupling studies at 60 and 100 MHz with 1-diethoxyphosphonyl-2-phenylaziridine (2) and 1-diethoxyphosphonyl-*trans*-2-phenyl-3-methylaziridine (5) were carried out to determine and confirm the *cis*, *trans*, *geminal*, and PNCH couplings. In the p.m.r. spectrum of 2, proton H_A is coupled with the *gem* proton H_B , with the *trans* proton H_X , and with phosphorus (the usual PNCH coupling). A combination of these couplings gives rise to four doublets [$J_{AB} (gem) = 1.5$ Hz, $J_{AX} (trans) = 3$ Hz and $J_{PNCH_A} = 15$ Hz] for the proton H_A (Figure 1, peaks 17 to 24). Similarly, a combination of *gem*, *cis* and PNCH coupling gives rise to four doublets [$J_{AB} (gem) = 1.5$ Hz, $J_{BX} (cis) = 6$ Hz and $J_{PNCH_B} = 18$ Hz] for the proton H_B (Figure 1, peaks 9 to 16). In reference to proton H_X , four doublets [Figure 1, peaks 1 to 8, $J_{AX} (trans) = 3$ Hz, $J_{BX} (cis) = 6$ Hz and $J_{PNCH_X} = 15$ Hz] are observed.

TABLE I

P.m.r. Data of the Aziridine Ring Protons;
 δ (TMS) Values to Multiplet-Center.

Compound	H_X	H_B	H_A
1	3.7	2.79	2.12
2	3.4	2.57	2.05
3	(a)	(a)	1.89
4	3.6	—	2.67
5	3.33	—	3.53
6	2.83	2.02	1.64
7	2.47	—	1.87

(a) Part of the multiplet was merged in the methylene multiplet of $-N(C_2H_5)_2$ group.

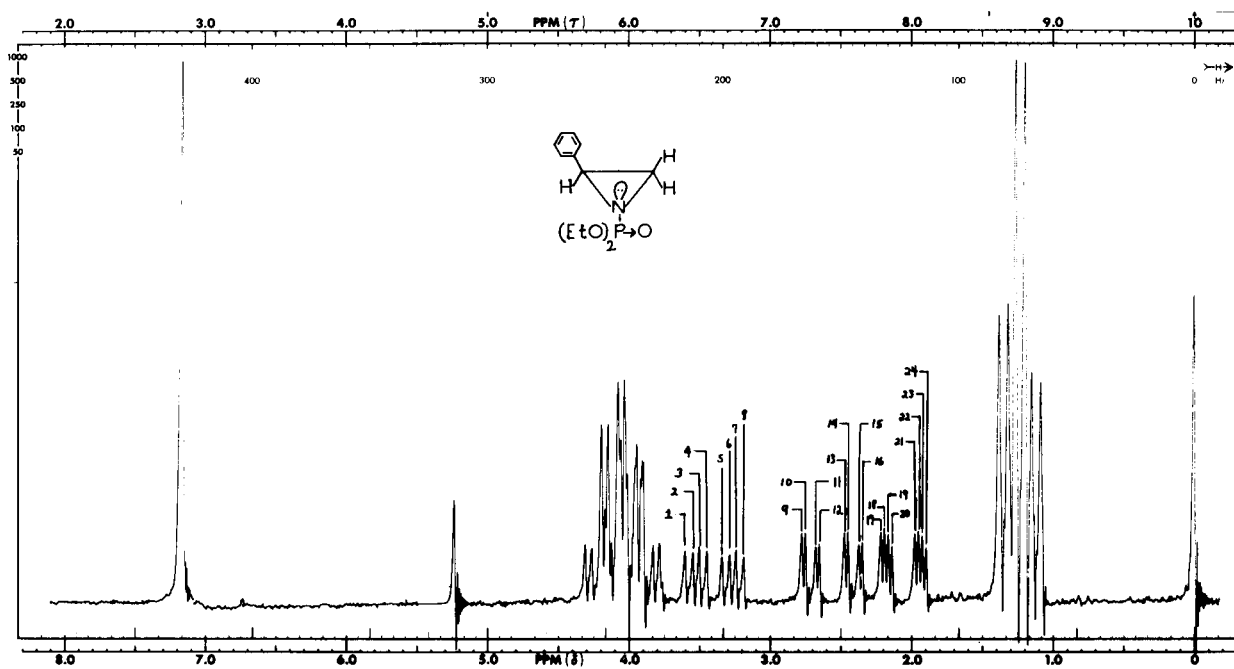


Figure 1. P.m.r. spectrum of 2 at 60 MHz in dichloromethane (δ 5.22) with TMS.

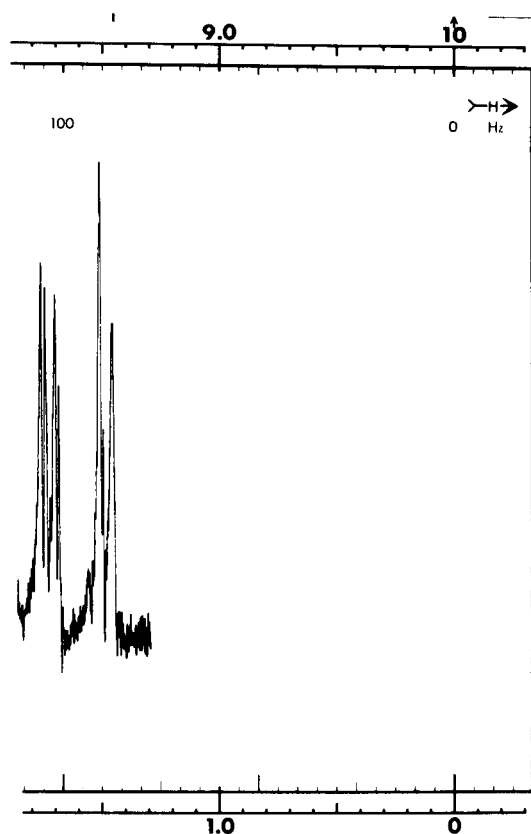


Figure 2. P.m.r. spectrum of part of the pattern of H_A (observe higher field doublet) while irradiating H_B (peaks 13,14).

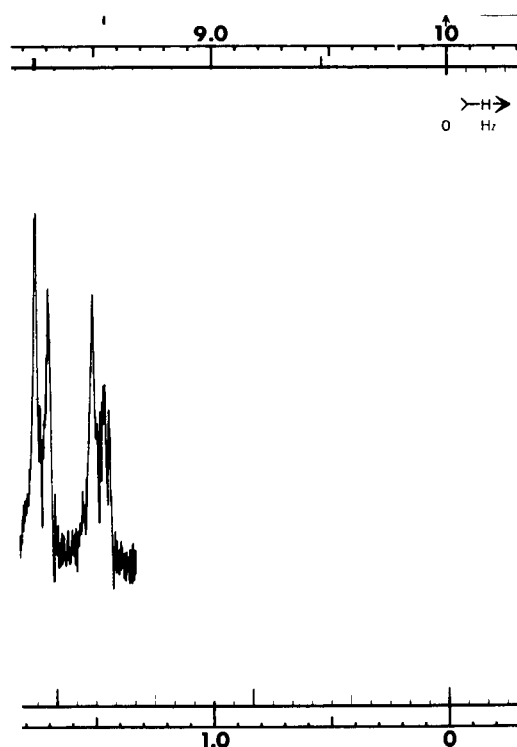


Figure 3. P.m.r. spectrum of part of the pattern of H_A while irradiating peaks 9,10 of the H_B pattern.

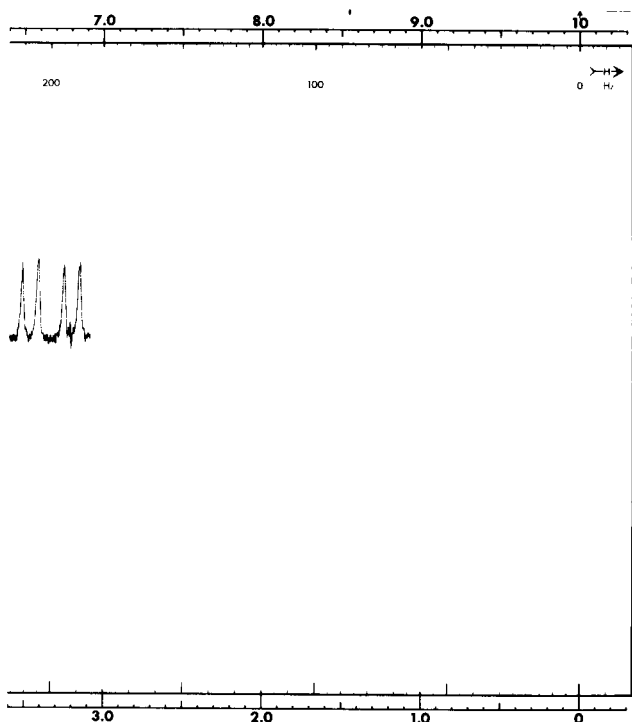


Figure 4. P.m.r. pattern for H_X observed while irradiating H_A .

On irradiation of one of the doublets of H_B (peaks 13,14 with a difference frequency of -33.5 Hz) the two doublets (peaks 21,22 and 23,24) of H_A coalesced (Figure 2) to give a single doublet. The coalescence is due to the removal of the *gem* coupling. The coupling constant of the new doublet is 3 Hz, the value of *trans* $H_A H_X$ coupling. On irradiation of the peaks 9,10 with a difference frequency of -37 Hz, the other two doublets of H_A (peaks 17,18 and 19,20) coalesced (Figure 3) into a doublet [J (*trans*) = 3 Hz]. From the separation of the new doublets observed by the irradiation of peaks 9,10 and 13,14, it was possible to obtain J_{PNCH_A} as 15 Hz.

The identification of the *cis* $H_B H_X$ coupling was made by irradiating H_A with a difference frequency of $+74$ Hz. Thus, elimination of *trans* coupling between H_A and H_X resulted in the four pairs of doublets (peaks 1,2;3,4;5,6 and 7,8) being converted into two pairs of doublets (Figure 4) with a value of 6 Hz, the value for $H_B H_X$ coupling. These two doublets are separated by 15 Hz, due to the $PNCH_X$ coupling.

A theoretical spectrum (treated ABCX) of **2** was calculated (Figure 5) using the published computer program (5). For use on the IBM 360-50 computer, two subroutines (invert and matrix) had to be made double precision.

Similar decoupling studies with 1-diethoxyphosphinyl-*trans*-2-phenyl-3-methylaziridine (**5**) revealed the *trans*

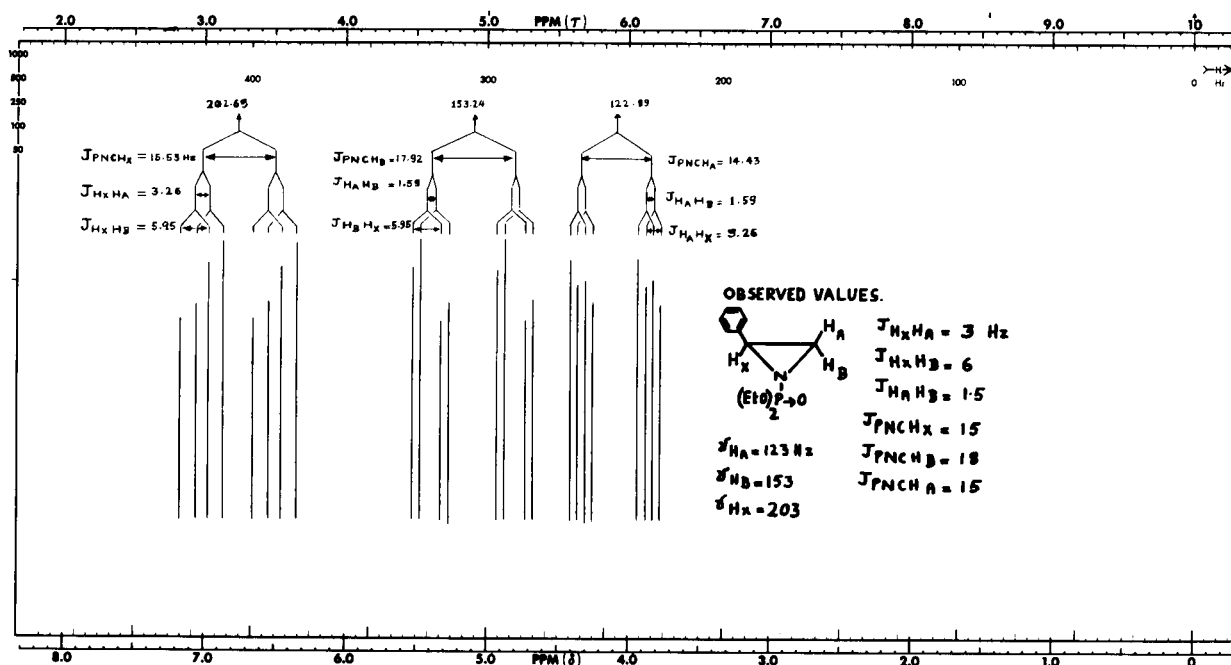


Figure 5. Calculated p.m.r. spectrum (lines 1-24) for **2**.

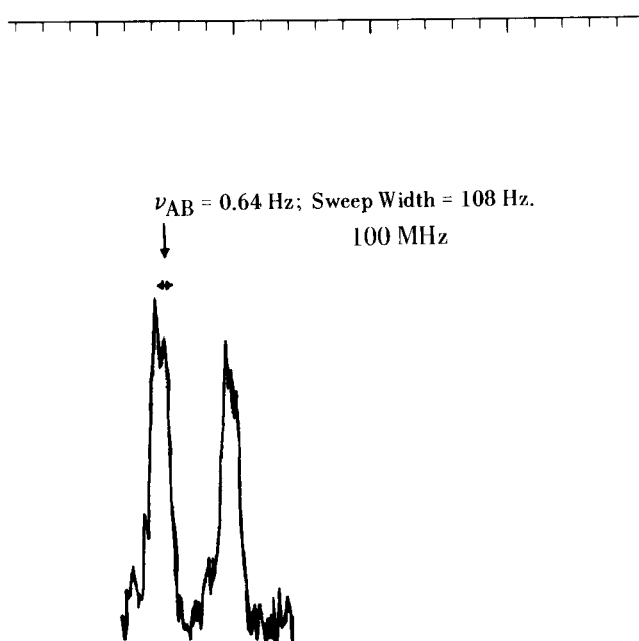


Figure 6. P.m.r. spectrum (protons of CH_3 groups only) of **4** at 0°C .

$\text{H}_\text{A}\text{H}_\text{X}$ coupling as 3 Hz, $\text{J}_{\text{PNCH}_\text{X}}$ as 15.5 Hz and $\text{J}_{\text{PNCH}_\text{A}}$ as 15 Hz. This is in excellent agreement with the *trans* $\text{H}_\text{A}\text{H}_\text{X}$ coupling on **2**

In view of the previous suggestion that phosphorylated aziridines may *not* show significant population of invertomers on the n.m.r. time scale because of rapid inversion even at quite low temperatures (6), **4** was cooled to 0° . At this temperature (Figure 6) a change in the p.m.r. spectrum was detected at 100 MHz. The two lines for the methyl protons were separated (ν_{AB}) by 0.64 cps. Rough estimates of k (sec^{-1}) and E_a (kcal/mole) were made from equation (1) (6) and equation (2) (7), respectively, and gave values of 1.41 sec^{-1} and 15.6 kcal/mole

$$k = \pi \nu_{\text{AB}}/\sqrt{2} \quad (1)$$

$$k = \kappa \left(\frac{kT}{h}\right) e^{-E_\text{a}/RT} \quad (2)$$

at 273°K (8). Work is continuing on possible isolation of invertomers of P-aziridines.

The phosphorylated aziridines **1-5** were made *via* phosphorylation of the parent aziridines in presence of triethylamine. Treatment of *trans*-2-phenyl-3-methylaziridine (**7**) with nitrosyl chloride under conditions reported (4)

TABLE II

Coupling Constants in Hz.

Compound	J (<i>gem</i>)	J (<i>trans</i>)	J (<i>cis</i>)	$\text{J}_{\text{PNCH}_\text{X}}$	$\text{J}_{\text{PNCH}_\text{A}}$	$\text{J}_{\text{PNCH}_\text{B}}$
1	1.5	3	6	16	13	18
2	1.5	3	6	15.5	15	18
3	---	---	---	---	15	Ca 18
4	---	3	--	15.5	15	---
5	---	3	--	15.5	15	---
6	1	3	6	---	---	---
7	---	3	--	---	---	---

TABLE III

Phosphorylated Aziridines

Compound	Yield %	Molecular Formula	B.p. (mm) or M.p. $^\circ\text{C}$	Calcd., %		Found, %	
				P	N	P	N
1	74	$\text{C}_{20}\text{H}_{18}\text{NOP}$	124°	9.71	4.39	9.65	4.29
2	66	$\text{C}_{12}\text{H}_{18}\text{NO}_3\text{P}$	135-136 (0.25)	12.15	5.49	11.92	5.27
3	32	$\text{C}_{16}\text{H}_{28}\text{N}_3\text{OP}$	196-197 (0.25)	13.59	10.03	13.86	9.83
4	81	$\text{C}_{21}\text{H}_{20}\text{NOP}$	119-120	9.29	4.20	9.22	4.24
5	75	$\text{C}_{12}\text{H}_{20}\text{NO}_3\text{P}$	130-131 (0.1)	11.52	5.20	11.70	5.13

gave exclusively *trans*-1-phenylpropene confirming the *trans* configuration assignment in the aziridine **7**.

EXPERIMENTAL (9)

2-Phenylaziridine (**6**) and *trans*-2-phenyl-3-methylaziridine (**7**) were prepared by a known procedure (3b). All phosphorus acid chlorides are available (Aldrich Chemical Co. and Columbia Organic Chemicals Co.) as are samples of *cis* and *trans* 1-phenylpropene (Chemical Samples Co.), except *N,N,N',N'*-tetraethylphosphorodiamidic chloride which was prepared by a known procedure (10).

The General Procedure for the Phosphorylation of Aziridines.

To a mixture of aziridine (0.01 mole) and triethylamine (0.01 mole) in dry ether (20-30 ml.) cooled in an ice-salt mixture was added the corresponding phosphorus acid chloride (0.01 mole) in dry ether (20-30 ml.) (11) in the course of 30 minutes under nitrogen and with stirring. The reaction mixture was maintained below 0° during addition. After the addition, stirring was continued for 2 hours at 0-5° after which time the precipitate of triethylamine hydrochloride was filtered off. The ether solution was washed with water and dried (sodium sulfate). The ether was evaporated and the residue was crystallized in the case of a solid or distilled in the case of a liquid (Table III).

Acknowledgment.

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REFERENCES

- (1) O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines," Academic Press, New York and London, 1969, Chapter 6.
- (2) *Ibid.*, 1, p. 100.
- (3a) H. S. Gutowsky, C. H. Holm, A. Saika and G. A. Williams, *J. Am. Chem. Soc.*, **79**, 4596 (1957). (b) S. J. Brois, *J. Org. Chem.*, **27**, 3532 (1962). (c) S. J. Brois and G. P. Beardsley, *Tetrahedron Letters*, 5113 (1966).
- (4) K. D. Berlin, L. G. Williams and O. C. Dermer, *Tetrahedron Letters*, 873 (1968) and references therein.
- (5) A. A. Bothner-By and S. M. Castellano, LAOCN 3, in "Computers Programs for Chemistry," D. F. Detar, Ed., W. A. Benjamin, Inc., N. Y., N. Y., 1968, Chapter 3.
- (6) F. A. L. Anet, R. D. Trepka and D. J. Cram, *J. Am. Chem. Soc.*, **89**, 357 (1967).
- (7) A. T. Bottini and J. D. Roberts, *ibid.*, **80**, 5203 (1958).
- (8) For a listing of the few recorded values for simple aziridines (none are recorded for *N*-phosphorylated aziridines) see reference 1, page 98.
- (9) Melting points are uncorrected. I.R. spectra were recorded on a Beckman IR-5A instrument. P.m.r. spectra were obtained on Varian A-60, Varian HA-100, and Jeolco PS-100 units in dichloromethane.
- (10) F. L. Scott, R. Riordan and P. D. Morton, *J. Org. Chem.*, **27**, 4255 (1962).
- (11) In the preparation of **3**, benzene was used as a solvent and the reaction was carried out at 24-30° for 24 hours.

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