A New Phosphorus Heterocycle. Crystal and Molecular Structure of 7,8-Dimethyl-5-methoxy-5-oxo-λ^5-5-phospha-6-oxaindolizine

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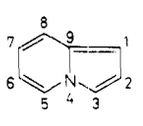
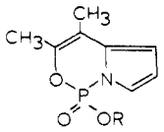
A new heterocycle, in which one pair of sp^2 carbon atoms of indolizine is replaced by the –OP– group of the –OP(O)(OR)– function, has been synthesized. The structure of a member of the family has been solved by X-ray crystallographic methods. 7,8-Dimethyl-5-methoxy-5-oxo-λ^5-5-phospha-6-oxaindolizine [$(CH_3)_2(OCH_3)(O)(C_6H_3NPO)$] crystallizes from hexane–ether in space group $P2_1/c$ of the monoclinic system, with eight molecules, $C_9H_{12}O_3NP$, in a unit cell of dimensions a = 17.334 (4), b = 7.773 (1), and c = 15.731 (4) Å; β = 105.30 (2)°; D_{calcd} = 1.38 g cm^{-3} and D_{meas} = 1.38 (1) g cm^{-3}. There are two independent molecules in the asymmetric unit. Data were obtained on a computer-controlled CAD-4 diffractometer. A multiple solution direct methods technique was employed, and the structure was refined by full-matrix least-squares methods to a final R value of 4.1% on F based on 2252 independent structure amplitudes. The P–N, P–O, and P=O bond distances are 1.65, 1.57, and 1.44 Å, respectively. The conjugated C–C triene in the ring has alternating bond distances of ~1.33 and 1.45 Å. The bicyclo[4.3.0]-nonane skeleton consists of a planar, regular pyrrole ring (all angles near 109°) fused to a nonplanar, irregular six-membered ring with bond angles ranging from 102 (O–P–N) to 123 (P–N–C) and 126° (P–O–C) values. The data suggest the occurrence of p–d π bonding in the O–P and N–P groups, but no significant electron delocalization within the C–C triene in the ground state of the molecule. Nevertheless, the phosphaoxaindolizine ring has relatively high thermal stability and retains its integrity in the vapor phase under electron impact.

Indolizine or pyrrocoline is an aromatic heterocycle isomeric with indole.[2-5a] This paper describes the synthesis and properties of a new type of ring system, **1**, in which one of the



Indolizine



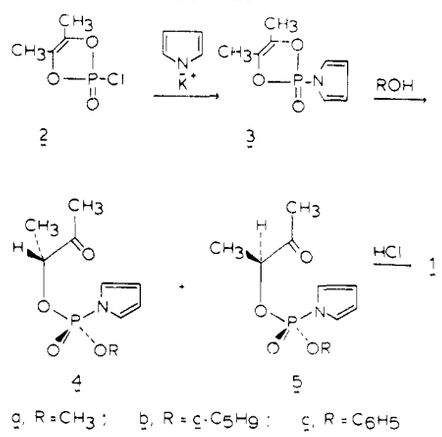
1 a, R = CH_3
b, R = c-C_5H_9
c, R = C_6H_5

pairs of sp^2 carbons of indolizine is replaced by the –OP– group of the –OP(O)(OR)– function. We present also data on the molecular structure of one of these 5-phospha-6-oxaindolizine (POI) derivatives, **1a**, obtained by X-ray crystallographic methods.

The synthesis of POI (**1**) involves the steps shown in Scheme I. Reaction of potassium pyrrole with the cyclic enediol phosphorochloridate, **2**, produces the corresponding *N*-phosphorylpyrrole,[6] **3**. Reaction of alcohols with compound **3** generates two diastereomers of an acyclic phosphoramide, **4a,b** and **5a,b**, with an α-hydroxy ketone ester function. This step is susceptible to catalysis by imidazole, and the proportion of diastereomers **4** and **5** formed in the absence and in the presence of the catalyst varies somewhat.[6] Both diastereomers are converted into derivatives of the POI ring, **1a,b**, under catalysis by hydrogen chloride. Phenols react with *N*-phosphorylpyrrole **3** at a practical rate only in the presence of the imidazole catalyst, and the resulting acyclic esters, **4c** and **5c**, also undergo cyclization to the corresponding POI derivative, **1c**. A preliminary communication describing these observations has appeared.[7]

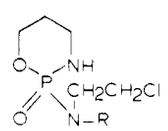
The POI ring provides an opportunity for studies on electron delocalizations in phosphorus heterocycles,[5b,8-10] which could result from the ability of the –OP(=O)< unit to transmit electronic effects. Moreover, this ring system shares some structural features with the experimental cancer drug cyclophosphamide.[11] Apparently, this DNA alkylating agent acts on tumors after ring hydroxylation and further degradations.[12-14] In principle, the incorporation of the 2-chloroethylamino group in the POI ring is feasible, and the chemotherapeutic properties of the resulting compound should be of interest. One of the relevant questions in this respect, in particular in connection with DNA–drug intercalation phenomena, is the degree of planarity of the ring, as revealed by X-ray crystallographic techniques.

Scheme I



2 **3** **4** **5**

a, R = CH_3; b, R = c-C_5H_9; c, R = C_6H_5



Cyclophosphamide

The molecular structure of cyclophosphamide is known.[15] Several other structures relevant to the present investigation have also been solved: sodium phosphoramidate,[16] PO_3NH_3Na; calcium 1,3-diphosphorylimidazole hexahydrate,[17] $Ca_{1.5}C_3H_3N_2(PO_3)_2 \cdot 6H_2O$; diphenyl phosphindimethylamidate,[18] $(C_6H_5)_2P(O)N(CH_3)_2$, trichlorobis(diethylphenylphosphine)(diethylphenylphosphineiminato)-ruthenium(IV),[19] and phosphocreatine.[20] The nature of the P–N bond has been discussed in those publications and elsewhere.[21-24]

Experimental Section

Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn. Mass spectra were determined on a Hewlett Packard

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5980A instrument operating at 70 eV; samples were introduced via the solid probe at ambient temperature.

Synthesis of 7,8-Dimethyl-5-methoxy-5-oxo-λ⁵-5-phospha-6-oxaindolizine (1a). Methanol (0.51 g, 16 mmol) was added to a solution of *N*-(1,2-dimethylethenylenedioxyphosphoryl)pyrrole[6] (**3**; 3.22 g, 16 mmol) in anhydrous CH_2Cl_2 (40 mL) at 20 °C. After 2 h at 20 °C, the solvent was evaporated first at 30 mm and finally at 0.1 mm. The residue, which contained the two diastereomers of *N*-[methoxy(3-oxo-2-butoxy)phosphoryl]pyrrole[6] (**4a** and **5a**) in 60:40 proportion, was dissolved in CH_2Cl_2 (50 mL) at 20 °C; hydrogen chloride was bubbled through the solution until the ^1H NMR spectrum revealed no further conversion of the acyclic phosphoramidates, **4a** and **5a**, into methoxy-POI (**1a**). Evaporation, first at 30 mm and then at 0.1 mm, left a residue which was submitted to evaporative distillation at 0.1 mm in a sublimation apparatus immersed in a 100 °C bath. The distillate solidified and was recrystallized from hexane–benzene or hexane–diethyl ether: mp 67–69 °C; yield, 70% of the theory.

Anal. Calcd for $C_9H_{12}O_3NP$: C, 50.7; H, 5.7; N, 6.6; P, 14.5. Found: C, 50.5; H, 5.7; N, 6.6; P, 14.3. (See Discussion section for spectral data.)

Synthesis of 7,8-Dimethyl-5-cyclopentyloxy-5-oxo-λ⁵-5-phospha-6-oxaindolizine (1b). Cyclopentanol (0.60 g, 7.0 mmol) was added to a solution of the phosphorylpyrrole[6] (**3**, 1.40 g, 7.0 mmol) and imidazole (0.47 g, 7.0 mmol), added as catalyst, in CH_2Cl_2 (25 mL) at 20 °C. After 0.5 h at 20 °C, the solution was diluted with CH_2Cl_2 (75 mL), extracted with ice-cold 3% aqueous HCl, washed with cold 1% aqueous Na_2CO_3, and evaporated to yield the diastereomers of *N*-[cyclopentyloxy(3-oxo-2-butoxy)phosphoryl]pyrrole[6] (**4b** and **5b**) in a 50:50 proportion. Conversion of **4b** and **5b** into cyclopentyloxy-POI (**1b**) was carried out as for the methoxy analogue. Compound **1b** underwent some decomposition during evaporative distillation at 0.2 mm in a 130 °C bath; the yield was 43% of the theory.

Anal. Calcd for $C_{13}H_{18}O_3NP$: C, 58.4; H, 6.8; N, 5.2; P, 11.6. Found: C, 58.4; H, 6.8; N, 5.1; P, 11.5.

Synthesis of 7,8-Dimethyl-5-phenoxy-5-oxo-λ⁵-5-phospha-6-oxaindolizine (1c). From phenol (1.25 g, 13 mmol), the phosphorylpyrrole[6] (**3**; 2.68 g, 13 mmol), and imidazole (0.90 g, 13 mmol), in CH_2Cl_2 (15 mL), there was obtained, after 20 h at 20 °C, the diastereomers of *N*-[phenoxy(3-oxo-2-butoxy)phosphoryl]pyrrole[6] (**4c** and **5c**) in a 50:50 proportion, as described for the cyclopentyloxy analogue. The conversion of **4c** and **5c** into phenoxy-POI (**1c**) was carried out as previously described. Compound **1c** was purified by chromatography through a 2 × 30 cm column of Merck's silica gel 60 (70 g), using diethyl ether as eluting solvent. The chromatographed material was recrystallized from benzene–hexane (2:5) at −10 °C. Pure **1c** (*ca.* 50% yield) had mp 66–68 °C.

Anal. Calcd for $C_{14}H_{14}O_3NP$: C, 61.1; H, 5.1; N, 5.1; P, 11.3. Found: C, 60.9; H, 5.1; N, 5.0; P, 11.5. Mass spectrum: main peak m/e = 275 due to the molecular ion. λ_{max} 270 nm (ϵ 27 700), in CH_3CN.

Crystal Data. 7,8-Dimethyl-5-methoxy-5-oxo-λ⁵-5-phospha-6-oxaindolizine (**1a**), $C_9H_{12}O_3NP$: monoclinic; $P2_1/c$; a = 17.334 (4), b = 7.773 (1), and c = 15.731 (4) Å; β = 105.30 (2)°; V = 2044.5 Å^3 ($\lambda_{Cu\ K\alpha}$ = 1.5418 Å at 21 °C); Z = 8 (two molecules per asymmetric unit); D_{calcd} = 1.38 g cm^{-3}, D_{meas} (by flotation in aqueous $ZnCl_2$) = 1.38 (1) g cm^{-3}; and μ(Cu Kα) = 22.44 cm^{-1}.

Data Collection and Structure Refinement. Precession photographs of the ($h0l$), ($h1l$), ($0kl$), and ($1kl$) zones showed systematic absences ($h0l$) for l odd and ($0k0$) for k odd implying space group $C_{2h}^5 = P2_1/c$. The cell dimensions were determined by a least-squares fit of the observed 2θ angles for 17 reflections centered automatically.

Three-dimensional intensity data were measured from a colorless crystal of roughly hexagonal prismatic habit and dimensions 0.11 × 0.16 × 0.43 mm, obtained by cooling to 5 °C a solution of 135 mg of compound **1a** in 4 mL of hexane and 1 mL of diethyl ether. The data crystal was coated with epoxy resin, mounted on a glass fiber, and oriented along b^*, the prism axis. Data were collected on a computer-controlled Enraf-Nonius CAD-4 diffractometer using Cu Kα radiation monochromatized by reflection from a highly oriented graphite monochromator. A total of 8417 observations was collected by θ–2θ scans to 2θ (Cu Kα) < 124° and an absorption correction was applied using BNLABS, a local version of ORABS.[25] The minimum and maximum corrections to F_o^2 were 0.631 and 0.801, respectively, and agreement between symmetry equivalent intensities was R = 0.037. These intensities were averaged to give 2252 independent structure amplitudes with $F_o^2 > 3\sigma_{count}(F_o^2)$ where $\sigma(F_o^2)$ is based on Poisson counting statistics. The intensities of three standard reflections were measured periodically and were found to have decayed to approximately 45% of their original values by the end of data collection. The decrease in intensity was uniform over the exposure time and the individual standards were scaled to the zero time standards. Background was measured on one-sixth of the total scan width and normal scans which did not result in sufficiently high precision on net intensity measurements were repeated at a slower scan speed. The takeoff angle was 6.2° and the diffracted beam was automatically corrected for coincidence losses.

Structure factors were derived in the usual way and normalized structure factors (E's) were used in a multiple solution direct methods technique as described by Germain, Main, and Woolfson[26] to determine phases from which an E map revealed the coordinates of all nonhydrogen atoms.

The structure was refined by full-matrix least squares, minimizing the function $\Sigma w\Delta^2$ with $\Delta = |F_o| - |F_c|$ with weights $w = 4F_o^2/\sigma^2(F_o^2)$ and $\sigma^2(F_o^2) = \sigma^2_{count}(I) + (0.03F^2)^2$. All but three of the hydrogen atom positions were located by difference Fourier synthesis. These three were placed in idealized positions and all hydrogen atom positions were refined with isotropic thermal parameters fixed at 5.5 Å^2. Atomic scattering factors for all nonhydrogen atoms were taken from a standard source,[27] while that for hydrogen was the best spherically averaged value of Stewart et al.[28]

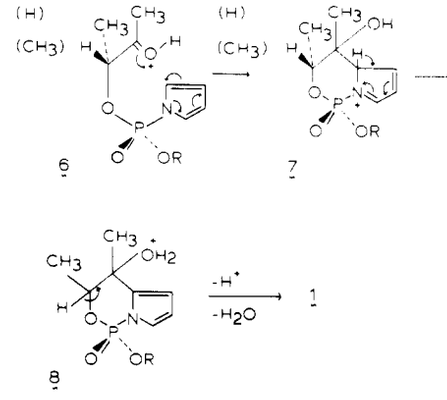
The final least-squares cycles included anisotropic thermal parameters for the nonhydrogen atoms and fixed contributions from the hydrogen atoms. The final values of $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_2 = \{[\Sigma w||F_o| - |F_c|^2]/\Sigma w|F_o^2|\}^{1/2}$ were 0.041 and 0.055, respectively, and the error in an observation of unit weight was 1.73. The maximum density in a final difference electron density synthesis was 0.27 electron Å^{-3}, approximately 7% of the height of a carbon atom peak. The final parameters are presented in Tables VI, VII, and VIII (see paragraph at end of paper regarding supplementary material).

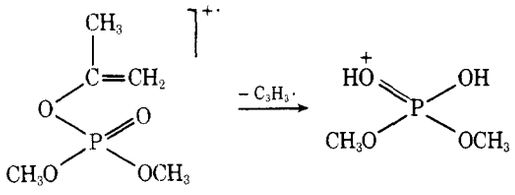
Discussion of Results

Synthesis and Properties of POI Derivatives. A possible mechanism for the synthesis of the POI ring is shown in Scheme II. The two diastereomers, **4** and **5**, undergo cyclization at significantly different rates, as would be expected from steric effects in the rate-limiting step, which is probably a nucleophilic attack of the pyrrole Cα atom on the carbonyl carbon, **6** → **7**. The closest analogy we have found for this reaction is the acid-catalyzed cyclization of *N*-(3-cyanoalkyl)-pyrrole.[29,30]

The methoxy-POI, **1a**, is a crystalline substance with considerable thermal stability in the liquid and vapor phases, as shown by recovery of the compound after distillation under vacuum. The heterocyclic ring preserves its integrity under electron impact, and the most intense peak in its mass spectrum corresponds to m/e = 213, i.e., to the molecular ion[31] $[C_9H_{12}O_3NP]^{+\cdot}$. Most of the ion current is carried by this species and by a fragment with m/e = 198, $[C_8H_9O_3NP]^+$, which results from the loss of a methyl radical from the parent ion. This spectrum is reminiscent of those obtained from related polycyclic aromatic and heterocyclic compounds, which consist of strong parent and parent-CH_3 peaks, without evidence of extensive fragmentation. In contrast, the mass spectrum of dimethyl (2-propenyl)phosphate,[32] which has an enol phosphate function similar to that present in compound **1a**, is quite different. The enol phosphate generates a molec-

Scheme II





ular ion which undergoes fragmentation with exclusive loss of the elements of methylacetylene radical and formation of protonated dimethyl phosphate.

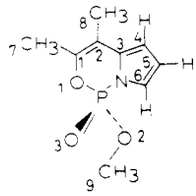
The main chromophore present in POI derivatives is associated with the triene system, which absorbs strongly at 269 nm in methoxy-POI, **1a** (ϵ = 30 000 in CH_3CN solution).[33]

The ^1H NMR signals of the methyl groups in POI derivatives appear at τ = 7.90 and 8.04 ppm relative to $(CH_3)_4Si$ = 10, which is typical of CH_3 groups bound to olefinic sp^2 carbons. The ^{31}P NMR signals in these compounds, **1a–c,** occur respectively at $\delta^{31}P$ = −8.4, −11.2, and −14.8 ppm relative to 85% H_3PO_4 = 0 (in the convention that positive values refer to signals at lower magnetic field than the reference). Hence, the ^{31}P nucleus is more effectively shielded by surrounding electrons in the POI ring than in related compounds, e.g., *N*-(1,2-dimethylethenylenedioxyphosphoryl)pyrrole (**3**), $\delta^{31}P$ = +8.8 ppm, and the acyclic esters **4a–c, 5a–c,** which have $\delta^{31}P$ = −2.0, −3.0, and −8.0 ppm, respectively (all compounds in $CDCl_3$ solutions).

The ^{13}C NMR spectrum of methoxy-POI is summarized in Table I. The tentative assignments are based on comparisons with the cyclic enediol *N*-phosphorylpyrrole, **3.**

Molecular Structure of Methoxy-POI, 1a. The asymmetric unit of the crystal contains two independent molecules, A and B, depicted in Figure 1. The contents of the unit cell are displayed in Figure 2. Table II gives the bond distances and angles, and Table III emphasizes some significant nonbonded distances. Several dihedral angles between three atom planes are collected in Table IV, and the best least-squares planes in Table V.

Molecules A and B differ slightly in their conformations, e.g., in the degree of rotation around the P–O(2) bond (cf.



1a'

Table I. ^{13}C NMR Signals[a] of *N*-(1,2-Dimethylethenylenedioxyphosphoryl)pyrrole (3) and 7,8-Dimethyl-5-methoxy-5-oxo-λ⁵-5-phospha-6-oxa-indolizine (1a)

compd 3[b,e]		compd 1a[b,f]	
$\delta^{13}C$, ppm (J)	assignment	$\delta^{13}C$, ppm (J)	assignment
		12.8	CH_3–C_8;[c] C(8)[d]
11.2 (10.3)	CH_3(C=C)	16.5 (7.6)	CH_3–C_7; C(7)
		54.5 (6.7)	CH_3–OP; C(9)
		106.0 (5.8)	C_8; C(2)
		108.3 (8.0)	C_1; C(4)
113.9 (12.4)	pyrrole C_β	114.3 (12.1)	C_2; C(5)
122.7 (7.0)	pyrrole C_α	119.1 (5.7)	C_3; C(6)
136.8 (1.2)	C=C	135.0 (3.8)	C_7; C(1)
		142.3 (11.7)	C_9; C(3)

[a] $\delta^{13}C$ in parts per million downfield from $(CH_3)_4Si$ = 0. *J* = ^{13}C, ^{31}P coupling constants in Hz (^1H decoupled). [b] In C_6D_6. [c] Indolizine numbering. [d] X-ray structure numbering. [e] Registry no. 65696-85-7. [f] Registry no. 68051-02-5.

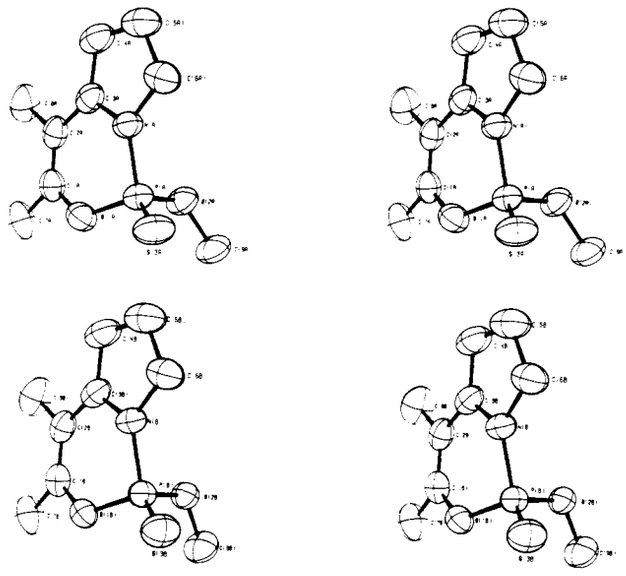


Figure 1. Stereoscopic drawing of the two independent isolated molecules of compound **1a.** The 50% probability ellipsoids are shown.

formula **1a'**) which alters the nonbonded C(9)···O(3) distance a little, and in the angle formed by planes N, C(3), C(6) and N, P, O(3), which differ from orthogonality to a greater extent in B than in A. The angle formed by planes N, P, O(3) and O(1), P, O(2) is perfectly orthogonal in both molecules.

The structure consists of a six-membered and a five-membered ring fused in a bicyclo[4.3.0]nonane framework, which contains a conjugated C–C triene spanned by the O–P–N atomic group, with N and C atoms at the bridgehead. The triene system contains alternating bond distances (ca. 1.33 and 1.45 Å) reflecting little bond delocalization in the carbon skeleton.

As expected, the P=O bond distance is significantly shorter (1.44 Å) than the exo- and endo-cyclic P–O distances, which are about the same (~1.57 Å). In relation to the estimated pure single P–O bond distance[23,24] (1.76 Å), this may represent some p–d π bonding[34] involving the lone electron pairs on oxygen and the phosphorus d orbitals. The P–N bond distance of 1.65 Å is somewhat shorter than that in phosphocreatine, sodium phosphoramidate (1.77 Å), and calcium 1,3-diphosphorylimidazole (av 1.78 Å), but of about the same length as that in diphenylphosphindimethylamide (1.68 Å), which also suggests some p–d π bonding in the ring P–N bond.

An adequate description of the POI ring is that of a six-membered cyclic enol phosphoramidate in which the nitrogen function is part of a pyrrole ring. The best least-squares plane in the molecule contains the pyrrole atoms (planes 1A and 1B in Table V). Reasonably good planes can also be obtained by inclusion of the phosphorus atom or the vinyl group, C(1), C(2), in the plane of the pyrrole, cf. respectively, planes 2A, 2B, and 3A, 3B. An examination of the dihedral angle formed by planes which contain atoms C(1), C(2), C(3) and C(2), C(3), C(4) (Table IV) reveals a slight bending at bond C(2)–C(3) which connects the vinyl group to the pyrrole Cα position. There is also some rotation about the C(2)–C(3) bond, with the net effect that, upon closure of the six-membered ring, the endocyclic O(1) atom protrudes from the best molecular plane.

The six-membered ring in POI is irregular, with bond angles ranging from ca. 102° (O–P–N) to ca. 123° (P–N–C) and 125° (P–O–C) values. The five-membered ring is quite regular, with all angles close to 109°. The phosphate group, PO_3N, is a distorted tetrahedron, with angles ranging from 102° for O(1)–P–N to about 115° for O(3)–P–N and O(2)–P–O(3). In

Table II. Bond Distances (Å) and Angles (deg) Involving Nonhydrogen Atoms[a]

molecule A		molecule B	
P(A)–O(1A)	1.568 (2)	P(B)–O(1B)	1.570 (2)
P(A)–O(2A)	1.569 (2)	P(B)–O(2B)	1.572 (2)
P(A)–O(3A)	1.444 (2)	P(B)–O(3B)	1.446 (2)
P(A)–N(A)	1.647 (2)	P(B)–N(B)	1.644 (2)
O(1A)–C(1A)	1.410 (4)	O(1B)–C(1B)	1.420 (4)
O(2A)–C(9A)	1.434 (4)	O(2B)–C(9B)	1.436 (4)
N(A)–C(3A)	1.404 (4)	N(B)–C(3B)	1.405 (3)
N(A)–C(6A)	1.399 (4)	N(B)–C(6B)	1.402 (4)
C(1A)–C(2A)	1.330 (5)	C(1B)–C(2B)	1.324 (4)
C(2A)–C(3A)	1.451 (4)	C(2B)–C(3B)	1.452 (4)
C(3A)–C(4A)	1.365 (4)	C(3B)–C(4B)	1.363 (4)
C(4A)–C(5A)	1.409 (4)	C(4B)–C(5B)	1.412 (5)
C(5A)–C(6A)	1.352 (4)	C(5B)–C(6B)	1.352 (4)
C(7A)–C(1A)	1.487 (4)	C(7B)–C(1B)	1.492 (4)
C(8A)–C(2A)	1.518 (4)	C(8B)–C(2B)	1.516 (4)
O(1A)–P(A)–O(2A)	106.6 (1)	O(1B)–P(B)–O(2B)	106.1 (1)
O(1A)–P(A)–O(3A)	113.4 (1)	O(1B)–P(B)–O(3B)	113.4 (1)
O(1A)–P(A)–N(A)	101.8 (1)	O(1B)–P(B)–N(B)	101.8 (1)
O(2A)–P(A)–O(3A)	115.0 (1)	O(2B)–P(B)–(3B)	115.6 (1)
O(2A)–P(A)–N(A)	102.7 (1)	O(2B)–P(B)–N(B)	102.4 (1)
O(3A)–P(A)–N(A)	115.9 (1)	O(3B)–P(B)–N(B)	116.0 (1)
P(A)–O(1A)–C(1A)	126.2 (2)	P(B)–O(1B)–C(1B)	123.0 (2)
P(A)–O(2A)–C(9A)	121.5 (2)	P(B)–O(2B)–C(9B)	119.6 (2)
P(A)–N(A)–C(3A)	123.3 (2)	P(B)–N(B)–C(3B)	121.8 (2)
P(A)–N(A)–C(6A)	127.6 (2)	P(B)–N(B)–C(6B)	128.5 (2)
C(3A)–N(A)–C(6A)	108.5 (3)	C(3B)–N(B)–C(6B)	108.8 (3)
O(1A)–C(1A)–C(2A)	120.0 (3)	O(1B)–C(1B)–C(2B)	120.4 (3)
O(1A)–C(1A)–C(7A)	110.0 (3)	O(1B)–C(1B)–C(7B)	109.8 (3)
C(2A)–C(1A)–C(7A)	130.0 (3)	C(2B)–C(1B)–C(7B)	129.8 (3)
C(1A)–C(2A)–C(3A)	122.5 (3)	C(1B)–C(2B)–C(3B)	122.2 (3)
C(1A)–C(2A)–C(8A)	121.7 (3)	C(1B)–C(2B)–C(8B)	121.9 (3)
C(3A)–C(2A)–C(8A)	115.9 (3)	C(3B)–C(2B)–C(8B)	115.8 (3)
C(2A)–C(3A)–N(A)	119.7 (3)	C(2B)–C(3B)–N(B)	119.6 (3)
C(4A)–C(3A)–N(A)	106.7 (3)	C(4B)–C(3B)–N(B)	106.8 (3)
C(4A)–C(3A)–C(2A)	133.6 (3)	C(4B)–C(3B)–C(2B)	133.4 (3)
C(3A)–C(4A)–C(5A)	108.8 (3)	C(3B)–C(4B)–C(5B)	108.3 (3)
C(4A)–C(5A)–C(6A)	108.4 (3)	C(4B)–C(5B)–C(6B)	109.2 (3)
C(5A)–C(6A)–N(A)	107.7 (3)	C(5B)–C(6B)–N(B)	106.9 (3)

[a] Numbers in parentheses here and in succeeding tables are estimated standard deviations in the least significant digits.

general, O–P–O and O–P–N angles which involve the phosphoryl oxygen, P=O(3), are the largest of their kind. This effect has also been noted in several derivatives of the 1,3,2-dioxaphospholene ring[35] with PO_4 and PO_3N groups, and may be related to the increased degree of p–d π bonding in the phosphoryl group, and/or the size of this oxygen atom.

Table III. Significant Nonbonded Distances <3.2 Å

Intramolecular			
C(9A)···O(3A)	3.029 (4)	C(8A)···H(4A)	3.034
C(9B)···O(3B)	3.141 (4)	C(8B)···H(4B)	3.058
C(7A)···C(8A)	3.085 (4)	O(3A)···H(6A)	3.024
C(7B)···C(8B)	3.083 (4)	O(3B)···H(6B)	3.087
Shortest Intermolecular			
O(2B)···C(9B)	3.173 (4)		

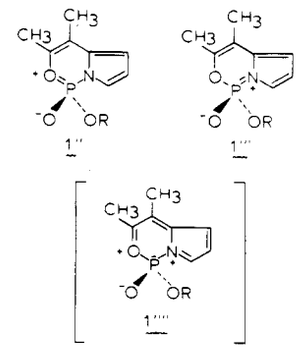
Table IV. Some Dihedral Angles between Planes Defined by Three Atoms

plane α	plane β	angle, deg
N(A), C(3A), C(6A)	N(A), P(A), O(3A)	141.8 (2)
N(B), C(3B), C(6B)	N(B), P(B), O(3B)	147.6 (2)
N(A), P(A), O(3A)	O(1A), P(A), O(2A)	90.1 (1)
N(B), P(B), O(3B)	O(1B), P(B), O(2B)	89.8 (1)
C(1A), C(2A), C(3A)	C(2A), C(3A), C(4A)	172.8 (3)
C(1B), C(2B), C(3B)	C(2B), C(3B), C(4B)	169.7 (3)
C(1A), C(2A), C(8A)	C(1A), C(2A), C(7A)	0.1 (6)
C(1B), C(2B), C(8B)	C(1B), C(2B), C(7B)	1.8 (6)

The environment around the vinyl group, C(1), C(2), reveals considerable crowding among the methyl groups, C(7) and C(8), and among C(8) and the hydrogen atom bound to C(4). This can be deduced from the corresponding bond angles and nonbonded distances.[36]

Conclusions

The POI ring has a reasonable degree of thermal stability in the vapor phase and preserves its integrity even under electron impact. The data from various sources suggest that electron delocalizations associated with the group –Ö–P(O)(OR)–N̈– in the POI heterocycle are limited to p–d π bonding involving the lone electron pairs on oxygen and nitrogen and the d orbitals of the phosphorus. These electron delocalizations do not seem to extend to the conjugated C–C triene system of the ring, since the effects on C–C bond orders and bond distances expected from such phenomena are not, in fact, reflected in the structure of the molecule in its ground state. In terms of possible resonance structures to describe the POI ring, we conclude that formulas 1″ and 1‴ are significant; however, formula 1⁗, which includes triene bond delocalization, is not justified by the results of the X-ray crystallographic analysis.



The molecules of methoxy-POI, **1a**, stack themselves nicely in the crystal, with the POI rings parallel to each other. The closest contacts between neighboring molecules involve oxygen and carbon atoms of their respective methoxy groups. It is conceivable that molecules which give rise to this type of crystal may also engage in the type of intercalation phenomena which has been observed in certain DNA–drug interactions, e.g., with the planar proflavin. The replacement of the methoxy group in POI by 2-chloroethylamino groups, and the chemotherapeutic properties of the resulting compounds as analogues of cyclophosphamide, are under investigation.

Registry No.—**1b**, 68051-03-6; **1c**, 68051-04-7; **4a**, 68107-83-5; **4b**, 68107-84-6; **4c**, 68107-85-7; **5a**, 68107-86-8; **5b**, 68107-87-9; **5c**, 68107-88-0; methanol, 67-56-1; cyclopentanol, 96-41-3; phenol, 108-95-2.

Supplementary Material Available: Figure 2, unit cell contents;

Table V, equations of best least-squares planes; Table VI, positional parameters for nonhydrogen atoms; Table VII, anisotropic thermal parameters; and Table VIII, hydrogen atom positions (5 pages). Ordering information is given on any current masthead page.

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Phosphoric Amides. 1. Phosphorus–Nitrogen vs. Nitrogen–Carbon Bond Cleavage in Acidic Solvolysis of *N*-Alkyl Phosphoramidates and Phosphinamidates

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N-tert-Butyl phosphinamidates and phosphoramidates, $X_2P(O)NH$-*t*-Bu (X = alkyl, aryl, *O*-alkyl, *O*-aryl), solvolyze in acidic media with both P–N and N–C bond cleavage. The relative contribution of these two pathways depends upon the substrate structure and the proton-donating and nucleophilic properties of the reaction medium. Rates of P–N and N–C bond fission were measured in solutions of $HClO_4$, TFA, and HCO_2H. Rate profiles and KSIE are interpreted in terms of an A2 mechanism for substitution at phosphorus, and a mechanism involving solvent electrophilic assistance for the de-*tert*-butylation pathway. For other *N*-alkyl-substituted phosphoramidates the competition between the P–N and N–R bond cleavage is a function of the ability of the *N*-alkyl group to generate the corresponding carbonium ion. N–C bond fission predominates for R = $CH(CH_3)Ph$ and $CH_2C_6H_4OCH_3$-*p*, but for R = *i*-Pr, CH_2Ph, $CH_2C_6H_4CH_3$-*p*, or CH_2-c-C_3H_5 only the substitution at phosphorus was observed.

The remarkably facile cleavage of the P–N bond under acidic conditions is receiving much attention in terms of mechanistic[1] and stereochemical[2] studies as well as synthetic application.[3] For the phosphacyl[4] derivatives $X(Y)P(O)NR_2$ (**1**), the principal mechanistic problems involve the structure of substrate conjugate acid (N vs. O protonation) and the nature of the rate-determining step (bimolecular displacement vs. unimolecular collapse of the protonated substrate). Although the direct evidence for the N protonation is still lacking, the N-protonated **1** is presently considered as the most probable reactive form of the substrate in solvolysis reaction.[6] The excellent leaving group (amine molecule or ammonia) is then in most cases displaced by the nucleophile in the bimolecular, S_N2-like process; the participation of the unimolecular mechanism can be a function of the leaving group nucleophilicity[7] and perhaps the acidity of the medium[2] (Scheme I).

The postulated structure of the conjugate acid (**1a**) has some additional implications. In the N-substituted system the full charge localized on nitrogen can in principle facilitate both P–N and N–C bond fission (Scheme II), and the reaction pathway should depend upon the relative stability of the intermediates formed and the nucleophilic (and possibly electrophilic) participation of the medium. It is reasonable to expect that these two cleavage patterns should be a function of the properties of the reaction medium and the detailed structure of the organophosphorus amide.

In order to gain some insight into the structure–reactivity

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