

Cyclic Organophosphorus Compounds. Part 6.¹ Synthesis of *N*-Methyl-2-phenoxy-1,3,2-oxazaphosphorinan-2-thione and Its Crystal and Molecular Structures

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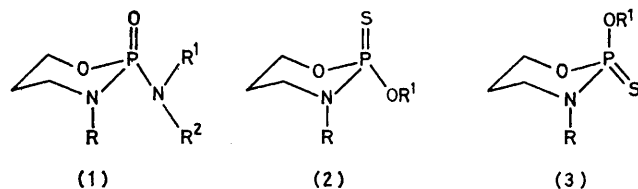
2-Chloro-1,3,2-oxazaphosphorinan-2-thione (1) was prepared by treatment of phosphorothioic trichloride with 3-aminopropan-1-ol in the presence of triethylamine. Treatment of (1) with sodium phenoxide afforded the 2-phenoxy-derivative (2) from which the title compound (3) could be obtained by the action of sodium hydride followed by alkylation with an excess of methyl iodide. The structure of the title compound has been determined by the direct method and refined by least-squares to $R = 0.037$, $a = 7.240(3)$, $b = 10.705(4)$, $c = 15.327(4)$ Å, $\beta = 91.475(5)^\circ$, space group $P2_1/n$. The oxazaphosphorinan ring is in the chair form with the P=S bond in the equatorial position.

STEREOCHEMISTRY and conformational preferences in various 1,3,2-dioxaphosphorinan-2-ones and -2-thiones have been extensively investigated over the past decade.²⁻¹² In contrast to this most of the information on the preferred conformation of 1,3,2-oxazaphosphorinan derivatives had involved only the 2-oxo-2-disubstituted amido-system.¹³⁻¹⁸

This ring system received some attention in connection with the increasing interest in the synthesis of cyclic adenosine monophosphates¹⁹ and monothiophosphates.²⁰

As a result of ingenious stereospecific syntheses of various optically active phosphates and thiophosphates from carbohydrate precursors which have been recently reported by Inch *et al.*,²¹ 2-substituted 1,3,2-oxazaphosphorinan-2-thiones became an important class of accessible cyclic organophosphorus compounds.

The structure of *N*-methyl-2-phenoxy-1,3,2-oxazaphosphorinan-2-thione, selected as a model compound, can throw some light on the preferred conformation of the thiophosphoryl group in 1,3,2-oxazaphosphorinan ring for which there are two possible conformations (2)



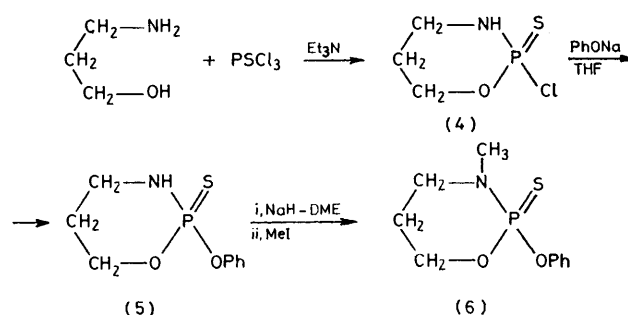
and (3). An *X*-ray structural determination clearly shows the existence of the latter in the solid state.

RESULTS AND DISCUSSION

N-Methyl-2-phenoxy-1,3,2-oxazaphosphorinan-2-thione. —2-Chloro-1,3,2-oxazaphosphorinan-2-thione (4) was prepared in 73% yield from phosphorothioic trichloride and 3-aminopropan-1-ol in the presence of triethylamine. Our modification of the original procedure²² allowed both a doubling of the yield and improved purity of the product.

The 2-phenoxy-derivative (5) was obtained in moderate yield (37%) when the 2-chloro-compound (4) was treated

with sodium phenoxide in tetrahydrofuran at 35–40 °C. No attempt was made to optimize the yield of



this reaction. As expected, the reaction of 2-phenoxy-derivative (5) with sodium hydride in dimethoxyethane

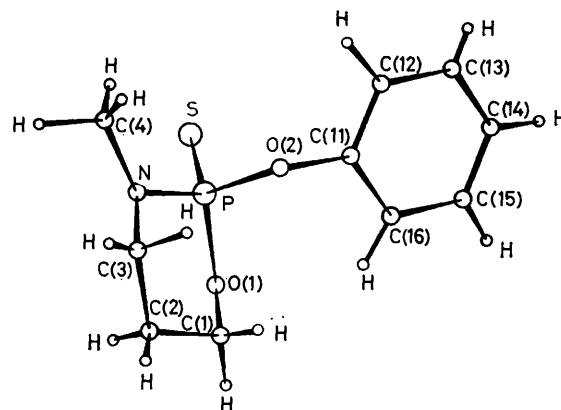


FIGURE 1 The molecule projected perpendicularly to *b*

afforded the corresponding *N*-sodio-derivative from which *N*-methyl-2-phenoxy-1,3,2-oxazaphosphorinan-2-thione (6) was formed almost quantitatively (96% yield) by treatment with an excess of methyl iodide. We determined the crystal structure of the final compound (6), *N*-methyl-2-phenoxy-1,3,2-oxazaphosphorinan-2-thione, by *X*-ray analysis.

Crystal Structure of N-Methyl-2-phenoxy-1,3,2-oxazaphosphorinan-2-thione.—The geometry of the mole-

cule is shown in Figure 1. The six-membered oxazaphosphorinan ring has a chair conformation as indicated by the dihedral angles (Figure 2). The first two angles of C(1)-O(1)-P-N(1) and O(1)-P-N(1)-C(3) are significantly smaller as a result of flattening of this ring at the P end. The angle between the planes through P(1),N(1),O(1) and O(1),N(1),C(3),C(1) is 37.36° and that between the latter plane and the plane through C(1),C(2),C(3) is 52.57° . In the ring having a chair conformation the P=S bond is in an equatorial and the phenoxy-group in an axial position. The ring nitrogen atom N(1) is 0.26 \AA from the plane through its three substituents P, C(3), and C(4). The sum of the angles around the nitrogen atom is 350.3° . The benzene ring from the phenoxy-group is planar. Maximum deviation from the mean plane for the C(11) atom is 0.0038 \AA .

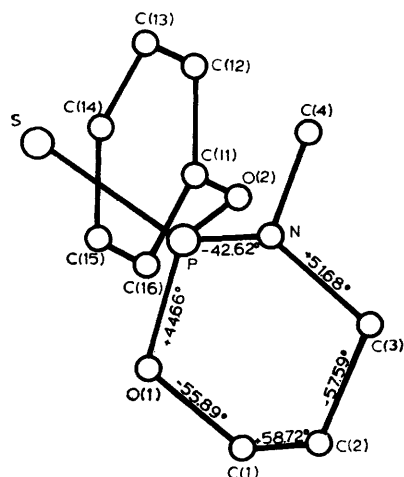


FIGURE 2 The dihedral angles in oxazaphosphorinan ring

The angle between the mean plane through the atoms of benzene ring and the O(1),N(1),C(3),C(1) plane is 54.2° .

The phosphorus co-ordination tetrahedron is not very different from that found in similar compounds such as cyclophosphamides¹³⁻¹⁸ and dioxaphosphorinans.²⁻⁹ The P=S bond length $1.918(1) \text{ \AA}$ is slightly shorter than normally observed average value 1.94 \AA .¹² The two P-O bonds: $1.576(2) \text{ \AA}$ (ring bond) and $1.605(2) \text{ \AA}$ (exocyclic bond) differ considerably in length, but both correspond to the average value 1.59 ± 0.02 ²³ for a number of compounds.

The P-N bond length $1.638(2) \text{ \AA}$ is substantially shorter than the generally accepted single bond distance of 1.769 \AA in NaH_2NPO_4 .²⁴ This value is similar to average value 1.640 \AA found in many cyclophosphamides^{13,15-18} for P-N ring bonds. The exocyclic P-N bond in cyclophosphamides and dioxaphosphorinans is shorter (average value 1.628 \AA).^{8,9,12,13,15-18} This difference is quite understandable since the exocyclic nitrogen atom and its three substituents form a planar system; on the other hand the ring nitrogen atom deviates from a trigonal configuration (the sum of the angles for the oxazaphosphorinan ring is equal to 350.3°).

Its substituents are less planar than for the exocyclic atom and the degree of $p_\pi-d_\pi$ P-N bonding is not appreciable. In the consequence the ring P-N bond is longer.

The other bond distances in the oxazaphosphorinan ring are normal. Only the bond lengths in the benzene ring are slightly but not significantly shorter than expected, but this is undoubtedly due to high thermal motion of this ring.

The intermolecular distances suggested only van der Waals interaction between the molecules.

EXPERIMENTAL

¹H N.m.r. spectra were measured with a JEOL-JNM-C-60 HL spectrometer with deuteriochloroform as solvent and tetramethylsilane as internal standard. I.r. spectra were recorded for liquid films or Nujol mulls using an UR-10 spectrophotometer (C. Zeiss, Jena). All solvents were dried and purified according to standard procedures.

2-Chloro-1,3,2-oxazaphosphorinan-2-thione (4).—To a solution of phosphorothioic trichloride (16.95 g, 0.1 mol) in benzene (150 ml), a mixture of 3-aminopropan-1-ol (7.5 g, 0.1 mol), triethylamine (20.2 g, 0.2 mol), and methylene chloride (15 ml) was added dropwise at $5-10^\circ \text{C}$. The mixture was then stirred at room temperature for 2 h and left overnight. Triethylamine hydrochloride was filtered off and the filtrate evaporated. The residue was dissolved in benzene (150 ml) and washed successively with 5% aqueous sodium hydrogencarbonate and water. The crude product (12.5 g, 73%), obtained on evaporation of solvent, had m.p. $83-85^\circ \text{C}$. A sample purified by crystallization from ethyl acetate had m.p. $84-86^\circ$ (lit.,²² m.p. $84-86^\circ$) (Found: C, 30.0; H, 4.0; N, 8.1; P, 18.3. $\text{C}_3\text{H}_7\text{ClNOPS}$ requires C, 29.9; H, 4.1; N, 8.2; P, 18.1%).

2-Phenoxy-1,3,2-oxazaphosphorinan-2-thione (5).—To a solution of sodium phenoxide prepared from phenol (6.6 g, 0.07 mol) and sodium hydride (1.68 g, 0.07 mol) in tetrahydrofuran (100 ml), a solution of 2-chloro-1,3,2-oxazaphosphorinan-2-thione (12.0 g, 0.07 mol) in tetrahydrofuran (50 ml) was added dropwise and the resulting mixture was then kept at $35-40^\circ \text{C}$ for 3 h. After being set aside overnight at room temperature the solution was evaporated, and the residue diluted with chloroform (100 ml) and washed successively with 5% aqueous sodium hydroxide (30 ml), water (30 ml), 5% hydrochloric acid (30 ml), and water (30 ml). The residue obtained on evaporation was distilled under reduced pressure to give (5) (6.0 g, 37%) as a thick oil which crystallized with time, b.p. 162°C at 0.05 mmHg, m.p. $38-39^\circ \text{C}$, $n_D^{20} 1.5840$ (Found: C, 47.5; H, 5.3; P, 13.2. $\text{C}_9\text{H}_{12}\text{NO}_2\text{PS}$ requires C, 47.2; H, 5.2; P, 13.5%), $\nu_{\text{N-H}}$ (film) 3230 and 3430 cm^{-1} ; δ_{H} 1.15-2.50 (2 H, m), 2.80-3.55 (2 H, m), 4.10-4.77 (3 H, m, changing into 2 H, m on deuteration), and 6.85-7.40 (5 H, m).

N-Methyl-2-phenoxy-1,3,2-oxazaphosphorinan-2-thione (6).—A solution of (5) (3.2 g, 0.014 mol) in dimethoxyethane (30 ml) was added dropwise below 25°C to a suspension of sodium hydride (0.336 g, 0.014 mol) in dimethoxyethane (20 ml). When evolution of hydrogen had ceased methyl iodide (8.0 g, 0.056 mol) was added and the mixture was refluxed for 2 h. On evaporation of solvent the residue was diluted with benzene (100 ml) and washed with 5% hydrochloric acid (30 ml) and water ($2 \times 30 \text{ ml}$). The product (3.25 g, 96%), obtained on evaporation of solvent,

was recrystallized from light petroleum to give an analytically pure sample, m.p. 65–66 °C (Found: C, 49.3; H, 5.7; N, 5.8; P, 12.7. $C_{10}H_{14}NO_2PS$ requires C, 49.4; H, 5.8; N, 5.8; P, 12.75%); $\nu(P-O-C_{arom})$ (Nujol) 1192 cm^{-1} ; $\nu(P-O-C_{aliph})$ (Nujol) 1030 and 780 cm^{-1} ; δ_H 1.50–2.50 (2 H, m), 2.85 (1 H, NMe, J_{P-N-Me} 14.3 Hz), 3.20–3.60 (2 H, m), 4.10–4.70 (2 H, m), and 7.00–7.60 (5 H, m).

Crystal Data.— $C_{10}H_{14}NO_2PS$, $M = 243.26$. Monoclinic, $a = 7.240(3)$ Å, $b = 10.705(4)$ Å, $c = 15.327(4)$ Å, $\beta = 91.475(5)^\circ$, $V = 1187.51$ Å³, $D_m = 1.364$ g cm^{-3} , $D_c = 1.377$ g cm^{-3} , $Z = 4$, $F(000) = 512$, space group $P2_1/n$, Mo- K_α radiation.

Data were collected at room temperature, on a CAD-4 four-circle diffractometer using Mo- K_α radiation. 1733 Reflections were measured of which 60 had $F_o < 3.0\sigma(F_o)$, and these were not used in the refinement.

The structure was solved by direct method with the multiple-solution programme from SHELX-76 system using 337 normalized structure factors with $E > 1.2$. The E -map calculated from the phase set with the highest figure of merit (1.011) revealed 14 of 15 non-hydrogen atoms. With these atoms in the model, the discrepancy index $R = \Sigma[|F_o| - |F_c|]/\Sigma|F_o|$ was 0.33. A Fourier map, computed at this stage, showed the position of the remained carbon atom.

The atomic position and anisotropic thermal parameters were refined by full-matrix least squares, where the function minimized was $\Sigma w[|F_o| - |F_c|]^2$. Unit weights were initially chosen but for final refinement statistical weight was $w = [\sigma^2 F + 0.001F^2]^{-1}$. A Fourier difference map showed the positions of all hydrogen atoms. Further refinement of all atom positions with anisotropic temperature parameters for non-hydrogen atoms and isotropic para-

map showed no misplaced electron density. All computations were made with SHELX-76 system on the ODR-1305 computer. Atomic fractional co-ordinates are given in Table 1. The observed and calculated structure factors together with the thermal parameters are deposited as Supplementary publication SUP No. 22265 (13 pp.).*

Bond angles and lengths are listed in Tables 2 and 3.

TABLE 2
Bond angles

Atoms	Angles (°)	Atoms	Angles (°)
O(1)–P(1)–S(1)	112.6(1)	C(2)–C(1)–O(1)	110.7(2)
O(2)–P(1)–S(1)	113.8(1)	C(3)–C(2)–C(1)	111.2(2)
O(2)–P(1)–O(1)	104.2(1)	C(2)–C(3)–N(1)	111.1(2)
O(1)–P(1)–N(1)	104.3(1)	C(12)–C(11)–O(2)	117.5(2)
N(1)–P(1)–S(1)	116.8(1)	C(16)–C(11)–O(2)	120.5(2)
N(1)–P(1)–O(2)	103.8(1)	C(16)–C(11)–C(12)	121.9(2)
C(1)–O(1)–P(1)	119.0(2)	C(13)–C(12)–C(11)	118.8(3)
P(1)–O(2)–C(11)	122.5(1)	C(14)–C(13)–C(12)	120.6(3)
C(3)–N(1)–P(1)	117.7(2)	C(15)–C(14)–C(13)	120.0(3)
C(4)–N(1)–P(1)	119.7(2)	C(16)–C(15)–C(14)	115.6(3)
C(4)–N(1)–C(3)	113.9(2)	C(15)–C(16)–C(11)	118.2(3)
H(11)–C(1)–O(1)	108.4(3)	H(42)–C(4)–N(1)	115.5(3)
H(11)–C(1)–C(2)	112.3(3)	H(42)–C(4)–H(41)	114.1(3)
H(12)–C(1)–O(1)	116.0(3)	H(43)–C(4)–N(1)	115.4(2)
H(12)–C(1)–C(2)	104.7(3)	H(43)–C(4)–H(41)	110.6(2)
H(12)–C(1)–H(11)	104.6(3)	H(43)–C(4)–H(42)	96.9(2)
H(21)–C(2)–C(1)	117.7(3)	H(2)–C(12)–C(11)	118.2(2)
H(21)–C(2)–C(3)	107.2(3)	H(2)–C(12)–C(13)	123.1(3)
H(22)–C(2)–C(1)	95.4(2)	H(3)–C(13)–C(12)	121.3(3)
H(22)–C(2)–C(3)	110.3(3)	H(3)–C(13)–C(14)	118.0(3)
H(22)–C(2)–H(21)	114.7(3)	H(4)–C(14)–C(13)	123.5(4)
H(31)–C(3)–N(1)	106.3(2)	H(4)–C(14)–C(15)	115.9(4)
H(31)–C(3)–C(2)	110.5(3)	H(5)–C(15)–C(14)	123.7(6)
H(32)–C(3)–N(1)	102.1(3)	H(5)–C(15)–C(16)	115.6(6)
H(32)–C(3)–C(2)	116.7(4)	H(6)–C(16)–C(11)	114.2(2)
H(32)–C(3)–H(31)	109.4(3)	H(6)–C(16)–C(15)	127.6(3)
H(41)–C(4)–N(1)	104.6(2)		

TABLE 1

Fractional atomic co-ordinates

Atom	x	y	z
P(1)	0.015 2(1)	0.893 9(1)	0.216 0(0)
S(1)	0.158 3(1)	0.745 9(1)	0.197 8(0)
O(1)	–0.195 5(2)	0.864 9(2)	0.229 3(1)
O(2)	0.076 8(2)	0.971 0(1)	0.301 7(1)
N(1)	0.015 0(3)	0.998 8(2)	0.138 2(1)
C(1)	–0.327 2(4)	0.969 4(3)	0.232 8(2)
C(2)	–0.316 7(4)	1.048 5(3)	0.152 4(2)
C(3)	–0.122 8(4)	1.100 5(2)	0.141 8(2)
C(4)	0.188 4(4)	1.035 8(3)	0.100 1(2)
C(11)	0.111 1(3)	0.913 2(2)	0.382 8(1)
C(12)	0.290 1(4)	0.914 3(3)	0.415 5(2)
C(13)	0.326 4(5)	0.863 0(3)	0.497 0(2)
C(14)	0.187 1(6)	0.812 0(2)	0.544 2(2)
C(15)	0.008 6(6)	0.812 4(3)	0.510 8(2)
C(16)	–0.031 7(4)	0.863 7(2)	0.429 0(2)
H(11)	–0.446(6)	0.937(4)	0.240(3)
H(12)	–0.312(5)	1.019(4)	0.274(3)
H(21)	–0.394(5)	1.111(4)	0.147(3)
H(22)	–0.340(6)	0.978(4)	0.110(2)
H(31)	–0.083(4)	1.157(4)	0.197(2)
H(32)	–0.109(5)	1.129(4)	0.109(3)
H(41)	0.277(5)	0.957(3)	0.109(2)
H(42)	0.239(5)	1.110(3)	0.121(2)
H(43)	0.179(5)	1.064(4)	0.028(3)
H(2)	0.386(5)	0.951(3)	0.380(2)
H(3)	0.436(5)	0.864(3)	0.520(2)
H(4)	0.201(4)	0.789(3)	0.598(2)
H(5)	–0.094(8)	0.774(6)	0.540(4)
H(6)	–0.153(4)	0.868(3)	0.398(2)

meters for hydrogen atoms resulted in a final $R = 0.037$ 2 (omitting 16 reflections). A computed Fourier difference

* For details of the Supplementary publications scheme see Notice to Authors No. 7, *J.C.S. Perkin I*, 1977, Index issue.

TABLE 3

Bond lengths

Atoms	Distance (Å)	Atoms	Distance (Å)
P(1)–S(1)	1.918(1)	C(1)–C(2)	1.498(4)
P(1)–O(1)	1.576(2)	C(2)–C(3)	1.522(4)
P(1)–O(2)	1.605(2)	C(11)–C(12)	1.378(4)
P(1)–N(1)	1.638(2)	C(11)–C(16)	1.374(3)
O(1)–C(1)	1.472(3)	C(12)–C(13)	1.383(4)
O(2)–C(11)	1.404(2)	C(13)–C(14)	1.370(5)
N(1)–C(3)	1.479(3)	C(14)–C(15)	1.378(6)
N(1)–C(4)	1.453(4)	C(15)–C(16)	1.394(4)
C(1)–H(11)	0.935	C(4)–H(42)	0.927
C(1)–H(12)	0.824	C(4)–H(43)	1.161
C(2)–H(21)	0.874	C(12)–H(2)	0.979
C(2)–H(22)	1.002	C(13)–H(3)	0.857
C(3)–H(31)	1.074	C(14)–H(4)	0.857
C(3)–H(32)	0.605	C(15)–H(5)	0.976
C(4)–H(41)	1.067	C(16)–H(6)	0.984

This structure research was supported by project MR I-9 from the Polish Academy of Sciences.

[7/1875 Received, 25th October, 1977]

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