

Heterocyclic Compounds containing Phosphorus. Part 30.† Synthesis of Mixed Phosphorohydrazides and of Some New Mono-, Bi-, and Tri-cyclic Derivatives

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Mixed phosphorohydrazides have been synthesized. They react with formaldehyde and with acetone to give new mono- or bi-cyclic compounds. In one case, the carbonyl group reacted with a nitrogen atom directly linked to phosphorus, thus forming a chiral tricyclic compound.

WE have previously described,^{1,2} the synthesis of phosphoric di- and tri-hydrazides in which both or all three hydrazino-groups are identical; the reaction between such compounds and aldehydes or ketones leads

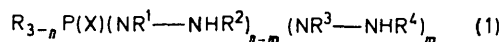
† Part 29, J. P. Majoral, R. Kraemer, J. Navech, and F. Mathis, *Tetrahedron*, in the press.

to new families of heterocyclic compounds. We have now undertaken the synthesis of phosphorohydrazides of

¹ J. P. Majoral, R. Kraemer, J. Navech, and F. Mathis, *Tetrahedron Letters*, 1975, 1481.

² J. P. Majoral, R. Kraemer, J. Navech, and F. Mathis, *Tetrahedron*, in the press.

type (1) and studied their reactions with formaldehyde and with acetone.



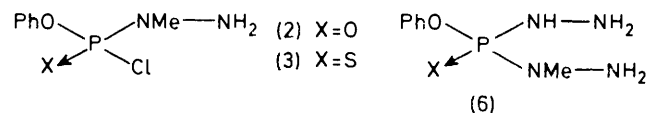
X = O or S

n = 3, m = 1 or 2

n = 2, m = 1

Synthesis of Mixed Phosphoric Di- and Tri-hydrazides.

—We envisaged the synthesis of mixed phosphoric di- and tri-hydrazides *via* intermediate phosphorohydrazidic

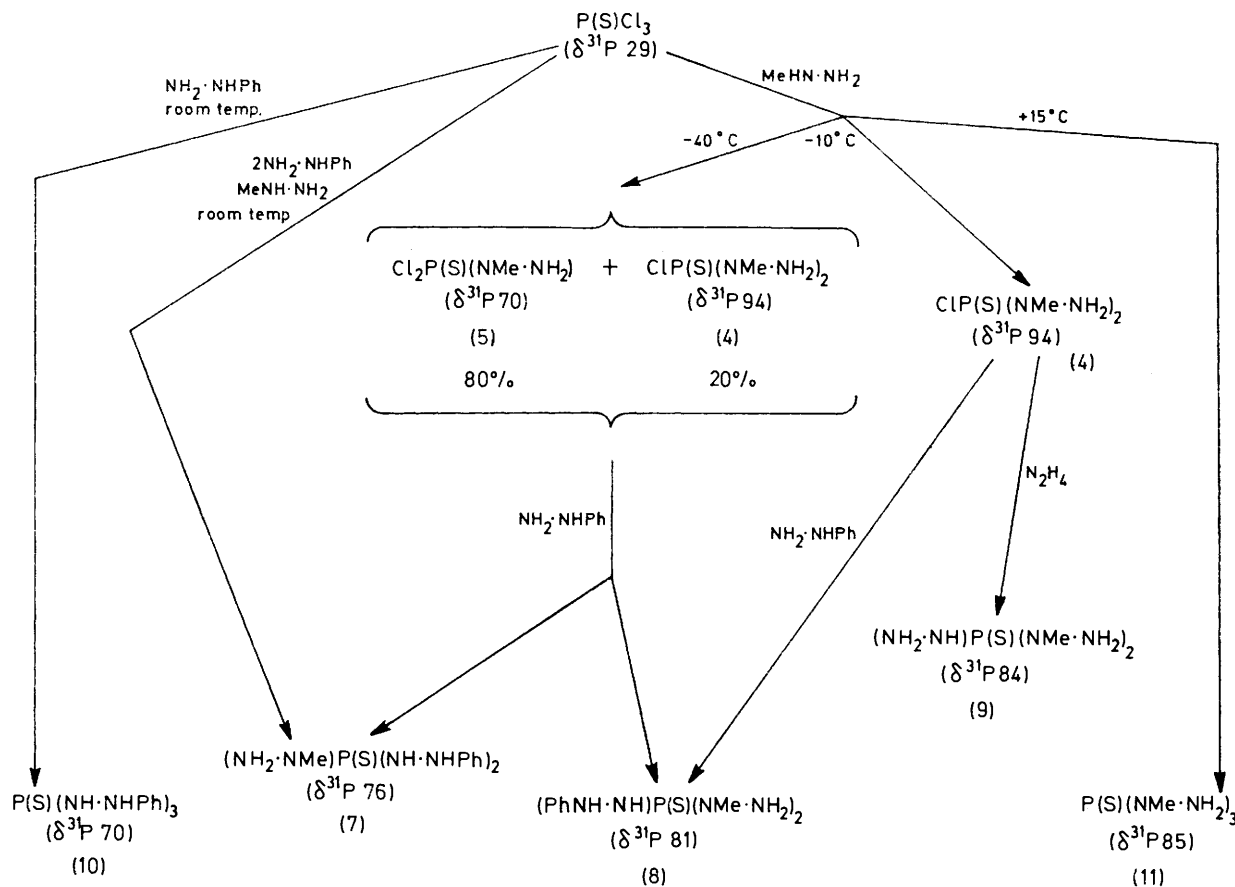


chlorides. We had previously treated phenyl phosphorodichloridate and its thio-analogue with methylhydrazine at low temperature to give the hydrazidochloridates (2) and (3),³ and therefore tried to achieve

derivatives; these compounds can be thought of as intermediates in the formation of the phosphoric trihydrazide.

At -40°C , compounds (4) and (5) were formed in the ratio 20 : 80. This ratio is insensitive to the initial ratio of the reactants. At -10°C , only the monochloro-dihydrazide (4) is formed, and could be isolated and identified [$\delta^{31}\text{P}$ 94 p.p.m. (in chloroform), M^+ 188]; the ^1H n.m.r. spectrum of this compound in CDCl_3 exhibits signals due to methyl protons [δ 2.92, $J(\text{PNCH})$ 13.9 Hz] and to the protons linked to the β -nitrogen atom (δ 3.7) (ratio 3 : 2); the PNNH spin coupling does not appear, presumably because of rapid chemical exchange.

The dichloro-monohydrazide (5) could not be isolated because at room temperature the reaction mixture violently decomposes. However, its structure was confirmed by its ^{31}P chemical shift (70 p.p.m. in CDCl_3), intermediate between those of thiophosphoryl chloride (29 p.p.m.) and the monochloride (4), and by the fact



SCHEME

a similar partial substitution with thiophosphoryl chloride (Scheme). At room temperature, a 3 : 1 molar ratio of a monosubstituted hydrazine and thiophosphoryl chloride gives a phosphoric trihydrazide with three identical hydrazino-residues.^{1,2} At low temperature, however, thiophosphoryl chloride reacts with methylhydrazine to give the monochloro- (4) and dichloro- (5)

that the reaction of phenylhydrazine with the already mentioned 80 : 20 mixture gives a mixture of both phosphoric trihydrazides (7) and (8) (Scheme) in the same (80 : 20) proportions. Compounds (7) and (8) were prepared independently and identified as described later.

³ J. P. Majoral, R. Kramer, J. Navech, and F. Mathis, *Bull. Soc. chim. France*, 1975, 2367.

The monochloride (4) reacted with phenylhydrazine to give the expected mixed phosphoric dihydrazide (8) (Scheme).

We had supposed that mixed phosphoric trihydrazides could not be obtained without preliminary preparation of a phosphorohydrazidic chloride. This proved too pessimistic, as we could prepare compound (7) directly by treating thiophosphoryl chloride at room temperature with phenylhydrazine (2 mol. equiv.) and methylhydrazine (1 mol. equiv.).

However, it is easier to extract compound (7) from the mixture of (7) and (8) already described.

detected only when the NH group is connected to a phenyl group.

Reactions of Aldehydes and Ketones with Mixed Phosphoric Trihydrazides.—Reactions of symmetrical phosphoric trihydrazides (three identical hydrazino-groups) with aldehydes and ketones lead in most cases to cyclic compounds.² Hydrazones were obtained in only a few cases. In the present work, the mixed phosphoric trihydrazides underwent only cyclisation reactions.

Compound (8) and acetone gave only one perhydro-1,2,4,5,3-tetra-azaphosphorine (14) (Table 2), with a free

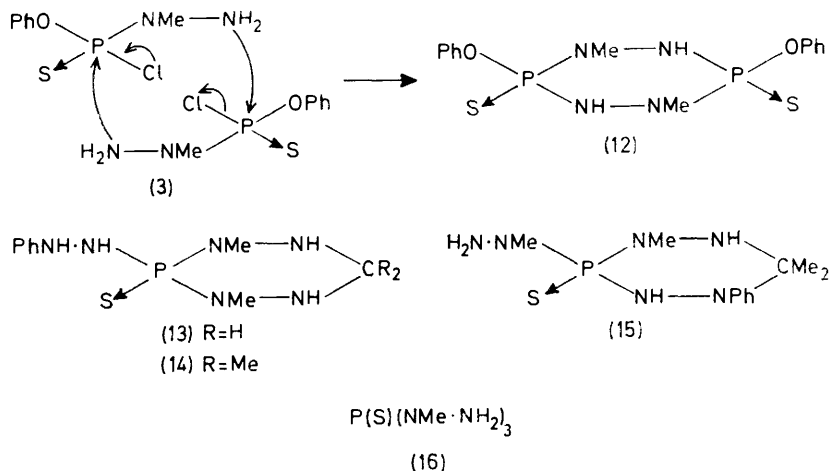


TABLE I

³¹P and ¹H n.m.r. spectral parameters for the mixed phosphoric hydrazides (6)–(9)

Compd.	$\delta^{31}P$	δ^1H			J/Hz		
		PNH	PNNH	PNCH ₃	PNH	PNNH	PNCH ₃
(6)	78 *	5.30	3.84	2.97	28	0	10.6
(7)	76 †	4.88	3.34 ^a 5.60 ^b	2.74	26.5	0	11.25
(8)	81 *	4.81	3.81 ^a 5.51 ^b	2.81	30	0 ^a 4.3 ^b	10.9
(9)	84 ‡	5.62	3.60	2.90	30	0	10

* Solvent ethanol. † Solvent CHCl₃. ‡ Solvent ether.

^a MeNH-NH₂. ^b PhNH; coupling constant at -40 °C.

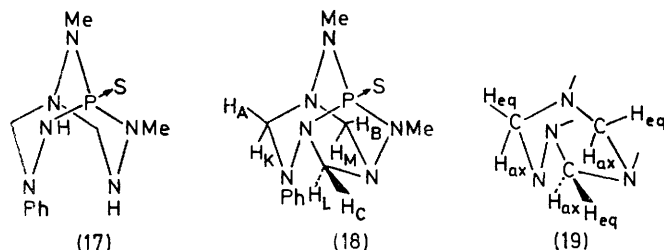
We have reported that, when a solution of hydrazine is added dropwise to the hydrazido chloridate (3), the latter condenses intermolecularly with itself to give a perhydro-1,2,4,5,3,6-tetra-azadiphosphorine³ (12). If the hydrazine is added all at once, a different reaction takes place: hydrazine is phosphorylated and compound (6) (Table I) is formed. Hydrazine reacts in a similar way with the monochloro derivative (4) to give the mixed phosphoric trihydrazide (9) (Scheme).

N.m.r. data (Table I) are in good agreement with the structures assigned. The ³¹P signal shifts to lower field in the order: thiophosphoric tris(phenylhydrazide) (10), mixed trihydrazide (7), mixed trihydrazide (8), thiophosphoric tris(methylhydrazide) (11), suggesting that the phenyl groups exert a strong anisotropic effect on the phosphorus nucleus. As in phosphoric trihydrazides previously described,³ the PNNH coupling can be

phenylhydrazino-group directly linked to phosphorus. Formaldehyde and (8) reacted similarly to form the monocyclic compound (13), provided that the aldehyde (1 mol. equiv.) was added dropwise and very slowly (Table 2). In both cases, the carbonyl group reacts with the nitrogen atoms β to phosphorus but not with the less nucleophilic phenylamino nitrogen atom. The ¹H n.m.r. spectrum of compound (13) exhibits a single doublet (PNCH₃ coupling) for both methyl groups, which rules out structure (15), and the protons linked to the β -nitrogen atoms give only one peak.

The thiophosphoric tris(*N*-methylhydrazide) (16) can react with aldehydes to give tricyclic compounds of adamantane-like structure.^{2,3} Such a reaction cannot occur with compound (8) because of the lack a third NH₂ group β to phosphorus; however formation of a bicyclic compound might be expected. In fact, treatment

of compound (13) with 1 mol. equiv. of formaldehyde gave two compounds ($\delta^{31}\text{P}$ 66 and 87 p.p.m.). Mass spectral (M^+ 284), ^1H n.m.r. (Table 3), and i.r. (two different NH groups) data proved that the structure of the first ($\delta^{31}\text{P}$ 66 p.p.m.) was (17). The other product was identified by (a) a molecular ion at m/e 296, (b) a 1 : 1 methylene : methyl proton ratio in the ^1H n.m.r. spectrum, and (c) the lack of an NH band in the i.r. spectrum as 8,9-dimethyl-3-phenyl-2,3,5,7,8,9-hexa-aza-1-phosphatrimethylcyclo[3.3.1.1^{2,7}]decane *P*-sulphide (18). This struc-



ture is strongly supported by the ^1H n.m.r. spectrum (Table 4). The signals due to the methylene protons appear as the ABCMKL part of an ABCMKMX system (X is phosphorus). This complex spectrum can be analysed under three hypotheses (based on previous results²): (a) the long-distance H,H-coupling constants are equal to zero except those between equatorial protons in the perhydro-1,2,4,6-tetra-azepine part struc-

ture (19); (b) protons linked to this ring (19) have non-zero coupling constants with the ^{31}P nucleus only if they are in axial orientation; (c) there are only two non-zero long distance H,H-coupling constants, coupling constants through the C-N-N-C fragment being negligible. The observed methylene proton spectrum should then appear as the superposition of three ABX systems. INDOR experiments allowed us to determine those systems (AKX, BMX, and CLX). All the subspectra were reconstructed; the J and δ parameters were calculated and refined with the help of the LAOCOON III iterative program (Table 4). The three geminal proton pairs being defined by the three systems AKX, BMX, and CLX, assignment of the symbols to the six methylene protons arises as follows. (a) J_{AX} , J_{BX} , and J_{CX} being zero, A, B, and C are equatorial relative to the 1,2,4,6-tetra-azepine ring (19). The fact that A and B on the one hand and B and C on the other are coupled corroborates this interpretation. (b) The comparatively high value of J_{LX} implies that the proton L is bound to the five membered ring. (c) The position of A (and hence that of B) is fixed by J_{AO} being zero.

The formation of the tricyclic molecule (18) implies a nucleophilic attack by a nitrogen atom directly linked to phosphorus, a type of reaction which we had never observed before. Compound (18) is the only one in which we have a NH group linked to a phosphorus atom and a PhNH group. We suggest therefore that the

TABLE 2
 ^{31}P and ^1H n.m.r. spectral parameters for perhydro-1,2,4,5,3-tetra-azaphosphorines in CDCl_3

Compd.	$\delta^{31}\text{P}$ *	$\delta^1\text{H}$				J/Hz		
		PNH	PNNH	PNCH ₃	Others	PNH	PNNH	PNCH ₃
(13)	76	4.77	4.25 ^a 5.47 ^b	2.79	CH ₂ 3.79	30.6	0 ^a 4.1 ^b	11.8
(14)	76.5	4.95	3.98 ^a 5.38 ^b	2.84	CCH ₃ 1.08	34.6	0 ^a 4.3 ^b	11.4

* Solvent CHCl_3 .
^a MeN·NH. ^b PhNH; J_{PNNH} evaluated at -40°C .

TABLE 3
 ^{31}P and ^1H n.m.r. spectral parameters for the bicyclo[3.3.1]nonanes (17) and (21)

Compd.	$\delta^{31}\text{P}$ *	$\delta^1\text{H}$				J/Hz				
		NCH ₃	CH ₂	PNH	PNNH	PNCH ₃	PNH	PNNH	HCH	HCCH
(17)	66	2.88 3.14 ^a	<i>b</i>	5.10	5.36	9.1, 10.9 ^a	20.8	4.8	<i>b</i>	<i>b</i>
(21)	66	3.18	4.80 4.64	4.70		10.9	22.9		-12.5	0

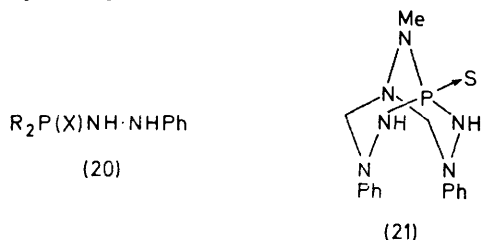
* Solvent CHCl_3 .
^a Me at position 9. ^b Poor resolution prevented assignments of this part of the spectrum.

TABLE 4
 ^{31}P and ^1H n.m.r. spectral parameters for the tricyclodecane (18)

$\delta^{31}\text{P}$	$\delta^1\text{H}$ (in CDCl_3)								J/Hz										
	CH ₃	H _A	H _B	H _C	H _K	H _L	H _M		PNCH ₃	AB	BC	AC	KX *	LX	MX	AX, BX, CX	AK	BM	CL
87	2.87 2.86	5.00	4.90	4.61	4.12	3.80	3.74		12.0 13.1	1.51	2.02	0	2.01	11.44	1.50	0	-10.42	-14.16	-11.40

* X is phosphorus.

presence of the anilino-group renders the neighbouring α -nitrogen atom more nucleophilic. This hypothesis can be related to observations of Arbuzov *et al.*,⁴ who have shown that a nitrogen atom α to phosphorus is a comparatively strong nucleophile in compounds of type (20).



We consider that (18) is formed *via* the intermediate (17).

The phosphoric hydrazide (7) reacted with 2 mol. equiv. of formaldehyde to give 9-methyl-3,7-diphenyl-2,3,5,7,8,9-hexa-aza-1-phosphabicyclo[3.3.1]nonane *P*-sulphide (21) as the sole product. Structure (21) is supported by n.m.r. data. Methylene protons give rise to one AB spectrum, showing that the molecule possesses a plane of symmetry, at least on a time averaged basis, and that the coupling constants of these protons with each other and with phosphorus are zero.

EXPERIMENTAL

³¹P N.m.r. spectra were recorded with a Perkin-Elmer R10 spectrometer operating at 24.3 MHz; chemical shifts are reported in p.p.m. to low field of external H₃PO₄. ¹H N.m.r. spectra were obtained with a Varian HA-100 spectrometer (tetramethylsilane as internal standard), for solutions in CDCl₃ unless otherwise stated. I.r. spectra were run with a Perkin-Elmer 125 spectrophotometer. Mass spectra were obtained on an RIBER quadrupole spectrometer at 70 eV ionization energy. M.p.s were determined with a Büchi hot-stage apparatus.

Chloro-(1-methylhydrazino)phenoxyphosphine Sulphide (3).—To a solution of phenyl phosphorodichloridate (6.81 g, 0.03 mol) in ether (150 ml) at -70°C , a solution of methylhydrazine (2.76 g, 0.06 mol) in ether was added dropwise with stirring. Stirring at this temperature was continued for 2 h. The mixture was allowed to warm to room temperature. Methylhydrazine hydrochloride was filtered off and washed with ether. The combined ethereal solutions were evaporated under reduced pressure to 5 ml and the resulting mixture was kept overnight at 0°C . The product (3) crystallised as *needles* (5 g, 79%), m.p. $53-55^\circ\text{C}$ (Found: C, 35.8; H, 4.2; N, 11.8; P, 13.2. C₇H₁₀ClN₂OPS requires C, 35.5; H, 4.25; N, 11.85; P, 13.1%).

Chlorobis-(1-methylhydrazino)phosphine Sulphide (4).—To a solution of thiophosphoryl chloride (4.25 g, 0.025 mol) in ether (200 ml) at -10°C , a solution of methylhydrazine (4.6 g, 0.1 mol) in ether was added dropwise with stirring. The mixture was allowed to warm to room temperature. Methylhydrazine hydrochloride was filtered off and the ethereal solution was evaporated. The residue crystallised from 1:3 benzene-hexane to give the product (4) (3 g, 63%), m.p. $114-116^\circ\text{C}$ (Found: C, 12.9; H, 5.6; N, 29.9; P 16.1. C₂H₁₀ClN₄PS requires C, 12.75; H, 5.3; N, 29.7; P, 16.4%).

Dichloro-(1-methylhydrazino)phosphine Sulphide (5).—To a solution of methylhydrazine (4.6 g; 0.1 mol) in ether

(200 ml) was added dropwise, with stirring and cooling, at -50°C , an ethereal solution of thiophosphoryl chloride (8.5 g 0.05 mol). The mixture was allowed to warm to room temperature. Methylhydrazine hydrochloride was filtered off and the filtrate was carefully evaporated under reduced pressure to 10 ml. The ³¹P n.m.r. spectrum (CHCl₃) showed two signals (4:1), δ 70.10 (5) and 94.10 p.p.m. (4). This solution was used without further purification to minimize the explosion hazard.

Hydrazino-(1-methylhydrazino)phenoxyphosphine Sulphide (6).—To a solution of the chloro-hydrazide (3) (5 g, 0.021 mol) in chloroform (150 ml) was quickly added, at 0°C , with vigorous stirring, a solution of hydrazine hydrate (0.14 g 0.042 mol) in chloroform. Stirring at 0°C was continued for 3 h. Hydrazine hydrochloride was filtered off and the filtrate was dried (Na₂SO₄) and evaporated under reduced pressure. The ³¹P n.m.r. spectrum (CHCl₃) showed the presence of compounds (6) (80%, δ 78 p.p.m.) and (12) (20%, δ 73 p.p.m.). The mixture was crystallised from hexane yielding the *dihydrazide* (6) (2.9 g, 60%), m.p. $50-52^\circ\text{C}$ (Found: C, 36.4; H, 5.8; N, 24.4; P, 13.5. C₇H₁₃N₄PS requires C, 36.2; H, 5.6; N, 24.1; P, 13.3%).

1-Methylhydrazinobis-(2-phenylhydrazino)phosphine Sulphide (7).—To a solution of thiophosphoryl chloride (16.95 g, 0.1 mol) in chloroform (200 ml) was added dropwise with stirring and cooling (0°C) a solution in chloroform of methylhydrazine (9.2 g, 0.2 mol) and phenylhydrazine (43.6 g, 0.4 mol). After 3 h stirring, the methylhydrazine and phenylhydrazine hydrochlorides were filtered off and the solvent removed. The residue was washed several times with chloroform and crystallised from ethanol to give (7) as *needles* (1.6 g, 5%), m.p. $104-105^\circ\text{C}$ (Found: C, 49.0; H, 6; N, 26.0; P, 9.5. C₁₃H₁₉N₆PS requires C, 48.4; H, 5.95; N, 26.05; P, 9.6%).

Bis-(N¹-methylhydrazino)-2-phenylhydrazinophosphine Sulphide (8).—To a solution of the chloro-hydrazide (4) (2.6 g, 0.014 mol) in chloroform was added dropwise with stirring a solution of phenylhydrazine (3 g, 0.027 mol) in chloroform. Stirring was continued at 30°C during 1 h. Phenylhydrazine hydrochloride was filtered off and the solution evaporated to 5 ml. The resulting oil was washed several times with ether to remove phenylhydrazine hydrochloride, and the residue was crystallised from hexane to give the *product* (8) (0.7 g, 20%), m.p. $165-168^\circ\text{C}$ (Found: C, 36.3; H, 6.5; N, 32.4; P, 11.7. C₈H₁₇N₆PS requires C, 36.9; H, 6.6; N, 32.3; P, 11.9%).

Hydrazinobis-(1-methylhydrazino)phosphine Sulphide (9).—To a solution of the chloro-hydrazide (4) (4.3 g, 0.022 mol) in ether was added dropwise hydrazine hydrate (1.43 g, 0.044 mol). The resulting mixture was stirred for 2 h at 50°C . Hydrazine hydrochloride was filtered off and the solvent removed. The residue was an *oil* (9) (1.2 g, 30%) (Found: C, 13.25; H, 7.3; N, 45.75; P, 16.6. C₂H₁₃N₆PS requires C, 13.05; H, 7.1; N, 45.6; P, 16.8%).

2,4-Dimethyl-3-(2-phenylhydrazino)perhydro-1,2,4,5,3-tetra-azaphosphorine P-Sulphide (13).—To an alcoholic solution of compound (8) (3 g, 0.015 mol) was added very slowly (10 h) aqueous formaldehyde (30%; 1.5 g, 0.015 mol). The mixture was kept overnight at room temperature; the product (13) crystallised directly as *needles* (3.00 g, 75%), m.p. $139-140^\circ\text{C}$ (Found: C, 39.6; H, 6.5;

⁴ A. E. Arbuzov, F. G. Validotva, N. G. Gazetdinova, and L. P. Petrova, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 1646.

N, 31.0; P, 11.2. $C_9H_{17}N_6PS$ requires C, 39.7; H, 6.3; N, 30.9; P, 11.35%.

2,4,6-Tetramethyl-3-(2-phenylhydrazino)perhydro-1,2,4,5,3-tetra-azaphosphorine P-Sulphide (14).—The same procedure as for (13) gave the *product* (14) (70%), m.p. 144–145 °C (Found: C, 44.3; H, 7.15; N, 27.7; P, 10.1. $C_{11}H_{21}N_6PS$ requires C, 44.0; H, 7.05; N, 28.0; P, 10.3%).

2,9-Dimethyl-7-phenyl-2,3,5,7,8,9-hexa-aza-1-phosphabicyclo[3.3.1]nonane P-Sulphide (17).—To a solution of compound (7) (1 g, 0.0038 mol) in chloroform (10 ml) was added dropwise aqueous formaldehyde (30%; 0.1 g, 0.0038 mol). The solvent was evaporated off to give a mixture of products (17) ($\delta^{31}P$ 66 p.p.m.) and (18) ($\delta^{31}P$ 87 p.p.m.). This was washed with 1:1 alcohol-ether; the residue consisted solely of the *product* (17) (0.054 g, 5%), m.p. 179–180 °C (Found C, 42.5; H, 6.1; N, 29.3; P, 10.7. $C_{10}H_{17}N_6PS$ requires C, 42.25; H, 6.0; N, 29.55; P, 10.9%).

8,9-Dimethyl-3-phenyl-2,3,5,7,8,9-hexa-aza-1-phospha-

tricyclo[3.3.1.1^{2,7}]decane P-Sulphide (18).—To a solution of compound (13) (3.6 g, 0.013 mol) in chloroform was added very slowly (8 h) aqueous formaldehyde (30%; 2.6 g, 0.026 mol). The solvent was removed under reduced pressure and the residue crystallised from hexane to give the *product* (18) (0.38 g, 10%), m.p. 144–146 °C (Found: C, 44.4; H, 5.6; N, 28.1; P, 10.4. $C_{11}H_{17}N_6PS$ requires C, 44.6; H, 5.8; N, 28.4; P, 10.45%).

9-Methyl-3,7-diphenyl-2,3,5,7,8,9-hexa-aza-1-phosphabicyclo[3.3.1]nonane P-Sulphide (21).—To a solution of compound (7) (0.25 g, 0.0008 mol) in chloroform was added aqueous formaldehyde (30%; 0.16 g, 0.0016 mol) at 0 °C with stirring. The mixture was then stirred at this temperature for 3 h. The solvent was evaporated off and the residue was crystallised from ethanol to give the *product* (21) (0.22 g, 80%), m.p. 136–139 °C (Found: C, 51.4; H, 5.2; N, 24.8; P, 8.6. $C_{15}H_{19}N_6PS$ requires C, 52.0; H, 5.5; N, 24.3; P, 8.95%).

[6/041 Received, 7th January, 1976]