Studies on the Synthesis of Phosphorus Heterocyles II. Preparation of Some New Tetrahydro-[1,4,3]thiazaphosphorino[3,4-*b*][1,3,2]benzodiazaphosphorine 12-Oxides

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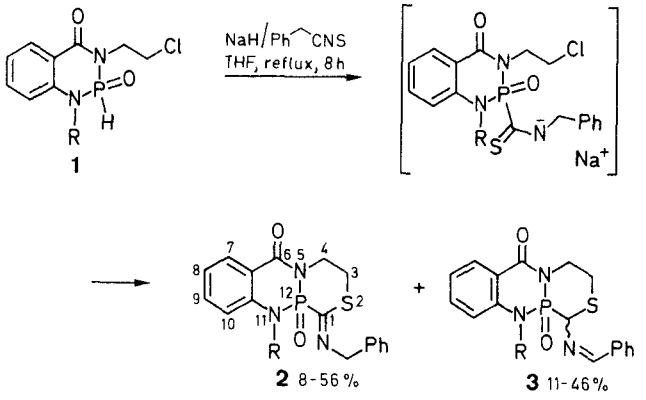
Reaction of 1,3,2-benzodiazaphosphorine derivatives **1** with benzyl isothiocyanate in the presence of base gave a tautomeric mixture of **2** and **3**. The preparation of new heterocycles **6** and **7** obtained from the reaction of **1** with carbon disulfide in the presence of sodium hydride is described.

In a previous paper,[1] we reported the synthesis of a new type of fused tricyclic phosphorus compounds by reaction of tetrahydro-1,3,2-benzodiazaphosphorines **1** with aryl isothiocyanates. We have now found that, when benzyl isothiocyanate was used instead of phenyl isothiocyanate, benzylimines **2** and benzylideneamines **3** were obtained at the same time. The tautomerization of **2** to **3** was observed for all the cases studied except for R = CH_3. The new compounds were characterized by spectral analytical data (Table 1). The molecular structure of **3** was further confirmed by X-ray diffraction data of **3a**.

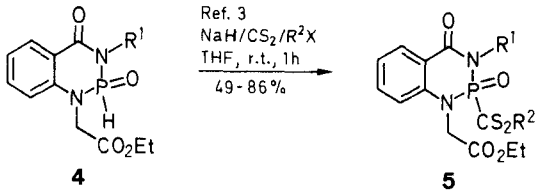
From X-ray data,[2] it was confirmed that the ring C in **3** has a chair conformation and C=N bond length is 1.265 Å with *E* stereochemistry of the substituents. The P=O and C–N bonds are found to be in *trans* position and axially substituted.



1–3	a	b	c	d
R	CH_2CO_2Et	Me	Et	n-C_3H_7

[a] **2c**, not given in Table 1. Tautomer **3b** not formed.

In search of novel fused phosphorus heterocycles we have carried out the reaction of **1** with carbon disulfide in the presence of sodium hydride, which afforded a mixture of two hitherto unknown phosphorus heterocycles **6** and **7**. Earlier work[3] (see experimental) on the reaction of tetrahydro-1,3,2-benzodiazaphosphorines **4** with carbon disulfide and an alkyl halide in the presence of sodium hydride at room temperature yielded only the *p*-substituted products **5** (Table 2).



4	R^1	5	R^1	R^2
a	Me	a	Pr	Me
b	Pr	b	Pr	CH_2Ph
		c	Pr	CH_2CO_2Et
		d	Me	Me

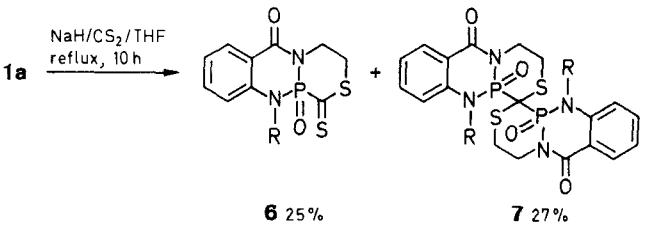


Table 1. Compounds **2** and **3** Prepared

Product	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]	IR (KBr) ν (cm^{-1})					^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS, M^+ m/z (%)
				C=O	C=N	P–C	P=O	P–N		
2a	30	165–166	$C_{21}H_{22}N_3O_4PS$ (443.5)	1755	1670	1335	1240	700	1.1 (t, 3H, J = 5, $OCH_2C\underline{H}_3$), 3.3 (dt, 1H, $J_{gemHa,e}$ = 14.4, SCH*a*), 3.7–4.4 (m, 5H, $SCH_2C\underline{H}_2$, SCH*e*, OCH_2), 4.42, 4.48 (dd, 2H, $PhC\underline{H}_2$), 6.7–8.3 (m, 9H_{arom})	443 (34)
2b	56	163–164	$C_{18}H_{18}N_3O_2PS$ (371.5)	1755	1670	1340	1245	700	3.3 (dt, 1H, $J_{gemHa,e}$ = 14.4, SCH*a*), 3.44 (d, 3H, $J_{P,H}$ = 7.2, NCH_3), 3.9–4.4 (m, 3H, $SCH_2C\underline{H}_2$, SCH*e*), 4.4, 4.5 (dd, 2H, $PhC\underline{H}_2$), 6.9–8.24 (m, 9H_{arom})	371 (15)
2d	8	97–98	$C_{20}H_{22}N_3O_2PS$ (399.5)	1760	1670	1335	1245	700	0.9 (t, 3H, J = 4.5, $CH_2C\underline{H}_3$), 1.7 (m, 2H, $NCH_2C\underline{H}_2$), 3.2–4.2 (m, 6H, $SC\underline{H}_2C\underline{H}_2$, NCH_2), 4.4, 4.5 (dd, $PhC\underline{H}_2$), 6.8–8.2 (m, 9H_{arom})	399 (30)
3a	11	185–186	$C_{21}H_{22}N_3O_4PS$ (443.5)	1670	1630	1340	1240	695	1.3 (t, 3H, J = 3, $OCH_2C\underline{H}_3$), 2.3 (dd, 1H, $J_{gemHa,e}$ = 14.14, SCH*a*), 3.4 (dt, 1H, $J_{gemHa,e}$ = $J_{vicHa,e}$ = 14.14, SCH*a*), 3.4 (dt, 1H, $J_{gemHa,e}$ = $J_{vicHa,e}$ = 13.34, SCH*e*), 3.8–5.3 (m, 7H, CH, NCH_2, OCH_2, $SCH_2C\underline{H}_2$), 6.38–8.2 (m, 9H_{arom}), 8.44 (d, 1H, J = 3, N=CH)	443 (30)
3c	46	174–176	$C_{19}H_{20}N_3O_2PS$ (385.5)	1680	1630	1340	1245	700	1.35 (t, 3H, J = 4.5, $CH_2C\underline{H}_3$), 2.3 (dd, 1H, $J_{gemHa,e}$ = 14.14, SCH*a*), 3.2 (dt, 1H, $J_{gemHa,e}$ = $J_{vicHa,e}$ = 13.34, SCH*e*), 3.6–5.3 (m, 5H, CH, NCH_2, $SCH_2C\underline{H}_2$), 6.8–8.2 (m, 9H_{arom}), 8.45 (d, 1H, J = 3, N=CH)	385 (65)
3d	31	66–68	$C_{20}H_{22}N_3O_2PS$ (399.5)	1680	1625	1340	1240	700	0.95 (t, 3H, J = 4.5, $CH_2C\underline{H}_3$), 1.7 (m, 2H, $NCH_2C\underline{H}_2$), 2.35 (d, 1H, $J_{gemHa,e}$ = 14.14, SCH*a*), 3.2 (dt, 1H, $J_{gemHa,e}$ = $J_{vicHa,e}$ = 13.34, SCH*e*), 3.4–5.2 (m, 5H, CH, NCH_2, $SCH_2C\underline{H}_2$), 6.6–8.2 (m, 9H_{arom}), 8.5 (d, 1H, J = 3, N=CH)	399 (10)

[a] Yield of isolated product.
[b] Recrystallized from petroleum ether (bp 60–90 °C)/EtOAc.
[c] Satisfactory microanalyses obtained: C ±0.32, H ±0.39, N ±0.37 (exception, **3c**: C +0.49).

Table 2. Compounds **5** Prepared

Product	Yield[a] (%)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS, m/z (%) M^+
5a	52	$C_{16}H_{21}N_2O_4PS_2$ (400.5)	0.9 (t, 3H, J = 4.5, $NCH_2CH_2C\underline{H}_3$), 1.15 (t, 3H, J = 5, $OCH_2C\underline{H}_3$), 1.7 (m, 2H, $NCH_2C\underline{H}_2$), 2.6 (s, 3H, SCH_3), 3.4, 3.7 (dm, 2H, NCH_2), 4.1 (q, 2H, J = 5, OCH_2), 4.5 (dq, 2H, $J_{H,H}$ = 18, $J_{P,H}$ = 9, $PhNC\underline{H}_2$), 6.15–8.15 (m, 4H_{arom})	400 (38)
5b	64	$C_{22}H_{25}N_2O_4PS_2$ (476.6)	0.92 (t, 3H, J = 4.5, $NCH_2CH_2C\underline{H}_3$), 1.25 (t, 3H, J = 5, $OCH_2C\underline{H}_3$), 1.7 (m, 2H, $NCH_2C\underline{H}_2$), 3.4, 4.6 (dm, 2H, NCH_2), 4.2 (m, 4H, OCH_2, SCH_2), 4.55 (dq, 2H, $J_{H,H}$ = 9, $PhNC\underline{H}_2$), 6.6–8.2 (m, 9H_{arom})	476 (18)
5c	49	$C_{19}H_{25}N_2O_6PS_2$ (472.5)	1.1 (m, 9H, $NCH_2CH_2C\underline{H}_3$, 2 × $OCH_2C\underline{H}_3$), 1.5 (m, 2H, $NCH_2C\underline{H}_2$), 3.8 (s, 2H, SCH_2), 4.0 (m, 6H, $PhNC\underline{H}_2$, 2 × OCH_2), 6.3–8.0 (m, 4H_{arom})	472 (17)
5d	86	$C_{14}H_{17}N_2O_4PS_2$ (372.4)	1.1 (t, 3H, J = 4.5, $OCH_2C\underline{H}_3$), 2.7 (s, 3H, SCH_3), 3.15 (dd, 3H, J = 7.2, NCH_3), 4.1 (t, 2H, J = 4.5, OCH_2), 4.55 (dq, 2H, $J_{H,H}$ = 18, $J_{P,H}$ = 9, $PhNC\underline{H}_2$), 6.65–8.25 (m, 4H_{arom})	372 (10)

[a] Yield of pure isolated product. All products were oils and not distilled.
[b] Satisfactory microanalyses obtained: C ±0.32, H ±0.44, N ±0.34.

In summary, we have prepared and characterized new and interesting phosphorus heterocyclic and spirocyclic compounds, which may be useful for biological testing.[1]

Melting points are uncorrected. THF was dried with NaH. PCl_3 was distilled freshly before use. Microanalyses were obtained using a CHN CORDERD MT-3 element analyser. IR spectra were obtained using a NICOLET 5DX spectrophotometer (KBr). ^{1}H-

NMR, ^{13}C-NMR, ^{31}P-NMR spectra were obtained using a JEOL FX-90Q spectrometer.

Compounds **4a** and **4b** were prepared according to Ref. 4.

4a; yield: 76%; mp 128–130 °C.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.2 (t, 3 H, J = 5 Hz, $OCH_2C\underline{H}_3$), 2.1 (d, 3 H, J = 1.2 Hz, NCH_3), 4.1 (q, 2 H, J = 5 Hz, $OC\underline{H}_2CH_3$), 4.3 (dq, 2 H, $J_{H,H}$ = 18 Hz, $J_{P,H}$ = 9 Hz, NCH_2), 6.4–8.0 (m, 4 H_{arom}), 8.5 (d, 1 H, J = 640 Hz, PH)

MS: m/z (%) = 282 (M^+, 17).

4b; yield: 78%; mp 105–106 °C.

$C_{14}H_{19}N_2O_4P$	calc.	C 54.19	H 6.17	N 9.03
(310.3)	found	54.43	6.29	9.05

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.9 (t, 3 H, J = 4.5 Hz, CH_3), 1.25 (t, 3 H, J = 5 Hz, $OCH_2C\underline{H}_3$), 1.7 (m, 2 H, $NCH_2C\underline{H}_2$), 3.7 (dm, 2 H, $NC\underline{H}_2$), 4.19 (dq, 2 H, $J_{H,H}$ = 18 Hz, $J_{P,H}$ = 9, $PhNC\underline{H}_2$), 4.2 (q, 2 H, J = 5, $OC\underline{H}_2$), 6.7–8.1 (m, 4 H_{arom}), 7.8 (d, 1 H, J = 649 Hz, PH)

MS: m/z (%) = 310 (M^+, 20).

11-Substituted 1-Benzylimino- and 1-Benzylideneamino-6-oxo-3,4,6,11-tetrahydro[1,4,3]thiazaphosphorino[3,4-*b*][1,3,2]benzodiazaphosphorine 12-Oxides 2 and 3; General Procedure:

To a 100 mL 4-necked flask containing **1** (3 mmol) and anhydrous THF (40 mL) is added NaH (80% dispersion in oil, 90 mg, 3 mmol) at 0 °C. The mixture is stirred for 0.5 h at 0 °C and 0.5 h at r.t. During this time formation of copious precipitate is noted. To the mixture is added dropwise benzyl isothiocyanate (0.45 g, 3 mmol), and stirring is continued at r.t. util the solids have disappeared. The mixture is refluxed for 8 h, cooled to r.t. and treated with EtOAc (2 × 40 mL) and ice/water (40 mL). The organic layer is separated, the aqueous layer is extracted with EtOAc (2 × 40 mL) and the combined organic extracts are dried (Na_2SO_4). The solvent is removed under reduced pressure and the pale yellow oil obtained is chromatographed on a silica gel column (80 × 3.5 cm, 250–300 mesh) using petroleum ether (60–90 °C)/EtOAc (2:1, 1.5 L) as the eluent. By evaporating the solvent under reduced pressure, from appropriate fractions products **2** and **3** are obtained as colorless solids (Table 1).

2b; ^{13}C-NMR ($CDCl_3$/TMS): δ = 25.35 ($\underline{C}H_2Ph$), 25.52 (d, $^2J_{PC}$ = 7.33 Hz, C-4), 32.40 (CH_3), 44.74 (C-3), 113.60 (d, $^3J_{PC}$ = 7.32 Hz), 115.71, 121.56, 130.56, 135.00, 141.83 (d, $^2J_{PC}$ = 4.89 Hz) (C_6H_4), 126.98, 127.42, 128.39, 138.25 (C_6H_5), 162.30 (d, $^1J_{PC}$ = 205.08, C-1), 162.95 (C=O).

3a; ^{13}C-NMR ($CDCl_3$/TMS): δ = 14.19 (CH_3), 23.51 (d, $^2J_{PC}$ = 5.28 Hz, C-4), 46.23 (C-3), 47.24 (d, $^2J_{PC}$ = 4.88 Hz, $\underline{C}H_2CO_2$), 62.41 ($CO_2\underline{C}H_2$), 65.33 (d, $^2J_{PC}$ = 151.57 Hz (C-1), 114.36 (d, $^3J_{PC}$ = 7.32 Hz), 118.75, 121.89, 128.39, 135.10, 142.82 (C_6H_4), 128.17, 130.88, 131.32, 134.29 (C_6H_5), 163.93, 165.55 (d, N = CH), 166.31 (CO_2), 169.78 (C=O).

3-(Alkyl)-1-(ethoxycarbonylmethyl)-2-(alkyldithioyl)-4-oxo-1,2,3,4-tetrahydro-1,3,2-benzodiazaphosphorine 2-Oxides 5; General Procedure: (Translated from Chinese, Ref. 4).

To a solution of **4** (1 mmol) in THF (20 mL) kept in a 50 mL 4-necked flask is added NaH (80% dispersion in oil, 30 mg, 1 mmol) at r.t. A copious white precipitate is formed immediately, which disappears and the solution becomes violet when CS_2 (1.5 mL) is added dropwise. After stirring for 15 min at r.t., the alkyl halide (1 mmol) is added. The mixture is stirred for 30–60 min, poured into ice/water (40 mL) and extracted with Et_2O (3 × 30 mL). The organic phase is dried (Na_2SO_4), the solvent is evaporated at reduced pressure, and the residual violet oil is chromatographed on a silica gel column (80 × 3 cm, 250–300 mesh) using petroleum ether (60–90 °C)/EtOAc (5:1, 1000 mL) as the eluent (Table 2).

11-Ethoxycarbonylmethyl-1-thio-6-oxo-3,4,6,11-tetrahydro[1,4,3]thiazaphosphorino[3,4-*b*][1,3,2]benzodiazaphosphorine 12-Oxide (6) and 1,1-Bisspiro{11-ethoxycarbonyl-6-oxo-3,4,6,11-tetrahydro-[1,4,3]thiazaphosphorino[3,4-*b*][1,3,2]benzodiazaphosphorine 12-Oxide} (7):

To a 100 mL 4-necked flask containing **1a** (0.6 g, 1.8 mmol) and anhydrous THF (60 mL) is added NaH (80% suspension in oil, 50 mg, 1.8 mmol) at −10 °C. Stirring the mixture for 1 h at −10 °C produces a dense white precipitate. The mixture is treated with CS_2 (3 mL) dropwise, stirred 1 h at r.t. till the solids disappear. The mixture is then refluxed for 10 h, cooled, poured into ice/water (50 mL) and extracted with EtOAc (3 × 40 mL). The combined organic extracts are dried (Na_2SO_4) and the solvent is removed under reduced pressure to obtain a violet oil, which is chromatographed on a silica gel column (80 × 3.5 cm, 250–300 mesh) using petroleum ether (60–90 °C)/EtOAc (2:1, 1.5 L) as the eluent. By evaporating the solvent under reduced pressure from the appropriate fractions, the products **6** and **7** are obtained. **6**; yield: 25%; mp 279–280 °C.

$C_{14}H_{15}N_2O_4PS_2$	calc.	C 45.41	H 4.05	N 7.57
(370.4)	found	45.69	4.32	7.34

IR (KBr): ν = 1750 (C=O), 1320 (P–C), 1240 (P=O), 690 cm^{-1} (P–N).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.16 (t, 3 H, J = 5 Hz, CH_3), 2.4, 4.0 (dd, 2 H, $J_{gem\ Ha,e}$ = 16.18 Hz, SCH_2), 3.17, 5.0 (dt, 2 H, $J_{gem\ Ha,e}$ = 11.59 Hz, $SCH_2C\underline{H}_2$), 4.0 (m, 2 H, OCH_2), 4.6, 5.3 (dq, 2 H, $J_{gem\ H,H}$ = 8.39 Hz, $J_{P,H}$ = 8.97, 18.31, 18.61 Hz, $PhNC\underline{H}_2$), 6.75–8.2 (m, 4 H_{arom}).

^{31}P-NMR ($CDCl_3$/H_3PO_4): δ = 10.26.

MS (70 eV): m/z (%) = 370 (M^+, 5).

7; yield: 27%; mp 281–282 °C.

$C_{27}H_{30}N_4O_8P_2S_2$	calc.	C 48.87	H 4.52	N 8.45
(664.3)	found	49.06	4.79	8.75

IR (KBr): ν = 1750 (C=O), 1320 (P–C), 1240 (P=O), 690 cm^{-1} (P–N).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.16 (t, 6 H, J = 5, CH_3), 2.4 (d, 2 H, $J_{gem\ Ha,e}$ = 14.4 Hz, SCH*a*), 3.16 (t, 2 H, $J_{gem\ Ha,e}$ = $J_{P,Ha}$ = 10.8 Hz, $SCH_2C\underline{H}a$), 3.9–54 (m, 12 H, SCH*e*, $SCH_2C\underline{H}e$, OCH_2, $PhNC\underline{H}_2$), 6.9–8.2 (m, 8 H, C_6H_4).

^{13}C-NMR ($CDCl_3$/TMS): δ = 13.97 (CH_3), 25.35 (d, $^2J_{PC}$ = 4.88 Hz, $SCH_2C\underline{H}_2$), 45.5 (SCH_2), 46.69 ($PLN\underline{C}H_2$), 59.80 (t, $^1J_{PC}$ = 125 Hz, PCP), 61.64 (OCH_2), 115.06, 117.98, 122.86, 131.1, 134.99, 141.82 (C_6H_4), 126.84 (CO_2), 168.26 (C=O).

^{31}P-NMR ($CDCl_3$/H_3PO_4): δ = 11.79.

MS (70 eV): m/z (%) = 664 (M^+, 100).

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(2) Further data on the X-ray analysis of **3a** can be obtained from the authors.
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