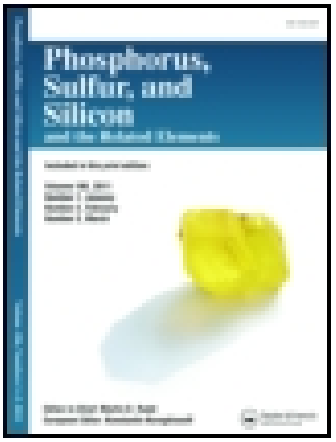

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

PREPARATION OF N-PHOSPHORYLATED NITROGEN MUSTARDS WITH THE BENZODIAZA- AND OXAZAPHOSPHORINONE RING SYSTEMS;HYDROLYSIS OF 2-CHLORO BENZODIAZAPHOSPHORINONES

Ion Neda [a] , Ralf Sonnenburg [a] , Axel Fischer [a] , Peter G. Jones [a] & Reinhard Schmutzler [a]

[a] Institut für Anorganische und Analytische Chemie der Technischen Universität , Postfach 3329, D-38023, Braunschweig, Germany

Published online: 04 Oct 2006.

To cite this article: Ion Neda , Ralf Sonnenburg , Axel Fischer , Peter G. Jones & Reinhard Schmutzler (1996) PREPARATION OF N-PHOSPHORYLATED NITROGEN MUSTARDS WITH THE BENZODIAZA- AND OXAZAPHOSPHORINONE RING SYSTEMS;HYDROLYSIS OF 2-CHLORO BENZODIAZAPHOSPHORINONES, Phosphorus, Sulfur, and Silicon and the Related Elements, 113:1-4, 287-294, DOI: 10.1080/10426509608046400

To link to this article: http://dx.doi.org/10.1080/10426509608046400

Phosphorus, Sulfur, and Silicon, 1996, Vol. 113, pp. 287–294
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PREPARATION OF N-PHOSPHORYLATED NITROGEN MUSTARDS WITH THE BENZODIAZA- AND OXAZAPHOSPHORINONE RING SYSTEMS; HYDROLYSIS OF 2-CHLORO BENZODIAZAPHOSPHORINONES

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Institut für Anorganische und Analytische Chemie der Technischen Universität, Postfach 3329, D-38023 Braunschweig, Germany

(Received February 13, 1996)

The reaction of N-*p*-ethoxyphenylanthranilic acid **1** with phosphorus trichloride furnished the 2-chloro-1,3,2-benzoxazaphosphorin-6-one **2**, which was allowed to react with bis-(2-chloroethyl)amine hydrochloride to form **3** by substitution at phosphorus. Treatment of **3** and the previously known N-*p*-fluorobenzyl-, N-*p*-chlorobenzyl- and N-*o*-chlorobenzyl-substituted 1,3,2-benzodiazaphosphorin-4-ones **4–6** with the hydrogen peroxide/urea 1:1 adduct led to the phosphoryl species **7–10**. The phosphoryl derivatives **14–16** were obtained by hydrolysis of the previously known λ^3P-chloro derivatives **11–13** with small amounts of water. For the N-*p*-fluorobenzyl substituted compound **14** a single crystal X-ray structure determination showed a weak intermolecular P—H···O contact.

Key words: 2-Chloro-3-*p*-ethoxyphenyl-4,5-benzo-1,3,2-oxazaphosphorin-6-one, 2-bis(2-chloroethyl)-amino-3-*p*-ethoxyphenyl-4,5-benzo-1,3,2-oxazaphosphorin-6-one, 2-bis(2-chloroethyl)amino-4,5-benzo-1,3,2-oxazaphosphorin-6-on-2-oxide, 2-bis(2-chloroethyl)amino-5,6-benzo-1,3,2-diazaphosphorin-4-on-2-oxides, 2-hydro-1,3,2-diazaphosphorin-4-on-2-oxides, x-ray analysis.

INTRODUCTION

Phosphoric amides containing bis-(2-chloroethyl)amino or 2-chloroethylamino groups (nitrogen mustards) exhibit biological activity and are therefore of interest as cytostatic agents. The alkylating activity of nitrogen mustards is attributed to the high mobility of the chlorine atom, which leads to the cyclisation of the 2-chloroethylamino group with formation of aziridinium derivatives.[1] Cyclophosphamide (Figure 1) is a typical and frequently employed alkylating agent used in antitumor chemotherapy.[2,3] The "cross-linking" of cellular nucleophilic centers (Figure 1) leads to the inhibition of cellular growth.[4,5] The blocking of DNA also causes healthy cells with high proliferation rates, such as bone-marrow, hair and germ-cells, to be attacked. Further side-effects result from toxic degradation products (4-hydroxycyclophosphamide, acrolein) of the known activation process of cyclophosphamide.[6]

By synthesizing new bis-(2-chloroethyl)amino-substituted phosphorus-containing heterocycles we hope to prepare cytostatic agents of higher specific activity and lower toxicity of their degradation products, because the annelation of the benzene ring to the oxaza- and diazaphosphorinone rings makes the formation of acrolein impossible.

Further, the hydrolysis of λ^3P-chlorodiazaphosphorinones to λ^4P-hydrodiazaphosphorinone oxides is described.

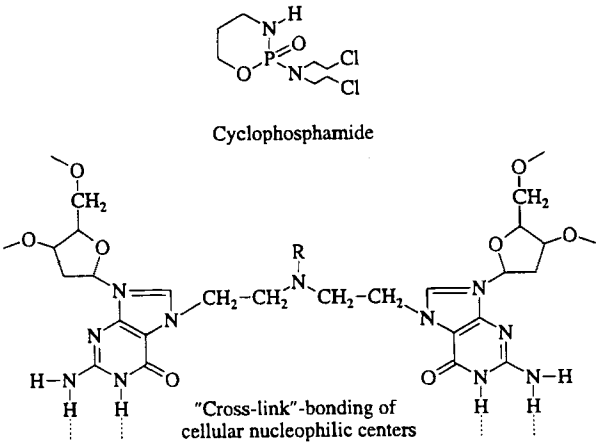
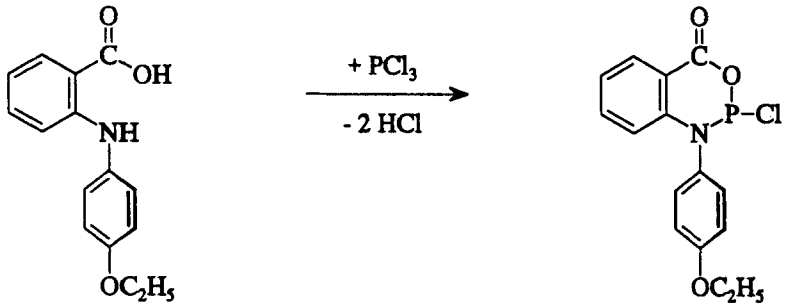


FIGURE 1

RESULTS AND DISCUSSION

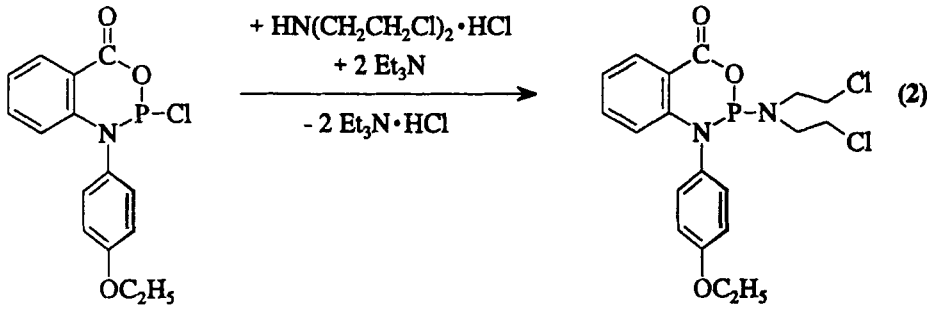
Anthranilic acid and its N-substituted derivatives are known to react with phosphorus trichloride to form bicyclic benzoxazaphosphorin-4-ones.[7-10] The λ^3P-derivatives could be isolated if air and moisture were excluded.[11-14] Thus, the P-chlorooxazaphosphorinone **2** was obtained in good yield by reaction of N-*p*-ethoxyphenylanthranilic acid with PCl_3 (Equation 1). Because of the low basicity of the N-atom it was not necessary to use an auxiliary base. The HCl formed during the reaction was simply bled off by refluxing the reaction mixture.



(1)

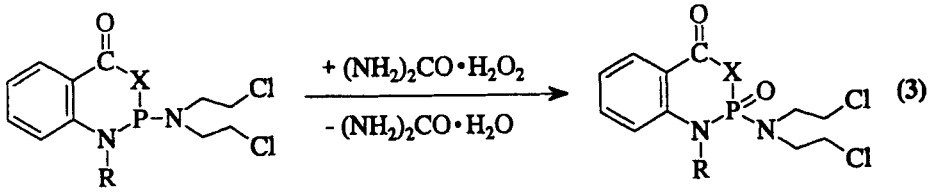
1 **2**

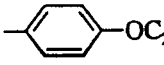
Halogen substitution of phosphorinones with amines has previously been described.[11,14-16] Treatment of **2** with bis-(2-chloroethyl)amine hydrochloride in the presence of triethylamine led to **3** (Equation 2). Because of the instability of bis-(2-chloroethyl)amine it was released from its hydrochloride during the reaction by slow addition of triethylamine at 0°C. Compound **3** was separated from triethylammonium chloride by extraction with diethyl ether.

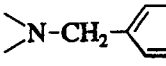


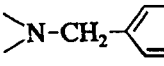
2 **3**

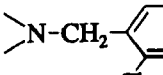
Compounds **3–6** were allowed to react with the hydrogen peroxide/urea 1:1 adduct, a well known reagent for the oxidation of phosphorus(III) compounds in the absence of water,[17,18] to form the phosphoryl species **7–10** (Equation 3). Typical high-field shifts were observed in the ^{31}P-NMR-spectra of **7–10**.

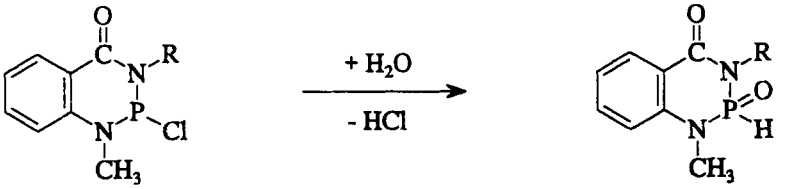


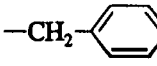
3 R =  , X = O **7**

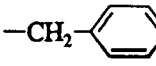
4 R = CH_3 , X =  **8**

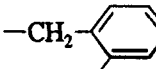
5 R = CH_3 , X =  **9**

6 R = CH_3 , X =  **10**



11 R =  **14**

12 R =  **15**

13 R =  **16**

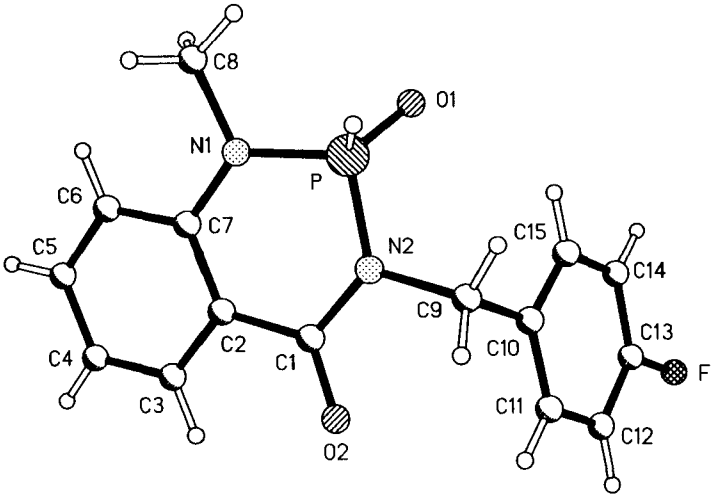


FIGURE 2 The molecule of compound **14** in the crystal. Radii are arbitrary.

The phosphoryl derivatives **14–16** were obtained by hydrolysis of the λ^3P-chloro derivatives **11–13**[21] with small amounts of water in diethyl ether (Equation 4).[7,19] The identity of **14–16** was established by NMR spectroscopy (^{1}H, ^{13}C, ^{19}F (where applicable), and ^{31}P). In the ^{1}H- and ^{31}P-NMR spectra ^1J(PH) coupling constants between 644.2–652.4 Hz were observed. The structure of the N-*p*-fluorobenzyl substituted compound **14** was confirmed by a single crystal X-ray structure determination.

X-RAY CRYSTAL STRUCTURE DETERMINATION OF **14**

The heterocycle is almost planar (mean deviation 6 pm); however, a more accurate description is that P, N2, C1 and C7 are coplanar within 1 pm, with N1 18 pm above and C2 10 pm below this plane. The phosphorus atom possesses the expected distorted tetrahedral configuration; the exocyclic angle O1—P—N1 [116.63(7)°] represents the largest and the endocyclic angle [103.00(6)°] the smallest value. The bond lengths at phosphorus are in the usual range [P—O1 146.87(11) pm, P—N1 164.68(13) pm, P—N2 166.89(13) pm]. The *p*-fluorophenyl group shows an interplanar angle of 72° with respect to the plane of N1, N2, C1, C2 and C7. Loose centrosymmetric dimers are formed via weak P—H···O contacts [P—H0···O1 (at 1-x, 1-y, 1-z) 121(1)°, P···O1 346.8(1) pm, H0···O1 262.1(17) pm, P···H0 128.4(17) pm] (Figure 2).

EXPERIMENTAL

All experiments were carried out with exclusion of air and moisture; solvents were purified and dried according to the usual methods.[20] "In vacuo" (i. v.) refers to a pressure of 0.1 mm Hg at 25°C.

NMR spectra were recorded on a Bruker AC 200 spectrometer at 200.1 MHz (^{1}H), 50.3 MHz (^{13}C), 188.3 MHz (^{19}F), and 81.0 MHz (^{31}P). Chemical shifts δ are given relative to $Si(CH_3)_4$, (TMS) (^{1}H, ^{13}C);

$CFCl_3$ (^{19}F); 85% H_3PO_4 (^{31}P). High-field shifts were given negative, low-field shifts positive signs. MS: Finnigan MAT 8430.

Elemental analyses: Analytisches Laboratorium des Instituts für Anorganische und Analytische Chemie der Technischen Universität, Braunschweig.

Compounds **4–6** and **11–13** were prepared according to Reference 21.

2-Chloro-3-p-ethoxyphenyl-4,5-benzo-1,3,2-oxazaphosphorin-6-one (**2**). 5.0 g (19.4 mmol) **1** were dissolved in 50 ml of anhydrous toluene. PCl_3 (2.7 g; 19.7 mmol) was added and the mixture was refluxed for 5 h. After removing the solvent and volatile components i. v. **2** was left as a colourless oil. Yield: 4.7 g (75.6%); b.p.: >200°C (0.1 mm Hg).

$C_{15}H_{13}ClNO_3P$ (321.70); calc.: C 56.00; H 4.07; N 4.35; found: C 55.42; H 3.90; N 4.76.—^{1}H-NMR ($CDCl_3$): δ = 1.40 (t, 3 H, ^3J(HH) = 7.0 Hz, $CH_2\underline{CH_3}$); 4.07 (q, 2 H, ^3J(HH) = 7.0 Hz, $C\underline{H_2}CH_3$); 6.30–6.41, 6.75–7.29, 7.71–8.03 (3 m, 8 H, $\underline{H}_{Ar}$).—^{13}C-NMR ($CDCl_3$): δ = 14.81 (s, $CH_2\underline{C}H_3$); 62.97 (s, $\underline{C}H_2CH_3$); 109.49–145.88 (11 s, $\underline{C}_{Ar}$); 156.62 (s, $\underline{C}_{Ar}OCH_2CH_3$); 161.49 (d, ^2J(PC) = 13.1 Hz, PO$\underline{C}$(:O)).—^{31}P-NMR ($CDCl_3$): δ = 135.33 (s).—EI-MS: m/z (%): 321 (8) $[M]^+$; 286 (25) $[M—Cl]^+$; 276 (12) $[M—OCH_2CH_3]^+$; 200 (26) $[M—C_6H_4OCH_2CH_3]^+$; 121 (100) $[C_6H_4OCH_2CH_3]^+$.

2-Bis(2-chloroethyl)amino-3-p-ethoxyphenyl-4,5-benzo-1,3,2-oxazaphosphorin-6-one (**3**). A solution of 2.2 g (22.0 mmol) of triethylamine in 30 ml of dichloromethane was added dropwise at 0°C over 0.5 h to a solution of 3.5 g (10.9 mmol) **2** and 1.3 g (10.9 mmol) of bis(2-chloroethyl)amine hydrochloride in 70 ml of dichloromethane. After stirring for 3 h at room temperature the solvent and volatile components were removed i. v. The residue was extracted with 100 ml of diethyl ether, and triethyl-ammonium chloride was filtered off. After removing the diethyl ether i. v. **3** was left as a colourless solid. Yield: 2.5 g (53.4%); m.p.: 55°C.

$C_{19}H_{21}Cl_2N_2O_3P$ (427.27); calc.: C 53.41; H 4.95; N 6.55; found: C 54.47; H 5.05; N 6.25.—^{1}H-NMR ($CDCl_3$): δ = 1.36 (t, 3H, ^3J(HH) = 6.9 Hz, $CH_2\underline{CH_3}$); 3.16–3.40 (m, 8 H, $PN(\underline{CH_2}\underline{CH_2}Cl)_2$); 3.99 (q, 2 H, ^3J(HH) = 6.9 Hz, $C\underline{H_2}CH_3$); 6.35–6.47, 6.78–7.33, 7.75–7.98 (3 m, 8 H, $\underline{H}_{Ar}$).—^{13}C-NMR ($CDCl_3$): δ = 14.72 (s, $CH_2\underline{C}H_3$); 41.90 (d, ^3J(PC) = 3.3 Hz, $PN(CH_2\underline{C}H_2Cl)_2$); 48.86 (d, ^2J(PC) = 19.5 Hz, $PN(\underline{C}H_2CH_2Cl)_2$); 63.75 (s, $\underline{C}H_2CH_3$); 112.14–135.67 (10 s, $\underline{C}_{Ar}$); 148.10 (d, ^2J(PC) = 3.4 Hz, $PN\underline{C}_{Ar}$); 158.67 (s, $\underline{C}_{Ar}OCH_2CH_3$); 159.74 (d, ^2J(PC) = 12.5 Hz, $PO\underline{C}$(:O)).—^{31}P-NMR ($CDCl_3$): δ = 116.28 (s).—EI-MS: m/z (%): 426 (4) $[M]^+$; 286 (12) $[M—N(CH_2CH_2Cl)_2]^+$; 239 (100) $[M—OPN(CH_2CH_2Cl)_2]^+$; 211 (82) $[M—C(:O)OPN(CH_2CH_2Cl)_2]^+$; 182 (22) $[M—C(:O)OPN(CH_2CH_2Cl)—C_2H_5]^+$.

2-Bis(2-chloroethyl)amino-4,5-benzo-1,3,2-oxazaphosphorin-6-on-2-oxide (**7**) *and 2-Bis(2-chloroethyl)-amino-5,6-benzo-1,3,2-diazaphosphorin-4-on-2-oxides* (**8–10**); *(general method)*. Hydrogen peroxide/urea 1:1 adduct (0.78 g; 10 mmol) was added to solutions of 5 mmol (2.1 g **3**, 2.1 g **4**, 2.2 g **5**, 2.2 g **6**) in 50 ml of dichloromethane. After stirring for 1 d at room temperature the mixtures were filtered, and from the filtrates the solvent and other volatiles were removed i. v. The residues were dissolved in 20 ml of diethyl ether and left overnight at −20°C. The precipitates were filtered off and dried i. v.

(**7**). Yield: 1.6 g (72.2%); m.p.: 45°C.
$C_{19}H_{21}Cl_2N_2O_4P$ (443.26); calc.: C 51.48; H 4.78; N 6.31; found: C 53.34; H 4.87; N 6.77.—^{1}H-NMR ($CDCl_3$): δ = 1.35 (t, 3 H, ^3J(HH) = 7.0 Hz, $CH_2C\underline{H_3}$); 3.04–3.52 (m, 8 H, $PN(C\underline{H_2}C\underline{H_2}Cl)_2$); 3.98 (q, 2 H, ^3J(HH) = 7.0 Hz, $C\underline{H_2}CH_3$); 6.36–6.47, 6.74–7.37, 7.98–8.03 (3 m, 8 H, $\underline{H}_{Ar}$).—^{13}C-NMR ($CDCl_3$): δ = 14.70 (s, $CH_2\underline{C}H_3$); 41.18 (s, $PN(CH_2\underline{C}H_2Cl)_2$); 48.98 (d, ^2J(PC) = 12.8 Hz, $PN(\underline{C}H_2CH_2Cl)_2$); 64.00 (s, $\underline{C}H_2CH_3$); 111.83–146.96 (11 s, $\underline{C}_{Ar}$); 157.49 (d, ^2J(PC) = 3.4 Hz, $PO\underline{C}$(:O)); 159.74 (s, $\underline{C}_{Ar}OCH_2CH_3$).—^{31}P-NMR ($CDCl_3$): δ = 2.33 (s).—EI-MS: m/z (%): 442 (8) $[M]^+$; 393 (6) $[M—CH_2Cl]^+$; 302 (6) $[M—N(CH_2CH_2Cl)_2]^+$; 257 (62) $[M—N(CH_2CH_2Cl)_2—OC_2H_5]^+$; 239 (58) $[M—OP(:O)N(CH_2CH_2Cl)_2]^+$; 211 (100) $[M—C(:O)OP(:O)N(CH_2CH_2Cl)_2]^+$; 182 (48) $[M—C(:O)-OP(:O)N(CH_2CH_2Cl)_2—C_2H_5]^+$.

(**8**). Yield: 1.4 g (63.0%); m.p.: 55°C.
$C_{19}H_{21}Cl_2FN_3O_2P$ (444.27); calc.: C 51.37; H 4.76; N 9.46; found: C 51.27; H 4.89; N 9.32.—^{1}H-NMR ($CDCl_3$): δ = 3.16–3.32 (m, 4 H, $PN(C\underline{H_2}CH_2Cl)_2$); 3.25 (d, 3 H, ^3J(PH) = 8.0 Hz, $PNC\underline{H_3}$); 3.51 (t, 4 H, ^3J(HH) = 6.3 Hz, $PN(CH_2C\underline{H_2}Cl)_2$); 4.81–4.91 (m, 2 H, $PNC\underline{H_2}$); 6.93–7.12, 7.51–7.58, 8.16–8.21 (3 m, 8 H, $\underline{H}_{Ar}$).—^{13}C-NMR ($CDCl_3$): δ = 30.19 (d, ^2J(PC) = 4.2 Hz, $PN\underline{C}H_3$); 42.05 (s, $PN(CH_2\underline{C}H_2Cl)_2$); 44.48 (d, ^2J(PC) = 3.8 Hz, $PN\underline{C}H_2$); 49.62 (d, ^2J(PC) = 4.9 Hz, $PN(\underline{C}H_2CH_2Cl)_2$); 112.86–135.10 (10 s, $\underline{C}_{Ar}$); 142.27 (d, ^2J(PC) = 6.2 Hz, $PN\underline{C}_{Ar}$); 162.14 (d, ^1J(CF) = 246.1 Hz, $\underline{C}_{Ar}F$); 163.62 (d, ^2J(PC) = 3.8 Hz, $PN\underline{C}$(:O)).—^{31}P-NMR ($CDCl_3$): δ = 9.69 (s).—^{19}F-NMR ($CDCl_3$): δ = −115.44 (s).—EI-MS: m/z (%): 443 (22) $[M]^+$; 394 (22) $[M—CH_2Cl]^+$; 303 (26) $[M—N(CH_2CH_2Cl)_2]^+$; 132 (8) $[(C_6H_4)C(:O)NCH_2]^+$; 109 (100) $[CH_2C_6H_4F]^+$.

(**9**). Yield: 1.3 g (56.4%); m.p.: 62°C.
$C_{19}H_{21}Cl_3N_3O_2P$ (460.73); calc.: C 49.53; H 4.59; N 9.12; found: C 50.28; H 4.63; N 8.95.—^{1}H-NMR ($CDCl_3$): δ = 3.02–3.32 (m, 4 H, $PN(C\underline{H}_2CH_2Cl)_2$); 3.21 (d, 3 H, ^3J(PH) = 8.1 Hz, $PNC\underline{H}_3$); 3.48 (t, 4 H, ^3J(HH) = 6.0 Hz, $PN(CH_2C\underline{H}_2Cl)_2$); 4.68–4.96 (m, 2 H, $PNC\underline{H}_2$); 6.92–7.54, 8.08–8.19 (2 m, 8 H, $\underline{H}_{Ar}$).—^{13}C-NMR ($CDCl_3$): δ = 30.43 (d, ^2J(PC) = 4.1 Hz, $PN\underline{C}H_3$); 42.30 (s, $PN(CH_2\underline{C}H_2Cl)_2$); 44.79 (d, ^2J(PC) = 3.7 Hz, $PN\underline{C}H_2$); 49.86 (d, ^2J(PC) = 4.8 Hz, $PN(\underline{C}H_2CH_2Cl)_2$); 113.09–135.36 (11 s, $\underline{C}_{Ar}$); 142.50 (d, ^2J(PC) = 6.0 Hz, $PN\underline{C}_{Ar}$); 163.83 (d, ^2J(PC) = 3.6 Hz, $PN\underline{C}(:O)$).—^{31}P-NMR ($CDCl_3$): δ = 9.69 (s).—EI-MS: m/z (%): 459 (24) $[M]^+$; 424 (8) $[M—Cl]^+$; 410 (22) $[M—CH_2Cl]^+$; 319 (28) $[M—N(CH_2CH_2Cl)_2]^+$; 285 (10) $[M—CH_2C_6H_4Cl—CH_2Cl]^+$; 125 (100) $[CH_2C_6H_4Cl]^+$; 104 (12) $[(C_6H_4)C(:O)]^+$.

(**10**). Yield: 1.6 g (69.5%); m.p.: 144°C.
$C_{19}H_{21}Cl_3N_3O_2P$ (460.73); calc.: C 49.53; H 4.59; N 9.12; found: C 49.30; H 4.56; N 9.17.—^{1}H-NMR ($CDCl_3$): δ = 3.21–3.38 (m, 4 H, $PN(C\underline{H}_2CH_2Cl)_2$); 3.27 (d, 3 H, ^3J(PH) = 8.1 Hz, $PNC\underline{H}_3$); 3.53 (t, 4 H, ^3J(HH) = 6.8 Hz, $PN(CH_2C\underline{H}_2Cl)_2$); 4.69–4.81, 5.22–5.35 (2 m, 2 H, $PNC\underline{H}_2$); 7.02–7.36, 7.55–7.63, 8.19–8.24 (3 m, 8 H, $\underline{H}_{Ar}$).—^{13}C-NMR ($CDCl_3$): δ = 30.34 (d, ^2J(PC) = 4.2 Hz, $PN\underline{C}H_3$); 42.10 (s, $PN(CH_2\underline{C}H_2Cl)_2$); 42.41 (d, ^2J(PC) = 4.0 Hz, $PN\underline{C}H_2$); 49.66 (d, ^2J(PC) = 4.8 Hz, $PN(\underline{C}H_2CH_2Cl)_2$); 113.01–135.27 (11 s, $\underline{C}_{Ar}$); 142.45 (d, ^2J(PC) = 6.0 Hz, $PN\underline{C}_{Ar}$); 163.56 (d, ^2J(PC) = 3.6 Hz, $PN\underline{C}(:O)$).—^{31}P-NMR ($CDCl_3$): δ = 9.67 (s).—EI-MS: m/z (%): 459 (1.6) $[M]^+$; 424 (100) $[M—Cl]^+$; 319 (28) $[M—N(CH_2CH_2Cl)_2]^+$; 285 (12) $[M—CH_2C_6H_4Cl—CH_2Cl]^+$; 125 (58) $[CH_2C_6H_4Cl]^+$; 104 (10) $[C_6H_4C(:O)]^+$.

2-Hydro-1,3,2-diazaphosphorin-4-on-2-oxides (**14**–**16**); *(general method).* Water (0.3 ml; 16.6 mmol) was added to solutions of 10 mmol (2.9 g **11**, 3.0 g **12**, 3.0 g **13**) in 50 ml of diethyl ether and the mixture stirred for 1 d. The precipitates were filtered off, washed three times with 10 ml of diethyl ether and dried i. v.

(**14**). Yield: 1.9 g (62.4%); m.p.: 75°C.
$C_{15}H_{14}FN_2O_2P$ (304.26); calc.: C 59.21; H 4.63; N 9.20; found: C 58.83; H 4.90; N 9.05.—^{1}H-NMR ($CDCl_3$): δ = 3.18 (d, 3 H, ^3J(PH) = 9.2 Hz, $PNC\underline{H}_3$); 4.65–5.12 (m, 2 H, $PNC\underline{H}_2$); 6.88–7.07, 7.31–7.53, 8.07–8.12 (3 m, 8 H, $\underline{H}_{Ar}$); 7.69 (d, 1 H, ^1J(PH) = 644.2 Hz, $P\underline{H}$).—^{13}C-NMR ($CDCl_3$): δ = 30.89 (d, ^2J(PC) = 6.8 Hz, $PN\underline{C}H_3$); 44.60 (d, ^2J(PC) = 5.5 Hz, $PN\underline{C}H_2$); 113.69–135.08 (10 s, $\underline{C}_{Ar}$); 141.37 (d, ^2J(PC) = 4.4 Hz, $PN\underline{C}_{Ar}$); 162.36 (d, ^1J(CF) = 246.7 Hz, $\underline{C}_{Ar}F$); 162.74 (d, ^2J(PC) = 3.3 Hz, $PN\underline{C}(:O)$).—^{19}F-NMR ($CDCl_3$): δ = −114.53 (s).—^{31}P-NMR ($CDCl_3$): δ = 3.57 (s).—EI-MS: m/z (%): 304 (8) $[M]^+$; 285 (6) $[M—F]^+$; 151 (100) $[C(:O)NCH_2C_6H_4F]^+$; 133 (28) $[C(:O)C_6H_4NCH_3]^+$; 105 (78) $[C_6H_4NCH_3]^+$.

(**15**). Yield: 1.6 g (49.9%); m.p.: 98°C.
$C_{15}H_{14}ClN_2O_2P$ (320.71); calc.: C 56.17; H 4.40; N 8.73; found: C 56.91; H 4.87; N 9.13.—^{1}H-NMR ($CDCl_3$): δ = 3.24 (d, 3 H, ^3J(PH) = 9.3 Hz, $PNC\underline{H}_3$); 4.72–5.17 (m, 2 H, $PNC\underline{H}_2$); 6.95–7.76, 8.13–8.18 (2 m, 8 H, $\underline{H}_{Ar}$); 7.76 (d, 1 H, ^1J(PH) = 644.3 Hz, $P\underline{H}$).—^{13}C-NMR ($CDCl_3$): δ = 31.03 (d, ^2J(PC) = 6.7 Hz, $PN\underline{C}H_3$); 44.65 (d, ^2J(PC) = 5.7 Hz, $PN\underline{C}H_2$); 112.14–142.18 (11 s, $\underline{C}_{Ar}$); 141.53 (d, ^2J(PC) = 4.1 Hz, $PN\underline{C}_{Ar}$); 161.95 (d, ^2J(PC) = 3.7 Hz, $PN\underline{C}(:O)$).—^{31}P-NMR ($CDCl_3$): δ = 3.64 (s).—EI-MS: m/z (%): 320 (28) $[M]^+$; 303 (42) $[M—OH]^+$; 133 (28) $[H_3CNC_6H_4C(:O)]^+$; 125 (100) $[CH_2C_6H_4Cl]$; 105 (76) $[C_6H_4NCH_3]^+$.

(**16**). Yield: 1.7 g (53.0%); m.p.: 105°C.
$C_{15}H_{14}ClN_2O_2P$ (320.71); calc.: C 56.17; H 4.40; N 8.73; found: C 54.97; H 4.08; N 8.30.—^{1}H-NMR ($CDCl_3$): δ = 3.23 (d, 3 H, ^3J(PH) = 9.2 Hz, $PNC\underline{H}_3$); 4.94–5.23 (m, 2 H, $PNC\underline{H}_2$); 6.97–7.67, 8.15–8.33 (2 m, 8 H, $\underline{H}_{Ar}$); 7.83 (d, 1 H, ^1J(PH) = 652.4 Hz, $P\underline{H}$).—^{13}C-NMR ($CDCl_3$): δ = 31.25 (d, ^2J(PC) = 7.3 Hz, $PN\underline{C}H_3$); 43.26 (d, ^2J(PC) = 5.9 Hz, $PN\underline{C}H_2$); 113.69–135.14 (11 s, $\underline{C}_{Ar}$); 141.60 (d, ^2J(PC) = 3.6 Hz, $PN\underline{C}_{Ar}$); 162.84 (d, ^2J(PC) = 4.3 Hz, $PN\underline{C}(:O)$).—^{31}P-NMR ($CDCl_3$): δ = 3.28 (s).—EI-MS: m/z (%): 320 (0.6) $[M]^+$; 303 (100) $[M—OH]^+$; 285 (58) $[M—Cl]^+$; 125 (56) $[CH_2C_6H_4Cl]$.

Crystal Structure Analysis of **14**

Crystal data: $C_{15}H_{14}FN_2O_2P$, M = 304.25, triclinic, space group $P\bar{1}$, a = 729.2(2), b = 974.1(2), c = 1027.9(2) pm, α = 105.03(2)°, β = 92.23(2)°, γ = 94.67(2)°, U = 0.7014(3) nm^3, Z = 2, D_x = 1.441 Mg m^{-3}, λ(MoK$_\alpha$) = 71.073 pm, μ = 0.21 mm^{-1}, F(000) = 316, T = −130°C.

Data collection and reduction: A colourless prism 0.6 × 0.45 × 0.45 mm was mounted on a glass fibre in inert oil and transferred to the cold gas stream of the diffractometer (Stoe STADI-4 with Siemens LT-2 low temperature attachment).

3507 intensities were registered in the 2θ-range of 6–55° (3241 independent reflections, R_{int} = 0.016). The cell constants were refined from $\pm\omega$ angles of 60 reflections in the 2θ range 20–23°.

TABLE I

Selected bond lengths [pm] and angles [°] for **14**

P-O(1)	146.87(11)	P-N(1)	164.68(13)
P-N(2)	166.89(13)	F-C(13)	135.6(2)
O(2)-C(1)	122.2(2)	N(1)-C(7)	139.8(2)
N(1)-C(8)	147.3(2)	N(2)-C(1)	138.6(2)
N(2)-C(9)	148.8(2)	C(1)-C(2)	147.4(2)

O(1)-P-N(1)	116.63(7)	O(1)-P-N(2)	115.79(7)
N(1)-P-N(2)	103.00(6)	C(7)-N(1)-C(8)	119.79(13)
C(7)-N(1)-P	125.45(10)	C(8)-N(1)-P	114.46(10)
C(1)-N(2)-C(9)	116.99(12)	C(1)-N(2)-P	127.47(10)
C(9)-N(2)-P	115.53(10)	O(2)-C(1)-N(2)	119.85(14)
O(2)-C(1)-C(2)	122.28(13)	N(2)-C(1)-C(2)	117.87(12)

TABLE II

Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($pm^2 \times 10^{-1}$) for **14**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij}-tensor

	x	y	z	U(eq)
P	4025.2(5)	3137.5(4)	5336.2(4)	23.9(1)
F	-2436(2)	3807.7(15)	133.0(13)	62.0(4)
O(1)	2979(2)	4397.5(11)	5616.2(11)	31.5(2)
O(2)	2744(2)	-131.9(12)	2331.7(11)	34.6(3)
N(1)	3780(2)	2089.9(13)	6356.0(12)	27.7(3)
N(2)	3597(2)	2004.6(13)	3809.7(12)	24.7(3)
C(1)	2938(2)	574.6(15)	3507.1(15)	25.5(3)
C(2)	2487(2)	-37.3(15)	4638.8(15)	25.1(3)
C(3)	1604(2)	-1423(2)	4321(2)	29.9(3)
C(4)	1155(2)	-2087(2)	5311(2)	34.6(4)
C(5)	1595(2)	-1366(2)	6646(2)	34.9(4)
C(6)	2457(2)	11(2)	6997(2)	31.7(3)
C(7)	2911(2)	699.3(15)	6000.9(15)	25.1(3)
C(8)	4385(3)	2782(2)	7776(2)	38.6(4)
C(9)	3998(2)	2610(2)	2650.9(15)	28.2(3)
C(10)	2284(2)	2940(2)	1963.3(15)	27.9(3)
C(11)	1553(3)	2051(2)	739(2)	37.5(4)
C(12)	-27(3)	2335(2)	104(2)	43.8(4)
C(13)	-868(2)	3526(2)	726(2)	40.6(4)
C(14)	-203(2)	4437(2)	1939(2)	37.5(4)
C(15)	1382(2)	4134(2)	2549(2)	32.0(3)

Structure solution and refinement: The structure was solved by direct methods and was refined anisotropically on F^2 (program system: SHELXL-93, G.M. Sheldrick, Universität Göttingen). The H atom at phosphorus was refined freely. All other H atoms were included using a riding model or rigid methyl groups. The final R(F) value was 0.037, with $wR(F^2) = 0.105$ for all reflections. 195 parameters; $S = 1.1$; max $\Delta/\sigma = 0.001$; max $\Delta\rho = 305$ e. nm^{-3}.

Bond lengths and angles are presented in Table I, atomic coordinates in Table II.

Full details of the structure determination have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Germany, from where this material may be obtained on quoting the full literature citation and the reference number CSD 404760.

ACKNOWLEDGEMENTS

The authors are grateful to ASTA Medica AG, BASF AG, BAYER AG and HOECHST AG for generous gifts of chemicals. The Fonds der Chemischen Industrie is thanked for financial support. Dipl. Chem. Holger Thönnessen assisted in the preparation of the manuscript.

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