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N-PHOSPHORYLATED NITROGEN MUSTARDS; PREPARATION OF 2-CHLOROETHYL- AND BIS(2-CHLOROETHYL)-AMIDES WITH THE BENZODIAZAPHOSPHORINONE RING SYSTEM

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N-PHOSPHORYLATED NITROGEN MUSTARDS; PREPARATION OF 2-CHLOROETHYL- AND BIS(2-CHLOROETHYL)-AMIDES WITH THE BENZODIAZAPHOSPHORINONE RING SYSTEM

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The reaction of isatoic acid anhydride **1** with NaH/BrCH₂CH₂Cl furnished the N-(2-chloroethyl) substituted derivative **2**, which was allowed to react with methylamine to form N-(2-chloroethyl)-N'-methylantranilamide **3**. Treatment of **3** with PCl₃ furnished the 1,3,2-diazaphosphorin-4-one **4**, which reacted with bis(2-chloroethyl) amine hydrochloride to form the P-bis(2-chloroethyl)amino derivative **5** by substitution at phosphorus. Oxidation of **5** with the hydrogen peroxide/urea 1:1 adduct led to the phosphoryl species **6**. The σ^4 P-derivative **7** was formed by hydrolysis of **4** with small amounts of water. Treatment of the P-chloro derivative **8** with (CH₃)₃SiOCH₃ furnished the methoxy-substituted compound **9**, which formed the phosphoryl derivative **10** upon reaction with SO₂Cl₂. The previously known bis(2-chloroethyl)amino-substituted 1,3,2-benzodiazaphosphorin-4-on-2-oxide **11** was synthesized by reaction of **10** with bis(2-chloroethyl)amine hydrochloride/triethylamine. The P-2-chloroethylamino-substituted derivative **12** was obtained by treatment of **8** with 2-chloroethylamine hydrochloride/triethylamine. The structures of **3**, **4** and **5** were confirmed by single crystal X-ray structure determination. In **3** the molecules are linked into chains by hydrogen bonds of the form N-H...O=C between amide groups. The heterocycles of **4** and **5** display half-boat conformation with the P atom out of plane.

Keywords: Anthranilamide; 1,3,2-benzodiazaphosphorinones; 2-chloroethyl substituent; 4-fluorobenzyl substituent; oxidation; hydrolysis; X-ray analysis.

INTRODUCTION

Cyclophosphamide, Ifosfamide and Trofosfamide (Fig. 1) are well known and highly effective alkylating agents used in antitumor chemotherapy.¹⁻³ Therapeu-

* R. Schmutzler, Institut für Anorganische und Analytische Chemie der Technischen Universität, Postfach 3329, D-38023 Braunschweig, Germany. Dedicated to Professor Gottfried Huttner on the occasion of his 60th birthday.

tic side-effects result from toxic degradation products (especially acrolein) of the thoroughly investigated activation pathway of these drugs.^{3,4} Thus, the synthesis of bis(2-chloroethyl)amino- or 2-chloroethylamino-phosphoric amides (phosphorylated nitrogen mustards), bearing a skeleton that renders formation of acrolein impossible, is an important task in preparing cytostatic agents of lower toxicity.

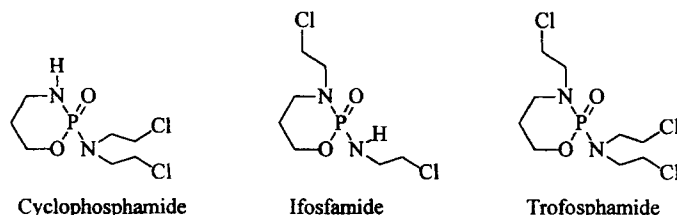


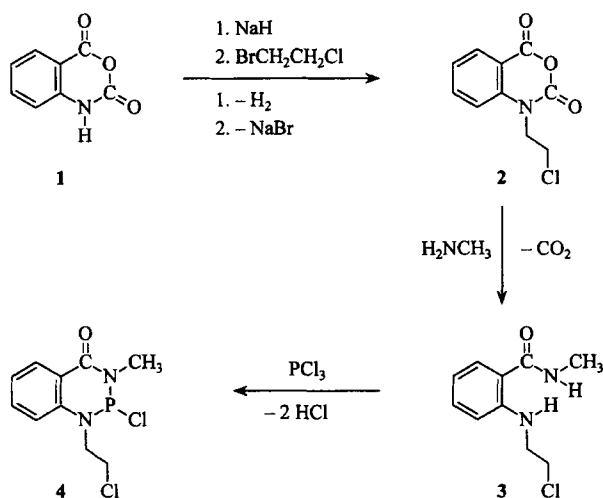
FIGURE 1

In our previously reported investigations we described several 2-bis(2-chloroethyl)amino- and 2-(2-chloroethylamino)-5,6-benzo-1,3,2-diazaphosphorin-4-ones with various substituents at the amido group.⁵⁻⁹ The present paper reports the synthesis of 1-(2-chloroethyl)-substituted 5,6-benzo-1,3,2-diazaphosphorin-4-ones. The preparation of a 2-chloro-5,6-benzo-1,3,2-diazaphosphorin-4-on-2-oxide is also described.

RESULTS AND DISCUSSION

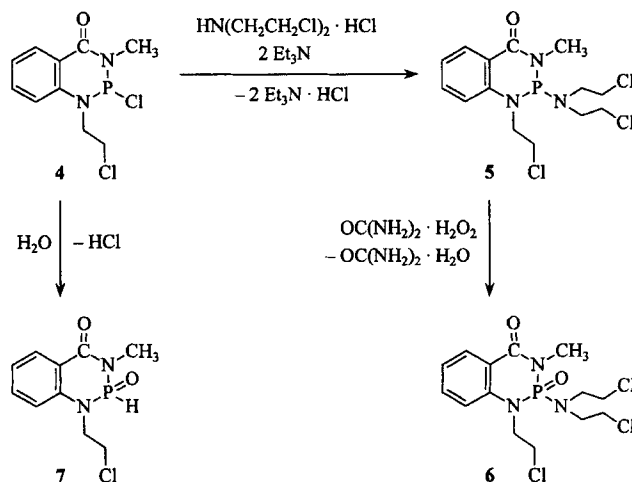
Isatoic acid anhydride is known to form N-substituted derivatives by treatment with sodium hydride and alkyl or aryl halides.¹⁰ Whereas N-(2-bromoethyl)isatoic acid anhydride was synthesized by Hardtmann *et al.* in only 26% yield,¹⁰ the N-(2-chloroethyl)-substituted derivative **2** was now prepared in 63% yield by varying the molar ratio of the starting compounds (Scheme 1). Isatoic acid anhydride and its N-substituted derivatives react with amines to form anthranilamides.¹¹⁻¹³ Thus, N-(2-chloroethyl)-N'-methylantranilamide **3** was obtained in good yield by reaction of **2** with methylamine (Scheme 1). Based on a known synthesis of benzodiazaphosphorinones by treatment of anthranilamides with PCl_3 ,^{5-9,11-15} the P-chloro-benzodiazaphosphorinone **4** was synthesized by refluxing compound **3** with PCl_3 in toluene to drive off the HCl formed during the reaction (Scheme 1). The identity of **4** was established by NMR-spectroscopy, mass spectrometry and a single-crystal X-ray structure determination.

The formation of **5** took place upon reaction of **4** with bis(2-chloroethyl)amine hydrochloride (Scheme 2). Because of the instability of bis(2-chloroethyl)amine



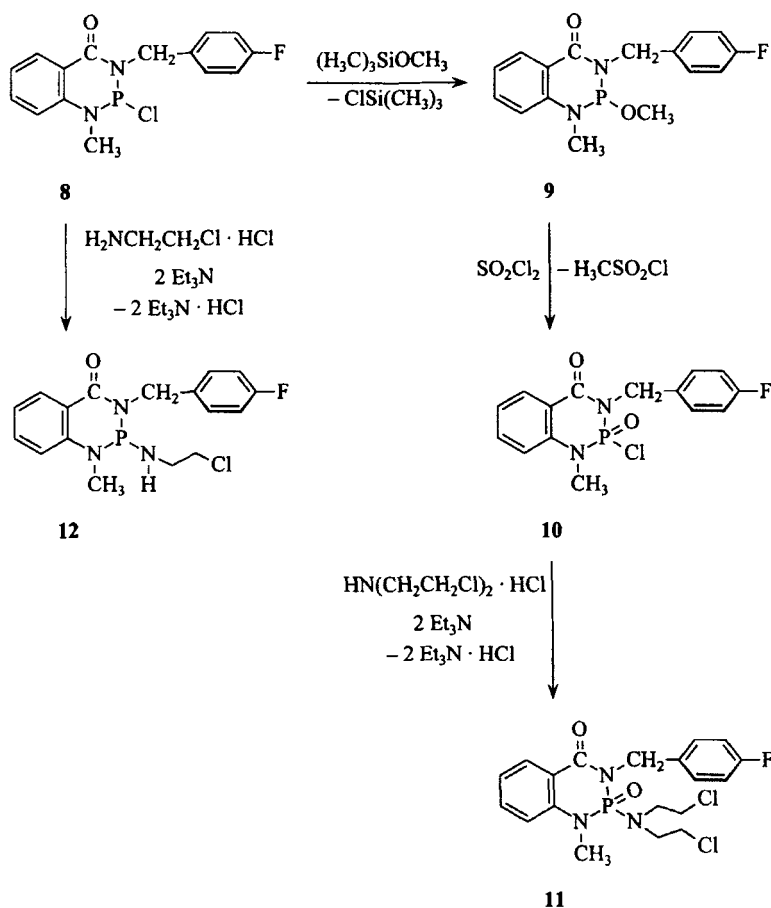
SCHEME 1

at room temperature it was formed from its hydrochloride during the reaction by slow addition of triethylamine. As in the case of **4**, a single-crystal X-ray structure determination confirmed the identity of **5**. The σ^3 -phosphorinone **5** was 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,^{8,16} to form the phosphoryl species **6** (Scheme 2). The phosphoryl derivative **7** was obtained by hydrolysis of the σ^3 P-chloro derivative **4** in diethyl ether with small amounts of water.



SCHEME 2

The preparation of σ^3 P-methoxy derivatives by treatment of phosphorus(III)-halogen compounds with trimethylsilylmethyl ether is a known method.^{17,18} Compound **9** was formed in this reaction in almost quantitative yield (Scheme 3). It was allowed to react with sulfonyl chloride to form the phosphoryl chloride **10** in high yield. Treatment of **10** with bis(2-chloroethyl)amine hydrochloride/triethylamine led to the known compound **11**, which was previously synthesized by the reaction of **8** with bis(2-chloroethyl)amine hydrochloride/triethylamine and subsequent oxidation with the hydrogen peroxide/urea 1:1 adduct in good yield.^{8,9} Compared to **8**, the reactivity of **10** seems to be much lower. Thus **11**, formed as described, was obtained in only 36% yield. Furthermore, **8** was allowed to react with 2-chloroethylamine hydrochloride/triethylamine to form the N-methyl-N'-4-fluorophenyl-substituted σ^3 -phosphorus derivative **12**.



SCHEME 3

X-RAY CRYSTAL STRUCTURE DETERMINATION OF 3

Both nitrogen atoms of compound **3** display a nearly planar coordination with angle sums of 350° (N1) and 359° (N2). N1 lies 22 pm outside of the plane of the α -substituents. The C-N-C angles at the nitrogen atoms [$122.4(2)^\circ$ C7-N1-C8 and $122.2(2)^\circ$ C1-N2-C10] are larger than those involving hydrogen [$113(2)^\circ$ C7-N1-H1, $114(2)^\circ$ C8-N1-H1, $120(2)^\circ$ C1-N2-H2 and $118(2)^\circ$ C10-N2-H2]. The 2-chlorethylamino group displays a staggered configuration with a torsion angle of $56.9(3)^\circ$. The amido group (H2-N2-C1-O) is antiperiplanar configured, the corresponding torsion angle is -177° .

Compound **3** displays intramolecular hydrogen bonds of the form N1-H1...O [N1-H1 84(2) pm; N1...O 273.3(3) pm; H1...O 207(2) pm; N1-H1...O $136(2)^\circ$] and also intermolecular H bonds that link the molecules in chains in the y-direction [N2-H2...O; symmetry operator $1.5-x, -0.5+y, +z$; N2-H2 75(3) pm; N2...O 294.8(3) pm; H1...O 224(3) pm; N2-H2...O $154(3)^\circ$].

X-RAY CRYSTAL STRUCTURE DETERMINATION OF 4 AND 5

The six-membered heterocyclic rings of both compounds show the typical half-boat conformation, in which the phosphorus atoms lie 42.3 pm (**4**) (Fig. 3) or

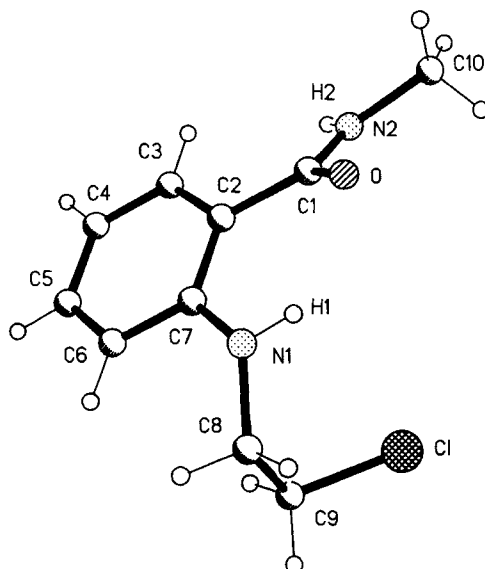


FIGURE 2: The molecule of compound **3** in the crystal. Radii are arbitrary.

45.7 pm (5) (Fig. 4) outside the plane formed by N1, N2, C1, C2 and C7 [mean deviation 2.0 pm (4) and 4.4 pm (5)]. Both phosphorus atoms display a pyramidal configuration and lie 83 pm (4) and 75 pm (5) out of the plane of their α -substituents. The angles at the phosphorus atoms vary for 4 from 99.54(8)° (N2-P-C11) to 101.61(8)° (N1-P-C11) and for 5 from 96.60(13)° (N1-P-N2) to 105.74(13)° (N1-P-N3).

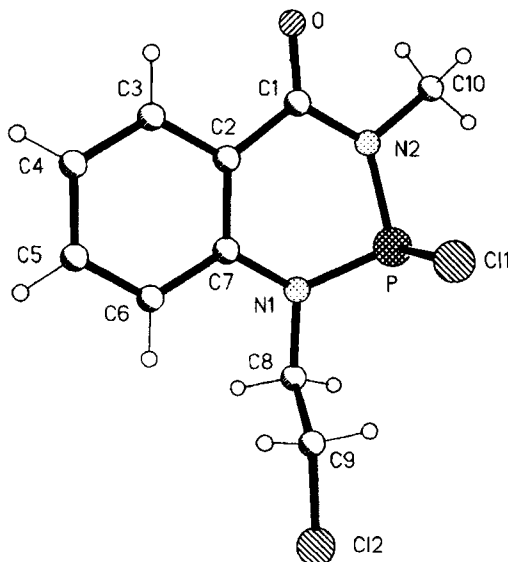


FIGURE 3: The molecule of compound 4 in the crystal. Radii are arbitrary.

Possibly because of the electron-withdrawing chlorine atom Cl1, the P-N bond lengths of 4 [P-N1 166.8(2) pm and P-N2 167.8(2) pm] are significantly shorter than those of 5 [P-N1 170.6(3) pm and P-N2 173.9(3) pm]. All nitrogen atoms display a planar coordination with angle sums between 358.9° and 359.9°.

All 2-chloroethylamino groups display an antiperiplanar configuration, with absolute torsion angles from 169.3° to 179.7°. In compound 4 intermolecular chlorine contacts (C11...Cl2 338.8 pm, symmetry operator of Cl1 1-x, -0.5+y, 0.5-z) are observed.

EXPERIMENTAL

All experiments were carried out with exclusion of air and moisture; solvents were purified and dried according to the usual methods.¹⁹ "In vacuo" (i. v.) refers to a pressure of 0.1 mm Hg at 25°C.

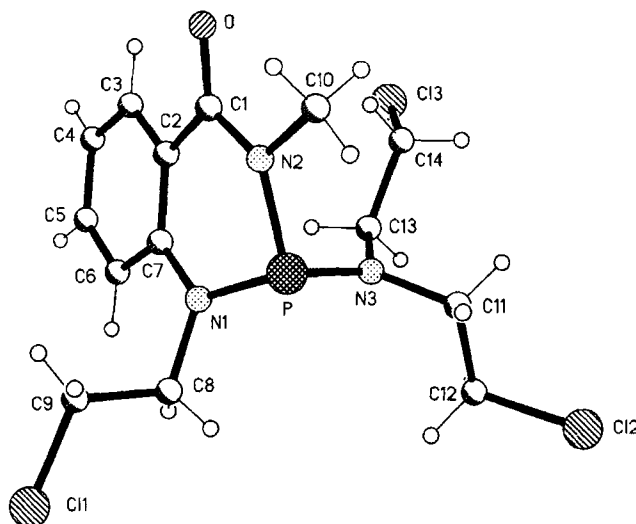


FIGURE 4: The molecule of compound **5** in the crystal. Radii are arbitrary.

NMR spectra were recorded on a Bruker AC 200 spectrometer at 200.1 MHz (^1H), 50.3 MHz (^{13}C), 188.3 MHz (^{19}F), and 81.0 MHz (^{31}P). Chemical shifts (δ) are given, relative to $\text{Si}(\text{CH}_3)_4$ (TMS) (^1H , ^{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.

N-(2-Chloroethyl)isatoic acid anhydride (**2**). To a solution of 10.0 g (61 mmol) of isatoic acid anhydride in 150 ml of dimethylformamide, sodium hydride (2.2 g; 92 mmol) was added in small portions. After the formation of hydrogen ceased, the suspension was stirred for 3 h at room temperature. 1,2-Bromochloroethane (16.5 g; 115 mmol) was added and stirring was continued for 48 h. The reaction mixture was concentrated to one third of its volume and poured onto 150 ml of ice water. The resulting precipitate of **2** was filtered off and dried i. v. Yield: 8.7 g (63.2 %); m.p.: 107°C.

$\text{C}_{10}\text{H}_8\text{ClNO}_3$ (225.63); calc.: C 53.23; H 3.57; N 6.21; found: C 52.80; H 3.53; N 6.53. – ^1H -NMR (CDCl_3): δ = 3.84 (t, 2 H, $^3J(\text{HH})$ = 6.7 Hz, $\text{CH}_2\text{CH}_2\text{Cl}$); 4.40 (t, 2 H, $^3J(\text{HH})$ = 6.7 Hz, $\text{CH}_2\text{CH}_2\text{Cl}$); 7.27–7.36, 7.75–7.82, 8.15–8.19 (3 m, 4 H, H_{Ar}). – ^{13}C -NMR (CDCl_3): δ = 39.38, 45.99 (2 s, $\text{CH}_2\text{CH}_2\text{Cl}$); 111.73–141.23 (6 s, C_{Ar}); 147.72, 157.99 (2 s, $\text{C}(\text{:O})\text{OC}(\text{:O})$). – EI-MS: m/z (%): 225 (12) $[\text{M}]^+$; 181 (10) $[\text{M} - \text{CO}_2]^+$; 146 (27) $[\text{M} - \text{CO}_2 - \text{Cl}]^+$; 132 (100) $[\text{C}(\text{O})\text{C}_6\text{H}_4\text{NCH}_2]^+$; 104 (10) $[\text{C}(\text{O})\text{C}_6\text{H}_4]^+$.

N-(2-Chloroethyl)-*N*'-methylantranilamide (**3**). Methylamine was bubbled for 45 min. through a solution of 8.0 g (35 mmol) of **2** in 200 ml of dioxane. Subsequently the reaction mixture was stirred at room temperature overnight. The solvent and all volatile components were removed i. v. and the viscous residue was dissolved in 100 ml of toluene. The clear solution was separated from insoluble oil, using a syringe. After removing the solvent i. v., **3** was obtained as a pale brown solid. Yield: 5.6 g (75.1 %); m.p.: 61°C.

$C_{10}H_{13}ClN_2O$ (212.68); calc.: C 56.47; H 6.16; N 13.17; found: C 55.65; H 6.29; N 13.01. – 1H -NMR ($CDCl_3$): δ = 2.91 (d, 3 H, $^3J(HH)$ = 4.8 Hz, $NHCH_3$); 3.52 (t, 2H, $^3J(HH)$ = 5.3 Hz, CH_2CH_2Cl); 3.61 – 3.70 (m, 2 H, CH_2CH_2Cl); 6.18 (br., 1 H, $NHCH_2CH_2Cl$); 6.56 – 6.69, 7.24 – 7.34 (2 m, 4 H, H_{Ar}); 7.85 (br., 1 H, $C(=O)NHCH_3$). – ^{13}C -NMR ($CDCl_3$): δ = 26.39 (s, NCH_3); 42.44, 44.49 (2 s, CH_2CH_2Cl); 111.16 – 148.42 (6 s, C_{Ar}); 170.29 (s, $C(=O)$). – EI-MS: m/z (%): 212 (26) $[M]^+$; 177 (10) $[M - Cl]^+$; 132 (100) $[C(O)C_6H_4NCH_2]^+$; 104 (8) $[C(O)C_6H_4]^+$, 91 (9) $[C_6H_4NH]^+$.

2-Chloro-1-(2-chloroethyl)-3-methyl-5,6-benzo-1,3,2-diazaphosphorin-4-one (**4**). 3.2 g (15 mmol) of **3** were dissolved in 70 ml of anhydrous toluene. PCl_3 (2.1 g; 15 mmol) was added and the mixture was refluxed for 5 h. The solvent and volatile components were removed i. v. and the residue was recrystallized from dichloromethane/diethyl ether (1:9) at –20°C. Colourless crystals of **4** were obtained. Yield: 3.2 g (76.8 %); m.p.: 78°C.

$C_{10}H_{11}Cl_2N_2OP$ (277.09); calc.: C 43.35; H 4.00; N 10.11; found: C 44.19; H 4.10; N 10.00. – 1H -NMR ($CDCl_3$): δ = 3.20 (d, 3 H, $^3J(PH)$ = 15.4 Hz, $PNCH_3$); 3.72 (t, 2H, $^3J(HH)$ = 6.4 Hz, CH_2CH_2Cl); 3.95 – 4.16 (m, 2 H, $PNCH_2CH_2Cl$); 6.95 – 7.00, 7.14 – 7.25, 7.50 – 7.50, 8.23 – 8.28 (4 m, 4 H, H_{Ar}). – ^{13}C -NMR ($CDCl_3$): δ = 32.38 (d, $^2J(PC)$ = 37.8 Hz, $PNCH_3$); 40.24 (d, $^3J(PC)$ = 6.9 Hz, $PNCH_2CH_2Cl$); 49.81 (d, $^2J(PC)$ = 41.3 Hz, $PNCH_2CH_2Cl$); 115.16 – 133.94 (5 s, C_{Ar}); 141.57 (d, $^2J(PC)$ = 9.1 Hz, $C_{Ar}NP$); 162.87 (d, $^2J(PC)$ = 7.1 Hz, $PNC(=O)$). – ^{31}P -NMR ($CDCl_3$): δ = 127.77 (s). – EI-MS: m/z (%): 276 (46) $[M]^+$; 241 (100) $[M - Cl]^+$; 227 (33) $[M - CH_2Cl]^+$; 184 (17) $[M - CH_2CH_2Cl - NCH_3]^+$; 146 (12) $[M - Cl - CH_3NPCl]^+$; 132 (82) $[C(O)C_6H_4NCH_2]^+$.

1-(2-Chloroethyl)-2-bis(2-chloroethyl)amino-3-methyl-5,6-benzo-1,3,2-diazaphosphorin-4-one (**5**). A solution of 2.3 g (23.0 mmol) of triethylamine in 30 ml of dichloromethane was added dropwise at 0°C over 0.5 h to a solution of 3.2 g (11.5 mmol) of **4** and 2.05 g (11.5 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 triethylammonium chloride was filtered off. The solution was

concentrated i. v. to one half of its volume and left at -20°C overnight. **5** was obtained as colourless crystals. Yield: 3.2 g (72.7 %); m.p.: 82°C .

$\text{C}_{14}\text{H}_{19}\text{Cl}_3\text{N}_3\text{OP}$ (382.66); calc.: C 43.94; H 5.00; N 10.98; found: C 43.95; H 5.19; N 10.41. – ^1H -NMR (CDCl_3): δ = 3.14 (d, 3 H, $^3J(\text{PH}) = 12.3$ Hz, PNCH_3); 3.17 - 3.44 (m, 8 H, $\text{PN}(\text{CH}_2\text{CH}_2\text{Cl})_2$); 3.61 (t, 2 H, $^3J(\text{HH}) = 6.9$ Hz, $\text{NCH}_2\text{CH}_2\text{Cl}$); 3.68 - 4.05 (m, 2 H, $\text{PNCH}_2\text{CH}_2\text{Cl}$); 6.82 - 6.86, 6.95 - 7.02, 7.40 - 7.48, 8.14 - 8.18 (4 m, 4 H, H_{Ar}). – ^{13}C -NMR (CDCl_3): δ = 33.50 (d, $^2J(\text{PC}) = 37.3$ Hz, PNCH_3); 40.49 (d, $^3J(\text{PC}) = 4.5$ Hz, $\text{PNCH}_2\text{CH}_2\text{Cl}$); 42.10 (d, $^3J(\text{PC}) = 2.4$ Hz, $\text{PN}(\text{CH}_2\text{CH}_2\text{Cl})_2$); 49.34 (d, $^2J(\text{PC}) = 19.4$ Hz, $\text{PN}(\text{CH}_2\text{CH}_2\text{Cl})_2$); 50.43 (d, $^2J(\text{PC}) = 43.1$ Hz, $\text{PNCH}_2\text{CH}_2\text{Cl}$); 114.07 - 133.77 (5 s, C_{Ar}); 143.86 (d, $^2J(\text{PC}) = 9.3$ Hz, PNC_{Ar}); 164.15 (d, $^2J(\text{PC}) = 7.8$ Hz, $\text{PNC}(\text{:O})$). – ^{31}P -NMR (CDCl_3): δ = 92.84 (s). – EI-MS: m/z (%): 381 (1) $[\text{M}]^+$; 261 (16) $[\text{M} - \text{CH}_2\text{CH}_2\text{Cl} - \text{C}(\text{O})\text{NCH}_3]^+$; 241 (18) $[\text{M} - \text{N}(\text{CH}_2\text{CH}_2\text{Cl})_2]^+$; 212 (29) $[\text{M} - \text{N}(\text{CH}_2\text{CH}_2\text{Cl})_2 - \text{NCH}_3]^+$; 132 (100) $[\text{C}(\text{O})\text{C}_6\text{H}_4\text{NCH}_2]^+$.

1-(2-Chloroethyl)-2-bis(2-chloroethyl)amino-3-methyl-5,6-benzo-1,3,2-diazaphosphorin-4-on-2-oxide (6). Hydrogen peroxide/urea 1:1 adduct (0.94 g; 10 mmol) was added to a solution of 1.6 g (4.2 mmol) of **5** in 50 ml of dichloromethane. After stirring for 1 d at room temperature, insoluble components were filtered off. Subsequently the solvent and other volatiles were removed from the filtrate i. v. The residue was dissolved in 50 ml of diethyl ether and kept overnight at -20°C . The colourless precipitate of **6** was filtered off and dried i. v. Yield: 1.1 g (66.0 %); m.p.: 127°C .

$\text{C}_{14}\text{H}_{19}\text{Cl}_3\text{N}_3\text{O}_2\text{P}$ (398.66); calc.: C 42.18; H 4.80; N 10.54; found: C 41.67; H 4.79; N 10.39. – ^1H -NMR (CDCl_3): δ = 3.23 (d, 3 H, $^3J(\text{PH}) = 7.3$ Hz, PNCH_3); 3.31 - 3.52 (m, 8 H, $\text{PN}(\text{CH}_2\text{CH}_2\text{Cl})_2$); 3.58 (t, 2 H, $^3J(\text{HH}) = 5.8$ Hz, $\text{NCH}_2\text{CH}_2\text{Cl}$); 3.63 - 4.06 (m, 2 H, $\text{PNCH}_2\text{CH}_2\text{Cl}$); 7.03 - 7.18, 7.55 - 7.65, 8.23 - 8.28 (3 m, 4 H, H_{Ar}). – ^{13}C -NMR (CDCl_3): δ = 27.75 (d, $^2J(\text{PC}) = 3.6$ Hz, PNCH_3); 39.35 (s, $\text{PNCH}_2\text{CH}_2\text{Cl}$); 42.09 (s, $\text{PN}(\text{CH}_2\text{CH}_2\text{Cl})_2$); 44.34 (d, $^2J(\text{PC}) = 4.0$ Hz, $\text{PNCH}_2\text{CH}_2\text{Cl}$); 49.49 (d, $^2J(\text{PC}) = 4.9$ Hz, $\text{PN}(\text{CH}_2\text{CH}_2\text{Cl})_2$); 112.88 - 135.14 (5 s, C_{Ar}); 140.39 (d, $^2J(\text{PC}) = 6.1$ Hz, PNC_{Ar}); 166.61 (d, $^2J(\text{PC}) = 4.7$ Hz, $\text{PNC}(\text{:O})$). – ^{31}P -NMR (CDCl_3): δ = 93.34 (s). – EI-MS: m/z (%): 397 (24) $[\text{M}]^+$; 348 (38) $[\text{M} - \text{CH}_2\text{Cl}]^+$; 291 (100) $[\text{M} - \text{CH}_2\text{Cl} - \text{C}(\text{O})\text{NCH}_3]^+$; 257 (53) $[\text{M} - \text{N}(\text{CH}_2\text{CH}_2\text{Cl})_2]^+$; 194 (10) $[\text{M} - \text{N}(\text{CH}_2\text{CH}_2\text{Cl})_2 - \text{CH}_2\text{CH}_2\text{Cl}]^+$; 132 (12) $[\text{C}(\text{O})\text{C}_6\text{H}_4\text{NCH}_2]^+$.

1-(2-Chloroethyl)-2-hydro-3-methyl-5,6-benzo-1,3,2-diazaphosphorin-4-on-2-oxide (7). To a solution of 1.4 g (5 mmol) of **4** in 30 ml of diethyl ether, 0.1 ml (5.5 mmol) of water was added and the mixture was stirred for 1 d. The precipitate thus formed was collected by filtration, washed three times with 10 ml portions of diethyl ether and dried i. v. Yield: 0.8 g (61.9 %); m.p.: 108°C .

$C_{10}H_{12}ClN_2O_2P$ (258.64); calc.: C 46.44; H 4.68; N 10.83; found: C 46.27; H 4.72; N 10.61. – 1H -NMR ($CDCl_3$): δ = 3.24 (d, 3 H, $^3J(PH)$ = 8.3 Hz, $PNCH_3$); 3.76 (t, 2 H, $^3J(HH)$ = 6.6 Hz, CH_2CH_2Cl); 4.03 - 4.15 (m, 2 H, $PNCH_2CH_2Cl$); 6.98 - 7.02, 7.12 - 7.19, 7.49 - 7.61, 8.18 - 8.23 (4 m, 4 H, H_{Ar}); 7.87 (d, 1 H, $^1J(PH)$ = 650.1 Hz, PH). – ^{13}C -NMR ($CDCl_3$): δ = 28.55 (d, $^2J(PC)$ = 6.0 Hz, $PNCH_3$); 40.09 (s, CH_2CH_2Cl); 45.35 (d, $^2J(PC)$ = 5.9 Hz, $PNCH_2CH_2Cl$); 113.95 - 134.90 (5 s, C_{Ar}); 139.42 (d, $^2J(PC)$ = 4.6 Hz, $C_{Ar}NP$); 162.71 (d, $^2J(PC)$ = 3.7 Hz, $PNC(:O)$). – ^{31}P -NMR ($CDCl_3$): δ = 4.64 (s). – EI-MS: m/z (%): 258 (30) $[M]^+$; 209 (94) $[M - CH_2Cl]^+$; 146 (30) $[M - Cl - NCH_3P(O)H]^+$; 132 (100) $[C(O)C_6H_4NCH_2]^+$; 77 (23) $[NCH_2CH_2Cl]^+$.

3-(4-Fluorobenzyl)-2-methoxy-1-methyl-5,6-benzo-1,3,2-diazaphosphorin-4-one (9). A solution of 0.62 g (6.0 mmol) of trimethylsilyl methyl ether in 20 ml of dichloromethane was added dropwise to 1.93 g (6.0 mmol) of **8**⁹, dissolved in 30 ml of dichloromethane. Subsequently the reaction mixture was stirred for 7 h. After removing the solvent and all volatile components i. v., the product **9** was obtained as a non-crystallizing oil. Yield: 1.8 g (94.2 %); dec.: 196°C.

$C_{16}H_{16}FN_2O_2P$ (318.27); calc.: C 60.38; H 5.07; N 8.80; found: C 60.02; H 5.13; N 8.53. – 1H -NMR ($CDCl_3$): δ = 3.01 (d, 3 H, $^3J(PH)$ = 9.0 Hz, $POCH_3$), 3.28 (d, 3 H, $^3J(PH)$ = 12.9 Hz, $PNCH_3$), 4.65 - 5.08 (m, 2 H, NCH_2), 6.80 - 7.26, 7.33 - 7.70, 8.12 - 8.33 (3 m, 8 H, H_{Ar}). – ^{13}C -NMR ($CDCl_3$): δ = 36.17 (d, $^2J(PC)$ = 43.9 Hz, $PNCH_3$), 48.81 (d, $^2J(PC)$ = 34.6 Hz, $PNCH_2$), 51.66 (s, $POCH_3$), 113.73 - 146.13 (11 s, C_{Ar}), 162.18 (d, $^1J(FC)$ = 245.6 Hz, $C_{Ar}F$), 161.32 (s, $C(O)$). – ^{31}P -NMR ($CDCl_3$): δ = 103.57 (s). – EI-MS: m/z (%): 318 (43) $[M]^+$, 287 (4) $[M - OCH_3]^+$, 109 (100) $[CH_2C_6H_4F]^+$.

2-Chloro-3-(4-fluorobenzyl)-1-methyl-5,6-benzo-1,3,2-diazaphosphorin-4-on-2-oxide (10). Sulfuryl chloride (0.66 g; 4.9 mmol) was added dropwise at 0°C to a solution of 1.54 g (4.8 mmol) of **9** in 20 ml of dichloromethane. The reaction mixture was allowed to warm up to room temperature and was stirred for 18 h. After removing the solvent and all volatile components i. v., **10** was left as a non-crystallizing oil. Yield: 1.4 g (86.1 %); dec.: 170°C.

$C_{15}H_{13}ClFN_2O_2P$ (338.69); calc.: C 53.19; H 3.87; N 8.27; found: C 53.02; H 3.64; N 8.04. – 1H -NMR ($CDCl_3$): δ = 3.36 (d, 3 H, $^3J(PH)$ = 11.4 Hz, $PNCH_3$), 4.95 - 5.11 (m, 2 H, CH_2), 6.93 - 7.18, 7.50 - 7.69, 8.17 - 8.22 (3 m, 8 H, H_{Ar}). – ^{13}C -NMR ($CDCl_3$): δ = 30.20 (d, $^2J(PC)$ = 3.1 Hz, $PNCH_3$), 44.83 (d, $^2J(PC)$ = 3.32 Hz, $PNCH_2$), 114.46 - 140.41 (11 s, C_{Ar}), 162.51 (d, $^1J(FC)$ = 246.6 Hz, $C_{Ar}F$), 162.76 (d, $^2J(PC)$ = 4.4 Hz, $PNC(:O)$). – ^{31}P -NMR ($CDCl_3$): δ = 13.82 (s). – EI-MS: m/z (%): 338 (18) $[M]^+$, 132 (18) $[C(O)C_6H_4NCH_2]^+$, 109 (100) $[CH_2C_6H_4F]^+$, 105 (16) $[C_6H_4NCH_3]^+$.

2-Bis(2-chloroethyl)amino-3-(4-fluorobenzyl)-1-methyl-5,6-benzo-1,3,2-diazaphosphorin-4-on-2-oxide (11). To a suspension of 0.85 g (2.5 mmol) of **10** and 0.45 g (2.5 mmol) of bis(2-chloroethyl)amine hydrochloride in 25 ml of dichloromethane, 0.51 g (5.0 mmol) of triethylamine was added dropwise over 30 min. After the reaction mixture was stirred for 18 h, the solvent and all volatile components were removed i. v. The residue was extracted with 50 ml of diethyl ether in order to separate the product from triethylamine hydrochloride. The extract was concentrated by evaporation of the solvent and was kept for 2 d at -20°C . The resulting colourless precipitate of **11** was collected by filtration and dried i. v. Yield: 0.4 g (36.0 %); The identity of the known compound **11** was established by NMR-spectroscopy. For experimental data see ref. 8.

2-(2-Chloroethylamino)-3-(4-fluorobenzyl)-1-methyl-5,6-benzo-1,3,2-diazaphosphorin-4-one (12). 2-Chloroethylamine hydrochloride (1.30 g; 11.2 mmol) and 3.60 g (11.1 mmol) of **8** were suspended in 50 ml of dichloromethane. Triethylamine (2.28 g; 22.5 mmol) was added dropwise with stirring over 45 min. After stirring for 6 h, the solvent and all volatile components were removed i. v. The residue was extracted with 100 ml of diethyl ether, in order to separate the product from triethylamine hydrochloride. The extract was concentrated by evaporation and kept for 1 d at -20°C . The resulting colourless precipitate of **12** was filtered off and dried i. v. Yield: 2.1 g (51.2 %); m.p. : 87°C .

$\text{C}_{17}\text{H}_{18}\text{ClFN}_3\text{OP}$ (365.76); calc.: C 55.82; H 4.96; N 11.49; found: C 55.93; H 5.03; N 10.88. – ^1H -NMR (CDCl_3): δ = 3.17 (d, 3 H, $^3J(\text{PH}) = 14.3$ Hz, PNCH_3), 3.22 - 3.67 (m, 4 H, $\text{PNHCH}_2\text{CH}_2\text{Cl}$), 4.55 - 5.10 (m, 2 H, PNCH_2), 6.79 - 7.30, 7.32 - 7.68, 8.12 - 8.21 (3 m, 8 H, H_{Ar}), 8.20 (br., 1 H, NH). – ^{13}C -NMR (CDCl_3): δ = 35.98 (d, $^2J(\text{PC}) = 42.9$ Hz, PNCH_3), 43.70 (d, $^2J(\text{PC}) = 4.6$ Hz, $\text{PNHCH}_2\text{CH}_2\text{Cl}$), 45.88 (d, $^3J(\text{PC}) = 2.6$ Hz, $\text{PNHCH}_2\text{CH}_2\text{Cl}$), 48.44 (d, $^2J(\text{PC}) = 33.8$ Hz, $\text{PNCH}_2\text{C}_6\text{H}_4\text{F}$), 113.71 - 135.10 (11 s, C_{Ar}), 162.04 (d, $^1J(\text{FC}) = 245.5$ Hz, CF), 164.30 (d, $^2J(\text{PC}) = 7.4$ Hz, $\text{PNC}(\text{:O})$). – ^{31}P -NMR (CDCl_3): δ = 80.69 (s). – EI-MS: m/z (%): 365 (32) $[\text{M}]^+$, 287 (79) $[\text{M} - \text{NHCH}_2\text{CH}_2\text{Cl}]^+$; 109 (100) $[\text{CH}_2\text{C}_6\text{H}_4\text{F}]^+$.

X-RAY Crystal Structure Determination of 3, 4 and 5:

Data collection and reduction: Crystals were mounted on glass fibres in inert oil and transferred to the cold gas stream of the diffractometer (Siemens P4 for **3** and **5**, Stoe STADI-4 for **4**, both with LT2 low temperature attachment). The orientation matrix for **3** and **5** was refined from setting angles of 64 (63) reflections in the 2θ range $5-25^{\circ}$. The cell constants for **4** were refined from $\pm\omega$ angles of 52 reflections in the 2θ range $20-23^{\circ}$ (monochromated Mo K_{α} radiation).

Structure solution and refinement: The structures were solved by direct methods and refined anisotropically on F^2 (program system: SHELXL-93, G.M.Shel-

drick, University of Göttingen). H atoms were included using a riding model or rigid methyl groups, except that N-H of compound **3** was freely refined. Weighting schemes of the form $w^{-1} = [\sigma^2(F_o^2) + (aP)^2 + bP]$ were employed, with $P = (F_o^2 + 2F_c^2)/3$. Full details of the structure determinations 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 406059 (**3**), CSD 406060 (**4**) and CSD 406061 (**5**).

TABLE I Crystal data and structure refinement for **3**, **4** and **5**

Compound	3	4	5
Formula	C ₁₀ H ₁₃ ClN ₂ O	C ₁₀ H ₁₁ Cl ₂ N ₂ OP	C ₁₄ H ₁₉ Cl ₃ N ₃ OP
<i>M_r</i>	212.67	277.09	382.66
Crystal habit	colourless tablet	colourless prism	colourless tablet
Crystal size (mm)	0.60 × 0.40 × 0.15	0.50 × 0.30 × 0.20	0.40 × 0.30 × 0.05
Temperature (°C)	− 100	− 130	− 100
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	Pbca	P2 ₁ /c	P2 ₁ /n
Cell constants			
α(pm)	793.78(8)	967.9(2)	1039.78(14)
β(pm)	922.56(10)	1548.8(3)	829.45(10)
c(pm)	2836.6(3)	798.82(12)	1994.4(2)
a (°)	90	90	90
b (°)	90	94.30(2)	91.137(8)
γ (°)	90	90	90
<i>U</i> (nm ^{−3})	2.0772(4)	1.1941(4)	1.7198(4)
<i>Z</i>	8	4	4
<i>D_x</i> (Mg m ³)	1.360	1.541	1.478
μ (mm ^{−1})	0.336	0.656	0.630
<i>F</i> (000)	896	568	792
2θ _{max} (°)	50	50	50
No. of reflns.:			
measured	2348	3681	3367
independent	1825	2110	3023
<i>R_{int}</i>	0.024	0.023	0.024
<i>wR</i> (<i>F</i> ² , all refl.)	0.1038	0.095	0.072
<i>R</i> (<i>F</i> , >4σ(<i>F</i>))	0.040	0.037	0.041
No. of parameters	136	146	200
<i>S</i>	0.886	1.057	0.806
max. Δ/σ	< 0.001	< 0.001	< 0.001
max. Δρ (e nm ^{−3})	283	373	283

TABLE II Selected bond lengths [pm] and angles [°] for **3**.

Cl-C(9)	178.0(3)	O-C(1)	125.2(3)
N(1)-C(7)	138.6(3)	N(1)-C(8)	144.4(3)
N(2)-C(1)	132.4(3)	N(2)-C(10)	145.3(3)
C(1)-C(2)	148.7(3)	C(2)-C(3)	139.1(3)
C(2)-C(7)	142.3(3)	C(3)-C(4)	137.7(3)
C(4)-C(5)	137.6(4)	C(5)-C(6)	137.5(4)
C(6)-C(7)	140.4(3)	C(8)-C(9)	151.2(4)
C(7)-N(1)-C(8)	122.4(2)	C(1)-N(2)-C(10)	122.2(2)
O-C(1)-N(2)	120.4(2)	O-C(1)-C(2)	121.3(2)
N(2)-C(1)-C(2)	118.3(2)	C(3)-C(2)-C(7)	118.6(2)
C(3)-C(2)-C(1)	120.4(2)	C(7)-C(2)-C(1)	120.9(2)
C(4)-C(3)-C(2)	122.2(2)	C(5)-C(4)-C(3)	119.1(2)
C(6)-C(5)-C(4)	120.7(2)	C(5)-C(6)-C(7)	121.4(2)
N(1)-C(7)-C(6)	120.4(2)	N(1)-C(7)-C(2)	121.6(2)
C(6)-C(7)-C(2)	118.0(2)	N(1)-C(8)-C(9)	114.9(2)
C(8)-C(9)-Cl	111.4(2)		

TABLE III Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{pm}^2 \times 10^{-1}$) for **3**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} -tensor.

	x	y	z	$U(\text{eq})$
Cl	1077.8(12)	9140.0(10)	4121.3(3)	64.1(3)
O	6162(2)	10406.5(16)	4295.7(6)	34.5(5)
N(1)	3995(3)	10576(2)	3548.9(9)	34.6(6)
N(2)	7031(3)	8148(3)	4446.2(8)	34.6(6)
C(1)	6469(3)	9151(2)	4151.7(8)	26.0(6)
C(2)	6201(3)	8741(2)	3650.2(8)	23.7(5)
C(3)	7163(3)	7651(2)	3444.5(8)	25.8(6)
C(4)	6928(3)	7217(3)	2984.7(8)	30.2(6)
C(5)	5697(3)	7875(3)	2718.9(9)	31.8(6)
C(6)	4727(3)	8968(3)	2906.1(8)	31.5(6)
C(7)	4952(3)	9442(2)	3372.2(8)	25.8(6)
C(8)	2272(3)	10820(3)	3406.5(10)	39.1(7)
C(9)	1078(3)	9585(3)	3510.7(9)	36.4(7)
C(10)	7467(4)	8476(3)	4932.1(8)	45.8(8)

TABLE IV Selected bond lengths [pm] and angles [°] for **4**.

P-N(1)	166.8(2)	P-N(2)	167.8(2)
P-Cl(1)	216.07(10)	Cl(2)-C(9)	178.4(3)
O-C(1)	122.0(3)	N(1)-C(7)	140.6(3)
N(1)-C(8)	147.4(3)	N(2)-C(1)	138.4(3)
N(2)-C(10)	147.1(3)		
N(1)-P-N(2)	100.39(10)	N(1)-P-Cl(1)	101.61(8)
N(2)-P-Cl(1)	99.54(8)	C(7)-N(1)-C(8)	120.5(2)
C(7)-N(1)-P	124.5(2)	C(8)-N(1)-P	113.9(2)
C(1)-N(2)-C(10)	116.4(2)	C(1)-N(2)-P	127.1(2)
C(10)-N(2)-P	115.9(2)		

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

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq)
P	6815.9(7)	5509.5(4)	3992.4(8)	31.7(2)
Cl(1)	5947.8(7)	5804.3(4)	1486.7(9)	40.8(2)
Cl(2)	6049.1(7)	2491.8(4)	2483.5(9)	38.8(2)
O	9706.3(19)	7201.2(11)	3880(3)	41.1(5)
N(1)	7979.3(19)	4753.7(12)	3613(2)	27.1(4)
N(2)	7856(2)	6369.0(13)	4324(2)	29.3(5)
C(1)	9136(2)	6501.4(15)	3704(3)	27.9(5)
C(2)	9782(2)	5759.3(15)	2913(3)	25.5(5)
C(3)	11048(3)	5905.9(17)	2238(3)	32.7(6)
C(4)	11794(3)	5245.5(19)	1603(3)	38.8(6)
C(5)	11264(3)	4418.3(18)	1616(3)	38.7(6)
C(6)	10021(3)	4250.5(16)	2259(3)	32.4(6)
C(7)	9246(2)	4916.1(15)	2918(3)	24.9(5)
C(8)	7460(3)	3863.4(16)	3747(3)	32.9(6)
C(9)	6786(3)	3522.6(17)	2100(4)	42.2(7)
C(10)	7254(3)	7108.7(18)	5165(4)	41.8(7)

TABLE VI Selected bond lengths [pm] and angles [°] for **5**.

P-N(3)	168.1(3)	P-N(1)	170.6(3)
P-N(2)	173.9(3)	Cl(1)-C(9)	178.3(3)
Cl(2)-C(12)	180.3(3)	Cl(3)-C(14)	179.2(3)
N(1)-C(7)	141.3(4)	N(1)-C(8)	146.6(4)
N(2)-C(1)	136.7(4)	N(2)-C(10)	147.3(4)
N(3)-C(13)	146.3(4)	N(3)-C(11)	147.3(4)
O-C(1)	122.9(4)		
N(3)-P-N(1)	105.74(13)	N(3)-P-N(2)	103.76(13)
N(1)-P-N(2)	96.60(13)	C(7)-N(1)-C(8)	119.4(3)
C(7)-N(1)-P	125.0(2)	C(8)-N(1)-P	115.5(2)
C(1)-N(2)-C(10)	116.1(3)	C(1)-N(2)-P	129.9(2)
C(10)-N(2)-P	113.4(2)	C(13)-N(3)-C(11)	115.8(2)
C(13)-N(3)-P	125.1(2)	C(11)-N(3)-P	118.3(2)

TABLE VII Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{pm}^2 \times 10^{-1}$) for **5**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} -tensor.

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq)
P	9791.0(9)	2808.3(11)	914.1(4)	22.6(2)
Cl(1)	6529.8(9)	5398.0(12)	-786.6(4)	40.2(3)
Cl(2)	11388.8(10)	7054.6(12)	2597.2(5)	48.1(3)
Cl(3)	8609.9(9)	-290.9(12)	3046.9(4)	40.0(3)
N(1)	8224(2)	2682(3)	648.7(12)	22.2(7)
N(2)	10137(3)	764(3)	850.8(13)	21.8(7)
N(3)	9747(2)	3134(3)	1745.4(12)	22.9(7)
O	9752(2)	-1921(3)	862.3(11)	34.2(6)
C(1)	9330(3)	-537(4)	859.6(15)	23.8(8)
C(2)	7932(3)	-185(4)	870.7(14)	21.1(8)
C(3)	7107(3)	-1484(4)	980.1(15)	29.9(9)
C(4)	5802(4)	-1303(5)	975.3(16)	34.5(10)
C(5)	5291(3)	196(5)	849.1(16)	35.3(10)
C(6)	6069(3)	1514(4)	737.4(15)	27.6(9)
C(7)	7408(3)	1349(4)	755.0(15)	20.5(8)
C(8)	7702(3)	4132(4)	323.4(15)	26.8(9)
C(9)	7434(3)	3795(4)	-413.2(15)	29.0(9)
C(10)	11523(3)	405(4)	892.2(16)	32.3(9)
C(11)	10708(3)	4229(4)	2050.2(16)	28.3(9)
C(12)	10125(3)	5824(4)	2235.1(18)	35.3(10)
C(13)	8964(3)	2223(4)	2214.9(15)	23.1(8)
C(14)	9681(3)	793(4)	2517.5(16)	31.7(9)

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