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Bromination of benzo[*e*]-1,2-oxaphosphorinine derivatives

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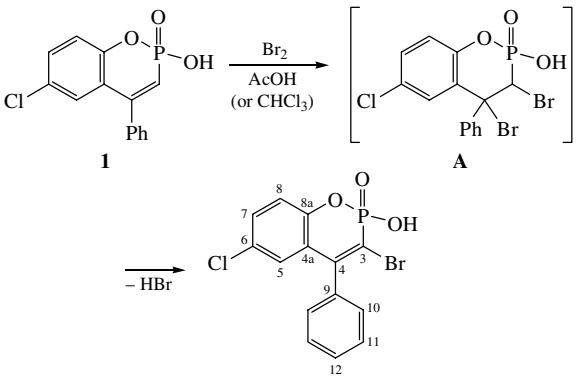
Using NMR spectroscopy, we found that the reactions of 6-chloro-2-hydroxy-2-oxo-4-phenyl- and 2,6-dichloro-2-oxo-4-phenylbenzo[*e*]-1,2-oxaphosphorinines with molecular bromine result in 3-bromo-6-chloro-2-hydroxy-2-oxo-4-phenyl- and 3-bromo-2,6-dichloro-2-oxo-4-phenylbenzo[*e*]-1,2-oxaphosphorinines in high yields.

The reactions of 2,2,2-trihalobenzo[*d*]-1,3,2-dioxaphospholes and their methyl, chlorocarbonyl, and halo derivatives substituted in the phenylene fragment[1–4] with arylacetylenes can serve as a convenient method for the synthesis of rare benzo[*e*]-1,2-oxaphosphorinines,[5–7] *i.e.*, phosphorus-containing analogues of natural heterocycles, coumarin and α-chromene,[8–12] which possess diverse types of bioactivity. Unlike the latter compounds, the chemical properties of benzo[*e*]-1,2-oxaphosphorinine derivatives have not been studied.

We were the first to study the regiochemistry of bromination for 6-chloro-2-hydroxy-2-oxo-4-phenyl- and 2,6-dichloro-2-oxo-4-phenylbenzo[*e*]-1,2-oxaphosphorinines **1** and **2** as examples. The reaction of oxaphosphorinine **1** with an excess of molecular bromine in acetic acid or chloroform under mild conditions (keeping at room temperature or heating in chloroform) results in single compound **3**.† The doublet of original phosphorinine **1** (δ_P 17.4, $^2J_{PCH}$ 23.8 Hz) in the ^{31}P NMR spectrum is transformed into a singlet (δ_P 2.4) corresponding to compound **3**. Similarly, the ^{1}H NMR spectrum of the latter does not contain a proton signal from the P–CH=C fragment in the characteristic region (δ 5.5–6.5). The structure of the compound was determined from ^{13}C and ^{13}C-{^{1}H} NMR data. Note that the ^{13}C-{^{1}H} NMR spectrum contains the signals of all 14 carbon atoms in the weak-field region (δ 120–150) typical of carbon atoms in sp^2 hybridization. The C^3, C^4, C^{4a}, C^8 and C^{8a} nuclei participate in the spin–spin coupling with the phosphorus atom; the values of the constants are characteristic of cyclic compounds. The doublet of the C^3 carbon (δ 114.54, $^1J_{PC^3}$ 183.8 Hz) remains unchanged in the ^{13}C NMR spectrum; hence, it can be concluded that the proton at the third carbon atom is replaced by a bromine atom to give a C^4=C^3(Br)–P fragment. The absence of a proton at the C^3 atom is also reflected in the multiplicity of the signals from the C^{4a} and C^9 nuclei in the ^{13}C NMR spectrum, *viz*., a doublet of doublets and a doublet of doublet of doublets, respectively; the $^3J_{HC^3CC^{4a}}$ constant is absent. The multiplicity of other nuclei of the benzo fragment and the phenyl substituent remains unchanged (in comparison with the multiplicity of the signals of these carbon nuclei in phosphorinine **1**), which suggests that only one reaction direction occurs to give 3-bromo-



1 **A** **3**

Scheme 1

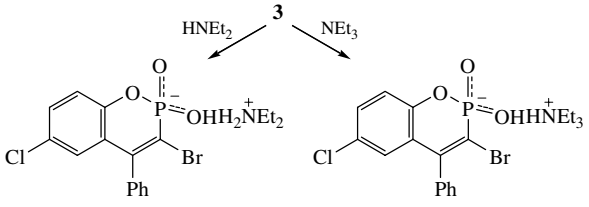
† *Reaction of 6-chloro-2-hydroxy-2-oxo-4-phenylbenzo[*e*]-1,2-oxaphosphorinine* **1** *with bromine.* (*a*) A solution of bromine (0.75 ml, 0.0147 mol) in acetic acid (15 ml) was added dropwise to a solution of phosphonic acid **1** (2.0 g, 0.0068 mol) in acetic acid (30 ml). After stirring for 2 h, the reaction mixture was evacuated until half of acetic acid remained. The beige-coloured precipitate was filtered off, washed with diethyl ether and dried *in vacuo* (12 Torr). The yield of **3** is 1.14 g (45%), mp 215 °C. IR (ν/cm^{-1}): 423, 469, 486, 536, 564, 615, 657, 670, 697, 729, 760, 779, 827, 891, 929, 958, 998, 1038, 1074, 1099, 1122, 1167, 1242, 1337, 1377, 1393, 1469, 1490, 1548, 1583, 2248, 2361, 2598, 2854, 2924, 3060, 3380. ^{31}P-{^{1}H} NMR (AcOH) δ_P: 2.4 (s). ^{1}H NMR (CDCl$_3$) δ: 11.40 (br. s, OH), 6.84 (d, 1H, H^5, $^4J_{H^7CCCH^5}$ 2.5 Hz), 7.35 (dd, 1H, H^7, $^3J_{H^8CCH^7}$ 8.7 Hz, $^4J_{H^5CCCH^7}$ 2.3–2.4 Hz), 7.21 (d, 1H, H^8, $^3J_{H^7CCH^8}$ 8.7 Hz), 7.24 (m, H^{10}, $^3J_{HCCH}$ 7.8 Hz), 7.54–7.56 (m, H^{11}, H^{12}). (*b*) A solution of **1** with bromine in chloroform was refluxed for 8 h (68 °C). The resultant mixture was cooled, and the precipitate formed was filtered off and dried. The yield of **3** was 85%, mp 214–216 °C. ^{13}C NMR spectrum ([^{2}H$_6$]DMSO) of **3** (henceforth, the multiplicity of the signal in the ^{13}C-{^{1}H} spectrum is given in parentheses) δ_C: 114.54 [d (d), C^3, $^1J_{PC^3}$ 183.8 Hz], 148.66 [m (d), C^4, $^2J_{PCC^4}$ 7.2 Hz], 124.64 [br. dd (d), C^{4a}, $^3J_{PCCC^{4a}}$ 12.5 Hz, $^3J_{HC^8CC^{4a}}$ 6.1 Hz], 127.56 [br. dd (s), C^5, $^1J_{HC^5}$ 166.0 Hz, $^3J_{HC^7CC^5}$ 5.6 Hz], 127.33 [br. ddd (s), C^6, $^3J_{HC^8CC^6}$ 11.5 Hz, $^2J_{HC^7C^6}$ 3.5–4.1 Hz, $^2J_{HC^5C^6}$ 3.5–4.1 Hz], 130.06 [dd (s), C^7, $^1J_{HC^7}$ 169.9 Hz, $^3J_{HC^5CC^7}$ 6.3 Hz], 120.78 [dd (d), C^8, $^1J_{HC^8}$ 167.5 Hz, $^3J_{POCC^8}$ 7.5 Hz], 147.55 [m (d), C^{8a}, $^2J_{POC^{8a}}$ 10.1 Hz], 136.34 [ddd (d), C^9, $^3J_{PCCC^9}$ 12.3 Hz, $^3J_{HC^{11}CC^9}$ 7.8 Hz, $^3J_{HC^{11'}CC^9}$ 7.8 Hz], 128.28 [ddd (s), C^{10}, $^1J_{HC^{10}}$ 160.7 Hz, $^3J_{HC^{10}CC^{10}}$ 6.9–7.0 Hz, $^3J_{HC^{12}CC^{10}}$ 6.9–7.0 Hz], 128.87 [dd (s), C^{11}, $^1J_{HC^{11}}$ 161.1 Hz, $^3J_{HC^{11'}CC^{11}}$ 7.4 Hz], 128.69 [ddd (s), C^{12}, $^1J_{HC^{12}}$ 162.0 Hz, $^3J_{HC^{10}CC^{12}}$ 7.6 Hz, $^3J_{HC^{10'}CC^{12}}$ 7.6 Hz]. Found (%): C, 45.33; H, 2.67; P, 8.17. Calc. for C$_{14}$H$_9$BrClO$_3$P (%): C, 45.22; H, 2.42; P, 8.34.

Melting points are uncorrected; the measurements involved a Boetius melting point apparatus. NMR spectra were recorded on Bruker Avance-600 (^{1}H, 600 MHz; ^{13}C, 150.9 MHz) and Bruker CXP-100 (^{31}P, 36.48 MHz) spectrometers. The δ_H and δ_P values were determined relative to an internal (HMDS) or external (H$_3$PO$_4$) standard. The δ_C values were determined relative to the signal of the deuterated solvent. IR spectrum was recorded on a Bruker Vector-22 instrument in Nujol. The EI mass spectra were obtained on a TRACE MS Finnigan MAT instrument; the electron energy was 70 eV, the ion source temperature was 200 °C. The samples were introduced into the ion source using a direct inlet system. Heating of the evaporator tube was programmed from 35 to 150 °C at a rate of 35 K min^{-1}. The mass-spectrometric data were processed using the Xcalibur system program.

6-chloro-2-hydroxy-2-oxo-4-phenylbenzo[*e*]-1,2-oxaphosphorinine **3** (Scheme 1).

The reaction probably starts with the addition of bromine to the C^3=C^4 bond and the formation of intermediate compound **A**, which was not detected by spectral methods. It is known that, unlike phosphorinine **1**, similar products of bromine addition to coumarin are stable and can be isolated in a pure form.[14] The regioselectivity of the C^3–C^4 bond bromination is probably consistent with the benzophosphorinine electronic structure. The heterocyclic molecule is likely to have less pronounced 'aromatic' properties than its benzo fragment.

The reaction of bromophosphonic acid **3** with amines gave diethyl- and triethylammonium salts **4** and **5**,‡ respectively (Scheme 2), as thick glassy oils; the corresponding chemical shifts δ_P in the ^{31}P NMR spectrum are –3.8 and –6.5, respectively.

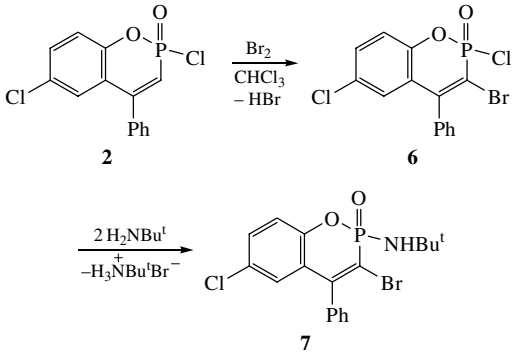


Scheme 2

The structure of compound **4** was also confirmed by ^{13}C and ^{13}C-{^{1}H} NMR spectroscopy. The spectra of compounds **3** and **4** are similar, except the upfield region where resonance of alkyl groups of the ammonium salt is observed. Note that the C^3 and C^4 carbon nuclei in salt **4** are descreened to a noticeably greater extent.

The bromination of chlorophosphorinine **2** occurs in a similar way. The fact that one bromine atom was incorporated was also confirmed by mass spectrometry for the aminolysis product of chlorophosphorinine **6**, *viz*., *tert*-butylamide **7** (Scheme 3).§

Thus, the reaction of 6-chloro-2-hydroxy-2-oxo-4-phenyl- and 2,6-dichloro-2-oxo-4-phenylbenzo[*e*]-1,2-oxaphosphorinine **1** and **2** with molecular bromine gives high yields of products of proton replacement at the 3-position with bromine.



Scheme 3

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‡ *Diethylammonium 3-bromo-6-chloro-2-oxo-4-phenylbenzo[e]-1,2-oxaphosphorinin-2-oate* **4**. Diethylamine (0.29 g, 0.004 mol) was added to a suspension of phosphorinine **3** (1.0 g, 0.003 mol) in benzene (15 ml). After stirring for 1 h, the solvent and an excess of the amine were removed *in vacuo*. Compound **4** was obtained as a colourless glassy oil. Yield 98%. Found (%): C, 48.67; H, 4.88; N, 2.99; P, 7.05. Calc. for $C_{18}H_{20}BrClNO_3P$ (%): C, 48.59; H, 4.50; N, 3.15; P, 6.97. IR (ν/cm^{-1}): 429, 472, 504, 543, 612, 657, 674, 695, 733, 771, 811, 834, 866, 881, 915, 994, 1103, 1143, 1180, 1227, 1263, 1377, 1465, 1549, 1584, 1610, 2503, 2562, 2854, 2924, 2954, 3450. ^{31}P-{^{1}H} NMR ([$^2H_6$]DMSO) δ_P: –3.8 (s). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.20 (t, 6H, 2Me, $^3J_{HCCH}$ 7.2 Hz), 2.91 (q, 4H, 2CH$_2$, $^3J_{HCCH}$ 7.2 Hz), 6.50 (d, 1H, H^5, $^4J_{H^7CCH^5}$ 2.6 Hz), 7.04 (d, 1H, H^8, $^3J_{H^8CCH^7}$ 8.5 Hz), 7.21 (dd, 1H, H^7, $^3J_{H^8CCH^7}$ 8.5 Hz, $^4J_{H^7CCCH^5}$ 2.6 Hz), 7.15 (m, H^{10}, $^3J_{HCCH}$ 7.1 Hz), 7.43–7.54 (2m, H^{11}, H^{12}), 8.58 (br. s, 2H, NH$_2$). ^{13}C NMR ([$^2H_6$]DMSO) δ_C: 122.98 [d (d), C^3, $^1J_{PC^3}$ 171.9 Hz], 151.18 [m (d), C^4, $^2J_{PCC^4}$ 7.8 Hz], 126.80 [br. dt (d), C^{4a}, $^3J_{PCCC^{4a}}$ 12.2 Hz, $^3J_{HC^8CC^{4a}}$ 4.0 Hz], 127.36 [dd (s), C^5, $^1J_{HC^5}$ 164.0–164.9 Hz, $^3J_{HC^7CC^5}$ 5.4 Hz], 125.88 [ddd (s), C^6, $^3J_{HC^8CC^6}$ 11.9 Hz, $^2J_{HC^7C^6}$ 4.7 Hz, $^2J_{HC^5C^6}$ 4.7 Hz], 129.36 [dd (s), C^7, $^1J_{HC^7}$ 167.8 Hz, $^3J_{HC^5CC^7}$ 6.2 Hz], 121.32 [dd (d), C^8, $^1J_{HC^8}$ 163.8 Hz, $^3J_{POCC^8}$ 6.2 Hz], 143.12 [m (d), C^{8a}, $^2J_{POC^{8a}}$ 8.5 Hz], 138.32 [br. dt (d), C^9, $^3J_{PCCC^9}$ 10.2 Hz, $^3J_{HC^{11,11'}CC^9}$ 8.1 Hz], 129.20 [ddd (s), C^{10}, $^1J_{HC^{10}}$ 169.1 Hz, $^3J_{HC^{10}CC^{10}}$ 7.1 Hz, $^3J_{HC^{12}CC^{10}}$ 7.1 Hz], 129.33 [dd (s), C^{11}, $^1J_{HC^{11}}$ 161.0 Hz, $^3J_{HC^{11'}CC^{11}}$ 7.7 Hz], 128.65 [ddd (s), C^{12}, $^1J_{HC^{12}}$ 161.5 Hz, $^3J_{HC^{10}CC^{12}}$ 7.2 Hz, $^3J_{HC^{10'}CC^{12}}$ 7.2 Hz], 41.86 [t (s), CH$_2$, $^1J_{HC}$ 140.0 Hz], 11.38 [s (q), Me, $^1J_{HC}$ 127.8 Hz].

Triethylammonium 3-bromo-6-chloro-2-oxo-4-phenylbenzo[e]-1,2-oxaphosphorinin-2-oate **5** (a light brown glassy oil) was obtained in the same manner as compound **4**. Found (%): C, 50.45; H, 5.13; N, 3.07; P, 6.49. Calc. for $C_{20}H_{24}BrClNO_3P$ (%): C, 50.79; H, 5.08; N, 2.96; P, 6.56. Dioxane was used as the solvent. ^{31}P-{^{1}H} NMR (dioxane) δ_P: –6.5 (s). ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.51 (d, 1H, H^5, $^4J_{H^7CCCH^5}$ 2.4 Hz), 7.28 (dd, 1H, H^7, $^3J_{H^8CCH^7}$ 8.5 Hz, $^4J_{HC^5CCH^7}$ 2.4 Hz), 7.10 (d, 1H, H^8, $^3J_{H^7CCH^8}$ 8.5 Hz), 3.19 (m, 6H, 3CH$_2$), 1.19 (t, 9H, 3Me, $^3J_{HCCH}$ 7.2 Hz).

§ *3-Bromo-2-*tert*-butylamino-6-chloro-2-oxo-4-phenylbenzo[e]-1,2-oxaphosphorinine* **7**. A mixture of 2,6-dichloro-2-oxo-4-phenylbenzo[*e*]-1,2-oxaphosphorinine **2** (6.81 g, 0.0218 mol), $CHCl_3$ (25 ml) and bromine (3.36 ml, 0.0659 mol) was refluxed for 4 h. 3-Bromo-2,6-dichloro-2-oxo-4-phenylbenzo[*e*]-1,2-oxaphosphorinine **6** was obtained as a light-brown glassy oil (yield 95%). ^{31}P NMR ($CHCl_3$) δ_P: 10.8 (s). Compound **6** was dissolved in benzene (35 ml) and treated with *tert*-butylamine (5.69 ml, 0.0548 mol). After stirring for 6 h, the reaction mixture was filtered and then washed with water to remove *tert*-butylammonium chloride and an excess of the amine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated after drying. Compound **7** was obtained as a light brown glassy oil. Yield 93%. Found (%): C, 50.49; H, 4.51; N, 3.39. P, 7.33. Calc. for $C_{18}H_{18}BrClNO_2P$ (%): C, 50.64; H, 4.22; N, 3.28; P, 7.27. IR (ν/cm^{-1}): 407, 427, 474, 488, 532, 564, 604, 648, 664, 681, 704, 729, 749, 763, 794, 814, 836, 846, 887, 927, 957, 1039, 1071, 1091, 1114, 1154, 1179, 1204, 1219, 1242, 1304, 1316, 1339, 1380, 1493, 1554, 1575, 1592, 1604, 1674, 1771, 1826, 1919, 1960, 2725, 2855, 2926, 3056, 3451. ^{31}P NMR (C_6H_6) δ_P: 3.4 (d, $^2J_{PNH}$ 7.7 Hz). ^{1}H NMR ($CDCl_3$) δ: 1.31 (s, 9H, Bu^t, $^4J_{HCCCH}$ 2.5 Hz), 6.80 (d, 1H, H^5, X-part of ABX-spectrum, $^4J_{AX}$ 2.5 Hz), 7.05 (dm, 1H, NH, $^2J_{PNH}$ 7.7 Hz), 7.18 and 7.26 (d and dd, 2H, H^8 and H^7, AB-part of ABX-spectrum, $^3J_{AB}$ 9.2 Hz, $^4J_{AX}$ 2.5 Hz), 7.50–7.55 (m, Ph). ^{13}C NMR ([$^2H_6$]DMSO) δ_C: 117.36 [d (d), C^3, $^1J_{PC^3}$ 168.1 Hz], 148.84 [ddd (d), C^4, $^2J_{PCC^4}$ 8.1 Hz, $^3J_{HC^{10}CC^4}$ 2.0–3.6 Hz, $^3J_{HC^{10'}CC^4}$ 2.0–3.6], 124.26 [dd (d), C^{4a}, $^3J_{PCCC^{4a}}$ 12.2 Hz, $^3J_{HC^8CC^{4a}}$ 6.5 Hz], 128.06 [s (dd), C^5, $^1J_{HC^5}$ 166.4 Hz, $^3J_{HC^7CC^5}$ 5.7 Hz], 127.84 [ddd (s), C^6, $^3J_{HC^8CC^6}$ 11.3 Hz, $^2J_{HC^7C^6}$ 4.4 Hz, $^2J_{HC^5C^6}$ 4.4 Hz], 130.92 [ddd (s), C^7, $^1J_{HC^7}$ 169.7 Hz, $^3J_{HC^5CC^7}$ 6.2 Hz, $^2J_{HC^8C^7}$ 4.8 Hz], 121.52 [ddd (d), C^8, $^1J_{HC^8}$ 167.2 Hz, $^3J_{POCC^8}$ 7.6 Hz, $^2J_{HC^7C^8}$ 3.8 Hz], 148.68 [dddd (d), C^{8a}, $^2J_{POC^{8a}}$ 10.2 Hz, $^3J_{HC^7CC^{8a}}$ 5.2–6.2 Hz, $^3J_{HC^5CC^{8a}}$ 5.2–6.2 Hz, $^2J_{HC^8C^{8a}}$ 1.1–1.2 Hz], 137.10 [ddd (d), C^9, $^3J_{PCCC^9}$ 11.7 Hz, $^3J_{HC^{11}CC^9}$ 7.5–8.2 Hz, $^3J_{HC^{11'}CC^9}$ 7.5–8.2 Hz], 128.71 [dm (s), C^{10}, $^1J_{HC^{10}}$ 157.0–161.6 Hz], 129.56 [dd (s), C^{11}, $^1J_{HC^{11}}$ 161.6 Hz, $^3J_{HC^{11'}CC^{11}}$ 7.8 Hz], 129.32 [ddd (s), C^{12}, $^1J_{HC^{12}}$ 161.8 Hz, $^3J_{HC^{10}CC^{12}}$ 7.4 Hz, $^3J_{HC^{10'}CC^{12}}$ 7.4 Hz]. MS, *m/z*: 429, 427, 425 [M]$^{+\cdot}$, 414, 412, 410 [M – Me], 355, 332, 239, 199, 163, 98, 97, 73, 69, 58, 41.

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