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Regioselective chlorination of 4- and 5-methyl-2,2,2-trichlorobenzo[*d*]-1,3,2-dioxaphospholes

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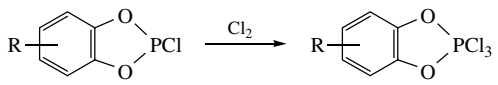
The reactions of 4- and 5-methyl-2,2,2-trichlorobenzo[*d*]-1,3,2-dioxaphospholes with molecular chlorine in an 1:1 ratio occur selectively to give 4-methyl-2,2,2,5-tetrachloro- and 5-methyl-2,2,2,6-tetrachlorobenzo[*d*]-1,3,2-dioxaphospholes, which undergo hydrolysis to 4-chloro-3-methyl- and 4-chloro-5-methyl-1,2-dihydroxybenzenes, respectively.

1,2-Dihydroxybenzenes (catechols or pyrocatechols) and their derivatives are important compounds in organic synthesis.[1] Despite numerous publications on the synthesis of these compounds, the selective introduction of functional groups and halogens into catechol molecules remains a problem of current interest.[2,3] Electrophilic replacement in 3-methoxy-4-hydroxytoluene with chlorine and bromine occurs non-selectively; an excess of a halogen results in corresponding 2,5,6-trihalo derivatives.[4,5] Mono- and dihalo derivatives of pyrocatechols were obtained in moderate yields[6] using milder halogenating agents ($SOCl_2$, SO_2Cl_2, MeCOCl, *etc.*) in various solvents. Cyclic ethers based on pyrocatechol, such as benzo[*d*]-1,3-dioxolane[7–9] and benzo[*e*]-1,4-dioxane,[10] were efficient. Examples of facile selective halogenation of cyclic systems in which the catechol fragment is involved in the P-heterocycle (benzo[*d*]-1,3,2-dioxaphosphole) are unknown (a review of the chemical properties of these compounds is available[11]).

In this study, we found that, under certain conditions, benzo[*d*]-1,3,2-dioxaphospholes undergo highly regioselective electrophilic chlorination at the phenylene fragment.

5-Methyl- and 4-methyl-2-chlorobenzo[*d*]-λ^3-1,3,2-dioxaphospholanes **1** and **2**† can react with chlorine in a molar ratio of 1:2. The first equivalent of the halogen adds very readily to the phosphorus atom similarly to the behaviour of other related phospholes[11] to give derivatives of pentacoordinate phosphorus, namely, 2,2,2-trichlorobenzo[*d*]-λ^5-1,3,2-dioxaphospholes **3** and **4**,‡ which can be isolated in high yields and purified by distillation *in vacuo*.



1, **2** **3**, **4**

In the presence of an excess of chlorine, phospholes **3** and **4** unexpectedly undergo a further selective chlorination at the aromatic ring to give phospholes **5** and **6**, respectively. The structures of compounds **3**–**6** were determined by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. In the ^{31}P NMR spectrum, the signal of phospholes **5** and **6** chlorinated at the ring is somewhat shifted towards weaker fields in comparison with that of non-substituted derivatives **3** and **4**, which suggests the retention of a pentacoordinate environment of the phosphorus atom and the cyclic structure of the phosphole. The stability of compounds **5** and **6** in the presence of free chlorine and the hydrogen halide molecule formed suggest that the aromaticity of the benzene ring is preserved. The relative positions of substituents in the phenylene fragment was determined based on the ^{1}H NMR spectra of phospholes **5** and **6**. These compounds showed spectra typical of 1,2,3,4- and 1,2,4,5-tetrasubstituted benzenes (the AB system of the H^6 and H^7 protons and two singlets of the H^4 and H^7 protons, respectively) in the weak-field region.

The weak-field region of the ^{13}C–{^{1}H} NMR spectra of compounds **5** and **6**§ contains signals from four carbon atoms that do not undergo direct spin-spin coupling with protons. The resonance of the C^7 carbon atom in the ^{13}C–{^{1}H} spectrum manifests itself as a doublet with $^3J_{POCC^7}$ 17.4 Hz. The nuclei of *ipso* C^{3a} and C^{7a} atoms are also easily distinguishable due to not

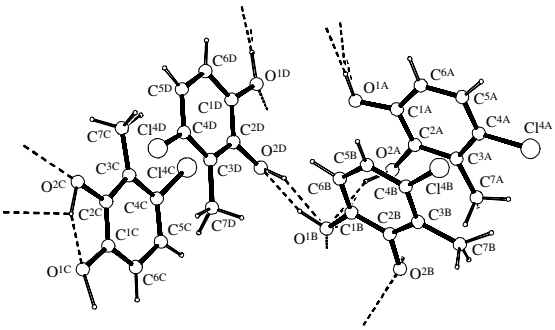
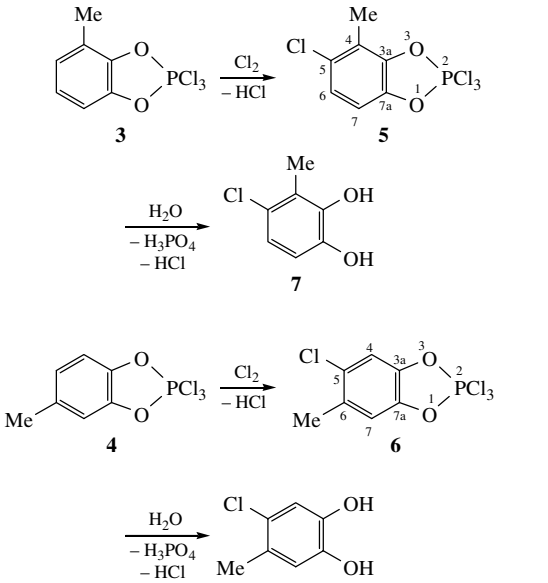


Figure 1 Geometry of four independent molecules of pyrocatechol **7** in a crystal.



† *2-Chloro-4-methylbenzo[*d*]-1,3,2-dioxaphosphole* **1**. A mixture of 1,2-dihydroxy-3-methylbenzene (12.8 g), PCl_3 (14 ml) and a few drops of water was stirred for 1.5 h at 100 °C. An excess of PCl_3 was removed *in vacuo* (12 Torr). The residue (phosphole **1**) was distilled to give 17.3 g (89%), bp 65 °C (1 Torr), n_D^{20} 1.5630. ^{1}H NMR ($CDCl_3$) δ: 2.41 (s, 3H, Me), 6.99–7.10 (m, 3H, H^5, H^6, H^7, ABC spectrum). ^{31}P-{^{1}H} NMR (36.46 MHz, $CDCl_3$) δ_P: 174.2.

*2-Chloro-5-methylbenzo[*d*]-1,3,2-dioxaphosphole* **2**. A mixture of 1,2-dihydroxy-4-methylbenzene (10 g), PCl_3 (22.2 ml) and a few drops of water was stirred for 1 h at 100–110 °C and kept *in vacuo* to remove an excess of PCl_3. The residue (phosphole **3**) was distilled, yield 13.7 g (91%), bp 65 °C (1 Torr). ^{31}P-{^{1}H} NMR, δ_P: 176.6.

‡ *2,2,2-Trichloro-4-methylbenzo[*d*]-1,3,2-dioxaphosphole* **3**. A solution of chlorine (1.45 g) in dichloromethane (10 ml) was added to a solution of dioxaphosphole **1** (3.85 g) in dichloromethane (15 ml) with stirring at –70 °C in an argon atmosphere. The reaction mixture was kept *in vacuo* in order to remove an excess of chlorine and the solvent. The residue consisted of phosphole **3**, viscous yellowish oil, yield 97%, bp 97–101 °C (0.8 Torr). ^{1}H NMR ($CDCl_3$) δ: 2.41 (s, Me), 7.17 (br. d, H^7, $^3J_{H^6CCH^7}$ 8.8 Hz), 6.99–7.04 (br. m, H^5, H^6, $^3J_{H^6CCH^5}$ 8.5 Hz). ^{13}C NMR (the parameters of the ^{13}C-{^{1}H} NMR spectrum in $CDCl_3$ are given in parentheses) δ: 140.10 [m (d), C^{3a}, $^2J_{POC^{3a}}$ 1.3 Hz], 121.28 [ddqd (d), C^4, $^3J_{POCC^4}$ 17.0 Hz, $^3J_{HCCC^4}$ 6.7–6.8 Hz, $^3J_{HC^6CC^4}$ 7.1 Hz, $^2J_{HC^5C^4}$ 2.0 Hz], 124.81 [ddq (s), C^5, $^1J_{HC^5}$ 160.4 Hz, $^3J_{HC^7CC^5}$ 7.6 Hz, $^3J_{HCCC^5}$ 5.0 Hz], 122.74 [d (s), C^6, $^1J_{HC^6}$ 163.9 Hz], 107.99 [ddd (d), C^7, $^1J_{HC^7}$ 167.6 Hz, $^3J_{POCC^7}$ 18.0 Hz, $^3J_{HC^5CC^7}$ 8.8 Hz], 142.23 [br. d (br. s), C^{7a}, $^3J_{HC^6CC^{7a}}$ 10.2 Hz], 14.62 [br. qd (d), Me, $^4J_{HC}$ 128.2 Hz, $^3J_{POCCC}$ 1.1 Hz]. ^{31}P-{^{1}H} NMR (36.46 MHz, $CDCl_3$) δ_P: –25.7.

*2,2,2-Trichloro-5-methylbenzo[*d*]-1,3,2-dioxaphosphole* **4**. A solution of chlorine (2.8 g) in dichloromethane (15 ml) was added to phosphite **2** (7.4 g) at –60 °C; then, the solvent and an excess of chlorine were removed. The residue consisted of phosphole **4** as a viscous yellowish oil. Yield 97%, bp 95–100 °C (0.8 Torr). ^{13}C NMR (the parameters of the ^{13}C-{^{1}H} NMR spectrum in $CDCl_3$ are given in parentheses), δ: 142.84 [ddd (d), C^{3a}, $^3J_{HC^7CC^{3a}}$ 7.1 Hz, $^2J_{HC^4C^{3a}}$ 3.6 Hz, $^2J_{POC^{3a}}$ 0.8 Hz], 111.32 [dddqd (d), C^4, $^1J_{HC^4}$ 164.0 Hz, $^3J_{POCC^4}$ 17.6 Hz, $^3J_{HC^6CC^4}$ 7.7 Hz, $^3J_{HCCC^4}$ 5.1 Hz, $^4J_{HC^7CCC^4}$ 1.4 Hz], 133.81 [dq (s), C^5, $^3J_{HC^7CC^5}$ 7.8 Hz, $^2J_{HCC^5}$ 6.1 Hz], 123.51 [ddqd (s), C^6, $^1J_{HC^6}$ 161.4 Hz, $^3J_{HC^4CC^6}$ 7.0 Hz, $^3J_{HCCC^6}$ 5.1 Hz, $^2J_{HC^7C^6}$ 1.1 Hz], 110.43 [dd (d), C^7, $^1J_{HC^7}$ 166.7 Hz, $^3J_{POCC^7}$ 17.7 Hz], 140.40 [m (d), C^{7a}, $^2J_{POC^{7a}}$ 0.8 Hz], 21.21 [qdd (d), Me, $^1J_{HC}$ 127.2 Hz, $^3J_{HC^4CC}$ 4.7 Hz, $^3J_{HC^6CC}$ 4.7 Hz]. ^{31}P-{^{1}H} NMR (36.46 MHz, C_6H_6) δ_P: –27.3.

§ *2,2,2,5-Tetrachloro-4-methylbenzo[*d*]-1,3,2-dioxaphosphole* **5**. A solution of chlorine (4 g) in dichloromethane (20 ml) was added to a solution of dioxaphosphole **1** (3.6 g) in dichloromethane (15 ml) with stirring at –60 °C. The reaction mixture was slowly heated to 20 °C and kept for six days. The solvent and an excess of chlorine were removed *in vacuo* (12 Torr) to give a residue of phosphole **5**, viscous yellowish oil, yield 97%. ^{1}H NMR ($CDCl_3$) δ: 2.32 (s, Me), 6.87 (br. dd, H^7, $^3J_{H^6CCH^7}$ 8.6 Hz, $^4J_{POCCCH^7}$ 1.0 Hz), 7.04 (br. dd, H^6, $^3J_{H^6CCH^7}$ 8.6 Hz, $^5J_{POCCCCH^7}$ 1.4 Hz). ^{13}C NMR (the parameters of the ^{13}C-{^{1}H} NMR spectrum in $CDCl_3$ are given in parentheses) δ: 141.87 [m (d), C^{3a}, $^2J_{POC^{3a}}$ 2.1 Hz], 120.27 [ddq (d), C^4, $^3J_{POCC^4}$ 16.5 Hz, $^3J_{HC^6CC^4}$ 6.0–6.2 Hz, $^2J_{HCC^4}$ 6.0–6.2 Hz], 129.02 [dqd (s), C^5, $^3J_{HC^7CC^5}$ 10.7 Hz, $^3J_{HCCC^5}$ 5.4 Hz, $^2J_{HC^6C^5}$ 4.4 Hz], 122.89 [d (s), C^6, $^1J_{HC^6}$ 168.5 Hz], 108.77 [dd (d), C^7, $^1J_{HC^7}$ 170.2 Hz, $^3J_{POCC^7}$ 17.4 Hz], 140.33 [br. dd (br. s), C^{7a}, $^3J_{HC^6CC^{7a}}$ 12.0 Hz, $^2J_{HC^7C^{7a}}$ 3.6 Hz], 12.74 [qd (d), Me, $^1J_{HC}$ 129.9 Hz, $^4J_{POCCC}$ 1.1 Hz]. ^{31}P-{^{1}H} NMR ($CDCl_3$) δ_P: –22.8.

*2,2,2,6-Tetrachloro-5-methylbenzo[*d*]-1,3,2-dioxaphosphole* **6**. A solution of chlorine (5 g) in dichloromethane (25 ml) was added to a solution of phosphite **2** (6.2 g) in dichloromethane (30 ml) with stirring at –60 °C. The resulting mixture was slowly heated to 20 °C and kept for three days. The solvent and an excess of chlorine were removed *in vacuo*. The residue (phosphole **6**) was a viscous yellowish oil, yield 96% (9.3 g). ^{13}C NMR (the parameters of the ^{13}C-{^{1}H} NMR spectrum in $CDCl_3$ are given in parentheses) δ: 141.04 [ddd (d), C^{7a}, $^2J_{POC^{7a}}$ 0.9 Hz, $^3J_{HC^4CC^{7a}}$ 7.5 Hz, $^2J_{HC^7C^{3a}}$ 4.3 Hz], 111.62 [dd (d), C^7, $^1J_{HC^7}$ 170.8 Hz, $^3J_{POCC^7}$ 17.7 Hz, $^4J_{HCCCC^7}$ 0.8–0.9 Hz], 131.28 [qd (s), C^5, $^2J_{HCC^5}$ 6.0 Hz, $^3J_{HC^7CC^5}$ 12.0 Hz], 128.08 [dqd (s), C^6, $^3J_{HC^4CC^6}$ 10.3 Hz, $^2J_{HC^7C^6}$ 5.1 Hz, $^3J_{HCCC^6}$ 5.2 Hz], 112.63 [ddqd (d), C^4, $^1J_{HC^4}$ 166.4 Hz, $^3J_{POCC^4}$ 17.3 Hz, $^3J_{HCCC^4}$ 5.2 Hz, $^3J_{HC^7CCC^4}$ 1.3 Hz], 141.03 [ddd (d), C^{7a}, $^3J_{HC^4CC^{7a}}$ 7.5 Hz, $^2J_{HC^7C^{7a}}$ 4.3 Hz, $^2J_{POC^{7a}}$ 0.9 Hz], 20.03 [qd (s), Me, $^1J_{HC}$ 132.6 Hz, $^3J_{HC^4CC}$ 3.0 Hz]. ^{31}P-{^{1}H} NMR ($CDCl_3$) δ_P: –24.1.

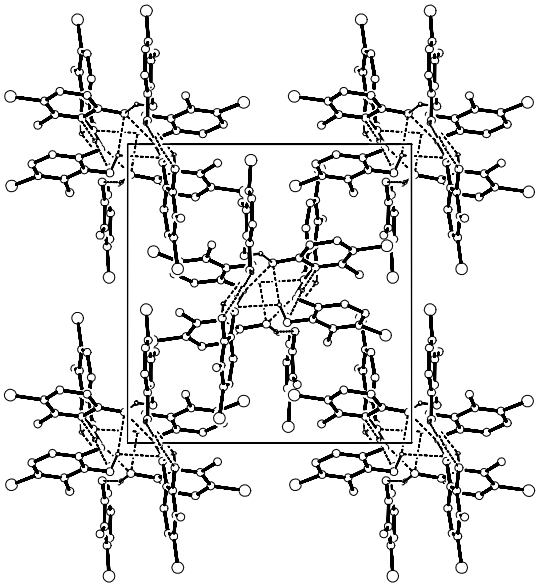


Figure 2 Supramolecular cylindrical aggregates of pyrocatechol **7** molecules in a crystal.

only the larger difference in the total effect of chlorine and methyl (stronger unshielding of the C^{3a} atom) but also the multiplicity of signals in the ^{13}C NMR spectrum (a doublet of doublets for C^{7a} and a multiplet for C^{3a}). The same difference in the *para* and *ortho* shielding effects between chlorine and methyl makes it possible to reliably assign signals to the C^4, C^7 and C^{3a}, C^{7a} nuclei in phosphole **6**. In this case, the multiplicity of signals from the C^7 and C^{7a} nuclei in the ^{13}C NMR spectrum caused by the spin-spin coupling with methyl protons also serves as an additional criterion.

In general, the regiochemistry of chlorination agrees with the electrophilic character of the process and can be explained by the coordinated orientation of two first-kind (*i.e.*, donor-type) substituents, that is, the methyl group and one of the oxygen atoms. Iron and aluminium chlorides are generally used as catalysts in the electrophilic chlorination of aromatic compounds with chlorine, but the halogenation of phenols and dihydroxybenzenes is uncatalysed. The hitherto unknown easiness of such a process in benzo[*d*]-1,3,2-dioxaphospholes is unusual and may be due to the catalytic effect of the phosphorus centre, which serves as a Lewis acid, on the polarization of the chlorine molecule.

Hydrolysis of phospholes **5** and **6** gave pyrocatechols **7** and **8**. Compound **8** was obtained previously[3] by a more complex method and isolated as a metabolite of microorganisms.[12,13] Catechol **7** has not been synthesised; however, it was mentioned as a minor metabolite of 3-chloro-2-methylaniline by *Phodococeus prodochrous* bacteria.[14]

The structure of 4-chloro-3-methylpyrocatechol was confirmed by X-ray diffraction analysis. The crystal contains four independent molecules of compound **7** (**A**, **B**, **C**, **D**), the difference between which lies within the experimental error (Figure 1). The lengths of the C–C, C–Cl and C–O bonds are within the standard values for this type of bonds. There is only one molecule where the C–Cl bond is somewhat shortened [1.579(8) Å] due to the partial occupation (50%) of this position by the chlorine atom. The benzene rings in all of the molecules are planar to within 0.01 Å; the substituents slightly deviate in alternating directions from the ring planes (alternation of substituents in 1,2,3,4-tetrasubstituted benzene). The exocyclic angles at the methyl group in four independent molecules of substituted pyrocatechol are within the ideal value for an sp^2-hybridised carbon atom. The $Cl^4C^4C^5$ bond angles at the chlorine atom in the molecules of **7A**,**B** and **7D** are somewhat decreased, whereas in the molecule of **7C**, this angle is within standard values. Multiple classic hydrogen bonds of the O–H···O type occur in a crystal of compound **7**; this results in the formation of a spiral structure along the axis 0*x* through an infinite chain of hydrogen-bonded molecules (Figure 2). The loops of these spiral structures penetrate each other. The chlorine atoms that are located outside these spiral structures form 'chlorine channels'. Classic O–H···O hydrogen bonds are responsible for the formation of supramolecular cylindrical aggregates shown in Figure 2 (view along the axis 0*x*; only the hydrogen atoms involved in the bonds are shown).

Thus, we found that the facile regioselective chlorination of *P,P,P*-trichlorobenzo[*d*]-1,3,2-dioxaphospholes **3** and **4** at the benzene ring followed by hydrolysis is a convenient method for the synthesis of methylchloropyrocatechols **7** and **8**.¶

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¶ *4-Chloro-1,2-dihydroxy-3-methylbenzene* **7**. Phosphole **5** (5.4 g) was carefully added dropwise to a mixture of water (7 ml) and HCl (1.5 ml) with stirring at 20 °C. A strong exothermic effect and the liberation of hydrogen chloride were observed. The product was extracted with hexane under reflux conditions. The hexane layer was separated and kept to precipitate crystals, which were filtered off and dried *in vacuo* at 12 Torr to give 1.1 g of pyrocatechol **7** (yield 38%), mp 53–54 °C. ^1H NMR ($[^2H_6]$DMSO) δ: 2.19 (s, 3H, Me), 6.66–6.70 (m, 2H, H^5, H^6, AB-spectrum, $^3J_{HCCH}$ 8.6 Hz), 8.54 and 9.37 (2br. s, 2H, OH). IR, ν/cm^{-1}: 454, 544, 584, 655, 727, 817, 839, 854, 893, 1003, 1034, 1113, 1143, 1185, 1209, 1295, 1377, 1461, 1509, 1603, 2855, 2925, 3299.

5-Chloro-1,2-dihydroxy-4-methylbenzene **8**. Phosphorane **6** (9.3 g) was added to a solution containing water (10.0 ml) and hydrochloric acid (0.5 ml) with intense stirring at 20 °C. The resulting reaction mixture was heated for 1 h with stirring in a water bath (60 °C). The crystals precipitated on cooling were filtered off and recrystallised from hexane to give 2.3 g (46%) of compound **8**, mp 106–107 °C. ^1H NMR ($[^2H_6]$DMSO) δ: 2.16 (s, 3H, Me), 6.71 and 6.77 (2s, 2H, H^3, H^6). IR, ν/cm^{-1}: 453, 544, 586, 656, 726, 817, 837, 857, 892, 943, 1002, 1035, 1113, 1143, 1185, 1209, 1292, 1350, 1377, 1462, 1511, 1603, 1658, 1721, 1932, 2855, 2925, 2955, 3298.