o-Hydroxyaryl Diphosphonic Acids

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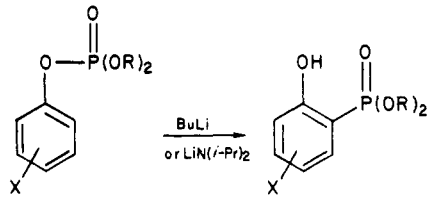
Treatment of dialkyl aryl phosphates with *n*-butyllithium or lithium diisopropylamide results in a rearrangement that involves the fission of an oxygen–phosphorus bond and formation of a C–P bond yielding dialkyl (2-hydroxyaryl)phosphonates. A dialkyl (2-hydroxyaryl)phosphonate on reaction with dialkyl phosphorochloridate yields a phosphate–phosphonate which on treatment with lithium diisopropylamide gives a tetraalkyl (2-hydroxy-1,3-arenediyl)bis(phosphonate). Tetraalkyl 1,4-phenylene bis(phosphate) on treatment with the strong base yields exclusively tetraalkyl (2,5-dihydroxy-1,4-phenylene)bis(phosphonate) and tetraalkyl 1,2-phenylene bis(phosphate) gives (2,3-dihydroxy-1,4-phenylene)bis(phosphonate). These phosphonate esters on treatment with trimethylsilyl chloride and sodium iodide in acetonitrile undergo transesterification to give trimethylsilyl phosphonate esters that readily undergo hydrolysis to the corresponding phosphonic acids on contact with water at room temperature.

Our interest in the synthesis of phosphonic acid derivatives led us to investigate reports from two laboratories[1,2] on the rearrangement of dialkyl aryl phosphates to dialkyl arylphosphonates (eq 1). Treatment of the phosphate



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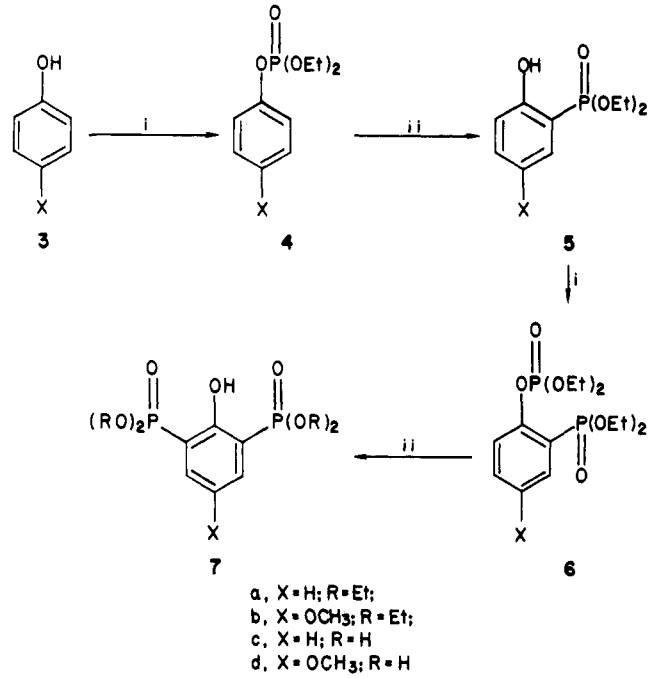
esters with lithium diisopropylamide or butyllithium generates an anion which undergoes a migration of phosphorus from oxygen to carbon. Although O → C migrations of phosphorus are not without precedent[3] C → O migrations of phosphorus moieties are much more commonly encountered (e.g., Horner-Emmons reaction).[4]

The work reported here extends this useful phosphate–phosphonate rearrangement to the prepn. of aryldiphosphonic acid derivatives in two ways: (i) phosphorylation of (*o*-hydroxyaryl)phosphonates **2** followed by treatment with base to induce a second O → C phosphorus migration; (ii) base treatment of bis(phosphates) derived from hydroquinone or catechol to induce a double migration. In addition the conversion of the phosphonates to the corresponding phosphonic acids is reported.

2-Hydroxy 1,3-Bis(phosphonates). From phenol (**3a**) or *p*-methoxyphenol (**3b**) the corresponding 2-hydroxy phosphonates **7a** and **7b** have been obtained by the sequence depicted in Scheme I. Each step in the sequence proceeded in at least 80% yield resulting in overall yields for the conversion of **3** to **7** of 40–55%. It was found that the formation of phosphonate–phosphates **6a** and **6b** and their rearrangement to **7a** and **7b** occurred as efficiently as the formation and rearrangement of **4**. Phosphorus, carbon, and proton NMR provided convincing evidence for the structures assigned. Phosphonate phosphates **6** exhibited two phosphorus peaks: the phosphate at −7 to −8 ppm and the phosphonate function at ≈15 ppm. The

Scheme I[a]



[a] Reagents: (i) $(EtO)_2P{=}OH/CCl_4/NEt_3$; (ii) $(i\text{-}Pr)_2NLi$.

rearrangement products **7a** and **7b** showed a single phosphorus resonance at ≈19 ppm.

Conversion of the esters **7a** and **7b** into the corresponding acids **7c** and **7d** provided further confirmation of the structure. These acids were conveniently converted into their anilinium salts for analysis.

1,4-Bis(phosphonates) from Dihydric Phenols. Hydroquinone and catechol were readily converted into their phosphate esters **8** and **9**, respectively, upon treatment with diethyl phosphite and CCl_4 in the presence of triethylamine.[5] Treatment of diphosphate **8** with the strong base gave a surprisingly clean rearrangement to a single crystalline product **10a**. The spectral properties clearly established the structure of the product to be **10a** rather than the alternative **11**. The aromatic proton in the ^1H NMR is a doublet of doublets J = 15 Hz, J = 9 Hz, (J_{3H}, J_{4H}). The magnitude of the coupling is consistent with ortho and meta P–H coupling but too large for meta and para P–H coupling.[6] Compound **11** would be ex-

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(3) (a) Sturtz, G.; Corbel, B. *C. R. Acad. Sci. Paris* **1973**, *276* C, 1807. (b) Sturtz, G.; Corbel, B. *C. R. Acad. Sci. Paris* **1973**, *277* C, 395. (c) Sturtz, G. In "Colloque International Sur la Chimie Organique du Phosphore" 1970, No. 82, p 217.
(4) (a) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87. (b) Wadsworth, W. S. *Org. React.* **1977**, *25*, 73.
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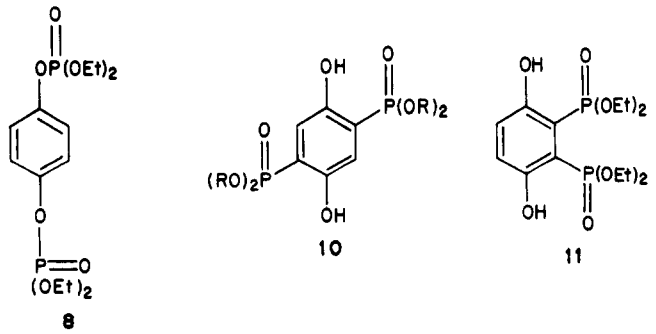
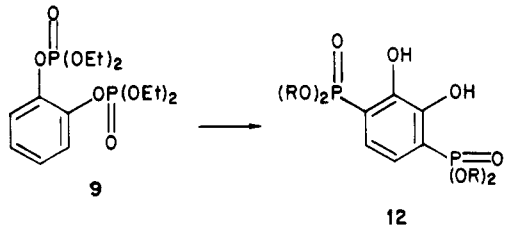


a, R = Et; b, R = H

pected to show couplings of 7–8 Hz and 2–3 Hz. The ^{13}C NMR spectrum is also consistent with **10a** but not **11**; the carbon atom bearing the phosphorus substituent is a doublet, J = 178 Hz, but would be expected to be a doublet of doublets in **11** $^1J_{C-P}$ = 175, $^2J_{C-P}$ = 6–10 Hz.[7]

Hydrolysis of **10a** to the acid **10b** provided further support for the assignment of structure: NMR spectra supported the assignment of structure **10b** to the diphosphonic acid.

The rearrangement of bis(phosphate) **9** induced by lithium diisopropylamide proceeds quite cleanly to produce diphosphonate **12a**. Phosphorus NMR exhibits a major



a, R = Et; b, R = H

peak at 21.1 ppm characteristic of the phosphonate. Confirmation of the structure was obtained by hydrolysis with HCl in aqueous dioxane whereupon bis(phosphonic acid) **12b** was isolated as its anilinium salt.

Conversion of the Phosphonate Esters to Phosphonic Acids. The standard procedure for the conversion of diethyl phosphonates to the corresponding acids is heating at reflux with aqueous hydrochloric acid.[8] Although this procedure is satisfactory for many phosphonates it is not suitable for molecules containing acid-sensitive functions or where the resulting phosphonic acid is not stable to acid or elevated temperatures. The generally accepted procedure where mild conditions are required is treatment of the ester with trimethylsilyl bromide or iodide in acetonitrile followed by hydrolysis, both at room temperature.[9] When the conversion of the phosphonate esters

$$RP{=}O(OEt)_2 + 2Me_3SiX \rightarrow RP{=}O(OSiMe_3)_2 \xrightarrow{H_2O} RP{=}O(OH)_2$$

5, **7**, **10**, and **12** into the corresponding acids was attempted with aqueous hydrochloric acid significant differences in behavior were observed. Although **10** and **12** were converted virtually quantitatively to the diphosphonic acids with HCl the other esters suffered C–P bond cleavage. By the use of the trimethylsilyl halide procedure these esters yielded the acids.

There seems to be no obvious explanation for the greater acid stability of the diphosphonic acid from **10** or **12** in comparison with the other phenolic phosphonic acids.

Experimental Section

Melting points were obtained on a Melt Temp melting point apparatus and are uncorrected. The elemental analyses were performed by Galbraith laboratories, Knoxville, TN and Petrolite Corporation, Analytical Section. ^{31}P and ^{13}C spectra were obtained with a Jeol FX-60 spectrometer operating at 24.15 and 15.04 MHz, respectively. The chemical shift (+δ) values are downfield from H_3PO_4 (cap) for ^{31}P spectra and from Me_4Si for ^{13}C spectra. ^1H NMR spectra were obtained with a Perkin-Elmer R-32 spectrometer (90 MHz) using Me_4Si for $CDCl_3$ solutions and the sodium salt of 3-(trimethylsilyl)propionic acid for D_2O solutions as internal standards.

Diethyl phenyl phosphate (**4a**) and diethyl 4-methoxyphenyl phosphate (**4b**) were prepared by the method of Kenner and Williams.[5]

Diethyl (2-Hydroxyphenyl)phosphonate (5a). To 22.2 g of diisopropylamine in THF (100 mL) under nitrogen atmosphere at −78 °C was added *n*-butyllithium (137.6 mL of a 1.6 M solution). The mixture was stirred for 30 min when a white slurry was formed. Diethyl phenyl phosphate (23.0 g) dissolved in 100 mL of THF was next syringed into the reaction mixture. The mixture was stirred at −78 °C for 1 h and then poured over a mixture of 300 mL of saturated aqueous NH_4Cl and 300 mL of ether. The ether layer was separated and dried over anhydrous Na_2SO_4. The solvent was next removed on a rotary evaporator and the crude product was distilled to give 18.7 g (81%) of pure diethyl (2-hydroxyphenyl)phosphonate; bp 110–111 °C (0.7 mm) (lit.[1] bp 92–97 °C (0.05 mm)); ^1H NMR (CCl_4/Me_4Si) 1.30 (t, J = 7 Hz, 6 H, CH_3), 3.80–4.30 (m, 4 H, CH_2), 6.70–6.95 (m, 2 H, Ar), 7.15–7.45 (m, 2 H, Ar), 9.60 (s, OH); ^{13}C NMR 16.10 (d, J = 7.82 Hz, CH_3), 62.52 (d, J = 5.86, CH_2), 108.95 (d, J = 179.69, C_1), 117.39 (d, J = 11.71, C_3), 119.40 (d, J = 13.67, C_5), 131.61 (d, J = 5.85, C_6), 135.06 (C_4), 161.93 (d, J = 7.81, C_2); ^{31}P NMR +22.30.

Diethyl (2-Hydroxy-5-methoxyphenyl)phosphonate (5b). Starting with 0.1 mol of diethyl 4-methoxyphenyl phosphate, the yield was 21.4 g (82%): bp 145–147 °C (0.65–0.70 mm) (lit.[1] bp 117–121 °C (0.05 mm); ^1H NMR ($CDCl_3/Me_4Si$) 1.30 (t, J = 7 Hz, 6 H, CH_3), 3.75 (s, 3 H, OCH_3), 3.90–4.30 (m, 4 H, CH_2), 6.75–7.10 (m, 3 H, Ar), 8.85 (OH); ^{13}C NMR ($CDCl_3/Me_4Si$) 16.16 (d, J = 5.86, CH_3), 55.71 (s, OCH_3), 62.78 (d, J = 5.86, CH_2), 110.31 (d, J = 201.17, C_1), 115.22 (d, J = 6.83 Hz, C_6) 119.70 d, J = 14.65, C_3), 123.76 (C_4), 153.46 (d, J = 16.6, C_5), 157.23 (d, J = 7.84, C_2); ^{13}P NMR +21.90.

(2-Hydroxyphenyl)phosphonic Acid (5c). To a mixture of diethyl (2-hydroxyphenyl)phosphonate (4.6 g), acetonitrile (30 mL), and sodium iodide (9.0 g) under nitrogen was added chlorotrimethylsilane (6.5 g). The mixture was stirred at 40 °C for 1 h and then at room temperature for 1.5 h. It was next filtered to remove sodium chloride and volatiles were removed on a rotary exaporator. Chloroform (30 mL) was added to the residue when some more sodium chloride precipitated out. After the removal of NaCl by filtration, chloroform was removed on a rotary evaporator. Water (20 mL) was added to the crude silyl ester. After 2 h stirring at room temperature the aqueous layer was separated. A 7-mL sample of the aqueous solution was freeze-dried to yield crude (2-hydroxyphenyl)phosphonic acid. The crude acid was dissolved in ethanol (16 mL) and aniline (0.48 g in 16 mL of ethanol) was added. The mixture was warmed and on cooling the anilinium salt of (2-hydroxyphenyl)phosphonic acid crystallized out slowly. After one crystallization from 95% ethanol, the yield was 1.11 g (65%): mp 169–170 °C; ^1H NMR (D_2O) 6.88–7.18 (m, 2 H, Ar), 7.24–7.72 (m, 7 H, Ar); ^{13}C NMR (D_2O), 117.1 (11), 119.2 (172), 121.1 (14), 133.0 (8), 134.5, 158.5 (6) (aniline, 123.8, 130.0, 131.2); ^{31}P NMR +13.54. Anal. Calcd for $C_{12}H_{14}NO_4P$: C, 53.93; H, 5.24; N, 5.24; P, 11.61. Found: C, 53.84; H, 5.42; N, 5.17; P, 11.60.

(2-Hydroxy-5-methoxyphenyl)phosphonic Acid (5d). This was isolated as an anilinium salt in 54.3% yield: mp 163–165 °C; ^1H NMR (D_2O) 3.80 (s, 3 H, OCH_3), 6.75–7.65 (m, 8 H, Ar); ^{13}C NMR (D_2O), 117.0 (8), 118.2 (12), 119.7 (172), 120.6, 152.6 (8), 153.0 (12), (aniline, 123.8, 130.0, 131.0); ^{31}P NMR +13.01. Anal.

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Calcd for $C_{13}H_{16}NO_5P$: C, 52.52; H, 5.39; N, 4.71; P, 10.43. Found: C, 52.06; H, 5.40; N, 4.25; P, 10.75.

Diethyl 2-(Diethoxyphosphinyl)phenyl Phosphate (6a). To a mixture of diethyl (2-hydroxyphenyl)phosphonate (23.0 g), carbon tetrachloride (30 mL), and diethyl phosphite (14.35 g) cooled to 0 °C was carefully added dropwise triethylamine (10.5 g). The mixture was stirred overnight at room temperature. Water was next added and the organic layer was separated and dried over anhydrous Na_2SO_4. Removal of solvent on rotary evaporator gave diethyl 2-(diethoxyphosphinyl)phenyl phosphate as an oil: 25.5 g (80%); ^1H NMR ($CDCl_3/Me_4Si$) 1.32 (m, 12 H, CH_3), 3.95–4.50 (m, 8 H, CH_2), 7.10–7.35 (m, 1 H, Ar), 7.40–7.65 (m, 2 H, Ar), 7.75–8.05 (m, 1 H, Ar); ^{31}P NMR +15.02 (d, J_{P-P} = 2.9 Hz), –7.92 (d, J_{P-P} = 2.9 Hz).

Tetraethyl (2-Hydroxy-1,3-phenylene)bis(phosphonate) (7a). To 8.88 g of diisopropylamine dissolved in 100 mL of THF at –78 °C under nitrogen was added 55.04 mL of *n*-butyllithium. The mixture was stirred for 30 min and diethyl 2-(diethoxyphosphinyl)phenyl phosphate (14.64 g) dissolved in 100 mL of THF was added with a syringe. The mixture was stirred at –78 °C for 1 h. The dry ice–acetone bath was then removed and the reaction mixture was allowed to stir for an additional 1 h. It was next poured over a mixture of 300 mL of saturated aqueous ammonium chloride and 300 mL of ether. The ether layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic extracts were dried over anhydrous Na_2SO_4. Removal of solvents on a rotary evaporator left tetraethyl (2-hydroxyphenylene)-1,3-bis(phosphonate) as an oil: 11.6 g (78%); ^1H NMR ($CDCl_3/Me_4Si$) 1.32 (t, J = 7 Hz, 12 H, CH_3), 3.95–4.40 (m, 8 H, CH_2), 6.80–7.05 (m, 1 H, Ar), 7.65–7.95 (q, 2 H, J_{H-H} = 8 Hz, J_{P-H} = 15 Hz); ^{31}P NMR +18.70.

(2-Hydroxy-1,3-phenylene)bis(phosphonic acid) (7c). When the procedure as described above for (2-hydroxyphenyl)-phosphonic acid was followed, this acid was isolated as a bis-(anilinium salt) in 50% yield: mp 179–181 °C (from 95% ethanol); ^{31}P NMR +12.86; ^1H NMR 7.25–7.85 (m, Ar); ^{13}C NMR (D_2O) 120.3 (14), 120.8 (173,8), 136.6 (4), 160.6 (aniline, 123.9, 130.1, 131.3). Anal. Calcd for $C_{18}H_{22}N_2O_7P_2$: C, 49.09; H, 5.00; N, 6.36; P, 14.09. Found: C, 49.23; H, 5.24; N, 6.23; P, 14.02.

Diethyl 2-(Diethoxyphosphinyl)-4-methoxyphenyl Phosphate (6b). When the starting material was 13.0 g of diethyl (2-hydroxy-5-methoxyphenyl)phosphonate, the yield was 18.3 g (92.5%): ^1H NMR ($CDCl_3/Me_4Si$) 1.23 (t, 12 H, CH_3), 3.80 (s, 3 H, OCH_3), 3.95–4.50 (m, 8 H, CH_2), 6.72–7.65 (m, 3 H, Ar); ^{31}P NMR +14.84 (d, J_{P-P} = 2 Hz), –7.34 (d, J_{P-P} = 2 Hz) with a small amount of impurity at +21.96.

Tetraethyl (2-Hydroxy-5-methoxy-1,3-phenylene)bis-(phosphonate) (7b). When the starting material was 15.84 g of diethyl 2-(diethoxyphosphinyl)-4-methoxyphenyl phosphate, the yield of crude product was 14.8 g (93%): ^1H NMR ($CDCl_3/Me_4Si$) 1.34 (t, J = 7 Hz, 12 H, CH_3), 3.80 (s, 3 H, OCH_3), 3.95–4.45 (m, 8 H, CH_2), 7.32 (d, J = 16 Hz, 2 H). In addition, signals from the probable impurity diethyl 2-hydroxy-5-methoxyphenyl phosphate were evident at 3.78 and 6.72–7.05 (m, Ar). ^{31}P NMR +18.96, +21.96 (impurity).

(2-Hydroxy-5-methoxy-1,3-phenylene)bis(phosphonic acid) (7d). This was isolated as the bis(anilinium salt) in 29% yield: mp 178–179 °C (from 95% ethanol); ^1H NMR (D_2O) 3.80 (s, 3 H, OCH_3), 7.15–7.65 (m, 12 H, Ar); ^{31}P NMR +12.61; ^{13}C NMR (D_2O) 121.8 (4), 122.0 (172,10), 152.0 (17), 154.8, (aniline, 123.9, 130.1, 131.2). Anal. Calcd for $C_{19}N_{24}N_2O_8P_2$: C, 48.51; N, 5.10; H, 5.96; P, 13.19. Found: C, 48.11; H, 5.24; N, 5.75; P, 13.36.

Tetraethyl 1,4-Phenylene Bis(phosphate) (8). To a mixture of hydroquinone (33 g), carbon tetrachloride (180 mL), and diethyl phosphite (86.6 g) cooled to 0 °C was added triethylamine (63 g) dropwise. The mixture was stirred overnight at room temperature, water (200 mL) was added, and the organic layer was separated and dried over anhydrous Na_2SO_4. Removal of solvent on a rotary evaporator left tetraethyl 1,4-phenylene bis(phosphate) as a colorless liquid, 84.5 g (75%): ^1H NMR ($CDCl_3/Me_4Si$) 1.30 (t, J = 7 Hz, 12 H, CH_3), 3.95–4.20 (m, 8 H, CH_2), 7.16 (s, 4 H, Ar); ^{13}C NMR ($CDCl_3/Me_4Si$) 17.20 (d, J = 5.9 Hz, $POCH_2CH_3$), 65.77 (d, J = 5.9 Hz, $POCH_2CH_3$), 122.20 (d, J = 3.9 Hz, C_2, C_3, C_5, C_6), 148.69 (d, J = 7.8 Hz, C_1 and C_4); ^{31}P NMR –6.35.

Tetraethyl (2,5-Dihydroxy-1,4-phenylene)bis(phosphonate) (10a). To a solution of diisopropylamine (22.4 g) in THF (100 mL) at –78 °C under nitrogen was added *n*-butyllithium (136.6 mL). The mixture was stirred for 30 min and tetraethyl 1,4-phenylene bis(phosphate) (19 g) dissolved in 100 mL THF was then added with a syringe. The mixture was stirred at –78 °C for 1 h. Dry ice–acetone bath was next removed and the mixture was allowed to stir for an additional 1 h. It was next poured over a mixture of a saturated solution of ammonium chloride (150 mL) and ether (200 mL). The ether layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic extracts were dried over anhydrous Na_2SO_4. Removal of solvent on a rotary evaporator gave tetraethyl (2,5-dihydroxy-1,4-phenylene)bis(phosphonate) as a pinkish solid which was purified by recrystallization from methylene chloride/petroleum ether. The yield of white crystalline solid was 10.60 g (55.7%): mp 219–220 °C; ^1H NMR ($CDCl_3/Me_4Si$) 1.34 (t, J = 7 Hz, 12 H, CH_3) 4.16 (q, J = 7 Hz, 8 H, CH_2), 7.00 (q, 2 H, $J_{P-C-C-H}$ = 15 Hz, $J_{P-C-C-C-H}$ = 8 Hz), 9.65 (s, 2 H, OH, exchangeable with D_2O); ^{13}C NMR ($CDCl_3/Me_4Si$) 17.3 (d, J = 5.9 Hz, CH_3), 64.3 (d, J = 5.9 Hz, CH_2), 117.6 (d, J = 177.7 Hz, C_1 and C_4), 120.5 (dd, J_{P-C-C} = 5.8 Hz and $J_{P-C-C-C}$ = 13.8 Hz, C_3 and C_6), 154.7 (dd, J_{P-C-C} = 5.9 Hz, $J_{P-C-C-C}$ = 18.5 Hz, C_2 and C_5); ^{31}P NMR +19.37. Anal. Calcd for $C_{14}H_{24}O_8P_2$: C, 43.97; H, 6.28; P, 16.23. Found: C, 43.90; H, 6.20; P, 16.45.

(2,5-Dihydroxy-1,4-phenylene)bis(phosphonic acid) (10b). A mixture of tetraethyl (2,5-dihydroxy-1,4-phenylene)bis(phosphonate) (5 g), 18% HCl (50 mL), and dioxane (50 mL) was refluxed for 16 h. The solvents were removed on a rotary evaporator and the residue was refluxed with 18% HCl (50 mL) for 2 h. Removal of water and HCl on a rotary evaporator gave a syrup which solidified on trituration with acetonitrile. The solid was collected by filtration and crystallized from water–acetonitrile to yield colorless long needles. The yield was quantitative: mp 219–220 °C; ^1H NMR 7.10 (d,d $J_{P-C-C-H}$ = 16 Hz, $J_{P-C-C-CH}$ = 7 Hz); ^{31}P NMR (D_2O) + 12.94; ^{13}C NMR (D_2O), 120.4 (10,10), 122.7 (178,2), 152.0 (17,2). Anal. Calcd for $C_6H_8O_8P_2$: C, 26.66; H, 2.96; P, 22.96. Found: C, 26.60; H, 3.09; P, 22.10.

Tetraethyl 1,2-Phenylene Bis(phosphate) (9). From 16.5 g of catechol, the yield was 54.2 g (94.5%): ^{31}P NMR –6.47; ^{13}C NMR ($CDCl_3/Me_4Si$) 17.02 (d, J = 6.7 Hz, CH_3), 65.94 (d, J = 6.11 Hz, CH_2), 122.43 (C_3 and C_6), 126.65 (C_4, C_5), 142.70 (t, J = 6.7 Hz, J_{POCC} = 6.7 Hz, C_1 and C_2).

Tetraethyl (2,3-Dihydroxy-1,4-phenylene)bis(phosphonate) (12a). The procedure was essentially the same as for tetraethyl (2,5-dihydroxy-1,4-phenylene)bis(phosphonate) except that after the removal of dry ice–acetone bath, it was found preferable to let the mixture stir for 2 additional hours. After 1 h a solid started to separate and increased as the reaction progressed. When the reaction began with 19.0 g of tetraethyl phenyl-1,2-diphosphate, the yield of the crude product was 18.3 g (96%): ^1H NMR (D_2O) 1.30 (t, CH_3), 3.85–4.30 (m, CH_2), 6.65–6.90 (dd, J = 11 Hz, J = 6 Hz); ^{31}P NMR +21.10 with impurities at +22.36 and +18.95.

(2,3-Dihydroxy-1,4-phenylene)bis(phosphonic acid) (12b). Tetraethyl (2,3-dihydroxy-1,4-phenylene)bisphosphonate) (13.6 g) was dissolved in a mixture of 136 mL of dioxane and 136 mL of 18% HCl. The solution was refluxed for 16 h. The solvents were removed on a rotary evaporator. The residue was refluxed for 2 h with 136 mL of 18% HCl. The solvent was again removed on a rotary evaporator. The residue was taken up in 100 mL of water and filtered to remove black material. The filtrate was concentrated to a small volume on a rotary evaporator and acetonitrile was next added to cloudiness. On allowing to stand, a white solid slowly crystallized out (1.7 g, 17.7%); mp >300 °C; ^{13}C NMR (D_2O/dioxane) 121.10 (dd, J = 2.4 Hz, J = 173.34 Hz), 122.88 (dd, J = 6.1 Hz, J = 15.87 Hz), 147.51 (dd, J = 3.66 Hz, J = 14.65 Hz).

For analytical characterization an alternative workup was followed.

The filtrate on removal of solvents gave 8.8 g of dark oil which was dissolved in 95% ethanol (50 mL). Aniline (6.06 g) dissolved in 50 mL of 95% ethanol was added and the mixture was warmed and set aside when a white crystalline solid 6.7 g (41%) precipitated out which was collected by filtration. A portion recrystallized from ethanol melted at 211–213 °C: ^{31}P NMR +12.71; ^1H NMR 7.02 (dd, $J_{P-C-C-H}$ = 12 Hz, $J_{P-C-C-C-H}$ = 6 Hz, 2 H, Ar), 7.15–7.55 (m, 10 H, Ar). Analysis Calcd for $C_{18}H_{22}N_2O_8P_2$: C 47.37;

H, 4.82; N, 6.14; P, 13.60. Found: C, 47.54, H, 5.00; N, 6.06; P, 13.90.

Registry No. **4a**, 2510-86-3; **4b**, 5076-68-6; **5a**, 69646-14-6; **5b**, 80615-41-4; **5c**, 53104-46-4; **5d** anilinium salt, 91633-06-6; **6a**, 91633-07-7; **6b**, 91633-08-8; **7a**, 91633-09-9; **7b**, 91633-10-2; **7c** anilinium salt, 91633-12-4; **7d** anilinium salt, 91633-14-6; **8**, 57246-14-7; **9**, 37521-98-5; **10a**, 91633-15-7; **10b**, 91633-16-8; **12a**, 91633-17-9; **12b**, 91633-18-0; $(i\text{-Pr})_2NH$, 108-18-9; BuLi, 109-72-8; $(EtO)_2POH$, 762-04-9; $(i\text{-Pr})_2NLi$, 4111-54-0; sodium iodide, 7681-82-5; chlorotrimethylsilane, 75-77-4; hydroquinone, 123-31-9; catechol, 120-80-9.

Structural Alteration of Nucleic Acid Bases by Bromomalonaldehyde[1]

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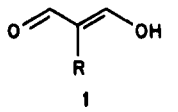
Bromomalonaldehyde (BMDA), prepared by bromination of malonaldehyde with elemental bromine, has been employed to modify a number of nucleic acid bases. These reactions transform pyrimidine and purine bases into modified systems containing etheno and etheno carboxaldehyde moieties, among other products. The structures of these modified bases were established by UV, mass spectral, and high-field NMR data. Fluorescence emission data for some of the adducts are of significance. The general mechanism of modification is discussed.

In the course of some work in our laboratory on the behavior of the ubiquitous natural compound malonaldehyde (MDA, 1, R = H) toward biomolecules,[2,3] we needed some information on the comparative reactivity of 2-substituted malonaldehydes. In particular, the structural nature of modification of nucleic acid bases was of interest in this work. The chemical modification of the base moiety of nucleic acids is also of synthetic and biological interest. For example, 1,N^6-ethenoadenosine and 3,N^4-ethenocytidine are both able to substitute for adenine nucleotides in some biological systems.[4] The observation that some modified bases are fluorescent has generated considerable interest in their use as biological probes in the structure and mechanism of action of nucleic acids and some enzymes and coenzymes.[4-15] Ethenoadenine derivatives exhibit fluorescence emission in the range of 410 nm with quantum yields of the order of 0.56. However, the use of ethenocytidine derivatives as biological probes has been limited by their inappropriate fluorescence emission wavelengths and low quantum yields.[4,16] The search therefore continues for cytidine derivatives which possess fluorescence characteristics that allow for ready detection in biological systems. In this paper we report on the interesting modifications of a number of purine and pyrimidine bases by bromomalonaldehyde (BMDA).



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Results and Discussion

Although the chemistry of halogenated malonaldehydes (1, R = Cl, Br, I, F) has been explored to some extent mainly for the synthesis of heterocycles,[17-20] little is known about the reactivity of these compounds toward nucleic acid bases. Bromomalonaldehyde can be prepared by bromination of MDA with elemental bromine as described by Trofimenko.[21] Modification of the pyrimidine and purine bases was accomplished by stirring the substrate in an aqueous acidic medium with BMDA at 60 °C. The reactions were followed by UV spectral methods and terminated when the absorption for the bathochromically shifted product peak had maximized. Separation and purification of the modified bases and derivatives were achieved by preparative-layer chromatography on silica gel or by HPLC on Amberlite XAD-4 resin.

The reaction of BMDA with cytidine afforded a yellow crystalline compound in 43% yield (mp 202–204 °C) with UV absorption shifted to 325 nm (ϵ 10 500) which is indicative of more extended conjugation. The molecular ion in its mass spectrum at m/z 295 suggested the formation of a 1:1 adduct in which bromine was not present. The 360-MHz ^1H NMR spectrum in Me_2SO-d_6 showed the presence of 4 non-ribosyl protons at δ 6.91 (d, J = 7.8 Hz), 8.12 (d, J = 7.8 Hz), 8.16 (s), and 10.57 (s). Three additional carbon resonances (compared to cytidine) at δ 130.0, 139.6, and 181.0 suggesting the presence of a bicyclic base carrying an exocyclic vinylogous amide carbonyl group were present in its high-field ^{13}C NMR spectrum in

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