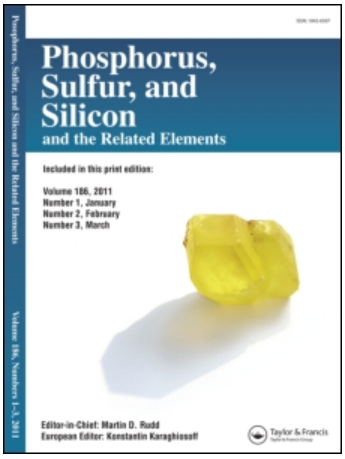

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NITRIC ACID OXIDATION OF 3-PHOSPHONO-3,5,5-TRIMETHYLCYCLOHEXANONE

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Ammonium metavanadate catalysed nitric acid oxidation of 3-phosphono-3,5,5-trimethylcyclohexanone **1** gave a mixture of the three dicarboxylic acids **2**, **3** and **4** which were characterised by isolation (**2**) or synthesis (**3**, **4**).

INTRODUCTION

Alkylphosphonic acids containing one or more carboxylic acid substituents have valuable properties as ferrous corrosion inhibitors and scale control additives for circulating water systems. One successful approach to the synthesis of such molecules has been the elaboration of triethylphosphonoacetate[1] and tetraethylphosphonosuccinate[2] by alkylation with alkyl halides and/or olefins. In a new approach to sterically congested phosphono-carboxylic acids we have examined the oxidative cleavage of the readily accessible γ-ketophosphonic acids. We report here the nitric acid oxidation of 3-phosphono-3,5,5-trimethylcyclohexanone and the characterisation of the three major oxidation products.

RESULTS AND DISCUSSION

Ammonium metavanadate catalysed nitric acid oxidation of 3-phosphono-3,5,5-trimethylcyclohexanone **1** gave, after evaporation of the reaction mixture a pale green glass whose ^{31}P-NMR spectrum showed two broad resonances in the phosphonic acid region at 32 and 25 ppm and a smaller amount (ca. 5% of total) of phosphoric acid ($\delta = 0$). On standing, a concentrated aqueous solution of the oxidation product deposited crystals of 3-phosphono-3,5,5-trimethylhexanedioic acid **2**, which had a ^{31}P chemical shift of 31.3 and in its ^{1}H-NMR spectrum showed a characteristic phosphorus coupled doublet (δ 2.7, $J_{P-C-CH_2} = 20$ Hz) for the 2-CH_2 group. After treatment to remove further **2**, phosphoric acid and metavanadate ion the residue was reexamined by ^{31}P-NMR. **2** was still present (ca. 5%) and the 25 ppm signal was now sharply resolved into two signals at 24.06 (ca. 20%) and 24.92 (ca. 70%). GC/MS examination of the methyl esters of this mixture indicated that the major component was the expected isomeric hexanedioic acid **3** and the minor component the homologous pentanedioic acid **4**[3] (Scheme 1).

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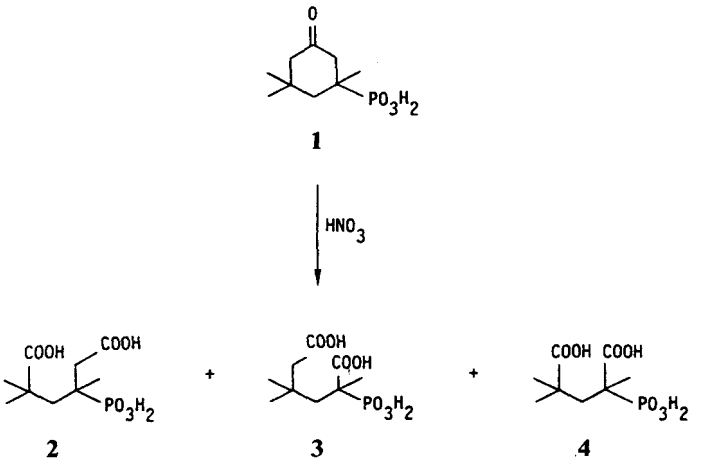


SCHEME 1

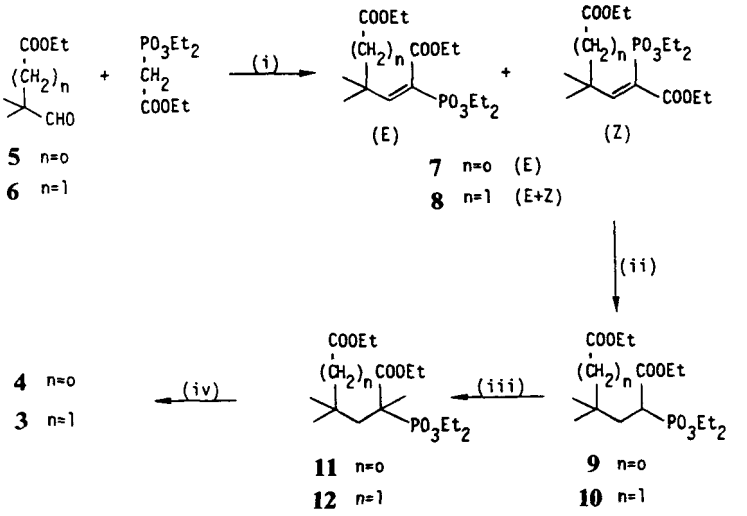
The samples of **3** and **4** required for characterisation, corrosion testing, and development of analytical methods for the mixture were synthesised according to Scheme 2. Condensation of the aldehyde **5** with triethylphosphono acetate using Lehnerts procedure[4] gave specifically the E-olefin **7** ($J_{P\overset{\frown}{=}H}$ = 23 Hz) in 68% yield. The E-stereospecificity of the reaction with a range of aldehydes was reported by Lehnert.[4] With aldehyde **6** a 1:1 mixture of E-**8** ($J_{P\overset{\frown}{=}H}$ = 26 Hz) and Z-**8** ($J_{P}{}^{H}\!\!=\!\!\diagup$ = 47 Hz) was formed in 60% yield. This reaction neatly overcame the difficulty of forming the 2,3-bond in **7** and **8** as a single bond eg. by alkylation of triethyl 2-phosphonopropionate with alkyl halides of neopentyl-type structure.

Hydrogenation of the olefins **7** and **8** gave the substituted phosphonoacetates **9** and **10**. It was important at this stage to achieve a complete methylation of the anions of **9** and **10**, since separation of **11** from **9** or **12** from **10** was extremely difficult. This was achieved by addition of **9** or **10** to a mixture of sodium hydride and a tenfold excess of MeI in dioxan. The sterically congested esters **11** and **12** required a full 24 hr reflux in conc. HCl to achieve complete hydrolysis to the acids **4** and **3** which had ^{31}P chemical shifts of 23.0 and 24.4 ppm, respectively.

The mixture of acids **2**, **3** and **4** and particularly the acid **2** were very active corrosion inhibitors for ferrous metals in circulating industrial water systems, complete protection against corrosion being achieved with concentrations of between 5 and 10 ppm in the circulating water.[5]

EXPERIMENTAL PART

1. *General.* Melting points (mp) are uncorrected. ^1H-NMR. spectra were recorded on Varian-T60 and EM-360A, Jeol MH-100 and Perkin Elmer R-34 instruments and are reported in ppm from internal tetramethylsilane or 3-(trimethylsilyl)-1-propane sulphonic acid, sodium salt (for aqueous solutions). ^{31}P-NMR. spectra were recorded on a Jeol FX-60 instrument at 24.15 MHz in the Fourier transform mode and are reported in ppm from external H_3PO_4 (downfield signals positive). Coupling constants are given in Hz.



(i) $TiCl_4$, N-methylmorpholine;
(ii) H_2, PtO_2;
(iii) NaH, MeI;
(iv) cHCl.

SCHEME 2

2. *Preparation of starting materials.*

2.1. Ethyl 2-formyl-2-methylpropionate **5** (b.p. 56–60°C/12 Torr, Lit.[6] 65–66°C/20 Torr) was prepared by Rosenmund reduction in toluene of the acid chloride (b.p. 64°C/12 Torr) prepared from ethyl dimethylmalonate and thionylchloride.

2.2. Ethyl 3-formyl-3-methylpropionate **6** (b.p. 86–88°C/12 Torr) was prepared by Rosenmund reduction in toluene of the acid chloride prepared as described by Julia *et al.*[7]

2.3. 3-Phosphono-3,5,5-trimethylcyclohexanone **1**: 100 g (0.36 mol) diethyl 3-phosphono-3,5,5-trimethylcyclohexanone[8] in 1000 ml 18% hydrochloric acid was refluxed 18 hr then evaporated i.V. and the solid residue triturated with ether and filtered to give 69 g (86%) **1**, m.p. 168–170°C. ^{1}H-NMR. (100 MHz, $DMSOd_6$): 1.0 (s, 3 H, CH_3—C(5)); 1.05 (s, 3 H, CH_3—C(5)); 1.2 (d, J_{P-C-CH_3} = 18, 3 H, CH_3—C(3)); 1.4–2.9 (m, 6 H, 3 × CH_2); ^{31}P-NMR. (DMSO): 29.1. $C_9H_{17}O_4P$(220.21): Calc.: C, 49.09; H, 7.78; P, 14.06. Found: C, 49.59; H, 8.03; P, 13.93.

3. *Nitric acid oxidation of* **1** *and isolation of 2,2,4-trimethyl-4-phosphonohexanedioic acid* **2**. A hot solution (80–90°C) of 18 g (0.082 mol) of **1** in 18 ml water was added dropwise over 45 min. from a steam-jacketed dropping funnel to a stirred solution of 0.05 g ammonium metavanadate in 19 ml (0.43 mol) 70% nitric acid at 55–60°C. The exothermic reaction was maintained at 55–60°C by a controlled rate of addition and occasional water cooling. The resulting solution was heated at 55–60°C for a further 5 hr then evaporated i.V. to give 21.4 g of a pale green hygroscopic glass ^{31}P-NMR. (H_2O): 32 and 25 (broad).

On standing, a concentrated aqueous solution of this oxidation mixture deposited crystals which were recrystalised from water to give **2**, m.p. 167–169° ^{1}H-NMR. (60 MHz, D_2O): 1.3 (s, 6 H, $C(CH_3)_2$); 1.33 (d, J_{P-C-CH_3} = 17, 3 H, CH_3—C(4)); 2.17 and 2.2 (inner doublets of ABP system for —CH_AH_B—$C(CH_3)PO_3H_2$—, J_{AB} not discernable, J_{AP} = 8, J_{BP} = 11, 2 H); 2.72 (d, J_{P-C-CH_2} = 20, 2 H, H_2C(5)); ^{31}P-NMR. (H_2O): 31.3. $C_9H_{17}O_7P$ 1.5 H_2O (295.23): Calc.: C, 36.62; H, 6.83; P, 10.50. Found: C, 36.79; H, 6.84; P, 10.55.

A further crop of **2** was obtained by prolonged storage of the liquors at 0°C. The filtrate was then evaporated, dissolved in ethanol and cyclohexylamine added. The insoluble cyclohexylaminephosphate was filtered and the filtrate evaporated. The residue was then dissolved in water and passed down a column of IR120 ion exchange resin in the acid form. The acidic eluates were evaporated and the residue examined by ^{31}P-NMR. The 32 ppm signal for 2 was much reduced (~ 7% of total) and the 25 ppm

signal now sharply resolved into two signals at 24.06 (~ 20%) and 24.92 (~ 70%). A sample of this residue was dissolved in trimethylorthoformate (5 ml/g) and heated at 100°C for 24 hr. Volatiles were removed i.V. and the methyl esters distilled in a Kugelrohr at 150–160°C/0.1 Torr. GC/MS examination of these methyl esters (AEI MS/30 coupled with Pye 104 with silicon membrane interface, 5% OV-1, 200–300°C at 12°/min.) showed the more volatile component with a $M^+ - 15$ ion at 295 and the less volatile component with an $M^+ - 15$ ion at 309.

4. *Synthesis of 2,4,4-trimethyl-2-phosphonopentanedioic acid* (**4**).

4.1. (E)-Tetraethyl 4,4-dimethyl-2-phosphonopent-2-enedioate (**7**). To 400 ml dry tetrahydrofuran at 0°C were added successively 38 g (0.2 mol) titaniumtetrachloride in 50 ml carbontetrachloride, 14.4 g (0.1 mol) aldehyde **5**, and 22.4 g (0.115 mol) triethylphosphonoacetate, then after 10 minutes stirring at 0° 40.4 g (0.4 mol) *N*-methylmorpholine in 60 ml tetrahydrofuran was added dropwise over 30 min. The dark red mixture was kept at 0°C for 22 hr then hydrolysed by pouring onto 100 ml ice and extracted with ether. The ether solutions were dried (Na_2SO_4), evaporated and the residue distilled i.V. to give 24.0 g. (68%) (E)-**7** as a colourless oil, b.p. 120–122°C/0.05 Torr ^{1}H-NMR. (100 MHz, CCl_4): 1.1–1.4 (m, 12 H, $OCH_2\underline{CH_3}$); 1.36 (s, 6 H, $(CH_3)_2C$); 3.7–4.2 (m, 8 H, $O\underline{CH_2}CH_3$); 6.6 (d, $J_{P-C=CH}$ = 23, 1 H, $C=\underline{CH}$). ^{31}P-NMR. (CCl_4): 13.3 (m, $J_{P-C=CH}$ = 23, J_{POCH_2} = 7.3). $C_{15}H_{27}O_7P$ (350.34): Calc.: C, 51.42; H, 7.77; P, 8.84. Found: C, 52.01; H, 7.88; P, 8.55.

4.2. Tetraethyl 4,4-dimethyl-2-phosphonopentanedioate **9**. 9.0 g (0.026 mol) **7** dissolved in 115 ml absolute ethanol was hydrogenated over 0.5 g platinum dioxide at 100°C and 100 atmospheres pressure with stirring for 7 hr. The solution was filtered, evaporated i.V. and the residue distilled i.V. to give 6.6 g (73%) **9** as a colourless oil, b.p. 116–118°C/0.05 Torr. ^{1}H-NMR. (220 MHz, CCl_4): 1.1 (s, 3 H, CH_3); 1.15 (s, 3 H, CH_3); 1.2–1.4 (m, 12 H, $OCH_2\underline{CH_3}$); 2.1 and 2.8 (ABXP system for $-CH_AH_BCH_XPO_3R_2-$ J_{AB} = 14, J_{AX} = 10, J_{AP} = 4, J_{BX} = 2, J_{BP} = 14, J_{XP} = 24, 3 H); 3.9–4.2 (m, 8 H, $O\underline{CH_2}CH_3$). ^{31}P-NMR. (CCl_4): 22.4. $C_{15}H_{29}O_7P$ (352.36): Calc.: C, 51.13; H, 8.3; P, 8.79. Found: C, 50.68; H, 8.46; P, 8.63.

4.3. Tetraethyl 2,4,4-trimethyl-2-phosphonopentanedioate **11**. 17.6 g (0.05 mol) **9** in 100 ml dry dioxan was added dropwise over 2 hr to a stirred suspension of 1.44 g (0.06 mol) sodium hydride in 400 ml dry dioxan containing 71 g (0.5 mol) methyliodide. The mixture was stirred a further 4 hr at room temperature and finally heated at reflux 2 hr. The mixture was filtered and evaporated i.V. and the residue distilled i.V. to give 10.5 g (57%) **11** as a colourless oil, b.p. 120–124°C/0.1 Torr ^{1}H-NMR. (60 MHz, $CDCl_3$): 1.1 (s, 3 H, CH_3—C(4)); 1.2 (s, 3 H, CH_3—C(4)); 1.35 (d, J_{P-C-CH_3} = 18, 3 H, CH_3—C(2)); 1.1–1.4 (3xt, 12 H, $OCH_2\underline{CH_3}$): 2.45 and 2.5 (inner doublets of ABP system for $-CH_AH_B-C(CH_3)PO_3R_2-$ J_{AB} not discernable, J_{AP} = 6, J_{BP} = 10); 3.9–4.5 (m, 8 H, $O\underline{CH_2}CH_3$). ^{31}P-NMR (CCl_4): 25.7. $C_{16}H_{31}O_7P$ (366.38): Calc.: C, 52.45; H, 8.53; P, 8.45. Found: C, 52.78; H, 8.91; P, 8.16.

4.4. 2,4,4-Trimethyl-2-phosphonopentanedioic acid **4**. 1.83 g (0.005 mol) **11** and 500 ml conc. hydrochloric acid were heated under reflux for 24 hr. The solution was evaporated i.V., the residue re-dissolved in 20 ml water and re-evaporated, then dissolved in 20 ml H_2O and treated with acid washed charcoal to remove the brown coloration, filtered and re-evaporated. The residue was dried i.V. over P_2O_5 and triturated with acetonitrile to give 0.8 g (69%) **4** as a white solid m.p. 185–186°C. ^{1}H-NMR. (100 MHz, D_2O): 1.08 (s, 3 H, CH_3—C(4)); 1.20 (s, 3 H, CH_3—C(4)); 1.25 (d, J_{P-C-CH_3} = 18, 3 H, CH_3—C(2)); 2.3 and 2.36 (unsymmetrical d, 2 H, $H_2C(3)$). ^{31}P-NMR. (H_2O): 23.0. $C_8H_{15}O_7P$ (254.17): Calc.: C, 37.8; H, 5.95; P, 12.19. Found: C, 37.10; H, 5.87; P, 11.81.

5. *Synthesis of 2,4,4-trimethyl-2-phosphonohexanedioic acid* **3**.

5.1. (E + Z)-Tetraethyl 4,4-dimethyl-2-phosphonohex-2-enedioate **8**. Using the method described in 4.1 with aldehyde **6** gave 60% of a ca. 1:1 mixture of (E) and (Z) **8** as a colourless oil, b.p. 140–142°C/0.05 Torr. ^{1}H-NMR. (60 MHz, CCl_4): 1.1–1.5 (m, 18 H, $OCH_2\underline{CH_3}$ and $C(CH_3)_2$); 2.4 (s, 1 H, CH_2 of Z-isomer) and 2.9 (s, 1 H, CH_2 of E-isomer); 3.7–4.4 (m, 8 H, $O\underline{CH_2}CH_3$); 6.6 (d, $J_{P-C=CH}$ = 26, 0.5 H, C=CH of E-isomer) and 7.2 (d, $J_{P-C=CH}$ = 46, 0.5 H, $C=\underline{CH}$ of Z-isomer). ^{31}P-NMR. (CCl_4): 10.5 (m, $J_{P-C=CH}$ = 47, J_{POCH_2} = 8.6, Z-isomer) and 13.8 (m, $J_{P-C=CH}$ = 27, J_{POCH_2} = 8.6, E-isomer).

5.2. Tetraethyl 4,4-dimethyl-2-phosphonohexanedioate **10**. Using the method described in 4.2 with **8** gave 76% **10** as a colourless oil, b.p. 138–140°C/0.05 Torr ^{1}H-NMR. (220 MHz, CCl_4): 0.95 (s, 6 H, $C(CH_3)_2$); 1.1–1.4 (m, 12 H, $OCH_2\underline{CH_3}$); 2.1 (s, 2 H, $H_2C(5)$); 1.9 and 2.85 (ABXP system for $-CH_AH_B-CH_XPO_3Et_2-$, J_{AB} = 16, J_{AX} = 11, J_{AP} = 3, J_{BX} = 15, J_{BP} = 14, J_{XP} = 24, 3 H); 3.9–4.2 (m, 8 H, $O\underline{CH_2}CH_3$). ^{31}P-NMR. (CCl_4): 22.9. $C_{16}H_{31}O_7P$ (366.38): Calc.: C, 52.45; H, 8.53; P, 8.45. Found: C, 51.64; H, 8.82; P, 8.48.

5.3. Tetraethyl 2,4,4-trimethyl-2-phosphonohexanedioate **12**. Using the method described in 4.3 with **10** gave 83% **12** as a colourless oil b.p. 130–132°C/0.02 Torr ^{1}H-NMR. (60 MHz, CCl_4): 1.0 (s, 6 H, $C(CH_3)_2$); 1.1–1.6 (m, 12 H, $OCH_2\underline{CH_3}$); 1.45 (d, J_{P-C-CH_3} = 18, CH_3—C(2)); 2.2 (s, 2 H, $H_2C(5)$);

1.6–2.6 (ABP multiplet for $-CH_AH_B-C(CH_3)PO_3Et_2-$, J_{AB} = 14, J_{AP} = 6, J_{BP} = 10 2 H); 3.8–4.5 (m, 8 H, OCH_2CH_3). ^{31}P-NMR. (CCl_4): 26.4. $C_{17}H_{33}O_7P$ (380.41): Calc.: C, 53.67; H, 8.74; P, 8.14. Found: C, 53.52; H, 8.94; P, 8.28.

5.4. 2,4,4-Trimethyl-2-phosphonohexanedioic acid **3**. Using the method described in 4.4 with **12** gave 81% **3** as a white solid, m.p. 199–201°C. ^{1}H-NMR (60 MHz, D_2O): 1.1 (s, 6 H, $C(CH_3)_2$); 1.53 (d, J_{P-C-CH_3} = 18, 3 H, $CH_3C(2)$); 2.35 (s, 2 H, $CH_2-C(4)$); 1.6–2.6 (ABP multiplet for $-CH_AH_B-C(CH_3)PO_3H_2-$, J_{AB} = 16, J_{AP} = 6, J_{BP} = 11, 2 H). ^{31}P-NMR. (H_2O): 24.7. $C_9H_{17}O_7P$ (268.2): Calc.: C, 40.3; H, 6.39; P, 11.55. Found: C, 40.06; H, 6.48; P, 11.74.

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