Stereochemical Studies on Some *vic*-Bisphosphonates

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The *erythro*- and racemic *threo*-forms of tetramethyl 1,2-dihydroxyethane-1,2-diylbisphosphonate have been identified and characterised by NMR analysis of their 2-ethoxy-1,3-dioxolane derivatives and by their independent conversion into tetramethyl *cis*- and *trans*-ethene-1,2-diylbisphosphonates respectively. Optimal conditions for the partial *cis*-reduction of tetraethyl ethyne-1,2-diylbisphosphonate have been identified. NMR data for the AA'XX' spectra of this range of two-carbon *gem*- and *vic*-bisphosphonates are provided and discussed.

We have recently used a range of *gem*-bisphosphonates in the synthesis of analogues of nucleoside di- and tri-phosphates,[1] dinucleoside tetraphosphates,[2] and dinucleoside triphosphates.[3] In particular, the *cis*-[4] and *trans*-[5] ethene-1,2-diylbisphosphonates possess significant potential as stretched transition state analogues for scission of the pyrophosphate linkage. At the same time, we have investigated the use of 1,2-dihydroxyethane-1,2-diylbisphosphonic acid, derived from the tetramethyl ester described by Mikroyannidis,[6] as a ligand for technetium-99m in bone scintigraphy.[7] This material was of undetermined stereochemistry and, in the light of the present growing demand for identification of the stereochemistry of pharmaceutically active compounds, we have reinvestigated that condensation process and now report some diastereoisomeric relationships involving a number of *vic*-bisphosphonates.

Results and Discussion

Tetramethyl 1,2-dihydroxyethane-1,2-diylbisphosphonate was prepared by the reaction between trimethyl phosphite and anhydrous glyoxal as described by Mikroyannidis.[6] We found that fractional crystallisation of the crude reaction product provided two isomers, rather than the single species reported. Isomer A **1a**, m.p. 170–172 °C, was spectroscopically identical with the product previously described of m.p. 190–192°C[6] while isomer B **4a**, m.p. 113–115 °C, had completely different spectroscopic features. Neither the ^{1}H nor the ^{31}P NMR spectra of these compounds permitted their stereochemical identification. Thus they were converted separately into the corresponding 2-ethoxy-1,3-dioxolanes **2a** and **5a** by reaction with triethyl orthoformate at elevated temperature. ^{1}H NMR analysis of **2a** identified its C_S symmetry by the magnetic equivalence of 4-H and 5-H, giving a phosphorus-coupled doublet at δ_H 4.46, $^2J_{PH}$ 14 Hz. We favour the *trans*-geometry at C-2 on the basis of steric considerations and the fact that we were unable to observe an NOE relating the different alkoxy groups. This analysis thus identifies **1a** as the *meso*-isomer, tetramethyl *erythro*-1,2-dihydroxyethane-1,2-diylbisphosphonate (Scheme 1).

On the other hand, the isomer **5a** showed dissymmetry through the non-equivalence of 4-H and 5-H, δ_H 4.74 and 4.90 (multiplets) (unexpectedly the proton-decoupled phosphorus NMR spectrum showed a singlet at δ_P + 20.1).†

† One possible explanation for this apparent magnetic equivalence of the phosphorus atoms of **5** is a rapid and reversible opening of one of the ring O–C(OEt) bonds to permit epimerisation at C-2 in the ring, as has been pointed out by a Referee.

Accordingly, isomer **4a** can be identified as the racemic modification of tetramethyl *threo*-1,2-dihydroxyethane-1,2-diylbisphosphonate (Scheme 1).

We further sought both to provide an independent means of identification of the stereochemistry of **1a** and **4a** and also to try to employ one of these species as an intermediate for the preparation of the *cis*-bisphosphonic acid **3c**. The *erythro*-isomer **1a** appeared to be a convenient precursor for this purpose through the application of one of a range of methods for the stereospecific *syn*-elimination processes by which *vic*-diols can be converted into alkenes. In the event, we found the acid catalysed fragmentation of 2-alkoxy-1,3-dioxolanes to be the most convenient for our purpose.[8] However, the conversion of **2a** into **3a** by heating with terephthalic acid at 170 °C provided the desired tetramethyl (*Z*)-ethenediylbisphosphonate **3a** only in admixture with partially de-esterified materials. This transformation, nonetheless, did provide the additional proof we sought for identification of the stereochemistry of **1a** since the mixed products all showed the δ_H 6.45 NMR signal characteristic of authentic **3a**. In the same way, the isomeric **5a** was converted into tetramethyl (*E*)-ethene-1,2-diylbisphosphonate **6a** in admixture with partially de-esterified material, and characterised by its δ_H 6.78 pseudotriplet (Scheme 1).

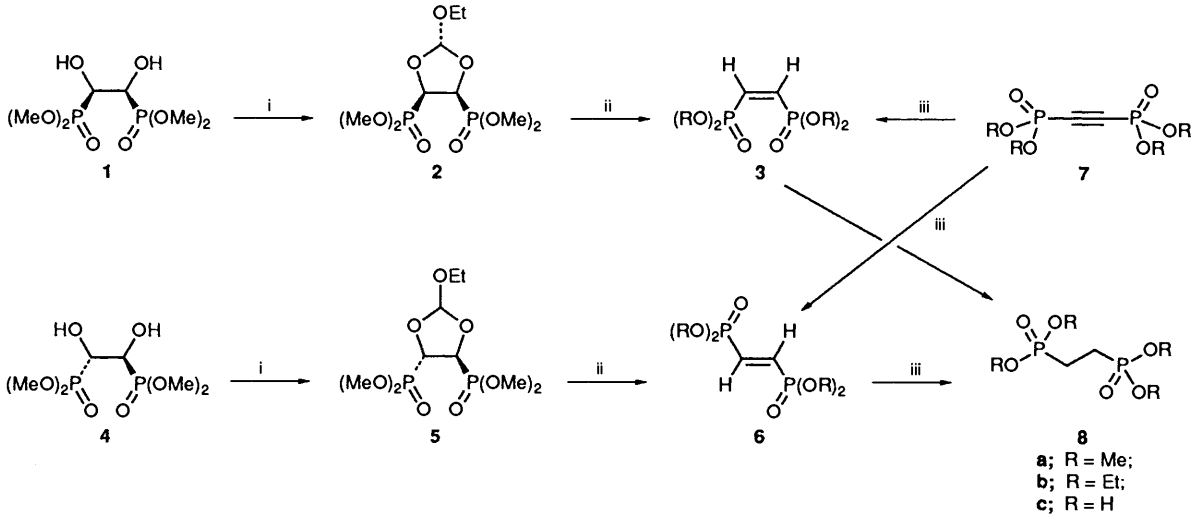
The tetraethyl ester of (*E*)-ethene-1,2-diylbisphosphonate **6b** is known to be readily accessible through a Michaelis–Arbusov reaction of (*E*)-1,2-dichloroethene catalysed by nickel(II) chloride.[5] As we were unable to achieve any reaction between triethyl phosphite and (*Z*)-1,2-dichloroethene under the same conditions, we carried out the preparation of (*Z*)-ethene-1,2-diylbisphosphonate by a Lindlar catalytic reduction[9] of tetraethyl ethyne-1,2-diylbisphosphonate **7b** with 10% palladium on barium sulphate as described by Honing and Martin.[4] In our hands, their procedure led to a mixture of the desired *cis*-product admixed with large amounts of the *trans*-isomer and also fully reduced tetraethyl ethane-1,2-diylbisphosphonate **8b** and starting material. Accordingly, we undertook a systematic analysis of the relative formation of these three products from the reduction of **7b** using a range of catalysts (Table 1).

It is evident that under the conditions used, palladium(0) on barium sulphate poisoned by quinoline is superior to any other catalyst for the selective reduction of the alkyne to the desired *cis*-alkenebisphosphonate. The alkyne is surprisingly resistant to reduction and we found that longer reaction times did not in any way improve the proportion of the desired *cis*-alkene material. Fortunately, it proved possible to achieve a good separation of the *cis*- and *trans*-alkenes both from the starting alkyne and from the fully reduced alkane bisphosphonates by the use of silica gel chromatography. The *trans*-alkene ester

Table 1 Hydrogenation of tetraethyl ethyne-1,2-diylbisphosphonate **7b**

Catalyst[a]	Product: tetraethyl 1,2-bisphosphonate			
	(*E*)-Alkene **6b**	(*Z*)-Alkene **3b**	Alkane **8b**	Alkyne **7b**
$Pd/CaCO_3$	0	0	0	100
Lindlar	0	0	0	100
$Pd/BaSO_4/Pb$	0	0	0	100
$Pd/BaSO_4$	6	48	32	14
$Pd/SrCO_3$	3	25	8	64
$Pd/BaCO_3$	2	19	4	75
Nickel P2	0	0	0	100

Substrate 10% (w/v) in MeOH, 3% catalyst (w/w) and 3% quinoline (w/v) hydrogenated 2 h at 1 bar and 20 °C. [a] All catalysts 5% Pd.



Scheme 1 *Reagents:* i, $(EtO)_3CH$, 150 °C; ii, $p\text{-}C_6H_4(CO_2H)_2$; iii, $H_2/PdC/BaSO_4$/quinoline

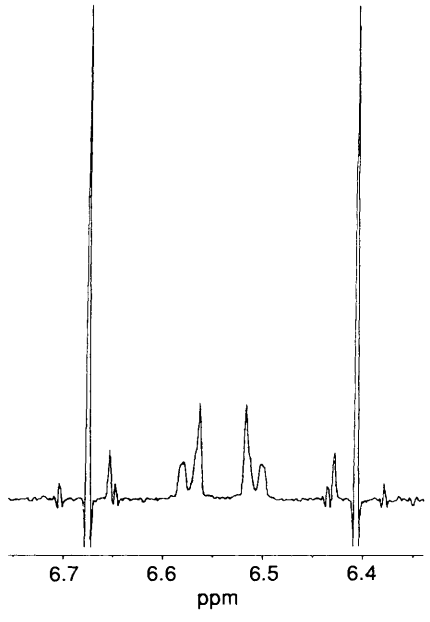


Fig. 1 ^1H NMR spectrum, giving only the AA′XX′ component, for tetraethyl (*Z*)-ethene-1,2-diylbisphosphonate **3b** (chemical shifts as in Table 2)

proved to be identical with that prepared by the method of Tavs and Weitkamp[5] and the two diastereoisomers were further identified on the basis of their NMR PH-coupling constants (*vide infra*). Finally, these products provided ^1H and ^{31}P NMR spectra that were used to identify the alkenebisphosphonates **3a** and **6a** produced by fragmentation of the 1,3-dioxolanes **2a** and **5a** respectively and thus confirm the assignment of relative stereochemistry to **1a** and **4a** (Scheme 1).

All of these four esters (**1a**, **3b**, **4a** and **6b**) were smoothly and quantitatively converted into the corresponding free bisphosphonic acids (**1c**, **3c**, **4c** and **6c**), either through transesterification using bromotrimethylsilane[10] or by hydrochloric acid hydrolysis. The free acids can conveniently be isolated as their triscyclohexylammonium or trisodium salts. Results on the incorporation of these species into nucleotide analogues will be described in the sequel.

Both the *cis*- and *trans*-esters **3b** and **6b** as well as tetraethyl vinylidenebisphosphonate[11] **9b** are expected to show 10-line ^1H NMR spectra¶ having half (either AA′ or XX′) of a typical 20-line AA′XX′ pattern.[12] The second half of the system would reside in the ^{31}P NMR spectrum either as a simple proton-decoupled singlet or in a 10-line signal further coupled to protons in the four ester ethyl groups. In practice, while the ^1H NMR spectra of all three isomeric ethenebisphosphonate esters give distinctly characteristic 'fingerprints' in chemical shift and multiplet pattern, only that for the *cis*-isomer **3b** is able fully to support a resolution of the 10-line proton spectrum (Fig. 1) which can be solved to provide all four coupling constants, $^3J_{PP}$, $^3J_{HH}$, $^2J_{PH}$ and $^3J_{PH}$ (**3b**; Table 2). The spectrum calculated from these four constants by the use of PANIC§ software, operated on the Aspect 2000 computer of a Bruker WP80SY instrument, provides an excellent fit to the experimentally observed spectrum. It is to be noted that the mathematical analysis of this system is not able to differentiate between the assignment of the AA′ and XX′ couplings, $^3J_{PP}$ and $^3J_{HH}$. These can,

¶ Effects of natural-abundance ^{13}C couplings are ignored.
§ Bruker software for PANIC.

Table 2 NMR data for 2-carbon *gem*- and *vic*-bisphosphonate esters*

Tetraethyl bisphosphonate	NMR data					
	δ_P	J_{PP}/Hz	$^2J_{PH}$/Hz	$^3J_{PH}$/Hz	δ_H	J_{HH}/Hz
Ethane-1,2-diyl[14] **8b**	+28.23	71.3[a]	N.d.	N.d.	1.97	N.d.
(*E*)-Ethene-1,2-diyl **6b**	+13.34	74.1[a]	23.9	23.9	6.81	18.9[c]
(*Z*)-Ethene-1,2-diyl **3b**	+10.69	26.5	18.0	49.0	6.54	6.55
gem-Vinylidene **9b**	+12.98	35	—	44, 29	6.11	0
		52	—	46, 24		3
Ethene-1,2-diyl **7b**	−10.7	11.5[b]	—	—	—	—
Diethyl ethenylphosphonate[d] **10b**	+15.01	—	18	50 (*trans*), 13 (*cis*)	6.20 (*cis*), 5.90 (*gem*), 5.71 (*trans*)	3 (*gem*), 13 (*cis*), 22 (*trans*)

* Values in italics derived from nucleotide esters. [a] Value for α,β-analogue of ADP.[15] [b] Value for β,γ-acetylene analogue of ATP.[1a] [c] Value for β,γ-ethenyl analogue of ATP.[15] [d] Refs. 5 and 15.

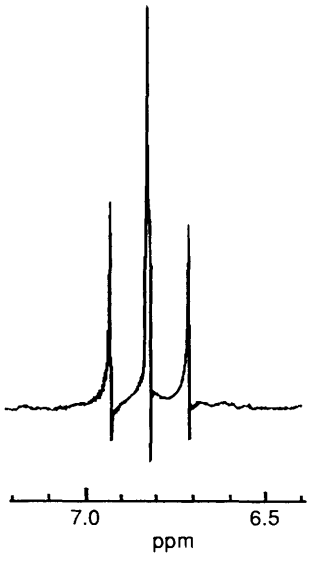


Fig. 2 ^{1}H NMR spectrum, AA′XX′ component only, for tetraethyl (*E*)-ethene-1,2-diylbisphosphonate **6b**

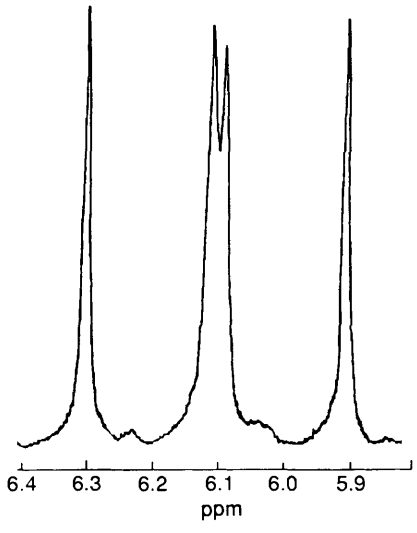


Fig. 3 ^{1}H NMR spectrum, AA′XX′ component only, for tetraethyl vinylidenebisphosphonate **9b**

however, be apportioned reliably on the basis of generally established values for *cis*-ethylene proton–proton couplings.[13] The same algebraic analysis similarly leads to ambiguity in the assignment of the $^2J_{PH}$ and $^3J_{PH}$ couplings. Based on our previous evaluation of the ^{1}H NMR spectra of di-isopropyl 1-fluoroethenyl- and 1-fluoro-2-phenylethenyl-phosphonates,[14] we can confidently assign the larger value to $^3J_{PH\,trans}$ and the smaller to $^2J_{PH\,gem}$ (**3b**, Table 2).

In the case of tetraethyl (*E*)-ethene-1,2-diylbisphosphonate, both the proton spectrum and the ^{1}H-coupled phosphorus spectrum of the sodium salt of the corresponding free acid **6c** appear as triplets (Fig. 2). This is a result of coalescence of the four central lines† of the spectrum (lines 6, 7, 9 and 12), for which the necessary condition is the coincidence of values for $^2J_{PH}$ and $^3J_{PH}$ (in this case found to be 23.9 Hz). The 'outside' lines of both spectra were found to be too indeterminate for evaluation of $^3J_{PP}(^3J_{HH})$. However, the calculated§ spectrum is a triplet regardless of the values assigned to these couplings.

Finally, for the case of tetraethyl vinylidenebisphosphonate **9b** yet a third ^{1}H NMR pattern is seen (Fig. 3). The central four lines converge to give a central doublet, though they do not coalesce. Line 6 merges with 9 and line 7 with 12, for which the condition is that $J_{XX'}$ (*i.e.* $^2J_{HH'}$) vanishes.† The 'outside lines' of the spectrum (lines 5, 8, 10 and 11) are insufficiently well resolved for accurate analysis of coupling constants. A simulation of this spectrum using PANIC shows that values of the *cis*- and *trans*-$^3J_{PH}$ coupling constants must have a mean value close to 34 Hz but are tolerant of a range of values for $^2J_{PP'}$ with $^2J_{HH'}$ being rather small. Two alternative sets of values can be combined to reproduce this spectrum. On the one hand, coupling constants can be found which place the four 'outside' lines as 'satellites' of the principal lines, *i.e.* lines 1,2 and 3,4 (Table 2, **9b**, upper row). On the other hand, a spectrum can be generated with widely separated outside lines of weak intensity (Table 2, **9b**, lower row). Experience leads us to favour the latter solution, though both accord well with observation.

In all of these cases, the calculated spectra provided line positions essentially identical with those observed in several observed ^{1}H NMR spectra and with intensities of comparable amplitude. It is to be noted that all the simulations have been performed using positive values for the 2- and 3-bond coupling constants. In practice, we established experimentally that changing the sign for either $^2J_{PP}$ or $^2J_{HH}$ resulted in no evident change in the spectrum calculated using PANIC. Nonetheless, significantly different spectra were produced in cases where $^2J_{PH}$ and $^3J_{PH}$ were given either the same or opposite signs. It appears that the mathematical analysis of the AA′XX′ system§ permits a negative sign for either J_{AX} or $J_{AX'}$ only when the central lines of the spectrum do not converge. Clearly, this is not the case for either **3b** or **9b**, and therefore neither $^2J_{PH}$ nor $^3J_{PH}$ can realistically be negative. While we cannot exclude the possibility of $^2J_{PH}$ having a negative value for **6b**, we were not able to identify scalar values which simulated the observed

† The lines of the spectrum are numbered according to ref. 12, *i.e.* from left to right: 5, 10, 1(2), 9, 6; 7, 12, 3(4), 11 and 8.

§ See footnote on p. 2868.

spectrum by having a negative coupling constant for $^2J_{PH}$. We therefore present only positive values for the coupling constants in Table 2.

In the case of tetraethyl ethane-1,2-diylbisphosphonate [16] the observed complex ^1H NMR spectrum is not sufficiently well-resolved to permit a solution of the $A_2A'_2XX'$ system.

The ^1H and ^{31}P NMR data (Table 2) follow expected patterns for P–P coupling constants, which increase in the order $^2J_{gem} \leqslant {}^3J_{cis} < {}^3J_{trans}$. These data are in line with observations we have made on the nucleotide di- and triphosphate and the dinucleoside tetraphosphate analogues we have prepared which incorporate these and other bisphosphonates.[1–3,15]

The stereochemical and spectroscopic characterisation of this range of two-carbon bisphosphonates first identifies as the *meso*-isomer the 1,2-dihydroxyethane-1,2-diylbisphosphonic acid, which we have investigated as an agent for technetium-99m bone scintigraphy.[7] Secondly, it underpins the evaluation of the role of these *vic*-bisphosphonates as analogues of pyrophosphoric acid both for incorporation into nucleotide analogues as enzyme inhibitors [1–3] and, potentially, for use as stretched transition state analogues for the generation of catalytic antibodies. Results on the incorporation of **1c**, **3c**, **6c** and **8c** into analogues of ADP, ATP and Ap_4A will be reported elsewhere.

Experimental

Materials.—Triethyl and trimethyl phosphite, tetraethyl methylenebisphosphonate, triethyl orthoformate, and terephthalic acid were obtained from Lancaster Synthesis. 1,2-*trans*-Dichloroethene and palladium catalysts were obtained from Aldrich Chemicals and $NiCl_2 \cdot 6H_2O$ from B.D.H., Poole, England. Merck Kieselgel 60H was used for column chromatography. Melting points were determined on a Kofler heated stage micro-melting point apparatus and are otherwise uncorrected. ^1H NMR spectra were recorded on a Perkin-Elmer R34 spectrometer at 220 MHz or with a Bruker AM250 spectrometer at 250 MHz. Chemical shifts are quoted in ppm downfield from tetramethylsilane as internal reference in $CDCl_3$ or, in the case of phosphonic acids, using Bu^{t}OH as internal reference in D_2O. ^{31}P NMR spectra were recorded on a Bruker WP80SY spectrometer at 32.438 MHz in the proton decoupled mode unless otherwise specified and chemical shifts are in ppm downfield from 85% H_3PO_4 as external reference. Low resolution mass spectra were recorded on a Kratos MS80 instrument in conjunction with a Kratos DS55 data station, using chemical ionisation (CI) with ammonia as the reagent gas [17] or electron impact (EI).

Tetramethyl erythro- **1a** *and* threo- **4a** 1,2-*Dihydroxyethane*-1,2-*diylbisphosphonate.*—Trimeric glyoxal dihydrate (52.5 g, 0.25 mol) was dissolved in anhydrous methanol (1.2 l). Methanol was distilled off to remove water and was replaced by more methanol (450 ml) and the procedure repeated. The glyoxal was precipitated on the dropwise addition of concentrated sulphuric acid (300 mg). Trimethyl phosphite (186.2 g, 1.5 mol) was then added dropwise to the methanolic suspension heated under reflux in a nitrogen atmosphere and heating continued for a further 20 h. Volatiles were removed by rotary evaporation, after which acetone (1 l) was added, and the mixture was set aside at 0 °C overnight. Crystals formed and were filtered off to give crude tetramethyl *erythro*-1,2-dihydroxyethane-1,2-diylbisphosphonate **1a**. The mother liquors were retained (*vide infra*). This material recrystallised from ethanol as fine needles (29.3 g, 42%), m.p. 170–172 °C (lit.,[6] 190–192 °C (decomp.)), $\delta_P([^2H_6]\text{-DMSO})$ +26.1; $\delta_H(D_2O)$ 4.20 [2 H, m, PC*H*(OH)C*H*(OH)P], 3.82 (12 H, m, 4POCH_3) (Found: C, 26.5; H, 6.2. $C_6H_{16}O_8P_2$ requires C, 25.9; H, 5.8%); *m/z* (+ve CI) 279 (100%, $[M + 1]^+$) and 169 {70%, $[M - (CH_3O)_2POH]^+$}.

Evaporation of the mother liquors from the above reaction provided a second solid fraction of different crystal morphology. This was crystallised repeatedly from ethanol to give racemic *threo*-1,2-dihydroxyethane-1,2-diylbisphosphonate **4a** (15 g, 22%), m.p. 113–115 °C; δ_P(d[$^2H_6$]-DMSO) +24.7; $\delta_H(D_2O)$ 4.50 [2 H, m, PC*H*(OH)C*H*(OH)P] and 3.83 (12 H, m, 4POCH_3) (Found: C, 26.1; H, 5.6. $C_6H_{16}O_8P_2$ requires C, 25.9; H, 5.8%); *m/z* (+ve CI) 279 (100%, $[M + 1]^+$) and 169 (57%, $[M - (CH_3O)_2POH]^+$).

(±)-threo-1,2-*Dihydroxyethane*-1,2-*diylbisphosphonic Acid* **4c**.—This compound was obtained from the above tetramethyl ester **4a** (240 mg, 1 mmol) by heating with hydrochloric acid (20% v/v; 10 ml) under reflux for 24 h. Repeated evaporation under reduced pressure with water (4 × 10 ml) afforded the product as an oil (180 mg, 98%); $\delta_P(D_2O)$ +20.4; $\delta_H([^2H_6]\text{-DMSO})$ 3.62.

meso-2-*Ethoxy*-4,5-*bis*(*dimethoxyphosphono*)-1,3-*dioxolane* **2a**.—The above *erythro*-isomer **1a** (5.0 g, 0.18 mol) was heated with freshly distilled triethyl orthoformate (16 g, 0.108 mol) under a reflux condenser maintained at 100 °C in a nitrogen atmosphere with exclusion of moisture for 14 h at 170–180 °C. A distillate of ethanol, ethyl formate, and methyl formate was collected. The cooled reaction mixture was evaporated under reduced pressure (1 mmHg) to remove excess of triethyl orthoformate and leave the product as a viscous oil (6.0 g, 99%), which could be neither distilled nor chromatographed without decomposition; $\delta_P([^2H_6]\text{-DMSO})$ +16.7; $\delta_H(C_6D_6)$ 5.83 [1 H, s, $O_2 > CH(OEt)$], 4.46 (2 H, d, $^2J_{PH}$ 14, 2PCH),‡ 3.98 (2 H, q, $^3J_{HH}$ 8, OCH_2CH$_3$), 3.75 (12 H, m, 4POCH_3) and 1.15 (3 H, t, $^3J_{HH}$ 8, OCH$_2$CH_3); *m/z* (+ve CI) 335 (44% $[M + H]^+$) and 289 (100%, $[M - EtOH + H]^+$) ($C_9H_{20}O_9P_2$ requires *M*, 334).

threo-2-*Ethoxy*-4,5-*bis*(*dimethoxyphosphono*)-1,3-*dioxolane* **5a**.—This compound was prepared by heating **4a** (5.0 g, 0.18 mol) with triethyl orthoformate (16 g, 0.108 mol) at 140–150 °C for 14 h as above and worked up in the same fashion to provide the product as a viscous oil (6.0 g, 99%); $\delta_P[^2H_6]$-DMSO) +20.1; $\delta_H(C_6D_6)$ 6.11 [1 H, s, $O_2 > CH(OEt)$], 4.90 (1 H, m, PCH), 4.70 (1 H, m, PCH), 3.98 (12 H, m, 4POCH_3), 3.75 (2 H, q, $^3J_{HH}$ 7, OCH_2CH$_3$) and 1.23 (3 H, t, $^3J_{HH}$ 7, OCH$_2$CH_3); *m/z* (+ve CI) 335 (22% $[M + H]^+$) and 289 (100%, $[M - EtOH + H]^+$) ($C_9H_{20}O_9P_2$ requires *M*, 334).

Decomposition of the 1,3-*Dioxolanes.*—The *meso*-2-ethoxy-1,3-dioxolane **2a** (3.8 g, 13.7 mmol) was heated with terephthalic acid (1.5 g, 9 mmol) in anhydrous benzene at 170 °C for 14 h under a condenser maintained at 100 °C. A white sublimate collected in the condenser, identified as dimethyl terephthalate. The flask residues were dissolved in water (50 ml), filtered, and washed with ether (3 × 100 ml). The resulting aqueous solution was evaporated under reduced pressure and the solid residue examined by ^1H NMR in [$^2H_6$]-DMSO. The products showed a multiplet at δ_H 6.5 with the same line-pattern as that of an authentic sample of tetraethyl (*Z*)-ethene-1,2-diylbisphosphonate **3b**, prepared as described below. Integration of the ^1H NMR spectrum at δ_H 3.52 showed some loss of CH_3O groups as a result of partial de-esterification. The proton-coupled ^{31}P NMR spectrum gave a broad multiplet at δ_P +10.6–10.8.

‡ The unexpected simplicity of this PCH signal, when an AA'XX' spectrum might have been expected, must be attributed to a very small value for $^3J_{PH}$. That is, in turn, a probable consequence of a P–C–C–H torsion angle close to 100° for *trans*-substituents in a 5-membered ring.

The *threo*-2-ethoxy-1,3-dioxolane **5a** was treated in an identical fashion to give a mixture of products showing a triplet at δ_H 6.75 (J_{PH} 24), corresponding to tetramethyl (*E*)-ethene-1,2-diylbisphosphonate **6a**. The proton-coupled ^{31}P NMR spectrum showed a broad signal δ_P +13.3–13.4.

Tetraethyl Ethyne-1,2-diylbisphosphonate **7b**.—This compound was prepared as described[18] by a Michaelis–Arbusov reaction from dichloroethyne[19] and triethyl phosphite to give an oil (62%), b.p. 170–180 °C (0.005 mmHg) (lit.,[18] b.p. 181–184 °C, 2.5 mmHg); $\delta_P(CDCl_3)$ −10.7; $\delta_H(CDCl_3)$ 4.23 (8 H, m, $POCH_2CH_3$), 1.40 (12 H, t, $^3J_{HH}$ 7.8, $POCH_2CH_3$); *m/z* (+ve CI) 316 (72%, $[M + NH_4]^+$), 299 (68%, $[M + H]^+$) ($C_{10}H_{20}O_6P_2$ requires *M*, 298).

Tetraethyl (E)-*Ethene-1,2-diylbisphosphonate* **6b**.—Anhydrous $NiCl_2$ (1.1 g, 8.5 mmol), *trans*-1,2-dichloroethene (27.6 g, 28 mmol), and triethyl phosphite (157 g, 945 mmol) were brought into reaction at 200 °C for 8 h in an autoclave and worked up as previously described[5] to give tetraethyl (*E*)-ethene-1,2-diylbisphosphonate **6b** (65 g, 77%), b.p. 150–160 °C (0.8 mmHg); $\delta_P(CDCl_3)$ +13.3; $\delta_H(CDCl_3)$ 6.81 (2 H, t, $^2J_{PH} = {}^3J_{PH}$ 23.9, PCH=CHP), 4.12 (8 H, m, $4POCH_2CH_3$), 1.29 (12 H, t, $^3J_{HH}$ 7, $4POCH_2CH_3$) (Found: C, 40.2; H, 7.1. $C_{10}H_{22}O_6P_2$ requires C, 40.2; H, 7.3%).

Tetraethyl (Z)-*Ethene-1,2-diylbisphosphonate* **3b**.—Tetraethyl ethyne-1,2-diylbisphosphonate **7b** (10 g, 33.6 mmol) was stirred under hydrogen (1 bar) with quinoline (300 mg) and $Pd/BaSO_4$ (300 mg) in dry methanol (100 ml). After 2 h (hydrogen absorption 680 ml, 90% of theoretical) the solution was filtered (Celite) and evaporated under reduced pressure to give an oil which ^1H NMR analysis showed to contain alkyne **7b** (36%), *cis*-alkene **3b** (38%), *trans*-alkene **6b** (9%) and tetraethyl ethane-1,2-diylbisphosphonate **8b** (17%). This mixture was flash chromatographed on a column of Merck Kieselgel 60H (70 × 50 mm) and eluted with acetone. Fractions containing the desired product were monitored by TLC, combined and evaporated to give **3b** (2.2 g, 22%); $\delta_P(CDCl_3)$ +10.69; $\delta_H(CDCl_3$, 250 MHz) 6.54 (2 H, m, $^2J_{PH}$ 18.0, $^3J_{HH}$ 6.55, $^3J_{PH}$ 49.0, $^3J_{PP}$ 26.5, PCH=CHP), 4.20 (8 H, m, $4POCH_2CH_3$) and 1.36 (12 H, t, J_{HH} 7.5, $4POCH_2CH_3$); *m/z* (+ve CI) 301 (100%, $(M + H)^+$) ($C_{10}H_{22}O_6P_2$ requires *M*, 300).

(Z)-*Ethene-1,2-diylbisphosphonic Acid* **3c**.—The above ester **3b** (300 mg, 1 mmol) was stirred with bromotrimethylsilane[10] (765 mg, 5 mmol) in tetrachloromethane (25 ml) at 35 °C for 24 h under nitrogen. Volatiles were removed under reduced pressure to afford a residue which was treated with distilled water (20 ml) and washed with diethyl ether (3 × 20 ml). The aqueous solution was evaporated under reduced pressure and the residue redissolved in water (20 ml) and re-evaporated to give the product as an oil (204 mg, 100%); $\delta_P(D_2O)$ 10.25 (AA'XX', $^2J_{PH}$ 17.5, $^3J_{PH}$ 49.5, $^3J_{HH}$ 8.0, $^3J_{PP}$ 26.0); $\delta_H(D_2O)$ 6.56 (AA'XX', $^2J_{PH}$ 17.5, $^3J_{PH}$ 51, $^3J_{HH}$ 82, $^3J_{PP}$ 26.0).

Tetraethyl Ethane-1,2-diylbisphosphonate **8b**.—This compound was prepared from 1,2-dibromoethane (distilled off CaH_2, 63.7 g, 339 mmol) and triethyl phosphite (100 g, 602 mmol) as described[16] to give the product (49 g, 54%), b.p. 140–148 °C (0.01 mmHg) (lit.,[16] b.p. 167 °C 1 mmHg); $\delta_P(CDCl_3)$ +28.23; $\delta_H(CDCl_3)$ 4.12 (8 H, m, $4POCH_2CH_3$), 1.97 (4 H, m, PCH_2CH_2P), 1.31 (12 H, t, $^3J_{HH}$ 8, $4POCH_2CH_3$); *m/z* (+ve CI) 303 (100% $[M + H]^+$) ($C_{10}H_{24}O_6P_2$ requires *M*, 302).

Tetraethyl Vinylidenebisphosphonate **9b**.—This compound was prepared as described by Burdsall and Degenhardt[11] from tetraethyl methylenebisphosphonate; $\delta_P(CDCl_3)$ +12.98; $\delta_H(CDCl_3)$ 6.11 (2 H, AA'XX', CH_2=C), 4.18 (8 H, m, $4POCH_2CH_3$), 1.34 (12 H, t, $^3J_{HH}$ 7, $4POCH_2CH_3$).

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