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NMR Studies of the Bishydroxy Bisphosphonate Synthesis from *o*-Phthalic Aldehyde and Diethyl Phosphite

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ABSTRACT: *The reaction of the o-phthalic aldehyde with diethyl phosphite leading to the bishydroxy bisphosphonate has been studied. It was found that the reaction is complex and a cyclic acetal formed from the monohydroxyphosphonate is the first relatively stable product. It slowly transforms to the bishydroxy bisphosphonate. The latter compound undergoes intramolecular nucleophilic substitution of the phosphorus atom by the hydroxy group which results in a cyclic structure, a phosphonate-hydroxyphosphate compound.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:157–164, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10014

INTRODUCTION

α-Hydroxy phosphoryl compounds (phosphonates and phosphonic acids) are very important because of their biological activity [1,2]. In this group there are some compounds that inhibit enzymes such as renin [3,4], EPSP synthetase [5,6], and HIV protease [7,8]. Hydroxyphosphonates are also used as intermediates in the synthesis of other α- and γ-substituted phosphonates and phosphonic acids [9–13].

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The hydroxyphosphonates have valuable properties as ferrous corrosion inhibitors and scale control additives for circulating water systems. They are well-known to retard or block effectively the growth process [14]. Their usefulness is also known as extractants in the recovery of some metal ions [15,16].

The above mentioned compounds, in general, can be easily prepared by thermal noncatalyzed addition [17–20] or base catalyzed addition [21–30] of a dialkyl phosphite to aldehydes or ketones or in the presence of potassium or cesium fluorides [31]. Strong acid conditions were also applied successfully [32]. By use of a chiral base as catalyst, enantiomerically enriched products were obtained [33].

Synthesis of 1-hydroxyphosphonates in alkaline solutions suffer some disadvantages due to reversibility of the reaction and the possibility of the rearrangement of hydroxyphosphonates to phosphates [17,19,30,34,35]. For the recent work on the hydroxyphosphonates synthesis and their applications see [36–39] and references cited therein.

The reaction becomes even more complicated if the substrate possesses an additional reactive functional group. Recently the synthesis of various substituted 1,2-dihydroxy-1,2-bisphosphonoethanes was reported [17]. The reaction in this case proceeds through the intermediate 2-hydroxy-2-phosphonoethanals. Aromatic bisaldehydes, such as *meta*- and *para*-phenylene bisaldehydes, react with diethyl phosphite forming the expected bishydroxy

bisphosphonates [18]. To our best knowledge, no synthesis of 1,2-bis-α-hydroxyphosphonates from *o*-benzenedicarboxaldehyde has been reported so far. The possible explanation of this fact is that the reaction is complicated in this case because of the presence of a reactive neighbouring group in close proximity. It is known that *o*-carboxybenzaldehyde reacts with dimethyl phosphite in the presence of an amine to yield an oily amido-amino-phosphonic acid monomethyl ester [19]. The bishydroxy bisphosphonates that we decided to obtain are potentially interesting; some for example are complexing agents and others serve as intermediates in the synthesis of other phosphonic derivatives, for example bisamino bisphosphonates. The synthesis of the latter compounds failed, in spite of numerous attempts [20]. It was therefore decided by us to undertake systematic studies on the reaction mechanism in order to rationalise the synthesis of *o*-phenylene bishydroxy bisphosphonates from an *o*-phenylene biscarboxaldehyde.

RESULTS AND DISCUSSION

We started our investigations by adopting the typical procedure of monohydroxyphosphonate synthesis, ie, amine-catalysed addition of a dialkyl phosphite to a bisaldehyde. *o*-Benzenedicarboxaldehyde reacts with diethyl phosphite in the presence of triethylamine yielding, however, a very complex reaction mixture. The number of the compounds, and their relative ratio as observed by ^{31}P NMR analysis strongly depends on the reaction conditions (molar ratio of the reagents, their concetrations, the nature of the solvent, time of the reaction, and the temperature of the reaction). The typical ^{31}P NMR spectrum of the reaction mixture is shown in Fig. 1.

The problem of the identification of particular mixture components is enlarged because of the fact that most of the products are present in a state of dynamic equilibrium. Because of the problem of isolation of the reaction mixture components, the course of the reaction was followed by NMR methods. At some chosen reaction stages, the mixture was partially purified by washing it with basic and acidic water solutions. This procedure allowed us to remove some dealkylated products and most of the substrates (amine and diethyl phosphite). Finally, we analysed this mixture by ^{1}H, ^{13}C, ^{31}P, HHCosy, HCCosy, and PPCosy NMR methods. We succeeded also in the isolation of some reaction products in a form suitable for crystal structure analysis. In this manner, we were able to identify the main products of the reaction and consequently to establish the reaction path, which is shown in Fig. 2.

We observed that, at the beginning of the reaction, one molecule of the diethyl phosphite reacts with *o*-benzenedicarboxaldehyde forming compounds **2a** and **2b**, but they quickly react further yielding more stable compounds **3a** and **3b**.

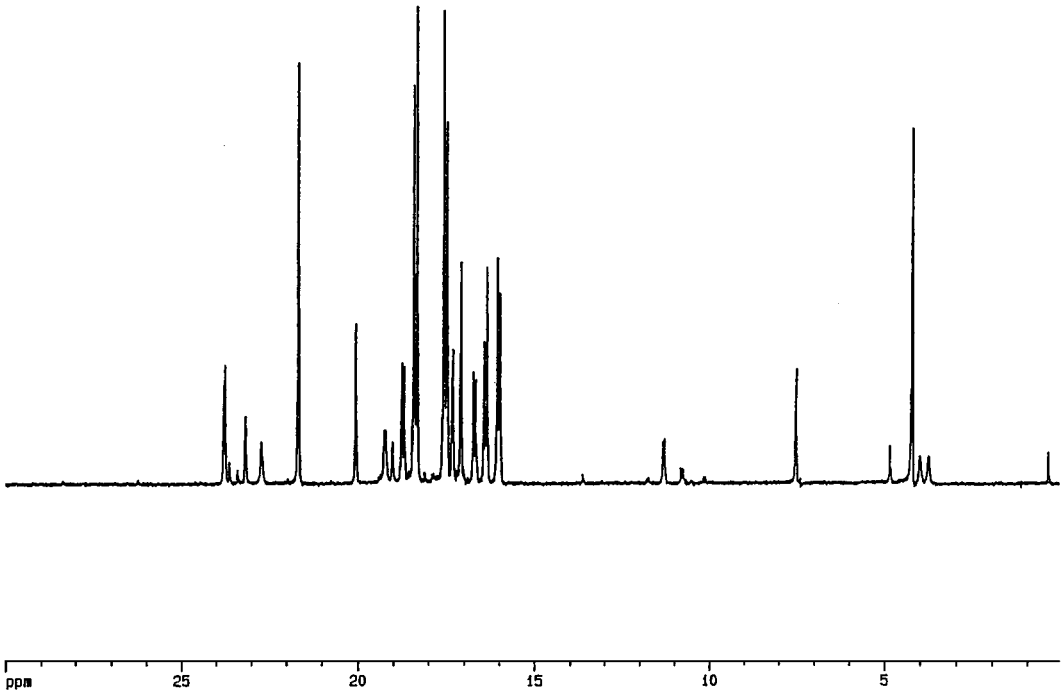

FIGURE 1 ^{31}P NMR spectrum of the reaction mixture.

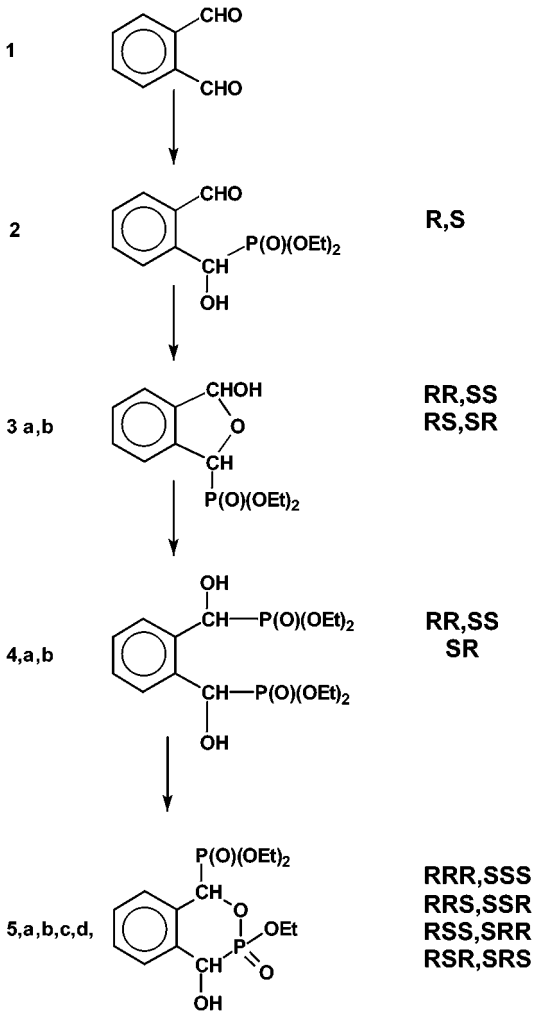

FIGURE 2 Products of the reaction between *o*-phthalic aldehyde and diethyl phosphite.

The last reaction is so fast that the compounds **2a** and **2b** could not be isolated by any method. ^{1}H NMR spectroscopy showed that, when the bisaldehyde disappeared ($\delta = 10.52$), a new carbonyl compound ($\delta = 10.15$) was formed. At the same time a new phosphorus signal displayed by ^{31}P NMR ($\delta = 20.40$) spectroscopy indicated the formation of a new compound. The ^{31}P NMR chemical shift allows us to identify it as the expected two enantiomeric hydroxyphosphonates, compounds **2a** and **2b**. Their fast transfomation into two other phosphorus compounds (**3a, 3b**) was accompanied by the disapperance of the aldehyde proton ($\delta = 10.15$ in the ^{1}H NMR spectrum and appearance of new signals ($\delta = 20.37$ and 19.38) in the ^{31}P NMR spectrum.

The mixture containing mainly compounds **3a** and **3b** was stable enough to be purified by removal of some dealkylated products formed during an aqueous work up, and could be fully characterized by NMR spectroscopic techniques (^{1}H, ^{31}P, ^{13}C, H–H COSY, H–C COSY). The analysis of the ^{1}H NMR spectra indicated that compounds **3a** and **3b** are diastereomers of cyclic hemiacetals present in a ratio of 6:4. Especially characteristic are the signals of ^{13}C NMR spectra at $\delta = 102.79$ (d, $J_{PC} = 1.5$ Hz) and 102.32 (d, $J_{PC} = 6.8$ Hz), which are typical of the acetal carbon nuclei. The full spectral data nicely correspond to the proposed structures and are given in the experimental part.

When the reaction mixture was kept at room temperature for a period of several hours new phosphorus signals appeared in the ^{31}P NMR spectrum ($\delta = 21.85$ and 23.38), which we identified as arising from compounds **4a** and **4b**. Both of these compounds posses similar ^{1}H, ^{13}C, and ^{31}P spectra and the identity of one diastereomer of **4** was confirmed by a crystal structure analysis (see Fig. 6 and Table 1). Parallel with formation of these compounds a new complex NMR pattern was evolved in the ^{31}P NMR spectrum at $\delta = 15$–19 which indicated further reaction. During the next few hours the signals at $\delta = 21.25$ and 23.18 slowly disappeared and compounds forming a complex pattern at $\delta = 15$–19 dominated in the reaction mixture. ^{31}P NMR spectrum of the component of the mixture, purified analogously to those described above, showed the interesting pattern of 8 doublets at a: $\delta = 17.96$ (d, $J_{PP} = 5.25$ Hz); b: 17.48 (d, $J_{PP} = 6.00$ Hz); c: 16.67 (d, $J_{PP} = 6.00$ Hz); d: 16.27 (d, $J_{PP} = 6.10$ Hz); e: 16.05 (d, $J_{PP} = 6.10$ Hz); f: 15.61 (d, $J_{PP} = 5.25$ Hz); g: 15.28 (d, $J_{PP} = 6.00$ Hz); h: 15.18 (d, $J_{PP} = 6.00$ Hz) and one singlet at $\delta =$ 20.67 ppm.

The ^{31}P–^{31}P COSY spectrum showed that these doublets are coupled pairwise, (a-f, g-h, b-c, d-e) (see Fig. 3) indicating that they come from the four molecules, each containing two symmetry nonequivalent phosphorus atoms situated closely enough so that they can couple to each other.

Two of the compounds displaying doublets at $\delta = 17.48$, 16.67, and 15.28, 15.18 formed crystals suitable for X-ray analysis and they were identified as two diastereomeric cyclic phosphonate-hydroxyphosphonates (**5b, 5d**), see Figs. 4 and 5 and Table 1.

Their ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra are similar and are given in the experimental part. In each diastereomer of compound **5**, there are three stereogenic centers (two on —CH carbon atoms and one on the phosphorus atoms) so there are possible four enantiomeric pairs of diastereoisomers, each containing two nonequivalent phosphorus atoms coupled together. This gives two doublets in their ^{31}P NMR spectra for each diastereomeric

TABLE 1 Summary of Crystal Data for Compounds **4a**, **5b**, and **5d**

	4a	**5b**	**5d**
Formula	$C_{16}H_{28}O_8P_2$	$C_{14}H_{22}O_7P_2$	$C_{14}H_{22}O_7P_2$
Molecular weight	410.32	364.26	364.26
T (K)	100(5)	293(2)	100(5)
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1/c$	$P2_1$
a (Å)	9.045(2)	8.8562)	8.672(2)
b (Å)	11.505(2)	12.896(3)	14.319(3)
c (Å)	10.136(2)	15.416(3)	26.666(5)
β (°)	106.16(3)	92.03(3)	90.36(3)
V (Å^3)	1013.1(3)	1759.3(7)	3323.6(7)
Z	2	4	8
D_c (mg/m^3)	1.345	1.456	1.456
F(000)	436	768	1356
Radiation (λ) (Å)	0.71073	1.5418	0.71073
Crystal dimensions (mm)	$0.10 \times 0.20 \times 0.22$	$0.29 \times 0.25 \times 0.24$	$0.20 \times 0.20 \times 0.25$
Reflections measured	7112	3578	21347
θ range (°)	3.54–28.5	4.5–80.0	3.56–27.6
Independent reflection	4643 [$R_{int} = 0.029$]	3578[$R_{int} = 0.023$]	9656 [$R_{int} = 0.032$]
μ (mm^{-1})	0.253	0.328	0.294
Extinction correction	0.0092(5)	0.003(6)	0.003(6)
No. of parameters varied	348	225	845
Weights (a, b)[a]	0.0196, 0.026	0.1136, 1.93	0.0249, 0.020
Goodness of fit	0.999	1.095	0.856
$R1$[b]	0.0272	0.0582	0.0412
$wR2$[c]	0.052	0.160	0.0709
$R1$[b] (all data)	0.0368	0.0865	0.0643
$wR2$[c] (all data)	0.0543	0.2277	0.0753
Flack parameter	−0.10(5)	–	0.15(8)
$\Delta\rho$(e/Å^3)	0.329, −0.250	0.36, −0.26	0.46, −0.27

[a] $w = 1/[\sigma^2(F_o^2) + (aP) + bP]$, where $P = \max(0, F_o^2) + (2F_o^2)/3$.
[b] $R1 = \Sigma(|F_o| - |F_c|)/|F_o|)$.
[c] $wR2 = \{(\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

pair of enantiomers, exactly as seen in the ^{31}P–^{31}P COSY spectra.

Isomer **5b** has the same configuration on both stereogenic carbon atoms. Such stereochemistry makes it possible to form an intramolecular hydrogen bond between the hydroxy group residing on one stereogenic carbon atom and the phosphoryl oxygen atom from the phosphonic group attached to the second stereogenic carbon atom. There are two such diastereomeric pairs of enantiomers, **5a** and **5b**, depending on the configuration of the stereogenic phosphorus atom. The one, which crystallized easily (compound **5b**), has the relatively large ethoxy group away from the more crowded side of the plane defined by an aromatic ring (see Fig. 4).

The second isolated isomer of compound **5d**, the structure of which had been determined by X-ray studies, has opposite configurations on both carbon atoms attached to the phosphorus atom. Such a stereochemistry prevents the formation of intramolecular hydrogen bonds as in the compound previously studied (see Fig. 5). This difference of two diastereomeric esters is manifested by their different behaviour in solution. Depending on their concentration in $CDCl_3$, we have observed substantial changes in the ^{31}P and ^{1}H NMR spectra only for the diastereomer having the same configuration at both stereogenic carbon atoms, and almost no changes for the second one. This can be explained by the shift in the equilibrium between inter- and intramolecular hydrogen bonding only in diastereomers **5a** and **5b** having the same configuration on stereogenic carbon atoms.

When the mixture containing all four diastereomeric pairs of enantiomers of **5** was studied by NMR spectroscopy at different concentrations, only two compounds giving doublets at 16.27, 16.05 and 15.28, 15.18 showed changes with concentration. The first is the one studied above and the second should have the same configuration at the CH carbon atoms, since only this allows equilibrium between intra- and intermolecular hydrogen bonding.

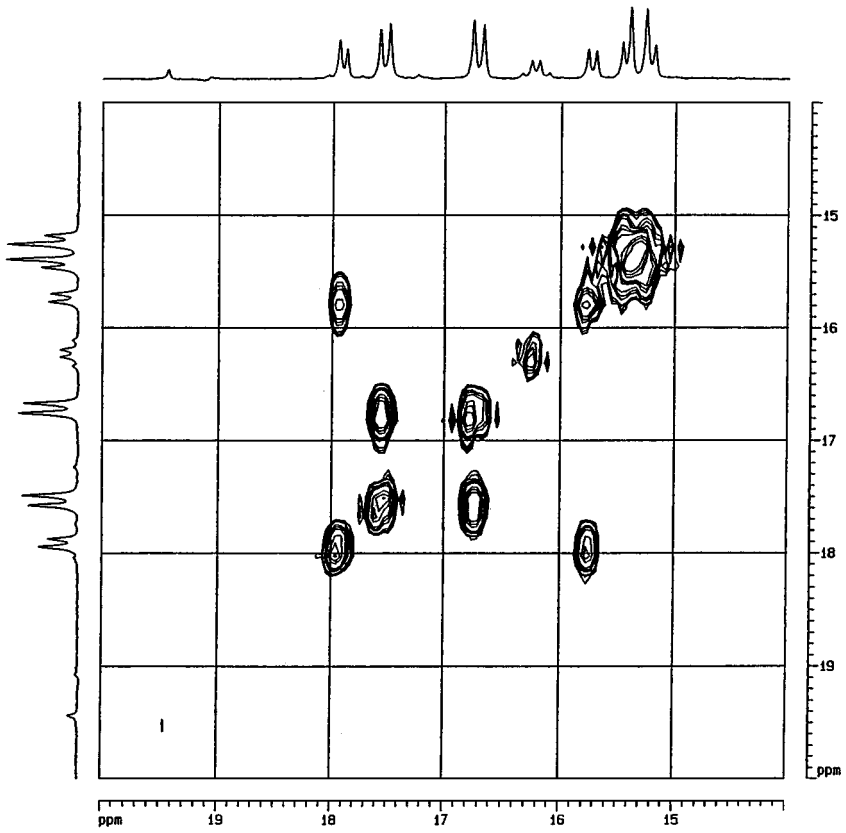

FIGURE 3 ^{31}P–^{31}P COSY NMR spectrum of the main reaction products.

Consequently, the remaining doublets at 17.96, 15.61 and 17.48, 16.67 we assign to diastereomers **5c** and **5d**.

Performing the addition of diethyl phosphite to *o*-phthalic aldehyde in the presence of quinine as a basic catalyst, we succeeded in the isolation of pure compound **4a**. This was the only compound that crystallized from the complex reaction mixture. We succeeded also in obtaining useful crystals of it which showed a singlet at $\delta = 20.67$ in the

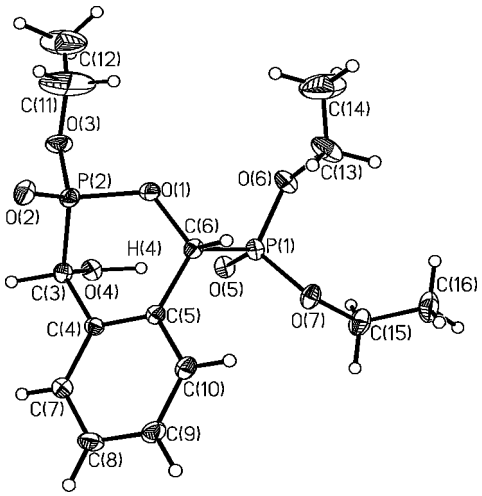

FIGURE 4 Structure of compound **5b** showing the atom labeling scheme and 20% probability displacement ellipsoids.

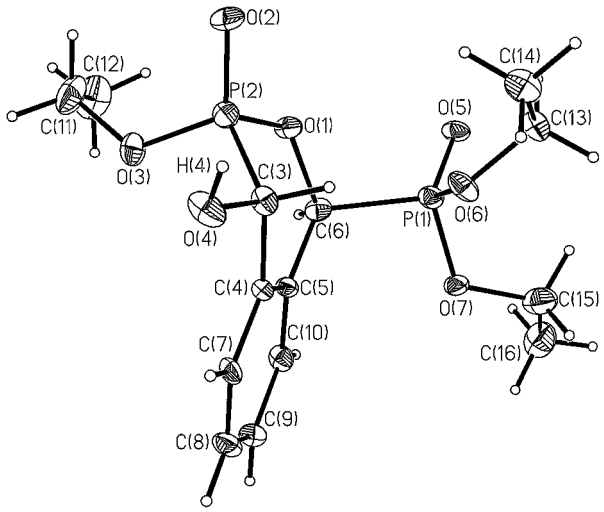

FIGURE 5 Structure of compound **5d** (molecule A) showing the atom labeling scheme and 40% probability displacement ellipsoids.

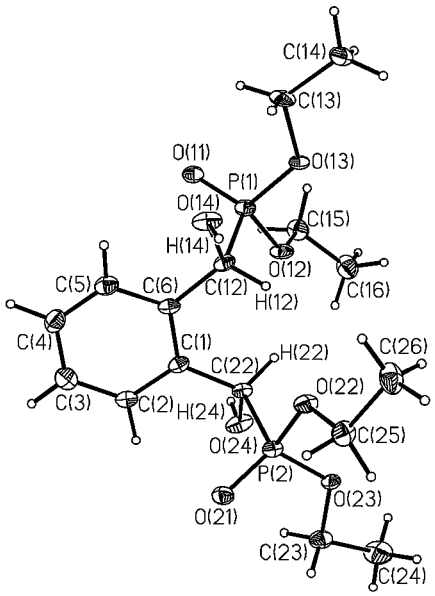

FIGURE 6 Stereoview of compound **4** showing the atom labeling scheme and 50% probability displacement ellipsoids.

^{31}P NMR spectrum. By X-ray analysis, it was found, indeed, that it is a noncyclic bishydroxy bisphosphonate with the configuration *RR* at both carbon atoms (see Fig. 6).

EXPERIMENTAL

NMR spectra were recorded on an AMX 300 MHz Bruker instrument operating at 300.13 MHz (^{1}H) and 121.499 (^{31}P). Measurements were made in $CDCl_3$ (chloroform-d, isotopic purity 99.8 atom %, Dr. Glaser AG Basel).

Reaction of o-Phthalic Aldehyde with Diethyl Phosphite and Isolation of the Reaction Products

A mixture of *o*-phtalic aldehyde, 5.36 g (0.04 mol), diethyl phosphite, 12.4 g (11.6 ml; 0.088 mol) and 4 ml of triethylamine was kept at room temperature for 2 h. Then a 1 ml sample of the mixture was dissolved in 2 ml of diethyl ether, washed with 2 ml of a 5% solution of sodium bicarbonate, then 2 ml of water, and finally the diethyl ether solution was evaporated to dryness yielding an oily residue. NMR analysis revealed that this is a 2:1 mixture of diastereomeric hemiacetals of compound **3**. Their ^{1}H NMR showed 7.49–7.25 (m, 4H, Ar<u>H</u>), 6.42 (d, 1H, C<u>H</u>, $J_{HP} = 5.40$ Hz), 5.32 (d, 1H, C<u>H</u>, $J_{HP} = 4.20$ Hz), 4.30–4.10 (m, 4H, C<u>H</u>$_2$O), 1.32 (t, 3H, C<u>H</u>$_3$, $J_{HH} = 7.12$ Hz) for major isomer and 7.49–7.25 (m, 4H, ArH), 6.59 (t, 1H, C<u>H</u>, $J_{HH} = 1.86$ Hz, $J_{HP} = 1.86$ Hz), 5.61 (t, 1H, C<u>H</u>, $J_{HH} = 6.9$ Hz, $J_{HP} = 6.9$ Hz), 4.30–4.10 (m, 4H, CH_2O), 1.32 (t, 3H, CH_3, $J_{HH} = 7.10$ Hz) for minor isomer; whereas on ^{31}P{^{1}H} NMR 20.26 (s) for major and 19.14 (s) for minor isomers, and on ^{13}C.NMR 140.33 (d, $J_{CP} = 5.29$ Hz), 135.30 (d, $J_{CP} = 2.27$ Hz), 129.11 (d, $J_{CP} = 3.02$ Hz), 128.87 (d, $J_{CP} = 3.02$ Hz), 123.11 (d, $J_{CP} = 3.02$ Hz), 122.39 (d, $J_{CP} = 3.02$ Hz), for six aromatic carbon atoms, 102.79 (d, $J_{CP} = 1.51$ Hz), for hemiacetal carbon atom, 78.06 (d, $J_{CP} = 168.02$ Hz), for <u>C</u>HP, 64.36 (d, $J_{CP} = 6.61$ Hz), 63.51 (d, $J_{CP} = 7.60$ Hz), for <u>C</u>H$_2$O, 16.36 (d, $J_{CP} = 5.51$ Hz), 16.32 (d, $J_{CP} = 5.74$ Hz) for <u>C</u>H$_3$ for major isomer and, 139.59 (d, $J_{CP} = 6.04$ Hz), 135.60 (d, $J_{CP} = 3.76$ Hz), 129.16 (d, $J_{CP} = 4.53$ Hz), 128.54 (d, $J_{CP} = 3.02$ Hz), 123.66 (d, $J_{CP} = 4.53$ Hz), 122.18 (d, $J_{CP} = 3.02$ Hz), for six aromatic carbon atoms, 102.32 (d, $J_{CP} = 6.70$ Hz), for hemiacetal carbon atom, 77.69 (d, $J_{CP} = 170.78$ Hz), for <u>C</u>HP, 63.35 (d, $J_{CP} = 6.80$ Hz), 62.84 (d, $J_{CP} = 7.56$ Hz), for <u>C</u>H$_2$O, 16.20 (d, $J_{CP} = 6.49$ Hz), 16.17 ($J_{CP} = 5.51$ Hz, $J_{CP} = 7.60$ Hz), for <u>C</u>H$_2$O, 16.36 (d, $J_{CP} = 5.51$ Hz), 16.32 (d, $J_{CP} = 5.74$ Hz), for minor isomer.

After 48 h, 10 ml of ethyl alcohol was added and the mixture was to stand in a freezer. After 24 h the, white crystals which had precipated were filtered off yielding 6.38 g (44%) of compound **5d**. Repeated crystallisation of **5d** from ethyl alcohol gave the pure compound in a crystal form suitable for X-ray analysis.

mp. = 152–153°C. ^{1}H NMR [$CDCl_3$] 7.49–7.38 (m, 3H, Ar<u>H</u>), 7.19 (d, 1H, Ar<u>H</u>, $J_{HH} = 5.01$ Hz), 5.86 (d, 1H, O<u>H</u>, $J_{HH} = 10.78$ Hz), 5.64 (dd, 1H, C<u>H</u>, $J_{HP} = 13.45$, 8.39 Hz), 4.83 (dd, 1H, C<u>H</u>, $J_{HH} = 10.80$ Hz, $J_{HP} = 9.93$ Hz), 4.45–4.33 (m, 4H, C<u>H</u>$_2$O), 4.00–4.05 (m, 1H, C<u>H</u>$_2$O), 3.89–3.83 (m, 1H, C<u>H</u>$_2$O), 1.45 (t, C<u>H</u>$_3$, $J_{HH} = 7.23$ Hz), 1.42 (t, C<u>H</u>$_3$, $J_{HH} = 7.17$ Hz), 1.21 (d, $J_{HH} = 7.08$ Hz). ^{31}P{^{1}H} NMR [$CDCl_3$] 19.41 (d, $J_{PP} = 10.33$ Hz), 18.67 (d, $J_{PP} = 10.37$ Hz). ^{13}C{^{1}H} NMR 135.27 (d, <u>Ar</u>, $J_{PC} = 10.33$ Hz), 132.96 (dd, <u>Ar</u>, $J_{PC} = 3.02$ Hz, 12.84 Hz), 129.87 (dd, <u>Ar</u>, $J_{PC} = 3.78$ Hz, 3.78 Hz), 129.30 (d, <u>Ar</u>, $J_{PC} = 3.02$ Hz), 128.19 (dd, <u>Ar</u>, $J_{PC} = 3.78$ Hz, 14.35 Hz), 127.69 (d, <u>Ar</u>, $J_{PC} = 4.53$ Hz), 77.47 (dd, <u>C</u>HP, $J_{PC} = 165.27$ Hz, 3.25 Hz), 64.60 (d, C<u>H</u>P, $J_{PC} = 140.51$ Hz), 65.14 (d, <u>C</u>H$_2$O, $J_{PC} = 6.87$ Hz), 64.64 (d, <u>C</u>H$_2$O, $J_{PC} = 6.64$ Hz), 64.21 (d, <u>C</u>H$_2$O, $J_{PC} = 7.47$ Hz), 16.60 (d, <u>C</u>H$_3$, $J_{PC} = 5.29$ Hz), 16.44 (d, <u>C</u>H$_3$, $J_{PC} = 5.29$Hz), 16.16 (d, <u>C</u>H$_3$, $J_{PC} = 6.04$ Hz).

When, to the solution obtained after filtration of **5d** 10 ml of diethyl ether was added and the mixture was allowed to stand in a freezer over night, 0.79 g of pure crystals of **5b** had precipitated in a form suitable for X-ray analysis.

mp. = 183–184°C. ^{1}H NMR [$CDCl_3$] 7.84 (d, 1H, Ar<u>H</u>, $J_{HH} = 7.71$ Hz), 7.44 (dd, 1H, Ar<u>H</u>, $J_{HH} = 7.71$ Hz, 7.65 Hz), 7.31 (dd, 1H, Ar<u>H</u>, $J_{HH} = 7.63$ Hz,

7.65 Hz), 7.34 (d, 1H, ArH, $J_{HH} = 7.53$ Hz), 5.68 (d, 1H, OH, $J_{HP} = 10.35$ Hz), 5.55 (t, 1H, CH, $J_{HP} = 12.93$ Hz, 12.93 Hz), 5.10 (b.s., 1H, OH). $^{31}P\{^1H\}$ NMR [$CDCl_3$] 16.36 (d, $J_{PP} = 9.20$ Hz), 15.95 (d, $J_{PP} = 9.20$ Hz). $^{13}C\{^1H\}$ NMR 136.29 (d, Ar, $J_{PC} = 1.5$ Hz), 129.13 (d, Ar, $J_{PC} = 2.27$ Hz), 126.98 (s), 126.78 (d, Ar, $J_{PC} = 2.27$ Hz), 126.39 (d, Ar, $J_{PC} = 7.55$ Hz), 124.20 (d, Ar, $J_{PC} = 4.53$ Hz), 78.58 (dd, CHP, $J_{PC} = 161.00$ Hz, 8.38 Hz), 63.80 (dd, CHP, $J_{PC} = 149.00$ Hz,1.51 Hz), 64.56 (d, CH_2O, $J_{PC} = 6.72$ Hz), 64.34 (d, CH_2O, $J_{PC} = 6.72$ Hz), 63.75 (d, CH_2O, $J_{PC} = 7.02$ Hz), 16.41 (d, CH_3, $J_{PC} = 6.64$ Hz), 16.39 (d, CH_3, $J_{PC} = 6.64$ Hz), 16.29 (d, CH_3, $J_{PC} = 7.93$ Hz).

In another experiment, a mixture of *o*-phtalic aldehyde, 1.00 g (0.05 mol), diethyl phosphite, 2.00 ml (0.016 mol) and 0.25 g (0.8 mmol) of quinine, added as a basic catalyst, was kept for 48 h. After that time crystals suitable for X-ray analysis had precipitated (40%). They were found to be identical with compound **4b**.

mp. = 125°C. ^1H NMR [$CDCl_3$] 7.67 (b.s., 2H, ArH), 7.31 (t, 2H, ArH, $J_{HH} = 4.56$ Hz), 5.43 (d, 2H, CH, $J_{HP} = 12.99$ Hz), 5.00 (b.s, 2H, OH), 4.18–3.82 (m, 8H, CH_2O), 1.45 (t, CH_3, $J_{HH} = 7.23$ Hz), 1.26 (t, 6H, CH_3, $J_{HH} = 7.05$ Hz), 1.19 (t, 6H, CH_3 $J_{HH} = 7.05$ Hz). $^{31}P\{^1H\}$ NMR [$CDCl_3$] 22.61 (s). $^{13}C\{^1H\}$ NMR 135.09 (dd, $J_{PC} = 3.02$ Hz for two tertiary aromatic carbons), 128.13 (b.s. for other four aromatic carbons), 67.13 (d, CH, $J_{PC} = 163.84$ Hz), 63.68 (dd, CH_2O, $J_{PC} = 3.40$ Hz, $J_{PC} = 3.40$ Hz), 63.13 (dd, CH_2O, $J_{PC} = 3.32$ Hz, $J_{PC} = 3.32$ Hz), 16.32 (s, CH_3).

X-ray Diffraction Analysis of **4a, 5b***, and* **5d**

Preliminary examination and intensities data collections were carried out on a KUMA KM4 four-circle diffractometer for **5b**, and KUMA KM4 CCD four-circle diffractometer [40] with an Oxford Cryosystem Cooler for **4a** and **5d**. Details of the data collection, refinement and crystal data are summarized in Table 1. All data were corrected for Lorentz and polarization effects.

The structures were solved by direct methods SHELXS-86 [41] and refined by full matrix least-squares on F^2 using SHELXL-97 [42] with anisotropic thermal parameters for non-hydrogen atoms. During the refinement, an extinction correction was applied. For compound 4a all hydrogen atoms were found from a Fourier-difference synthesis and refined isotropically. For **5b** and **5d**, carbon-bound hydrogen atoms were initially placed in calculated positions (with the thermal parameters being 1.2 times U_{eq} of the parent carbon atom) and the remainder were found from the difference synthesis. In the case of compound **5d**, the absolute structure cannot be determined reliably since the value of the Flack parameter was 0.15(8) and the refined data on the inverted structure gave $R = 0.0415$ and $wR = 0.0716$. Scattering factors and real, as well as imaginary, components of anomalous dispersion were those incorporated with SHELXL-97.

REFERENCES

[1] Brienne, M. J.; Jacques, J.; Brianso, M. C.; Surcouf, E. Nouv J Chim 1978, 2, 19–20.

[2] Abramov, V. S.; Zh Obshch Khim 1952, 22, 647; Chem Abstr 1953, 47, 5351.

[3] Patel, D. V.; Rielly-Gauvin, K. D.; Ryono, E. Tetrahedron Lett 1990, 31, 5587–5590.

[4] Patel, D. V.; Rielly-Gauvin, K. D.; Ryono, E. Tetrahedron Lett 1990, 31, 5591–5594.

[5] Sikorski, J. A.; Miller, M. J.; Braccolino, D. S.; Cleary, D. G.; Corey, S. D.; Font, J. L.; Gruys, K. J.; Han, Y.; Lin, K. C.; Pansegrau, P. D.; Ream, J. E.; Schnur, D.; Shah, A.; Walker, M. C. Phosphorus Sulfur Silicon 1993, 76, 115–118.

[6] Peterson, M. L.; Corney, S. D.; Sikorski, A.; Walker, M. C. In 203rd American Chemical Society National Meeting, San Francisco, 1992. ORGN 469 (Abstracts).

[7] Stowasser, B.; Budt, K. H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. Tetrahedron Lett 1992, 33, 6625–6628.

[8] Moore, M. L.; Dreyer G. B. Perspective in Drug Discovery and Design 1993, 1, 85.

[9] Hammerschmidt, F.; Vollenkle, H. Liebigs Ann Chem 1989, 577–583.

[10] Yokomatsu, T.; Shibuya, S. Tetrahedron Assym 1992, 2, 377–378.

[11] Baraldi, P. G.; Guarneri, M.; Moroder, F.; Pollini, G. P.; Simoni, D. Synthesis 1982, 653–655.

[12] Maier, L. Phosphorus Sulfur Silicon 1993, 76, 119–122.

[13] Ohler, E.; Kotzinger, S. Synthesis 1993, 497–502 and references cited therein.

[14] Mikroyannidis, J. A. Phosphorus Sulphur 1987, 32, 113–118.

[15] Petrov, K. A.; Parshina, V. A. Russ Chem Rev 1968, 37, 1218–1242.

[16] Chiarizia, R.; Herlinger, A. W.; Horwitz, E. P. Solvent Extr Ion Exch 1997, 15, 417–413.

[17] Karasch, M. S.; Mosher, R. A.; Bengelsdorf, I. S. J Org Chem 1960, 25, 1000–1006.

[18] Abramov, V. S.; Kapustina, A. S. Zh Obshch Khim 1957, 27, 1012–1015.

[19] Janzen, A. F.; Pollit, R. Can J Chem 1970, 48, 1987–1990.

[20] Abramov, V. S.; Shalman, A. L.; Bulgakova, A. P. Khim Org Soedin Fosfora Akad Nauk SSSR Otd Obshch Tech Khim 1967,132–135.

[21] Ruveda, M. A.; Licastro, S. A. Tetrahedron 1972, 28, 6013–6018.

[22] Agawa, T.; Kubo, T.; Ohshiro, Y. Synthesis 1971, 27–28.

[23] Arbuzov, B. A.; Vinogradova, V. S.; Polezhaeva, N. A. Dokl Akad Nauk SSSR 1956, 111, 107–109.

[24] Meisters, A.; Swan, J. M. Aust J Chem 1965, 18, 155–162.

[25] Springs, B.; Haake, P. J Org Chem 1976, 41, 1165–1168.

[26] Pudovik, A. N.; Konovalova, J. V. Synthesis 1979,81–96.
[27] Pudovik, A. N. Dokl Akad Nauk SSSR 1950, 73, 499–502.
[28] Timmler, H.; Kurz, J. Chem Ber 1971, 104, 3740–3749.
[29] Kozlowski, J. K.; Rath, N. P.; Spilling, C. D. Tetrahedron Lett 1995, 51, 6385–6396.
[30] Gancarz, R.; Gancarz, I.; Walkowiak, U. Phosphorus Sulfur Silicon 1995, 104, 45–52.
[31] Fexier-Bouleet, T.; Foucand, A. Synthesis 1982, 165–166.
[32] Consiglio, G.; Failla, S.; Finochiaro, P. Phosphorus Sulfur Silicon 1996, 117, 37–54.
[33] Wynberg, H.; Smaardijk, A. A. Tetrahedron Lett 1983, 24, 5899–5900.
[34] Jaszay, Z. M.; Petnehazy, I.; Toke, L. Phosphorus Sulfur Silicon 1993, 77, 198.
[35] Gancarz, R.; Gancarz, I. Tetrahedron Lett 1993, 34, 145–148.
[36] Wiemar, D. F. Tetrahedron 1997, 53, 16609–16644.
[37] Ohler, E.; Kanzler, S. Liebigs Ann Chem 1997, 1437–1445.
[38] Ward, C. V.; Jiang, M.; Kee, T. P. Tetrahedron Lett 2000, 41, 6181–6184.
[39] Shabany, H.; Spilling, C. D. Tetrahedron Lett 1998, 39, 1465–1468.
[40] Kuma Diffraction. KM4CCD™ SYSTEM SOFTWARE. User's Guide Version 1.161.; Kuma Diffraction Instuments GmbH: Wrocław, Poland, 1995–1999.
[41] Sheldrick, G. M. Acta Crystallogr, Sect A 1990, 46, 467.
[42] (a) Sheldrick, G. M. SHELXL93, University of Gottingen, 1993; (b) Sheldrick, G. M. SHELXL97, University of Gottingen, 1997.