Synthesis and Structure Assignment of the Diastereoisomeric 1,2-*O*-Cyclohexylidene-α-D-xylofuranose 3,5-*O*-Methylphosphonates and the Related Thiono- and Selenono-phosphonates

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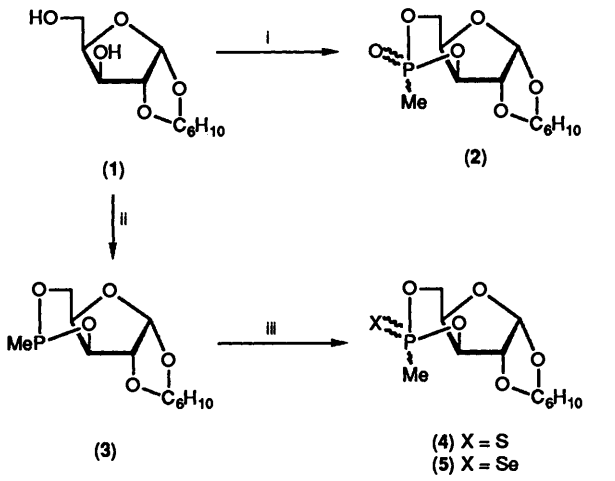
The diastereoisomeric 1,2-*O*-cyclohexylidene-α-D-xylofuranose 3,5-*O*-methylphosphonates have been synthesized as a mixture and separated by chromatography to give the pure (R_P) and (S_P) forms. The related thiono- and selenono-phosphonates have also been obtained. Their ^{13}C, ^{1}H, ^{31}P, and ^{77}Se NMR spectra are discussed and NOE experiments have been used to determine the chirality at phosphorus.

Cyclonucleotides, nucleotide 3',5'-phosphates, *e.g.* cAMP and cGMP, are important components of biological systems.[1] There is much interest in synthesizing analogues of these nucleotides, and Bajwa and Bentrude have reported methylphosphonate forms.[2] Thus thymidine 3',5'-cyclic methylphosphonate was obtained as a mixture of diastereoisomers because of the chirality at the phosphorus atom. Structural assignments were based on comparison of the ^{13}C NMR spectra of these compounds with those of related cyclic methyl phosphonates whose structure had been unequivocally assigned by X-ray crystallography.[2] These analogues, like the natural forms, contain a relatively rigid, strained[3] *trans*-fused arrangement of the 1,2,3-dioxaphosphorinane ring and the furanoid ring of the nucleoside. The *cis*-fused system in the related D-xylofuranose compounds is less strained and cyclonucleotides of this form have been synthesized.[4] Tronchet and co-workers[5] have synthesized and compared the phenyl esters of the 3,5-cyclic phosphates of 1,2-*O*-isopropylidene-α-D-ribofuranose and 1,2-*O*-isopropylidene-α-D-xylofuranose. We now report on the synthesis and structure assignment of the 1,2-*O*-cyclohexylidene-α-D-xylofuranose 3,5-*O*-methylphosphonates (**2**) and the corresponding thionophosphonates (**4**) and selenonophosphonates (**5**).



Scheme. *Reagents:* i, $MePOCl_2$; ii, $MePCl_2$; iii, S or Se. C_6H_{10} = cyclohexylidene.

Results and Discussion

Treatment of 1,2-*O*-cyclohexylidene-α-D-xylofuranose (**1**)[6] with methylphosphonic dichloride in 1,4-dioxane in the presence of triethylamine gave a pair of diastereoisomeric cyclic phosphonates (**2**), one crystalline and the other as a syrup, in approximately equal amounts which were readily separated by column chromatography.

Similar treatment of compound (**1**) with dichloro(methyl)-phosphine gave a product, presumed to be the cyclic ester (**3**), which was not isolated but which was immediately allowed to react with elemental sulphur or selenium to give the diastereoisomeric cyclic thionophosphonates (**4**) or selenonophosphonates (**5**) (Scheme). As before, the diastereoisomers were separated by column chromatography, all four were obtained in crystalline form and, like the phosphonates (**2**), gave elemental analyses, IR spectra, and mass spectra in keeping with the expected structures. Diastereoisomeric assignments were made on the basis of NMR studies.

The ^{1}H and ^{13}C NMR data are given in Tables 1 and 2; ^{1}H signals were identified by appropriate decoupling experiments and ^{13}C assignments were confirmed for selenonophosphates (**5a**) and (**5e**) by ^{13}C–^{1}H correlation spectroscopy (COSY). It is seen that the pairs of diastereoisomers divide into two sets, each with remarkably similar values within the sets for chemical shifts and coupling constants, indicating that the conformations are unaffected by the heteroatom (oxygen, sulphur, or selenium) on the phosphorus atom. It is also clear from the small values of $J_{4,5a}$ and $J_{4,5e}$ in both sets of diasteroisomers that they have the 1,3,2-dioxaphosphorinane ring in the same conformation as shown in structures (**2a**)–(**5a**) and (**2e**)–(**5e**). The alternative conformation (**6**), which would show a large diaxial coupling between 4-H and 5-H^a, contains an unfavourable *syn*-diaxial interaction between C-2 and one of the phosphorus substituents (methyl or heteroatom). In the earlier work[2] on the *trans*-fused ring systems, the diastereoisomer with an axial methyl group was recognised by consideration of a number of factors: the smaller chemical shifts of the methyl group (^{13}C) and the phosphorus atom (^{31}P); the smaller value of $^{1}J_{C,P}$; and the larger chemical shifts (^{13}C) of C-3 and C-5. Applying these considerations (see Tables 1, 2, and 3) to the two sets gives a

Table 1. ^{1}H NMR spectral data.[a,b]

Compound	1-H	2-H	3-H	4-H	5-H^a	5-H^e	Me	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5e}$	$J_{5a,5e}$	$^3J_{3,P}$	$^4J_{4,P}$	$^3J_{5a,P}$	$^3J_{5e,P}$	$^2J_{Me,P}$
(**2a**)	5.90	4.53	4.62	4.14	4.33	4.44	1.44	3.5	0	2.5	2.5	<1	13.5	2.5	1.5	2.5	19.5	17.0
(**4a**)	6.02	4.68	4.65	4.25	4.39	4.54	1.88	3.5	0	2.0	1.5	2.5	13.5	2.5	2.0	4.5	20.5	14.5
(**5a**)	6.05	4.71	4.64	4.33	4.39	4.53	2.07	3.5	0	3.0	3.0	2.2	13.0	3.0	2.0	6.0	19.5	13.5
(**2e**)	5.94	4.55	4.86	4.17	4.68	4.35	1.53	3.5	0	<1	2.5	<1	13.0	<1	<1	2.5	19.5	15.0
(**4e**)	5.93	4.55	4.92	4.10	4.81	4.32	1.90	3.5	0	1.5	2.0	0	13.0	1.5	1.5	4.0	24.0	16.0
(**5e**)	5.93	4.55	4.95	4.11	4.83	4.29	2.05	3.5	0	2.0	2.0	1.0	13.0	2.0	1.0	4.0	25.0	15.0

[a] δ_H/ppm and J/Hz, measured at 300 MHz. [b] J-values measured to nearest 0.5 Hz.

Table 2. ^{13}C NMR spectral data.[a]

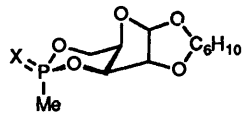
Compound	C-1	C-2	C-3	C-4	C-5	Me	$O_2C(CH_2)_2$	$O_2C(CH_2)_2$	$(CH_2)_3$
(**2a**)	104.4	83.9 (7.6)[b]	81.2 (6.4)	72.2 (8.9)	66.0 (6.0)	8.4 (134.1)	113.0	36.2, 35.5	24.6, 23.7, 23.3
(**4a**)	104.6	83.9 (8.2)	80.8 (8.6)	72.2 (8.7)	63.8 (8.2)	17.6 (106.0)	113.2	36.3, 35.7	24.7, 23.8, 23.5
(**5a**)	104.8	83.8 (8.0)	80.5 (9.7)	72.6 (8.9)	65.3 (9.3)	21.75 (80.5)	113.4	36.4, 35.6	24.8, 23.9, 23.6
(**2e**)	104.3	83.8 (9.7)	77.6 (5.8)	72.7 (6.9)	62.9 (5.9)	10.8 (144.7)	113.1	36.2, 35.5	24.6, 23.6, 23.3
(**4e**)	104.2	83.7 (11.0)	76.4 (4.7)	72.8 (6.9)	62.3 (5.4)	20.9 (110.0)	112.9	36.1, 35.6	24.7, 23.7, 23.4
(**5e**)	104.4	83.7 (11.0)	77.0 (4.5)	73.1 (7.2)	63.0 (5.1)	24.5 (94.7)	113.2	36.3, 35.7	24.8, 23.8, 23.5

[a] δ_C/ppm, measured at 75.47 MHz. [b] Figures in parentheses are $J_{C,P}$-values (Hz).

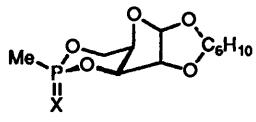
Table 3. ^{31}P and ^{77}Se NMR spectral data.[a,b]

Compound	P	Se
(**2a**)	21.9	
(**4a**)	88.6	
(**5a**)	92.3	140.9 (914)
(**2e**)	29.7	
(**4e**)	97.2	
(**5e**)	100.1	199.8 (862)

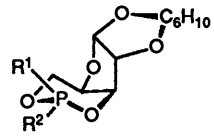
[a] δ-Values/ppm measured at 121.5 MHz (^{31}P) and 57.27 MHz (^{77}Se). [b] Figures in parentheses are $J_{P,Se}$-values (in Hz).



(**2a**) X = O
(**4a**) X = S
(**5a**) X = Se



(**2e**) X = O
(**4e**) X = S
(**5e**) X = Se



(**6**) R^1R^2 = Me, X or X, Me
(X = O, S, or Se)

consistent indication that compounds (**2a**), (**4a**), and (**5a**) all possess an axial methyl group. It also suggests that the considerations are independent of the nature of the heteroatom on phosphorus and it is interesting that the selenium resonance in compound (**5a**) is, like that of the phosphorus, at higher field than in its isomer (**5e**) (see Table 3).

A clear distinction in the ^{1}H NMR spectra of the two sets of diastereoisomers lies in the chemical shifts of 3-H and 5-H^a. The set with the higher chemical shifts is, by the earlier considerations, the one with an equatorial methyl group and thus an axial heteroatom which deshields the *syn*-diaxial 3-H and 5-H^a. In both sets 5-H^e is clearly identified by the large $^3J_{H,P}$-values (19.5–25.0 Hz) arising from the antiperiplanar arrangement of 5-H^e and phosphorus. The other $^3J_{H,P}$-values are smaller (0–6.0 Hz) as are the $^4J_{H,P}$-values (0–2 Hz); no coupling was observed between 1-H and phosphorus in either set. The $^2J_{H,P}$-values are also consistently lower (16.8–13.5 Hz) for the axial methyl compounds than for the equatorial methyl diastereoisomers (18.2–15.1 Hz) as were the $^1J_{C,P}$-values. There are also uniform trends in the $^2J_{C,P}$- and $^3J_{C,P}$-values involving C-2, C-3, C-4, and C-5 and phosphorus.

The axial methyl assignments for compounds (**4a**) and (**5a**) and, by implication, for compound (**2a**) were confirmed by NOE experiments. For compound (**4a**) irradiation of either axial hydrogen atom, 3-H or 5-H^a, produced enhancement of the methyl signal (1.5 and 1.6%, respectively) and irradiation of the methyl had a strong effect (5.6%) on 3-H and a weaker one (2.2%) on 5-H^a. No such NOE effects were observed in the equatorial diastereoisomer (**4e**). Similarly irradiation of the methyl signal in the selenonophosphonate (**5a**) caused enhancement of the 3-H signal (6%) and the 5-H^a signal (2%).

Finally it is to be noted that in the pairs (**2a**)/(**2e**), (**4a**)/(**4e**), and (**5a**)/(**5e**), the diastereoisomer containing the axial methyl group has (where applicable) the higher melting point and the higher optical rotation.

Experimental

The NMR spectral data given in Tables 1–3 were obtained with a Brucker WM-300 spectrometer. Compounds were dissolved in $CDCl_3$ with either $SiMe_4$ as internal standard (^{13}C and ^{1}H) or 85% H_3PO_4 or aqueous H_2SeO_3 as external standards (^{31}P and ^{77}Se, respectively). Light petroleum refers to the fraction boiling in the range 40–60 °C. Optical rotations were measured on a Polamat A (Karl–Zeiss Jena) polarimeter in chloroform solution.

1,2-O-*Cyclohexylidene*-α-D-*xylofuranose* 3,5-O-*Methylphosphonates* (**2**).—A solution of 1,2-*O*-cyclohexylidene-α-D-xylofuranose (**1**) (2.3 g, 10 mmol) and triethylamine (2.2 g, 22 mmol) in 1,4-dioxane (40 cm^3) was added dropwise at room

temperature to a stirred solution of methylphosphonic dichloride (1.33 g, 10 mmol) in 1,4-dioxane (1 cm^3) under nitrogen. After 6 h, precipitated triethylamine hydrochloride was filtered off and the filtrate was evaporated under reduced pressure to an oil, which was partitioned between water (50 cm^3) and chloroform (4 × 25 cm^3). The combined chloroform extracts were dried (Na_2SO_4) and evaporated to give an oil, which was dissolved in dichloromethane. On addition of hexane the (S_P)-*isomer* (**2a**) (1.8 g, 31%) crystallised out, with m.p. 196–198 °C; $[\alpha]_D$ +15.4° (*c* 1.1) (Found: C, 49.4; H, 6.7. $C_{12}H_{19}O_6P$ requires C, 49.65; H, 6.55%).

The mother liquours were concentrated to give an oil, which was purified by chromatography on silica and elution with ethyl acetate–acetic acid (10:1) to give the (R_P)-*isomer* (**2e**) (1.5 g, 26%) as a viscous oil, $[\alpha]_D$ +13.9° (*c* 1.5) (Found: C, 49.45; H, 6.5%).

1,2-O-*Cyclohexylidene*-α-D-*xylofuranose* 3,5-O-*Methylthionophosphonates* (**4**).—A solution of the acetal (**1**) (2.3 g, 10 mmol) and triethylamine (2.2 g, 22 mmol) in 1,4-dioxane (40 cm^3) was added dropwise at room temperature to a stirred solution of methyldichlorophosphine (1.17 g, 10 mmol) in 1,4-dioxane (10 cm^3) under nitrogen. After 6 h precipitated salts were filtered off and the filtrate was concentrated to yield the crude phosphite (**3**) as an oil to which sulphur (0.5 g, 15 mmol) was added. The mixture was stirred at 80–90 °C for 2 h, cooled, and partitioned between water (50 cm^3) and chloroform (4 × 25 cm^3). The combined chloroform extracts were dried (Na_2SO_4), concentrated, taken up in diethyl ether, and filtered to remove remaining sulphur. Evaporation yielded a mixture of thionophosphonates (**4**), which was separated by chromatography on silica and elution with benzene–light petroleum–ethyl acetate (10:7:3). The (S_P)-*isomer* (**4a**) (0.95 g, 31%) eluted first, and had m.p. 141–143 °C (from dichloromethane–hexane); $[\alpha]_D$ +36.6° (*c* 1.5) (Found: C, 47.0; H, 6.2; S, 10.7. $C_{12}H_{19}O_5PS$ requires C, 47.05; H, 6.25; S, 10.5%). The (R_P)-*isomer* (**4e**) (0.67 g, 22%) had m.p. 108–110 °C; $[\alpha]_D$ +18.1° (*c* 1.3) (Found: C, 47.0; H, 6.4; S, 10.7%).

1,2-O-*Cyclohexylidene*-α-D-*xylofuranose* 3,5-O-*Methylselenonophosphonates* (**5**).—Powdered selenium (1 g) was added to the crude phosphite (**3**), prepared as in the previous experiment from the acetal (**1**) (2.3 g, 10 mmol). The mixture was stirred under nitrogen at room temperature for 4 h and then partitioned between water (50 cm^3) and chloroform (4 × 25 cm^3). The combined chloroform extracts were dried (Na_2SO_4) and concentrated to give an oil. This was dissolved in benzene and absorbed onto a column of silica and left for 12 h (immediate development of the column resulted in the elution of colloidal selenium) during which time an intense red colour appeared. Subsequent elution with benzene–light petroleum–ethyl acetate (10:7:3) gave the (S_P)-*isomer* (**5a**) (0.9 g, 31%), m.p. 145–147 °C (from hexane); $[\alpha]_D$ +40.30° (*c* 1.5) (Found: C, 41.35; H, 5.4. $C_{12}H_{19}O_5PSe$ requires C, 40.8; H, 5.4%). Eluted second was the (R_P)-*isomer* (**5e**) (0.67 g, 22%), m.p. 97–99 °C; $[\alpha]_D$ +25.8° (*c* 0.7) (Found: C, 41.0; H, 5.55%).

Acknowledgements

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