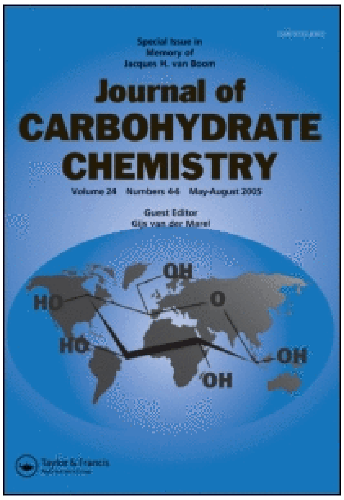

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Synthesis and Stereochemistry of Some new Derivatives of 1,2-O-Cyclohexylidene-α-D-Xylofuranuronic Acid

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SYNTHESIS AND STEREOCHEMISTRY OF SOME NEW DERIVATIVES OF 1,2-O-CYCLOHEXYLIDENE-α-D-XYLOFURANURONIC ACID[1]

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ABSTRACT

1,2-O-Cyclohexylidene-α-D-xylofuranuronic acid (2) has been converted into its 3-O-acetyl derivative and consecutively to the corresponding acid chloride and ethyl ester. Direct reaction of 2 with ethanol in the presence of p-toluene sulphonic acid gave the ethyl ester. Reaction of 2 with phosphorus pentachloride in dry ether gave the acid chloride of 1,2-O-cyclohexylidene-3-O-dichlorophosphoryl-α-D-xylofuranuronic acid. Conformational data have been obtained from ^{1}H and ^{13}C NMR measurements.

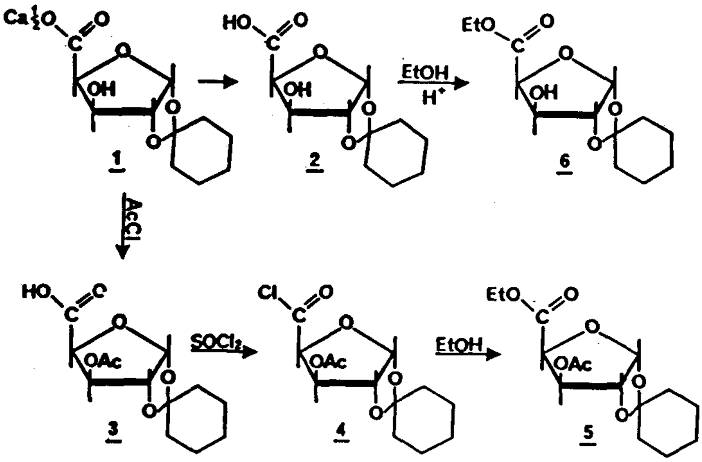
INTRODUCTION

In the previous communications[2,3] from this laboratory, synthesis of 5-deoxy- and 5-bromo-5-deoxy- derivatives of 1,2-O-cyclohexylidene-α-D-xylofuranose[4,5] have been described. In the present report we discuss some further transformations of 1,2-O-cyclohexylidene-α-D-xylofuranose into simple derivatives of 1,2-O-cyclohexylidene-α-D-xylofuranuronic acid. These derivatives, owing to their polar and solubility properties, could potentially serve as starting building blocks in the preparation of various pharmaceuticals.

RESULTS AND DISCUSSION

The starting compounds 1,2-O-cyclohexylidene-α-D-xylofuranuronic acid (2) and its calcium salt(1) were obtained by O_2-oxidation of 1,2-O-cyclohexylidene-α-D-xylofuranose using Pt/C as the catalyst.[6] The preparation of D-xylofuranuronic acid derivatives is given in Scheme 1.

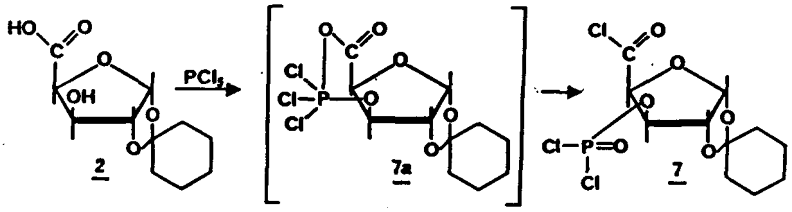
SCHEME 1



Direct esterification of acid 2 with ethanol, in the presence of catalytic amounts of p-toluenesulphonic acid, takes place without any change of the 1,2-O-cyclohexylidene acetal function.

Treating acid 2 with phosphorus pentachloride give 1,2-O-cyclohexylidene-3-O-dichlorophosphoryl-α-D-xylofuranuronoyl chloride (7) as shown in Scheme 2. It is probable that 7 is formed via the cyclic intermediate 7a. A similar reaction sequence has been described for salicylic acid when it is converted into O-dichlorophosphorylsalicyl chloride.[7]

SCHEME 2



^{1}H and ^{13}C NMR parameters are given in Table 1. According to the notation of Altona and Sundaralingam[8] the proton coupling constants are compatible with a twist conformation $^{3}T_{2}$ of the furanose ring. These results are consistent with the conclusions of Abraham et al.[9] and Neeser et al.,[10] concerning the predominant conformations of 1,2-O-isopropylidene-α-D-xyloses.

The preferred conformation around the C_3-O_3 phosphoester bond of 7 follows from the observed coupling constants between phosphorus-31 and both protons ($^{3}J_{POCH}$, $^{4}J_{POCCH}$) and carbon-13 ($^{3}J_{POCC}$). The low value of $^{3}J_{POCC(2)}$ is characteristic of a gauche orientation[11] of phosphorus with respect to the carbon at position 2 and indicates that the preferred conformation has C_4-C_3-O-P in a zig-zag arrangement. The high value of $^{4}J_{POCCH(4)}$ confirms a zig-zag coupling pathway, which

TABLE 1

Chemical Shifts and Coupling Constants of Compounds 2-7 in $CDCl_3$

NMR Parameters	Compounds					
	2[a]	3	4	5	6	7[b]
δ ^1H, ppm						
H-1	6.16	6.05	6.05	5.99	6.08	6.06
H-2	4.86	4.53	4.53	4.47	4.57	4.82
H-3	5.17	5.58	5.66	5.41	4.76	5.43
H-4	4.75	5.11	5.13	4.78	4.48	5.07
CH_3(Ac)	-	1.92	1.92	1.93	-	-
CH_2(Et)	-	-	-	4.22	4.26	-
CH_3(Et)	-	-	-	1.24	1.20	-
$J_{H,H}$-Hz						
$J_{1,2}$	3.5	3.3	3.3	3.3	3.5	3.3
$J_{3,4}$	3.1	3.6	3.6	3.6	3.1	3.1
$J_{2,3}$	0	$\leqslant$0.4	$\leqslant$0.4	$\leqslant$0.4	0	$\leqslant$0.6
δ ^{13}C, ppm						
C-1	103.7	103.9	104.0	103.3	103.3	105.6
C-2	79.7	75.6	74.9	75.2	78.1	81.6
C-3	74.6	76.7	80.2	76.3	74.5	83.6
C-4	83.4	81.4	83.2	80.7	82.4	85.2
C-5	169.3	167.3	167.2	167.2	167.0	166.8
CO (Ac)	-	165.9	166.3	165.1	-	-
CH_3(Ac)	-	18.5	18.6	18.6	-	-
CH_2(Et)	-	-	-	59.4	59.7	-
CH_3(Et)	-	-	-	12.3	12.3	-

a. C_5D_5N as solvent

b. $J_{H_1,P}=0.2$ Hz, $J_{H_2,P}=0.3$ Hz, $J_{H_3,P}=10.4$ Hz and $J_{H_4,P}=4.2$ Hz. $J_{C_1,P}=0.5$ Hz, $J_{C_2,P}=1.5$ Hz, $J_{C_3,P}=7.8$ Hz and $J_{C_4,P}=9.8$ Hz.

is generally observed in similar cases.[12,13] On the basis of $^3J_{PH(trans)}$ = 23 Hz and $^3J_{PH(gauche)}$ = 2.1 Hz,[12] as well as $^3J_{PC(trans)}$ = 10 Hz and $^3J_{PC(gauche)}$ = 2.5 Hz,[11] the molar fraction of this rotamer is estimated to be more than 0.7.

EXPERIMENTAL

General Methods. IR spectra were recorded as KBr pelletson a Perkin-Elmer 577 Spectrophotometer.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (TMS as interal standard) at 80 and 20 MHz respectively, using a Varian CFT-20 instrument. Assignements of the protons of the furanose ring were done by homodecoupling experiments and confirmed by simulation of the spectra using SIMEQ.[14] ^{13}C NMR spectral assignements were based on the cross-correlation experiments.

High resolution mass spectrometry was performed on Varian MAT 311A, using direct a probe and 70 eV ionizing energy. Melting points are not corrected.

1,2-O-Cyclohexylidene-3-O-acetyl-α-D-xylofuranuronic acid (3). A suspension of calcium 1,2-O-cyclohexylidene-α-D-xylofuranuronate[6] 1 (1 g, 1,9 mmol) in acetyl chloride (10 mL) was stirred at room temperature for 12 h. After removing acetyl chloride in vacuo, the resulting mixture was diluted with cold water and extracted with ethyl acetate. The combined extracts were dried over anhyd sodium sulfate. After filtration of Na_2SO_4 and evaporation of ethyl acetate in vacuo, the residue was directly crystallized from methylene chloride-n-hexane to yield 0.75 g (69.4%) of 3 with mp 137 °C. IR (KBr) 3200, 2970, 1740, 1680, 1370, 1230, 1060, 930 cm^{-1}; ^1H NMR ($CDCl_3$) see Table 1.; MS 286 (M^+, 78), 257 (32), 243 (100), 171 (26), 99 (48), 43 (96).

Anal. Calcd for $C_{13}H_{18}O_7$: C,54.54; H,6.43. Found: C,54.48; H,6.20.

1,2-O-Cyclohexylidene-3-O-acetyl-α-D-xylofuranuranoyl chloride (4). A mixture of 3 (2.86 g, 0.01 mmol) and thionyl chloride (20 mL) was refluxed for 2 h. Thionyl chloride was removed in vacuo, petroleum ether was added to the residue and the solution concentrated to dryness. This was repeated three times in order to remove last traces of thionyl chloride. The product was crystallized from methylene chloride-n-hexane to give 1.8 g (58%) of 4 with mp 97 °C.

A sample for microanalysis was purified by low-pressure distillation followed by crystallization. IR (KBr) 2940, 1800, 1740, 1370, 1225, 1075, 780 cm^{-1}; ^1H NMR ($CDCl_3$) see Table 1.; MS 304 (M^+, 100), 261 (95), 241 (45), 189 (30), 169 (30), 143 (85), 99 (97).

Anal. Calcd for $C_{13}H_{17}O_6Cl$: C,51.23; H,5.58. Found: C,51.28; H,5.33.

Ethyl 1,2-O-cyclohexylidene-3-O-acetyl-α-D-xylofuranuronate (5). A solution of 4 (0.85 g, 2.8 mmol) in ethanol (3 mL) was concentrated to dryness at 40 °C. This procedure was repeated twice. The crude ester was dissolved in water and the resulting solution extracted with ether. The dried (sodium sulfate) extracts were concentrated and petroleum ether was added to yield 0.49 g (61%) of 5 with mp 64 °C IR (KBr) 2930, 2860, 1760, 1740, 1320, 1250, 1060, 960 cm^{-1}; ^1H NMR ($CDCl_3$) see Table 1.; MS 314 (M^+, 45), 271 (52), 225 (22), 134 (18), 107 (34), 43 (100).

Anal. Calcd for $C_{15}H_{22}O_7$: C,57.31; H,7.06. Found: C,57.45; H,7.23.

Ethyl 1,2-O-cyclohexylidene-α-D-xylofuranuronate (6). A solution of 2 (0.25 g, 1 mmol) in ethanol (5 mL) was refluxed with p-toluenesulphonic acid (0.05 g, 0.3 mmol) for 6 h. The reaction mixture was concentrated and poured into water (10 mL). The aqueous solution was neutralized with sodium bicarbonate and extracted with chloroform. The combined extracts were dried (sodium sulfate) and concentrated in vacuo. The crude product was crystallized from methylene chloride-n-hexane to give 0.068 g (25%) of 6 with mp 115 °C: IR (KBr) 3480, 2920, 1374, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) see Table 1.; MS 272 (M^+, 40), 229 (90), 169 (6), 139 (10), 55 (100).

Anal. Calcd for $C_{13}H_{20}O_6$: C,57.33; H,7.40. Found: C,56.59; H,7.44.

1,2-O-Cyclohexylidene-3-O-dichlorophosphoryl-α-D-xylofuranuranoyl chloride (7). A mixture of 2 (0.15 g 0.6 mmol) and phosphorus pentachloride (0.15 g, 0.7 mmol) in dry ether (4 mL) was stirred at room temperature for 6 h. Concentration of the reaction mixture followed by cooling at -10 °C gave 0.112 g (48%) of 7 with mp 120 °C (decomposition): IR (KBr) 2930, 1790, 1280, 1040, 610 cm^{-1}; ^1H NMR ($CDCl_3$) see Table 1.; MS 378 (M^+, 24), 335 (82), 181 (30), 135 (11), 55 (100).

Anal. Calcd for $C_{11}H_{14}O_6Cl_3P$: Cl,28.02. Found: Cl,27.81.

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