NOVEL PHOSPHORUS DERIVATIVES OF SUGARS

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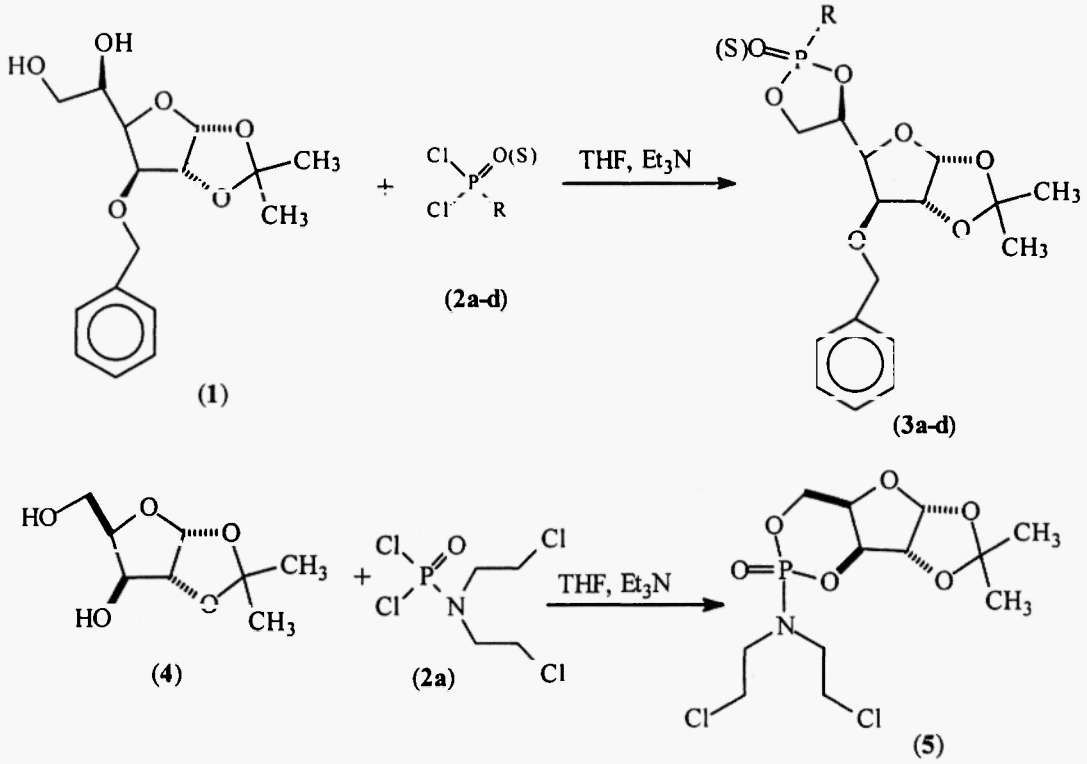
Abstract: Novel 1,2-O-(1-methylethylidene)-3-O-(phenylmethyl)-α-D-glucofuranose cyclic phosphoramidate/phosphates/ phosphorothioate (3a-d) and 1,2-O-(1-methylethylidene)-α-D-xylofuranose cyclic bis(2-chloroethyl)phosphoramidate (5) have been synthesized from reactions of equimolar quantities of 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (1) or 1,2-isopropylidene-D-xylofuranose (4) with bis(2-chloroethyl)phosphoramidic dichloride (2a), O-2-chloroethyl phosphoryl dichloride (2b), trichloromethyl phosphonic dichloride (2c) and phenylphosphorothioic dichloride (2d) in the presence of triethylamine in dry tetrahydrofuran. The structures are characterized by IR, ^{1}H, ^{31}P NMR and mass spectral data.

Introduction

Phospha sugars are one kind of pseudo sugar derivatives having a phosphorus atom in the hemiacetal ring of the sugar[1,2]. Like aza or thia sugars,whose hemiacetal rings has a nitrogen or a sulfur atom respectively, phospha sugars have been expected to exert biological activities by their affinity to organs[3]. Therefore phospha sugars are of interest in the aspects related to not only syntheses but also structures and biological activities. They are mainly prepared from sugar starting materials with suitable protections, functional group interconversions, cyclisations and deprotections[4-5]. N-Phosphorylated nitrogen mustard compounds are proven drugs in cancer chemotherapy[6-9]. In view of this, the title compounds 3&5 were synthesized and characterized by elemental, IR, NMR (^{1}H and ^{31}P) and mass spectral data.

Results and Discussion

3-O-Benzyl-1,2-O-isopropylidene-α-glucofuranose (1) was prepared from D-glucose[10] and reacted with members of 2 namely bis(2-chloroethyl)phosphoramidic dichloride (2a), O-2-chloroethyl phosphoryl dichloride (2b), trichloromethyl phosphonic dichloride (2c) and phenylphosphorothioic dichloride (2d) to obtain members of 3 (Scheme 1). 1,2-Isopropylidene-D-xylofuranose (4) was prepared from xylose[11] and treated with 2a to get 5. Two equivalents of triethylamine served as the base with tetrahydrofuran as the solvent. Purification of members of 3&5 was achieved by filtering off the triethylamine hydrochloride, removing the solvent under reduced pressure and treating the residue obtained, with increasing gradients of hexane-ethylacetate mixture. The compounds 3&5 were obtained as liquids. Attempts to determine their boiling points even under reduced pressure failed due to their thermal sensitivity. Physical and spectral data for the products obtained are found in Tables 1-3.



Compd.	R	Compd.	R
a	$N(CH_2CH_2Cl)_2$	c	CCl_3
b	OCH_2CH_2Cl	d	$OC_6H_5(P=S)$

IR spectra[12] of 3a-c & 5 (Table 1) showed bands at 1253-1279 cm^{-1} (P=O) and 3d showed band at 759 cm^{-1} (P=S). The ^1H NMR spectra (Table 2) of 3a and 5 shows that they are mixture of diastereomers judging from a pair of doublets at δ 5.87 (J=3.3 Hz), 5.94 (J=3.4 Hz) and (6.00 (J=3.7 Hz), 6.18 (J=3.7 Hz), respectively for H-1. The evidence shows that both R- and S- stereoisomers on the phosphorus atom were produced during the present reaction[13]. However, these diastereomers could not be separated by flash chromatography on silica gel. But 3b-d showed only one doublet at δ 5.83-5.91 (J=3.4-3.7 Hz) for H-1, which suggests that the nucleophilic attack of oxygen atom of the sugar at the phosphorus atom proceeds with inversion of configuration and only one stereoisomer might be formed as the major product[14]. In 3, the other protons of sugar moiety H-2 to H-6, H-6' and the benzylic protons of O-CH_2-Ph resonated as complex multiplet at δ 3.50-4.85 while in 5, H-2 to 5&5' resonated as multiplet at δ 4.08-4.97. The other protons chemical shifts appeared in the expected regions.

The appearance of two phosphorus resonance signals with equal intensities for the compounds 3a and 5 at 23.65 and 24.53 ppm and at 5 1.46 and 4.36 ppm, respectively suggest that they may include a pair of diastereomers. The appearance of two signals with varying intensities in the other compounds (3b,3c) may be due to the existence of other conformers[15].

The EI mass spectrum of 3a and CI-MS of 5 were recorded and interpreted. The molecular ions are detected as protonated species ($M^{+\cdot} + H$)^{1}. Appearance of [($M^{+\cdot} + H$)+2], [($M^{+\cdot} + H$)+4], along with their characteristic daughter ions [M^{+}-$N(CH_2CH_2Cl)_2$], [M^{+}-CH_2Cl], [M^{+}-CH_3], [M^{+}-Cl] confirm the structures proposed for them.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were run as KBr pellets using a Perkin-Elmer 283 double beam spectrophotometer (ν_{max} in cm^{-1}). The ^{1}H and ^{31}P NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 using Brucker 400 MHz instrument and chemical shifts were referenced to TMS (^{1}H) and 85% H_3PO_4 (^{31}P). Microanalytical data were obtained from Central Drug Research Institute, Lucknow, India. Mass spectral data were collected on a Auto Spec Q instrument from University of Kuwait, Kuwait. Compounds 1 & 4 were prepared according to literature procedure[10,11] and are characterised by ^{1}H NMR (Table 2).

Synthesis of 1,2-O-(1-methylethylidene)-3-O-(phenylmethyl)-α-D-glucofuranose cyclic bis(2-chloroethyl)phosphoramidate (3a): General procedure:

A solution of bis(2-chloroethyl)phosphoramidic dichloride (2a, 2.59 g, 0.01 mole) in 15 ml of dry tetrahydrofuran was added dropwise to the cooled (0°C) and stirred solution of 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (1, 3.10g, 0.01 mole) and triethylamine (2.02 g, 0.02 mole) in 50 ml of tetrahydrofuran for twenty minutes. After completion of the addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred for four hours to effect completion of the condensation. The completion of the reaction was monitored by TLC analysis. The solid triethylamine hydrochloride formed was filtered off, and the filtrate was evaporated under reduced pressure. The residue obtained was purified by flash chromatography with hexane-ethylacetate (8:2) mixture as eluent to get light yellow dense liquid of 3a, yield 1.39g (28%). Physical and spectral data of 3a-d and 5 are given in Tables 1-3.

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Table 1: Physical and IR (cm-1) data of compounds 3 & 5

Compd	Molecular formula	Yield (%)	$[\alpha]_D$	Found (Calcd.) %			P=O	P=S
				C	H	N		
3a	$C_{20}H_{28}Cl_2NO_7P$	28	-19.5	48.32 (48.40)	5.76 (5.69)	2.80 (2.82)	1267	
3b	$C_{18}H_{24}ClO_8P$	20	-17.5	49.66 (49.72)	5.52 (5.56)		1253	
3c	$C_{17}H_{20}Cl_3O_7P$	22	-16.6	43.18 (43.11)	4.21 (4.26)		1279	
3d	$C_{22}H_{25}O_7PS$	26	-14.4	59.12 (58.89)	5.40 (5.43)			759
5	$C_{12}H_{20}Cl_2NO_6P$	28	+4.20	38.29 (38.31)	5.38 (5.36)	3.70 (3.72)	1256	

Table 2: ^{1}H and ^{31}P NMR data of compounds 3 & 5

Compd.	H-1	H-2-6,6' & OCH_2Ph	Ar-H	$C(CH_3)_2$	R'-H	OH	^{31}P NMR[c]
1	5.92 (d,4.0,1H)	4.60 (d,4.0,1H,H-2) 3.60-4.20 (m,5H,H-3-6&6') 4.55 (d,13.0,1H,OCH_2Ph) 4.75 (d,13.0,1H,OCH_2Ph)	7.20-7.50 (m,5H)	1.40 (s,3H) 1.49 (s,3H)		2.40 (br s, 2H)	
3a	5.87 (d,3.3,1H) 5.94 (d,3.4,1H)	3.98-4.80 (m,8H)	7.20-7.34 (m,5H)	1.29 (s,3H) 1.46 (s,3H)	3.34-3.47 (m,4H,$N(CH_2)_2$) 3.54-3.59 (m,4H,$(CH_2Cl)_2$)		23.65, 24.53
3b	5.91 (d,3.4,1H)	4.04-4.72 (m,8H)	7.26-7.35 (m,5H)	1.31 (s,3H) 1.47 (s,3H)	3.82 (t,2H,OCH_2) 3.72 (t,2H, CH_2Cl)		-10.77, -11.37
3c	5.81 (d,3.4,1H)	3.85-4.70 (m,8H)	7.20-7.41 (m, 5H)	1.30 (s,3H) 1.48 (s,3H)			7.63, 17.24
3d	5.83 (d,3.7,1H)	3.50-4.85 (m,8H)	6.80 (d,8.0,2H) 7.15-7.50 (m,8H)	1.29 (s,3H) 1.48 (s,3H)			
4	5.95 (d,4.0,1H)	3.95-4.50 (m,5H,H-2-5&5')		1.30 (s,3H) 1.45 (s,3H)		3.70 (br s, 2H)	
5	6.00 (d,3.7,1H) 6.18 (d,3.7,1H)	4.08-4.97 (m,5H,H-2-5&5')		1.40 (s,3H) 1.54 (s,3H)	3.32-3.48 (m,4H,$N(CH_2)_2$) 3.56-3.66 (m,4H, $(CH_2Cl)_2$)		1.14, 4.36

[a]Chemical shifts in δ from TMS, *J* (Hz) given in parentheses
[b]Recorded in $CDCl_3$
[c]Chemical shifts in δ from 85% H_3PO_4

Table 3. Mass spectral data of 3a & 5

Compd.	m/z (relative abundance)
3c CIMS	500 [5.7, (M^+ +H)+4], 498 [29.7, (M^++H)+2], 496 [45.6, (M^+ +H)], 480 [1.8, (M^+-CH_3)], 460 [9.3 (M^+-Cl)], 446 [18.1, (M^+-CH_2Cl)], 355 [5.7, (M^+-$N(CH_2CH_2Cl)_2$], 297 (12.4), 91 (100)
5 EIMS	380 [0.2, (M^+ + H)+4], 378 [1.1, (M^+ +H)+2], 376 [1.8 (M^+ +H)], 360 [7.1, (M^+ -CH_3), 340 [0.9, (M^+-Cl)], 326 [100, (M^+-CH_2Cl)], 235 [34.8, (M^+-$N(CH_2CH_2Cl)_2$], 177 (7.1), 172 (8.9), 149 (7.1), 139 (51.3), 97 (43.7)

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