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SOME 3-*C*-(DIMETHOXY)PHOSPHINYL DERIVATIVES OF D-GLUCOSE, D-ALLOSE, AND D-RIBOSE*

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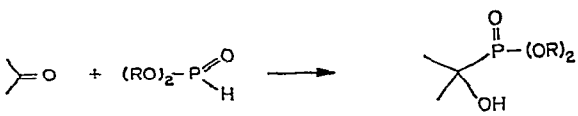
ABSTRACT

Reaction of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose with dimethyl phosphite affords preponderantly 3-*C*-(dimethoxy)phosphinyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose; lesser quantities of the C-3 epimer have also been isolated. The structural assignments of these derivatives are based on detailed n.m.r. analyses. A similar reaction has been applied to 1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-*erythro*-pentofuranos-3-ulose to give 3-*C*-(dimethoxy)phosphinyl-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-ribofuranose.

INTRODUCTION

Recent interest[2–4] in the chemistry of organo-phosphonate derivatives has been prompted partly by the isolation[5] of one such compound from natural sources and partly by the speculation that some phosphonates may have interesting biological properties. Our interest in phosphonate derivatives of carbohydrates was also enhanced by the possibility that they might give further insight into the angular dependencies of ^{31}P nuclear magnetic resonance (n.m.r.) parameters.

The present paper describes the synthesis of three carbohydrate hydroxyphosphonates, by an application of the Abramov reaction[6], a reaction which has also been used by Paulsen's group[4].



RESULTS AND DISCUSSION

The original, small-scale reaction between 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[7,8] (**1**) and dimethyl phosphite, in benzene solution con-

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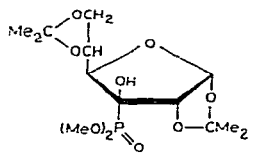
taining a catalytic amount of sodium methoxide, afforded, directly from the reaction mixture and in low yield (~26%), a crystalline derivative, "isomer *A*", m.p. 85°. Subsequent preparative-scale experiments afforded, as major product, a different crystalline derivative, "isomer *B*", m.p. 102°, in somewhat higher yield (64%).

The ^{1}H n.m.r. spectra of isomers *A* and *B* demonstrated that each derivative retained both isopropylidene groups (12 protons at τ ~8.6), and contained, effectively, one equivalent of dimethyl phosphite (6 protons at τ ~6.2). Evidently, *A* and *B* are the epimeric 3-*C*-(dimethoxy)phosphinyl-1,2:5,6-di-*O*-isopropylidene-α-D-hexofuranoses **2** and **3**.



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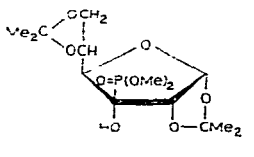

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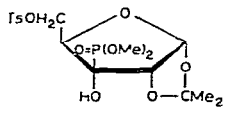

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Assignment of the configuration at C-3 was based on the parameters derived from the ^{1}H n.m.r. spectra shown in Figs. 1 and 2. The coupling constants obtained by computer analysis* of these spectra are summarised in Table I. We shall assume, for the present, that the furanoid rings of the phosphonates **2** and **3** have, to a first approximation, the $^3T_2$(D) conformations (see Figs. 1 and 2). If this is correct, it is possible to predict the *relative* magnitudes of the vicinal ^{31}P–^{1}H couplings of **2** and **3**, using the previously established[9,10], angular dependence of $^3J_{P,H}$ couplings. For the D-*gluco* derivative (**2**) in the $^3T_2$(D) conformation (Fig. 1), both $J_{P,2}$ and $J_{P,4}$ should be small (<8 Hz); for the D-*allo* derivative (**3**) in the $^3T_2$(D) conformation (Fig. 2), $J_{P,2}$ should again be small, but $J_{P,4}$ should now be much larger (~30 Hz).

Inspection of the vicinal ^{31}P–^{1}H couplings in Table I indicates that isomer *A*, m.p. 85°, has couplings in accord with those expected for the D-*gluco* configuration (**2**), while those of isomer *B*, m.p. 102°, agree with the D-*allo* configuration (**3**). Thus, isomer *A* has the structure 3-*C*-(dimethoxy)phosphinyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) and isomer *B* the structure 3-*C*-(dimethoxy)phosphinyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**).

To our dismay, we have never been able to repeat successfully the *first* experiment which afforded isomer *A*** *in crystalline form directly from the reaction mixture.* Instead, every subsequent reaction has afforded crystalline isomer *B directly* from the reaction mixture, together with lesser quantities of isomer *A*, isolable only with difficulty by column chromatography. In spite of the uncertainty associated with our failure to repeat the first experiment, the observation that the major course of the

*It will be noted that the value quoted for $J_{P,4}$ differs from that given in ref. 1. The original value was based on an incorrect first-order assignment made by L.D.H.

We still have a crystalline sample of this elusive compound. It was suggested to us by Dr. Gordon Jones (Syntex, Palo Alto) that isomer *A* might have arisen from epimerisation of **1 at C-4; we attempted to induce this epimerisation without success.

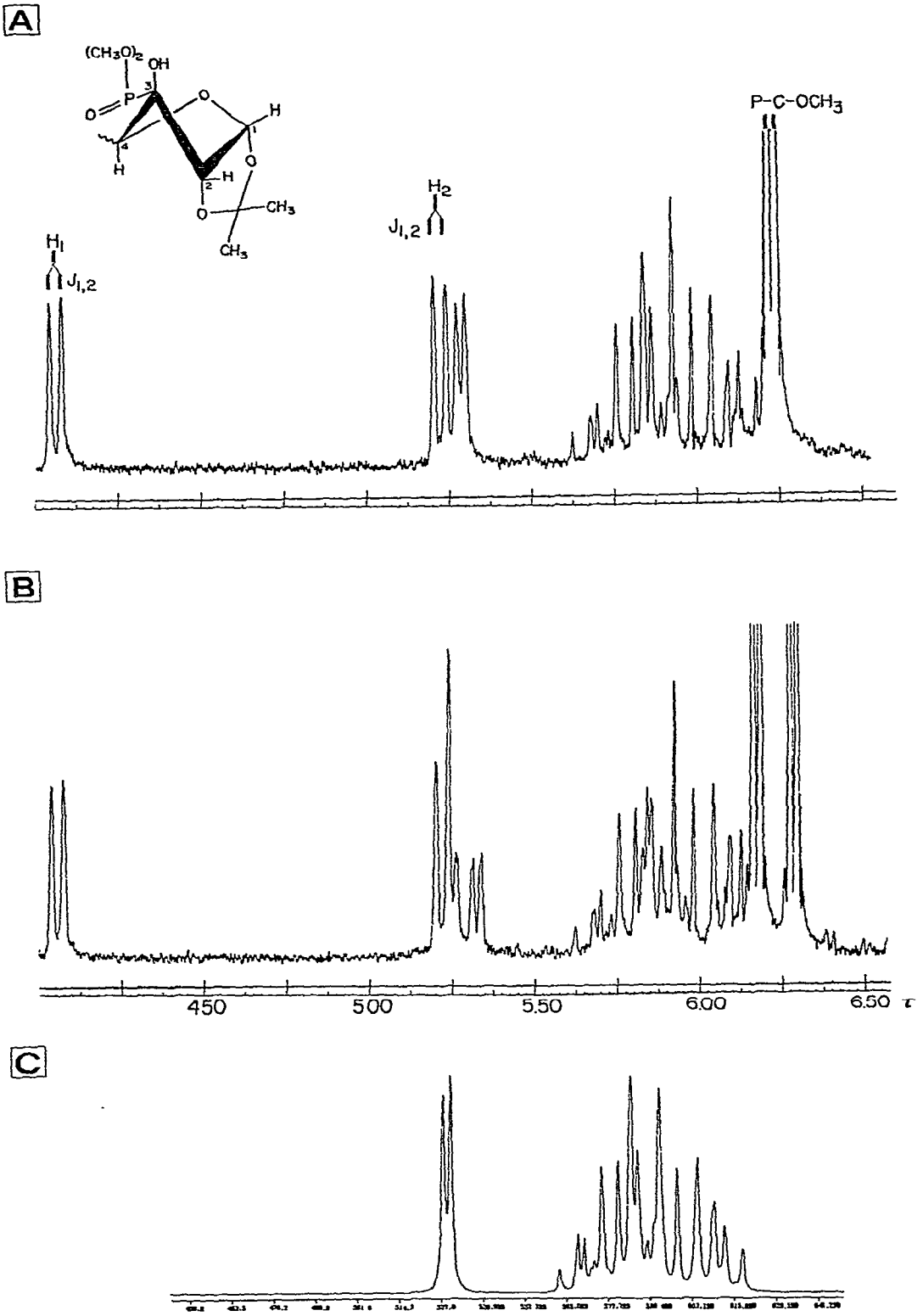

Fig. 1. Partial ^{1}H n.m.r. spectra (100 MHz) of compound 2 in deuterioacetone solution. The normal spectrum is shown in (A); the spectrum in (B) was measured with simultaneous irradiation at the ^{31}P resonance frequency (40,480,800.0 Hz). (C) A computer-based simulation of the ^{31}P-decoupled spectra based on the parameters listed in Tables I and II.

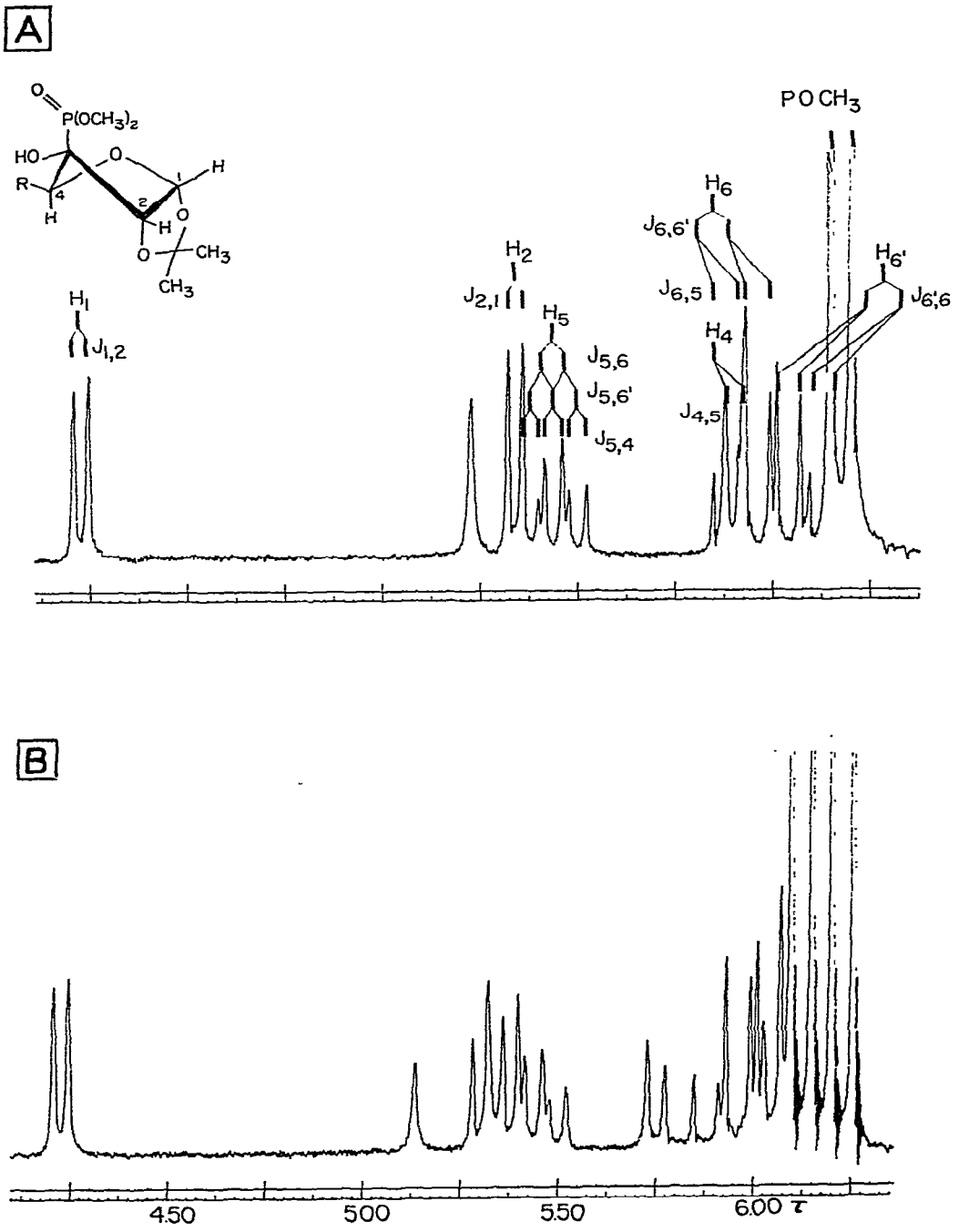

Fig. 2. Partial ^{1}H n.m.r. spectra (100 MHz) of compound **3** in deuterioacetone solution. The normal spectrum is shown in (A). That shown in (B) was measured with simultaneous irradiation at the ^{31}P resonance frequency (40,481,615.0 Hz). The first-order assignment is based on the parameters listed in Tables I and II.

TABLE I

COUPLING CONSTANTS (Hz) FOR THE HYDROXY-PHOSPHONATE DERIVATIVES **2**, **3**, AND **6**

Compound	$J_{1,2}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{P,2}$	$J_{P,4}$	J_{P,OCH_3}	$J_{P,OH}$
2[a]	3.7	7.6	5.9	5.4	−8.7	<0.5	2.8	11.0	8.0; $J_{4,OH}$ 2.5
3[a]	3.8	4.8	6.5	5.9	−8.3	7.8	29.7	10.4	17.0
6[b]	3.8	2.0 8.5	$J_{5,5'}$ −10.5	—	—	8.1	26.8	10.5	—

[a]Measured in deuterioacetone solution. [b]Measured in deuteriochloroform solution.

TABLE II

CHEMICAL SHIFTS (τ-VALUES, δ-VALUES) FOR THE HYDROXY-PHOSPHONATE DERIVATIVES **2**, **3**, AND **6**

Compound	*H-1*	*H-2*	*H-4*	*H-5*	*H-6*	*OH*	*OMe*	*C-CH*$_3$	δ_P
								8.51 (1)	
2[a]	4.04	5.20	5.88	5.74	5.92	5.29	6.20	8.58 (1)	112.2
					6.10		6.22	8.69 (2)	
								8.50 (1)	
3[a]	4.22	5.34	5.91	5.45	5.93	5.22	6.13	8.65 (1)	91.5
					6.07		6.23	8.70 (2)	
6[b]	4.24	5.37	5.85	5.46	—	—	6.17	8.48 (1)	92.2
				5.70			6.23	8.65 (1)	

[a]Measured in deuterioacetone solution. [b]Measured in deuteriochloroform solution.

reaction favours formation of the D-*allo* configuration is in accord with many previous observations. It is well known that nucleophilic attack at C-3 of the 1,2-*O*-isopropylidene-α-D-xylofuranose ring-system occurs more readily from the *exo* side; for example, reduction of the 3-keto derivative **1** by sodium borohydride affords[7] preponderantly the D-*allo* product.

Subsequent to the above experiments, we (L. Lynn) applied essentially the same reaction conditions to 1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-*erythro*-pentofuranos-3-ulose[11]. A single, crystalline product was obtained, and no evidence (n.m.r., t.l.c.) for the presence of an epimeric product could be obtained. Examination of the ^{1}H n.m.r. spectrum of the crystalline product showed it to be 3-*C*-(dimethoxy)phosphinyl-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-ribofuranose (**4**) ($J_{P,2}$ 8.1, $J_{P,4}$ 26.8 Hz). Thus, this reaction also resulted in the preferential nucleophilic attack of the phosphonate anion from the *exo* direction.

We are continuing a study of the synthesis of other derivatives of carbohydrates having a carbon–phosphorus bond and with their use as intermediates to novel phosphorus-containing systems.

EXPERIMENTAL AND SPECTRAL ASSIGNMENTS

The general methods used in this study have been summarised previously[10].

Reaction of dimethyl phosphite with 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (**1**). — (*a*) The *first* reaction, which resulted in the direct formation of crystalline "isomer *A*", involved the addition of dimethyl phosphite (0.4 ml) and 10 drops of a saturated solution of sodium methoxide in methanol to a solution of **1**[7] (1.0 g) in benzene (15 ml). The solution was left overnight, the solvent was removed, and the resultant syrup was induced to crystallise from ether–light petroleum (b.p. 30–60°) to give **2** as colourless needles (0.38 g, 24%), m.p. 85°, $[\alpha]_D^{25}$ −41.7° (*c* 1.7, chloroform).

Anal. Calc. for $C_{14}H_{25}O_9P$: C, 45.65; H, 6.84. Found: C, 45.66; H, 6.81.

Analysis of the ^1H n.m.r. spectrum (Fig. 1) of isomer *A* in $(CD_3)_2CO$ solution showed (see below) that it had the structure 3-*C*-(dimethoxy)phosphinyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**).

(*b*) The large-scale reaction, which resulted in the predominant formation of "isomer *B*", involved mixing a solution of **1** (12 g) in benzene (10 ml) with dimethyl phosphite (5 ml), followed by addition of a saturated solution of sodium methoxide in methanol (~1 ml). An exothermic reaction immediately ensued and the mixture was left at ambient temperature overnight. The solution was then diluted with benzene, washed with water, dried (Na_2SO_4), and concentrated to a syrup. Crystallisation from methanol afforded large, colourless prisms (11.0 g, 64%), m.p. 102°, $[\alpha]_D^{25}$ +14.5° (*c* 1.7, chloroform).

Anal. Calc. for $C_{14}H_{25}O_9P$: C, 45.65; H, 6.84. Found: C, 45.72; H, 7.07.

A detailed analysis of the ^1H n.m.r. spectrum (Fig. 2) of this crystalline product showed it to have the structure 3-*C*-(dimethoxy)phosphinyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**).

Thin-layer chromatography (t.l.c.) [Silica Gel G, according to Stahl; methanol–chloroform (1:19)] showed that isomer *A* had a higher R_F value than isomer *B*. T.l.c. of the mother liquors remaining after crystallisation of isomer *B* from reaction (*b*) showed the presence of a small quantity of isomer *A*, together with larger amounts of isomer *B* and unreacted dimethyl phosphite. Column chromatography (Mallinckrodt Silicar CC-7), using graded elution by ether (5→100%)–benzene, afforded, with some difficulty, a small quantity of isomer *A*, identical with that obtained from the initial reaction (*a*).

In view of the unexpected difference between the reactions (*a*) and (*b*), many attempts were made to repeat the preparation of isomer *A* such that the material could be obtained in crystalline form directly from the reaction mixture; none of these were successful. Various solvents, including ethyl ether and acetonitrile were used; the concentration of both **1** and the sodium methoxide were varied over wide limits, and in several instances solid sodium methoxide was used. The 3-ketone **1** was prepared by a variety of methods, including the methyl sulphoxide–acetic anhydride method[7], the methyl sulphoxide–phosphorus pentaoxide method[11], and the

ruthenium dioxide–sodium metaperiodate method[8]. The 3-ketone **1** or the hydrate could be used, without any noticeable effect on the course of the reaction.

Proof of structure for isomers A *and* B. — The partial ^{1}H n.m.r. spectra of the two crystalline products, isomers *A* and *B*, are shown in Figs. 1 and 2, respectively.

The first-order assignments were made by the usual methods and were confirmed by the ^{31}P–[^{1}H] decoupling experiments also shown in Figs. 1 and 2. The first-order parameters, obtained by direct measurement of the spectra, formed the input data for computer simulation, using LAOCN3 programme in conjunction with the U.B.C., I.B.M. 360-67.

*Reaction of dimethyl phosphite with 1,2-*O*-isopropylidene-5-*O*-tosyl-α-*D*-erythro-pentofuranos-3-ulose*[11]. — A solution of the keto-sugar (6 g) in benzene (50 ml) was mixed with dimethyl phosphite (2 g), and a saturated solution of sodium methoxide (15 drops) was added. The solution was left overnight at room temperature during which time crystals formed. Recrystallization from ethanol–light petroleum (b.p. 30–60°) gave **6** (5 g, 63%), m.p. 149°, $[\alpha]_D^{25}$ +21° (*c* 0.9, chloroform).

Anal. Calc. for $C_{17}H_{25}O_{10}PS$: C, 45.20; H, 5.54. Found: C, 45.02; H, 5.63.

The ^{1}H n.m.r. spectrum of the product was closely similar to that of isomer *B*, and it was assigned the structure 3-*C*-(dimethoxy)phosphinyl-1,2-*O*-isopropylidene-5-*O*-tosyl-α-*D*-ribofuranose (**6**).

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