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3-Oxo-3-phosphapentopyranoses

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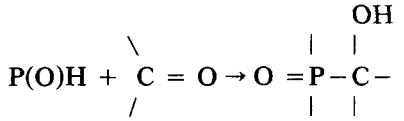
ABSTRACT

Addition of methyl phosphinate to 2(R)-methoxy 3-oxapentanedial gives all eight possible diastereoisomeric 3-phosphapentopyranoses in very poor yield. Structures and stereochemistry are assigned on the basis of ^1H, ^{31}P NMR, and mass spectroscopy of their acetates.

INTRODUCTION

The concept of preparing analogs of compounds of known biological activity as a path to new and more useful substances is as old as chemotherapy itself. In recent times, with a better understanding of metabolic processes, the concept has been refined somewhat to place greater emphasis on the shape and size of target molecules as well as their gross chemical features. A popular approach is to replace a single atom or small group of atoms in a bioactive molecule with another of similar size. The rationale behind this isosteric approach is that the new molecule will become involved in similar pathways to the parent if the normally strict spatial requirements of enzymic processes are only minimally affected. Replacement of carbon by phosphorus has been employed in steroids [1], alkaloids [2], cannabinoids [3], and sugars [4]. We were attracted to the last of these groups essentially because of the ubiquity of sugars in living systems. Much work in the area of phosphasugars has been carried out over the last 30 years, initially by Whistler [4a], very largely concerned with replacing the hemiacetal ring oxygen or, in a few instances, the anomeric carbon with phosphorus. For reasons of synthetic convenience, the phosphorus atom also usually carries an alkyl or aryl group. It seemed to us that replacing CH(OH) by P(O)H would be of interest since this would provide a better isosteric fit and would have the further advantage that the P=O is strongly hydrogen bonding and might reasonably be expected to mimic the COH group in this regard. It would be difficult, however, to carry the HP=O group through a synthetic sequence, and, since the conversion AlkOP=O to HP=O is feasible, we made the esters our first target. Total synthesis of sugars is a laborious process because of the multiplicity of chiral centers generated, though in recent years, elegant stereoselective reactions have been developed to make this approach more practical [5]. We have explored the possibility of applying some of the methods used to phosphasugar synthesis but with no success, and our recent progress [6] resulted from the discovery of a highly selective addition of the type



In this article, we describe an earlier attempt to synthesize a carbohydrate system directly by making use of a double addition of this type with phosphinate (hypophosphite) esters as the phosphorus source.

Dedicated to Prof. L. D. Quin in honor of his long and distinguished career.

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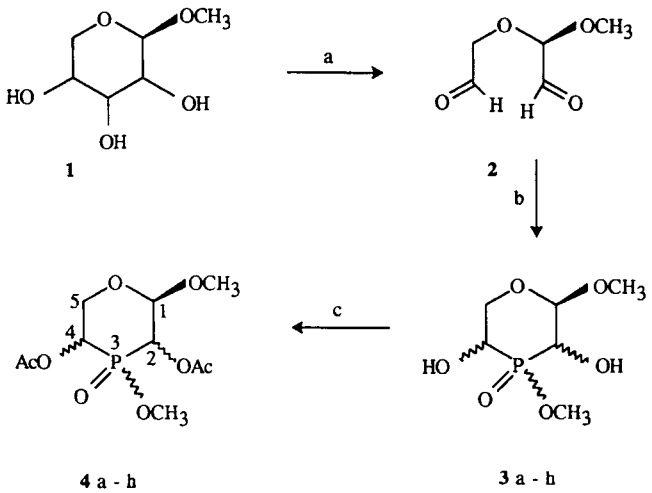
RESULTS AND DISCUSSION

The dialdehyde, **2**, is readily accessible by periodate cleavage of methyl β-D-arabinoside [7,8], an easily prepared crystalline material. The yield of **2** is higher than theoretical, so it is very probable that acetal formation has occurred during workup, and it exists as a mixture of cyclic and polymeric forms. We hoped, however, that the self-condensation would be reversible in solution and that a useful yield of 3-oxo-3-phosphapentopyranoses, **3a–h**, would be obtained (Figure 1).

In the event, the phosphinate ester was completely consumed, but {^{1}H} ^{31}P, NMR spectroscopy showed that 90–95% of the product was present as a very broad complex multiplet centered about δ 46.6 due, we assume, to polymer. In addition, eight sharp peaks in the range δ 34.6–41.6 were observed. These latter peaks were easily separated from the polymer by chromatography, but the mixture of isomers thus obtained resisted all attempts at further chromatographic resolution. Acetylation of the reaction mixture and chromatography of the resulting acetates (δ ^{31}P 23.5–31.2) was more successful, and the first isomer eluted from the column was obtained as a hygroscopic oil in a state of reasonable purity and was identified as a diacetate, **4**, by high-resolution mass spectrometry. Its stereochemistry and structure were assigned as **4e** from its ^{1}H-NMR spectrum on the assumption that the ring is a chair. The angular vicinal relationships of $^3J_{HH}$ and $^3J_{PH}$ are well established



a, $NaIO_4$; b, $MeOP(O)H_2$, Et_3N; c, AcONa / Ac_2O

FIGURE 1

[9a], and, with the exception of stereochemistry at phosphorus, angular relationships were clear. The second isomer, **4f**, off the column was not quite so clean, but stereochemical assignment was still straightforward. Thereafter, only overlapping fractions could be obtained, but, by careful comparison of successive fractions using ^{31}P-NMR spectroscopy to determine composition and approximate proportions, and selective decoupling and subtraction techniques to clarify multiplicities, it has been possible to assign structures to all eight isomers **4a–h** on the basis of their ^{1}H-NMR spectra. The data on which the assignments are based are presented in Tables 1 and 2, and the assigned principal conformers **4a–h** are shown in Figure 2. Since the stereochemistry at C_1 is (R), the absolute stereochemistry at the carbons is as shown. Surprisingly, ^{13}C-NMR data were of little use here since peak overlaps and intensity uncertainties made assignments in the overlapping fractions much more difficult. We examined base-catalyzed equilibration of the later fractions in the hope of increasing yields of individual isomers. Equilibration occurred rapidly, but the resulting isomer distribution was the same as in the preparation. None of the isomers was obtained crystalline, and hence the absolute stereochemistry at phosphorus could not be directly assigned. However, the data are internally self-consistent, e.g., all isomers with P=O axial absorb at higher field than isomers with P=O equatorial. This is observed in less complex phosphorus heterocycles [9b] and has been observed also in 2-deoxy-3-phosphahexoses [6] for which a solid-state structure is available. Similarly, δ $POCH_{3ax}$ is at higher field than δ $POCH_{3eq}$. Further, Inokawa and his colleagues have observed an angular dependance of $^1J_{PCH}$ in the (O)PCH system of phosphasugars of established structure [10]. They observed that, where the dihedral angle between P=O and CH is 180° (anti or axial–axial), $^2J_{PCH}$ is small (ca. 2–6 Hz) compared to other geometries (10–20 Hz). In agreement with this, we observe that those conformers with a *gauche* H–C–P=O arrangement fall in the range 6–15.7 Hz. Unfortunately, the two isomers **4a** and **4e**, in which there is an anti H–C–P=O geometry, have $^2J_{PCH}$ 7.9 and 7.0, respectively, overlapping with the bottom end of the *gauche* range. Though there appears to be a useful $^2J_{PCH}$ angular relationship for phosphoryl compounds [9a], the data base is as yet too small to be confident in making assignments on this basis. In our case, also, we have no crystallographic data on the 4-phosphapyran ring system to make more direct comparisons with other ring systems. If our assignments are correct, then we find H_{ax}–C–P=$O_{(ax\ or\ eq)}$ to be 6–7.9 Hz and H_{eq}–C–

TABLE 1 Methyl 3-Methoxy-3-oxo-3-phosphapentopyranoside Diacetates

Chemical Shift Data Isomer	^{31}P	H_1	H_2	H_3	H_{5ax}	H_{4eq}	$COCH_3$	$POCH_3$	$OCOCH_3$
4a	28.85	5.04	5.29	5.28	4.48	3.87	3.47	3.76	—
4b	26.8	5.08	5.44	5.21	4.24	3.87	3.43	3.95	2.20, 2.22
4c	24.34	4.89	5.19	5.15	3.95	4.53	3.49	3.76	2.19, 2.20
4d	23.54	4.86	5.21	5.13	4.31	3.95	3.44	3.88	2.235, 2.24
4e	33.2	4.72	5.27	5.29	4.05	4.16	3.49	3.82	2.18, 2.20
4f	31.7	4.58	5.44	5.22	3.84	4.20	3.49	3.91	—
4g	30.9	4.91	5.39	5.15	4.09	4.26	3.52	3.83	2.17, 2.20
4h	30.1	4.67	5.46	5.13	3.88	4.30	3.51	3.89	2.21, 2.24

TABLE 2 Methoxy-3-oxo-3-phosphapentopyranoside Diacetates

Coupling Constant Data Isomer	$^2J_{PH_2}$	$^2J_{PH_3}$	$^3J_{PH_1}$	$^3J_{PH_5}$	$^3J_{PH_4}$	$^3J_{H_1H_2}$	$^3J_{H_3H_4}$	$^2J_{H_3H_5}$	$^2J_{H_4H_5}$	$^3J_{POCH_3}$	$^4J_{H_{2eq}-H_{3\ eq}}$
4a	7.9	15.3	20.8	4.0	26.5	3.9	1.9	3.6	13.5	10.7	
4b	7.7	15.7	19.7	4.3	24.6	4.0	2.0	3.7	13.6	10.7	
4c	12.7	14.5	16.3	4.7	24.0	2.9	2.1	3.6	13.6	10.7	1.9
4d	12.5	15.6	15.3	2.3	22.5	2.3	2.3	2.8	13.7	10.9	1.9
4e	7.0	10.5	7.0	10.0	23.1	7.0	2.8	5.0	13.2	11.1	
4f	6.0	11.5	6.9	8.9	22.3	6.9	2.9	5.0	13.2	10.4	
4g	13.1	11.8	5.7	8.2	23.5	2.0	2.7	4.6	13.5	11.1	1.7
4h	13.3	11.9	4.3	6.9	22.1	2.2	2.8	4.2	13.5	10.6	1.5

$P=O_{(ax\ or\ eq)}$ to fall in the range 11.8–15.7 Hz, but many more data will be necessary to confirm this as a generality. In agreement with Inokawa and his collaborators, we also observe a small W equatorial–equatorial $^4J_{HCPCH}$ (<2 Hz). Despite the uncertainty, we feel that the absolute configuration at phosphorus is as shown, though we cannot completely exclude the possibility that all configurations at P may be reversed.

Some of the assignments may appear surprising and even rather improbable in view of the 1,3-diaxial disposition of the substituents. However, the increased length of the P–C bond when compared with a C–C bond will flatten and widen the ring at the phosphoryl end, and the resulting increase in distance between the two carbons attached to phosphorus will make substituent nonbonded interactions less energetically important. We have no reason to suppose, however, that the rings are not flipping rapidly, though the nonequilibrium values of the coupling constants are consistent with the conformers shown being the most important ones.

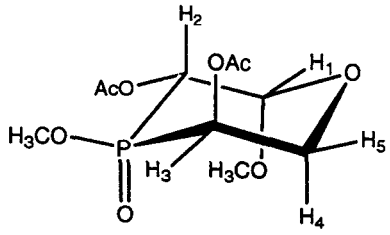
It is clear from the ^{31}P-NMR spectra of the crude reaction mixtures that the formation of the phosphasugars has no useful stereoselectivity, and the overall yield (ca. 6% of the mixture of diacetates) means that some method of suppressing or eliminating polymer formation would have to be found to make the reaction preparatively useful. We have not to date found any such method.

EXPERIMENTAL

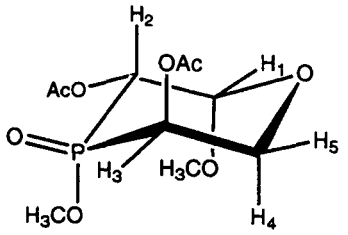
^{1}H, ^{13}C, and ^{31}P spectra were measured at 300, 75.43, and 24.29 MHz, respectively, on Bruker machines. TMS and H_3PO_4 were zero references. Solvents were distilled before use, and reaction mixtures were dried with anhydrous Na_2SO_4 before removal of solvent at water-pump vacuum. Anhydrous crystalline H_3PO_2 was prepared from commercial 40% aqueous solution by low-temperature vacuum distillation followed by freeze-drying. Other reagents were used as received. Chromatography was performed on silica gel H.

Methyl β-D-Arabinopyranoside[10] 1

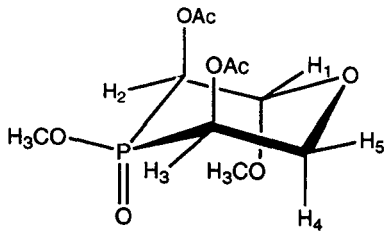
A suspension of D-arabinose (50 g) in MeOH (225 mL) containing concentrated aqueous HCl (10 mL) was stirred and heated under reflux (1 hour). The clear solution was seeded and kept at 5° overnight to yield colorless flakes (8.4 g). Four further crops were obtained by concentrating and cooling giving a final yield of 39.6 g (72%) mp. ^{1}H NMR (D_2O) δ 3.3 (3H, s, OMe), 3.57 (1H, dd, J 12.8, 2.2, H-5), 3.75 (2H, m,



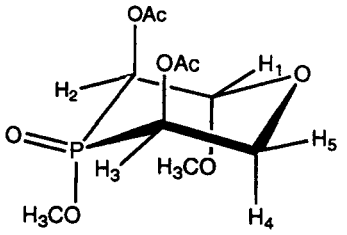
4a
1R2S3S4R



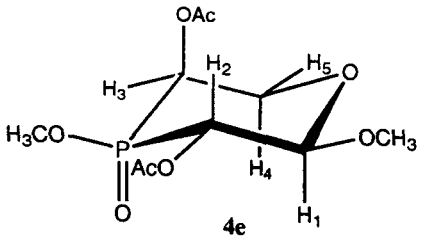
4b
1R2S3R4S



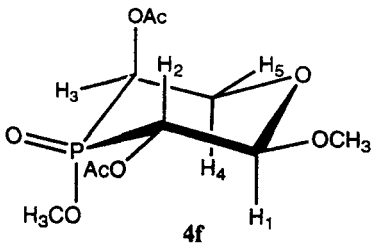
4c
1R2R3S4S



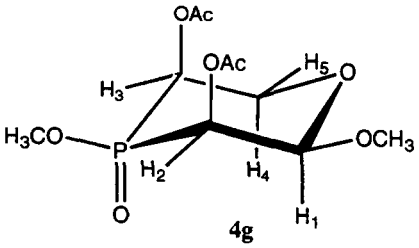
4d
1R2R3R4S



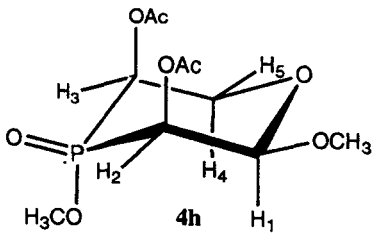
4e
1R2R3R4R



4f
1R2R3S4R



4g
1R2S3R4R



4h
1R2S3S4R

FIGURE 2

H-2 and H-3), 3.79 (1H, dd, *J* 12.8, 1.6, H-5), 3.91 (1H, m, H-4), 4.75 (1H, H-1 approx d, *J* ca. 2.7).

R-2-Methoxy-3-oxapentandial, 2

To a stirred solution of $NaIO_4$ (8.56 g, 40 mmol) in H_2O (60 mL) at 5°, methyl b-D-arabinopyranoside (3.28 g, 20 mmol) was added during 5 minutes and stirring continued (5 minutes). The flask was removed from the ice bath, and the reaction mixture was neutralized with $NaHCO_3$ solution (1M), keeping the pH < 6 (18 mL, 90% theoretical). The mixture was diluted with an equal volume of ethanol and filtered. Filtrate plus washings were evaporated (<45°), and the residue was diluted with absolute EtOH (50 mL), filtered, and evaporated. The oily residue was diluted ($CHCl_3$, 20 mL), filtered, and again evaporated to give *product,* an oil (3.45 g, expected

for dialdehyde: 2.64 g). ^{1}H-NMR spectroscopy clearly showed the presence of ethyl groups, and it seems likely that acetal formation has occurred.

3-Oxo-3-phosphapentopyranoses 3

Methyl phosphinate was prepared by the method of Fitch [11] and hence was contaminated with the byproducts of that reaction [12]. Trimethyl orthoformate (23.4 g, 0.22 mol) was added to crystalline H_3PO_2 (13.2 g, 0.2 mol) and shaken till a homogeneous solution was obtained (2 minutes). ^{1}H and ^{31}P spectra showed the previously described mixture of $MeOP(O)H_2$ (ca. 90%) $MeOP(O)HCH(OMe)_2$ (ca. 5–10%) plus small amounts of the other byproducts.

The *"dialdehyde"* obtained earlier (3.64 g, ca. 20 mmol) in dry MeOH (20 mL) was stirred at room temperature, and the crude *ester* (3.66 g, ca. 20 mmol) was added. Monitoring the reaction by ^{1}H-NMR spectroscopy showed a slow reduction of the P–H peak after 24 hours. Et_3N (3 g, 30 mmol) was added, and the solution warmed spontaneously, and ^{1}H-NMR spectroscopy showed the disappearance of the PH peak, and [^{1}H] ^{31}P-NMR spectroscopy showed the presence of polymer and 5–10% of eight discrete peaks (δ ^{31}P 34.6, 35.9, 37.2, 38.8, 39.3, 40.1, 40.4, 41.6). Chromatography of the colorless gum obtained by evaporation (ca. 7 g) on silica gel (35 g) and elution with CH_2Cl_2 gradually increasing to 20% MeOH eluted the phosphasugars as a series of badly overlapping fractions (TLC, NMR). Repeated chromatography failed to give useful resolution.

Varying the base, the method of preparation of $MeOP(O)H_2$, temperature, duration, and solvents did not produce any useful changes in yield or product ratios.

3-Oxo-3-phosphapentopyranose Diacetates

The combined fractions from the first chromatography (ca. 650 mg) were stirred with Ac_2O (10 mL) containing anhydrous AcONa (2 g) at room temperature (16 hours). The mixture was then heated to 75° (10 minutes) and stirred at this temperature (10 minutes), cooled to room temperature, and treated with MeOH (20 mL) for 30 minutes and the volatiles removed (>50°). The residue was partitioned between saturated aqueous $NaHCO_3$ (100 mL) and $CHCl_3$ (50 mL). The organic layer was separated, and the aqueous layer was extracted again (3 × 50 mL). Evaporation of the combined, dried, organic extracts afforded eight phosphasugar diacetates (δ ^{31}P 23.5, 24.3, 26.8, 28.85, 30.1, 30.9, 31.7, 33.2), as a pale-yellow gum (600 mg). CI (H_2) mass spectrum of the mixture showed a peak at 297 (100%, MH^+), high-resolution, 297.0761. $C_{10}H_{18}O_8P$ requires 297.0739.

In subsequent preparations, the acetylation was carried out on the crude reaction mixture, and separation from polymer was carried out on the acetylated product.

Partial Separation of Phosphasugar Diacetates

The mixture of diacetates (600 mg) in CH_2Cl_2/hexanes (1:1 10 mL) was chromatographed on silica gel (30 g) and eluted with CH_2Cl_2/hexanes (2:1) followed by CH_2Cl_2/MeOH (97:3). Fractions were monitored by TLC and ^{1}H NMR. The first fraction (150 mg) contained no $POCH_3$ and was discarded, the second fraction was **4e**, contaminated with only small amounts of other isomers. [δ ^{31}P 33.2; ^{13}C ($CDCl_3$) δ CH_3 20.6 (2 × $COCH_3$), 53.2 (d, J 6.9 Hz, $POCH_3$), 56.7 ($COCH_3$), 63.3 (C-5), 67.5 (d, J 99.4) and 68.5 (d, J = 99) (C2 and C4), 102.4 (d, J = 6.5, C-1); *m/z* (C.I., isobutane), 297 (100% M^+ + 1); (C.I., H_2), 297 47.6% M^+ + 1; E.I. 297 0.4% M^+ + 1. High resolution (C.I., H_2) 297.0722, $C_{10}H_{18}O_8P$ requires: 297.0740]. The subsequent fraction was enriched in **4f** [ca. 80%; δ ^{31}P 31.7; ^{13}C ($CDCl_3$) δ 20.6, 20.65 (2 × $COCH_3$), 52.9 (d, J = 6.2, $POCH_3$), 56.2 (C–OCH_3), 61.0 (s, C-5), 67.6 (d, J 101.9) 68.1 (d, J = 96.4) (C2 and C4), 101.6 (s, C-1) *m/z* (C.I., H_2) 297, 100%, MH^+. High-resolution *m/z* MH^+ 297.0761, $C_{10}H_{18}O_8P$ requires 297.0740.

Further elution resulted in a series of overlapping fractions in the order **4b**, **4a**, **4c**, **4g**, **4d**, **4h**.

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