Synthesis of Sugar Analogs with Phosphorus as the Ring Heteroatom

ROY L. WHISTLER AND CHIH-CHENG WANG

Department of Biochemistry, Purdue University, West Lafayette, Indiana 47907

Received May 27, 1968

Reaction of 5-bromo-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose or 5-*O*-*p*-tolylsulfonyl-3-*O*-methyl-α-D-xylofuranose with triethyl phosphite yields the corresponding diethyl phosphonate. Reduction of the phosphonate with lithium aluminum hydride gives, presumably, 5-deoxy-5-phosphine-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose, which upon treatment with acid followed by air oxidation produces a mixture of stable crystalline 5-deoxy-3-*O*-methyl-5-(phosphine oxide)-D-xylopyranose and 5-deoxy-3-*O*-methyl-5-(phosphinic acid)-D-xylopyranose. The former is converted into the latter by oxidation with bromine.

As a part of a program to examine the behavior of carbon-bonded phosphorus in sugar derivatives,[1] our interest has been directed toward the preparation of sugar analogs wherein phosphorus replaces the oxygen heteroatom in the D-xylopyranose ring. D-Xylose has served previously as a satisfactory starting material for the introduction of sulfur into the pyranose ring.[2] Phosphorus is introduced at position C-5 through application of the Michaelis–Arbuzov reaction. The ester obtained is reduced with lithium aluminum hydride to the phosphine[3] which reacts intramolecularly with the aldehydic function to form a phosphorus hemiacetal[4] with phosphorus in the sugar ring.

The starting compound for the Michaelis–Arbuzov reaction requires a reactive leaving group, such as halogen or tosylate,[5] at C-5. The hydroxyl group at C-3 is blocked with a methyl group to prevent its participation in the displacement reaction. As can be anticipated, substantially higher yields of desired product are obtained when the C-3 hydroxyl is blocked with a methyl than with an acetyl group.

Methylation of 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose with methyl iodide and silver oxide in *N*,*N*-dimethylformamide affords 1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose (I). This compound is converted into 5-bromo-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (II) by nucleophilic displacement of the tosyloxy group using tetraethylammonium bromide in N,N-dimethylformamide. 5-Deoxy-5-(diethyl phosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (III) is obtained in nearly quantitative yield by treating II with a large excess of triethyl phosphite. The same phosphonate ester is obtained in lower yield when the corresponding tolylsulfonyl ester, I, is treated with an excess of triethyl phosphite. Hydrolysis of the phosphonate ester with aqueous acetic acid yields 5-deoxy-5-(diethyl phosphonate)-3-*O*-methyl-D-xylofuranose (VIII), which is characterized as the osazone.

Reduction of III with lithium aluminum hydride in ether furnishes, presumably, 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-5-phosphine-α-D-xylofuranose (IV), which rapidly produces acidic materials during isolation, but is relatively stable in ether after washing with essentially oxygen-free water. Only one component is initially present in the ether solution as shown by thin layer chromatography.

On acid treatment, the furanose ring in IV shifts to a cyclic six-membered ring containing a secondary phosphine group. This compound, 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-5-phosphine-D-xylopyranose (V), reacts readily with oxygen. It is converted immediately by air oxidation into the stable crystalline secondary phosphine oxide, IV, and phosphinic acid, VII (Scheme I).

Secondary phosphine oxides and phosphinic acids are readily obtainable by air oxidation of secondary phosphines.[6,7] Rauhut and Currier,[6] on oxidizing secondary phosphines with air, produced phosphine oxides, but found no phosphinic acids among the products. Other workers,[8] on the other hand, have oxidized certain secondary phosphines in air directly to phosphinic acids without obtaining secondary phosphine oxides.

5-Deoxy-3-*O*-methyl-5-(phosphine oxide)-D-xylopyranose (VI) and 5-deoxy-3-*O*-methyl-5-(phosphinic acid)-D-xylopyranose (VII) are obtained in an over-all yield of 15 and 3.5%, respectively, from the phosphonate ester. The phosphinic acid is obtained also from the oxide by bromine oxidation[9] at 25°.

The ^{1}H nmr spectra of compound VI in deuterium oxide is shown in Figure 1. The spectrum determined at 40° shows a triplet centered at τ 5.40, which represents only half of the H-1 proton resonance. The signal of another half-proton is only partially observable because of interference by the HOD signals. The latter signal is shifted upfield[10] in the spectrum measured at 80° and the triplets appeared at τ 5.15 and 5.30.

The splitting pattern of the signals suggests that compound VI has phosphorus in the ring. H-1 is split by phosphorus into two peaks, each of which is further split into two peaks by the phosphorus-bonded deuterium. Each of these four peaks are again split by H-2 to give eight peaks. Only six (two triplets) of the theoretical eight peaks (two quartets) are observed. The wide coupling (8.5 Hz) is assigned to the phosphorus and H-1 interaction on the basis that it was not affected when decoupling was attempted at −220 to −440 Hz and at +47 to +160 Hz. Because of complex second-order effects from long-range coupling,

(1) For example, see R. L. Whistler, C. C. Wang, and S. Inokawa, *J. Org. Chem.*, **33**, 2495 (1968).

(2) (a) R. L. Whistler, M. S. Feather, and D. L. Ingles, *J. Amer. Chem. Soc.*, **84**, 122 (1962); (b) T. J. Adley and L. N. Owen, *Proc. Chem. Soc.*, 418 (1961); (c) J. C. P. Schwarz and K. C. Yule, *ibid.*, 417 (1961); (d) J. K. N. Jones and W. A. Szarek, *Can. J. Chem.*, **41**, 636 (1963).

(3) F. Pass and H. Schindbauer, *Monatsh. Chem.*, **90**, 148 (1959).

(4) (a) H. Hellman and O. Schumacher, *Angew. Chem.*, **72**, 211 (1960); (b) S. A. Buckler and M. Epstein, *J. Org. Chem.*, **27**, 1090 (1962); (c) S. A. Buckler and M. Epstein, *Tetrahedron*, **18**, 1231 (1962).

(5) L. Horner, H. Hoffmann, and P. Beck, *Ber.*, **91**, 1583 (1958).

(6) M. M. Rauhut and H. A. Currier, *J. Org. Chem.*, **26**, 4626 (1961).

(7) K. D. Berlin and G. B. Butler, *Chem. Rev.*, **60**, 243 (1960).

(8) (a) C. Dorken, *Ber.*, **21**, 1505 (1888). (b) A. W. Hoffmann, *ibid.*, **4**, 605 (1871); **6**, 292 (1873). (c) S. A. Buckler and V. P. Wystrach, *J. Amer. Chem. Soc.*, **83**, 168 (1961).

(9) P. Nylen, *Z. Anorg. Allg. Chem.*, **235**, 161 (1938).

(10) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **44**, 249 (1966).

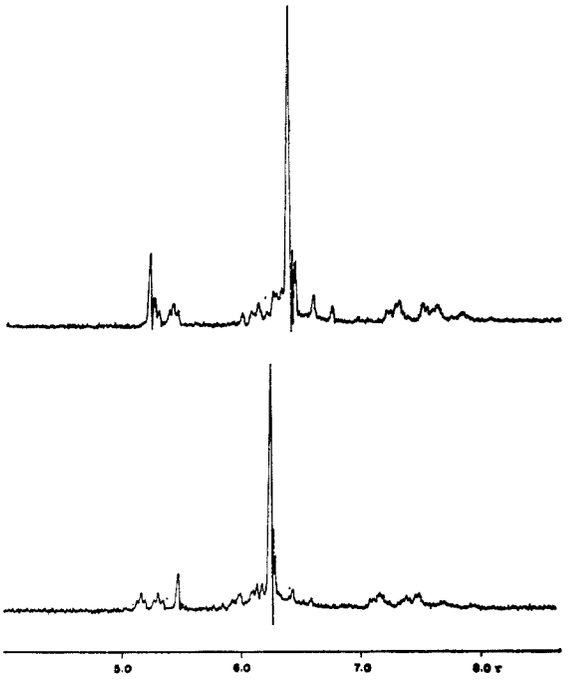


Figure 1.—^{1}H nmr spectra of 5-deoxy-3-*O*-methyl-5-(phosphine oxide)-D-xylopyranose in deuterium oxide at 40° (upper) and 80° (lower).

the line-spacing values for $J_{1,2}$ (2.5 Hz) and $J_{1,D}$ (2.0 Hz) are only rough estimates. Two one-proton multiplets at τ 7.24 and 7.54 might be assigned to the 5 hydrogens.

The signals for the phosphorus-bonded hydrogen[11] appear when the spectrum is determined in water. They are observed as two half-proton multiplets centered at τ −1.42 and 6.88, which shows a coupling constant of 498 Hz for the interaction between phosphorus and its proton.[12]

Although the two half-proton triplets at τ 5.15 and 5.30 and the absence of mutarotation indicate that compound VI constitutes only one anomer both in the crystalline form and in solution, it is not possible to assign the configuration of the anomeric carbon. On the assumption that the ring adopts a *C1* conformation, the sugar would have, most likely, an α-D configuration, since the coupling constant $J_{1,2}$ is relatively small. On the other hand, if a *1C* conformation should predominate, the small coupling constant could account for both α-D and β-D configurations, since H-2 bisects the hydrogen and hydroxyl on C-1 producing about the same dihedral angle for both α-D and β-D forms.

The infrared spectra of compound VI in a Nujol mull shows a P–H stretching vibration[13] at 2430 cm^{-1} which disappears on deuteration. A strong absorption at 1237 cm^{-1} is attributed to the phosphoryl group.

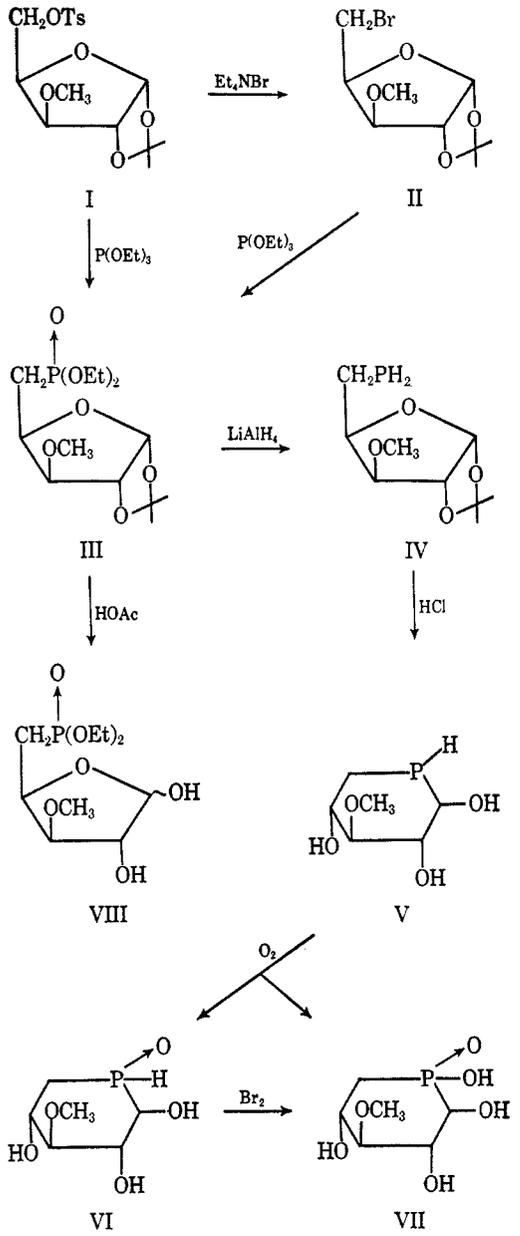
The secondary phosphine oxide structure of VI is supported also by its neutrality and relative stability toward air oxidation.[8] On exposing to a dry atmosphere at 25° for several weeks, compound VI does not show a change in melting point.

(11) D. D. Magnelli, G. Tesi, T. U. Lowe, Jr., and W. E. McQuistion, *Inorg. Chem.*, **5**, 457 (1966).

(12) J. R. Dyer, Applications of Absorption Spectroscopy of Organic Compounds, Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 96.

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958, p 320.

SCHEME I



Although the nmr spectral results obtained with the phosphinic acid, VII, are difficult to interpret because of their complexity, a spectrum in methyl sulfoxide-d_6 shows that, while other signals remain at about the same regions as those of VI, the signals of both C-1 and C-5 protons become evident because they occur farther upfield. C-1 proton signals appear at τ 7.07 and 7.20 (5.70 and 5.85 for VI) and C-5 protons appear at 7.85–8.14 and 8.17–8.50 (7.55–7.76 and 7.80–8.10 for VI). These observations are consistent with the structures assigned since the protons on C-1 and C-5 would be those most affected by the substitution of P–OH (VII) for P–H (VI).

The infrared spectra of this acid shows a broad shallow absorption at 2260 cm^{-1} which is clearly to be associated with the phosphinic acid group as it disappears on salt formation.[14] The phosphoryl group was observed at 1224 cm^{-1}. Such characteristic phosphoryl group and phosphinic acid group vibration

(14) Reference 13, p 319.

positions indicate an enhanced hydrogen-bonding effect.[14]

When compounds VI and VII are subjected to sodium metaperiodate oxidation at room temperature, the former consumes 3 mol of oxidant with the liberation of 0.79 mol of formic acid, and the latter consumes 2 mol of oxidant with the production of 0.77 mol of formic acid. The yield of formic acid agrees reasonably with the theoretical value of 1 mol. These results indicate that α-hydroxy phosphinic acids are susceptible to periodate cleavage. Since VI can be readily converted into VII by oxidation, the extra mole of periodate consumed by VI can be accounted for by the oxidation of the P–H bond. These results greatly substantiate the assigned structures.

The titration curve and neutralization equivalent of VII are consistent with a monobasic acid. Its pK_a is calculated from apparent dissociation constants, uncorrected for activities, to be 1.61. This indicates that it is a stronger acid than orthophosphoric acid which has a pK_1 of 2.1.[15] The increase in acidity can be rationalized in terms of internal hydrogen bonding of the phosphinic acid group with an adjacent hydroxyl group in a manner analogous to the sugar phosphates.[16]

Although a phosphorus atom cannot be proven to be in the ring in compound V, the isolation and characterization of VI and VII indicate that V has the structure shown.

Experimental Section

Melting points were determined by a Fisher-Johns apparatus. Infrared spectra were measured on a Perkin-Elmer 521 grating spectrophotometer. Nuclear magnetic resonance spectra were recorded at 40° unless otherwise stated on a Varian A-60A spectrometer, with tetramethylsilane as an external or internal reference; the samples were saturated solutions. The first-order coupling constants recorded are the measured peak spacings and are considered accurate to ±0.5 Hz. Deuteration of the samples was performed by double evaporation in deuterium oxide. Evaporation was performed in a water bath at 40° unless otherwise stated. Thin layer chromatograms were run on silica gel in (a) ethyl acetate–Skellysolve B (1:1 v/v), (b) isopropyl alcohol–ethyl acetate–water (7:1:2 v/v), and (c) ethanol–ammonium hydroxide–water (5:3:1 v/v). Compounds on the chromatograms were detected by spraying with 5% sulfuric acid in ethanol and heating.

1,2-*O*-Isopropylidene-3-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose (I).—1,2-*O*-Isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose[17] (2.0 g) was dissolved in 20 ml of dry *N*,*N*-dimethylformamide[18] and to this was added 3.0 g of silver oxide and 2 ml of iodomethane. The mixture was shaken in the dark at 25° for 20 hr. It was then filtered and the residue extracted several times with chloroform. The combined chloroform extracts were filtered to remove a white precipitate and were concentrated to a thick syrup which crystallized readily from ethanol–Skellysolve B. The yield was 95%, mp 113–114°, $[\alpha]^{25}D$ −27.0° (*c* 1.87, chloroform). The following constants for this compound, prepared by another procedure,[19] have been recorded: mp 114°, $[\alpha]D$ −27.2° (*c* 2.173, chloroform).

5-Bromo-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (II).—1,2-*O*-Isopropylidene-3-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose (5.0 g) was dissolved in 100 ml of *N*,*N*-dimethylformamide and to this was added 10 g of tetraethylammonium bromide. The solution was heated at 100° in an oil bath for 15 hr. Water (200 ml) was added after cooling and it was extracted four times with 60-ml portions of chloroform. The chloroform extracts were combined and washed with water, dried over sodium sulfate, filtered and the last trace of *N*,*N*-dimethylformamide was removed by evaporation at 90° (6 mm). The remaining residue was then distilled at 100° (bath temperature) (0.2 mm) to give a pure product, yield 3.5 g (90%), $[\alpha]^{25}D$ −94.8° (*c* 1.80, ethanol).

Anal. Calcd for $C_9H_{15}O_4Br$: C, 40.48; H, 5.66; Br, 29.92. Found: C, 40.68; H, 5.80; Br, 29.87.

5-Deoxy-5-(diethyl phosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (III).—A mixture of 4 g of 5-bromo-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose and 12 ml of freshly distilled triethyl phosphite was refluxed gently under nitrogen for 7 hr at 165°. Excess phosphite was distilled at 70° (0.3 mm) and the desired phosphonate ester was obtained as a colorless oil in nearly quantitative yield which was sufficiently pure for subsequent conversion. An analytical sample was obtained by distillation at 140° (5×10^{-3} mm): $[\alpha]^{25}D$ −36.3° (*c* 1.63, methanol).

Anal. Calcd for $C_{13}H_{25}O_7P$: C, 48.09; H, 7.72; P, 9.56. Found: C, 47.64; H, 7.71; P, 9.08.

The phosphonate ester was also obtained in 30% yield by substituting 1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose for the bromoxylose derivative above. ^1H nmr data (chloroform-*d*) were as follows: τ 4.16 (one-proton doublet, $J_{1,2}$ = 3.5 Hz, H-1), 5.41 [one-proton doublet, partially overlaps with $P(OCH_2-)$ signals, H-3], 5.86 [four-proton multiplet, J_{P,H^α} = 7.5 Hz, J_{H^α,H^β} = 7.0 Hz, $P(OCH_2-)$], 6.56 (three-proton singlet, OCH_3), 7.61, 7.93 (two-proton multiplets, $J_{5,P}$ = 18 Hz, H-5,5′), 8.53, 8.68 (three-proton singlets, CMe_2), 8.55, 8.68, 8.79 [six-proton triplets, $J_{P,4}$ = 0 Hz, $P(OCH_3)_2$].

5-Deoxy-5-(diethyl phosphonate)-3-*O*-methyl-D-xylofuranose (VIII).—5-Deoxy-5-(diethyl phosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-D-xylofuranose (1 g) was dissolved in 50 ml of 20% acetic acid. After heating for 6 hr at 80°, the solvent was evaporated to a syrupy residue. Examination by thin layer chromatography showed a single component, R_f 0.1 in solvent a. The product was dissolved in 20 ml of 50% ethanol and, by addition of 2 g of phenylhydrazine hydrochloride and 3 g of sodium acetate, was converted into the yellow osazone which was recrystallized from methanol: mp 86–88°.

Anal. Calcd for $C_{22}H_{31}O_5N_4P$: N, 12.11. Found: N, 11.94.

5-Deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-5-phosphino-α-D-xylofuranose (IV).—5-Deoxy-5-(diethyl phosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (1.0 g) was dissolved in 10 ml of ether and the solution was cooled to 0° in an ice bath. A suspension of 0.4 g of lithium aluminum hydride in 10 ml of ether was added and the reaction mixture was stirred at 0° for 15 min in a nitrogen atmosphere. The ice bath was removed and reaction was continued for an additional 15 min. At this point, tlc revealed one product at an approximate R_f of 0.82 in solvent a but no starting material was detected. Excess lithium aluminum hydride was cautiously destroyed with dilute sulfuric acid while maintaining the reaction mixture at 0°. The ether layer was washed with nitrogen-saturated water (10 ml) three times and then dried over anhydrous sodium sulfate. It was used immediately for the following conversion.

5-Deoxy-3-*O*-methyl-5-phosphino-D-xylopyranose (V).—The ether solution obtained above was filtered in a nitrogen atmosphere into a flask equipped with a gas inlet tube which extended to near the bottom of the flask and 25 ml of 2.4 *N* hydrochloric acid, previously saturated with nitrogen, was added. The flask was kept at 40° in a water bath for 3–7 hr, while a stream of nitrogen was passed through the solution. The water level in the bath was maintained at about or below the same height as that inside the reaction flask. Compound IV gradually went into the aqueous layer as ether was carried away by the nitrogen stream. At the end of the reaction tlc showed one spot at the base line in solvent a but with an R_f of 0.8 in solvent b. This compound could not be isolated without contaminating oxidized products. Since the latter compounds were more stable and easier to handle, procedures were developed to isolate the oxidized products as described below. No special effort was made to characterize the unoxidized product.

5-Deoxy-3-*O*-methyl-5-(phosphine oxide)-D-xylopyranose (VI). Method A.—The solution obtained above was cooled, diluted with 200 ml of water, and neutralized by passing through a column containing 100 ml of Amberlite IR-45. The column was then washed with 800 ml of water and the effluent was evaporated

(15) J. R. Van Wager, "Phosphorus and Its Compounds," Vol. I, Interscience Publishers, New York, N. Y., 1958, p 360.

(16) (a) J. X. Khym, D. G. Doherty, and W. E. Cohn, *J. Amer. Chem. Soc.*, **76**, 5523 (1954); (b) W. D. Kumber and J. J. Eiler, *ibid.*, **65**, 2355 (1943).

(17) P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, **102**, 317 (1942).

(18) M. L. Wolfrom, Y-L. Hung, P. Chakravarty, G. U. Yuen, and D. Horton, *J. Org. Chem.*, **31**, 2227 (1966).

(19) G. T. Robertson and D. Gall, *J. Chem. Soc.*, 1600 (1937).

to dryness under reduced pressure in a rotatory evaporator at 40–50°. The yellow residue was taken up in 20 ml of methanol. Examination by thin layer chromatography in solvent b showed the presence of one major spot at R_f 0.8, one minor spot at R_f 0.6, corresponding to the phosphine oxide VI, a very light streak centered around R_f 0.2, corresponding to the phosphinic acid VII, and a trace spot at the base line. The methanolic solution was filtered and made cloudy by adding ether. Traces of peroxides contained in the ether solution were sufficient to catalyze the oxidation. It was then kept at −5° for 2 days. Crystalline material was collected and washed with cold methanol. A second crop was obtained from the mother liquor by similar treatment. The products were combined (0.1 g) and recrystallized from hot methanol: mp 208–210°, $[\alpha]^{25}D$ +35.0° (*c* 1.10, water, no mutarotation in 48 hr).

Anal. Calcd for $C_6H_{13}O_5P$: C, 36.73; H, 6.68; P, 15.79. Found: C, 36.50; H, 6.71; P, 15.50.

Method B.—The solution was cooled, diluted, neutralized, and washed in the same way as described above. The effluent was evaporated in a glass circulating evaporator[20] under reduced pressure (6 mm) to about 50 ml. The solution was removed and further concentrated under reduced pressure in a rotatory evaporator at 40° to produce a brown residue. The residue was dissolved in 10 ml of methanol and the compound was crystallized at 5°, yield 0.095 g. Melting point and infrared and nmr spectra proved that compounds obtained by methods A and B were identical.

Method B was convenient for larger scale preparations in which solvent could be removed readily. VI had an approximate R_f value of 0.6 in solvent b and 0.73 in c on thin layer chromatograms. It had an approximate R_{xyl} value of 0.90 by descending chromatography on Whatman No. 1 in pyridine–ethyl acetate–acetic acid–water (5:5:1:3 v/v);[21] ammoniacal silver nitrate was used as the indicator.[22] On periodate oxidation[23] it consumed 3.0 mol of periodate and liberated 0.79 mol of formic acid/mol of compound in 12 hr.

^1H nmr data of VI in solvent a, deuterium oxide at 80°, follow, τ 5.15, 5.30 (half-proton triplets, $J_{1,2}$ = 2.5 Hz, $J_{1,D}$ = 2.0 Hz, H-1), 6.72 (three-proton singlet, OCH_3), 5.84–6.66 (three-proton multiplet, H-2, -3, -4), 7.24, 7.54 (one-proton multiplets, H-5, -5′); in b, water, −1.42, 6.88 (half-proton multiplets, P–H, $J_{P,H}$ = 498 Hz); in c, methyl sulfoxide, −0.60 (half-proton multiplet, P–H); in d, methyl sulfoxide-d_6, 5.09 (three-proton broad singlet, disappears on deuteration and shifts with change in concentration, OH-1, -2, -4), 5.70, 5.85 (half-proton singlets, H-1), 6.51 (three-proton singlet, OCH_3), 7.55–7.76, 7.80–8.10 (one-proton multiplets, H-5, -5′).

5-Deoxy-3-*O*-methyl-5-(phosphinic acid)-D-xylopyranose (VII).—The mother liquor obtained above from either method A or method B could be used. As a typical example, the mother liquor obtained from method B, [starting from 5 g of 5-deoxy-5-(diethyl phosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose] was evaporated to a syrup which was taken up in 20 ml of water and passed through a column containing 20 ml of Amberlite IR-45 ion-exchange resin. The column was washed successively with 50 ml of water, 25 ml of 5% NH_3 and finally water to neutrality. The effluent was evaporated to a brown residue. Water (10 ml) and cyclohexylamine (1 ml) was added. A white amorphous solid resulted upon evaporation. The solid was dissolved in methanol and precipitated by adding acetone and cooling. The fluffy precipitate was centrifuged, washed with methanol–acetone, redissolved in water, and passed through Amberlite IR-120 (5 ml). The column was washed with water to neutrality. The effluent was evaporated to a syrup which crystallized upon scratching. It was recrystallized from methanol–ether: yield 0.12 g, mp 192° dec, $[\alpha]^{28}D$ −25.8° (*c* 1.02, water, no mutarotation in 48 hr).

Anal. Calcd for $C_6H_{13}O_6P$: C, 33.97; H, 6.18; P, 14.60; neut equiv, 212. Found: C, 34.35; H, 6.33; P, 14.17; neut equiv, 210.

The same phosphinic acid was obtained also from 5-deoxy-3-*O*-methyl-5-(phosphine oxide)-D-xylopyranose (VI) by bromine oxidation. VI (100 mg) was dissolved in 10 ml of water, to which was added 3 drops of bromine and 100 mg of barium carbonate. The mixture was shaken until a clear yellow solution resulted and was stored at 25° in the dark for 2–5 days. Excess bromine was removed by aeration. The solution was neutralized with silver carbonate, filtered, and passed through a column containing 10 ml of Amberlite IR-120. The effluent was evaporated to a colorless syrup which crystallized upon scratching. The compound was recrystallized from methanol–ether: yield 93 mg (90%). It had the same decomposition point and infrared spectrum as the compounds indicated above.

On periodate oxidation[23] the compound consumed 2.0 mol of periodate and produced 0.77 mol of formic acid/mol of sugar in 11.5 hr.

^1H nmr data of VII in solvent a, deuterium oxide, follows, τ 5.50–7.00 (seven-proton multiplets, H-1, -2, -3, -4, $-OCH_3$), 7.18–8.30 (two-proton multiplets, H-5, -5′); b, methyl sulfoxide-d_6, 3.49 (four-proton singlet, disappears on deuteration and shifts with change in concentration, OH-1, -2, -4, P–OH). 6.48 (three-proton singlet, OCH_3), 7.07, 7.20 (broad half-proton singlets, H-1), 7.85–8.14, 8.17–8.50 (one-proton multiplets, H-5, -5′).

Acid Strength of 5-Deoxy-3-*O*-methyl-5-(phosphinic acid)-D-xylopyranose.—Titration was made at 25°. Several points near the middle of the curve were used and the variation of the pK_a values gave an estimate of their accuracy. The over-all error was perhaps greater than the differences indicated. Results are presented in Table I.

TABLE I

Molality × 10^{-3}	$[N^+]$ × 10^{-3}	pH	pK_a	Average pK_a
1.47	0.19	2.30	1.63	
0.84	0.40	2.50	1.57	1.61
0.55	0.47	2.70	1.61	
0.27	0.54	3.00	1.63	

Registry No.—I, 17954-92-6; II, 17954-93-7; III 17968-56-8; VI, 17954-42-6; VII, 17953-91-2; VIII 17953-63-8.

Acknowledgment.—This work was supported by the Agricultural Research Service, U. S. Department of Agriculture, Grant No. 12-14-100-7662(71) (Journal Paper No. 3376 of the Purdue Agricultural Experiment Station, Lafayette, Ind.) administered by the Northern Regional Research Laboratory, Peoria, Ill.

(20) M. Beroza, *Anal. Chem.*, **26**, 1251 (1954).
(21) F. G. Fischer and H. J. Nebel, *Z. Physiol. Chem.*, **302**, 10 (1955).
(22) L. Hough, *Nature*, **165**, 400 (1950).
(23) R. D. Guthrie in "Methods in Carbohydrate Chemistry," R. L. Whistler and M. L. Wolfrom, Ed., Academic Press, New York, 1962, p 432.