Photochemical Addition of Phosphines to 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose

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Photochemical addition of phosphine to 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose produces, presumably, a mixture of 5,6-dideoxy-1,2-*O*-isopropylidene-6-phosphine-α-D-*xylo*-hexofuranose and bis-6-(5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose)phosphine. They are characterized as the cyclohexylamine salt of the corresponding phosphonous acid and phosphine oxide, respectively. Phenylphosphine also adds photochemically to produce phenyl-6-(5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose)phosphine which is converted into its oxide for isolation.

Synthesis of sugars containing a carbon–phosphorus bond in various positions of hexose and pentose sugars by the addition of phosphines to carbon–carbon double bonds has not been reported. However, addition of phosphines to olefin hydrocarbons has been accomplished in the presence of radical initiators[1-3] or under the influence of acid catalysts.[4,5] Carbohydrate phosphines would possess phosphorus in its lowest oxidation state and could be used as starting materials for the synthesis of a variety of phosphorus containing sugar derivatives by modification of either the phosphorus group or the sugar moiety. Consequently, an investigation of the addition of phosphines to the 5,6-unsaturated bond in a hexose was undertaken and the results are reported here.

5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enfuranose (I) was used as the olefinic substrate because it has an exposed terminal exocyclic double bond which would aid the addition.

When compound I is exposed to ultraviolet radiation in the presence of phosphine a reaction takes place with the formation of two major products, as indicated by thin layer chromatography. With ethyl ether as the irrigant they had approximate R_f values of 0.25 (component A) and 0.02 (component B), respectively. A minor amount of material remained stationary (component C). Addition of ether to the reaction product caused precipitation of component B. After recrystallization from ethanol, it was identified as bis(5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose-6)-phosphine oxide (V). The isolation of V suggests that phosphine adds to I, producing the secondary phosphine, III, which during isolation takes up an oxygen atom to form the oxide. It is known that secondary phosphines readily undergo air oxidation to their corresponding secondary phosphine oxides.[6]

An attempt to separate component A from component C by fractionation on silica gel yielded no pure fractions. Passage of air or oxygen through the alcoholic solution slowly converts component A into an oxidized product (component C) which causes the solution to become acidic. After application to an anion-exchange column, component C is eluted with ammonia and converted into a crystalline cyclohexylamine salt. The isolation and identification of this material suggests that component A and C are the corresponding primary phosphine (II) and phosphonous acid (IV), respectively. Primary phosphines have been shown to undergo air oxidation readily to the corresponding phosphonous acid.[7]

Reaction conditions and yields of the phosphine addition are shown in Table I. Higher yields of the primary phosphine (II) result when a high ratio of phosphine to compound I is employed.

TABLE I

PHOTOCHEMICAL ADDITION OF PHOSPHINE TO 5,6-DIDEOXY-1,2-*O*-ISOPROPYLIDENE-α-D-*xylo*-HEX-5-ENOFURANOSE

Compound I, mol	Phosphine, mol	Irradiation time, hr	Yield, %	
			IV[a]	V
0.01	0.01	11	1	15
0.01	0.06	40	24	6

[a] Based on the isolated cyclohexylamine salt.

Phenylphosphine behaves similarly with phosphine when treated with compound I in the presence of ultraviolet light to produce an unstable syrupy material which was not characterized. An attempt to crystallize it from benzene and Skellysolve B slowly produced crystalline material which was identified as the secondary phosphine oxide (VII), obtained in 75% over-all yield. Although phenylphosphine has been shown to be readily added to various olefinic compounds in the presence of peroxides and/or at high temperatures,[8-11] its addition by photochemical irradiation has not been reported.

The infrared spectra of all three isolated phosphine derivatives exhibits an absorption maximum between 2300 and 2340 cm^{-1}, which is attributed to the P-H stretching vibration.[12] The infrared spectra of compound VII has a phosphoryl absorption at 1210 cm^{-1}, in agreement with absorptions shown by Bellamy.[12] However, the phosphoryl absorptions of compound V and the cyclohexylamine salt of IV are observed at 1630 and 1635 cm^{-1}, respectively. 5-Deoxy-5-(diethyl

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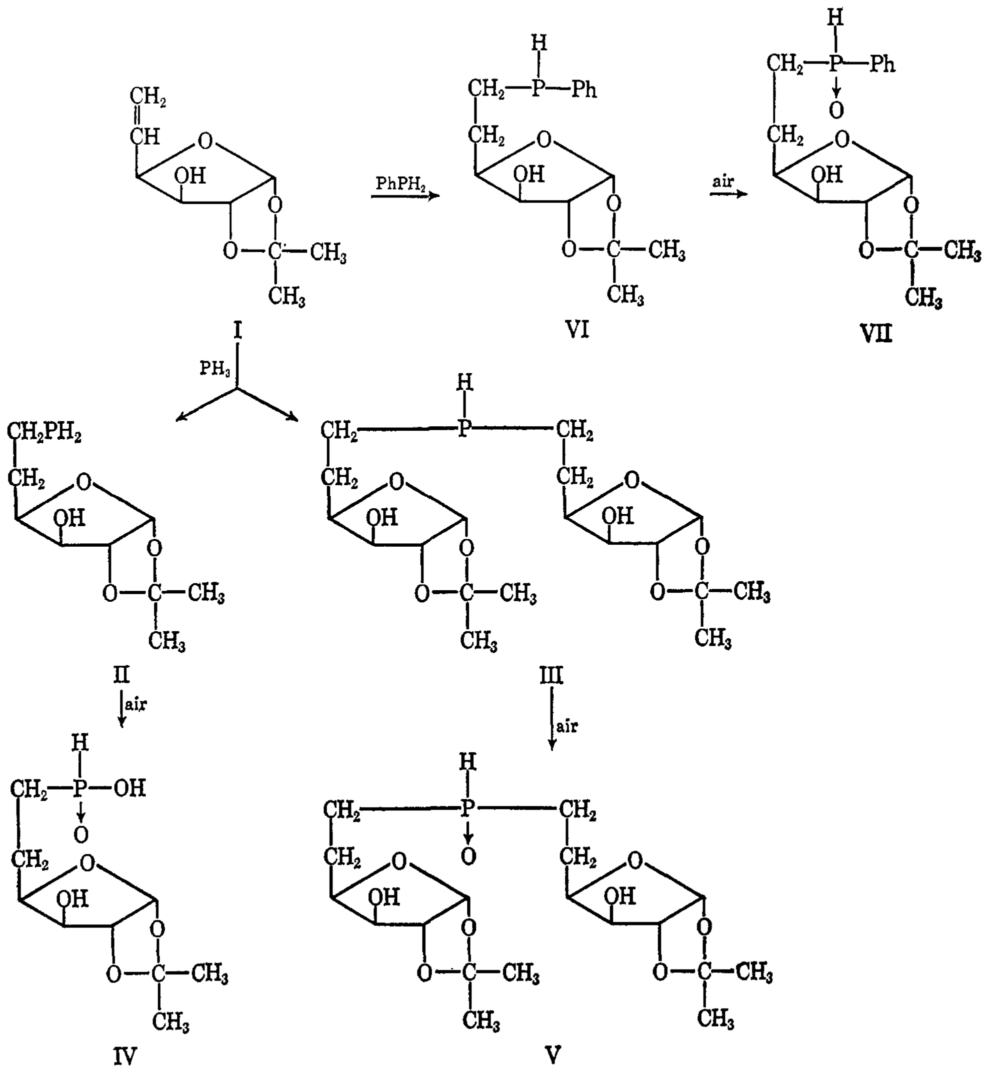

phosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose and 5,6-dideoxy-6-(diethyl phosphonate)-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose,[13] recently synthesized in this laboratory, also exhibit phosphoryl absorptions in the region of 1630–1640 cm^{-1}. Other deviations of the phosphoryl absorption from those shown by Bellamy are reported by Rauhut and Currier,[6] who showed that the phosphoryl absorptions appear at 1655 to 1670 cm^{-1}.

None of these isolated phosphine derivatives shows an nmr signal in the region τ 8.9, where a doublet for a terminal methyl group would be expected[14–17] had the addition produced a 6-deoxy-5-phosphino structure. Thus, the addition takes place in anti-Markownikoff fashion as has been observed by others examining phosphine addition to terminal olefins.[2,3]

Experimental Section

Analytical Methods.—Melting points measured on a calibrated Fisher-Johns melting point apparatus were corrected. Infrared spectra were obtained on a Perkin-Elmer Model 521 and nmr spectra on a Varian A-60 spectrometer. Chemical-shift values are given on the τ scale, and correspond to the midpoint of each singlet or symmetrical multiplet. For unsymmetrical multiplets, the chemical shifts are given as weighted mean values. Purity of products was determined by thin layer chromatography on silica gel G[18] after activation of plates for 1 hr at 105°. Phosphorus compounds were detected by spraying the plates with cobalt chloride solution[19] and heating.

Materials.—Phenylphosphine was prepared as described by Mann and Millar[20] and stored in sealed weighed ampoules. Liquid phosphine, obtained from the Matheson Co., Inc., was used without additional purification.

5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (1) was prepared by a modification of the procedure of Hall, Hough, and Pritchard.[21] 5,6-Di-*O*-*p*-tolylsulfonyl-1,2-*O*-isopropylidene-α-D-glucofuranose (1.70 g) and sodium iodide (8.0 g) were refluxed for 3 hr with constant stirring in ethyl methyl ketone (50 ml) which was previously dried over calcium sulfate. Sodium tosylate was filtered off and the filtrate was concentrated to a brown residue which was partitioned between a 10% aqueous solution of sodium thiosulfate (50 ml) and chloroform (30 ml). The aqueous layer was extracted twice with 30-ml portions of chloroform and the combined chloroform extracts were washed twice with water and dried over calcium sulfate. Concentration produced a yellow syrup. Methanol (20 ml) was added and the insoluble material removed by filtration. The filtrate was evaporated to a dry solid (0.55 g, 93% yield), mp 58–62°. Sublimation at 60° (bath) (0.3 mm) produced needles (0.5 g, 85%), mp 62–66°. Resublimation gave compound I: mp 65–66°, $[\alpha]^{26}_{D}$ −56.4° (*c* 1.7, chloroform).

Literature values reported for I are as follows: mp 61–65°,

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$[\alpha]_D$ −51.5° (*c* 11., chloroform);[21] mp 64°, $[\alpha]^{25}_D$ −60.5° (*c* 2.0, water);[22] mp 70–71°, $[\alpha]^{22}_D$ −57.3° (*c* 2.8, chloroform).[23]

Reaction of Phosphine with 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose.—Reactions involving phosphine were conducted in a closed glass system. Measured amounts of compound I and phosphine were introduced together in a small Vycor tube cooled in liquid nitrogen, cyclohexanol (5 ml) being used as the solvent. After sealing, the tubes were allowed to warm to 25° in an iron pipe containing a 2 × 10 cm slit and irradiated from a 200-W Hanovia S 654A-36 lamp at a distance of about 15 cm. At the end of irradiation, the unreacted phosphine was evacuated and cyclohexanol was distilled off. Addition of four volumes of ethyl ether precipitated a crude amorphous compound (V). The ether soluble portion was filtered and the filtrates were combined with the washings and evaporated to a yellow syrup which was dissolved in ethanol and oxidized by passing air or oxygen through the solution for 4–6 hr. The solution was then flowed through an Amberlite IR-45 column, eluted with 5% ammonium hydroxide solution and finally washed with water to neutrality. Redistilled cyclohexylamine was added to the collected effluent which was concentrated to a crystalline solid, and was recrystallized from an ethanol–acetone mixture to yield the pure cyclohexylammonium salt of 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose-6-phosphonous acid (IV): mp 166°, $[\alpha]^{25}_D$ −10.9° (*c* 1.46, methanol).

Anal. Calcd for $C_{15}H_{30}NO_6P$: C, 51.25; H, 8.55; N, 3.99; P, 8.83. Found: C, 51.03; H, 8.47; N, 4.12; P, 8.47.

The infrared spectrum of the compound (potassium bromide pellet) showed absorption maxima at ν 3230 (OH), 2300 (P—H), 1635 (P=O), 1382, 1370 (CMe_2) cm^{-1}. Nmr data in deuterium oxide gave signals at τ 4.09 (one-proton doublet, $J_{1,2}$ = 3.6 Hz, H-1), 5.44 (one-proton doublet overlapping with OD peak), 5.91 (two-proton multiplet, H-3,4), 8.35 (15-proton multiplet, H-5,5′, H-6,6′, C_6H_{11}), 8.58, 8.75 (three-proton singlet, CMe_2), and 2.76 (one-proton doublet, J_{P-H} = 550 Hz, P–H).

The ether-insoluble material was recrystallized from hot ethanol to yield bis(5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose-6)phosphine oxide (V): mp 190°, $[\alpha]^{25}_D$ −22.5° (*c* 1.70 in water).

Anal. Calcd for $C_{18}H_{31}O_9P$: C, 51.18; H, 7.35; P, 7.35; mol wt, 422. Found: C, 51.60; H, 7.46; P, 6.91; mol wt 412.

The infrared spectrum of the compound (potassium bromide pellet) exhibited absorption maxima at ν 3350 (OH), 2340 (P—H), 1630 (P=O), 1368, 1380 (CMe_2) cm^{-1}.

Reaction of Phenylphosphine with 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose.—A 10-ml quartz tube was charged with 1.2 g of I, 6 g of phenylphosphine, and 0.5 ml of methanol and sealed with a rubber cap. The tube was irradiated with uv light from a 200-W Hanovia S 654-36 lamp at a distance of about 10 cm. After 48 hr, 50 ml of methanol was added and the azeotropic mixture of phenylphosphine and methanol was removed under reduced pressure (6 mm, 50°) to give a syrupy residue which was dissolved in benzene, and Skellysolve B was added to near turbidity. Compound VII slowly crystallized in the refrigerator to yield 1.56 g (75%). It was recrystallized from methanol–benzene–Skellysolve B: mp 145–147°, $[\alpha]^{25}_D$ −13.2° (*c* 0.64, methanol).

Anal. Calcd for $C_{15}H_{21}O_5P$: C, 57.70; H, 6.73; P, 10.06. Found: C, 57.74; H, 6.69; P, 9.58.

The infrared spectrum of the compound (potassium bromide pellet) exhibited absorption maxima at ν 3190 (OH), 2330 (P—H), 1590 (C_6H_5), 1382, 1370 (CMe_2), 1210 (P=O) cm^{-1}.

The nmr spectra in methanol showed one peak at τ −1.68, which is due to the phosphorus-bonded hydrogen. H-1 was observed at τ 4.08 as a doublet ($J_{1,2}$ = 3.05 Hz); isopropylidene protons were observed at τ 8.43 and 8.58. The rest of protons were obscured by the solvent peaks. Yields were not changed in several other runs using one-fourth the amount of reactants without the addition of methanol.

Preparations on a smaller scale, with irradiation from an ultraviolet handlamp, gave comparable yields of VII after longer periods of irradiation.

Registry No.—I, 7284-07-3; IV cyclohexylamine, 16355-03-6; V, 16355-04-7; VII, 16355-05-8.

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The Pyrolysis and Structure of Jesaconitine

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The structure of jesaconitine has been determined by an examination of the nmr spectrum of this alkaloid and its pyrolysis products. The pyrolysis was carried out in an nmr tube and continuously monitored by nmr spectroscopy to provide evidence for the elimination product. This method of pyrolysis constitutes a rapid and convenient way of establishing the presence of certain C-8 ester groups in these diterpene alkaloids using small amounts of material.

Jesaconitine (*Aconitum fischeri* Reich,[2] A. subcunlatum,[3,4] A. sachalinense,[3,4] A. yesoense,[3] and A. mitakense[5]) on hydrolysis affords acetic acid, anisic acid, and the amino alcohol aconine (I).[4] Since the absolute stereochemistry of aconine (Figure 1) is known from X-ray crystallographic studies,[6] the structure of jesaconitine follows once the placement of the two ester groups on the aconine skeleton is determined.

Jesaconitine has been reported to undergo pyrolysis to form pyrojesaconitine.[4] Pyrolysis is a well-characterized reaction for aconitine-type alkaloids bearing an ester functional group at C-8.[7,8] When a C-16 hydroxyl is present, the pyrolytic product exists in the keto form.[9,10] Unfortunately, early workers did not report whether acetic acid or anisic acid was the elimination product of the pyrolysis. However, as a

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