[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA]

D-Glucopyranose 6-Deoxy-6-phosphonic Acid

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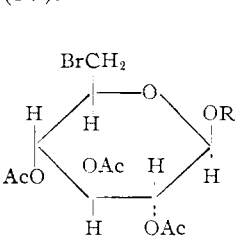
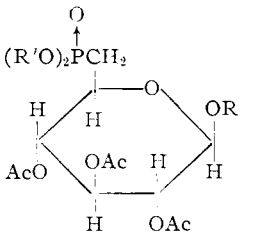
The synthesis of D-glucopyranose 6-deoxy-6-phosphonic acid from 1,2,3,4-tetra-*O*-acetyl-6-bromo-6-deoxy-β-D-glucopyranose *via* 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose 6-deoxy-6-(diphenyl phosphonate) has been accomplished.

In the glycolytic process which provides energy for mechanical work, the creation of heat, and for synthetic metabolic processes, glucose-6-phosphoric acid commands a central position. It may be converted to glucose, glucose-1-phosphoric acid and fructose-6-phosphoric acid in reversible reactions under the influence of appropriate enzymes, and seems to be oxidizable to 6-phosphogluconic acid by an alternative pathway.[2] Since little is known about the substrate specificity of these reactions beyond certain steric requirements of the carbohydrate moieties, it was of interest to explore the effect of structural changes of phosphorylated monosaccharides upon the biochemical behavior of such substances. A minimal structural alteration has been performed in the present study which describes D-glucopyranose-6-deoxy-6-phosphonic acid (X). This compound resembles the metabolite, glucose-6-phosphoric acid, in solubility, polarity, over-all chemical reactivity and molecular shape but differs from it by its inability to be dephosphorylated under ordinary conditions. It was hoped that its reactions with glycolytic and related enzymes would shed some light on structural limitations of substrate analogs in glycolysis. Inhibitory analogs might, in turn, influence neoplastic growth since the tumor cell derives considerable energy from rapid glycolysis under anaerobic and even aerobic conditions.

The synthesis of 6-phosphonate derivatives of glucose started from 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-α-D-glucopyranosyl bromide (acetodibromoglucose), prepared[3] by warming triacetyllevoglucosan[4] with phosphorus pentabromide[5] in an open vessel on a steam-bath. Acetodibromoglucose was converted to 1,2,3,4-tetra-*O*-acetyl-6-bromo-6-deoxy-β-D-glucopyranose (I),[6] as well as to benzyl 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-β-D-glucopyranoside (II).[7] These compounds served as the halides for the subsequent introduction of the phosphonate ester groups. The singular inertness of 6-halogenoglucose derivatives recorded by earlier workers,[8–10] was confirmed when attempts to subject I or II to the Nylen reaction[11] with sodium dialkylphosphites in hydrocarbons remained unsuccessful. However, when the Michaelis–Arbuzov-method[11] was applied, compound I being heated with a large excess of triethyl phosphite for six hours, 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose 6-deoxy-6-(diethyl phosphonate) (III) was obtained in near-quantitative yield. Under analogous conditions, II furnished benzyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside 6-deoxy-6-(diethyl phosphonate) (IV).



I, R = Ac
II, R = $CH_2C_6H_5$



III, R = Ac, R′ = C_2H_5
IV, R = $CH_2C_6H_5$, R′ = C_2H_5
VI, R = Ac, R′ = C_6H_5
VII, R = $CH_2C_6H_5$, R′ = C_6H_5
VIII, R = Ac, R′ = H
IX, R = R′ = H

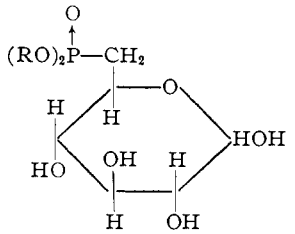
The ester III was also formed in lesser yields when 1,2,3,4-tetra-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranose[12] or the corresponding methylsulfonyl ester[13] were heated with triethyl phosphite in a manner described for simple alkanol arylsulfonates in the recent literature.[14]

Deacetylation of III with 0.65 *N* hydrobromic acid gave amorphous D-glucopyranose-6-deoxy-6-(diethyl phosphonate) (V) which was characterized as the osazone. Hydrolysis of the diethyl phosphonate ester group with strong acids could not be effected because the products suffered decomposition under these conditions. Likewise, attempts to hydrolyze IV with alkali were unsuccessful although model experiments to saponify phosphonate esters[15,16] using diethyl benzhydrylphosphonate available in this Laboratory[17] furnished low yields of ethyl hydrogen benzhydrylphosphonate. Therefore, the hydrogenolysis of glucopyranose-6-deoxy-6-(dibenzyl or diphenyl phosphonates) appeared as the only feasible route to the desired glucose-phosphonic acids.

While benzyl and phenyl phosphate esters have been hydrogenolyzed as a means of preparing otherwise inaccessible derivatives of phosphoric

(1) Virginia-Carolina Chemical Corporation Fellow, 1952-1955.
(2) J. S. Fruton and S. Simmonds, "General Biochemistry," John Wiley and Sons, Inc., New York, N. Y., 1953.
(3) J. C. Irvine and J. W. H. Oldham, *J. Chem. Soc.*, **127**, 2729 (1925).
(4) G. H. Coleman, C. M. McCloskey and R. Kirby, *Ind. Eng. Chem.*, **36**, 1040 (1944).
(5) A. I. Popov and N. E. Skelly, THIS JOURNAL, **76**, 3916 (1954).
(6) E. Fischer, B. Helferich and P. Ostmann, *Ber.*, **53**, 873 (1920).
(7) E. Fischer and K. Zach, *ibid.*, **45**, 456 (1921).
(8) W. S. Mills, *Chem. News*, **88**, 218 (1903).
(9) B. Helferich and H. Collatz, *Ber.*, **61**, 1640 (1928).
(10) B. Helferich and J. F. Leete, *ibid.*, **62**, 1549 (1929).
(11) See G. M. Kosolapoff, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951.
(12) E. Hardegger and R. M. Montavon, *Helv. Chim. Acta*, **29**, 1199 (1946).
(13) B. Helferich, H. Dressler and R. Griebel, *J. prakt. Chem.*, **153**, 285 (1939).
(14) T. C. Myers, S. Preis and E. V. Jensen, THIS JOURNAL, **76**, 4172 (1954).
(15) N. Mikhaĭlova, *Uchenye Zapiski Kazan. Gosudarst. Univ. im. V. I. Ul'yanova-Lenina*, **101**, No. 3, *Sbornik, Studencheskikh Rabot*, No. 2, 58 (1941); *C. A.*, **40**, 555 (1946).
(16) M. Janczak, *Rocz. Chem.*, **6**, 774 (1926); *C. A.*, **21**, 3599 (1927).
(17) B. E. Smith and A. Burger, THIS JOURNAL, **75**, 5891 (1953).

acid,[18] hydrogenolysis has never been applied to phosphonate esters. When the 6-bromoglucose derivatives I and II were heated with ethyl diphenyl phosphite at 160–170° for 48 to 60 hours, the diphenyl phosphonate esters VI and VII, respectively, were formed in satisfactory yields as crystalline solids. Hydrogenolysis of VI in absolute ethanol solution under the influence of Adams catalyst furnished 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose-6-deoxy-6-phosphonic acid (VIII), and the analogous procedure with VII led to 2,3,4-tri-*O*-acetyl-β-D-glucopyranose 6-deoxy-6-phosphonic acid (IX). Acid deacetylation of VIII gave a water-soluble material whose osazone could not be completely purified. Deacetylation with potassium methoxide furnished D-glucopyranose-6-deoxy-6-phosphonic acid (X), isolated as the potassium salt.



V, R = C_2H_5
X, R = H

This salt did not inhibit appreciably choline acetylase, histidine decarboxylase, xanthine oxidase, and hyaluronidase at concentrations of 1 mg./ml. In the complete absence of ATP, the ester III caused production of acetylcholine by choline acetylase as measured by tissue contraction, and increased acetylcholine formation on addition of suboptimal amounts of ATP.[19]

Acknowledgment.—We are grateful to Virginia–Carolina Chemical Corporation for support of this investigation.

Experimental[20]

Ethyl Diphenyl Phosphite.[21]—A solution of 57.5 g. (0.23 mole) of diphenyl phosphorochloridite (b.p. 140–170° (0.55 mm.))[22,23] in 100 ml. of dry hexane was added, with stirring and over a period of four hours, to an ice-cold solution of 18.2 g. (0.23 mole) of pyridine and 11.0 g. (0.24 mole) of absolute ethanol in 100 ml. of dry hexane, the temperature being maintained below 10°. After another 30 minutes stirring the precipitated pyridinium chloride was filtered, the hexane solution was dried over potassium hydroxide for 2 hours, the solvent was removed under 15 mm. pressure, and the residual pale oil fractionated. The fraction boiling at 110–116° (0.35 mm.) was redistilled to yield 36.4 g. (60%) of colorless oil, b.p. 108–109° (0.3 mm.), 129–132° (0.73 mm.), 149–152° (1.8 mm.), $n^{28}D$ 1.5250.

Anal. Calcd. for $C_{14}H_{15}O_3P$: C, 64.12; H, 5.76. Found: C, 64.31; H, 5.86.

1,2,3,4-Tetra-*O*-acetyl-β-D-glucopyranose-6-deoxy-6-(diethyl Phosphonate) (III).—(a) A mixture of 4.25 g. (0.0103 mole) of tetra-*O*-acetyl-6-bromo-6-deoxy-β-D-glucopyranose[6] and a fivefold excess (8.65 g.) of freshly distilled triethyl phosphite was refluxed slowly for six hours, removing ethyl bromide as it was formed. Excess phosphite was distilled off at 70° (15 mm.) and the remaining colorless oil was mixed with 100 ml. of ligroin; it solidified on stirring. The material was dissolved in 125 ml. of dry ether and crystallized on standing after the addition of some pentane. The yield of short, colorless needles was 4.2 g. (88%), m.p. 119–120°, $[\alpha]^{27}D$ +2.5° (chloroform, *c* 6.00).

Anal. Calcd. for $C_{18}H_{29}O_{12}P$: C, 46.15; H, 6.24. Found: C, 46.21; H, 6.16.

(b) The same phosphonate ester was also obtained in 50% yield by substituting 1,2,3,4-tetra-*O*-acetyl-6-*O*-tolylsulfonyl-β-D-glucopyranose[12] or the corresponding methylsulfonyl ester[13] for the bromoglucose derivative above. Melting point, mixture melting point, and rotation ($[\alpha]^{25}D$ +2.2° (chloroform, *c* 2.22)) proved the identity of the two materials.

Anal. Found: C, 45.95; H, 6.00.

D-Glucopyranose-6-deoxy-6-(diethyl Phosphonate) (V).—A mixture of 3 g. (0.0064 mole) of III and 150 ml. of 0.65 *N* hydrobromic acid was heated at 95° for 3 hours, buffered to *p*H 7 with 5% sodium carbonate solution, and evaporated at 50–60° (15 mm.). The viscous yellow oil solidified to a semi-solid on standing in a desiccator; extraction with three 50-ml. portions of absolute ethanol and evaporation gave a hygroscopic semi-solid; 0.5 g. of the product was dissolved in 4 ml. of water and, by means of 0.4 g. of phenylhydrazine and 1.35 g. of sodium acetate, converted to the yellow osazone which was recrystallized from benzene, m.p. 171–172°.

Anal. Calcd. for $C_{29}H_{31}N_4O_8P$: C, 55.22; H, 6.53. Found: C, 55.23; H, 6.64.

Benzyl 2,3,4-Tri-*O*-acetyl-β-D-glucopyranoside-6-deoxy-6-(diethyl Phosphonate) (IV).—A mixture of 2.5 g. (0.0054 mole) of benzyl 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-β-D-glucopyranoside[7] and a 5-molar excess of triethyl phosphite was refluxed at 160–170° for eight hours, and worked up as described for III above. From the residual straw-colored oil, toluene was distilled repeatedly at 15 mm. until, on stirring with 30 ml. of petroleum ether, crystallization occurred. Recrystallization from dry ether–pentane gave 2.25 g. (81%) of colorless material, m.p. 132.5–134°; $[\alpha]^{27}D$ −38.6° (chloroform, *c* 1.97).

Anal. Calcd. for $C_{23}H_{33}O_{11}P$: C, 53.48; H, 6.44. Found: C, 53.32; H, 6.27.

1,2,3,4-Tetra-*O*-acetyl-β-D-glucopyranose-6-deoxy-6-(diphenyl Phosphonate) (VI).—A mixture of 2.2 g. (0.0054 mole) of I and a fourfold excess of diphenyl ethyl phosphite was heated at 165–170° for 62 hours under constant observation. The cooled solution was washed with 30 ml. of cold petroleum ether; the remaining oil solidified on stirring with 20 ml. of cold dry pentane. Recrystallization from dry ether–pentane (1:1) gave 1.6 g. (52%) of colorless product, m.p. 130–131°, $[\alpha]^{25}D$ +1.1° (*c* 3.44, chloroform).

Anal. Calcd. for $C_{26}H_{29}O_{12}P$: C, 55.32; H, 5.18; P, 5.49. Found: C, 55.37; H, 5.22; P, 5.87.

In several other runs using two to three times the amounts of material just given, purification of VI could only be achieved by chromatography over activated alumina and charcoal as shown in Table I.

TABLE I

ELUTION OF VI FROM ALUMINA COLUMN

Fraction	Solvent	Volume, ml.	Product	Characteristics
1–4	Petroleum ether–ether (1:1)	100	I	M.p. 126–127°; positive bromine test
5–6	Benzene	50	VI	M.p. 130–131°
7–9	Benzene–ether (1:1)	75	VI	M.p. 130–131°
10–11	Ether	75		Traces of material only

Benzyl 2,3,4-Tri-*O*-acetyl-β-D-glucopyranoside 6-Deoxy-6-(diphenyl Phosphonate) (VII).—A mixture of 3.2 g. (0.007 mole) of benzyl tri-*O*-acetyl-6-bromo-6-deoxy-β-D-glucopyranoside[7] and 11.0 g. of diphenyl ethyl phosphite was

(18) F. R. Atherton, H. T. Howard and A. R. Todd, *J. Chem. Soc.*, 1106 (1948).

(19) We are obliged to Dr. M. Beiler of the National Drug Co., for these results.

(20) All melting points are corrected. Microanalyses by Miss May Lai and Strauss and Weiler Laboratories, Oxford.

(21) Conditions for the preparation of this ester were suggested by C. L. Harowitz of Virginia-Carolina Chemical Corporation.

(22) R. Anschütz and W. O. Emery, *Ann.*, **239**, 301 (1887), *cf.* p. 308.

(23) H. B. Gottlieb, THIS JOURNAL, **54**, 748 (1932) lists b.p. 165–174° (1 mm.).

heated and worked up as described above in the preparation of VI. The yield of colorless product, recrystallized from ether–pentane, was 2.65 g. (61.8%), m.p. 113–114.5°, $[\alpha]^{27}D$ −51° (*c* 5.03, chloroform).

Anal. Calcd. for $C_{31}H_{33}O_{11}P$: C, 60.78; H, 5.43. Found: C, 60.80; H, 5.57.

2,3,4-Tri-*O*-acetyl-D-glucopyranose-6-deoxy-6-phosphonic Acid (IX).—A solution of 0.4 g. (0.65 millimole) of VII in 20 ml. of absolute ethanol was hydrogenated at a pressure of 40 pounds in the presence of 0.06 g. of Adams catalyst. The calculated amount of hydrogen was absorbed in 20 minutes, the catalyst was filtered, and the filtrate concentrated at 40° *in vacuo*. The residual viscous oil gave a positive Fehling test, and solidified on stirring with 5 ml. of pentane. It was recrystallized from ether–pentane. The colorless material darkened at 175° and had m.p. 187–191° dec. It contained two moles of ether of crystallization which could not be removed at 110° *in vacuo* without decomposition of the compound.

Anal. Calcd. for $C_{12}H_{19}O_{11}P \cdot 2(C_4H_{10}O)$: C, 46.33; H, 7.58. Found: C, 46.21; H, 7.60.

1,2,3,4-Tetra-*O*-acetyl-β-D-glucopyranose-6-deoxy-6-phosphonic Acid (VIII).—Hydrogenolysis of 1.5 g. (0.0027 mole) of VI in 40 ml. of absolute ethanol in the presence of 0.15 g. of platinum dioxide was carried out as described in the preceding experiment. The reaction required from 30–90 minutes. The product (0.92 g., 76%) crystallized slowly from absolute ethanol, m.p. 171–172° dec., $[\alpha]^{25}D$ +9.5° (*c* 3.27, chloroform). It was dried at 56° over phosphorus pentoxide.

Anal. Calcd. for $C_{14}H_{21}O_{12}P \cdot 2H_2O$: C, 37.50; H, 5.62. Found: C, 37.83; H, 5.77.

Further drying at 78° for four days removed all but 0.5 mole of water of crystallization.

Anal. Calcd. for $C_{14}H_{21}O_{12}P \cdot {}^1/_2H_2O$: C, 39.91; H, 5.27. Found: C, 39.94; H, 5.01.

The acid gave a lead salt insoluble in water, and a somewhat water-soluble barium salt.

D-Glucopyranose-6-deoxy-6-phosphonic Acid (X).—(a) To a solution of 1.1 g. (2.6 millimoles) of tetra-*O*-acetyl-β-D-glucopyranose-6-deoxy-6-phosphonic acid in 25 ml. of cold anhydrous methanol was added dropwise 5.2 millimoles of 1 *N* potassium methoxide in order to neutralize the compound. Cleavage of the acetoxy groups by addition of further 3.9 mmoles of potassium methoxide was accompanied by immediate precipitation of a colorless, hygroscopic *potassium salt*. After standing at −10° for 24 hours, the salt was centrifuged, washed four times with absolute methanol, twice with ether–methanol (1:1), and then with dry ether. The yield was 0.4 g. (*ca.* 50%), $[\alpha]^{25}D$ +28.7° (*c* 4.9, water).

Anal. Calcd. for $C_6H_{11}K_2O_8P \cdot H_2O$: C, 21.30; H, 3.87; P, 9.16. Found: C, 21.56; H, 4.21; P, 9.17.

From the combined mother liquors and washings of the potassium salt, 0.5 g. of a colorless barium salt was obtained with barium hydroxide, but some contaminating barium carbonate could not be separated.

Anal. Calcd. for $C_6H_{11}BaO_8P$: Ba, 36.20. Found: Ba, 35.47.

(b) A solution of 0.7 g. (1.6 mmoles) of VIII in 50 ml. of 0.65 *N* hydrobromic acid was heated on a steam-bath for 3 hours, cooled and neutralized to *p*H 3 with 50 ml. of 0.65 *N* sodium hydroxide solution. A mixture of 1.2 g. of phenylhydrazine hydrochloride, 1.8 g. of anhydrous sodium acetate and 1 ml. of a saturated sodium bisulfite solution was added, and the whole heated at 95° for 2 hours. A somewhat gelatinous yellow precipitate appeared on cooling. It was recrystallized from 75% ethanol to melting point 162–169°, and purified further by sublimation at 65° (1.5 × 10^{-4} mm.). The osazone melted at 170–172°.

Anal. Calcd. for $C_{18}H_{23}N_4O_6P$: N, 13.27; neut. equiv., 422. Found: N, 12.63; neut. equiv., 438.[24]

(24) The analyses of this osazone were performed by Dr. Claibourne E. Griffin.

CHARLOTTESVILLE, VIRGINIA

COMMUNICATIONS TO THE EDITOR

NEW SYNTHETIC CRYSTALLINE ZEOLITES

Sir:

The outstanding characteristic of some natural hydrated zeolites is their ability to undergo removal of water of crystallization with little or no change in crystal structure. The dehydrated crystals are then interlaced with regularly spaced channels of molecular dimensions in which adsorption may occur.

Because of the interesting adsorptive properties of these rare natural minerals, a research program was initiated in this laboratory in 1949 to study the synthesis and properties of zeolites. Between 1949 and 1953, twenty crystalline zeolites were synthesized. These included: synthetic counterparts of the minerals chabazite, gmelinite, erionite, and mordenite, a species very similar to gismondite, and a species isostructural with faujasite but quite different in chemical composition. In addition, fourteen zeolite species were synthesized which have no natural counterparts known to us.

These new synthetic zeolites have been the subject of intensive study in this and other laboratories, and a number of papers describing their properties in detail will appear shortly.

Chemically, these zeolites may be represented by the generalized formula: $Me_{x/n}[(AlO_2)_x(SiO_2)_y] \cdot MH_2O$, where x/n is the number of exchangeable cations of valence n, and M is the number of water molecules, removal of which produces the characteristic pore system.

One of the new synthetic zeolites, designated as zeolite "A," which has no known natural counterpart has the composition: $Me_{12/n}[(AlO_2)_{12}(SiO_2)_{12} \cdot 27H_2O$. When Me is Na^+ or Ca^{++} the adsorption volume is about 0.30 cc. per gram of dehydrated zeolite. When Me is Na^+ the dehydrated zeolite readily adsorbs molecules having a critical dimension up to 4 Å., the critical molecular dimension being defined as the diameter of the smallest cylinder which will accommodate a model of the molecule constructed using the best available van der Waals radii, bond angles, and bond lengths. When $^1/_3$ of the sodium ions are exchanged for calcium ions, the effective pore diameter increases to about 5 Å. For example, straight-chain hydrocarbons are adsorbed readily whereas branched-chain hydrocarbons are excluded. Replacement of sodium by potassium decreases the effective pore diameter. These and other phenomena are explained on the