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Note

Synthesis of sugar phosphinimine derivatives from amino sugars

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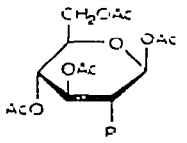
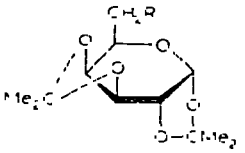
We have applied[1] the Staudinger reaction for the formation of phosphinimines[2] to *O*-acetylaldosyl azides to obtain the first aldosyl phosphinimines. The compounds permitted the simple synthesis of a number of new aldosyl derivatives, for example, sugar carbodi-imides[1] that are percursors of heterocyclic and urea derivatives.

We now describe the use of the Appel reaction[3], namely, the conversion of amino compounds into substituted aminophosphonium salts using triphenylphosphine–carbon tetrachloride, for the synthesis of sugar phosphinimines containing the reactive group at C-1 and elsewhere in the molecule.

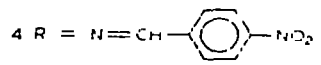
Reaction of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose or 6-amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose with triphenylphosphine and carbon tetrachloride in dichloromethane gave the crystalline hydrochlorides of the corresponding triphenylphosphonioamino sugars **1** and **2** (78 and 68%, respectively); their structures were supported by i r. data.

Treatment of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(triphenylphosphonioamino)-β-D-glucopyranose hydrochloride (**1**) with triethylamine in anhydrous media afforded the phosphinimine **3** which yielded the same Schiff base (**4**) with *p*-nitrobenzaldehyde as did the starting amine. With methyl iodide, **3** gave the *N*-methylaminotriphenylphosphonium iodide **5**.





1 R = NH—$\overset{+}{P}Ph_3Cl^-$
3 R = N=PPh_3



5 R = N(Me)$\overset{+}{P}Ph_3$ I^-

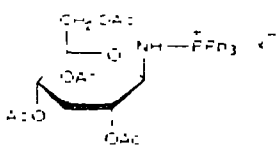
2 R = NH—$\overset{+}{P}Ph_3Cl^-$
6 R = N=PPh_3
7 R = N(Me)$\overset{+}{P}Ph_3$ I^-

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-(triphenylphosphonioamino)-α-D-galactopyranose hydrochloride (**2**) could not be converted into the phosphinimine in anhydrous media even with strong organic bases such as triethylamine and 1,8-bis(dimethylamino)naphthalene. The structure of **2** was established when the phosphinimine **6**, prepared by the Staudinger reaction from 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[4] by treatment with hydrochloric acid, gave a product which was identical to **2**. The phosphinimine **6** is not crystalline, but forms a stable *N*-methylaminotriphenylphosphonium iodide **7** with methyl iodide.

When 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine was treated under the conditions of the Appel reaction, the expected triphenyl(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)phosphonium chloride (**8a**) was formed as a by-product (13%) and could be isolated only *via* the fluoroborate salt (**8b**). The two main products were di-(D-glucopyranosyl)amine octa-acetate[5] and aminotriphenylphosphonium chloride[6]. Small amounts of tetra-*O*-acetyl-D-glucopyranosylammonium chloride[7] were also isolated.

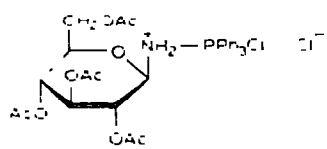
The structure of **8b** was established by the fact that it was identical with the salt prepared from triphenyl-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)phosphine imide[1] by treatment with hydrogen fluoroborate.

If, instead of using equimolar amounts of triphenylphosphine and carbon tetrachloride, the reagents are used in a molar ratio of 2:1, the aminophosphonium salt **8a** is the main product formed from 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosylamine, and chloromethyltriphenylphosphonium chloride[8] is also formed. The latter compound is a characteristic by-product of the chlorination of alcohols with triphenylphosphine–carbon tetrachloride[9]. Its formation indicates that the Appel reaction involves an intermediate (*e.g.*, **9**) of similar structure. If fast deprotonation of **9** is ensured by the presence of a strong proton-acceptor, *e.g.*, 1,8-bis(dimethylamino)-naphthalene, no di-(D-glucopyranosyl)amine octa-acetate is formed and the main product is the aminotriphenylphosphonium salt **8a**, together with chloromethyltriphenylphosphonium chloride.



8a X = Cl

8b X = BF_4



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The Appel reaction is a useful preparative method in carbohydrate chemistry when the starting amines are available by routes other than azide reduction.

EXPERIMENTAL

General. — I.r. spectra were recorded, for KBr discs, using a Unicam SP200 spectrophotometer. Microanalyses were performed by Dr. Eva Boromissza and her co-workers in the Microanalytical Laboratory of the Institute.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-(triphenylphosphonioamino)-β-D-glucopyranose hydrochloride (**1**) — A mixture of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose[10] (8.67 g, 25 mmol), triphenylphosphine (6.55 g, 25 mmol), carbon tetrachloride (3.85 g, 25 mmol), and anhydrous dichloromethane (75 ml) was boiled under reflux for 30 h. 1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-D-glucopyranose hydrochloride (0.3 g, 3%) was removed from the cooled mixture. Addition of dry ether (3 vol.) to the filtrate gave **1** (13.5 g, 84%), m.p. 193°, $[\alpha]_D$ +16° (*c* 2, dichloromethane); ν_{max}^{KBr} 3000–2500 (⁺NH), 1745 (C=O acetyl), 1440 and 1118 cm^{-1} (P-phenyl).

Anal. Calc. for $C_{32}H_{35}ClNO_9P$: P, 4.81; Cl, 5.51; Ac, 26.76. Found: P, 4.81; Cl, 5.93; Ac, 26.11.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-(triphenylphosphoranylideneamino)-β-D-glucopyranose (**3**). — To a solution of **1** (10 g, 15.5 mmol) in anhydrous dichloromethane (30 ml), anhydrous triethylamine (7.05 g, 69.7 mmol) was added dropwise with stirring. After stirring for 3 h, the triethylamine hydrochloride [1.8 g, 85%; m.p. 251–253° (from ethanol)] was removed and the filtrate was concentrated. Treatment of the residue with dry benzene (40 ml) yielded **1** (1.7 g, 17%). Concentration of the mother liquor and treatment of the residue with dry ether (20 ml) gave **3** (5.5 g, 58.5%), m.p. 154–155°. Recrystallization from cyclohexane (900 ml) afforded the pure product (4.3 g, 46%), m.p. 155–156°, $[\alpha]_D$ −16.5 (*c* 2, dichloromethane). From the mother liquors, more **3** (1.0 g, 10%) was isolated, m.p. 153–155°, $[\alpha]_D$ −16 (*c* 1, dichloromethane); ν_{max}^{KBr} 1745 (C=O acetyl) and 1440 cm^{-1} (P-phenyl).

Anal. Calc. for $C_{32}H_{34}NO_9P$: P, 5.10; N, 2.31; Ac, 28.35. Found: P, 5.59; N, 2.55; Ac, 27.30.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-(p-nitrobenzylideneamino)-β-D-glucose (**4**). — (*a*) To a solution of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose[10] (0.70 g, 2 mmol) in warm, anhydrous ethanol (7 ml), was added a warm solution of *p*-nitrobenzaldehyde (0.32 g, 2.1 mmol) in ethanol (3 ml). The mixture was kept at 40° for 4 h and then at room temperature overnight. The product (0.6 g, 63%; m.p. 173–174°) was collected, washed with ethanol, and recrystallised from ethanol (12 ml) to give **4** (0.5 g), m.p. 176–178°, $[\alpha]_D$ +101° (*c* 1, chloroform).

(*b*) A mixture of **3** (1 g, 1.65 mmol), *p*-nitrobenzaldehyde (0.26 g, 1.72 mmol), and dry 1,2-dimethoxyethane (10 ml) was boiled under reflux for 20 h, and then concentrated *in vacuo*. Recrystallization of the residue (1.5 g) from ethanol (11 ml) afforded **4** (0.65 g, 82%), m.p. 175–176° alone or in admixture with the product from (*a*).

Addition of water to the mother liquor gave triphenylphosphine oxide (0.4 g, 87%), m.p. 152–153° (from cyclohexane).

1,3,4,6-Tetra-O-acetyl-2-deoxy-N-methyl-2-(triphenylphosphonioamino)-β-D-

glucopyranose iodide (**5**). — A solution of **3** (0.61 g, 1 mmol) in methyl iodide (3 ml) was stored for 1 h and then mixed with dry ether (10 ml) to give crude **5** (0.46 g, 61.5%), m.p. 235–236°. Precipitation with ether from a dichloromethane solution afforded the pure product (0.4 g, 53.5%), m.p. 236–237°, $[\alpha]_D$ −2° (*c* 2, acetonitrile); ν_{max}^{KBr} 1740 (C=O acetyl), 1440 and 1110 cm^{-1} (P-phenyl).

Anal. Calc. for $C_{33}H_{37}INO_9P$: I, 16.93; P, 4.13. Found: I, 16.96; P, 4.08.

*6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-(triphenylphosphonioamino)-α-*D*-galactose hydrochloride* (**2**). — (*a*) A mixture of 6-amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[4] (7.50 g, 29 mmol), triphenylphosphine (7.59 g, 29 mmol), carbon tetrachloride (4.46 g, 29 mmol), and dry dichloromethane (90 ml) was kept at 40° for 20 h. Addition of ether (500 ml) gave the crude salt (10.9 g, 68%), m.p. 213–214°. Repeated dissolution in anhydrous dichloromethane (40 ml) and precipitation with dry ether (200 ml) gave **2** (8.5 g, 53%), m.p. 212–213° (from water), $[\alpha]_D$ −58° (*c* 1, dichloromethane); ν_{max}^{KBr} 3000–2600 ($^+$NH), 1445 and 1115 cm^{-1} (P-phenyl).

Anal. Calc. for $C_{30}H_{35}ClNO_5P$: Cl, 6.38; P, 5.57. Found: Cl, 6.47; P, 5.55.

(*b*) To a solution of **6** (0.5 g, 0.96 mmol) in dry ether (6 ml), dry ether saturated with hydrogen chloride (2 ml) was added. The resulting precipitate (0.45 g, 84%), m.p. 211°, was repeatedly precipitated with ether from solution in dichloromethane to give **2** (0.38 g, 71%), m.p. 211–212° alone or in admixture with the product from (*a*).

*6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-(triphenylphosphoranylideneamino)-α-*D*-galactopyranose* (**6**). — To a solution of 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[4] (3.4 g, 11.9 mmol) in dry ether (50 ml), a solution of triphenylphosphine (3.12 g, 11.9 mmol) in dry ether (20 ml) was added. Nitrogen evolution ceased within 3 h. The mixture was stored overnight, and then concentrated *in vacuo* to yield **6** as an amorphous, glassy product (6.3 g), $[\alpha]_D$ −82° (*c* 1, benzene); $\nu_{max}^{benzene}$ 1440, 1105, and 745 cm^{-1} (P-phenyl).

Anal. Calc. for $C_{30}H_{34}NO_5P$: N, 2.70; P, 5.96. Found: N, 2.63; P, 5.80.

*6-Deoxy-1,2:3,4-di-*O*-isopropylidene-*N*-methyl-6-(triphenylphosphonioamino)-α-*D*-galactopyranose iodide* (**7**). — To a solution of **6** (0.78 g, 1.5 mmol) in methyl iodide (3 ml), dry ether (10 ml) was added after 1 h. The resulting precipitate (0.92 g, 93%), m.p. 228–230°, was repeatedly precipitated with ether from solution in dichloromethane to give **7** (0.8 g, 81%), m.p. 230–231°, $[\alpha]_D$ −49° (*c* 1, chloroform).

Anal. Calc. for $C_{31}H_{37}INO_5P$: I, 19.18; P, 4.68. Found: I, 19.37; P, 4.81.

*Reaction of 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosylamine with triphenylphosphine–carbon tetrachloride.* — (*a*) A mixture of the title compound (1.04 g, 3 mmol), triphenylphosphine (0.79 g, 3 mmol), carbon tetrachloride (0.46 g, 3 mmol), and dry dichloromethane (10 ml) was boiled under reflux for 7 h and then stored overnight at room temperature. 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylamine hydrochloride (0.09 g, 8%), m.p. 163–164°, was removed and the filtrate was concentrated. The residue (2.2 g) was extracted with hot dry ether. The extract contained a small amount of di-(D-glucopyranosyl)amine octa-acetate, m.p. 190–192°, and triphenylphosphine oxide, m.p. 150–152°.

The residue (1.7 g) insoluble in ether was extracted briefly with boiling ethyl

acetate (50 ml), and then recrystallized from acetonitrile to yield aminotriphenylphosphonium chloride[6] (0.25 g, 27%), m.p. 219–220°.

Concentration of the ethyl acetate extract and treatment of the residue with water (5 ml), followed by recrystallization of the product (0.53 g) from ethanol, gave di-(D-glucopyranosyl)amine octa-acetate (0.27 g, 27%), m.p. 212–213°, $[\alpha]_D$ +85° (*c* 1, chloroform); lit.[5] m.p. 216–217°, $[\alpha]_D$ +87° (chloroform).

To the water-soluble substance, a solution of sodium fluoroborate (0.4 g) in water (2.5 ml) was added to yield triphenyl(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)phosphonium fluoroborate (**8b**; 0.19 g, 9%), m.p. 185–186°, $[\alpha]_D$ +6° (*c* 2, chloroform).

(*b*) A mixture of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (1.04 g, 3 mmol), triphenylphosphine (1.57 g, 6 mmol), carbon tetrachloride (0.46 g, 3 mmol), and dry dichloromethane (10 ml) was boiled under reflux for 7 h, and then stored overnight at room temperature. The mixture was concentrated to dryness, and to a solution of the syrupy residue (3 g) in dry benzene (20 ml), dry ether (40 ml) was added to give a light-yellow, hygroscopic, amorphous substance (2.35 g). The mother liquor was concentrated and the residue was crystallized from ethanol to afford di-(D-glucopyranosyl)amine octa-acetate (0.1 g, 10%). Concentration of the alcoholic solutions and crystallization of the residue from cyclohexane yielded triphenylphosphine oxide (0.14 g, 8.5%), m.p. 149–152°.

The foregoing, amorphous product was extracted with boiling ethyl acetate (60 ml). Recrystallization of the residue (0.7 g) from acetonitrile afforded chloromethyltriphenylphosphonium chloride[8] (0.27 g, 26%), m.p. 256–258°.

Concentration of the ethyl acetate extract, followed by dissolution of the residue in water and treatment with aqueous sodium fluoroborate yielded triphenyl-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosylamino)phosphonium fluoroborate (0.70 g, 33.6%), m.p. 185–187°, $[\alpha]_D$ +5.5° (*c* 2, chloroform).

(*c*) A mixture of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (1.04 g, 3 mmol), triphenylphosphine (0.79 g, 3 mmol), carbon tetrachloride (0.46 g, 3 mmol), 1,8-bis(dimethylamino)naphthalene (0.13 g, 0.6 mmol), and dry dichloromethane (10 ml) was boiled under reflux for 7 h and then stored overnight at room temperature. The mixture was concentrated and a solution of the amorphous residue (2.2 g) in dry benzene (20 ml) was treated with dry ether (40 ml) to give a hygroscopic substance (1.55 g).

Concentration of the mother liquor and recrystallization of the residue (0.9 g) from ethanol gave starting amine (0.1 g), m.p. 115–118°.

The amorphous, ether-insoluble product was extracted briefly with boiling ethyl acetate (60 ml) to leave a product (0.4 g), m.p. 208–210°. Precipitation from solution in chloroform with ethyl acetate, followed by crystallization from acetonitrile, afforded chloromethyltriphenylphosphonium chloride (0.08 g, 8%), m.p. 256–258°. Concentration of the ethyl acetate extract and treatment of the residue with aqueous sodium fluoroborate gave triphenyl(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosylamino)-phosphonium fluoroborate (0.66 g, 32%), m.p. 189–191°, $[\alpha]_D$ +6° (*c* 2, chloroform).

Triphenyl(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)phosphonium fluoroborate (**8b**) — (*a*) A solution of triphenyl-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)phosphine imide (1.22 g, 2 mmol) in a mixture (8 ml) of acetic anhydride and 40% fluoroboric acid (5:1) was mixed with dry ether (80 ml) with stirring. The crude product (1.4 g), m.p. 181–184°, was precipitated from chloroform solution with ether or recrystallised from water to give **8b**, m.p. 192–193°, $[\alpha]_D$ +6.5° (*c* 5, chloroform).

Anal. Calc. for $C_{32}H_{35}BF_4NO_9P$: C, 55.27; H, 5.07; P, 4.45; F, 10.93. Found: C, 54.75; H, 5.24; P, 3.92; F, 10.58.

(*b*) Upon dissolution of triphenyl-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-phosphine imide (1 g, 1.65 mmol) in conc. HCl–acetic anhydride (1:5, 4 ml), followed by the addition of dry ether (40 ml), the phosphinimine hydrochloride was obtained as an oil which solidified upon trituration with dry ether. The product (0.9 g) had m.p. 105–106°, $[\alpha]_D$ −5° → +25° (*c* 5, dichloromethane). Upon storage, more product (0.15 g) separated from the mother liquor (overall yield, 98%).

The crude phosphinimine hydrochloride (0.4 g) was briefly extracted with boiling ethyl acetate (12 ml). The extract was concentrated, and a solution of the residue in water (3 ml) was mixed with a solution of sodium fluoroborate (0.2 g) in water (2 ml) to give **8b** (0.29 g, 67%), m.p. 191–193°, $[\alpha]_D$ +6.5° (*c* 5, chloroform).

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