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INTERACTION OF DIISOPROPYLIDENEGLUCOSE WITH HALIDE COMPLEXES OF TRIPHENYL PHOSPHITE

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The very limited possibilities for synthetic transformations in the monosaccharide series, and the absence of sufficiently convenient and general methods for the synthesis of the most important representatives of carbohydrates—amino and deoxy sugars—make it essential to study reactions involving the replacement of one of the hydroxyl groups of a monosaccharide by a halide, which would subsequently open the way to both deoxy and amino sugars. Up to the present time, reactions of this type have been known only for the primary hydroxyl group (at C_6 in hexoses and C_5 in pentoses); the conditions for replacing secondary alcohol groups located in a pyranose or furanose ring by halide have not yet been found. In this connection, we turned our attention to the interaction, described by Rydon (^{1}), of triphenyl phosphite complexes with halides of the type $(C_6H_5O)_3PX_2$ (where $X = \mathrm{Cl, Br, J}$) with the simplest alcohols, leading to alkyl halides. It could be hoped that, with the aid of this reaction, which proceeds very vigorously and under mild conditions, it would be possible to replace a hydroxyl group by halide in the molecule of a monosaccharide as well. As the first object for testing this possibility in the carbohydrate series, we chose 1,2 : 5,6-diisopropylideneglucofuranose (I), which has a single free hydroxyl group at C_3.

The interaction of I with the complex of triphenyl phosphite and bromine in absolute benzene readily occurs spontaneously at room temperature and is accompanied by almost no evolution of hydrogen bromide. The reaction product, obtained after appropriate treatment and removal of the isopropylidene protection by hydrolysis with dilute acid, is a mixture of sugars, the main component of which, by its R_f value, corresponds to bromodeoxyhexose (II). The latter substance was indeed isolated in 16% yield by partition chromatography on cellulose from the total mixture of sugars formed. Quite analogously, in the interaction of I with the complex of triphenyl phosphite with iodine, iododeoxyhexose (III) was obtained.

To establish the structure of the halodeoxyhexoses obtained, the conversion of them into the corresponding deoxy sugars by hydrogenolysis of the halogen atom in the presence of skeletal nickel was studied. On hydrogenation of the bromo- (II) and iodo-derivative (III), one and the same deoxy sugar (IV) was obtained; upon oxidation of it with periodic acid on a paper chromatogram, only acetaldehyde, but not malondialdehyde, could be identified. Similarly, as a result of Ruff degradation of deoxy sugar IV, a single product was isolated, different from 2-deoxyribose, upon oxidation of which with periodic acid on a paper chromatogram only acetaldehyde, but not malondialdehyde, was likewise identified. These results give grounds to suppose that deoxy sugar IV is not 3-deoxyglucose, but 6-deoxyglucose (D-chinovose), and consequently that the product of the first-

the initial reaction was not the expected 3-halogenoglucose, but 6-halogenoglucose. In order finally to exclude the remaining doubts connected with possible changes in the structure of the halogenosugar during hydrolysis and subsequent treatment, we subjected to hydrogenolysis the reaction product obtained directly after interaction of I with the triphenyl phosphite complex with bromine, without isolating the latter from the reaction mixture. After removal of the hydrogen halide and solvent, the reaction mass was hydrogenated in methanol over skeletal nickel in the presence of caustic alkali, taken in some excess. When all the alkali was added to the reaction mixture before the start of hydrogenation, the hydrogenation process was complicated, since paper chromatography showed that, in the reaction products after hydrolysis, along with D-quinovose and the starting glucose, there was also a considerable amount of a substance with a higher R_f value, arising either as a side product of the reaction or as a product of further transformation of II or IV. If, during hydrogenation, alkali is added gradually, the process, on the contrary, proceeds very smoothly and almost exclusively IV is formed, with a small admixture of glucose and the above-mentioned side product. In this case D-quinovose was isolated after hydrolysis by chromatography on cellulose and identified in the form of its osazone, whose properties agreed with literature data. On the other hand, the tetraacetate of the iodo derivative III was obtained, corresponding in its properties to α-tetraacetate of 6-iodo-6-deoxyglucose. Thus it has been finally proved that, in the interaction of diacetone glucose with halide complexes of triphenyl phosphite, replacement by halogen occurs at the hydroxyl group of glucose situated in position 6. Accordingly, the transformations described above may be represented by the following scheme:

$$\mathrm{I} \xrightarrow[\text{2) } \mathrm{H}^+]{\text{1) } (\mathrm{C_6H_5O})_3\mathrm{PX}_2} \begin{matrix} \mathrm{II},\ X = \mathrm{Br} \\ \mathrm{III},\ X = \mathrm{J} \end{matrix} \longrightarrow \mathrm{IV}$$

It should be noted that the same result was obtained by Smith (^{2}) in the interaction of I with phosphorus pentachloride, where formation of 6-chloro-6-deoxyglucose was observed; recently, an analogous substitution at C_6 was also established in the action of acetobromoglucose on I in the presence of mercuric cyanide (^{3}). The data available to us are insufficient to make an unambiguous choice between two possible reaction pathways:

1) as a result of acid-catalyzed migration of the isopropylidene group (possibly reversible), 1,2–3,5-diisopropylideneglucofuranose is formed from I, which then reacts with substitution of the hydroxyl liberated at C_6 (path A);
2) direct substitution at C_6 with simultaneous displacement of the isopropylidene group by means of a reaction involving transfer of the reaction center according to the scheme proposed earlier by Smith (path B). It should be borne in mind, however, that this scheme was not supported by any experimental data.

The data presented show that the use of halide complexes of triphenyl phosphite for replacement of a hydroxyl group in monosaccharides is of considerable interest, even if it does not acquire great preparative significance.

Experimental Part

The reported R_f values are average values obtained on ascending chromatograms in the solvent system *n*-butanol–water–acetic acid, $4:2:1$, which was also used for partition chromatography on cellulose. Chromatographic paper "M" of the Leningrad factory No. 2 was used. For detection of spots, *p*-anisidine–H_3PO_4 was used, and for elucidating the structure of deoxy sugars, a 2.5% solution of $NaIO_4$ in combination with nitroprusside or *p*-nitroaniline reagents (^{4}) was used.

6-Bromo-6-deoxyglucose. To 9.3 g (0.03 mole) of triphenyl phosphite is added a solution of 2.4 g (0.015 mole) of bromine in 25 ml of abs. benzene; after warming is complete, a benzene solution of 7.8 g (0.03 mole) of diacetone glucose is added to the precipitated complex; the mixture is shaken for a short time until a homogeneous solution is formed and is left for 48 hr at room temperature; it is then poured into an equal volume of $2\,N$ NaOH, the benzene layer is washed with water and evaporated in vacuo, and to the residue is added a solution of 2 ml of conc. H_2SO_4 in 200 ml of 50% methanol, followed by boiling for 4 hr. After heating is complete, the aqueous-methanolic layer is carefully neutralized with a solution of $Ba(OH)_2$ and, after centrifugation and brief boiling with activated charcoal, the colorless neutral solution is evaporated in vacuo. The solid mass thus obtained (3.9 g) is a mixture of sugars, the principal component of which has $R_f 0.48$. Chromatography on cellulose afforded chromatographically pure 6-bromo-6-deoxyglucose, yield 1.2 g (16.5%).

6-Iodo-6-deoxyglucose. Obtained analogously to the 6-bromo derivative from 6.5 g (0.025 mole) of diacetone glucose, using dry chloroform free of alcohol as the solvent. After chromatography on cellulose, the yield of chromatographically pure product was 1.53 g (21%), $R_f 0.56$.

α-Tetraacetyl-6-iodo-6-deoxyglucopyranose. 0.5 g of 6-iodo-6-deoxyglucose is dissolved in a mixture of 14 g of acetic anhydride and 7 g of glacial acetic acid, cooled to 0°, 16 drops of conc. H_2SO_4 are added, and the mixture is left for 24 hr at 0°. The resulting solution is poured into ice water; the α-tetraacetate formed is extracted with chloroform, the chloroform is evaporated in vacuo, and the residue is recrystallized three times from methanol and dried in high vacuum; yield 0.08 g, m.p. 177.5–178°. Literature data: m.p. 182° ([5]).

6-Deoxyglucose (D-xylose). a) An aqueous solution of 1 g of 6-iodo-6-deoxyglucose and 0.5 g of $NaHCO_3$ is hydrogenated for two days over Raney nickel at room temperature, absorbing the liberated carbon dioxide with solid KOH; the D-xylose formed is then subjected, without isolation, to Ruff degradation. For this purpose the catalyst is filtered off; 3 g of iodine is added to the solution, and then, dropwise over 15 min with stirring, a solution of 1.4 g of NaOH in 50 ml of water is added. The solution is kept for 20 min, then acidified with dilute H_2SO_4; the liberated iodine is extracted with carbon tetrachloride; the aqueous solution is neutralized with silver carbonate, treated with a large excess of cation exchanger KU-1 in the H^+ form, neutralized with $Ca(OH)_2$, evaporated in vacuo to a volume of 10 ml, 0.11 g of $Ba(OCOCH_3)_2$ and 0.06 g of $Fe_2(SO_4)_3$ are added, and the mixture is heated to boiling. The precipitate that forms is filtered off, and to the filtrate cooled to 40° there is added 0.7 ml of 30% H_2O_2. When, after the end of warming and vigorous evolution of gases, the temperature of the solution again falls to 40°, a further 0.7 ml of 30% H_2O_2 is added; to remove volatile products, after 15 min air is drawn through the solution under reduced pressure, and it is then diluted with an equal volume of methanol and centrifuged. The centrifugate contained, as the sole product, a sugar with R_f 0.50, in which acetaldehyde, but not malondialdehyde, was detected on oxidation on paper with $NaJO_4$ ([4]); the 2-deoxy-D-ribose taken for comparison had R_f 0.39.

b) To 3.1 g (0.01 mole) of triphenyl phosphite there is added a solution of 0.8 g (0.005 mole) of bromine in 10 ml of abs. benzene, and then, after cooling to 0°, a benzene solution of 2.6 g (0.01 mole) of diacetoneglucose (see experiment No. 1). After completion of the reaction, the benzene solution is washed with NaOH solution and with water and evaporated. The residue is dissolved in 30 ml of abs. methanol and hydrogenated at room temperature over Raney nickel, adding during the hydrogenation, dropwise, a solution of 0.6 g of KOH in methanol until hydrogen absorption ceases. The catalyst is filtered off; the filtrate is neutralized with dilute H_2SO_4 and evaporated in vacuo. The residue is dissolved in a mixture of 50 ml of 50% methanol and 0.5 ml of conc. H_2SO_4 and boiled for 4 h. After cooling, the solution is neutralized with $Ba(OH)_2$, the precipitate is filtered off, the solution is boiled with a small amount of activated carbon, the carbon is filtered off, the filtrate is evaporated, and from the remaining syrup D-xylose is isolated by chromatography on cellulose; yield 0.2 g (8%

of theory), R_f 0.36.

If, during the hydrogenation, the alkali is added all at once at the beginning, considerable amounts of a by-product of undetermined structure with R_f 0.70 are formed. With gradual addition of the alkali, this process is suppressed.

Phenylosazone of D-xylose. To a mixture of 2.5 ml of 4 N acetic acid and 0.5 g of phenylhydrazine there is added a solution of 0.2 g of D-xylose in 2 ml of water. The mixture is boiled for 30 min in a stream of CO_2; after cooling, the light-yellow precipitate that separates is filtered off and dried; yield 0.2 g, m.p. 175-176° (from aqueous alcohol with rapid heating), $[\alpha]_D^{20} - 75.5 \pm 2°$ (c 2, alcohol—pyridine 3 : 2).

Found, %: C 63.29; 63.25; H 6.54; 6.52
$C_{18}H_{22}O_3N_4$. Calculated, %: C 63.14; H 6.48

Literature data (^{6}): m.p. 189-191°; $[\alpha]_D^{20} - 77°$ (c 2; alcohol—pyridine 3 : 2).

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