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Abstract

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CHEMISTRY

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THE WITTIG REACTION IN THE CARBOHYDRATE SERIES

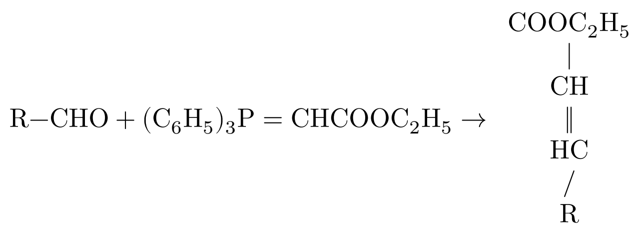
One of the main problems of the synthetic chemistry of carbohydrates remains, up to the present time, the problem of synthetic routes for passing from lower monosaccharides to higher ones. The existing routes—the classical cyanohydrin method of Kiliani–Fischer (^{1}) and the Sowden–Fischer method (^{2})—have a number of shortcomings, one of which is the possibility of extending the carbon chain of a monosaccharide by only one unit.

We recently proposed (^{3}) a new route for passing to higher sugars from lower ones through 2,3-dehydro-2,3-dideoxy-aldonic acids, which makes it possible to lengthen the carbon chain of a monosaccharide by two units at once. The factor determining the preparative value and breadth of the proposed method proves to be the accessibility of 2,3-dehydro-2,3-dideoxy-aldonic acids. The original method for obtaining them had a number of serious limitations. Therefore we developed (^{4}) a general method for the synthesis of 2,3-dehydro-2,3-dideoxy-aldonic acids on the basis of the Wittig reaction and readily available acetates of aldose forms of monosaccharides with carbethoxymethylenetriphenylphosphorane.

It turned out, however, that the monosaccharides themselves, containing no protective groups of any kind, also readily enter into reaction with carbethoxymethylenetriphenylphosphorane, opening up entirely new possibilities in the synthetic chemistry of carbohydrates. The reaction proceeds smoothly on heating the monosaccharide with a 1.5–3-fold excess of the phosphorane in a solution of dimethylformamide at 90°, the unreacted phosphorane being readily regenerated. The reaction is general in character and applicable to various reducing sugars. We have carried it out with *D*-arabinose, *D*-ribose, *D*-glucose, *D*-galactose, and *D*-glycero-*D*-gulo-heptose. Data were also obtained showing that amino sugars readily enter into the Wittig reaction (using *N*-acetyl-*D*-glucosamine as an example):

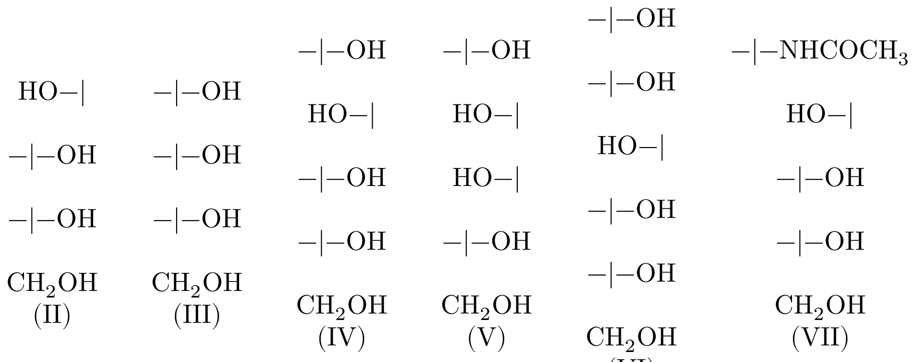
Fig. 1

Figure 1: Fig. 1



$$R{-}CHO + (C_6H_5)_3P = CHCOOC_2H_5 \rightarrow \begin{array}{c} COOC_2H_5 \\ | \\ CH \\ \| \\ HC \\ / \\ R \end{array} \qquad (I)$$

where R:



HO–|
–|–OH
–|–OH
CH_2OH
(II)

–|–OH
–|–OH
–|–OH
CH_2OH
(III)

–|–OH
HO–|
–|–OH
–|–OH
CH_2OH
(IV)

–|–OH
HO–|
HO–|
–|–OH
CH_2OH
(V)

–|–OH
–|–OH
HO–|
–|–OH
–|–OH
CH_2OH
(VI)

–|–$NHCOCH_3$
HO–|
–|–OH
–|–OH
CH_2OH
(VII)

Chromatographic examination of the reaction mixture shows that the initial monosaccharide disappears completely after only 3-4 hours and that two new substances are formed. The substance with the greater chromatographic mobility—an ester of trans-2,3-dehydro-2,3-dideoxy-aldonic acid—is the main reaction product, which can readily be isolated from the mixture by preparative chromatography on cellulose. As a rule, the trans isomer is isolated in crystalline form from the reaction mixture even without the use of chromatographic methods.

Fig. 1. IR spectrum of the ethyl ester of trans-2,3-dehydro-2,3-dideoxy-*D*-arabino-heptonic acid

The structure of the esters of trans-2,3-dehydro-2,3-dideoxy-aldonic acids was proved as follows. Compounds I and V, obtained by the interaction of phosphorane I with *D*-arabinose and *D*-galactose, upon acetylation with acetic anhydride in pyridine were converted into the complete acetates, identical in properties with the acetates of the esters of trans-2,3-dehydro-2,3-dideoxy-aldonic acids obtained by us earlier from the acetates of the alb-forms of the same monosaccharides and phosphorane I, the structure of which had been rigorously proved (^{4}). In addition, in the IR spectra of esters I and V there are frequencies corresponding to a trans double bond conjugated with a carbonyl group, an ester group, and a hydroxyl group (Fig. 1).

The structure of the second reaction product of monosaccharides with phosphorane I has not yet been elucidated. The IR spectrum of the second reaction product isolated in the experiment with *D*-ribose does not contain frequencies characteristic of a double bond and an ester, but does contain frequencies characteristic of a γ-lactone ring (1778 cm^{-1}) and a hydroxyl group (3405 cm^{-1}). It is possible that a more detailed study of the course of the Wittig reaction in the sugar series will make it possible to increase the yield of the desired trans isomer. The simplicity of this reaction and the availability of the starting substances fully solve the problem of obtaining 2,3-dehydro-2,3-dideoxy-aldonic acids and make the new route we have proposed for the synthesis of higher sugars (^{3}) extremely convenient preparatively and broad in its possibilities. Besides its preparative significance for the synthesis of higher sugars and its undoubted interest for the development of other synthetic methods in the chemistry of monosaccharides, the reaction studied is also important in principle, since it represents an example of a reaction of monosaccharides leading to the formation of a new carbon-carbon bond and giving monosaccharide derivatives with an open chain. At present it is difficult to express a definite judgment concerning its mechanism; however, it seems most probable to us that the monosaccharide reacts with phosphorane I in the acyclic aldehyde form. Important additional information on the reaction mechanism can be obtained by establishing the structure of the second reaction product and by studying in detail the factors affecting the ratio of the two substances.

Since monosaccharides are capable of entering into the Wittig reaction, interesting synthetic possibilities may be opened by the reaction of sugars with other phosphoranes. Data on the study of the reaction mechanism and on its use for the synthesis of sugars will be reported later.

Experimental Part

(Carried out with the participation of B. O. Akhunbaeva)

Ascending paper chromatography; mobile phase *n*-butanol—acetic acid—water in the ratio 4 : 1 : 2, Leningrad paper of

Goznak factory. To detect substances on paper, an alkaline solution of potassium periodate-cuprate (^{5}) and a neutral solution of potassium permanganate were used. Chromatography on a cellulose column was carried out in the systems *n*-butanol saturated with water (A) and *n*-butanol—alcohol—water in the ratio 40 : 12 : 18 (B).

Ethyl ester of trans-2,3-dehydro-2,3-dideoxy-D-arabino-heptonic acid

(II). 350 mg of D-arabinose is dissolved with heating in 15 ml of dimethylformamide; 1.2 g of carbethoxymethylenetriphenylphosphorane is added to the solution, and the mixture is heated for 4 h at 90°. After cooling, the solution is evaporated in vacuo to dryness; the residue is treated with 25 ml of water, the crystalline precipitate formed is filtered off and washed with water, and the filtrate is extracted with chloroform (3 × 15 ml), decolorized with charcoal, and evaporated in vacuo to dryness. The residue obtained is heated with 10 ml of ethyl acetate; the hot solution is filtered and left to crystallize. This gives 310 mg of unsaturated ester II, yield 60.5%, mp 133–135°, $[\alpha]_D^{18} + 14.45°$ (C 2.97, water), R_f 0.52. IR spectral data (in a paste with petrolatum oil): 3382, 1727, 1667, 970 cm^{-1}.

Found, %: C 48.90, 48.95; H 7.25, 7.37
$C_9H_{16}O_6$. Calculated, %: C 49.09; H 7.32

Tetraacetate. To a solution of 100 mg of unsaturated ester II in 2 ml of abs. pyridine, 1 ml of acetic anhydride is added, and the mixture is left for 24 h at room temperature. The solution is evaporated in vacuo to dryness; 2 ml of water is added to the residue, and the oil that separates soon crystallizes. The crystals are filtered off and recrystallized from alcohol, giving 120 mg of tetraacetate, yield 57%, mp 84–85°, $[\alpha]_D^{20} + 35.9°$ (C 4.9, chloroform). Literature data for the L-isomer (^{4}): mp 83–84°, $[\alpha]_D^{20} - 35.9°$ (C 5.25, chloroform).

Ethyl ester of trans-2,3-dehydro-2,3-dideoxy-D-ribo-heptonic acid (III). To a heated solution of 750 mg of D-ribose in 30 ml of dimethylformamide, 2.6 g of phosphorane I is added; the mixture is heated for 3 h at 90° and worked up as described above. The syrup obtained after evaporation of the aqueous solution is dissolved in 5 ml of *n*-butanol saturated with water and chromatographed on 150 g of cellulose in system A, collecting 13-ml fractions. Fractions 16–20 are evaporated in vacuo; traces of butanol are removed with water in vacuo; the residue is dissolved in 10 ml of water, decolorized with charcoal, and evaporated in vacuo to dryness. The unsaturated ester III obtained, as a colorless syrup, crystallized after drying in vacuo over P_2O_5; yield 45.5%, mp 61–64° with softening at 56° (from ethyl acetate), $[\alpha]_D^{19} - 21.0°$ (C 4.3, CH_3COOH), R_f 0.67.

Found, %: C 48.91, 48.95; H 7.34, 7.35
$C_9H_{16}O_6$. Calculated, %: C 49.09; H 7.32

Ethyl ester of trans-2,3-dehydro-2,3-dideoxy-D-gluco-octonic acid (IV). A mixture of 900 mg of D-glucose and 3.48 g of phosphorane I in 40 ml of dimethylformamide is heated for 4 h at 90° and worked up as usual. The syrupy product obtained (1.25 g) is dissolved in 5 ml of aqueous butanol and chromatographed on a cellulose column in system A. Fractions containing the substance with R_f 0.59 are combined and evaporated in vacuo; traces of butanol are removed with water; the residue is dissolved in water, the solution is decolorized with charcoal, evaporated in vacuo to dryness, and dried over P_2O_5 in vacuo. This gives 0.65 g of unsaturated ester IV, which soon crystallized;

yield 46.5%, mp 115–116° (from an ethyl acetate–methanol mixture, 4 : 1); $[\alpha]_D^{18} - 11.6°$ (C 4.64, CH_3COOH).

Found, %: C 47.98, 48.01; H 7.28, 7.28
$C_{10}H_{18}O_7$. Calculated, %: C 47.99; H 7.25

Ethyl ester of trans-2,3-didehydro-2,3-dideoxy-D-galacto-octonic acid (V). A solution of 1 g of D-galactose and 2.9 g of phosphorane I in 50 ml of dimethylformamide is heated for 5 hours at 90°, evaporated in vacuo to dryness, treated as usual, and a crystalline residue is obtained. The residue is heated to boiling with 25 ml of ethyl acetate and 5 ml of alcohol; the hot solution is filtered and left to crystallize. This gives 400 mg of unsaturated ester V. The mother liquor is evaporated in vacuo to dryness; the residue (0.84 g) is chromatographed on 150 g of cellulose in system A. The fractions containing the substance with $R_f 0.62$ are evaporated in vacuo to dryness, decolorized with charcoal, and 200 mg of unsaturated ester V is obtained; total yield 43%, m.p. 158-159° (from an ethyl acetate-alcohol mixture, 2 : 1), $[\alpha]_D^{16} - 12.6°$ (C 4.11, water). IR spectrum data (in a paste with Vaseline oil): 3300, 1728, 1667, 967 cm^{-1}.

Found, %: C 48.17, 47.90; H 7.30, 7.30
$C_{10}H_{18}O_7$. Calculated, %: C 47.99; H 7.25

Pentaacetate was obtained by the action of acetic anhydride in pyridine in the usual manner, m.p. 160° (from alcohol), $[\alpha]_D^{20} + 11.5°$ (C 4.2, chloroform). A mixed sample with an authentic specimen gives no depression of the melting point. Literature data (4): m.p. 160-161°, $[\alpha]_D^{20} + 11.25°$ (C 4.27, chloroform).

Ethyl ester of trans-2,3-didehydro-2,3-dideoxy-D-glycero-D-gulo-nononic acid (VI). A mixture of 1 g of D-glycero-D-gulo-heptose and 4 g of phosphorane I is heated for 4 hours at 90° in 30 ml of dimethylformamide; the mixture is treated as usual, and the syrupy product obtained (1.3 g) is chromatographed on a cellulose column in system B. The fractions containing the substance with $R_f 0.51$ are evaporated in vacuo, decolorized with charcoal, and 0.42 g of unsaturated ester VI is obtained as a colorless syrup, which soon crystallized completely; yield 31.5%, m.p. 108-110° (from a methanol-ethyl acetate mixture, 3 : 1); $[\alpha]_D^{20} - 24.15°$ (C 2.65, CH_3COOH).

Found, %: C 47.07, 47.32; H 7.31, 7.06
$C_{11}H_{20}O_8$. Calculated, %: C 47.12; H 7.19

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CITED LITERATURE

1. C. S. Hudson, *Adv. Carbohydrate Chem.*, **1**, 1 (1945).

2. J. C. Sowden, *Adv. Carbohydrate Chem.*, **6**, 291 (1951).
3. N. K. Kochetkov, B. A. Dmitriev, *Chem. and Ind.*, **1962**, 2147.
4. N. K. Kochetkov, B. A. Dmitriev, *Chem. and Ind.*, **1963**, 864.
5. T. G. Bonner, *Chem. and Ind.*, **1960**, 13, 345.

Note: Figure translations are in progress. See original paper for figures.