ORTHOESTERS OF SUGARS

COMMUNICATION 2. BICYCLIC AND TRICYCLIC ORTHOBENZOATES OF α-D-XYLOPYRANOSE

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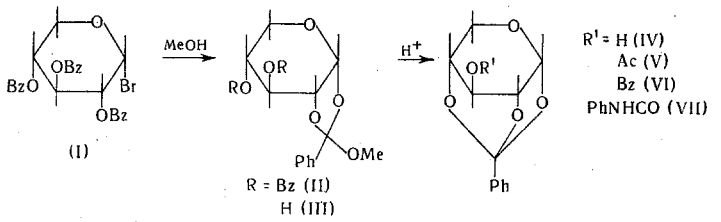
The preparation and properties of the bicyclic and tricyclic orthoacetates of α-D-xylopyranose were reported in the previous paper of this series [1]. In connection with solving one of the complex synthetic problems the need arose of obtaining and studying the properties of the bicyclic and tricyclic orthobenzoates of α-D-xylopyranose, which is the subject of the present paper



Starting with the previously described [2] 2,3,4-tri-O-benzoyl-α-D-xylopyranosyl, bromide (I), and using the modified Helferich method [3], were prepared 1,2-O-methylorthobenzoyl-3,4-di-O-benzoyl-α-D-xylopyranose (II). The same as in the synthesis of the bicyclic orthoacetates of α-D-xylopyranose [1], in order to isolate the bicyclic methyl orthobenzoate it proved convenient to saponify the obtained mixture of substances, after which the isolation of 1,2-O-methylorthobenzoyl-α-D-xylopyranose was easily achieved by extraction with chloroform from the reaction mixture. The orthobenzoate (III) obtained in this manner in 48% yield was then reconverted to dibenzoate (II).

Both orthoesters (II) and (III) are chromatographically homogeneous, and are hydrolyzed completely under the conditions of the analytical test for the orthoesters of sugars [4, 5]. The NMR spectrum* of (II) contains a doublet at 7.99 ppm† and $J_{1,2}$ 4.5 Hz, which corresponds to the α-configuration of the glycoside center. The two singlets at 3.09 and 3.44 ppm, respectively correspond to the exo- and endo-configurations of the methoxyl group. Based on the NMR data, the ratio of the exo- and endo-isomers is equal to 7 : 2.

In the synthesis of (II) and (III) the side formation of intensely colored products of undetermined nature was observed, which arise during the treatment of the reaction mixture after the synthesis of (II) (see Experimental Method). All attempts to remove thecolored impurity (filtration through Al_2O_3, extraction with various solvents) proved unsuccessful. Since during the saponification of this mixture with sodium methylate the polarity of the colored impurity increases sharply, compound (III) can be easily purified by washing the chloroform solution of the saponification products with water. The nature of the colored impurity was not studied in greater detail; however, it is possible to assume that its formation is responsible for the comparatively low yield of (III) (48%) and is specific for the orthobenzoates of D-xylose, since previously neither in the synthesis of the orthoacetates of D-xylose (I), nor in the synthesis of the orthoacetates and

*The NMR spectra of the orthoesters of D-xylose will be discussed in another communication.
†All of the chemical shifts are given on the δ scale.

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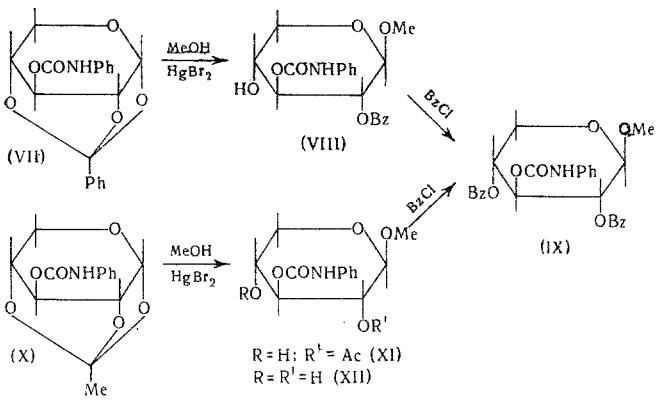
orthobenzoates of other sugars (see, for example, [3-8]), carried out by an analogous scheme, was the formation of similar colored products observed.

In its properties the bicyclic orthobenzoate (III) resembles 1,2-O-methylorthoacetyl-α-D-xylopyranose [1]. It undergoes cyclization when stored, and is converted with comparative ease to 1,2,4-orthobenzoyl-α-D-xylopyranose (IV) under transesterification conditions (see below). 1,2,4-Orthobenzoyl-α-D-xylopyranose (IV) was obtained in 60% yield under the conditions for the cyclization of bicyclic orthoesters, proposed by us on the example of the synthesis of the tricyclic orthoacetates of α-D-xylopyranose (I) and the macrocyclic orthoacetate of α-D-glucopyranose [9].

In contrast to the orthoacetates of α-D-xylopyranose, together with the main compound (IV), a side product is formed during the cyclization, which gives a positive hydrolytic test for the orthoester group. The by-product has R_f 1.2 relative to (IV) (SiO_2, system A). The yield of the by-product is about 10% (visually). The nature of the by-product was not studied in greater detail by us. In the preparation of (IV) we took special precautions to protect the reaction mixture from moisture, since in the opposite case a decomposition of the starting orthoester (III) is observed. Using conventional procedures, from (IV) were obtained the 3-O-acetate (V), the 3-O-benzoate (VI) and the 3-O-carbanilate (VII). Compounds (IV)-(VII) are chromatographically homogeneous, and they give a positive hydrolytic test for orthoesters. In the NMR spectra of orthobenzoates (IV)-(VII) is present a doublet of the anomeric proton at 5.88-5.92 ppm, $J_{1,2}$ 4.5-4.7 Hz, which corroborates the α-configuration of the glycoside center. In the spectrum of (V) is additionally present the singlet of the acetyl group at 2.1 ppm. On the whole, the NMR spectra of (IV)-(VII) are analogous to the NMR spectra of the tricyclic orthoacetates of α-D-xylopyranose [1].

In order to confirm the structure of orthobenzoates (IV)-(VII) we ran a number of transformations according to the following scheme



Under the conditions of the orthoester method [4], from (VII) was obtained 2-O-benzoyl-3-O-carbamoyl-β-methyl-D-xylopyranoside (VIII), the benzoylation of which gave dibenzoate (IX) in 72% yield when based on (VII). The same product was also obtained by starting with the previously described [1], 1,2,4-orthoacetyl-3-O-carbamoyl-α-D-xylopyranose (X). Under conditions, analogous to those used to prepare (VIII), was obtained 2-O-acetyl-3-O-carbamoyl-β-methyl-D-xylopyranoside (XI), the saponification of which with sodium methylate gives 3-O-carbamoyl-β-methyl-D-xylopyranoside (XII)

The benzoylation of (XII) leads to 2,4-di-O-benzoyl-3-O-carbamoyl-β-methyl-D-xylopyranoside (IX) in 57% yield when based on (X). The identity of the β-D-xylopyranose derivatives (IX) obtained by the two routes, which follows from a comparison of the IR spectra, analytical data, angles of rotation, and the absence of depression of the mixed melting point, unequivocally proves the structure of orthobenzoates (IV)-(VII), since in the above performed transformations the position of the carbamoyl group could not change.

EXPERIMENTAL METHOD

The CH_3NO_2 was purified as described in [4], while the dichloroethane (DCE) was purified as described in [1].

The thin-layer chromatography (TLC) was run in a bound layer of silica gel or on Al_2O_3 (neutral, degree of activity III according to Brockmann) in a loose layer in the systems: $CHCl_3$–Me_2CO (95 : 5) – A, $CHCl_3$–Me_2CO (90 : 10) – B, $CHCl_3$–Me_2CO (80 : 20) – C, $CHCl_3$–Me_2CO (60 : 40) – D. The spots were

detected with conc. H_2SO_4. The evaporation of the solutions was done in vacuo at a temperature not exceeding 40°C. The melting points were determined on a Kofler block. The NMR spectra were taken in $CDCl_3$ on a Varian D-60-A1L spectrometer.

The obtained compounds are chromatographically homogeneous in the appropriate systems of solvents. All of the orthoesters are hydrolyzed completely under the conditions of the analytical test for orthoesters [4, 5]. In order to avoid hydrolysis, the obtained orthoesters are stored in the presence of a small amount of pyridine or in a desiccator over caustic.

1,2-O-Methylorthobenzoyl-α-D-xylopyranose (III). A solution of 92.4 mmoles of (I) [2] in a mixture of 120 ml of CH_3NO_2, 60 ml of lutidine and 4.5 ml of CH_3OH was allowed to stand at 37° for two days. To the reaction mixture was then added 500 ml of $CHCl_3$, and the solution was washed in succession with 100 ml of water, saturated $NaHCO_3$ solution (3 × 100 ml), and water (3 × 100 ml), and evaporated in vacuo. Here the formerly clear solution acquires a green color, which becomes dark brown toward the end of the evaporation. Any residual lutidine was removed by azeotropic distillation with toluene and heptane. The dark brown residue was dissolved in 100 ml of absolute methanol, 10 ml of a 1 N solution of CH_3ONa in absolute methanol was added, and the mixture was allowed to stand for 2 h. The solution assumes an intense raspberry color.

To the reaction mixture was added 150 ml of water and the whole was extracted with $CHCl_3$ (4 × 150 ml), after which the extract was washed with water (3 × 100 ml), in which connection all of the colored substance is washed out with the water. The clear chloroform solution was evaporated in vacuo. To the residue was added 150 ml of heptane, and the mixture was shaken well and allowed to stand for 5-6 h, after which the heptane was decanted.

In this connection nearly all of the methyl benzoate is removed with the heptane; in case of need the operation was repeated. The $C_6H_5CO_2CH_3$ can also be removed by rough chromatography on Al_2O_3: the residue after evaporation was deposited on Al_2O_3; the $C_6H_5CO_2CH_3$ was eluted with CCl_4, and the substance was washed out with a $CHCl_3$ – acetone mixture (1 : 1). The yield of (III) was 12.0 g (48%); $[\alpha]_D^{22}$ + 32° (1.0; $CHCl_3$). Found: C 58.31; H 6.12%. $C_{13}H_{16}O_6$. Calculated: C 58.24; H 6.00%. TLC on silica gel in systems B and C.

1,2-O-Methylorthobenzoyl-3,4-di-O-benzoyl-α-D-xylopyranose (II). To a solution of 4.44 mmoles of (III) in 30 ml of pyridine, cooled to 0°, was carefully added 3.8 ml of C_6H_5COCl, and the mixture was allowed to stand at room temperature for 3 h. Then the reaction mixture was diluted with 250 ml of $CHCl_3$, washed in succession with 50 ml of water, saturated $NaHCO_3$ solution (3 × 50 ml) and water (3 × 50 ml), and evaporated in vacuo. The yield of (II) was 1.8 g (86%). TLC on silica gel in system A.

1,2,4-Orthobenzoyl-α-D-xylopyranose (IV). A solution of 15 mmoles of (III) in 100 ml of dichloroethane was boiled in a flask connected to a descending condenser, at the same time distilling off and adding the solvent in drops in such a manner that the volume of the solution remained constant. At the same time a solution of 0.09 mmole of TsOH in 40 ml of DCE was boiled, distilling off about 15 ml of the solvent. After about 20 ml of DCE had been distilled from the solution of (III), to the (III) solution was added the TsOH solution, after which the process was continued under the above indicated conditions (dropwise addition and distillation of the solvent) until reaction was complete (about 30 min, the composition of the reaction mixture was periodically checked by TLC on Al_2O_3 in system D). Then 1.0 ml of pyridine was added, and the mixture was cooled and evaporated in vacuo. The residue was recrystallized from benzene. The yield of (IV) was 2.1 g (60%); mp 144-145°; $[\alpha]_D^{22}$ + 67° (1.16; $CHCl_3$). Found: C 61.30; H 5.30%. $C_{12}H_{12}O_5$. Calculated: C 61.02; H 5.08%. TLC on silica gel in system B.

1,2,4-Orthobenzoyl-3-O-acetyl-α-D-xylopyranose (V). To a solution of 1.70 mmoles of (IV) in 10 ml of pyridine was added 1.5 ml of $(CH_3CO_2)O$ and the mixture was allowed to stand overnight. The mixture was evaporated with toluene, while the residue was evaporated with a 5% solution of pyridine in toluene (3 × 15 ml). The residue was dissolved in 80 ml of $CHCl_3$, washed in succession with saturated $NaHCO_3$ solution (3 × 15 ml) and water (3 × 15 ml), and evaporated in vacuo. The residue was recrystallized from MeOH. The yield of (V) was 0.43 g (73%); mp 159-161°; $[\alpha]_D^{22}$ + 55° (0.98; $CHCl_3$). Found: C 60.71; H 5.18%. $C_{14}H_{14}O_6$. Calculated: C 60.43; H 5.04%. TLC on silica gel in system A.

1,2,4-Orthobenzoyl-3-O-benzoyl-α-D-xylopyranose (VI). To a solution of 25.42 mmoles of (IV) in 50 ml of pyridine at 0° was carefully added 4.6 ml of C_6H_5COCl, after which the mixture was let stand at room temperature for 2 h. The reaction mixture was diluted with 200 ml of $CHCl_3$, washed in succession

with 50 ml of water, saturated $NaHCO_3$ solution (3 × 50 ml) and water (3 × 50 ml), and evaporated in vacuo. Traces of pyridine were removed by azeotropic distillation with toluene and heptane. The residue was recrystallized from methanol. The yield of (VI) was 7.9 g (91%); mp 136-137°; $[\alpha]_D^{22}$ + 52° (0.92; $CHCl_3$). Found: C 67.10; H 4.82%. $C_{19}H_{16}O_6$. Calculated: C 67.06; H 4.71%. TLC on silica gel in system A.

1,2,4-Orthobenzoyl-3-O-carbamoyl-α-D-xylopyranose (VII). To a solution of 14.8 mmoles of (IV) in 30 ml of freshly distilled pyridine (over P_2O_5) was added 16.5 mmoles of phenyl isocyanate. The reaction mixture was kept at 100° for 2 h without the admittance of moisture. The mixture was evaporated in vacuo to dryness, and the residue was dissolved in 20 ml of ether and kept at 0° for 2 h. The crystals of diphenylurea were separated, and the filtrate was evaporated in vacuo to dryness. The residue was recrystallized from toluene–heptane. The yield of (VII) was 3.8 g (71%); mp 128-129°; $[\alpha]_D^{22}$ + 53° (1.05; $CHCl_3$). Found: C 64.13; H 5.08; N 4.03%. $C_{19}H_{17}O_6N$. Calculated: C 64.23; H 4.78; N 3.94%. TLC on silica gel in system A.

2,4-Di-O-benzoyl-3-O-carbamoyl-β-methyl-D-xylopyranoside (IX). From a solution of 6.62 mmoles of (VII) in 70 ml of CH_3NO_2 was distilled off about 25 ml of solvent, after which 0.25 mmole of $HgBr_2$ and 1.0 ml of CH_3OH were added, and the mixture was refluxed without the admittance of moisture for 3 h (the composition of the reaction mixture was checked periodically by TLC on silica gel in system B). The mixture was cooled, 1.0 ml of pyridine was added, and the mixture was evaporated in vacuo to dryness. The residue, namely 2-O-benzoyl-3-O-carbamoyl-β-methyl-D-xylopyranoside (VIII), does not give a hydrolytic test for the orthoester group and, based on the TLC data (on silica gel in systems A and B), contains one free OH group.

Compound (VIII) was dissolved in 20 ml of pyridine, 9 mmoles of C_6H_5COCl was added, and the mixture was allowed to stand at room temperature for 2 h. The reaction mixture was diluted with 100 ml of $CHCl_3$, washed in succession with water (30 ml), saturated $NaHCO_3$ solution (3 × 30 ml) and H_2O solution (3 × 30 ml), and evaporated in vacuo to dryness. The residue was recrystallized from toluene. The yield of (IX) was 2.32 g [72.5%, when based on (VII)]; mp 197-198°; $[\alpha]_D^{22}$ – 25° (0.96; $CHCl_3$). Found: C 66.35; H 5.25; N 2.91%. $C_{27}H_{25}O_8N$. Calculated: C 66.00; H 5.09; N 2.83%. TLC on silica gel in system A.

Under conditions, analogous to those used for the preparation of (VIII), from 3.27 mmoles of 1,2,4-orthoacetyl-3-O-carbamoyl-α-D-xylopyranose (X) [1] in 20 ml of CH_3NO_2, 0.14 mmole of $HgBr_2$ and 0.5 ml of CH_3OH was obtained 2-O-acetyl-3-O-carbamoyl-β-methyl-D-xylopyranoside (XI). The reaction time was 2 h. Compound (XI) does not give a hydrolytic test for the orthoester group and, based on the TLC data (silica gel in system B), it contains one free hydroxyl group.

To a solution of (XI) in 10 ml of absolute CH_3OH was added 0.5 ml of a 1 N solution of CH_3ONa in absolute CH_3OH, and the mixture was allowed to stand at room temperature for 90 min. To the reaction mixture was added 100 ml of water, and the mixture was washed with $CHCl_3$, neutralized with KU-2 (H^+), and evaporated in vacuo to dryness. Traces of water were removed by azeotropic distillation with pyridine. The residue, being 3-O-carbamoyl-α-methyl-D-xylopyranoside (XII), was dissolved in 10 ml of pyridine, 10 mmoles of C_6H_5COCl was added, and the mixture was allowed to stand at room temperature for 4 h.

The reaction mixture was diluted with 100 ml of $CHCl_3$, washed in succession with water (30 ml), saturated $NaHCO_3$ solution (3 × 30 ml), H_2O (3 × 30 ml), and evaporated in vacuo to dryness. The residue was recrystallized from toluene. The yield of (XI) was 0.62 g [57%, when based on (X)]; mp 194-196°. After recrystallization from CH_3OH, mp 196.5-197°; $[\alpha]_D^{22}$ – 24° (0.83; $CHCl_3$).

The IR spectra of the (IX) compounds, obtained by the two methods, were identical, and the mixed melting point was not depressed. The compounds are chromatographically homogeneous (TLC on silica gel in systems A and B, and on Al_2O_3 in system A).

CONCLUSIONS

1. The bicyclic and tricyclic orthobenzoates of α-D-xylopyranose were obtained.

2. A study was made of the behavior of the tricyclic orthoesters of α-D-xylopyranose under the conditions of the orthoester method for the synthesis of glycosides.

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