TETRAMETHYLACETAL OF THE RACEMIC STREPTOSE*

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2,5-Dimethoxy-3-(dimethoxymethyl)-2-methyl-2,5-dihydrofuran (*I*), the product of the electrolytical methoxylation of 3-formyl-2-methylfuran, and the dimethylacetal of *trans*-4-acetoxy-3-(dimethoxymethyl)-2-penten-1-al (*VIII*), the product of the anodic oxidation of 3-(1-acetoxyethyl)thiophene, were used as the staring material in the synthesis of the tetramethylacetal of the racemic streptose (*VI*) and its *ribo*-isomer *VII*.

While the existing syntheses of streptose[1] have been mainly based on the formation of the branched carbon chain by means of addition reactions at the keto group of the starting ketonic sugar[1-5], an attempt has been now made to create the carbon chain of streptose from heterocyclic compounds of the furan and thiophene series. 3-Formyl-2-methylfuran[6,7] (a satisfactory preparation of this compound has been accomplished in this Laboratory[8]) and 3-(1-hydroxyethyl)thiophene[9] were used as the starting material in the present synthesis.

Electrolytical oxidations in methanol (investigated in this Laboratory from the standpoint of the sugar synthesis both in the furan[10-12] and the thiophene[13] series) constituted the first step in both alternatives of our synthesis. Thus, 3-formyl-2-methylfuran is converted by this reaction to 2,5-dimethoxy-3-(dimethoxymethyl)-2-methyl-2,5-dihydrofuran (*I*), the yield of which (75%) is favourably influenced by the use of ammonium bromide as electrolyte[11]. On the basis of NMR spectrum, *i.e.*, nonequivalent protons in methyl groups at position 2 (1·38 and 1·45δ) as well as protons at position 5 (5·32 and 5·56δ), the ratio of isomers differing in the mutual position of the methoxyl groups may be inferred from the intensity of both signals. This ratio of the *cis*- to the *trans*-isomer was found 1 : 3. The spectrum was measured at 60 and 80 MHz; as indicated by the direct dependence of the difference of both proton signals in the methyl group at position 2 on the frequency, there are involved signals of two nonequivalent methyl groups, not a doublet. We did not pay attention to the separation of the geometrical isomers, since the isomerism at carbon atoms 2 and 5 disappears in the subsequent synthetic steps.

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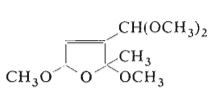
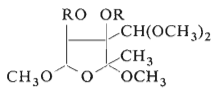
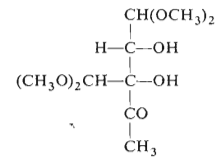
The hydroxylation of the double bond of the acetal *I* is preferably accomplished with potassium permanganate in the presence of magnesium sulfate in aqueous acetone (for the earlier applications to analogous types of compounds see ref.[10,12]). We obtain the crude 3,4-dihydroxy-2,5-dimethoxy-3-(dimethoxymethyl)-2-methyltetrahydrofuran (*III*) which is unstable when distilled and must be therefore purified through the diacetyl derivative *II*. Transesterification according to Zemplén[14] liberated the pure diol. As indicated by analysis and gas chromatography in combination



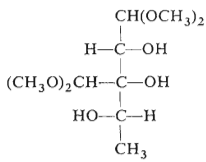
I



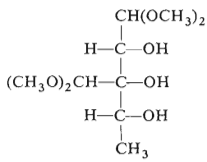
II, R = $COCH_3$
III, R = H
IV, R = $Si(CH_3)_3$



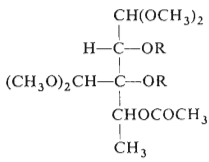
V



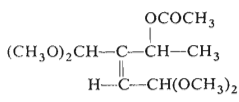
VI



VII



IX, R = H
X, R = $COCH_3$



VIII

In formulae *V*—*X* only one of the enantiomers is demonstrated.

with mass spectrometry, the purity is of at least 90%. The analysis was performed after conversion to the trimethylsilyloxy derivative *IV*. The product *III* obtained *via* the diacetyl derivative *II* was composed from three configurational isomers. This reaction step confirmed the suitability of the choice of 3-formyl-2-methylfuran as the starting compound since this route leads to a mixture of the *lyxo*- and *ribo*-isomer of the final product (*VI* and *VII*) while 3-acetylfuran would afford the *arabino*- and *xylo*-isomer[15]. The *trans*-hydroxylation of the latter types of compounds was shown to furnish very low yields of diols[16].

The cyclic acetal bonds were cleaved without any complications when compound *III* in methanol was stirred at room temperature for 4 days in the presence of Dowex 50W ion exchange resin. The IR spectrum of the resulting dimethylacetal of 5-deoxy--3-C-(dimethoxymethyl)-DL-*erythro*-4-pentulose (*V*) exhibits a marked absorption of the ketonic group. The lithium aluminum hydride or sodium borohydride reduction of compound *V* afforded a mixture of the *lyxo*- and *ribo*-isomers (*VI* and *VII*) of 5-deoxy-3-C-(dimethoxymethyl)pentose. As determined by gel filtration after conversion to the triacetyl derivative, the mixture contained 64% of the *ribo*- and *lyxo*-isomers in the ratio 7 : 13. The composition of this mixture was identical with that obtained with the use of 3-(1-hydroxyethyl)thiophene as the starting material.

The *ribo-lyxo* mixture was separated by column chromatography on silica gel and gradient elution into DL-streptose tetramethylacetal (*VI*) and the isomeric 5-deoxy-3-C-(dimethoxymethyl)-DL-ribose dimethylacetal (*VII*). The structure of compounds *VI* and *VII* was confirmed by NMR spectra. The R_F values 0·43 (*VI*) and 0·39 (*VII*) were determined by thin-layer chromatography on silica gel in the solvent system benzene–2-propanol–ethyl acetate (17 : 1 : 2). The order of components does not change when the thin-layer chromatography is performed on silica gel impregnated with a borate complex; the R_F value 0·39 was therefore ascribed to the *ribo* compound *VII* (*cf.*[17]).

In the thiophene series, the synthesis was started from 3-(1-hydroxyethyl)thiophene which is preferably accessible by reaction of 3-thienyllithium with acetaldehyde[9]. The use of 3-formyl-2-methylthiophene is less suitable because of its difficult preparation[18,19]. 3-Acetylthiophene cannot be taken into consideration since its anodic oxidation is accompanied by addition of one molecule of methanol to the double bond[13]. The anodic oxidation of 3-(1-acetoxyethyl)thiophene (obtained by acetylation with acetic anhydride in pyridine) was found to afford better yields than of the free alcohol. The oxidation was performed analogously to the preparation of compound *III* except for the use of sulfuric acid as the electrolyte. *trans*-4-Acetoxy--3-(dimethoxymethyl)-2-penten-1-al dimethylacetal (*VIII*) is obtained as the main product. The double bond is isomerised by the action of the mineral acid[16,20]. Under these circumstances, compound *VIII* was subjected to the *cis*-hydroxylation leading to a mixture of 4-acetoxy-2,3-dihydroxy-3-(dimethoxymethyl)-1-pentanal (*IX*) *lyxo*- and *ribo*-isomers. Both potassium permanganate and osmium tetraoxide in the presence of sodium chlorate proved as suitable reagens. The crude compounds *IX* were then converted to a mixture of the configurational isomers of the triacetate *X*. This mixture was identical with that obtained in the furan series as shown by NMR spectroscopy and gel filtration. The acetals *VI* and *VII* are resistant towards Dowex 50W ion exchange resin in aqueous media as well as towards acetic acid. On the other hand, complicated reactions occur in 10% aqueous hydrochloric acid.

EXPERIMENTAL

Temperature data are uncorrected. Anodic oxidations were performed in an electrolysis apparatus (volume, 300 ml) with a graphite electrode at 25 V. IR spectra were taken in tetrachloromethane on a Zeiss UR 10 apparatus. NMR spectra were measured in tetrachloromethane on a BS 477 Tesla Brno 60 MHz and BS 487A Tesla 80 MHz apparatus (hexamethyldisiloxane as internal standard). Mass spectra were recorded on a Gas Chromatograph-Mass Spectrometer LKB 9000 (AB Stockholm) apparatus.

3-(Dimethoxymethyl)-2,5-dimethoxy-2-methyl-2,5-dihydrofuran (*I*)

The electrolytical methoxylation of 3-formyl-2-methylfuran (38 g; 0·35 mol) was performed in methanol (300 ml) in the presence of ammonium bromide (6 g) at 20—25 V, 45 A. h, —35°C (the end of the reaction manifests itself by increase of the solution resistance). The reaction mixture was then adjusted to pH 8 with methanolic sodium methoxide and the methanol was evaporated under diminished pressure. The residue was dissolved in ether, the salts filtered off, the filtrate dried over anhydrous sodium sulfate, evaporated, and the residue distilled to afford 39·5 g (75·5%) of compound *I*, b.p. 106°/11 Torr. For $C_{10}H_{18}O_5$ (218·2) calculated: 55·03% C, 8·31% H, 45·17% OCH_3; found: 55·09% C, 8·38% H, 44·97% OCH_3. IR spectrum: 958, 980, 1 020, 1 085, 1 398, 1 445, 1 479, 1 553, 2 826, 2 938, and 2 998 cm^{-1}. NMR spectrum: 1·38 and 1·45 (total 3 H, nonequivalent CH_3 protons), 2·80 and 3·15 (total 12 H, CH_3O), 5·32 and 5·56 (1 H, position 5), 4·74 and 5·94 (total 2 H) δ. The methoxylation can be performed directly with the crude mixture of products from the condensation of chloroacetaldehyde with sodium hydroxymethylacetone; after the rectification, there is obtained a 60% yield of compound *I*.

3,4-Diacetoxy-2,5-dimethoxy-3-(dimethoxymethyl)-2-methyltetrahydrofuran (*II*)

A solution of the acetal *I* (9 g; 0·042 mol) in acetone (200 ml) was cooled down to —15°C and treated dropwise under stirring over 45 min with 160 ml of an aqueous solution containing potassium permanganate (5·8 g; 0·01 mol) and magnesium sulfate heptahydrate (4·6 g; 0·01 mol). The mixture was stirred under cooling for additional 30 min and then kept at room temperature overnight. Gaseous sulfur dioxide was introduced into the cooled mixture to dissolve the precipitate of manganese dioxide. The reaction mixture was then extracted with three 20 ml portions of light petroleum to recover 1·7 g of compound *I*. The aqueous phase was concentrated under diminished pressure to the volume of 150 ml, the concentrate saturated with potassium carbonate, and extracted continuously with ether for 100 h. The extract was dried over anhydrous sodium sulfate and evaporated to yield 3·5 g (36·4%) of the crude diol *III*. The crude material was dissolved in pyridine (40 ml) and the solution treated at 0°C with acetic anhydride (10 g). The mixture was kept at room temperature for 2 days and poured onto crushed ice (300 g). The product was extracted with three 50 ml portions of ether, the extract dried over anhydrous sodium sulfate, and evaporated under diminished pressure to remove pyridine and ether. Distillation of the residue yielded 68% of the diacetate *II*, b.p. 145°C/0·2 Torr. IR spectrum: 898, 998, 1 222, 1 376, 1 442, 1 752, 2 832, 2 951, and 3 001 cm^{-1}.

3,4-Dihydroxy-2,5-dimethoxy-3-(dimethoxymethyl)-2-methyl-tetrahydrofuran (*III*)

A solution of the diacetate *II* (4 g) in methanol (200 ml) was treated with methanolic sodium methoxide (from 1 g of sodium) and the mixture kept at room temperature for 4 days. Gaseous carbon dioxide was then introduced for 2 h, the methanol evaporated under diminished pressure, and the residue extracted with chloroform. The extract was filtered and the filtrate evaporated to afford 2·8 g (96%) of a viscous mixture of the configurational isomers of compound *III*. For

$C_{10}H_{20}O_7$ (252·3) calculated: 47·61% C, 7·99% H, 49·21% OCH_3; found: 47·41% C, 7·85% H, 48·65% OCH_3. IR spectrum: 895, 996, 1386, 1455, 2828, 2936, 3011, 3500, and 3576 cm^{-1}.

Analysis of the isomeric mixture. A solution of the crude product *III* (10 mg) in pyridine (1 ml) was treated with hexamethyldisilazane (0·2 ml) and trimethylchlorosilane (0·1 ml), the whole mixture vigorously shaken, kept at room temperature for 15 min, and examined by gas chromatography in combination with mass spectrometry (3 m column packed with 5% SE-30, programmed temperature 120—170°C, helium as carrier gas. In addition to a small amount of a lower fraction, the product contained 3 configurational isomers of 2,5-dimethoxy-3-(dimethoxymethyl)-2-methyl-3,4-bis(trimethylsilyloxy)tetrahydrofuran (*IV*) of identical mass spectra, differing somewhat only in intensities of ionic species. The mass spectrum shows a characteristic $(M\text{-}90)^+$ ion, 306 *m/e*. Further ionic species: 72 (100%), 75 (86%), 85 (42%), 43 (40%), 99 (38%), 79 (28%), 45 (27%), 89 (24%), 143 (19%), 159 (17%), 187 (16%), 275 (16%), 93 (14%), 147 (14%), 157 (14%), 93 (13%), and 173 (12%) *m/e*.

5-Deoxy-3-C-(dimethoxymethyl)-DL-*erythro*-4-pentulose Dimethylacetal (*V*)

A solution of the diol *III* (5 g; 0·02 mol) in methanol (300 ml) was treated with Dowex 50W ion exchange resin (50 ml) and the whole stirred at room temperature for 4 days. The resin was filtered off and washed with two 30 ml portions of methanol. The filtrate and washings were combined and evaporated under diminished pressure to afford 4·6 g (92%) of compound *V* as a viscous sirup. For $C_{10}H_{20}O_7$ (252·3) calculated: 47·61% C, 7·99% H, 49·21% OCH_3; found: 47·39% C, 7·92% H, 48·86% OCH_3. IR spectrum: 805, 895, 990, 1376, 1448, 1721, 2828, 2928, 2945, 2987, 3460, and 3570 cm^{-1}.

Reduction. To a solution of compound *V* (2·5 g; 0·01 mol) in ether (50 ml), there was added under stirring lithium aluminum hydride (0·4 g) in ether (20 ml), the whole mixture stirred for 2 h, and decomposed successively with 0·4 ml of water, 0·4 ml of 15% aqueous sodium hydroxide, and 1·2 ml of water. The inorganic salts were filtered off and the filtrate was evaporated under diminished pressure to afford 1·6 g (63%) of 5-deoxy-3-C-(dimethoxymethyl)pentose dimethylacetal isomers differing in configuration at carbon atom 4. For $C_{10}H_{22}O_7$ (254·3) calculated: 47·24% C, 8·72% H, 48·82% OCH_3; found: 47·12% C, 8·79% H, 49·15% OCH_3. IR spectrum: 886, 992, 1197, 1228, 1379, 1463, 2821, 2931, 3009, 3440, and 3560 cm^{-1}. The isomeric mixture (700 mg) was chromatographed on a column (30 cm of length and 25 mm of diameter) of silica gel (Merck). The column was washed with pure benzene and then with the use of a gradient, 2% to 10% of ethyl acetate per each 200 ml. 2-Propanol (0·2—2·0%) was then added per each 500 ml. The 100 ml fractions of the effluent were separately evaporated and checked by thin-layer chromatography on silica gel G (Merck) in the solvent system benzene–ethyl acetate–2-propanol (17 : 2 : 1). Two products were obtained. DL-Streptose tetramethylacetal (*VI*), yield 240 mg, R_F value 0·43, NMR spectrum: 1·29 (J = 6·5 Hz) (3 H, d, $C_{(5)}$), 3·20 (3 H, s, OH), 3·37 (6 H, s, OCH_3), 3·38 (6 H, s, OCH_3), 3·88 (J = 1·2 Hz) (1 H, d, $C_{(2)}$), 4·43 (1 H, q, $C_{(4)}$), 4·79 (J = = 1, 2 Hz) (1 H, d, $C_{(1)}$), and 5·04 (1 H, s, $C_{(3)}$H) δ; and 5-deoxy-3-C-(dimethoxymethyl)-DL-ribose dimethylacetal (*VII*), yield 130 mg, R_F value 0·39, NMR spectrum: 1·24 (J = 6·5 Hz) (3 H, d, $C_{(5)}$), 3·20 (3 H, s, OH), 3·51 (6 H, s, OCH_3), 3·52 (6 H, s, OCH_3), 3·84 (J = 1·2 Hz) (1 H, d, $C_{(2)}$), 4·26 (1 H, q, $C_{(4)}$), 4·65 (J = 1·2 Hz) (1 H, d, $C_{(1)}$), and 5·01 (1 H, s, $C_{(3)}$) δ.

trans-4-Acetoxy-3-(dimethoxymethyl)-2-penten-1-al Dimethylacetal (*VIII*)

A mixture of 3-(1-acetoxyethyl)thiophene[13] (29 g; 0·17 mol), conc. sulfuric acid (1 ml), and methanol (300 ml) was electrolysed (graphite anode) at-20°C, 20 V and 45 Amp. h, and the products

were isolated analogously to preparation of compound *I*. The rectification afforded 10·3 g (23%) of compound *VIII*, b.p. 105—110°C/0·5 Torr. For $C_{12}H_{22}O_6$ (262·3) calculated: 54·93% C, 8·46% H; found: 55·01% C, 8·45% H. IR spectrum: 915, 978, 1245, 1381, 1457, 1698, 1749, 2830, 2905, 2930, 2944, and 2995 cm^{-1}. NMR spectrum: 1·32 (J = 5·2 Hz) (3 H, d, CH_3), 2·00 (3 H, s, CH_3CO), 3·24, 3·36, 3·41 (total 12 H, s, OCH_3), 5·37 (1 H, q, CHOCO—), 4·98, 5·15, and 5·59 (total 3 H, remaining protons) δ.

4-Acetoxy-2,3-*erythro*-dihydroxy-3-(dimethoxymethyl)-1-pentanal Dimethylacetal (*IX*)

A. A solution of osmium tetraoxide (0·5 g) in water (35 ml) was treated with the acetal *VIII* (14 g; 0·054 mol) and to this mixture a solution of sodium chlorate (5 g) in water (50 ml) was added dropwise under stirring. The stirring was continued for 10 h at 50—60°C, the mixture cooled down, extracted with benzene, and the extract evaporated to afford 4·2 g (27%) of the acetal *IX*.

B. The acetal *VIII* (26·2 g; 0·1 mol) was hydroxylated with potassium permanganate in aqueous acetone analogously to the preparation of compound *II*. There was obtained 7·2 g (45·3%) of the acetal *IX* and recovered 12·2 g of the starting compound *VIII*.

2,3,4-Triacetoxy-3-(dimethoxymethyl)-1-pentanal Dimethylacetal (*X*)

Acetylation of the monoacetyl derivative *IX* (4·2g) (*cf.* the preparation of compound *II*) afforded 2·1 g (39%) of the triacetate *X*, a viscous sirup, b.p. 130°C/0·3 Torr. For $C_{16}H_{28}O_{10}$ (380·4) calculated: 50·52% C, 7·42% H, 31·84% OCH_3; found: 50·68% C, 7·33% H, 31·56% OCH_3.

Deacetylation. The triacetate *X* (4 g) was added to methanolic sodium methoxide (from 1 g of sodium and 200 ml of methanol) and the mixture kept at room temperature for 4 days. Carbon dioxide was then introduced for 2 h, the methanol evaporated under diminished pressure, and the residue extracted with chloroform. The extract was filtered and evaporated to afford a mixture (2·8 g; 92%) of isomers *VI* and *VII*. The IR spectrum of this mixture was identical with that of the isomeric mixture obtained in the furan series from compound *V*. For $C_{10}H_{22}O_7$ (254·3) calculated: 47·24% C, 8·72% H, 48·82% OCH_3; found: 47·40% C, 8·75% H, 48·12% OCH_3.

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