Methylthiomethyl ethers of methyl α-L-rhamnopyranoside

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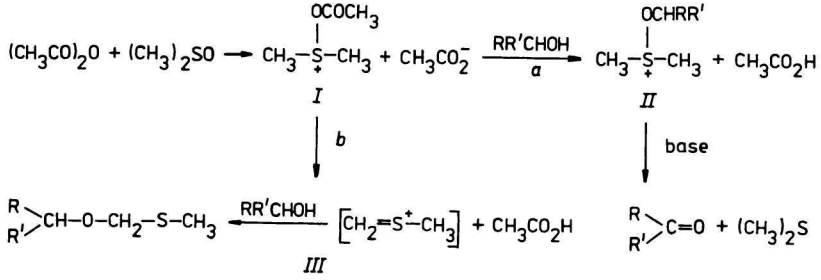
Under suitable conditions, the mixture of dimethyl sulfoxide and acetic anhydride can be applied for effective methylthiomethylation of the hydroxyl groups in a sugar unit. Thus from methyl 2,3-di-*O*-methyl-, methyl 3-*O*-methyl-, and methyl α-L-rhamnopyranoside, the corresponding methylthiomethyl ethers have been obtained in good yields.

Смесь диметилсульфоксида и ацетангидрида можно при подходящих условиях применить для эффективного метилтиометилирования гидроксильной группы сахаров. Так, например, из метил-2,3-ди-*O*-метил-, метил-3-*O*-метил- и метил-α-L-рамнопиранозида были получены соответствующие метилтиометиловые эфиры с хорошим выходом.

In connection with the studies on the sugar derivatives having antibacterial effect, our attention was focused on the preparation of sulfur derivatives of saccharides which were supposed to exhibit this effect. Methylthiomethylation using chloromethyl methyl sulfide and sodium hydride [1] represents relatively simple method of sulfur atom introduction into a sugar molecule. Nevertheless, it is inapplicable to base-sensitive compounds and only modest yields obtained from secondary alcohols have been reported [2]. Methylthiomethyl ethers, were, however, often isolated as by-products of the oxidation of saccharides with dimethyl sulfoxide and acetic anhydride [3] (DMSO—Ac_2O) affording, in some cases, relatively high yields [4]. It is generally accepted [3] that the nucleophilic reaction

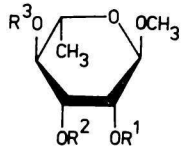


Scheme 1

between dimethyl sulfoxide and acetic anhydride takes place at first, giving rise to a sulfonium ion *I* (Scheme 1). This may further react: *a*) with an alcohol to give the intermediate *II* with subsequent conversion to a carbonyl derivative, or *b*) unsaturated sulfonium ylid *III*, formed after elimination of acetic acid, reacts with alcohol giving rise to the corresponding methylthiomethyl ether.

The yield of methylthiomethyl ethers depends, *inter alia*, on the steric arrangement of hydroxyl groups in a sugar residue [3, 5] and on the reaction temperature applied [5, 6]. It is also reported [5] that a small addition of acetic acid stimulates the methylthiomethyl ether formation.

The present work shows that the reaction of DMSO—Ac_2O with methyl 2,3-di-*O*-methyl-α-L-rhamnopyranoside *IV*, methyl 3-*O*-methyl-α-L-rhamnopyranoside *V*, and methyl α-L-rhamnopyranoside *VI* affords very practical synthesis of the corresponding methylthiomethyl ethers *VII*, *VIII*, and *IX* in a good yield.



	R^1	R^2	R^3
IV	CH_3	CH_3	H
V	H	CH_3	H
VI	H	H	H
VII	CH_3	CH_3	CH_2SCH_3
VIII	CH_2SCH_3	CH_3	CH_2SCH_3
IX	CH_2SCH_3	CH_2SCH_3	CH_2SCH_3

Reaction of DMSO—Ac_2O with *IV* at room temperature for 48 h and subsequent chromatography on a column of silica gel afforded a major product *VII* in the yield of 87%. Its i.r. spectrum did not contain absorption bands characteristic of the carbonyl or hydroxyl groups. ^{1}H-N.m.r. spectrum revealed, except of signals characteristic of the methylated methyl α-L-rhamnopyranosides [7], a 3-proton singlet (δ 2.19) that can be assigned to the —SCH_3 group and a 2-proton singlet (δ 4.85) that belongs to the protons of the —OCH_2S— group.

Similarly, the reaction of DMSO—Ac_2O with *V* and *VI* gave the compounds *VIII* (yield 72%) and *IX* (58%) which did not give bands characteristic of the carbonyl and hydroxyl groups in the i.r. spectrum, too.

^{1}H-N.m.r. spectrum of compound *VIII* contained a sharp 6-proton singlet (δ 2.21) belonging to two —SCH_3 groups and two 2-proton singlets (δ 4.84, 4.79)

assigned to the protons of two —OCH_2S— groups. The compound *IX* gave, *inter alia*, a 3-proton singlet (δ 2.19) and a 6-proton broadened siglet (δ 2.22) that may be assigned to three —SCH_3 groups and a 2-proton singlet (δ 4.84) and a 4-proton broadened singlet (δ 4.78) that belong to three —OCH_2S— groups.

Structure of compounds *VII*, *VIII*, and *IX* was confirmed by mass spectrometry, too. In accordance with the previous results showing that the presence of sulfur in methyl derivatives of the thiosaccharides results in an increased stability of molecular ions [8], the spectra of methylthiomethyl ethers *VII*, *VIII*, and *IX* also contain strong peaks of the molecular ions at *m/z* 266, 312, and 358. The high-resolution measurements confirmed their elemental composition: $C_{11}H_{22}O_5S$ for *VII*, $C_{12}H_{24}O_5S_2$ for *VIII*, and $C_{13}H_{26}O_5S_3$ for *IX*. Spectra of the compounds *VII* and *VIII*, contained peaks of ions of the same origin [8, 9], A_1 at *m/z* 235 and 281, B_1 at *m/z* 222 and 268, $[M-CH_3S\bullet]^+$ at *m/z* 219 and 265, $[M-CH_3SCH_2OH]^{\bullet+}$ at *m/z* 188 and 234, $[M-CH_3SCH_2OH—HCOOCH_3]^{\bullet+}$ at *m/z* 128 and 174, C_2 at *m/z* 129 and 175. The peaks of ions F_1 are at *m/z* 101 and 147 for compound *VII*, 101 and 193 for *VIII*, H_1 at *m/z* 88 appears with compound *VII* only. J_1 at *m/z* 75 was present in both cases.

Structure of the compound *IX* was confirmed by the following fragmentation: $[M-CH_3S\bullet]^+$ at *m/z* 311, $[M-CH_3SCH_2\bullet]^+$ at *m/z* 297, $[M-\bullet OCH_3—CH_3SCH_2OH]^+$ at *m/z* 249, $[M-CH_3SCH_2OH—CH_3SCH_2O\bullet]^+$ at *m/z* 229, C_2 at *m/z* 231, and F_1 at *m/z* 193. The main peak of spectra comprises $CH_2=S^+—CH_3$ ions at *m/z* 61.

The compounds *V* and *VI* having the axial hydroxyl groups at C_2 reacted slower than *IV* and a lower reaction yield was especially with *VI* accompanied by the formation of a higher amount of by-products, mainly of ketonic nature. The temperature increase had a negative influence on the reaction course. For example, at 50°C, the yield of *VIII* was ~10% only. Addition of a small amount of acetic acid to the reaction mixture (Ac_2O : AcOH = 1 : 0.6) had not a substantial influence on the yield increase. On the other hand, the prolongation of the reaction time had a positive effect on the formation of desired product. The optimal yields of *VII* have already been obtained after 48 h and of *VIII* and *IX* after 72 h.

The compounds *VII*, *VIII*, and *IX* manifested remarkable antibacterial effect, *e.g.* towards *Micrococcus luteus, Bacillus licheniformis, Lactobacillus casei, Streptococcus aureus, Escherichia coli* (according to the decreasing effect). More detailed results on a larger number of tested microorganisms will be published later [10].

Experimental

Syntheses of the compounds *IV*, *V*, and *VI* were described elsewhere [7, 11]. Optical rotations were measured on solutions in chloroform with a Perkin—Elmer Model 141

polarimeter at 25°C. T.l.c. was performed on Silufol plates (Kavalier, Votice) with *A*, light petroleum (b.p. 35—50°C)—acetone (5:1) and *B*, light petroleum—acetone (7:1), and detection by charring after spraying with 20% aqueous ammonium sulfate. Preparative chromatography was accomplished on the dry columns of Silica gel L (40—56 μm; Lachema, Brno) using the solvent systems *A* and *B*.

^{1}H-N.m.r. spectra were recorded in chloroform-d at 80 MHz (internal standard Me_4Si) with a Tesla BS 487 B spectrometer. The proton-signal assignments were made by the Indor technique. Mass spectra were measured at 70 eV and 100 μA with a JMS-D 100 (JEOL) instrument. The temperature at the site of sample evaporation, measured with a direct-probe temperature-control unit MS-DPT-01, was 30—40°C. The temperature of ionization chamber was 185°C. Exact mass measurements were performed at a resolution of 10 000. Solutions were concentrated below 50°C under reduced pressure.

Methyl 2,3-di-O-methyl-4-O-methylthiomethyl-α-L-rhamnopyranoside (VII)

To a solution of the compound *IV* (0.67 g) in dry dimethyl sulfoxide (10 ml), acetic anhydride (3 ml) was added and the reaction mixture was stirred at room temperature for 48 h. Solution was then carefully poured into cold saturated aqueous sodium hydrogen carbonate solution (50 ml) and after 30 min the reaction mixture was extracted with chloroform (3 × 30 ml). The extract was washed several times with water (5 × 20 ml), dried ($MgSO_4$) and evaporated to yield a sirupy product. T.l.c. with *A* showed the product to contain a major component, R_f 0.72 together with minor components having slower chromatographic mobility. A sirupy material (0.6 g) was resolved by chromatography on a column (3 × 30 cm) of silica gel with solvent *A*. The obtained main product (0.58 g; 87%) had $[\alpha]_D = -260°$ (*c* 0.42). ^{1}H-N.m.r. data: δ 4.85 (s, 2H, OCH_2S); 4.73 (d, 1H, $J_{1,2}$ 1.7 Hz, H-1); 3.65—3.58 (m, 2H, H-2, H-3); ~3.54 overlapped signals H-4 and H-5; 3.49, 3.44, 3.35 (3s, 9H, CH_3O-1, CH_3O-3, CH_3O-2); 2.19 (s, 3H, SCH_3); 1.27 (d, 3H, J_{5,CH_3} 6.8 Hz, CH_3).

Methyl 3-O-methyl-2,4-di-O-methylthiomethyl-α-L-rhamnopyranoside (VIII)

To a mixture of the compound *V* (0.36 g) and dry dimethyl sulfoxide (5 ml), acetic anhydride (1.5 ml) was added and the reaction run at room temperature for 72 h. After usual work-up, as described above, a sirup was obtained that on t.l.c. in solvent *B* showed to contain a major component having R_f 0.48 and a small amount of other slower-moving components. A sirup (0.32 g) was applied onto a column (3 × 25 cm) of silica gel and eluted with *B*. The obtained main product (0.26 g; 72%) had $[\alpha]_D = -178.3°$ (*c* 1.31). ^{1}H-N.m.r. data: δ 4.84, 4.79 (2s, 4H, $2OCH_2S$); 4.70 (d, 1H, $J_{1,2}$ 1.7 Hz, H-1); 4.31—4.06 (m, 2H, H-2, H-3); ~3.56 overlapped signals H-4 and H-5; 3.46, 3.39 (2s, 6H, CH_3O-1, CH_3O-3); 2.21 (s, 6H, $2SCH_3$); 1.29 (d, 3H, J_{5,CH_3} 6.7 Hz, CH_3).

Methyl 2,3,4-tri-O-methylthiomethyl-α-L-rhamnopyranoside (IX)

Methylthiomethylation of the compound *VI* (1 g) and subsequent chromatography on a column (3.5 × 40 cm) of silica gel with solvent *B* afforded desired product *IX* (0.58 g;

58%), $[\alpha]_D = -181.7°$ (c 1.09), R_f 0.58 (t.l.c., solvent B). ^{1}H-N.m.r. data: δ 4.94—4.63 overlapped signals H-1, H-2, and H-3; 4.84 (s, 2H, OCH_2S); 4.78 (bs, 4H, $2OCH_2S$); 4.04 (q, 1H, $J_{4,5}$ 9 Hz, $J_{4,3}$ 3 Hz, H-4); ~3.66 (q, 1H, $J_{5,4}$ 9 Hz, J_{5,CH_3} 6.5 Hz, H-5); 3.37 (s, 3H, CH_3O-1); 2.22 (bs, 6H, $2SCH_3$); 2.19 (s, 3H, SCH_3); 1.38 (d, 3H, J_{5,CH_3} 6.5 Hz, CH_3).

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